Supplementary Materials

SUPPLEMENTARY METHODS

Public data used in this study

TCGA-LIHC cohort

The TCGA-LIHC cohort comprises 275 HCC and 50 non-tumor liver tissues analyzed using Illumina Infinium HumanMethylation450 arrays, whole exome and RNA sequencing. Clinical annotations, DNA methylation (QC metrics and methylation beta values) and RNA-seq data (raw read counts per gene) were obtained from the TCGA data portal (https://tcga-data.nci.nih.gov). Cholangiocarcinomas and mixed forms of HCC were discarded to keep only pure HCC and non-tumor samples. Single somatic mutations and TERT promoter mutation were retrieved from the original article (1). HCC cases in this cohort are predominantly of American, Canadian or Vietnamese origin, mostly males (64%), with a median of 63 years and related to diverse risk factors: alcohol (34%), HBV (14%), HCV (17%). Detailed clinical characteristics and sequencing details for each sample are available at the TCGA website.

HEPTROMIC cohort

The HEPTROMIC cohort comprises 221 surgically resected HCC and 19 non-tumor liver tissues analyzed using Illumina Infinium HumanMethylation450 arrays (2). HCC cases in this cohort come from two institutions of the HCC Genomic Consortium: IRCCS Istituto Nazionale Tumori (Milan, Italy) and Hospital Clínic (Barcelona, Spain). HEPTROMIC cases are mostly males (78%), with a median of 66 years and a predominance of viral-related etiologies (HCV, 47%; HBV, 20%). No additional molecular data was available for this cohort

Description of (epi)genomic features analyzed for correlation with methylation components

For each component, we examined the association of the following (epi)genomic features were considered:

- CpG island-based features: CpG islands retrieved from UCSC database (release 19, GRCh37), shores (2 kb on each side of the islands) and shelves (2 kb outside shores)
- gene-based features: promoter (defined as transcription start site (TSS) +/- 500 bp) and gene body for each gene in GENCODE database (release 19 - GRCh37.p13)
- chromatin states in normal liver as defined by the ROADMAP consortium (3). Eighteen chromatin states were defined by the consortium based on the genome-wide analysis of 6 histone marks (H3K4me3, H3K4me1, H3K36me3, H3K27me3, H3K9me3 and H3K27ac) using

a multivariate Hidden Markov model (ChromHMM tool (4)). Each chromatin state corresponds to a particular combination of histone marks and is associated with a specific type of functional element (e.g. active TSS, genic enhancers, heterochromatin…). We downloaded the bed file of chromatin states in normal liver through the ROADMAP epigenomics website (http://www.roadmapepigenomics.org).

- DNA methylation domains derived from whole genome bisulfite sequencing of normal hepatocytes (5). Genome-wide CpG methylation analyses have shown that the epigenome is organized in megabase-scale partially methylated domains (PMD, methylation between 50% and 80%) and highly methylated domains (HMD, methylation > 80%), as well as short (regulatory) lowly methylated (LMR, methylation between 10% and 50%) and unmethylated regions (UMR, methylation < 10%) (6,7). We retrieved these domains in normal liver defined by Salhab *et al.* (5) using a Hidden Markov Model-based detection method called methylSeekR (7).
- replication timing in the liver cancer cell line HepG2. We used Repli-seq data generated by the ENCODE project (8) to characterize the replication timing of each CpG site. To do so, we downloaded the wavelet-smoothed Repli-seq signals for HepG2 cell line through the UCSC genome browser, and we segmented this signal into 10 deciles from the earliest (decile 1) to the latest (decile 10) replicated regions.

Description of clinico-molecular annotations analyzed for correlation with methylation components

Clinical features for the LICA-FR cohort are detailed in Supporting Table S1 and included patient information (gender, geographic origin, age), risk factors (alcohol intake, HBV or HCV infection, metabolic syndrome), underlying liver disease (METAVIR fibrosis stage; F0-F1: no fibrosis, F2-F3: moderate fibrosis, F4: cirrhotic liver) and various tumor characteristics like the number of nodules and size of the largest nodule, vascular invasion, Barcelona Clinic Liver Cancer stage (BCLC 0, A, B, C and D from the earliest to the terminal stage) and Edmonson grade (I-II = well differentiated, III-IV = poorly differentiated). In the TCGA cohort, the same features were analyzed except the following that were not available: metabolic syndrome, number of nodules and largest nodule size, vascular invasion, BCLC stage and Edmonson grade. The Ishak fibrosis score was converted to METAVIR for comparison with

the LICA-FR series as follows: “0,1,2 - No Fibrosis or Portal Fibrosis” = F0-F1; “3,4 - Fibrous Speta” = F2-F3; “5,6 - Nodular Formation, Incomplete Cirrhosis” and “Established Cirrhosis” = F4).

Molecular features analyzed in both cohorts included:

- driver alterations of 27 HCC driver genes defined by Schulze *et al.* (9) or characterized recently in the lab (10,11): *TERT*, *CTNNB1*, *TP53*, *ARID1A*, *AXIN1*, *CDKN2A*, *ARID2*, *RPS6KA3*, *NFE2L2*, *KEAP1*, *PTEN*, *HNF1A*, *ALB*, *ACVR2A*, *RPL22*, *CDKN1A*, *RB1*, *TSC2*, *ATP10B*, *FGA*, *MEF2C*, *ZNRF3*, *EPHA4*, *TSC1*, *CCNA2*, *CCNE1*, *BAP1*). Mutational status for these 27 genes was derived from whole exome or whole genome sequencing, completed by *TERT* promoter screening by Sanger sequencing for both the TCGA-LIHC (1) and LICA-FR (12) cohorts.
- molecular subgroups of HCC, G1 to G6, defined by Boyault *et al.* from gene expression data (13). In the LICA-FR cohort, G1-G6 groups were predicted using a combination of 16 marker genes analyzed in qRT-PCR, as previously described (14). We used the *MS.liverK* package (15) to predict the G1-G6 groups based on RNA-seq expression data in the TCGA LIHC cohort.
- selected transcriptional signatures related to hepatocellular carcinoma phenotypes were analyzed, including differentiation (*ALB*, *CDH1*, *APOF*, *CYP1A1*, *CYP2A6*, *UGT2B7*, *HNF1A*, *HNF4A*) and proliferation (*CDC20*, *GMNN*, *MKI67*, *RRM2*, *CCNA2*, *CCND1*, *CCNE1*, *AURKA*, *BUB1*, *PCNA*, *RAN*, *BIRC5*, *SPP1*) signatures defined by Nault *et al.* (14), as well as liver progenitor (*PROX1*, *AFP*, *EPCAM*, *IGF2*, *SALL4*, *PROM1*, *LGR5*, *GPC3*, *LIN28B*), stem cell (*CD47*, *CD44*, *KDR*, *IL6*, *NCAM2*, *THY1*, *KIT*) and epithelial-mesenchymal transition/metastasis (*SNAI2*, *ITGB3*, *TWIST1*, *ZEB2*, *PLAUR*, *VIM*) signatures defined by Caruso *et al.* (16). For each signature, a score was computed in each tumor as the mean expression of marker genes.
- immune infiltrate estimated from RNA-seq data using the MCPcounter tool (17). The overall immune infiltrate was obtained by summing MCPcounter scores for all immune cell populations.

Linking CpG methylation with transcriptional networks

We used ELMER tool (18) to identify CpG-gene pairs, i.e. correlations between the methylation level of a CpG site and the expression of one or more nearby genes, leveraging samples with matched methylation array and RNA-seq data. The *get.pair* function of ELMER v2 package (19) was used in unsupervised mode to compare the expression of the 10 genes closest to each CpG site between the

40% samples with the highest/lowest methylation level for that CpG. We used a permutation size of 10,000 and selected CpG-gene pairs with an empirical p-value *Pe* < 0.001. We used an in-house adaptation of the GSEA (Gene Set Enrichment Analysis) method (20), modified to take as input a ranked gene list instead of an expression matrix, to identify gene sets associated with each methylation component (MC). For each MC, genes were ranked according to the contribution of their paired CpG. Genes paired with several CpGs were assigned to the CpG with the strongest contribution to the component (in absolute value). GSEA was then used to identify gene sets from the MSigDB v6 database overrepresented among genes paired with the most contributing CpGs. We used the *get.enriched.motif* of ELMER v2 package to identify transcription factor binding motifs enriched around the most contributing CpGs of each MC.

DNA methylation-based classification of hepatocellular carcinomas and non-tumor liver tissues

We used consensus clustering (21) to identify HCC subgroups on the basis of their DNA methylation profiles. A same set of CpGs was used for the LICA-FR and TCGA LIHC cohorts, corresponding to the union of the 10,000 most variant probes (based on standard deviation) in each series. We then established consensus partitions of the data set in K clusters (for K = 2, 3, …, 8), based on 1,000 resampling iterations of hierarchical clustering, with Pearson's dissimilarity as the distance metric and Ward's method for linkage analysis. We used the cumulative distribution functions (CDF) of the consensus matrices to determine the optimal number of clusters, considering both the shape of the functions and the area under the CDF curves. The Bioconductor ConsensusClusterPlus package was used for consensus clustering analysis. T-stochastic neighbor embedding (tSNE) was used to project the data set in two dimensions using the *Rtsne* package (https://github.com/jkrijthe/Rtsne). t-SNE was applied to a Pearson correlation matrix of CpGs with standard deviation > 0.25, with a theta value of zero over 2,000 iterations and perplexity of 9 for TCGA-LIHC and 6 for LICA-FR.

We also performed an unsupervised classification of non-tumor liver tissues from the LICA-FR cohort. Hierarchical clustering was done on the 15 000 most variant probes (based on standard deviation) using R function *hclust* with Pearson's dissimilarity as distance metric and Ward.D2 linkage method.

