

A functional m 6 A-RNA methylation pathway in the oyster Crassostrea gigas assumes epitranscriptomic regulation of lophotrochozoan development

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A functional m⁶A-RNA methylation pathway in the oyster Crassostrea gigas assumes epitranscriptomic regulation of lophotrochozoan development

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Running title

m⁶A-RNA methylation pathway in oyster development

Abbreviations

*N*⁶-methyladenosine (m⁶A), 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 m⁶A-interacting protein (Cg-m⁶A-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

N⁶-methyladenosine (m⁶A) is a prevalent epitranscriptomic mark in eukaryotic RNA, with crucial roles for mammalian and ecdysozoan development. Indeed, m⁶A-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 m⁶A-RNA pathway remains unknown in more distant animals, questioning the evolution and significance of the epitranscriptomic regulation. Therefore, we investigated the m⁶A-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 m⁶A-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 m⁶A-machinery. The expression levels of the identified putative m⁶A 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 m⁶A-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*⁶-methyladenosine (m⁶A) is the prevalent chemical RNA modification in all eukaryotic coding and non-coding RNAs [1]. Messenger RNAs are the most heavily m⁶A methylated RNAs, with m⁶A 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*⁶-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 m⁶A 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 m⁶A 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 6th nitrogen of RNA adenosines is catalysed by m⁶A 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 m⁶A-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 m⁶A readers involved in m⁶A-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 m⁶A-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 cap-

independent translation [5].

The m⁶A 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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A 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 m⁶A pathway in *C. gigas* and its significance in oyster early development.

To investigate this, we measured m⁶A 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 m⁶A-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 m⁶A-RNA oligonucleotide coupled to liquid chromatography and mass spectrometry (LC-MS/MS) to characterize potential oyster m⁶A-binding proteins. To our knowledge, this study is the first report unravelling epitranscriptomic mechanisms outside vertebrate and ecdyzosoan animal models.

Results:

m⁶A is present in oyster RNA, differentially affects distinct RNA populations and displays variations during embryonic life.

Mass spectrometry measurements revealed that m⁶A is present in oyster RNA, with global m⁶A/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 m⁶A during oyster development and that these variations display distinct profiles suggesting specific methylation patterns between RNA populations. Indeed, N⁶A-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, m⁶A levels in polyA+ RNA are hardly detected in early stages but display a peak in the gastrula and trochophore stages (Figure 1C).

m⁶A machinery is conserved at the molecular level in the oyster.

In silico analyses led to the identification of oyster sequences encoding putative orthologues of m⁶A writers, erasers and readers that are present in the human and/or in the human and the fruit fly.

All the eight m⁶A-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 m⁶A-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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A-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 m⁶A-RNA machinery in the oyster. The complete list of the identified genes encoding the conserved m⁶A machinery actors and their isoforms, as well as the related information is given in the supplementary data (Data S1).

Oyster putative m⁶A actors display expression level variations across development.

RNAseq data analyses showed that all the oyster m⁶A-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 m⁶A 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 m⁶A-RNA interacting proteins bind m⁶A RNA in vitro.

To determine whether oyster proteins can bind m⁶A-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 m⁶A-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 m⁶A-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 m⁶A-RNA, and suggest an important compartmentalization of m⁶A-related processes. Among the identified proteins in this assay, four of the putative oyster m⁶A readers are found, YTHDC1, hnRNPA2B1, IGF2BP and eIF3. In the nuclear extracts YTHDC1 is uncovered as

m⁶A-specific whereas hnRNPA2B1 and IGF2BP were present complexed with both the m⁶A-and A-oligos. In the cytoplasmic extracts, YTHDC1 and eIF3a are m⁶A-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 m⁶A-RNA and that the putative m⁶A reader orthologues in the oyster are conserved at the protein level and are able to interact with m⁶A-RNA.

The m⁶A-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 m⁶A-interacting protein (Cg-m⁶A-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-m⁶A-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 m⁶A-RNA is present and variable during the embryo-larval life of the oyster, and that *C. gigas* exhibits putative conserved and functional m⁶A-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.

m⁶A-RNA levels vary across oyster development.

Using mass spectrometry and immunological measurements, we showed that oyster RNA is m⁶A-methylated. The global proportion of N⁶-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 m⁶A-RNA amounts between taxa, in contrast to DNA methylation [46], may indicate conserved biological significance of epitranscriptomic processes between groups. The amount of m⁶A 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 m⁶A decrease in total RNA during cleavage, i.e.

before the transcription of the zygotic genome starts, reflects a degradation of maternal m⁶A-RNAs or their demethylation. However, all RNA populations do not exhibit the same pattern, indeed polyA+ RNAs are m⁶A 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 m⁶A-RNA levels are variable and affecting distinct RNA populations across embryonic stages strongly favours an important biological significance of m⁶A-RNA in oyster development. We hypothesize that oyster maternal messenger RNAs are poorly polyadenylated, and that m⁶A, 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 m⁶A RNA after cleavage could therefore be the result of the methylation of the increasingly transcribed RNAs from the blastula stage, including polyadenylated mRNAs.

The m⁶A-RNA machinery is conserved in the oyster and regulated during development. The important regulation of m⁶A levels during oyster development assumes the presence of a related protein machinery. We identified *in silico* cDNA sequences encoding conserved putatively functional orthologues of m⁶A-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 m⁶A

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 m⁶A-RNA readers are also present at the molecular level in the oyster and are putatively able to bind m⁶A 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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A levels observed at the same time. The correlation between the increasing METTL3 expression and m⁶A-RNA levels after cleavage strongly favours the conservation of the methyltransferase activity of the oyster MT-A70 domain. Interpreting the regulation of the m⁶A 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 m⁶A-RNA erasure during oyster development, consistent with the normal embryonic phenotype of ALKBH5 knockdown mice [16]. Overall, the m⁶A 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 m⁶A 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 m⁶A-RNA targets [27], thereby possibly acting in oyster MZT, bringing new perspectives into this process which remains poorly understood in lophotrochozoans. In mammals m⁶A 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 m⁶A peak, suggesting similar implications.

Putative oyster m⁶A readers actually bind m⁶A-RNA in vitro.

To better approach the developmental processes involving m⁶A in the oyster, we characterized the proteins that can interact with m⁶A-RNA using a methylated-RNA-pulldown / mass spectrometry assay. We identified 162 proteins able to specifically bind the m⁶A-RNA oligo in embryonic cell extracts, demonstrating the actual presence of genuine m⁶A-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 m⁶A 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 m⁶A via a limited number of 'scaffold' m⁶A readers. Such authentic readers that only bind the m⁶A-RNA oligo in our assay likely include YTHDC1 and elF3a, which have been demonstrated to directly bind m⁶A in other species, demonstrating the conservation of the m⁶A-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 m⁶A-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 m⁶A-mediated translation processes, such as cap-independent translation [5].

Possible functions of m⁶A-RNA in oyster development.

We investigated the expression level and the functional annotation of the 162 genes encoding the m⁶A-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 m⁶A in oyster development. First, during cleavage the decrease of m⁶A-RNA, the weak expression of methyltransferase complex genes, the maximum of YTHDF gene expression and the expression of *Cg*-m⁶A-BPs

related to the initiation of the translation strongly suggest the implication of m⁶A in MZT in C. gigas. Second, the increasing m⁶A 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 m⁶A implication in gastrulation. Finally, the highest m⁶A 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-m⁶A-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 m⁶A in development from the indirect and incomplete functional annotation of the oyster genome is only limited. Characterization of the precise targets of m⁶A and how their individual methylation is regulated across development, for example using high throughput sequencing of precipitated m⁶A-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 m⁶A-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 m⁶A and the accumulation of RNA in oocytes, we are at present investigating our hypothesis that m⁶A 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 m⁶A-RNA erasers could be related to a sub-functionalization of the DMAD [41] and NMAD-1 [42] N⁶-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 m⁶A 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 m⁶A levels are variable across oyster development and that m⁶A differentially affects distinct RNA populations. Expression levels of the related enzymatic machinery is consistent with the observed m⁶A level variations. We demonstrate the m⁶A binding capacity and specificity of putative oyster m⁶A 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 m⁶A 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 m⁶A-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/10⁶ 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).

m⁶A 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.

• m⁶A quantification:

The apparatus was composed of a NexeraX² 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 m⁶A (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 m⁶A. For both nucleosides, a quadratic regression with 1/C weighting resulted in standard curves with R²>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.

m⁶A/A ratios were calculated for each single sample using the determined concentrations.

Final results are the average of three technical replicates.

m⁶A quantification by immunoblotting:

Immunological quantification of m⁶A 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-m⁶A 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 m⁶A 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 m⁶A 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 m⁶A 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 m⁶A-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-m⁶A: 5'Biotin-AGAAAAGACAACCAACGAGRR-m⁶A-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-m⁶A 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 m⁶A-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 m⁶A-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.

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Figure legends

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, 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 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).

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.

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.

977	Supporting information:
978	Data S1: Complete list of in silico identified putative m ⁶ A 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 ⁶ A or
981	A-oligo, in nuclear or cytosolic protein extracts
982	Data S3: Complete list of GO terms of clustered genes of m ⁶ 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 m⁶A-RNA methylation pathway in the oyster Crassostrea gigas
- 2 assumes epitranscriptomic regulation of lophotrochozoan development
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Running title

m⁶A-RNA methylation pathway in oyster development

Abbreviations

N°-methyladenosine (m°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°A-interacting protein (Cg-m°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

N⁶-methyladenosine (m⁶A) is a prevalent epitranscriptomic mark in eukaryotic RNA, with crucial roles for mammalian and ecdysozoan development. Indeed, m⁶A-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 m⁶A-RNA pathway remains unknown in more distant animals, questioning the evolution and significance of the epitranscriptomic regulation. Therefore, we investigated the m⁶A-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 m⁶A-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 m⁶A-machinery. The expression levels of the identified putative m⁶A 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 m⁶A-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*⁶-methyladenosine (m⁶A) is the prevalent chemical RNA modification in all eukaryotic coding and non-coding RNAs [1]. Messenger RNAs are the most heavily m⁶A methylated RNAs, with m⁶A 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*⁶-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 m⁶A 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 m⁶A 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 6th nitrogen of RNA adenosines is catalysed by m⁶A 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 m⁶A-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 m⁶A readers involved in m⁶A-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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A 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 m⁶A pathway in *C. gigas* and its significance in oyster early development.

To investigate this, we measured m⁶A 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 m⁶A-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 m⁶A-RNA oligonucleotide coupled to liquid chromatography and mass spectrometry (LC-MS/MS) to characterize potential oyster m⁶A-binding proteins. To our knowledge, this study is the first report unravelling epitranscriptomic mechanisms outside

144 Results:

vertebrate and ecdyzosoan animal models.

displays variations during embryonic life.

