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Human Hepatocellular Carcinomas with a Peripoportal Phenotype Have the Lowest Potential for Early Recurrence after Curative Resection

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List of abbreviations: APC, adenomatous polyposis coli; AUROC, area under the receiver operating curve; BIO, 6-bromoindirubin-3'-oxime; DF, disease-free survival; ECM, extracellular matrix; GSEA, gene set enrichment analysis; HAL, histidine ammonia lyase; HCC, hepatocellular carcinoma; ODAM, odontogenic ameloblast-associated protein; PCA, principal component analysis; PP, periportal; PV, perivenous; SPLS-DA, sparse partial least squares discriminant analysis; TCF, T-cell factor; VNN1, vanin 1.

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ABSTRACT

Hepatocellular carcinomas (HCCs) exhibit a diversity of molecular phenotypes, raising major challenges in clinical management. HCCs detected by surveillance programs at an early stage are candidates for potentially curative therapies (local ablation, resection or transplantation). In the long term, transplantation provides the lowest recurrence rates. Treatment allocation is based on tumor number, size, vascular invasion, performance status, functional liver reserve and on the prediction of early (< 2 years) recurrence, which reflects the intrinsic aggressiveness of the tumor. Well-differentiated, potentially low-aggressiveness tumors form the heterogeneous molecular class of non-proliferative HCCs, characterized by an approximate 50% β -catenin (*CTNNB1*) mutation rate. To define the clinical, pathological, molecular features and the outcome of non-proliferative HCCs, we constructed an 1133-HCC transcriptomic metadata set and validated findings in a publically available 210-HCC RNAseq set. We show that non-proliferative HCCs preserve the zonation program that distributes metabolic functions along the porto-central axis in normal liver. More precisely, we identified two well-differentiated, non-proliferation subclasses, namely *Periportal-type* (wild-type *CTNNB1*) and *Perivenous-type* (mutant *CTNNB1*), which expressed negatively correlated gene networks. The new *Periportal-type* subclass represented 29% of all HCCs; expressed an HNF4A-driven gene network, which was down-regulated in mouse *Hnf4a*-KO mice; were early-stage tumors by BCLC, CLIP and TNM staging systems; had no macrovascular invasion and showed the lowest metastasis-specific gene expression levels and *TP53* mutation rates. Also, we identified an 8-gene *Periportal-type* HCC signature, which was independently associated with the highest 2-year recurrence-free survival by multivariate analyses in two independent cohorts of 247 and 210 patients.

Conclusion: Well-differentiated HCCs display mutually exclusive periportal or perivenous zonation programs. Among all HCCs, *Periportal-type* tumors have the lowest intrinsic potential for early recurrence after curative resection.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related death worldwide. HCC is endemic in East Asia and sub-Saharan Africa, and its incidence has doubled over the past 20 years in Western countries. Projections anticipate a further increase in incidence, despite recent breakthroughs in the management of chronic hepatitis.(1) More than 80% of HCCs arise in a field of chronic liver disease resulting from viral hepatitis, alcohol, hemochromatosis, obesity and metabolic syndrome or genotoxins. This diversity in etiology and natural history results in high HCC heterogeneity, raising major challenges in clinical management.(1)

Current therapeutic strategies are based upon tumor number, size, vascular invasion, performance status and functional reserve of the liver. These variables have been integrated in the Barcelona Clinic Liver Cancer (BCLC) classification to match the best candidates with the best therapies available.(1) Surveillance programs currently detect early-stage tumors (single or ≤ 3 nodules ≤ 3 cm) that are candidates for potentially curative therapies (local ablation, resection or transplantation) with 5-year survival rates of 50-70%. Five-year recurrence rates after HCC resection (up to 70%) or even higher after percutaneous ablation make liver transplantation the best possible treatment, with a recurrence rate of 10% and the additional advantage of eliminating the underlying liver disease.(1) Treatment allocation for early-stage HCCs might be improved by identifying homogeneous molecular subclasses with predictable outcomes.(2, 3)

The molecular landscape of HCCs is emerging as a result of global gene expression analyses and the discovery of crucial driver tumor mutations.(1, 2) At present, HCCs are split into two molecular classes, each representing 50% of tumors: proliferative

and non-proliferative HCCs.(2) Proliferative HCCs include two subclasses enriched in WNT/TGFB signals and stem/progenitor cell markers, respectively.(1, 2) Among non-proliferative HCCs, half of the tumors form a homogeneous subclass with a high rate of activating β -catenin (*CTNNB1*) exon 3 mutations.(2, 4-6) These tumors are well-differentiated,(2, 4-8) but patient survival rates do not differ from HCCs carrying wild-type *CTNNB1* (reviewed in Supporting Table S1). The rest of non-proliferative HCCs carry wild-type *CTNNB1*,(5) but no evidence to date allowed them to qualify as a homogeneous HCC subclass.

This study was conducted to determine whether non-proliferative HCCs carrying wild-type *CTNNB1* warrant consideration as a distinct, clinically relevant tumor subclass.

To analyze a large and statistically powerful population, we constructed an 1133-HCC transcriptomic metadata set and identified four HCC subclasses by discriminant analyses and hierarchical clustering. As the 1133 HCCs were not annotated for *CTNNB1* mutations, we developed a reliable method to predict *CTNNB1* mutations in an independent set of 225 β -catenin-sequenced HCCs. *CTNNB1* mutation prediction, HCC classification and survival analyses were further validated in an external RNAseq dataset of 210 HCC patients (Fig. 1).

Altogether, analysis of data from 1568 HCC patients identified two new well-differentiated, mutually exclusive, low-proliferation subclasses of HCCs. Both subclasses showed favorable outcomes and preserved metabolic liver zonation programs. They respectively displayed *periportal* (wild-type β -catenin) or *perivenous* (mutant β -catenin) phenotypes. *Periportal-type* HCCs showed the highest 2-year recurrence-free survival rates by multivariate analysis, suggesting that these tumors have the lowest potential for early recurrence among all HCCs.

Patients and Methods

Patients, study design and data management

The study design is presented in Fig. 1. Nine public transcriptomic datasets passing the quality control analyses were integrated into a metadata set totalizing 1133 HCCs and 9542 genes (Supporting Tables S2 and S3). As HCCs in these datasets were not annotated for *CTNNB1* mutations, we developed a robust prediction method. Complying with REMARK guidelines, identification of *CTNNB1* mutation predictors in a training set (n=87) was confirmed in a validation set (n=56) and in our recently described in-house independent cohort (n=82).(9) The three datasets (Supporting Table S2) were annotated for Sanger-sequenced *CTNNB1* exon 3 mutations (Supporting Table S4). We thus predicted *CTNNB1* mutational status in the 1133-HCC transcriptomic metadata set. Independently, hierarchical cluster analysis was used in this metadata set to identify robust HCC subclasses. Then, the resulting tumor classification was validated in a 210-HCC patient dataset from The Cancer Genome Atlas (TCGA) consortium(10) (normalized RNAseq genome-wide mRNA expression, whole genome sequencing and clinical data downloaded in June 2016 from the TCGA website). Out of 294 HCCs with available RNAseq and clinical annotations, 84 met our exclusion criteria (Supporting Fig. S1A). Quality control of clinical annotations was performed by studying the relationship between tumor staging and overall/disease-free survival by Kaplan-Meier plots and Log Rank tests (Supporting Fig. S1B).

Raw data from publically available transcriptome profiling experiments were extracted from Gene Expression Omnibus. Probes detected over background in at least one HCC were quantile normalized (R package preprocessCore) and log₂ intensity

expression values for each probe set were calculated by Robust Multi-array Average Cross-platform and batch-dependent variances were corrected with COMBAT(11) (R package sva) in the 1133-HCC metadata set and with YuGene(12) (R package YuGene) in the datasets used for *CTNNB1* mutation prediction.

Statistical analyses

To optimize the identification of stable gene predictors of *CTNNB1* activating mutations, we applied Sparse Partial Least Squares Discriminant Analysis (sPLS-DA) with bootstrap subsampling (Supporting Fig. S2), as described.(13) After further marker validation in the in-house cohort by real-time PCR, we established a score to predict *CTNNB1* mutations. Independently, robust HCC subclasses were identified using hierarchical cluster analysis defined by a stepwise algorithm (see Supporting Materials and Methods). Survival analyses were performed using the Log Rank test, Kaplan-Meier curves and Cox models. Statistical analyses were performed with R (version 3.3.0).

See Supporting Materials and Methods for: tissue banking, fully detailed statistics, functional genomics, detection of β -catenin exon 3 mutations/deletions, tissue micro-array-based immunohistochemistry, antibodies, cell culture, nucleic acid extraction, real-time PCR, primers, and RNA interference.

RESULTS

A robust 5-gene score predicts *CTNNB1* mutations in large transcriptomic datasets

As described in the *Patients and Methods* section and Fig. 1, nine public transcriptomic datasets were integrated into a metadata set of 1133 HCCs and 9542 genes (Supporting Tables S2 and S3). The 1133-HCC transcriptomic dataset was not annotated for *CTNNB1* mutational status; thus, we set up a robust pipeline to predict *CTNNB1* activating mutations (Fig. 1). The model achieved a prediction accuracy of 87% in the training set and 93% in the independent validation sets (Supporting Fig. S2). The analysis identified Histidine Ammonia-Lyase (*HAL*) and Vanin 1 (*VNN1*) (selected in >85% of the models after 300 bootstrap runs), which were both downregulated in HCCs carrying mutant *CTNNB1*. In addition, a search for the top upregulated genes in HCCs carrying *CTNNB1* mutations identified *ODontogenic AMeloblast-associated protein (ODAM)*. Then, to construct a score predicting *CTNNB1* mutations, we combined *HAL*, *VNN1* and *ODAM* with two well-known markers of *CTNNB1* activating mutations in HCCs: *GLUL* and *LGR5*.⁽¹⁴⁾ RNA expression levels of the five biomarkers were significantly associated with mutant *CTNNB1* in the three datasets (Fig. 2A,B). *AXIN2*, which reflects Wnt/ β -catenin pathway activation,⁽¹⁵⁾ was positively correlated with *GLUL*, *LGR5* and *ODAM* and negatively correlated with *HAL* and *VNN1* (Fig. 2A,B; Supporting Fig. S3A). Cluster analyses confirmed the association of the five markers with *CTNNB1* mutation (Fig. 2, B1,B2,B3). In the external validation set, *CTNNB1* mutation was negatively associated with invasive (Gamma= -0.83, $p<10^{-3}$) and multinodular (Gamma= -0.56, $p=0.02$) tumors (Fig. 2B3). In turn, nuclear β -catenin immunostaining was positively correlated with *CTNNB1* mutations, *GLUL*, *ODAM* and *LGR5* and negatively with

VNN1 and *HAL* and (Supporting Fig. S3B). Combination of the five markers into an arithmetic score resulted in a reliable prediction in the three datasets (AUROC=0.87-0.90; Sensitivity=0.86-0.91; Specificity=0.83-1; Fig. 2C-E).

Tissue microarray-based immunohistochemistry in 20 HCCs carrying mutant *versus* 20 HCCs carrying wild-type *CTNNB1* revealed a clear-cut difference in GLUL expression between HCCs showing mutant *versus* wild-type *CTNNB1* at low power microscopic examination, whereas *HAL* and *VNN1* were globally higher in wild-type samples (Fig. 2F). *ODAM* protein expression was low in all samples (not shown), but detected in HCCs carrying mutant *CTNNB1* and expressing high GLUL (Fig. 2G).

In the external validation set, analysis of matching HCC and non-tumor samples showed that tumor/non-tumor ratios were highly predictive of *CTNNB1* mutations (AUROC=0.90, Se 0.87; Sp 0.88) (Supporting Fig. S3C-F). As data from non-tumor tissues were not available in all the transcriptomic datasets, further predictions of *CTNNB1* mutations were performed with tumor samples. Thus, we predicted *CTNNB1* mutations in the 1133 HCCs of the metadata set (Supporting Table S5). Predicted mutation rates between 20-40% matched the previously described *CTNNB1* mutation rates in HCC.(16)

To better understand the association of the newly discovered biomarkers (*HAL*, *VNN1* and *ODAM*) with *CTNNB1* activating mutations, we analyzed human HCC cell lines (Supporting Fig. S4). *HAL* was expressed at higher levels in HCC cell lines carrying wild-type *CTNNB1*, *i.e.*, Huh7 or HepaRG, than in those carrying activating *CTNNB1* mutations, *i.e.*, B16, BC2, HepG2 and Huh-6. *VNN1* was expressed at much higher levels in HepaRG cells than in the cell lines carrying mutant *CTNNB1*. By contrast, Huh7 expressed *VNN1* at low levels. Last, *ODAM* was clearly expressed

at higher levels in cell lines carrying mutant than in those carrying wild-type *CTNNB1*. The GSK3 β inhibitor 6-bromoindirubin-3'-oxime (BIO), which activates β -catenin signaling,(17) strongly upregulated β -catenin-dependent transcriptional activity (Supporting Fig. S5A). BIO upregulated *GLUL*, *LGR5* and *ODAM* (Supporting Fig. S5B) and attenuated the increase in *HNF4A*, *ALDOB*, *HAL* and *VNN1* mRNA expression over the 30 days required for differentiation of HepaRG progenitors to hepatocyte-like cells (Supporting Fig. S5C-F). Conversely, HepaRG cells transfected with β -catenin targeting siRNA downregulated *AXIN2* and *ODAM* and upregulated *HAL* and *VNN1* mRNA expression (Supporting Fig. S5G). In addition, *in silico* analysis of the 5000 base pairs upstream the transcription start site of *ODAM* DNA (NM_017855; PROMO program,(18) TRANSFAC database), revealed three putative TCF-4/LEF-1 consensus transcription factor binding sites in the *ODAM* 5'UTR region at positions -99; -1262 and -3956. Taken together, these data suggest that β -catenin signaling regulates *HAL*, *VNN1* and *ODAM* mRNA expression.

Predicted *CTNNB1* mutations cluster within a homogeneous tumor subclass after analysis of transcriptomic data from 1343 HCCs.

We integrated the nine datasets into an 1133 HCC metadata set with 9542 common genes and performed cross-platform normalization with the COMBAT algorithm(11) (Supporting Fig. S6). Identification of the 1618 most discriminant genes by partial least squares discriminant analysis (PLS-DA), using a VIP score threshold >1, followed by stepwise hierarchical cluster analysis, identified four subclasses. Subclasses were named *red*, *green*, *blue* and *purple* before further functional characterization (Supporting Fig. S7). The *red* subclass had a predicted *CTNNB1*

mutation rate of 84% (Supporting Fig. S7). The predicted *CTNNB1* mutation rates in this subclass were high in all datasets (65% to 100%, Supporting Table S6). These findings are consistent with previous evidence that HCCs carrying *CTNNB1* mutation are a homogeneous subclass.(4, 6)

Reproducibility (Supporting Fig. S8) and robustness (Supporting Fig. S9A,B) analyses showed that the *red* and *green* subclasses had similarly low intra-cluster inertia, indicating high homogeneity of HCC samples within each cluster. In terms of gene expression profiles, the *purple* cluster was highly different from the *red* and *green* ones, whereas the *blue* cluster was intermediate between the green and purple ones (Supporting Fig. S9C). To further test the robustness of the HCC classification, we repeated PLS-DA-based identification of the most discriminant genes with a more stringent VIP score threshold (>1.5), which yielded 550 top discriminant genes and confirmed the four tumor subclasses (Supporting Fig. S9D). Further, the value of the 550-geneset as a classifier was confirmed in the external validation RNAseq dataset (n= 210 HCCs; Supporting Fig. 9E). Thus, using the top 550 genes, both the 1133-HCC transcriptomic (Fig. 3A) and the 210-HCC RNAseq (Supporting Fig. 9E) datasets confirmed four HCC subclasses and three gene sets. In the *red* subclass, *CTNNB1* was predicted to be mutated in 89% of HCCs (Fig. 3A). In consistency with the high rate of predicted *CTNNB1* mutations, the red subclass showed the highest levels of *GLUL*, *LGR5* and *ODAM* and the lowest levels of *VNN1* and *HAL* (Fig. 3B).

By immunohistochemistry in human liver (Fig. 3C-D), *GLUL* showed a clear perivenous localization, as expected.(19) *HAL* showed a clear-cut periportal distribution, consistently with its expression by periportal hepatocytes in mice.(20) *VNN1* was panlobular and was abundantly detected in the cytoplasm and in bile

canaliculi in normal liver and in well-differentiated HCCs (Fig. 3C,D), which goes well with the evidence that VNN1 is one of the 59 major proteins in human bile.(21). Further, anti-VNN1 staining of bile canaliculi was totally suppressed by the immunogen polypeptide (Fig. 3D). In consistency with the above findings, full genome sequencing data from the independent RNAseq 210-HCC TCGA dataset confirmed that 81% of HCCs within the *red* subclass carried *CTNNB1* mutations (Supporting Fig. S9E).

Well-differentiated HCCs display a preserved metabolic liver zonation program.

Functional genomics studies by gene set enrichment analysis (GSEA) (Fig. 4; Supporting Table S7) revealed that the HCC subclass containing the highest rate of predicted *CTNNB1* mutations (84%) was enriched in signatures of HCCs carrying mutant *CTNNB1*, such as the G6(6) and the *CTNNB1* subclasses,(4) as well as perivenous hepatocyte signatures, such as fatty acid and bile salt metabolism.(20) We thus called this subclass “Perivenous-type HCCs” (*PV*). The HCC subclass enriched in signatures of differentiated periportal hepatocytes (gluconeogenesis, amino acid catabolism, HNF4A-induced genes),(20) good prognosis, (hepatocyte-like (S3) subclass HCCs)(5) and low recurrence,(5, 22) was called “Periportal-type HCCs” (*PP*). Both PP and PV subclasses were enriched in signatures of favorable survival(23) and low proliferation in HCCs.(4) The HCC subclass featuring signatures of cancer extracellular matrix (ECM) remodeling and epithelial mesenchymal transition(24) was called “ECM-type HCCs”. It was characterized by integrin cell-surface interactions, *KRAS*, *TGFB*, *IL6*, and the *MMP14* network typical of invasive tumors. The last HCC subclass was associated with high grade metastasis

signatures, tumor aggressiveness with decreased patient survival,(23) the cancer stem cell program predicting metastasis and death(25) and upregulation of p53 mutation markers (Supporting Fig. S10). It was also enriched in signatures of cell cycle progression (*MYC*, *RAC*, *AURKA*, *RB1* and *PDGFRB* pathways), HCCs displaying stem cell features(26) and extrahepatic undifferentiated cancers of various origins, as well as cancer cell resistance to doxorubicin and vincristine. Thus, we called this subclass “STEM-type HCCs”. Both ECM- and STEM-type HCCs shared signatures of high tumor cell proliferation(4) and were associated with the Wnt/TGF- β (S1) HCC subclass,(5) indicating bad prognosis.(27) Also, they were both associated with early recurrence(28). Expression levels of representative genes in HCC subclasses and in gene clusters are illustrated in Fig. 4B and in Supporting Fig. S11, respectively. Functional genomics findings were confirmed by gene ontology analysis of gene clusters (Supporting Table S8). The mean $\pm$ 95%CI mRNA expression level of the top 550 genes in the four HCC subclasses is shown in Supporting Table S9.

We observed differences in the percentage of samples in each subclass according to the dataset of origin (Supporting Table S10). The sampling technique (1060 resections *versus* 73 biopsy specimens) had no impact on tumor classification (Supporting Table S11). By contrast, cohorts containing >95% HCV (+) HCCs showed a higher rate of PV samples than cohorts with >95% HBV (+) ($p=10^{-3}$), in agreement with the well-known positive association of *CTNNB1* mutation with HCV and its negative association with HBV.(2)

The metabolic program of Periportal-type HCCs is regulated by HNF4A

The interplay between TCF4, β -catenin and HNF4A(20) governs the differential distribution of metabolic liver functions along the porto-central axis of the liver, which is known as “liver zonation”.(29) Using the ortholog genes of the mouse liver periportal and perivenous signatures,(20) we clustered the 326 Periportal-type and the 210 Perivenous-type HCCs from the 1133 HCC metadata set. We observed a remarkable matching of mouse normal liver perivenous genes with Perivenous-type HCCs and mouse normal liver periportal genes with Periportal-type HCCs, thus confirming the identity of both HCC subclasses described above (Supporting Fig. S12A). Subsequently, network analysis in the 1133 patient metadata set revealed that periportal and perivenous genes were negatively correlated and respectively upregulated in Periportal-type and Perivenous-type HCCs (Fig. 5A). Predictive markers of *CTNNB1* mutation showed high connectivity within this network. *GLUL*, *HAL* and *LGR5* were connected respectively with 60 (42%), 54 (38%) and 54 (38%) of genes in the network. Although mouse *Odam* and *Vnn1* were not present in the original periportal and perivenous signatures,(20) human *ODAM* and *VNN1* were connected respectively with 47 (33%) and 28 (20%) of the genes in human HCCs.

Suppression of HNF4A in mouse liver has profound effects on zoned metabolic functions,(30, 31) cell proliferation(30) and oncogenesis.(32, 33) Consistent with this, the top 550 genes representative of the four HCC subclasses perfectly discriminated *Hnf4a*-KO and *Hnf4a*-WT(31) mouse livers (Fig. 5B). Among the 550 genes, a first cluster was strongly upregulated in *Hnf4a*-KO mice and clearly enriched in genes upregulated in ECM/STEM HCCs. A second cluster was downregulated in *Hnf4a*-KO mice and enriched in genes upregulated in Periportal-type HCCs. The rest of the genes (20%) were poorly affected by HNF4A. Finally, we extracted from the *Hnf4a*-KO dataset the genes showing the highest modulation (fold change >2 or <0.5 and

Bonferroni adjusted P value <0.01) to look at the expression of their orthologs in the 1133 HCC metadata set (Supporting Fig. S12B). Hierarchical clustering of these genes showed a good discrimination of the four subclasses (80% of samples correctly classified), with a strong enrichment of genes highly downregulated by *Hnf4a*-KO in Periportal-type HCCs. Conversely, genes highly upregulated by *Hnf4a*-KO were remarkably enriched in the STEM-type HCC subclass. These findings are in line with the notion that HNF4A induces hepatocyte differentiation of cancer stem cells, suppressing hepatocyte proliferation and oncogenesis.(30, 32, 33)

Periportal-type HCCs show the most favorable clinical features and the highest early (2-year) disease-free and overall survival rates after resection.

Comparative analysis of the clinical outcome of the four HCC subclasses in a 247-HCC transcriptomic dataset(34) (dataset C, Supporting Table S2) revealed increasingly aggressive tumor phenotypes from Periportal through Perivenous → ECM → STEM HCCs (Fig. 6A). These subclasses showed a progressive increase in metastatic signature(34) rates, CLIP and BCLC scores as well as serum AFP concentrations. Survival curves (Fig. 6B) showed a progressive decrease in overall and disease free survival (DF) rates from Periportal through Perivenous → ECM → STEM HCCs. Thus, the Periportal-type is a well-differentiated, favorable-outcome HCC subclass carrying wild-type *CTNNB1*, displaying a periportal liver metabolic program and expressing HNF4A target genes. In turn, the Perivenous-type is a well-differentiated HCC subclass carrying mutant *CTNNB1*, displaying a perivenous liver metabolic program and expressing β -catenin target genes.

The above data were further validated using an external 210-HCC RNAseq dataset. Tumor aggressiveness was inferred from increasing AFP serum levels, tumor grade, TNM staging, vascular invasion, TP53 mutation rates, tumor onset in younger patients (Fig. 6C), as well as survival (Supporting Fig. S13). This analysis confirmed the existence of increasingly aggressive tumor phenotypes from Periportal-type through Perivenous-type → ECM-type → STEM-type HCCs. The overall survival of Perivenous-type HCCs was significantly more favorable than that of STEM-type HCCs in both the 247-HCC transcriptomic (Fig. 6B) and in the 210-HCC RNAseq (Supporting Fig. S13) datasets.

To obtain a *Periportal-type HCC gene signature*, we searched for genes meeting the following criteria: >2 fold change between the Periportal and the other HCC subclasses; high connectivity within the periportal gene network in HCCs (>0.30 correlation coefficient with >50% of the genes) and association with survival ($p < 0.05$ in $\geq 7/8$ tests; Supporting Materials and Methods). The resulting 8-gene *Periportal-type HCC signature* (Fig. 6D) was associated with favorable overall and disease-free outcome in the 247-HCC transcriptomic (34) (Fig. 6E) and in the 210-HCC RNAseq (Fig. 6F) datasets. Periportal-type HCCs showed the lowest early (2-year) recurrence and the highest overall survival rates after resection among all other HCCs taken together. Univariate and multivariate survival analysis revealed that the *Periportal-type HCC signature* was independently associated with low early recurrence after HCC resection (Table 1).

Of note, the *Periportal-type HCC signature* was predominantly expressed in normal liver, as shown by analysis of their mRNA expression levels in 84 tissues,(35, 36) from the GSE1133 microarray dataset (Supporting Fig. S14,A-H). In addition, the expression levels of the eight genes constituting the signature were highly correlated

(Supporting Table S12). These genes were expressed at higher levels in Periportal-type HCCs than in the other HCC subclasses (Fig. 6D). The expression levels of these genes in 70 Periportal HCCs were closer to those detected in 232 non-tumor livers than in 167 non-Periportal HCCs. Two of these genes (*AGXT* and *OTC*) were not significantly different in non-tumor livers from Periportal HCCs (Supporting Fig. S15).

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DISCUSSION

Our study revealed that preservation of the liver zonation program is an important feature of well-differentiated HCCs. Periportal-type HCCs showed the most favorable patient outcome in two independent cohorts of 247 and 210 patients. Further, they displayed the lowest rates of *Metastasis Signature*,⁽³⁴⁾ BCLC, CLIP, TNM staging, vascular invasion and TP53 mutations. We identified an 8-gene *Periportal-type HCC signature* composed of liver-enriched genes involved in periportal liver functions, such as amino-acid catabolism (GLS2, AGXT and GNMT), biliary acid transport (SLC10A1 and SLC22A7), lipid (SLC27A5) and glucose (FETUB) metabolism, as well as the urea cycle (OTC). These genes were expressed at higher levels in non-tumor livers and in Periportal-type than in non-Periportal-type HCCs.

In normal liver, β -catenin is transiently activated in perivenous zones to meet homeostatic needs.⁽¹⁵⁾ Therefore, turning *OFF* β -catenin in adult mouse liver constitutively leads to a default periportal metabolic program, with a normal liver function. Conversely, turning *ON* β -catenin leads to liver hyperplasia, hyperammonemia and death.⁽²⁰⁾ Considered in this context, Periportal-type HCCs preserve the default metabolic program of normal liver. Therefore, converging evidence indicates that the periportal program embodies the lowest level of aggressiveness in HCCs.

Recently, no association was detected between β -catenin mutations and survival in 362 HCC patients,⁽⁷⁾ in line with data summarized in Supporting Table S1. We confirmed these findings by analyzing two independent cohorts of 247 and 210 HCC patients (Fig. 7A). Noteworthy, subclass-specific survival analyses in these two cohorts revealed that Periportal-type and Perivenous-type HCC patients had a more favorable outcome than STEM-type HCC patients (Fig. 6B; Supporting Fig. S13).

Also, discriminant analysis confirmed that Perivenous-type HCCs lie between Periportal-type and ECM-type HCCs in terms of aggressiveness (Fig. 7B). This body of evidence suggests that HCCs carrying β -catenin mutations are moderately aggressive (Fig. 7C). *De novo* expression of cancer stem/progenitor cell genes such as *ODAM* and *LGR5* in *CTNNB1*-mutated HCCs goes well with the moderate aggressiveness of this tumor subclass. *ODAM* is a basement membrane component of the periodontal junctional epithelium secreted by ameloblasts, repressed in adult tissues, but expressed *de novo* in cancers.(37) *LGR5*, in turn, is expressed by liver stem cells or progenitors in response to stimuli calling for tissue renewal or tumor cell growth.(38)

Perivenous-type HCCs match the G6(6) and *CTNNB1*(4) subclasses that carry *CTNNB1* mutations, but not the S3(5) subclass. In turn, the S3 subclass matches Periportal-type HCCs. Indeed, S3 HCCs are well-differentiated, hepatocyte-like, and approximately 50% of them carry *CTNNB1* mutations.(5) Further, S3 HCC patients have a more favorable survival than S1 and S2 HCC patients.(27) As the main feature of S3 HCCs is preserved hepatocyte differentiation, S3's may include both Periportal-type and Perivenous-type HCCs.

GLUL, *HAL* and *VNN1* are involved in metabolic liver zonation. *HAL* is an enzyme that degrades the amino acid histidine(39) and we showed that it was restricted to periportal hepatocytes in normal liver. Likewise, Periportal-type HCCs expressed a host of amino acid degrading enzymes, such as *ARG1* (arginase 1) and *GLS2* (glutaminase 2), which were major hubs in the periportal gene network in HCCs (Fig. 5A). Some of these amino acid degrading enzymes, such as *SDS* (serine dehydratase) and *GLDC* (glycine decarboxylase), yield the end-product oxaloacetate, which is used for gluconeogenesis, a periportal metabolic pathway.(20, 40) *VNN1* is

a key activator of hepatic gluconeogenesis, transcriptionally activated by HNF4A.(41) By immunohistochemistry, VNN1 had a panlobular distribution, in consistency with unsupervised transcriptomic data,(20, 40) suggesting that *VNN1* probably responds to dynamic zonation.(29)

Cross-talks between HNF4A and β -catenin control the transcription of genes involved in periportal and perivenous zonation in normal liver.(29) Our data suggest that this cross-talk is preserved in well-differentiated HCCs. The 5-gene score predicting *CTNNB1* mutation was composed of genes known to be upregulated by β -catenin (*LGR5*, *GLUL* and *ODAM*) or by HNF4A (*VNN1* and *HAL*). (20, 41) By *in vitro* experiments, we confirmed that β -catenin activation enhanced *GLUL*, *LGR5* and *ODAM*, but inhibited *HAL* and *VNN1* expression. Conversely, β -catenin knockdown silenced *AXIN2* and *ODAM*, but enhanced *HAL* and *VNN1* expression. Further, we showed that β -catenin activation attenuated the gain in the expression of *HNF4A*, *ALDOB*, *HAL* and *VNN1* upon the 30-day time course of differentiation of HepaRG progenitors into hepatocyte-like cells (Supporting Fig. S5C-F). These observations suggest that β -catenin mutations divert the default periportal metabolic program of well-differentiated HCC cells toward a perivenous one (Fig. 7B).

In summary, we identified a new well-differentiated HCC subclass, Periportal-type HCCs, which has the most favorable clinical outcome among all HCCs. Accordingly, the Periportal-type HCC signature was associated with low early HCC recurrence (< 2 years after resection) independently of tumor size and vascular invasion in multivariate analyses. Given the heterogeneity of HCC phenotypes shown in Fig 7B, the question arises whether early, well-differentiated HCC types (Periportal and Perivenous) ultimately progress to a more aggressive, progenitor-like phenotype spontaneously or in response to treatments that may spare cancer progenitor cells.

Prediction of patient survival impacts the indication of liver transplantation for HCC. In particular, early recurrence is one of the principles governing patient staging within the spectrum of eligibility for liver transplantation.(3) Thus, it would be interesting to test whether identification of Periportal-type HCCs contributes to adapt indications of liver transplantation beyond current criteria. This issue will gain importance in the near future, because the control of the hepatitis C virus epidemics with direct antiviral agents will increase donor liver availability.

The major limitation to the direct translation of these basic findings to the clinical arena is the exclusion of diagnostic liver biopsy from current guidelines for HCC diagnosis and allocation to treatments. However, in view of exciting results demonstrating the clinical relevance of metabolic imaging in early-stage HCCs(42) and of the association of the transporter of gadoxetic acid OATP1B3 with Wnt/ β -catenin signaling in HCCs(43), the Periportal-type molecular phenotype raises a new challenge to metabolic imaging of HCCs.

FIGURE LEGENDS

Fig. 1. Flowchart of the study. (A) Construction of a transcriptomic metadata set for subclass-specific analyses after curative resection of 1133 HCCs. Nine public transcriptomic datasets (*A to I*) were merged into a metadata set. As the 1133-HCCs were not annotated for *CTNNB1* mutations, we developed a *CTNNB1* mutation prediction score from transcriptomic data. The most stable markers were identified by sPLS-DA modeling in training and validation sets. Mutation prediction was validated in an external in-house HCC collection(9); then, *CTNNB1* mutations were predicted in 1133 HCCs after cross-platform normalization. Subclass-specific survival analyses were performed in dataset C (n= 247 HCCs)(34) and validated in an external RNAseq, full-genome sequenced, dataset (LIHC-US; TCGA consortium, n= 210 HCCs).(10) (B) Transcriptomic datasets used: 1, yes or present; 0, no or absent. References: Training set(4); Validation set(6); A(44); B(45); C(34); D(46); E(47); F(48); G(49); H(49); I(28); RNAseq dataset(10). Major endpoints are indicated by bold arrows. External validation sets are represented by black boxes.

Fig. 2. A 5-gene score reliably predicts *CTNNB1* mutations using mRNA expression data in HCCs. (A) Gene expression of the five biomarkers in the training (n=87), validation (n=56) and the external validation (n=82) sets, according to Sanger-sequenced *CTNNB1* mutational status. *AXIN2* was included as a Wnt pathway activation marker (missing in A2). (B) Heatmaps showing mRNA expression of the five biomarkers plus *AXIN2* and *CTNNB1* mutational status (B1, training set; B2, validation set; B3, external HCC collection). Low and high gene expressions (median as cut-off) are represented in green and red, respectively. (C) Formula; (D)

Performance and (E) ROC curves of the *CTNNB1* mutation prediction score. (F) Tissue micro array-based immunostainings (*brown*) for GLUL, HAL and VNN1 in 20 *CTNNB1* mutant and 20 *CTNNB1* wild-type HCCs. Insets on the right: β -catenin cell membrane staining in *CTNNB1* wild-type (*arrowheads, upper right*), or cytoplasmic and nuclear staining in *CTNNB1* mutant HCCs (*arrowheads, lower right*). (G) Immunostaining (*brown*) for ODAM and GLUL in serial sections in a *CTNNB1* mutant HCC. Images were acquired with a tissue slide scanner at 20X original magnification. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Wilcoxon tests). AUROC, Area under the receiver operating curve; qPCR, real-time PCR (a pool of five normal liver samples was used as calibrator); CI, Confidence interval; Se, Sensitivity; Sp, Specificity.

Fig. 3. (A) Hierarchical clustering of transcriptomic metadata from 1133 HCCs reveals four tumor subgroups (*green, red, purple, & blue*) with different proportions of predicted *CTNNB1* mutations. Lowest and highest gene expression values are represented in *green* and *red*, respectively. (B) Gene expression levels of the five *CTNNB1* mutation predictors. Results are relative to the green subclass, arbitrarily set to $1 \pm 95\%$ CI. Green, $n=326$; Red, $n=210$; Blue, $n=420$; Purple, $n=177$. NS, non-significant. ** $P < 0.01$, *** $P < 0.001$, after Student's *t* tests. (C) Immunostainings (*brown*) of β -catenin, GLUL, VNN1 and HAL in serial sections of normal human liver illustrates clear-cut perivenous and periportal zonation of GLUL and HAL, respectively. β -catenin is predominantly membranous and highlights bile ducts (*BD*). Arrows show portal tracts (*PT*) and central veins (*CV*). VNN1 is panlobular. (D) VNN1 is detected in bile canaliculi in normal liver and in a well-differentiated HCC. VNN1 signal is totally suppressed by the immunogen polypeptide.

Fig. 4. Well-differentiated HCCs display a preserved metabolic liver zonation program. (A) Gene Set Enrichment Analysis (GSEA) in the four HCC subclasses. (B) Expression of relevant genes in the 1133-HCC metadata set. Color code keys are shown at the bottom of the heatmap. Samples (columns) are ordered by HCC subclass. *Green*, low; *red*, high expression. *PP*, Periportal-type; *PV*, Perivenous-type; *ECM*, Extracellular matrix-type; *STEM*, Stem cell-type.

Fig. 5. The metabolic program of Periportal-type HCCs is regulated by HNF4A. (A) Periportal (*PP*, *green*) and Perivenous (*PV*, *red*) gene networks constructed by Weighted Gene Correlation Analysis and shown with Cytoscape graphics. Networks consist of human orthologs of mouse liver periportal and perivenous gene signatures,(20) detected in 326 Periportal-type and 210 Perivenous-type HCCs from the 1133 HCC set. *Node border colors (Green/red)* denote periportal/perivenous attributes of mouse genes, respectively.(20) *Node core colors* are proportional to the PV/PP fold-change in the HCC set (*Color key: lower right*). *Link thickness* is proportional to correlation coefficients (>0.30 in all networks; *blue*, positive; *red*, negative correlation). (B) The 550 genes representative of the four HCC subclasses discriminate between *Hnf4a*-KO and *Hnf4a*-WT mice.(31). Three gene clusters (*black nodes on the left*) denote: 1, upregulation in *Hnf4a*-KO's and enrichment in human HCC STEM/ECM signatures; 2, upregulation in *Hnf4a*-WT's and enrichment in HCC PP genes; 3, genes poorly affected by *Hnf4a* status. *Red*, high expression, *green*, low expression.

Fig. 6. Periportal-type HCCs show the most favorable clinical features and the highest early (2-year) disease-free and overall survival rates after resection. (A) Clinical features of HCC subclasses in a 247-patient dataset(34). (B) Kaplan-Meier plots of subclass-specific overall and disease-free survival; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (C) Subclass-specific clinical features, *CTNNB1* and *TP53* mutation rates (full genome sequencing) in an external validation 210-HCC RNAseq dataset (TCGA-LIHC-US). (D) Subclass-specific mRNA expression levels of *Periportal HCC signature* genes in 1133 HCCs. (E, F) Kaplan-Meier plots of overall and disease-free survival in HCC patients with and without the *Periportal HCC signature* in two datasets. AFP, serum alpha-fetoprotein; NA, not available; BCLC (Barcelona Clinic Liver Cancer); CLIP (Cancer of the Liver Italian Program). Statistics: Fisher exact test (categorical variables); Student's *t* test (continuous variables); Log-rank test (survival analyses).

Fig. 7. Periportal-type HCCs and the survival paradox between *CTNNB1*-mutated and wild-type HCCs. (A) Kaplan-Meier plots and log-rank tests in two independent HCC datasets confirm similar outcome of HCCs carrying mutated (*red*) or wild-type (*black*) *CTNNB1*. Mutational status results from prediction in dataset C and full-genome sequencing in TCGA-LIHC-US. (B) Multivariate discriminant analysis of the four HCC subclasses. In the first component, there is a grading from Periportal-type (*green*), through Perivenous- (*red*) and ECM-types (*blue*), to STEM-type (*purple*). In the second component, Perivenous-type differs from other HCC subclasses. (C) HCCs with predominantly mutated *CTNNB1* are moderately aggressive. (D) HCCs with predominantly wild-type *CTNNB1* include mildly, moderately and highly aggressive subclasses. The % of HCCs in each subclass is indicated in parentheses.

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Contributors: Study design, RD, OM, FR, K-A LC, CP, BC; statistics, RD, FR, K-A LC; experiments, RD, FC, MS, SR, PB, CP, OM; anatomic pathology data, BT, OM; tissue banking and quality control, MD, OM; manuscript preparation, RD, OM; manuscript editing, all authors.

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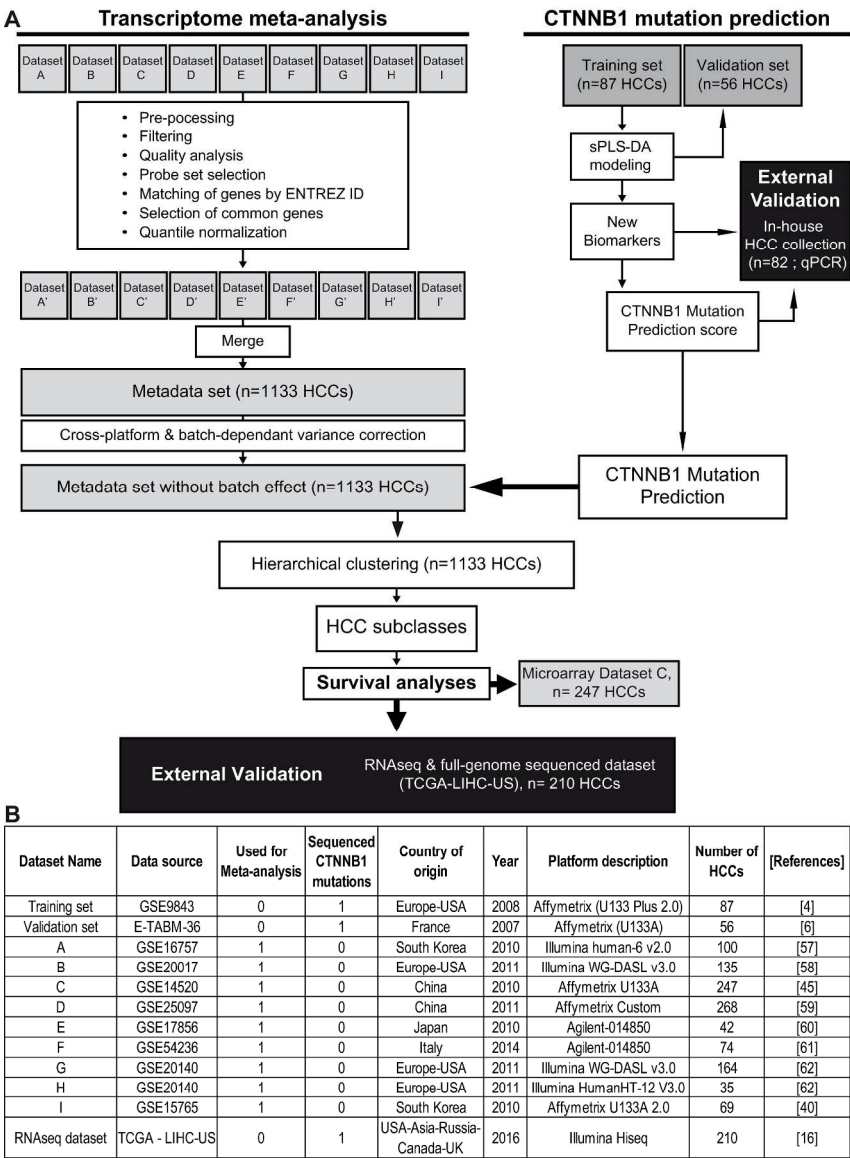
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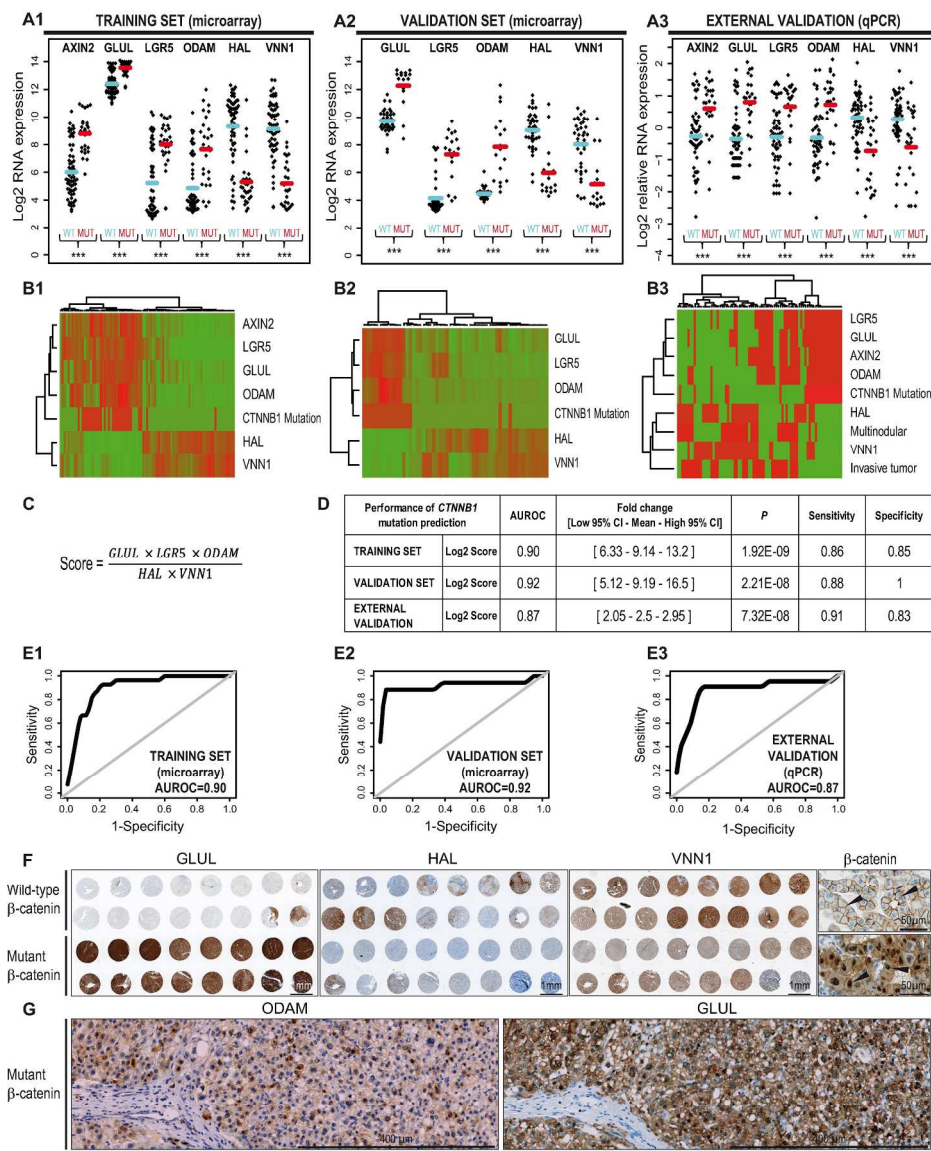


Désert et al., Figure 1

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Désert et al., Figure 2

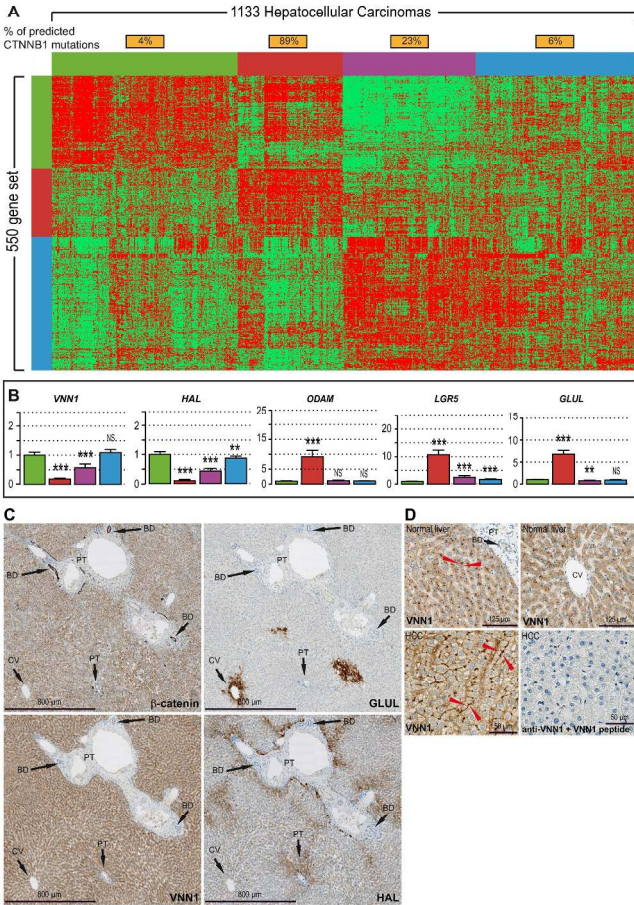
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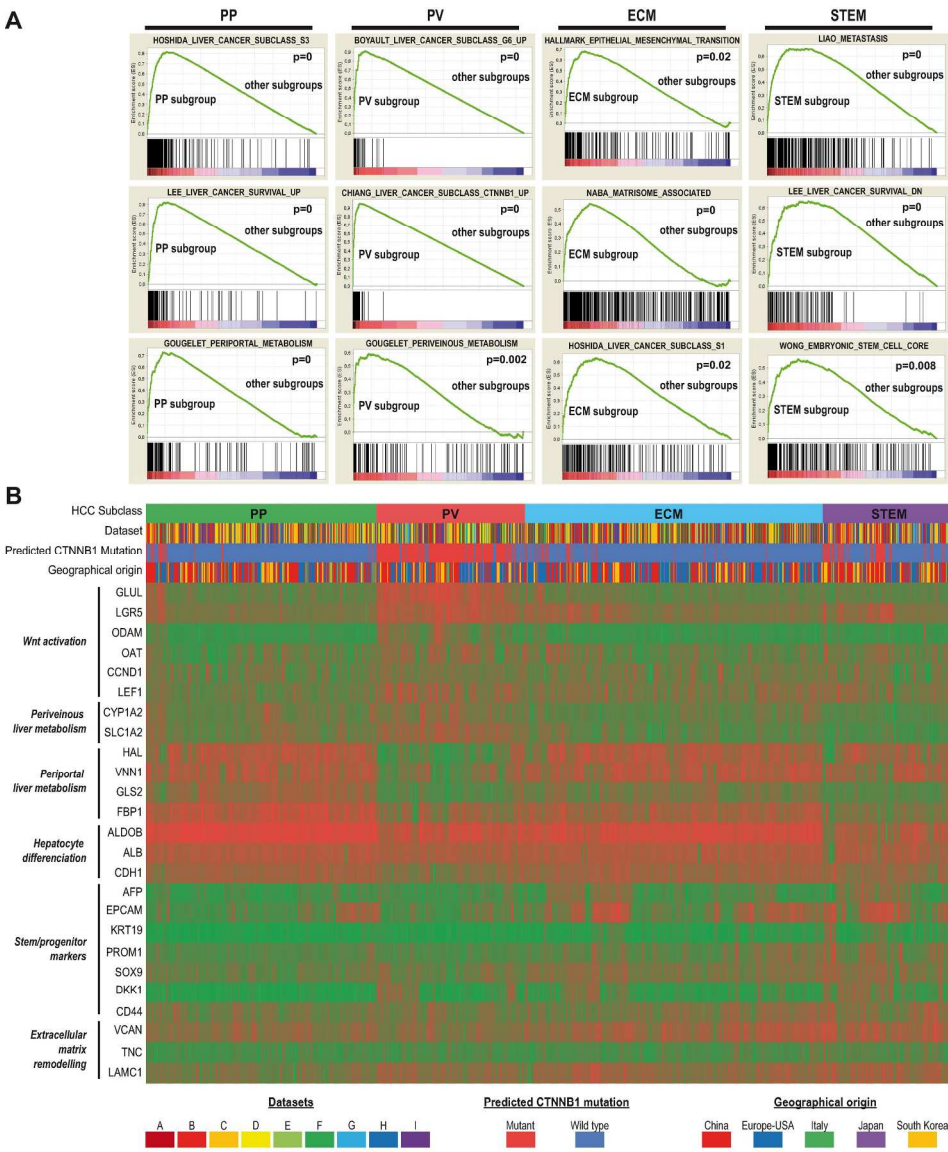


Désert et al., Figure 3

Fig. 3. (A) Hierarchical clustering of transcriptomic metadata from 1133 HCCs reveals four tumor subgroups (green, red, purple, & blue) with different proportions of predicted CTNNB1 mutations. Lowest and highest gene expression values are represented in green and red, respectively. (B) Gene expression levels of the five CTNNB1 mutation predictors. Results are relative to the green subclass, arbitrarily set to $1 \pm 95\%$ CI. Green, $n=326$; Red, $n=210$; Blue, $n=420$; Purple, $n=177$. NS, non-significant. $**P<0.01$, $***P<0.001$, after Student's t tests. (C) Immunostainings (brown) of β -catenin, GLUL, VNN1 and HAL in serial sections of normal human liver illustrates clear-cut perivenous and periportal zonation of GLUL and HAL, respectively. β -catenin is predominantly membranous and highlights bile ducts (BD). Arrows show portal tracts (PT) and central veins (CV). VNN1 is panlobular. (D) VNN1 is detected in bile canaliculi in normal liver and in a well-differentiated HCC. VNN1 signal is totally suppressed by the immunogen polypeptide.