Supplementary Methods References

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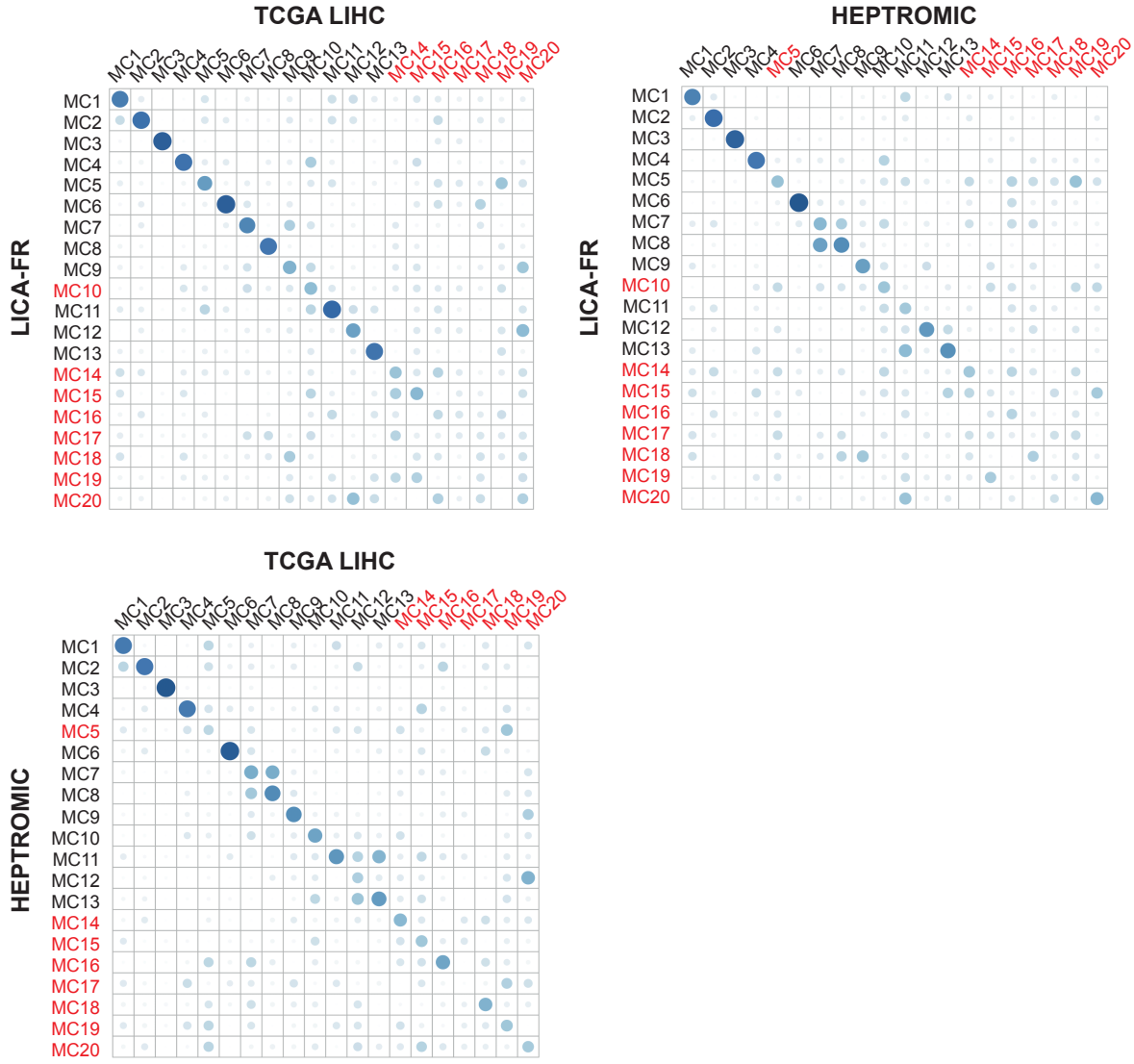
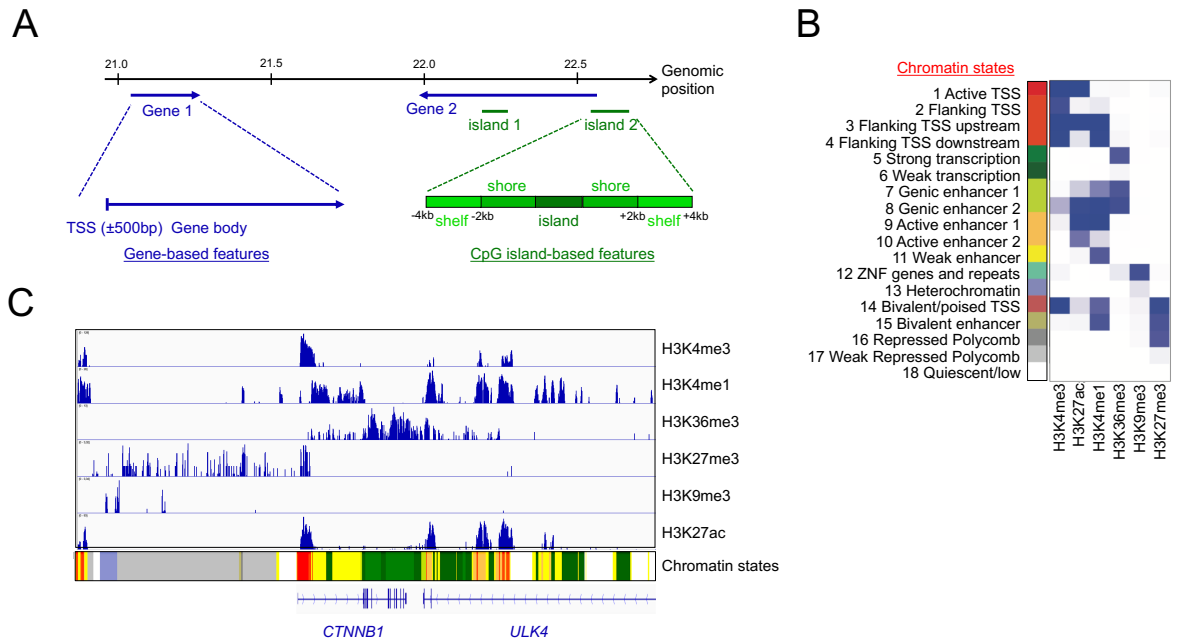
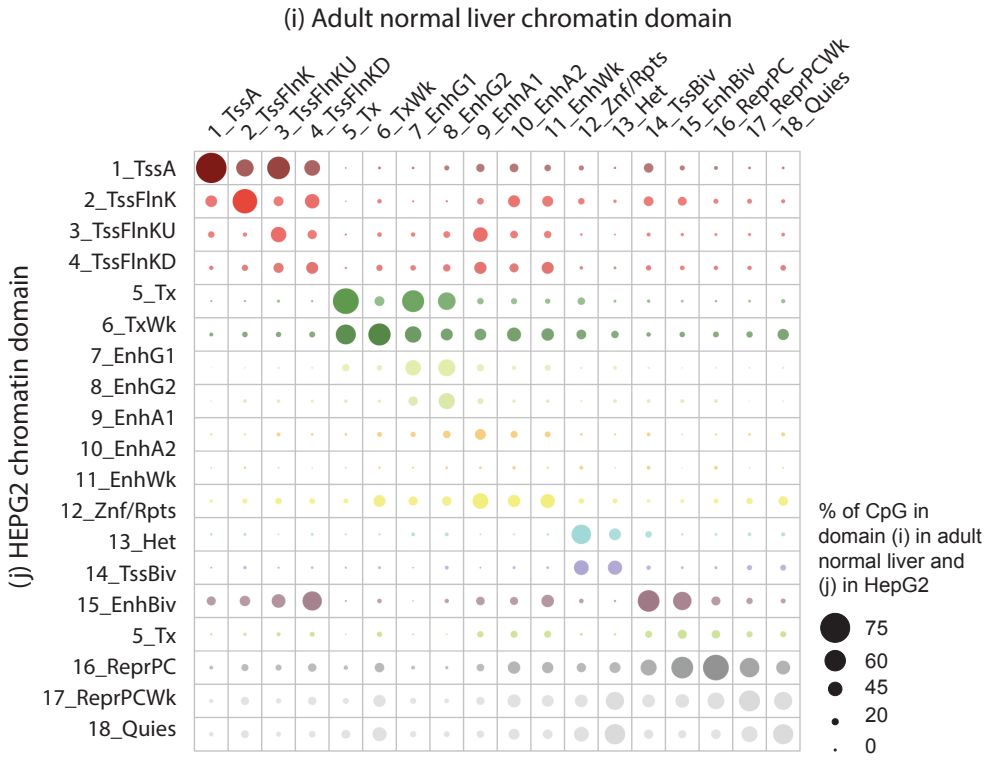
SUPPORTING FIGURES



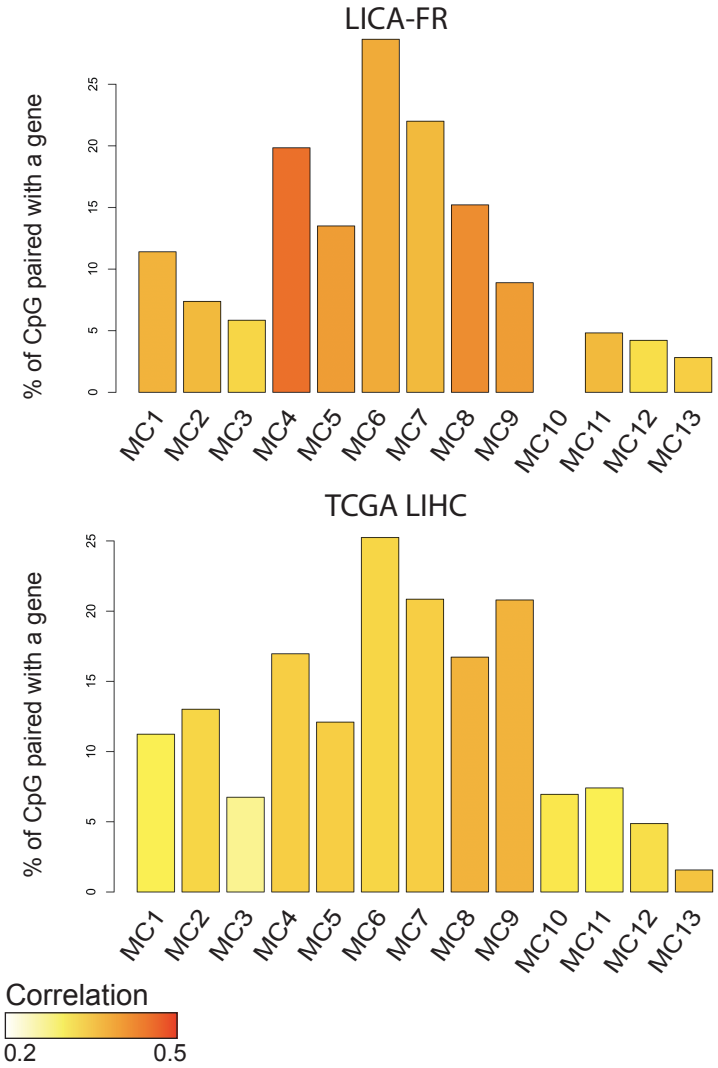
Supporting FIG. S1. Reproducibility of methylation components across the three data sets. Pearson correlation coefficients were used to link each methylation component (MC) extracted in one cohort with its closest equivalent in the other two cohorts. The figure displays the Pearson correlation scores between each MC pair. MCs identified in one series without a match in the second are indicated in red. Abbreviations: LICA-FR, Liver Cancer (France); MC, methylation component; TCGA-LIHC, The Cancer Genome Atlas Liver Hepatocellular Carcinoma.



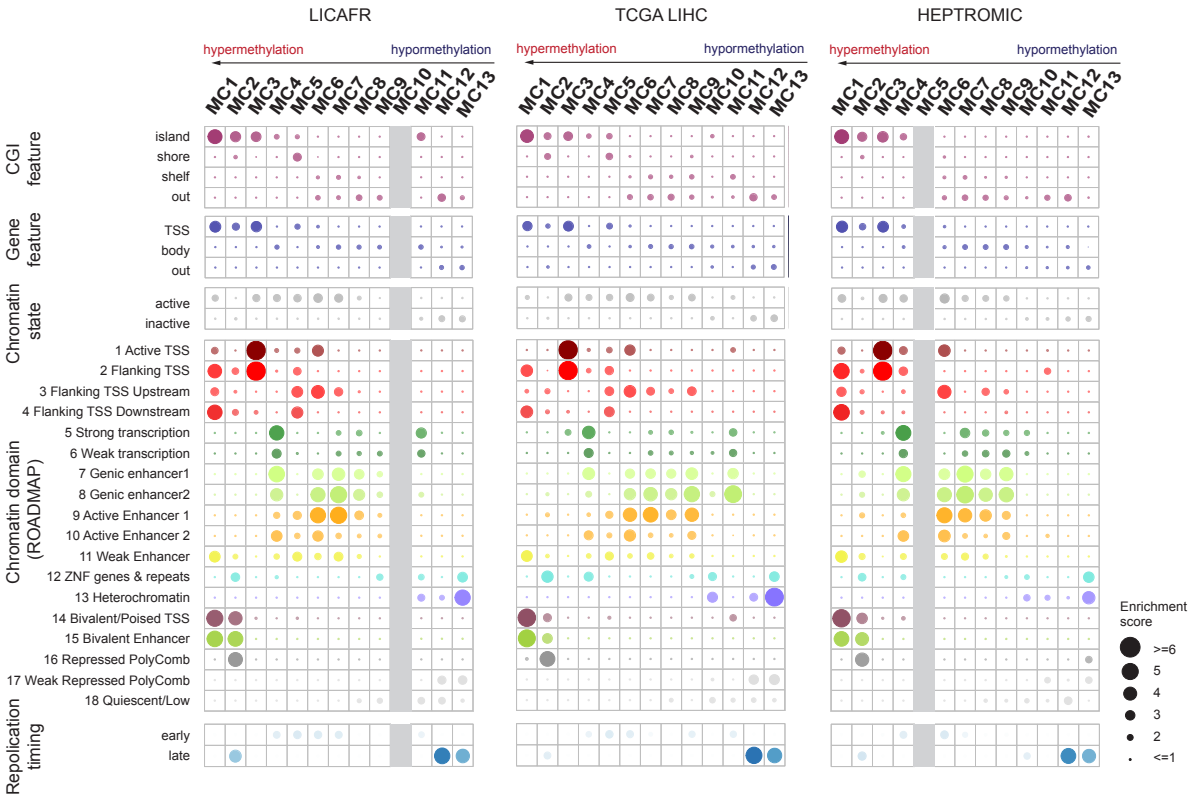
Supporting FIG. S2. Definition of CGI-based, gene-based features and chromatin states. Each CpG site was annotated relative to its position with respect to genes, CGIs and chromatin states. (A) Gene-based features comprise transcription start sites (TSS) +/- 500 bp and gene bodies for each gene in GENCODE database (release 19 - GRCh37.p13). CGI-based features comprise CpG islands (UCSC database release 19, GRCh37), shores (2 kb on each side of the islands) and shelves (2 kb outside shores). (B) Chromatin states were defined in various cell types by the Roadmap consortium based on the genome-wide analysis of 6 histone marks (H3K4me3, H3K4me1, H3K36me3, H3K27me3, H3K9me3 and H3K27ac). This panel, adapted from Kundaje *et al.*, indicates the combination of histone marks associated with each chromatin state. (C) Integrative Genomics Viewer (IGV) visualization of histone marks and chromatin states across the *CTNNB1* locus in liver tissue (Roadmap data).