Mass spectrometry measurements revealed that m⁶A is present in oyster RNA, with global m⁶A/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 m⁶A during oyster development and that these variations display distinct profiles

m⁶A is present in oyster RNA, differentially affects distinct RNA populations and

suggesting specific methylation patterns between RNA populations. Indeed, N^6 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, m⁶A levels in polyA+ RNA are hardly detected in early stages but display a peak in the gastrula and trochophore stages (Figure 1C).

In silico analyses led to the identification of oyster sequences encoding putative orthologues

m⁶A machinery is conserved at the molecular level in the oyster.

of m⁶A writers, erasers and readers that are present in the human and/or in the human and the fruit fly. All the eight m⁶A-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 m⁶A-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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A-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 m⁶A-RNA machinery in the oyster. The complete list of the identified genes encoding the conserved m⁶A machinery actors and their isoforms, as well as the related information is given in the supplementary data (Data

S1).

Oyster putative m⁶A actors display expression level variations across development.

RNAseq data analyses showed that all the oyster m⁶A-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 m⁶A 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 m⁶A-RNA interacting proteins bind m⁶A RNA *in vitro*.

To determine whether oyster proteins can bind m⁶A-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 m⁶A-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 m⁶A-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 m⁶A-RNA, and suggest an important compartmentalization of m⁶A-related processes. Among the identified proteins in this assay, four of the putative oyster m⁶A readers are found, YTHDC1, hnRNPA2B1, IGF2BP and eIF3. In the nuclear extracts YTHDC1 is uncovered as

m⁶A-specific whereas hnRNPA2B1 and IGF2BP were present complexed with both the m⁶A-and A-oligos. In the cytoplasmic extracts, YTHDC1 and eIF3a are m⁶A-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 m⁶A-RNA and that the putative m⁶A reader orthologues in the oyster are conserved at the protein level and are able to interact with m⁶A-RNA.

The m⁶A-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 m⁶A-interacting protein (Cg-m⁶A-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-m⁶A-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 m⁶A-RNA is present and variable during the embryo-larval life of the oyster, and that *C. gigas* exhibits putative conserved and functional m⁶A-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.

m⁶A-RNA levels vary across oyster development.

Using mass spectrometry and immunological measurements, we showed that oyster RNA is m⁶A-methylated. The global proportion of N⁶-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 m⁶A-RNA amounts between taxa, in contrast to DNA methylation [46], may indicate conserved biological significance of epitranscriptomic processes between groups. The amount of m⁶A 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 m⁶A decrease in total RNA during cleavage, i.e.

before the transcription of the zygotic genome starts, reflects a degradation of maternal m⁶A-RNAs or their demethylation. However, all RNA populations do not exhibit the same pattern, indeed polyA+ RNAs are m⁶A 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 m⁶A-RNA levels are variable and affecting distinct RNA populations across embryonic stages strongly favours an important biological significance of m⁶A-RNA in oyster development. We hypothesize that oyster maternal messenger RNAs are poorly polyadenylated, and that m⁶A, 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 m⁶A RNA after cleavage could therefore be the result of the methylation of the increasingly transcribed RNAs from the blastula stage, including polyadenylated mRNAs.

The m⁶A-RNA machinery is conserved in the oyster and regulated during development.

The important regulation of m⁶A levels during oyster development assumes the presence of a related protein machinery. We identified *in silico* cDNA sequences encoding conserved putatively functional orthologues of m⁶A-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 m⁶A

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 m⁶A-RNA readers are also present at the molecular level in the oyster and are putatively able to bind m⁶A 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 m⁶A-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 m⁶A 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 m⁶A-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 m⁶A levels observed at the same time. The correlation between the increasing METTL3 expression and m⁶A-RNA levels after cleavage strongly favours the conservation of the methyltransferase activity of the oyster MT-A70 domain. Interpreting the regulation of the m⁶A 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 m⁶A-RNA erasure during oyster development, consistent with the normal embryonic phenotype of ALKBH5 knockdown mice [16]. Overall, the m⁶A 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 m⁶A 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 m⁶A-RNA targets [27], thereby possibly acting in oyster MZT, bringing new perspectives into this process which remains poorly understood in lophotrochozoans. In mammals m⁶A 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 m⁶A peak, suggesting similar implications.

Putative oyster m⁶A readers actually bind m⁶A-RNA in vitro.

To better approach the developmental processes involving m⁶A in the oyster, we characterized the proteins that can interact with m⁶A-RNA using a methylated-RNA-pulldown / mass spectrometry assay. We identified 162 proteins able to specifically bind the m⁶A-RNA oligo in embryonic cell extracts, demonstrating the actual presence of genuine m⁶A-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 m⁶A 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 m⁶A via a limited number of 'scaffold' m⁶A readers. Such authentic readers that only bind the m⁶A-RNA oligo in our assay likely include YTHDC1 and elF3a, which have been demonstrated to directly bind m⁶A in other species, demonstrating the conservation of the m⁶A-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 m⁶A-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 m⁶A-mediated translation processes, such as cap-independent translation [5].

Possible functions of m⁶A-RNA in oyster development.

We investigated the expression level and the functional annotation of the 162 genes encoding the m⁶A-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 m⁶A in oyster development. First, during cleavage the decrease of m⁶A-RNA, the weak expression of methyltransferase complex genes, the maximum of YTHDF gene expression and the expression of *Cg*-m⁶A-BPs

related to the initiation of the translation strongly suggest the implication of m⁶A in MZT in C. gigas. Second, the increasing m⁶A 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 m⁶A implication in gastrulation. Finally, the highest m⁶A 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-m⁶A-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 m⁶A in development from the indirect and incomplete functional annotation of the oyster genome is only limited. Characterization of the precise targets of m⁶A and how their individual methylation is regulated across development, for example using high throughput sequencing of precipitated m⁶A-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 m⁶A-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 m⁶A and the accumulation of RNA in oocytes, we are at present investigating our hypothesis that m⁶A 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 m⁶A-RNA erasers could be related to a sub-functionalization of the DMAD [41] and NMAD-1 [42] N⁶-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 m⁶A 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 m⁶A levels are variable across oyster development and that m⁶A differentially affects distinct RNA populations. Expression levels of the related enzymatic machinery is consistent with the observed m⁶A level variations. We demonstrate the m⁶A binding capacity and specificity of putative oyster m⁶A 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 m⁶A 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 m⁶A-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/10⁶ 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).

m⁶A quantification by LC-MS/MS:

RNA hydrolysis

To generate nucleosides for quantification against standard curves, 5 μ 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/ μ L, Promega, Madison, WI, USA) in Nuclease S1 buffer (Promega) in a final reaction volume of 25 μ 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.

• m⁶A quantification:

The apparatus was composed of a NexeraX² 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 m⁶A (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 m⁶A. For both nucleosides, a quadratic regression with 1/C weighting resulted in standard curves with R²>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.

m⁶A/A ratios were calculated for each single sample using the determined concentrations.

Final results are the average of three technical replicates.

m⁶A quantification by immunoblotting:

Immunological quantification of m⁶A 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-m⁶A 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 m⁶A 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 m⁶A 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 m⁶A 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 m⁶A-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-m⁶A: 5'Biotin-AGAAAAGACAACCAACGAGRR-m⁶A-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-m⁶A 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 m⁶A-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 m⁶A-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.

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Figure legends

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, 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 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).

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.

<u>Figure 4: Characterization of m⁶A-RNA binding proteins in oyster development.</u>

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.

Supporting information:

- <u>Data S1</u>: Complete list of *in silico* identified putative m⁶A machinery proteins and their respective BLAST results
- 979 <u>Data S2</u>: Identified proteins by RNA pull down coupled with mass spectrometry with m⁶A or
- 980 A-oligo, in nuclear or cytosolic protein extracts

Data S3: Complete list of GO terms of clustered genes of m⁶A interacting proteins (p value<0,05)
 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

985 GigaTON database.



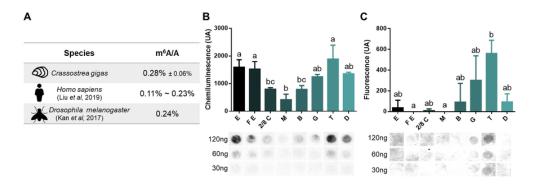


Figure 1: m6A levels across oyster development.

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).

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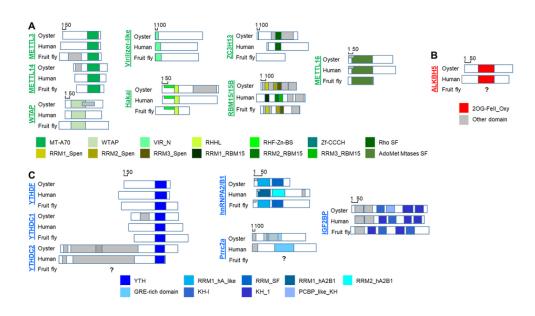


Figure 2: The putative conserved m6A machinery in Crassostrea gigas.

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).

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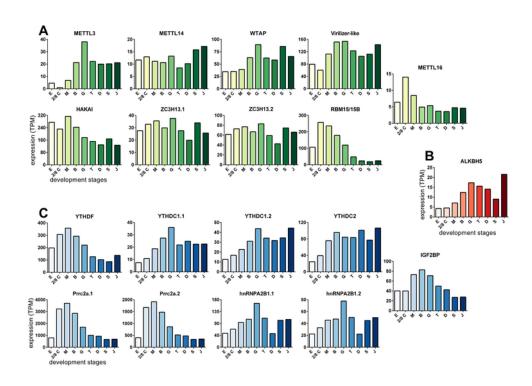


Figure 3: Gene expression of the putative m6A machinery throughout oyster development Expression levels of writers (A), eraser (B) and readers (C) identified by in silico analysis at each development stage were inferred from the GigaTON database. Expression levels are given in Transcripts Per kilobases 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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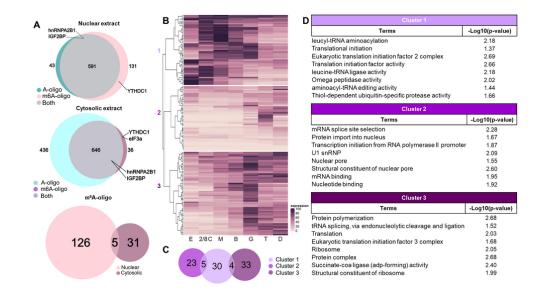


Figure 4: Characterization of m6A-RNA binding proteins in oyster development.