304x463mm (300 x 300 DPI)

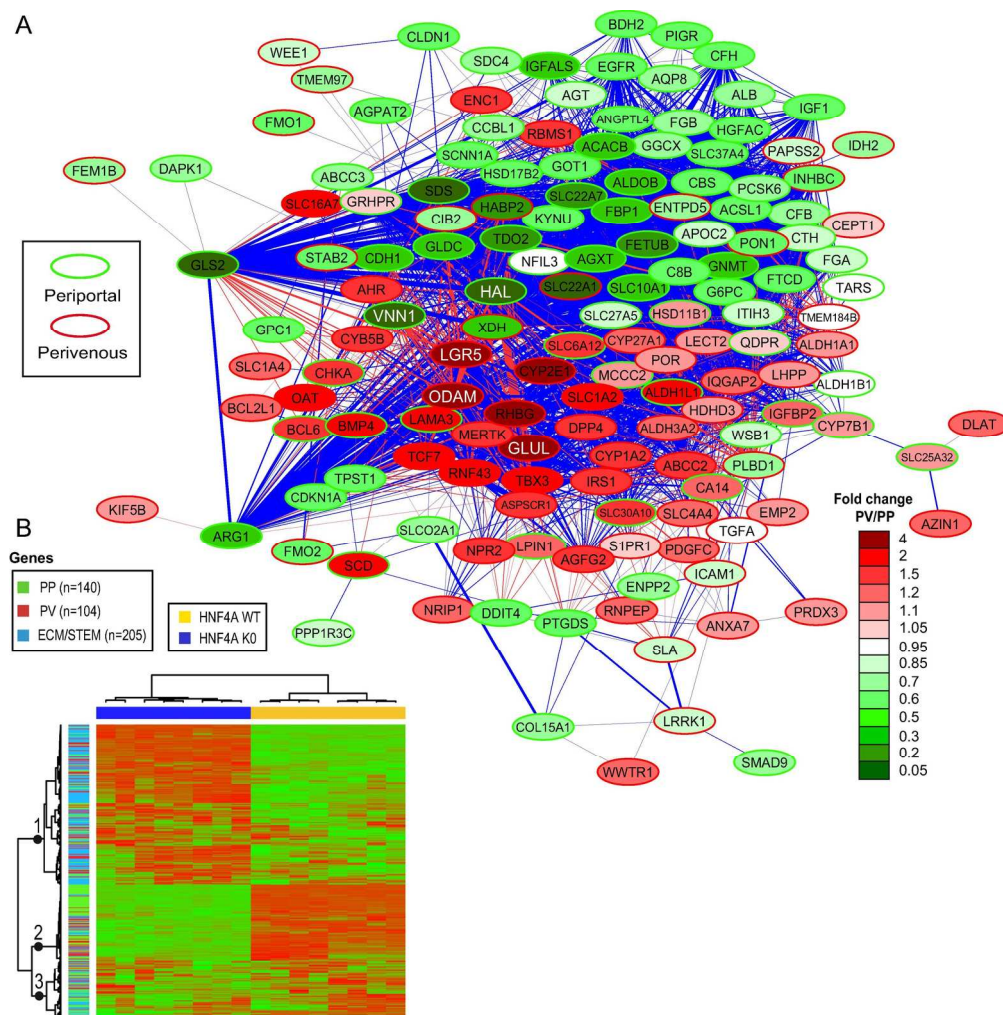
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Désert et al., Figure 4

Fig. 4. Well-differentiated HCCs display a preserved metabolic liver zonation program. (A) Gene Set Enrichment Analysis (GSEA) in the four HCC subclasses. (B) Expression of relevant genes in the 1133-HCC metadata set. Color code keys are shown at the bottom of the heatmap. Samples (columns) are ordered by HCC subclass. Green, low; red, high expression. PP, Periportal-type; PV, Perivenous-type; ECM, Extracellular matrix-type; STEM, Stem cell-type.

212x269mm (300 x 300 DPI)



Désert et al., Figure 5

Fig. 5. The metabolic program of Periportal-type HCCs is regulated by HNF4A. (A) Periportal (PP, green) and Perivenous (PV, red) gene networks constructed by Weighted Gene Correlation Analysis and shown with Cytoscape graphics. Networks consist of human orthologs of mouse liver periportal and perivenous gene signatures,(20) detected in 326 Periportal-type and 210 Perivenous-type HCCs from the 1133 HCC set. Node border colors (Green/red) denote periportal/perivenous attributes of mouse genes genes, respectively.(20) Node core colors are proportional to the PV/PP fold-change in the HCC set (Color key: lower right). Link thickness is proportional to correlation coefficients (>0.30 in all networks; blue, positive; red, negative correlation). (B) The 550 genes representative of the four HCC subclasses discriminate between Hnf4a-KO and Hnf4a-WT mice.(31). Three gene clusters (black nodes on the left) denote: 1, upregulation in Hnf4a-KO's and enrichment in human HCC STEM/ECM signatures; 2, upregulation in Hnf4a-WT's and enrichment in HCC PP genes; 3, genes poorly affected by Hnf4a status. Red, high expression, green, low expression.

179x191mm (300 x 300 DPI)

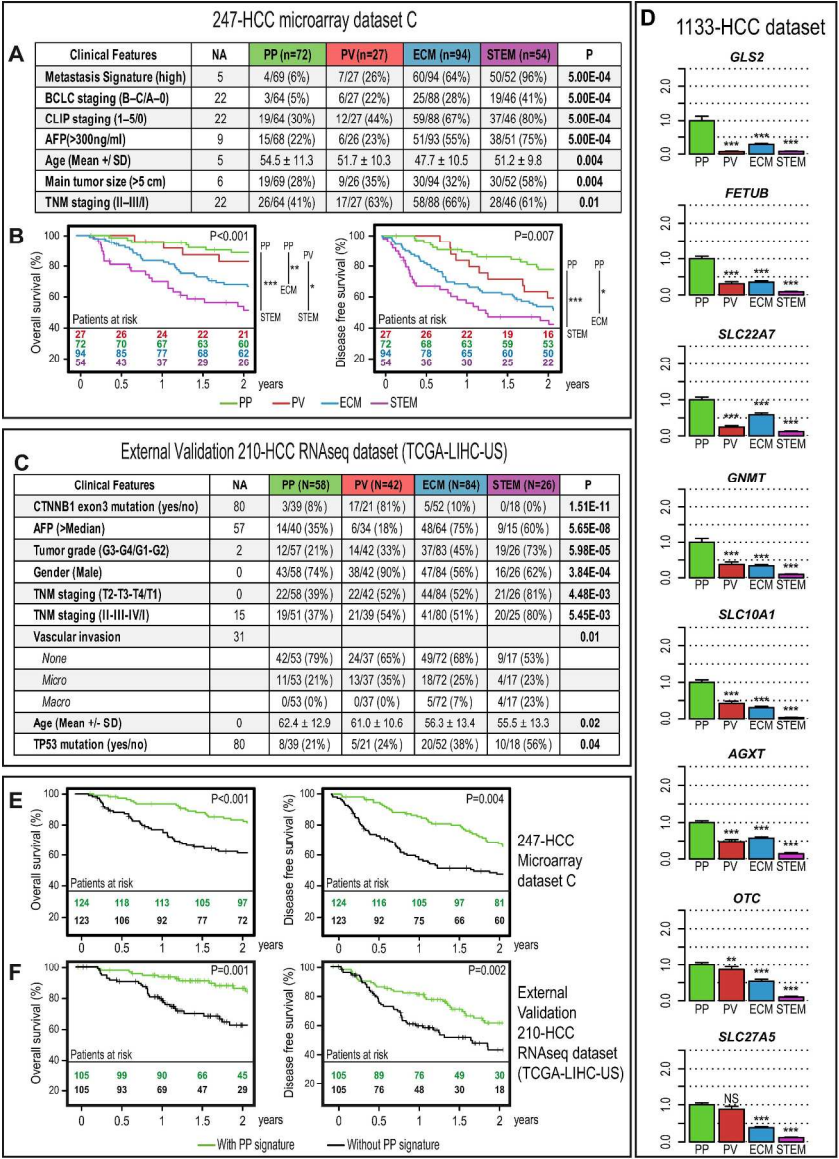
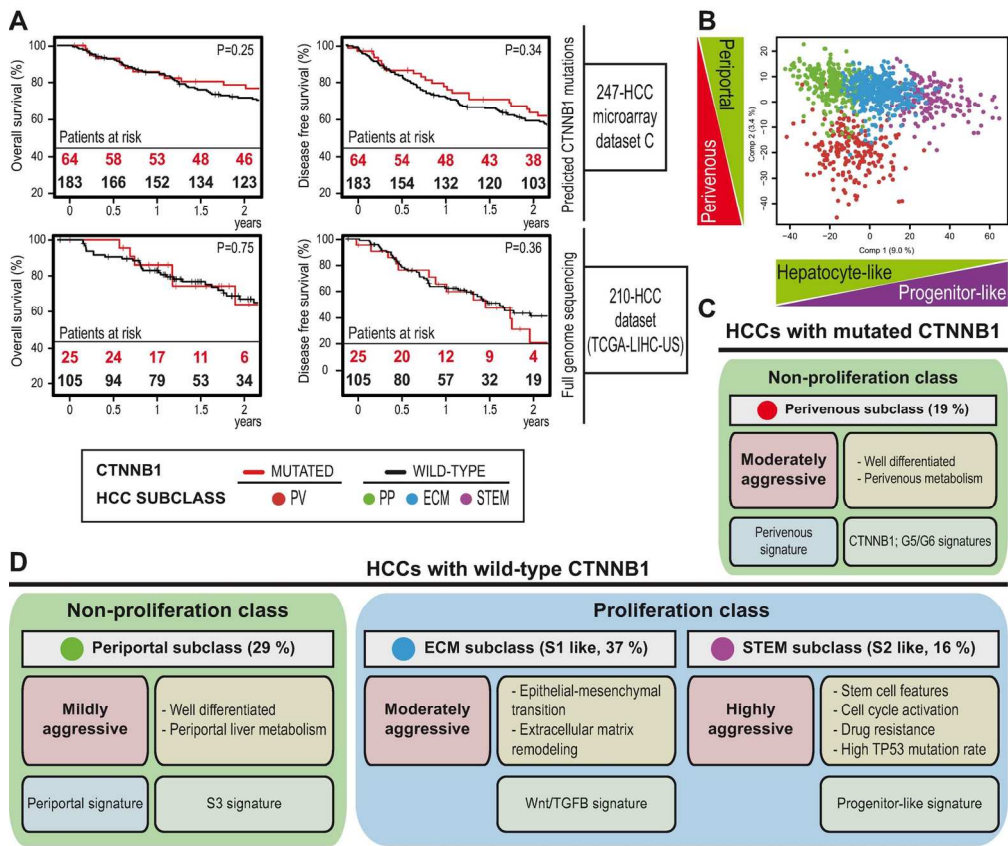


Fig. 6. Periportal-type HCCs show the most favorable clinical features and the highest early (2-year) disease-free and overall survival rates after resection. (A) Clinical features of HCC subclasses in a 247-patient dataset(34). (B) Kaplan-Meier plots of subclass-specific overall and disease-free survival; *P<0.05, **P<0.01, ***P<0.001. (C) Subclass-specific clinical features, CTNNB1 and TP53 mutation rates (full genome sequencing) in an external validation 210-HCC RNAseq dataset (TCGA-LIHC-US). (D) Subclass-specific mRNA expression levels of Periportal HCC signature genes in 1133 HCCs. (E, F) Kaplan-Meier plots of overall and disease-free survival in HCC patients with and without the Periportal HCC signature in two datasets. AFP, serum alpha-fetoprotein; NA, not available; BCLC (Barcelona Clinic Liver Cancer); CLIP (Cancer of the Liver Italian Program). Statistics: Fisher exact test (categorical variables); Student's t test (continuous variables); Log-rank test (survival analyses).

227x327mm (300 x 300 DPI)

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Désert et al., Figure 7

Fig. 7. Periportal-type HCCs and the survival paradox between CTNNB1-mutated and wild-type HCCs. (A) Kaplan-Meier plots and log-rank tests in two independent HCC datasets confirm similar outcome of HCCs carrying mutated (red) or wild-type (black) CTNNB1. Mutational status results from prediction in dataset C and full-genome sequencing in TCGA-LIHC-US. (B) Multivariate discriminant analysis of the four HCC subclasses. In the first component, there is a grading from Periportal-type (green), through Perivenous- (red) and ECM-types (blue), to STEM-type (purple). In the second component, Perivenous-type differs from other HCC subclasses. (C) HCCs with predominantly mutated CTNNB1 are moderately aggressive. (D) HCCs with predominantly wild-type CTNNB1 include mildly, moderately and highly aggressive subclasses. The % of HCCs in each subclass is indicated in parentheses.

155x139mm (300 x 300 DPI)

A

Table 1. Univariate and multivariate Cox's 2-year disease-free survival analyses in two independent HCC datasets.

Variables	Missing values	N (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	Wald <i>P</i> value	HR (95% CI)	Wald <i>P</i> value
247-HCC microarray dataset C						
Sex (male)	5	211 (87%)	2.38 (1.25-4.53)	8.41E-03	2.25 (1.16-4.33)	0.01
Age (> 60 y)	5	46 (19%)	1.02 (0.66-1.56)	0.94		
HBV viral status (AVR)	23	58 (26%)	1.34 (0.91-1.96)	0.14		
ALT (>50 U/L.)	5	100 (41%)	1.4 (1-1.96)	0.05		
Main tumor size (>5 cm)	6	88 (37%)	1.38 (0.97-1.94)	0.07	1.14 (0.79-1.65)	0.47
Multinodular	5	52 (21%)	1.33 (0.9-1.98)	0.15	1.10 (0.73-1.66)	0.63
Cirrhosis	5	223 (92%)	1.99 (0.93-4.27)	0.08		
AFP (>300ng/ml)	9	110 (46%)	1.31 (0.93-1.83)	0.12	1.22 (0.85-1.74)	0.26
Periportal 8-gene signature	0	124 (50%)	0.62 (0.45-0.88)	6.37E-03	0.69 (0.48-0.97)	0.03
External validation 210-HCC RNAseq dataset (TCGA-LIHC-US)						
Sex (male)	0	144 (69%)	0.84 (0.55-1.27)	0.40		
Age (> 60 y)	0	104 (50%)	0.8 (0.53-1.19)	0.26		
Patients from Asia	6	71 (35%)	0.96 (0.63-1.47)	0.87		
Patients from USA	6	101 (50%)	1.09 (0.73-1.63)	0.67		
Obesity	18	32 (17%)	0.85 (0.48-1.51)	0.59		
Tumor sample weight (>median)	0	69 (33%)	1.73 (1.11-2.7)	0.02	0.98 (0.54-1.8)	0.96
Vascular invasion	31	55 (31%)	1.68 (1.05-2.69)	0.03	1.52 (0.92-2.5)	0.10
Child pugh (>A)	68	15 (11%)	1.44 (0.65-3.18)	0.36		
AFP (>median)	57	76 (50%)	1.16 (0.72-1.85)	0.55		
Platelet count (>median)	34	87 (49%)	1.49 (0.95-2.34)	0.08		
Hepatic inflammation of adjacent tissue	68	76 (54%)	1.03 (0.64-1.65)	0.92		
Performance Status (>0)	40	77 (45%)	1.53 (0.99-2.35)	0.05		
CTNNB1 exon3 mutation	80	25 (19%)	1.33 (0.74-2.36)	0.34		
TP53 mutation	80	43 (33%)	1.4 (0.84-2.32)	0.20		
Periportal 8-gene signature	0	105 (50%)	0.53 (0.36-0.8)	0.003	0.59 (0.37-0.94)	0.02

Supporting Table S1. See Supplementary Data.docx file for caption.

Study number	1	2	3	4	5	6	7	8	9	10	11	12
First author name	Rebouissou et al.	Kawai-Kitahata et al.	Schulze et al.	Lu et al.	Ding et al.	Kan et al.	Cleary et al.	Nault et al.	Guichard et al.	Yuan et al.	Peng et al.	Hsu et al.
Year of publication	2016	2015	2015	2014	2014	2013	2013	2013	2012	2011	2004	2000
Bibliographic reference	Hepatology, 10.1002/hep.28638	J Gastroenterol, 51:473	Nat Genet, 47:505	Oncology, 87:159	PLoS One, 9:e95307	Genome Res, 23:1422	Hepatology, 58:1693	Gastroenterology, 145:176	Nat Genet, 44:694	J Gastrointest Surg, 15:321	Int. J. Cancer, 112:44	Am J Pathol, 157:763
Geographical origin of patients and etiology	HCCs from France, mainly alcoholics (36%)	HCCs from Japan, mainly HCV positive	HCCs from France, mainly alcoholics (41%)	HCCs from Taiwan, mainly HBV positive (68%)	HCCs from China, mainly HBV positive	HCCs from China, mainly HBV positive	HCCs from USA - 40% HBV, 20% HCV	HCCs from France, mainly alcoholics (39%)	HCCs from France, mainly alcoholics (34%)	HCCs from Taiwan, mainly HBV positive	HCCs from Taiwan, mainly HBV positive	HCCs from Taiwan, mainly HBV positive
Number of HCCs carrying mutant CTNNB1	137	28	82	21	13	14	20	100	41	26	44	47
Number of HCCs carrying wild-type CTNNB1	225	54	154	94	123	74	60	207	84	145	281	319
% of CTNNB1 mutations	38%	34%	35%	18%	10%	16%	25%	33%	33%	15%	14%	13%
Total number of HCCs studied	362	104	236	115	136	88	80	307	125	171	325	366
Overall survival	HR	NA	NS	NA	NS	NA	NA	NA	NA	NA	NS	NA
	P=	NA	0.15	NA	0.81	0.23	NA	NA	NA	NA	0.06	<0.001
Disease-free survival	HR	NA	NS	NA	NA	NA	NS	NA	NA	NA	NA	NA
	P=	NA	0.68	NA	NA	NA	0.51	NA	NA	NA	NA	NA
Disease-specific survival	HR	NS	NA	NS	NA	NA	NA	NS	NA	NA	NA	NA
	P=	0.85	NA	0.61	NA	NA	NA	0.06	NA	NA	NA	NA
Other clinical or pathological associations of CTNNB1 mutations	Positively associated with male gender, alcohol, low AFP, low Edmondson score, larger nodule size, capsular invasion and cholestasis. Negatively associated with HBV and cirrhosis.	Negatively associated with HBV. No association with tumor size, tumor differentiation, number of tumors, vascular invasion or AFP.		No association with tumor stage nor with metastasis			Association with HCV. No association with microvascular invasion, tumor size or tumor differentiation		Negatively associated with AFP and HBV. No association with tumor size or tumor differentiation.	Early tumor recurrence is negatively associated with mutant CTNNB1 by logistic regression (OR=0.25, p=0.03)	Negatively associated with AFP.	Negatively associated with tumor grade, tumor stage, AFP and HBV. HBV in liver tissues: mutant CTNNB1, 9%; wild-type CTNNB1, 24% (p<10 ⁻⁶). HBsAg in serum: mutant CTNNB1, 46.8%; wild-type CTNNB1, 71.5% (p=0.0013).
Different patient survival between HCCs carrying mutant versus wild-type CTNNB1?	No	No	No	No	No	NA	No	No	NA	NA	No	Yes
Comments						S3 HCCs show more favorable survival than S2 and S1 HCCs. S3 HCCs have a relatively higher proportion of CTNNB1 mutations.				Same cohort as Hsu et al.	Same cohort as Hsu et al.	Lack of multivariate survival analysis. Potential confusion bias: differences in etiology between patients carrying wild-type and mutant CTNNB1 (more HBV-infected patients in wild-type CTNNB1 tumors).

Supporting Table S2. See Supplementary Data.docx file for caption.

Dataset Name	Training set	Validation set	External Validation in-house HCC collection	Dataset A	Dataset B	Dataset C	Dataset D	Dataset E	Dataset F	Datasets G-H	Dataset I	External validation RNAseq dataset
First author or consortium & project names	Chiang D.	Boyault S.	Mebarki S.	Kim SM.	Minguez B.	Roessler S.	Sung WK.	Tsuchiya M.	Villa E.	Villanueva A.	Woo HG.	TCGA-LIHC
Patients in cohort (n=)	91	57	70	100	135	247	268	43	78	244	70	380
Available HCC samples (n=)	91	57	70	100	135	247	268	43	81	164+35=199	70	294
Samples excluded after quality analysis (n=)	0	0	0	0	0	0	0	1	8	0	1	84
Samples excluded because of unavailable mutational status (n=)	4	1	0	/	/	/	/	/	/	/	/	/
Included HCC samples (n=)	87	56	82	100	135	247	268	42	73	164+35=199	69	210
Inclusion criteria	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection	HCV-associated HCCs after surgical resection	Child-Pugh class A liver cirrhosis diagnosed as HCC based on histological criteria. Samples are liver biopsies.	HCCs after surgical resection	HCCs after surgical resection	HCCs after surgical resection
Country of origin	Europe-USA	France	France	South Korea	Europe-USA	China	China	Japan	Italy	Europe-USA	South Korea	USA-Asia-Russia-Canada-UK
Gender (Male)	54 (66.7%)	45 (82%)	64 (94%)	83 (83%)	102 (75.6%)	214 (87%)	80%	32 (74.4%)	61 (78.2%)	179 (73.3%)	57 (81.4%)	144 (69%)
Age												
Mean, SD	65.1 ± 68.9	62.0 ± 13.8	63.6 ± 9.3	NA	NA	50.8 ± 10.8	56.0 ± 12.0	66.5 ± 7.9	NA	NA	NA	58.8 ± 13
Median, range	NA	NA	64 (56.5-71)	55 (25-70)	67 (36-83)	NA	NA	NA	66 (44-88)	NA	NA	60 (51-68)
>55 years	NA	NA	54 (80%)	NA	NA	NA	NA	NA	NA	NA	41 (58.6%)	134 (64%)
>60 years	NA	NA	39 (58%)	NA	NA	NA	NA	NA	NA	150 (62.4%)	NA	104 (49%)
HCV positive	81 (100%)	11 (19%)	4 (6%)	NA	54 (40.0%)	5 (2%)	NA	43 (100%)	44 (56.4%)	150 (61.9)	1 (1.4%)	52 (56%)
HBV positive	NA	17 (30%)	3 (4%)	58 (58%)	45 (33.3%)	241 (99%)	NA	0 (0%)	10 (12.8%)	56 (23.1)	69 (98%)	87 (93%)
HBV active viral replication	NA	NA	NA	NA	NA	62 (26%)	NA	0 (0%)	NA	NA	NA	9 (10%)
Alcohol	NA	18 (32%)	56 (80%)	NA	9 (6.7%)	NA	40%	NA	12 (15.4%)	8 (3.3)	62 (29%)	NA
Hemochromatosis	NA	3 (5%)	4 (6%)	NA	NA	NA	NA	NA	NA	NA	NA	3 (1%)
Cirrhosis	NA	36 (63%)	59 (89%)	64 (64%)	NA	224 (91%)	57%	NA	NA	NA	NA	NA
Intact capsule	NA	13 (23%)	30 (42.86%)	NA	NA	129 (53%)	NA	NA	NA	NA	NA	NA
Satellite nodule	NA	23 (40%)	NA	NA	NA	NA	NA	NA	NA	36 (14.9%)	NA	NA
CTNNB1 mutation	27 (31%)	17 (30%)	23 (33%)	NA	NA	NA	NA	NA	NA	NA	NA	25 (19%)
TP53 mutation	11 (13%)	14 (24%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	43 (33%)
Tumor size												
cm, mean, SD	NA	7.9 ± 5.1	4.4 ± 2.8	NA	NA	NA	7.6 ± 4.1	2.95 ± 1.37	NA	NA	NA	NA
cm, median, range	3.5 (2.5-6.0)	NA	3.5 (3.0-4.5)	NA	3.5 (2.3-5)	NA	NA	NA	NA	NA	NA	NA
Tumour volume (cm3) (mean, SD)	NA	NA	NA	NA	NA	NA	NA	NA	12.1 ± 19.7	NA	NA	NA
Less than 2.0 cm	8 (9.9%)	NA	7 (10%)	NA	NA	NA	NA	NA	NA	61 (25%)	NA	NA
Between 2.0 cm and 3.0 cm	NA	NA	NA	NA	NA	NA	NA	NA	NA	68 (27.9%)	NA	NA
Greater than 3.0 cm	48 (59.2%)	NA	45 (65%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Greater than 5.0 cm	NA	NA	45 (65%)	NA	75 (55.6%)	NA	NA	NA	NA	115 (47.1%)	NA	NA
Number of tumor nodules	25 (30.9%)	NA	11 (16%)	NA	NA	89 (36%)	NA	NA	NA	NA	31 (44.2%)	NA
Mean, SD	NA	NA	3.2 ± 1.7	NA	NA	NA	NA	1.30 ± 0.51	NA	NA	NA	NA
Single	68 (84.0%)	68 (84.0%)	38 (43%)	NA	50 (37.0%)	193 (78%)	76%	NA	66 (84.6%)	NA	32 (45.7%)	NA
Multiple	13 (16.0%)	13 (16.0%)	30 (56%)	NA	18 (13.3%)	52 (21%)	24%	NA	12 (15.4%)	NA	38 (54.3%)	NA
Vascular invasion												
None	34 (42.0%)	33 (58%)	42 (61%)	52 (52%)	95 (70.4%)	90 (46%)	51%	38 (88.4%)	NA	154 (64.4%)	34 (51.4%)	124 (69%)
Microscopic	38 (46.9%)	17 (30%)	NA	NA	40 (29.6%)	107 (54%)	NA	NA	NA	85 (35.5%)	NA	46 (26%)
Macroscopic	8 (9.9%)	7 (12%)	NA	NA	0 (0.0%)	0 (0%)	NA	NA	9 (11.5%)	0 (0%)	NA	9 (5%)
TNM staging												
I	NA	NA	NA	85 (44%)	NA	97 (43%)	44%	8 (18.6%)	NA	NA	NA	94 (48%)
I-II	NA	NA	NA	161 (84%)	NA	NA	NA	NA	NA	NA	16 (23.9%)	139 (71%)
II-III	NA	NA	NA	107 (56%)	NA	130 (57%)	56%	34 (89.1%)	NA	NA	NA	96 (50%)
III-IV	NA	NA	NA	31 (16%)	NA	NA	NA	NA	NA	NA	51 (76.1%)	56 (29%)
IV	NA	NA	NA	0 (0%)	NA	0 (0%)	0%	1 (2.3%)	NA	NA	NA	3 (1%)
CLIP Staging												
0	NA	NA	NA	NA	NA	99 (44%)	NA	NA	NA	NA	NA	NA
1-5	NA	NA	NA	NA	NA	128 (56%)	NA	NA	NA	NA	NA	NA
Tumor differentiation												
Well differentiated	20 (24.7%)	NA	NA	NA	NA	NA	NA	6 (14.0%)	NA	60 (24.9%)	NA	NA
Moderately differentiated	43 (53.1%)	NA	NA	NA	NA	NA	NA	29 (67.4%)	NA	140 (58.1%)	NA	NA
Poorly differentiated	17 (21.0%)	NA	NA	NA	NA	NA	NA	8 (18.6%)	NA	41 (17%)	NA	NA
Edmondson grade												
I	NA	4 (7%)	4 (6%)	10 (10%)	NA	NA	21.3%	NA	24 (30.8%)	NA	NA	NA
I-II	NA	33 (59%)	37 (53%)	61 (61%)	NA	NA	80.5%	NA	54 (69.2%)	NA	37 (52.8%)	NA
II	NA	29 (51%)	33 (48%)	51 (51%)	NA	NA	59.2%	NA	30 (38.4%)	NA	NA	NA
III	NA	20 (35%)	32 (46%)	33 (33%)	NA	NA	18.3%	NA	24 (30.8%)	NA	NA	NA
III-IV	NA	24 (43%)	32 (46%)	39 (39%)	NA	NA	19.6%	NA	24 (30.8%)	NA	33 (47.1%)	NA
IV	NA	4 (7%)	0 (0%)	6 (6%)	NA	NA	1.3%	NA	0 (0%)	NA	NA	NA
Child-Pugh class												
A	NA	NA	42 (79%)	92 (92%)	NA	NA	97.3%	NA	78 (100%)	NA	NA	127 (89%)
B	NA	NA	6 (11%)	4 (4%)	NA	NA	2.7%	NA	0 (0%)	NA	NA	15 (11%)
C	NA	NA	5 (9%)	4 (4%)	NA	NA	0%	NA	0 (0%)	NA	NA	0 (0%)
Fibrosis score												
F0	NA	NA	3 (4%)	NA	NA	NA	NA	0 (0%)	NA	NA	NA	NA
F1	NA	NA	2 (3%)	NA	NA	NA	NA	3 (7.0%)	NA	NA	NA	NA
F2	NA	NA	1 (2%)	NA	NA	NA	NA	6 (14.0%)	NA	NA	NA	NA
F3	NA	NA	1 (2%)	NA	NA	NA	NA	12 (27.9%)	NA	NA	NA	NA
F4	NA	NA	62 (90%)	NA	NA	NA	NA	22 (51.2%)	NA	NA	NA	NA
Barcelona Clinic Liver Cancer stage												
0	9 (11.1%)	NA	NA	0 (0%)	NA	0 (0%)	NA	NA	0 (0%)	39 (16%)	NA	NA
0-A	NA	NA	NA	53 (53%)	NA	174 (77%)	NA	NA	56 (71.8%)	244 (100%)	NA	NA
A	56 (69.1%)	NA	NA	53 (53%)	NA	NA	NA	NA	56 (71.8%)	205 (84%)	NA	NA
B	7 (8.6%)	NA	NA	37 (37%)	NA	NA	NA	NA	0 (0%)	0 (0%)	NA	NA
B-C	NA	NA	NA	43 (43%)	NA	53 (23%)	NA	NA	22 (28.1%)	0 (0%)	NA	NA

C		8 (9.9%)	NA	NA	6 (6%)	NA	NA	NA	NA	9 (11.5%)	0 (0%)	NA	NA
D		0 (0%)	NA	NA	4 (4%)	NA	0 (0%)	NA	NA	0 (0%)	0 (0%)	NA	NA
	Serum AFP levels (ng/ml)												
	Mean, SD	NA	NA	39.4 ± 92.2	NA	NA	NA	151.3 ± 107.1	345 ± 962	NA	NA	NA	NA
	Less than 10	24 (29.6%)	NA	41 (69%)	NA	53 (41.4%)	NA	NA	NA	NA	NA	NA	NA
	Between 10 and 100	25 (30.9%)	NA	12 (20%)	NA	41 (32%)	NA	NA	NA	NA	NA	NA	NA
	Less than 100	NA	38 (67%)	54 (91%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Between 100 and 1000	11 (13.6%)	NA	5 (8%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Greater than 100	NA	NA	5 (8%)	NA	21 (16.4%)	NA	NA	NA	NA	63 (26.7%)	NA	NA
	Greater than 300	NA	NA	4 (6%)	32 (32%)		111 (46%)	NA	NA	NA	22 (31.4%)	NA	NA
	Greater than 400	NA	NA	1 (2%)	NA	NA	NA	NA	NA	7 (9.6%)	NA	NA	NA
	Greater than 1000	10 (12.3%)	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Laboratory procedure outcome value (Mean, SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	17125 ± 164991
	Albumin (g/dl)												
	Mean, SD	NA	NA	3.6 ± 0.8	NA	NA	NA	4 ± 0.4	NA	3.8 ± 0.5	NA	NA	NA
	Median, range	NA	NA	3.7 (3.2-4.0)	NA	4 (3.8-4.4)	NA	NA	NA	NA	NA	NA	NA
	Less than 3.5	NA	NA	20 (42%)	NA	NA	NA	NA	NA	NA	29 (12.2%)	NA	NA
	Laboratory procedure outcome value (Mean, SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	35 ± 400
	Platelets (x1000/ml)												
	Mean, SD	NA	NA	146 ± 71.5	NA	NA	NA	NA	128 ± 42	111 ± 64	NA	NA	NA
	Median, range	NA	NA	136.5 (86.0-189.5)	NA	160 (120-209)	NA	NA	NA	NA	NA	NA	NA
	Less than 100	NA	NA	19 (30%)	NA	NA	NA	NA	NA	NA	49 (20.4)	NA	NA
	Greater than 150	NA	NA	26 (41%)	NA	NA	NA	NA	NA	NA	37 (57%)	NA	NA
	Laboratory procedure outcome value (Mean, SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	22656 ± 79098
	Bilirubin												
	mg/dl, mean, SD	NA	NA	1.34 ± 1.34	NA	NA	NA	0.85 ± 0.65	0.80 ± 0.35	1.1 ± 0.9	NA	NA	0.94 ± 1.61
	mg/dl, median, range	NA	NA	0.88 (0.60-1.52)	NA	0.8 (0.6-1.1)	NA	NA	NA	NA	NA	NA	0.70 (0.50-1.0)
	Greater than 1 mg/dl	NA	NA	26 (44%)	NA	NA	NA	NA	NA	NA	85 (35.4%)	NA	32 (18%)
	ALT (U/L)												
	Mean, SD	NA	NA	44.3 ± 24.6	NA	NA	NA	61.0 ± 51.4	51.7 ± 33.1	66 ± 61	NA	NA	NA
	Greater than 50	NA	NA	21 (33%)	NA	NA	101 (41%)	NA	NA	NA	NA	NA	NA
	ASAT (U/L), mean, SD	NA	NA	48.6 ± 21.0	NA	NA	NA	64.3 ± 53.9	NA	87 ± 72	NA	NA	NA

Supporting Table S3. See Supplementary Data.docx file for caption.

Data source	Number of probes in the array	Number of genes expressed over background	Pearson's Correlations										
			EPCAM-KRT19	GS-HAL	GS-LGR5	GS-ODAM	GS-VNN1	LGR5-HAL	LGR5-ODAM	LGR5-VNN1	HAL-ODAM	HAL-VNN1	ODAM-VNN1
A	48701	18758	0.67	-0.52	0.58	0.67	-0.43	-0.49	0.56	-0.54	-0.57	0.38	-0.51
B	24526	18277	0.27	-0.51	0.42	0.71	-0.42	-0.48	0.33	-0.36	-0.50	0.28	-0.43
C	22277	12509	0.51	-0.46	0.58	0.55	-0.20	-0.29	0.43	-0.34	-0.51	0.33	-0.30
D	37582	18918	0.46	-0.66	0.54	0.68	-0.38	-0.55	0.58	-0.42	-0.68	0.56	-0.53
E	43376	18883	0.57	-0.81	0.74	0.78	-0.68	-0.63	0.62	-0.63	-0.63	0.59	-0.59
F	43376	18962	0.84	-0.50	0.41	0.42	-0.51	-0.64	0.62	-0.53	-0.45	0.50	-0.46
G	24526	18344	0.42	-0.58	0.61	0.79	-0.49	-0.51	0.56	-0.47	-0.60	0.33	-0.54
H	48781	24919	0.78	-0.56	0.82	0.68	-0.72	-0.54	0.51	-0.57	-0.55	0.63	-0.73
I	22277	12138	0.49	-0.62	0.74	0.51	-0.49	-0.64	0.58	-0.47	-0.72	0.47	-0.48

Supporting Table S4. See Supplementary Data.docx file for caption.

Training set		Validation set		External Validation: in-house HCC collection	
ID	CTNNB1 exon3 mutational status	ID	CTNNB1 exon3 mutational status	ID	CTNNB1 exon3 mutational status
GSM248688	WT	HCC253	beta-catenin_not_mutated	1	WT
GSM248689	WT	HCC399	beta-catenin_mutated	2	WT
GSM248690	WT	HCC373	beta-catenin_not_mutated	3	c.A121C/p.T41P
GSM248691	233A>AG,p.D32D/G	HCC189	beta-catenin_not_mutated	4	c.C134T/p.S45F
GSM248692	239G>GA,p.G34G/E	HCC210	beta-catenin_not_mutated	5	c.A121C/p.T41P
GSM248693	239G>GT,p.G34G/V	HCC313	beta-catenin_not_mutated	6	WT
GSM248694	WT	HCC198	beta-catenin_not_mutated	7	c.del107-109 p.H36-S37>P
GSM248695	259A>AG,p.T41T/A	HCC320	beta-catenin_not_mutated	8	c.A121C/p.T41P
GSM248696	WT	HCC437	beta-catenin_not_mutated	9	WT
GSM248697	WT	HCC060	beta-catenin_not_mutated	10	WT
GSM248698	WT	HCC218	beta-catenin_mutated	11	c.A95T/p.D32V
GSM248699	233A>AG,p.D32D/G	HCC121	beta-catenin_mutated	12	WT
GSM248700	WT	HCC204	beta-catenin_not_mutated	13	c.C134T/p.S45F
GSM248701	WT	HCC231	beta-catenin_mutated	14	c.A107C/p.H36P
GSM248702	236C>CT S33S/F	PoolL	beta-catenin_not_mutated	15	c.C134T/p.S45F
GSM248703	WT	HCC441	beta-catenin_mutated	16	WT
GSM248704	271T>TG,p.S45S/A	PoolJ	beta-catenin_not_mutated	17	WT
GSM248705	WT	HCC237	beta-catenin_mutated	18	WT
GSM248706	232G>GA D32D/N	HCC206	beta-catenin_not_mutated	19	WT
GSM248707	247T>TG S37S/A	HCC229	beta-catenin_mutated	20	WT
GSM248708	272C>T S45F	HCC013	beta-catenin_mutated	21	WT
GSM248709	WT	HCC137	beta-catenin_mutated	22	WT
GSM248710	248C>CG S37S/C	HCC205	beta-catenin_not_mutated	23	c.G94T/p.D32Y
GSM248711	WT	HCC335	beta-catenin_not_mutated	24	c.A107C/p.H36P
GSM248712	WT	PoolH	beta-catenin_mutated	25	WT
GSM248713	WT	HCC438	beta-catenin_mutated	26	WT
GSM248714	WT	HCC322	beta-catenin_not_mutated	27	WT
GSM248715	WT	HCC107	beta-catenin_mutated	28	WT
GSM248716	WT	HCC242	beta-catenin_not_mutated	29	WT
GSM248717	236C>CG S33S/C	HCC333	beta-catenin_not_mutated	30	WT
GSM248718	WT	HCC304	beta-catenin_not_mutated	31	c.G94T/p.D32Y
GSM248719	WT	HCC433	beta-catenin_not_mutated	32	WT
GSM248720	247T>TG S37S/A	HCC081	beta-catenin_mutated	33	WT
GSM248721	WT	HCC168	beta-catenin_not_mutated	34	WT
GSM248722	WT	HCC230	beta-catenin_not_mutated	35	WT
GSM248723	WT	HCC405	beta-catenin_not_mutated	36	WT
GSM248724	WT	HCC197	beta-catenin_not_mutated	37	c.A107C/p.H36P
GSM248725	WT	HCC314	beta-catenin_not_mutated	38	WT
GSM248726	248C>CT S37S/F	HCC208	beta-catenin_not_mutated	39	c.C122T/p.T41I
GSM248727	WT	HCC301	beta-catenin_mutated	40	WT
GSM248728	WT	HCC016	beta-catenin_not_mutated	41	WT
GSM248729	WT	HCC164	beta-catenin_not_mutated	42	WT
GSM248731	271T>TG,p.S45S/A	HCC010	beta-catenin_not_mutated	43	c.A121C/p.T41P
GSM248732	WT	HCC252	beta-catenin_mutated	44	WT
GSM248733	233A>AT D32D/V	HCC170	beta-catenin_not_mutated	45	WT
GSM248734	233A>AG,p.D32D/G	HCC358	beta-catenin_mutated	46	WT
GSM248735	0	HCC195	beta-catenin_not_mutated	47	c.C122T/p.T41I
GSM248736	236C>CT,p.S33S/F	HCC402	beta-catenin_not_mutated	48	WT
GSM248737	WT	HCC305	beta-catenin_not_mutated	49	WT
GSM248738	WT	PoolI	beta-catenin_not_mutated	50	WT
GSM248739	WT	HCC018	beta-catenin_not_mutated	51	WT
GSM248740	WT	HCC429	beta-catenin_not_mutated	52	WT
GSM248741	WT	HCC432	beta-catenin_not_mutated	53	c.G101T/p.G34V
GSM248742	260C>CT T41T/I	PoolK	beta-catenin_not_mutated	54	WT
GSM248743	232G>GA,p.D32D/N	HCC309	beta-catenin_not_mutated	55	WT
GSM248744	235T>TC S33S/P	HCC191	beta-catenin_mutated	56	WT
GSM248745	WT			57	WT
GSM248746	WT			58	WT
GSM248747	232G>GT D32D/Y			59	WT

GSM248748	WT
GSM248749	248C>CT S37S/F
GSM248750	WT
GSM248751	WT
GSM248753	WT
GSM248754	WT
GSM248755	WT
GSM248756	WT
GSM248757	WT
GSM248758	WT
GSM248759	234_245het_delCTCTGGAATCCA
GSM248760	WT
GSM248761	WT
GSM248762	WT
GSM248763	WT
GSM248764	232G>GA D32D/N
GSM248765	WT
GSM248766	WT
GSM248767	248C>CG S37S/C
GSM248769	WT
GSM248771	WT
GSM248772	WT
GSM248773	WT
GSM248774	239G>GT G34G/V
GSM248775	WT
GSM248776	WT
GSM248777	WT
GSM248778	WT

60	WT
61	WT
62	WT
63	WT
64	c.C134A/p.S45Y
65	WT
66	WT
67	c.A95T/p.D32V
68	c.A95G/p.D32G
69	WT
70	c.G101T/p.G34V
71	c.A121G/p.T41A
72	WT
73	WT
74	WT
75	c.A95G/p.D32G
76	WT
77	WT
78	c.C110G/p.S37C
79	WT
80	WT
81	WT
82	c.G94T/p.D32Y

Accepted

Supporting Table S5. See Supplementary Data.docx file for caption.

