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Lorane Le Franc, Benoit Bernay, Bruno Petton, Marc Since, Pascal Favrel, et al.. A functional m 6 A-RNA methylation pathway in the oyster Crassostrea gigas assumes epitranscriptomic regulation of lophotrochozoan development. FEBS Journal, In press, 10.1111/febs.15500. hal-02952460

# HAL Id: hal-02952460

https://hal.sorbonne-universite.fr/hal-02952460v1

Submitted on 29 Sep 2020

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# A functional m<sup>6</sup>A-RNA methylation pathway in the oyster Crassostrea gigas assumes epitranscriptomic regulation of lophotrochozoan development

Journal:	The FEBS Journal
Manuscript ID	FJ-20-0151.R1
Manuscript Type:	Regular Paper
Date Submitted by the Author:	n/a
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Key Words:	

SCHOLARONE™ Manuscripts

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# Running title

m<sup>6</sup>A-RNA methylation pathway in oyster development

Abbreviations

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A), Methyltransferase like (METTL), Wilms' tumor 1-associated protein (WTAP), RNA-binding motif 15 (RBM15), Ring finger E3 ubiquitin ligase (HAKAI), Zinc finger CCCH-type containing 13 (ZC3H13), AlkB homologue 5 (ALKBH5), Fat mass and obesity associated protein (FTO), YTH domain family protein (YTHDF), YTH domain containing protein (YTHDC), Heterogeneous nuclear ribonucleoproreins A2 B1 (HNRNPA2B1), Proline rich coiled-coil 2a (Prrc2a), Eukaryotic initiation factor 3 (eIF3), Sterile sea water (SSW), Oocytes (E), Fertilized oocytes (F E), Two to eight cell embryos (2/8 C), Hours post fertilization (hpf), Morula (M), Blastula (B), Gastrula (G), D larvae (D), solid-phase reversible immobilization (SPRI), TPM (Transcripts Per Million), Gene ontology (GO), oyster m<sup>6</sup>A-interacting protein (Cg-m<sup>6</sup>A-BPs), S-adenosyl-methionine (SAM), maternal-to-zygotic transition (MZT), acetonitrile (ACN)

Keywords

40 RNA, methylation, epitranscriptomics, oyster, development.

**Conflicts of interest** 

The authors declare they have no competing conflict of interest

#### **Abstract**

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is a prevalent epitranscriptomic mark in eukaryotic RNA, with crucial roles for mammalian and ecdysozoan development. Indeed, m<sup>6</sup>A-RNA and the related protein machinery are important for splicing, translation, maternal-to-zygotic transition and cell differentiation. However, to date, the presence of an m<sup>6</sup>A-RNA pathway remains unknown in more distant animals, questioning the evolution and significance of the epitranscriptomic regulation. Therefore, we investigated the m<sup>6</sup>A-RNA pathway in the oyster *Crassostrea gigas*, a lophotrochozoan model whose development was demonstrated under strong epigenetic influence. Using mass spectrometry and dot blot assays, we demonstrated that m<sup>6</sup>A-RNA is actually present in the oyster and displays variations throughout early oyster development, with the lowest levels at the end of cleavage. In parallel, by in silico analyses, we were able to characterize at the molecular level a complete and conserved putative m<sup>6</sup>A-machinery. The expression levels of the identified putative m<sup>6</sup>A writers, erasers and readers were strongly regulated across oyster development. Finally, RNA pull-down coupled to LC-MS/MS allowed us to prove the actual presence of readers able to bind m<sup>6</sup>A-RNA and exhibiting specific developmental patterns. Altogether, our results demonstrate the conservation of a complete m<sup>6</sup>A-RNA pathway in the oyster and strongly suggest its implication in early developmental processes including MZT. This first demonstration and characterization of an epitranscriptomic regulation in a lophotrochozoan model, potentially involved in the embryogenesis, brings new insights into our understanding of developmental epigenetic processes and their evolution.

# Introduction

The *N*<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is the prevalent chemical RNA modification in all eukaryotic coding and non-coding RNAs [1]. Messenger RNAs are the most heavily m<sup>6</sup>A methylated RNAs, with m<sup>6</sup>A bases lying mostly in their 3' UTRs, at the vicinity of their stop codon [2–4] and also in 5' UTRs and long internal exons [4,5]. *N*<sup>6</sup>-methylation of RNA adenosines is responsible for RNA processing and, like DNA methylation or histone modifications, contributes to the regulation of gene expression without changing the DNA or mRNA sequence. Therefore m<sup>6</sup>A constitutes a new layer of post-transcriptional gene regulation, which is emerging or has been proven critical in various biological processes, and referred to as epitranscriptomic [2].

The dynamics and biological outcomes of m<sup>6</sup>A levels are the results of the activity of a complex protein machinery comprising writers, erasers and readers. The addition of a methyl group to the 6<sup>th</sup> nitrogen of RNA adenosines is catalysed by m<sup>6</sup>A writers with distinct properties. Methyltransferase like 16 (METTL16) is a 'stand-alone' class I methyltransferase that recognizes the UACA\*GAGAA consensus sequence (with \* indicating the target adenosine) [6]. By contrast, METTL3 transfers methyl groups to adenosines within the RRA\*CH motif [2,3,7]. METTL3 is only active within a tripartite 'core complex' [8] comprising METTL3, METTL14 which enhances the methyltransferase activity supported by the MTA-70 domain of METTL3 [9,10] and the regulator protein Wilms' tumor 1-associated protein (WTAP) [4,9,11]. This core complex can interact with Virilizer-like (or KIAA1429) [12], ring finger E3 ubiquitin

independent translation [5].

ligase (HAKAI) [12,13], zinc finger CCCH-type containing 13 (ZC3H13) [12,14], RNA-binding motif 15 (RBM15) and RBM15B [7,15] which are suspected to intervene in the core complex activity and target specificity. The demethylation of adenosines has been demonstrated to be an active process catalysed by eraser enzymes belonging to the Fe(II)/2-oxoglutarate dioxygenase family: AlkB homologue 5 (ALKBH5) [16,17] and the fat mass and obesity associated protein (FTO) [17,18].

A growing number of reader proteins which recognize the m<sup>6</sup>A-RNA mark is being described. They may be divided into two classes depending on the presence of a YT521 B Homology (YTH) domain in their primary sequence. The YTH protein family includes YTH domain family protein 1-3 (YTHDF1-3) and YTH domain containing protein 2 (YTHDC2), which are cytosolic m<sup>6</sup>A readers involved in m<sup>6</sup>A-RNA stability and translation [19–22]. The fifth YTH member is YTHDC1, which is present in the nucleus and controls splicing [23] and nuclear export [24] of m<sup>6</sup>A-RNA. The second class of readers comprises proteins without YTH domain which are

The m<sup>6</sup>A epitranscriptomes underlie important biological functions, most of which being related to developmental processes, including the control of cell differentiation [27–32], maternal to zygotic transition (MZT) [33], sex determination [7,34] and gametogenesis [16,21,35,36]. Such

involved in several molecular mechanisms. For example, the heterogeneous nuclear

ribonucleoprotein A2 B1 (HNRNPA2B1) is important for miRNA processing [25]. Insulin-like

growth factor 2 mRNA binding protein 1-3 (IGF2BP 1-3) [26] and proline-rich coiled-coil 2a

(Prrc2a) [27] participate in RNA stability while eukaryotic initiation factor 3 (eIF3) guides cap-

critical epitransriptomic outcomes are conserved in the animal evolution and were characterized in both vertebrates and ecdysozoans, i.e. mammals and drosophila. However, such conserved biological significance originates in diverse epitranscriptomic mechanisms. Indeed, not all ecdysozoans bear a complete m<sup>6</sup>A-RNA machinery, such as C. elegans whose genome is devoid of the related protein machinery with the exception of a putative orthologue of METTL16 [37,38]. In addition, no m<sup>6</sup>A eraser has been described to date in non-vertebrate models, and especially ecdysozoans such as the drosophila or C. elegans [38–40], where it cannot be excluded that m<sup>6</sup>A-RNA methylation could be removed by the activity of characterised 6mA-DNA demethylases [41,42]. This situation may illustrate a growing complexity of epitranscriptomic mechanisms during the animal phylogeny and raises fundamental questions about its evolution and its presence in organisms distant from mammals and ecdysozoans. However, to date, no data about a possible epitranscriptomic regulation is available to our knowledge in lophotrochozoans, the understudied sister group of ecdysozoans within protostomes, although representing an important range of metazoan biodiversity. The Pacific oyster Crassostrea gigas (i.e. Magallana gigas) is a bivalve mollusc whose great ecological an economical significance allowed its emergence as a model species within lophotrochozoan organisms. As such, an important amount of genetic, transcriptomic and epigenetic data have been generated in this model. Interestingly, the embryolarval development of C. gigas is described to be under the strong epigenetic influence of DNA methylation [43–47] and histone marks [48–50]. Besides, oyster development occurs exposed

to external environmental conditions, and in other models the m<sup>6</sup>A methylation of RNA and/or

the expression of its machinery can be induced by heat stress, UV exposure or endocrine disruptors [5,51–54], questioning the presence of an m<sup>6</sup>A pathway in *C. gigas* and its significance in oyster early development.

To investigate this, we measured m<sup>6</sup>A levels in RNA across the entire embryolarval life of the oyster using mass spectrometry and dot-blot. We also searched the available *in silico* resources for putative conserved m<sup>6</sup>A-related proteins in *C. gigas* genomic data as well as their cognate expression kinetics using RNAseq assembly analyses. We also performed RNA-pulldown with a synthetic m<sup>6</sup>A-RNA oligonucleotide coupled to liquid chromatography and mass spectrometry (LC-MS/MS) to characterize potential oyster m<sup>6</sup>A-binding proteins. To our knowledge, this study is the first report unravelling epitranscriptomic mechanisms outside vertebrate and ecdyzosoan animal models.

# Results:

m<sup>6</sup>A is present in oyster RNA, differentially affects distinct RNA populations and displays variations during embryonic life.

Mass spectrometry measurements revealed that m<sup>6</sup>A is present in oyster RNA, with global m<sup>6</sup>A/A levels of ca. 0.3%, a value comparable to what has been found in the human and the fruit fly (Figure 1A). Immunoblot assays indicate that total and polyA+ RNA present variable amounts of m<sup>6</sup>A during oyster development and that these variations display distinct profiles suggesting specific methylation patterns between RNA populations. Indeed, N<sup>6</sup>A-methylation in total RNA is the highest in the early stages (oocytes and fertilized oocytes) then gradually

decreases until the morula stage before gradually increasing again up to the trochophore stage when it recovers its maximum (Figure 1B). In contrast, m<sup>6</sup>A levels in polyA+ RNA are hardly detected in early stages but display a peak in the gastrula and trochophore stages (Figure 1C).

# m<sup>6</sup>A machinery is conserved at the molecular level in the oyster.

In silico analyses led to the identification of oyster sequences encoding putative orthologues of m<sup>6</sup>A writers, erasers and readers that are present in the human and/or in the human and the fruit fly.

All the eight m<sup>6</sup>A-RNA writers characterized in the human and/or drosophila at the time of the study, namely METTL3, METTL14, WTAP, Virilizer-like, HAKAI, ZC3H13, RBM15/15B and METTL16, were present in the oyster at the gene level. The encoded protein primary sequences all display the specific domains required for enzymatic activity and/or binding. They include MT-A70 and AdoMetMtases SF domains for METTL3, METTL14 and METTL16, respectively, that bear the methyltransferase activity. Oyster WTAP and Virilizer-like orthologues exhibit WTAP and VIR N domains, respectively, that are required in their human counterparts to bind and activate the catalytic subunit of the m<sup>6</sup>A-RNA methyltransferase complex. Oyster Hakai and RBM15/15B present RHHL, RHF-Zn-BS and specific RRM domains, respectively, similar to human and fruit fly orthologues. Besides, the oyster ZC3H13 bears the Rho SF domain present in the human, but not in the fruit fly orthologue (Figure 2A). C. gigas also presents a putative m<sup>6</sup>A-RNA eraser, ALKBH5, which is present in the human but has not been characterized in drosophila. The oyster ALKBH5 exhibits a 20G-FeII Oxy domain suggestive of a presumably conserved catalytic functionality through fe2+-dependent

oxoglutarate oxidation. Of note, no orthologue of the human FTO eraser could be identified in the oyster genomic or transcriptomic databases available to date (Figure 2B).

Many m<sup>6</sup>A reader orthologues have also been found in the oyster, including proteins containing a YTH domain, such as YTHDF, YTHDC1 and YTHDC2. An oyster Prrc2a-like protein produces homology with the human Prrc2a, especially within the m<sup>6</sup>A-binding GRE-rich domain. Oyster readers also include a heterogeneous nuclear ribonucleoprotein-coding gene, hnRNPA2B1 with greater sequence similarity with the drosophila counterpart than with the human orthologue. Similarly, the IGF2BP-coding sequence has also been found in *C. gigas* (Figure 2C). Five oyster sequences display homologies with eIF3a which is able to bind m<sup>6</sup>A-RNA [5] but it was not possible to discriminate whether a unique oyster predicted protein was an eIF3a orthologue.

Overall, these results indicate the conservation of a complete m<sup>6</sup>A-RNA machinery in the oyster. The complete list of the identified genes encoding the conserved m<sup>6</sup>A machinery actors and their isoforms, as well as the related information is given in the supplementary data (Data S1).

## Oyster putative m<sup>6</sup>A actors display expression level variations across development.

RNAseq data analyses showed that all the oyster m<sup>6</sup>A-related genes were expressed during the early life (Figure 3). Their expression level displayed gene-specific profiles, most of them being variable throughout oyster development.

The expression of writers belonging to the core methylation complex is weak overall. METTL3 and WTAP share similar profiles with little expression increasing up to the gastrulation and

remaining stable afterwards. In contrast METTL14 displays a weak expression level across the embryo larval life. The expression profile of Virilizer-like resembles WTAP, while HAKAI, RBM15/15B and METTL16 seem to have mRNA levels which decrease after cleavage, whereas those of ZC3H13 transcript variants seem to drop at the D larva stage. Interestingly, METTL16 mRNA levels display an opposite developmental profile when compared to METTL3 expression; with the highest values during cleavage which decrease later on (Figure 3A). ALKBH5 transcripts are weakly represented within oyster early embryos and the higher TPM values are found in gastrulas. However, maximum levels are observed after metamorphosis in juveniles (Figure 3B). Regarding m<sup>6</sup>A putative readers, the expression of YTH family genes during development showed different patterns. In fact, YTHDF is the most represented YTH-domain bearing actor and YTHDF TPM values are ca. 5-fold higher than all the other oyster YTH readers. YTHDF is strongly expressed at the beginning of development until a peak at the morula stage. Prrc2a is the most represented reader at the mRNA level in oyster embryos, and the sum of the TPM of the two Prrc2a oyster isoforms are at most ca. 20-fold higher than those of YTH family. However, Prrc2a and YTHDF transcript content profiles are similar across oyster development, and also remind of the IGF2BP mRNA levels. By contrast, the two isoforms of YTHDC1 identified by in silico analysis, YTHDC1.1 and YTHDC1.2, display similar patterns together with YTHDC2, with a maximum representation in gastrulas. The expression of hnRNPA2B1 isoforms has likewise patterns except for a marked drop at the D larvae stage (Figure 3 C).

Oyster orthologues of m<sup>6</sup>A-RNA interacting proteins bind m<sup>6</sup>A RNA in vitro.

To determine whether oyster proteins can bind m<sup>6</sup>A-RNA, we performed RNA-pulldown of cytoplasmic and nuclear embryonic cell extracts using a methylated versus a non-methylated oligonucleotide, followed by LC/MS-MS characterisation and identification of the captured proteins with the Mascot software. In nuclear extracts, we detected 591 proteins able to bind both the methylated and unmethylated oligos. We identified 43 proteins specific to unmethylated RNA while 131 proteins specifically bind the m6A-methylated oligo. In cytosolic extracts, there were respectively 646, 436 and 36 of such proteins, respectively. Regardless of the methylation status, more proteins in the cytoplasmic extracts can bind to the RNA oligonucleotides than in the nuclear extracts (1118 proteins vs. 765, respectively). However, more nuclear proteins are found exclusively bound to the m<sup>6</sup>A-containing oligo than cytoplasmic proteins (131 vs. 36, i.e. 17 % vs. 3 %, respectively). In addition, many nuclear and cytoplasmic proteins can bind both the methylated and the non-methylated oligo (591 vs. 646, i.e. 77 % vs. 58 %). An important number of proteins in the cytoplasmic extract were found exclusively bound to the nonmethylated oligo, whereas only a limited number of nuclear proteins display such a specificity (436 vs. 43, i.e. 39 % vs. 6 %). Among the 167 m<sup>6</sup>A-specific proteins in oyster extracts, only 5 were found in both the nuclear and cytoplasmic extracts. These results show that oyster proteins can directly or indirectly bind m<sup>6</sup>A-RNA, and suggest an important compartmentalization of m<sup>6</sup>A-related processes. Among the identified proteins in this assay, four of the putative oyster m<sup>6</sup>A readers are found, YTHDC1, hnRNPA2B1, IGF2BP and eIF3. In the nuclear extracts YTHDC1 is uncovered as

m<sup>6</sup>A-specific whereas hnRNPA2B1 and IGF2BP were present complexed with both the m<sup>6</sup>A-and A-oligos. In the cytoplasmic extracts, YTHDC1 and eIF3a are m<sup>6</sup>A-specific while hnRNPA2B1, IGF2BP were pulled down by both methylated and unmethylated oligos (Figure 4A).

These results demonstrate that some proteins in the oyster can specifically bind m<sup>6</sup>A-RNA and that the putative m<sup>6</sup>A reader orthologues in the oyster are conserved at the protein level and are able to interact with m<sup>6</sup>A-RNA.

# The m<sup>6</sup>A-interacting protein-coding genes display clustered expression regulation and

# functional annotation during oyster development.

The mRNA expression level of the genes encoding the 162 oyster m<sup>6</sup>A-interacting protein (Cg-m<sup>6</sup>A-BPs) was examined using RNAseq databases. Most of them display a specific and regulated expression level across oyster developmental stages. However, three main expression clusters could be distinguished according to their developmental mRNA expression level profile. Cluster 1 includes genes that show high expression at the beginning of the embryo life (i.e. cleavage) and strongly decrease after gastrulation; the second cluster contains weakly expressed genes except in the latest examined larval phases, after gastrulation (i.e. Trochophore and D Larvae); cluster 3 groups genes that show an expression peak during gastrulation (Figure 4B).

related to distinct functional pathways as indicated by the little - if any - common GO terms between them (Figure 4C). However, the functional pathways of all three gene clusters point

out to their implication in translation and its regulation, although the terms enriched in each cluster illustrate different aspects of translation, such as translation initiation (cluster 1), splicing and nuclear export (cluster 2) and ribosomal and mitochondrial processes (cluster 3) respectively (Figure 4D).

# **Discussion**

This work demonstrates that m<sup>6</sup>A-RNA is present and variable during the embryo-larval life of the oyster, and that *C. gigas* exhibits putative conserved and functional m<sup>6</sup>A-RNA writers, eraser and readers. The dynamics of such mark and of its actors strongly suggest a biological significance of the epitranscriptomic pathway in the control of development of a lophotrochozoan species, which has, to date, never been demonstrated to our knowledge.

## m<sup>6</sup>A-RNA levels vary across oyster development.

Using mass spectrometry and immunological measurements, we showed that oyster RNA is m<sup>6</sup>A-methylated. The global proportion of *N*<sup>6</sup>-methyladenosine in RNA in the developing oyster (0.28 %) is similar to those observed elsewhere in the animal kingdom, such as in the fruit fly (0.24 %) [34] or the human (0.11- 0.23 %) [55] (Figure 1A), despite those values are difficult to compare because they were not measured within the same developmental phase (adult flies and human cell lines vs. oyster embryos). However, the comparable magnitude of m<sup>6</sup>A-RNA amounts between taxa, in contrast to DNA methylation [46], may indicate conserved biological significance of epitranscriptomic processes between groups. The amount of m<sup>6</sup>A in total RNA displays a striking decrease during cleavage and then recovers its maximum levels at the end of the gastrulation (Figure 1B). Therefore, the m<sup>6</sup>A decrease in total RNA during cleavage, i.e.

before the transcription of the zygotic genome starts, reflects a degradation of maternal m<sup>6</sup>A-RNAs or their demethylation. However, all RNA populations do not exhibit the same pattern, indeed polyA+ RNAs are m<sup>6</sup>A methylated only after cleavage. The extent of polyadenylation of oyster maternal messenger RNAs accumulating during vitellogenesis is unknown. Therefore, which maternal RNA population(s) is methylated in oyster oocytes is unclear. Nevertheless, the observation that m<sup>6</sup>A-RNA levels are variable and affecting distinct RNA populations across embryonic stages strongly favours an important biological significance of m<sup>6</sup>A-RNA in oyster development. We hypothesize that oyster maternal messenger RNAs are poorly polyadenylated, and that m<sup>6</sup>A, aside polyadenylation, might play a role in the stability of quiescent maternal mRNAs. Alternatively, other maternal RNA populations such as snRNA, miRNA, rRNA or IncRNA might be methylated [6,15,25,56], which become demethylated or degraded up to the morula stage. The later increase in m<sup>6</sup>A RNA after cleavage could therefore be the result of the methylation of the increasingly transcribed RNAs from the blastula stage, including polyadenylated mRNAs.

The m<sup>6</sup>A-RNA machinery is conserved in the oyster and regulated during development. The important regulation of m<sup>6</sup>A levels during oyster development assumes the presence of a related protein machinery. We identified *in silico* cDNA sequences encoding conserved putatively functional orthologues of m<sup>6</sup>A-RNA writers, eraser and readers in the oyster, with great confidence (homologies ranging from ca. 30 to 65 % with their human counterpart, see Data S1). The writers include all the members of the methylation complex (METTL3, METTL14, WTAP, Virilizer-like, Hakai, ZC3H13, RBM15/15B) identified to date in the human and the fruit

fly [7,11,12,14,15,57]. We also identified an orthologue of the stand-alone METTL16 m<sup>6</sup>A

methyltransferase. Each orthologue bears the conserved domain(s) demonstrated to be implicated in the catalytic and/or binding activity of their cognate counterpart in other species, such as the MT-A70 domain which transfers methyl groups from the S-adenosyl-methionine (SAM) to the No nitrogen of RNA adenines [57]. Of the two proteins that can erase RNA methylation, only ALKBH5, which is important for mouse spermatogenesis [16], was identified at the cDNA level in the oyster. Indeed, no C. gigas sequence displayed significant homology with the mammalian FTO protein, whose functional significance remains controversial [17]. Most the characterized m<sup>6</sup>A-RNA readers are also present at the molecular level in the oyster and are putatively able to bind m<sup>6</sup>A regarding their primary sequence, such as the YTHDC and YTHDF family members [19,21,23,58], Prrc2A [27], HnRNPA2B1 [25] and IGF2BP [26]. Of note, some of these readers have not been characterized to date in D. melanogaster but display strong homologies between humans and oysters. In mammals, eIF3a has important functional outcomes in cap-independent translational stress response [5]. However, it was not possible to ascribe a single oyster sequence as a unique eIF3a orthologue (Data S1), although its presence was demonstrated by RNA pull down (see below) (see Data S2). Altogether, in silico results show the conservation of a complete m<sup>6</sup>A-RNA machinery in the oyster. To date to our knowledge, this is the first demonstration in a lophotrochozoan organism of an epitranscriptomic pathway. Its presence suggests its ancestral origin, and questions its biological significance in oyster development. To investigate this, we analysed the expression level of the m<sup>6</sup>A machinery genes using RNAseq data. Our results indicate that the core methylation complex (METTL3, METTL14 and WTAP) would not be active during cleavage because of the absence of METTL3 and little

WTAP expression. METTL16 catalyses the downregulation of SAM methyl donor availability in mammals [59]. If METTL16 function is conserved in the oyster as suggested by the high sequence homology, the peak in METTL16 expression, together with the weak expression of the core complex in 2/8 cell embryos is consistent with an absence of m<sup>6</sup>A-RNA up to the blastula stage. Then, the core complex would likely be active as soon as the end of cleavage (i.e. since the blastula stage), in line with the increase in m<sup>6</sup>A levels observed at the same time. The correlation between the increasing METTL3 expression and m<sup>6</sup>A-RNA levels after cleavage strongly favours the conservation of the methyltransferase activity of the oyster MT-A70 domain. Interpreting the regulation of the m<sup>6</sup>A activity by the other methyltransferase complex members (i.e. Virilizer-like, HAKAI, ZC3H13 and RBM15/15B) is difficult because how - or even if - oyster orthologues act within the complex is not known. Nevertheless, their specific expression profiles may reflect their implication in the regulation of distinct biological contexts. There might be little functional significance of active m<sup>6</sup>A-RNA erasure during oyster development, consistent with the normal embryonic phenotype of ALKBH5 knockdown mice [16]. Overall, the m<sup>6</sup>A readers display distinct developmental expression patterns. While YTHDF and Prrc2a peak during cleavage, YTHDC1, YTHDC2, IGF2BP and hnRNPA2B1 mRNA levels gradually increase up to the gastrulation and remain mostly highly expressed afterwards (except for hnRNPA2B1 and IGF2BP). These profiles evoke the mediation of distinct biological functions depending on the reader and the developmental phases. Therefore, we hypothesized that YTHDF and Prrc2a might participate in the blastulean transition in the oyster. Indeed, in the zebrafish, a YTHDF reader triggers the maternal-tozygotic transition through the decay of the maternal m<sup>6</sup>A RNAs during cleavage [33]. The role

in the axon myelination and specification of mouse oligodendrocytes [27] is unlikely conserved for Prrc2a because the oyster orthologue is expressed before the neurogenesis is detected in trochophore stages [60]. Alternatively, the early expression of Prrc2a suggests that it might rather compete with YTHDF for m<sup>6</sup>A-RNA targets [27], thereby possibly acting in oyster MZT, bringing new perspectives into this process which remains poorly understood in lophotrochozoans. In mammals m<sup>6</sup>A is implicated in the embryonic cell fate [30,31] notably via the regulation of cell differentiation by YTHDC2 [32] or hnRNPA2B1 [29]. In the oyster, YTHDC1, YTHDC2, IGF2BP and hnRNPA2B1 have their maximum expression during gastrulation correlated to the second m<sup>6</sup>A peak, suggesting similar implications.

## Putative oyster m<sup>6</sup>A readers actually bind m<sup>6</sup>A-RNA in vitro.

To better approach the developmental processes involving m<sup>6</sup>A in the oyster, we characterized the proteins that can interact with m<sup>6</sup>A-RNA using a methylated-RNA-pulldown / mass spectrometry assay. We identified 162 proteins able to specifically bind the m<sup>6</sup>A-RNA oligo in embryonic cell extracts, demonstrating the actual presence of genuine m<sup>6</sup>A-readers in the oyster. Most (ca. 75 %) of these proteins were found in nuclear extracts and only 5 were found in both the cytoplasmic and nuclear fractions, showing an important compartmentalization of the epitranscriptomic pathway. Regarding the little number of m<sup>6</sup>A readers in other animals, and because the assay conditions do not discriminate between direct and indirect interactions, we hypothesize that most these proteins indirectly bind m<sup>6</sup>A via a limited number of 'scaffold' m<sup>6</sup>A readers. Such authentic readers that only bind the m<sup>6</sup>A-RNA oligo in our assay likely include YTHDC1 and elF3a, which have been demonstrated to directly bind m<sup>6</sup>A in other species, demonstrating the conservation of the m<sup>6</sup>A-binding capacity and specificity of the YTH

domain in the oyster. Besides, YTHDC1 is found in both cell fractions, suggesting its implication in the trafficking of m<sup>6</sup>A-RNA across the nuclear envelope [24], and reinforcing the hypothesis that YTH proteins could participate in oyster MZT and cell differentiation. The presence of the oyster eiF3a in the cytoplasm is consistent with a conserved role in m<sup>6</sup>A-mediated translation processes, such as cap-independent translation [5].

## Possible functions of m<sup>6</sup>A-RNA in oyster development.

We investigated the expression level and the functional annotation of the 162 genes encoding the m<sup>6</sup>A-interacting proteins across oyster early life. These genes can be clustered into three successive expression phases corresponding to three distinct functional pathways, which are independent albeit all mostly related to translation regulation. The cluster 1 is mostly expressed during the cleavage and the associated GO terms are related to the initiation of translation, consistent with maternal RNA consumption before MZT is complete and the zygotic genome becomes fully activated. The genes within cluster 3 show an expression peak during gastrulation. Their ontology terms evoke ribosomal and mitochondrial processes, the latter being required for energy supply and signalling integration during gastrulation [61–64]. The cluster 2 contains genes that peak after gastrulation and which are related to splicing and nuclear export. Such functional annotations are in line with a fine regulation of transcript variant translation within the distinct cell lineages in the three cell layers of the late embryos.

Taken together, our findings bring to light a possible implication of m<sup>6</sup>A in oyster development. First, during cleavage the decrease of m<sup>6</sup>A-RNA, the weak expression of methyltransferase complex genes, the maximum of YTHDF gene expression and the expression of *Cg*-m<sup>6</sup>A-BPs

related to the initiation of the translation strongly suggest the implication of m<sup>6</sup>A in MZT in C. gigas. Second, the increasing m<sup>6</sup>A level during gastrula stage is correlated to the increase of methyltransferase complex gene expression. In addition, the increased RNA level of readers putatively related to cell differentiation and the peak of gene expression of Cg-m6A-BPs associated to ribosomal and mitochondrial processes, support the hypothesize of a m<sup>6</sup>A implication in gastrulation. Finally, the highest m<sup>6</sup>A level at the trochophore stage, the gene expression of the methyltransferase complex and of readers associated to cell differentiation, as well as high RNA level of Cg-m<sup>6</sup>A-BPs related to splicing and nuclear export is correlated with the fine cell differentiation taking place at this stage. However, inferring the biological significance of m<sup>6</sup>A in development from the indirect and incomplete functional annotation of the oyster genome is only limited. Characterization of the precise targets of m<sup>6</sup>A and how their individual methylation is regulated across development, for example using high throughput sequencing of precipitated m<sup>6</sup>A-RNA (MeRIP-seq), could be extremely relevant to better understand this issue. In addition, despite sequence conservation and binding ability of oyster actor orthologues strongly suggest functional conservation, future dedicated studies such as biochemical inhibition or gene inactivation could help demonstrate their genuine biological function. Besides, there seems to be an inverse correlation between m<sup>6</sup>A-RNA and 5mC-DNA levels during the considered oyster developmental window [46]. This may suggest an interplay between epigenetic and epitranscriptomic marks, possibly reflecting competition for methyldonor availability [59] or a link by histone epigenetic pathways [65,66]. Regarding the potential influence of the environment on m<sup>6</sup>A and the accumulation of RNA in oocytes, we are at present investigating our hypothesis that m<sup>6</sup>A may convey intergenerational

epitranscriptomic inheritance of maternal life traits in the oyster. On an evolutionary perspective, the presence of a putatively fully conserved epitranscriptomic pathway in the oyster suggests that it was already present in the bilaterian common ancestor thereby in favour of an important biological significance. Why *Drosophila* and *Caenorhabditis* seem to have lost specific m<sup>6</sup>A-RNA erasers could be related to a sub-functionalization of the DMAD [41] and NMAD-1 [42] N<sup>6</sup>-methyladenine DNA demethylase activity broadened towards RNA. However, more work in required to better understand the evo-devo implications of our results.

To conclude, in this work we report the discovery and characterisation of a putatively complete epitranscriptomic pathway in a lophotrochozoan organism, the oyster Crassostrea gigas. This pathway includes the m<sup>6</sup>A mark in RNA and the actors of all the aspects of its regulation (writers, eraser, readers) which are conserved at the molecular level and putatively functional. We show that m<sup>6</sup>A levels are variable across oyster development and that m<sup>6</sup>A differentially affects distinct RNA populations. Expression levels of the related enzymatic machinery is consistent with the observed m<sup>6</sup>A level variations. We demonstrate the m<sup>6</sup>A binding capacity and specificity of putative oyster m<sup>6</sup>A readers in the cytoplasm and nucleus of embryolarval cells. These readers mediate distinct putative biological outcomes depending on the development stage considered. From these results we hypothesize that early decay of maternal m<sup>6</sup>A RNA participates in maternal-to-zygotic transition during cleavage and that later de novo zygotic m6A methylation contributes to gastrulation and cell differentiation. This first characterisation of an m<sup>6</sup>A-epitranscriptomic pathway in a lophotrochozoan organism, together with its potential implication in development, opens new perspectives on the evolution of

epigenetic mechanisms and on the potential epitranscriptomic inheritance of environmentally-induced life traits.

# **Methods:**

## Animals:

Broodstock oysters [67] and oyster embryos [46] were obtained at the IFREMER marine facilities (Argenton, France) as previously described. Briefly, gametes of mature broodstock oysters were obtained by stripping the gonads and filtering the recovered material on a 60 µm mesh to remove large debris. Oocytes were collected as the remaining fraction on a 20 µm mesh and spermatozoa as the passing fraction on a 20 µm mesh. Oocytes were pre-incubated in 5 L of UV-treated and 1 µm filtered sterile sea water (SSW) at 21 °C until germinal vesicle breakdown. Fertilization was triggered by the addition of ca.10 spermatozoids per oocyte. After the expulsion of the second polar body was assessed by light microscopy, embryos were transferred in 150 L tanks of oxygenated SSW at 21 °C. The development stages were determined by light microscopy observation. The stages collected were oocytes (E, immediately before sperm addition), fertilized oocytes (F E, immediately before transfer to 150L tanks), two to eight cell embryos (2/8 C, ca. 1.5 hours post fertilization (hpf)), morula (M, ca. 4 hpf), blastula (B, ca. 6 hpf), gastrula (G, ca. 10 hpf), trochophore (T, ca 16 hpf) and D larvae (D, ca. 24 hpf). For each development stage, 3 million embryos were collected as the remaining fraction on a 20 µm mesh and centrifuged at 123 g for 5min at room temperature. Supernatant was discarded and samples of 1 million embryos were then snap-frozen in liquid nitrogen directly of after resuspension in Tri-Reagent (Sigma-Aldrich, St Louis, MO, USA) (1 mL/10<sup>6</sup> embryos) and stored at -80 °C. Three distinct experiments were realized (February to May 2019) using the gametes of 126 to 140 broodstock animals, respectively.

#### **RNA** extraction:

total RNA extraction

RNA was extracted using phenol-chloroform followed by affinity chromatography as previously described [68]. Briefly, embryos were ground in Tri-Reagent (Sigma-Aldrich) and RNA was purified using affinity chromatography (Nucleospin RNA II kit, Macherey-Nagel, Duren, Germany). Potential contaminating DNA was removed by digestion with rDNase (Macherey-Nagel) according to the manufacturer's instructions for 15 min at 37 °C then RNA was purified using Beckman Coulter's solid-phase reversible immobilization (SPRI) paramagnetic beads (AgencourtAMPure XP, Beckman Coulter, Brea, CA, USA) according to the manufacturer's instructions. Briefly, paramagnetic beads and RNAs were mixed slowly and incubated 5 min at room temperature followed by 2 min on a magnetic rack. Cleared supernatant was removed, and beads were washed three times with 70 % ethanol. After 4 min of drying at room temperature, RNAs were mixed slowly with RNase free water and incubated for 1 min at room temperature on the magnetic rack. Eluted total RNA was stored at -80 °C.

PolyA RNA enrichment

Poly-A RNA was extracted from total RNA by oligo-dT affinity chromatography (NucleoTrap mRNA kit, Macherey-Nagel) according to the manufacturer's instructions. Briefly, up to 130 µg

of total RNAs were mixed with oligo-dT latex beads and incubated for 5 min at 68 °C then 10 min at room temperature. After centrifugation (2,000 g then 11,000 g), the pellets were washed three times on the microfilter and dried by centrifugation at 11,000 g for 1 min. Finally, polyA+RNA was incubated with RNAse-free water for 7 min at 68 °C then centrifuged at 11,000 g for 1 min. Eluted polyA+RNA was stored at -80 °C until needed.

Total and polyA-enriched RNA purity and concentrations were assayed by spectrophotometry (Nanodrop, Thermo Scientific, Waltham, MA, USA).