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			
Crassostrea gigas	GIGATON	CHOYP_PHUM_PHUM423190.1.1	554	MT-A70			
Crassostrea gigas	NCBI	gi 762092209 (XP_011428532.1)	555	MT-A70			
		METT	<u>L14</u>				
Homo sapiens	NCBI	gi 24308265 (NP_066012.1)	456	MT-A70			
Drosophila melanogaster (CG7818)	NCBI	gi 19920926 (NP_609205.1)	397	MT-A70			
	GIGATON -	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>AP</u>	プ カル			
		gi 395455090 (NP_001257460.1)	396	WTAP			
Homo sapiens	NCBI	gi 23199974 (NP_690596.1)	151	WTAP			
		gi 395455092 (NP_001257461.1)	170	WTAP			
Drosonhila malanogastor (EL (2)D)	NCBI -	gi 24653459 (NP_523732.2)	536	WTAP			
Drosophila melanogaster (FL(2)D)	NOBI	gi 24653461 (NP_725327.1)	412	WTAP			
		CHOYP_FL2D.1.1	406	WTAP IncA			
Crassostroa gigas	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 (viniizer-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

	NCDI	gi 209180481 (NP_079090.2)	491	RHF-Zn-BS RHHL
Homo sapiens	NCBI	gi 546230945 (NP_001271220.1)	490	RHF-Zn-BS RHHL
		gi 19921556 (NP_609993.1)	302	RHF-Zn-BS RHHL
Drosophila melanogaster	NCBI	gi 24585301 (NP_724217.1)	311	RHF-Zn-BS RHHL
Diosophila melanogastel		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
	INCDI	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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		gi 116008442 (NP_055885.3)	1564	Zf-CCCH Rho SF
		gi 24643154 (NP_573339.1)	1150	
Drosophila melanogaster (CG7358)	NCBI	gi 665392303 (NP_001285418.1)	1139	
		gi 665392305 (NP_001285419.1)	842	
	GIGATON	CHOYP_BRAFLDRAFT_120702.1.1	1631	Zf-CCCH Rho SF dnaA super family PTZ00121
	GIGATON	CHOYP_LOC100568158.1.1	1611	Zf-CCCH Rho SF dnaA super family PTZ00121
Crassostroa gigas		gi 762096734 (XP_011430912.1)	1400	Rho SF dnaA super family PTZ00121
Crassostrea gigas	NCBI -	gi 762096736 (XP_011430913.1)	1400	Rho SF dnaA super family PTZ00121
		gi 762096738 (XP_011430914.1)	1380	Rho SF PHA03307 PTZ00121
		gi 762096740 (XP_011430915.1)	1329	Rho SF PTZ00121

RBM15/15B

		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	
		gi 24586450 (NP_724633)	793	RRM1_Spen RRM2_Spen RRM SPOC	
Drosophila melanogaster (SPENITO/NITO)	NCBI	gi 19921778 (NP_610339)	793	RRM1_Spen RRM2_Spen RRM SPOC	
		gi 665399388 (NP_001286174)	793	RRM1_Spen RRM2_Spen RRM SPOC	
Crannostron gigan	GIGATON	CHOYP_LOC663518.1.1	717	RRM1_Spen RRM2_Spen RRM SPOC PTZ00449 SF	
Crassostrea gigas NCBI	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 gigas	NCBI	gi 762141911 (XP_011454156.1)	538	AdoMet Mtases SF S-adenosylmethionine binding site				
	NODI	gi 762141913 (XP_011454157.1)	527	AdoMet Mtases SF S-adenosylmethionine binding site				
		ALKBI	<u> 15</u>					
Homo sapiens	NCBI	gi 148539642 (NP_060228.3)	394	2OG-FeII_Oxy				
Drosophila melanogaster								
Crossostros gigos	GIGATON	CHOYP_BRAFLDRAFT_126925.1.1	403	2OG-FeII_Oxy				
Crassostrea gigas	NCBI	gi 762097205 (XP_011431161.1)	374	2OG-FeII_Oxy				
	YTHDC1							
		gi 72534750 (NP_001026902.1)	727	YTH				
Homo sapiens	NCBI	gi 94536805 (NP_588611.2)	709	YTH				
		gi 1061213987 (NP_001317627.1)	735	YTH				
Drosophila melanogaster (YT521)	NCBI	gi 24656811 (NP_647811.2)	721	YTH				
Diosophila melanogaster (11321)	NCBI	gi 24656816 (NP_728876.1)	710	YTH				
	GIGATON	CHOYP_YTDC1.2.2	636	YTH CDC27				
Crassostrea gigas	GIGATON	CHOYP_LOC586835.1.1	545	YTH CDC27				
	NCBI	gi 762070401 (XP_011447601.1)	636	YTH CDC27				
		YTHDO	<u>C2</u>					
		gi 269847874 (NP_073739.3)	1430	YTH HrpA R3H_DEXH_helicase DEXHc_YTHDC2 OB_NTP_bind				
Homo sapiens	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 melanogaster								
Crassostrea gigas	GIGATON	CHOYP_YTDC2.1.1	1572	YTH HrpA R3H super family Ank_2				
Grassosirea gigas	NCBI	gi 762086858 (XP_011425711.1)	1572	YTH HrpA R3H super family Ank_2				

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YTHDF

		gi 29791407 (AAH50284.1)	559	YTH RPA_2b-aaRSs_OBF_like PHA03247 super family
Homo sapiens	NCBI	gi 12803469 (AAH02559.1)	579	YTH
		gi 31419299 (AAH52970.1)	585	YTH
		gi 21356147 (NP_651322.1)	700	YTH
Drosophila melanogaster (CG6422)		gi 24649883 (NP_733067.1)	699	YTH
		gi 161078590 (NP_001097905.1)	694	YTH
	01017011	CHOYP_COX1.6.15	532	YTH
Crassostrea gigas	GIGATON	CHOYP_LOC100371022.1.1	531	YTH
	NCBI	gi 762146089 (XP_011456337.1)	522	YTH

hnRNPA2B1

	T	10/2	ı	
Homo sapiens	NCBI	gi 4504447 (NP_002128.1)	341	RRM1_hA2B1 RRM2_hA2B1 Putative DNA binding site hnRNPA1
Пото заренз	NODI	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
Drosophila melanogaster (hrb98DE)	NCBI	gi 17738267 (NP_524543.1)	365	RRM1_hA_like RRM_SF Putative DNA binding site
Drosophila melanogaster (111090DE)	NODI	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
		CHOYP_LOC100748395.3.7	315	RRM1_hA_like RRM_SF Putative DNA binding site
	GIGATON	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		INCDI	gi 762104366 (XP_011434717.1)	363 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			Prrc2	<u>c2a</u>
24 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 34		GIGATON	CHOYP_LOC100559941.1.2	2578 GRE-rich domain BAT2_N PTZ00121 PTZ00449
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	<u>2BP</u>
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 57			gi 56118219 (NP_001007226.1)	556 KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM2_IGF2BP2
58 59	Homo sanions		gi 631226390 (NP_001278798.1)	605 KH-I KH-1 PCBP_like_KH RRM1_IGF2BP2 RRM_SF super family
60	Homo sapiens	NCBI	ail621226202 (ND 001278801 1)	542 KILL KILA DODD like KIL DDM OF super femily