PREDICTION OF CTNNB1 MUTATIONS	Predicted CTNNB1 mutations					Sanger-sequenced CTNNB1
Data source	AUROC (Score)	Best common threshold	Sensitivity	Specificity	% of predicted CTNNB1 mutations	% of CTNNB1 mutations
Training set	0.90	8	0.82	0.83	38%	31%
Validation set	0.92	8	0.88	0.89	28%	30%
A					24%	NA
B					30%	NA
C					25%	NA
D					25%	NA
E					40%	NA
F					20%	NA
G					31%	NA
H					34%	NA
I					28%	NA

Supporting Table S6. See Supplementary Data.docx file for caption.

Dataset	HCC Subclasses				Number of HCCs
	GREEN	RED	BLUE	PURPLE	
A	3%	79%	0%	19%	100
B	10%	78%	3%	0%	135
C	10%	89%	6%	50%	247
D	4%	98%	12%	28%	268
E	9%	100%	17%	20%	42
F	7%	89%	12%	18%	73
G	3%	65%	6%	0%	164
H	17%	67%	0%	0%	35
I	5%	93%	0%	29%	69
<u>Total</u>	6%	84%	7%	28%	1133

Supporting Table S7. See Supplementary Data.docx file for caption.

PERIPORTAL CLUSTER			
Unsupervised GSEA			
NAME	SIZE	NES	NOM p-val
HOSHIDA_LIVER_CANCER_SURVIVAL_DN	90	2.19	0
ACEVEDO_LIVER_CANCER_DN	334	2.10	0
HOSHIDA_LIVER_CANCER_SUBCLASS_S3	217	2.10	0
CAIRO_LIVER_DEVELOPMENT_DN	178	2.03	0
BURTON_ADIPOGENESIS_6	136	2.02	0
REACTOME_METABOLISM_OF_AMINO_ACIDS_AND_DERIVATIVES	137	2.00	0
HALLMARK_XENOBIOTIC_METABOLISM	157	1.99	0
REACTOME_LIPID_DIGESTION_MOBILIZATION_AND_TRANSPORT	34	1.99	0
BOCHKIS_FOXA2_TARGETS	265	1.96	0
ACEVEDO_LIVER_TUMOR_VS_NORMAL_ADJACENT_TISSUE_DN	180	1.95	0
REACTOME_GLUCOSE_METABOLISM	45	1.95	0
HALLMARK_ADIPOGENESIS	145	1.94	0.0041
CAIRO_HEPATOBLASTOMA_DN	203	1.94	0
HALLMARK_OXIDATIVE_PHOSPHORYLATION	142	1.92	0.030
HALLMARK_FATTY_ACID_METABOLISM	108	1.92	0
CHIANG_LIVER_CANCER_SUBCLASS_POLYSOMY7_UP	43	1.91	0
BOYALT_LIVER_CANCER_SUBCLASS_G1_DN	35	1.91	0
REACTOME_GLUONEOGENESIS	21	1.91	0
HSIAO_LIVER_SPECIFIC_GENES	193	1.90	0
LUCAS_HNF4A_TARGETS_UP	44	1.89	0.0060
BOYALT_LIVER_CANCER_SUBCLASS_G3_DN	39	1.87	0
LEE_LIVER_CANCER_MYC_TGFA_DN	54	1.87	0
KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	24	1.86	0.0021
HALLMARK_BILE_ACID_METABOLISM	85	1.86	0
CHIANG_LIVER_CANCER_SUBCLASS_UNANNOTATED_UP	51	1.86	0
HALLMARK_PEROXISOME	80	1.81	0.0043
LEE_LIVER_CANCER_SURVIVAL_UP	112	1.79	0
BOYALT_LIVER_CANCER_SUBCLASS_G123_DN	40	1.78	0
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	59	1.78	0.0020
KEGG_PYRUVATE_METABOLISM	30	1.77	0.0060
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_DN	121	1.75	0
LEE_LIVER_CANCER_MYC_E2F1_DN	51	1.73	0
LEE_LIVER_CANCER_MYC_DN	44	1.72	0.0041
LEE_LIVER_CANCER_E2F1_DN	47	1.70	0
YAMASHITA_LIVER_CANCER_STEM_CELL_DN	59	1.70	0.0020
REACTOME_PHASE_II_CONJUGATION	36	1.70	0.0021
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM	108	1.69	0.0079
REACTOME_COMPLEMENT_CASCADE	24	1.69	0.0059
KEGG_DRUG_METABOLISM_OTHER_ENZYMES	24	1.69	0.0020
PID_HNF3B_PATHWAY	31	1.69	0.012
HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN	51	1.69	0.0020
LEE_LIVER_CANCER_DENA_DN	58	1.67	0.0060
CAIRO_HEPATOBLASTOMA_CLASSES_DN	166	1.65	0.012
KEGG_HISTIDINE_METABOLISM	20	1.64	0.011
MOOTHA_GLUONEOGENESIS	25	1.63	0.014
TANG_SENESCENCE_TP53_TARGETS_UP	27	1.63	0.0040
WANG_CLASSIC_ADIPOGENIC_TARGETS_OF_PPARG	17	1.63	0.017
REACTOME_HDL_MEDIATED_LIPID_TRANSPORT	15	1.62	0.029
BOYALT_LIVER_CANCER_SUBCLASS_G6_DN	16	1.60	0.033

HALLMARK_COAGULATION	119	1.57	0.024
REACTOME_BILE_ACID_AND_BILE_SALT_METABOLISM	22	1.51	0.031

Supervised GSEA			
GOUGELET_PERIPORTAL_METABOLISM	142	1.95	0

PERIVENOUS CLUSTER			
Unsupervised GSEA			
NAME	SIZE	NES	NOM p-val
BOYALT_LIVER_CANCER_SUBCLASS_G6_UP	51	2.06	0
CHIANG_LIVER_CANCER_SUBCLASS_CTNNB1_UP	110	1.97	0
SMITH_LIVER_CANCER	31	1.86	0.002
BOYALT_LIVER_CANCER_SUBCLASS_G1_DN	35	1.86	0.008
CHIANG_LIVER_CANCER_SUBCLASS_INTERFERON_DN	26	1.84	0
BIOCARTA_WNT_PATHWAY	24	1.79	0.0095
WOO_LIVER_CANCER_RECURRENCE_DN	61	1.78	0
LEE_LIVER_CANCER_DENA_DN	58	1.74	0.0020
LEE_LIVER_CANCER_MYC_UP	37	1.73	0
KANG_DOXORUBICIN_RESISTANCE_DN	17	1.72	0.016
WANG_CLASSIC_ADIPOGENIC_TARGETS_OF_PPARG	17	1.71	0.0020
LEE_LIVER_CANCER_SURVIVAL_UP	112	1.70	0.0040
KEGG_ADHERENS_JUNCTION	60	1.68	0.0061
KEGG_FATTY_ACID_METABOLISM	29	1.67	0.0081
REACTOME_METABOLISM_OF_VITAMINS_AND_COFACTORS	34	1.65	0.014
BIOCARTA_MTOR_PATHWAY	18	1.63	0.047
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_DN	121	1.61	0.010
BOYALT_LIVER_CANCER_SUBCLASS_G123_DN	40	1.61	0.016
REACTOME_BILE_ACID_AND_BILE_SALT_METABOLISM	22	1.61	0.014
PID_HDAC_CLASSII_PATHWAY	24	1.61	0.041
PID_MYC_PATHWAY	21	1.60	0.056
LIU_LIVER_CANCER	21	1.58	0.040
CAIRO_HEPATOBLASTOMA_CLASSES_DN	166	1.56	0.042
KEGG_PPAR_SIGNALING_PATHWAY	52	1.51	0.048
PARENT_MTOR_SIGNALING_UP	408	1.38	0.033

Supervised GSEA			
GOUGELET_PERIVEINOUS_METABOLISM	379	1.57	0.002

EXTRACELLULAR MATRIX CLUSTER			
Unsupervised GSEA			
NAME	SIZE	NES	NOM p-val
BOYALT_LIVER_CANCER_SUBCLASS_G1_UP	77	2.06	0.0020
ZHONG_SECRETOME_OF_LUNG_CANCER_AND_FIBROBLAST	96	2.01	0
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS	65	1.88	0.0019
BIOCARTA_MYOSIN_PATHWAY	25	1.87	0.0019
LIAO_METASTASIS	300	1.84	0
BORLAK_LIVER_CANCER_EGF_UP	39	1.84	0
LANDIS_BREAST_CANCER_PROGRESSION_UP	30	1.82	0.0039
GOTZMANN_EPITHELIAL_TO_MESENCHYMAL_TRANSITION_UP	59	1.82	0
BOYALT_LIVER_CANCER_SUBCLASS_G12_UP	32	1.82	0.0062
CHIANG_LIVER_CANCER_SUBCLASS_CTNNB1_DN	118	1.81	0
HOSHIDA_LIVER_CANCER_SURVIVAL_UP	61	1.81	0
REACTOME_DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX	19	1.78	0
NABA_ECM_REGULATORS	138	1.78	0.001980198

HUMMERICH_SKIN_CANCER_PROGRESSION_UP	66	1.78	0
HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_UP	43	1.78	0.0019
ROZANOV_MMP14_TARGETS_SUBSET	26	1.77	0.0040
REACTOME_HEPARAN_SULFATE_HEPARIN_HS_GAG_METABOLISM	30	1.77	0
WOO_LIVER_CANCER_RECURRENCE_UP	83	1.76	0
REACTOME_GLYCOSAMINOGLYCAN_METABOLISM	67	1.75	0.0019
PID_RHOA_REG_PATHWAY	33	1.75	0.0078
LI_WILMS_TUMOR_VS_FETAL_KIDNEY_2_DN	43	1.75	0.0039
JECHLINGER_EPITHELIAL_TO_MESENCHYMAL_TRANSITION_UP	60	1.75	0
LEE_TARGETS_OF_PTCH1_AND_SUFU_DN	57	1.74	0
NABA_CORE_MATRISOME	143	1.72	0.0038
RAMASWAMY_METASTASIS_UP	43	1.72	0.011
PID_INTEGRIN3_PATHWAY	34	1.71	0.0078
RUIZ_TNC_TARGETS_UP	121	1.71	0.011
NABA_ECM_GLYCOPROTEINS	101	1.71	0.0038
COULOUARN_TEMPORAL_TGFB1_SIGNATURE_UP	71	1.70	0.0078
LEE_LIVER_CANCER_DENA_UP	52	1.70	0.0020
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION	56	1.70	0.0078
PID_SYNDECAN_1_PATHWAY	36	1.69	0.0039
TURASHVILI_BREAST_LOBULAR_CARCINOMA_VS_DUCTAL_NORMAL_UP	45	1.69	0.0019
GERHOLD_ADIPOGENESIS_DN	52	1.68	0.013
CHARAFE_BREAST_CANCER_BASAL_VS_MESENCHYMAL_UP	70	1.68	0.0040
ROESSLER_LIVER_CANCER_METASTASIS_DN	30	1.68	0.0020
BOYALT_LIVER_CANCER_SUBCLASS_G2	21	1.68	0.012
LIEN_BREAST_CARCINOMA_METAPLASTIC	22	1.67	0.0019
VERHAAK_GLIOMASTOMA_MESENCHYMAL	170	1.67	0.015
CROONQUIST_STROMAL_STIMULATION_UP	42	1.67	0.004
HARRIS_BRAIN_CANCER_PROGENITORS	26	1.67	0.0040
LEE_LIVER_CANCER_MYC_TGFA_UP	45	1.67	0.0061
NGUYEN_NOTCH1_TARGETS_DN	61	1.67	0.0020
REACTOME_NCAM1_INTERACTIONS	25	1.66	0.0039
NABA_MATRISOME_ASSOCIATED	394	1.66	0
KEGG_ECM_RECEPTOR_INTERACTION	65	1.65	0.0059
HOSHIDA_LIVER_CANCER_SUBCLASS_S1	192	1.65	0.017
KEGG_FOCAL_ADHESION	151	1.65	0.010
REACTOME_AXON_GUIDANCE	177	1.65	0.0039
VERRECCHIA_EARLY_RESPONSE_TO_TGFB1	43	1.64	0.025
BOQUEST_STEM_CELL_UP	197	1.64	0.008
PID_INTEGRIN1_PATHWAY	52	1.64	0.023
ASTIER_INTEGRIN_SIGNALING	37	1.63	0.018
BOYALT_LIVER_CANCER_SUBCLASS_G6_DN	16	1.63	0.028
LEE_LIVER_CANCER_E2F1_UP	50	1.63	0.010
VERRECCHIA_DELAYED_RESPONSE_TO_TGFB1	29	1.62	0.0077
ALONSO_METASTASIS_EMT_UP	27	1.62	0.038
PID_IL6_7_PATHWAY	40	1.62	0.010
GENTLES_LEUKEMIC_STEM_CELL_UP	15	1.62	0.0079
DASU_IL6_SIGNALING_UP	47	1.61	0.010
PID_INTEGRIN2_PATHWAY	21	1.61	0.029
PID_AVB3_INTEGRIN_PATHWAY	55	1.61	0.021
TONKS_TARGETS_OF_RUNX1_RUNX1T1_FUSION_ERYTHROCYTE_UP	126	1.61	0.010
ROZANOV_MMP14_TARGETS_UP	151	1.61	0.0093
BOYALT_LIVER_CANCER_SUBCLASS_G123_UP	32	1.61	0.045
ANASTASSIOU_CANCER_MESENCHYMAL_TRANSITION_SIGNATURE	53	1.61	0.0077
BYSTRYKH_HEMATOPOIESIS_STEM_CELL_SCP2_QTL_TRANS	15	1.60	0.012

REACTOME_NCAM_SIGNALING_FOR_NEURITE_OUT_GROWTH	45	1.60	0.014
LEE_AGING_MUSCLE_DN	33	1.57	0.032
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_UP	118	1.57	0.046
NABA_COLLAGENS	25	1.56	0.029
HALLMARK_IL2_STAT5_SIGNALING	144	1.54	0.028
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	160	1.53	0.030
HALLMARK_KRAS_SIGNALING_UP	159	1.51	0.017

STEM CLUSTER			
Unsupervised GSEA			
NAME	SIZE	NES	NOM p-val
REACTOME_INFLUENZA_LIFE_CYCLE	79	2.16	0.0065
LEE_LIVER_CANCER_SURVIVAL_DN	112	2.08	0
LE_EGR2_TARGETS_UP	74	2.07	0
BENPORATH_ES_CORE_NINE_CORRELATED	81	2.05	0
REACTOME_TRANSLATION	77	2.04	0.0085
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_UP	118	2.00	0
LIAO_METASTASIS	300	2.00	0
REACTOME_MITOTIC_M_M_G1_PHASES	122	1.97	0.0083
CAIRO_HEPATOBLASTOMA_CLASSES_UP	428	1.97	0.0063
RHODES_UNDIFFERENTIATED_CANCER	53	1.95	0.0063
HALLMARK_MYC_TARGETS_V1	127	1.95	0.016
BOYALT_LIVER_CANCER_SUBCLASS_G3_UP	134	1.94	0.010
SARRIO_EPITHELIAL_MESENCHYMAL_TRANSITION_UP	106	1.92	0.0062
WONG_EMBRYONIC_STEM_CELL_CORE	229	1.92	0.0084
HALLMARK_G2M_CHECKPOINT	149	1.91	0
REACTOME_CELL_CYCLE_MITOTIC	209	1.91	0.0063
SHIPP_DLBCL_VS_FOLLICULAR_LYMPHOMA_UP	27	1.90	0.0082
BHATTACHARYA_EMBRYONIC_STEM_CELL	55	1.87	0
WHITFIELD_CELL_CYCLE_G2	90	1.86	0.0020
COULOUARN_TEMPORAL_TGFB1_SIGNATURE_UP	71	1.85	0
HOLLEMAN_VINCRIStINE_RESISTANCE_B_ALL_UP	28	1.85	0.0021
KOBAYASHI_EGFR_SIGNALING_24HR_DN	186	1.85	0.0063
REACTOME_METABOLISM_OF_MRNA	132	1.85	0.039
REACTOME_CELL_CYCLE	261	1.85	0.0063
BASSO_B_LYMPHOCYTE_NETWORK	96	1.85	0.0020
PID_MYC_ACTIV_PATHWAY	55	1.83	0.0083
REACTOME_MITOTIC_G1_G1_S_PHASES	92	1.83	0.013
CHEMNITZ_RESPONSE_TO_PROSTAGLANDIN_E2_UP	90	1.82	0.011
ZAMORA_NOS2_TARGETS_UP	45	1.82	0.011
BENPORATH_PROLIFERATION	98	1.81	0.0062
REACTOME_SIGNALING_TO_RAS	18	1.81	0.0082
HALLMARK_MITOTIC_SPINDLE	134	1.81	0.0040
TARTE_PLASMA_CELL_VS_PLASMABLAST_DN	213	1.80	0.020
HALLMARK_MYC_TARGETS_V2	36	1.80	0.010
BILD_MYC_ONCOGENIC_SIGNATURE	107	1.79	0
KEGG_SPLICEOSOME	72	1.79	0.026
SCHLOSSER_MYC_TARGETS_AND_SERUM_RESPONSE_UP	34	1.79	0.010
GRADE_COLON_AND_RECTAL_CANCER_UP	182	1.78	0.012
WHITFIELD_CELL_CYCLE_G2_M	144	1.78	0.010
BIOCARTA_CASPASE_PATHWAY	21	1.77	0.004
BENPORATH_CYCLING_GENES	412	1.77	0.0062
LEE_EARLY_T_LYMPHOCYTE_UP	69	1.77	0.0041
BOYALT_LIVER_CANCER_SUBCLASS_G23_UP	40	1.77	0.010

ROSTY_CERVICAL_CANCER_PROLIFERATION_CLUSTER	110	1.76	0.0062
BIOCARTA_FAS_PATHWAY	26	1.76	0.0082
BIDUS_METASTASIS_UP	128	1.76	0.015
MORI_IMMATURE_B_LYMPHOCYTE_DN	61	1.76	0.010
REACTOME_G1_S_TRANSITION	78	1.75	0.027
SENGUPTA_NASOPHARYNGEAL_CARCCINOMA_UP	181	1.75	0.013
BORCZUK_MALIGNANT_MESOTHELIOMA_UP	233	1.75	0.031
KEGG_CELL_CYCLE	91	1.74	0.0085
BOYAUULT_LIVER_CANCER_SUBCLASS_G123_UP	32	1.74	0.010
ZHANG_BREAST_CANCER_PROGENITORS_UP	241	1.73	0.014
PATIL_LIVER_CANCER	458	1.73	0.026
HALLMARK_E2F_TARGETS	140	1.72	0.016
RODRIGUES_THYROID_CARCCINOMA_POORLY_DIFFERENTIATED_UP	384	1.71	0.015
WOO_LIVER_CANCER_RECURRENCE_UP	83	1.71	0
HOSHIDA_LIVER_CANCER_SUBCLASS_S1	192	1.71	0.021
ZHENG_GLIOMBLASTOMA_PLASTICITY_UP	168	1.70	0.0083
PARK_HSC_MARKERS	27	1.70	0.022
WINNEPENINCKX_MELANOMA_METASTASIS_UP	94	1.70	0.033
KANG_DOXORUBICIN_RESISTANCE_UP	42	1.70	0.0062
RAMASWAMY_METASTASIS_UP	43	1.70	0.012
EGUCHI_CELL_CYCLE_RB1_TARGETS	19	1.69	0.0020
CHIARADONNA_NEOPLASTIC_TRANSFORMATION_KRAS_UP	93	1.69	0.0044
VANTVEER_BREAST_CANCER_POOR_PROGNOSIS	34	1.69	0.0061
CAIRO_PML_TARGETS_BOUND_BY_MYC_UP	16	1.69	0.024
CHICAS_RB1_TARGETS_GROWING	165	1.68	0.011
YU_MYC_TARGETS_UP	28	1.68	0.0043
REACTOME_SYNTHESIS_OF_DNA	68	1.67	0.073
PID_P38_MK2_PATHWAY	15	1.67	0.019
CHNG_MULTIPLE_MYELOMA_HYPERPLOID_UP	29	1.67	0.045
LU_TUMOR_ANGIOGENESIS_UP	21	1.66	0.011
STONER_ESOPHAGEAL_CARCCINOGENESIS_UP	23	1.64	0.025
ZHAN_MULTIPLE_MYELOMA_PR_UP	26	1.64	0.0062
LI_WILMS_TUMOR_ANAPLASTIC_UP	15	1.64	0.017
PRAMOONJAGO_SOX4_TARGETS_UP	39	1.64	0.044
PID_AURORA_A_PATHWAY	21	1.64	0.038
CAIRO_HEPATOBLASTOMA_UP	146	1.63	0.034
LINDGREN_BLADDER_CANCER_CLUSTER_3_UP	211	1.63	0.043
PID_PDGRFB_PATHWAY	100	1.63	0.029
DANG_MYC_TARGETS_UP	90	1.62	0.048
PID_RAC1_PATHWAY	40	1.62	0.026
HOLLEMAN_VINCRIStINE_RESISTANCE_ALL_UP	16	1.62	0.029
BIOCARTA_CELLCYCLE_PATHWAY	18	1.62	0.011
WINTER_HYPOXIA_UP	47	1.62	0.027
YAMASHITA_LIVER_CANCER_WITH_EPCAM_UP	37	1.61	0.049
FEVR_CTNNB1_TARGETS_DN	336	1.61	0.040
KAUFFMANN_MELANOMA_RELAPSE_UP	44	1.61	0.043
WANG_TUMOR_INVASIVENESS_UP	233	1.60	0.022
HALLMARK_MTORC1_SIGNALING	160	1.51	0.048

Supporting Table S8. See Supplementary Data.docx file for caption.

OVERREPRESENTED ATTRIBUTES IN PERIVENOUS GENES			
LOD	P_adj	attrib ID	Overrepresented GO terms
2.16	0.017	GO:0016098	monoterpenoid metabolic process
1.96	0.049	GO:0061045	negative regulation of wound healing
1.55	0.041	GO:0008299	isoprenoid biosynthetic process
1.52	0.001	GO:0006695	cholesterol biosynthetic process
1.45	0.001	GO:0016126	sterol biosynthetic process
1.40	0.012	GO:0016709	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen
1.13	0.001	GO:0046165	alcohol biosynthetic process
1.11	0.002	GO:0008203	cholesterol metabolic process
1.10	0.002	GO:0006694	steroid biosynthetic process
1.06	0.005	GO:0016125	sterol metabolic process
1.04	0.031	GO:0061041	regulation of wound healing
1.01	0.043	GO:0006720	isoprenoid metabolic process
1.01	0.043	GO:0042579	microbody
1.00	0.012	GO:0046906	tetrapyrrole binding
0.97	0.019	GO:1901617	organic hydroxy compound biosynthetic process
0.97	<0.001	GO:0008202	steroid metabolic process
0.81	0.001	GO:0044283	small molecule biosynthetic process
0.76	0.04	GO:0006066	alcohol metabolic process
0.69	0.014	GO:0008610	lipid biosynthetic process
0.60	0.001	GO:0044711	single-organism biosynthetic process
0.56	0.04	GO:0044255	cellular lipid metabolic process
0.54	0.011	GO:0006629	lipid metabolic process
0.49	0.001	GO:0044281	small molecule metabolic process
0.37	0.005	GO:0044444	cytoplasmic part
0.37	0.005	GO:0044237	cellular metabolic process
0.37	0.01	GO:0044710	single-organism metabolic process
0.37	0.04	GO:0044699	single-organism process
0.34	0.044	GO:0008152	metabolic process
0.34	0.04	GO:0071704	organic substance metabolic process

OVERREPRESENTED ATTRIBUTES IN PERIportal GENES			
LOD	P_adj	attrib ID	Overrepresented GO terms
3.06	<0.001	GO:0006572	tyrosine catabolic process
2.86	0.001	GO:0006116	NADH oxidation
2.38	0.004	GO:0008391	arachidonic acid monooxygenase activity
2.38	0.004	GO:0008392	arachidonic acid epoxygenase activity
2.16	0.018	GO:0016841	ammonia-lyase activity
2.13	0.001	GO:0005579	membrane attack complex

2.11	<0.001	GO:0006558	L-phenylalanine metabolic process
2.11	<0.001	GO:0006559	L-phenylalanine catabolic process
2.11	<0.001	GO:0006570	tyrosine metabolic process
2.11	<0.001	GO:1902221	erythrose 4-phosphate/phosphoenolpyruvate family amino acid metabolic process
2.11	<0.001	GO:1902222	erythrose 4-phosphate/phosphoenolpyruvate family amino acid catabolic process
2.09	<0.001	GO:0019373	epoxygenase P450 pathway
1.93	0.001	GO:0097267	omega-hydroxylase P450 pathway
1.89	<0.001	GO:0019627	urea metabolic process
1.83	<0.001	GO:0071941	nitrogen cycle metabolic process
1.80	<0.001	GO:0009074	aromatic amino acid family catabolic process
1.80	0.003	GO:0000050	urea cycle
1.67	<0.001	GO:0009072	aromatic amino acid family metabolic process
1.65	0.013	GO:0006525	arginine metabolic process
1.65	0.013	GO:0034185	apolipoprotein binding
1.63	<0.001	GO:0034364	high-density lipoprotein particle
1.60	0.001	GO:0034308	primary alcohol metabolic process
1.55	<0.001	GO:0017144	drug metabolic process
1.54	0.041	GO:0000097	sulfur amino acid biosynthetic process
1.49	<0.001	GO:0034358	plasma lipoprotein particle
1.46	<0.001	GO:0032994	protein-lipid complex
1.45	<0.001	GO:1901606	alpha-amino acid catabolic process
1.42	<0.001	GO:0009063	cellular amino acid catabolic process
1.42	<0.001	GO:0000096	sulfur amino acid metabolic process
1.39	<0.001	GO:0016054	organic acid catabolic process
1.39	<0.001	GO:0046395	carboxylic acid catabolic process
1.38	<0.001	GO:0006094	gluconeogenesis
1.34	<0.001	GO:0046364	monosaccharide biosynthetic process
1.34	<0.001	GO:0019319	hexose biosynthetic process
1.34	0.024	GO:0006730	one-carbon metabolic process
1.31	0.001	GO:0008206	bile acid metabolic process
1.31	0.001	GO:0009066	aspartate family amino acid metabolic process
1.31	<0.001	GO:0051289	protein homotetramerization
1.30	0.029	GO:0009069	serine family amino acid metabolic process
1.29	<0.001	GO:0072329	monocarboxylic acid catabolic process
1.28	<0.001	GO:0044282	small molecule catabolic process
1.26	<0.001	GO:0009064	glutamine family amino acid metabolic process
1.26	0.047	GO:0016709	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen
1.25	<0.001	GO:1901605	alpha-amino acid metabolic process
1.23	0.001	GO:0030170	pyridoxal phosphate binding
1.22	<0.001	GO:0019395	fatty acid oxidation

1.21	<0.001	GO:0009062	fatty acid catabolic process
1.21	<0.001	GO:0034440	lipid oxidation
1.21	<0.001	GO:0006805	xenobiotic metabolic process
1.21	<0.001	GO:0043648	dicarboxylic acid metabolic process
1.20	<0.001	GO:1901607	alpha-amino acid biosynthetic process
1.17	<0.001	GO:0016597	amino acid binding
1.15	<0.001	GO:0008652	cellular amino acid biosynthetic process
1.15	0.026	GO:0016627	oxidoreductase activity, acting on the CH-CH group of donors
1.15	0.026	GO:0019369	arachidonic acid metabolic process
1.13	0.03	GO:0042632	cholesterol homeostasis
1.12	<0.001	GO:0001676	long-chain fatty acid metabolic process
1.12	0.038	GO:0055092	sterol homeostasis
1.12	<0.001	GO:0019752	carboxylic acid metabolic process
1.11	0.041	GO:1901616	organic hydroxy compound catabolic process
1.11	<0.001	GO:0051262	protein tetramerization
1.11	<0.001	GO:0032787	monocarboxylic acid metabolic process
1.10	<0.001	GO:0016614	oxidoreductase activity, acting on CH-OH group of donors
1.09	0.001	GO:0004497	monooxygenase activity
1.09	<0.001	GO:0072562	blood microparticle
1.08	0.011	GO:0072376	protein activation cascade
1.07	0.013	GO:0005319	lipid transporter activity
1.05	<0.001	GO:0006082	organic acid metabolic process
1.05	<0.001	GO:0043436	oxoacid metabolic process
1.05	<0.001	GO:0006732	coenzyme metabolic process
1.03	<0.001	GO:0016051	carbohydrate biosynthetic process
1.03	<0.001	GO:0016616	oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor
1.02	<0.001	GO:0006520	cellular amino acid metabolic process
1.02	<0.001	GO:0048037	cofactor binding
1.02	<0.001	GO:0006631	fatty acid metabolic process
1.02	0.004	GO:0033559	unsaturated fatty acid metabolic process
1.02	<0.001	GO:0006575	cellular modified amino acid metabolic process
1.00	0.041	GO:0006641	triglyceride metabolic process
1.00	<0.001	GO:0016053	organic acid biosynthetic process
1.00	<0.001	GO:0046394	carboxylic acid biosynthetic process
0.99	0.007	GO:0009108	coenzyme biosynthetic process
0.99	<0.001	GO:0031406	carboxylic acid binding
0.99	<0.001	GO:0043177	organic acid binding
0.99	0.001	GO:0030258	lipid modification
0.98	<0.001	GO:0050662	coenzyme binding
0.98	<0.001	GO:0051186	cofactor metabolic process
0.98	0.05	GO:0006639	acylglycerol metabolic process
0.97	0.05	GO:0006638	neutral lipid metabolic process
0.97	0.05	GO:0055088	lipid homeostasis

0.96	<0.001	GO:0006006	glucose metabolic process
0.95	0.001	GO:0043603	cellular amide metabolic process
0.94	<0.001	GO:0044283	small molecule biosynthetic process
0.94	0.005	GO:0020037	heme binding
0.93	0.007	GO:0044242	cellular lipid catabolic process
0.93	0.007	GO:0051188	cofactor biosynthetic process
0.93	0.029	GO:0042579	microbody
0.92	0.001	GO:0016829	lyase activity
0.91	0.011	GO:0046906	tetrapyrrole binding
0.91	<0.001	GO:0005759	mitochondrial matrix
0.89	<0.001	GO:0016491	oxidoreductase activity
0.89	0.003	GO:0016705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen
0.86	<0.001	GO:0051260	protein homooligomerization
0.86	0.001	GO:0019318	hexose metabolic process
0.85	<0.001	GO:0008202	steroid metabolic process
0.84	<0.001	GO:0055114	oxidation-reduction process
0.84	<0.001	GO:0044281	small molecule metabolic process
0.82	0.019	GO:0006869	lipid transport
0.82	0.001	GO:0005996	monosaccharide metabolic process
0.80	0.001	GO:0006790	sulfur compound metabolic process
0.76	0.025	GO:0016042	lipid catabolic process
0.75	<0.001	GO:0006629	lipid metabolic process
0.75	<0.001	GO:0044255	cellular lipid metabolic process
0.75	<0.001	GO:0044710	single-organism metabolic process
0.73	<0.001	GO:0044712	single-organism catabolic process
0.72	0.001	GO:0051259	protein oligomerization
0.70	<0.001	GO:0043233	organelle lumen
0.69	0.001	GO:1901615	organic hydroxy compound metabolic process
0.69	0.025	GO:0015711	organic anion transport
0.69	<0.001	GO:0044711	single-organism biosynthetic process
0.67	<0.001	GO:1901565	organonitrogen compound catabolic process
0.67	<0.001	GO:0070013	intracellular organelle lumen
0.66	<0.001	GO:0031974	membrane-enclosed lumen
0.66	<0.001	GO:1901564	organonitrogen compound metabolic process
0.65	<0.001	GO:1901566	organonitrogen compound biosynthetic process
0.65	0.005	GO:0006820	anion transport
0.61	<0.001	GO:0048878	chemical homeostasis
0.61	<0.001	GO:0044248	cellular catabolic process
0.57	<0.001	GO:0009056	catabolic process
0.57	<0.001	GO:1901575	organic substance catabolic process
0.56	<0.001	GO:0044699	single-organism process
0.55	0.009	GO:0014070	response to organic cyclic compound
0.55	<0.001	GO:0003824	catalytic activity

0.52	<0.001	GO:0043230	extracellular organelle
0.52	<0.001	GO:0065010	extracellular membrane-bounded organelle
0.52	<0.001	GO:0070062	extracellular vesicular exosome
0.51	0.018	GO:0044429	mitochondrial part
0.51	0.001	GO:0042592	homeostatic process
0.50	<0.001	GO:0008152	metabolic process
0.48	0.024	GO:1901361	organic cyclic compound catabolic process
0.48	<0.001	GO:0044421	extracellular region part
0.45	<0.001	GO:0031988	membrane-bounded vesicle
0.45	<0.001	GO:0031982	vesicle
0.43	<0.001	GO:0071704	organic substance metabolic process
0.43	<0.001	GO:0043168	anion binding
0.40	<0.001	GO:0044238	primary metabolic process
0.39	<0.001	GO:0044444	cytoplasmic part
0.39	0.001	GO:0036094	small molecule binding
0.38	0.001	GO:0065008	regulation of biological quality
0.37	<0.001	GO:0044237	cellular metabolic process
0.33	0.001	GO:0044763	single-organism cellular process

OVERREPRESENTED ATTRIBUTES IN STEM GENES			
LOD	P adj	attrib ID	Overrepresented GO terms
2.22	0.036	GO:0000778	condensed nuclear chromosome kinetochore
1.69	0.025	GO:0000779	condensed chromosome, centromeric region
1.63	0.042	GO:0005583	fibrillar collagen
1.17	0.042	GO:0030834	regulation of actin filament depolymerization
1.05	0.004	GO:1901879	regulation of protein depolymerization
0.96	0.027	GO:0043244	regulation of protein complex disassembly
0.86	0.044	GO:0008064	regulation of actin polymerization or depolymerization
0.85	0.05	GO:0030832	regulation of actin filament length
0.82	0.01	GO:0005819	spindle
0.76	<0.001	GO:0030335	positive regulation of cell migration
0.75	<0.001	GO:2000147	positive regulation of cell motility
0.74	<0.001	GO:0051272	positive regulation of cellular component movement
0.72	<0.001	GO:0040017	positive regulation of locomotion
0.71	<0.001	GO:0051493	regulation of cytoskeleton organization
0.70	<0.001	GO:0030198	extracellular matrix organization
0.70	<0.001	GO:0043062	extracellular structure organization
0.69	0.029	GO:0050900	leukocyte migration
0.68	<0.001	GO:0022411	cellular component disassembly
0.66	<0.001	GO:0007599	hemostasis
0.65	<0.001	GO:0007017	microtubule-based process
0.65	<0.001	GO:0007596	blood coagulation
0.65	<0.001	GO:0050817	coagulation
0.61	<0.001	GO:0050878	regulation of body fluid levels

0.59	0.002	GO:0000278	mitotic cell cycle
0.59	<0.001	GO:0030334	regulation of cell migration
0.56	<0.001	GO:2000145	regulation of cell motility
0.56	<0.001	GO:0033043	regulation of organelle organization
0.56	<0.001	GO:0016477	cell migration
0.55	0.036	GO:0051129	negative regulation of cellular component organization
0.54	0.001	GO:0040012	regulation of locomotion
0.53	<0.001	GO:0008092	cytoskeletal protein binding
0.53	0.008	GO:0051270	regulation of cellular component movement
0.52	<0.001	GO:0005856	cytoskeleton
0.52	<0.001	GO:0006928	cellular component movement
0.52	<0.001	GO:0048870	cell motility
0.50	<0.001	GO:0044699	single-organism process
0.50	0.003	GO:0032403	protein complex binding
0.50	0.001	GO:0022603	regulation of anatomical structure morphogenesis
0.49	<0.001	GO:0043230	extracellular organelle
0.49	<0.001	GO:0065010	extracellular membrane-bounded organelle
0.49	<0.001	GO:0070062	extracellular vesicular exosome
0.48	<0.001	GO:0031988	membrane-bounded vesicle
0.47	<0.001	GO:0031982	vesicle
0.46	<0.001	GO:0022402	cell cycle process
0.46	<0.001	GO:0051128	regulation of cellular component organization
0.46	<0.001	GO:0044430	cytoskeletal part
0.45	<0.001	GO:0005829	cytosol
0.45	0.044	GO:0008284	positive regulation of cell proliferation
0.45	0.02	GO:0040011	locomotion
0.45	<0.001	GO:0016043	cellular component organization
0.44	<0.001	GO:0044421	extracellular region part
0.44	<0.001	GO:0071840	cellular component organization or biogenesis
0.44	<0.001	GO:0044763	single-organism cellular process
0.43	<0.001	GO:0043228	non-membrane-bounded organelle
0.43	<0.001	GO:0043232	intracellular non-membrane-bounded organelle
0.43	<0.001	GO:0042981	regulation of apoptotic process
0.43	<0.001	GO:0043067	regulation of programmed cell death
0.42	<0.001	GO:0010941	regulation of cell death
0.41	0.008	GO:0005615	extracellular space
0.41	<0.001	GO:0065008	regulation of biological quality
0.41	<0.001	GO:0042127	regulation of cell proliferation
0.40	<0.001	GO:0048522	positive regulation of cellular process
0.39	<0.001	GO:0048518	positive regulation of biological process
0.38	<0.001	GO:0005515	protein binding
0.38	<0.001	GO:0044424	intracellular part
0.38	0.044	GO:0071822	protein complex subunit organization
0.36	<0.001	GO:0048523	negative regulation of cellular process

0.35	<0.001	GO:0048519	negative regulation of biological process
0.35	0.025	GO:0002376	immune system process
0.34	<0.001	GO:0005737	cytoplasm
0.33	0.042	GO:0032879	regulation of localization
0.32	0.014	GO:0010033	response to organic substance
0.32	0.014	GO:0009987	cellular process
0.31	<0.001	GO:0043226	organelle
0.31	<0.001	GO:0065007	biological regulation
0.30	<0.001	GO:0044444	cytoplasmic part
0.28	<0.001	GO:0043227	membrane-bounded organelle
0.27	0.001	GO:0050794	regulation of cellular process
0.25	0.014	GO:0050789	regulation of biological process

Accepted Article



Supporting Table S9. See Supplementary Data.docx file for caption.