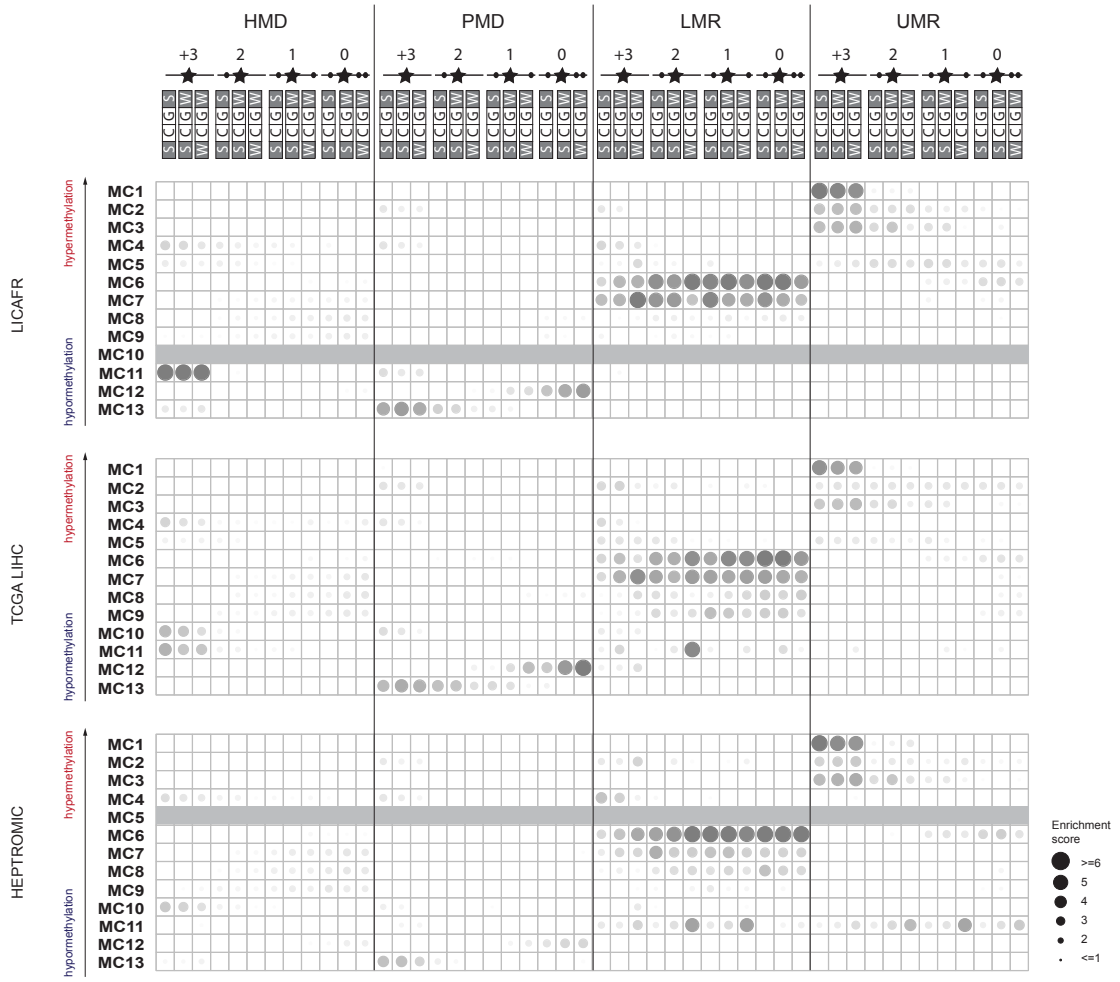
Supporting FIG. S3. Correlation matrix of Roadmap chromatin domains between normal liver and the cancerous HepG2 cell line. Chromatin states (numbered as in Figure 2A) display a highly significant overlap between normal liver and HepG2 (P < 2.2e-16, Chi-square test). When considering the 18 chromatin state categories, 37% of CpG sites analyzed with the Illumina Infinium 450k Beadchip have the same state in normal liver and HepG2. However, most discrepancies involve very close chromatin states, e.g. “TssA” in normal liver and “TssFlnk” in HepG2. When grouping chromatin states into more general categories (namely TSS, enhancer, transcription, and inactive chromatin), 71% of CpG sites have the same state in normal liver and HepG2.



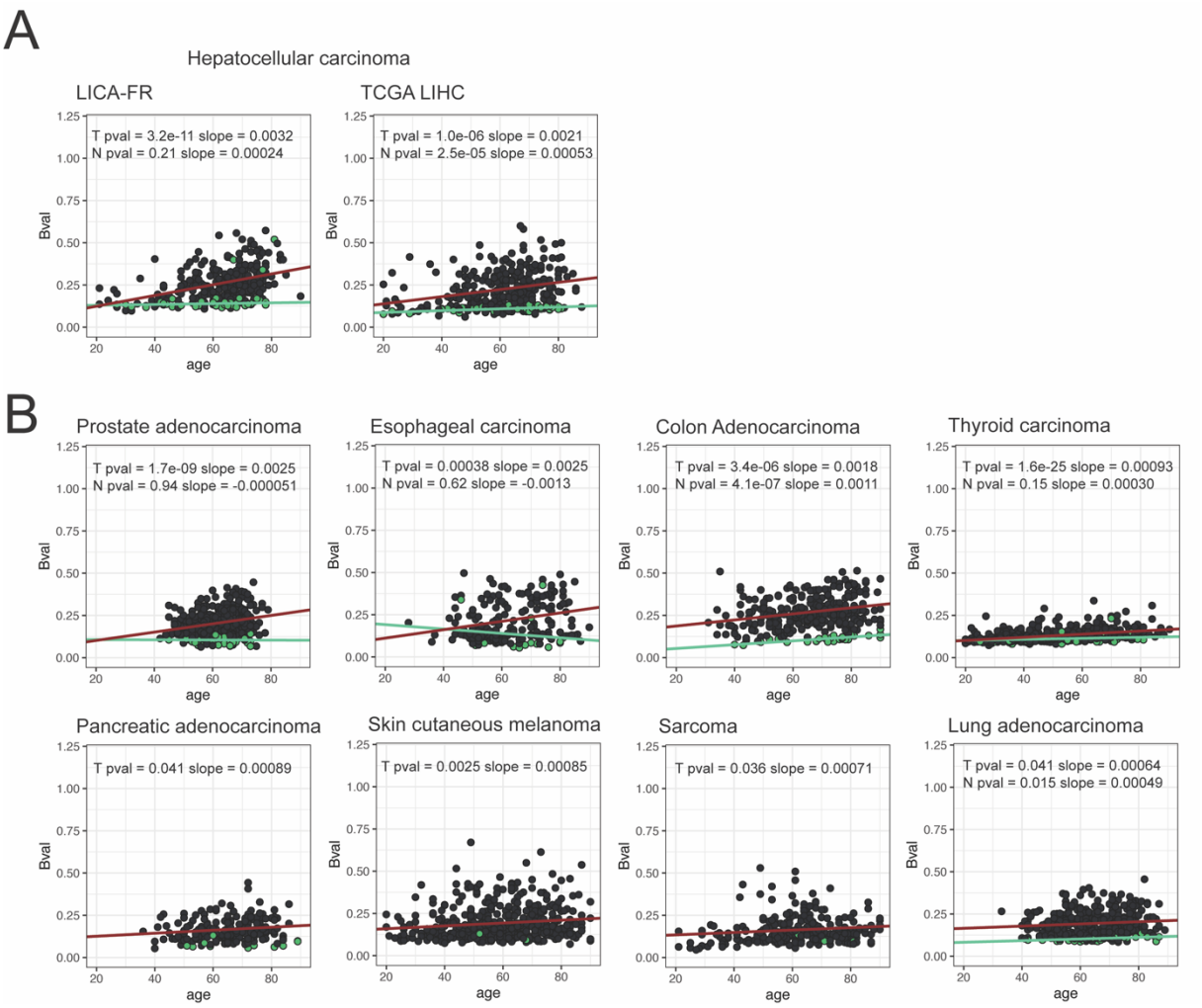
Supporting FIG. S4. Transcriptional impact of each methylation component. Genes "paired" with each CpG (whose expression is correlated with CpG methylation) were identified using the ELMER tool. The bar plots represent the proportion of the most contributing CpG sites of each component with a "paired" gene. The color of each bar indicates the average Pearson correlation score between CpG methylation and the expression of their paired gene. Abbreviation: ELMER, Enhancer Linking by Methylation/Expression Relationships.



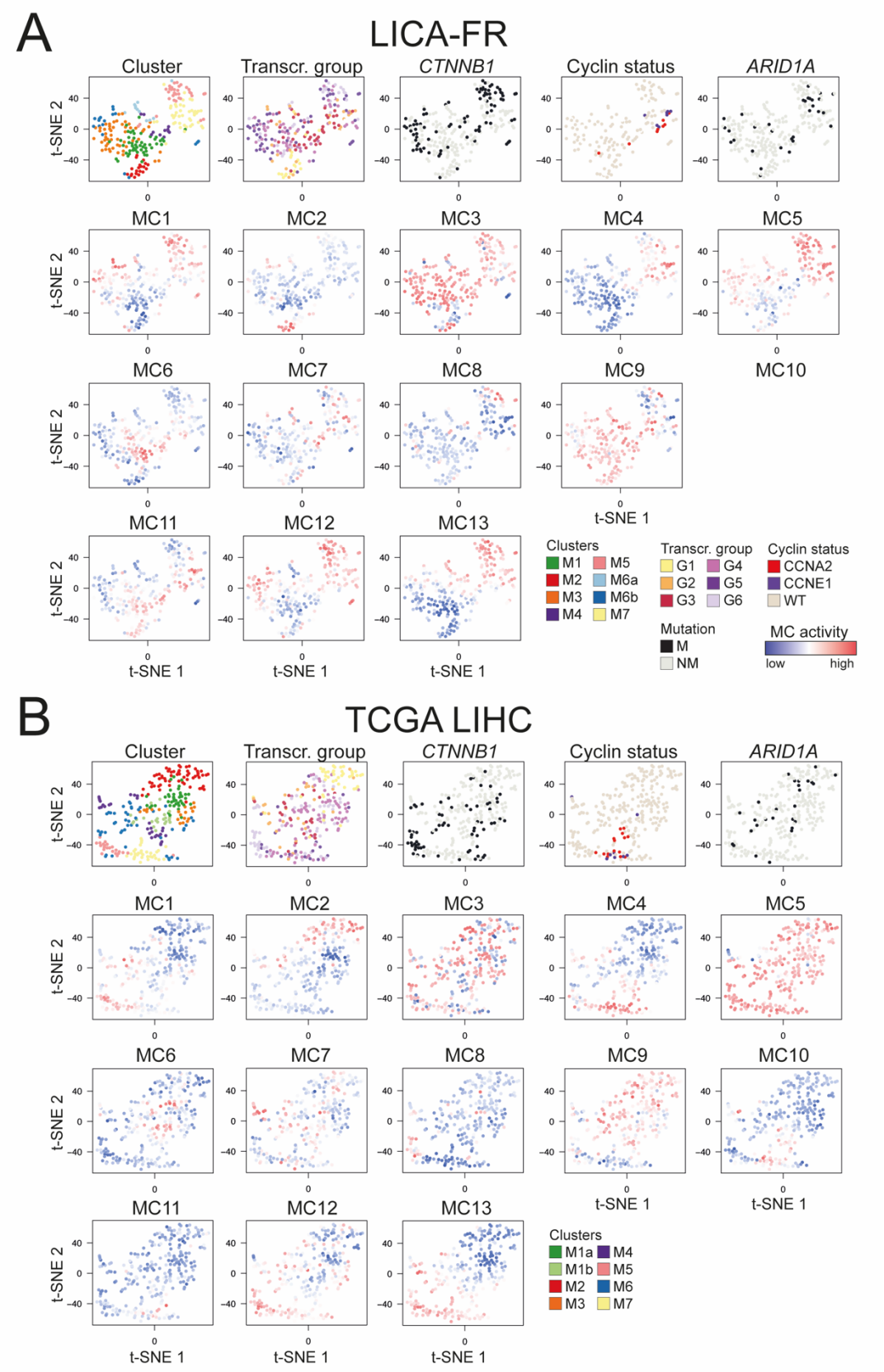
Supporting FIG. S5. Association of MCs with CGI- and gene-based features, chromatin states, and replication timing in the LICA-FR, TCGA-LIHC and HEPTROMIC cohorts. The most contributing CpG sites of each component were extracted in each cohort, and the enrichment of these CpG sites across CGI features, gene-based features, chromatin states, and replication deciles are shown below. Abbreviations: CGI, CpG island; TSS, transcription start site; ZNF, zinc finger.



Supporting FIG. S6. Association of MCs with CpG context in the LICA-FR, TCGA-LIHC and HEPTROMIC cohorts. The most contributing CpG sites of each component were extracted in each cohort, and the enrichment of these CpG sites across 48 CpG categories are shown below. Methylation categories are defined based on the methylation domain in normal liver (HMD: Highly Methylated Domain; PMD: Partially Methylated Domain; LMR: Lowly Methylated Region; UMR: UnMethylated Region), local CpG density (number of flanking CpGs within 35 base pairs on each side of the dyad), and sequence context (SCGS, SCGW, or WCGW, with S denoting C or G and W denoting A or T). Abbreviations: HMD, highly methylated domain; LMR, lowly methylated region; PMD, partially methylated domain; UMR, unmethylated region.