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

Data S1: Complete list of in silic	co identified putative m6A machinery protein	s and their respective BLAST results														
	Crassostrea gigas					Homo sap	iens							Drosophila melanogaster		
METTL3	CHOYP_PHUM_PHUM423190.1.1	gi 21361827 (NP_062826.2) 52.3%										gi 21355141 (NP_651204.1) 73.26%				
WILTIES	gi 762092209 (XP_011428532.1)	52.81%										73.96%				
		gi 24308265 (NP_066012.1)										gi 19920926 (NP_609205.1)				
METTL14	CHOYP_MET14.1.1 CHOYP_LOC100743733.1.1	62.03% 60.88%										58.05% 57.76%				
	gi 762082967 (XP_011424173.1)	61.58%										58.05%				
		gi 395455090 (NP_001257460.1)	gi 23199974 (NP_690596.1)	gi 395455092 (NP_001257461.1)								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%			
		gi 33946282 (NP_056311.2)	gi 33946280 (NP_892121.1)									gi 17864576 (NP_524900.1)				
	CHOYP_VIR.1.1	30.70%	29.59%									25.49%				
VIRILIZER-like	gi 762120202 (XP_011443024.1) gi 762120200 (XP_011443023.1)	30.85% 30.85%	30.17% 30.17%									25.49% 25.49%				
VIIVIELET IIIO	gi 1139822239 (XP_019927346.1)	30.89%	30.17%									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)	
HAICAL	CHOYP_LOC100864501.1.1	43.27%	43.96%									60.45%	60.45%	60.45%	60.45%	
HAKAI	gi 762140345 (XP_011453340.1)	29.43%	29.68%									56.29%	60.45%	56.29%	60.45%	
	gi 762140347 (XP_011453341.1)	29.28% gi 1060099240 (NP_001317493.1)	29.68%	ail116009442 (ND 055995 2)								57.14%	60.45%	57.14% gi 665392305 (NP_001285419.1)	60.45%	
	CHOYP_BRAFLDRAFT_120702.1.1	37.11%	gi 1060099108 (NP_001317496.1) 37.11%	gi 116008442 (NP_055885.3) 37.11%								gi 24643154 (NP_573339.1) N/A	gi 665392303 (NP_001285418.1) N/A	911003392303 (NF_001285419.1) N/A		
	CHOYP_LOC100568158.1.1	37.11%	37.11%	37.11%								N/A	N/A	N/A		
ZC3H13	gi 762096734 (XP_011430912.1) gi 762096736 (XP_011430913.1)	31.48% 31.48%	31.48% 31.48%	40.00% 40.00%								N/A	N/A N/A	N/A		
	gi 762096736 (XP_011430913.1) gi 762096738 (XP_011430914.1)	31.48%	31.48%	40.00%								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)	gi 319996623 (NP_001188474)	gi 54607124 (NP_037418)								gi 24586450 (NP_724633)	gi 19921778 (NP_610339)	gi 665399388 (NP_001286174)		
KBWI13/13B	gi 762129377 (XP_011447812)	56.73% 41.64%	56.73% 41.64%	61.59% 34.94%								59.22% 42.75%	59.22% 42.75%	59.22% 42.75%		
		gi 122114654 (NP_076991.3)										gi 19922302 (NP_611015.1)				
METTL16	CHOYP_LOC100561572.1.1	38.05% 37.68%										38.81%				
	gi 762141911 (XP_011454156.1) gi 762141913 (XP_011454157.1)	37.68%										39.16% 39.16%				
		gi 148539642 (NP_060228.3)														
ALKBH5	CHOYP_BRAFLDRAFT_126925.1.1 gi 762097205 (XP_011431161.1)	72.43% 72.43%														
	gi 102091203 (XF_011431101.1)	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	46.61%	46.61%	45.30%								57.74%	57.74%			
1111201	CHOYP_LOC586835.1.1	51.52% 43.92%	51.52% 44.52%	52.27% 42.86%								57.74% 46.53%	57.74% 46.53%			
	gi 762070401 (XP_011447601.1)	gi 269847874 (NP_073739.3)	gi 1066536696 (NP_001332904.1)									40.5576	40.55%			
YTHDC2	CHOYP_YTDC2.1.1	52.99%	53.66%	51.83%												
	gi 762086858 (XP_011425711.1)	53.09%	53.77%	52.05%								gi 21356147 (NP_651322.1)	qi 24649883 (NP 733067.1)	gi 161078590 (NP 001097905.1)		
	CHOYP_COX1.6.15	gi 29791407 (AAH50284.1) 53.09%	gi 12803469 (AAH02559.1) 53.77%	gi 31419299 (AAH52970.1) 52.05%								71.51%	gij24649883 (NP_733067.1) 71.51%	71.51%		
YTHDF	CHOYP_LOC100371022.1.1	53.09%	53.77%	52.05%								71.51%	71.51%	71.51%		
	gi 762146089 (XP_011456337.1)	43.49%	71.21%	71.72%								71.20%	71.20%	71.20%	(10.4050000 (NID. 700050.4)	
	CHOYP LOC100748395.1.7	gi 4504447 (NP_002128.1) 55.37%	gi 14043072 (NP_112533.1) 54.71%									gi 24650831 (NP_733249.1) 58.14%	gi 17738267 (NP_524543.1) 58.14%	gi 24650838 (NP_733252.1) 58.14%	gi 24650833 (NP_733250.1) 58.14%	
	CHOYP_LOC100748395.2.7	55.37%	54.71%									58.14%	58.14%	58.14%	58.14%	
	CHOYP_LOC100748395.3.7	55.37%	54.71%									58.14%	57.71%	58.14%	58.14%	
	CHOYP_LOC100748395.4.7 CHOYP_LOC100748395.6.7	55.37% 55.37%	54.71% 54.71%									58.14% 58.14%	58.14% 57.71%	58.14% 58.14%	58.14% 58.14%	
hnRNPA2B1	CHOYP_AGAP_AGAP002374.1.1	54.24%	53.53%									58.72%	58.29%	58.29%	56.83% 58.14%	
	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%	55.37%									50.63%	50.63%	50.63%	50.63%	
	CHOYP_LOC100559941.1.2	gi 314122241 (NP_004629.3) 46.02%														
Prrc2a	CHOYP_LOC100559941.2.2	46.02%														
	gi 1139830093 (XP_019928978.1)	34.66%	1100000 105- (117- 101-111)	110 400 20 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1150440040 (215 40400	11004000000 (117)	11004000000 (117)	11004000000 (117 001070000	11004000004 (117	1100400000 (11 0	110070704040	1000=04400 (01=	1100000011101101101	114	110 10 110 110 110 110 110 110 110 110	1100400000 (117)
	CHOYP_LOC100114171.1.1	gi 56237027 (NP_006537.3) 34.87%	gi 238624257 (NP_001153895.1) 35.71%	gi 64085377 (NP_006539.3) 35.86%	gi 56118219 (NP_001007226.1)	gi 631226390 (NP_001278798.1) 35.50%	gi 631226392 (NP_001278801.1) 34.93%	gi 631226396 (NP_001278802.1) 35.34%	gi 631226394 (NP_001278803.1) 35.85%	gi 631226398 (NP_001278804.1) 38.61%	gi 30795212 (NP_006538.2) 33.16%	gi 386764188 (NP_001036268.2) 42.72%	40.000/	gi 17530887 (NP_511111.1) 44.89%	gi 24641097 (NP_727451.1) 44.89%	gi 281360685 (NP_001162717.1) 44.20%
IGF2BP	gi 762079091 (XP_0114171.1.1	34.80%	36.39%	35.86% 35.96%	36.52%	35.50% 35.61%	34.93% 35.53%	35.34%	36.38%	39.76%	33.78%	42.72%	42.26% 42.83%	44.89% 45.07%	44.69% 45.07%	44.20% 44.37%
	gi 762079093 (XP_011412008.1)	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%	44.52%
	gi 762079095 (XP_011412017.1)	34.80%	36.39%	35.96%	36.52%	35.88%	35.53%	36.24%	36.38%	39.76%	33.78%	42.83%	42.83%	45.07%	45.07%	44.37%
	CHOYP_BRAFLDRAFT_75590.1.1	gi 4503509(NP_003741.1) 40.86%										gi 665393171 (NP_730838.3) 45.97%	gi 24643988 (NP_649470.2) 45.97%			
elF3a	CHOYP_UBP47.2.2	63.83%										50.89%	50.89%			
CII Ja	CHOYP_MROH1.1.1	63.71%										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%			
<u> </u>	5,	33370							<u> </u>							

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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

Proteins ide	entified in nuclear ext	racts
Oligo	Accession	Description
m6A	K1PTY5_CRAGI	Protocadherin Fat 4
m6A	K1QNA2_CRAGI	Vitellogenin-6
m6A	K1QBR5_CRAGI	Uncharacterized protein
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	·
m6A	K1PQP2 CRAGI	·
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	
m6A	K1RWS2_CRAGI	Transcriptional activator protein Pur-alpha
m6A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
m6A	K1R3U2_CRAGI	
m6A	K1QQ68 CRAGI	
	_	·
m6A	K1QVJ8_CRAGI	Piwi-like protein 1
m6A	K1PVA1_CRAGI	Transitional endoplasmic reticulum ATPase
m6A	K1QKB5_CRAGI	Uncharacterized protein
m6A	_	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 2
m6A	K1QII6_CRAGI	Tubulin alpha chain
m6A	-	Putative ATP-dependent RNA helicase an3
m6A	K1QQ27_CRAGI	
m6A	_	RRP5-like protein
m6A	-	40S ribosomal protein S8
m6A	K1QXX7_CRAGI	Myosin heavy chain, non-muscle (Fragment)
m6A	K1QK56_CRAGI	Uncharacterized protein
m6A	K1PNR3_CRAGI	Uncharacterized protein 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	·
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	-
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	-	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

K1PJ06_CRAGI Importin subunit alpha-1 m6A K1QA13_CRAGI Calcium-transporting ATPase m6A m6A K1R0L4_CRAGI Sodium/potassium-transporting ATPase subunit alpha m6A K1R115_CRAGI Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial 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 m6A K1QFW9 CRAGI Uncharacterized protein 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 m6A K1PUL2_CRAGI Long-chain-fatty-acid--CoA 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 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 m6A K1QYB3_CRAGI Ig-like and fibronectin type-III domain-containing protein C25G4.10 m6A K1QI14_CRAGI 40S ribosomal protein S3a 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 m6A K1RAJ1_CRAGI T-complex protein 1 subunit alpha K1QH74 CRAGI Splicing factor, arginine/serine-rich 1 m6A K1QRL6_CRAGI Methenyltetrahydrofolate synthetase domain-containing protein m6A m6A K1QUC6 CRAGI Uncharacterized protein K1RIT6 CRAGI NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial m6A K1RBF6_CRAGI Uncharacterized protein yfeX m6A m6A K1PCS4 CRAGI Eukaryotic translation initiation factor 2 subunit 3, Y-linked m6A K1Q620 CRAGI Uncharacterized protein K1QWX2_CRAGI 60S acidic ribosomal protein P0 m6A K1PD57_CRAGI Constitutive coactivator of PPAR-gamma-like protein 1-like protein m6A m6A K1Q4S5 CRAGI Cadherin-87A K1RQA0_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2 m6A m6A K1QMX8_CRAGI DNA replication licensing factor MCM7 m6A K1QPX8_CRAGI Alkyl/aryl-sulfatase BDS1 K1QZW0_CRAGI Polyadenylate-binding protein 2 m6A m6A K1RWX7_CRAGI Metabotropic glutamate receptor 3 K1RFT1_CRAGI Band 4.1-like protein 3 m6A K1RNB5_CRAGI Propionyl-CoA carboxylase beta chain, mitochondrial m6A K1QBK6_CRAGI Splicing factor 3B subunit 1 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 m6A K1QWT8 CRAGI Uncharacterized protein K1Q0L1_CRAGI 60S ribosomal protein L23a m6A m6A K1Q260 CRAGI Nucleolar protein 58 m6A K1QT04 CRAGI Uncharacterized protein K1Q9K6_CRAGI Histone H3 m6A

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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 Ribonuelo ocido diabonabata noductora
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 Caprin-1
m6A m6A	K1QP17_CRAGI K1R7A2_CRAGI	Uncharacterized protein
m6A	K1R/AZ_CRAGI 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	
m6A	K1RSZ6_CRAGI	40S ribosomal protein S7
m6A	K1QDZ5_CRAGI	Cytochrome c1, heme protein, mitochondrial
m6A	K1PGW7 CRAGI	Transmembrane protein 2
m6A	_	Eukaryotic translation initiation factor 3 subunit A
m6A	K1RNZ6_CRAGI	Eukaryotic translation initiation factor 3 subunit D
m6A	-	T-complex protein 1 subunit eta
m6A	K1Q404 CRAGI	DNA topoisomerase 2
m6A	K1R7J6 CRAGI	Putative sodium/potassium-transporting ATPase subunit beta-2
m6A	_	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 m6A	K1R005_CRAGI	Filamin-C (Fragment) Splicing factor, argining/spring-rich 7
m6A m6A	K1RA35_CRAGI K1R2V1_CRAGI	Splicing factor, arginine/serine-rich 7 Importin subunit beta-1
m6A	K1R2V1_CRAGI K1QAH9_CRAGI	H/ACA ribonucleoprotein complex subunit
m6A	K1QAH9_CRAGI K1QET2 CRAGI	Coatomer subunit alpha
m6A	K1QE12_CRAGI K1RAB9_CRAGI	Epoxide hydrolase 4
m6A	K1QGK2_CRAGI	Coatomer subunit beta
HOA	KIQGKZ_CRAGI	Coatomer Subullit 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
```

K1QT61_CRAGI NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial (Fragment)

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 m6A