# m<sup>6</sup>A quantification by LC-MS/MS:

RNA hydrolysis

To generate nucleosides for quantification against standard curves, 5 μg of total RNA were denatured for 10 min at 70 °C followed by 10 min on ice, and hydrolyzed with 100 U Nuclease S1 (50 U/μL, Promega, Madison, WI, USA) in Nuclease S1 buffer (Promega) in a final reaction volume of 25 μL for 2 h at 37 °C under gentle shaking. Samples were then incubated with alkaline phosphatase buffer (Promega) for 5 min at room temperature, before 10 U alkaline phosphatase (Promega) were added and incubated further for 2 h at 37 °C under gentle shaking. Ten extra units of alkaline phosphatase were added after 1 hour of incubation to complete the reaction. Finally, samples were centrifuged at 13,000 rpm for 10 min at 4 °C and the supernatant containing digested total RNA was collected and kept at -20 °C before quantification.

• m<sup>6</sup>A quantification:

The apparatus was composed of a NexeraX<sup>2</sup> UHPLC system coupled with LCMS8030 Plus (Shimadzu, Kyoto, Japan) mass spectrometer using an electrospray interface in positive mode. The column (1.7 µm, 100x3 mm) was a HILIC Aquity® Amide (Waters, Millford, MA, USA) maintained at 35 °C. The injection volume and run-to-run time were 3 µL and 10 min, respectively. The flow rate was set to 1 mL/min. Mobile phase was initially composed of a mixture of ammonium formate solution (10 mM) containing 0.2 % (v/v) formic acid and 95 % acetonitrile (ACN) and it was maintained for 1 min. Then, a linear gradient was applied to reach 83 % ACN for 6 min. The composition returned to the initial conditions and the column was equilibrated for 3 min. The mass spectrometer was running in the Multiple Reaction Monitoring (MRM) acquisition mode. LabSolutions 5.86 SP1 software was used to process the data. The desolvatation temperature was 230 °C, source temperature was 400 °C and nitrogen flows were 2.5 L/min for the cone and 15 L/min for the desolvatation. The capillary voltage was +4.5 kV. For each compound, two transitions were monitored from the fragmentation of the [M+H]+ ion. The first transition (A in Table S1) was used for quantification and the second one (B in Table S1) for confirmation of the compound according to European Commission Decision 2002/657/EC (Table S1). Blank plasma samples were analysed to check specificity. Calibrators were prepared using diluted solutions of A (Toronto Research Chemical, Toronto, Canada) and m<sup>6</sup>A (Carbosynth, Berkshire, UK) in water at 1, 2, 5, 10, 20 50, 100 ng/mL The calibration curves were drawn by plotting the ratio of the peak area of A and m<sup>6</sup>A. For both nucleosides, a quadratic regression with 1/C weighting resulted in standard curves with R<sup>2</sup>>0.998 and more than 75% of standards

with back-calculated concentrations within 15% of their nominal values as recommended for by the European medicines agency for bioanalytical methods [69]. The limits of quantifications for both compounds were considered as the lowest concentrations of the calibration curve.

m<sup>6</sup>A/A ratios were calculated for each single sample using the determined concentrations.

Final results are the average of three technical replicates.

# m<sup>6</sup>A quantification by immunoblotting:

Immunological quantification of m<sup>6</sup>A was performed by dot-blot using total and polyA+ RNAs. Dogfish total RNA (Dr. A. Gautier, personal communication) and a synthetic unmethylated RNA oligo (Eurogentec, Liege, Belgium) were used as positive and negative controls, respectively. RNA samples were denatured for 15 min at 55 °C with gentle shaking in denaturing solution (2.2 M formaldehyde, 50 % formamide, 0.5X MOPS, DEPC water) followed by 2 min on ice. Blotting was performed on a vacuum manifold as follows: a nylon membrane (Amersham Hybond-N+, GE Healthcare life Sciences, Chicago, IL, USA) was pre-hydrated in DEPC water for 5 min, then each well was washed twice with 10X SSC (Sigma-Aldrich) before RNA was spotted onto the membrane and incubated for 15 min at room temperature. Then, vacuum aspiration was applied and each well was washed twice with 10X SSC. After heat crosslinking for 2 h at 70 °C, the membrane was rehydrated with DEPC water for 5 min, washed with PBS then PBST (PBS, 0.1 % Tween-20) for 5 min each and blocked with two 5 min incubations with blocking buffer (PBS, 0.1 % Tween-20, 10 % dry milk, 1 % BSA) at room temperature. The blocked membrane was incubated overnight at 4 °C under gentle shaking with the anti-m<sup>6</sup>A primary antibody (Total RNA: Millipore (Burlington, MA, USA) ABE572, 1:

1,000 dilution in blocking buffer; polyA+ RNA: Diagenode (Liege, Belgium) C15200082, 1:500 dilution in blocking buffer) followed by four washes of PBST for 5 min. The secondary antibody (Total RNA: Dako (Santa Clara, CA, USA) P0447 goat anti-mouse HRP antibody, 1: 10,000 dilution; polyA+ RNA: Invitrogen (Carlsbad, CA, USA) A21202 donkey anti-mouse Alexa 488, 1 : 250 dilution) was diluted in PBST supplemented with 5 % dry milk and added onto the membrane for 1 h 30 (total RNA) or 1 h (polyA+ RNA) at room temperature under gentle shaking. Membranes were extensively washed in PBST (at least 4 washes of 5 min for total RNA and 5 min then 1 h for polyA+ RNA) then total and polyA+ RNA immunoblots were visualized using chemiluminescence (ECL kit, Promega) or fluorescence scanning at 480-530 nm (Pro Xpress, Perkin-Elmer, Waltham, MA, USA), respectively. The amount of m<sup>6</sup>A was inferred from dot intensity measurements using ImageJ (v.1.49). Signal intensities were determined as 'integrated densities as a percentage of the total' which corresponds to the area under the curve of the signal of each dot after membrane background and negative control signal subtraction.

# In silico analyses:

All protein and RNA sequences of the m<sup>6</sup>A machinery of *Homo sapiens* and *Drosophila melanogaster* (Data S1) were recovered by their published designation (i.e., 'METTL3' or 'YTHDF' etc.) and their identified protein sequence (ie. RefSeq accession number NP...) collected from NCBI and used as query sequences to search for putative homologue sequences in *Crassostrea gigas* databases. The presence of oyster orthologue RNA and protein sequences were investigated by reciprocal

BLAST(https://blast.ncbi.nlm.nih.gov/Blast.cgi) on the *Crassostrea gigas* GigaTON [70] and NCBI databases and results were compared between the two oyster databases. Domain prediction was performed with CD-search software (https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi) with default settings on protein sequences of *Homo sapiens*, *Drosophila melanogaster* and *Crassostrea gigas*. The GRE-rich domain identified in vertebrate Prrc2a sequence [27] was performed with ProtParam (https://web.expasy.org/cgi-bin/protparam/protparam).

## Protein machinery mRNA expression analyses:

The transcriptome data of the different development stages are available on the GigaTON database [70,71]. The correspondence between development stages in our study, and the GigaTON database were assessed using light microscopy based on the morphological description by Zhang et al., 2012 [71] (Table S2). Expression data was expressed in TPM (Transcripts Per Million) [72] to provide a normalized comparison of gene expression between all samples. The actual presence of some transcripts that display unclear or chimeric sequences within available oyster databases was assessed using RT-PCR (Data S1).

#### Protein m<sup>6</sup>A RNA pull down:

Protein extraction and RNA affinity chromatography

Protein extraction and RNA affinity chromatography were performed as described previously [27] with some modifications as follows. Equal amounts (1 million individuals) of each developmental stage (oocyte to D larvae) were pooled together then homogenized in 3.5

volumes of buffer A (10 mM KCl, 1.5 mM MgCl2, 10 mM HEPES, pH 7.9, DEPC water, 1X Protease inhibitor cocktail, DTT 0.5 mM) by extensive pipetting (ca. 30 times) and incubated 10 min at 4 °C. Embryos were ground with 10 slow 23G-needle syringe strokes and centrifuged at 2,000 rpm for 10 min at 4 °C. The supernatant was diluted in 0.11 volume of buffer B (1.4 M KCI, 0.03 M MgCI2, HEPES 0.3 M, pH 7.9, DEPC water), centrifuged at 10,000 g for 1 h at 4 °C and the supernatant containing cytosolic proteins was stored at -80 °C. The pellet of the first centrifugation, containing nuclei, was re-suspended in two volumes of buffer C (0.42 M NaCl, 1.5 mM MgCl2, 0.2 mM EDTA, 25 % glycerol, 20 mM HEPES, pH 7.9, 0.5 mM PMSF, 0.5 mM DTT, water DEPC). Nuclei were then lysed with a 23 G needle (10 vigorous syringe strokes) followed by centrifugation at 30,000 rpm for 30 min at 4 °C and the supernatant containing nuclear proteins was stored at -80 °C. To identify putative proteins able to bind m<sup>6</sup>A-RNA, the cytosolic and nuclear fractions were submitted to affinity chromatography using 5'-biotin-labelled RNA oligonucleotides either bearing  $N^6$ -methylated adenosines or not. The methylated adenosines were designed to lie within RRACH motifs, according to the conserved methylated consensus sequence in other organisms [2,3,7,33,73] (oligo-m<sup>6</sup>A: 5'Biotin-AGAAAAGACAACCAACGAGRR-m<sup>6</sup>A-CWCAUCAU-3', oligo-A: 5'Biotin-AGAAAAGACAACCAACGAGRRACWCAUCAU-3', R = A or G, W = A or U, Eurogentec).For RNA pull down, streptavidin-conjugated magnetic beads (Dynabeads Myone Streptavidin, Invitrogen) were pre-blocked with 0.2 mg/mL tRNA (Sigma-Aldrich) and 0.2 mg/mL BSA for 1 h at 4 °C under gentle rotation followed by three washes with 0.1 M NaCl. To avoid the

identification of non-target proteins, cytosolic and nuclear protein extracts were cleared with

pre-blocked magnetic beads in binding buffer (50 mM Tris-HCl, 250 mM NaCl, 0.4 mM EDTA, 0.1 % NP-40, DEPC water, 1 mM DTT, 0.4 U/µL RNAsin) for 1 h at 4 °C under gentle rotation. After incubation on magnetic rack, the supernatants containing putative target proteins were collected and mixed with pre-blocked magnetic beads and oligo-m<sup>6</sup>A or oligo-A for 2 h at 4 °C under gentle rotation. The beads binding putative target proteins were washed three times with binding buffer and diluted in 50 mM ammonium bicarbonate.

Identification of m<sup>6</sup>A-binding proteins by LC-MS/MS:

Protein samples were first reduced, alkylated and digested with trypsin then desalted and concentrated onto a µC18 Omix (Agilent, Santa Clara, CA, USA) before analysis.

The chromatography step was performed on a NanoElute (Bruker Daltonics, Billerica, MA, USA) ultra-high pressure nano flow chromatography system. Peptides were concentrated onto a C18 pepmap 100 (5 mm x 300 µm i.d.) precolumn (Thermo Scientific) and separated at 50 °C onto a reversed phase Reprosil column (25 cm x 75 µm i.d.) packed with 1.6 µm C18 coated porous silica beads (Ionopticks, Parkville, Victoria, Australia). Mobile phases consisted of 0.1 % formic acid, 99.9 % water (v/v) (A) and 0.1 % formic acid in 99.9 % ACN (v/v) (B). The nanoflow rate was set at 400 nL/min, and the gradient profile was as follows: from 2 to 15 % B within 60 min, followed by an increase to 25 % B within 30 min and further to 37 % within 10 min, followed by a washing step at 95 % B and re-equilibration.

MS experiments were carried out on an TIMS-TOF pro mass spectrometer (Bruker Daltonics) with a modified nano-electrospray ion source (CaptiveSpray, Bruker Daltonics). The system was calibrated each week and mass precision was better than 1 ppm. A 1600 spray voltage with a capillary temperature of 180 °C was typically employed for ionizing. MS spectra were

acquired in the positive mode in the mass range from 100 to 1700 m/z. In the experiments described here, the mass spectrometer was operated in PASEF mode with exclusion of single charged peptides. A number of 10 PASEF MS/MS scans was performed during 1.16 seconds from charge range 2-5.

The fragmentation pattern was used to determine the sequence of the peptide. Database searching was performed using the Mascot 2.6.1 program (Matrix Science) with a *Crassostrea gigas* Uniprot database (including 25,982 entries). The variable modifications allowed were as follows: C-Carbamidomethyl, K-acetylation, methionine oxidation, and Deamidation (NQ). The 'Trypsin' parameter was set to 'Semispecific'. Mass accuracy was set to 30 ppm and 0.05 Da for MS and MS/MS mode respectively. Mascot data were then transferred to Proline validation

software (http://www.profiproteomics.fr/proline/) for data filtering according to a significance

threshold of <0.05 and the elimination of protein redundancy on the basis of proteins being

# Gene ontology analysis:

evidenced by the same set or a subset of peptides (Data S2).

The mRNA sequences of the characterized m<sup>6</sup>A-binding proteins were identified using tBlastn [74–76] against the GigaTON database [70] with default settings. Gene ontology (GO) analyses were carried out with the GO annotations obtained from GigaTON database gene universe [70]. GO term-enrichment tests were performed using the goseq (V1.22.0) R package [77] with p-values calculated by the Wallenius method and filtered using REVIGO [78]. GO terms with a p-value < 0.05 were considered significantly enriched (Data S3).

Statistical analyses and graph production:

Results are given as the mean ± SD of three independent experiments unless otherwise stated. They were analysed using one-way ANOVA or Kruskall-wallis tests when required, depending on the normality of result distribution. The normality was tested using the Shapiro-Wilk's test and homoscedasticity of variances with Bartlett's tests. Statistics and graphics were computed with Prism v.6 (Graphpad), R (v.3.6.1) and RStudio (v.1.0.153) softwares. The R packages eulerr [79] and Complexheatmap [80] were used for production of specific figures.

## **Author contribution**

- 667 Experiment design: GR, LLF.
- Benchwork and bioinformatics: LLF, GR, BB, BP, MS.
- Data analysis: LLF, GR, BB, MS.
- 670 Manuscript writing and editing: LLF, GR, PF, BB, MS, BP.

#### **Acknowledgements**

- The authors would like to acknowledge PRISMM core facility collaborators R. Delepée and S.
- Lagadu for their expertise in m<sup>6</sup>A/A UHPLC-MS/MS quantification. We also thank J. Pontin for
- 675 technical assistance and J. Le Grand for help with sampling.

# Funding sources and disclosure of conflicts of interest

This work was supported by the French National program CNRS EC2CO (Ecosphère Continentale et Côtière 'HERITAGe' to G. Rivière) and the council of the Normandy Region (RIN ECUME to P. Favrel). The authors declare they have no conflict of interest.



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#### Figure legends

Figure 1: m<sup>6</sup>A levels across oyster development.

**A.** m<sup>6</sup>A level quantified by LC-MS/MS in *Crassostrea gigas* embryo-larval stages pooled from oocytes to D-larvae (n= 3) is compared to the m<sup>6</sup>A level in *Homo sapiens* and *Drosophila melanogaster*, **B.** Dot blot quantification of m<sup>6</sup>A in total RNA throughout oyster development (n=3); **C.** Dot blot quantification of m<sup>6</sup>A in polyA+ RNAs throughout oyster development (n=3) Kruskal-Wallis test, α < 0,05. E: Egg, F E: fertilized egg, 2/8C: two to eight cell embryos, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae. Chemiluminescence (B) and fluorescence (C) are measured as a ratio between dot intensity of development stages and their respective controls for each amount of RNA (120ng, 60ng and 30ng).

Figure 2: The putative conserved m<sup>6</sup>A machinery in *Crassostrea gigas*.

Domain architecture of actors of the m<sup>6</sup>A machinery identified by *in silico* analyses in the oyster compared to the fruit fly and human, **A.** Writer proteins; **B.** Eraser protein; **C.** Reader proteins. Putative domains involved in m<sup>6</sup>A processes are coloured (writers, green; eraser, red; readers, blue). Other domains identified but not involved in m<sup>6</sup>A processes are indicated in grey. Only one isoform is represented for each protein and each species for clarity (see supplementary figure S2 for other isoforms).

Figure 3: Gene expression of the putative m<sup>6</sup>A machinery throughout oyster development

Expression levels of writers (**A**), eraser (**B**) and readers (**C**) identified by *in silico* analysis at each development stage were inferred from the GigaTON database. Expression levels are given in Transcripts Per kilobases per Million Reads (TPM) as the mean of the GigaTON values according to the table S2. E: Egg, 2/8C: two to eight cell, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

Figure 4: Characterization of m<sup>6</sup>A-RNA binding proteins in oyster development.

**A.** Venn diagrams representation of proteins bound to the A- and/or m<sup>6</sup>A- oligos in nuclear and cytosolic fractions of oyster embryo-larval stages. The number of proteins identified is indicated. Some actors characterized in this study are highlighted: eIF3, YTHC1, hnRNPA2B1 and IGF2BP. **B.** Heatmap of gene expression levels of the proteins that bind specifically to the m<sup>6</sup>A-oligo throughout oyster development. The expression level is normalized regarding the maximum value for each gene according to the GigaTON database. **C.** GO term distribution among the three expression clusters in B. **D.** Examples of GO term enrichment within the expression clusters of the m<sup>6</sup>A-bound proteins. The –log10(p-value) associated to each term is given. E: Egg, 2/8C: two to eight cells, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

977	Supporting information:
978	Data S1: Complete list of in silico identified putative m6A machinery proteins and their
979	respective BLAST results
980	<u>Data S2</u> : Identified proteins by RNA pull down coupled with mass spectrometry with m <sup>6</sup> A or
981	A-oligo, in nuclear or cytosolic protein extracts
982	<u>Data S3</u> : Complete list of GO terms of clustered genes of m <sup>6</sup> A interacting proteins (p-
983	value<0,05)
984	Table S1: Transitions used for each compound. A: first transition, B: second transition
985	Table S2: Table of correspondence between development stages in our study, and the
986	GigaTON database.
987	
	GigaTON database.

- 1 A functional m<sup>6</sup>A-RNA methylation pathway in the oyster Crassostrea gigas
- 2 assumes epitranscriptomic regulation of lophotrochozoan development
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# Running title

m<sup>6</sup>A-RNA methylation pathway in oyster development

#### **Abbreviations**

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A), Methyltransferase like (METTL), Wilms' tumor 1-associated protein (WTAP), RNA-binding motif 15 (RBM15), Ring finger E3 ubiquitin ligase (HAKAI), Zinc finger CCCH-type containing 13 (ZC3H13), AlkB homologue 5 (ALKBH5), Fat mass and obesity associated protein (FTO), YTH domain family protein (YTHDF), YTH domain containing protein (YTHDC), Heterogeneous nuclear ribonucleoproreins A2 B1 (HNRNPA2B1), Proline rich coiled-coil 2a (Prrc2a), Eukaryotic initiation factor 3 (eIF3), Sterile sea water (SSW), Oocytes (E), Fertilized oocytes (F E), Two to eight cell embryos (2/8 C), Hours post fertilization (hpf), Morula (M), Blastula (B), Gastrula (G), D larvae (D), solid-phase reversible immobilization (SPRI), TPM (Transcripts Per Million), Gene ontology (GO), oyster m<sup>6</sup>A-interacting protein (Cg-m<sup>6</sup>A-BPs), S-adenosyl-methionine (SAM), maternal-to-zygotic transition (MZT), acetonitrile (ACN)

#### Keywords

40 RNA, methylation, epitranscriptomics, oyster, development.

# **Conflicts of interest**

The authors declare they have no competing conflict of interest

#### **Abstract**

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is a prevalent epitranscriptomic mark in eukaryotic RNA, with crucial roles for mammalian and ecdysozoan development. Indeed, m<sup>6</sup>A-RNA and the related protein machinery are important for splicing, translation, maternal-to-zygotic transition and cell differentiation. However, to date, the presence of an m<sup>6</sup>A-RNA pathway remains unknown in more distant animals, questioning the evolution and significance of the epitranscriptomic regulation. Therefore, we investigated the m<sup>6</sup>A-RNA pathway in the oyster *Crassostrea gigas*, a lophotrochozoan model whose development was demonstrated under strong epigenetic influence. Using mass spectrometry and dot blot assays, we demonstrated that m<sup>6</sup>A-RNA is actually present in the oyster and displays variations throughout early oyster development, with the lowest levels at the end of cleavage. In parallel, by in silico analyses, we were able to characterize at the molecular level a complete and conserved putative m<sup>6</sup>A-machinery. The expression levels of the identified putative m<sup>6</sup>A writers, erasers and readers were strongly regulated across oyster development. Finally, RNA pull-down coupled to LC-MS/MS allowed us to prove the actual presence of readers able to bind m6A-RNA and exhibiting specific developmental patterns. Altogether, our results demonstrate the conservation of a complete m<sup>6</sup>A-RNA pathway in the oyster and strongly suggest its implication in early developmental processes including MZT. This first demonstration and characterization of an epitranscriptomic regulation in a lophotrochozoan model, potentially involved in the embryogenesis, brings new insights into our understanding of developmental epigenetic processes and their evolution.

# Introduction

The *N*<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is the prevalent chemical RNA modification in all eukaryotic coding and non-coding RNAs [1]. Messenger RNAs are the most heavily m<sup>6</sup>A methylated RNAs, with m<sup>6</sup>A bases lying mostly in their 3' UTRs, at the vicinity of their stop codon [2–4] and also in 5' UTRs and long internal exons [4,5]. *N*<sup>6</sup>-methylation of RNA adenosines is responsible for RNA processing and, like DNA methylation or histone modifications, contributes to the regulation of gene expression without changing the DNA or mRNA sequence. Therefore m<sup>6</sup>A constitutes a new layer of post-transcriptional gene regulation, which is emerging or has been proven critical in various biological processes, and referred to as epitranscriptomic [2].

The dynamics and biological outcomes of m<sup>6</sup>A levels are the results of the activity of a complex protein machinery comprising writers, erasers and readers. The addition of a methyl group to the 6<sup>th</sup> nitrogen of RNA adenosines is catalysed by m<sup>6</sup>A writers with distinct properties. Methyltransferase like 16 (METTL16) is a 'stand-alone' class I methyltransferase that recognizes the UACA\*GAGAA consensus sequence (with \* indicating the target adenosine) [6]. By contrast, METTL3 transfers methyl groups to adenosines within the RRA\*CH motif [2,3,7]. METTL3 is only active within a tripartite 'core complex' [8] comprising METTL3, METTL14 which enhances the methyltransferase activity supported by the MTA-70 domain of METTL3 [9,10] and the regulator protein Wilms' tumor 1-associated protein (WTAP) [4,9,11]. This core complex can interact with Virilizer-like (or KIAA1429) [12], ring finger E3 ubiquitin

ligase (HAKAI) [12,13], zinc finger CCCH-type containing 13 (ZC3H13) [12,14], RNA-binding motif 15 (RBM15) and RBM15B [7,15] which are suspected to intervene in the core complex activity and target specificity. The demethylation of adenosines has been demonstrated to be an active process catalysed by eraser enzymes belonging to the Fe(II)/2-oxoglutarate dioxygenase family: AlkB homologue 5 (ALKBH5) [16,17] and the fat mass and obesity associated protein (FTO) [17,18]. A growing number of reader proteins which recognize the m<sup>6</sup>A-RNA mark is being described. They may be divided into two classes depending on the presence of a YT521 B Homology (YTH) domain in their primary sequence. The YTH protein family includes YTH domain family protein 1-3 (YTHDF1-3) and YTH domain containing protein 2 (YTHDC2), which are cytosolic m<sup>6</sup>A readers involved in m<sup>6</sup>A-RNA stability and translation [19–22]. The fifth YTH member is YTHDC1, which is present in the nucleus and controls splicing [23] and nuclear export [24] of m<sup>6</sup>A-RNA. The second class of readers comprises proteins without YTH domain which are involved in several molecular mechanisms. For example, the heterogeneous nuclear ribonucleoprotein A2 B1 (HNRNPA2B1) is important for miRNA processing [25]. Insulin-like growth factor 2 mRNA binding protein 1-3 (IGF2BP 1-3) [26] and proline-rich coiled-coil 2a (Prrc2a) [27] participate in RNA stability while eukaryotic initiation factor 3 (eIF3) guides capindependent translation [5].

The m<sup>6</sup>A epitranscriptomes underlie important biological functions, most of which being related to developmental processes, including the control of cell differentiation [27–32], maternal to

zygotic transition (MZT) [33], sex determination [7,34] and gametogenesis [16,21,35,36]. Such

critical epitransriptomic outcomes are conserved in the animal evolution and were characterized in both vertebrates and ecdysozoans, i.e. mammals and drosophila.

However, such conserved biological significance originates in diverse epitranscriptomic mechanisms. Indeed, not all ecdysozoans bear a complete m<sup>6</sup>A-RNA machinery, such as *C. elegans* whose genome is devoid of the related protein machinery with the exception of a putative orthologue of METTL16 [37,38]. In addition, no m<sup>6</sup>A eraser has been described to date in non-vertebrate models, and especially ecdysozoans such as the drosophila or *C. elegans* [38–40], where it cannot be excluded that m<sup>6</sup>A-RNA methylation could be removed by the activity of characterised 6mA-DNA demethylases [41,42]. This situation may illustrate a growing complexity of epitranscriptomic mechanisms during the animal phylogeny and raises fundamental questions about its evolution and its presence in organisms distant from mammals and ecdysozoans. However, to date, no data about a possible epitranscriptomic regulation is available to our knowledge in lophotrochozoans, the understudied sister group of ecdysozoans within protostomes, although representing an important range of metazoan biodiversity.

The Pacific oyster *Crassostrea gigas* (i.e. *Magallana gigas*) is a bivalve mollusc whose great ecological an economical significance allowed its emergence as a model species within lophotrochozoan organisms. As such, an important amount of genetic, transcriptomic and epigenetic data have been generated in this model. Interestingly, the embryolarval development of *C. gigas* is described to be under the strong epigenetic influence of DNA methylation [43–47] and histone marks [48–50]. Besides, oyster development occurs exposed to external environmental conditions, and in other models the m<sup>6</sup>A methylation of RNA and/or

the expression of its machinery can be induced by heat stress, UV exposure or endocrine disruptors [5,51–54], questioning the presence of an m<sup>6</sup>A pathway in *C. gigas* and its significance in oyster early development.

To investigate this, we measured m<sup>6</sup>A levels in RNA across the entire embryolarval life of the oyster using mass spectrometry and dot-blot. We also searched the available *in silico* resources for putative conserved m<sup>6</sup>A-related proteins in *C. gigas* genomic data as well as their cognate expression kinetics using RNAseq assembly analyses. We also performed RNA-pulldown with a synthetic m<sup>6</sup>A-RNA oligonucleotide coupled to liquid chromatography and mass spectrometry (LC-MS/MS) to characterize potential oyster m<sup>6</sup>A-binding proteins. To our knowledge, this study is the first report unravelling epitranscriptomic mechanisms outside

## Results:

vertebrate and ecdyzosoan animal models.

m<sup>6</sup>A is present in oyster RNA, differentially affects distinct RNA populations and displays variations during embryonic life.

Mass spectrometry measurements revealed that m<sup>6</sup>A is present in oyster RNA, with global m<sup>6</sup>A/A levels of ca. 0.3%, a value comparable to what has been found in the human and the fruit fly (Figure 1A). Immunoblot assays indicate that total and polyA+ RNA present variable amounts of m<sup>6</sup>A during oyster development and that these variations display distinct profiles suggesting specific methylation patterns between RNA populations. Indeed, N<sup>6</sup>A-methylation in total RNA is the highest in the early stages (oocytes and fertilized oocytes) then gradually

decreases until the morula stage before gradually increasing again up to the trochophore stage when it recovers its maximum (Figure 1B). In contrast, m<sup>6</sup>A levels in polyA+ RNA are hardly detected in early stages but display a peak in the gastrula and trochophore stages (Figure 1C).

### m<sup>6</sup>A machinery is conserved at the molecular level in the oyster.

In silico analyses led to the identification of oyster sequences encoding putative orthologues of m<sup>6</sup>A writers, erasers and readers that are present in the human and/or in the human and the fruit fly. All the eight m<sup>6</sup>A-RNA writers characterized in the human and/or drosophila at the time of the study, namely METTL3, METTL14, WTAP, Virilizer-like, HAKAI, ZC3H13, RBM15/15B and

METTL16, were present in the oyster at the gene level. The encoded protein primary sequences all display the specific domains required for enzymatic activity and/or binding. They include MT-A70 and AdoMetMtases SF domains for METTL3, METTL14 and METTL16, respectively, that bear the methyltransferase activity. Oyster WTAP and Virilizer-like orthologues exhibit WTAP and VIR N domains, respectively, that are required in their human counterparts to bind and activate the catalytic subunit of the m<sup>6</sup>A-RNA methyltransferase complex. Oyster Hakai and RBM15/15B present RHHL, RHF-Zn-BS and specific RRM domains, respectively, similar to human and fruit fly orthologues. Besides, the oyster ZC3H13 bears the Rho SF domain present in the human, but not in the fruit fly orthologue (Figure 2A). C. gigas also presents a putative m<sup>6</sup>A-RNA eraser, ALKBH5, which is present in the human

but has not been characterized in drosophila. The oyster ALKBH5 exhibits a 20G-FeII Oxy

domain suggestive of a presumably conserved catalytic functionality through fe2+-dependent

oxoglutarate oxidation. Of note, no orthologue of the human FTO eraser could be identified in the oyster genomic or transcriptomic databases available to date (Figure 2B). Many m<sup>6</sup>A reader orthologues have also been found in the oyster, including proteins containing a YTH domain, such as YTHDF, YTHDC1 and YTHDC2. An oyster Prrc2a-like protein produces homology with the human Prrc2a, especially within the m<sup>6</sup>A-binding GRE-rich domain. Oyster readers also include a heterogeneous nuclear ribonucleoprotein-coding gene, hnRNPA2B1 with greater sequence similarity with the drosophila counterpart than with the human orthologue. Similarly, the IGF2BP-coding sequence has also been found in C. gigas (Figure 2C). Five oyster sequences display homologies with eIF3a which is able to bind m<sup>6</sup>A-RNA [5] but it was not possible to discriminate whether a unique oyster predicted protein was an eIF3a orthologue. Overall, these results indicate the conservation of a complete m<sup>6</sup>A-RNA machinery in the oyster. The complete list of the identified genes encoding the conserved m<sup>6</sup>A machinery actors and their isoforms, as well as the related information is given in the supplementary data (Data

S1).

#### Oyster putative m<sup>6</sup>A actors display expression level variations across development.

RNAseq data analyses showed that all the oyster m<sup>6</sup>A-related genes were expressed during the early life (Figure 3). Their expression level displayed gene-specific profiles, most of them being variable throughout oyster development.

The expression of writers belonging to the core methylation complex is weak overall. METTL3 and WTAP share similar profiles with little expression increasing up to the gastrulation and

drop at the D larvae stage (Figure 3 C).

remaining stable afterwards. In contrast METTL14 displays a weak expression level across the embryo larval life. The expression profile of Virilizer-like resembles WTAP, while HAKAI, RBM15/15B and METTL16 seem to have mRNA levels which decrease after cleavage, whereas those of ZC3H13 transcript variants seem to drop at the D larva stage. Interestingly, METTL16 mRNA levels display an opposite developmental profile when compared to METTL3 expression; with the highest values during cleavage which decrease later on (Figure 3A). ALKBH5 transcripts are weakly represented within oyster early embryos and the higher TPM values are found in gastrulas. However, maximum levels are observed after metamorphosis in juveniles (Figure 3B). Regarding m<sup>6</sup>A putative readers, the expression of YTH family genes during development showed different patterns. In fact, YTHDF is the most represented YTH-domain bearing actor and YTHDF TPM values are ca. 5-fold higher than all the other oyster YTH readers. YTHDF is strongly expressed at the beginning of development until a peak at the morula stage. Prrc2a is the most represented reader at the mRNA level in oyster embryos, and the sum of the TPM of the two Prrc2a oyster isoforms are at most ca. 20-fold higher than those of YTH family. However, Prrc2a and YTHDF transcript content profiles are similar across oyster development, and also remind of the IGF2BP mRNA levels. By contrast, the two isoforms of YTHDC1 identified by in silico analysis, YTHDC1.1 and YTHDC1.2, display similar patterns together with YTHDC2, with a maximum representation in gastrulas. The expression of hnRNPA2B1 isoforms has likewise patterns except for a marked

Oyster orthologues of m<sup>6</sup>A-RNA interacting proteins bind m<sup>6</sup>A RNA in vitro.

To determine whether oyster proteins can bind m<sup>6</sup>A-RNA, we performed RNA-pulldown of cytoplasmic and nuclear embryonic cell extracts using a methylated versus a non-methylated oligonucleotide, followed by LC/MS-MS characterisation and identification of the captured proteins with the Mascot software. In nuclear extracts, we detected 591 proteins able to bind both the methylated and unmethylated oligos. We identified 43 proteins specific to unmethylated RNA while 131 proteins specifically bind the m6A-methylated oligo. In cytosolic extracts, there were respectively 646, 436 and 36 of such proteins, respectively. Regardless of the methylation status, more proteins in the cytoplasmic extracts can bind to the RNA oligonucleotides than in the nuclear extracts (1118 proteins vs. 765, respectively). However, more nuclear proteins are found exclusively bound to the m<sup>6</sup>A-containing oligo than cytoplasmic proteins (131 vs. 36, i.e. 17 % vs. 3 %, respectively). In addition, many nuclear and cytoplasmic proteins can bind both the methylated and the non-methylated oligo (591 vs. 646, i.e. 77 % vs. 58 %). An important number of proteins in the cytoplasmic extract were found exclusively bound to the nonmethylated oligo, whereas only a limited number of nuclear proteins display such a specificity (436 vs. 43, i.e. 39 % vs. 6 %). Among the 167 m<sup>6</sup>A-specific proteins in oyster extracts, only 5 were found in both the nuclear and cytoplasmic extracts. These results show that oyster proteins can directly or indirectly bind m<sup>6</sup>A-RNA, and suggest an important compartmentalization of m<sup>6</sup>A-related processes. Among the identified proteins in this assay, four of the putative oyster m<sup>6</sup>A readers are found, YTHDC1, hnRNPA2B1, IGF2BP and eIF3. In the nuclear extracts YTHDC1 is uncovered as

m<sup>6</sup>A-specific whereas hnRNPA2B1 and IGF2BP were present complexed with both the m<sup>6</sup>A-and A-oligos. In the cytoplasmic extracts, YTHDC1 and eIF3a are m<sup>6</sup>A-specific while hnRNPA2B1, IGF2BP were pulled down by both methylated and unmethylated oligos (Figure 4A).

These results demonstrate that some proteins in the oyster can specifically bind m<sup>6</sup>A-RNA and that the putative m<sup>6</sup>A reader orthologues in the oyster are conserved at the protein level and are able to interact with m<sup>6</sup>A-RNA.

# The m<sup>6</sup>A-interacting protein-coding genes display clustered expression regulation and

## functional annotation during oyster development.

The mRNA expression level of the genes encoding the 162 oyster m<sup>6</sup>A-interacting protein (Cg-m<sup>6</sup>A-BPs) was examined using RNAseq databases. Most of them display a specific and regulated expression level across oyster developmental stages. However, three main expression clusters could be distinguished according to their developmental mRNA expression level profile. Cluster 1 includes genes that show high expression at the beginning of the embryo life (i.e. cleavage) and strongly decrease after gastrulation; the second cluster contains weakly expressed genes except in the latest examined larval phases, after gastrulation (i.e. Trochophore and D Larvae); cluster 3 groups genes that show an expression peak during gastrulation (Figure 4B).

The Gene Ontology annotation of the Cg-m<sup>6</sup>A-BP genes reveal that the distinct clusters are related to distinct functional pathways as indicated by the little - if any - common GO terms between them (Figure 4C). However, the functional pathways of all three gene clusters point

out to their implication in translation and its regulation, although the terms enriched in each cluster illustrate different aspects of translation, such as translation initiation (cluster 1), splicing and nuclear export (cluster 2) and ribosomal and mitochondrial processes (cluster 3) respectively (Figure 4D).