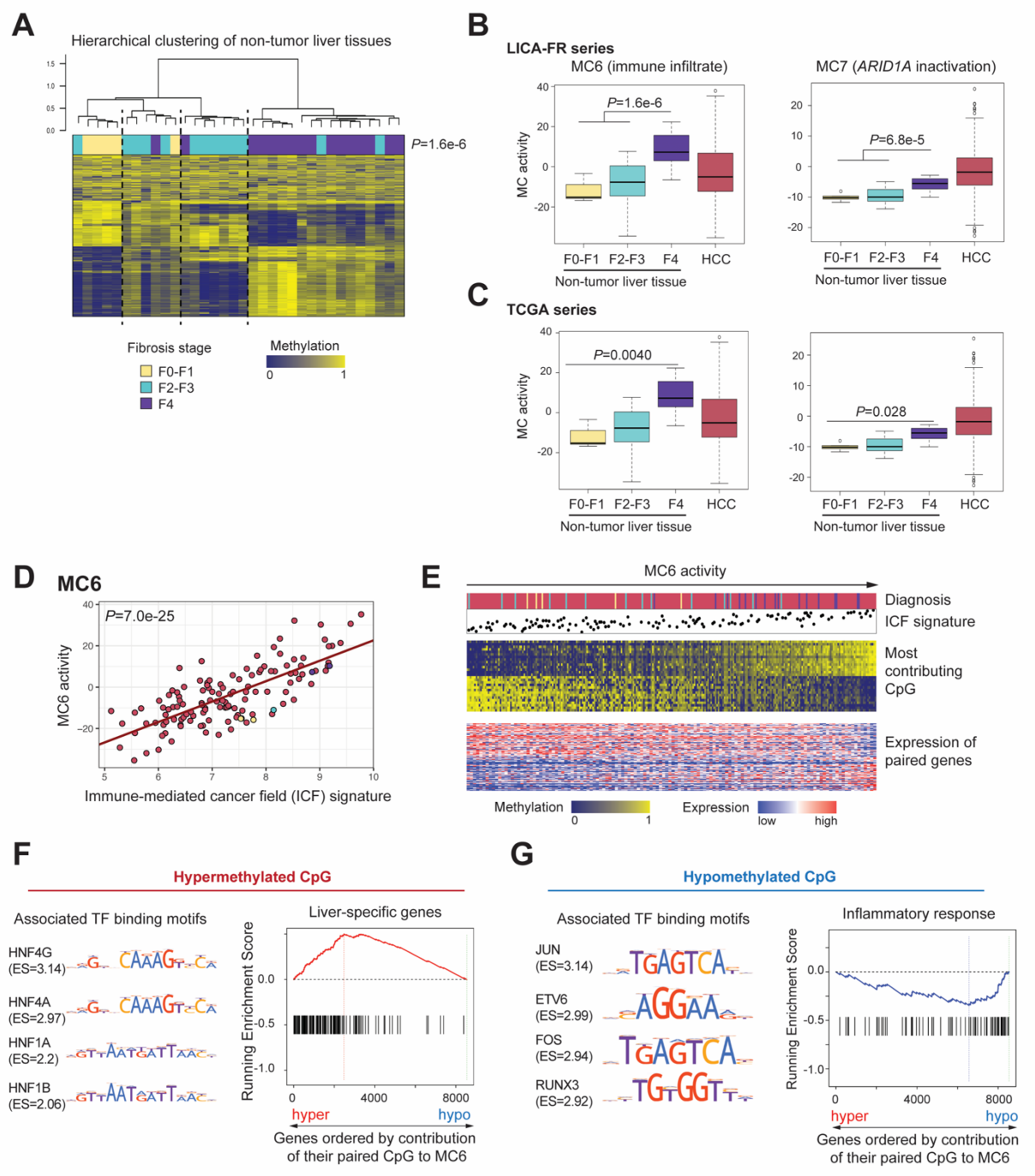


Supporting FIG. S7. Correlation of MC1 with age across diverse normal and tumor tissues. (A) The average methylation across the most contributing CpG sites of MC1 was calculated in hepatocellular carcinomas and normal liver tissues from the LICA-FR (left) and TCGA-LIHC (right) series. Linear regression was used to estimate the *P* value and slope, indicating the beta-value increase per year. (B) Similar analysis in various cancer types and matched normal tissues from the TCGA project. Linear regression for normal samples was only calculated when 10 or more samples were available. Abbreviations: bval, beta value; N, normal tissue; T, tumors.



Supporting FIG. S8. t-SNE plots showing the methylation-based classification of HCC with associated clinico-molecular features and MCs. t-SNE plots depict the classification of HCC from the (A) LICA-FR and (B) TCGA cohorts based on their DNA methylation profiles. Associated clinical and

molecular features and the intensity of each MC are represented by color codes. Abbreviations: ARID1A, AT-rich interactive domain-containing protein 1A; CCNA2, cyclin A2; CCNE1, cyclin E1; CTNNB1, catenin beta 1; M, mutated ; NM, non-mutated; t-SNE, t-distributed stochastic neighbor embedding; transcr., transcriptomic; WT, wild-type.



Supporting FIG. S9. Pre-neoplastic DNA methylation changes in cirrhotic liver. (A) Hierarchical clustering of non-tumor liver tissues reveals four homogenous subgroups strongly associated with fibrosis stage. (B) Activity of components MC6 and MC7 in HCC and adjacent non-tumor liver tissues with different levels of fibrosis (METAVIR stages) in the LICA-FR series. (C) Activity of components MC6 and MC7 in HCC and adjacent non-tumor liver tissues with different levels of fibrosis (METAVIR stages) in the TCGA series. (D) MC6 activity is strongly correlated to the immune-mediated cancer field (ICF) signature evaluated from RNA-seq data. Sample type (HCC or non-tumor liver with diverse fibrosis stage) is indicated with a color code as in panel (B). (E) Heatmap representing the methylation of the

MC6 MRCpGs and the expression of paired genes identified with ELMER. Samples are ordered according to MC6 activity (color code for sample type as in (B)), and the ICF gene expression signature is represented below. (F) Left: Transcription factor binding motif enrichment around CpG sites hypermethylated in samples with the highest activity of MC6. Right: Gene set enrichment analysis of genes paired with CpG sites hypermethylated in samples with the highest activity of MC6. (G) Same as (F) for hypomethylated CpG sites. Activity of components MC6 and MC7 in HCC and adjacent non-tumor liver tissues with different levels of fibrosis (METAVIR stages) in TCGA-LIHC series. Abbreviations: ETV6, ETS variant TCF 6; HNF1A/B, hepatocyte nuclear factor 1 alpha/beta; HNF4A/G, HNF 4 alpha/gamma; ICF, immune-mediated cancer field; MRCpGs, most representative CpG sites;; RNA-seq, RNA sequencing; RUNX3, RUNX family transcription factor 3; TF, transcription factor.

Table S1: Clinical and molecular annotations for the 274 samples of the LICA-FR series

Sample	Sample type	Gender	Age at sampling	Geographical origin
CHC018T	HCC	F	35	Africa
CHC229T	HCC	F	65	Europe
CHC231T	HCC	M	66	Europe
CHC013T	HCC	M	63	Europe
CHC441T	HCC	M	77	Europe
CHC333T	HCC	M	73	Europe
CHC239T	HCC	F	21	Africa
CHC399T	HCC	M	67	Europe
CHC014T	HCC	M	30	Africa
CHC043T	HCC	M	56	Asia
CHC037T	HCC	M	51	Africa
CHC339T	HCC	F	26	Africa
CHC245T	HCC	M	64	Europe
CHC253T	HCC	M	67	Europe
CHC158T	HCC	M	65	Europe
CHC445T	HCC	M	55	Europe
CHC080T	HCC	M	43	Europe
CHC335T	HCC	M	68	Europe
CHC230T	HCC	M	70	Europe
CHC228T	HCC	M	48	Europe
CHC010T	HCC	F	18	Europe
CHC137T	HCC	M	71	Europe
CHC205T	HCC	M	46	Europe
CHC218T	HCC	M	69	Europe
CHC081T	HCC	F	76	Asia
CHC031T	HCC	M	67	Europe
CHC242T	HCC	M	70	Europe
CHC059T	HCC	M	40	Europe
CHC220T	HCC	M	73	Europe
CHC206T	HCC	M	64	Europe
CHC152T	HCC	M	64	Europe
CHC046T	HCC	M	61	Europe
CHC211T	HCC	M	69	Europe
CHC437T	HCC	M	59	Europe
CHC725T	HCC	M	60	Europe
CHC317T	HCC	F	69	Europe
CHC789T	HCC	M	54	Europe

CHC195T	HCC	M	71	Europe
CHC1196T	HCC	M	27	Africa
CHC398T	HCC	M	50	Africa
CHC1010T	HCC	F	53	Europe
CHC1035T	HCC	M	68	Europe
CHC1040T	HCC	M	73	Europe
CHC1041T	HCC	M	69	Europe
CHC1044T	HCC	M	78	Europe
CHC1052T	HCC	M	75	Europe
CHC1055T	HCC	M	68	Europe
CHC1060T	HCC	M	66	Europe
CHC1061T	HCC	F	79	Europe
CHC1062T	HCC	M	65	Europe
CHC1065T	HCC	M	77	Europe
CHC1146T	HCC	M	60	Europe
CHC1154T	HCC	M	43	Africa
CHC1162T	HCC	M	60	Europe
CHC1192T	HCC	M	40	Africa
CHC1199T	HCC	M	62	Europe
CHC1201T	HCC	M	73	Europe
CHC255T	FLC	F	39	Europe
CHC320T	HCC	M	65	Europe
CHC334T	FLC	F	24	Europe
CHC412T	FLC	F	51	NA
CHC429T	HCC	F	64	Europe
CHC442T	FLC	F	27	Europe
CHC451T	HCC	M	75	Europe
CHC613T	HCC	M	70	Europe
CHC614T	HCC	M	61	Europe
CHC703T	HCC	M	55	Europe
CHC734T	HCC	M	65	Europe
CHC736T	HCC	M	77	Europe
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CHC314T	HCC	M	71	Europe
CHC322T	HCC	M	74	Europe
CHC433T	HCC	M	70	Europe
CHC794T	HCC	M	73	Europe
CHC798T	HCC	M	73	Europe
CHC961T	HCC	M	57	Europe
CHC060T	HCC	M	68	Europe
CHC1137T	HCC	M	57	Europe
CHC1568T	HCC	M	71	Asia
CHC1604T	HCC	M	57	Europe
CHC1717T	HCC	M	50	Africa
CHC1763T	HCC	M	75	Europe
CHC097T	HCC	M	56	Europe
CHC1148T	HCC	M	69	Europe
CHC1744T	HCC	M	50	Africa
CHC1152T	HCC	M	63	Europe
CHC1205T	HCC	M	72	Africa
CHC1616T	HCC	F	77	Europe
CHC1720T	HCC	M	81	Europe
CHC1745T	HCC	F	69	Europe
CHC432T	HCC	M	70	Europe

CHC1207T	HCC	M	60	Europe
CHC1626T	HCC	M	75	Europe
CHC1725T	HCC	F	83	Africa
CHC1746T	HCC	M	75	Europe
CHC1209T	HCC	M	66	Europe
CHC1594T	HCC	F	76	Europe
CHC1629T	HCC	M	64	Europe
CHC1731T	HCC	F	55	Europe
CHC1747T	HCC	M	54	Europe
CHC801T	HCC	M	78	Europe
CHC1211T	HCC	F	32	Africa
CHC1700T	HCC	M	62	Asia
CHC1732T	HCC	M	49	Europe
CHC1749T	HCC	M	66	Asia
CHC1183T	HCC	M	60	Europe
CHC1597T	HCC	M	41	Europe
CHC1704T	HCC	M	43	Africa
CHC1734T	HCC	M	76	Europe
CHC1185T	HCC	M	53	Asia
CHC1531T	HCC	M	78	Europe
CHC1598T	HCC	F	76	Europe
CHC1705T	HCC	M	83	Europe
CHC1736T	HCC	M	58	Europe
CHC1751T	HCC	M	52	Europe
CHC1186T	HCC	M	56	Africa
CHC1539T	HCC	M	45	Europe
CHC1600T	HCC	M	69	Europe
CHC1708T	HCC	M	56	NA
CHC1028T	HCC	M	62	Europe
CHC1189T	HCC	M	62	Europe
CHC1545T	HCC	M	77	Europe
CHC1739T	HCC	M	55	Europe
CHC1754T	HCC	M	34	Africa
CHC1190T	HCC	F	68	Europe
CHC1602T	HCC	M	71	Europe
CHC1741T	HCC	M	57	Europe
CHC1756T	HCC	M	73	Europe
CHC1079T	HCC	M	60	Europe
CHC1566T	HCC	M	68	Europe
CHC1603T	HCC	M	78	Europe
CHC1715T	HCC	M	72	Europe

CHC1742T	HCC	M	67	Europe
CHC1757T	HCC	M	41	Europe
CHC2025T	HCC	F	58	Europe
CHC2112T	HCC	F	48	Europe
CHC2029T	HCC	M	74	Europe
CHC2113T	HCC	M	61	Europe
CHC2215T	HCC	M	65	Europe
CHC2034T	HCC	M	80	Europe
CHC2115T	HCC	M	75	Europe
CHC2127T	HCC	M	57	Europe
CHC2043T	HCC	F	21	Europe
CHC2128T	HCC	F	53	Europe
CHC2048T	HCC	M	65	Europe
CHC2134T	HCC	F	57	Europe
CHC2052T	HCC	M	61	Europe
CHC2141T	HCC	M	74	Europe
CHC2098T	HCC	M	85	Europe
CHC2099T	HCC	M	73	Europe
CHC2202T	HCC	F	48	Europe
CHC2103T	HCC	M	57	Europe
CHC2206T	HCC	M	90	Europe
CHC2111T	HCC	F	56	Europe
CHC2211T	HCC	F	37	Europe
CHC2216T	HCC	M	62	Europe
CHC2208T	HCC	M	53	Europe
CHC1743T	HCC	M	64	Europe
CHC1569T	HCC	M	84	Europe
CHC1611T	HCC	M	75	Europe
CHC1719T	HCC	M	57	Europe
CHC1591T	HCC	M	60	Europe
CHC2200T	HCC	M	69	Europe
CHC1053T	HCC	M	74	Europe
CHC1595T	HCC	M	74	Europe
CHC1601T	HCC	M	75	Europe
CHC1596T	HCC	M	66	Europe
CHC1624T	early.HCC	M	59	Europe
CHC2351T	early.HCC	M	69	NA
CHC1177T	HCC	M	62	Europe
CHC1712T	HCC	M	76	Europe
CHC2358T	early.HCC	M	65	NA
CHC1180T	HCC	M	65	Europe