```
1
                 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
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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 K1QNUO 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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m6A	K1Q3V9_CRAGI	Mitochondrial carnitine/acylcarnitine carrier protein
m6A	K1QN55_CRAGI	60S acidic ribosomal protein P1
m6A	K1R3G0_CRAGI	Transformer-2-like protein beta
m6A	K1PWM3_CRAGI	MICOS complex subunit MIC13
m6A	K1QKL8_CRAGI	V-type proton ATPase subunit a
m6A	K1S6T6_CRAGI	UPF0480 protein C15orf24-like protein
m6A	K1R0W0_CRAGI	Ferritin
m6A	K1PGK7_CRAGI	Uncharacterized protein
m6A	K1QY71_CRAGI	Histone H2B
m6A	K1QNT7_CRAGI	Aldehyde dehydrogenase, mitochondrial
m6A	K1RJ96_CRAGI	Sphere organelles protein SPH-1
m6A	K1RZE2_CRAGI	Isocitrate dehydrogenase [NADP]
m6A	K1PPV1_CRAGI	Atlastin-2
m6A	K1P9F1_CRAGI	Insulin-like growth factor-binding protein complex acid labile chain
m6A	K1QVU0_CRAGI	Synaptojanin-2-binding protein
m6A	K1QX44_CRAGI	Ras-related protein Rab-11B
m6A	K1QKU6_CRAGI	mRNA export factor
m6A	K1QDV6_CRAGI	Protein argonaute-2
m6A	K1R5B9_CRAGI	DNA-directed RNA polymerase, mitochondrial
m6A	K1RCT2_CRAGI	Translocon-associated protein subunit delta
m6A	K1PKD4_CRAGI	40S ribosomal protein S30
m6A	K1PP50_CRAGI	Golgi integral membrane protein 4
m6A	K1PG60_CRAGI	60S ribosomal protein L17
m6A	K1QWJ4_CRAGI	Splicing factor 3B subunit 5
m6A	K1RB91_CRAGI	Neutral alpha-glucosidase AB
m6A	K1RD12_CRAGI	Uncharacterized protein
m6A	K1PQE3_CRAGI	RNA-binding protein Raly
m6A	K1Q2Y1_CRAGI	40S ribosomal protein S15
m6A	K1PQF1_CRAGI	Neural cell adhesion molecule L1
m6A	K1QKJ0_CRAGI	Aldehyde dehydrogenase family 3 member B1
m6A	K1PUQ5_CRAGI	
m6A	_	Uncharacterized protein
m6A	_	Uncharacterized protein
m6A	K1RNH1_CRAGI	
m6A	· -	Anoctamin
m6A	K1P8B7_CRAGI	Ubiquitin-conjugating enzyme E2-17 kDa (Fragment)
m6A	K1Q1D7_CRAGI	Putative rRNA-processing protein EBP2
m6A	K1PY30_CRAGI	Septin-2
m6A	K1Q1R1_CRAGI	Exostosin-3
m6A	K1RHP3_CRAGI	Proliferation-associated protein 2G4
m6A	K1PZI3_CRAGI	SWI/SNF complex subunit SMARCC2
m6A	K1QT97_CRAGI	N(G),N(G)-dimethylarginine dimethylaminohydrolase 1
m6A	K1QQQ5_CRAGI	·
m6A	K1PA61_CRAGI	Actin-like protein 6A
m6A	K1PNL0_CRAGI	Microtubule-associated protein futsch
m6A	K1QI28_CRAGI	V-type proton ATPase subunit B
m6A	K1PYL5_CRAGI	Uncharacterized protein
m6A m6A	K1PJ65_CRAGI	Dual specificity mitogen-activated protein kinase kinase 7 Proteasome subunit alpha type
m6A	_	·
m6A	K1Q2L4_CRAGI K1Q8C1_CRAGI	Transmembrane emp24 domain-containing protein 9 Putative RNA-binding protein Luc7-like 2
m6A	K1Q8C1_CRAGI K1PS71 CRAGI	Uncharacterized protein
m6A	K1Q900_CRAGI	Galectin
m6A	K1Q900_CRAGI K1RKR8_CRAGI	Pumilio-like protein 2
m6A	K1RKR6_CRAGI	IQ and AAA domain-containing protein 1
m6A	K1RRE3_CRAGI	Importin-5
m6A	_	Fatty-acid amide hydrolase 2
m6A	K1RD83_CRAGI	Serine hydroxymethyltransferase
m6A	K1RFA3_CRAGI	Lamin Dm0
m6A	-	Phosphatidylinositide phosphatase SAC1
	4, 137_617101	

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
53
       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
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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

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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	_	Puratrophin-1
m6A	K1PUF0_CRAGI	G-protein coupled receptor moody
m6A	-	Zinc finger protein 26
m6A	K1QXP9_CRAGI	Uncharacterized protein
m6A	K1P6M6_CRAGI	Cerebellin-1
Α	K1QNA2_CRAGI	-
A	K1PTY5_CRAGI	Protocadherin Fat 4
A	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	-	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
Α	K1R3U2_CRAGI	Uncharacterized protein Tubulin beta chain
A	K1R7V7_CRAGI K1QMX5_CRAGI	Uncharacterized protein
A A	K1R9B6_CRAGI	H/ACA ribonucleoprotein complex subunit 4
A	K1QQ68_CRAGI	Tubulin alpha chain
A	K1QQ00_CRAGI	Nucleolin
A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
A	K1R164_CRAGI	Galectin-4
Α	K1QVJ8_CRAGI	Piwi-like protein 1
Α	K1RGT5_CRAGI	Metalloendopeptidase
Α	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	K1QK56_CRAGI	Uncharacterized protein
Α	K1QKB5_CRAGI	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
A	K1PNR3_CRAGI	Clathrin heavy chain
A	_	RRP5-like protein
A	-	Dolichyl-diphosphooligosaccharideprotein glycosyltransferase subunit 2
A	K1QU53_CRAGI	NAD(P) transhydrogenase, mitochondrial
Α	K1PJC1_CRAGI K1RG73_CRAGI	Adipophilin Acetyl-CoA carboxylase
A 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
Α	K1RD58_CRAGI	Uncharacterized protein
Α	K1QLS3_CRAGI	Cytochrome b-c1 complex subunit 2, mitochondrial
Α	K1S1S1_CRAGI	Insulin-like growth factor 2 mRNA-binding protein 1
Α	K1R0L4_CRAGI	Sodium/potassium-transporting ATPase subunit alpha
Α	_	ATP synthase subunit beta
Α	K1QA13_CRAGI	·
Α	K1QFN2_CRAGI	Uncharacterized protein
Α	K1R545_CRAGI	Pre-mRNA-processing-splicing factor 8 (Fragment)
Α	K1R252_CRAGI	Putative methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial
Α	K1PMT6_CRAGI	Heterogeneous nuclear ribonucleoprotein U-like protein 1
Α	K1RGB7_CRAGI	Epidermal retinal dehydrogenase 2

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K1R466_CRAGI T-complex protein 1 subunit gamma Α K1R294_CRAGI T-complex protein 1 subunit beta Α Α K1RIT6_CRAGI NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial Α K1QIR8_CRAGI 78 kDa glucose-regulated protein K1RI55_CRAGI Insulin-like growth factor 2 mRNA-binding protein 3 K1QH74_CRAGI Splicing factor, arginine/serine-rich 1 Α K1S2N7_CRAGI Innexin Α K1R435_CRAGI Splicing factor, arginine/serine-rich 4 K1R5U4_CRAGI Acetyl-CoA carboxylase 1 Α K1QBK6_CRAGI Splicing factor 3B subunit 1 Α K1Q988_CRAGI Band 4.1-like protein 3 Α Α K1R420_CRAGI Non-specific serine/threonine protein kinase A5LGH1_CRAGI Voltage-dependent anion channel Α Α K1PHW2_CRAGI Uncharacterized protein Α K1REG6 CRAGI DNA helicase Α K1QAE5_CRAGI Uncharacterized protein Α K1QWT8_CRAGI Uncharacterized protein K1QRL6_CRAGI Methenyltetrahydrofolate synthetase domain-containing protein Α K1QYB3_CRAGI Ig-like and fibronectin type-III domain-containing protein C25G4.10 Α K1QKD6_CRAGI Uncharacterized protein Α K1R115_CRAGI Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial Α Α K1S4Q2_CRAGI T-complex protein 1 subunit delta (Fragment) Α K1QWK2_CRAGI MAM domain-containing glycosylphosphatidylinositol anchor protein 2 K1ROS3 CRAGI T-complex protein 1 subunit theta Α K1QFW9 CRAGI Uncharacterized protein Α K1Q0Z3_CRAGI Estradiol 17-beta-dehydrogenase 11 Α K1PNQ5_CRAGI Heat shock protein HSP 90-alpha 1 K1RBF6 CRAGI Uncharacterized protein yfeX Α K1R4D4_CRAGI 40S ribosomal protein SA Α K1QI14_CRAGI 40S ribosomal protein S3a K1PUL2_CRAGI Long-chain-fatty-acid--CoA ligase 1 Α K1RFT1_CRAGI Band 4.1-like protein 3 Α K1PJ06_CRAGI Importin subunit alpha-1 K1QT21_CRAGI Putative ATP-dependent RNA helicase DDX5 Α K1QM19_CRAGI Uncharacterized protein Α Α K1QXS6_CRAGI Heterogeneous nuclear ribonucleoprotein A2-like protein 1 Α K1QMX8_CRAGI DNA replication licensing factor MCM7 K1PD57_CRAGI Constitutive coactivator of PPAR-gamma-like protein 1-like protein Α K1R953_CRAGI Acetyl-CoA carboxylase Α Α K1RJH5 CRAGI Polyadenylate-binding protein K1RSZ6_CRAGI 40S ribosomal protein S7 Α Α K1R7A2_CRAGI Uncharacterized protein Α K1QUC6_CRAGI Uncharacterized protein Α K1QWX2_CRAGI 60S acidic ribosomal protein P0 K1RNB5_CRAGI Propionyl-CoA carboxylase beta chain, mitochondrial Α K1PCS4_CRAGI Eukaryotic translation initiation factor 2 subunit 3, Y-linked Α K1Q923_CRAGI Putative ATP-dependent RNA helicase DDX4 Α K1QPX8_CRAGI Alkyl/aryl-sulfatase BDS1 Α Α K1R4R9_CRAGI Mitotic apparatus protein p62 Α K1RAJ1_CRAGI T-complex protein 1 subunit alpha K1Q0L1_CRAGI 60S ribosomal protein L23a Α K1Q620_CRAGI Uncharacterized protein Α Α K1QG58_CRAGI Actin K1Q4H2_CRAGI Nodal modulator 3 Α Α K1Q260_CRAGI Nucleolar protein 58 Α K1QF01 CRAGI 40S ribosomal protein S4 K1PUM2_CRAGI Histone H2A Α Α K1QNN9_CRAGI MICOS complex subunit MIC60 Α K1RQA0_CRAGI Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2 Α K1QZW0_CRAGI Polyadenylate-binding 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)
```

K1PM76_CRAGI NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial Α K1PRL4_CRAGI 60S ribosomal protein L38 (Fragment) Α Α K1RW85_CRAGI Adenosylhomocysteinase Α K1PAY7_CRAGI Propionyl-CoA carboxylase alpha chain, mitochondrial 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 K1RSS3_CRAGI Myosin heavy chain, striated muscle Α K1QGK2_CRAGI Coatomer subunit beta Α K1PV79_CRAGI Importin subunit alpha Α K1QN79_CRAGI 40S ribosomal protein S11 Α K1PV49_CRAGI RuvB-like helicase Α Α K1QG65_CRAGI rRNA 2'-O-methyltransferase fibrillarin Α K1PK85 CRAGI Cullin-associated NEDD8-dissociated protein 1 Α K1QVN9_CRAGI T-complex protein 1 subunit eta Α K1QGB4_CRAGI 40S ribosomal protein S17 K1QK18_CRAGI Cytochrome b5 Α K1QVW3_CRAGI Alkylglycerone-phosphate synthase Α Α K1QN11_CRAGI Pre-mRNA-processing-splicing factor 8 K1RJS5_CRAGI Uncharacterized protein Α K1Q6W5_CRAGI FACT complex subunit spt16 Α Α K1QQB6_CRAGI 40S ribosomal protein S14 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 K1R2V1 CRAGI Importin subunit beta-1 Α Α K1PV86_CRAGI Phosphoglycerate mutase family member 5 K1QJ08_CRAGI 60S ribosomal protein L26 Α K1QLU6_CRAGI Poly [ADP-ribose] polymerase K1QDN1_CRAGI Heat shock protein 75 kDa, mitochondrial (Fragment) Α Α K1QPP2_CRAGI Elongation factor Tu, mitochondrial Α K1R834 CRAGI 60S ribosomal protein L9 K1R005_CRAGI Filamin-C (Fragment) Α Α K1QET2_CRAGI Coatomer subunit alpha K1RKC1 CRAGI Far upstream element-binding protein 3 Α K1RG19_CRAGI Protein FAM98A Α Α K1Q056_CRAGI Calpain-A Α K1QKJ0 CRAGI Aldehyde dehydrogenase family 3 member B1 Α K1QDZ5_CRAGI Cytochrome c1, heme protein, mitochondrial K1PPP8_CRAGI Vigilin Α Α K1RHB2_CRAGI Nucleolar RNA helicase 2 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 Α K1S2S8_CRAGI Signal recognition particle 54 kDa protein Α K1R1T8_CRAGI Nucleolar protein 56 K1QRZ3_CRAGI 40S ribosomal protein S13 Α Α K1PMP3_CRAGI Protoporphyrinogen oxidase Α K1P9N7_CRAGI 14-3-3 protein zeta K1Q0R4_CRAGI ATP-binding cassette sub-family F member 2 Α Α K1QWC3_CRAGI 40S ribosomal protein S3 Α K1Q812_CRAGI NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial K1P5V7_CRAGI Eukaryotic translation initiation factor 3 subunit C Α 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
```