			[Low 95% CI - Mean - High 95% CI]				P=
Gene symbol	Gene clustering	Gene description	Cluster PP	Cluster PV	Cluster ECM	Cluster STEM	
CYP2E1	PERIVENOUS	cytochrome P450, family 2, subfamily E, polypeptide 1	[12.31 - 12.53 - 12.75]	[14.52 - 14.62 - 14.73]	[12.9 - 13.1 - 13.29]	[11.43 - 11.73 - 12.04]	6.33E-23
AOX1	PERIVENOUS	aldehyde oxidase 1	[11.75 - 11.91 - 12.06]	[13.21 - 13.28 - 13.35]	[11.7 - 11.86 - 12.01]	[10.58 - 10.78 - 10.99]	7.43E-92
SPCS1	PERIVENOUS	signal peptidase complex subunit 1 homolog (S. cerevisiae)	[12.69 - 12.72 - 12.76]	[12.93 - 12.98 - 13.03]	[12.63 - 12.68 - 12.73]	[12.69 - 12.74 - 12.79]	2.62E-58
GLUL	PERIVENOUS	glutamate-ammonia ligase	[9.59 - 9.7 - 9.81]	[12.71 - 12.83 - 12.96]	[9.59 - 9.7 - 9.81]	[9.47 - 9.58 - 9.7]	8.39E-15
GGH	PERIVENOUS	gamma-glutamyl hydrolase (conjugase, folic polygamma glutamyl hydrolase)	[11.96 - 12.02 - 12.09]	[12.72 - 12.82 - 12.92]	[11.9 - 12 - 12.09]	[11.53 - 11.65 - 11.77]	5.72E-21
ATOX1	PERIVENOUS	ATX1 antioxidant protein 1 homolog (yeast)	[12.34 - 12.39 - 12.44]	[12.61 - 12.69 - 12.76]	[12.19 - 12.26 - 12.32]	[11.75 - 11.81 - 11.88]	4.06E-43
CERS2	PERIVENOUS	LAG1 homolog, ceramide synthase 2	[12.08 - 12.12 - 12.16]	[12.22 - 12.28 - 12.34]	[12.07 - 12.12 - 12.17]	[11.82 - 11.9 - 11.98]	5.68E-07
TAX1BP1	PERIVENOUS	Tax1 (human T-cell leukemia virus type I) binding protein 1	[11.97 - 12 - 12.04]	[12.19 - 12.24 - 12.3]	[11.92 - 11.97 - 12.01]	[11.93 - 11.99 - 12.04]	1.05E-14
EFR3A	PERIVENOUS	EFR3 homolog A (S. cerevisiae)	[11.68 - 11.73 - 11.78]	[12.12 - 12.18 - 12.25]	[11.8 - 11.86 - 11.92]	[11.58 - 11.65 - 11.71]	6.13E-74
HMGCS1	PERIVENOUS	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	[11.8 - 11.89 - 11.99]	[11.93 - 12.02 - 12.12]	[11.91 - 11.99 - 12.08]	[11.72 - 11.85 - 11.97]	9.29E-65
CEBPA	PERIVENOUS	CCAAT/enhancer binding protein (C/EBP), alpha	[11.89 - 11.97 - 12.05]	[11.84 - 11.94 - 12.04]	[12.16 - 12.24 - 12.31]	[11.84 - 11.99 - 12.14]	1.52E-58
PPAP2A	PERIVENOUS	phosphatidic acid phosphatase type 2A	[11.29 - 11.34 - 11.4]	[11.75 - 11.84 - 11.93]	[11.33 - 11.4 - 11.47]	[10.81 - 10.9 - 10.99]	6.25E-101
DSP	PERIVENOUS	desmoplakin	[11.26 - 11.31 - 11.36]	[11.77 - 11.84 - 11.9]	[11.37 - 11.42 - 11.48]	[11.49 - 11.58 - 11.67]	4.41E-63
AP3S1	PERIVENOUS	adaptor-related protein complex 3, sigma 1 subunit	[11.45 - 11.49 - 11.53]	[11.75 - 11.81 - 11.88]	[11.57 - 11.61 - 11.65]	[11.53 - 11.59 - 11.65]	6.13E-03
GNPAT	PERIVENOUS	glyceronephosphate O-acyltransferase	[11.11 - 11.15 - 11.2]	[11.71 - 11.77 - 11.83]	[11.38 - 11.43 - 11.48]	[11.48 - 11.55 - 11.62]	1.02E-33
MPC2	PERIVENOUS	mitochondrial pyruvate carrier 2	[11.67 - 11.72 - 11.78]	[11.62 - 11.68 - 11.75]	[11.66 - 11.73 - 11.8]	[11.43 - 11.53 - 11.62]	1.03E-39
CADM1	PERIVENOUS	cell adhesion molecule 1	[11.22 - 11.3 - 11.38]	[11.56 - 11.66 - 11.76]	[11.04 - 11.14 - 11.24]	[10.24 - 10.38 - 10.52]	5.59E-18
IARS2	PERIVENOUS	isoleucyl-tRNA synthetase 2, mitochondrial	[11.28 - 11.33 - 11.38]	[11.59 - 11.65 - 11.72]	[11.37 - 11.42 - 11.48]	[11.38 - 11.45 - 11.52]	1.17E-20
CYP3A4	PERIVENOUS	cytochrome P450, family 3, subfamily A, polypeptide 4	[10.2 - 10.35 - 10.51]	[11.47 - 11.64 - 11.81]	[9.25 - 9.4 - 9.56]	[8 - 8.17 - 8.34]	1.40E-101
SMYD2	PERIVENOUS	SET and MYND domain containing 2	[10.41 - 10.47 - 10.54]	[11.48 - 11.56 - 11.65]	[10.54 - 10.6 - 10.67]	[10.7 - 10.77 - 10.84]	4.22E-43
LBR	PERIVENOUS	lamin B receptor	[11.04 - 11.1 - 11.17]	[11.39 - 11.47 - 11.54]	[11.48 - 11.55 - 11.61]	[11.74 - 11.82 - 11.91]	1.31E-25
MRPL24	PERIVENOUS	mitochondrial ribosomal protein L24	[11.01 - 11.07 - 11.12]	[11.3 - 11.37 - 11.45]	[11.04 - 11.11 - 11.17]	[10.86 - 10.94 - 11.03]	2.19E-01
FAT1	PERIVENOUS	FAT tumor suppressor homolog 1 (Drosophila)	[10.9 - 10.97 - 11.04]	[11.2 - 11.3 - 11.4]	[10.7 - 10.78 - 10.87]	[10.61 - 10.7 - 10.79]	1.82E-01
PRPSAP1	PERIVENOUS	phosphoribosyl pyrophosphate synthetase-associated protein 1	[11.1 - 11.15 - 11.2]	[11.18 - 11.25 - 11.31]	[11.05 - 11.11 - 11.17]	[10.92 - 10.98 - 11.04]	1.46E-13
OAT	PERIVENOUS	ornithine aminotransferase	[9.63 - 9.77 - 9.91]	[10.97 - 11.18 - 11.39]	[10.1 - 10.25 - 10.41]	[10.33 - 10.5 - 10.67]	3.16E-01
CYP51A1	PERIVENOUS	cytochrome P450, family 51, subfamily A, polypeptide 1	[11.1 - 11.16 - 11.23]	[11.1 - 11.18 - 11.25]	[11.07 - 11.14 - 11.2]	[10.87 - 10.96 - 11.05]	9.97E-78
SCCPDH	PERIVENOUS	saccharopine dehydrogenase (putative)	[11.38 - 11.45 - 11.52]	[11.05 - 11.16 - 11.26]	[11.3 - 11.38 - 11.47]	[10.76 - 10.87 - 10.98]	2.16E-42
SAMM50	PERIVENOUS	sorting and assembly machinery component 50 homolog (S. cerevisiae)	[10.5 - 10.56 - 10.62]	[11.02 - 11.1 - 11.17]	[10.58 - 10.64 - 10.7]	[10.56 - 10.63 - 10.7]	2.84E-30
REG3A	PERIVENOUS	regenerating islet-derived 3 alpha	[6.93 - 7.17 - 7.4]	[10.64 - 11.03 - 11.42]	[7.18 - 7.43 - 7.69]	[7.56 - 7.89 - 8.21]	6.38E-36
HIST1H2AC	PERIVENOUS	histone cluster 1, H2ac	[10.36 - 10.46 - 10.56]	[10.91 - 11.03 - 11.14]	[10.27 - 10.38 - 10.48]	[10.5 - 10.62 - 10.74]	2.79E-51
RAB4A	PERIVENOUS	RAB4A, member RAS oncogene family	[10.47 - 10.52 - 10.57]	[10.96 - 11.02 - 11.09]	[10.47 - 10.53 - 10.6]	[10.35 - 10.43 - 10.51]	4.42E-25
IDI1	PERIVENOUS	isopentenyl-diphosphate delta isomerase 1	[10.81 - 10.88 - 10.96]	[10.89 - 10.98 - 11.06]	[10.86 - 10.94 - 11.02]	[10.73 - 10.83 - 10.93]	5.72E-30
ATP6V0A1	PERIVENOUS	ATPase, H+ transporting, lysosomal V0 subunit a1	[10.59 - 10.64 - 10.69]	[10.89 - 10.95 - 11.01]	[10.69 - 10.74 - 10.79]	[10.54 - 10.6 - 10.67]	4.46E-50
ROCK2	PERIVENOUS	Rho-associated, coiled-coil containing protein kinase 2	[10.21 - 10.26 - 10.31]	[10.88 - 10.95 - 11.01]	[10.35 - 10.4 - 10.46]	[10.43 - 10.5 - 10.56]	5.20E-28
DUT	PERIVENOUS	deoxyuridine triphosphatase	[10.21 - 10.27 - 10.33]	[10.84 - 10.93 - 11.02]	[10.12 - 10.19 - 10.25]	[10.1 - 10.19 - 10.28]	2.18E-51

PREB	PERIVENOUS	prolactin regulatory element binding	[10.1 - 10.14 - 10.19]	[10.8 - 10.88 - 10.96]	[10.1 - 10.15 - 10.2]	[10.04 - 10.1 - 10.16]	9.99E-23
LPPR1	PERIVENOUS	lipid phosphate phosphatase-related protein type 1	[9.03 - 9.12 - 9.21]	[10.76 - 10.87 - 10.99]	[9.21 - 9.32 - 9.44]	[9.15 - 9.34 - 9.53]	3.09E-24
TBCE	PERIVENOUS	tubulin folding cofactor E	[10.19 - 10.25 - 10.3]	[10.76 - 10.82 - 10.88]	[10.48 - 10.54 - 10.61]	[10.39 - 10.47 - 10.55]	4.12E-17
CD36	PERIVENOUS	CD36 molecule (thrombospondin receptor)	[9.7 - 9.78 - 9.87]	[10.62 - 10.75 - 10.89]	[9.29 - 9.4 - 9.52]	[9.29 - 9.44 - 9.6]	1.71E-06
PIR	PERIVENOUS	pirin (iron-binding nuclear protein)	[9.97 - 10.05 - 10.13]	[10.61 - 10.71 - 10.81]	[9.87 - 9.98 - 10.08]	[9.62 - 9.76 - 9.9]	7.57E-45
SLCO1B3	PERIVENOUS	solute carrier organic anion transporter family, member 1B3	[7.55 - 7.79 - 8.03]	[10.37 - 10.7 - 11.02]	[8.07 - 8.33 - 8.58]	[7.89 - 8.15 - 8.41]	1.54E-30
TKT	PERIVENOUS	transketolase	[9.87 - 9.97 - 10.06]	[10.53 - 10.67 - 10.8]	[10.26 - 10.37 - 10.47]	[10.64 - 10.75 - 10.86]	7.76E-30
SYF2	PERIVENOUS	SYF2 homolog, RNA splicing factor (<i>S. cerevisiae</i>)	[10.28 - 10.33 - 10.37]	[10.61 - 10.66 - 10.71]	[10.27 - 10.32 - 10.38]	[10.28 - 10.34 - 10.4]	2.43E-21
PEX19	PERIVENOUS	peroxisomal biogenesis factor 19	[10.42 - 10.47 - 10.52]	[10.58 - 10.64 - 10.71]	[10.22 - 10.29 - 10.35]	[9.9 - 9.98 - 10.06]	9.67E-31
MCUR1	PERIVENOUS	mitochondrial calcium uniporter regulator 1	[10.23 - 10.28 - 10.33]	[10.54 - 10.63 - 10.72]	[10.03 - 10.1 - 10.16]	[9.97 - 10.05 - 10.12]	5.84E-30
PMVK	PERIVENOUS	phosphomevalonate kinase	[10.34 - 10.39 - 10.45]	[10.51 - 10.58 - 10.66]	[10.26 - 10.32 - 10.38]	[10.02 - 10.1 - 10.17]	2.96E-20
ELOVL2	PERIVENOUS	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 2	[10.17 - 10.25 - 10.33]	[10.4 - 10.54 - 10.68]	[10.23 - 10.32 - 10.42]	[9.89 - 10.04 - 10.19]	2.16E-26
PBXIP1	PERIVENOUS	pre-B-cell leukemia homeobox interacting protein 1	[10.05 - 10.11 - 10.16]	[10.43 - 10.5 - 10.58]	[10.11 - 10.17 - 10.23]	[10.12 - 10.19 - 10.27]	1.37E-17
LGALS8	PERIVENOUS	lectin, galactoside-binding, soluble, 8	[9.84 - 9.9 - 9.96]	[10.43 - 10.5 - 10.57]	[10.01 - 10.08 - 10.15]	[9.83 - 9.91 - 10]	5.49E-23
TTC1	PERIVENOUS	tetratricopeptide repeat domain 1	[10.27 - 10.31 - 10.35]	[10.44 - 10.5 - 10.55]	[10.28 - 10.32 - 10.36]	[10.1 - 10.15 - 10.2]	1.89E-16
CUL1	PERIVENOUS	cullin 1	[10.13 - 10.18 - 10.23]	[10.4 - 10.48 - 10.55]	[10.07 - 10.13 - 10.2]	[9.99 - 10.06 - 10.13]	9.99E-15
LANCL1	PERIVENOUS	LanC lantibiotic synthetase component C-like 1 (bacterial)	[10.3 - 10.35 - 10.41]	[10.4 - 10.48 - 10.55]	[10.39 - 10.45 - 10.52]	[10.23 - 10.31 - 10.38]	8.13E-14
KLHL21	PERIVENOUS	kelch-like 21 (<i>Drosophila</i>)	[9.83 - 9.9 - 9.97]	[10.38 - 10.47 - 10.55]	[9.81 - 9.89 - 9.97]	[9.8 - 9.89 - 9.98]	3.84E-46
HMGCR	PERIVENOUS	3-hydroxy-3-methylglutaryl-CoA reductase	[10.35 - 10.42 - 10.5]	[10.37 - 10.46 - 10.55]	[10.43 - 10.51 - 10.59]	[10.39 - 10.5 - 10.6]	2.95E-15
RNPEP	PERIVENOUS	arginyl aminopeptidase (aminopeptidase B)	[10.04 - 10.09 - 10.14]	[10.39 - 10.46 - 10.53]	[10.05 - 10.12 - 10.18]	[9.9 - 9.97 - 10.04]	1.74E-14
EIF2B4	PERIVENOUS	eukaryotic translation initiation factor 2B, subunit 4 delta, 67kDa	[9.68 - 9.74 - 9.8]	[10.36 - 10.44 - 10.53]	[9.76 - 9.83 - 9.91]	[9.87 - 9.96 - 10.05]	2.97E-25
ATRN	PERIVENOUS	atractin	[10.58 - 10.64 - 10.71]	[10.35 - 10.44 - 10.53]	[10.41 - 10.49 - 10.57]	[10 - 10.11 - 10.21]	7.96E-92
CYP1A2	PERIVENOUS	cytochrome P450, family 1, subfamily A, polypeptide 2	[9.17 - 9.32 - 9.47]	[10.19 - 10.4 - 10.61]	[8.6 - 8.75 - 8.9]	[8.02 - 8.14 - 8.26]	8.21E-16

TIMM17A	PERIVENOUS	translocase of inner mitochondrial membrane 17 homolog A (yeast)	[9.64 - 9.7 - 9.77]	[10.31 - 10.4 - 10.48]	[9.6 - 9.66 - 9.73]	[9.35 - 9.43 - 9.51]	1.03E-40
CYB5B	PERIVENOUS	cytochrome b5 type B (outer mitochondrial membrane)	[9.61 - 9.66 - 9.71]	[10.26 - 10.35 - 10.43]	[9.65 - 9.72 - 9.78]	[9.72 - 9.8 - 9.88]	1.35E-45
LGTN	PERIVENOUS	ligatin	[9.86 - 9.92 - 9.97]	[10.27 - 10.34 - 10.42]	[10.06 - 10.12 - 10.18]	[10.01 - 10.08 - 10.16]	7.23E-43
CAP2	PERIVENOUS	CAP, adenylate cyclase-associated protein, 2 (yeast)	[9.4 - 9.5 - 9.59]	[10.23 - 10.34 - 10.45]	[9.54 - 9.64 - 9.74]	[9.4 - 9.52 - 9.65]	1.34E-16
TGIF1	PERIVENOUS	TGFB-induced factor homeobox 1	[9.51 - 9.6 - 9.69]	[10.21 - 10.31 - 10.41]	[9.67 - 9.76 - 9.84]	[9.72 - 9.82 - 9.93]	2.97E-33
ZNF238	PERIVENOUS	zinc finger protein 238	[9.51 - 9.58 - 9.65]	[10.19 - 10.3 - 10.4]	[9.59 - 9.67 - 9.75]	[9.25 - 9.37 - 9.49]	1.46E-63
HNRNP2	PERIVENOUS	heterogeneous nuclear ribonucleoprotein H2 (H')	[10.03 - 10.07 - 10.11]	[10.21 - 10.27 - 10.33]	[9.96 - 10.01 - 10.05]	[9.93 - 9.98 - 10.03]	1.74E-20
PDHX	PERIVENOUS	pyruvate dehydrogenase complex, component X	[9.95 - 9.99 - 10.03]	[10.16 - 10.23 - 10.3]	[9.85 - 9.9 - 9.95]	[9.8 - 9.86 - 9.92]	1.16E-51
NEDD4	PERIVENOUS	neural precursor cell expressed, developmentally down-regulated 4	[9.51 - 9.59 - 9.67]	[10.11 - 10.21 - 10.3]	[9.3 - 9.39 - 9.48]	[8.8 - 8.92 - 9.04]	4.91E-46
PFDN6	PERIVENOUS	prefoldin subunit 6	[9.77 - 9.82 - 9.88]	[10.11 - 10.19 - 10.27]	[9.7 - 9.76 - 9.83]	[9.87 - 9.95 - 10.03]	5.65E-10
SMAD3	PERIVENOUS	SMAD family member 3	[9.4 - 9.45 - 9.5]	[10.07 - 10.12 - 10.18]	[9.55 - 9.61 - 9.67]	[9.74 - 9.81 - 9.89]	3.15E-38
HEXA	PERIVENOUS	hexosaminidase A (alpha polypeptide)	[9.58 - 9.63 - 9.68]	[10.01 - 10.09 - 10.17]	[9.47 - 9.53 - 9.59]	[9.58 - 9.66 - 9.74]	2.93E-31
CYP7A1	PERIVENOUS	cytochrome P450, family 7, subfamily A, polypeptide 1	[10.05 - 10.24 - 10.44]	[9.84 - 10.07 - 10.31]	[9.06 - 9.27 - 9.49]	[7.07 - 7.31 - 7.55]	1.46E-24
LGR5	PERIVENOUS	leucine-rich repeat-containing G protein-coupled receptor 5	[6.24 - 6.36 - 6.49]	[9.86 - 10.04 - 10.22]	[6.81 - 6.99 - 7.16]	[7.64 - 7.89 - 8.13]	2.12E-18
ABLIM1	PERIVENOUS	actin binding LIM protein 1	[9.36 - 9.42 - 9.48]	[9.95 - 10.03 - 10.11]	[9.31 - 9.37 - 9.43]	[9.5 - 9.57 - 9.64]	4.13E-54
TCEAL1	PERIVENOUS	transcription elongation factor A (SII)-like 1	[9.18 - 9.24 - 9.29]	[9.9 - 9.99 - 10.08]	[9.08 - 9.15 - 9.22]	[8.94 - 9.03 - 9.11]	4.18E-20
TNFAIP3	PERIVENOUS	tumor necrosis factor, alpha-induced protein 3	[9.24 - 9.31 - 9.38]	[9.83 - 9.95 - 10.06]	[9.63 - 9.7 - 9.77]	[9.55 - 9.65 - 9.74]	4.77E-20
WIPI2	PERIVENOUS	WD repeat domain, phosphoinositide interacting 2	[9.65 - 9.69 - 9.73]	[9.88 - 9.94 - 10]	[9.59 - 9.64 - 9.69]	[9.64 - 9.7 - 9.75]	5.04E-04
OSER1	PERIVENOUS	oxidative stress responsive serine-rich 1	[9.51 - 9.57 - 9.63]	[9.87 - 9.93 - 9.98]	[9.42 - 9.47 - 9.53]	[9.33 - 9.4 - 9.46]	1.27E-35
CBFB	PERIVENOUS	core-binding factor, beta subunit	[9.65 - 9.71 - 9.77]	[9.84 - 9.91 - 9.97]	[9.82 - 9.88 - 9.94]	[10.12 - 10.19 - 10.27]	3.13E-49
NARS2	PERIVENOUS	asparaginyl-tRNA synthetase 2, mitochondrial (putative)	[9.37 - 9.42 - 9.48]	[9.82 - 9.88 - 9.94]	[9.4 - 9.46 - 9.52]	[9.37 - 9.44 - 9.51]	2.84E-14
ICK	PERIVENOUS	intestinal cell (MAK-like) kinase	[8.41 - 8.48 - 8.55]	[9.73 - 9.87 - 10.01]	[8.37 - 8.46 - 8.55]	[8.51 - 8.61 - 8.7]	1.62E-32
LAMA3	PERIVENOUS	laminin, alpha 3	[7.91 - 8 - 8.09]	[9.71 - 9.86 - 10.02]	[7.92 - 8.01 - 8.11]	[7.61 - 7.74 - 7.87]	9.73E-25
YAP1	PERIVENOUS	Yes-associated protein 1	[9.11 - 9.17 - 9.23]	[9.77 - 9.86 - 9.94]	[9.25 - 9.32 - 9.4]	[9.47 - 9.55 - 9.64]	3.67E-22
DNAJC12	PERIVENOUS	DnaJ (Hsp40) homolog, subfamily C, member 12	[8.6 - 8.73 - 8.86]	[9.66 - 9.85 - 10.05]	[8.34 - 8.48 - 8.63]	[8.3 - 8.48 - 8.67]	4.58E-16
TMCC1	PERIVENOUS	transmembrane and coiled-coil domain family 1	[9 - 9.09 - 9.18]	[9.72 - 9.85 - 9.98]	[9.12 - 9.22 - 9.32]	[9.25 - 9.36 - 9.46]	6.55E-27
ANKRA2	PERIVENOUS	ankyrin repeat, family A (RFXANK-like), 2	[9.36 - 9.41 - 9.47]	[9.76 - 9.84 - 9.92]	[9.24 - 9.3 - 9.36]	[9.04 - 9.12 - 9.19]	4.93E-38
THEM6	PERIVENOUS	thioesterase superfamily member 6	[9.43 - 9.5 - 9.56]	[9.73 - 9.81 - 9.9]	[9.42 - 9.5 - 9.57]	[9.14 - 9.23 - 9.32]	3.81E-58
MTR	PERIVENOUS	5-methyltetrahydrofolate-homocysteine methyltransferase	[9.04 - 9.1 - 9.16]	[9.69 - 9.78 - 9.86]	[9.32 - 9.39 - 9.47]	[9.23 - 9.31 - 9.39]	8.16E-23
AIMP1	PERIVENOUS	aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	[9.21 - 9.26 - 9.32]	[9.67 - 9.75 - 9.84]	[9.18 - 9.26 - 9.33]	[9.31 - 9.39 - 9.47]	1.17E-28

ARHGAP12	PERIVENOUS	Rho GTPase activating protein 12	[8.84 - 8.9 - 8.97]	[9.64 - 9.73 - 9.82]	[9.13 - 9.21 - 9.28]	[9.16 - 9.24 - 9.33]	3.69E-22
THAP11	PERIVENOUS	THAP domain containing 11	[9.26 - 9.31 - 9.35]	[9.62 - 9.67 - 9.72]	[9.26 - 9.31 - 9.36]	[9.43 - 9.49 - 9.55]	1.97E-41
PARN	PERIVENOUS	poly(A)-specific ribonuclease (deadenylation nuclease)	[9.35 - 9.4 - 9.44]	[9.61 - 9.66 - 9.71]	[9.27 - 9.32 - 9.38]	[9.15 - 9.22 - 9.29]	1.29E-24
ASAP2	PERIVENOUS	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	[8.56 - 8.64 - 8.72]	[9.53 - 9.63 - 9.73]	[8.84 - 8.91 - 8.98]	[8.99 - 9.09 - 9.2]	9.05E-03
GNAI1	PERIVENOUS	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	[8.6 - 8.67 - 8.74]	[9.48 - 9.6 - 9.71]	[8.6 - 8.69 - 8.78]	[8.61 - 8.7 - 8.79]	5.70E-22
PPP1R2	PERIVENOUS	protein phosphatase 1, regulatory (inhibitor) subunit 2	[9.01 - 9.05 - 9.1]	[9.47 - 9.54 - 9.61]	[9.06 - 9.12 - 9.17]	[9.21 - 9.28 - 9.35]	1.60E-11
NCOA2	PERIVENOUS	nuclear receptor coactivator 2	[8.83 - 8.9 - 8.96]	[9.38 - 9.48 - 9.58]	[8.88 - 8.97 - 9.05]	[8.71 - 8.81 - 8.9]	4.13E-12
PRKCA	PERIVENOUS	protein kinase C, alpha	[8.95 - 9.01 - 9.07]	[9.36 - 9.44 - 9.52]	[8.95 - 9.02 - 9.09]	[8.86 - 8.95 - 9.04]	1.63E-39
SOX13	PERIVENOUS	SRY (sex determining region Y)-box 13	[9.2 - 9.26 - 9.31]	[9.36 - 9.42 - 9.49]	[9.46 - 9.52 - 9.58]	[9.43 - 9.52 - 9.61]	4.73E-17
TLE1	PERIVENOUS	transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	[8.9 - 8.95 - 9]	[9.34 - 9.42 - 9.49]	[8.95 - 9.02 - 9.09]	[8.93 - 9.02 - 9.11]	1.01E-27
MTMR11	PERIVENOUS	myotubularin related protein 11	[8.41 - 8.5 - 8.6]	[9.29 - 9.41 - 9.53]	[8.65 - 8.76 - 8.86]	[8.51 - 8.64 - 8.77]	6.69E-09
SLC30A10	PERIVENOUS	solute carrier family 30, member 10	[8.61 - 8.69 - 8.76]	[9.26 - 9.38 - 9.5]	[8.57 - 8.67 - 8.77]	[8.22 - 8.36 - 8.51]	2.43E-23
RRNAD1	PERIVENOUS	ribosomal RNA adenine dimethylase domain containing 1	[9.09 - 9.14 - 9.19]	[9.3 - 9.37 - 9.43]	[8.92 - 8.98 - 9.04]	[8.81 - 8.88 - 8.95]	3.97E-18
HEATR1	PERIVENOUS	HEAT repeat containing 1	[8.66 - 8.72 - 8.78]	[9.24 - 9.33 - 9.41]	[9.14 - 9.2 - 9.27]	[9.34 - 9.42 - 9.5]	5.01E-16
TERF2	PERIVENOUS	telomeric repeat binding factor 2	[8.88 - 8.92 - 8.96]	[9.23 - 9.28 - 9.34]	[8.85 - 8.9 - 8.95]	[8.81 - 8.86 - 8.92]	6.92E-32
NBAS	PERIVENOUS	neuroblastoma amplified sequence	[8.87 - 8.91 - 8.96]	[9.18 - 9.25 - 9.32]	[8.89 - 8.93 - 8.97]	[8.9 - 8.95 - 9]	6.65E-17
PARVB	PERIVENOUS	parvin, beta	[8.25 - 8.32 - 8.4]	[9.08 - 9.22 - 9.37]	[8.61 - 8.7 - 8.79]	[8.66 - 8.76 - 8.86]	1.40E-30
RCBTB1	PERIVENOUS	regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1	[8.51 - 8.57 - 8.63]	[9.13 - 9.21 - 9.29]	[8.5 - 8.57 - 8.63]	[8.63 - 8.7 - 8.78]	1.47E-19
PTPRG	PERIVENOUS	protein tyrosine phosphatase, receptor type, G	[8.29 - 8.35 - 8.4]	[9.08 - 9.16 - 9.25]	[8.35 - 8.42 - 8.5]	[8.67 - 8.75 - 8.84]	1.31E-67
NAGPA	PERIVENOUS	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase	[8.73 - 8.79 - 8.85]	[9.05 - 9.14 - 9.22]	[8.63 - 8.69 - 8.76]	[8.61 - 8.69 - 8.76]	9.66E-06
TRAPPC6A	PERIVENOUS	trafficking protein particle complex 6A	[8.95 - 9.01 - 9.08]	[9.01 - 9.09 - 9.17]	[8.75 - 8.82 - 8.89]	[8.59 - 8.67 - 8.76]	2.16E-27
RAB11FIP2	PERIVENOUS	RAB11 family interacting protein 2 (class I)	[8.2 - 8.26 - 8.32]	[8.92 - 8.99 - 9.07]	[8.38 - 8.45 - 8.51]	[8.43 - 8.5 - 8.58]	2.15E-44
HS1BP3	PERIVENOUS	HCLS1 binding protein 3	[8.54 - 8.6 - 8.66]	[8.89 - 8.97 - 9.05]	[8.53 - 8.59 - 8.66]	[8.38 - 8.45 - 8.52]	3.44E-34
THADA	PERIVENOUS	thyroid adenoma associated	[8.16 - 8.22 - 8.28]	[8.83 - 8.92 - 9]	[8.41 - 8.47 - 8.53]	[8.6 - 8.66 - 8.73]	3.53E-26
AP2B1	PERIVENOUS	adaptor-related protein complex 2, beta 1 subunit	[8.34 - 8.4 - 8.46]	[8.8 - 8.88 - 8.96]	[8.34 - 8.41 - 8.47]	[8.62 - 8.71 - 8.79]	1.11E-13
CASK	PERIVENOUS	calcium/calmodulin-dependent serine protein kinase (MAGUK family)	[8.39 - 8.44 - 8.5]	[8.8 - 8.88 - 8.96]	[8.45 - 8.51 - 8.57]	[8.49 - 8.57 - 8.65]	1.60E-27
NUP93	PERIVENOUS	nucleoporin 93kDa	[8.48 - 8.54 - 8.6]	[8.79 - 8.87 - 8.96]	[8.71 - 8.78 - 8.85]	[9.13 - 9.22 - 9.3]	4.22E-64
STAM2	PERIVENOUS	signal transducing adaptor molecule (SH3 domain and ITAM motif) 2	[8.43 - 8.49 - 8.55]	[8.8 - 8.87 - 8.94]	[8.35 - 8.41 - 8.48]	[8.43 - 8.5 - 8.57]	1.21E-25
DIEXF	PERIVENOUS	digestive organ expansion factor homolog (zebrafish)	[8.39 - 8.45 - 8.51]	[8.77 - 8.85 - 8.93]	[8.42 - 8.49 - 8.57]	[8.45 - 8.54 - 8.62]	1.36E-13
CYP1A1	PERIVENOUS	cytochrome P450, family 1, subfamily A, polypeptide 1	[6.64 - 6.77 - 6.9]	[8.53 - 8.77 - 9.01]	[6.23 - 6.36 - 6.5]	[5.89 - 6.02 - 6.16]	6.72E-35
IMPAD1	PERIVENOUS	inositol monophosphatase domain containing 1	[8.03 - 8.09 - 8.14]	[8.51 - 8.58 - 8.66]	[7.98 - 8.04 - 8.1]	[8.04 - 8.11 - 8.18]	3.61E-43
KATNB1	PERIVENOUS	katanin p80 (WD repeat containing) subunit B 1	[8.01 - 8.07 - 8.12]	[8.42 - 8.49 - 8.56]	[8.05 - 8.11 - 8.17]	[8.11 - 8.18 - 8.25]	8.02E-22
SLC7A6	PERIVENOUS	solute carrier family 7 (cationic amino acid transporter, y+ system), member 6	[7.51 - 7.57 - 7.62]	[8.37 - 8.45 - 8.53]	[7.92 - 7.99 - 8.05]	[8.16 - 8.24 - 8.32]	5.35E-18
CEP68	PERIVENOUS	centrosomal protein 68kDa	[7.82 - 7.89 - 7.97]	[8.36 - 8.44 - 8.51]	[7.96 - 8.03 - 8.11]	[8.12 - 8.2 - 8.28]	2.55E-14
RAD50	PERIVENOUS	RAD50 homolog (S. cerevisiae)	[8.09 - 8.16 - 8.22]	[8.31 - 8.4 - 8.5]	[7.91 - 7.98 - 8.04]	[7.81 - 7.9 - 7.98]	2.40E-12
MID1	PERIVENOUS	midline 1 (Opitz/BBB syndrome)	[7.47 - 7.54 - 7.6]	[8.11 - 8.21 - 8.3]	[7.62 - 7.71 - 7.8]	[7.69 - 7.78 - 7.88]	4.67E-25
GREB1	PERIVENOUS	growth regulation by estrogen in breast cancer 1	[6.87 - 6.95 - 7.03]	[7.97 - 8.11 - 8.25]	[6.88 - 6.98 - 7.07]	[7.08 - 7.22 - 7.36]	5.19E-35

LEF1	PERIVENOUS	lymphoid enhancer-binding factor 1	[6.37 - 6.45 - 6.52]	[7.28 - 7.42 - 7.55]	[6.8 - 6.89 - 6.98]	[6.82 - 6.92 - 7.03]	1.29E-40
RPL8	ECM/STEM	ribosomal protein L8	[12.99 - 13.05 - 13.1]	[13.24 - 13.33 - 13.41]	[13.37 - 13.43 - 13.49]	[13.66 - 13.72 - 13.78]	8.23E-13
RPS3	ECM/STEM	ribosomal protein S3	[12.62 - 12.67 - 12.72]	[12.79 - 12.86 - 12.93]	[12.91 - 12.97 - 13.02]	[13.41 - 13.47 - 13.52]	6.53E-24
PABPC1	ECM/STEM	poly(A) binding protein, cytoplasmic 1	[12.7 - 12.75 - 12.8]	[13.07 - 13.15 - 13.22]	[13.11 - 13.17 - 13.22]	[13.39 - 13.45 - 13.51]	3.67E-56
TUBA1C	ECM/STEM	tubulin, alpha 1c	[12.34 - 12.39 - 12.44]	[12.37 - 12.44 - 12.5]	[12.65 - 12.69 - 12.74]	[12.99 - 13.05 - 13.1]	7.80E-54
EIF3H	ECM/STEM	eukaryotic translation initiation factor 3, subunit H	[12.36 - 12.4 - 12.45]	[12.72 - 12.79 - 12.86]	[12.59 - 12.65 - 12.71]	[12.91 - 12.97 - 13.04]	1.07E-60
ENO1	ECM/STEM	enolase 1, (alpha)	[12.33 - 12.38 - 12.43]	[12.41 - 12.49 - 12.57]	[12.37 - 12.45 - 12.53]	[12.87 - 12.96 - 13.05]	1.40E-54
HSPA5	ECM/STEM	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	[12.55 - 12.6 - 12.65]	[12.27 - 12.33 - 12.39]	[12.66 - 12.71 - 12.76]	[12.67 - 12.72 - 12.77]	6.14E-43
DYNLL1	ECM/STEM	dynein, light chain, LC8-type 1	[12.31 - 12.35 - 12.38]	[12.37 - 12.42 - 12.47]	[12.52 - 12.55 - 12.58]	[12.64 - 12.68 - 12.72]	2.57E-53
ARPC2	ECM/STEM	actin related protein 2/3 complex, subunit 2, 34kDa	[11.94 - 11.97 - 12.01]	[11.95 - 12 - 12.06]	[12.23 - 12.28 - 12.33]	[12.5 - 12.56 - 12.61]	3.73E-48
CFL1	ECM/STEM	cofilin 1 (non-muscle)	[12.15 - 12.19 - 12.23]	[12.16 - 12.21 - 12.26]	[12.31 - 12.35 - 12.39]	[12.5 - 12.54 - 12.59]	2.21E-44
GPI	ECM/STEM	glucose-6-phosphate isomerase	[12.26 - 12.32 - 12.37]	[12.01 - 12.09 - 12.16]	[12.41 - 12.46 - 12.51]	[12.44 - 12.51 - 12.57]	8.89E-41
YWHAZ	ECM/STEM	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	[11.72 - 11.78 - 11.83]	[11.82 - 11.9 - 11.98]	[12.1 - 12.17 - 12.23]	[12.42 - 12.49 - 12.56]	8.79E-55
PPA1	ECM/STEM	pyrophosphatase (inorganic) 1	[12.08 - 12.13 - 12.18]	[12.21 - 12.28 - 12.35]	[12.37 - 12.43 - 12.48]	[12.42 - 12.49 - 12.56]	3.30E-12
SPP1	ECM/STEM	secreted phosphoprotein 1	[10.14 - 10.34 - 10.55]	[11.19 - 11.5 - 11.81]	[11.64 - 11.85 - 12.06]	[12.13 - 12.34 - 12.55]	8.59E-57
SPINK1	ECM/STEM	serine peptidase inhibitor, Kazal type 1	[10.68 - 10.96 - 11.25]	[9.32 - 9.71 - 10.11]	[12.45 - 12.68 - 12.91]	[11.94 - 12.23 - 12.51]	5.54E-30
IFI30	ECM/STEM	interferon, gamma-inducible protein 30	[11.61 - 11.68 - 11.75]	[11.44 - 11.54 - 11.65]	[11.91 - 11.99 - 12.08]	[12.11 - 12.22 - 12.33]	2.40E-60
CLIC1	ECM/STEM	chloride intracellular channel 1	[11.17 - 11.23 - 11.29]	[11.4 - 11.47 - 11.53]	[11.55 - 11.6 - 11.65]	[12.14 - 12.19 - 12.25]	7.00E-41
MAT2A	ECM/STEM	methionine adenosyltransferase II, alpha	[11.72 - 11.77 - 11.82]	[11.48 - 11.56 - 11.63]	[11.92 - 11.97 - 12.02]	[12.13 - 12.19 - 12.26]	3.86E-40
CAP1	ECM/STEM	CAP, adenylate cyclase-associated protein 1 (yeast)	[11.62 - 11.66 - 11.7]	[11.69 - 11.73 - 11.77]	[11.71 - 11.76 - 11.8]	[11.93 - 11.99 - 12.05]	5.81E-28
SPATS2L	ECM/STEM	spermatogenesis associated, serine-rich 2-like	[11.32 - 11.37 - 11.43]	[11.13 - 11.2 - 11.27]	[11.5 - 11.56 - 11.62]	[11.84 - 11.91 - 11.99]	2.48E-35
ANXA5	ECM/STEM	annexin A5	[11 - 11.07 - 11.15]	[10.67 - 10.8 - 10.93]	[11.35 - 11.45 - 11.55]	[11.83 - 11.91 - 11.99]	1.30E-46

EIF3E	ECM/STEM	eukaryotic translation initiation factor 3, subunit E	[11.25 - 11.31 - 11.37]	[11.86 - 11.95 - 12.04]	[11.58 - 11.64 - 11.7]	[11.82 - 11.9 - 11.99]	2.96E-86
NDRG1	ECM/STEM	N-myc downstream regulated 1	[10.73 - 10.82 - 10.91]	[10.96 - 11.07 - 11.17]	[11.33 - 11.43 - 11.53]	[11.78 - 11.9 - 12.02]	5.17E-22
BCAP31	ECM/STEM	B-cell receptor-associated protein 31	[11.45 - 11.5 - 11.54]	[11.95 - 12.02 - 12.08]	[11.67 - 11.72 - 11.78]	[11.77 - 11.83 - 11.88]	2.41E-33
ATIC	ECM/STEM	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase	[11.01 - 11.06 - 11.1]	[11.28 - 11.34 - 11.41]	[11.28 - 11.33 - 11.39]	[11.69 - 11.76 - 11.82]	1.09E-30
H2AFZ	ECM/STEM	H2A histone family, member Z	[11.03 - 11.11 - 11.18]	[11.05 - 11.13 - 11.22]	[11.18 - 11.27 - 11.35]	[11.67 - 11.75 - 11.83]	6.60E-32
TM4SF1	ECM/STEM	transmembrane 4 L six family member 1	[10.69 - 10.78 - 10.86]	[10.88 - 11 - 11.13]	[11 - 11.11 - 11.22]	[11.59 - 11.73 - 11.87]	2.10E-44
CBX3	ECM/STEM	chromobox homolog 3	[11.06 - 11.11 - 11.15]	[11.28 - 11.34 - 11.4]	[11.26 - 11.31 - 11.36]	[11.63 - 11.69 - 11.75]	5.85E-36
TFRC	ECM/STEM	transferrin receptor (p90, CD71)	[10.93 - 11 - 11.08]	[10.61 - 10.72 - 10.82]	[11.26 - 11.34 - 11.42]	[11.59 - 11.68 - 11.77]	1.17E-24
BAMBI	ECM/STEM	BMP and activin membrane-bound inhibitor homolog (<i>Xenopus laevis</i>)	[10.04 - 10.18 - 10.32]	[11.35 - 11.48 - 11.61]	[10.81 - 10.92 - 11.03]	[11.54 - 11.65 - 11.77]	1.00E-40
KPNB1	ECM/STEM	karyopherin (importin) beta 1	[11.05 - 11.1 - 11.15]	[11.21 - 11.27 - 11.33]	[11.21 - 11.26 - 11.31]	[11.57 - 11.63 - 11.69]	9.91E-52
WDR1	ECM/STEM	WD repeat domain 1	[11.1 - 11.14 - 11.17]	[11.28 - 11.33 - 11.39]	[11.36 - 11.41 - 11.46]	[11.55 - 11.61 - 11.67]	1.36E-66
GRN	ECM/STEM	granulin	[11.32 - 11.37 - 11.42]	[11.21 - 11.27 - 11.34]	[11.34 - 11.4 - 11.46]	[11.51 - 11.59 - 11.68]	8.10E-32
HIF1A	ECM/STEM	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	[10.86 - 10.91 - 10.96]	[10.73 - 10.8 - 10.86]	[11.2 - 11.26 - 11.31]	[11.51 - 11.59 - 11.66]	8.89E-32
ACTR3	ECM/STEM	ARP3 actin-related protein 3 homolog (yeast)	[11.13 - 11.17 - 11.2]	[11.16 - 11.21 - 11.26]	[11.3 - 11.34 - 11.38]	[11.54 - 11.58 - 11.63]	1.11E-41
ALDOA	ECM/STEM	aldolase A, fructose-bisphosphate	[10.81 - 10.87 - 10.94]	[10.85 - 10.94 - 11.03]	[11.01 - 11.09 - 11.18]	[11.44 - 11.55 - 11.67]	6.64E-25
MSN	ECM/STEM	moesin	[11.06 - 11.12 - 11.19]	[11.14 - 11.24 - 11.34]	[11.3 - 11.39 - 11.48]	[11.45 - 11.55 - 11.65]	1.32E-41
CLNS1A	ECM/STEM	chloride channel, nucleotide-sensitive, 1A	[11.14 - 11.18 - 11.23]	[11.41 - 11.46 - 11.52]	[11.3 - 11.35 - 11.4]	[11.47 - 11.54 - 11.6]	3.43E-53
DHRS7	ECM/STEM	dehydrogenase/reductase (SDR family) member 7	[11.33 - 11.4 - 11.47]	[10.93 - 11.04 - 11.16]	[11.54 - 11.62 - 11.71]	[11.4 - 11.48 - 11.57]	6.16E-28
SCD	ECM/STEM	stearoyl-CoA desaturase (delta-9-desaturase)	[10.58 - 10.71 - 10.84]	[11.5 - 11.64 - 11.78]	[11.4 - 11.51 - 11.62]	[11.33 - 11.46 - 11.58]	1.16E-50
NREP	ECM/STEM	neuronal regeneration related protein	[10.48 - 10.57 - 10.65]	[10.2 - 10.32 - 10.44]	[10.98 - 11.07 - 11.16]	[11.33 - 11.45 - 11.57]	1.18E-49
LGALS3	ECM/STEM	lectin, galactoside-binding, soluble, 3	[10.78 - 10.89 - 11]	[10.11 - 10.24 - 10.37]	[11.18 - 11.29 - 11.41]	[11.31 - 11.45 - 11.58]	1.78E-48

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ACSL4	ECM/STEM	acyl-CoA synthetase long-chain family member 4	[9.93 - 10.09 - 10.25]	[9.8 - 9.99 - 10.19]	[11.29 - 11.43 - 11.56]	[11.3 - 11.44 - 11.59]	1.07E-29
MARCKSL1	ECM/STEM	MARCKS-like 1	[10.14 - 10.21 - 10.27]	[10.26 - 10.37 - 10.48]	[10.62 - 10.69 - 10.76]	[11.34 - 11.44 - 11.54]	3.03E-18
IARS	ECM/STEM	isoleucyl-tRNA synthetase	[10.62 - 10.66 - 10.71]	[10.86 - 10.92 - 10.99]	[10.92 - 10.98 - 11.03]	[11.34 - 11.39 - 11.45]	1.53E-34
MARCKS	ECM/STEM	myristoylated alanine-rich protein kinase C substrate	[10.05 - 10.13 - 10.2]	[9.94 - 10.05 - 10.17]	[10.6 - 10.69 - 10.77]	[11.31 - 11.39 - 11.46]	5.66E-07
CALU	ECM/STEM	calumenin	[10.88 - 10.92 - 10.96]	[10.81 - 10.87 - 10.93]	[11.02 - 11.07 - 11.11]	[11.32 - 11.37 - 11.43]	4.27E-31
SPON2	ECM/STEM	spondin 2, extracellular matrix protein	[10.58 - 10.68 - 10.77]	[11.27 - 11.38 - 11.48]	[11.22 - 11.32 - 11.42]	[11.23 - 11.34 - 11.46]	3.47E-56
BZW2	ECM/STEM	basic leucine zipper and W2 domains 2	[10.49 - 10.53 - 10.57]	[10.81 - 10.87 - 10.94]	[10.7 - 10.76 - 10.82]	[11.27 - 11.34 - 11.41]	6.49E-60
HIST1H4C	ECM/STEM	histone cluster 1, H4c	[10.71 - 10.78 - 10.85]	[10.35 - 10.44 - 10.54]	[10.77 - 10.85 - 10.93]	[11.25 - 11.34 - 11.43]	1.57E-48
DYNC1I2	ECM/STEM	dynein, cytoplasmic 1, intermediate chain 2	[10.81 - 10.85 - 10.89]	[11.04 - 11.09 - 11.14]	[11.01 - 11.06 - 11.1]	[11.28 - 11.34 - 11.39]	2.16E-22
CDK4	ECM/STEM	cyclin-dependent kinase 4	[10.55 - 10.59 - 10.64]	[10.6 - 10.67 - 10.74]	[10.78 - 10.83 - 10.89]	[11.26 - 11.32 - 11.39]	3.05E-61
EPRS	ECM/STEM	glutamyl-prolyl-tRNA synthetase	[10.64 - 10.7 - 10.75]	[10.94 - 11.02 - 11.09]	[11.07 - 11.12 - 11.18]	[11.24 - 11.31 - 11.38]	3.30E-61
HDAC2	ECM/STEM	histone deacetylase 2	[10.52 - 10.56 - 10.6]	[10.66 - 10.73 - 10.8]	[10.74 - 10.8 - 10.86]	[11.22 - 11.28 - 11.35]	3.02E-42
PPT1	ECM/STEM	palmitoyl-protein thioesterase 1	[10.63 - 10.69 - 10.74]	[10.54 - 10.62 - 10.71]	[10.78 - 10.85 - 10.93]	[11.16 - 11.24 - 11.32]	7.27E-37
SERPINE2	ECM/STEM	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	[9.95 - 10.08 - 10.2]	[9.59 - 9.82 - 10.04]	[10.71 - 10.85 - 10.98]	[11.09 - 11.24 - 11.39]	2.45E-66
TNFRSF21	ECM/STEM	tumor necrosis factor receptor superfamily, member 21	[9.84 - 9.92 - 10]	[9.72 - 9.9 - 10.08]	[10.38 - 10.47 - 10.56]	[11.14 - 11.24 - 11.34]	4.31E-18
COL1A2	ECM/STEM	collagen, type I, alpha 2	[10.43 - 10.54 - 10.65]	[9.61 - 9.8 - 9.99]	[10.83 - 10.98 - 11.13]	[11.04 - 11.21 - 11.38]	3.13E-49
SH3BGR13	ECM/STEM	SH3 domain binding glutamic acid-rich protein like 3	[10.7 - 10.76 - 10.82]	[10.53 - 10.61 - 10.69]	[10.88 - 10.95 - 11.02]	[11.09 - 11.19 - 11.29]	6.94E-40
ZMIZ1	ECM/STEM	zinc finger, MIZ-type containing 1	[10.53 - 10.58 - 10.62]	[10.4 - 10.46 - 10.52]	[10.85 - 10.91 - 10.96]	[11.05 - 11.12 - 11.19]	3.14E-57
TSPAN3	ECM/STEM	tetraspanin 3	[10.65 - 10.71 - 10.78]	[10.08 - 10.16 - 10.25]	[10.75 - 10.82 - 10.89]	[11.02 - 11.1 - 11.18]	1.91E-57
SSB	ECM/STEM	Sjogren syndrome antigen B (autoantigen La)	[10.41 - 10.46 - 10.5]	[10.69 - 10.75 - 10.81]	[10.68 - 10.73 - 10.77]	[11 - 11.06 - 11.13]	5.57E-29
TUBA4A	ECM/STEM	tubulin, alpha 4a	[10.49 - 10.57 - 10.65]	[10.22 - 10.32 - 10.42]	[10.85 - 10.93 - 11.01]	[10.93 - 11.03 - 11.13]	3.47E-35