CHC1714T	HCC	M	72	Europe
CHC2362T	early.HCC	M	49	Europe
CHC1737T	HCC	M	73	Europe
CHC1210T	HCC	F	44	Asia
CHC1738T	HCC	F	68	Europe
CHC1081T	HCC	M	53	Europe
CHC1750T	HCC	M	54	Europe
CHC1530T	HCC	M	64	Europe
CHC1753T	HCC	M	65	Africa
CHC902T	HCC	M	73	Europe
CHC1534T	HCC	M	67	Europe
CHC1774T	early.HCC	M	65	Europe
CHC923T	HCC	M	74	Europe
CHC1085T	HCC	M	49	Europe
CHC1556T	HCC	F	54	Europe
CHC1775T	early.HCC	M	65	Europe
CHC1592T	HCC	F	69	Europe
CHC2449T	HCC	M	81	Europe
CHC2695T	HCC	M	94	Europe
CHC2415T	HCC	M	68	Europe
CHC2448T	HCC	M	82	Europe
CHC2687T	HCC	M	76	Europe
CHC2707T	HCC	M	79	Europe
CHC1606T	HCC	F	77	Europe
CHC2539T	HCC	F	41	Europe
CHC2686T	HCC	F	52	NA
CHC2207T	HCC	M	49	Europe
CHC2560T	HCC	M	74	Europe
CHC2132T	HCC	M	57	Europe
CHC2491T	HCC	M	66	Europe
CHC2558T	HCC	M	70	Europe
CHC2697T	HCC	M	64	Europe
CHC2135T	HCC	F	57	Europe
CHC2706T	HCC	M	70	Europe
CHC2210T	HCC	M	66	Europe
CHC2538T	HCC	F	76	Europe
CHC2443T	HCC	M	74	Europe
CHC2691T	HCC	M	68	Europe
CHC014N	NT	M	30	Africa
CHC013N	NT	M	63	Europe
CHC898N	NT	M	71	Europe

CHC235N	NT	F	66	Europe
CHC591N	NT	F	37	NA
CHC152N	NT	M	64	Europe
CHC469N	NT	F	32	Europe
CHC229N	NT	F	65	Europe
CHC028N	NT	M	64	Europe
CHC566N	NT	F	55	NA
CHC245N	NT	M	64	Europe
CHC333N	NT	M	73	Europe
CHC239N	NT	F	21	Africa
CHC226N	NT	M	42	Africa
CHC046N	NT	M	61	Europe
CHC081N	NT	F	76	Asia
CHC168N	NT	M	67	Europe
CHC173N	NT	M	61	Europe
CHC043N	NT	M	56	Asia
CHC934N	NT	F	44	NA
CHC1196N	NT	M	27	Africa
CHC203N	NT	M	46	Europe
CHC1040N	NT	M	73	Europe
CHC1044N	NT	M	78	Europe
CHC1052N	NT	M	75	Europe
CHC1055N	NT	M	68	Europe
CHC1062N	NT	M	65	Europe
CHC1069N	NT	M	78	Europe
CHC1162N	NT	M	60	Europe
CHC789N	NT	M	54	Europe
CHC326N	NT	M	49	Europe
CHC051N	NT	F	69	Europe
CHC302N	NT	M	72	Europe
CHC306N	NT	M	68	Europe
CHC313N	NT	F	43	Europe

Alcohol intake	Hepatitis B	Hepatitis C	Tobacco	Fibrosis stage
no	yes	no	no	F2-F3
no	no	yes	no	F4
yes	no	no	NA	F4
no	no	yes	no	F4
no	no	no	NA	F0-F1
yes	no	no	NA	F4
no	yes	no	no	F2-F3
no	no	no	NA	F2-F3
no	yes	no	no	F2-F3
no	yes	no	NA	F2-F3
no	no	no	NA	F0-F1
no	yes	no	NA	F2-F3
no	yes	no	NA	F4
no	no	no	NA	F4
yes	yes	no	NA	F4
yes	no	yes	NA	F4
yes	yes	yes	yes	F4
no	yes	no	NA	F2-F3
no	no	no	no	F0-F1
no	no	no	NA	F0-F1
no	yes	no	NA	F2-F3
no	yes	no	NA	F2-F3
yes	no	no	yes	F0-F1
no	no	no	no	F0-F1
no	yes	no	no	F4
yes	no	no	yes	F2-F3
no	no	no	no	F0-F1
yes	no	no	NA	F0-F1
no	no	no	NA	F0-F1
no	yes	no	NA	F4
no	yes	no	yes	F4
no	yes	no	NA	F4
yes	no	no	NA	F0-F1
yes	no	no	yes	F4
no	yes	no	no	F4
no	no	yes	NA	F4
no	no	no	NA	F2-F3

yes	no	no	yes	F0-F1
no	yes	no	yes	F2-F3
no	yes	no	NA	F4
yes	no	no	yes	F0-F1
yes	yes	no	NA	F2-F3
yes	no	no	NA	F2-F3
no	no	no	no	F0-F1
yes	no	no	NA	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	NA	F2-F3
no	no	no	NA	F4
no	no	no	NA	F0-F1
no	no	no	no	F2-F3
no	no	no	no	F0-F1
yes	no	no	no	F2-F3
no	yes	no	yes	F0-F1
yes	no	no	no	F4
no	yes	no	NA	F4
no	no	no	no	F0-F1
yes	no	no	no	F4
no	no	no	yes	F0-F1
yes	no	yes	NA	F4
no	no	no	NA	F0-F1
NA	no	NA	NA	NA
no	no	no	no	F0-F1
no	no	no	yes	F0-F1
yes	no	yes	NA	F2-F3
yes	no	no	NA	F0-F1
no	no	no	no	F0-F1
yes	no	no	NA	F4
yes	no	no	no	F0-F1
no	yes	no	no	F0-F1
no	no	no	no	F0-F1
yes	no	no	NA	F2-F3
no	no	no	no	F0-F1
no	no	no	NA	F0-F1
yes	no	no	NA	F2-F3
no	no	no	NA	F2-F3
no	no	no	NA	F4
no	no	no	no	F0-F1
yes	no	no	yes	F0-F1

no	no	no	no	F2-F3
no	no	no	yes	F0-F1
yes	no	yes	yes	F0-F1
yes	no	no	NA	F4
no	no	yes	NA	F4
yes	no	no	yes	F0-F1
yes	no	no	yes	F4
no	no	no	NA	F0-F1
no	no	no	NA	F2-F3
no	no	yes	NA	F2-F3
yes	no	no	NA	F4
no	no	yes	NA	F4
yes	no	no	NA	F4
no	yes	no	NA	F4
no	no	yes	NA	F4
no	no	no	no	F0-F1
yes	yes	no	yes	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	yes	F0-F1
no	no	yes	no	F0-F1
yes	no	yes	NA	F2-F3
yes	no	no	NA	F4
yes	no	no	NA	F0-F1
no	no	no	no	F0-F1
yes	no	no	yes	F0-F1
yes	no	no	no	F0-F1
yes	no	no	NA	F4
no	no	yes	no	F4
no	yes	no	yes	F4
no	no	no	yes	F2-F3
no	yes	no	NA	F4
yes	no	no	yes	F0-F1
no	no	yes	no	F0-F1
yes	no	no	yes	F0-F1
no	yes	yes	no	F4
yes	no	no	yes	F4
yes	yes	no	yes	F4
no	no	yes	no	F4
no	no	yes	yes	F4
no	no	yes	yes	F4
yes	no	no	yes	F2-F3

yes	no	no	yes	F0-F1
yes	no	no	no	F0-F1
no	no	yes	yes	F2-F3
no	no	no	no	F2-F3
no	no	yes	yes	F2-F3
yes	no	no	yes	F0-F1
yes	no	no	yes	F0-F1
no	no	no	no	F0-F1
yes	no	yes	yes	F4
no	no	no	no	F0-F1
no	yes	no	no	F0-F1
no	yes	no	yes	F4
yes	no	yes	yes	F4
no	yes	no	yes	F0-F1
no	no	no	no	F2-F3
yes	yes	no	yes	F4
no	yes	no	no	F2-F3
no	no	no	yes	F0-F1
yes	yes	no	yes	F4
yes	no	no	yes	F0-F1
no	yes	no	no	F0-F1
no	no	no	yes	F0-F1
no	yes	no	yes	F4
yes	no	no	yes	F4
no	no	yes	no	F2-F3
no	no	yes	NA	F4
yes	no	no	yes	F0-F1
NA	NA	NA	NA	F2-F3
yes	no	no	NA	F4
yes	no	no	no	F4
yes	no	yes	yes	F4
yes	no	no	yes	F4
no	yes	no	no	F2-F3
yes	no	yes	yes	F2-F3
no	no	no	yes	F0-F1
yes	no	no	yes	F4
yes	yes	no	no	F4
no	yes	no	NA	F2-F3
yes	no	yes	yes	F4
yes	no	no	yes	F4
yes	no	no	yes	F0-F1

no	no	no	yes	F0-F1
yes	no	no	no	F4
yes	no	no	yes	F0-F1
no	no	no	no	F0-F1
yes	no	no	yes	F0-F1
yes	no	no	no	F0-F1
no	no	no	yes	F0-F1
yes	no	no	yes	F0-F1
yes	no	no	yes	F0-F1
no	no	yes	yes	F0-F1
no	no	no	no	F0-F1
no	no	no	yes	F0-F1
yes	no	no	no	F0-F1
no	no	yes	yes	F0-F1
yes	no	no	yes	F0-F1
yes	no	no	yes	F2-F3
yes	no	no	no	F0-F1
no	no	no	yes	F0-F1
no	no	no	yes	F0-F1
yes	no	yes	yes	F0-F1
no	no	no	no	F0-F1
no	no	no	yes	F0-F1
no	no	no	no	F0-F1
yes	no	no	no	F0-F1
no	no	no	yes	F0-F1
yes	no	no	yes	F4
yes	no	no	yes	F0-F1
no	no	no	NA	F0-F1
yes	no	no	no	F4
no	no	no	no	F0-F1
no	no	no	yes	F0-F1
yes	no	no	no	F4
no	no	no	yes	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	NA	F4
yes	no	no	NA	F4
yes	no	no	NA	F4
no	no	yes	yes	F4
yes	no	no	no	F2-F3
no	no	yes	NA	F4
yes	no	no	no	F2-F3

no	no	yes	yes	F0-F1
yes	no	no	NA	F4
no	no	no	yes	F2-F3
no	yes	no	no	F2-F3
no	no	yes	no	F4
yes	no	no	NA	F4
yes	no	no	yes	F4
yes	yes	no	NA	F2-F3
no	no	yes	yes	F2-F3
yes	no	no	no	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	NA	F4
yes	no	no	yes	F2-F3
yes	yes	yes	NA	F4
no	no	no	yes	F2-F3
yes	no	no	NA	F4
no	no	yes	no	F4
no	no	no	yes	F0-F1
no	no	no	NA	F0-F1
no	no	no	no	F0-F1
no	no	no	no	F0-F1
no	no	no	yes	F0-F1
no	no	no	yes	F0-F1
no	no	no	NA	F0-F1
no	no	no	yes	F0-F1
no	no	no	NA	F0-F1
no	no	no	yes	F0-F1
no	no	no	yes	F0-F1
no	no	no	yes	F0-F1
yes	no	no	NA	F4
yes	no	no	no	F0-F1
yes	no	no	no	F0-F1
yes	yes	no	yes	F0-F1
yes	no	no	yes	F4
no	no	no	no	F0-F1
no	no	no	no	F2-F3
yes	no	no	yes	F0-F1
yes	no	no	NA	F0-F1
no	yes	no	no	F2-F3
no	no	yes	no	F4
no	no	no	no	F2-F3

no	no	yes	no	F4
no	no	no	no	F0-F1
no	yes	no	yes	F4
no	no	no	NA	F0-F1
no	no	yes	no	F4
no	no	yes	NA	F4
no	no	no	NA	F0-F1
no	yes	no	NA	F4
yes	no	no	NA	F4
no	yes	no	no	F2-F3
no	yes	no	NA	F2-F3
no	yes	no	NA	F4
no	yes	no	no	F4
yes	no	no	NA	F4
no	no	no	NA	F4
no	yes	no	NA	F2-F3
no	no	no	NA	F0-F1
no	yes	no	yes	F2-F3
yes	no	no	NA	F4
yes	no	no	NA	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	NA	F2-F3
no	no	no	no	F2-F3
yes	no	no	NA	F2-F3
yes	no	no	no	F4
no	no	no	NA	F2-F3
no	yes	no	NA	F4
no	no	yes	NA	F4
no	no	yes	NA	F2-F3
no	no	yes	NA	F4
no	no	yes	no	F0-F1