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 Α K1QK68_CRAGI Myosin-2 essential light chain

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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
Α	K1Q2Z5_CRAGI	Putative ATP-dependent RNA helicase DDX46
Α	K1PYA0_CRAGI	Cytoplasmic dynein 2 heavy chain 1
Α	K1QAV0_CRAGI	Guanine nucleotide-binding protein G(Q) subunit alpha
Α	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
Α	K1P8I1_CRAGI	Pleckstrin-like protein domain-containing family F member 2 (Fragment)
Α	K1Q1N1_CRAGI	Alpha-mannosidase
Α	K1PXB6_CRAGI	Cadherin-23
Α	K1QXA9_CRAGI	Sortilin-related receptor
Α	K1PVG0_CRAGI	Long-chain fatty acid transport protein 4
Α	K1PBG6_CRAGI	·
Α	K1PP50_CRAGI	Golgi integral membrane protein 4
Α	K1QCQ5_CRAGI	SuccinateCoA ligase [ADP-forming] subunit beta, mitochondrial
Α	K1PK87_CRAGI	Putative E3 ubiquitin-protein ligase TRIP12
A	K1Q373_CRAGI	Splicing factor, arginine/serine-rich 7
A	K1Q151_CRAGI	60S ribosomal protein L32
A	K1QZ95_CRAGI	Nuclear pore complex protein
A	K1PPH0_CRAGI	Gamma-tubulin complex component
A	K1R0R7_CRAGI	Putative ATP-dependent RNA helicase DHX36
A	K1R247_CRAGI K1QIB2_CRAGI	Condensin complex subunit 1 Mitogen-activated protein kinase
A A	K1QG61_CRAGI	Acetolactate synthase-like protein
A	K1QG01_CRAGI	Transketolase-like protein 2
Α	K1RCW5_CRAGI	
Α	K1PQZ3_CRAGI	Armadillo repeat-containing protein 4
Α	K1PYJ8_CRAGI	Uncharacterized protein
Α	K1QQP1_CRAGI	Programmed cell death protein 4
Α	K1PQY0_CRAGI	Protein quiver
Α	K1PLC6_CRAGI	Nucleolar protein 14
Α	K1QV25_CRAGI	Transcription elongation factor B polypeptide 2
Α	K1QZ50_CRAGI	RNA-dependent RNA polymerase
Α	K1QXH7_CRAGI	DNA replication licensing factor mcm4-B
Α	K1PDE4_CRAGI	Protein arginine N-methyltransferase Golgi resident protein GCP60 Mannosyl-oligosaccharide glucosidase Putative tyrosinase-like protein tyr-3
Α	K1QT36_CRAGI	Golgi resident protein GCP60
A	K1PZ89_CRAGI	Mannosyl-oligosaccharide glucosidase
A	K1Q7A7_CRAGI	rational tyrical map protein tyric
A	K1R481_CRAGI	Epimerase family protein SDR39U1
A	K1RJ35_CRAGI Q70MT4_CRAGI	All-trans-retinol 13,14-reductase 40S ribosomal protein S10
A A	K1REV3_CRAGI	DNA polymerase delta subunit 2
A	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	K1QZ58_CRAGI	Splicing factor U2AF 26 kDa subunit
Α	K1RR98_CRAGI	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4-like 2
Α	K1QMT2_CRAGI	Signal peptidase complex catalytic subunit SEC11
Α	K1PWM3_CRAGI	MICOS complex subunit MIC13
Α		Leucine zipper transcription factor-like protein 1
Α	-	V-type proton ATPase subunit D
Α	K1QKI1_CRAGI	Tudor domain-containing protein 1
A	K1P0H0_CRAGI	Aspartyl/asparaginyl beta-hydroxylase
A	K1PVQ8_CRAGI	Eukaryotic translation initiation factor 3 subunit K
Α	K1Q5P0_CRAGI	60S ribosomal protein L17 Muscla, skalatal recentor tyrasina protein kinasa
A	K1QJ36_CRAGI K1PHS4_CRAGI	Muscle, skeletal receptor tyrosine protein kinase Ribosome-binding protein 1
Α	KIPH34_CKAGI	Whosome-ninding brotein T

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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	-	
8		K1QFG2_CRAGI	Telomere-associated protein RIF1
9	A	K1Q5J7_CRAGI	Uncharacterized protein
10 11	A	K1QKA9_CRAGI	•
12	A	K1P7Q6_CRAGI	·
13	A	K1QYV5_CRAGI	
14	Α	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	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	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	-	Afadin-and alpha-actinin-binding protein
38	A	-	Toll-like receptor 3
39 40	A	K1PZCO CRAGI	Structural maintenance of chromosomes protein
41	A	K1PT69_CRAGI	
42		K1RE67 CRAGI	Methylated-DNAprotein-cysteine methyltransferase
43	A	-	
44	A	K1QCX5_CRAGI	
45	A	K1QBT8_CRAGI	·
46 47	A	K1RFF1_CRAGI	Uncharacterized protein
48	A	K1RS40_CRAGI	•
49	Α	K1R8V1_CRAGI	Puratrophin-1
50			
51			
52			
53 54			
55			
56			
57			
58			
59			
60			