CKS2	ECM/STEM	CDC28 protein kinase regulatory subunit 2	[9.97 - 10.06 - 10.14]	[10.12 - 10.21 - 10.31]	[10.22 - 10.32 - 10.42]	[10.93 - 11.03 - 11.13]	2.21E-32
PKM2	ECM/STEM	pyruvate kinase, muscle	[9.56 - 9.63 - 9.7]	[9.42 - 9.52 - 9.63]	[10.09 - 10.18 - 10.27]	[10.91 - 11.03 - 11.15]	5.65E-24
ITGA5	ECM/STEM	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	[10.4 - 10.46 - 10.51]	[9.95 - 10.02 - 10.08]	[10.74 - 10.8 - 10.85]	[10.89 - 10.97 - 11.06]	8.95E-14
CCL20	ECM/STEM	chemokine (C-C motif) ligand 20	[8.81 - 8.97 - 9.14]	[8.16 - 8.4 - 8.64]	[10.29 - 10.44 - 10.59]	[10.8 - 10.97 - 11.15]	6.59E-31
MMD	ECM/STEM	monocyte to macrophage differentiation-associated	[9.88 - 9.94 - 10.01]	[9.56 - 9.68 - 9.81]	[10.26 - 10.34 - 10.42]	[10.88 - 10.97 - 11.05]	5.99E-88
PTK2	ECM/STEM	PTK2 protein tyrosine kinase 2	[10.51 - 10.56 - 10.61]	[10.91 - 10.98 - 11.05]	[10.79 - 10.86 - 10.92]	[10.9 - 10.96 - 11.03]	7.22E-38
IFNGR2	ECM/STEM	interferon gamma receptor 2 (interferon gamma transducer 1)	[10.08 - 10.14 - 10.19]	[10.27 - 10.36 - 10.44]	[10.48 - 10.53 - 10.59]	[10.88 - 10.95 - 11.02]	2.04E-28
ITGAV	ECM/STEM	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	[10.37 - 10.44 - 10.51]	[10.26 - 10.35 - 10.44]	[10.57 - 10.66 - 10.75]	[10.84 - 10.95 - 11.06]	9.29E-40
LAMC1	ECM/STEM	laminin, gamma 1 (formerly LAMB2)	[9.68 - 9.77 - 9.85]	[10.3 - 10.41 - 10.52]	[10.38 - 10.47 - 10.56]	[10.83 - 10.93 - 11.03]	1.28E-58
CDC25B	ECM/STEM	cell division cycle 25 homolog B (S. pombe)	[10.4 - 10.46 - 10.53]	[10.11 - 10.19 - 10.28]	[10.58 - 10.65 - 10.72]	[10.83 - 10.92 - 11]	3.45E-58
SOX4	ECM/STEM	SRY (sex determining region Y)-box 4	[8.81 - 8.92 - 9.02]	[8.69 - 8.87 - 9.04]	[9.91 - 10.03 - 10.16]	[10.76 - 10.91 - 11.06]	1.46E-13
ROBO1	ECM/STEM	roundabout, axon guidance receptor, homolog 1 (Drosophila)	[9.35 - 9.48 - 9.62]	[10.4 - 10.57 - 10.75]	[10.24 - 10.38 - 10.53]	[10.77 - 10.91 - 11.04]	1.20E-26
MAPRE1	ECM/STEM	microtubule-associated protein, RP/EB family, member 1	[10.04 - 10.08 - 10.13]	[10.15 - 10.21 - 10.27]	[10.29 - 10.35 - 10.4]	[10.83 - 10.89 - 10.95]	2.49E-43
CKAP4	ECM/STEM	cytoskeleton-associated protein 4	[9.79 - 9.86 - 9.93]	[9.91 - 10.01 - 10.12]	[10.33 - 10.41 - 10.49]	[10.8 - 10.89 - 10.98]	3.80E-64
PTPN12	ECM/STEM	protein tyrosine phosphatase, non-receptor type 12	[10.21 - 10.25 - 10.3]	[10.36 - 10.43 - 10.49]	[10.49 - 10.55 - 10.6]	[10.78 - 10.84 - 10.89]	1.45E-29
SERPINF1	ECM/STEM	serpin peptidase inhibitor, clade B (ovalbumin), member 1	[10.08 - 10.16 - 10.23]	[10.38 - 10.46 - 10.54]	[10.49 - 10.54 - 10.6]	[10.72 - 10.8 - 10.88]	4.05E-38
COL1A1	ECM/STEM	collagen, type I, alpha 1	[9.73 - 9.87 - 10]	[8.92 - 9.11 - 9.3]	[10.38 - 10.56 - 10.74]	[10.6 - 10.8 - 11]	7.65E-77
ARPC5L	ECM/STEM	actin related protein 2/3 complex, subunit 5-like	[10.25 - 10.3 - 10.35]	[10.21 - 10.27 - 10.33]	[10.37 - 10.43 - 10.48]	[10.7 - 10.77 - 10.83]	5.58E-20
INTS8	ECM/STEM	integrator complex subunit 8	[10.01 - 10.06 - 10.11]	[10.24 - 10.31 - 10.38]	[10.46 - 10.52 - 10.57]	[10.7 - 10.76 - 10.83]	1.04E-30
ATP1B3	ECM/STEM	ATPase, Na+/K+ transporting, beta 3 polypeptide	[9.7 - 9.77 - 9.85]	[9.9 - 10.03 - 10.16]	[10.17 - 10.25 - 10.34]	[10.65 - 10.75 - 10.86]	4.15E-89
MDK	ECM/STEM	midkine (neurite growth-promoting factor 2)	[9.36 - 9.49 - 9.63]	[10.08 - 10.26 - 10.44]	[10.05 - 10.18 - 10.32]	[10.59 - 10.75 - 10.9]	7.09E-30

CDC42EP4	ECM/STEM	CDC42 effector protein (Rho GTPase binding) 4	[10.57 - 10.62 - 10.67]	[10.86 - 10.93 - 11.01]	[10.47 - 10.53 - 10.59]	[10.62 - 10.71 - 10.79]	3.59E-47
UBE2I	ECM/STEM	ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)	[10.11 - 10.17 - 10.22]	[10.2 - 10.27 - 10.34]	[10.23 - 10.3 - 10.37]	[10.61 - 10.69 - 10.77]	3.10E-23
PVRL2	ECM/STEM	poliovirus receptor-related 2 (herpesvirus entry mediator B)	[10.56 - 10.62 - 10.68]	[10.14 - 10.21 - 10.28]	[10.68 - 10.75 - 10.82]	[10.6 - 10.68 - 10.77]	7.84E-11
AMD1	ECM/STEM	adenosylmethionine decarboxylase 1	[9.96 - 10.01 - 10.06]	[9.99 - 10.06 - 10.13]	[10.29 - 10.35 - 10.4]	[10.61 - 10.68 - 10.75]	4.77E-21
MID1IP1	ECM/STEM	MID1 interacting protein 1 (gastrulation specific G12 homolog (zebrafish))	[9.71 - 9.79 - 9.88]	[10.18 - 10.27 - 10.36]	[10.41 - 10.48 - 10.55]	[10.59 - 10.68 - 10.77]	3.67E-43
TMED3	ECM/STEM	transmembrane emp24 protein transport domain containing 3	[9.26 - 9.37 - 9.48]	[8.78 - 8.95 - 9.11]	[10.03 - 10.14 - 10.26]	[10.53 - 10.65 - 10.78]	5.02E-48
S100A11	ECM/STEM	S100 calcium binding protein A11	[9.63 - 9.7 - 9.78]	[9.52 - 9.64 - 9.77]	[10.08 - 10.19 - 10.29]	[10.5 - 10.64 - 10.78]	5.38E-72
TOP2A	ECM/STEM	topoisomerase (DNA) II alpha 170kDa	[8.96 - 9.1 - 9.25]	[9.14 - 9.3 - 9.46]	[9.64 - 9.76 - 9.88]	[10.46 - 10.59 - 10.73]	9.81E-52
CAPZA1	ECM/STEM	capping protein (actin filament) muscle Z-line, alpha 1	[10.04 - 10.11 - 10.18]	[10.07 - 10.17 - 10.28]	[10.15 - 10.23 - 10.31]	[10.49 - 10.58 - 10.68]	4.00E-23
IGF2BP2	ECM/STEM	insulin-like growth factor 2 mRNA binding protein 2	[8.91 - 9.03 - 9.16]	[8.39 - 8.58 - 8.76]	[10.06 - 10.17 - 10.29]	[10.43 - 10.57 - 10.72]	1.54E-31
GNPMB	ECM/STEM	glycoprotein (transmembrane) nmb	[9.77 - 9.87 - 9.97]	[9.52 - 9.65 - 9.78]	[10 - 10.14 - 10.27]	[10.43 - 10.57 - 10.71]	5.78E-33
XPNPEP1	ECM/STEM	X-prolyl aminopeptidase (aminopeptidase P) 1, soluble	[10.12 - 10.16 - 10.2]	[10.28 - 10.34 - 10.39]	[10.39 - 10.43 - 10.48]	[10.51 - 10.56 - 10.62]	1.35E-59
ELF3	ECM/STEM	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	[9.86 - 9.95 - 10.03]	[9.43 - 9.54 - 9.65]	[10.35 - 10.45 - 10.54]	[10.42 - 10.54 - 10.66]	5.69E-25
S100P	ECM/STEM	S100 calcium binding protein P	[8.75 - 8.99 - 9.24]	[8.07 - 8.32 - 8.56]	[10.15 - 10.41 - 10.68]	[10.25 - 10.54 - 10.84]	9.63E-76
ADM	ECM/STEM	adrenomedullin	[9.88 - 9.97 - 10.07]	[10.33 - 10.45 - 10.57]	[9.93 - 10.05 - 10.17]	[10.38 - 10.53 - 10.68]	1.61E-62
SLC38A1	ECM/STEM	solute carrier family 38, member 1	[9.1 - 9.24 - 9.37]	[8.83 - 9 - 9.18]	[9.77 - 9.91 - 10.05]	[10.37 - 10.53 - 10.69]	8.70E-88
S100A6	ECM/STEM	S100 calcium binding protein A6	[9.22 - 9.32 - 9.41]	[8.89 - 9.02 - 9.14]	[9.97 - 10.1 - 10.23]	[10.35 - 10.52 - 10.69]	1.71E-43
RHOQ	ECM/STEM	ras homolog gene family, member Q	[10.1 - 10.15 - 10.21]	[9.99 - 10.07 - 10.15]	[10.32 - 10.39 - 10.46]	[10.43 - 10.51 - 10.6]	2.03E-38
UBE2Z	ECM/STEM	ubiquitin-conjugating enzyme E2Z	[9.81 - 9.86 - 9.91]	[9.96 - 10.02 - 10.09]	[10.01 - 10.07 - 10.12]	[10.39 - 10.47 - 10.54]	2.34E-33
VNN1	ECM/STEM	vanin 1	[11.01 - 11.15 - 11.3]	[8.34 - 8.58 - 8.82]	[11.1 - 11.25 - 11.4]	[10.24 - 10.46 - 10.69]	3.46E-45
SERPINH1	ECM/STEM	serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)	[9.58 - 9.64 - 9.7]	[9.25 - 9.33 - 9.41]	[9.82 - 9.9 - 9.98]	[10.36 - 10.46 - 10.56]	3.52E-44

GNPDA1	ECM/STEM	glucosamine-6-phosphate deaminase 1	[9.74 - 9.79 - 9.85]	[9.87 - 9.95 - 10.03]	[10.11 - 10.18 - 10.25]	[10.37 - 10.45 - 10.52]	1.97E-43
DNMT1	ECM/STEM	DNA (cytosine-5-)-methyltransferase 1	[9.54 - 9.61 - 9.68]	[9.3 - 9.38 - 9.47]	[9.86 - 9.94 - 10.01]	[10.28 - 10.36 - 10.44]	1.79E-47
PELI1	ECM/STEM	pellino homolog 1 (Drosophila)	[9.58 - 9.65 - 9.71]	[9.07 - 9.15 - 9.23]	[9.88 - 9.94 - 10.01]	[10.27 - 10.34 - 10.42]	4.14E-30
UBE2C	ECM/STEM	ubiquitin-conjugating enzyme E2C	[9.13 - 9.24 - 9.35]	[9.02 - 9.16 - 9.3]	[9.58 - 9.68 - 9.78]	[10.21 - 10.34 - 10.46]	1.08E-34
DAB2	ECM/STEM	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	[9.54 - 9.62 - 9.7]	[9.08 - 9.21 - 9.33]	[9.8 - 9.9 - 10]	[10.2 - 10.31 - 10.43]	1.29E-57
VPS37C	ECM/STEM	vacuolar protein sorting 37 homolog C (S. cerevisiae)	[9.68 - 9.72 - 9.76]	[9.65 - 9.71 - 9.78]	[9.97 - 10.02 - 10.07]	[10.23 - 10.29 - 10.35]	1.75E-28
CAMSAP2	ECM/STEM	calmodulin regulated spectrin-associated protein family, member 2	[9.53 - 9.59 - 9.65]	[9.99 - 10.07 - 10.15]	[10.02 - 10.08 - 10.15]	[10.2 - 10.27 - 10.35]	4.59E-23
GLS	ECM/STEM	glutaminase	[9.49 - 9.57 - 9.66]	[8.93 - 9.07 - 9.21]	[10.1 - 10.19 - 10.28]	[10.12 - 10.22 - 10.33]	8.30E-29
KIAA0196	ECM/STEM	KIAA0196	[9.74 - 9.8 - 9.86]	[10.15 - 10.23 - 10.32]	[10.09 - 10.16 - 10.24]	[10.11 - 10.19 - 10.27]	2.26E-21
CHD7	ECM/STEM	chromodomain helicase DNA binding protein 7	[9.31 - 9.36 - 9.42]	[9.79 - 9.87 - 9.95]	[9.57 - 9.64 - 9.72]	[10.09 - 10.19 - 10.29]	1.54E-37
PNMA1	ECM/STEM	paraneoplastic antigen MA1	[8.95 - 9.03 - 9.1]	[8.92 - 9.02 - 9.12]	[9.55 - 9.62 - 9.7]	[10.09 - 10.18 - 10.27]	1.34E-32
CTSC	ECM/STEM	cathepsin C	[9.11 - 9.2 - 9.29]	[9.14 - 9.28 - 9.41]	[9.4 - 9.49 - 9.58]	[10.05 - 10.17 - 10.28]	7.29E-15
LGALS4	ECM/STEM	lectin, galactoside-binding, soluble, 4	[11.39 - 11.56 - 11.72]	[9.43 - 9.71 - 9.98]	[11.25 - 11.46 - 11.68]	[9.86 - 10.16 - 10.45]	2.00E-34
CORO1C	ECM/STEM	coronin, actin binding protein, 1C	[9.4 - 9.45 - 9.5]	[9.54 - 9.63 - 9.71]	[9.64 - 9.7 - 9.77]	[10.08 - 10.15 - 10.22]	5.65E-54
MMP9	ECM/STEM	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	[8.19 - 8.32 - 8.44]	[8.17 - 8.32 - 8.48]	[9.2 - 9.36 - 9.52]	[9.94 - 10.13 - 10.31]	7.23E-43
HN1	ECM/STEM	hematological and neurological expressed 1	[9.27 - 9.33 - 9.39]	[9.31 - 9.4 - 9.48]	[9.47 - 9.53 - 9.6]	[10.04 - 10.12 - 10.2]	1.65E-32
SUCO	ECM/STEM	SUN domain containing ossification factor	[9.43 - 9.51 - 9.58]	[9.83 - 9.92 - 10.01]	[9.86 - 9.94 - 10.01]	[10.02 - 10.1 - 10.17]	3.54E-34
LRRC1	ECM/STEM	leucine rich repeat containing 1	[8.53 - 8.66 - 8.79]	[8.11 - 8.3 - 8.49]	[9.52 - 9.62 - 9.72]	[9.96 - 10.08 - 10.21]	2.13E-53
COL5A2	ECM/STEM	collagen, type V, alpha 2	[9.11 - 9.22 - 9.32]	[8.75 - 8.87 - 8.99]	[9.51 - 9.63 - 9.75]	[9.91 - 10.06 - 10.22]	1.52E-35
VCAN	ECM/STEM	versican	[8.51 - 8.65 - 8.79]	[7.77 - 7.96 - 8.15]	[9.3 - 9.49 - 9.68]	[9.83 - 10.04 - 10.24]	7.34E-42
SOX9	ECM/STEM	SRY (sex determining region Y)-box 9	[8.32 - 8.46 - 8.6]	[8.51 - 8.72 - 8.93]	[9.37 - 9.5 - 9.64]	[9.84 - 10.04 - 10.23]	4.08E-38
DRAM1	ECM/STEM	DNA-damage regulated autophagy modulator 1	[9.25 - 9.31 - 9.37]	[9.34 - 9.41 - 9.49]	[9.56 - 9.62 - 9.68]	[9.95 - 10.04 - 10.12]	5.33E-37
PLBD1	ECM/STEM	phospholipase B domain containing 1	[8.78 - 8.87 - 8.96]	[8.2 - 8.33 - 8.45]	[9.09 - 9.21 - 9.32]	[9.87 - 10.03 - 10.18]	2.70E-44
TPX2	ECM/STEM	TPX2, microtubule-associated, homolog (Xenopus laevis)	[8.94 - 9.03 - 9.12]	[8.92 - 9.04 - 9.15]	[9.18 - 9.27 - 9.37]	[9.91 - 10.02 - 10.13]	3.64E-59
TMEM165	ECM/STEM	transmembrane protein 165	[9.4 - 9.44 - 9.49]	[9.41 - 9.48 - 9.55]	[9.65 - 9.7 - 9.75]	[9.94 - 10.01 - 10.08]	6.13E-52
PAFAH1B3	ECM/STEM	platelet-activating factor acetylhydrolase 1b, catalytic subunit 3 (29kDa)	[8.89 - 8.97 - 9.05]	[8.8 - 8.9 - 9]	[9.41 - 9.48 - 9.56]	[9.91 - 10 - 10.09]	1.15E-51

CTNNAL1	ECM/STEM	catenin (cadherin-associated protein), alpha-like 1	[9.43 - 9.5 - 9.56]	[10.18 - 10.26 - 10.34]	[9.59 - 9.67 - 9.76]	[9.91 - 10 - 10.09]	3.11E-12
UBR5	ECM/STEM	ubiquitin protein ligase E3 component n-recognin 5	[9.25 - 9.31 - 9.37]	[9.62 - 9.71 - 9.79]	[9.62 - 9.69 - 9.76]	[9.87 - 9.94 - 10.01]	4.67E-18
ZNF189	ECM/STEM	zinc finger protein 189	[9.19 - 9.26 - 9.32]	[9.9 - 9.98 - 10.06]	[9.58 - 9.66 - 9.73]	[9.84 - 9.92 - 10.01]	2.15E-77
IL8	ECM/STEM	interleukin 8	[8.28 - 8.45 - 8.62]	[7.69 - 7.86 - 8.03]	[9.24 - 9.43 - 9.63]	[9.67 - 9.9 - 10.12]	3.32E-49
WARS	ECM/STEM	tryptophanyl-tRNA synthetase	[9.33 - 9.39 - 9.45]	[9.41 - 9.49 - 9.56]	[9.57 - 9.64 - 9.71]	[9.78 - 9.89 - 9.99]	9.56E-76
VIL1	ECM/STEM	villin 1	[8.25 - 8.42 - 8.59]	[7.76 - 7.98 - 8.2]	[9.24 - 9.42 - 9.6]	[9.66 - 9.88 - 10.11]	8.27E-36
SPAG5	ECM/STEM	sperm associated antigen 5	[9.51 - 9.58 - 9.66]	[8.96 - 9.07 - 9.18]	[9.45 - 9.54 - 9.62]	[9.78 - 9.88 - 9.98]	5.44E-43
VAT1	ECM/STEM	vesicle amine transport protein 1 homolog (T. californica)	[9.26 - 9.32 - 9.38]	[9.55 - 9.65 - 9.75]	[9.58 - 9.65 - 9.72]	[9.78 - 9.86 - 9.94]	1.20E-42
ETV5	ECM/STEM	ets variant 5	[8.88 - 8.95 - 9.02]	[8.69 - 8.79 - 8.88]	[9.27 - 9.36 - 9.45]	[9.74 - 9.84 - 9.94]	1.72E-34
AGO2	ECM/STEM	argonaute RISC catalytic component 2	[9 - 9.06 - 9.12]	[9.34 - 9.43 - 9.51]	[9.45 - 9.52 - 9.58]	[9.73 - 9.81 - 9.9]	6.42E-52
LHFPL2	ECM/STEM	lipoma HMGIC fusion partner-like 2	[8.62 - 8.7 - 8.78]	[8.76 - 8.89 - 9.02]	[9.23 - 9.33 - 9.43]	[9.67 - 9.79 - 9.91]	6.40E-31
LAMB1	ECM/STEM	laminin, beta 1	[8.65 - 8.73 - 8.81]	[8.24 - 8.35 - 8.46]	[9.08 - 9.19 - 9.3]	[9.65 - 9.78 - 9.9]	1.58E-25
NCAPG	ECM/STEM	non-SMC condensin I complex, subunit G	[8.39 - 8.5 - 8.61]	[8.6 - 8.72 - 8.84]	[8.87 - 8.97 - 9.08]	[9.61 - 9.72 - 9.83]	1.65E-47
LPCAT1	ECM/STEM	lysophosphatidylcholine acyltransferase 1	[8.55 - 8.62 - 8.7]	[8.65 - 8.77 - 8.89]	[9.08 - 9.17 - 9.25]	[9.61 - 9.7 - 9.8]	1.49E-41
ARID5B	ECM/STEM	AT rich interactive domain 5B (MRF1-like)	[8.84 - 8.9 - 8.97]	[8.79 - 8.87 - 8.96]	[9.25 - 9.31 - 9.38]	[9.6 - 9.69 - 9.78]	6.84E-21
YEATS2	ECM/STEM	YEATS domain containing 2	[8.69 - 8.75 - 8.8]	[8.72 - 8.79 - 8.86]	[9.1 - 9.15 - 9.2]	[9.59 - 9.66 - 9.73]	8.61E-36
LCN2	ECM/STEM	lipocalin 2	[8.66 - 8.87 - 9.08]	[10.6 - 10.84 - 11.09]	[9.98 - 10.19 - 10.41]	[9.39 - 9.64 - 9.89]	5.34E-38
LUM	ECM/STEM	lumican	[9.18 - 9.37 - 9.57]	[7.45 - 7.72 - 7.99]	[9.37 - 9.65 - 9.92]	[9.37 - 9.64 - 9.91]	9.72E-44
SLC52A2	ECM/STEM	solute carrier family 52 (riboflavin transporter), member 2	[8.92 - 8.98 - 9.04]	[9.02 - 9.1 - 9.18]	[9.26 - 9.34 - 9.42]	[9.54 - 9.63 - 9.72]	5.86E-46
GPD1L	ECM/STEM	glycerol-3-phosphate dehydrogenase 1-like	[8.66 - 8.75 - 8.84]	[8.41 - 8.52 - 8.63]	[9.23 - 9.32 - 9.41]	[9.5 - 9.61 - 9.71]	7.01E-65
MTHFD2	ECM/STEM	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	[8.6 - 8.68 - 8.75]	[8.38 - 8.49 - 8.6]	[8.79 - 8.89 - 9]	[9.45 - 9.6 - 9.74]	1.73E-36
TIMELESS	ECM/STEM	timeless homolog (Drosophila)	[9.3 - 9.36 - 9.43]	[9.1 - 9.17 - 9.25]	[9.18 - 9.25 - 9.32]	[9.48 - 9.56 - 9.64]	4.79E-38
TESC	ECM/STEM	tescalcin	[8.22 - 8.32 - 8.42]	[8.08 - 8.22 - 8.37]	[8.89 - 9.03 - 9.17]	[9.38 - 9.55 - 9.72]	1.37E-46
PLEKHB2	ECM/STEM	pleckstrin homology domain containing, family B (evectins) member 2	[8.85 - 8.91 - 8.97]	[8.92 - 9 - 9.08]	[9.11 - 9.17 - 9.24]	[9.43 - 9.51 - 9.59]	2.70E-40
RFC5	ECM/STEM	replication factor C (activator 1) 5, 36.5kDa	[9.3 - 9.37 - 9.45]	[9.11 - 9.17 - 9.24]	[9.13 - 9.2 - 9.27]	[9.4 - 9.48 - 9.56]	5.91E-47
ARHGEF2	ECM/STEM	Rho/Rac guanine nucleotide exchange factor (GEF) 2	[8.35 - 8.42 - 8.48]	[8.32 - 8.4 - 8.49]	[8.88 - 8.95 - 9.03]	[9.4 - 9.48 - 9.56]	3.44E-27
TUBB3	ECM/STEM	tubulin, beta 3	[8.54 - 8.61 - 8.68]	[8.48 - 8.56 - 8.65]	[8.98 - 9.07 - 9.16]	[9.35 - 9.48 - 9.6]	9.81E-22
COLGALT1	ECM/STEM	collagen beta(1-O)galactosyltransferase 1	[9.22 - 9.27 - 9.32]	[9.1 - 9.17 - 9.23]	[9.19 - 9.25 - 9.31]	[9.4 - 9.48 - 9.55]	7.94E-21
ASNS	ECM/STEM	asparagine synthetase (glutamine-hydrolyzing)	[7.67 - 7.79 - 7.9]	[7.67 - 7.85 - 8.02]	[8.75 - 8.89 - 9.04]	[9.31 - 9.47 - 9.64]	1.32E-49
CLSTN1	ECM/STEM	calsyntenin 1	[8.75 - 8.82 - 8.89]	[8.73 - 8.83 - 8.92]	[9.03 - 9.1 - 9.17]	[9.36 - 9.45 - 9.54]	2.40E-21
MST4	ECM/STEM	serine/threonine protein kinase MST4	[8.91 - 9 - 9.09]	[8.33 - 8.49 - 8.65]	[9.28 - 9.38 - 9.48]	[9.34 - 9.45 - 9.56]	6.88E-25
CAPG	ECM/STEM	capping protein (actin filament), gelsolin-like	[8.17 - 8.28 - 8.38]	[7.78 - 7.92 - 8.06]	[8.9 - 9.02 - 9.15]	[9.3 - 9.44 - 9.57]	5.54E-26
KRT23	ECM/STEM	keratin 23 (histone deacetylase inducible)	[7.85 - 8.04 - 8.23]	[7.85 - 8.11 - 8.36]	[9.2 - 9.43 - 9.65]	[9.16 - 9.43 - 9.7]	1.14E-29
MAPK13	ECM/STEM	mitogen-activated protein kinase 13	[7.55 - 7.65 - 7.75]	[7.14 - 7.25 - 7.36]	[8.44 - 8.57 - 8.7]	[9.26 - 9.41 - 9.55]	5.09E-76
UGCG	ECM/STEM	UDP-glucose ceramide glucosyltransferase	[9.13 - 9.2 - 9.28]	[8.59 - 8.7 - 8.8]	[9.15 - 9.23 - 9.31]	[9.3 - 9.39 - 9.48]	3.20E-30
PHF21A	ECM/STEM	PHD finger protein 21A	[8.62 - 8.67 - 8.73]	[8.69 - 8.76 - 8.84]	[9.02 - 9.07 - 9.13]	[9.32 - 9.39 - 9.45]	4.63E-62
SOBP	ECM/STEM	sine oculis binding protein homolog (Drosophila)	[8.05 - 8.17 - 8.29]	[7.51 - 7.69 - 7.87]	[8.69 - 8.84 - 8.98]	[9.17 - 9.36 - 9.55]	9.15E-45
MTMR2	ECM/STEM	myotubularin related protein 2	[8.45 - 8.52 - 8.59]	[8.17 - 8.28 - 8.4]	[8.77 - 8.85 - 8.93]	[9.28 - 9.36 - 9.44]	3.23E-28
G6PC3	ECM/STEM	glucose 6 phosphatase, catalytic, 3	[8.97 - 9.01 - 9.06]	[9.07 - 9.12 - 9.17]	[8.99 - 9.06 - 9.12]	[9.26 - 9.35 - 9.44]	1.17E-42
P2RX4	ECM/STEM	purinergic receptor P2X, ligand-gated ion channel, 4	[8.65 - 8.72 - 8.79]	[8.46 - 8.55 - 8.64]	[8.98 - 9.05 - 9.12]	[9.25 - 9.33 - 9.42]	8.07E-34

RNF44	ECM/STEM	ring finger protein 44	[8.67 - 8.72 - 8.76]	[9.09 - 9.17 - 9.24]	[9.02 - 9.07 - 9.13]	[9.24 - 9.31 - 9.39]	6.16E-30
STX3	ECM/STEM	syntaxin 3	[8.27 - 8.34 - 8.41]	[8.22 - 8.34 - 8.45]	[8.69 - 8.79 - 8.88]	[9.19 - 9.3 - 9.4]	5.37E-43
H2AFY2	ECM/STEM	H2A histone family, member Y2	[7.72 - 7.82 - 7.92]	[8.19 - 8.34 - 8.5]	[8.73 - 8.86 - 8.99]	[9.14 - 9.3 - 9.46]	8.42E-43
ARID3A	ECM/STEM	AT rich interactive domain 3A (BRIGHT-like)	[7.74 - 7.81 - 7.88]	[7.79 - 7.89 - 7.99]	[8.55 - 8.67 - 8.78]	[9.13 - 9.29 - 9.45]	4.17E-27
CDC42EP1	ECM/STEM	CDC42 effector protein (Rho GTPase binding) 1	[8.68 - 8.74 - 8.8]	[8.46 - 8.54 - 8.62]	[8.99 - 9.06 - 9.13]	[9.16 - 9.26 - 9.35]	1.15E-69
VNN2	ECM/STEM	vanin 2	[8.37 - 8.51 - 8.65]	[7.31 - 7.47 - 7.63]	[9.02 - 9.18 - 9.35]	[9.05 - 9.23 - 9.42]	1.59E-62
TRAF5	ECM/STEM	TNF receptor-associated factor 5	[7.97 - 8.06 - 8.15]	[8.05 - 8.17 - 8.29]	[8.77 - 8.87 - 8.97]	[9.11 - 9.23 - 9.34]	3.95E-42
POSTN	ECM/STEM	periostin, osteoblast specific factor	[7.81 - 7.98 - 8.15]	[7.21 - 7.41 - 7.61]	[8.58 - 8.78 - 8.98]	[9 - 9.22 - 9.45]	1.68E-49
TP53BP1	ECM/STEM	tumor protein p53 binding protein 1	[8.71 - 8.75 - 8.8]	[8.8 - 8.86 - 8.92]	[8.92 - 8.96 - 9.01]	[9.15 - 9.21 - 9.28]	2.09E-38
KDEL3	ECM/STEM	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	[8.61 - 8.73 - 8.85]	[7.88 - 8.03 - 8.19]	[8.97 - 9.08 - 9.2]	[9.07 - 9.21 - 9.35]	1.98E-41
TACC3	ECM/STEM	transforming, acidic coiled-coil containing protein 3	[8.23 - 8.3 - 8.37]	[8.21 - 8.3 - 8.4]	[8.55 - 8.62 - 8.69]	[9.11 - 9.2 - 9.3]	5.84E-68
S100A9	ECM/STEM	S100 calcium binding protein A9	[8.03 - 8.15 - 8.28]	[7.6 - 7.76 - 7.92]	[8.42 - 8.56 - 8.7]	[8.96 - 9.2 - 9.44]	1.66E-19
DKK1	ECM/STEM	dickkopf homolog 1 (Xenopus laevis)	[5.73 - 5.86 - 5.99]	[7.28 - 7.64 - 8.01]	[6.89 - 7.1 - 7.31]	[8.86 - 9.18 - 9.49]	1.70E-35
RAB15	ECM/STEM	RAB15, member RAS oncogene family	[8.66 - 8.74 - 8.81]	[9.25 - 9.34 - 9.44]	[9.09 - 9.16 - 9.23]	[9.08 - 9.17 - 9.26]	1.94E-71
UCHL1	ECM/STEM	ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)	[7.8 - 7.92 - 8.03]	[7.43 - 7.58 - 7.73]	[8.2 - 8.35 - 8.5]	[8.92 - 9.17 - 9.42]	2.77E-14
LYN	ECM/STEM	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	[8.62 - 8.69 - 8.77]	[8.92 - 9.01 - 9.11]	[8.93 - 9.01 - 9.08]	[9.06 - 9.16 - 9.26]	1.18E-45
DLG5	ECM/STEM	discs, large homolog 5 (Drosophila)	[8.24 - 8.32 - 8.4]	[9.07 - 9.16 - 9.26]	[8.68 - 8.75 - 8.82]	[9.04 - 9.13 - 9.22]	2.90E-29
GPX7	ECM/STEM	glutathione peroxidase 7	[8.21 - 8.32 - 8.44]	[7.76 - 7.89 - 8.03]	[8.55 - 8.66 - 8.77]	[8.99 - 9.13 - 9.27]	9.60E-57
NSMAF	ECM/STEM	neutral sphingomyelinase (N-SMase) activation associated factor	[8.26 - 8.32 - 8.39]	[8.57 - 8.66 - 8.75]	[8.86 - 8.93 - 8.99]	[9.05 - 9.13 - 9.2]	4.83E-25
ZNF532	ECM/STEM	zinc finger protein 532	[8.07 - 8.13 - 8.2]	[7.89 - 7.97 - 8.05]	[8.55 - 8.64 - 8.72]	[9.03 - 9.13 - 9.22]	1.12E-43
STK17A	ECM/STEM	serine/threonine kinase 17a	[8.32 - 8.39 - 8.46]	[8.61 - 8.7 - 8.79]	[8.79 - 8.87 - 8.94]	[9.03 - 9.12 - 9.2]	9.31E-10
ADAM9	ECM/STEM	ADAM metalloproteinase domain 9	[8.18 - 8.25 - 8.33]	[8.49 - 8.58 - 8.68]	[8.34 - 8.42 - 8.5]	[8.98 - 9.09 - 9.19]	2.32E-53
GTF2IRD1	ECM/STEM	GTF2I repeat domain containing 1	[8.6 - 8.68 - 8.76]	[9.15 - 9.24 - 9.33]	[8.68 - 8.75 - 8.82]	[9 - 9.08 - 9.15]	3.24E-42
C1orf106	ECM/STEM	chromosome 1 open reading frame 106	[7.7 - 7.85 - 8.01]	[6.96 - 7.16 - 7.35]	[8.62 - 8.79 - 8.95]	[8.89 - 9.07 - 9.25]	7.52E-66
VRK1	ECM/STEM	vaccinia related kinase 1	[8.5 - 8.56 - 8.63]	[8.28 - 8.36 - 8.43]	[8.62 - 8.68 - 8.74]	[8.98 - 9.06 - 9.14]	1.19E-45
BICC1	ECM/STEM	bicaudal C homolog 1 (Drosophila)	[7.38 - 7.5 - 7.63]	[7.06 - 7.25 - 7.45]	[8.26 - 8.4 - 8.55]	[8.83 - 9.01 - 9.18]	5.05E-64
TPM4	ECM/STEM	tropomyosin 4	[8.1 - 8.17 - 8.23]	[7.94 - 8.04 - 8.15]	[8.43 - 8.51 - 8.6]	[8.85 - 8.97 - 9.09]	5.02E-34
MMP12	ECM/STEM	matrix metalloproteinase 12 (macrophage elastase)	[5.95 - 6.1 - 6.25]	[6.59 - 6.82 - 7.04]	[7.34 - 7.56 - 7.78]	[8.66 - 8.95 - 9.24]	5.79E-18
CEP55	ECM/STEM	centrosomal protein 55kDa	[7.44 - 7.52 - 7.61]	[7.48 - 7.59 - 7.71]	[8.06 - 8.15 - 8.24]	[8.83 - 8.95 - 9.07]	2.24E-34
PDGFRA	ECM/STEM	platelet-derived growth factor receptor, alpha polypeptide	[8.24 - 8.37 - 8.5]	[7.15 - 7.32 - 7.49]	[8.44 - 8.62 - 8.8]	[8.72 - 8.92 - 9.12]	1.11E-48
DSG2	ECM/STEM	desmoglein 2	[8.33 - 8.42 - 8.52]	[7.53 - 7.69 - 7.84]	[8.43 - 8.53 - 8.64]	[8.78 - 8.91 - 9.05]	8.79E-22
TCF7L1	ECM/STEM	transcription factor 7-like 1 (T-cell specific, HMG-box)	[8.98 - 9.05 - 9.11]	[8.14 - 8.23 - 8.33]	[8.74 - 8.82 - 8.9]	[8.81 - 8.91 - 9.01]	1.13E-47
SPHK1	ECM/STEM	sphingosine kinase 1	[7.41 - 7.5 - 7.6]	[7.22 - 7.37 - 7.52]	[7.94 - 8.07 - 8.19]	[8.73 - 8.89 - 9.05]	8.91E-59
HK2	ECM/STEM	hexokinase 2	[7.3 - 7.39 - 7.48]	[7.22 - 7.34 - 7.46]	[7.96 - 8.1 - 8.24]	[8.68 - 8.85 - 9.03]	3.30E-37
RIT1	ECM/STEM	Ras-like without CAAX 1	[8.28 - 8.34 - 8.39]	[8.28 - 8.34 - 8.41]	[8.46 - 8.53 - 8.6]	[8.76 - 8.85 - 8.95]	4.85E-25
NDUFA4L2	ECM/STEM	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2	[8.06 - 8.13 - 8.21]	[8.01 - 8.09 - 8.18]	[8.26 - 8.36 - 8.46]	[8.7 - 8.85 - 9]	1.11E-15
SALL2	ECM/STEM	sal-like 2 (Drosophila)	[7.24 - 7.35 - 7.46]	[6.91 - 7.05 - 7.19]	[8.1 - 8.24 - 8.38]	[8.67 - 8.85 - 9.02]	2.48E-29
ARHGEF3	ECM/STEM	Rho guanine nucleotide exchange factor (GEF) 3	[8.16 - 8.24 - 8.31]	[8.09 - 8.21 - 8.34]	[8.69 - 8.78 - 8.88]	[8.75 - 8.84 - 8.93]	3.12E-54
SULF1	ECM/STEM	sulfatase 1	[7.54 - 7.68 - 7.82]	[6.89 - 7.05 - 7.22]	[8.51 - 8.72 - 8.92]	[8.62 - 8.84 - 9.06]	2.65E-39
STEAP1	ECM/STEM	six transmembrane epithelial antigen of the prostate 1	[8.08 - 8.23 - 8.38]	[8.79 - 8.99 - 9.19]	[8.39 - 8.55 - 8.71]	[8.67 - 8.84 - 9.01]	1.31E-30
CENPA	ECM/STEM	centromere protein A	[7.77 - 7.87 - 7.97]	[7.74 - 7.85 - 7.97]	[8.08 - 8.17 - 8.27]	[8.73 - 8.83 - 8.93]	1.57E-55

SLC25A24	ECM/STEM	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 24	[8.13 - 8.22 - 8.31]	[7.81 - 7.95 - 8.08]	[8.33 - 8.44 - 8.55]	[8.68 - 8.82 - 8.96]	4.98E-39
G6PD	ECM/STEM	glucose-6-phosphate dehydrogenase	[7.35 - 7.43 - 7.52]	[7.75 - 7.89 - 8.02]	[7.95 - 8.05 - 8.15]	[8.66 - 8.8 - 8.95]	4.50E-71
SLC12A8	ECM/STEM	solute carrier family 12 (potassium/chloride transporters), member 8	[8.15 - 8.24 - 8.33]	[7.5 - 7.63 - 7.75]	[8.53 - 8.63 - 8.73]	[8.69 - 8.8 - 8.91]	2.79E-67
C12orf49	ECM/STEM	chromosome 12 open reading frame 49	[7.91 - 7.97 - 8.03]	[7.79 - 7.88 - 7.98]	[8.3 - 8.37 - 8.44]	[8.67 - 8.76 - 8.85]	3.18E-69
HILPDA	ECM/STEM	hypoxia inducible lipid droplet-associated	[7.83 - 7.9 - 7.97]	[7.82 - 7.91 - 8]	[7.96 - 8.03 - 8.11]	[8.6 - 8.72 - 8.84]	4.33E-15
TRIP13	ECM/STEM	thyroid hormone receptor interactor 13	[7.54 - 7.63 - 7.73]	[7.66 - 7.79 - 7.91]	[7.88 - 7.96 - 8.05]	[8.6 - 8.72 - 8.84]	7.44E-38
PSRC1	ECM/STEM	proline/serine-rich coiled-coil 1	[7.93 - 7.99 - 8.05]	[8.05 - 8.13 - 8.21]	[8.15 - 8.23 - 8.3]	[8.62 - 8.71 - 8.81]	6.52E-51
AGPAT5	ECM/STEM	1-acylglycerol-3-phosphate O-acyltransferase 5 (lysophosphatidic acid acyltransferase, epsilon)	[8.72 - 8.83 - 8.93]	[8.05 - 8.17 - 8.29]	[8.49 - 8.58 - 8.67]	[8.58 - 8.7 - 8.81]	5.26E-47
MUC13	ECM/STEM	mucin 13, cell surface associated	[8.61 - 8.79 - 8.96]	[7.02 - 7.21 - 7.4]	[8.97 - 9.19 - 9.41]	[8.42 - 8.68 - 8.95]	2.42E-52
SMOX	ECM/STEM	spermine oxidase	[7.66 - 7.72 - 7.78]	[7.68 - 7.78 - 7.87]	[8.07 - 8.15 - 8.23]	[8.57 - 8.67 - 8.77]	1.09E-81
DLGAP5	ECM/STEM	discs, large (Drosophila) homolog-associated protein 5	[7.24 - 7.34 - 7.45]	[7.33 - 7.47 - 7.6]	[7.76 - 7.87 - 7.98]	[8.54 - 8.67 - 8.81]	2.31E-48
BLM	ECM/STEM	Bloom syndrome, RecQ helicase-like	[7.57 - 7.66 - 7.76]	[7.29 - 7.4 - 7.51]	[8.04 - 8.14 - 8.23]	[8.55 - 8.66 - 8.77]	2.69E-40
ASAP1	ECM/STEM	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1	[7.52 - 7.59 - 7.67]	[7.9 - 8.02 - 8.14]	[8.18 - 8.27 - 8.35]	[8.54 - 8.66 - 8.77]	3.12E-30
CDC7	ECM/STEM	cell division cycle 7 homolog (S. cerevisiae)	[7.94 - 8.03 - 8.12]	[7.62 - 7.71 - 7.81]	[8.18 - 8.27 - 8.36]	[8.54 - 8.64 - 8.74]	1.37E-15
SLC4A7	ECM/STEM	solute carrier family 4, sodium bicarbonate cotransporter, member 7	[7.9 - 7.97 - 8.04]	[7.6 - 7.7 - 7.8]	[8.12 - 8.21 - 8.29]	[8.46 - 8.56 - 8.66]	7.83E-72
BUB1B	ECM/STEM	budding uninhibited by benzimidazoles 1 homolog beta (yeast)	[7.33 - 7.42 - 7.52]	[7.37 - 7.48 - 7.59]	[7.69 - 7.78 - 7.87]	[8.38 - 8.49 - 8.61]	4.78E-54
KIF2C	ECM/STEM	kinesin family member 2C	[7.37 - 7.45 - 7.54]	[7.42 - 7.53 - 7.63]	[7.79 - 7.88 - 7.97]	[8.37 - 8.47 - 8.58]	3.01E-46
KIF11	ECM/STEM	kinesin family member 11	[7.16 - 7.25 - 7.35]	[7.32 - 7.43 - 7.54]	[7.58 - 7.68 - 7.79]	[8.34 - 8.46 - 8.57]	1.84E-45
F2RL1	ECM/STEM	coagulation factor II (thrombin) receptor-like 1	[8.51 - 8.66 - 8.8]	[7.25 - 7.43 - 7.61]	[8.67 - 8.83 - 8.98]	[8.28 - 8.45 - 8.63]	1.25E-75
SHCBP1	ECM/STEM	SHC SH2-domain binding protein 1	[7.56 - 7.65 - 7.73]	[7.71 - 7.81 - 7.91]	[7.93 - 8.02 - 8.1]	[8.32 - 8.43 - 8.54]	8.28E-35
KIF4A	ECM/STEM	kinesin family member 4A	[7.34 - 7.43 - 7.53]	[7.3 - 7.44 - 7.58]	[7.7 - 7.81 - 7.93]	[8.28 - 8.42 - 8.56]	4.19E-45
GNAZ	ECM/STEM	guanine nucleotide binding protein (G protein), alpha z polypeptide	[7.78 - 7.89 - 7.99]	[7.38 - 7.49 - 7.6]	[8.24 - 8.35 - 8.46]	[8.3 - 8.42 - 8.54]	3.61E-31
STK39	ECM/STEM	serine threonine kinase 39	[7.25 - 7.35 - 7.45]	[7.42 - 7.57 - 7.71]	[8.19 - 8.29 - 8.39]	[8.27 - 8.41 - 8.55]	2.34E-08
MGAT4A	ECM/STEM	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme A	[7.85 - 7.92 - 8]	[7.58 - 7.69 - 7.79]	[8.21 - 8.28 - 8.34]	[8.31 - 8.4 - 8.5]	3.22E-51
SFI1	ECM/STEM	Sfi1 homolog, spindle assembly associated (yeast)	[7.64 - 7.69 - 7.74]	[7.51 - 7.58 - 7.66]	[7.93 - 8 - 8.07]	[8.3 - 8.4 - 8.5]	1.77E-27
BUB1	ECM/STEM	budding uninhibited by benzimidazoles 1 homolog (yeast)	[6.92 - 7.02 - 7.13]	[7.14 - 7.28 - 7.42]	[7.44 - 7.55 - 7.67]	[8.26 - 8.39 - 8.51]	7.51E-50
EPS8L3	ECM/STEM	EPS8-like 3	[6.77 - 6.89 - 7]	[7.92 - 8.12 - 8.32]	[7.84 - 7.98 - 8.13]	[8.2 - 8.37 - 8.54]	9.11E-55
KIF23	ECM/STEM	kinesin family member 23	[6.99 - 7.09 - 7.19]	[6.91 - 7.02 - 7.13]	[7.31 - 7.41 - 7.5]	[8.19 - 8.31 - 8.43]	2.50E-51
SSUH2	ECM/STEM	ssu-2 homolog (C. elegans)	[7.07 - 7.21 - 7.35]	[7.68 - 7.9 - 8.12]	[8.1 - 8.28 - 8.47]	[8.04 - 8.25 - 8.46]	8.93E-25
CENPE	ECM/STEM	centromere protein E, 312kDa	[7.02 - 7.12 - 7.22]	[7.07 - 7.19 - 7.31]	[7.43 - 7.53 - 7.64]	[8.11 - 8.24 - 8.37]	2.71E-43
ASRGL1	ECM/STEM	asparaginase like 1	[7.58 - 7.69 - 7.8]	[6.95 - 7.06 - 7.16]	[7.64 - 7.76 - 7.88]	[7.99 - 8.14 - 8.28]	3.10E-32
MEP1A	ECM/STEM	mepirin A, alpha (PABA peptide hydrolase)	[6.32 - 6.53 - 6.74]	[5.52 - 5.68 - 5.84]	[7.17 - 7.41 - 7.64]	[7.79 - 8.09 - 8.39]	3.09E-31
SLC7A1	ECM/STEM	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	[6.65 - 6.73 - 6.82]	[6.84 - 6.96 - 7.09]	[7.43 - 7.52 - 7.61]	[7.9 - 8.01 - 8.12]	3.59E-20
SYNGR1	ECM/STEM	synaptogyrin 1	[7.25 - 7.36 - 7.47]	[7.92 - 8.08 - 8.23]	[7.83 - 7.95 - 8.07]	[7.76 - 7.9 - 8.03]	1.42E-49
HOMER1	ECM/STEM	homer homolog 1 (Drosophila)	[6.9 - 7.04 - 7.17]	[6.26 - 6.43 - 6.6]	[7.47 - 7.6 - 7.72]	[7.65 - 7.78 - 7.92]	2.55E-44
COCH	ECM/STEM	coagulation factor C homolog, cochlin (Limulus polyphemus)	[7.28 - 7.47 - 7.65]	[6.11 - 6.29 - 6.48]	[7.59 - 7.78 - 7.96]	[7.57 - 7.78 - 7.99]	2.94E-33