# Discussion

This work demonstrates that m<sup>6</sup>A-RNA is present and variable during the embryo-larval life of the oyster, and that *C. gigas* exhibits putative conserved and functional m<sup>6</sup>A-RNA writers, eraser and readers. The dynamics of such mark and of its actors strongly suggest a biological significance of the epitranscriptomic pathway in the control of development of a lophotrochozoan species, which has, to date, never been demonstrated to our knowledge.

#### m<sup>6</sup>A-RNA levels vary across oyster development.

Using mass spectrometry and immunological measurements, we showed that oyster RNA is m<sup>6</sup>A-methylated. The global proportion of N<sup>6</sup>-methyladenosine in RNA in the developing oyster (0.28 %) is similar to those observed elsewhere in the animal kingdom, such as in the fruit fly (0.24 %) [34] or the human (0.11- 0.23 %) [55] (Figure 1A), despite those values are difficult to compare because they were not measured within the same developmental phase (adult flies and human cell lines vs. oyster embryos). However, the comparable magnitude of m<sup>6</sup>A-RNA amounts between taxa, in contrast to DNA methylation [46], may indicate conserved biological significance of epitranscriptomic processes between groups. The amount of m<sup>6</sup>A in total RNA displays a striking decrease during cleavage and then recovers its maximum levels at the end of the gastrulation (Figure 1B). Therefore, the m<sup>6</sup>A decrease in total RNA during cleavage, i.e.

before the transcription of the zygotic genome starts, reflects a degradation of maternal m<sup>6</sup>A-RNAs or their demethylation. However, all RNA populations do not exhibit the same pattern, indeed polyA+ RNAs are m<sup>6</sup>A methylated only after cleavage. The extent of polyadenylation of oyster maternal messenger RNAs accumulating during vitellogenesis is unknown. Therefore, which maternal RNA population(s) is methylated in oyster oocytes is unclear. Nevertheless, the observation that m<sup>6</sup>A-RNA levels are variable and affecting distinct RNA populations across embryonic stages strongly favours an important biological significance of m<sup>6</sup>A-RNA in oyster development. We hypothesize that oyster maternal messenger RNAs are poorly polyadenylated, and that m<sup>6</sup>A, aside polyadenylation, might play a role in the stability of quiescent maternal mRNAs. Alternatively, other maternal RNA populations such as snRNA, miRNA, rRNA or IncRNA might be methylated [6,15,25,56], which become demethylated or degraded up to the morula stage. The later increase in m<sup>6</sup>A RNA after cleavage could therefore be the result of the methylation of the increasingly transcribed RNAs from the blastula stage, including polyadenylated mRNAs.

The m<sup>6</sup>A-RNA machinery is conserved in the oyster and regulated during development.

The important regulation of m<sup>6</sup>A levels during oyster development assumes the presence of a related protein machinery. We identified *in silico* cDNA sequences encoding conserved putatively functional orthologues of m<sup>6</sup>A-RNA writers, eraser and readers in the oyster, with great confidence (homologies ranging from ca. 30 to 65 % with their human counterpart, see Data S1). The writers include all the members of the methylation complex (METTL3, METTL14, WTAP, Virilizer-like, Hakai, ZC3H13, RBM15/15B) identified to date in the human and the fruit fly [7,11,12,14,15,57]. We also identified an orthologue of the stand-alone METTL16 m<sup>6</sup>A

methyltransferase. Each orthologue bears the conserved domain(s) demonstrated to be implicated in the catalytic and/or binding activity of their cognate counterpart in other species, such as the MT-A70 domain which transfers methyl groups from the S-adenosyl-methionine (SAM) to the No nitrogen of RNA adenines [57]. Of the two proteins that can erase RNA methylation, only ALKBH5, which is important for mouse spermatogenesis [16], was identified at the cDNA level in the oyster. Indeed, no C. gigas sequence displayed significant homology with the mammalian FTO protein, whose functional significance remains controversial [17]. Most the characterized m<sup>6</sup>A-RNA readers are also present at the molecular level in the oyster and are putatively able to bind m<sup>6</sup>A regarding their primary sequence, such as the YTHDC and YTHDF family members [19,21,23,58], Prrc2A [27], HnRNPA2B1 [25] and IGF2BP [26]. Of note, some of these readers have not been characterized to date in D. melanogaster but display strong homologies between humans and oysters. In mammals, eIF3a has important functional outcomes in cap-independent translational stress response [5]. However, it was not possible to ascribe a single oyster sequence as a unique eIF3a orthologue (Data S1), although its presence was demonstrated by RNA pull down (see below) (see Data S2). Altogether, in silico results show the conservation of a complete m<sup>6</sup>A-RNA machinery in the oyster. To date to our knowledge, this is the first demonstration in a lophotrochozoan organism of an epitranscriptomic pathway. Its presence suggests its ancestral origin, and questions its biological significance in oyster development. To investigate this, we analysed the expression level of the m<sup>6</sup>A machinery genes using RNAseq data. Our results indicate that the core methylation complex (METTL3, METTL14 and WTAP) would not be active during cleavage because of the absence of METTL3 and little

WTAP expression. METTL16 catalyses the downregulation of SAM methyl donor availability in mammals [59]. If METTL16 function is conserved in the oyster as suggested by the high sequence homology, the peak in METTL16 expression, together with the weak expression of the core complex in 2/8 cell embryos is consistent with an absence of m<sup>6</sup>A-RNA up to the blastula stage. Then, the core complex would likely be active as soon as the end of cleavage (i.e. since the blastula stage), in line with the increase in m<sup>6</sup>A levels observed at the same time. The correlation between the increasing METTL3 expression and m<sup>6</sup>A-RNA levels after cleavage strongly favours the conservation of the methyltransferase activity of the oyster MT-A70 domain. Interpreting the regulation of the m<sup>6</sup>A activity by the other methyltransferase complex members (i.e. Virilizer-like, HAKAI, ZC3H13 and RBM15/15B) is difficult because how - or even if - oyster orthologues act within the complex is not known. Nevertheless, their specific expression profiles may reflect their implication in the regulation of distinct biological contexts. There might be little functional significance of active m<sup>6</sup>A-RNA erasure during oyster development, consistent with the normal embryonic phenotype of ALKBH5 knockdown mice [16]. Overall, the m<sup>6</sup>A readers display distinct developmental expression patterns. While YTHDF and Prrc2a peak during cleavage, YTHDC1, YTHDC2, IGF2BP and hnRNPA2B1 mRNA levels gradually increase up to the gastrulation and remain mostly highly expressed afterwards (except for hnRNPA2B1 and IGF2BP). These profiles evoke the mediation of distinct biological functions depending on the reader and the developmental phases. Therefore, we hypothesized that YTHDF and Prrc2a might participate in the blastulean transition in the oyster. Indeed, in the zebrafish, a YTHDF reader triggers the maternal-tozygotic transition through the decay of the maternal m<sup>6</sup>A RNAs during cleavage [33]. The role

in the axon myelination and specification of mouse oligodendrocytes [27] is unlikely conserved for Prrc2a because the oyster orthologue is expressed before the neurogenesis is detected in trochophore stages [60]. Alternatively, the early expression of Prrc2a suggests that it might rather compete with YTHDF for m<sup>6</sup>A-RNA targets [27], thereby possibly acting in oyster MZT, bringing new perspectives into this process which remains poorly understood in lophotrochozoans. In mammals m<sup>6</sup>A is implicated in the embryonic cell fate [30,31] notably via the regulation of cell differentiation by YTHDC2 [32] or hnRNPA2B1 [29]. In the oyster, YTHDC1, YTHDC2, IGF2BP and hnRNPA2B1 have their maximum expression during gastrulation correlated to the second m<sup>6</sup>A peak, suggesting similar implications.

#### Putative oyster m<sup>6</sup>A readers actually bind m<sup>6</sup>A-RNA in vitro.

To better approach the developmental processes involving m<sup>6</sup>A in the oyster, we characterized the proteins that can interact with m<sup>6</sup>A-RNA using a methylated-RNA-pulldown / mass spectrometry assay. We identified 162 proteins able to specifically bind the m<sup>6</sup>A-RNA oligo in embryonic cell extracts, demonstrating the actual presence of genuine m<sup>6</sup>A-readers in the oyster. Most (ca. 75 %) of these proteins were found in nuclear extracts and only 5 were found in both the cytoplasmic and nuclear fractions, showing an important compartmentalization of the epitranscriptomic pathway. Regarding the little number of m<sup>6</sup>A readers in other animals, and because the assay conditions do not discriminate between direct and indirect interactions, we hypothesize that most these proteins indirectly bind m<sup>6</sup>A via a limited number of 'scaffold' m<sup>6</sup>A readers. Such authentic readers that only bind the m<sup>6</sup>A-RNA oligo in our assay likely include YTHDC1 and eIF3a, which have been demonstrated to directly bind m<sup>6</sup>A in other species, demonstrating the conservation of the m<sup>6</sup>A-binding capacity and specificity of the YTH

domain in the oyster. Besides, YTHDC1 is found in both cell fractions, suggesting its implication in the trafficking of m<sup>6</sup>A-RNA across the nuclear envelope [24], and reinforcing the hypothesis that YTH proteins could participate in oyster MZT and cell differentiation. The presence of the oyster eiF3a in the cytoplasm is consistent with a conserved role in m<sup>6</sup>A-mediated translation processes, such as cap-independent translation [5].

#### Possible functions of m<sup>6</sup>A-RNA in oyster development.

We investigated the expression level and the functional annotation of the 162 genes encoding the m<sup>6</sup>A-interacting proteins across oyster early life. These genes can be clustered into three successive expression phases corresponding to three distinct functional pathways, which are independent albeit all mostly related to translation regulation. The cluster 1 is mostly expressed during the cleavage and the associated GO terms are related to the initiation of translation, consistent with maternal RNA consumption before MZT is complete and the zygotic genome becomes fully activated. The genes within cluster 3 show an expression peak during gastrulation. Their ontology terms evoke ribosomal and mitochondrial processes, the latter being required for energy supply and signalling integration during gastrulation [61–64]. The cluster 2 contains genes that peak after gastrulation and which are related to splicing and nuclear export. Such functional annotations are in line with a fine regulation of transcript variant translation within the distinct cell lineages in the three cell layers of the late embryos.

Taken together, our findings bring to light a possible implication of m<sup>6</sup>A in oyster development. First, during cleavage the decrease of m<sup>6</sup>A-RNA, the weak expression of methyltransferase complex genes, the maximum of YTHDF gene expression and the expression of *Cg*-m<sup>6</sup>A-BPs

related to the initiation of the translation strongly suggest the implication of m<sup>6</sup>A in MZT in C. gigas. Second, the increasing m<sup>6</sup>A level during gastrula stage is correlated to the increase of methyltransferase complex gene expression. In addition, the increased RNA level of readers putatively related to cell differentiation and the peak of gene expression of Cg-m<sup>6</sup>A-BPs associated to ribosomal and mitochondrial processes, support the hypothesize of a m<sup>6</sup>A implication in gastrulation. Finally, the highest m<sup>6</sup>A level at the trochophore stage, the gene expression of the methyltransferase complex and of readers associated to cell differentiation, as well as high RNA level of Cg-m<sup>6</sup>A-BPs related to splicing and nuclear export is correlated with the fine cell differentiation taking place at this stage. However, inferring the biological significance of m<sup>6</sup>A in development from the indirect and incomplete functional annotation of the oyster genome is only limited. Characterization of the precise targets of m<sup>6</sup>A and how their individual methylation is regulated across development, for example using high throughput sequencing of precipitated m<sup>6</sup>A-RNA (MeRIP-seq), could be extremely relevant to better understand this issue. In addition, despite sequence conservation and binding ability of oyster actor orthologues strongly suggest functional conservation, future dedicated studies such as biochemical inhibition or gene inactivation could help demonstrate their genuine biological function. Besides, there seems to be an inverse correlation between m<sup>6</sup>A-RNA and 5mC-DNA levels during the considered oyster developmental window [46]. This may suggest an interplay between epigenetic and epitranscriptomic marks, possibly reflecting competition for methyldonor availability [59] or a link by histone epigenetic pathways [65,66]. Regarding the potential influence of the environment on m<sup>6</sup>A and the accumulation of RNA in oocytes, we are at present investigating our hypothesis that m<sup>6</sup>A may convey intergenerational

epitranscriptomic inheritance of maternal life traits in the oyster. On an evolutionary perspective, the presence of a putatively fully conserved epitranscriptomic pathway in the oyster suggests that it was already present in the bilaterian common ancestor thereby in favour of an important biological significance. Why *Drosophila* and *Caenorhabditis* seem to have lost specific m<sup>6</sup>A-RNA erasers could be related to a sub-functionalization of the DMAD [41] and NMAD-1 [42] N<sup>6</sup>-methyladenine DNA demethylase activity broadened towards RNA. However, more work in required to better understand the evo-devo implications of our results.

To conclude, in this work we report the discovery and characterisation of a putatively complete epitranscriptomic pathway in a lophotrochozoan organism, the oyster Crassostrea gigas. This pathway includes the m<sup>6</sup>A mark in RNA and the actors of all the aspects of its regulation (writers, eraser, readers) which are conserved at the molecular level and putatively functional. We show that m<sup>6</sup>A levels are variable across oyster development and that m<sup>6</sup>A differentially affects distinct RNA populations. Expression levels of the related enzymatic machinery is consistent with the observed m<sup>6</sup>A level variations. We demonstrate the m<sup>6</sup>A binding capacity and specificity of putative oyster m<sup>6</sup>A readers in the cytoplasm and nucleus of embryolarval cells. These readers mediate distinct putative biological outcomes depending on the development stage considered. From these results we hypothesize that early decay of maternal m<sup>6</sup>A RNA participates in maternal-to-zygotic transition during cleavage and that later de novo zygotic m6A methylation contributes to gastrulation and cell differentiation. This first characterisation of an m<sup>6</sup>A-epitranscriptomic pathway in a lophotrochozoan organism, together with its potential implication in development, opens new perspectives on the evolution of epigenetic mechanisms and on the potential epitranscriptomic inheritance of environmentallyinduced life traits.

# **Methods:**

#### Animals:

Broodstock oysters [67] and oyster embryos [46] were obtained at the IFREMER marine facilities (Argenton, France) as previously described. Briefly, gametes of mature broodstock oysters were obtained by stripping the gonads and filtering the recovered material on a 60 µm mesh to remove large debris. Oocytes were collected as the remaining fraction on a 20 µm mesh and spermatozoa as the passing fraction on a 20 µm mesh. Oocytes were pre-incubated in 5 L of UV-treated and 1 µm filtered sterile sea water (SSW) at 21 °C until germinal vesicle breakdown. Fertilization was triggered by the addition of ca.10 spermatozoids per oocyte. After the expulsion of the second polar body was assessed by light microscopy, embryos were transferred in 150 L tanks of oxygenated SSW at 21 °C. The development stages were determined by light microscopy observation. The stages collected were oocytes (E, immediately before sperm addition), fertilized oocytes (F E, immediately before transfer to 150L tanks), two to eight cell embryos (2/8 C, ca. 1.5 hours post fertilization (hpf)), morula (M, ca. 4 hpf), blastula (B, ca. 6 hpf), gastrula (G, ca. 10 hpf), trochophore (T, ca 16 hpf) and D larvae (D, ca. 24 hpf). For each development stage, 3 million embryos were collected as the remaining fraction on a 20 µm mesh and centrifuged at 123 g for 5min at room temperature.

Supernatant was discarded and samples of 1 million embryos were then snap-frozen in liquid nitrogen directly of after resuspension in Tri-Reagent (Sigma-Aldrich, St Louis, MO, USA) (1 mL/10<sup>6</sup> embryos) and stored at -80 °C. Three distinct experiments were realized (February to May 2019) using the gametes of 126 to 140 broodstock animals, respectively.

#### **RNA** extraction:

total RNA extraction

RNA was extracted using phenol-chloroform followed by affinity chromatography as previously described [68]. Briefly, embryos were ground in Tri-Reagent (Sigma-Aldrich) and RNA was purified using affinity chromatography (Nucleospin RNA II kit, Macherey-Nagel, Duren, Germany). Potential contaminating DNA was removed by digestion with rDNase (Macherey-Nagel) according to the manufacturer's instructions for 15 min at 37 °C then RNA was purified using Beckman Coulter's solid-phase reversible immobilization (SPRI) paramagnetic beads (AgencourtAMPure XP, Beckman Coulter, Brea, CA, USA) according to the manufacturer's instructions. Briefly, paramagnetic beads and RNAs were mixed slowly and incubated 5 min at room temperature followed by 2 min on a magnetic rack. Cleared supernatant was removed, and beads were washed three times with 70 % ethanol. After 4 min of drying at room temperature, RNAs were mixed slowly with RNase free water and incubated for 1 min at room temperature on the magnetic rack. Eluted total RNA was stored at -80 °C.

PolyA RNA enrichment

Poly-A RNA was extracted from total RNA by oligo-dT affinity chromatography (NucleoTrap mRNA kit, Macherey-Nagel) according to the manufacturer's instructions. Briefly, up to 130 µg

of total RNAs were mixed with oligo-dT latex beads and incubated for 5 min at 68 °C then 10 min at room temperature. After centrifugation (2,000 g then 11,000 g), the pellets were washed three times on the microfilter and dried by centrifugation at 11,000 g for 1 min. Finally, polyA+RNA was incubated with RNAse-free water for 7 min at 68 °C then centrifuged at 11,000 g for 1 min. Eluted polyA+RNA was stored at -80 °C until needed.

Total and polyA-enriched RNA purity and concentrations were assayed by spectrophotometry (Nanodrop, Thermo Scientific, Waltham, MA, USA).

## m<sup>6</sup>A quantification by LC-MS/MS:

RNA hydrolysis

To generate nucleosides for quantification against standard curves, 5  $\mu$ g of total RNA were denatured for 10 min at 70 °C followed by 10 min on ice, and hydrolyzed with 100 U Nuclease S1 (50 U/ $\mu$ L, Promega, Madison, WI, USA) in Nuclease S1 buffer (Promega) in a final reaction volume of 25  $\mu$ L for 2 h at 37 °C under gentle shaking. Samples were then incubated with alkaline phosphatase buffer (Promega) for 5 min at room temperature, before 10 U alkaline phosphatase (Promega) were added and incubated further for 2 h at 37 °C under gentle shaking. Ten extra units of alkaline phosphatase were added after 1 hour of incubation to complete the reaction. Finally, samples were centrifuged at 13,000 rpm for 10 min at 4 °C and the supernatant containing digested total RNA was collected and kept at -20 °C before quantification.

m<sup>6</sup>A quantification:

The apparatus was composed of a NexeraX<sup>2</sup> UHPLC system coupled with LCMS8030 Plus (Shimadzu, Kyoto, Japan) mass spectrometer using an electrospray interface in positive mode. The column (1.7 µm, 100x3 mm) was a HILIC Aquity® Amide (Waters, Millford, MA, USA) maintained at 35 °C. The injection volume and run-to-run time were 3 µL and 10 min, respectively. The flow rate was set to 1 mL/min. Mobile phase was initially composed of a mixture of ammonium formate solution (10 mM) containing 0.2 % (v/v) formic acid and 95 % acetonitrile (ACN) and it was maintained for 1 min. Then, a linear gradient was applied to reach 83 % ACN for 6 min. The composition returned to the initial conditions and the column was equilibrated for 3 min. The mass spectrometer was running in the Multiple Reaction Monitoring (MRM) acquisition mode. LabSolutions 5.86 SP1 software was used to process the data. The desolvatation temperature was 230 °C, source temperature was 400 °C and nitrogen flows were 2.5 L/min for the cone and 15 L/min for the desolvatation. The capillary voltage was +4.5 kV. For each compound, two transitions were monitored from the fragmentation of the [M+H]+ ion. The first transition (A in Table S1) was used for quantification and the second one (B in Table S1) for confirmation of the compound according to European Commission Decision 2002/657/EC (Table S1). Blank plasma samples were analysed to check specificity. Calibrators were prepared using diluted solutions of A (Toronto Research Chemical, Toronto, Canada) and m<sup>6</sup>A (Carbosynth, Berkshire, UK) in water at 1, 2, 5, 10, 20 50, 100 ng/mL The calibration curves were drawn by plotting the ratio of the peak area of A and m<sup>6</sup>A. For both nucleosides, a quadratic regression

with 1/C weighting resulted in standard curves with R<sup>2</sup>>0.998 and more than 75% of standards

with back-calculated concentrations within 15% of their nominal values as recommended for by the European medicines agency for bioanalytical methods [69]. The limits of quantifications for both compounds were considered as the lowest concentrations of the calibration curve.

m<sup>6</sup>A/A ratios were calculated for each single sample using the determined concentrations.

Final results are the average of three technical replicates.

### m<sup>6</sup>A quantification by immunoblotting:

Immunological quantification of m<sup>6</sup>A was performed by dot-blot using total and polyA+ RNAs. Dogfish total RNA (Dr. A. Gautier, personal communication) and a synthetic unmethylated RNA oligo (Eurogentec, Liege, Belgium) were used as positive and negative controls, respectively. RNA samples were denatured for 15 min at 55 °C with gentle shaking in denaturing solution (2.2 M formaldehyde, 50 % formamide, 0.5X MOPS, DEPC water) followed by 2 min on ice. Blotting was performed on a vacuum manifold as follows: a nylon membrane (Amersham Hybond-N+, GE Healthcare life Sciences, Chicago, IL, USA) was pre-hydrated in DEPC water for 5 min, then each well was washed twice with 10X SSC (Sigma-Aldrich) before RNA was spotted onto the membrane and incubated for 15 min at room temperature. Then, vacuum aspiration was applied and each well was washed twice with 10X SSC. After heat crosslinking for 2 h at 70 °C, the membrane was rehydrated with DEPC water for 5 min, washed with PBS then PBST (PBS, 0.1 % Tween-20) for 5 min each and blocked with two 5 min incubations with blocking buffer (PBS, 0.1 % Tween-20, 10 % dry milk, 1 % BSA) at room temperature. The blocked membrane was incubated overnight at 4 °C under gentle shaking with the anti-m<sup>6</sup>A primary antibody (Total RNA: Millipore (Burlington, MA, USA) ABE572, 1:

1,000 dilution in blocking buffer; polyA+ RNA: Diagenode (Liege, Belgium) C15200082, 1:500 dilution in blocking buffer) followed by four washes of PBST for 5 min. The secondary antibody (Total RNA: Dako (Santa Clara, CA, USA) P0447 goat anti-mouse HRP antibody, 1: 10,000 dilution; polyA+ RNA: Invitrogen (Carlsbad, CA, USA) A21202 donkey anti-mouse Alexa 488, 1 : 250 dilution) was diluted in PBST supplemented with 5 % dry milk and added onto the membrane for 1 h 30 (total RNA) or 1 h (polyA+ RNA) at room temperature under gentle shaking. Membranes were extensively washed in PBST (at least 4 washes of 5 min for total RNA and 5 min then 1 h for polyA+ RNA) then total and polyA+ RNA immunoblots were visualized using chemiluminescence (ECL kit, Promega) or fluorescence scanning at 480-530 nm (Pro Xpress, Perkin-Elmer, Waltham, MA, USA), respectively. The amount of m<sup>6</sup>A was inferred from dot intensity measurements using ImageJ (v.1.49). Signal intensities were determined as 'integrated densities as a percentage of the total' which corresponds to the area under the curve of the signal of each dot after membrane background and negative control signal subtraction.

## In silico analyses:

All protein and RNA sequences of the m<sup>6</sup>A machinery of *Homo sapiens* and *Drosophila melanogaster* (Data S1) were recovered by their published designation (i.e., 'METTL3' or 'YTHDF' etc.) and their identified protein sequence (ie. RefSeq accession number NP...) collected from NCBI and used as query sequences to search for putative homologue sequences in *Crassostrea gigas* databases. The presence of oyster orthologue RNA and protein sequences were investigated by reciprocal

BLAST(https://blast.ncbi.nlm.nih.gov/Blast.cgi) on the *Crassostrea gigas* GigaTON [70] and NCBI databases and results were compared between the two oyster databases. Domain prediction was performed with CD-search software (https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi) with default settings on protein sequences of *Homo sapiens*, *Drosophila melanogaster* and *Crassostrea gigas*. The GRE-rich domain identified in vertebrate Prrc2a sequence [27] was performed with ProtParam (https://web.expasy.org/cgi-bin/protparam/protparam).

#### Protein machinery mRNA expression analyses:

The transcriptome data of the different development stages are available on the GigaTON database [70,71]. The correspondence between development stages in our study, and the GigaTON database were assessed using light microscopy based on the morphological description by Zhang et al., 2012 [71] (Table S2). Expression data was expressed in TPM (Transcripts Per Million) [72] to provide a normalized comparison of gene expression between all samples. The actual presence of some transcripts that display unclear or chimeric sequences within available oyster databases was assessed using RT-PCR (Data S1).

#### Protein m<sup>6</sup>A RNA pull down:

Protein extraction and RNA affinity chromatography

Protein extraction and RNA affinity chromatography were performed as described previously [27] with some modifications as follows. Equal amounts (1 million individuals) of each developmental stage (oocyte to D larvae) were pooled together then homogenized in 3.5

volumes of buffer A (10 mM KCl, 1.5 mM MgCl2, 10 mM HEPES, pH 7.9, DEPC water, 1X Protease inhibitor cocktail, DTT 0.5 mM) by extensive pipetting (ca. 30 times) and incubated 10 min at 4 °C. Embryos were ground with 10 slow 23G-needle syringe strokes and centrifuged at 2,000 rpm for 10 min at 4 °C. The supernatant was diluted in 0.11 volume of buffer B (1.4 M KCI, 0.03 M MgCI2, HEPES 0.3 M, pH 7.9, DEPC water), centrifuged at 10,000 g for 1 h at 4 °C and the supernatant containing cytosolic proteins was stored at -80 °C. The pellet of the first centrifugation, containing nuclei, was re-suspended in two volumes of buffer C (0.42 M NaCl, 1.5 mM MgCl2, 0.2 mM EDTA, 25 % glycerol, 20 mM HEPES, pH 7.9, 0.5 mM PMSF, 0.5 mM DTT, water DEPC). Nuclei were then lysed with a 23 G needle (10 vigorous syringe strokes) followed by centrifugation at 30,000 rpm for 30 min at 4 °C and the supernatant containing nuclear proteins was stored at -80 °C. To identify putative proteins able to bind m<sup>6</sup>A-RNA, the cytosolic and nuclear fractions were submitted to affinity chromatography using 5'-biotin-labelled RNA oligonucleotides either bearing  $N^6$ -methylated adenosines or not. The methylated adenosines were designed to lie within RRACH motifs, according to the conserved methylated consensus sequence in other organisms [2,3,7,33,73] (oligo-m<sup>6</sup>A: 5'Biotin-AGAAAAGACAACCAACGAGRR-m<sup>6</sup>A-CWCAUCAU-3', oligo-A: 5'Biotin-AGAAAAGACAACCAACGAGRRACWCAUCAU-3', R = A or G, W = A or U, Eurogentec).For RNA pull down, streptavidin-conjugated magnetic beads (Dynabeads Myone Streptavidin, Invitrogen) were pre-blocked with 0.2 mg/mL tRNA (Sigma-Aldrich) and 0.2 mg/mL BSA for 1 h at 4 °C under gentle rotation followed by three washes with 0.1 M NaCl. To avoid the identification of non-target proteins, cytosolic and nuclear protein extracts were cleared with

pre-blocked magnetic beads in binding buffer (50 mM Tris-HCl, 250 mM NaCl, 0.4 mM EDTA, 0.1 % NP-40, DEPC water, 1 mM DTT, 0.4 U/µL RNAsin) for 1 h at 4 °C under gentle rotation. After incubation on magnetic rack, the supernatants containing putative target proteins were collected and mixed with pre-blocked magnetic beads and oligo-m<sup>6</sup>A or oligo-A for 2 h at 4 °C under gentle rotation. The beads binding putative target proteins were washed three times with binding buffer and diluted in 50 mM ammonium bicarbonate.

Identification of m<sup>6</sup>A-binding proteins by LC-MS/MS:

Protein samples were first reduced, alkylated and digested with trypsin then desalted and concentrated onto a µC18 Omix (Agilent, Santa Clara, CA, USA) before analysis.

The chromatography step was performed on a NanoElute (Bruker Daltonics, Billerica, MA,

USA) ultra-high pressure nano flow chromatography system. Peptides were concentrated onto

a C18 pepmap 100 (5 mm x 300 µm i.d.) precolumn (Thermo Scientific) and separated at 50

°C onto a reversed phase Reprosil column (25 cm x 75 µm i.d.) packed with 1.6 µm C18 coated

porous silica beads (Ionopticks, Parkville, Victoria, Australia). Mobile phases consisted of 0.1

% formic acid, 99.9 % water (v/v) (A) and 0.1 % formic acid in 99.9 % ACN (v/v) (B). The

nanoflow rate was set at 400 nL/min, and the gradient profile was as follows: from 2 to 15 % B

within 60 min, followed by an increase to 25 % B within 30 min and further to 37 % within 10

min, followed by a washing step at 95 % B and re-equilibration.

MS experiments were carried out on an TIMS-TOF pro mass spectrometer (Bruker Daltonics)

with a modified nano-electrospray ion source (CaptiveSpray, Bruker Daltonics). The system

was calibrated each week and mass precision was better than 1 ppm. A 1600 spray voltage

with a capillary temperature of 180 °C was typically employed for ionizing. MS spectra were

acquired in the positive mode in the mass range from 100 to 1700 m/z. In the experiments described here, the mass spectrometer was operated in PASEF mode with exclusion of single charged peptides. A number of 10 PASEF MS/MS scans was performed during 1.16 seconds from charge range 2-5.

The fragmentation pattern was used to determine the sequence of the peptide. Database searching was performed using the Mascot 2.6.1 program (Matrix Science) with a *Crassostrea gigas* Uniprot database (including 25,982 entries). The variable modifications allowed were as follows: C-Carbamidomethyl, K-acetylation, methionine oxidation, and Deamidation (NQ). The 'Trypsin' parameter was set to 'Semispecific'. Mass accuracy was set to 30 ppm and 0.05 Da for MS and MS/MS mode respectively. Mascot data were then transferred to Proline validation

software (http://www.profiproteomics.fr/proline/) for data filtering according to a significance

threshold of <0.05 and the elimination of protein redundancy on the basis of proteins being

#### Gene ontology analysis:

evidenced by the same set or a subset of peptides (Data S2).

The mRNA sequences of the characterized m<sup>6</sup>A-binding proteins were identified using tBlastn [74–76] against the GigaTON database [70] with default settings. Gene ontology (GO) analyses were carried out with the GO annotations obtained from GigaTON database gene universe [70]. GO term-enrichment tests were performed using the goseq (V1.22.0) R package [77] with p-values calculated by the Wallenius method and filtered using REVIGO [78]. GO terms with a p-value < 0.05 were considered significantly enriched (Data S3).

Statistical analyses and graph production:

Results are given as the mean ± SD of three independent experiments unless otherwise stated. They were analysed using one-way ANOVA or Kruskall-wallis tests when required, depending on the normality of result distribution. The normality was tested using the Shapiro-Wilk's test and homoscedasticity of variances with Bartlett's tests. Statistics and graphics were computed with Prism v.6 (Graphpad), R (v.3.6.1) and RStudio (v.1.0.153) softwares. The R packages eulerr [79] and Complexheatmap [80] were used for production of specific figures.

#### **Author contribution**

- 667 Experiment design: GR, LLF.
- Benchwork and bioinformatics: LLF, GR, BB, BP, MS.
- Data analysis: LLF, GR, BB, MS.
- 670 Manuscript writing and editing: LLF, GR, PF, BB, MS, BP.

#### **Acknowledgements**

- The authors would like to acknowledge PRISMM core facility collaborators R. Delepée and S.
- Lagadu for their expertise in m<sup>6</sup>A/A UHPLC-MS/MS quantification. We also thank J. Pontin for
- technical assistance and J. Le Grand for help with sampling.

#### Funding sources and disclosure of conflicts of interest

This work was supported by the French National program CNRS EC2CO (Ecosphère Continentale et Côtière 'HERITAGe' to G. Rivière) and the council of the Normandy Region (RIN ECUME to P. Favrel). The authors declare they have no conflict of interest.

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#### Figure legends

Figure 1: m<sup>6</sup>A levels across oyster development.

**A.** m<sup>6</sup>A level quantified by LC-MS/MS in *Crassostrea gigas* embryo-larval stages pooled from oocytes to D-larvae (n= 3) is compared to the m<sup>6</sup>A level in *Homo sapiens* and *Drosophila melanogaster*, **B.** Dot blot quantification of m<sup>6</sup>A in total RNA throughout oyster development (n=3); **C.** Dot blot quantification of m<sup>6</sup>A in polyA+ RNAs throughout oyster development (n=3) Kruskal-Wallis test,  $\alpha$  < 0,05. E: Egg, F E: fertilized egg, 2/8C: two to eight cell embryos, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae. Chemiluminescence (B) and fluorescence (C) are measured as a ratio between dot intensity of development stages and their respective controls for each amount of RNA (120ng, 60ng and 30ng).

Figure 2: The putative conserved m<sup>6</sup>A machinery in *Crassostrea gigas*.

Domain architecture of actors of the m<sup>6</sup>A machinery identified by *in silico* analyses in the oyster compared to the fruit fly and human, **A.** Writer proteins; **B.** Eraser protein; **C.** Reader proteins. Putative domains involved in m<sup>6</sup>A processes are coloured (writers, green; eraser, red; readers, blue). Other domains identified but not involved in m<sup>6</sup>A processes are indicated in grey. Only one isoform is represented for each protein and each species for clarity (see supplementary figure S2 for other isoforms).

Figure 3: Gene expression of the putative m<sup>6</sup>A machinery throughout oyster development

Expression levels of writers (**A**), eraser (**B**) and readers (**C**) identified by *in silico* analysis at each development stage were inferred from the GigaTON database. Expression levels are given in Transcripts Per kilobases per Million Reads (TPM) as the mean of the GigaTON values according to the table S2. E: Egg, 2/8C: two to eight cell, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

<u>Figure 4: Characterization of m<sup>6</sup>A-RNA binding proteins in oyster development.</u>

**A.** Venn diagrams representation of proteins bound to the A- and/or m<sup>6</sup>A- oligos in nuclear and cytosolic fractions of oyster embryo-larval stages. The number of proteins identified is indicated. Some actors characterized in this study are highlighted: eIF3, YTHC1, hnRNPA2B1 and IGF2BP. **B.** Heatmap of gene expression levels of the proteins that bind specifically to the m<sup>6</sup>A-oligo throughout oyster development. The expression level is normalized regarding the maximum value for each gene according to the GigaTON database. **C.** GO term distribution among the three expression clusters in B. **D.** Examples of GO term enrichment within the expression clusters of the m<sup>6</sup>A-bound proteins. The –log10(p-value) associated to each term is given. E: Egg, 2/8C: two to eight cells, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

#### **Supporting information:**

- <u>Data S1</u>: Complete list of *in silico* identified putative m<sup>6</sup>A machinery proteins and their respective BLAST results
- 979 <u>Data S2</u>: Identified proteins by RNA pull down coupled with mass spectrometry with m<sup>6</sup>A or
- 980 A-oligo, in nuclear or cytosolic protein extracts

Data S3: Complete list of GO terms of clustered genes of m<sup>6</sup>A interacting proteins (p-value<0,05)</li>
 Table S1: Transitions used for each compound. A: first transition, B: second transition

Table S2: Table of correspondence between development stages in our study, and the

GigaTON database.



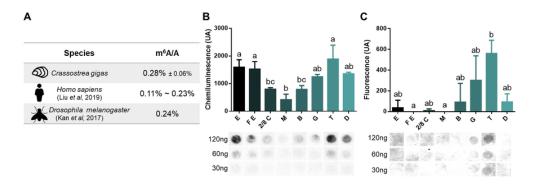


Figure 1: m6A levels across oyster development.

A. m6A level quantified by LC-MS/MS in Crassostrea gigas embryo-larval stages pooled from oocytes to D-larvae (n= 3) is compared to the m6A level in Homo sapiens and Drosophila melanogaster; B. Dot blot quantification of m6A in total RNA throughout oyster development (n=3); C. Dot blot quantification of m6A in polyA+ RNAs throughout oyster development (n=3) Kruskal-Wallis test, a < 0,05. E: Egg, F E: fertilized egg, 2/8C: two to eight cell embryos, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae. Chemiluminescence (B) and fluorescence (C) are measured as a ratio between dot intensity of development stages and their respective controls for each amount of RNA (120ng, 60ng and 30ng).