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
-	m6A	K1QHK9_CRAGI	Dynein heavy chain, cytoplasmic
11	m6A	K1QQ68_CRAGI	Tubulin alpha chain
12	m6A	K1RLF8_CRAGI	Splicing factor 3B subunit 3
13 14	m6A	K1R473_CRAGI	Tubulin alpha chain
	m6A	K1QII6_CRAGI	Tubulin alpha chain
	m6A	K1PNR3_CRAGI	Clathrin heavy chain
17	m6A	K1R7V7_CRAGI	Tubulin beta chain
18	m6A	K1PNI6_CRAGI	Heterogeneous nuclear ribonucleoprotein A/B
19 20	m6A	K1QMX5_CRAGI	Uncharacterized protein
	m6A	K1QHI5_CRAGI	Pyruvate carboxylase, mitochondrial
	m6A	K1PE00_CRAGI	Tubulin alpha chain
23	m6A	K1R294_CRAGI	T-complex protein 1 subunit beta
24	m6A	K1S4Q2_CRAGI	T-complex protein 1 subunit delta (Fragment)
25 26	m6A	K1PQP2_CRAGI	Nucleolin
	m6A	K1R466_CRAGI	T-complex protein 1 subunit gamma
	m6A	K1PN21_CRAGI	Tubulin beta chain
29	m6A	K1R164_CRAGI	Galectin-4
30	m6A	K1S2N7_CRAGI	Innexin
31 32	m6A	K1R6Z7_CRAGI	ATP synthase subunit alpha
	m6A	K1R5B4_CRAGI	Proteasome activator complex subunit 4
	m6A	K1PVA1_CRAGI	Transitional endoplasmic reticulum ATPase
	m6A	K1QFW9_CRAGI	Uncharacterized protein
36 37	m6A	K1R0S3_CRAGI	T-complex protein 1 subunit theta
38	m6A	K1QMA4_CRAGI	RRP5-like protein
	m6A	K1R3U2_CRAGI	Uncharacterized protein
	m6A	K1Q9W5_CRAGI	T-complex protein 1 subunit eta
41	m6A	K1QBK6_CRAGI	Splicing factor 3B subunit 1
42 43	m6A	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
	m6A	K1Q350_CRAGI	Glyceraldehyde-3-phosphate dehydrogenase
47	m6A	K1RGT5_CRAGI	Metalloendopeptidase
48 49	m6A	K1PJ85_CRAGI	26S protease regulatory subunit 6A
50	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
	m6A	K1RZE2_CRAGI	Isocitrate dehydrogenase [NADP]
53 54	m6A	K1PNQ5_CRAGI	Heat shock protein HSP 90-alpha 1
55	m6A	K1R866_CRAGI	Puromycin-sensitive aminopeptidase
56	m6A	K1P9D0_CRAGI	Stress-70 protein, mitochondrial
	m6A	K1QXX7_CRAGI	Myosin heavy chain, non-muscle (Fragment)
	m6A	K1RG73_CRAGI	Acetyl-CoA carboxylase
59 60	m6A	K1R420_CRAGI	Non-specific serine/threonine protein kinase
00	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
   m6A
3
                K1QVN9 CRAGI
                                 T-complex protein 1 subunit eta
4
   m6A
5
   m6A
                K1PLF9_CRAGI
                                 Arginine kinase
6
   m6A
                Q8TA69_CRAGI
                                 Actin 2
7
                K1QG58_CRAGI
                                 Actin
   m6A
8
                K1QSB2_CRAGI
                                 26S protease regulatory subunit 6B
   m6A
9
                K1R401_CRAGI
                                 Spectrin alpha chain
10 m6A
11
   m6A
                K1Q1I2_CRAGI
                                 26S protease regulatory subunit 7
12
   m6A
                K1Q4I9_CRAGI
                                 D-3-phosphoglycerate dehydrogenase (Fragment)
13
   m6A
                K1RJH5_CRAGI
                                 Polyadenylate-binding protein
14
<sub>15</sub> m6A
                K1RWD4_CRAGI
                                 Actin, cytoplasmic
16 m6A
                K1QI14_CRAGI
                                 40S ribosomal protein S3a
17 m6A
                K1RWW5_CRAGI
                                 ATP synthase subunit beta
18
   m6A
                K1QET2_CRAGI
                                 Coatomer subunit alpha
19
   m6A
                K1QVS3 CRAGI
                                 Thimet oligopeptidase
20
21 m6A
                K1QSQ9_CRAGI
                                 Putative ATP-dependent RNA helicase an3
22 m6A
                K1Q923_CRAGI
                                 Putative ATP-dependent RNA helicase DDX4
23
   m6A
                K1QXR4_CRAGI
                                 Pancreatic lipase-related protein 2
24
   m6A
                K1R512_CRAGI
                                 Uncharacterized protein
25
   m6A
                K1R8L1_CRAGI
                                 Exportin-2
26
27 m6A
                                 Dynein beta chain, ciliary
                K1PAG1_CRAGI
28 m6A
                K1Q988_CRAGI
                                 Band 4.1-like protein 3
29
   m6A
                K1PJ06_CRAGI
                                 Importin subunit alpha-1
30
   m6A
                                 60S acidic ribosomal protein P0
                K1QWX2 CRAGI
31
   m6A
                K1PH76_CRAGI
                                 Y-box factor-like protein (Fragment)
32
33 m6A
                K1PW06_CRAGI
                                 Filamin-C
34 m6A
                K1RNB5 CRAGI
                                 Propionyl-CoA carboxylase beta chain, mitochondrial
35
  m6A
                K1QWT8_CRAGI
                                 Uncharacterized protein
36
   m6A
                                 Bifunctional aminoacyl-tRNA synthetase
                K1QNW9_CRAGI
37
38 m6A
                K1QCC1_CRAGI
                                 Phosphoglycerate kinase
39 m6A
                K1QBN0 CRAGI
                                 Methylcrotonoyl-CoA carboxylase beta chain, mitochondrial
40 m6A
                K1Q3S7_CRAGI
                                 Cytosolic carboxypeptidase 1
41
   m6A
                K1PMT6_CRAGI
                                 Heterogeneous nuclear ribonucleoprotein U-like protein 1
42
   m6A
                K1Q9Z6_CRAGI
                                 26S proteasome non-ATPase regulatory subunit 7
43
44 m6A
                                 Fibrinolytic enzyme, isozyme C
                K1PH66_CRAGI
45 m6A
                K1R1M7_CRAGI
                                 Ubiquitin-like modifier-activating enzyme 1
46 m6A
                K1Q7G8_CRAGI
                                 Fatty acid synthase
47
                                 Phosphoenolpyruvate carboxykinase [GTP]
   m6A
                K1QEA6_CRAGI
48
   m6A
                K1QRL4_CRAGI
                                 Importin-5
49
<sub>50</sub> m6A
                K1RFT1 CRAGI
                                 Band 4.1-like protein 3
51 m6A
                K1QR72_CRAGI
                                 Dipeptidyl peptidase 3
52 m6A
                K1R5R4_CRAGI
                                 Dynein heavy chain 10, axonemal
53
   m6A
                K1QLK6 CRAGI
                                 E3 ubiquitin-protein ligase HUWE1
54
   m6A
                K1R5U4_CRAGI
                                 Acetyl-CoA carboxylase 1
55
                                 Heterogeneous nuclear ribonucleoprotein A2-like protein 1
   m6A
                K1QXS6_CRAGI
56
57 m6A
                K1R953_CRAGI
                                 Acetyl-CoA carboxylase
58 m6A
                                 Eukaryotic translation initiation factor 2 subunit 3, Y-linked
                K1PCS4_CRAGI
59
                                 78 kDa glucose-regulated protein
   m6A
                K1QIR8_CRAGI
60
                                 Methylcrotonoyl-CoA carboxylase subunit alpha, mitochondrial
   m6A
                K1RSA6_CRAGI
                K1R2V1_CRAGI
                                 Importin subunit beta-1
   m6A
                K1QZW0_CRAGI
                                 Polyadenylate-binding protein 2
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                                  Importin-4
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56 A
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58 A
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                K1QRW4_CRAGI
                                  Coronin
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                                  Replication protein A subunit
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                K1PGW7_CRAGI
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                                  Methenyltetrahydrofolate synthetase domain-containing protein
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                                  Intron-binding protein aquarius
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                                  Aldehyde dehydrogenase, mitochondrial
                K1QLZ1_CRAGI
                                  Actin-related protein 3
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K1R9T2_CRAGI Eukaryotic translation initiation factor 3 subunit B 3 K1PS27 CRAGI **DNA** helicase 4 5 K1Q5G6_CRAGI 60 kDa heat shock protein, mitochondrial 6 K1QRM1_CRAGI Nuclear pore protein 7 K1QGC9_CRAGI Acetyl-coenzyme A synthetase 8 K1RLT4_CRAGI Signal recognition particle subunit SRP68 Α 9 K1PAR4_CRAGI Unc-45-like protein A 10 A 11 A K1QVE8_CRAGI Phosphoacetylglucosamine mutase 12 K1Q4Z4_CRAGI Bifunctional purine biosynthesis protein PURH 13 K1P8W6_CRAGI 60S ribosomal protein L4 14 15 A K1QQK1_CRAGI 26S proteasome non-ATPase regulatory subunit 12 16 A K1RIT6_CRAGI NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial 17 A K1R2L7_CRAGI Glutaminyl-tRNA synthetase (Fragment) 18 Α K1QRQ2_CRAGI Glutamate dehydrogenase 1, mitochondrial 19 20 A K1RKZ5_CRAGI DNA damage-binding protein 1 21 A K1QC10_CRAGI GTP-binding protein 1 22 A K1PGZ0_CRAGI Thyroid adenoma-associated protein 23 A K1QUK0_CRAGI NEDD8-activating enzyme E1 catalytic subunit 24 Programmed cell death protein 4 K1QQP1_CRAGI 25 26 A K1PM50_CRAGI 40S ribosomal protein S16 27 A Poly [ADP-ribose] polymerase K1PJS7_CRAGI 28 A K1QX37_CRAGI **Enolase** 29 A K1QCA7_CRAGI Valyl-tRNA synthetase 30 K1Q811 CRAGI Alpha-centractin 31 32 A K1QRZ3_CRAGI 40S ribosomal protein S13 33 A K1QG70_CRAGI Katanin p60 ATPase-containing subunit A1 34 A 60S ribosomal protein L6 K1QW36 CRAGI 35 A K1R8S7_CRAGI Phospholipase A-2-activating protein 36 K1P9N7_CRAGI 14-3-3 protein zeta 37 38 A K1PG07_CRAGI Lupus La-like protein 39 A K1QFZ8 CRAGI Ceramide kinase-like protein 40 A Alpha-aminoadipic semialdehyde synthase, mitochondrial K1Q1Q9_CRAGI 41 A K1PX83_CRAGI Dynein heavy chain 5, axonemal 42 Α K1PCV0_CRAGI Severin 43 44 A K1QP17_CRAGI Caprin-1 45 A K1PS13_CRAGI Coatomer subunit beta (Fragment) 46 A K1Q273_CRAGI 60S ribosomal protein L14 47 Α K1PBU0_CRAGI L-fucose kinase 48 K1QVV5_CRAGI Periostin 49 50 A K1P112_CRAGI ATP synthase subunit gamma, mitochondrial 51 A K1QKN4_CRAGI Dynein heavy chain 6, axonemal 52 A K1P2B8_CRAGI GDP-mannose 4,6 dehydratase 53 A K1QC11 CRAGI AP-1 complex subunit gamma 54 K1QPD6_CRAGI Ubiquitin conjugation factor E4 B 55 56 A K1QWZ0_CRAGI Tetratricopeptide repeat protein 38 57 A K1QKF8_CRAGI S-(hydroxymethyl)glutathione dehydrogenase 58 A K1RD83_CRAGI Serine hydroxymethyltransferase 59 K1R1F0_CRAGI ATP-dependent DNA helicase 2 subunit 1 60 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