PLXNC1	ECM/STEM	plexin C1	[7.44 - 7.54 - 7.64]	[6.58 - 6.69 - 6.81]	[7.66 - 7.75 - 7.85]	[7.6 - 7.71 - 7.83]	2.31E-62
NRCAM	ECM/STEM	neuronal cell adhesion molecule	[6.12 - 6.27 - 6.43]	[7.12 - 7.44 - 7.75]	[7.29 - 7.48 - 7.66]	[7.36 - 7.57 - 7.78]	1.42E-08
LRRC8B	ECM/STEM	leucine rich repeat containing 8 family, member B	[6.8 - 6.88 - 6.95]	[6.37 - 6.47 - 6.58]	[7.13 - 7.22 - 7.31]	[7.33 - 7.45 - 7.57]	7.62E-23
APOA1	PERIPORTAL	apolipoprotein A-I	[14.26 - 14.31 - 14.37]	[13.27 - 13.42 - 13.58]	[13.66 - 13.77 - 13.89]	[12.64 - 12.87 - 13.11]	4.32E-89
HRG	PERIPORTAL	histidine-rich glycoprotein	[14.23 - 14.28 - 14.34]	[12.72 - 12.94 - 13.17]	[13.34 - 13.46 - 13.58]	[11.28 - 11.52 - 11.77]	6.81E-113
ALDOB	PERIPORTAL	aldolase B, fructose-bisphosphate	[14.15 - 14.2 - 14.25]	[12.76 - 12.93 - 13.1]	[13.61 - 13.68 - 13.75]	[11.58 - 11.82 - 12.06]	7.62E-55
HPX	PERIPORTAL	hemopexin	[13.95 - 14 - 14.06]	[13.19 - 13.32 - 13.45]	[13.33 - 13.43 - 13.52]	[11.85 - 12.04 - 12.23]	2.20E-76
PLG	PERIPORTAL	plasminogen	[13.44 - 13.51 - 13.57]	[13.26 - 13.38 - 13.49]	[12.66 - 12.76 - 12.87]	[11.12 - 11.35 - 11.59]	3.79E-95
CPS1	PERIPORTAL	carbamoyl-phosphate synthase 1, mitochondrial	[13.33 - 13.42 - 13.51]	[12.93 - 13.11 - 13.28]	[12.6 - 12.75 - 12.9]	[10.84 - 11.1 - 11.36]	2.87E-48
ARG1	PERIPORTAL	arginase, liver	[13.33 - 13.41 - 13.48]	[11.88 - 12.07 - 12.25]	[12.75 - 12.85 - 12.96]	[10.92 - 11.15 - 11.37]	3.81E-47
AGXT	PERIPORTAL	alanine-glyoxylate aminotransferase	[13.28 - 13.34 - 13.41]	[12.18 - 12.34 - 12.5]	[12.59 - 12.69 - 12.79]	[10.77 - 11.01 - 11.24]	3.09E-90
F9	PERIPORTAL	coagulation factor IX	[13.19 - 13.27 - 13.36]	[11.67 - 11.88 - 12.09]	[12.24 - 12.36 - 12.48]	[9.77 - 10.04 - 10.32]	8.12E-65
ADH1A	PERIPORTAL	alcohol dehydrogenase 1A (class I), alpha polypeptide	[13.15 - 13.25 - 13.35]	[13.08 - 13.25 - 13.42]	[12.96 - 13.07 - 13.17]	[11.26 - 11.51 - 11.75]	6.34E-76
DCXR	PERIPORTAL	dicarbonyl/L-xylulose reductase	[13.14 - 13.2 - 13.26]	[13.49 - 13.57 - 13.65]	[12.2 - 12.28 - 12.35]	[11.21 - 11.32 - 11.44]	8.45E-86
ASS1	PERIPORTAL	argininosuccinate synthase 1	[12.97 - 13.04 - 13.12]	[12.56 - 12.64 - 12.71]	[12.43 - 12.5 - 12.56]	[11.76 - 11.87 - 11.98]	2.56E-73
BHMT	PERIPORTAL	betaine--homocysteine S-methyltransferase	[12.9 - 13 - 13.11]	[12.41 - 12.55 - 12.69]	[11.74 - 11.88 - 12.01]	[9.97 - 10.18 - 10.4]	5.33E-108
SLC10A1	PERIPORTAL	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	[12.65 - 12.73 - 12.82]	[11.49 - 11.68 - 11.86]	[11.2 - 11.34 - 11.48]	[8.17 - 8.4 - 8.63]	6.82E-23
C6	PERIPORTAL	complement component 6	[12.64 - 12.73 - 12.82]	[12.07 - 12.24 - 12.4]	[11.92 - 12.03 - 12.14]	[10.15 - 10.34 - 10.53]	8.37E-97
APCS	PERIPORTAL	amyloid P component, serum	[12.62 - 12.72 - 12.82]	[12.69 - 12.85 - 13.02]	[12.34 - 12.49 - 12.64]	[10.71 - 10.97 - 11.23]	1.03E-37
HGD	PERIPORTAL	homogentisate 1,2-dioxygenase	[12.64 - 12.71 - 12.77]	[12.61 - 12.71 - 12.81]	[11.91 - 11.99 - 12.08]	[10.83 - 10.97 - 11.11]	3.10E-47
FBP1	PERIPORTAL	fructose-1,6-bisphosphatase 1	[12.58 - 12.66 - 12.74]	[11.11 - 11.26 - 11.42]	[11.92 - 12.01 - 12.1]	[10.67 - 10.81 - 10.94]	3.31E-130
AZGP1	PERIPORTAL	alpha-2-glycoprotein 1, zinc-binding	[12.59 - 12.65 - 12.71]	[12.38 - 12.47 - 12.55]	[11.7 - 11.79 - 11.87]	[10.55 - 10.72 - 10.9]	2.53E-141
ECHDC2	PERIPORTAL	enoyl CoA hydratase domain containing 2	[12.59 - 12.65 - 12.7]	[12.5 - 12.58 - 12.65]	[12.12 - 12.18 - 12.23]	[11.39 - 11.47 - 11.55]	3.60E-41

C8A	PERIPORTAL	complement component 8, alpha polypeptide	[12.57 - 12.63 - 12.7]	[12.26 - 12.37 - 12.49]	[11.79 - 11.88 - 11.97]	[10.4 - 10.57 - 10.73]	2.91E-91
HRSP12	PERIPORTAL	heat-responsive protein 12	[12.53 - 12.59 - 12.65]	[11.88 - 11.99 - 12.1]	[11.76 - 11.85 - 11.95]	[10.71 - 10.83 - 10.95]	1.96E-62
HSD11B1	PERIPORTAL	hydroxysteroid (11-beta) dehydrogenase 1	[12.44 - 12.58 - 12.73]	[12.92 - 13.1 - 13.28]	[10.51 - 10.72 - 10.93]	[8.8 - 9.04 - 9.27]	2.94E-104
APOC4	PERIPORTAL	apolipoprotein C-IV	[12.48 - 12.57 - 12.66]	[12.94 - 13.05 - 13.15]	[11.59 - 11.72 - 11.85]	[9.4 - 9.6 - 9.8]	9.87E-101
TD02	PERIPORTAL	tryptophan 2,3-dioxygenase	[12.45 - 12.55 - 12.66]	[10.52 - 10.75 - 10.98]	[11.89 - 12.03 - 12.17]	[10.63 - 10.85 - 11.06]	7.29E-90
SAA4	PERIPORTAL	serum amyloid A4, constitutive	[12.38 - 12.47 - 12.55]	[10.87 - 11.08 - 11.28]	[11.87 - 11.99 - 12.12]	[9.79 - 10.01 - 10.23]	2.16E-108
SDS	PERIPORTAL	serine dehydratase	[12.26 - 12.4 - 12.54]	[9.03 - 9.26 - 9.49]	[10.96 - 11.14 - 11.31]	[8.98 - 9.18 - 9.37]	2.19E-96
HPD	PERIPORTAL	4-hydroxyphenylpyruvate dioxygenase	[12.25 - 12.37 - 12.5]	[12.92 - 13.06 - 13.21]	[10.85 - 11.09 - 11.32]	[8.5 - 8.74 - 8.98]	1.01E-49
G6PC	PERIPORTAL	glucose-6-phosphatase, catalytic subunit	[12.29 - 12.37 - 12.45]	[11.77 - 11.94 - 12.1]	[11.8 - 11.92 - 12.03]	[10.16 - 10.38 - 10.6]	2.44E-70
FMO3	PERIPORTAL	flavin containing monooxygenase 3	[12.27 - 12.36 - 12.45]	[12.89 - 12.96 - 13.04]	[11.77 - 11.89 - 12]	[9.94 - 10.16 - 10.38]	3.36E-55
C8B	PERIPORTAL	complement component 8, beta polypeptide	[12.29 - 12.36 - 12.42]	[11.39 - 11.52 - 11.65]	[11.62 - 11.7 - 11.79]	[10.05 - 10.23 - 10.41]	8.18E-60
LECT2	PERIPORTAL	leukocyte cell-derived chemotaxin 2	[12.22 - 12.35 - 12.49]	[12.51 - 12.68 - 12.85]	[11.76 - 11.95 - 12.14]	[9.8 - 10.1 - 10.39]	2.68E-35
DPYS	PERIPORTAL	dihydropyrimidinase	[12.28 - 12.35 - 12.42]	[12 - 12.15 - 12.29]	[11.62 - 11.74 - 11.86]	[10 - 10.2 - 10.41]	1.90E-95
CYP2C9	PERIPORTAL	Cytochrome P450, family 2, subfamily C, polypeptide 9	[12.2 - 12.32 - 12.43]	[12.24 - 12.41 - 12.57]	[11.51 - 11.64 - 11.78]	[9.54 - 9.77 - 10]	1.33E-65
GRHPR	PERIPORTAL	glyoxylate reductase/hydroxypyruvate reductase	[12.22 - 12.28 - 12.34]	[12.43 - 12.5 - 12.58]	[11.6 - 11.67 - 11.73]	[11.01 - 11.1 - 11.18]	9.98E-13
MAT1A	PERIPORTAL	methionine adenosyltransferase I, alpha	[12.21 - 12.28 - 12.34]	[12.39 - 12.47 - 12.55]	[11.9 - 11.98 - 12.06]	[10.73 - 10.89 - 11.04]	5.31E-21
AQP9	PERIPORTAL	aquaporin 9	[12.17 - 12.26 - 12.35]	[13.29 - 13.37 - 13.45]	[11.45 - 11.55 - 11.66]	[9.55 - 9.76 - 9.97]	3.89E-99
ABAT	PERIPORTAL	4-aminobutyrate aminotransferase	[12.15 - 12.21 - 12.26]	[11.82 - 11.92 - 12.02]	[11.43 - 11.51 - 11.58]	[10.27 - 10.4 - 10.53]	1.22E-95
SULT2A1	PERIPORTAL	sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1	[12 - 12.12 - 12.23]	[12.4 - 12.51 - 12.63]	[11.64 - 11.75 - 11.87]	[9.86 - 10.09 - 10.31]	1.85E-95
MTHFD1	PERIPORTAL	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase	[12.05 - 12.11 - 12.17]	[12.35 - 12.43 - 12.51]	[11.29 - 11.35 - 11.41]	[10.72 - 10.8 - 10.87]	3.71E-79
RDH16	PERIPORTAL	retinol dehydrogenase 16 (all-trans)	[11.98 - 12.07 - 12.17]	[10.59 - 10.77 - 10.94]	[10.54 - 10.66 - 10.79]	[8.64 - 8.82 - 9]	4.75E-67

CYP4A11	PERIPORTAL	cytochrome P450, family 4, subfamily A, polypeptide 11	[11.93 - 12.02 - 12.12]	[11.1 - 11.29 - 11.49]	[10.95 - 11.1 - 11.26]	[9.18 - 9.38 - 9.59]	1.44E-102
OTC	PERIPORTAL	ornithine carbamoyltransferase	[11.87 - 11.98 - 12.09]	[11.69 - 11.82 - 11.96]	[11.38 - 11.5 - 11.61]	[8.85 - 9.1 - 9.34]	4.83E-83
ANPEP	PERIPORTAL	alanyl (membrane) aminopeptidase	[11.9 - 11.97 - 12.04]	[11.12 - 11.24 - 11.35]	[11.74 - 11.81 - 11.89]	[11.47 - 11.59 - 11.72]	9.35E-85
CBS	PERIPORTAL	cystathionine-beta-synthase	[11.89 - 11.95 - 12.02]	[11.08 - 11.22 - 11.35]	[11.23 - 11.31 - 11.39]	[10.34 - 10.49 - 10.64]	2.19E-49
HPR	PERIPORTAL	haptoglobin-related protein	[11.83 - 11.95 - 12.07]	[12.31 - 12.44 - 12.58]	[10.96 - 11.1 - 11.24]	[9.39 - 9.6 - 9.8]	3.13E-79
SLC27A5	PERIPORTAL	solute carrier family 27 (fatty acid transporter), member 5	[11.86 - 11.94 - 12.02]	[11.77 - 11.88 - 11.99]	[10.67 - 10.77 - 10.86]	[8.92 - 9.03 - 9.14]	2.20E-113
ACAA1	PERIPORTAL	acetyl-CoA acyltransferase 1	[11.83 - 11.89 - 11.96]	[11.96 - 12.04 - 12.11]	[11.35 - 11.42 - 11.5]	[11.04 - 11.13 - 11.21]	7.39E-94
HAO1	PERIPORTAL	hydroxyacid oxidase (glycolate oxidase) 1	[11.79 - 11.86 - 11.92]	[11.63 - 11.74 - 11.85]	[11.01 - 11.11 - 11.21]	[9.53 - 9.71 - 9.89]	1.22E-80
FTCD	PERIPORTAL	formiminotransferase cyclodeaminase	[11.77 - 11.86 - 11.95]	[11.18 - 11.35 - 11.51]	[11.22 - 11.33 - 11.45]	[10.01 - 10.21 - 10.41]	1.91E-81
PCK2	PERIPORTAL	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	[11.79 - 11.86 - 11.92]	[11.36 - 11.49 - 11.62]	[10.83 - 10.91 - 11]	[9.8 - 9.89 - 9.99]	2.99E-110
AFM	PERIPORTAL	afamin	[11.72 - 11.82 - 11.91]	[10.94 - 11.12 - 11.3]	[11.08 - 11.22 - 11.35]	[8.91 - 9.14 - 9.37]	2.70E-59
SLC22A1	PERIPORTAL	solute carrier family 22 (organic cation transporter), member 1	[11.66 - 11.81 - 11.97]	[9.32 - 9.61 - 9.9]	[9.38 - 9.56 - 9.75]	[7.62 - 7.79 - 7.95]	2.71E-76
DHRS1	PERIPORTAL	dehydrogenase/reductase (SDR family) member 1	[11.74 - 11.81 - 11.87]	[11.08 - 11.18 - 11.28]	[11.02 - 11.09 - 11.16]	[10.19 - 10.28 - 10.37]	1.31E-98
TAT	PERIPORTAL	tyrosine aminotransferase	[11.66 - 11.75 - 11.84]	[10.8 - 10.99 - 11.19]	[10.48 - 10.61 - 10.75]	[8.45 - 8.62 - 8.8]	1.02E-100
SPP2	PERIPORTAL	secreted phosphoprotein 2, 24kDa	[11.61 - 11.73 - 11.86]	[10.48 - 10.67 - 10.87]	[10.84 - 11.04 - 11.23]	[8.72 - 8.98 - 9.23]	4.20E-54
TM4SF5	PERIPORTAL	transmembrane 4 L six family member 5	[11.65 - 11.73 - 11.82]	[11.01 - 11.12 - 11.23]	[11.87 - 11.98 - 12.1]	[10.9 - 11.07 - 11.24]	4.49E-41
CD14	PERIPORTAL	CD14 molecule	[11.64 - 11.73 - 11.83]	[10.67 - 10.82 - 10.98]	[11.04 - 11.15 - 11.26]	[10.13 - 10.27 - 10.41]	6.85E-88
CYP2C8	PERIPORTAL	cytochrome P450, family 2, subfamily C, polypeptide 8	[11.63 - 11.73 - 11.84]	[10.56 - 10.79 - 11.02]	[10.15 - 10.33 - 10.51]	[8.02 - 8.26 - 8.5]	7.36E-51
CPN2	PERIPORTAL	carboxypeptidase N, polypeptide 2	[11.65 - 11.71 - 11.78]	[11.84 - 11.92 - 12]	[11.05 - 11.14 - 11.23]	[9.94 - 10.11 - 10.28]	4.66E-79
FAH	PERIPORTAL	fumarylacetoacetate hydrolase (fumarylacetoacetase)	[11.6 - 11.65 - 11.71]	[10.96 - 11.05 - 11.14]	[11.13 - 11.2 - 11.27]	[10.37 - 10.46 - 10.56]	2.88E-73
NDRG2	PERIPORTAL	NDRG family member 2	[11.57 - 11.65 - 11.73]	[11.35 - 11.44 - 11.54]	[11.1 - 11.17 - 11.23]	[10.68 - 10.77 - 10.85]	2.10E-39

MTTP	PERIPORTAL	microsomal triglyceride transfer protein	[11.57 - 11.64 - 11.71]	[11.62 - 11.71 - 11.81]	[10.76 - 10.86 - 10.96]	[9.8 - 10.02 - 10.24]	5.23E-70
GADD45A	PERIPORTAL	growth arrest and DNA-damage-inducible, alpha	[11.56 - 11.63 - 11.69]	[11.45 - 11.53 - 11.61]	[10.97 - 11.03 - 11.09]	[10.45 - 10.53 - 10.6]	2.42E-134
SLC22A7	PERIPORTAL	solute carrier family 22 (organic anion transporter), member 7	[11.51 - 11.61 - 11.71]	[9.45 - 9.67 - 9.9]	[10.86 - 10.98 - 11.11]	[8.93 - 9.15 - 9.38]	2.54E-92
ALDH8A1	PERIPORTAL	aldehyde dehydrogenase 8 family, member A1	[11.5 - 11.58 - 11.67]	[10.34 - 10.53 - 10.72]	[10.89 - 10.99 - 11.08]	[9.34 - 9.52 - 9.7]	3.01E-99
CYP2J2	PERIPORTAL	cytochrome P450, family 2, subfamily J, polypeptide 2	[11.52 - 11.58 - 11.64]	[11.36 - 11.45 - 11.54]	[10.78 - 10.85 - 10.93]	[9.56 - 9.72 - 9.88]	2.60E-33
UPB1	PERIPORTAL	ureidopropionase, beta	[11.49 - 11.58 - 11.66]	[11.13 - 11.26 - 11.39]	[11.01 - 11.12 - 11.23]	[9.17 - 9.4 - 9.62]	1.30E-114
CTH	PERIPORTAL	cystathionase (cystathionine gamma-lyase)	[11.45 - 11.56 - 11.67]	[11.23 - 11.39 - 11.54]	[10.29 - 10.43 - 10.56]	[8.94 - 9.09 - 9.25]	1.14E-98
AGXT2L1	PERIPORTAL	alanine-glyoxylate aminotransferase 2-like 1	[11.43 - 11.55 - 11.67]	[10.32 - 10.47 - 10.61]	[10.03 - 10.18 - 10.32]	[8.16 - 8.35 - 8.55]	4.92E-90
HAL	PERIPORTAL	histidine ammonia-lyase	[11.4 - 11.51 - 11.63]	[7.74 - 7.93 - 8.13]	[11.07 - 11.21 - 11.34]	[10.29 - 10.5 - 10.71]	4.32E-101
EPHX2	PERIPORTAL	epoxide hydrolase 2, cytoplasmic	[11.44 - 11.51 - 11.59]	[11.04 - 11.15 - 11.26]	[10.62 - 10.7 - 10.78]	[9.75 - 9.87 - 9.98]	1.65E-119
SLC37A4	PERIPORTAL	solute carrier family 37 (glucose-6-phosphate transporter), member 4	[11.43 - 11.49 - 11.55]	[10.9 - 10.98 - 11.07]	[11.04 - 11.11 - 11.18]	[10.55 - 10.66 - 10.76]	1.62E-51
ABCB4	PERIPORTAL	ATP-binding cassette, sub-family B (MDR/TAP), member 4	[11.37 - 11.46 - 11.56]	[11.33 - 11.44 - 11.55]	[10.27 - 10.38 - 10.5]	[8.92 - 9.07 - 9.22]	1.93E-39
FETUB	PERIPORTAL	fetuin B	[11.35 - 11.44 - 11.53]	[9.51 - 9.78 - 10.04]	[10.04 - 10.18 - 10.33]	[7.98 - 8.15 - 8.33]	3.49E-64
C9	PERIPORTAL	complement component 9	[11.23 - 11.44 - 11.64]	[8.85 - 9.19 - 9.54]	[10.59 - 10.82 - 11.05]	[8.79 - 9.07 - 9.34]	3.32E-18
PON1	PERIPORTAL	paraoxonase 1	[11.33 - 11.43 - 11.53]	[10.63 - 10.82 - 11]	[10.42 - 10.54 - 10.67]	[8.63 - 8.84 - 9.05]	1.75E-78
RGN	PERIPORTAL	regucalcin (senescence marker protein-30)	[11.35 - 11.41 - 11.48]	[11.35 - 11.45 - 11.54]	[10.81 - 10.91 - 11]	[9.67 - 9.82 - 9.96]	1.49E-47
ACSL1	PERIPORTAL	acyl-CoA synthetase long-chain family member 1	[11.26 - 11.33 - 11.41]	[10.76 - 10.87 - 10.98]	[10.72 - 10.81 - 10.91]	[9.75 - 9.9 - 10.04]	2.28E-45
HAO2	PERIPORTAL	hydroxyacid oxidase 2 (long chain)	[11.19 - 11.32 - 11.46]	[8.79 - 9.02 - 9.25]	[9.51 - 9.68 - 9.84]	[7.53 - 7.71 - 7.88]	4.97E-45
CYP2C18	PERIPORTAL	cytochrome P450, family 2, subfamily C, polypeptide 18	[11.2 - 11.3 - 11.4]	[9.66 - 9.85 - 10.05]	[10.71 - 10.83 - 10.94]	[9.4 - 9.6 - 9.8]	1.32E-79
GNMT	PERIPORTAL	glycine N-methyltransferase	[11.1 - 11.25 - 11.4]	[9.69 - 9.95 - 10.2]	[9.72 - 9.88 - 10.03]	[8.09 - 8.26 - 8.44]	4.03E-131
ITIH4	PERIPORTAL	inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein)	[11.1 - 11.18 - 11.25]	[10.74 - 10.85 - 10.97]	[10.66 - 10.76 - 10.86]	[9.55 - 9.69 - 9.83]	8.67E-74
KLKB1	PERIPORTAL	kallikrein B, plasma (Fletcher factor) 1	[11.08 - 11.16 - 11.24]	[10.3 - 10.43 - 10.55]	[10.32 - 10.41 - 10.51]	[9.25 - 9.4 - 9.55]	7.72E-92

GLS2	PERIPORTAL	glutaminase 2 (liver, mitochondrial)	[11 - 11.15 - 11.3]	[6.86 - 7.07 - 7.28]	[9.25 - 9.4 - 9.54]	[7.37 - 7.53 - 7.69]	3.19E-100
MASP2	PERIPORTAL	mannan-binding lectin serine peptidase 2	[11.05 - 11.14 - 11.23]	[10.93 - 11.05 - 11.16]	[10.11 - 10.25 - 10.4]	[8.49 - 8.66 - 8.83]	5.15E-123
GBA3	PERIPORTAL	glucosidase, beta, acid 3 (cytosolic)	[11 - 11.11 - 11.23]	[8.84 - 9.05 - 9.25]	[9.24 - 9.41 - 9.58]	[7.85 - 8.06 - 8.26]	4.67E-119
AKR7A3	PERIPORTAL	aldo-keto reductase family 7, member A3 (aflatoxin aldehyde reductase)	[10.98 - 11.1 - 11.22]	[10.42 - 10.59 - 10.75]	[9.81 - 9.98 - 10.16]	[8.33 - 8.51 - 8.68]	1.77E-92
PPP2R1B	PERIPORTAL	protein phosphatase 2, regulatory subunit A, beta	[11.04 - 11.1 - 11.15]	[10.58 - 10.69 - 10.79]	[10.96 - 11.05 - 11.14]	[10.39 - 10.49 - 10.6]	1.02E-79
CYP4F2	PERIPORTAL	cytochrome P450, family 4, subfamily F, polypeptide 2	[10.98 - 11.07 - 11.17]	[10.63 - 10.76 - 10.88]	[10.16 - 10.27 - 10.38]	[8.59 - 8.76 - 8.92]	1.21E-89
EHHADH	PERIPORTAL	enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase	[11 - 11.07 - 11.14]	[11.08 - 11.18 - 11.29]	[10.14 - 10.23 - 10.32]	[9.01 - 9.14 - 9.28]	2.47E-24
NR1I3	PERIPORTAL	nuclear receptor subfamily 1, group I, member 3	[10.92 - 11.03 - 11.13]	[10.58 - 10.75 - 10.92]	[9.48 - 9.64 - 9.8]	[7.98 - 8.17 - 8.36]	1.21E-85
PCK1	PERIPORTAL	phosphoenolpyruvate carboxykinase 1 (soluble)	[10.88 - 11 - 11.13]	[10.27 - 10.43 - 10.59]	[9.67 - 9.82 - 9.97]	[7.88 - 8.05 - 8.22]	1.27E-84
ETFDH	PERIPORTAL	electron-transferring-flavoprotein dehydrogenase	[10.9 - 10.97 - 11.04]	[10.67 - 10.76 - 10.85]	[10.31 - 10.37 - 10.43]	[9.61 - 9.71 - 9.81]	1.69E-65
ACACB	PERIPORTAL	acetyl-CoA carboxylase beta	[10.89 - 10.96 - 11.04]	[9.98 - 10.07 - 10.17]	[10.43 - 10.51 - 10.59]	[9.53 - 9.66 - 9.78]	3.14E-137
GABARAPL1	PERIPORTAL	GABA(A) receptor-associated protein like 1	[10.85 - 10.93 - 11.01]	[11.17 - 11.27 - 11.36]	[10.4 - 10.48 - 10.55]	[9.93 - 10.02 - 10.12]	6.26E-114
FXYD1	PERIPORTAL	FXYD domain containing ion transport regulator 1	[10.81 - 10.92 - 11.02]	[8.74 - 8.98 - 9.21]	[9.64 - 9.78 - 9.91]	[8.54 - 8.72 - 8.89]	1.80E-62
GNE	PERIPORTAL	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase	[10.85 - 10.92 - 10.98]	[10.56 - 10.66 - 10.75]	[10 - 10.1 - 10.19]	[9.52 - 9.61 - 9.7]	5.54E-90
OGDHL	PERIPORTAL	oxoglutarate dehydrogenase-like	[10.79 - 10.89 - 10.98]	[9.9 - 10.08 - 10.26]	[9.94 - 10.05 - 10.16]	[8.48 - 8.62 - 8.77]	7.85E-43
ADH6	PERIPORTAL	alcohol dehydrogenase 6 (class V)	[10.79 - 10.88 - 10.97]	[11.53 - 11.63 - 11.73]	[10.28 - 10.39 - 10.51]	[9.18 - 9.34 - 9.51]	1.50E-85
ALDH1L1	PERIPORTAL	aldehyde dehydrogenase 1 family, member L1	[10.75 - 10.86 - 10.98]	[11.81 - 11.94 - 12.08]	[9.84 - 9.99 - 10.14]	[8.67 - 8.85 - 9.04]	5.84E-115
ABCA6	PERIPORTAL	ATP-binding cassette, sub-family A (ABC1), member 6	[10.78 - 10.86 - 10.94]	[10.74 - 10.85 - 10.96]	[9.89 - 9.99 - 10.09]	[8.62 - 8.79 - 8.95]	6.31E-62
AKR1D1	PERIPORTAL	aldo-keto reductase family 1, member D1 (delta 4-3-ketosteroid-5-beta-reductase)	[10.68 - 10.82 - 10.97]	[9.35 - 9.56 - 9.78]	[9.83 - 9.98 - 10.13]	[8.77 - 8.97 - 9.17]	1.79E-40
GLYAT	PERIPORTAL	glycine-N-acyltransferase	[10.7 - 10.82 - 10.94]	[10.67 - 10.84 - 11.01]	[8.65 - 8.81 - 8.97]	[6.52 - 6.7 - 6.89]	7.23E-95
ALDH2	PERIPORTAL	aldehyde dehydrogenase 2 family (mitochondrial)	[10.75 - 10.8 - 10.85]	[10.76 - 10.83 - 10.91]	[10.37 - 10.43 - 10.5]	[9.86 - 9.93 - 10]	2.59E-73
PEMT	PERIPORTAL	phosphatidylethanolamine N-methyltransferase	[10.63 - 10.74 - 10.85]	[10.36 - 10.48 - 10.6]	[10.1 - 10.2 - 10.29]	[9.48 - 9.6 - 9.72]	1.36E-125

SLC17A2	PERIPORTAL	solute carrier family 17 (sodium phosphate), member 2	[10.61 - 10.72 - 10.83]	[10.86 - 11.01 - 11.17]	[10.22 - 10.35 - 10.49]	[9.22 - 9.43 - 9.64]	2.06E-55
APOF	PERIPORTAL	apolipoprotein F	[10.45 - 10.59 - 10.73]	[8.52 - 8.73 - 8.94]	[8.88 - 9.05 - 9.23]	[7.24 - 7.42 - 7.61]	7.25E-56
ACADSB	PERIPORTAL	acyl-CoA dehydrogenase, short/branched chain	[10.46 - 10.55 - 10.63]	[10.59 - 10.69 - 10.8]	[10.01 - 10.1 - 10.2]	[9.28 - 9.42 - 9.56]	3.22E-109
PBLD	PERIPORTAL	phenazine biosynthesis-like protein domain containing	[10.42 - 10.51 - 10.61]	[10.04 - 10.21 - 10.38]	[9.64 - 9.76 - 9.88]	[8.64 - 8.8 - 8.97]	2.44E-29
SLCO1B1	PERIPORTAL	solute carrier organic anion transporter family, member 1B1	[10.39 - 10.49 - 10.58]	[10.17 - 10.33 - 10.49]	[9.95 - 10.08 - 10.2]	[8.27 - 8.5 - 8.73]	2.69E-78
ANXA10	PERIPORTAL	annexin A10	[10.33 - 10.46 - 10.58]	[8.88 - 9.09 - 9.3]	[8.79 - 8.91 - 9.04]	[7.63 - 7.81 - 7.98]	3.04E-111
ACSM5	PERIPORTAL	acyl-CoA synthetase medium-chain family member 5	[10.26 - 10.36 - 10.46]	[10.48 - 10.62 - 10.76]	[9.12 - 9.25 - 9.38]	[7.83 - 7.98 - 8.14]	1.30E-101
ABCA8	PERIPORTAL	ATP-binding cassette, sub-family A (ABC1), member 8	[10.16 - 10.28 - 10.4]	[9.97 - 10.15 - 10.34]	[9.14 - 9.3 - 9.47]	[7.95 - 8.17 - 8.39]	1.30E-86
ABCC6	PERIPORTAL	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	[10.17 - 10.25 - 10.32]	[10.24 - 10.32 - 10.4]	[9.8 - 9.89 - 9.98]	[9.23 - 9.35 - 9.47]	2.60E-12
CPE	PERIPORTAL	carboxypeptidase E	[10.13 - 10.24 - 10.36]	[9.07 - 9.19 - 9.32]	[10.27 - 10.39 - 10.51]	[9.89 - 10.04 - 10.2]	2.16E-105
GCDH	PERIPORTAL	glutaryl-CoA dehydrogenase	[10.16 - 10.24 - 10.31]	[10.09 - 10.18 - 10.28]	[9.47 - 9.55 - 9.62]	[8.9 - 8.99 - 9.07]	9.78E-21
GHR	PERIPORTAL	growth hormone receptor	[10.1 - 10.21 - 10.31]	[8.91 - 9.05 - 9.2]	[9.23 - 9.35 - 9.46]	[8.09 - 8.23 - 8.38]	2.05E-32
SLC46A3	PERIPORTAL	solute carrier family 46, member 3	[10.07 - 10.19 - 10.3]	[9.46 - 9.64 - 9.83]	[8.89 - 9.02 - 9.16]	[7.89 - 8.02 - 8.16]	9.41E-102
ANO1	PERIPORTAL	anoctamin 1, calcium activated chloride channel	[10.02 - 10.15 - 10.27]	[8.66 - 8.89 - 9.12]	[8.83 - 8.99 - 9.16]	[8.02 - 8.17 - 8.32]	6.60E-151
SEC14L2	PERIPORTAL	SEC14-like 2 (<i>S. cerevisiae</i>)	[10.04 - 10.13 - 10.22]	[10.26 - 10.37 - 10.49]	[8.76 - 8.85 - 8.94]	[7.59 - 7.7 - 7.8]	3.53E-59
SLC1A1	PERIPORTAL	solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	[9.99 - 10.12 - 10.25]	[8.78 - 8.98 - 9.19]	[8.71 - 8.9 - 9.08]	[7.49 - 7.7 - 7.91]	5.54E-43
DNASE1L3	PERIPORTAL	deoxyribonuclease I-like 3	[9.97 - 10.1 - 10.24]	[9.6 - 9.75 - 9.91]	[9.07 - 9.21 - 9.35]	[8.3 - 8.45 - 8.61]	2.78E-24
GPR37	PERIPORTAL	G protein-coupled receptor 37 (endothelin receptor type B-like)	[9.96 - 10.09 - 10.22]	[8.47 - 8.7 - 8.94]	[8.85 - 9.03 - 9.21]	[8.23 - 8.44 - 8.65]	5.54E-54
LRRC20	PERIPORTAL	leucine rich repeat containing 20	[10.02 - 10.08 - 10.15]	[9.89 - 9.97 - 10.05]	[9.99 - 10.07 - 10.15]	[9.3 - 9.4 - 9.5]	4.81E-36
GCH1	PERIPORTAL	GTP cyclohydrolase 1	[9.99 - 10.06 - 10.14]	[8.98 - 9.09 - 9.2]	[9.53 - 9.62 - 9.71]	[9.03 - 9.14 - 9.25]	1.19E-101
CYP2B7P1	PERIPORTAL	cytochrome P450, family 2, subfamily B, polypeptide 7 pseudogene 1	[9.89 - 10.05 - 10.2]	[7.32 - 7.51 - 7.69]	[8.34 - 8.51 - 8.69]	[7.22 - 7.38 - 7.53]	7.44E-104
GYS2	PERIPORTAL	glycogen synthase 2 (liver)	[9.92 - 10.03 - 10.15]	[8.92 - 9.11 - 9.3]	[8.07 - 8.2 - 8.34]	[6.33 - 6.5 - 6.66]	5.49E-49
CLDN15	PERIPORTAL	claudin 15	[9.93 - 10.03 - 10.12]	[9.82 - 9.94 - 10.06]	[9.67 - 9.77 - 9.87]	[8.91 - 9.03 - 9.14]	5.28E-82
KMO	PERIPORTAL	kynurenine 3-monooxygenase (kynurenine 3-hydroxylase)	[9.81 - 9.92 - 10.02]	[8.29 - 8.44 - 8.6]	[9.19 - 9.31 - 9.42]	[8.17 - 8.3 - 8.42]	4.38E-23
FEM1B	PERIPORTAL	fem-1 homolog b (<i>C. elegans</i>)	[9.86 - 9.9 - 9.95]	[9.55 - 9.62 - 9.68]	[9.76 - 9.81 - 9.85]	[9.67 - 9.73 - 9.78]	4.58E-111
ZGPAT	PERIPORTAL	zinc finger, CCCH-type with G patch domain	[9.68 - 9.8 - 9.91]	[9.2 - 9.32 - 9.43]	[9.03 - 9.12 - 9.21]	[8.81 - 8.89 - 8.98]	6.52E-158
CSTA	PERIPORTAL	cystatin A (stefin A)	[9.65 - 9.77 - 9.89]	[8.5 - 8.69 - 8.87]	[9.39 - 9.53 - 9.67]	[9.58 - 9.74 - 9.89]	1.66E-90
NR1I2	PERIPORTAL	nuclear receptor subfamily 1, group I, member 2	[9.67 - 9.76 - 9.85]	[8.91 - 9.06 - 9.21]	[8.29 - 8.43 - 8.57]	[7.14 - 7.29 - 7.44]	1.88E-22

CDA	PERIportal	cytidine deaminase	[9.65 - 9.74 - 9.84]	[8.32 - 8.45 - 8.58]	[8.99 - 9.1 - 9.21]	[8.35 - 8.5 - 8.65]	3.70E-72
LCAT	PERIportal	lecithin-cholesterol acyltransferase	[9.63 - 9.74 - 9.85]	[8.97 - 9.1 - 9.23]	[8.95 - 9.05 - 9.15]	[8.34 - 8.44 - 8.54]	4.92E-83
GRP88	PERIportal	G protein-coupled receptor 88	[9.47 - 9.7 - 9.93]	[7.01 - 7.24 - 7.48]	[8.58 - 8.84 - 9.09]	[7.31 - 7.55 - 7.78]	4.31E-18
CRY1	PERIportal	cryptochrome 1 (photolyase-like)	[9.6 - 9.66 - 9.73]	[9.18 - 9.27 - 9.35]	[9.53 - 9.6 - 9.67]	[9.51 - 9.58 - 9.65]	3.75E-103
IGF1	PERIportal	insulin-like growth factor 1 (somatomedin C)	[9.48 - 9.62 - 9.77]	[8.58 - 8.76 - 8.95]	[8.31 - 8.47 - 8.63]	[7.74 - 7.87 - 8.01]	2.63E-151
SOCS2	PERIportal	suppressor of cytokine signaling 2	[9.51 - 9.62 - 9.72]	[8.63 - 8.78 - 8.92]	[8.72 - 8.84 - 8.96]	[7.94 - 8.07 - 8.2]	8.94E-67
HMGB3	PERIportal	high-mobility group box 3	[9.5 - 9.59 - 9.69]	[8.38 - 8.5 - 8.62]	[9.1 - 9.23 - 9.35]	[9.01 - 9.16 - 9.31]	2.52E-33
GSTZ1	PERIportal	glutathione transferase zeta 1	[9.4 - 9.5 - 9.59]	[9.21 - 9.33 - 9.45]	[8.52 - 8.6 - 8.68]	[8.23 - 8.32 - 8.4]	7.16E-54
ACSM3	PERIportal	acyl-CoA synthetase medium-chain family member 3	[9.34 - 9.44 - 9.54]	[9.5 - 9.6 - 9.71]	[8.29 - 8.4 - 8.51]	[7.93 - 8.04 - 8.16]	2.03E-112
PXMP4	PERIportal	peroxisomal membrane protein 4, 24kDa	[9.36 - 9.43 - 9.5]	[9.22 - 9.3 - 9.39]	[9.17 - 9.24 - 9.32]	[8.8 - 8.88 - 8.96]	6.23E-29
GPN3	PERIportal	GPN-loop GTPase 3	[9.36 - 9.41 - 9.47]	[9.09 - 9.15 - 9.22]	[9.07 - 9.15 - 9.22]	[9.01 - 9.08 - 9.15]	2.82E-147
MLLT11	PERIportal	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11	[9.26 - 9.4 - 9.54]	[8.07 - 8.21 - 8.36]	[8.82 - 8.96 - 9.11]	[8.95 - 9.11 - 9.26]	1.28E-87
GPDI	PERIportal	glycerol-3-phosphate dehydrogenase 1 (soluble)	[9.26 - 9.38 - 9.49]	[8.45 - 8.59 - 8.72]	[8.47 - 8.57 - 8.67]	[7.59 - 7.7 - 7.82]	5.23E-117
BDH2	PERIportal	3-hydroxybutyrate dehydrogenase, type 2	[9.23 - 9.33 - 9.43]	[8.39 - 8.5 - 8.62]	[8.65 - 8.76 - 8.86]	[8.24 - 8.34 - 8.45]	5.61E-151
NAT2	PERIportal	N-acetyltransferase 2 (arylamine N-acetyltransferase)	[9.13 - 9.3 - 9.46]	[8.96 - 9.14 - 9.31]	[7.66 - 7.81 - 7.97]	[6.69 - 6.83 - 6.96]	1.50E-13
SCGN	PERIportal	secretagogin, EF-hand calcium binding protein	[9.09 - 9.27 - 9.45]	[7.56 - 7.73 - 7.9]	[8.47 - 8.65 - 8.83]	[8.38 - 8.57 - 8.77]	4.59E-61
CYP3A43	PERIportal	cytochrome P450, family 3, subfamily A, polypeptide 43	[9.06 - 9.21 - 9.36]	[9.35 - 9.51 - 9.67]	[8.29 - 8.43 - 8.57]	[7.11 - 7.25 - 7.38]	1.82E-45
ATP11B	PERIportal	ATPase, class VI, type 11B	[9.08 - 9.14 - 9.2]	[8.61 - 8.69 - 8.77]	[9.01 - 9.09 - 9.16]	[9.11 - 9.19 - 9.27]	1.51E-109
CYFIP2	PERIportal	cytoplasmic FMR1 interacting protein 2	[9.02 - 9.14 - 9.26]	[7.91 - 8.07 - 8.22]	[8.63 - 8.75 - 8.86]	[8.19 - 8.31 - 8.43]	8.09E-41
SRD5A2	PERIportal	steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)	[8.94 - 9.09 - 9.23]	[8.86 - 9.04 - 9.22]	[7.65 - 7.77 - 7.89]	[6.78 - 6.92 - 7.06]	2.91E-69
GRAMD1C	PERIportal	GRAM domain containing 1C	[8.94 - 9.04 - 9.14]	[7.71 - 7.85 - 7.99]	[8.11 - 8.21 - 8.31]	[7.4 - 7.52 - 7.64]	7.58E-111
ACADL	PERIportal	acyl-CoA dehydrogenase, long chain	[8.83 - 8.95 - 9.07]	[8.38 - 8.57 - 8.76]	[7.33 - 7.48 - 7.62]	[6.27 - 6.42 - 6.57]	8.19E-62
ESR1	PERIportal	estrogen receptor 1	[8.72 - 8.84 - 8.97]	[8.41 - 8.61 - 8.81]	[7.37 - 7.49 - 7.6]	[6.95 - 7.05 - 7.16]	1.33E-29
CPEB3	PERIportal	cytoplasmic polyadenylation element binding protein 3	[8.69 - 8.77 - 8.85]	[8.51 - 8.61 - 8.72]	[8.08 - 8.15 - 8.23]	[7.61 - 7.68 - 7.75]	1.60E-99
IGFALS	PERIportal	insulin-like growth factor binding protein, acid labile subunit	[8.64 - 8.77 - 8.91]	[7.51 - 7.62 - 7.73]	[7.89 - 7.99 - 8.09]	[7.65 - 7.76 - 7.88]	3.81E-31
MNS1	PERIportal	meiosis-specific nuclear structural 1	[8.59 - 8.74 - 8.89]	[7.6 - 7.72 - 7.84]	[7.86 - 7.99 - 8.11]	[7.56 - 7.66 - 7.75]	4.23E-95
FAM149A	PERIportal	family with sequence similarity 149, member A	[8.58 - 8.68 - 8.77]	[7.63 - 7.77 - 7.92]	[7.96 - 8.06 - 8.15]	[7.29 - 7.41 - 7.54]	1.56E-36
GNB5	PERIportal	guanine nucleotide binding protein (G protein), beta 5	[8.52 - 8.61 - 8.7]	[7.61 - 7.71 - 7.81]	[8.31 - 8.41 - 8.51]	[7.87 - 7.97 - 8.07]	1.60E-52
VIPR1	PERIportal	vasoactive intestinal peptide receptor 1	[8.41 - 8.53 - 8.65]	[7.85 - 7.99 - 8.13]	[7.73 - 7.84 - 7.95]	[7.26 - 7.37 - 7.47]	8.44E-105
KDM8	PERIportal	Lysine (K)-Specific Demethylase 8	[8.38 - 8.5 - 8.62]	[7.76 - 7.87 - 7.98]	[7.78 - 7.87 - 7.96]	[7.34 - 7.42 - 7.51]	1.24E-57
LRRC31	PERIportal	leucine rich repeat containing 31	[8.3 - 8.43 - 8.56]	[7.02 - 7.21 - 7.4]	[8.08 - 8.22 - 8.37]	[7.54 - 7.71 - 7.87]	2.97E-78
LPA	PERIportal	lipoprotein, Lp(a)	[8.25 - 8.38 - 8.51]	[7.19 - 7.34 - 7.48]	[7.43 - 7.55 - 7.67]	[6.81 - 6.96 - 7.11]	7.86E-81
SLC4A4	PERIportal	solute carrier family 4, sodium bicarbonate cotransporter, member 4	[8.1 - 8.21 - 8.32]	[8.73 - 8.88 - 9.02]	[7.22 - 7.34 - 7.47]	[7.15 - 7.32 - 7.49]	2.64E-112
FAM134B	PERIportal	family with sequence similarity 134, member B	[8.06 - 8.2 - 8.34]	[7.31 - 7.5 - 7.68]	[7.13 - 7.28 - 7.42]	[6.62 - 6.76 - 6.9]	3.25E-26
ADRA1A	PERIportal	adrenergic, alpha-1A-, receptor	[7.99 - 8.13 - 8.27]	[7.55 - 7.73 - 7.91]	[6.95 - 7.07 - 7.2]	[6.22 - 6.34 - 6.46]	1.73E-37
AASS	PERIportal	aminoadipate-semialdehyde synthase	[8 - 8.1 - 8.2]	[8.13 - 8.27 - 8.41]	[6.97 - 7.07 - 7.17]	[6.38 - 6.46 - 6.54]	1.36E-30
KCNN2	PERIportal	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	[7.7 - 7.86 - 8.02]	[6.85 - 6.96 - 7.08]	[7.04 - 7.14 - 7.24]	[6.91 - 6.99 - 7.07]	4.02E-100
FOLH1B	PERIportal	folate hydrolase 1B	[7.61 - 7.76 - 7.9]	[7 - 7.22 - 7.44]	[6.41 - 6.52 - 6.64]	[6.11 - 6.22 - 6.33]	4.55E-50
TENM1	PERIportal	Teneurin Transmembrane Protein 1	[7.41 - 7.59 - 7.76]	[6.38 - 6.6 - 6.82]	[6.37 - 6.52 - 6.67]	[6.46 - 6.64 - 6.83]	3.04E-84

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Supporting Table S10. See Supplementary Data.docx file for caption.