Largest nodule diameter (mm)	Edmonson grade	Vascular invasion	TERT
>50	III-IV	yes	NM
>50	III-IV	yes	MUT
<=50	I-II	no	MUT
<=50	I-II	yes	MUT
<=50	III-IV	no	MUT
<=50	I-II	no	MUT
>50	I-II	yes	NM
<=50	I-II	no	MUT
>50	III-IV	yes	NM
<=50	III-IV	no	NM
>50	I-II	no	MUT
>50	I-II	yes	NM
<=50	I-II	no	MUT
>50	III-IV	yes	MUT
<=50	I-II	no	NM
<=50	I-II	no	MUT
<=50	III-IV	no	ND
>50	I-II	yes	ND
>50	I-II	no	MUT
>50	III-IV	yes	NM
>50	III-IV	no	NM
<=50	III-IV	no	NM
>50	III-IV	no	MUT
>50	III-IV	yes	MUT
>50	I-II	no	NM
<=50	I-II	no	NM
>50	I-II	no	MUT
>50	III-IV	yes	NM
<=50	I-II	no	MUT
<=50	III-IV	no	NM
<=50	NA	no	MUT
>50	III-IV	yes	MUT
>50	I-II	yes	MUT
<=50	I-II	no	MUT
<=50	III-IV	no	MUT
<=50	III-IV	no	MUT
>50	I-II	yes	ND

>50	I-II	no	MUT
>50	III-IV	yes	NM
<=50	I-II	no	ND
>50	III-IV	no	NM
>50	I-II	no	NM
>50	III-IV	yes	NM
>50	I-II	no	MUT
<=50	III-IV	yes	MUT
>50	III-IV	yes	MUT
>50	III-IV	yes	MUT
<=50	III-IV	no	NM
>50	I-II	yes	NM
<=50	I-II	yes	NM
<=50	I-II	yes	MUT
>50	III-IV	yes	MUT
>50	I-II	yes	MUT
>50	I-II	no	NM
>50	III-IV	yes	NM
>50	I-II	yes	MUT
>50	I-II	no	NM
>50	NA	no	NM
<=50	III-IV	no	MUT
>50	NA	no	MUT
>50	NA	yes	NM
<=50	III-IV	yes	MUT
>50	NA	yes	MUT
<=50	I-II	no	MUT
>50	I-II	yes	MUT
<=50	III-IV	yes	NM
<=50	III-IV	yes	MUT
>50	III-IV	no	NM
>50	III-IV	yes	NM
>50	III-IV	yes	ND
<=50	I-II	no	MUT
<=50	I-II	yes	MUT
>50	I-II	no	MUT
>50	III-IV	yes	MUT
>50	I-II	yes	NM
<=50	III-IV	yes	MUT
>50	I-II	no	MUT
>50	I-II	yes	NM

>50	III-IV	yes	MUT
>50	III-IV	yes	MUT
>50	III-IV	yes	NM
<=50	I-II	no	MUT
>50	III-IV	no	NM
>50	I-II	no	MUT
<=50	I-II	no	MUT
>50	I-II	no	NM
<=50	III-IV	no	MUT
<=50	I-II	no	MUT
>50	III-IV	yes	NM
<=50	I-II	no	MUT
<=50	III-IV	yes	MUT
<=50	I-II	no	MUT
<=50	I-II	no	MUT
>50	III-IV	no	NM
<=50	III-IV	yes	MUT
>50	III-IV	yes	MUT
>50	III-IV	yes	MUT
>50	III-IV	yes	NM
<=50	I-II	no	MUT
<=50	III-IV	no	MUT
>50	I-II	yes	MUT
>50	III-IV	yes	NM
>50	I-II	no	MUT
>50	III-IV	yes	MUT
<=50	III-IV	yes	NM
>50	III-IV	yes	MUT
<=50	III-IV	yes	NM
<=50	III-IV	no	MUT
>50	I-II	yes	NM
>50	III-IV	no	MUT
>50	I-II	yes	MUT
>50	I-II	yes	MUT
>50	III-IV	yes	ND
>50	III-IV	yes	MUT
>50	III-IV	yes	MUT
>50	III-IV	no	MUT
>50	III-IV	no	MUT
>50	III-IV	yes	MUT
>50	I-II	yes	MUT

>50	I-II	yes	MUT
>50	III-IV	yes	MUT
>50	I-II	yes	MUT
<=50	III-IV	yes	NM
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NM	NM	NM	NM	G5

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ND	ND	ND	ND	G1
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NM	MUT	NM	NM	G4
NM	NM	NM	NM	G3

NM	NM	NM	NM	G4
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Immune infiltrate (MCPcounter estimate)	Cyclin status	Liver progenitor sco
3.72824391794859	WT	10.7465547370503
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3.93130340758771	WT	7.64142838662909
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5.12853163719204	WT	9.24644235908455
6.85408126548256	WT	9.60543934465568
6.10284584691055	WT	7.02121871464857
4.67829905111719	WT	9.19232584106968
NA	NA	NA
7.1465786771073	WT	5.81967601822757
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NA	NA	NA
7.16359453790011	WT	5.23561248929128
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NA	NA	NA
5.06263663618805	WT	8.19468783579839
3.5590935180149	WT	8.46750736603988
6.33559224125095	WT	7.99784108125666
4.8879383110081	WT	6.48702058438561
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7.42422134348545	WT	8.05574826824443
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6.57913576740609	WT	8.72946653958931
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6.84219484454753	WT	9.08639625149016
6.25994042125682	WT	6.02320952665446
4.49211870986198	WT	5.25485142422835
4.92090062318738	WT	5.8990162730977
NA	NA	NA
4.20977105246734	WT	5.40016313989591
8.00657464769479	CCNE1	5.81521058947908
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4.53919109805583	WT	5.19084760024085
5.41370563728124	CCNA2	6.3373690272837
NA	NA	NA
NA	NA	NA
5.52437551559362	WT	8.02944322460638
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5.31155098701609	WT	7.99221177621962
NA	NA	NA
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5.75742364251585	WT	8.05027596349255
6.50695552909929	WT	7.14110072476883
7.18230126524343	WT	6.22724992867762
NA	NA	NA
4.34501524856647	WT	7.07064752681346
6.79444603285544	WT	6.53815782509635
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4.58189366447301	WT	6.37157460518738
4.27607440849631	WT	7.27039309128663
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5.78911070650012	WT	5.49729886543503
5.49141660416506	WT	5.92498326456495
4.30149273848339	WT	6.42957773543943
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5.24290962558493	WT	5.08967731405754
4.38779814774171	WT	5.91666425931927
5.80479168035294	WT	9.57808735466283
5.97414367343292	WT	7.45373832979156
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4.42717698474437	WT	6.45767738008273
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5.14184939516668	WT	6.75677464622488
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5.17898492835664	WT	4.78133823613662
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5.68633532737475	WT	8.69171748521191
5.68458477540256	WT	10.1936944135387
3.58174657429698	WT	5.96710997415482
7.51071749793545	WT	6.06609680280162
4.76051941505015	WT	9.03241039389735
5.88035415774506	CCNA2	7.20297182145155
5.99893816571093	WT	5.13481724852164
5.89934075615097	WT	5.18316510521923
4.4735304026101	WT	5.54483031497137
5.11694695958629	WT	6.6317555095669
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4.88965368335298	CCNA2	6.25752812269289
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5.11972000676233	WT	6.99361575758988
5.58206234753379	WT	6.16677897051453
6.01804326713513	WT	5.2052301833447
6.04826778642928	WT	7.7887270406553
6.09012469744965	WT	6.94539511454561
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6.13563116037559	WT	7.32312023066901
4.83708754760122	WT	6.3014162119215
4.54870254655313	WT	6.03831228591358
6.46922547952408	WT	5.88570921283379
6.14278946251368	WT	6.80298859931973

4.0873775438817	WT	6.3193654497792
4.95330403560497	WT	3.83457535709012
4.99105012281805	WT	10.9031567364034
4.46956113947877	WT	6.48414601488175
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6.03900145296637	CCNE1	6.89427569492059
5.24734925859528	WT	6.97341165829248
4.7846164028281	WT	7.40863969162601
5.86458591300386	WT	6.4809911182852
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4.48880868916404	WT	10.5725309023044
6.85732473432141	WT	8.47803170407868
5.94657381459287	WT	8.10035487712543
5.15116561925653	WT	5.22681492949504
4.79117199391471	WT	6.57624633542579
5.35346193440622	WT	7.52816602179977
5.92667926664017	WT	8.41629428995287
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5.33059297541132	WT	11.3737935432965
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4.6219453647406	WT	6.24720036623245
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5.8812708876413	WT	10.3203986831568
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6.78364420463617	WT	7.78666528241344
7.98269672816239	WT	6.43797593695633
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7.20724923600456	WT	7.05158291434924
5.03595542904165	WT	5.96389378466042
4.79844251078237	WT	4.92896060300051
4.63810719268195	WT	10.5898206736593
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6.03749844724803	WT	6.94499059697318
5.75788029719322	WT	7.02115748737286
5.04046014605212	WT	7.5851090258647
5.83523757321575	WT	8.05471877255927
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4.83864383959345	WT	6.78350649319442
5.28886912323356	WT	5.92914463539061

4.94634206329893	WT	5.52017895028628
5.5054496642369	WT	6.18439479689041
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5.29277212951652	CCNA2	5.56104675028822
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6.5375067775325	WT	6.2648365369478
6.47701103140567	WT	7.80002675776607
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6.62488301657235	WT	8.9598434968061
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6.94963849117889	CCNA2	6.04063595333393
5.02400523695685	CCNE1	5.21211255274868
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4.81437988097336	WT	7.25598704882759
5.16622374417788	WT	8.50231913542114
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6.86465723147873	CCNE1	6.47642414019062
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4.09832204702135	CCNE1	7.11923811117606
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8.83219926320216	WT	3.4962345076087

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8.18816569897432	WT	5.68336660339979
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6.83145629615156	WT	8.76894934588989
6.59105854867388	WT	6.49443810161791
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7.00076377979082	WT	7.50470626265644
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7.74294065139673	CCNA2	8.42645417687649
6.57505284038713	WT	6.93021066080381
7.92519410684423	WT	4.4163029498647
5.28072918719659	WT	6.88550788530157
4.54591109121419	WT	6.29837076506728
5.85826432022386	WT	7.14644213502193
6.61049920500203	WT	6.95263732726946
5.21461307584279	WT	11.8557904494614
5.13391156253383	WT	4.58277703479269
4.58771788623014	CCNE1	5.1764161696947
6.015745105782	WT	5.75059123488373
6.2305227212537	WT	8.73993540904513
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4.55037918161186	WT	6.06558347489535
5.66756092464501	CCNA2	5.77130414269639
6.15246294635046	WT	9.84146946305097
6.08170775341932	WT	6.56278669483253
5.55067683108682	WT	6.41659935301764
5.85950751446197	WT	5.67505560855404
4.84803668866516	WT	7.12385916159242
5.25888370638408	WT	6.07772699824321
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6.40747390441143	NA	7.41905229890499
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6.35305012824697	NA	7.61081666796304
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6.733644585295	NA	7.52685661550489
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7.27117802446477	NA	8.3692878186425
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7.1180264982131	NA	8.29870431187253
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Stem cell score	EMT_metastasis sco	Differentiation scor	Proliferation score
5.74434868264597	5.96552701856367	10.4718700809757	9.1998527760453
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5.95260340158947	5.93122189880386	9.64556179410923	9.55642431073186
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5.46445457688407	5.32578248565868	10.6617338521485	10.2225137083363
8.51212981021379	7.29422665020632	10.3135897903951	10.4877606722331
6.82596197817972	6.83638967887083	12.797352178916	8.5537038319584
6.46324650340087	6.40450892074537	9.20877450603193	8.90576235332004
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9.8900455720016	10.4830582339789	5.20259356908594	10.6939123964948
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8.53448843618139	8.22548646936558	11.7387761493465	9.09974025183035
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6.9475654458028	5.60081248293068	11.2437255997048	9.39768621107351
6.66766165841722	6.67220600317461	11.1804002865185	10.2396284888538
8.48432551143894	8.7098005780872	12.5579843460461	9.36247063521169
7.28806402299846	7.76406009405162	12.4207135313366	9.10105200444148
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9.51472950280981	9.58896728715336	12.9188662940972	8.5062687861946
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9.02493895416002	8.85937691694908	10.9808415702654	9.75413817023518
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8.62734130610053	7.5927012133176	12.2535908755183	9.11851338004113
7.79391360764951	8.2933746380954	12.736297682233	8.89457357976477
6.75852853431665	7.63247101123877	12.787957560403	9.26570225882883
6.82797674032583	6.26406782789505	12.1665404669934	9.16375402443351
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7.95033920341148	6.87833231499979	13.5868400624293	8.38453053284427
6.74623803502467	6.70321440199519	9.07570413868819	10.2676518485542
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7.01986215219323	7.72534748763638	11.0410558528999	8.34377384330163
8.7184333473278	8.48683962951986	11.5346058449332	9.92934689650795
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7.93477974167183	6.61946352609457	12.9490951211853	8.87286854077669
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6.63035578732157	6.50273550462921	11.0737257756137	9.88703620865428
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7.72271862490551	8.37141982292686	8.75252615751562	8.48695858880622
7.27484458578888	7.28145394047493	12.6063046417975	8.99254442137677
9.51061161736984	9.15426870589037	9.86368593330279	8.30106027136327
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7.18533067911354	6.40188630997362	12.8757590407564	8.22881394955633
10.7214032221137	9.62835226350307	10.8515467432148	8.07326104690646
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7.70591433340121	7.23515656827149	10.8761575835649	9.04125965661208
6.12972816271214	6.62624158720137	13.2353591878059	9.16910477946144
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7.13773025777185	6.8259806939684	10.9632917357586	9.44007365148889
6.6036817119256	7.13426346020349	11.2972585001392	10.0998492097126
6.38015015732472	7.16948092976296	11.1435384008559	9.77609485838262
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6.73548758627339	6.48224390064309	12.1412764001274	9.32271677322212
7.36985097062338	6.41368925559818	12.5322195663335	8.09847500165129
7.9516762935075	7.24936802007233	9.73690272150947	10.0600378225507
7.82177166223793	7.5124233785592	13.3663781159428	8.18845543491714
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6.75336364888093	6.67108401944259	12.7984928410123	8.37458320434076
6.62925664966375	6.81069376709236	13.1027394949725	10.1694143914224
7.06323922462965	6.59331450747511	10.382138046715	8.87865456212197
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7.28333271442067	7.75611591127392	11.2811787005646	8.13098106574357
6.47993324472907	5.74543975374043	11.7643718425697	9.32870675828584
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8.37609255031423	7.98378830137945	11.6028067548153	9.24469442248212
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8.830127781107	7.97873941012244	12.918156070634	8.0635592574604
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7.34986604307226	7.25406197667707	13.7901692656033	8.04139741565506
7.75912813161663	7.13271479072835	11.9967303291592	10.1771613694895
8.1567926925151	7.17121926392249	11.7208226800577	9.52985748257572
5.98223129282144	6.2404535284625	13.4241252721334	8.99038721082184
7.10536255848935	6.96195751355548	11.4275171348962	9.43962136827724
5.99709019441023	7.18087827496154	10.8641172349482	10.3158827777275
7.36662589699978	7.21016163639938	12.1664299936487	8.46401098123892
7.30209979719839	7.15912144058615	12.352420707081	8.02159724586623
8.77933105636784	8.16871799557403	12.0971320043776	8.96511035828314
6.74983773596349	6.48804880979649	12.0707467610585	8.92884991086709
7.12458673931366	7.62034729653615	8.29095577410701	9.63870076319385
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7.20141351340075	7.30173924266808	13.0628632620287	9.83811303350543
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Table S2a: Association between methylation components and clinico-molecular features in LICA-FR