Dynein heavy chain 2, axonemal

K1PLD4_CRAGI

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K1QPC6_CRAGI
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                                  60S ribosomal protein L5
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38 A
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39 A
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44 A
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                                  60S ribosomal protein L23a
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1		
2	1/4 D000	
3 A	K1R008_CRAGI	Proteasome subunit alpha type
4 А 5 д	K1QBG8_CRAGI	Proteasome subunit beta type-4
6	K1R8B2_CRAGI	Isovaleryl-CoA dehydrogenase, mitochondrial
7	K1RNN9_CRAGI	Cytoskeleton-associated protein 5
8 A	K1QYG7_CRAGI	Glucosaminefructose-6-phosphate aminotransferase [isomerizing] 1
₉ A 10 A	K1PFK8_CRAGI K1PRD5_CRAGI	Uncharacterized protein Trifunctional purine biosynthetic protein adenosine-3
10 A 11 A	K1PBH3_CRAGI	Dynein heavy chain 3, axonemal
12 A	K1QVK0_CRAGI	Transaldolase
13 ^	K1PAM6_CRAGI	Uncharacterized protein
14 ^A 15 A	K1Q948_CRAGI	Alpha-1,4 glucan phosphorylase
16 A	K1RGG1_CRAGI	Alanyl-tRNA synthetase, cytoplasmic
17 A	K1Q9P5_CRAGI	Mitochondrial-processing peptidase subunit beta
18 _A	K1QTE3_CRAGI	ATP-binding cassette sub-family F member 1
19	K1PZ08_CRAGI	Ras-related protein Rab-7a
20 ^A 21 A	K1RGJ7_CRAGI	Neogenin
22 A	K1RK68_CRAGI	Uncharacterized protein
23 A	K1QEF9_CRAGI	Protein-glutamine gamma-glutamyltransferase K
24 A	K1RHB2_CRAGI	Nucleolar RNA helicase 2
25 A 26 A	K1QAF3_CRAGI	Alanine aminotransferase 2
₂₇ A	K1PB94_CRAGI	ATP-binding cassette sub-family E member 1
28 A	K1R488_CRAGI	Actin-related protein 2/3 complex subunit
²⁹ A	K1QC65_CRAGI	DNA polymerase alpha subunit B
³⁰ A 31	K1PCR9_CRAGI	Proteasome endopeptidase complex
32 A	K1RFU6_CRAGI	Proteasome activator complex subunit 3
33 A	K1R9R5_CRAGI	Proteasome subunit alpha type
34 A	K1PRQ5_CRAGI	Ubiquitin-like modifier-activating enzyme 1
35 д 36 _л	K1Q1L4_CRAGI	Uncharacterized protein
37 ^A	K1Q982_CRAGI	Malignant fibrous histiocytoma-amplified sequence 1
38 A	K1PKF6_CRAGI	26S proteasome non-ATPase regulatory subunit 13
39 A 40 A	K1QBT2_CRAGI K1P5Z3_CRAGI	Proteasome subunit beta Lysosomal aspartic protease
41 A	K1P7L9_CRAGI	Nucleolar GTP-binding protein 1
42 A	K1Q9M7_CRAGI	Histone H1-delta
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46 A	K1PZCO_CRAGI	Structural maintenance of chromosomes protein
47 A	K1PMJ9_CRAGI	Cleavage stimulation factor 77 kDa subunit
48 Δ	K1R4M7_CRAGI	Serine/threonine protein phosphatase 2A regulatory subunit
49 A 50 A	K1S3G2_CRAGI	HMGB1
51 A	K1PB82_CRAGI	Electron transfer flavoprotein subunit beta
52 A	K1PWP4_CRAGI	Phenylalanyl-tRNA synthetase alpha chain
⁵³ A	K1QNS4_CRAGI	DnaJ-like protein subfamily C member 9
54 55 A	K1Q7E4_CRAGI	Ubiquitin-conjugating enzyme E2 N
₅₆ A	K1R6F1_CRAGI	Proteasome subunit alpha type
57 A	K1Q667_CRAGI	tRNA-splicing ligase RtcB homolog
58 A	K1QWC3_CRAGI	40S ribosomal protein S3
⁵⁹ A 60 _A	K1RAH6_CRAGI	Ubiquitin-conjugating enzyme E2-17 kDa
А	K1RIM7_CRAGI	Methionine aminopeptidase 2
A	K1PXS8_CRAGI	Calreticulin
A	K1RIG6_CRAGI	LSM14-like protein A
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A A	K1QE83 CRAGI	CCR4-NOT transcription complex subunit 1
A	K1QFR9_CRAGI	Spectrin beta chain
A	K1RAP8_CRAGI	Malic enzyme
A	K1PK49_CRAGI	Myosin-Ic
		•

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3
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   Α
5
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55
56 A
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                                  Cytosolic Fe-S cluster assembly factor NUBP2 homolog
57 A
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58 A
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                                  Translin
                K1QQC1_CRAGI
                                  Dynein light chain roadblock
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50 A
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51 A
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52 A
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56 A
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                                  Intraflagellar transport protein 52-like protein
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                                  ATP-dependent DNA helicase II subunit 2
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                                  Putative RNA-binding protein 16
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                K1S5H7_CRAGI
                                  Cell division cycle 5-related protein
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11 A
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52 A
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                                  F-box only protein 36
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                K1P8Z1_CRAGI
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                                  Phosphatidylinositol-4-phosphate 5-kinase type-1 alpha
```

Page	1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 1 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 14 24 34 44 56 57 58 59 60 50 50 50 50 50 50 50 50 50 50 50 50 50	

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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
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K1QJN8 CRAGI	AP-3 complex subunit beta
K1PXA0_CRAGI	Uncharacterized protein
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K1QXY4_CRAGI	Kinase
K1PBW4_CRAGI	Uncharacterized protein
K1PUF0_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
_	

cluster Co0003272		<u>Data S3</u> : Con	nplete list of GO t	erms of clustered genes of m6A interacting proteins (p-value<0,05)		
California		Cluster	term_ID	description	log10 p-value	Class
Cutsiver		cluster1	GO:0006172	ADP biosynthetic process	-2,848	Biological process
Calabert				·		
Column				· · · · · · · · · · · · · · · · · · ·		- '
dataset)					
Cutsert						
Column	<u> </u>			·		
cluster1 600000419 Isusor/HANA aminosoy/attorn -2,1763 Biological process cluster1 6000006127 mixturbendral electron tramport, ubiquinol to eyotxhrome c -1,5328 Biological process cluster1 6000006127 mevicine fusion with Oliga paparatus -2,999 Loster1 6000006120 Loster1 1,9378 Biological process cluster1 6000003127 COPII vesicle coat -1,6934 Cellular component cluster1 600003137 COPII vesicle coat -1,5555 Cellular component cluster1 600003137 COPII vesicle coat -1,5555 Cellular component cluster1 600003137 Colonia component -1,5555 Cellular component cluster1 600003138 Cellular component -2,6246 Cellular component cluster1 60000350 cukanyotic canalisation initiation storal cravity -2,6366 Cellular component cluster1 60000350 mixtornomial regard instance storality -2,3716 Molecular function cluster1 600000350 mixtornomial regard instance storality -2,37	1			- · · · · · · · · · · · · · · · · · · ·		
dustert	5			·		
Cutsert) 7			·		
dustert	3	cluster1	GO:0006122	mitochondrial electron transport, ubiquinol to cytochrome c	-1,9328	Biological process
dustert G00003177 membrane coat 1,595 Cellular component dustert G00003117 GOBIVeside coat 1,595 Cellular component dustert G00003131 Clathrin adaptor complex 1,595 Cellular component dustert G00001105 septin complex 2,2039 Cellular component dustert G00001105 septin complex 2,2039 Cellular component dustert G00001105 evicano translation intation factor 2 complex 2,2039 Cellular component dustert G00001355 evicano translation intation factor 2 complex 2,2034 Cellular component dustert G00001355 evicano translation intation factor 2 complex 2,204 Cellular component dustert G00001355 mitodonordiar legistrative chain complex 1,205 dustert G00001341 translation of translation 1,205 dustert G00001342 translation 1,205 dustert G0000343 translation 1,205 dustert G0000343 glycine-bydrow-membrate activity 2,716 dustert G0000343 glycine-bydrow-membrate activity 2,716 dustert G0000343 glycine-fi8NA ligose activity 2,764 dustert G0000343 glycine-fi8NA ligose activity 2,716 dustert G0000343 glycine-fi8NA ligose activity 2,716 dustert G0000344 company perfect activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,716 dustert G0000341 glycine-fi8NA ligose activity 2,716 dustert G0000341 glycine-fi8NA ligose activity 2,716 dustert G0000341 glycine-fi8NA ligose activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,716 dustert G0000345 glycine-fi8NA ligose activity 2,426 dustert G0000345 glycine-fi8NA ligose activity 2,427 dustert G00003)	cluster1	GO:0048280	vesicle fusion with Golgi apparatus	-2,3699	Biological process
dustert) I			- · · · · · · · · · · · · · · · · · · ·		
Colusters	2					·
clusters 60,0003175 clusters 60,00031105 clusters 60,00031105 clusters 60,00031105 clusters 60,0003550 clustary clusters 60,0003550 clustary clusters 60,00005556 clusters 60,00005556 clusters 60,00005570 mitochondrial respiratory chain complex 1-1,9328 cellular component clusters 60,0000173 Golg membrane 1-1,9328 cellular component clusters 60,00003743 translation initiation factor activity 2,2654 Molecular function clusters 60,0003743 translation initiation factor activity 2,2766 Cellular component clusters 60,0003743 translation initiation factor activity 2,276 Cellular component clusters 60,0003574 glycine hydroxymethytransfersae activity 2,276 Molecular function clusters 60,0003548 binding 1-1,66 Molecular function clusters 60,0003548 binding 1-1,66 Molecular function clusters 60,0008423 leurine tRNA ligase activity 2,21763 Molecular function clusters 60,0008423 leurine tRNA ligase activity 2,21763 Molecular function clusters 60,0008542 mema perpitase activity 2,21763 Molecular function clusters 60,0003536 Fibration Fibration 60,0003536 hydrolese activity, acting on carbon mitrogen (but not peptide) bonds, in linear amidines 1,9675 Molecular function clusters 60,0001613 hydrolese activity, acting on carbon mitrogen (but not peptide) bonds, in linear amidines 1,9675 Molecular function clusters 60,0001613 hydrolese activity, posphafar group as acceptor 2,0557 Molecular function clusters 60,0001613 hydrolese activity, posphafar group as acceptor 2,0557 Molecular function clusters 60,0001613 hydrolese activity, posphafar group as acceptor 2,0557 Molecular function clusters 60,0001613 hydrolese activity, posphafar group as acceptor 2,0557 Molecular function clusters 60,0001613 hydrolese activity, posphafar group as acceptor 2,0557 Molecular function clusters 60,0001614 hydrolese activity,	3					•
dustral G0.0031105 septim complex 2,0349 Cellular component dustral G0.0003556 eukaryolit christation factor 2 complex 2,0349 Cellular component dustral G0.0003556 colonos Cellular component 1,0597 Cellular function 1,0597	4 -			·		
Column Col.	o S			···		•
cluster1 60.0003556 cytoskeleton 1,6667 Cellular component cluster1 60.0000139 mitochondrial respiratory chain complex III 1,328 Cellular component cluster1 60.0000139 Golg membrane 1,4287 Cellular component cluster1 60.000014372 glysine hydroxynethyltransferase activity 2,5564 Molecular function cluster1 60.00004372 glysine hydroxynethyltransferase activity 2,7664 Molecular function cluster1 60.0008585 protein transporter activity 2,7664 Molecular function cluster1 60.0008232 describer (ERNA) ligase activity 2,1753 Molecular function cluster1 60.0005252 Ran GTPase binding 1,385 Molecular function cluster1 60.0005255 Gro-0005255 GTP binding 1,9855 Molecular function cluster1 60.0001261 and Transporter activity postage activity 1,4387 Molecular function cluster1 60.0001261 and Transporter activity active postage activity 1,4387 Molecular function clus	7			·		•
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		cluster 3	GO:0008152	metabolic process	-1,9382	Biological process

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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	Biological process
cluster 3	GO:0007017	microtubule-based process	-2,4915	Biological process
cluster 3	GO:0006412	translation	-2,0331	Biological process
cluster 3	GO:0006122	mitochondrial electron transport, ubiquinol to cytochrome c	-2,0662	Biological process
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	Α	В
Α	3.07	268.0	135.9	119.0	-30	-12
m ⁶ 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)
2/8 Cells	TC (Two Cell embryos)
	FC (Four Cell embryos)
	EM (Early Morula)
Morula	M (Morula)
Blastula	B (Blastula)
	RM (Rotary Movement)
Gastrula	FS (Free Swimming)
	EG (Early Gastrula)
	G (Gastrula)
	T (Trochophore) 1
Trochophore	T2
	T3
	T4
	T5
	ED (Early D larvae) 1
D larvae	ED2
	D (D larvae)1
	D2
	D3
	D4
	D5
Spat	S (Spat)
Juvenile	J (Juvenile)