Datasets	HCC subclasses				Totals
	PP	PV	ECM	STEM	
A	32 (32%)	19 (19%)	28 (28%)	21 (21%)	100 (100%)
B	30 (22%)	27 (20%)	69 (51%)	9 (7%)	135 (100%)
C	72 (29%)	27 (11%)	94 (38%)	54 (22%)	247 (100%)
D	94 (35%)	50 (19%)	85 (32%)	39 (15%)	268 (100%)
E	11 (26%)	14 (33%)	12 (29%)	5 (12%)	42 (100%)
F	28 (38%)	9 (12%)	25 (34%)	11 (15%)	73 (100%)
G	34 (21%)	37 (23%)	82 (50%)	11 (7%)	164 (100%)
H	6 (17%)	12 (34%)	4 (11%)	13 (37%)	35 (100%)
I	19 (28%)	15 (22%)	21 (30%)	14 (20%)	69 (100%)
Totals	326 (29%)	210 (19%)	420 (37%)	177 (16%)	1133 (100%)

Supporting Table S11. See Supplementary Data.docx file for caption.**Sampling technique: metadata set, n= 1133 HCCs**

	PP	PV	ECM	STEM	Total
Tumor resection	298 (28%)	201 (19%)	395 (37%)	166 (15%)	1060 (100%)
Tumor biopsy	28 (38%)	9 (12%)	25 (34%)	11 (15%)	73 (100%)

Pearson's Chi-square test p value= 0.23

Etiology: metadata set, n= 1133 HCCs

	PP	PV	ECM	STEM	Total
HBV (>95% in original base)	91 (29%)	42 (13%)	115 (36%)	68 (21%)	316 (100%)
HCV (>95% in original base)	11 (26%)	14 (33%)	12 (28%)	5 (12%)	42 (100%)
Mixed etiology	224 (29%)	154 (20%)	293 (37%)	104 (13%)	775 (100%)

Pearson's Chi-square test p value= 0.001

Supporting Table S12. See Supplementary Data.docx file for caption.

N=210 HCCs	AGXT	FETUB	GLS2	GNMT	OTC	SLC10A1	SLC22A7	SLC27A5	KRT19	EPCAM	PROM1	LGR5	GLUL	ODAM	HAL
FETUB	0.66														
GLS2	0.47	0.53													
GNMT	0.58	0.56	0.52												
OTC	0.58	0.52	0.26	0.38											
SLC10A1	0.66	0.70	0.41	0.54	0.61										
SLC22A7	0.60	0.59	0.32	0.24	0.44	0.53									
SLC27A5	0.49	0.56	0.26	0.42	0.66	0.77	0.36								
KRT19	-0.25	-0.26	-0.02	-0.14	-0.32	-0.29	-0.15	-0.42							
EPCAM	-0.18	-0.24	0.08	-0.06	-0.20	-0.29	-0.10	-0.44	0.57						
PROM1	-0.36	-0.38	-0.12	-0.25	-0.32	-0.38	-0.24	-0.52	0.67	0.54					
LGR5	-0.17	-0.25	-0.46	-0.09	0.15	-0.15	-0.23	0.04	0.01	0.10	0.11				
GLUL	-0.04	-0.05	-0.54	-0.02	0.29	0.20	-0.04	0.34	-0.25	-0.19	-0.15	0.65			
ODAM	-0.22	-0.26	-0.57	-0.21	0.16	-0.03	-0.24	0.18	-0.13	-0.23	-0.02	0.61	0.71		
HAL	0.43	0.35	0.71	0.32	0.08	0.16	0.35	-0.11	0.15	0.27	0.07	-0.48	-0.66	-0.67	
VNN1	0.16	0.16	0.40	-0.04	0.04	0.00	0.27	-0.25	0.22	0.25	0.18	-0.42	-0.56	-0.51	0.61

PERIPORTAL GENE SIGNATURE

STEM CELL MARKERS

POSITIVE CTNNB1 MUTATION MARKERS

NEGATIVE CTNNB1 MUTATION MARKERS

Supporting Data to:

**Human Hepatocellular Carcinomas with a Periportal Phenotype Have the
Lowest Potential for Early Recurrence after Curative Resection**

Romain Désert, Florian Rohart, Frédéric Canal, Marie Sicard, Mireille Desille,
Stéphanie Renaud, Bruno Turlin, Pascale Bellaud, Christine Perret, Bruno Clément,
Kim-Anh Lê Cao, Orlando Musso

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SUPPORTING MATERIALS AND METHODS

Tissue banking of the external validation in-house HCC collection

The external validation in-house HCC collection (Fig. 1A) was recently described.⁽¹⁾

It included 70 HCC patients undergoing liver surgery with curative intention at Rennes University Hospital between January 1992 and December 2007. Fifty-one were treated by partial hepatectomy and 19 by orthotopic liver transplantation. Anatomic pathology features of HCCs were reviewed and annotated by a senior pathologist (BT). Demographic, clinical and biological data were retrieved from hospital charts by two experienced liver surgeons (LS & DB) and are described in online supporting table 2. Eighty-two frozen tumors from 70 patients were analyzed.

As controls, we included 66 matching non-tumor livers and 5 histologically normal livers from patients undergoing resection of liver metastases of extrahepatic primary cancers. Non-tumor and normal liver samples were obtained at >2 cm from the tumors. Frozen human tissue samples were processed by the Biological Resource Center, Rennes University Hospital (BB-0033-00056). Fresh tissues were frozen at -80°C in N₂-cooled isopentane and stored at -80°C under quality-controlled conditions. The study protocol complied with French laws and regulations and was approved by INSERM's Institutional Review Board (number 01-036) in the context of the National Network of Liver Biological Resource Centers. Sample collection was reported to the Ministry of Education and Research (No. DC-2008-338).

Statistical analysis

Transcriptomic data preprocessing

Raw feature data from Gene Expression Omnibus were normalized and $\log_2$ intensity expression summary values for each probe set were calculated using Robust Multiarray Average (RMA, packages Affy or Limma). Each dataset was assessed for the detection of outliers and inter-array, experiment-related batch effects by principal component analysis (PCA) and density plots. The outliers removed were: one sample from GSE17856, one sample from GSE15765 and two samples from GSE54236. When clear-cut inter-array experiment-related batch effects were observed within a dataset, this effect was corrected by the COMBAT method (package sva)(2). GSE25097 was corrected for 2-batch effect and GSE14520 for 3-batch effect. Then, probes being detected over the background noise in at least one HCC were retained and quantile normalized (package preprocessCore). When raw data were not available, normalized data were directly used (GSE20140, GSE20140 and TCGA-LIHC-US).

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Development of a score predicting CTNNB1 mutational status

To search for the best *CTNNB1* mutation predictors and to assess their predictive power (Fig. 1A, C), we used three HCC sets annotated for Sanger-sequenced *CTNNB1* exon 3 mutational status. The training set consisted of 87 HCCs (27 *CTNNB1*-mutant and 60 wild-type tumors) and the validation set contained 56 HCCs (17 *CTNNB1*-mutant and 39 wild-type tumors). *CTNNB1* mutation markers were further validated in an 82-HCC in-house independent cohort (23 *CTNNB1*-mutant and 59 wild-type tumors) (Fig. 1A and supporting table 2). Training (GSE9843) and validation (E-TABM-36) sets were obtained from publically available HCC mRNA expression profiling datasets. Cross-platform data transformation was performed with YuGene to reduce the variance attributable to platform or experimental batch.(3) The

external validation in-house HCC collection was analyzed by real-time PCR to validate the *CTNNB1* mutation predictors in an independent population.

To search for predictors of *CTNNB1* mutational status, we performed bootstrap over three PLS-DA principal components, whereby 300 rounds of bootstrap subsampling optimized the stability of predictors. Prediction was then validated on statistical tools based on one-tailed *t*-tests to objectively choose the number of optimal components and to identify the most robust set of predictors(4) (Supporting Fig. 2). The analysis identified Histidine Ammonia-Lyase (*HAL*) and Vanin 1 (*VNN1*) (selected in >85% of the models after 300 bootstrap runs). Histidine ammonia-lyase (*HAL*) was downregulated in *CTNNB1*-mutant HCCs by 17 folds in the training set [95% CI: (0.04-0.1), $p=2.8 \times 10^{-12}$] and by 8 folds in the validation set [95% CI: (0.06-0.23), $p=3.3 \times 10^{-6}$]. In turn, *Vanin 1* (*VNN1*) was downregulated in *CTNNB1*-mutant HCCs by 16 folds in the training set [95% CI: (0.04-0.11), $p=1.6 \times 10^{-12}$] and by 7 folds in the validation set [95% CI: (0.07-0.27), $p=1.4 \times 10^{-5}$] (Fig. 2A-B).

Odontogenic Ameloblast-Associated Protein (*ODAM*) was identified by exploratory analysis searching for the highest fold change between HCCs carrying mutant *versus* wild-type *CTNNB1*. *ODAM* was upregulated by about 7 folds in the training set [95% CI: (4-13), $p=3.8 \times 10^{-6}$] and by 10 folds in the validation set [95% CI: (4-24), $p=2.8 \times 10^{-5}$].

To develop a robust scoring method of prediction, we also included two well-known *CTNNB1* mutation markers, namely *GLUL* and *LGR5*.(5-8) *GLUL* was upregulated by about 2 folds in the training set [95% CI: (2-3); $p=6.4 \times 10^{-12}$] and by 6 folds in the validation set [95% CI: (4-10); $p=7.7 \times 10^{-7}$]; *LGR5* was upregulated by about 7 folds in the training set [CI: (4-11); $p=6.3 \times 10^{-8}$] and by 9 folds in the validation set [95% CI: (5-17); $p=8.3 \times 10^{-7}$]. After further validation of these markers in the external validation

in-house HCC collection by real-time PCR (Fig. 2A,B), we built an arithmetic score as shown in Fig. 2C.

Prediction of CTNNB1 mutational status in nine datasets

After extraction of gene expression values for *GLUL*, *LGR5*, *ODAM*, *HAL* and *VNN1* from the training and validation sets and from the nine datasets used for transcriptome meta-analysis, we compared:

- 1) Three normalization techniques (Autoscaling, Median Centering and Total-Sum Normalization).(9)
- 2) Several combinations of the five *CTNNB1* mutation markers: alternative scores with <5 genes were compared with the 5-gene score.

For each normalization technique and gene combination, the predictive score was calculated and the common threshold maximizing sensitivity and specificity in both training and validation sets was evaluated. Then, in each of the nine datasets, samples with a score higher than the threshold were predicted as mutated. To find the best method, we evaluated the performance of the score in the training and validation sets and the predicted mutation rate in each of the nine datasets, in comparison with the expected mutation rates in HCCs (20% to 40%).(5-7, 10, 11) This optimization process led us to choose the median centering technique and the 5-gene score. The performance of this method and the predicted mutation rate in the nine datasets is presented in supporting table 5.

Dataset quality control and combination for transcriptome meta-analysis

To assess the quality of each dataset, Pearson correlation coefficients were calculated for gene sets expected to be correlated: *KRT19-EPCAM*,⁽¹²⁾ *GLUL-LGR5*⁽⁷⁾ and *ODAM-HAL-VNN1* (supporting table 3). Datasets were discarded from the meta-classification analysis if Pearson correlations were <0.25 for at least one of the gene couples tested. Thus, nine datasets passing the quality control analysis were combined into a transcriptomic metadata set intended for meta-classification (Fig. 1B and supporting table 2), that totalized 1133 HCCs. Genes included in this metadata set were matched by ENTREZ ID (package org.Hs.eg.db). When multiple probe sets mapped a unique gene, we used the probe with a p-value detection <0.05 in most samples. The nine datasets had 9542 common genes. Probes were merged to the gene level and all nine datasets were normalized with the COMBAT algorithm to eliminate platform-related batch effect⁽²⁾ (Supporting Fig. 5). Thus, the metadata set consisted of 1133 HCCs with 9542 common genes.

Discriminating robust HCC subclasses by hierarchical cluster analysis

Hierarchical cluster analysis on the metadata set was performed with the Ward's method using 1-Pearson correlation as a distance metric. To highlight robust HCC subclasses, we applied the following four steps which are outlined below.

- 1) Identifying HCC samples highly associated with a subclass by individual reproducibility analysis.
- 2) Isolating the most highly associated gene sets within each HCC cluster by PLS-DA modeling.
- 3) Refining the HCC classification with the most highly associated gene sets within each HCC cluster.

- 4) Evaluating the robustness of the generated subclasses by several techniques, namely global reproducibility analysis, PCA, measure of inter-cluster and intra-cluster inertia and PLS-DA modeling.

Detailed description of the four steps applied to highlight robust HCC subclasses

1) Identifying HCC samples highly associated with a subclass by individual reproducibility analysis.

To isolate HCCs robustly linked to each cluster, we calculated an individual reproducibility score applying the following steps, modified from Boyault et al.,(13):

- A. Unsupervised gene selection based on the two following criteria:
- i. Variance test $p < 0.01$. For each gene (G) we tested whether its variance across samples was different from the median of the variances of the 9542 genes. The statistic used was $[(n-1) \times \text{Var}(G) / \text{Var}_{\text{med}}]$, where n refers to the number of samples. This statistic was compared to a percentile of the Chi-square distribution with $(n-1)$ degrees of freedom and yielded a p -value for each gene; and
 - ii. “robust” coefficient of variation (rCV) less than 10 and superior to a given rCV percentile threshold. Six rCV percentile thresholds were used: 60%; 70%; 80%; 90%; 95%; 97%, yielding six gene lists. The rCV for each gene was calculated by dividing

the standard deviation by the mean. It was called “robust” because the highest and the lowest expression values across the samples for each gene were deleted.

- B. Hierarchical clustering of the 1133 samples using the whole metadata set or data restricted to each of the six gene sets defined by the rCV percentile thresholds (see *ii* above) produced seven dendrograms. As the “elbow” method in the whole metadata set suggested a 4-cluster classification (not shown), the seven dendrograms were cut into four clusters.
- C. Individual reproducibility score: For each dendrogram, a sample was noted 1 for a given cluster (1-4) if it was classified in this cluster and 0 if it was not. The individual reproducibility score of clusters 1-4 was calculated with the mean of the scores of the seven dendrograms. Then, samples with a reproducibility score over 0.85 for a given cluster (which means that an HCC was classified in this cluster in at least six dendrograms out of seven) were considered to belong to this cluster in a robust way. Thus, 158 samples (14% of the metadata set) were robustly associated with cluster 1 (red); 123 (11% of the metadata set) were robustly associated with cluster 2 (purple); 228 (20% of the metadata set) were robustly associated with cluster 3 (green) and none of the samples were robustly associated with cluster 4 (blue).

2) Isolating the most highly associated gene sets within each HCC cluster by

PLS-DA modeling

Cluster-specific gene sets were determined by Partial Least Squares Discriminant Analysis (PLS-DA, package pls), following these steps:

A. Gene sets that were significantly different by a Tumor *versus* non-tumor *t* test, showing a fold difference either <0.5 or >2.0 , were considered to be tumor specific. For this test, the dataset GSE14520 was used and 2881 genes were selected.

B. Three PLS-DA models were obtained on the metadata set with 2881 differentially expressed genes for the prediction of the three subclasses defined by individual reproducibility analysis (red, purple and green). The best number of principal components *k* were evaluated after a cross-validation by the PRESS criteria ($k(\text{red})=8$, $k(\text{purple})=5$ and $k(\text{green})=7$). Then, *variable importance in the projection* (VIP) was calculated for each gene and each principal component. To refine the HCC classification, the mean of *k* VIPs in at least one PLS-DA model was set to >1 , yielding 1618 genes. For gene ontology analysis, the mean of *k* VIPs in at least one PLS-DA model was set to >1.5 , yielding 550 genes.

3) Refining the HCC classification with the most highly associated gene sets within each HCC cluster

The HCC classification was refined by a new hierarchical cluster analysis on the metadata set using the 1618 gene set (VIP>1). The dendrogram was cut into four clusters, as suggested by the “elbow” method (Supporting Fig. 8).

4) Evaluating the robustness of the generated subclasses from the 1618 gene set (VIP>1) by global reproducibility analysis, PCA, measure of inter-cluster and intra-cluster inertia and PLS-DA modeling.

A. Global reproducibility analysis included the following steps, modified from Boyault et al.,(13):

- i. Unsupervised gene selection was based on the two following criteria :
 - a. Variance test with a p-value <0.01.
 - b. Robust coefficient of variation (rCV) less than 10 and superior to a given rCV percentile from the following threshold list: 60%; 70%; 80%; 90%; 95%; 97%, 99%, 99.5%, yielding eight gene lists.
- ii. Hierarchical clustering of the 1133 samples using the entire metadata set or data restricted to each of eight gene set lists produced nine dendrograms. Each dendrogram was cut into four clusters.
- iii. For each dendrogram, the global reproducibility score was assessed by calculating the % of samples well classified.

- iv. The same score was calculated for each dendrogram restraining the data to a subclass of samples (red, purple, green and blue). These analyses showed that the red, green and purple subclasses were robust, with a global reproducibility higher than 70% in most of the cases. By contrast, the blue subclass was less robust, consistently with individual reproducibility analysis. The results of these analyses are presented in Supporting Fig. 6.

B. PCA analysis was performed with the FactoMineR package. Individual score plot in the first two principal components according to individual classification show noticeable discrimination (Supporting Fig. 7A).

C. The intra-cluster and the inter-cluster inertia were measured by Euclidean distances. The most homogenous cluster (with the weakest intra-cluster inertia) was the green one ($I=55.76$), then the red one ($I=58.18$), the blue one ($I=59.77$) and the purple one ($I=69.14$). The mean intra-cluster inertia, that can reflect dispersion, was weaker than the mean inter-cluster inertia, than can reflect distance between clusters. The green cluster was closest to the red cluster and both green and red clusters were distant from the purple one, the blue cluster occupying an intermediate position between them (Supporting Fig. 7B).

D. Multivariate PLS-DA analysis (package pls) was performed to measure the association between gene expression and the four subclasses. The model was validated by a 10-9 double cross-validation and the significance by a 1000-permutation test, as described.(14) The model was able to significantly discriminate the four subclasses, with a double cross-validated correct classification rate of 89% (SD: 0.03), ($p=10^{-3}$). In addition, the score plots in the first two or three principal components (2D-3D plot) according to the individual classification showed noticeable discrimination of the clusters. It also illustrated the distance between them, with intermediate position of the blue cluster as described in the inertia analysis (Supporting Fig. 7C-D).

Functional genomics analyses

Gene annotations based on gene ontology and enrichment for biological functions were done with the FuncAssociate 2.1 program.⁽¹⁵⁾ Gene set enrichment analysis (GSEA) was performed with the web-based tool developed at the Broad Institute.⁽¹⁶⁾

• Periportal-type HCC gene signature

After functional genomics analysis, the green cluster was defined as representative of a HCC subclass associated with periportal metabolism, thus called *Periportal-type*. Then, we searched the 9542 genes within the 1133 HCC metadata set for top *Periportal HCC* genes as good outcome predictors. Selected genes complied with the following four stringent criteria:

- 1) Fold change >2 between *Periportal-type* samples and the rest of the samples in the 1133 HCCs metadata set.
 - 2) *Periportal* gene, as defined by the periportal signature of normal mouse liver.⁽¹⁷⁾
 - 3) Hub gene in the network of metabolic liver zonation: connectivity (*i.e.*, Pearson's correlation coefficient >0.30) with >50% of 226 *periportal* or *perivenous* genes, as assessed by network analysis. *Periportal* and *perivenous* genes were defined according to normal mouse liver *periportal* and *perivenous* signatures.⁽¹⁷⁾
 - 4) Association with overall and disease-free survival analyses in 183 HCCs predicted as carrying wild-type *CTNNB1* from dataset C (n=247 patients).⁽¹⁸⁾
- To this end, a gene was retained when at least 7 out of the 8 univariate survival analyses detailed below were statistically significant ($p < 0.05$):

- a. Two Cox analyses (overall and disease-free survival analyses);
- b. Six log-rank analyses using three different gene-expression-level cutoffs: percentile 25, median and percentile 75 (overall and disease-free survival analyses).

Only eight genes complied with the above criteria and were retained to define the *Periportal signature*. The 247-HCC patients in dataset C and the 210-HCC patients in the external validation RNAseq cohort were then studied by PCA analysis of the 8-gene signature. HCCs with a score >median in the first principal component were defined as *Periportal HCCs*.

CTNNB1 exon 3 sequencing and search for CTNNB1 exon 3 deletions

CTNNB1 exon 3 sequencing was performed as described.⁽¹⁹⁾ For mutation analysis, exon 3 and the flanking intronic sequences of the *CTNNB1* gene were amplified by PCR using Kappa HiFi DNA polymerase (Kapa Biosystems, Wilmington, MA). Briefly, 50 ng of genomic DNA were used as template with β CATEX2F (5'-GAA-AAT-CCA-GCG-TGG-ACA-ATG-3') and β CATEX4R (5'-TCG-AGT-CAT-TGC-ATA-CTG-TCC-3') as oligonucleotide primers. The reaction included a 95°C denaturation step for 3 min followed by 35 cycles consisting of: 98°C denaturation for 15 sec, 60°C annealing for 15 sec, and elongation 72°C for 30 sec. Both strands of the amplified products were directly sequenced on an automated sequencer (ABI 3700; Perkin-Elmer, Boston, MA). Negative results on exon 3 mutations may overlook large exon 3 deletions in *CTNNB1*. Indeed, as somatic deletions are heterozygous, the wild-type allele may mask the deletion upon Sanger sequencing.^[40] To avoid this pitfall, HCCs showing no exon 3 mutation were screened for β -catenin deletion by PCR on

reverse-transcribed tumor cDNA. For PCR amplification of the exon 3 of *CTNNB1*, oligonucleotide primers (F1: 5'-GCG-TGG-ACA-ATG-GCT-ACT-CAA-G-3'; R1: 5'-TAT-TAA-CCA-CCA-CCT-GGT-CCT-C-3'; and R2: 5'-TTC-AGC-ACT-CTG-CTT-GTG-GTC-3') were used. The primer pairs F1-R1 and F1-R2 yielded 517 bp (169 aa) and 1043 bp (344 aa) amplicons, respectively. As positive control, HepG2-derived cDNA was used, as these cells harbor a large *CTNNB1* deletion (amino-acids 25-140).[40] PCR was performed using the GoTaq Green Master Mix (Promega) and amplicons migrated in 1.5% Nusieve agarose (LifeTechnologies) gels.

Tissue microarray

Tissue microarrays were set up and analyzed as previously described.(19, 20) For selection of tissue blocs for TMA construction, the whole set of archival HE-stained sections from formalin-fixed, paraffin-embedded tissue blocks from each one of the 67 available HCC patients and from five histologically normal livers were reviewed (Nikon 80i microscope) to ensure that the selected paraffin bloc was the mirror lesion of the frozen sample. A region of interest (ROI, 0.5 to 1 cm in diameter) was labeled with a permanent marker to precisely localize the punch zone. TMA construction was done with a MiniCore3 tissue arrayer (Alphelys, Plaisir, France). ROIs were punched in triplicate. Punch size was set at 1000 µm in diameter. HCC samples were randomly assigned to either one of two 132-punch receiver paraffin blocks. Randomization was performed with a “rand” function in Microsoft Excel. The five histologically normal liver controls were included in both array blocs #1 and #2 to control for signal and background intensities. Five-µm microtome sections were processed for immunohistochemistry with a Discovery XT from Ventana Medical Systems (Roche) slide staining system. See the table below for antibodies. Stained

slides were converted into high-resolution digital data with a NanoZoomer digital slide scanner (Hamamatsu, Massy, France). Digital slides were viewed using NDP.view software (Hamamatsu) in a Dell S2415H 24-Inch Screen LED-Lit Monitor.

Primary antibodies

PRIMARY ANTIBODIES		
GENE ID	CAT. #	Supplier
<i>β-catenin</i>	610154	BD Biosciences
GLUL	610518	BD Biosciences
HAL	HPA038547	Sigma Aldrich
ODAM	16509-1-AP	Proteintech
VNN1	sc-16776	Santa Cruz Biotechnology

Cell culture

297T, BC2, B16, Hep-G2, Huh-6 and Huh-7 cells were cultured in DMEM.(21) HepaRG cells were cultured as previously described.(1, 22, 23) For BIO assay, cells were treated with BIO (Merck Millipore) 2.5 μM during 72 h, applying a previously optimized protocol.(24)

Nucleic acid extraction from human tissues and from *in vitro* cultures

RNA and DNA were extracted from 10 μm cryosections obtained from frozen tissue blocks, as previously described(19, 20). Once tissues were placed on the specimen head of a Leica 3050S cryostat and trimmed to obtain a level and histologically controlled representative surface (hematoxylin or toluidine blue extemporaneous staining), the first two 5 μm sections were set aside as permanent histological

controls. Then, 10 μm cryosections were obtained and immediately lysed in RNA or DNA extraction buffers. Before removing the disk containing the specimen from the head, two 5 μm cryosections were set aside again as permanent histological controls. Lead and rear permanent histological controls were formalin-fixed, HE-stained in a Leica ST5020 routine stainer and representativity was assessed by two independent observers (BT & OM). Non-representative samples were removed from the RNA and DNA extraction process. Representative samples were extracted with NucleoSpin® RNA II (Macherey-Nagel) and with the DNeasy Blood & Tissue (Qiagen) kits, as recommended by the manufacturers. Quality control of the extracted nucleic acids was performed by dosing the eluents with a NanoDrop spectrophotometer and by checking 28S/18S ratios by gel electrophoresis. For in vitro cultured cell layers, total RNA was purified with an RNAeasy kit (Qiagen). Extracted RNA quality control was done as for human tissues.

Real-time PCR

Real-time PCR was performed as described.(19, 20) Reverse-transcribed cDNA was obtained with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's instructions. Expression of relevant genes was measured by quantitative real-time PCR using the StepOnePlus™ System or the ABI prism 7900HT, power SYBR Green PCR master mix or Taqman probe-based assays (Applied Biosystems), according to the experiments. Quantitative analyses of PCR data were conducted by the $2^{-\Delta\Delta C_t}$ method. See below for Sybr Green and TaqMan probes used.

Sybr Green primers and TaqMan probes

SYBR GREEN PRIMERS (Eurogentec, Seraing, Belgium)		
GENE ID	STRAND	Primer sequences 5'- 3'
ALDOB	Forward	GCATCTGTCAGCAGAATGGA
	Reverse	TAGACAGCAGCCAGGACCTT
AXIN2	Forward	TCAGCAGAGGGACAGGAATC
	Reverse	TCTTTGGCTCTTTGTGATCTTCTG
GLUL	Forward	AAGTGTGTGGAAGAGTTGCC
	Reverse	TGCTCACCATGTCCATTATC
HAL	Forward	CAACAAGCTCTCCACCAGTT
	Reverse	CTCCTTGTTGGTTTTAATCACCTC
HNF4A	Forward	ACATGGACATGGCCGACTAC
	Reverse	TCTGATGGGGACGTGTCATTG
HPRT1	Forward	TGACACTGGCAAAACAATGCA
	Reverse	GGTCCTTTTCACCAGCAAGCT
LGR5	Forward	GAAGCTCTGCAGAATTTGCGAAGCC
	Reverse	CAGGTGCCTCAGGGAATGCAGG
TBP	Forward	GAGCTGTGATGTGAAGTTTCC
	Reverse	TCTGGGTTTGATCATTCTGTAG
VNN1	Forward	GCACGCTACCATAAGCAAAAC
	Reverse	ACAATCTCAGGCTCCTTGGG

TAQMAN PRIMERS & PROBE	
GENE ID	Life Technologies cat. #
ODAM	Hs002152928m1

RNA interference and cDNA vector transfection

Routinely expanded HepaRG progenitor cells were detached by trypsinization, seeded at low density (2×10^4 cells/cm²), detached three days later and transfected in suspension with small interfering RNAs (siRNAs) by a MP100 Microporator (LabTech) and Neon™ Transfection System 100 µL Kit (Invitrogen) under optimized conditions (80 pmoles siRNA, 1500V, 20ms, 1 pulse), as we previously reported.(19)

Silencer negative control (D-001810-10-05, Thermo Fisher) and β -catenin (HSS102460, Invitrogen) siRNAs were used.

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SUPPORTING FIGURE LEGENDS

Supporting Fig. 1. Quality analysis of the external validation cohort (TCGA-LIHC-US). (A) Patient selection. (B) Assessment of the quality of extraction of clinical annotations by Kaplan-Meier plots of overall and disease-free survival as a function of TNM staging.

Supporting Fig. 2. Choosing predictive and stable gene signatures by sPLS-DA (A) Bootstrap subsampling evaluation of the stability of each gene predictor across three sPLS-DA components, where frequency of selection over 300 bootstrap subsamplings (Y-axis) is shown per gene (ENSEMBL ID, X-axis). Labels are provided for the 3 genes contributing to the signature across one component. Component 1 (blue rectangles), Component 2 (orange triangles), Component 3 (grey inverted triangles). (B) Evaluation of the contribution of each gene set to the informativeness of the first component. Each dot is a gene set ordered along the X-axis by decreasing stability (frequency of selection). The Y-axis represents the $-\log_{10}(P\text{-value})$ of a one tailed t -test indicating improvement in classification accuracy. (C) Classification accuracy of the 3-gene signature on both training and validation sets.

Comments to Supporting Fig. 2.

One PLS-DA component allowed the identification of three markers associated with *CTNNB1* mutations in HCCs, namely *HAL*, *VNN1* and *CCDC170*. Together, these three markers accurately classified more than 87% of the samples in both the training and the validation sets (see C). However, because of the low frequency of selection of *CCDC170* (see A), the analysis focused on both *HAL* and *VNN1* (frequency of selection >85%, see A).

Supporting Fig. 3. Predictive accuracy of the 5-gene score applied to tumor/non-tumor gene expression ratios on *CTNNB1* mutational status in the external validation HCC collection analyzed by qPCR. (A) Correlations between *GLUL*, *LGR5*, *ODAM*, *HAL* and *VNN1* in the training and validation sets and in the external validation HCC collection analyzed in HCCs (T); non-tumor samples (NT) and in tumor/non-tumor ratios. *AXIN2* is used as an indicator of high β -catenin pathway signaling.(25) (B) Heatmap showing the correlations of nuclear β -catenin (*Nu_* β -cat) with the mRNA expression of the five biomarkers and *CTNNB1* mutational status (*Mut_* β -cat), assessed by immunohistochemistry scoring as described,(1) in 82 HCCs. Each blue cell in the top row represents one HCC. Low and high gene expressions (using the median as the cut-off value) are represented in green and red, respectively. γ , Gamma correlation coefficient. (C) Log₂ of the Tumor/non-tumor ratios of mRNA expression levels for the indicated genes, according to *CTNNB1* mutational status. (D) Performance of the combined score of tumor/non-tumor gene expression ratios of *GLUL*, *LGR5*, *ODAM*, *HAL* and *VNN1* to predict *CTNNB1* mutated HCCs. The combined score was calculated as follows, using tumor/non-tumor ratios: $Score = (GLUL \times LGR5 \times ODA M) \div (HAL \times VNN1)$. (E) Receiver operating curve (ROC) showing predictive performance of the combined score on *CTNNB1* mutation. (F) Relative gene expression of the biomarkers in HCCs (*blue*) and non-tumor (*red*) samples according to *CTNNB1* mutational status ("*mutated*" and "*wild-type*" HCCs). *P<0.05, **P<0.01, ***P<0.001, after Wilcoxon tests. CI, Confidence interval; Se, Sensitivity; Sp, Specificity. AUROC, area under the ROC curve.

Supporting Fig. 4. Real-time PCR-based gene expression of *HAL*, *VNN1* and *ODAM* in HCC cell lines carrying mutant (B16, BC2, HepG2, Huh6) or wild-type (Huh7, HepaRG) *CTNNB1*, (10, 22) measured by real-time PCR. Results are expressed as relative to the 293T cell line (WT *CTNNB1*). Data are displayed as mean values $\pm$ SD. Experiments were done in triplicate.

Supporting Fig. 5. Functional analyses of the five mutation biomarkers by real-time PCR in HepaRG cells. (A) The GSK3 β inhibitor BIO (2.5 μ M) strongly upregulates β -catenin transcriptional activity, as shown in a β -catenin gene reporter assay, where 8x tandem TCF sites control the expression of the *Firefly luciferase* gene. (B) BIO upregulates *GLUL*, *LGR5* and *ODAM* mRNA expression, assessed by real-time PCR. (C-F) BIO attenuates the gain in the expression of *HNF4A*, *ALDOB*, *HAL* and *VNN1* mRNA upon differentiation of HepaRG liver progenitors into hepatocyte-like cells over a 30-day time course. (G) HepaRG cells transfected with β -catenin targeting siRNA downregulate *AXIN2* and *ODAM* and upregulate *HAL* and *VNN1* mRNA expression (real-time PCR). Data are relative to scrambled siRNA-transfected cells. Mean $\pm$ SD. Experiments were done in triplicate.

Supporting Fig. 6. Combat performance. The COMBAT algorithm effectively removes cross-platform variance effects after merging nine transcriptomic datasets into a metadata set. (A) Score plot of the individuals in the first two principal components of a principal component analysis (PCA). The 9542 common genes in the nine datasets are shown after preprocessing. PCA reveals cross-platform-dependent correlations. (B) Score plot of the individuals in the first two principal

components of PCA after removal of cross-platform variance using the COMBAT algorithm.(26)

Supporting Fig. 7. Unsupervised hierarchical cluster analysis reveals strong enrichment of HCCs with predicted *CTNNB1* mutations in one HCC subclass. (A)

The dendrogram was obtained with Ward's linkage and 1-Pearson correlation coefficient on the basis of the expression profile of 1618 genes, which were the most discriminant of the four subclasses (VIP>1 after PLS-DA analysis) in the metadata HCC set. *Top*, the four HCC subclasses (*purple, blue, red* and *green* nodes) are shown, as well as the predicted *CTNNB1* mutational status of each tumor (*red*: mutant; *blue*: wild-type). The % of predicted *CTNNB1* mutations in each HCC subclass is indicated in boxes. *Left*, for each gene, the lowest and highest intensity values are represented in *green* and *red*, respectively.

Supporting Fig. 8. Reproducibility analysis performed on the four HCC subclasses.

The numbers of HCCs in the whole metadata set and in each one of the subclasses are as follows: *whole metadata set* (n=1133), black curve; *subclasses*: *green* (n=326); *red* (n=210); *blue* (n=420); *purple* (n=177). The % of well-classified samples after hierarchical clustering using Ward's linkage and 1-Pearson correlation coefficient is shown as a function of gene sets containing different proportions of the most variable genes included in each analysis.

Comments to Supporting Fig. 8. The robustness of the four subclasses was measured by a global reproducibility score plotting the % of well-classified samples as a function of the gene sets containing variable percentages of the most variable

gene subsets. Thus, this analysis was performed on 100% of the genes (i.e., 9542-gene set) in the metadata set or on gene sets containing the most variable proportions of genes according to different thresholds (40%, 30%, 20%, 10%, 5%, 3%, 1%, 0.5%). The red, green and purple subclasses are homogenous, with a global reproducibility higher than 70% at different thresholds. By contrast, the blue subclass is less homogenous, consistently with individual reproducibility analysis.

Supporting Fig. 9. (A-D) Robustness analysis and distance measures between the four subclasses in the metadata set: (A) Principal component analysis (PCA) showing the individual score plot according to HCC subclasses. The four subclasses are noticeably discriminated. (B) Intra-cluster and inter-cluster inertia. Mean intra-cluster inertia (*orange cells*), that can reflect dispersion, is weaker than the mean of inter-cluster inertia (*yellow cells*), than can reflect distance between subclasses. (C) 3D representation of the score plot of multivariate PLS-DA in the first three principal components. The model is able to significantly discriminate the four subclasses, with 89% of samples correctly classified after a 10-9 double cross-validation (SD: 0.03, p -value = 10^{-3} after 1000 permutations). (D) Comparison of the 4-clusters obtained by two discriminant analysis cut-offs: (i) 1618 genes (VIP>1); and (ii) 550 genes (VIP>1.5 after PLS-DA analysis, see supporting materials and methods). Using either of the two cut-offs (VIP>1 & VIP>1.5), 81.6% of the samples fall within the same cluster. (E) Validation of the top discriminant 550 genes as HCC classifiers by unsupervised hierarchical clustering in the external validation cohort (210-HCC RNAseq dataset; TCGA, LIHC, US). HCC subclasses are indicated in color. For each gene, lowest and highest intensity values are represented in green and red, respectively.

Supporting Fig. 10. *TP53* gene expression and *TP53* mutation biomarkers in the transcriptomic subclasses from the HCC metadata set. Results are expressed as relative to the Periportal-type subclass. (A) Three markers of *TP53* mutation in cancer(27, 28) are overexpressed in the STEM-type subclass. (B) *TP53* gene expression in the individual datasets composing the metadata set. As *TP53* was missing in dataset D, its expression was explored separately in each of the remaining datasets composing the metadata set. *TP53* was significantly upregulated in STEM-type HCCs in some of the datasets and particularly in the dataset with the largest number of samples (Dataset C, n=247). Green, PP (n=326); Red, PV (n=210); Blue, ECM (n=420); Purple, STEM (n=177). NS, non-significant. *P<0.05, **P<0.01, ***P<0.001 after Student's *t* tests.

Supporting Fig. 11. Expression of hallmark genes representing the HCC subclasses. Gene expression results are shown as relative to Periportal-type HCCs. Green, PP (Periportal-type, n=326); red, PV (Perivenous-type, n=210); blue, ECM-type (extracellular matrix, n=420); purple, STEM-type (stem cell type, n=177). (A) Wnt pathway and perivenous zonation genes upregulated in the PV group. (B) Examples of genes expressed at higher levels in Periportal-type HCCs. (C) Tumor stem/progenitor cell (*AFP*, *EPCAM*, *PROM1*, *KRT19*, *SOX9*, *CD44*, *DKK1*) and extracellular matrix remodeling (*TGFB1*, *VCAN*, *TNC*, *LAMC1*, *VIM*) genes are overexpressed in STEM-type and ECM-type HCCs, respectively. NS, non-significant. *P<0.05, **P<0.01, ***P<0.001 after Student's *t* tests.

Supporting Fig. 12. Mouse liver zonation and HNF4A target genes discriminate human HCC subclasses. (A) Unsupervised hierarchical clustering of 210 Perivenous-type and 326 Periportal-type HCCs based on 93 periportal (*PP*) and 79 perivenous (*PV*) mouse ortholog genes.(17) Green indicates lower expression; red higher expression. Periportal-type and Perivenous-type HCC subclasses are remarkably discriminated. (B) Unsupervised hierarchical clustering of 1133 human HCCs based on the expression profile of the genes most tightly modulated by HNF4A in *Hnf4a*-KO mice(29) (fold change >2 or <0.5; Bonferroni adjusted *P* value<0.01). Over the 1868 genes identified in *Hnf4a*-KO mice, 603 orthologs were available in the human 1133-HCC metadata set. On the left panel, relative gene expression between *Hnf4a*-KO and *Hnf4a*-WT is indicated in color (*Green*: WT; *Red*: KO). On the top panel, the four HCC subclasses are indicated with the color keys under “Tumor (subclass)”. Hierarchical clustering discriminates the four subclasses, with 80% of samples correctly classified. Periportal-type HCCs group are strongly enriched in genes upregulated in *Hnf4a*-WT mice.

Supporting Fig. 13. Kaplan-Meier plot of overall survival of individuals in the external validation cohort (210-HCC RNAseq dataset; TCGA, LIHC, US) according to HCC subclass. HCC subclasses are indicated in color. *Green*, Periportal-type; *Red*, Perivenous-type; *Blue*, ECM-type; *Purple*, STEM-type HCCs. **P*<0.05, ***P*<0.01. after log-rank tests.

Supporting Fig. 14. The periportal signature is composed of liver-enriched genes. (A) *AGXT*, (B) *FETUB*, (C) *GLS2*, (D) *GNMT*, (E) *OTC*, (F) *SLC10A1*, (G) *SLC22A7*

and (H) *SLC27A5* mRNA expression data were extracted from the GSE1133 microarray dataset consisting of a panel of 158 samples including 84 different human tissues. Normalized background-corrected intensities of mRNA expression(30) were filtered to reveal the tissues expressing the highest (>3xmedian, >10xmedian or >30xmedian) mRNA levels for each gene. Histograms show mean±SEM for each tissue type. *AGXT*, *FETUB*, *GLS2*, *SLC10A1*, *SLC22A7* and *SLC27A5* are expressed over the threshold of 30x median only in liver samples. *GNMT* is expressed over this threshold in liver and pancreatic islets. *OTC* is expressed over the threshold of 3x median in liver, small intestine, fetal liver and ganglion samples.

Supporting Fig. 15. Expression of the components of the *Periportal HCC Signature* in non-tumor livers (NT), Periportal-type HCCs (PP) and the other HCC subclasses (other HCCs). “Other HCCs” include: Perivenous-type, ECM-type and STEM-type. Samples were extracted from the GSE14520 microarray dataset. Each individual dot corresponds to a tissue sample. The statistical differences between means (horizontal bars) were calculated by ANOVA.

SUPPORTING TABLES

Supporting Table 1. Bibliographic review of studies including HCC patients carrying sequence-verified exon 3 *CTNNB1* (β -catenin) mutations *versus* HCC patients carrying sequence-verified wild-type *CTNNB1* and performing survival analyses: *CTNNB1* exon 3 mutations were reported to be associated with survival in one cohort.(31) However, in this cohort,(31) patients with HCCs carrying wild-type *CTNNB1* were more frequently HBV-infected: [(HBV in liver tissues: mutant *CTNNB1*, 9%; wild-type *CTNNB1*, 24% ($p<10^{-6}$); HBsAg in serum: mutant *CTNNB1*, 46.8%; wild-type *CTNNB1*, 71.5% ($p=1.3\times10^{-3}$)].(31) Thus, HBV infection may constitute a confounding factor because HCCs carrying wild-type *CTNNB1* and arising in a background of HBV infection tend to meet the criteria for high-proliferation class HCCs with bad outcome.(11) In other publications, the association between *CTNNB1* mutation and overall, disease-free survival or disease-specific survival was not significant, even in large cohorts (two large cohort studies with 307(32) and 362(33) annotated patients, respectively). In three publications, *CTNNB1* exon 3 sequencing and patient survival data were available, but no survival analysis comparing HCCs carrying mutated *CTNNB1* *versus* those carrying wild-type *CTNNB1* were reported.(34-36) NA, information Not Available (*gray cells*); NS, non-significant (*light blue cells*); statistically significant ($p<0.05$, *green cells*); HR, Hazards ratio (Cox's Hazards regression); OR, Odds ratio (logistic regression).

Supporting Table 2. Clinical features of HCCs from public datasets and external validation in-house HCC collection used for biomarker search and transcriptome meta-analysis. NA, information Not Available (*gray cells*).

Supporting Table 3. Quality analysis of the nine datasets used for transcriptome meta-analysis. When available, raw data from Gene Expression Omnibus or Array-express were normalized and $\log_2$ intensity expression summary values for each probe set were calculated using robust multiarray average (RMA). When raw data were not available, normalized data were directly used. Then, the probes expressed over the background in at least one of the HCCs were selected and genes were matched by ENTREZ ID. To assess the quality of each dataset, Pearson's correlation coefficients were measured for gene pairs expected to be correlated, as indicated in the table headings.

Supporting Table 4. Sanger sequencing of *CTNNB1* exon 3 mutations in HCCs from the Training Set (n=87), Validation Set (n=56) and the external validation in-house HCC collection (n=82; Rennes Hospital, France).