75x25mm (300 x 300 DPI)

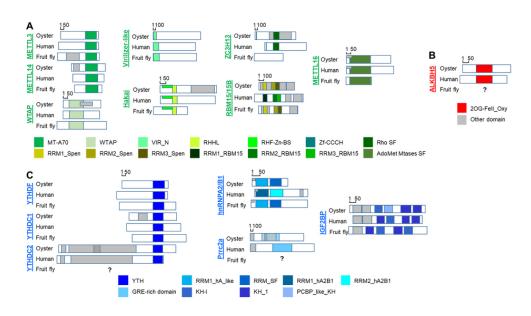


Figure 2: The putative conserved m6A machinery in Crassostrea gigas.

Domain architecture of actors of the m6A machinery identified by in silico analyses in the oyster compared to the fruit fly and human, A. Writer proteins; B. Eraser protein; C. Reader proteins. Putative domains involved in m6A processes are coloured (writers, green; eraser, red; readers, blue). Other domains identified but not involved in m6A processes are indicated in grey. Only one isoform is represented for each protein and each species for clarity (see supplementary figure S2 for other isoforms).

80x47mm (300 x 300 DPI)

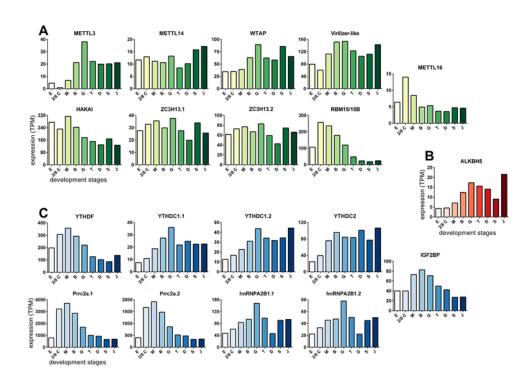


Figure 3: Gene expression of the putative m6A machinery throughout oyster development Expression levels of writers (A), eraser (B) and readers (C) identified by in silico analysis at each development stage were inferred from the GigaTON database. Expression levels are given in Transcripts Per kilobases per Million Reads (TPM) as the mean of the GigaTON values according to the table S2. E: Egg, 2/8C: two to eight cell, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

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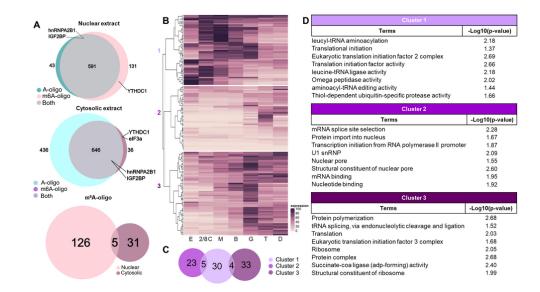


Figure 4: Characterization of m6A-RNA binding proteins in oyster development.

A. Venn diagrams representation of proteins bound to the A- and/or m6A- oligos in nuclear and cytosolic fractions of oyster embryo-larval stages. The number of proteins identified is indicated. Some actors characterized in this study are highlighted: eIF3, YTHC1, hnRNPA2B1 and IGF2BP. B. Heatmap of gene expression levels of the proteins that bind specifically to the m6A-oligo throughout oyster development. The expression level is normalized regarding the maximum value for each gene according to the GigaTON database. C. GO term distribution among the three expression clusters in B. D. Examples of GO term enrichment within the expression clusters of the m6A-bound proteins. The -log10(p-value) associated to each term is given. E: Egg, 2/8C: two to eight cells, M: Morula, B: Blastula, G: Gastrula, T: Trochophore, D: D larvae, S: Spat, J: Juvenile.

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<u>Data S1</u>: Complete list of in silico identified putative m6A machinery proteins and their respective BLAST results Probable assembly artefact highlighted in grey

Specie	database	sequence accession number	length	conserved domain			
METTL3							
Homo sapiens	NCBI	gi 21361827 (NP_062826.2)	580	MT-A70			
Drosophila melanogaster (IME4)	NCBI	gi 21355141 (NP_651204.1)	608	MT-A70 MDN1			
Crossostros gigos	GIGATON	CHOYP_PHUM_PHUM423190.1.1	554	MT-A70			
Crassostrea gigas	NCBI	gi 762092209 (XP_011428532.1)	555	MT-A70			
		METTI	L14				
Homo sapiens	NCBI	gi 24308265 (NP_066012.1)	456	MT-A70			
Drosophila melanogaster (CG7818)	NCBI	gi 19920926 (NP_609205.1)	397	MT-A70			
	CICATON	CHOYP_MET14.1.1	495	MT-A70 MttA_Hfc106			
Crassostrea gigas	GIGATON	CHOYP_LOC100743733.1.1	723	MT-A70 7tmA_NPR-like_invertebrate			
	NCBI	gi 762082967 (XP_011424173.1)	470	MT-A70 MttA_Hfc106			
		<u>WTA</u>	<u>IP</u>	70/1			
		gi 395455090 (NP_001257460.1)	396	WTAP			
Homo sapiens	NCBI	gi 23199974 (NP_690596.1)	151	WTAP			
		gi 395455092 (NP_001257461.1)	170	WTAP			
Dyna a mbila mada na sa ata n (FL (2)D)	NCDI	gi 24653459 (NP_523732.2)	536	WTAP			
Drosophila melanogaster (FL(2)D)	NCBI -	gi 24653461 (NP_725327.1)	412	WTAP			
		CHOYP_FL2D.1.1	406	WTAP IncA			
	GIGATON	CHOYP_SODM.1.2	252	WTAP IncA			
Crassostrea gigas		CHOYP_LOC100121674.1.1	290	WTAP IncA			
	NCBI	gi 762078268 (XP_011453082.1)	406	WTAP IncA			

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## **VIRILIZER-LIKE**

Homo sapiens (Virilizer-like, VIRMA)	NCBI	gi 33946282 (NP_056311.2)	1812	VIR_ N
nomo sapiens (vinilzer-like, vikivia)	INCDI	gi 33946280 (NP_892121.1)	1147	VIR_ N
Drosophila melanogaster (Virilizer)	NCBI	gi 17864576 (NP_524900.1)	1854	VIR_ N
	GIGATON	CHOYP_VIR.1.1	2021	VIR_ N
	NCBI	gi 762120202 (XP_011443024.1)	2023	VIR_ N
Crannostron gigan		gi 762120200 (XP_011443023.1)	2023	VIR_ N
Crassostrea gigas		gi 1139822239 (XP_019927346.1)	2022	VIR_ N
		gi 1139822241 (XP_019927347.1)	2021	VIR_ N
		gi 1139822243 (XP_019927348.1)	1717	VIR_ N PTZ00249 super family

### **HAKAI**

Home conione	NCBI	gi 209180481 (NP_079090.2)	491	RHF-Zn-BS RHHL
Homo sapiens	INCDI	gi 546230945 (NP_001271220.1)	490	RHF-Zn-BS RHHL
		gi 19921556 (NP_609993.1)	302	RHF-Zn-BS RHHL
Drosophila malanagastar	NCBI	gi 24585301 (NP_724217.1)	311	RHF-Zn-BS RHHL
Drosophila melanogaster	NCBI	gi 442628448 (NP_788075.2)	464	RHF-Zn-BS RHHL
		gi 442628450 (NP_001260593.1)	473	RHF-Zn-BS RHHL
	GIGATON	CHOYP_LOC100864501.1.1	504	RHF-Zn-BS RHHL PHA03247 super family
Crassostrea gigas	NCBI	gi 762140345 (XP_011453340.1)	498	RHF-Zn-BS RHHL PHA03247 super family
	NCBI -	gi 762140347 (XP_011453341.1)	497	RHF-Zn-BS RHHL PHA03247 super family

### **ZC3H13**

		gi 1060099240 (NP_001317493.1)	1669	Zf-CCCH Rho SF
Homo sapiens	NCBI	gi 1060099108 (NP_001317496.1)	1668	Zf-CCCH Rho SF

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Bill   16008442 (NP_055885.3)   1564   ZI-CCCH   Rho SF		<u> </u>		. –	
NCBI   gi 665392303 (NP_001285418.1)   1139	Zf-CCCH Rho SF	1564	gi 116008442 (NP_055885.3)		
GIGATON   CHOYP_BRAFLDRAFT_120702.1.1   1631   Zf-CCCH   Rho SF   dnaA super family   PTZ00121		1150	gi 24643154 (NP_573339.1)		
CHOYP_BRAFLDRAFT_120702.1.1   1631   Zf-CCCH   Rho SF   dnaA super family   PTZ00121		1139	gi 665392303 (NP_001285418.1)	NCBI	Drosophila melanogaster (CG7358)
CHOYP_LOC100568158.1.1   1611   Zf-CCCH   Rho SF   dnaA super family   PTZ00121		842	gi 665392305 (NP_001285419.1)		
CHOYP_LOC100568158.1.1 1611 Zf-CCCH Rho SF dnaA super family PTZ00121  gi 762096734 (XP_011430912.1) 1400 Rho SF dnaA super family PTZ00121  Crassostrea gigas  gi 762096736 (XP_011430913.1) 1400 Rho SF dnaA super family PTZ00121  NCBI gi 762096738 (XP_011430914.1) 1380 Rho SF PHA03307 PTZ00121	Zf-CCCH Rho SF dnaA super family PTZ00121	1631	CHOYP_BRAFLDRAFT_120702.1.1	CICATON	
Crassostrea gigas  gi 762096736 (XP_011430913.1) 1400 Rho SF dnaA super family PTZ00121  gi 762096738 (XP_011430914.1) 1380 Rho SF PHA03307 PTZ00121	Zf-CCCH Rho SF dnaA super family PTZ00121	1611	CHOYP_LOC100568158.1.1	GIGATON	
NCBI gi 762096736 (XP_011430913.1) 1400 Rho SF dnaA super family PTZ00121 gi 762096738 (XP_011430914.1) 1380 Rho SF PHA03307 PTZ00121	Rho SF dnaA super family PTZ00121	1400	gi 762096734 (XP_011430912.1)		Crassatras gigas
gi 762096738 (XP_011430914.1) 1380 Rho SF PHA03307 PTZ00121	Rho SF dnaA super family PTZ00121	1400	gi 762096736 (XP_011430913.1)	NCDI	Crassostrea gigas
n:/700000740 (VP 0444000454)	Rho SF PHA03307 PTZ00121	1380	gi 762096738 (XP_011430914.1)	NCBI -	
gi /62096/40 (XP_011430915.1) 1329 R10 SF P1200121	Rho SF PTZ00121	1329	gi 762096740 (XP_011430915.1)		
RBM15/15B		15B	RBM15		

		gi 47933339 (NP_073605)	977	RRM1_RBM15 RRM2_RBM15 RRM3_RBM15 SF-CC1 SPOC
Homo sapiens	NCBI	gi 319996623 (NP_001188474)	969	RRM1_RBM15 RRM2_RBM15 RRM3_RBM15 SF-CC1 SPOC
		gi 54607124 (NP_037418)	890	RRM1_RBM15 RRM2_RBM15 RRM3_RBM15 U2AF_Ig SF SPOC
Drosophila melanogaster (SPENITO/NITO)		gi 24586450 (NP_724633)	793	RRM1_Spen RRM2_Spen RRM SPOC
	NCBI	gi 19921778 (NP_610339)	793	RRM1_Spen RRM2_Spen RRM3_Spen RRM SPOC
		gi 665399388 (NP_001286174)	793	RRM1_Spen RRM2_Spen RRM3_Spen RRM SPOC
Crassostrea gigas	GIGATON	CHOYP_LOC663518.1.1	717	RRM1_Spen RRM2_Spen RRM SPOC PTZ00449 SF
	NCBI	gi 762129377 (XP_011447812)	717	RRM1_Spen RRM2_Spen RRM SPOC PTZ00449 SF

### METTL16

Homo sapiens	NCBI	gi 122114654 (NP_076991.3)	562	AdoMet Mtases SF S-adenosylmethionine binding site
Drosophila melanogaster (CG7544)	NCBI	gi 19922302 (NP_611015.1)	305	AdoMet Mtases SF
	GIGATON	CHOYP_LOC100561572.1.1	527	AdoMet Mtases SF S-adenosylmethionine binding site

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Crassostrea gi	gas NCBI	gi 762141911 (XP_011454156.1)	538	AdoMet Mtases SF S-adenosylmethionine binding site
	NCBI	gi 762141913 (XP_011454157.1)	527	AdoMet Mtases SF S-adenosylmethionine binding site
		ALKB	<u>H5</u>	
Homo sapier	ncbi NCBi	gi 148539642 (NP_060228.3)	394	2OG-FeII_Oxy
Drosophila meland	ogaster			
Crassastras di	GIGATON	CHOYP_BRAFLDRAFT_126925.1.1	403	2OG-FeII_Oxy
Crassostrea gi	NCBI	gi 762097205 (XP_011431161.1)	374	2OG-FeII_Oxy
		YTHD	<u>C1</u>	
		gi 72534750 (NP_001026902.1)	727	YTH
Homo sapier	ncBi NCBi	gi 94536805 (NP_588611.2)	709	YTH
		gi 1061213987 (NP_001317627.1)	735	YTH
Drosonhila melanogast	er (YT521) NCBI	gi 24656811 (NP_647811.2)	721	YTH
Drosophila melanogasi	Drosophila melanogaster ( YT521) NCBI	gi 24656816 (NP_728876.1)	710	YTH
	GIGATON	CHOYP_YTDC1.2.2	636	YTH CDC27
Crassostrea gi		CHOYP_LOC586835.1.1	545	YTH CDC27
	NCBI	gi 762070401 (XP_011447601.1)	636	YTH CDC27
		YTHD	<u>C2</u>	
		gi 269847874 (NP_073739.3)	1430	YTH HrpA R3H_DEXH_helicase DEXHc_YTHDC2 OB_NTP_bind
Homo sapier	NCBI	gi 1066536696 (NP_001332904.1)	1268	YTH HrpA DEXHc_YTHDC2 OB_NTP_bind
		gi 1066546270 (NP_001332905.1)	1130	YTH HrpA DEAD-like_helicase_N SF ANKYR OB_NTP_bind
Drosophila melano	gaster			
Crassostrea gi	GIGATON	CHOYP_YTDC2.1.1	1572	YTH HrpA R3H super family Ank_2
Sracecon ou gr	NCBI	gi 762086858 (XP_011425711.1)	1572	YTH HrpA R3H super family Ank_2

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## **YTHDF**

1 2 3 4					
5 6 7 8			<u>YTHI</u>	<u>DF</u>	
9 10 11			gi 29791407 (AAH50284.1)	559	YTH RPA_2b-aaRSs_OBF_like PHA03247 super family
12 13 14	Homo sapiens	NCBI	gi  12803469 (AAH02559.1)	579	YTH
15 16 17			gi 31419299 (AAH52970.1)	585	YTH
18 19 20 21			gi 21356147 (NP_651322.1)	700	YTH
22 23 24	Drosophila melanogaster (CG6422)		gi 24649883 (NP_733067.1)	699	YTH
25 26 27			gi 161078590 (NP_001097905.1)	694	YTH
28 29 30		GIGATON	CHOYP_COX1.6.15	532	YTH
31 32 33 34	Crassostrea gigas	GIOATON	CHOYP_LOC100371022.1.1	531	YTH
35 36 37		NCBI	gi 762146089 (XP_011456337.1)	522	YTH
38 39 40 41			hnRNP.	A2B1	·
42 43	Homo sapiens	NCBI	gi 4504447 (NP_002128.1)	341	RRM1_hA2B1 RRM2_hA2B1 Putative DNA binding site hnRNPA1
44 45 46 47	Trome dapterio	1105.	gi 14043072 (NP_112533.1)	353	RRM1_hA2B1 RRM2_hA2B1 Putative DNA binding site hnRNPA1
48 49			gi 24650831 (NP_733249.1)	364	RRM1_hA_like RRM_SF Putative DNA binding site
50 51 52 53	Drosophila melanogaster (hrb98DE)	NCBI -	gi 17738267 (NP_524543.1)	365	RRM1_hA_like RRM_SF Putative DNA binding site
54			gi 24650838 (NP_733252.1)	361	RRM1_hA_like RRM_SF Putative DNA binding site
55 56 57 58 59			gi 24650833 (NP_733250.1)	360	RRM1_hA_like RRM_SF Putative DNA binding site
60			CHOVE I OC100749305 1 7	220	RRM1 hA like RRM SE Putative DNA hinding site

## hnRNPA2B1

r				
Homo sapiens	NCBI -	gi 4504447 (NP_002128.1)	341	RRM1_hA2B1 RRM2_hA2B1 Putative DNA binding site hnRNPA1
riomo sapiens		gi 14043072 (NP_112533.1)	353	RRM1_hA2B1 RRM2_hA2B1 Putative DNA binding site hnRNPA1
		gi 24650831 (NP_733249.1)	364	RRM1_hA_like RRM_SF Putative DNA binding site
Droconhila malanagastar (hrh00DE)	NCBI	gi 17738267 (NP_524543.1)	365	RRM1_hA_like RRM_SF Putative DNA binding site
Drosophila melanogaster (hrb98DE)	INCBI	gi 24650838 (NP_733252.1)	361	RRM1_hA_like RRM_SF Putative DNA binding site
		gi 24650833 (NP_733250.1)	360	RRM1_hA_like RRM_SF Putative DNA binding site
		CHOYP_LOC100748395.1.7	229	RRM1_hA_like RRM_SF Putative DNA binding site
		CHOYP_LOC100748395.2.7	394	RRM1_hA_like RRM_SF Putative DNA binding site
	GIGATON	CHOYP_LOC100748395.3.7	315	RRM1_hA_like RRM_SF Putative DNA binding site
		CHOYP_LOC100748395.4.7	372	RRM1_hA_like RRM_SF Putative DNA binding site
		CHOYP_LOC100748395.6.7	315	RRM1_hA_like RRM_SF Putative DNA binding site
Crassostrea gigas		CHOYP_AGAP_AGAP002374.1.1	236	RRM_SF

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1 2 3 4								
5 6 7 8			CHOYP_LOC100748395.5.7	205 RRM_SF				
9 10 11			gi 762104361 (XP_011434715.1)	370 RRM1_hA_like RRM_SF Putative DNA binding site				
12 13 14		NCBI	gi 762104364 (XP_011434716.1)	RRM1_hA_like RRM_SF Putative DNA binding site				
15 16 17		INCBI	gi 762104366 (XP_011434717.1)	RRM1_hA_like RRM_SF Putative DNA binding site				
18 19 20 21			gi 762104368 (XP_011434718.1)	RRM1_hA_like RRM_SF Putative DNA binding site				
22 23 24	22 23 <b>Prrc2a</b>							
25 26 27	Homo sapiens	NCBI	gi 314122241 (NP_004629.3)	2157 GRE-rich domain BAT2_N				
28 29 30	Drosophila melanogaster							
31 32 33		GIGATON	CHOYP_LOC100559941.1.2	2578 GRE-rich domain BAT2_N PTZ00121 PTZ00449				
34 35 36 37	Crassostrea gigas	GIGATON	CHOYP_LOC100559941.2.2	2554 GRE-rich domain BAT2_N PTZ00121 PTZ00449				
38 39 40			gi 1139830093 (XP_019928978.1)	2922 GRE-rich domain BAT2_N PTZ00121 PTZ00449				
41 42 43			IGF2E	3P				
44 45 46			gi 56237027 (NP_006537.3)	577 KH-I KH-1 RRM1_IGF2BP1 RRM2_IGF2BP1				
47 48 49			gi 238624257 (NP_001153895.1)	438 KH-I KH-1 RRM1_IGF2BP1 RRM_SF super family				
50 51 52 53			gi 64085377 (NP_006539.3)	599 KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM2_IGF2BP2				
54 55 56			gi 56118219 (NP_001007226.1)	556 KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM2_IGF2BP2				
57 58 59	Homo soniono	NCBI	gi 631226390 (NP_001278798.1)	605 KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM_SF super family				
60	Homo sapiens	INCDI	a:1624226202 (NID 004278804 4)	542 KILL BODD III. KILL DDM OF annua (analla				

# IGF2BP

		gi 56237027 (NP_006537.3)	577	KH-I KH-1 RRM1_IGF2BP1 RRM2_IGF2BP1
		gi 238624257 (NP_001153895.1)	438	KH-I KH-1 RRM1_IGF2BP1 RRM_SF super family
		gi 64085377 (NP_006539.3)	599	KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM2_IGF2BP2
		gi 56118219 (NP_001007226.1)	556	KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM2_IGF2BP2
Homo sapiens	NCBI	gi 631226390 (NP_001278798.1)	605	KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM_SF super family
	-	gi 631226392 (NP_001278801.1)	542	KH-I KH-1 PCBP_like_KH RRM_SF super family
		gi 631226396 (NP_001278802.1)	536	KH-I KH-1 PCBP_like_KH RRM2_IGF2BP2
		gi 631226394 (NP_001278803.1)	493	KH-I KH-1 PCBP_like_KH RRM2_IGF2BP2
		gi 631226398 (NP_001278804.1)	463	KH-I KH-1 PCBP_like_KH RRM_SF super family
		gi 30795212 (NP_006538.2)	579	KH-I KH-1 PCBP_like_KH RRM1_IGF2BP3 RRM2_IGF2BP3
		gi 386764188 (NP_001036268.2)	631	KH-I KH-1 RRM2_VICKZ

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	NCBI	gi 386764191 (NP_001245616.1)	638	KH-I KH-1 RRM2_VICKZ
Drosophila melanogaster (IGF-II binding protein)		gi 17530887 (NP_511111.1)	566	KH-I KH-1
		gi 24641097 (NP_727451.1)	573	KH-I KH-1
		gi 281360685 (NP_001162717.1)	580	KH-I KH-1
	GIGATON	CHOYP_LOC100114171.1.1	607	KH-I KH-1 PCBP_like_KH RRM1_VICKZ RRM_SF super family
Crassostrea gigas	NCBI	gi 762079091 (XP_011412002.1)	611	KH-I KH-1 PCBP_like_KH RRM1_VICKZ RRM_SF super family
Orassosirea gigas		gi 762079093 (XP_011412008.1)	607	KH-I KH-1 PCBP_like_KH RRM1_VICKZ RRM_SF super family
		gi 762079095 (XP_011412017.1)	590	KH-I KH-1 PCBP_like_KH RRM1_VICKZ RRM_SF super family

## <u>elF3a</u>

Homo sapiens	NCBI	gi 4503509(NP_003741.1)	1382	PINT Smc super family U2AF_Ig super family dnaA super family Rho SF						
Drosonhila malanagastar (ICE II hinding protain)	NCBI	gi 665393171 (NP_730838.3)	1140	PINT DUF5401 Rho SF						
Drosophila melanogaster (IGF-II binding protein)	NCBI -	gi 24643988 (NP_649470.2)	gi 24643988 (NP_649470.2) 1140 PINT DUF5401 Rho SF							
	GIGATON NCBI	CHOYP_BRAFLDRAFT_75590.1.1	155							
Crassostrea gigas		CHOYP_UBP47.2.2	1253	PAM DUF5401						
		CHOYP_MROH1.1.1	1046	PAM DUF5401						
		gi 762160635 (XP_011418535.1)	759	PAM DUF5401						
		gi 762122193 (XP_011444042.1 )	1252	PAM DUF5401						

Data S1: Complete list of in silico	o identified putative m6A machinery proteins a	and their respective BLAST results														
Data O1. Complete list of lift sillet	Crassostrea gigas					Homo sa	piens							Drosophila melanogaster		
METTL3	CHOYP_PHUM_PHUM423190.1.1	gi 21361827 (NP_062826.2) 52.3%										gi 21355141 (NP_651204.1) 73.26%				
	gi 762092209 (XP_011428532.1)	52.81%										73.96%				
	CHOYP_MET14.1.1	gi 24308265 (NP_066012.1) 62.03%										gi 19920926 (NP_609205.1) 58.05%				
METTL14	CHOYP_LOC100743733.1.1	60.88%										57.76%				
	gi 762082967 (XP_011424173.1)	61.58% gi 395455090 (NP_001257460.1)	gi 23199974 (NP_690596.1)	gi 395455092 (NP_001257461.1)								58.05% gi 24653459 (NP_523732.2)	gi 24653461 (NP_725327.1)			
	CHOYP_FL2D.1.1	52.68%	47.55%	47.55%								56.16%	58.42%			
WTAP	CHOYP_SODM.1.2 CHOYP_LOC100121674.1.1	47.55% 52.68%	47.92% 47.55%	47.65% 47.55%								60.40% 56.16%	60.40% 58.42%			
	gi 762078268 (XP_011453082.1)	51.06%	47.55%	47.55%								53.49%	58.42%			
	CHOYP VIR.1.1	gi 33946282 (NP_056311.2) 30.70%	gi 33946280 (NP_892121.1) 29.59%									gi 17864576 (NP_524900.1) 25.49%				
	gi 762120202 (XP_011443024.1)	30.85%	30.17%									25.49%				
VIRILIZER-like	gi 762120200 (XP_011443023.1) gi 1139822239 (XP_019927346.1)	30.85% 30.89%	30.17% 30.17%									25.49% 25.49%				
	gi 1139822241 (XP_019927347.1)	30.95%	30.24%									25.49%				
	gi 1139822243 (XP_019927348.1)	30.62% gi 209180481 (NP_079090.2)	30.35% gi 546230945 (NP_001271220.1)									26.04% gi 19921556 (NP 609993.1)	gi 24585301 (NP_724217.1)	gi 442628448 (NP_788075.2)	gi 442628450 (NP_001260593.1)	
HAKAI	CHOYP_LOC100864501.1.1	43.27%	43.96%									60.45%	60.45%	60.45%	60.45%	
	gi 762140345 (XP_011453340.1) gi 762140347 (XP_011453341.1)	29.43% 29.28%	29.68% 29.68%									56.29% 57.14%	60.45% 60.45%	56.29% 57.14%	60.45% 60.45%	
		gi 1060099240 (NP_001317493.1)	gi 1060099108 (NP_001317496.1)									gi 24643154 (NP_573339.1)	gi 665392303 (NP_001285418.1)		33.1373	
	CHOYP_BRAFLDRAFT_120702.1.1 CHOYP_LOC100568158.1.1	37.11% 37.11%	37.11% 37.11%	37.11% 37.11%								N/A N/A	N/A N/A	N/A N/A		
ZC3H13	gi 762096734 (XP_011430912.1)	31.48%	31.48%	40.00%								N/A	N/A	N/A		
	gi 762096736 (XP_011430913.1) gi 762096738 (XP_011430914.1)	31.48% 31.48%	31.48% 31.48%	40.00% 40.00%								N/A N/A	N/A N/A	N/A N/A		
	gi 762096740 (XP_011430915.1)	31.68%	31.68%	40.58%								N/A	N/A	N/A		
RBM15/15B	CHOYP_LOC663518.1.1	gi 47933339 (NP_073605) 56.73%	gi 319996623 (NP_001188474) 56.73%	gi 54607124 (NP_037418) 61.59%								gi 24586450 (NP_724633) 59.22%	gi 19921778 (NP_610339) 59.22%	gi 665399388 (NP_001286174) 59.22%		
	gi 762129377 (XP_011447812)	41.64%	41.64%	34.94%								42.75%	42.75%	42.75%		
METTLAG	CHOYP_LOC100561572.1.1	gi 122114654 (NP_076991.3) 38.05%										gi 19922302 (NP_611015.1) 38.81%				
METTL16	gi 762141911 (XP_011454156.1)	37.68%										39.16%				
	gi 762141913 (XP_011454157.1)	37.68% gi 148539642 (NP_060228.3)										39.16%				
ALKBH5	CHOYP_BRAFLDRAFT_126925.1.1	72.43%														
	gi 762097205 (XP_011431161.1)	72.43% gi 72534750 (NP_001026902.1)	gi 94536805 (NP_588611.2)	gi 1061213987 (NP_001317627.1)								gi 24656811 (NP_647811.2)	gi 24656816 (NP_728876.1)			
YTHDC1	CHOYP_YTDC1.2.2 CHOYP_LOC586835.1.1	46.61%	46.61%	45.30%								57.74%	57.74%			
	gi 762070401 (XP_011447601.1)	51.52% 43.92%	51.52% 44.52%	52.27% 42.86%								57.74% 46.53%	57.74% 46.53%			
YTHDC2	CHOYP_YTDC2.1.1	gi 269847874 (NP_073739.3)	gi 1066536696 (NP_001332904.1) 53.66%													
TINDCZ	gi 762086858 (XP_011425711.1)	52.99% 53.09%	53.77%	51.83% 52.05%												
	CHOYP_COX1.6.15	gi 29791407 (AAH50284.1)	gi  12803469 (AAH02559.1)	gi 31419299 (AAH52970.1)								gi 21356147 (NP_651322.1)	gi 24649883 (NP_733067.1)	gi 161078590 (NP_001097905.1)		
YTHDF	CHOYP_LOC100371022.1.1	53.09% 53.09%	53.77% 53.77%	52.05% 52.05%								71.51% 71.51%	71.51% 71.51%	71.51% 71.51%		
	gi 762146089 (XP_011456337.1)	43.49% gi 4504447 (NP_002128.1)	71.21%	71.72%								71.20% gi 24650831 (NP 733249.1)	71.20% gi 17738267 (NP_524543.1)	71.20% gi 24650838 (NP_733252.1)	gi 24650833 (NP_733250.1)	
	CHOYP_LOC100748395.1.7	55.37%	gi 14043072 (NP_112533.1) 54.71%									58.14%	9i 17736267 (NP_524543.1) 58.14%	58.14%	58.14%	
	CHOYP_LOC100748395.2.7 CHOYP_LOC100748395.3.7	55.37% 55.37%	54.71% 54.71%									58.14% 58.14%	58.14% 57.71%	58.14% 58.14%	58.14% 58.14%	
	CHOYP_LOC100748395.4.7	55.37%	54.71%									58.14%	58.14%	58.14%	58.14%	
hnRNPA2B1	CHOYP_LOC100748395.6.7 CHOYP_AGAP_AGAP002374.1.1	55.37% 54.24%	54.71% 53.53%									58.14% 58.72%	57.71% 58.29%	58.14% 58.29%	58.14% 56.83%	
	CHOYP_LOC100748395.5.7	55.37%	54.71%									58.14%	58.14%	58.14%	58.14%	
	gi 762104361 (XP_011434715.1) gi 762104364 (XP_011434716.1)	55.37% 54.80%	55.37% 54.80%									58.14% 58.72%	58.14% 58.72%	58.14% 58.72%	58.14% 58.72%	
	gi 762104366 (XP_011434717.1)	55.37%	55.37%									58.14%	58.14%	58.14%	58.14%	
	gi 762104368 (XP_011434718.1)	55.37% gi 314122241 (NP_004629.3)	55.37%									50.63%	50.63%	50.63%	50.63%	
Prrc2a	CHOYP_LOC100559941.1.2	46.02%														
. 11 <b>02</b> 0	CHOYP_LOC100559941.2.2 gi 1139830093 (XP_019928978.1)	46.02% 34.66%														
		gi 56237027 (NP_006537.3)	gi 238624257 (NP_001153895.1)	gi 64085377 (NP_006539.3)	gi 56118219 (NP_001007226.1)	gi 631226390 (NP_001278798.1)	gi 631226392 (NP_001278801.1	gi 631226396 (NP_001278802.1)	gi 631226394 (NP_001278803.1)	J	gi 30795212 (NP_006538.2)	gi 386764188 (NP_001036268.2)	gi 386764191 (NP_001245616.1)	gi 17530887 (NP_511111.1)	gi 24641097 (NP_727451.1)	gi 281360685 (NP_001162717.1
IGF2BP	CHOYP_LOC100114171.1.1 gi 762079091 (XP_011412002.1)	34.87% 34.80%	35.71% 36.39%	35.86% 35.96% 36.20% 35.96%	N/A 36.52%	35.50% 35.61%	34.93% 35.53%	35.34% 35.93%	35.85% 36.38%	38.61% 39.76%	33.16% 33.78%	42.72% 42.83%	42.26% 42.83%	44.89% 45.07%	44.89% 45.07%	44.20% 44.37%
	gi 762079093 (XP_011412008.1) gi 762079095 (XP_011412017.1)	35.04%	36.39%	36.20%	36.77%	36.11%	35.83%	35.93%	36.38%	39.76%	34.01%	42.77%	42.45%	45.07%	45.07%	44.37% 44.52% 44.37%
		34.80% gi 4503509(NP_003741.1)	36.39%	35.96%	36.52%	35.88%	35.53%	36.24%	36.38%	39.76%	33.78%	42.83% gi 665393171 (NP_730838.3)	42.83% gi 24643988 (NP_649470.2)	45.07%	45.07%	44.37%
	CHOYP_BRAFLDRAFT_75590.1.1	40.86%										45.97%	45.97%			
elF3a	CHOYP_UBP47.2.2 CHOYP_MROH1.1.1	63.83% 63.71%										50.89% 50.89%	50.89% 50.89%			
	gi 762160635 (XP_011418535.1) gi 762122193 (XP_011444042.1)	54.20% 58.13%										44.99% 48.45%	44.99% 48.45%			
	911102122133 (AF_U11444042.1)	JO. 1370							97.			40.4070	40.4070			

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<u>Data S2</u>: Identified proteins by RNA pull down coupled with mass spectrometry with m6A or A-oligo, in nuclear or cytosolic protein extracts