P-values obtained with univariate linear models are indicated for each methylation component (MC) c

	MC1	MC2	MC3	MC4
Gender	0.000152641	0.00868459	5.02E-64	0.00010071
Geographical origin	0.001563705	0.00350529	0.86179639	0.51215794
Age at sampling	1.82E-20	0.11752311	0.04079449	0.00884404
Alcohol Intake	0.243823606	1	7.44E-05	0.05458358
Hepatitis B virus infection	1	0.17155004	0.77603975	1
Hepatitis C virus infection	0.132264922	0.74285724	1	1
Tobacco	1	1	0.06017705	1
Largest nodule diameter	1	1	1	1
Edmonson grade	0.095437141	0.3229948	0.46860316	0.84817688
Vascular invasion	1	1	0.50161517	1
Inflammation	1	0.04313596	1	0.0153666
***TERT* promoter**	1.42E-07	0.78238423	0.00103268	0.03287722
TP53	0.902463027	0.82003411	0.72848453	0.00019578
CTNNB1	1.69E-06	1	0.99307209	0.0001371
AXIN1	1	0.00589431	1	1
ALB	0.459420345	0.46251354	1	0.27095029
ARID2	1.39E-05	0.11543695	1	0.25085808
ARID1A	0.244870038	0.9299668	0.81940217	0.02055612
ACVR2A	0.579096727	0.87759946	0.22898597	0.20817161
NFE2L2	0.138892062	1	0.27438068	1
RPS6KA3	0.788831472	9.32E-05	1	1
KEAP1	0.432498906	0.31589178	1	0.18930362
RPL22	0.123803447	0.60534176	1	0.68467509
CDKN2A	0.487100451	1	0.56346054	0.78068977
CDKN1A	0.122590705	1	1	0.02760077
RB1	0.690286936	0.0396745	0.18200095	0.75625683
TSC2	1	1	0.98488951	1
ATP10B	0.400442534	0.95221754	0.91587205	0.01106201
FGA	0.584647236	0.2879121	0.47182484	0.14267254
MEF2C	1	1	0.92721928	0.19692704
HNF1A	0.551502431	0.90935497	1	0.08492951
ZNRF3	0.571220346	0.34162938	1	0.31259009
EPHA4	0.59887662	0.94579975	0.19409642	1
PTEN	0.560392251	1	1	0.04424528
TSC1	0.632257775	1	0.96385593	0.05547968
BAP1	1	0.01253311	1	1
Cyclin status	0.947142245	1	1	5.56E-07

Molecular group - G1	1	8.09E-08	1	1
Molecular group - G2	0.882311816	0.04323	1	0.07107371
Molecular group - G3	1	1	0.17812952	0.04608594
Molecular group - G4	1	1	0.10032055	1
Molecular group - G5	0.000259147	0.28359466	0.65993434	0.41029837
Molecular group - G6	0.091279454	1	1	0.06081306
Inflammation assessed from RNA-seq data (MCPcounter tool)	1	1	0.06972269	1
Liver progenitor transcriptional signature	1	0.01149652	1	1
Stem cell transcriptional signature	1	1	0.39096057	1
EMT/metastasis transcriptional signature	1	1	0.19101987	1
Differentiation transcriptional signature	2.45E-08	1	0.88322165	0.00355404
Proliferation transcriptional signature	1	0.10114817	0.0048384	0.03150257

series (univariate)

and each annotation.

MC5	MC6	MC7	MC8	MC9	MC11	MC12
0.00035308	0.02662413	0.05095424	0.84716758	0.66511285	0.76252606	0.00415826
0.10815199	0.35456297	0.04798611	0.85498439	0.44558665	0.0347655	0.0794497
2.40E-07	1	1	0.79497186	1	1	0.00022171
0.00273094	0.42158323	0.08204715	0.40946438	1	1	0.14128219
1	0.44750051	0.16740542	0.90257869	0.07534029	0.06657664	1
0.04765614	1	0.64523802	0.24862638	1	1	0.08014028
0.95455639	0.00585393	0.04487686	0.43564393	0.05863401	0.07906999	1
1	1	1	1	1	1	1
0.00119021	0.00985446	0.22239209	0.85594443	0.00158372	0.017369	0.0054695
1	9.33E-06	1	1	1	0.05039326	1
0.6008029	1	0.36834507	0.13764419	0.17439191	0.51985756	0.80832639
0.0032244	0.08853224	0.65646562	0.51818821	0.22348223	1	0.00011192
1	0.01061905	0.03942101	1	0.0109031	0.02809675	1
1.55E-08	1	0.17790703	1.45E-21	1	1	3.74E-17
1	1	0.04947647	1	1	1	1
0.74892682	1	0.68976438	1	0.8561672	0.99217905	1
0.22174086	1	1	0.15391932	1	1	5.33E-05
0.01180368	1	0.00117047	0.77967178	1	0.42159904	0.05448781
1	1	0.63016601	1	1	0.97349859	0.57048835
0.62271838	1	1	0.05223149	1	1	0.15242699
1	1	0.11235976	0.05546265	0.70283765	1	0.41214278
1	1	0.94322467	0.302995	0.06999128	1	1
0.07106782	1	1	0.21423248	1	1	0.01497033
0.4864166	1	0.78577628	0.48623651	0.21274988	1	0.30892869
0.01506444	0.9370591	1	1	0.86274604	0.28110817	0.13299514
0.86589163	1	1	1	0.3562119	0.25709612	1
1	1	1	0.66749596	0.0977919	1	1
0.19067187	1	0.00396741	1	1	1	0.4438262
0.10131669	1	0.80183885	0.37976569	0.38447706	0.8530977	0.12134234
0.37255578	1	1	0.38710805	0.04637475	1	0.54246364
0.30935837	1	0.05163965	1	1	0.45099726	0.91058481
0.0984226	1	0.26001505	1	0.90385705	0.43734979	1
0.28420113	1	0.77079557	1	1	0.97714108	0.50486844
0.13007165	1	1	1	1	1	0.09096669
1	0.04370514	0.10383075	1	0.09863367	0.00586022	1
1	0.838373	1	0.66034126	0.1799506	0.03692718	1
0.00397994	0.28304683	0.57151788	1	1	4.68E-06	0.86956015

1	1	0.01434322	0.50904134	0.13295136	0.0637912	1
0.52521566	1	0.07746856	1	1	0.00350885	1
1	6.50E-07	0.55348652	1	6.20E-05	0.01256124	1
1	0.00809854	1	1	1	0.28352848	1
0.02832826	1	1	0.00342742	1	1	8.23E-07
1.57E-05	1	1	4.76E-20	1	1	0.00539178
1	5.09E-22	0.8766761	1	0.78555094	2.08E-05	1
1	1	0.00309742	0.77094347	0.00766804	0.01288987	1
1	2.93E-18	0.95642674	1	0.24611295	7.12E-07	1
1	1.21E-17	1	1	0.22627547	0.00055644	1
1.38E-07	1	1	1	1	1	9.83E-09
1	3.20E-08	0.00771865	1	0.00061044	1.31E-05	1

MC13
4.94E-05
0.28706138
1.08E-06
0.0488825
1
0.05315126
1
1
0.43805172
1
0.04983613
0.00017236
0.19160375
2.63E-07
0.58171071
0.30213997
0.02978344
0.07720448
0.63641257
0.8322176
1
0.01770361
0.11841981
0.55166688
0.15435038
1
1
0.01719197
0.1112334
0.37607012
0.674015
0.30138721
0.86630309
0.11709941
0.53758653
1
0.31397827

1
1
0.50155763
1
0.28371714
0.00105165
1
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1
0.0003022
0.80724034

Table S2b: Association between methylation components and clinico-molecular features

P-values obtained with univariate linear models are indicated for each methylation compo

	MC1	MC2	MC3
Gender	0.02001832	0.009905777	7.57E-90
Geographical origin	0.005743652	0.012468626	0.081000835
Age at sampling	6.34E-12	1	1
Alcohol Intake	0.594570536	1	1.81E-05
Hepatitis B virus infection	0.800601676	0.005756959	0.020022996
Hepatitis C virus infection	7.85E-06	1	0.055918881
Tobacco	0.883735912	0.920127822	0.142271515
Edmonson grade	0.322794327	0.000428101	0.731179948
Vascular invasion	0.743507574	0.084119159	0.220622621
Inflammation	0.693246549	0.105256695	0.336466056
***TERT* promoter**	6.33E-08	1	0.263884245
TP53	0.17097474	0.383194059	0.017312953
CTNNB1	2.70E-06	1	0.032517451
AXIN1	0.896835901	0.005201998	0.285795845
ALB	0.000588547	1	0.24593835
ARID2	0.32926742	0.219240563	0.44612402
ARID1A	0.573438718	0.042003301	0.771334242
ACVR2A	0.408501793	1	1
NFE2L2	0.032536705	1	0.758666122
RPS6KA3	0.139677764	0.017873772	1
KEAP1	0.99770648	1	0.726748653
RPL22	0.330417892	0.026568644	1
CDKN2A	0.487551552	0.943569962	1
CDKN1A	0.271104609	0.436581955	1
RB1	1	7.52E-05	1
TSC2	1	0.918488645	0.170886812
ATP10B	0.847575846	0.720762885	0.18725942
FGA	0.410029259	1	0.507024738
MEF2C	1	1	0.925832075
HNF1A	1	1	1
ZNRF3	0.070754859	1	0.45858049
EPHA4	1	0.029373018	1
PTEN	0.318952696	0.176944612	0.899914584
TSC1	1	0.915652529	0.971014129
BAP1	1	0.003130553	1
Cyclin status	0.281381998	1	1
Molecular group - G1	1	3.04E-12	1
Molecular group - G2	0.124674619	0.035428904	1
Molecular group - G3	0.145529626	0.171760646	0.323463443

Molecular group - G4	1	1	0.581944431
Molecular group - G5	0.000689154	1	1
Molecular group - G6	0.048772507	1	0.082133007
Inflammation assessed from RNA-seq data (MCPcounter tool)	1	1	0.24028143
Liver progenitor transcriptional signature	1	1.48E-11	1
Stem cell transcriptional signature	1	1	0.008094434
EMT/metastasis transcriptional signature	1	1	0.11646267
Differentiation transcriptional signature	7.63E-07	1	0.817764833
Proliferation transcriptional signature	0.453963274	7.17E-12	0.584719794

; in TCGA LIHC series (univariate)

nent (MC) and each annotation.