Proteins identified in nuclear extracts

	intilied in fluciear ext	racts
Oligo	Accession	Description
m6A	K1PTY5_CRAGI	Protocadherin Fat 4
m6A	K1QNA2_CRAGI	-
m6A	K1QBR5_CRAGI	·
m6A	K1PFG1_CRAGI	Uncharacterized protein
m6A	K1P9A4_CRAGI	Beta-1,3-glucan-binding protein
m6A	K1QHI5_CRAGI	Pyruvate carboxylase, mitochondrial
m6A	K1QQ94_CRAGI	Uncharacterized protein
m6A	K1R5B4_CRAGI	Proteasome activator complex subunit 4
m6A	K1R164_CRAGI	Galectin-4
m6A	K1PNI6_CRAGI	Heterogeneous nuclear ribonucleoprotein A/B
m6A	K1QMX5_CRAGI	Uncharacterized protein
m6A	K1PQP2_CRAGI	Nucleolin
m6A	K1QXR4_CRAGI	Pancreatic lipase-related protein 2
m6A	K1R7V7_CRAGI	Tubulin beta chain
m6A	K1RGT5_CRAGI	Metalloendopeptidase
m6A	K1QSX8_CRAGI	ATPase family AAA domain-containing protein 2B
m6A	K1R9B6_CRAGI	H/ACA ribonucleoprotein complex subunit 4
m6A	K1RWS2_CRAGI	Transcriptional activator protein Pur-alpha
m6A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
m6A	K1R3U2_CRAGI	Uncharacterized protein
m6A	K1QQ68 CRAGI	Tubulin alpha chain
m6A	K1QVJ8 CRAGI	Piwi-like protein 1
m6A	K1PVA1_CRAGI	Transitional endoplasmic reticulum ATPase
m6A	K1QKB5_CRAGI	·
m6A	K1QHM2_CRAGI	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 2
m6A	K1QII6_CRAGI	Tubulin alpha chain
m6A	K1QSQ9_CRAGI	Putative ATP-dependent RNA helicase an3
m6A	K1QQ27_CRAGI	Pancreatic lipase-related protein 2
m6A	K1QMA4_CRAGI	RRP5-like protein
m6A	K1PEPO_CRAGI	40S ribosomal protein S8
m6A	K1QXX7_CRAGI	Myosin heavy chain, non-muscle (Fragment)
m6A	K1QK56_CRAGI	Uncharacterized protein
m6A	K1PNR3_CRAGI	Clathrin heavy chain Tubulin beta chain Acetyl-CoA carboxylase Uncharacterized protein
m6A	K1PN21_CRAGI	Tubulin beta chain
m6A	K1RG73_CRAGI	Acetyl-CoA carboxylase
m6A	K1RD58_CRAGI	Uncharacterized protein
m6A	K1QU53_CRAGI	NAD(P) transhydrogenase, mitochondrial
m6A	K1R473_CRAGI	Tubulin alpha chain
m6A	K1PH76_CRAGI	Y-box factor-like protein (Fragment)
m6A	K1PE00_CRAGI	Tubulin alpha chain
m6A	K1PJC1_CRAGI	Adipophilin
m6A	K1R6Z7_CRAGI	ATP synthase subunit alpha
m6A	K1R545_CRAGI	Pre-mRNA-processing-splicing factor 8 (Fragment)
m6A	K1RI55_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 3
m6A	K1QGS8_CRAGI	Elongation factor 1-alpha
m6A	K1QFM6_CRAGI	Vitellogenin
m6A	K1R6Q7_CRAGI	DNA topoisomerase I
m6A	K1Q988_CRAGI	Band 4.1-like protein 3
m6A	K1QLS3_CRAGI	Cytochrome b-c1 complex subunit 2, mitochondrial
m6A	K1RWW5_CRAGI	ATP synthase subunit beta
m6A	K1S2N7_CRAGI	Innexin
m6A	K1P421_CRAGI	Histone H2A
m6A	K1RK12_CRAGI	40S ribosomal protein S23
m6A	K1QKD6_CRAGI	Uncharacterized protein
m6A	K1QWZ6_CRAGI	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 1
m6A	K1QFN2_CRAGI	Uncharacterized protein
m6A	K1PHW2_CRAGI	Uncharacterized protein

m6A	K1PJ06_CRAGI	Importin subunit alpha-1
m6A	K1QA13_CRAGI	Calcium-transporting ATPase
m6A	K1R0L4_CRAGI	Sodium/potassium-transporting ATPase subunit alpha
m6A	K1R115_CRAGI	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
m6A	K1QB61_CRAGI	Protocadherin Fat 4
m6A	K1Q4H2_CRAGI	Nodal modulator 3
m6A	K1QWK2_CRAGI	MAM domain-containing glycosylphosphatidylinositol anchor protein 2
m6A	K1R466_CRAGI	T-complex protein 1 subunit gamma
m6A	K1QFW9_CRAGI	Uncharacterized protein
m6A	K1R5U4_CRAGI	Acetyl-CoA carboxylase 1
m6A	A5LGH1_CRAGI	Voltage-dependent anion channel
m6A	K1S4Q2_CRAGI	T-complex protein 1 subunit delta (Fragment)
m6A	K1REG6_CRAGI	DNA helicase
m6A	K1PUL2_CRAGI	Long-chain-fatty-acidCoA ligase 1
m6A	K1R294_CRAGI	T-complex protein 1 subunit beta
m6A	K1PMT6_CRAGI	Heterogeneous nuclear ribonucleoprotein U-like protein 1
m6A	K1RGB7_CRAGI	Epidermal retinal dehydrogenase 2
m6A	K1R435_CRAGI	Splicing factor, arginine/serine-rich 4
m6A	K1R252_CRAGI	Putative methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial
m6A	K1QAE5_CRAGI	Uncharacterized protein
m6A	K1QIR8_CRAGI	78 kDa glucose-regulated protein
m6A	K1QYB3_CRAGI	lg-like and fibronectin type-III domain-containing protein C25G4.10
m6A	K1QI14_CRAGI	40S ribosomal protein S3a
m6A	K1PNQ5_CRAGI	Heat shock protein HSP 90-alpha 1
m6A	K1S1S1_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 1
m6A	K1QM19_CRAGI	Uncharacterized protein
m6A	K1R420_CRAGI	Non-specific serine/threonine protein kinase
m6A	K1R4R9_CRAGI	Mitotic apparatus protein p62
m6A	K1R0S3_CRAGI	T-complex protein 1 subunit theta
m6A	K1RAJ1_CRAGI	T-complex protein 1 subunit alpha
m6A	K1QH74_CRAGI	
m6A	K1QRL6_CRAGI	Methenyltetrahydrofolate synthetase domain-containing protein
m6A	K1QUC6_CRAGI	Uncharacterized protein
m6A	K1RIT6_CRAGI	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial
m6A	K1RBF6_CRAGI	Uncharacterized protein yfeX
m6A	K1PCS4_CRAGI	Eukaryotic translation initiation factor 2 subunit 3, Y-linked
m6A	K1Q620_CRAGI	Uncharacterized protein
m6A	_	60S acidic ribosomal protein P0
m6A	K1PD57_CRAGI	Constitutive coactivator of PPAR-gamma-like protein 1-like protein
m6A	K1Q4S5_CRAGI	
m6A m6A	K1RQA0_CRAGI K1QMX8 CRAGI	
m6A	K1QPX8_CRAGI	
m6A	K1QZW0 CRAGI	
m6A	K1Q2W0_CRAGI	
m6A	K1RFT1_CRAGI	Band 4.1-like protein 3
m6A	K1RNB5_CRAGI	·
m6A	K1QBK6_CRAGI	
m6A	K1Q0Z3_CRAGI	Estradiol 17-beta-dehydrogenase 11
m6A	K1R953_CRAGI	Acetyl-CoA carboxylase
m6A	K1QNN9_CRAGI	MICOS complex subunit MIC60
m6A	K1QXS6_CRAGI	Heterogeneous nuclear ribonucleoprotein A2-like protein 1
m6A	K1RJH5_CRAGI	Polyadenylate-binding protein
m6A	K1R0Y9_CRAGI	ADP,ATP carrier protein
m6A	K1R4D4_CRAGI	40S ribosomal protein SA
m6A	K1QWT8 CRAGI	Uncharacterized protein
m6A	K1Q0L1_CRAGI	60S ribosomal protein L23a
m6A	K1Q260 CRAGI	Nucleolar protein 58
m6A	K1QT04_CRAGI	Uncharacterized protein
m6A	K1Q9K6_CRAGI	Histone H3

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m6A	K1QT21_CRAGI	Putative ATP-dependent RNA helicase DDX5
m6A	K1QBN0_CRAGI	Methylcrotonoyl-CoA carboxylase beta chain, mitochondrial
m6A	K1PLY1_CRAGI	DNA polymerase
m6A	K1QBH0_CRAGI	Uncharacterized protein
m6A	K1Q923_CRAGI	Putative ATP-dependent RNA helicase DDX4
m6A	K1QG58_CRAGI	Actin
m6A	K1QQB6_CRAGI	40S ribosomal protein S14
m6A	K1QDX9_CRAGI	Ribosome biogenesis protein BMS1-like protein
m6A	K1QF01_CRAGI	40S ribosomal protein S4
m6A	K1RLC5_CRAGI	T-complex protein 1 subunit epsilon
m6A	K1QY12_CRAGI	Dynamin-1-like protein
m6A	K1R0W4_CRAGI	Signal recognition particle subunit SRP72
m6A	K1QX26_CRAGI	Endoplasmin
m6A	K1QHS8_CRAGI	Ribonucleoside-diphosphate reductase
m6A	K1QQ05_CRAGI	Insulin-like growth factor-binding protein complex acid labile chain
m6A	K1QFP5_CRAGI	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial
m6A	K1QP17_CRAGI	Caprin-1
m6A	K1R7A2_CRAGI	Uncharacterized protein
m6A	K1R4L8_CRAGI	Electron transfer flavoprotein-ubiquinone oxidoreductase, mitochondrial
m6A	K1R591_CRAGI	Inter-alpha-trypsin inhibitor heavy chain H4
m6A	K1R7I9_CRAGI	Heterogeneous nuclear ribonucleoprotein Q
m6A	K1QBW8_CRAGI	Uncharacterized protein
m6A	K1RSZ6_CRAGI	40S ribosomal protein S7
m6A	K1QDZ5_CRAGI	Cytochrome c1, heme protein, mitochondrial
m6A	K1PGW7_CRAGI	Transmembrane protein 2
m6A	K1QMB9_CRAGI	Eukaryotic translation initiation factor 3 subunit A
m6A	K1RNZ6_CRAGI	Eukaryotic translation initiation factor 3 subunit D
m6A	K1Q9W5_CRAGI	T-complex protein 1 subunit eta
m6A	K1Q404_CRAGI	DNA topoisomerase 2
m6A	K1R7J6_CRAGI	Putative sodium/potassium-transporting ATPase subunit beta-2
m6A	K1P8W6_CRAGI	60S ribosomal protein L4
m6A	K1RSA6_CRAGI	Methylcrotonoyl-CoA carboxylase subunit alpha, mitochondrial
m6A	K1RW85_CRAGI	Adenosylhomocysteinase
m6A	K1PS27_CRAGI	DNA helicase
m6A	K1RH18_CRAGI	Sarcalumenin
m6A	K1Q5H6_CRAGI	FACT complex subunit SSRP1
m6A	K1PH66_CRAGI	Fibrinolytic enzyme, isozyme C
m6A	K1PF10_CRAGI	PAN2-PAN3 deadenylation complex catalytic subunit PAN2
m6A	K1Q358_CRAGI	60S acidic ribosomal protein P2
m6A	K1PXH5_CRAGI	Putative saccharopine dehydrogenase
m6A	K1Q8S0_CRAGI	Nucleolar complex protein 3 homolog
m6A	K1QYB6_CRAGI	Delta-1-pyrroline-5-carboxylate synthetase
m6A	K1PV79_CRAGI	Importin subunit alpha
m6A	K1PV49_CRAGI	RuvB-like helicase
m6A	K1PRL4_CRAGI	60S ribosomal protein L38 (Fragment)
m6A	K1QL67_CRAGI	60S ribosomal protein L7a
m6A	K1PAY7_CRAGI	Propionyl-CoA carboxylase alpha chain, mitochondrial
m6A	K1R6L5_CRAGI	NADH-cytochrome b5 reductase
m6A	K1R1B1_CRAGI	35 kDa SR repressor protein
m6A	K1QHQ6_CRAGI	Acyl-CoA dehydrogenase family member 9, mitochondrial
m6A	K1QZU8_CRAGI	Calcium-transporting ATPase
m6A	K1RN77_CRAGI	Nuclear autoantigenic sperm protein
m6A	K1PZ23_CRAGI	DnaJ-like protein subfamily C member 3
m6A	K1R005_CRAGI	Filamin-C (Fragment)
m6A	K1RA35_CRAGI	Splicing factor, arginine/serine-rich 7
m6A	K1R2V1_CRAGI	Importin subunit beta-1
m6A	K1QAH9_CRAGI	H/ACA ribonucleoprotein complex subunit
m6A	K1QET2_CRAGI	Coatomer subunit alpha
m6A	K1RAB9_CRAGI	Epoxide hydrolase 4
m6A	K1QGK2_CRAGI	Coatomer subunit beta

K1PXN5\_CRAGI T-complex protein 1 subunit zeta m6A K1QHX2\_CRAGI La-related protein 7 m6A m6A K1PZ08 CRAGI Ras-related protein Rab-7a m6A K1RK68\_CRAGI Uncharacterized protein K1Q0R4\_CRAGI ATP-binding cassette sub-family F member 2 m6A K1QW72\_CRAGI Catalase m6A K1PPP8\_CRAGI Vigilin m6A K1QVW3\_CRAGI Alkylglycerone-phosphate synthase m6A m6A K1PBZ4\_CRAGI Regulator of nonsense transcripts 1 K1Q6W5\_CRAGI FACT complex subunit spt16 m6A K1R5F2 CRAGI 14-3-3 protein epsilon m6A K1RLT4 CRAGI Signal recognition particle subunit SRP68 m6A K1RSS3\_CRAGI Myosin heavy chain, striated muscle m6A m6A K1RNN9\_CRAGI Cytoskeleton-associated protein 5 m6A K1QN11 CRAGI Pre-mRNA-processing-splicing factor 8 m6A K1PA54\_CRAGI Replication factor C subunit 3 m6A K1QC78\_CRAGI Ras-related protein Rab-14 m6A K1QW36\_CRAGI 60S ribosomal protein L6 m6A K1Q9P5\_CRAGI Mitochondrial-processing peptidase subunit beta m6A K1Q253\_CRAGI Neutral and basic amino acid transport protein rBAT K1QHK9\_CRAGI Dynein heavy chain, cytoplasmic m6A m6A K1QFN1 CRAGI 60S ribosomal protein L23 m6A K1P112\_CRAGI ATP synthase subunit gamma, mitochondrial K1QE71 CRAGI DNA helicase m6A K1PK85 CRAGI Cullin-associated NEDD8-dissociated protein 1 m6A K1QTD9\_CRAGI Nucleolar protein 56 m6A K1P9N7\_CRAGI 14-3-3 protein zeta m6A K1RG19 CRAGI Protein FAM98A m6A K1PMP3\_CRAGI Protoporphyrinogen oxidase m6A m6A K1QVN9\_CRAGI T-complex protein 1 subunit eta K1QG65 CRAGI rRNA 2'-O-methyltransferase fibrillarin m6A K1PM76\_CRAGI NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial m6A m6A K1PM50 CRAGI 40S ribosomal protein S16 m6A K1QEF9 CRAGI Protein-glutamine gamma-glutamyltransferase K K1RKC1\_CRAGI Far upstream element-binding protein 3 m6A m6A K1PY89 CRAGI Extracellular superoxide dismutase [Cu-Zn] m6A K1RIZ3 CRAGI Bone morphogenetic protein 7 K1RA95\_CRAGI Filamin-A m6A m6A K1PWZ3\_CRAGI Guanine nucleotide-binding protein subunit beta K1Q812 CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial m6A K1PFS5\_CRAGI Elongation factor 1-gamma m6A K1PX23\_CRAGI Eukaryotic peptide chain release factor subunit 1 m6A m6A K1QSV1\_CRAGI Uncharacterized protein K1Q6X5\_CRAGI Protein disulfide-isomerase m6A m6A K1RAU3\_CRAGI DNA ligase K1PXG6\_CRAGI Serine/threonine-protein phosphatase m6A K1RIG6\_CRAGI LSM14-like protein A m6A K1QWK6\_CRAGI Metalloendopeptidase m6A K1RCW3\_CRAGI Elongation factor 1-beta m6A K1QK18\_CRAGI Cytochrome b5 m6A K1Q056\_CRAGI Calpain-A m6A K1Q9M7\_CRAGI Histone H1-delta m6A K1P7L5\_CRAGI Transmembrane 9 superfamily member m6A K1QSU3\_CRAGI Protein I(2)37Cc m6A K1PLF9\_CRAGI Arginine kinase m6A m6A K1Q1F4\_CRAGI 60S ribosomal protein L3 (Fragment) K1R1T8\_CRAGI Nucleolar protein 56 m6A m6A K1QGB4 CRAGI 40S ribosomal protein S17 m6A K1QJ08 CRAGI 60S ribosomal protein L26 K1Q4Y8\_CRAGI Histone H1oo m6A

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m6A

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K1PKF5_CRAGI Protein-glutamine gamma-glutamyltransferase 4
       m6A
3
                 K1QYT5_CRAGI Phosphate carrier protein, mitochondrial
4
       m6A
5
      m6A
                 K1RHB2 CRAGI Nucleolar RNA helicase 2
6
       m6A
                 K1RJJ7_CRAGI Histone H5
7
                 K1PS84_CRAGI Alpha-crystallin B chain
       m6A
8
                 K1R2N0_CRAGI Histone H4
       m6A
9
                 K1PZP6_CRAGI Coatomer subunit gamma
10
       m6A
11
                 K1RGJ7_CRAGI Neogenin
       m6A
12
       m6A
                 K1R9P5_CRAGI Mitochondrial import receptor subunit TOM70
13
                K1RUM2_CRAGI Uncharacterized protein
       m6A
14
                 K1RJ97 CRAGI Multifunctional protein ADE2
       m6A
15
                 K1RJS5 CRAGI Uncharacterized protein
16
       m6A
17
                K1QW41_CRAGI Leucine-zipper-like transcriptional regulator 1
       m6A
18
       m6A
                 K1R834_CRAGI 60S ribosomal protein L9
19
      m6A
                 K1QLK8_CRAGI GTP-binding protein SAR1b
20
      m6A
                K1QDH9_CRAGI Myosin-11
21
22
       m6A
                 K1QEF2_CRAGI ADP-ribosylation factor-like protein 15
23
       m6A
                 K1PUX5_CRAGI Casein kinase II subunit alpha
24
                 K1QLU6_CRAGI Poly [ADP-ribose] polymerase
      m6A
25
       m6A
                K1QUK3_CRAGI Putative ATP-dependent RNA helicase DDX41
26
                 K1S2S8_CRAGI Signal recognition particle 54 kDa protein
       m6A
27
28
      m6A
                 K1PY73 CRAGI Basic leucine zipper and W2 domain-containing protein 1
29
       m6A
                 K1S6V7_CRAGI Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform
30
                 K1QPC6 CRAGI Nucleolar complex protein 2-like protein
       m6A
31
                 K1QPP2 CRAGI Elongation factor Tu, mitochondrial
      m6A
32
                K1QDN1_CRAGI Heat shock protein 75 kDa, mitochondrial (Fragment)
       m6A
33
                 K1R996_CRAGI Long-chain-fatty-acid--CoA ligase 4
34
       m6A
35
                K1RDW8 CRAGI Golgi apparatus protein 1
       m6A
36
                 K1S3G2_CRAGI HMGB1
       m6A
37
       m6A
                 K1QR48_CRAGI Calcium-binding mitochondrial carrier protein SCaMC-2
38
                 K1P5V7 CRAGI Eukaryotic translation initiation factor 3 subunit C
       m6A
39
                 K1PV86_CRAGI Phosphoglycerate mutase family member 5
40
       m6A
41
       m6A
                K1QWC3 CRAGI 40S ribosomal protein S3
42
                 K1PZ70_CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial
       m6A
43
                 K1PTL4_CRAGI Odr-4-like protein
       m6A
44
       m6A
                K1QRM1 CRAGI Nuclear pore protein
45
                 K1PVD7 CRAGI Cytochrome c oxidase subunit 5A, mitochondrial
46
       m6A
47
                 K1QFR2_CRAGI Calnexin
       m6A
48
       m6A
                 K1Q273_CRAGI 60S ribosomal protein L14
49
       m6A
                K1R0M2 CRAGI Uncharacterized protein
50
                K1R5W3_CRAGI Uncharacterized protein
      m6A
51
52
       m6A
                K1QXQ8_CRAGI DNA helicase
53
       m6A
                 K1QPY8_CRAGI Extracellular superoxide dismutase [Cu-Zn]
54
                 K1Q6V6_CRAGI Replication factor C subunit 4
       m6A
55
                K1QMS2_CRAGI Cadherin EGF LAG seven-pass G-type receptor 3
       m6A
56
                 K1Q7T5_CRAGI Protein disulfide-isomerase
       m6A
57
58
                 K1QRZ3_CRAGI 40S ribosomal protein S13
      m6A
59
                 K1R4Z3_CRAGI Malate dehydrogenase, mitochondrial
       m6A
60
                 K1PJ85_CRAGI 26S protease regulatory subunit 6A
       m6A
                 K1PB87_CRAGI Uncharacterized protein
      m6A
                 K1PXU6_CRAGI 60S ribosomal protein L24
      m6A
                 K1R6S5_CRAGI 40S ribosomal protein S9
       m6A
                 K1PVH5_CRAGI Centromere/kinetochore protein zw10-like protein
      m6A
                 K1R512_CRAGI Uncharacterized protein
      m6A
                 K1QK68_CRAGI Myosin-2 essential light chain
      m6A
      m6A
                 K1PUV4 CRAGI 40S ribosomal protein S24
                 K1R5U8_CRAGI UBX domain-containing protein 4
       m6A
       m6A
                K1PW39_CRAGI Glycerol-3-phosphate dehydrogenase, mitochondrial
       m6A
                 K1R790 CRAGI Retinol dehydrogenase 13
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K1QT61\_CRAGI NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial (Fragment)

m6A

K1RG28\_CRAGI Kinase C and casein kinase substrate in neurons protein 2 m6A K1QKV1\_CRAGI Cytochrome b-c1 complex subunit 6 m6A m6A K1P9S7 CRAGI Brix domain-containing protein 2 m6A K1QN79\_CRAGI 40S ribosomal protein S11 K1QEJ0\_CRAGI Ras GTPase-activating protein-binding protein 2 m6A K1S1X3\_CRAGI SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5 m6A K1R9T2\_CRAGI Eukaryotic translation initiation factor 3 subunit B m6A K1QED7\_CRAGI Replication protein A subunit m6A K1QQK5\_CRAGI Metabotropic glutamate receptor 2 m6A K1RN97\_CRAGI Hemagglutinin/amebocyte aggregation factor m6A K1PJS7\_CRAGI Poly [ADP-ribose] polymerase m6A K1R6F5 CRAGI Putative ATP-dependent RNA helicase DDX23 m6A K1R8R6\_CRAGI Fructose-bisphosphate aldolase m6A m6A K1QY85\_CRAGI Transport protein Sec31A m6A K1QF31 CRAGI Serine/threonine-protein kinase PLK K1Q5J7\_CRAGI Uncharacterized protein m6A m6A K1QPF0\_CRAGI Uncharacterized protein m6A K1P6Y1\_CRAGI Uncharacterized protein K1QJM1\_CRAGI 60S ribosomal protein L30 m6A m6A K1PXD4\_CRAGI Putative ATP-dependent RNA helicase DDX6 K1PH31\_CRAGI Protein arginine N-methyltransferase 1 m6A m6A K1PAM6 CRAGI Uncharacterized protein m6A K1RFU6\_CRAGI Proteasome activator complex subunit 3 K1Q324 CRAGI Heterogeneous nuclear ribonucleoprotein K m6A K1QRG9 CRAGI Uncharacterized protein m6A K1S6H7\_CRAGI Vacuolar protein sorting-associated protein 13C m6A K1QE94\_CRAGI Alpha-galactosidase m6A K1Q7Q2 CRAGI CCAAT/enhancer-binding protein zeta m6A K1Q7G8\_CRAGI Fatty acid synthase m6A m6A K1QXH3\_CRAGI Translational activator GCN1 K1P8G1 CRAGI Heterogeneous nuclear ribonucleoprotein H m6A K1QKQ8\_CRAGI THO complex subunit 4-A m6A m6A K1RA63 CRAGI Transmembrane protein 2 m6A K1QAA2 CRAGI Uncharacterized protein K1PLA7\_CRAGI Eukaryotic initiation factor 4A-II (Fragment) m6A m6A K1QIV3 CRAGI Uncharacterized protein m6A K1RAH2 CRAGI Superoxide dismutase [Cu-Zn] K1QXA9\_CRAGI Sortilin-related receptor m6A m6A K1QSD9\_CRAGI Uncharacterized protein K1Q3W3 CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial m6A K1R3T3 CRAGI Transcription factor BTF3 m6A m6A K1QMH5\_CRAGI Small nuclear ribonucleoprotein Sm D1 m6A K1R1R9\_CRAGI Pre-mRNA-processing factor 6 m6A K1PM66 CRAGI 60S ribosomal protein L12 m6A K1Q3W9\_CRAGI FAS-associated factor 2-B K1P9D0\_CRAGI Stress-70 protein, mitochondrial m6A K1R4F7\_CRAGI Ras-related protein Rab-6B m6A K1QGP7\_CRAGI Uncharacterized protein m6A K1REY2\_CRAGI Dysferlin m6A K1QSB2\_CRAGI 26S protease regulatory subunit 6B m6A K1RAU8\_CRAGI Eukaryotic translation initiation factor 3 subunit E m6A K1QAB1\_CRAGI AP-2 complex subunit alpha m6A K1RFU8\_CRAGI High mobility group protein DSP1 m6A K1QAA8\_CRAGI CAAX prenyl protease 1-like protein m6A K1PXS8\_CRAGI Calreticulin m6A m6A K1RV41\_CRAGI Guanine nucleotide-binding protein subunit beta-2-like 1 K1Q5Z6\_CRAGI Eukaryotic translation initiation factor 2 subunit 2 m6A m6A K1QYQ9 CRAGI Uncharacterized protein K1RCL2 CRAGI Mitochondrial import inner membrane translocase subunit Tim13-B m6A K1PI50 CRAGI 40S ribosomal protein S26

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K1QGP1_CRAGI Replication factor C subunit 2
       m6A
3
                 K1P541_CRAGI Alpha-soluble NSF attachment protein
4
       m6A
5
                 K1Q667_CRAGI tRNA-splicing ligase RtcB homolog
       m6A
6
       m6A
                 K1QBM3_CRAGI Ras-related protein Rab-2
7
                 K1R7L4_CRAGI Neural cell adhesion molecule 1
       m6A
8
                 K1PH13_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3B
       m6A
9
                 K1QAI2_CRAGI Ufm1-specific protease 2
10
       m6A
11
                 K1RJW8_CRAGI Protein DEK
       m6A
12
                 K1QKG8_CRAGI Upstream activation factor subunit spp27
       m6A
13
                 K1R150_CRAGI Ras-related protein Rab-1A
       m6A
14
                 K1PI40 CRAGI Uncharacterized protein
       m6A
15
                 K1PZT2 CRAGI Cytochrome c oxidase subunit 5B, mitochondrial
16
       m6A
17
                 K1PJB0_CRAGI Heat shock protein 70 B2
       m6A
18
       m6A
                 K1PR25_CRAGI Regulator of differentiation 1
19
       m6A
                K1QMV5 CRAGI Annexin
20
                 K1Q0N6_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A
       m6A
21
22
       m6A
                 K1QY58_CRAGI Eukaryotic translation initiation factor 3 subunit I (Fragment)
23
       m6A
                 K1RIJ1_CRAGI Synaptobrevin (Fragment)
24
                 K1PNC7_CRAGI AFG3-like protein 2
       m6A
25
       m6A
                 K1QQR1_CRAGI Major vault protein
26
                 K1R5V4_CRAGI GTP-binding nuclear protein
       m6A
27
                 K1QGA7_CRAGI Kynurenine formamidase
28
       m6A
29
       m6A
                 K1PTV1_CRAGI Splicing factor 3B subunit 4
30
                 K1P3Q5 CRAGI Programmed cell death 6-interacting protein
       m6A
31
                 K1R2G9 CRAGI SEC13-like protein
       m6A
32
                 K1PF96_CRAGI Spliceosome RNA helicase BAT1
       m6A
33
                 K1R1F0_CRAGI ATP-dependent DNA helicase 2 subunit 1
34
       m6A
35
                 K1Q5Z1 CRAGI Uncharacterized protein
       m6A
36
                 K1Q880_CRAGI Transportin-1
       m6A
37
       m6A
                 K1PDF8_CRAGI Splicing factor, arginine/serine-rich 6
38
                 K1PMY9 CRAGI Calmodulin
       m6A
39
40
                 K1PPW8_CRAGI Coatomer subunit beta
       m6A
41
       m6A
                 K1QZQ8_CRAGI Low-density lipoprotein receptor-related protein 8
42
       m6A
                 K1QE43 CRAGI Uncharacterized protein
43
                 K1RDS1_CRAGI Splicing factor, arginine/serine-rich 2
       m6A
44
       m6A
                 K1RAI3 CRAGI Annexin
45
                 K1PCR5 CRAGI KH domain-containing, RNA-binding, signal transduction-associated protein 2
46
       m6A
47
                K1QWP1_CRAGI Nucleoporin seh1
       m6A
48
                 K1QAL1_CRAGI Transmembrane emp24 domain-containing protein 7
       m6A
49
       m6A
                 K1Q2H5 CRAGI Uncharacterized protein
50
                 K1REPO_CRAGI Uncharacterized protein
       m6A
51
52
       m6A
                 K1PKI9_CRAGI Uncharacterized protein
53
       m6A
                 K1RG79_CRAGI Neuronal acetylcholine receptor subunit alpha-6
54
       m6A
                 K1Q1L4_CRAGI Uncharacterized protein
55
       m6A
                 K1QTP6_CRAGI Cation-transporting ATPase
56
                 K1Q615_CRAGI Peroxiredoxin-1
       m6A
57
58
                 K1QIZ7_CRAGI Programmed cell death protein 6
       m6A
59
                 K1R0D7_CRAGI Eukaryotic translation initiation factor 3 subunit M (Fragment)
       m6A
60
                 K1QTW3_CRAGI Murinoglobulin-2
       m6A
                 K1PDL3_CRAGI Ribosomal protein L19
       m6A
                 K1QW21_CRAGI 39S ribosomal protein L40, mitochondrial
       m6A
                 K1Q317_CRAGI Serine/threonine-protein kinase SRPK1
       m6A
                 K1QKG9_CRAGI Cysteine desulfurase, mitochondrial
       m6A
                 K1PS77_CRAGI Prostaglandin G/H synthase 1
       m6A
                 K1QJW6_CRAGI Translocon-associated protein subunit gamma
       m6A
       m6A
                 K1QTV1 CRAGI Uncharacterized protein
                 K1QTW6_CRAGI Eukaryotic translation initiation factor 3 subunit F
       m6A
       m6A
                 K1PNY5_CRAGI Splicing factor, proline-and glutamine-rich
       m6A
                 K1R100 CRAGI Metaxin-2
                 K1R8L1_CRAGI Exportin-2
       m6A
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K1QZ64\_CRAGI Nuclear pore complex protein Nup98-Nup96 m6A K1QWZ8\_CRAGI Catenin beta m6A m6A K1QAT9 CRAGI ATP-dependent RNA helicase DDX1 m6A K1P8Y9\_CRAGI Cytochrome b-c1 complex subunit 7 K1PIC5\_CRAGI Transmembrane protein 85 m6A K1QMV7\_CRAGI V-type proton ATPase subunit D m6A K1RC37\_CRAGI Uncharacterized protein m6A K1PEY4\_CRAGI 26S proteasome non-ATPase regulatory subunit 2 m6A m6A K1RG04\_CRAGI ALK tyrosine kinase receptor K1QG72\_CRAGI Hemagglutinin/amebocyte aggregation factor m6A K1RK83\_CRAGI Tyrosine-protein kinase BAZ1B m6A K1QMT1 CRAGI DnaJ-like protein subfamily B member 4 m6A K1P8I1\_CRAGI Pleckstrin-like protein domain-containing family F member 2 (Fragment) m6A K1R3I6\_CRAGI Nucleolar complex protein 2-like protein (Fragment) m6A m6A K1QDB9 CRAGI Transport protein Sec61 subunit alpha isoform 2 (Fragment) K1QMJ8\_CRAGI Transcription initiation factor IIA subunit 1 m6A m6A K1R5G4\_CRAGI 60S ribosomal protein L31 m6A K1R1W9\_CRAGI Nicalin-1 K1QDA7\_CRAGI Uracil phosphoribosyltransferase m6A K1QI02\_CRAGI Vesicle-trafficking protein SEC22b m6A K1QFZ8\_CRAGI Ceramide kinase-like protein m6A m6A K1Q151 CRAGI 60S ribosomal protein L32 m6A K1QNS4\_CRAGI DnaJ-like protein subfamily C member 9 K1REQ4 CRAGI Cytochrome c oxidase subunit 6B m6A K1R4B8 CRAGI Plexin domain-containing protein 2 m6A K1QC10\_CRAGI GTP-binding protein 1 m6A K1PJY2\_CRAGI Inositol polyphosphate 1-phosphatase m6A K1R983 CRAGI Protein transport protein SEC23 m6A K1Q5Y3\_CRAGI Annexin m6A m6A K1Q1N1\_CRAGI Alpha-mannosidase K1QNU0 CRAGI Non-specific serine/threonine protein kinase m6A K1R1Q8\_CRAGI Ras-related protein Rab-5C m6A m6A K1RH95 CRAGI Myosin-IIIB m6A K1QWE5 CRAGI Ras-related protein Rab-18-B K1QCB0\_CRAGI 40S ribosomal protein S5 m6A K1Q0I8\_CRAGI Putative splicing factor, arginine/serine-rich 7 m6A m6A K1QXF5 CRAGI Calcyphosin-like protein K1R8C6\_CRAGI 40S ribosomal protein S12 m6A K1QFA9\_CRAGI Low-density lipoprotein receptor-related protein 2 m6A m6A K1QYF5 CRAGI Apoptosis-inducing factor 1, mitochondrial K1QA50\_CRAGI V-type proton ATPase subunit H m6A m6A K1PY39\_CRAGI Protocadherin Fat 4 m6A K1Q330\_CRAGI Dihydrolipoyl dehydrogenase m6A K1Q350\_CRAGI Glyceraldehyde-3-phosphate dehydrogenase K1Q6U7\_CRAGI 78 kDa glucose-regulated protein m6A K1RBI9\_CRAGI Small nuclear ribonucleoprotein Sm D2 m6A K1P0H0\_CRAGI Aspartyl/asparaginyl beta-hydroxylase m6A K1QSR2\_CRAGI Apoptosis inhibitor 5 m6A K1RDV7\_CRAGI Cell division control protein 2-like protein (Fragment) m6A K1PD30\_CRAGI Putative histone-binding protein Caf1 m6A K1P7K8\_CRAGI Vesicle-fusing ATPase 1 m6A K1PVZ3\_CRAGI Cold shock domain-containing protein E1 m6A K1RKZ5\_CRAGI DNA damage-binding protein 1 m6A K1R0Z4\_CRAGI Uncharacterized protein m6A K1Q947\_CRAGI Dynein light chain m6A m6A K1PU46\_CRAGI Lethal(2) giant larvae-like protein 1 K1Q8K9\_CRAGI KRR1 small subunit processome component-like protein m6A m6A K1PQZ3 CRAGI Armadillo repeat-containing protein 4 m6A K1QL00 CRAGI Microsomal glutathione S-transferase 1 K1RDM2 CRAGI 60S ribosomal protein L18a m6A

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K1Q3V9_CRAGI Mitochondrial carnitine/acylcarnitine carrier protein
       m6A
3
                 K1QN55_CRAGI 60S acidic ribosomal protein P1
4
       m6A
5
       m6A
                 K1R3G0 CRAGI Transformer-2-like protein beta
6
       m6A
                K1PWM3_CRAGI MICOS complex subunit MIC13
                 K1QKL8_CRAGI V-type proton ATPase subunit a
       m6A
Я
                 K1S6T6_CRAGI UPF0480 protein C15orf24-like protein
       m6A
9
                K1R0W0_CRAGI Ferritin
10
       m6A
11
                 K1PGK7_CRAGI Uncharacterized protein
       m6A
12
       m6A
                 K1QY71 CRAGI Histone H2B
13
                 K1QNT7_CRAGI Aldehyde dehydrogenase, mitochondrial
       m6A
14
                 K1RJ96_CRAGI Sphere organelles protein SPH-1
       m6A
15
                 K1RZE2_CRAGI Isocitrate dehydrogenase [NADP]
16
       m6A
17
                 K1PPV1_CRAGI Atlastin-2
       m6A
18
                 K1P9F1_CRAGI Insulin-like growth factor-binding protein complex acid labile chain
       m6A
19
       m6A
                K1QVU0 CRAGI Synaptojanin-2-binding protein
20
       m6A
                 K1QX44_CRAGI Ras-related protein Rab-11B
21
22
       m6A
                K1QKU6_CRAGI mRNA export factor
23
       m6A
                K1QDV6_CRAGI Protein argonaute-2
24
                 K1R5B9_CRAGI DNA-directed RNA polymerase, mitochondrial
       m6A
25
       m6A
                 K1RCT2_CRAGI Translocon-associated protein subunit delta
26
                 K1PKD4_CRAGI 40S ribosomal protein S30
       m6A
27
28
       m6A
                 K1PP50 CRAGI Golgi integral membrane protein 4
29
       m6A
                 K1PG60_CRAGI 60S ribosomal protein L17
30
                 K1QWJ4 CRAGI Splicing factor 3B subunit 5
       m6A
31
                 K1RB91 CRAGI Neutral alpha-glucosidase AB
       m6A
32
                 K1RD12_CRAGI Uncharacterized protein
       m6A
33
                 K1PQE3_CRAGI RNA-binding protein Raly
34
       m6A
35
                 K1Q2Y1 CRAGI 40S ribosomal protein S15
       m6A
36
                 K1PQF1_CRAGI Neural cell adhesion molecule L1
       m6A
37
       m6A
                 K1QKJ0_CRAGI Aldehyde dehydrogenase family 3 member B1
38
                K1PUQ5_CRAGI Histone H2B
       m6A
39
40
                K1Q2W7_CRAGI Uncharacterized protein
       m6A
41
       m6A
                 K1Q412 CRAGI Uncharacterized protein
42
       m6A
                 K1RNH1_CRAGI 60S ribosomal protein L18 (Fragment)
43
                 K1QNT4_CRAGI Anoctamin
       m6A
44
                 K1P8B7_CRAGI Ubiquitin-conjugating enzyme E2-17 kDa (Fragment)
       m6A
45
                 K1Q1D7 CRAGI Putative rRNA-processing protein EBP2
46
       m6A
47
                 K1PY30_CRAGI Septin-2
       m6A
48
       m6A
                 K1Q1R1_CRAGI Exostosin-3
49
       m6A
                 K1RHP3 CRAGI Proliferation-associated protein 2G4
50
                 K1PZI3_CRAGI SWI/SNF complex subunit SMARCC2
       m6A
51
                 K1QT97_CRAGI N(G),N(G)-dimethylarginine dimethylaminohydrolase 1
52
       m6A
53
       m6A
                K1QQQ5_CRAGI Replication factor C subunit 5
54
       m6A
                 K1PA61_CRAGI Actin-like protein 6A
55
                 K1PNLO_CRAGI Microtubule-associated protein futsch
       m6A
56
                 K1QI28_CRAGI V-type proton ATPase subunit B
       m6A
57
58
                 K1PYL5_CRAGI Uncharacterized protein
       m6A
59
                 K1PJ65_CRAGI Dual specificity mitogen-activated protein kinase kinase 7
       m6A
60
                K1QMD8_CRAGI Proteasome subunit alpha type
       m6A
                 K1Q2L4_CRAGI Transmembrane emp24 domain-containing protein 9
      m6A
                 K1Q8C1_CRAGI Putative RNA-binding protein Luc7-like 2
       m6A
                 K1PS71_CRAGI Uncharacterized protein
       m6A
                 K1Q900_CRAGI Galectin
      m6A
                 K1RKR8_CRAGI Pumilio-like protein 2
      m6A
                 K1RKE5_CRAGI IQ and AAA domain-containing protein 1
       m6A
      m6A
                 K1QRL4 CRAGI Importin-5
                 K1PGN0_CRAGI Fatty-acid amide hydrolase 2
       m6A
       m6A
                 K1RD83_CRAGI Serine hydroxymethyltransferase
       m6A
                 K1RFA3 CRAGI Lamin Dm0
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K1QAG7 CRAGI Phosphatidylinositide phosphatase SAC1

m6A

K1PJP7\_CRAGI Surfeit locus protein 4 m6A m6A K1PG07\_CRAGI Lupus La-like protein m6A K1QVSO CRAGI Ras-like GTP-binding protein Rho1 m6A K1PWC3\_CRAGI Tetratricopeptide repeat protein 35 K1QZK9\_CRAGI Uncharacterized protein m6A K1QAG9\_CRAGI Ferritin m6A K1QHW8\_CRAGI Ferritin m6A K1PZF2\_CRAGI Exportin-7 m6A m6A K1RCF4\_CRAGI Translocon-associated protein subunit alpha K1QVIO\_CRAGI Isocitrate dehydrogenase [NAD] subunit, mitochondrial m6A K1PX47\_CRAGI Ubiquitin carboxyl-terminal hydrolase m6A K1P8G6 CRAGI Vesicular integral-membrane protein VIP36 m6A K1PNZ8\_CRAGI Ribosomal protein L37 m6A K1Q373\_CRAGI Splicing factor, arginine/serine-rich 7 m6A m6A K1R0U6 CRAGI Uncharacterized protein m6A K1QAV0\_CRAGI Guanine nucleotide-binding protein G(Q) subunit alpha m6A K1R8Y1\_CRAGI Obg-like ATPase 1 K1QBY6\_CRAGI Transmembrane protein Tmp21 m6A K1QZ58\_CRAGI Splicing factor U2AF 26 kDa subunit m6A m6A K1RAE9\_CRAGI ADP-ribosylation factor-like protein 8A K1RCW5\_CRAGI Eukaryotic translation initiation factor 4 gamma 3 m6A m6A K1PZ89 CRAGI Mannosyl-oligosaccharide glucosidase m6A K1PBG6\_CRAGI Uncharacterized protein K1QPS1 CRAGI Poly [ADP-ribose] polymerase m6A K1R1C5\_CRAGI Signal recognition particle receptor subunit beta m6A K1PVG0\_CRAGI Long-chain fatty acid transport protein 4 m6A K1QXA1\_CRAGI Retinol dehydrogenase 12 m6A K1R481 CRAGI Epimerase family protein SDR39U1 m6A K1QVP6\_CRAGI Developmentally-regulated GTP-binding protein 1 m6A m6A K1PWB7\_CRAGI Uncharacterized protein K1PNQ1 CRAGI Ankyrin repeat domain-containing protein 5 m6A K1Q8C5\_CRAGI Putative ATP-dependent RNA helicase DDX47 m6A m6A K1PR38 CRAGI TAR DNA-binding protein 43 m6A K1P7Q6 CRAGI 40S ribosomal protein S19 K1RFD2\_CRAGI Adenylate kinase m6A K1PQJ9\_CRAGI ATP synthase subunit delta, mitochondrial m6A m6A K1Q4U7 CRAGI AP-3 complex subunit delta-1 K1QM06\_CRAGI Prohibitin m6A K1QUW5\_CRAGI U2 snRNP auxiliary factor large subunit m6A m6A K1PD36 CRAGI Ubiquitin K1PBL2\_CRAGI Eukaryotic initiation factor 4A-III m6A m6A K1R3V8\_CRAGI COP9 signalosome complex subunit 4 m6A K1PII4\_CRAGI YTH domain-containing protein 1 K1PZL0\_CRAGI B-box type zinc finger protein ncl-1 m6A K1REW8\_CRAGI Ribosomal protein L15 m6A K1R9V5\_CRAGI Tetraspanin m6A K1QPX1\_CRAGI ATPase family AAA domain-containing protein 3 m6A K1QHI2\_CRAGI Heterogeneous nuclear ribonucleoprotein L m6A K1QZ95\_CRAGI Nuclear pore complex protein m6A K1R401\_CRAGI Spectrin alpha chain m6A K1PSA1\_CRAGI Transmembrane 9 superfamily member m6A K1Q486\_CRAGI Uncharacterized protein m6A K1PYA0\_CRAGI Cytoplasmic dynein 2 heavy chain 1 m6A K1QLC6\_CRAGI JmjC domain-containing protein 8 m6A K1RDG4\_CRAGI DNA helicase m6A m6A K1PQY0 CRAGI Protein guiver K1QTD5\_CRAGI Low-density lipoprotein receptor-related protein 12 m6A m6A K1PSP7\_CRAGI Uncharacterized protein m6A K1QAL3 CRAGI RNA-binding protein 28 K1QND2\_CRAGI Septin-2 m6A

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K1RMM6_CRAGI Centromere protein J
       m6A
3
                 K1R1K6_CRAGI Heat shock protein beta-1
4
       m6A
5
      m6A
                 K1R3Z4 CRAGI 5'-3' exoribonuclease 1
6
       m6A
                 K1RB56_CRAGI Ferritin
7
                 K1RIZ9_CRAGI Band 4.1-like protein 5
       m6A
8
                 K1RFB1_CRAGI Stomatin-like protein 2 (Fragment)
       m6A
9
                 K1RNI9_CRAGI Leucine-rich repeat-containing protein 59
10
       m6A
11
                 K1Q7U7_CRAGI Basigin
       m6A
12
                 K1RNX0_CRAGI Small nuclear ribonucleoprotein E
       m6A
13
                 K1P5F7_CRAGI Metastasis-associated protein MTA1
       m6A
14
                 K1PVG9 CRAGI Malectin
       m6A
15
                 K1R247 CRAGI Condensin complex subunit 1
16
       m6A
17
                 K1PSN0_CRAGI Pre-mRNA-processing factor 40-like protein A
       m6A
18
       m6A
                 K1PZV3_CRAGI Guanine nucleotide-binding protein-like 3-like protein (Fragment)
19
       m6A
                K1RWP3 CRAGI Peptidyl-tRNA hydrolase 2, mitochondrial
20
                 K1Q7E4_CRAGI Ubiquitin-conjugating enzyme E2 N
       m6A
21
22
       m6A
                 K1RK33_CRAGI Exportin-1
23
       m6A
                 K1RPP1_CRAGI Synaptophysin
24
                 K1Q5P0_CRAGI 60S ribosomal protein L17
       m6A
25
       m6A
                 K1PND7_CRAGI Fatty acid synthase
26
                 K1R0R7_CRAGI Putative ATP-dependent RNA helicase DHX36
       m6A
27
28
       m6A
                 K1QJL6 CRAGI Microtubule-associated protein RP/EB family member 3
29
       m6A
                 K1QKZ6_CRAGI Inosine-5'-monophosphate dehydrogenase
30
                Q70MT4 CRAGI 40S ribosomal protein S10
       m6A
31
                 K1RP91 CRAGI Putative RNA exonuclease NEF-sp
       m6A
32
                 K1PKK7_CRAGI AP-2 complex subunit mu-1
       m6A
33
                 K1PLR8_CRAGI Chromosome transmission fidelity protein 18-like protein (Fragment)
34
       m6A
35
                 K1PH10 CRAGI Polyadenylate-binding protein-interacting protein 1
       m6A
36
                 K1P2G0_CRAGI Strawberry notch-like protein 1
       m6A
37
       m6A
                K1PNU2_CRAGI Histone-arginine methyltransferase CARM1
38
                 K1QZJ6_CRAGI Uncharacterized protein (Fragment)
       m6A
39
                 K1PXB6_CRAGI Cadherin-23
40
       m6A
41
       m6A
                 K1QCK4_CRAGI CLIP-associating protein 1
42
       m6A
                 K1PPH0_CRAGI Gamma-tubulin complex component
43
                 K1Q105_CRAGI Ferrochelatase
       m6A
44
       m6A
                 K1QF52 CRAGI Uncharacterized protein
45
                 K1Q2Z5 CRAGI Putative ATP-dependent RNA helicase DDX46
46
       m6A
47
                 K1PXIO_CRAGI Angiopoietin-4
       m6A
48
       m6A
                 K1RPF7_CRAGI 60S ribosomal protein L5
49
                 K1QV25 CRAGI Transcription elongation factor B polypeptide 2
       m6A
50
                 K1PUJ1_CRAGI Radixin
       m6A
51
                K1QHT0_CRAGI Deoxyuridine 5'-triphosphate nucleotidohydrolase, mitochondrial
52
       m6A
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       m6A
                K1QMK5_CRAGI Kinesin-associated protein 3
54
                K1QQ16_CRAGI AP complex subunit beta
       m6A
55
                 K1QZ49_CRAGI Adipocyte plasma membrane-associated protein
       m6A
56
                 K1QIB2_CRAGI Mitogen-activated protein kinase
       m6A
57
58
                K1QXH7_CRAGI DNA replication licensing factor mcm4-B
       m6A
59
                K1QQV0_CRAGI Histone H1.2
       m6A
60
                K1QG61_CRAGI Acetolactate synthase-like protein
       m6A
                 K1R5R4_CRAGI Dynein heavy chain 10, axonemal
      m6A
                 K1R4J0_CRAGI MAGUK p55 subfamily member 2
       m6A
                 K1RR98_CRAGI NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4-like 2
       m6A
                 K1Q5E0_CRAGI Dual specificity protein kinase CLK2
      m6A
                 K1R275_CRAGI Putative ATP-dependent RNA helicase DDX52
      m6A
                 K1RFV5_CRAGI ATP-dependent RNA helicase DDX1
       m6A
      m6A
                 K1QNZ7 CRAGI Ubiquilin-1
                 K1QZ50_CRAGI RNA-dependent RNA polymerase
       m6A
                K1QHX4_CRAGI Uncharacterized protein
       m6A
       m6A
                 K1Q455 CRAGI Netrin-3
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K1QQL6\_CRAGI Leucyl-tRNA synthetase, cytoplasmic

m6A

m6A

K1RZM3\_CRAGI Cartilage acidic protein 1 m6A K1R065\_CRAGI Golgi membrane protein 1 m6A m6A K1RD19 CRAGI RNA-binding protein 4 m6A K1R969\_CRAGI Uncharacterized protein K1RE19\_CRAGI V-type proton ATPase subunit S1 m6A K1QGW5\_CRAGI WD repeat and SOF domain-containing protein 1 m6A K1QKI1\_CRAGI Tudor domain-containing protein 1 m6A K1PSH2\_CRAGI 28S ribosomal protein S12, mitochondrial m6A m6A K1QMT2\_CRAGI Signal peptidase complex catalytic subunit SEC11 K1QDI0\_CRAGI Transmembrane protein 49 m6A K1Q8T3 CRAGI Importin subunit alpha m6A K1Q525 CRAGI Mechanosensory protein 2 (Fragment) m6A K1Q5G6\_CRAGI 60 kDa heat shock protein, mitochondrial m6A m6A K1QHF0\_CRAGI 40S ribosomal protein S27 m6A K1Q7X3 CRAGI Pre-mRNA-splicing factor SYF1 m6A K1RRH1\_CRAGI Chromodomain-helicase-DNA-binding protein Mi-2-like protein m6A K1Q435\_CRAGI Eukaryotic translation initiation factor 2 subunit 1 K1RNS1\_CRAGI NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8 m6A K1QGF9\_CRAGI Rootletin m6A K1QJ36\_CRAGI Muscle, skeletal receptor tyrosine protein kinase m6A K1RNU5\_CRAGI Pre-mRNA-splicing factor RBM22 m6A m6A K1R916 CRAGI Structural maintenance of chromosomes protein m6A K1RUC9\_CRAGI Uncharacterized protein K1QR54 CRAGI Zinc finger RNA-binding protein m6A K1P9Q2 CRAGI Signal peptidase complex subunit 3 m6A K1RTR1\_CRAGI ATP-citrate synthase m6A K1Q050\_CRAGI Centrin-3 m6A K1QPA5 CRAGI Uncharacterized protein C16orf61-like protein m6A K1PSY2\_CRAGI Fragile X mental retardation syndrome-related protein 1 m6A m6A K1R7G0\_CRAGI Chromobox-like protein 5 K1QFG2 CRAGI Telomere-associated protein RIF1 m6A K1QYV5\_CRAGI Cytoplasmic polyadenylation element-binding protein 1-B m6A m6A K1R1I2 CRAGI Cation-independent mannose-6-phosphate receptor m6A K1R255 CRAGI Heterogeneous nuclear ribonucleoprotein L K1RB07\_CRAGI 60S ribosomal protein L27a m6A m6A K1RYF2\_CRAGI Enoyl-CoA hydratase domain-containing protein 3, mitochondrial m6A K1RJ53 CRAGI Tetratricopeptide repeat protein 12 K1QW73\_CRAGI Glycoprotein 3-alpha-L-fucosyltransferase A m6A K1RBC9\_CRAGI Transketolase-like protein 2 m6A K1QJ46 CRAGI Putative methylcrotonoyl-CoA carboxylase beta chain, mitochondrial m6A K1Q9V2\_CRAGI Antigen KI-67 m6A m6A K1PWQ2\_CRAGI 60 kDa neurofilament protein m6A K1QGF1\_CRAGI Splicing factor 3B subunit 2 K1QTE0\_CRAGI Epidermal retinal dehydrogenase 2 m6A K1PPQ1\_CRAGI 14-3-3 protein gamma m6A K1Q7A7\_CRAGI Putative tyrosinase-like protein tyr-3 m6A K1QHA2\_CRAGI Spectrin beta chain, brain 4 m6A K1Q6U0\_CRAGI Coatomer subunit zeta-1 m6A K1QU16\_CRAGI Protein polybromo-1 m6A K1P7W5\_CRAGI Histone H1-delta m6A K1QBL6\_CRAGI Tudor domain-containing protein 1 m6A K1QVS1\_CRAGI ER membrane protein complex subunit 3 m6A K1Q1L9\_CRAGI Interferon-induced protein 44-like protein m6A K1Q109\_CRAGI Neurexin-4 m6A K1PJN7\_CRAGI PC3-like endoprotease variant A m6A m6A K1RAH1 CRAGI Uncharacterized protein K1R472\_CRAGI Synaptobrevin-like protein YKT6 m6A m6A K1QMY9 CRAGI Uncharacterized protein m6A K1QBT8 CRAGI Uncharacterized protein K1Q1R2\_CRAGI Caprin-2

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m6A	K1R8V1_CRAGI	Puratrophin-1
m6A	K1PUF0_CRAGI	G-protein coupled receptor moody
m6A	K1Q4R2_CRAGI	Zinc finger protein 26
m6A	K1QXP9_CRAGI	Uncharacterized protein
m6A	K1P6M6_CRAGI	Cerebellin-1
Α	K1QNA2_CRAGI	Vitellogenin-6
Α	K1PTY5_CRAGI	Protocadherin Fat 4
Α	K1QBR5_CRAGI	Uncharacterized protein
A	K1PFG1_CRAGI	Uncharacterized protein
A	K1P9A4_CRAGI	Beta-1,3-glucan-binding protein
A	K1QHI5_CRAGI	Pyruvate carboxylase, mitochondrial
A	K1R5B4_CRAGI	Proteasome activator complex subunit 4
A	K1QQ94_CRAGI	Uncharacterized protein
A	K1QXR4_CRAGI	Pancreatic lipase-related protein 2
A	K1RWS2_CRAGI	Transcriptional activator protein Pur-alpha
A	K1PNI6_CRAGI	Heterogeneous nuclear ribonucleoprotein A/B
A	K1R3U2_CRAGI	Uncharacterized protein
A	K1R7V7_CRAGI	Tubulin beta chain
A	K1QMX5_CRAGI	Uncharacterized protein
A	K1R9B6_CRAGI K1QQ68_CRAGI	H/ACA ribonucleoprotein complex subunit 4  Tubulin alpha chain
A	K1PQP2_CRAGI	Nucleolin
A A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
A	K1R164_CRAGI	Galectin-4
A	K1QVJ8_CRAGI	Piwi-like protein 1
A	K1RGT5_CRAGI	Metalloendopeptidase
A	K1PH76_CRAGI	Y-box factor-like protein (Fragment)
Α	K1QII6_CRAGI	Tubulin alpha chain
Α	K1QSX8_CRAGI	ATPase family AAA domain-containing protein 2B
Α	<del>-</del>	Uncharacterized protein
Α	<del>-</del>	Uncharacterized protein
Α	K1PE00_CRAGI	Tubulin alpha chain
Α	K1QQ27_CRAGI	Pancreatic lipase-related protein 2
Α	K1PVA1_CRAGI	Transitional endoplasmic reticulum ATPase
Α	K1PEP0_CRAGI	40S ribosomal protein S8
Α	K1QXX7_CRAGI	Myosin heavy chain, non-muscle (Fragment)
Α	K1RK12_CRAGI	40S ribosomal protein S23
Α	K1QSQ9_CRAGI	Putative ATP-dependent RNA helicase an3
Α	K1PNR3_CRAGI	Clathrin heavy chain
Α	<del>_</del>	RRP5-like protein
Α	<del>-</del>	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 2
Α	K1QU53_CRAGI	NAD(P) transhydrogenase, mitochondrial
Α	K1PJC1_CRAGI	Adipophilin
A	K1RG73_CRAGI	Acetyl-CoA carboxylase
A	K1QFM6_CRAGI	
A	K1R6Q7_CRAGI	DNA topoisomerase I
A	K1R6Z7_CRAGI	ATP synthase subunit alpha
A	K1QGS8_CRAGI	Elongation factor 1-alpha
Α .	K1QWZ6_CRAGI	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 1
A	K1RD58_CRAGI K1QLS3_CRAGI	Uncharacterized protein Cytochrome b-c1 complex subunit 2, mitochondrial
A	K1GL35_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 1
A A	K1S1S1_CRAGI K1R0L4_CRAGI	Sodium/potassium-transporting ATPase subunit alpha
A	_	ATP synthase subunit beta
A	K1QA13_CRAGI	·
A	K1QFN2_CRAGI	Uncharacterized protein
A	K1R545_CRAGI	Pre-mRNA-processing-splicing factor 8 (Fragment)
A	K1R252_CRAGI	Putative methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial
A	K1PMT6_CRAGI	Heterogeneous nuclear ribonucleoprotein U-like protein 1
A	K1RGB7_CRAGI	Epidermal retinal dehydrogenase 2
		1

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Α	K1R466_CRAGI	T-complex protein 1 subunit gamma
Α	K1R294_CRAGI	T-complex protein 1 subunit beta
Α	K1RIT6_CRAGI	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial
Α	K1QIR8_CRAGI	78 kDa glucose-regulated protein
Α	K1RI55_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 3
Α	K1QH74_CRAGI	Splicing factor, arginine/serine-rich 1
A	K1S2N7_CRAGI	Innexin
A	K1R435_CRAGI	Splicing factor, arginine/serine-rich 4
A	K1R5U4_CRAGI	Acetyl-CoA carboxylase 1
A	K1QBK6_CRAGI	Splicing factor 3B subunit 1
A	K1Q988_CRAGI	Band 4.1-like protein 3
A	K1R420_CRAGI	
A	A5LGH1_CRAGI	Voltage-dependent anion channel
A	K1PHW2_CRAGI K1REG6_CRAGI	Uncharacterized protein  DNA helicase
A A	K1QAE5_CRAGI	
A	<del>-</del>	Uncharacterized protein
A	K1QW18_CRAGI	Methenyltetrahydrofolate synthetase domain-containing protein
A	K1QYB3 CRAGI	Ig-like and fibronectin type-III domain-containing protein C25G4.10
A	K1QKD6_CRAGI	
A	K1R115_CRAGI	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
Α	<del>-</del>	T-complex protein 1 subunit delta (Fragment)
Α	K1QWK2_CRAGI	MAM domain-containing glycosylphosphatidylinositol anchor protein 2
Α	K1R0S3_CRAGI	T-complex protein 1 subunit theta
Α	K1QFW9 CRAGI	
Α	K1Q0Z3_CRAGI	Estradiol 17-beta-dehydrogenase 11
Α	K1PNQ5_CRAGI	
Α	K1RBF6_CRAGI	Uncharacterized protein yfeX
Α	K1R4D4 CRAGI	40S ribosomal protein SA
Α	K1QI14_CRAGI	40S ribosomal protein S3a
Α	K1PUL2_CRAGI	Long-chain-fatty-acidCoA ligase 1
Α	K1RFT1_CRAGI	Band 4.1-like protein 3
Α	K1PJ06_CRAGI	Importin subunit alpha-1
Α	K1QT21_CRAGI	Putative ATP-dependent RNA helicase DDX5
Α	K1QM19_CRAGI	Uncharacterized protein
Α	K1QXS6_CRAGI	Heterogeneous nuclear ribonucleoprotein A2-like protein 1
Α	K1QMX8_CRAGI	DNA replication licensing factor MCM7
Α	K1PD57_CRAGI	Constitutive coactivator of PPAR-gamma-like protein 1-like protein
Α	K1R953_CRAGI	Acetyl-CoA carboxylase
Α	K1RJH5_CRAGI	Polyadenylate-binding protein
Α	K1RSZ6_CRAGI	40S ribosomal protein S7
Α	K1R7A2_CRAGI	Uncharacterized protein
Α	K1QUC6_CRAGI	Uncharacterized protein
Α	_	60S acidic ribosomal protein P0
A	K1RNB5_CRAGI	Propionyl-CoA carboxylase beta chain, mitochondrial
A	K1PCS4_CRAGI	Eukaryotic translation initiation factor 2 subunit 3, Y-linked
A	K1Q923_CRAGI	Putative ATP-dependent RNA helicase DDX4
A	K1QPX8_CRAGI	Alkyl/aryl-sulfatase BDS1
A	K1R4R9_CRAGI	Mitotic apparatus protein p62
A	K1RAJ1_CRAGI	T-complex protein 1 subunit alpha
A	K1Q0L1_CRAGI	60S ribosomal protein L23a
A	K1Q620_CRAGI	Uncharacterized protein
A	K1QG58_CRAGI	Actin Nedal modulator 2
A	K1Q4H2_CRAGI	Nodal modulator 3
A A	K1Q260_CRAGI K1QF01 CRAGI	Nucleolar protein 58 40S ribosomal protein S4
A	K1PUM2_CRAGI	Histone H2A
A	K1QNN9 CRAGI	MICOS complex subunit MIC60
A	K1RQA0_CRAGI	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 2
A	K1QZW0_CRAGI	Polyadenylate-binding protein 2
~	KIQZVVU_CNAGI	i organicingiate bilitating protein 2

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K1QBN0_CRAGI Methylcrotonoyl-CoA carboxylase beta chain, mitochondrial
        Α
3
                 K1Q8S0_CRAGI Nucleolar complex protein 3 homolog
4
        Α
5
        Α
                 K1RH18 CRAGI Sarcalumenin
6
        Α
                 K1QQ05_CRAGI Insulin-like growth factor-binding protein complex acid labile chain
7
                 K1QT04_CRAGI Uncharacterized protein
        Α
8
                 K1RLC5_CRAGI T-complex protein 1 subunit epsilon
        Α
9
                 K1Q9K6_CRAGI Histone H3
10
        Α
11
                 K1QBW8_CRAGI Uncharacterized protein
12
                 K1Q9W5_CRAGI T-complex protein 1 subunit eta
        Α
13
                 K1R0Y9_CRAGI ADP,ATP carrier protein
        Α
14
        Α
                 K1QP17_CRAGI Caprin-1
15
                 K1QYB6_CRAGI Delta-1-pyrroline-5-carboxylate synthetase
        Α
16
17
                 K1R7I9_CRAGI Heterogeneous nuclear ribonucleoprotein Q
        Α
18
        Α
                 K1QMB9_CRAGI Eukaryotic translation initiation factor 3 subunit A
19
        Α
                 K1PM50 CRAGI 40S ribosomal protein S16
20
        Α
                 K1P8W6_CRAGI 60S ribosomal protein L4
21
22
        Α
                 K1PXH5_CRAGI Putative saccharopine dehydrogenase
23
        Α
                 K1PBZ4_CRAGI Regulator of nonsense transcripts 1
24
                 K1R4L8_CRAGI Electron transfer flavoprotein-ubiquinone oxidoreductase, mitochondrial
        Α
25
                 K1QFP5_CRAGI NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial
        Α
26
                 K1RIG6_CRAGI LSM14-like protein A
27
28
        Α
                 K1R591_CRAGI Inter-alpha-trypsin inhibitor heavy chain H4
29
        Α
                 K1RSA6_CRAGI Methylcrotonoyl-CoA carboxylase subunit alpha, mitochondrial
30
                 K1R1B1 CRAGI 35 kDa SR repressor protein
        Α
31
                 K1QZU8_CRAGI Calcium-transporting ATPase
        Α
32
                 K1QX26_CRAGI Endoplasmin
        Α
33
                 K1Q358_CRAGI 60S acidic ribosomal protein P2
34
35
                 K1P112 CRAGI ATP synthase subunit gamma, mitochondrial
        Α
36
                 K1QHS8_CRAGI Ribonucleoside-diphosphate reductase
        Α
37
                 K1PXN5_CRAGI T-complex protein 1 subunit zeta
38
                 K1R7J6_CRAGI Putative sodium/potassium-transporting ATPase subunit beta-2
        Α
39
40
                 K1Q5H6_CRAGI FACT complex subunit SSRP1
        Α
41
                 K1QTD9_CRAGI Nucleolar protein 56
42
        Α
                 K1QC78 CRAGI Ras-related protein Rab-14
43
                 K1Q9M7_CRAGI Histone H1-delta
        Α
44
                 K1RNZ6_CRAGI Eukaryotic translation initiation factor 3 subunit D
        Α
45
46
        Α
                 K1QAH9 CRAGI H/ACA ribonucleoprotein complex subunit
47
                 K1RLT4_CRAGI Signal recognition particle subunit SRP68
        Α
48
        Α
                 K1RWX7_CRAGI Metabotropic glutamate receptor 3
49
                 K1RA35 CRAGI Splicing factor, arginine/serine-rich 7
        Α
50
                 K1QE71_CRAGI DNA helicase
        Α
51
52
        Α
                 K1PS27_CRAGI DNA helicase
53
        Α
                 K1Q4Y8_CRAGI Histone H1oo
54
                 K1PGW7_CRAGI Transmembrane protein 2
        Α
55
                 K1RAB9_CRAGI Epoxide hydrolase 4
        Α
56
                 K1Q9P5_CRAGI Mitochondrial-processing peptidase subunit beta
        Α
57
58
                 K1QL67_CRAGI 60S ribosomal protein L7a
        Α
59
                 K1PLY1_CRAGI DNA polymerase
        Α
60
        Α
                 K1R996_CRAGI Long-chain-fatty-acid--CoA ligase 4
        Α
                 K1Q404_CRAGI DNA topoisomerase 2
        Α
                 K1QBH0_CRAGI Uncharacterized protein
        Α
                 K1R0W4_CRAGI Signal recognition particle subunit SRP72
        Α
                 K1RN77_CRAGI Nuclear autoantigenic sperm protein
                 K1PA54_CRAGI Replication factor C subunit 3
        Α
        Α
                 K1Q4S5_CRAGI Cadherin-87A
        Α
                 K1QEF2 CRAGI ADP-ribosylation factor-like protein 15
        Α
                 K1QYT5_CRAGI Phosphate carrier protein, mitochondrial
        Α
                 K1QDX9_CRAGI Ribosome biogenesis protein BMS1-like protein
        Α
                 K1QB61 CRAGI Protocadherin Fat 4
        Α
                 K1R0D7_CRAGI Eukaryotic translation initiation factor 3 subunit M (Fragment)
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Α	K1PM76_CRAGI	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial
Α	K1PRL4_CRAGI	60S ribosomal protein L38 (Fragment)
Α	K1RW85_CRAGI	Adenosylhomocysteinase
Α	K1PAY7_CRAGI	Propionyl-CoA carboxylase alpha chain, mitochondrial
Α	K1PZ08_CRAGI	Ras-related protein Rab-7a
Α	K1QY12_CRAGI	Dynamin-1-like protein
Α	K1QFN1_CRAGI	60S ribosomal protein L23
Α	K1RDW8_CRAGI	Golgi apparatus protein 1
Α	K1RSS3_CRAGI	Myosin heavy chain, striated muscle
Α	K1QGK2_CRAGI	Coatomer subunit beta
A	K1PV79_CRAGI	Importin subunit alpha
A	K1QN79_CRAGI	40S ribosomal protein S11
A	K1PV49_CRAGI	RuvB-like helicase
A	K1QG65_CRAGI	rRNA 2'-O-methyltransferase fibrillarin
A	K1PK85_CRAGI	Cullin-associated NEDD8-dissociated protein 1
A	K1QVN9_CRAGI K1QGB4_CRAGI	T-complex protein 1 subunit eta 40S ribosomal protein S17
A A	K1QK18_CRAGI	Cytochrome b5
A	<del>-</del>	Alkylglycerone-phosphate synthase
Α	K1QVV3_CRAGI	Pre-mRNA-processing-splicing factor 8
Α	K1RJS5_CRAGI	Uncharacterized protein
Α	K1Q6W5_CRAGI	FACT complex subunit spt16
Α	K1QQB6_CRAGI	40S ribosomal protein S14
Α	K1PKF5_CRAGI	Protein-glutamine gamma-glutamyltransferase 4
Α	K1PH66_CRAGI	Fibrinolytic enzyme, isozyme C
Α	K1PY89_CRAGI	Extracellular superoxide dismutase [Cu-Zn]
Α	K1QUK3_CRAGI	Putative ATP-dependent RNA helicase DDX41
Α	K1R2V1_CRAGI	Importin subunit beta-1
Α	K1PV86_CRAGI	Phosphoglycerate mutase family member 5
Α	K1QJ08_CRAGI	60S ribosomal protein L26
Α	_	Poly [ADP-ribose] polymerase
Α	<del>_</del>	Heat shock protein 75 kDa, mitochondrial (Fragment)
Α	K1QPP2_CRAGI	Elongation factor Tu, mitochondrial
Α	K1R834_CRAGI	60S ribosomal protein L9
A	K1R005_CRAGI	Filamin-C (Fragment)
A	K1QET2_CRAGI	Coatomer subunit alpha Far upstream element-binding protein 3 Protein FAM98A Colonia A
A	K1RKC1_CRAGI	Far upstream element-binding protein 3
A	K1RG19_CRAGI	Protein FAM98A
A	K1Q056_CRAGI	Calpani-A
A	K1QKJ0_CRAGI	Aldehyde dehydrogenase family 3 member B1
A	K1QDZ5_CRAGI K1PPP8_CRAGI	Cytochrome c1, heme protein, mitochondrial Vigilin
A A	K1PPP8_CRAGI	Nucleolar RNA helicase 2
A	K1PH31_CRAGI	Protein arginine N-methyltransferase 1
Α	K1Q6V6_CRAGI	Replication factor C subunit 4
Α	K1PI50_CRAGI	40S ribosomal protein S26
Α	K1PX23_CRAGI	Eukaryotic peptide chain release factor subunit 1
Α	K1QFZ8_CRAGI	Ceramide kinase-like protein
Α	K1S2S8_CRAGI	Signal recognition particle 54 kDa protein
Α	K1R1T8_CRAGI	Nucleolar protein 56
Α	K1QRZ3_CRAGI	40S ribosomal protein S13
Α	K1PMP3_CRAGI	Protoporphyrinogen oxidase
Α	K1P9N7_CRAGI	14-3-3 protein zeta
Α	K1Q0R4_CRAGI	ATP-binding cassette sub-family F member 2
Α	K1QWC3_CRAGI	40S ribosomal protein S3
Α	K1Q812_CRAGI	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial
Α	K1P5V7_CRAGI	Eukaryotic translation initiation factor 3 subunit C
Α	K1R2N0_CRAGI	Histone H4
Α	K1QLK8_CRAGI	GTP-binding protein SAR1b
Α	K1QHX2_CRAGI	La-related protein 7