MC4	MC5	MC6	MC7	MC8	MC9	MC10
0.071926191	0.232159603	0.016431494	0.588921149	0.160620746	0.232428302	0.463359139
0.150559208	0.292025053	0.202851069	0.048798717	0.599075734	0.220896778	0.034072853
0.000250986	0.324039434	0.73980777	1	1	1	0.003184559
0.230258363	1	0.00187761	0.814478405	0.42594527	0.559305582	0.828331889
0.240268422	0.281699514	1	1	0.693609081	1	0.937372958
0.428917589	0.038509768	0.961651446	0.923274957	0.303672038	0.3458708	0.561026818
1	1	0.854082221	1	1	0.040470166	1
0.468451942	0.108759169	0.097514901	0.211015312	0.566769818	0.000570403	0.046148254
0.131850913	1	0.068783577	0.709118445	0.066056397	0.56558266	0.799365206
1	0.323464548	0.006103718	0.342245143	0.444323978	0.364353536	0.809461174
0.053764902	0.88934371	1	0.010277254	0.25494851	0.535543647	0.417404223
2.64E-05	1	0.067049739	0.352411885	1	0.394400435	0.000154669
0.003950444	0.182892314	1	0.627837608	9.78E-21	1	1
1	0.544381992	1	0.017987758	0.568530081	1	1
0.189640831	0.620634034	1	1	1	1	1
1	0.829710065	1	1	0.134072077	0.209394833	1
1	0.924229578	0.804968724	1.23E-05	0.152431883	1	1
0.215948247	1	1	1	1	1	1
0.897102668	0.313911476	0.732906007	0.877372487	0.221264669	0.356596377	1
1	0.076931235	1	0.033656068	0.155659023	1	0.990109936
0.216366126	1	0.015469876	0.107364497	0.162592474	0.548930149	0.236903493
1	0.108204296	1	1	1	0.233302227	1
0.586260368	0.304160538	1	1	1	1	1
0.218698205	0.32646482	1	1	1	0.901758418	0.264509828
1	0.110996241	1	1	1	0.047371923	1
1	0.671341239	0.001847173	0.742442389	0.945141862	0.222634882	1
0.375739174	1	1	1	0.199817018	0.247819028	1
0.382631033	1	1	0.870367659	0.134483369	0.89890355	0.615130389
0.277304535	0.846096289	0.566719179	0.933488466	1	0.799965689	0.343254223
0.472039069	1	0.908104951	0.723756709	1	1	1
1	0.382276846	0.510415214	0.324173363	0.767317901	0.059337204	1
1	1	0.675111879	1	1	0.221068919	1
0.089460902	1	1	1	1	1	1
0.975761012	0.578594071	0.628006858	1	1	0.482218309	1
1	0.114949211	1	1	0.141817652	0.142059872	1
3.67E-12	0.346083531	1	1	1	1	2.11E-10
1	0.936732987	1	0.155790783	0.592035554	0.100242693	1
0.651670198	1	1	0.030232145	1	0.685355133	0.049117141
0.268360598	1	0.00201811	6.39E-05	1	2.40E-06	0.030693212

1	0.123441615	0.020194595	1	1	1	1
1.98E-06	1	1	1	1	1	0.094814852
0.039939869	0.403319999	1	1	2.63E-27	1	1
1	0.521261504	1.49E-52	0.018375549	1	0.936717167	1
1	1	1	3.26E-11	0.000162715	0.320876682	0.24150507
1	0.940806278	3.29E-23	1	1	0.05056434	1
1	1	1.20E-30	1	1	0.01951798	1
5.49E-07	5.56E-05	1	1	1	1	0.878547021
0.002667898	1	0.000505167	8.29E-10	1	6.04E-05	2.67E-09

MC11	MC12	MC13
0.300853681	0.11242222	0.414126679
0.585553448	0.318412865	0.112155222
0.014875707	0.000851111	6.92E-11
0.079351313	1	0.408764119
1	0.066432315	0.722643309
0.574343751	0.001760288	0.005363047
0.677626137	1	1
0.570521776	0.154412716	0.140428184
0.075633592	0.315723703	0.679707365
0.208797345	1	1
0.967485289	0.000221705	2.67E-07
0.024241142	0.314886796	0.127695079
0.669098268	1.96E-07	2.27E-05
1	0.856790406	0.325097225
0.259023627	0.01825179	0.010839412
1	0.094904651	0.282245794
1	1	0.725149961
0.670773412	0.164111752	0.063439042
1	0.17377998	0.390184464
0.532720475	0.736184025	0.194023352
0.130848261	1	0.96436361
0.34823365	0.475132308	1
0.411206152	0.930970367	0.616182274
0.036775606	0.347780621	1
0.98871388	0.177815647	1
0.550423245	1	1
1	0.126828332	0.569628789
0.578597642	0.526219775	0.366416059
0.105999754	1	0.538808868
0.811512453	0.099225634	1
1	0.602571456	0.489488681
0.911998187	1	1
0.816961964	0.054172167	0.439434999
0.91046995	1	1
1	1	1
8.05E-06	0.311229008	3.01E-05
1	1	1
1	0.067035705	0.111515961
0.131967378	1	0.252816904

1	1	1
5.46E-06	0.000333112	0.000676118
1	0.000215617	0.08424002
0.716146818	1	1
1	1	1
1	1	1
1	1	1
0.188766696	1.72E-11	2.39E-09
0.000387415	1	0.274279805

Table S3a: Association between methylation components and clinico-molecular features in LICA-F

P-values obtained with multivariate linear models are indicated for each methylation component (M

Only features significant in univariate analyses of both LICA-FR and TCGA LIHC series were included i

	MC1	MC2	MC3	MC4
Gender	NA	NA	3.79E-59	NA
Geographical origin	NA	NA	NA	NA
Age at sampling	1.01E-09	NA	NA	NA
Alcohol Intake	NA	NA	0.57266976	NA
Hepatitis B virus infection	NA	NA	NA	NA
Hepatitis C virus infection	NA	NA	NA	NA
Tobacco	NA	NA	NA	NA
Largest nodule diameter	NA	NA	NA	NA
Edmonson grade	NA	NA	NA	NA
Vascular invasion	NA	NA	NA	NA
Inflammation	NA	NA	NA	NA
***TERT* promoter**	0.54251686	NA	NA	NA
TP53	NA	NA	NA	9.87E-08
CTNNB1	0.05825175	NA	NA	4.03E-06
AXIN1	NA	NA	NA	NA
ALB	NA	NA	NA	NA
ARID2	NA	NA	NA	NA
ARID1A	NA	NA	NA	NA
ACVR2A	NA	NA	NA	NA
NFE2L2	NA	NA	NA	NA
RPS6KA3	NA	NA	NA	NA
KEAP1	NA	NA	NA	NA
RPL22	NA	NA	NA	NA
CDKN2A	NA	NA	NA	NA
CDKN1A	NA	NA	NA	NA
RB1	NA	NA	NA	NA
TSC2	NA	NA	NA	NA
ATP10B	NA	NA	NA	NA
FGA	NA	NA	NA	NA
MEF2C	NA	NA	NA	NA
HNF1A	NA	NA	NA	NA
ZNRF3	NA	NA	NA	NA
EPHA4	NA	NA	NA	NA
PTEN	NA	NA	NA	NA
TSC1	NA	NA	NA	NA
BAP1	NA	NA	NA	NA

Cyclin status	NA	NA	NA	8.97E-12
Molecular group - G1	NA	8.09E-08	NA	NA
Molecular group - G2	NA	NA	NA	NA
Molecular group - G3	NA	NA	NA	NA
Molecular group - G4	NA	NA	NA	NA
Molecular group - G5	0.93210082	NA	NA	NA
Molecular group - G6	NA	NA	NA	NA
Inflammation assessed from RNA-seq data (MCPcounter tool)	NA	NA	NA	NA
Liver progenitor transcriptional signature	NA	NA	NA	NA
Stem cell transcriptional signature	NA	NA	NA	NA
EMT/metastasis transcriptional signature	NA	NA	NA	NA
Differentiation transcriptional signature	0.00023401	NA	NA	0.03241482
Proliferation transcriptional signature	NA	NA	NA	NA

R series (multivariate)

1C) and each annotation.

n multivariate models. For other features the p-value is NA (not applicable).

MC5	MC6	MC7	MC8	MC9	MC11	MC12
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	0.33294158
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	0.46342435	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	0.93467767
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	3.16E-12	NA	NA	1.18E-06
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	0.00021407	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA

NA	NA	NA	NA	NA	4.22E-05	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	0.02307316	NA	NA	0.07435151	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	0.34771929
NA	NA	NA	3.22E-10	NA	NA	NA
NA	3.04E-08	NA	NA	NA	NA	NA
NA	NA	0.00067088	NA	NA	NA	NA
NA	0.02185572	NA	NA	NA	NA	NA
NA	0.18597964	NA	NA	NA	NA	NA
1.38E-07	NA	NA	NA	NA	NA	0.00033629
NA	2.41E-07	NA	NA	0.17237211	0.00011834	NA

MC13
NA
NA
0.00179723
NA
NA
NA
NA
NA
NA
NA
NA
0.47773361
NA
8.73E-05
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
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NA
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NA
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NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
NA
0.09631478
NA

Table S3b: Association between methylation components and clinico-molecular features in TCGA

P-values obtained with multivariate linear models are indicated for each methylation component (M

Only features significant in univariate analyses of both LICA-FR and TCGA LIHC series were included i

	MC1	MC2	MC3	MC4
Gender	NA	NA	3.42E-80	NA
Geographical origin	NA	NA	NA	NA
Age at sampling	0.00082841	NA	NA	NA
Alcohol Intake	NA	NA	0.41819811	NA
Hepatitis B virus infection	NA	NA	NA	NA
Hepatitis C virus infection	NA	NA	NA	NA
Tobacco	NA	NA	NA	NA
Edmonson grade	NA	NA	NA	NA
Vascular invasion	NA	NA	NA	NA
Inflammation	NA	NA	NA	NA
***TERT* promoter**	3.91E-05	NA	NA	NA
TP53	NA	NA	NA	7.66E-08
CTNNB1	0.02912577	NA	NA	6.60E-06
AXIN1	NA	NA	NA	NA
ALB	NA	NA	NA	NA
ARID2	NA	NA	NA	NA
ARID1A	NA	NA	NA	NA
ACVR2A	NA	NA	NA	NA
NFE2L2	NA	NA	NA	NA
RPS6KA3	NA	NA	NA	NA
KEAP1	NA	NA	NA	NA
RPL22	NA	NA	NA	NA
CDKN2A	NA	NA	NA	NA
CDKN1A	NA	NA	NA	NA
RB1	NA	NA	NA	NA
TSC2	NA	NA	NA	NA
ATP10B	NA	NA	NA	NA
FGA	NA	NA	NA	NA
MEF2C	NA	NA	NA	NA
HNF1A	NA	NA	NA	NA
ZNRF3	NA	NA	NA	NA
EPHA4	NA	NA	NA	NA
PTEN	NA	NA	NA	NA
TSC1	NA	NA	NA	NA
BAP1	NA	NA	NA	NA
Cyclin status	NA	NA	NA	1.60E-13
Molecular group - G1	NA	3.04E-12	NA	NA
Molecular group - G2	NA	NA	NA	NA

Molecular group - G3	NA	NA	NA	NA	
Molecular group - G4	NA	NA	NA	NA	
Molecular group - G5	0.01785679	NA	NA	NA	
Molecular group - G6	NA	NA	NA	NA	
Inflammation assessed from RNA-seq data (MCPcounter tool)	NA	NA	NA	NA	
Liver progenitor transcriptional signature	NA	NA	NA	NA	
Stem cell transcriptional signature	NA	NA	NA	NA	
EMT/metastasis transcriptional signature	NA	NA	NA	NA	
Differentiation transcriptional signature	0.74781537	NA	NA		1.31E-05
Proliferation transcriptional signature	NA	NA	NA	NA	

LIHC series (multivariate)

1C) and each annotation.

n multivariate models. For other features the p-value is NA (not applicable).

MC5	MC6	MC7	MC8	MC9	MC10	MC11
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	0.00015921	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	0.08623843	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	0.03949437	NA
NA	NA	NA	1.01E-05	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	7.33E-06	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	3.95E-09	5.59E-05
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA

NA	0.0007412	NA	NA	0.0004619	NA	NA	
NA	NA	NA	NA	NA	NA	NA	
NA	NA	NA	NA	NA	NA	NA	
NA	NA	NA	3.15E-13	NA	NA	NA	
NA	6.01E-33	NA	NA	NA	NA	NA	
NA	NA	2.00E-11	NA	NA	NA	NA	
NA	0.0222163	NA	NA	NA	NA	NA	
NA	0.00035147	NA	NA	NA	NA	NA	
5.56E-05	NA	NA	NA	NA	NA	NA	
NA	1.12E-07	NA	NA	0.02494344	1.28E-06	0.00370631	

MC12	MC13
NA	NA
NA	NA
0.91751109	0.00090378
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
0.00339993	0.00033052
NA	NA
0.00410243	0.02186845
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA

NA	NA
NA	NA
0.04671933	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
0.00040335	0.00872875
NA	NA