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K1S6V7_CRAGI Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform
        Α
3
                K1Q3W9_CRAGI FAS-associated factor 2-B
4
        Α
5
        Α
                K1QG72_CRAGI Hemagglutinin/amebocyte aggregation factor
6
        Α
                K1QHQ6_CRAGI Acyl-CoA dehydrogenase family member 9, mitochondrial
7
                 K1QFR2_CRAGI Calnexin
        Α
8
                 K1S1X3_CRAGI SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5
        Α
9
                K1PWZ3_CRAGI Guanine nucleotide-binding protein subunit beta
10
        Α
11
                K1QW41_CRAGI Leucine-zipper-like transcriptional regulator 1
12
                 K1RK68_CRAGI Uncharacterized protein
        Α
13
                 K1RA95_CRAGI Filamin-A
        Α
14
                K1QMV5_CRAGI Annexin
        Α
15
        Α
                K1QW72_CRAGI Catalase
16
17
                K1QXQ8_CRAGI DNA helicase
        Α
18
                 K1P7L5_CRAGI Transmembrane 9 superfamily member
        Α
19
        Α
                 K1P8G1 CRAGI Heterogeneous nuclear ribonucleoprotein H
20
        Α
                 21
22
        Α
                 K1RIZ3_CRAGI Bone morphogenetic protein 7
23
        Α
                K1RNN9_CRAGI Cytoskeleton-associated protein 5
24
                 K1R6L5_CRAGI NADH-cytochrome b5 reductase
        Α
25
                 K1R5F2_CRAGI 14-3-3 protein epsilon
        Α
26
                 K1P9D0_CRAGI Stress-70 protein, mitochondrial
        Α
27
                 K1RGJ7_CRAGI Neogenin
28
        Α
29
        Α
                 K1PZP6_CRAGI Coatomer subunit gamma
30
                 K1RJ97 CRAGI Multifunctional protein ADE2
        Α
31
                 K1R6F5_CRAGI Putative ATP-dependent RNA helicase DDX23
        Α
32
                 K1PS84_CRAGI Alpha-crystallin B chain
        Α
33
                 K1P9S7_CRAGI Brix domain-containing protein 2
34
35
                 K1PI40_CRAGI Uncharacterized protein
        Α
36
                 K1QAI2_CRAGI Ufm1-specific protease 2
        Α
37
                 K1REPO_CRAGI Uncharacterized protein
38
                K1QJM1_CRAGI 60S ribosomal protein L30
        Α
39
                 K1S3G2_CRAGI HMGB1
40
        Α
41
                 K1PXD4_CRAGI Putative ATP-dependent RNA helicase DDX6
42
                 K1RJJ7 CRAGI Histone H5
        Α
43
                K1Q3W3_CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial
        Α
44
        Α
                K1RJW8 CRAGI Protein DEK
45
                 K1RN97_CRAGI Hemagglutinin/amebocyte aggregation factor
46
        Α
47
                K1QW36_CRAGI 60S ribosomal protein L6
        Α
48
                 K1RA63_CRAGI Transmembrane protein 2
        Α
49
                 K1R9T2 CRAGI Eukaryotic translation initiation factor 3 subunit B
        Α
50
        Α
                K1PM66_CRAGI 60S ribosomal protein L12
51
52
        Α
                 K1Q273_CRAGI 60S ribosomal protein L14
53
        Α
                 K1PXG6_CRAGI Serine/threonine-protein phosphatase
54
                 K1QPC6_CRAGI Nucleolar complex protein 2-like protein
        Α
55
                K1RCW3_CRAGI Elongation factor 1-beta
        Α
56
                 K1Q324_CRAGI Heterogeneous nuclear ribonucleoprotein K
        Α
57
58
                 K1PLA7_CRAGI Eukaryotic initiation factor 4A-II (Fragment)
        Α
59
                 K1RBI9_CRAGI Small nuclear ribonucleoprotein Sm D2
        Α
60
        Α
                 K1RCL2_CRAGI Mitochondrial import inner membrane translocase subunit Tim13-B
        Α
                 K1QKV1_CRAGI Cytochrome b-c1 complex subunit 6
        Α
                K1QVU0_CRAGI Synaptojanin-2-binding protein
        Α
                K1QRG9_CRAGI Uncharacterized protein
        Α
                 K1PZ70_CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial
                 K1Q350_CRAGI Glyceraldehyde-3-phosphate dehydrogenase
        Α
        Α
                 K1PXU6_CRAGI 60S ribosomal protein L24
        Α
                K1QZQ8_CRAGI Low-density lipoprotein receptor-related protein 8
        Α
                K1RUM2_CRAGI Uncharacterized protein
        Α
                 K1REY2_CRAGI Dysferlin
                 K1Q6X5 CRAGI Protein disulfide-isomerase
        Α
        Α
                K1QWK6_CRAGI Metalloendopeptidase
```

Α

K1QKL8\_CRAGI V-type proton ATPase subunit a

K1QDH9\_CRAGI Myosin-11 Α K1QQR1\_CRAGI Major vault protein Α Α K1RAH2\_CRAGI Superoxide dismutase [Cu-Zn] Α K1PH13\_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3B K1PY73\_CRAGI Basic leucine zipper and W2 domain-containing protein 1 Α K1Q7T5\_CRAGI Protein disulfide-isomerase Α K1PFS5\_CRAGI Elongation factor 1-gamma Α K1PW39\_CRAGI Glycerol-3-phosphate dehydrogenase, mitochondrial K1R1C5\_CRAGI Signal recognition particle receptor subunit beta Α K1Q1F4\_CRAGI 60S ribosomal protein L3 (Fragment) Α Α Α K1QY85\_CRAGI Transport protein Sec31A K1QWP1\_CRAGI Nucleoporin seh1 Α Α K1RAU3\_CRAGI DNA ligase Α K1R5W3\_CRAGI Uncharacterized protein Α K1QF31\_CRAGI Serine/threonine-protein kinase PLK Α K1Q667\_CRAGI tRNA-splicing ligase RtcB homolog Α K1QRM1\_CRAGI Nuclear pore protein K1R790\_CRAGI Retinol dehydrogenase 13 Α K1R0M2\_CRAGI Uncharacterized protein Α K1QNT7\_CRAGI Aldehyde dehydrogenase, mitochondrial Α Α K1QIV3\_CRAGI Uncharacterized protein Α K1QR48\_CRAGI Calcium-binding mitochondrial carrier protein SCaMC-2 K1R4F7 CRAGI Ras-related protein Rab-6B Α K1PIC5\_CRAGI Transmembrane protein 85 Α K1RKZ5\_CRAGI DNA damage-binding protein 1 Α K1QW21\_CRAGI 39S ribosomal protein L40, mitochondrial K1PB87 CRAGI Uncharacterized protein Α K1R150\_CRAGI Ras-related protein Rab-1A Α K1PVZ3\_CRAGI Cold shock domain-containing protein E1 K1QSD9\_CRAGI Uncharacterized protein Α K1PPW8\_CRAGI Coatomer subunit beta Α Α K1QKG9\_CRAGI Cysteine desulfurase, mitochondrial Α K1RK83\_CRAGI Tyrosine-protein kinase BAZ1B K1QE94\_CRAGI Alpha-galactosidase Α Α K1RIJ1\_CRAGI Synaptobrevin (Fragment) K1PJBO CRAGI Heat shock protein 70 B2 Α K1R6S5\_CRAGI 40S ribosomal protein S9 Α K1PAM6\_CRAGI Uncharacterized protein Α Α K1QY71 CRAGI Histone H2B K1P6Y1\_CRAGI Uncharacterized protein Α K1PNY5\_CRAGI Splicing factor, proline-and glutamine-rich Α Α K1PDL3\_CRAGI Ribosomal protein L19 K1RDG4\_CRAGI DNA helicase Α K1RV41\_CRAGI Guanine nucleotide-binding protein subunit beta-2-like 1 Α K1QMH5\_CRAGI Small nuclear ribonucleoprotein Sm D1 Α K1R4Z3\_CRAGI Malate dehydrogenase, mitochondrial Α K1R3T3\_CRAGI Transcription factor BTF3 Α Α K1QAB1\_CRAGI AP-2 complex subunit alpha Α K1QSU3\_CRAGI Protein I(2)37Cc K1PEY4\_CRAGI 26S proteasome non-ATPase regulatory subunit 2 Α Α K1PU46\_CRAGI Lethal(2) giant larvae-like protein 1 K1Q0N6\_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A Α Α K1QGP1\_CRAGI Replication factor C subunit 2 Α K1QDV6\_CRAGI Protein argonaute-2 Α K1S6H7\_CRAGI Vacuolar protein sorting-associated protein 13C K1PF10\_CRAGI PAN2-PAN3 deadenylation complex catalytic subunit PAN2 Α Α K1Q1L4\_CRAGI Uncharacterized protein Α K1PWC3 CRAGI Tetratricopeptide repeat protein 35

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```
K1QT61_CRAGI NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial (Fragment)
        Α
3
                 K1Q7G8_CRAGI Fatty acid synthase
4
        Α
5
        Α
                 K1QX44 CRAGI Ras-related protein Rab-11B
6
        Α
                 K1P7K8_CRAGI Vesicle-fusing ATPase 1
7
                 K1QHK9_CRAGI Dynein heavy chain, cytoplasmic
        Α
8
                 K1Q7Q2_CRAGI CCAAT/enhancer-binding protein zeta
        Α
9
                 K1Q880_CRAGI Transportin-1
10
        Α
11
                 K1Q253_CRAGI Neutral and basic amino acid transport protein rBAT
12
                 K1QGA7_CRAGI Kynurenine formamidase
        Α
13
                 K1QAL3_CRAGI RNA-binding protein 28
        Α
14
                 K1PXS8_CRAGI Calreticulin
        Α
15
        Α
                 K1QTP6_CRAGI Cation-transporting ATPase
16
17
                 K1PR25_CRAGI Regulator of differentiation 1
        Α
18
        Α
                 K1PA61_CRAGI Actin-like protein 6A
19
        Α
                 K1QAA8_CRAGI CAAX prenyl protease 1-like protein
20
        Α
                 K1PY30_CRAGI Septin-2
21
22
        Α
                 K1R100_CRAGI Metaxin-2
23
        Α
                 K1PTL4_CRAGI Odr-4-like protein
24
                 K1QA50_CRAGI V-type proton ATPase subunit H
        Α
25
                 K1PVH5_CRAGI Centromere/kinetochore protein zw10-like protein
        Α
26
                 K1PUQ5_CRAGI Histone H2B
        Α
27
28
        Α
                 K1RFB1_CRAGI Stomatin-like protein 2 (Fragment)
29
        Α
                 K1QAA2_CRAGI Uncharacterized protein
30
                 K1PNC7 CRAGI AFG3-like protein 2
        Α
31
                 K1PJS7_CRAGI Poly [ADP-ribose] polymerase
        Α
32
                 K1PLF9_CRAGI Arginine kinase
        Α
33
                 K1RC37_CRAGI Uncharacterized protein
34
35
                 K1PKD4 CRAGI 40S ribosomal protein S30
        Α
36
        Α
                 K1RDS1_CRAGI Splicing factor, arginine/serine-rich 2
37
                 K1Q5Z1_CRAGI Uncharacterized protein
38
        Α
                 K1PF96_CRAGI Spliceosome RNA helicase BAT1
39
40
                 K1QTW6_CRAGI Eukaryotic translation initiation factor 3 subunit F
        Α
41
        Α
                 K1RAU8_CRAGI Eukaryotic translation initiation factor 3 subunit E
42
        Α
                 K1RAI3 CRAGI Annexin
43
                 K1PUX5_CRAGI Casein kinase II subunit alpha
        Α
44
        Α
                 K1PDF8 CRAGI Splicing factor, arginine/serine-rich 6
45
                 K1QXH3 CRAGI Translational activator GCN1
46
        Α
47
                 K1PQE3_CRAGI RNA-binding protein Raly
        Α
48
        Α
                 K1QWE5_CRAGI Ras-related protein Rab-18-B
49
        Α
                 K1R5G4 CRAGI 60S ribosomal protein L31
50
        Α
                 K1RCT2_CRAGI Translocon-associated protein subunit delta
51
52
        Α
                 K1RFU6_CRAGI Proteasome activator complex subunit 3
53
        Α
                 K1R0W0_CRAGI Ferritin
54
        Α
                 K1Q5Z6_CRAGI Eukaryotic translation initiation factor 2 subunit 2
55
                 K1RKE5_CRAGI IQ and AAA domain-containing protein 1
        Α
56
                 K1P8G6_CRAGI Vesicular integral-membrane protein VIP36
        Α
57
58
                 K1P3Q5_CRAGI Programmed cell death 6-interacting protein
        Α
59
                 K1Q615_CRAGI Peroxiredoxin-1
        Α
60
        Α
                 K1RG04_CRAGI ALK tyrosine kinase receptor
        Α
                 K1QQK5_CRAGI Metabotropic glutamate receptor 2
                 K1R3G0_CRAGI Transformer-2-like protein beta
        Α
        Α
                 K1QCB0_CRAGI 40S ribosomal protein S5
        Α
                 K1REQ4_CRAGI Cytochrome c oxidase subunit 6B
        Α
                 K1QHI2_CRAGI Heterogeneous nuclear ribonucleoprotein L
        Α
                 K1PSH2_CRAGI 28S ribosomal protein S12, mitochondrial
        Α
                 K1R9P5_CRAGI Mitochondrial import receptor subunit TOM70
                 K1PGK7_CRAGI Uncharacterized protein
        Α
        Α
                 K1QPF0_CRAGI Uncharacterized protein
        Α
                 K1QT00 CRAGI ATP synthase subunit alpha, mitochondrial
        Α
                 K1RG28_CRAGI Kinase C and casein kinase substrate in neurons protein 2
```

Α

K1QK68\_CRAGI Myosin-2 essential light chain

K1PMY9\_CRAGI Calmodulin Α K1R1Q8\_CRAGI Ras-related protein Rab-5C Α K1RPP1\_CRAGI Synaptophysin Α Α K1RFU8\_CRAGI High mobility group protein DSP1 K1PJ85\_CRAGI 26S protease regulatory subunit 6A Α K1R2G9\_CRAGI SEC13-like protein Α K1QJW6\_CRAGI Translocon-associated protein subunit gamma Α K1R5B9\_CRAGI DNA-directed RNA polymerase, mitochondrial K1R8C6\_CRAGI 40S ribosomal protein S12 Α K1QSR2\_CRAGI Apoptosis inhibitor 5 Α K1Q5E0\_CRAGI Dual specificity protein kinase CLK2 Α Α K1QBM3\_CRAGI Ras-related protein Rab-2 K1Q8K9\_CRAGI KRR1 small subunit processome component-like protein Α Α K1QNU0\_CRAGI Non-specific serine/threonine protein kinase Α K1RDM2 CRAGI 60S ribosomal protein L18a Α K1RD12\_CRAGI Uncharacterized protein Α K1QGP7\_CRAGI Uncharacterized protein K1PBL2\_CRAGI Eukaryotic initiation factor 4A-III Α K1QAT9\_CRAGI ATP-dependent RNA helicase DDX1 Α K1QWJ4\_CRAGI Splicing factor 3B subunit 5 Α K1Q412\_CRAGI Uncharacterized protein Α Α K1R8R6\_CRAGI Fructose-bisphosphate aldolase Α K1RWP3\_CRAGI Peptidyl-tRNA hydrolase 2, mitochondrial K1PGN0 CRAGI Fatty-acid amide hydrolase 2 Α K1PUV4\_CRAGI 40S ribosomal protein S24 Α K1PJY2\_CRAGI Inositol polyphosphate 1-phosphatase Α K1QWZ8\_CRAGI Catenin beta K1R1F0 CRAGI ATP-dependent DNA helicase 2 subunit 1 Α K1PN47\_CRAGI Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial Α K1QYQ9\_CRAGI Uncharacterized protein K1PNZ8 CRAGI Ribosomal protein L37 Α K1PVD7\_CRAGI Cytochrome c oxidase subunit 5A, mitochondrial Α K1QEJ0\_CRAGI Ras GTPase-activating protein-binding protein 2 K1PYL5 CRAGI Uncharacterized protein Α K1QQQ5\_CRAGI Replication factor C subunit 5 Α Α K1RFA3\_CRAGI Lamin Dm0 K1RRH1\_CRAGI Chromodomain-helicase-DNA-binding protein Mi-2-like protein Α K1Q2Y1\_CRAGI 40S ribosomal protein S15 Α K1RIZ9\_CRAGI Band 4.1-like protein 5 Α K1QVI0\_CRAGI Isocitrate dehydrogenase [NAD] subunit, mitochondrial Α K1PS77\_CRAGI Prostaglandin G/H synthase 1 Α Α K1QZK9\_CRAGI Uncharacterized protein Α K1R9V5\_CRAGI Tetraspanin K1PPV1\_CRAGI Atlastin-2 Α K1R0Z4\_CRAGI Uncharacterized protein Α K1R1R9\_CRAGI Pre-mRNA-processing factor 6 Α K1QKU6\_CRAGI mRNA export factor Α K1PCR5\_CRAGI KH domain-containing, RNA-binding, signal transduction-associated protein 2 Α Α K1R7L4\_CRAGI Neural cell adhesion molecule 1 Α K1QAL1\_CRAGI Transmembrane emp24 domain-containing protein 7 K1QB65\_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1 Α Α K1QVP6\_CRAGI Developmentally-regulated GTP-binding protein 1 Α K1QNT4\_CRAGI Anoctamin Α Α K1RCF4\_CRAGI Translocon-associated protein subunit alpha Α K1QJL6\_CRAGI Microtubule-associated protein RP/EB family member 3 Α K1QPY8\_CRAGI Extracellular superoxide dismutase [Cu-Zn] Α K1R5V4\_CRAGI GTP-binding nuclear protein Α K1RNU5\_CRAGI Pre-mRNA-splicing factor RBM22

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```
K1QED7_CRAGI Replication protein A subunit
        Α
3
                 K1QPS1_CRAGI Poly [ADP-ribose] polymerase
4
5
        Α
                 K1PD36 CRAGI Ubiquitin
6
        Α
                 K1R4B8_CRAGI Plexin domain-containing protein 2
7
                 K1RHP3_CRAGI Proliferation-associated protein 2G4
8
                 K1QE43_CRAGI Uncharacterized protein
        Α
9
                 K1R3I6_CRAGI Nucleolar complex protein 2-like protein (Fragment)
10
        Α
11
                 K1QMJ8_CRAGI Transcription initiation factor IIA subunit 1
12
                 K1QXF5_CRAGI Calcyphosin-like protein
        Α
13
                 K1R512_CRAGI Uncharacterized protein
        Α
14
                 K1QM06_CRAGI Prohibitin
        Α
15
                 K1R275_CRAGI Putative ATP-dependent RNA helicase DDX52
        Α
16
17
                 K1QSB2_CRAGI 26S protease regulatory subunit 6B
        Α
18
        Α
                 K1QBW6_CRAGI Tudor domain-containing protein 1
19
        Α
                 K1PZT2_CRAGI Cytochrome c oxidase subunit 5B, mitochondrial
20
        Α
                 K1QIZ7_CRAGI Programmed cell death protein 6
21
22
        Α
                 K1QDA7_CRAGI Uracil phosphoribosyltransferase
23
                 K1R401_CRAGI Spectrin alpha chain
        Α
24
                 K1P541_CRAGI Alpha-soluble NSF attachment protein
        Α
25
                 K1PND7_CRAGI Fatty acid synthase
        Α
26
                 K1R8L1_CRAGI Exportin-2
        Α
27
28
        Α
                 K1QEF9_CRAGI Protein-glutamine gamma-glutamyltransferase K
29
        Α
                 K1Q2W7_CRAGI Uncharacterized protein
30
                 K1RYM7 CRAGI LAG1 longevity assurance-like protein 6
        Α
31
                 K1PY09_CRAGI Uncharacterized protein
        Α
32
                 K1Q105_CRAGI Ferrochelatase
        Α
33
                 K1PD30_CRAGI Putative histone-binding protein Caf1
34
35
                 K1QDB9 CRAGI Transport protein Sec61 subunit alpha isoform 2 (Fragment)
        Α
36
                 K1QTW3_CRAGI Murinoglobulin-2
        Α
37
                 K1PVG9_CRAGI Malectin
38
                 K1Q3V9 CRAGI Mitochondrial carnitine/acylcarnitine carrier protein
        Α
39
                 K1QVS0_CRAGI Ras-like GTP-binding protein Rho1
40
        Α
41
                 K1PX68_CRAGI Tyrosine-protein phosphatase non-receptor type 6
42
                 K1RPF7_CRAGI 60S ribosomal protein L5
        Α
43
                 K1QZ64_CRAGI Nuclear pore complex protein Nup98-Nup96
        Α
44
        Α
                 K1QSV1 CRAGI Uncharacterized protein
45
                 K1Q2L4 CRAGI Transmembrane emp24 domain-containing protein 9
46
        Α
47
                K1RMM6_CRAGI Centromere protein J
        Α
48
                 K1QKK2_CRAGI NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial
        Α
49
                 K1PNV6 CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit DAD1
        Α
50
        Α
                 K1PNQ1_CRAGI Ankyrin repeat domain-containing protein 5
51
52
        Α
                 K1QKQ8_CRAGI THO complex subunit 4-A
53
        Α
                 K1QAG9_CRAGI Ferritin
54
        Α
                 K1QHW8_CRAGI Ferritin
55
                 K1RFV5_CRAGI ATP-dependent RNA helicase DDX1
        Α
56
                 K1RNH1_CRAGI 60S ribosomal protein L18 (Fragment)
        Α
57
58
                 K1PPQ1_CRAGI 14-3-3 protein gamma
        Α
59
                 K1QQV0_CRAGI Histone H1.2
        Α
60
        Α
                 K1Q1R1_CRAGI Exostosin-3
        Α
                 K1QYF5_CRAGI Apoptosis-inducing factor 1, mitochondrial
                 K1RZE2_CRAGI Isocitrate dehydrogenase [NADP]
        Α
        Α
                 K1QL00_CRAGI Microsomal glutathione S-transferase 1
        Α
                 K1QTV1_CRAGI Uncharacterized protein
        Α
                 K1RZM3_CRAGI Cartilage acidic protein 1
        Α
                 K1Q0I8_CRAGI Putative splicing factor, arginine/serine-rich 7
        Α
                 K1RP91 CRAGI Putative RNA exonuclease NEF-sp
                 K1PG60_CRAGI 60S ribosomal protein L17
        Α
        Α
                 K1QTP4 CRAGI 5'-3' exoribonuclease
                 K1RG79_CRAGI Neuronal acetylcholine receptor subunit alpha-6
        Α
        Α
                 K1Q947_CRAGI Dynein light chain
```

Α K1RJ91\_CRAGI Ubiquitin-associated protein 2 K1Q2Z5\_CRAGI Putative ATP-dependent RNA helicase DDX46 Α K1PYA0\_CRAGI Cytoplasmic dynein 2 heavy chain 1 Α Α K1QAV0\_CRAGI Guanine nucleotide-binding protein G(Q) subunit alpha K1RKR8\_CRAGI Pumilio-like protein 2 Α K1QZI3\_CRAGI Myosin-le Α K1R5R4\_CRAGI Dynein heavy chain 10, axonemal Α K1QKG8\_CRAGI Upstream activation factor subunit spp27 K1P8I1\_CRAGI Pleckstrin-like protein domain-containing family F member 2 (Fragment) Α K1Q1N1\_CRAGI Alpha-mannosidase Α K1PXB6\_CRAGI Cadherin-23 Α Α K1QXA9\_CRAGI Sortilin-related receptor K1PVG0\_CRAGI Long-chain fatty acid transport protein 4 Α Α K1PBG6\_CRAGI Uncharacterized protein Α K1PP50\_CRAGI Golgi integral membrane protein 4 Α K1QCQ5\_CRAGI Succinate--CoA ligase [ADP-forming] subunit beta, mitochondrial Α K1PK87\_CRAGI Putative E3 ubiquitin-protein ligase TRIP12 Α K1Q373\_CRAGI Splicing factor, arginine/serine-rich 7 K1Q151\_CRAGI 60S ribosomal protein L32 Α K1QZ95\_CRAGI Nuclear pore complex protein Α K1PPH0\_CRAGI Gamma-tubulin complex component Α Α K1R0R7\_CRAGI Putative ATP-dependent RNA helicase DHX36 Α K1R247\_CRAGI Condensin complex subunit 1 K1QIB2 CRAGI Mitogen-activated protein kinase Α K1QG61\_CRAGI Acetolactate synthase-like protein Α K1RBC9\_CRAGI Transketolase-like protein 2 Α K1RCW5\_CRAGI Eukaryotic translation initiation factor 4 gamma 3 K1PQZ3 CRAGI Armadillo repeat-containing protein 4 Α K1PYJ8\_CRAGI Uncharacterized protein Α K1QQP1\_CRAGI Programmed cell death protein 4 K1PQY0\_CRAGI Protein quiver Α K1PLC6\_CRAGI Nucleolar protein 14 Α K1QV25\_CRAGI Transcription elongation factor B polypeptide 2 K1QZ50\_CRAGI RNA-dependent RNA polymerase Α K1QXH7\_CRAGI DNA replication licensing factor mcm4-B Α Α K1PDE4\_CRAGI Protein arginine N-methyltransferase Α K1QT36\_CRAGI Golgi resident protein GCP60 K1PZ89\_CRAGI Mannosyl-oligosaccharide glucosidase Α Α K1Q7A7\_CRAGI Putative tyrosinase-like protein tyr-3 Α K1R481 CRAGI Epimerase family protein SDR39U1 K1RJ35\_CRAGI All-trans-retinol 13,14-reductase Α Q70MT4\_CRAGI 40S ribosomal protein S10 Α Α K1REV3\_CRAGI DNA polymerase delta subunit 2 K1P9F1\_CRAGI Insulin-like growth factor-binding protein complex acid labile chain Α K1PJ65\_CRAGI Dual specificity mitogen-activated protein kinase kinase 7 Α K1Q2T0\_CRAGI ADP-dependent glucokinase Α K1PZI3\_CRAGI SWI/SNF complex subunit SMARCC2 Α K1Q8C5\_CRAGI Putative ATP-dependent RNA helicase DDX47 Α Α K1QZ58\_CRAGI Splicing factor U2AF 26 kDa subunit Α K1RR98\_CRAGI NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4-like 2 K1QMT2\_CRAGI Signal peptidase complex catalytic subunit SEC11 Α Α K1PWM3\_CRAGI MICOS complex subunit MIC13 Α K1QMM4\_CRAGI Leucine zipper transcription factor-like protein 1 Α K1QMV7\_CRAGI V-type proton ATPase subunit D Α K1QKI1\_CRAGI Tudor domain-containing protein 1 Α K1P0H0\_CRAGI Aspartyl/asparaginyl beta-hydroxylase Α K1PVQ8\_CRAGI Eukaryotic translation initiation factor 3 subunit K Α K1Q5P0\_CRAGI 60S ribosomal protein L17 Α K1QJ36\_CRAGI Muscle, skeletal receptor tyrosine protein kinase Α K1PHS4\_CRAGI Ribosome-binding protein 1

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1				
2	Α	K100B4 CRAGI	Long-chain-fatty-acidCoA ligase 1	
3 4	A	K1QYM4_CRAGI	,	
5	A	K1P2G0 CRAGI		
6	A	K1QCT0_CRAGI	Sideroflexin	
7	A	K1QFG2_CRAGI	Telomere-associated protein RIF1	
8	A	<del>-</del>	•	
9		K1Q5J7_CRAGI	Uncharacterized protein	
10 11	A	K1QKA9_CRAGI	•	
12	A	K1P7Q6_CRAGI	·	
13	A	K1QYV5_CRAGI		
14	A	K1QG84_CRAGI	THO complex subunit 2	
15	Α	K1R7G0_CRAGI	•	
16	Α	K1QHX4_CRAGI	•	
17 18	Α	_	Transmembrane protein Tmp21	
19	Α	K1PKK7_CRAGI	AP-2 complex subunit mu-1	
20	Α	K1P9V5_CRAGI	General transcription factor IIF subunit 1	
21	Α	K1Q9V2_CRAGI	Antigen KI-67	
22	Α	K1PNU2_CRAGI	Histone-arginine methyltransferase CARM1	
23	Α	K1Q109_CRAGI	Neurexin-4	
24 25	Α	K1P9Q2_CRAGI	Signal peptidase complex subunit 3	
25 26	Α	K1QCN0_CRAGI	Signal recognition particle 9 kDa protein	
27	Α	K1Q7E4_CRAGI	Ubiquitin-conjugating enzyme E2 N	
28	Α	K1Q5G6_CRAGI	60 kDa heat shock protein, mitochondrial	
29	Α	K1RUW0_CRAGI	E3 SUMO-protein ligase RanBP2	
30	Α	K1RB91_CRAGI	Neutral alpha-glucosidase AB	
31 32	Α	K1QGF1_CRAGI	Splicing factor 3B subunit 2	
32 33	Α	K1Q525_CRAGI	Mechanosensory protein 2 (Fragment)	
34	Α	K1RDB3_CRAGI		
35	Α	K1QI28_CRAGI		
36	Α	K1R4J0_CRAGI	MAGUK p55 subfamily member 2	
37	Α	<del>-</del>	Afadin-and alpha-actinin-binding protein	
38 39	Α	_	Toll-like receptor 3	
40	Α	K1PZCO CRAGI	Structural maintenance of chromosomes protein	
41	A	K1PT69_CRAGI		
42	A	K1RE67 CRAGI	Methylated-DNAprotein-cysteine methyltransferase	
43	A	K1QCX5 CRAGI		
44	A	K1QBT8_CRAGI		
45 46	A	K1RFF1 CRAGI	Uncharacterized protein	
47		_		
48	A	K1RS40_CRAGI	•	
49	Α	K1R8V1_CRAGI	Puratrophin-1	
50				
51				
52 53				
54				
55				
56				
57				
58 50				
59 60				
50				

Data S2: Identified proteins by RNA pull down coupled with mass spectrometry with m6A or A-oligo, in nuclear or cytosolic protein extracts 4 Proteins identified in cytosolic extracts

5 Oligo	Accession	Description
6 m6A	K1QNA2_CRAGI	Vitellogenin-6
7 8 m6A	K1QVJ8_CRAGI	Piwi-like protein 1
9 m6A	K1QQ94_CRAGI	Uncharacterized protein
10 m6A	K1QHK9_CRAGI	Dynein heavy chain, cytoplasmic
<sup>11</sup> m6A	K1QQ68_CRAGI	Tubulin alpha chain
<sup>12</sup> m6A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
13 14 m6A	K1R473_CRAGI	Tubulin alpha chain
<sub>15</sub> m6A	K1QII6_CRAGI	Tubulin alpha chain
16 m6A	K1PNR3_CRAGI	Clathrin heavy chain
<sup>17</sup> m6A	K1R7V7_CRAGI	Tubulin beta chain
<sup>18</sup> m6A	K1PNI6_CRAGI	Heterogeneous nuclear ribonucleoprotein A/B
19 20 m6A	K1QMX5_CRAGI	Uncharacterized protein
21 m6A	K1QHI5_CRAGI	Pyruvate carboxylase, mitochondrial
22 m6A	K1PE00_CRAGI	Tubulin alpha chain
<sup>23</sup> m6A	K1R294_CRAGI	T-complex protein 1 subunit beta
<sup>24</sup> m6A 25	K1S4Q2_CRAGI	T-complex protein 1 subunit delta (Fragment)
26 m6A	K1PQP2_CRAGI	Nucleolin
<sub>27</sub> m6A	K1R466_CRAGI	T-complex protein 1 subunit gamma
28 m6A	K1PN21_CRAGI	Tubulin beta chain
<sup>29</sup> m6A	K1R164_CRAGI	Galectin-4
<sup>30</sup> m6A 31	K1S2N7_CRAGI	Innexin
32 m6A	K1R6Z7_CRAGI	ATP synthase subunit alpha
33 m6A	K1R5B4_CRAGI	Proteasome activator complex subunit 4
34 m6A	K1PVA1_CRAGI	Transitional endoplasmic reticulum ATPase
<sup>35</sup> m6A	K1QFW9_CRAGI	Uncharacterized protein
<sup>36</sup> m6A 37	K1R0S3_CRAGI	T-complex protein 1 subunit theta
38 m6A	K1QMA4_CRAGI	RRP5-like protein
39 m6A	K1R3U2_CRAGI	Uncharacterized protein
40 m6A	K1Q9W5_CRAGI	T-complex protein 1 subunit eta
41 m6A 42 m6A	K1QBK6_CRAGI	Splicing factor 3B subunit 1
43	K1R545_CRAGI	Pre-mRNA-processing-splicing factor 8 (Fragment)
44 m6A	K1RAJ1_CRAGI	T-complex protein 1 subunit alpha
45 m6A	K1RWS2_CRAGI	Transcriptional activator protein Pur-alpha
46 m6A 47 m6A	K1Q350_CRAGI	Glyceraldehyde-3-phosphate dehydrogenase
11071	K1RGT5_CRAGI	Metalloendopeptidase
49 MOA	K1PJ85_CRAGI	26S protease regulatory subunit 6A
<sub>50</sub> m6A	K1S6V7_CRAGI	Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform
51 m6A	K1S1S1_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 1
52 m6A	K1RZE2_CRAGI	Isocitrate dehydrogenase [NADP]
<sup>53</sup> m6A <sup>54</sup> m6A	K1PNQ5_CRAGI	Heat shock protein HSP 90-alpha 1
55 m6A	K1R866_CRAGI	Puromycin-sensitive aminopeptidase Stross 70 protoin, mitochondrial
<sub>56</sub> m6A <sub>57</sub> m6A	K1P9D0_CRAGI K1QXX7_CRAGI	Stress-70 protein, mitochondrial Myosin heavy chain, non-muscle (Fragment)
58 m6A	K1RG73_CRAGI	Acetyl-CoA carboxylase
<sup>59</sup> m6A	K1R420_CRAGI	Non-specific serine/threonine protein kinase
60 m6A	K1PXN5_CRAGI	T-complex protein 1 subunit zeta
m6A	K1QGS8_CRAGI	Elongation factor 1-alpha
m6A	K1RLC5_CRAGI	T-complex protein 1 subunit epsilon
m6A	K1R6Q7_CRAGI	DNA topoisomerase I
m6A	K1RW85_CRAGI	Adenosylhomocysteinase
m6A	K1QSX8_CRAGI	ATPase family AAA domain-containing protein 2B
m6A	K1R4Z3_CRAGI	Malate dehydrogenase, mitochondrial
m6A	K1PEY4_CRAGI	26S proteasome non-ATPase regulatory subunit 2
m6A	K1RI55_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 3
m6A	K1PK85_CRAGI	Cullin-associated NEDD8-dissociated protein 1
m6A	K1R9B6_CRAGI	H/ACA ribonucleoprotein complex subunit 4
m6A	K1R252_CRAGI	Putative methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial
		, , , , , , , , , , , , , , , , , , , ,

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```
K1RK12_CRAGI
                                 40S ribosomal protein S23
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3
                K1QVN9 CRAGI
                                 T-complex protein 1 subunit eta
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5
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                                 Arginine kinase
6
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                                 Actin 2
7
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                                 Actin
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8
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                                 26S protease regulatory subunit 6B
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9
                K1R401_CRAGI
                                 Spectrin alpha chain
10 m6A
11
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12
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                                 D-3-phosphoglycerate dehydrogenase (Fragment)
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                                 Polyadenylate-binding protein
14
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16 m6A
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18
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                                 Coatomer subunit alpha
19
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                                 Thimet oligopeptidase
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21 m6A
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22 m6A
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24
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26
27 m6A
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28 m6A
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31
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                K1PH76_CRAGI
                                 Y-box factor-like protein (Fragment)
32
33 m6A
                K1PW06_CRAGI
                                 Filamin-C
34 m6A
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38 m6A
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                                 Phosphoglycerate kinase
39 m6A
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41
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42
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44 m6A
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45 m6A
                K1R1M7_CRAGI
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47
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57 m6A
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58 m6A
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                K1PCS4_CRAGI
59
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60
                                 Methylcrotonoyl-CoA carboxylase subunit alpha, mitochondrial
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                K1R2V1_CRAGI
                                 Importin subunit beta-1
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                K1QB04_CRAGI
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                                 Coatomer subunit beta
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                                 26S proteasome non-ATPase regulatory subunit 6
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   m6A
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                                 Fatty acid synthase
   m6A
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                                 26S proteasome non-ATPase regulatory subunit 3
7
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8
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   m6A
9
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10 m6A
11
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                                 Transketolase-like protein 2
12
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13
                                 AP-2 complex subunit mu-1
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14
<sub>15</sub> m6A
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16 m6A
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17 m6A
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                                 Spectrin beta chain, brain 4
18
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                K1REG6_CRAGI
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19
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                A7M7T7_CRAGI
                                 Non-selenium glutathione peroxidase
20
21 m6A
                K1QHX2_CRAGI
                                 La-related protein 7
22 m6A
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                                 Multifunctional protein ADE2
23
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24
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                                 Propionyl-CoA carboxylase alpha chain, mitochondrial
25
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                                 Pancreatic lipase-related protein 2
26
27 m6A
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28 m6A
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29
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30
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                                 Malate dehydrogenase (Fragment)
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31
                K1QF01_CRAGI
   m6A
                                 40S ribosomal protein S4
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33 m6A
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                                 Heat shock protein 75 kDa, mitochondrial (Fragment)
34 m6A
                                 Uncharacterized protein
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35 m6A
                                 V-type proton ATPase catalytic subunit A
                K1Q9V3_CRAGI
36
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38 m6A
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40 m6A
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41
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43
44 m6A
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45 m6A
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46 m6A
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                K1QQL6_CRAGI
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48
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                                 Extracellular superoxide dismutase [Cu-Zn]
49
<sub>50</sub> m6A
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51 m6A
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                                 Dynein heavy chain 5, axonemal
52 m6A
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                                 Hypoxia up-regulated protein 1
53
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54
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                                 Exportin-7
55
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                                 Vigilin
57 m6A
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58 m6A
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                K1QX26_CRAGI
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                                 Dynamin-1-like protein
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                                 Cytoplasmic dynein 2 heavy chain 1
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                                 PAN2-PAN3 deadenylation complex catalytic subunit PAN2
                K1PF10_CRAGI
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m6A
                K1PNP4_CRAGI
                                 26S proteasome non-ATPase regulatory subunit 11
3
                                 Eukaryotic translation initiation factor 3 subunit A
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   m6A
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6
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7
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                                 26S proteasome non-ATPase regulatory subunit 1
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8
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                                 Long-chain-fatty-acid--CoA ligase 1
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9
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10 m6A
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                                 26S proteasome non-ATPase regulatory subunit 12
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16 m6A
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                                 40S ribosomal protein S16
17 m6A
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                                 Ubiquitin carboxyl-terminal hydrolase
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                                 Tudor domain-containing protein 1
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27 m6A
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                                 Citrate synthase
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                                 Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
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31
                                 U3 small nucleolar RNA-associated protein 6-like protein
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32
33 m6A
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                                 Cysteine synthase
34 m6A
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                                 Severin
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38 m6A
                K1Q5G9_CRAGI
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                                 Coatomer subunit gamma
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                                 40S ribosomal protein S14
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                                 Exportin-1
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                K1PPW8_CRAGI
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                K1Q273_CRAGI
                                 60S ribosomal protein L14
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                                 DNA polymerase
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                K1QPC6_CRAGI
                                 Nucleolar complex protein 2-like protein
   m6A
                K1QP17_CRAGI
                                 Caprin-1
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                                 Histone H4
                K1R2N0_CRAGI
   m6A
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                                  LSM14-like protein A
4
   m6A
5
   m6A
                K1QY71_CRAGI
                                  Histone H2B
6
   m6A
                K1QAB1_CRAGI
                                  AP-2 complex subunit alpha
7
                K1QAF3_CRAGI
                                  Alanine aminotransferase 2
   m6A
8
                K1QI97_CRAGI
                                  Adenylyl cyclase-associated protein
   m6A
9
                                  Constitutive coactivator of PPAR-gamma-like protein 1-like protein
10 m6A
                K1PD57_CRAGI
11
   m6A
                K1Q0L1_CRAGI
                                  60S ribosomal protein L23a
12
   m6A
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                                  Epidermal retinal dehydrogenase 2
13
   m6A
                K1R0Y9_CRAGI
                                  ADP, ATP carrier protein
14
<sub>15</sub> m6A
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                                  Calcyphosin-like protein
16 m6A
                K1PA54_CRAGI
                                  Replication factor C subunit 3
17 m6A
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                                  DNA helicase
18
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                                  40S ribosomal protein S12
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21 m6A
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                                  Proteasome-associated protein ECM29-like protein
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                                  40S ribosomal protein S26
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26
27 m6A
                                  Signal recognition particle subunit SRP72
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19 A 20 A	K1QET2_CRAGI	Coatomer subunit alpha
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22 A	K1R9B6_CRAGI	H/ACA ribonucleoprotein complex subunit 4
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l '`	KIIGIIS_CNAGI	. or, a dony late of a line of protein

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Aspartate aminotransferase

N-acetyl-D-glucosamine kinase

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K1Q4E1\_CRAGI

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K1R9T2\_CRAGI Eukaryotic translation initiation factor 3 subunit B K1PS27 CRAGI **DNA** helicase K1Q5G6\_CRAGI 60 kDa heat shock protein, mitochondrial K1QRM1\_CRAGI Nuclear pore protein K1QGC9\_CRAGI Acetyl-coenzyme A synthetase K1RLT4\_CRAGI Signal recognition particle subunit SRP68 K1PAR4\_CRAGI Unc-45-like protein A K1QVE8\_CRAGI Phosphoacetylglucosamine mutase K1Q4Z4\_CRAGI Bifunctional purine biosynthesis protein PURH K1P8W6\_CRAGI 60S ribosomal protein L4 K1QQK1\_CRAGI 26S proteasome non-ATPase regulatory subunit 12 K1RIT6\_CRAGI NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial K1R2L7\_CRAGI Glutaminyl-tRNA synthetase (Fragment) K1QRQ2\_CRAGI Glutamate dehydrogenase 1, mitochondrial K1RKZ5\_CRAGI DNA damage-binding protein 1 K1QC10\_CRAGI GTP-binding protein 1 K1PGZ0\_CRAGI Thyroid adenoma-associated protein K1QUK0\_CRAGI NEDD8-activating enzyme E1 catalytic subunit Programmed cell death protein 4 K1QQP1\_CRAGI K1PM50\_CRAGI 40S ribosomal protein S16 Poly [ADP-ribose] polymerase K1PJS7\_CRAGI K1QX37\_CRAGI **Enolase** K1QCA7\_CRAGI Valyl-tRNA synthetase K1Q811 CRAGI Alpha-centractin K1QRZ3\_CRAGI 40S ribosomal protein S13 K1QG70\_CRAGI Katanin p60 ATPase-containing subunit A1 60S ribosomal protein L6 K1QW36 CRAGI K1R8S7\_CRAGI Phospholipase A-2-activating protein K1P9N7\_CRAGI 14-3-3 protein zeta K1PG07\_CRAGI Lupus La-like protein K1QFZ8 CRAGI Ceramide kinase-like protein Alpha-aminoadipic semialdehyde synthase, mitochondrial K1Q1Q9\_CRAGI K1PX83\_CRAGI Dynein heavy chain 5, axonemal K1PCV0\_CRAGI Severin K1QP17\_CRAGI Caprin-1 K1PS13\_CRAGI Coatomer subunit beta (Fragment) K1Q273\_CRAGI 60S ribosomal protein L14 K1PBU0\_CRAGI L-fucose kinase K1QVV5\_CRAGI Periostin K1P112\_CRAGI ATP synthase subunit gamma, mitochondrial K1QKN4\_CRAGI Dynein heavy chain 6, axonemal K1P2B8\_CRAGI GDP-mannose 4,6 dehydratase K1QC11 CRAGI AP-1 complex subunit gamma K1QPD6\_CRAGI Ubiquitin conjugation factor E4 B K1QWZ0\_CRAGI Tetratricopeptide repeat protein 38 K1QKF8\_CRAGI S-(hydroxymethyl)glutathione dehydrogenase K1RD83\_CRAGI Serine hydroxymethyltransferase K1R1F0\_CRAGI ATP-dependent DNA helicase 2 subunit 1 Proteasome subunit alpha type K1QMD8\_CRAGI K1Q8S0\_CRAGI Nucleolar complex protein 3 homolog K1PI50\_CRAGI 40S ribosomal protein S26 K1R8T6\_CRAGI Cullin-1 K1P6F0\_CRAGI **HEAT** repeat-containing protein 2 Serine/threonine-protein phosphatase K1PXG6\_CRAGI K1QG65\_CRAGI rRNA 2'-O-methyltransferase fibrillarin K1R5W3\_CRAGI Uncharacterized protein K1QB60\_CRAGI Uncharacterized protein K1R5D5\_CRAGI U3 small nucleolar RNA-associated protein 6-like protein K1REJ2\_CRAGI Lon protease homolog, mitochondrial K1PLD4\_CRAGI Dynein heavy chain 2, axonemal

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                K1R969_CRAGI
                                  Uncharacterized protein
18
   Α
                K1R1E4_CRAGI
                                  Serine/threonine-protein kinase Chk2
19
20 A
                K1QVL1_CRAGI
                                  Serine/threonine-protein phosphatase 4 regulatory subunit 4
21 A
                K1QYD8_CRAGI
                                  Trans-1,2-dihydrobenzene-1,2-diol dehydrogenase
22 A
                K1Q927_CRAGI
                                  Neurofibromin
23 A
                K1QAU3_CRAGI
                                  WD repeat-containing protein 63
24
                K1Q8P7_CRAGI
                                  Aspartyl aminopeptidase
25
26 A
                K1QZ64_CRAGI
                                  Nuclear pore complex protein Nup98-Nup96
27 A
                                  Chromosome transmission fidelity protein 18-like protein (Fragment)
                K1PLR8_CRAGI
28 A
                K1P752_CRAGI
                                  UPF0195 protein FAM96B
29 A
                K1QAY3_CRAGI
                                  Dipeptidyl-peptidase 1 (Fragment)
30
                K1R669 CRAGI
                                  Uncharacterized protein
31
32 A
                K1PWS8_CRAGI
                                  Mitotic spindle assembly checkpoint protein MAD2A
33 A
                K1PK87_CRAGI
                                  Putative E3 ubiquitin-protein ligase TRIP12
                                  mRNA export factor
34 A
                K1QKU6 CRAGI
35 A
                K1QQV0_CRAGI
                                  Histone H1.2
36
                                  Zinc finger RNA-binding protein
                K1QR54_CRAGI
37
38 A
                K1PE13_CRAGI
                                  Uncharacterized protein
39 A
                K1QUW5 CRAGI
                                 U2 snRNP auxiliary factor large subunit
40 A
                K1PTH4_CRAGI
                                  ADP-ribosylation factor
41 A
                K1Q3C3_CRAGI
                                  Lambda-crystallin-like protein
42
   Α
                K1RE82_CRAGI
                                  Uncharacterized protein
43
44 A
                K1P486_CRAGI
                                  Heat shock 70 kDa protein 12A
45 A
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                                  Peptidylprolyl isomerase
46 A
                K1PEC8_CRAGI
                                  Actin-related protein 8
47
  Α
                K1RAR8_CRAGI
                                  Protein FAM49B
48
                K1QZD2_CRAGI
                                  Tudor domain-containing protein 7
49
50 A
                K1QM54_CRAGI
                                  Activator of 90 kDa heat shock protein ATPase-like protein 1
51 A
                K1Q904_CRAGI
                                  PAN2-PAN3 deadenylation complex subunit PAN3
52 A
                K1P6N8_CRAGI
                                  Ubiquitin carboxyl-terminal hydrolase 7
53 A
                K1RBM7 CRAGI
                                  Ubiquitin-conjugating enzyme E2 variant 1
54
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                                  Hsp90 co-chaperone Cdc37
55
56 A
                K1PQU8_CRAGI
                                  Sperm-associated antigen 6
57 A
                                  Protein SET
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58 A
                                  Glutathione S-transferase A
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59
                                  Heat shock 70 kDa protein 12B
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60
                K1QNW5_CRAGI
                                 MAK10-like protein
                K1QZ84_CRAGI
                                  Thioredoxin domain-containing protein 3-like protein
                K1QXH7_CRAGI
                                  DNA replication licensing factor mcm4-B
                K1Q1L9_CRAGI
                                  Interferon-induced protein 44-like protein
                K1RGD5_CRAGI
                                  F-box only protein 36
                                  DNA topoisomerase
                K1Q3B4_CRAGI
                K1P8Z1_CRAGI
                                  Uncharacterized protein
                K1PYA2_CRAGI
                                  Host cell factor
                                  U2 small nuclear ribonucleoprotein A
                K1PZR3_CRAGI
                K1QB69_CRAGI
                                  Uncharacterized protein
                K1PI78_CRAGI
                                  Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1
                K1RKK2_CRAGI
                                  Phosphatidylinositol-4-phosphate 5-kinase type-1 alpha
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Pa	ge '	
1 2 3 4 5 6 7 8 9 10 11 2 3 14 15 16 17 18 19 20 21 22 23 24 25 6 27 28 29 30 31 32 33 34 35 36 37 8 9 40 41 42	ge AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
29 30 31 32 33 34 35 36 37	A A A A	
39 40 41 42 43 44 45 46 47		
48 49 50 51 52 53 54		

K1QLS5_CRAGI	Uncharacterized protein
K1QFI3_CRAGI	Apoptosis-inducing factor 3
K1QKB1_CRAGI	Tryptophanyl-tRNA synthetase, cytoplasmic
K1REU2_CRAGI	WD repeat and HMG-box DNA-binding protein 1
K1QUK3_CRAGI	Putative ATP-dependent RNA helicase DDX41
K1QBT8_CRAGI	Uncharacterized protein
K1QVX4 CRAGI	Glycogen synthase kinase-3 beta
K1PF20 CRAGI	Gamma-tubulin complex component
K1RFG1_CRAGI	Lipoxygenase-like protein domain-containing protein 1
K1PCI8_CRAGI	Cullin-2
K1QS27_CRAGI	UBX domain-containing protein 6
K1RFF1_CRAGI	Uncharacterized protein
K1Q4N9_CRAGI	Uncharacterized protein
K1QJN8 CRAGI	AP-3 complex subunit beta
K1PXA0 CRAGI	Uncharacterized protein
K1QA13_CRAGI	Calcium-transporting ATPase
K1QXY4_CRAGI	Kinase
K1PBW4_CRAGI	Uncharacterized protein
K1PUFO CRAGI	G-protein coupled receptor moody
K1QMY9_CRAGI	Uncharacterized protein
K1QZ54 CRAGI	Coiled-coil domain-containing protein 39
K1QWU8_CRAGI	Uncharacterized protein
K1Q3L1_CRAGI	Kielin/chordin-like protein
K1PGR2_CRAGI	G patch domain-containing protein 1
K1RXP9_CRAGI	Ventricular zone-expressed PH domain-containing-like protein 1
K1PIB2_CRAGI	Uncharacterized protein
K1R4U3_CRAGI	Uncharacterized protein

Outsite         formal Display         Class         Option Spring         A Pol Bologytheir arcress         2,848         Bological process           clastert         6000000000         1 Marcrashikan protein transport         4,1576         30logical process           ckstert         600000000         1 Marcrashikan protein transport         4,564         30logical process           ckstert         60000000         1 Control of the Control of the Control of Section (Control of Section Control of Sectio		Data S3: Con	nplete list of GO t	terms of clustered genes of m6A interacting proteins (p-value<0,05)		
dataset   Co-0000686   intracellular protein transport   Co-000686   intracellular protein transport   Co-0006861   Co-0006861   Dispute no removal protein carbotic process   La Port   Biological process   Co-0006861   Co-00			-		log10 p-value	Class
Custer   C0000551		cluster1	GO:0006172	ADP biosynthetic process	-2,848	Biological process
Columbia		cluster1	GO:0006886	intracellular protein transport	-6,1176	Biological process
Column   C		cluster1	GO:0015031	protein transport	-1,6944	Biological process
clustert	)	cluster1	GO:0006511	ubiquitin-dependent protein catabolic process	-1,8071	Biological process
duster1   G000016192   westle-mediatolic process   -1,00%   Biological process   duster1   G000016192   westle-mediated transport   -3,117   Biological process   duster1   G0000421   Inductional initiation   -1,278   Biological process   duster1   G0000421   Inductional electron transport, ubiquinot to cyclorime c   -1,937   Biological process   G000017   Government   -1,00%   Government   -	l	cluster1				
Custern	2			·		• .
Cutsert	3					
Catastert   G00000512	† 5			·		• .
dustert	5			·		
dustert	7					
Cutsert	3					
duster1	) )					
dustert         G00030137         CoPII weside coat         1-16,994         Cellular component           dustert         G00003131         Catharism or proposed         Classified         Cellular component           dustert         G00003105         sycophism         2-,3551         Cellular component           dustert         G00005550         eukaryotic translation initiation factor 2 complex         2-,684         Cellular component           dustert         G00005550         eukaryotic translation initiation factor 2 complex         1-1,932         Cellular component           dustert         G00005550         mitochondrial respiratory chain complex III         1-1,932         Cellular component           dustert         G00005550         mitochondrial respiratory chain complex III         1-1,932         Cellular component           dustert         G00000372         gold membrane         1-1,247         Cellular component           dustert         G0000373         Tomore membrane         1-1,247         Cellular component           dustert         G0000373         Tomore membrane         1-1,247         Cellular component           dustert         G0000373         Tomore membrane         1-1,247         Cellular component           dustert         G00000373         Tomore membrane         <	ĺ					
cluster	2					•
Custern	3					·
cluster         GO0031105         sequinomplex         2,0349         Cellular component           cluster         GO00008550         eukarport branisation initiation factor 2 complex         1,0697         Cellular component           cluster         GO00005750         mitochondriar irrepiratory chain complex III         1,1282         Cellular component           cluster         GO0000139         Golg membrane         1,4767         Cellular component           cluster         GO0000548         branishor initiation factor activity         2,2766         Molecular function           cluster         GO0005488         Budding         1,66         Molecular function           cluster         GO0005855         protein transporter activity         2,7964         Molecular function           cluster         GO0008242         omega peptidase activity         2,1058         Molecular function           cluster         GO000836         Ran GTPase binding         1,1387         Molecular function           cluster         GO0005151         prophotorarderse activity         1,1387         Molecular function           cluster         GO0005161         prophotorarderse activity, phosphate group as acceptor         1,1387         Molecular function           cluster         GO0005176         phosphatorarderse activ	+					·
clusters	5					·
cluster1         60.0003556         cytoskeleton         -1,9328         Cellular component           cluster1         60.0000139         mitochondral respiratory chain complex III         -1,9328         Cellular component           cluster1         60.0000139         Golgi membrane         -1,4267         Cellular component           cluster1         60.0003472         glycine hydroxynethyltransferase activity         -2,554         Molecular function           cluster1         60.0005485         piroten transporter activity         -2,764         Molecular function           cluster1         60.0008255         piroten transporter activity         -2,764         Molecular function           cluster1         60.0008232         description of the composition of the co	7			·		•
cluster1   G0 0000759	3			·		
Cluster1   G0.0000139   Golgi membrane   -1,4267   Cellular component   Cluster1   G0.0004372   glycine hydroxymethyl transferase activity   -2,2564   Molecular function   Cluster1   G0.0004372   glycine hydroxymethyl transferase activity   -2,2764   Molecular function   Cluster1   G0.0005555   grotein transporter activity   -2,7764   Molecular function   Cluster1   G0.0008232   Lejocine FRAN Igase activity   -2,1763   Molecular function   Cluster1   G0.0008232   Cluster2   G0.0008233   Cluster3   G0.0008234   Cluster3   G0.0008235   Gardinary   -2,0153   Molecular function   G0.0003525   Gardinary   -2,0153   Molecular function   G0.0003525   Gardinary   -2,0154   Molecular function   G0.0003525   Gardinary   -2,0007   Molecular function   G0.0003525   Gardinary   -2,0007   Molecular function   Guster1   G0.0003525   Mydrolase activity, acting on carbon-introgen (but not peptide) bonds, in linear amidines   -1,957   Molecular function   Guster1   G0.0003131   Mydrolase activity, acting on carbon-introgen (but not peptide) bonds, in linear amidines   -1,957   Molecular function   Guster1   G0.0003176   phosphotransferase activity, prosphotransferase activity   -2,005   Molecular function   Guster1   G0.0003177   phosphotransferase activity   -2,200   Molecular function   Guster1   G0.0003177   adenylate kinase activity   -2,200   Molecular function   Guster1   G0.000317   Guster2   G0.000317   Guster2   G0.000317   Guster3   G0.000318   Guster3   G0.000318   Guster3   G0.000318   Guster3   G0.000318   Guster3   G0.000318   Guster3   G0.000318   Guster3   G0.000333   Guster3   G0.000333   Guster3   G0.000333   Guster3   G0.000333   Guster3   G	} ``			·		·
cluster1         60 0009373         translation initiation factor activity         -2,6564         Molecular function           cluster1         60 0009488         Binding         -1,66         Molecular function           cluster1         60 00095488         Binding         -2,7964         Molecular function           cluster1         60 00098432         levicen-RNA ligase activity         -2,7964         Molecular function           cluster1         60 00098432         levicen-RNA ligase activity         -2,7963         Molecular function           cluster1         60 00098356         Ran GFBase binding         -1,496         Molecular function           cluster1         60 00098356         Ran GFBase binding         -1,496         Molecular function           cluster1         60 0008131         hydrolase activity, acting on carbon-nitrogen (but not peptide) blonds, in linear amidines         -1,985         Molecular function           cluster1         60 0001213         hydrolase activity, acting on carbon-nitrogen (but not peptide) blonds, in linear amidines         -1,985         Molecular function           cluster1         60 000177         phosphota phosphotal binding         -1,487         Molecular function           cluster1         60 000176         phosphota phosphota phosphotal binding         -1,487         Molecular function	l					
Cluster1   G.0.0005488	2			•		
Custer1   G.0.0008565   protein transporter activity   2,7864   Molecular function   Custer1   G.0.0008422   decine-HRN ligase activity   2,1253   Molecular function   Custer1   G.0.0008422   decine-HRN ligase activity   2,0138   Molecular function   G.0.0008536   Ran GTPase brinding   1,4386   Molecular function   G.0.0008536   Molecular function   G.0.0008536   Molecular function   G.0.0008536   Molecular function   G.0.0008541   G.0.0008542   G.0.0008542   G.0.0008542   G.0.0008542   G.0.0008542   G.0.0008542   G.0.0008542	3	cluster1	GO:0004372	glycine hydroxymethyltransferase activity	-2,3716	Molecular function
Custer1   G.0.004823	<del>1</del>	cluster1	GO:0005488	binding	-1,66	Molecular function
duster1   G.0.008242   omega peptidase activity   -2,0158   Molecular function   duster1   G.0.0008536   Ran GTRase binding   -1,2365   Molecular function   duster1   G.0.0008525   GTP binding   -1,2855   Molecular function   duster1   G.0.00081813   hydrolase activity, acting on carbon-integer fuot not peptide) bonds, in linear amidinas   -1,9675   Molecular function   duster1   G.0.00061813   hydrolase activity, acting on carbon-integer fuot not peptide) bonds, in linear amidinas   -1,9675   Molecular function   duster1   G.0.0006176   phosphotransferase activity, phosphate group as acceptor   -2,0567   Molecular function   duster1   G.0.000617   ademyste kinase activity   -1,3869   Molecular function   duster1   G.0.000917   ademyste kinase activity   -1,387   Molecular function   duster1   G.0.000917   uncleobase containing compound kinase activity   -1,596   Molecular function   duster1   G.0.000943   protein domain specific proteinse activity   -1,596   Molecular function   duster1   G.0.000343   thiol-dependent ubliquitin-specific protease activity   -1,596   Molecular function   duster1   G.0.0003779   dust-dependent ubliquitin-specific protease activity   -1,596   Molecular function   duster1   G.0.0003779   dust-dependent protein domain specific process   -1,434   Molecular function   duster2   G.0.0006376   m8NA splice site selection   -2,2802   Biological process   duster2   G.0.0006361   ubiquitin-dependent protein catabolic process   -1,434   Biological process   duster2   G.0.0006367   transcription initiation from RNA polymerase liprometer   -1,3872   Biological process   duster2   G.0.0006367   transcription initiation from RNA polymerase liprometer   -1,872   Biological process   duster2   G.0.0006363   protein import into nucleus   G.0.0006365	5	cluster1	GO:0008565	protein transporter activity	-2,7964	Molecular function
cluster   G.0.008336   Ran GTPase binding   -1,936   Molecular function   cluster   G.0.0005376   Molecular function   GTP binding   -1,985   Molecular function   cluster   G.0.0016813   hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in linear amidines   -1,9675   Molecular function   Guster   G.0.0001676   phosphotransferase activity, bushate group as acceptor   -2,0567   Molecular function   Guster   G.0.0001674   phosphotransferase activity, bushate group as acceptor   -2,0567   Molecular function   Guster   G.0.000543   phospholipid binding   -1,2869   Molecular function   Guster   G.0.0001671   Gadwylate kinase activity   -2,2504   Molecular function   Guster   G.0.0019905   nucleobase containing compound kinase activity   -2,2504   Molecular function   Guster   G.0.0019905   nucleobase containing compound kinase activity   -1,9387   Molecular function   Guster   G.0.0019904   protein domain specific protease activity   -1,6596   Molecular function   Guster   G.0.0019904   protein domain specific protease activity   -1,6596   Molecular function   Guster   G.0.0003779   actin binding   -1,333   Molecular function   Guster   G.0.0003779   actin binding   -1,334   Molecular function   -1,334   Molecular function   G.0.0003779   actin binding   -1,334   Molecular function   -1,345   G.0.000616192   ubiquitin-dependent protein catabolic process   -1,956   Biological process   G.0.000616192   G.0.000616192   G.0.000616192   G.0.000616193   G.0.000616193   G.0.000616193   G.0.000616193   G.0.000616193   G.0.000616194	7	cluster1	GO:0004823	leucine-tRNA ligase activity	-2,1763	Molecular function
Custer1   G0:00055255	3	cluster1	GO:0008242	omega peptidase activity	-2,0158	Molecular function
cluster1 GO:00168131 hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in linear amidines 1.1,9675 Molecular function cluster1 GO:0016776 phosphotransferase activity, phosphate group as acceptor 2.0,0567 Molecular function cluster1 GO:0016776 phosphotransferase activity, phosphate group as acceptor 2.0,0567 Molecular function cluster1 GO:0005431 phosphotransferase activity, phosphate group as acceptor 2.0,0567 Molecular function cluster1 GO:00019041 phosphotransferase activity 2.2,204 Molecular function cluster1 GO:00191055 nucleobase-containing compound kinase activity 1.1,9387 Molecular function cluster1 GO:0019104 protein domain specific binding 1.1,425 Molecular function cluster1 GO:0003790 actin binding 1.1,339 Molecular function cluster1 GO:0003790 actin binding 1.1,339 Molecular function cluster1 GO:0003779 actin binding 1.1,339 Molecular function cluster1 GO:000376 mRRNA splice site selection 2.2,2802 Biological process cluster 2 GO:0006376 mRRNA splice site selection 2.2,2802 Biological process cluster 2 GO:000511 ubiquitin-dependent protein catabolic process 1.8,95 Biological process cluster 2 GO:0005163 proteolysis involved in cellular protein catabolic process 1.8,95 Biological process cluster 2 GO:0006511 ubiquitin-dependent protein catabolic process 1.8,95 Biological process cluster 2 GO:0006664 purine nucleotide biosynthetic process 1.9,1312 Biological process cluster 2 GO:0006665 protein infinition from RRNA polymerase II promoter 1.8,729 Biological process cluster 2 GO:0006687 transcription infinition from RNA polymerase II promoter 1.8,729 Biological process cluster 2 GO:0005637 transcription infinition from RNA polymerase II promoter 1.8,729 Biological process cluster 2 GO:0005685 Urb active regulation of transcription, DNA-templated 1.8,802 Biological process cluster 2 GO:0005684 chromosome complex, alpha-subunit complex 1.1,7608 Cellular component cluster 2 GO:0005683 Biological process protein domain process protein domain protein domain protein domain protein domain p	9					
cluster   GO.0002161 aminoacyl-tRNA editing activity   -1,487 Molecular function cluster   GO.00016776 phosphategrase activity, phosphate group as acceptor   -2,0567 Molecular function cluster   GO.0000543 phosphotransferase activity   -1,3689 Molecular function cluster   GO.0001677 adenylate kinase activity   -1,2594 Molecular function cluster   GO.00019205 nucleobase-containing compound kinase activity   -1,9387 Molecular function cluster   GO.0019904 protein domain specific binding   -1,4245 Molecular function cluster   GO.0001843 thiol-dependent ublquith-specific protease activity   -1,6596 Molecular function cluster   GO.0003779 actin binding   -1,33 Molecular function cluster   GO.0003779 actin binding   -1,33 Molecular function cluster   GO.0001876 mRNA splice site selection   -2,2802 Biological process cluster   GO.0001876   ubiquitin-dependent protein catabolic process   -1,9467 Biological process cluster   GO.00016192 vesicie-mediated transport   -1,9467 Biological process cluster   GO.000511  ubiquitin-dependent protein catabolic process   -1,895 Biological process cluster   GO.0006163 protein protein catabolic process   -1,946 Biological process cluster   GO.0006164  purine rulcefueld be biosynthetic process   -1,946 Biological process cluster   GO.0006606  protein import into nucleus   -1,6687 Biological process cluster   GO.0006606  protein import into nucleus   -1,8729 Biological process cluster   GO.0006606  protein import into nucleus   -1,8729 Biological process cluster   GO.0005839  positive regulation of transcription, DNA-templated   -1,8902 Biological process cluster   GO.0005685  Ul snRIVP   -2,0889 Cellular component cluster   GO.0005848  binding   -1,5670 Cellular component cluster   GO.00005839  proteasome core complex   -1,7608 Cellular component cluster   GO.00005848  binding   -5,6024 Molecular function cluster   GO.00005849  protein transcription protein transcription   -1,2594 Molecular function cluster   GO.00005841  small protein activating enzyme activity   -2,4472 Molecular fu	) I				·	
Cluster1   G0.0016776   phosphotransferase activity, phosphate group as acceptor   2,0567   Molecular function cluster1   G0.0005543   phospholipid binding   -1,3689   Molecular function cluster1   G0.00019205   nucleobase-containing compound kinase activity   -2,2504   Molecular function cluster1   G0.0019904   protein domain specific binding   -1,4245   Molecular function cluster1   G0.0019904   protein domain specific binding   -1,4245   Molecular function cluster1   G0.0003479   actin binding   -1,433   Molecular function cluster1   G0.000379   actin binding   -1,333   Molecular function cluster2   G0.0006376   mRNA splice site selection   -2,2802   Biological process cluster   G0.00016192   vesicie-mediated transport   -1,9467   Biological process   Cluster   G0.00051603   proteolysis involved in cellular protein catabolic process   -1,4344   Biological process   Cluster   G0.00051603   proteolysis involved in cellular protein catabolic process   -1,4444   Biological process   Cluster   G0.0006606   purise nucleotide biosynthetic process   -1,9132   Biological process   Cluster   G0.0006606   protein import into nucleus   -1,6667   Biological process   Cluster   G0.0006606   protein import into nucleus   -1,6667   Biological process   Cluster   G0.0006606   protein import into nucleus   -1,8729   Biological process   Cluster   G0.00054893   positive regulation of transcription, DNA-templated   -1,8002   Biological process   Cluster   G0.0005685   U1 snRNP   -1,9322   Biological process   Cluster   G0.0005685   U1 snRNP   -1,6669   Cellular component   Cluster   G0.0005683   proteasome core complex   -1,6669   Cellular component   Cluster   G0.0005839   proteasome core complex   -1,4444   Cellular component   Cluster   G0.00005839   proteasome core complex   -1,4444   Cellular component   Cluster   G0.00005839   proteasome core complex   -1,4444   Cellular component   Cluster   G0.00005839   proteasome core complex   -1,4444   Cellular component   Cluster   G0.00005851   Ran GTPase binding   -1,9507   Mol	2				·	
ic cluster   G0:0005543   phospholipid binding   1,1688   Molecular function cluster   G0:0004017   adenylate kinase activity   2,2504   Molecular function cluster   G0:0019205   nucleobase-containing compound kinase activity   1,19387   Molecular function cluster   G0:0019904   protein domain specific binding   1,4245   Molecular function cluster   G0:00004843   thiol-dependent ublquith-specific protease activity   1,6596   Molecular function cluster   G0:00003779   actin binding   1,33   Molecular function cluster   G0:00003779   actin binding   1,33   Molecular function cluster   G0:0000676   mRNA splice site selection   2,2802   Biological process   cluster   G0:000676   mRNA splice site selection   2,2802   Biological process   cluster   G0:0006511   ublquitin-dependent protein catabolic process   1,895   Biological process   cluster   G0:0005163   proteolysis involved in cellular protein catabolic process   1,895   Biological process   cluster   G0:0006164   purine nucleotide biosynthetic process   1,9132   Biological process   cluster   G0:0006606   protein import into nucleus   1,6687   Biological process   cluster   G0:00066067   transcription initiation from RNA polymerase II promoter   1,8729   Biological process   cluster   G0:00066067   transcription initiation from RNA polymerase II promoter   1,8729   Biological process   cluster   G0:0005685   U1 snRNP   2,0889   Cellular component   cluster   G0:0005694   chromosome organization   1,9322   Biological process   cluster   G0:0005694   chromosome organization   1,2693   Cellular component   cluster   G0:0000583   proteasome core complex   1,2693   Cellular component   cluster   G0:0000583   proteasome core complex   1,2694   Cellular component   cluster   G0:0000583   proteasome core complex   1,2694   Molecular function   cluster   G0:0000583   proteasome core complex   1,2694   Molecular function   cluster   G0:0000583   RR GTPase binding   3,3815   Molecular function   cluster   G0:0000584   dama protein activative   1,2695   Molecular function	3					
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cluster 3 GO:0008152 metabolic process -1,9382 Biological process				·		
		cluster 3	GO:0008152	metabolic process	-1,9382	Biological process

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	1
28 29 30 31	
38 39 40 41 42	
42 43 44 45 46	

cluster 3	GO:0015986	ATP synthesis coupled proton transport	-4,8627	Biological process
cluster 3	GO:0006096	glycolytic process	-1,4156	Biological process
cluster 3	GO:0051258	protein polymerization	-2,6757	Biological process
cluster 3	GO:0044262	cellular carbohydrate metabolic process	-2,0966	Biological process
cluster 3	GO:0006388	tRNA splicing, via endonucleolytic cleavage and ligation	-1,523	Biological process
cluster 3	GO:0006879	cellular iron ion homeostasis	-1,4857	<b>Biological process</b>
cluster 3	GO:0007017	microtubule-based process	-2,4915	Biological process
cluster 3	GO:0006412	translation	-2,0331	<b>Biological process</b>
cluster 3	GO:0006122	mitochondrial electron transport, ubiquinol to cytochrome c	-2,0662	<b>Biological process</b>
cluster 3	GO:0000276	mitochondrial proton-transporting ATP synthase complex, coupling factor F(o)	-4,1068	Cellular component
cluster 3	GO:0005750	mitochondrial respiratory chain complex III	-2,0662	Cellular component
cluster 3	GO:0045261	proton-transporting ATP synthase complex, catalytic core F(1)	-2,0025	Cellular component
cluster 3	GO:0005874	microtubule	-2,2282	Cellular component
cluster 3	GO:0005882	intermediate filament	-1,9067	Cellular component
cluster 3	GO:0043231	intracellular membrane-bounded organelle	-2,1492	Cellular component
cluster 3	GO:0005852	eukaryotic translation initiation factor 3 complex	-1,6821	Cellular component
cluster 3	GO:0005737	cytoplasm	-1,9776	Cellular component
cluster 3	GO:0005840	ribosome	-2,0503	Cellular component
cluster 3	GO:0043234	protein complex	-2,6757	Cellular component
cluster 3	GO:0004739	pyruvate dehydrogenase (acetyl-transferring) activity	-2,8179	Molecular function
cluster 3	GO:0016624	oxidoreductase activity, acting on the aldehyde or oxo group of donors, disulfide as acceptor	-2,0554	Molecular function
cluster 3	GO:0005200	structural constituent of cytoskeleton	-2,3865	Molecular function
cluster 3	GO:0005525	GTP binding	-1,9304	Molecular function
cluster 3	GO:0015078	hydrogen ion transmembrane transporter activity	-3,0193	Molecular function
cluster 3	GO:0046961	proton-transporting ATPase activity, rotational mechanism	-1,6263	Molecular function
cluster 3	GO:0046933	proton-transporting ATP synthase activity, rotational mechanism	-1,7326	Molecular function
cluster 3	GO:0004775	succinate-CoA ligase (ADP-forming) activity	-2,3995	Molecular function
cluster 3	GO:0046912	transferase activity, transferring acyl groups, acyl groups converted into alkyl on transfer	-2,3982	Molecular function
cluster 3	GO:0016874	ligase activity	-1,4798	Molecular function
cluster 3	GO:0048037	cofactor binding	-1,6628	Molecular function
cluster 3	GO:0008199	ferric iron binding	-1,4607	Molecular function
cluster 3	GO:0005544	calcium-dependent phospholipid binding	-1,6049	Molecular function
cluster 3	GO:0003878	ATP citrate synthase activity	-2,3995	Molecular function
cluster 3	GO:0003735	structural constituent of ribosome	-1,9881	Molecular function

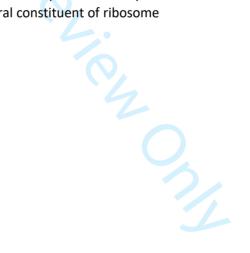


Table S1: Transitions used for each compound. A: first transition, B: second transition

Nucleoside	Retention time (min)	MRM precursor	MRM product (m/z)		Collision Energy (V)	
		(m/z)	Α	В	A	В
Α	3.07	268.0	135.9	119.0	-30	-12
m <sup>6</sup> A	2.12	282.0	150.1	123.1	-17	-46



<u>Table S2</u>: Correspondence between development stages in our study, and the GigaTON database.

Development stages : This Study	Development stages : GigaTON [53]		
Oocytes	E (Eggs)		
	TC (Two Cell embryos)		
2/8 Cells	FC (Four Cell embryos)		
	EM (Early Morula)		
Morula	M (Morula)		
Blastula	B (Blastula)		
Biastala	RM (Rotary Movement)		
	FS (Free Swimming)		
Gastrula	EG (Early Gastrula)		
	G (Gastrula)		
	T (Trochophore) 1		
	T2		
	T3		
Trochophore	T4		
	T5		
	ED (Early D larvae) 1		
	ED2		
	D (D larvae)1		
D larvae	D2		
	D3		
	D4		
	D5		
Spat	S (Spat)		
Juvenile	J (Juvenile)		