Supporting Table 5. Predicted *CTNNB1* mutation rates in the nine datasets used for transcriptome meta-analysis. Gene expression data for *GLUL*, *LGR5*, *ODAM*, *HAL* and *VNN1* were extracted from the training and validation sets and from the nine datasets (A to I) and normalized with a median centering in each dataset. Then, the predictive scores were calculated (as shown in Fig. 2C) and the “best common threshold” maximizing sensitivity and specificity in both the training and the validation sets was optimized. In each of the nine datasets, samples with a score higher than the fixed threshold were predicted as carrying mutant *CTNNB1*. AUROC, area under the receiver operating curve. NA, not available.

Supporting Table 6. Number and % of HCCs predicted to carry *CTNNB1* exon 3 mutations in each one of the transcriptomic subclasses (*green, red, blue* or *purple*) according to the individual datasets (A to I).

Supporting Table 7. Gene set expression analysis (GSEA) after classification of 1133 HCCs into four subclasses was performed with the web-based tool developed at the Broad Institute.(16)

Supporting Table 8. Search for Gene Ontology (GO) terms overrepresented in each one of the gene clusters performed with the FuncAssociate 2.0(15) software using *hgnc_symbol* as namespace and $p < 0.05$ as significance cutoff. *LOD* is the $\log_{10}$ of the odds value indicating overrepresentation. Gene subsets were obtained after hierarchical clustering on the basis of the expression profile of the 550 top discriminant genes ($VIP > 1.5$ after PLS-DA analysis) in the metadata set.

Supporting Table 9. RNA expression levels of the 550 genes in the four transcriptomic subclasses of the metadata set. *P* values were obtained by ANOVA. CI: Confidence interval.

Supporting Table 10. Numbers and (%) of HCCs in each one of the transcriptomic subclasses according to the individual datasets. *PP*, Periportal-type; *PV*, Perivenous-type; *ECM*, Extracellular-matrix-type; *STEM*, stem-cell-type.

Supporting Table 11. Number and (%) of HCCs in each one of the transcriptomic subclasses according to the sampling technique (tumor resection or biopsy) and etiology. Significantly predominant subclasses are highlighted in color.

Supporting Table 12. Quality analysis of RNAseq-based dataset extraction from the 210-HCC (TCGA-LICH-US) external validation set. Normalized data were extracted from the TCGA website. To assess the quality of dataset extraction, Pearson's correlation coefficients were measured for gene pairs expected to be correlated, as indicated in the table headings. Correlations are highlighted by a heatmap showing shades of *red*, indicating positive correlations and shades of *blue*, indicating negative correlations. The *Periportal HCC Signature* is highlighted in *green*, stem cell markers in *purple*, positive *CTNNB1* mutation markers in *red* and negative *CTNNB1* mutation markers in *grey*.

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A

Exclusion Criteria

- Cholangiocarcinoma (n=1)
- Fibrolamellar hepatocellular carcinoma (n=2)
- Mixed hepatocellular / cholangiocarcinoma (n=4)
- Unsure diagnosis (n=1)
- Low sample quality (n=2)
- No vital annotation (n=36)
- Patient treated by liver transplantation (n=1)
- History of prior malignancy (n=19)
- New primary tumor (n=7)
- Early death (< 90 days post resection, n=11)

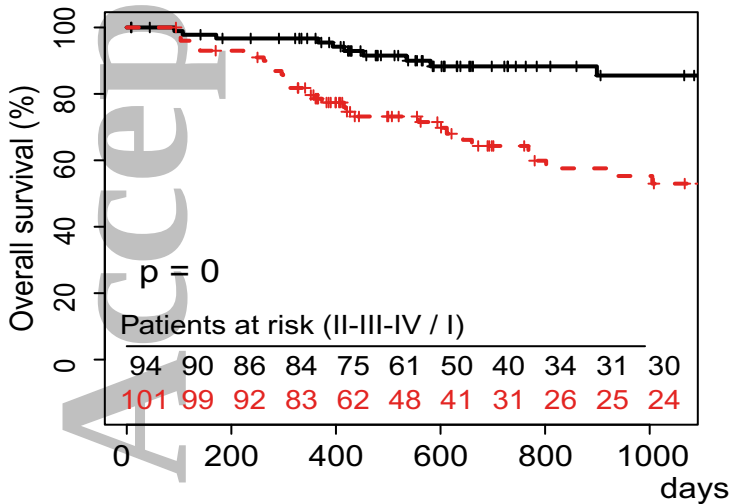
Available HCC samples

with RNAseq and clinical annotation data
(n=294)

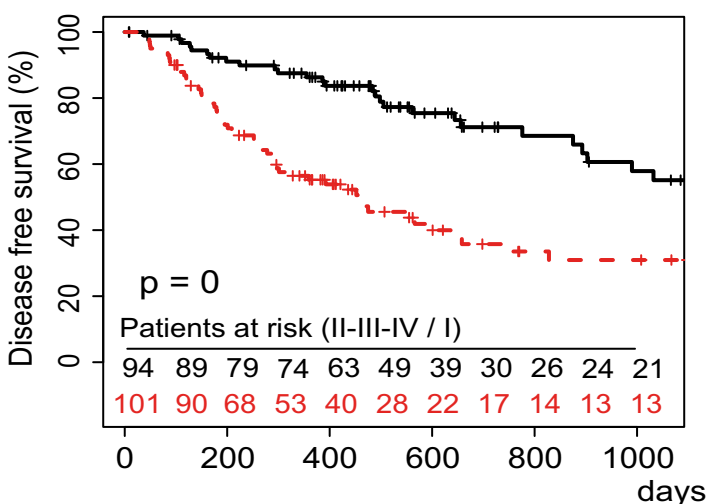
Analysed samples (n=210)

B

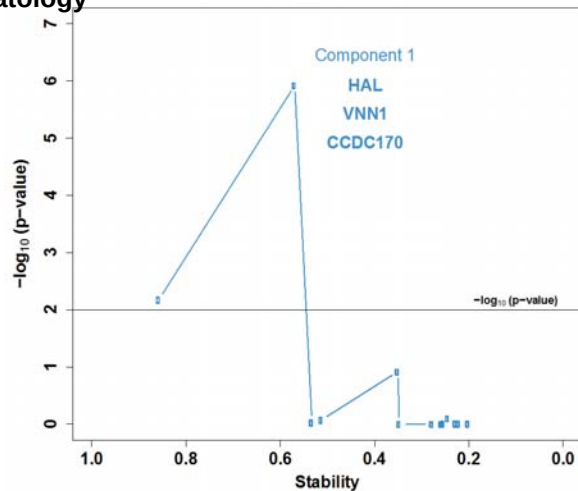
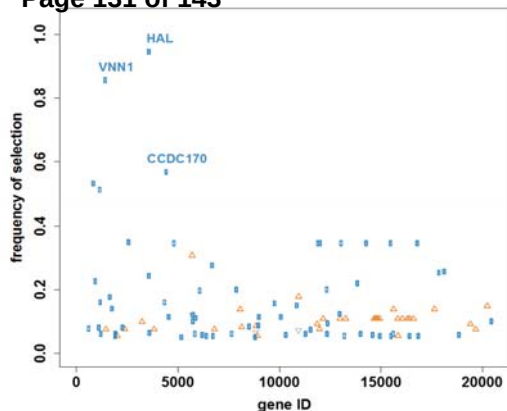
TNM staging (II-III-IV versus I)



TNM staging (II-III-IV versus I)



Hepatology



Classification accuracy (%)	wild type	mutated	Total
Training set	85.00	92.60	87.36
Validation set	97.44	82.35	92.86

Hepatology

External validation (in-house, qPCR)

Training set

HCCs, n=87	GLUL	LGR5	ODAM	HAL	VNN1
LGR5	0.71				
ODAM	0.65	0.71			
HAL	-0.76	-0.71	-0.68		
VNN1	-0.61	-0.67	-0.67	0.79	
AXIN2	0.78	0.83	0.74	-0.81	-0.73

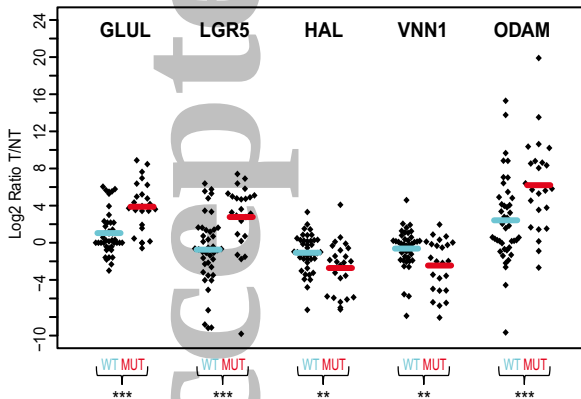
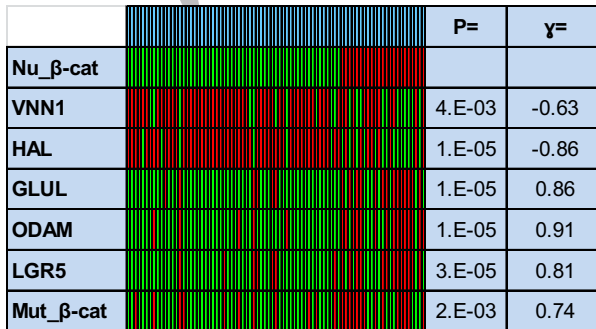
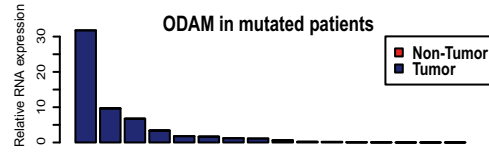
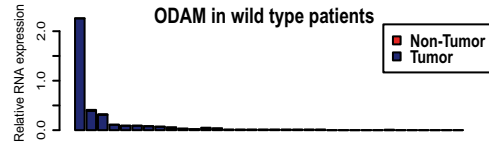
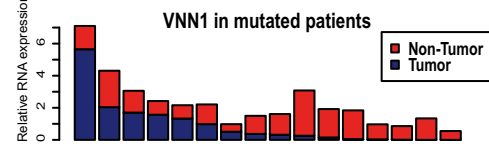
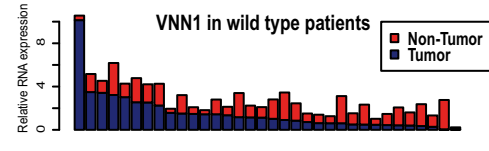
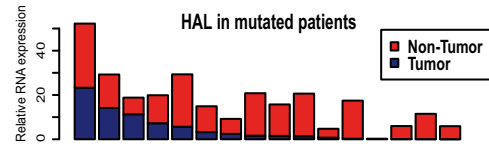
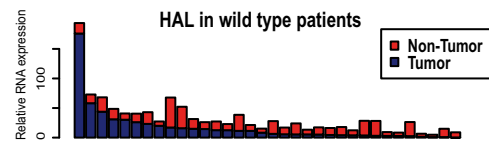
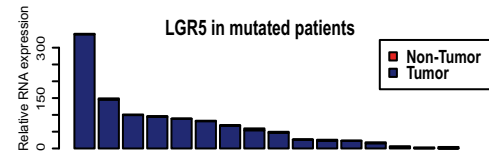
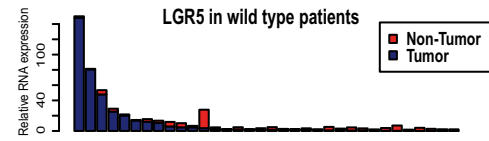
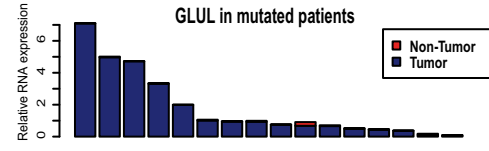
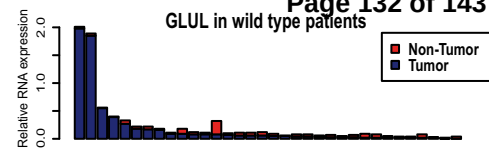
HCCs, n=82	GLUL	LGR5	ODAM	HAL	VNN1
LGR5	0.83				
ODAM	0.79	0.75			
HAL	-0.51	-0.49	-0.54		
VNN1	-0.35	-0.31	-0.33	0.48	
AXIN2	0.9	0.88	0.82	-0.5	-0.33

Validation set

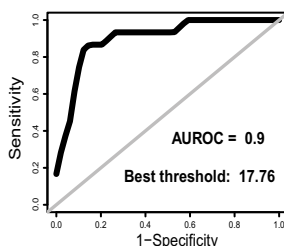
HCCs, n=8	GLUL	LGR5	ODAM	HAL
LGR5	0.80			
ODAM	0.77	0.75		
HAL	-0.68	-0.65	-0.72	
VNR1	-0.43	-0.50	-0.64	0.58

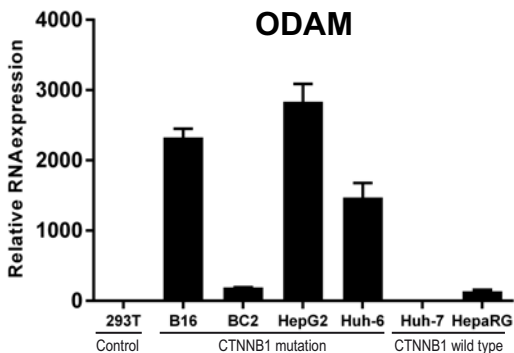
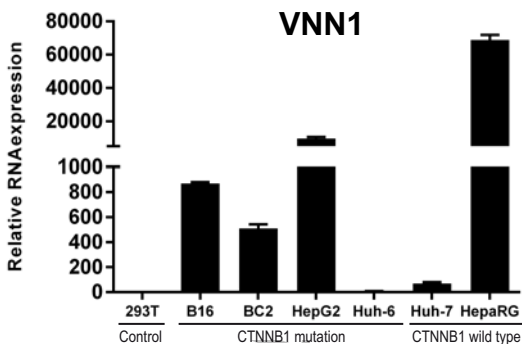
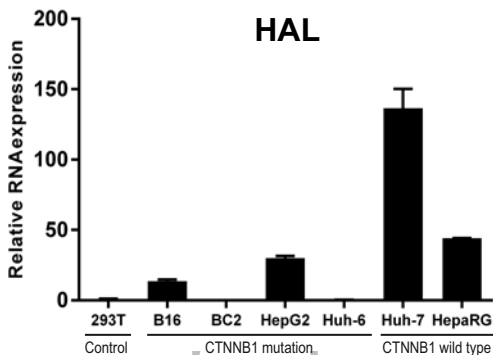
NT, n=66	GLUL	LGR5	ODAM	HAL
LGR5	0.49			
ODAM	0.44	0.4		
HAL	0.07	-0.12	0.17	
VNN1	0.48	0.21	0.01	0.15

Ratios, n=66	GLUL	LGR5	ODAM	HAL
LGR5	0.78			
ODAM	0.71	0.65		
HAL	-0.41	-0.41	-0.41	
VNN1	-0.19	-0.20	-0.12	0.41

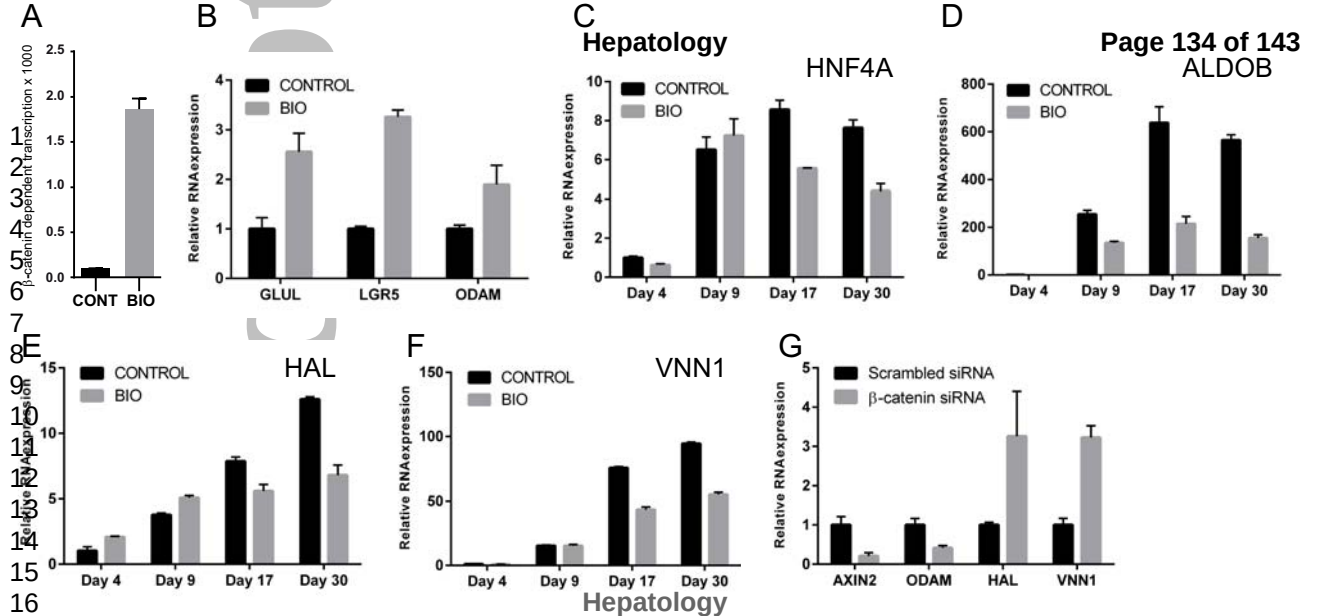
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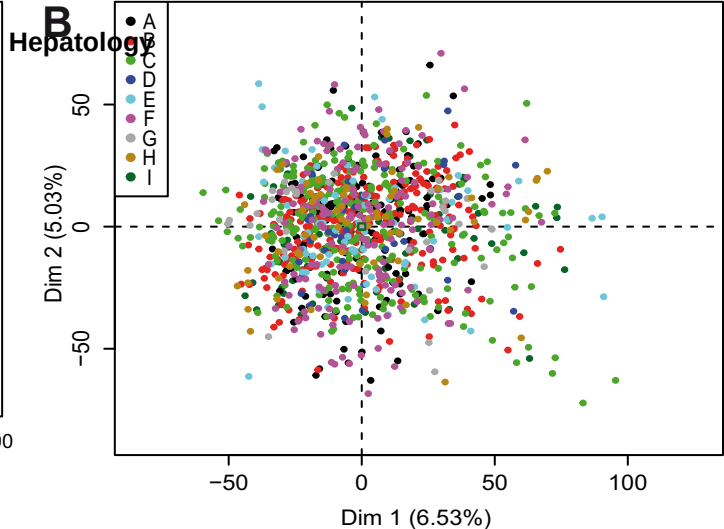
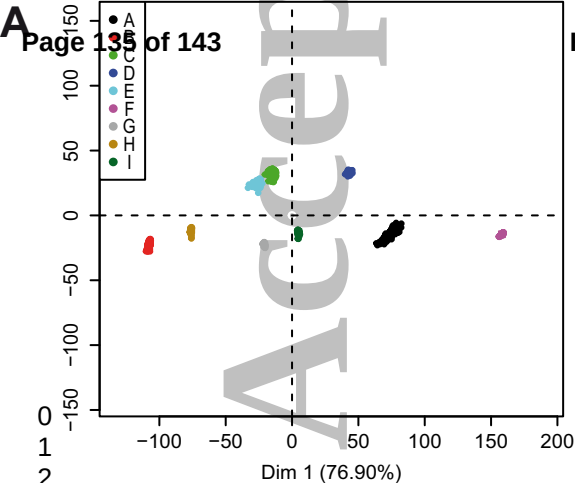
	AUROC	Fold change MUT/WT (95%CI)	p value	Se	Sp
44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	0.86	[1.65 - 23.81]	6.81E-05	0.80	0.88
GS ratio T/NT	0.81	[1.45 - 5.93]	3.12E-04	0.80	0.82
LS ratio T/NT	0.69	[0.11 - 0.7]	3.34E-02	0.82	0.60
HS ratio T/NT	0.65	[0.09 - 0.7]	9.29E-02	0.91	0.47
VM ratio T/NT	0.86	[2.07 - 26.16]	4.92E-05	0.80	0.76
QAM ratio T/NT	0.90	[2.04 - 3.08]	1.05E-06	0.87	0.88
Score ratio T/NT					





Hepatology





% of predicted
CTNNB1 mutation

Predicted mutation



Mutant



Wild type

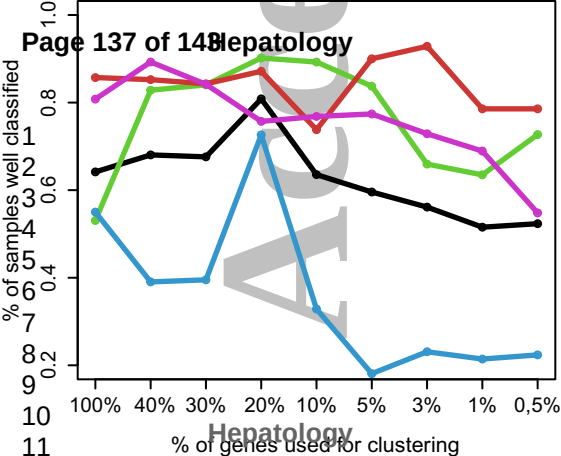
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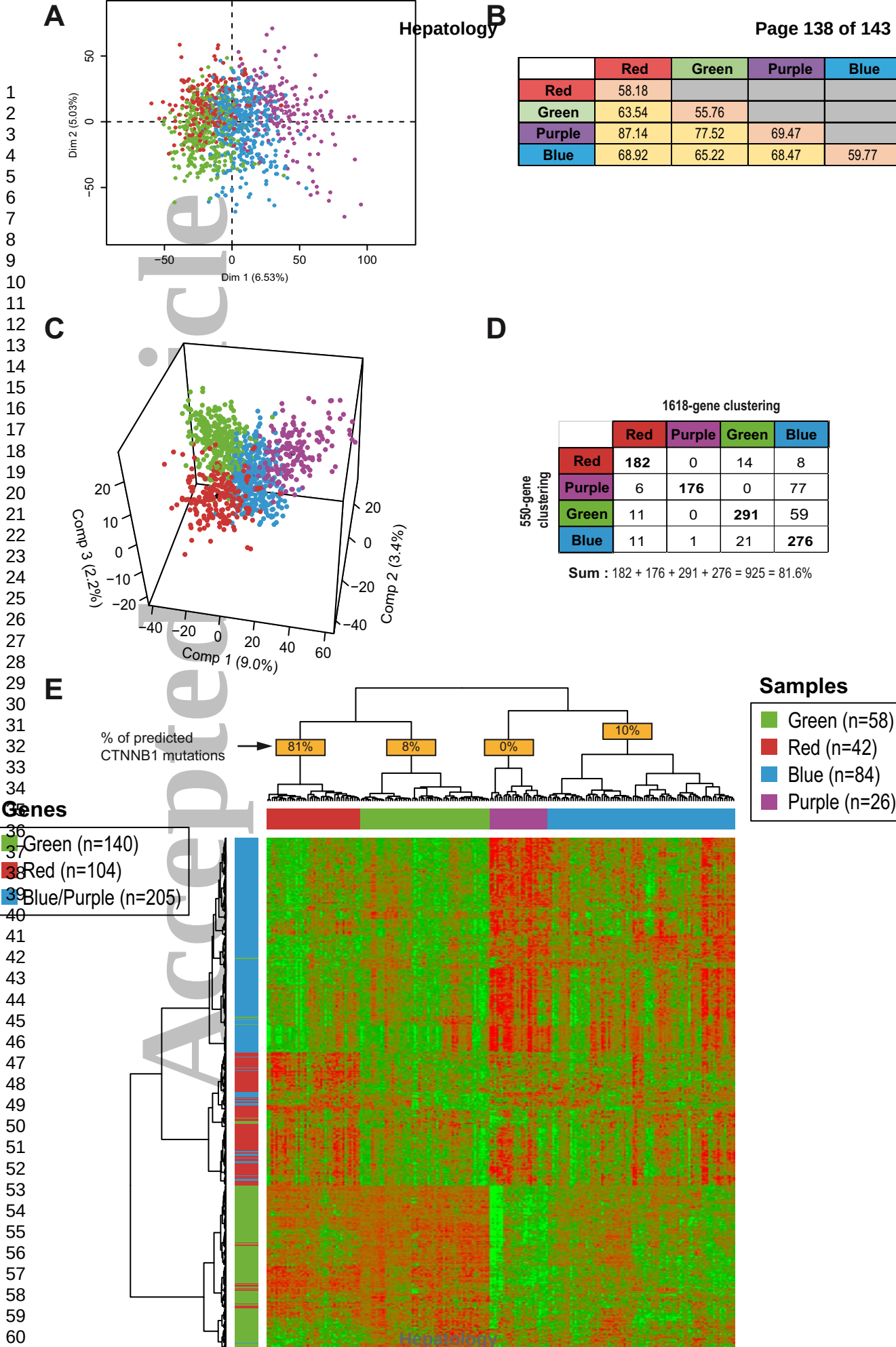
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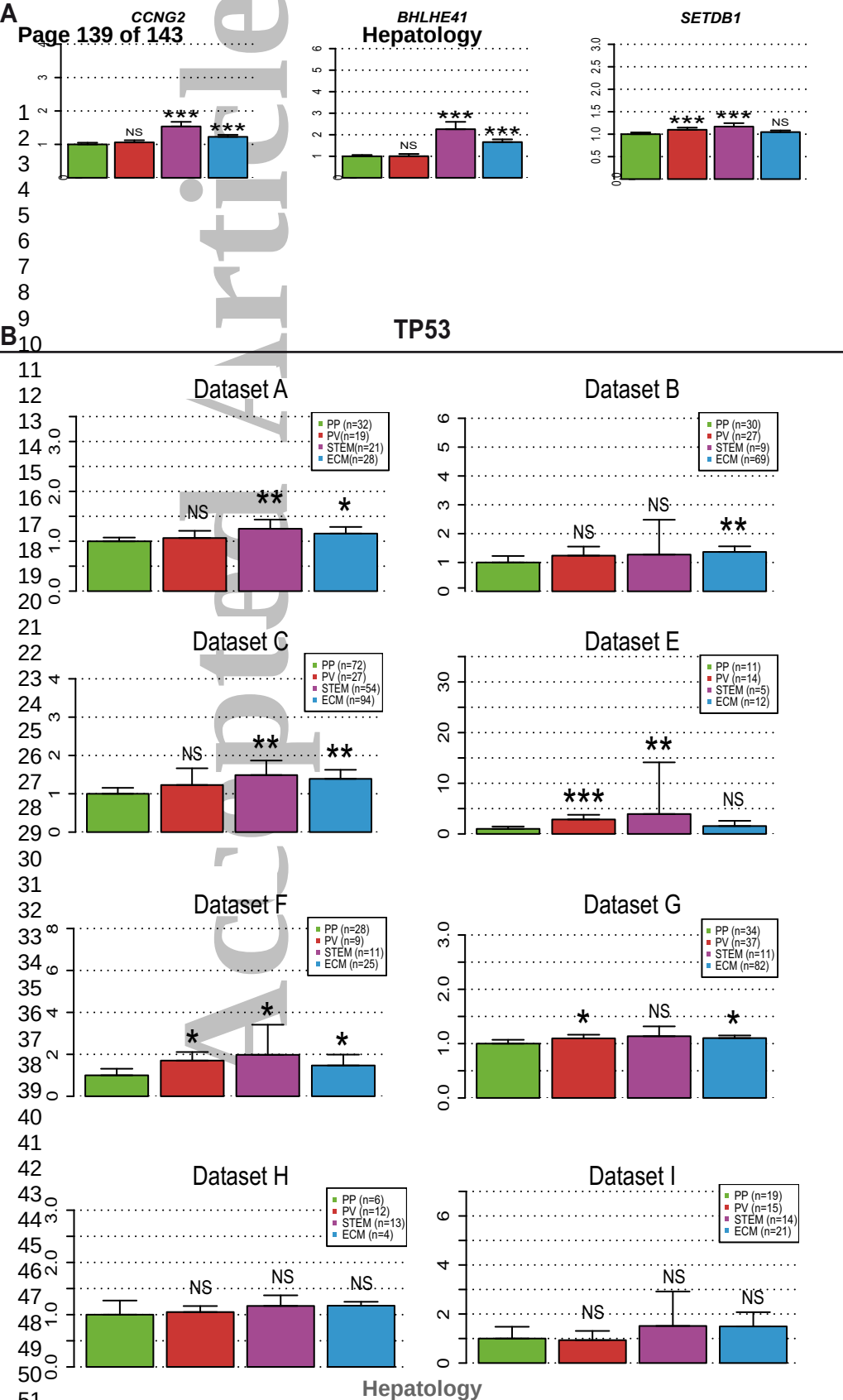
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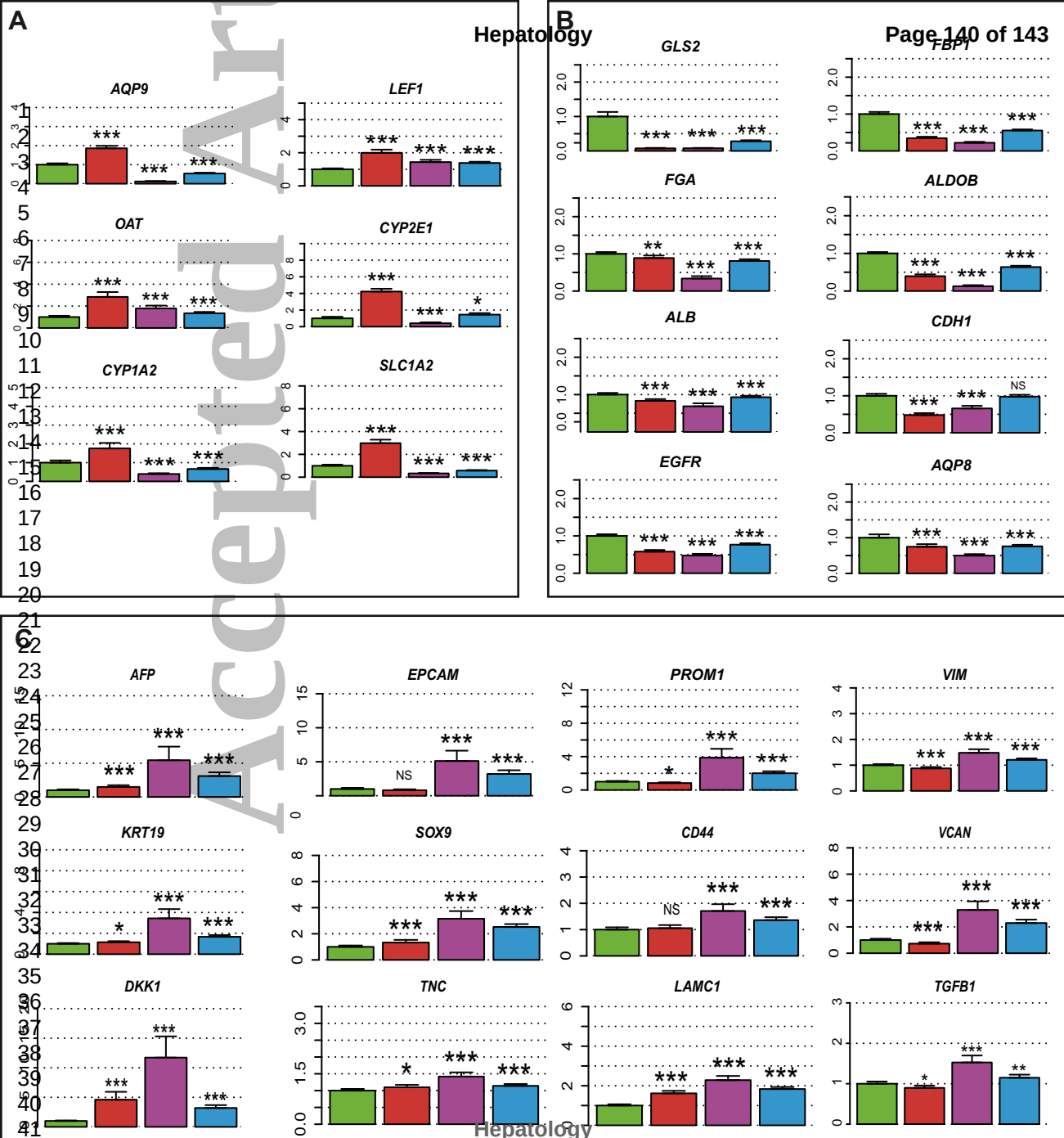
Hepatology

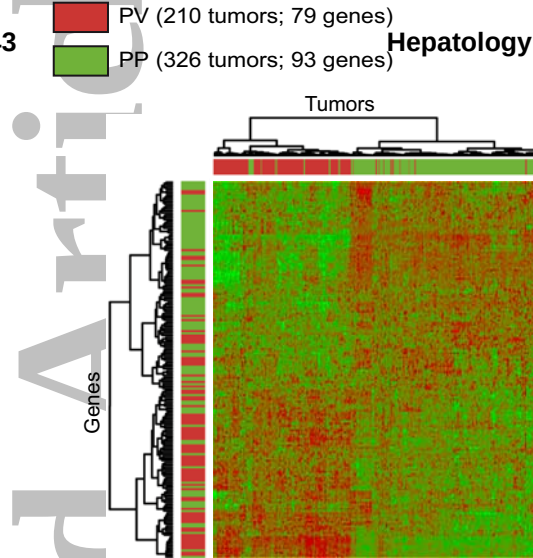


Hepatology

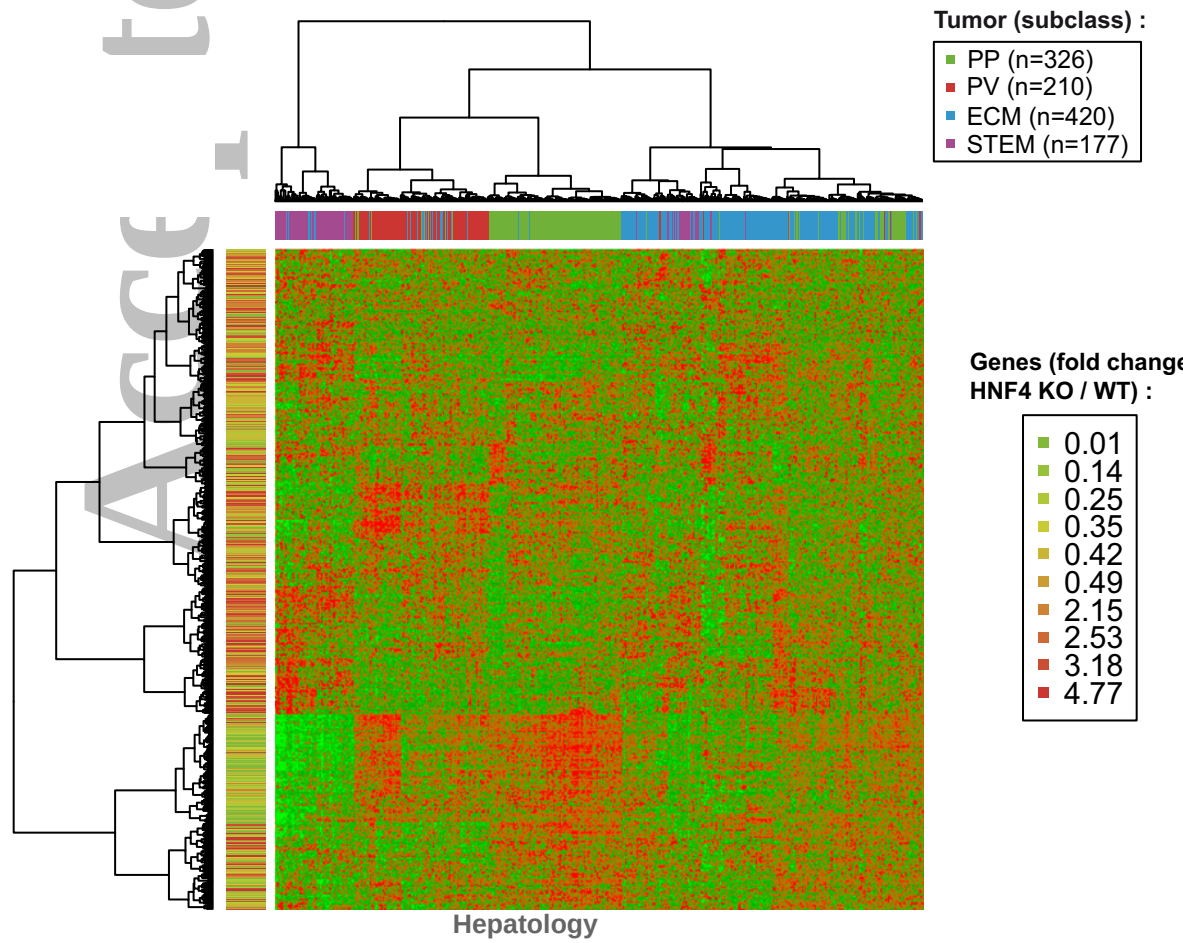


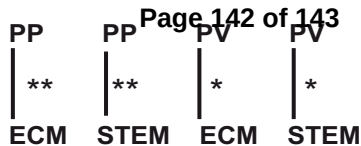
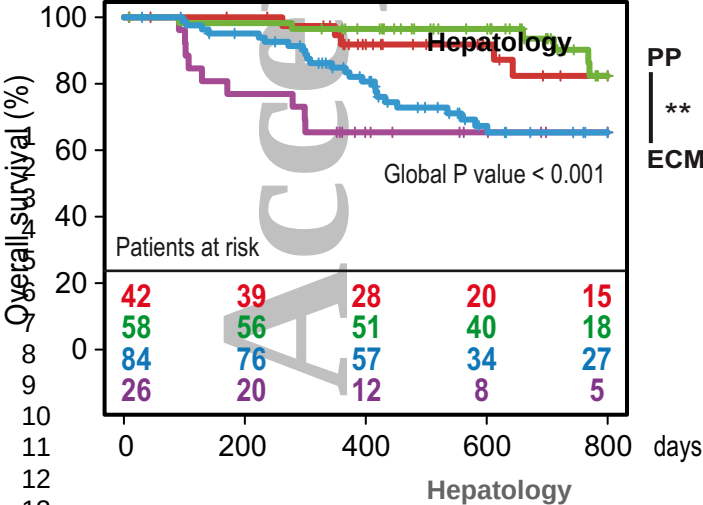


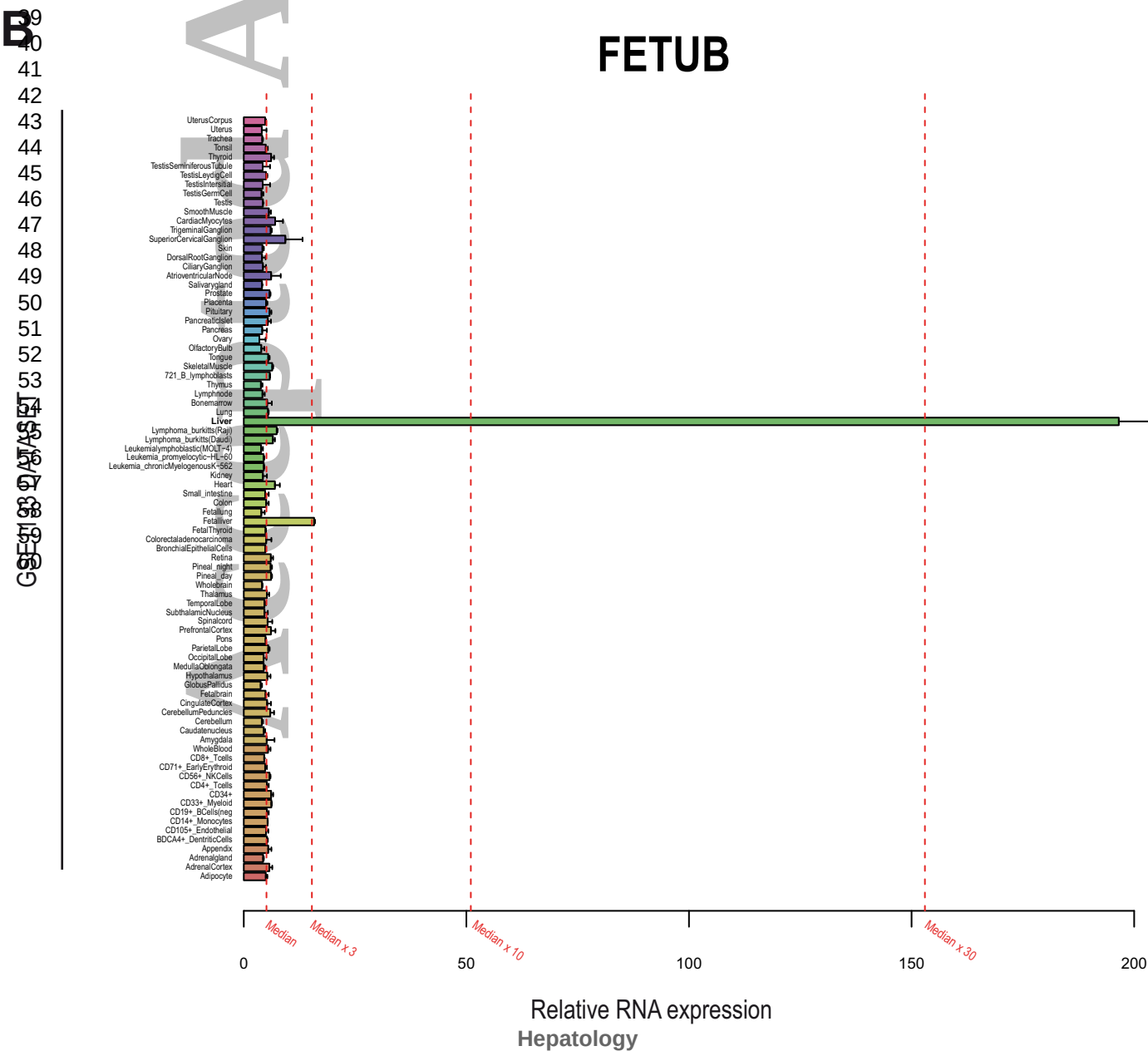
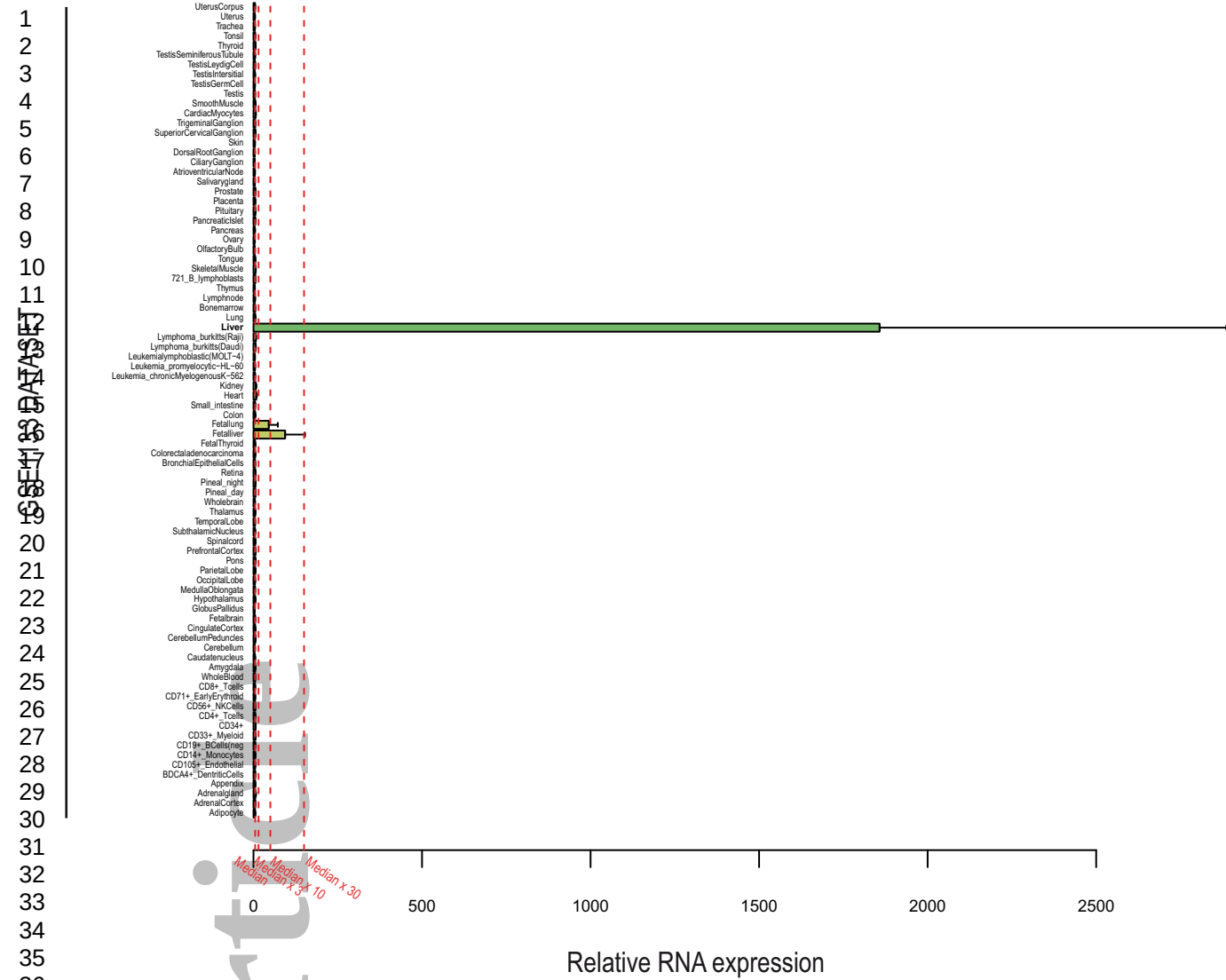




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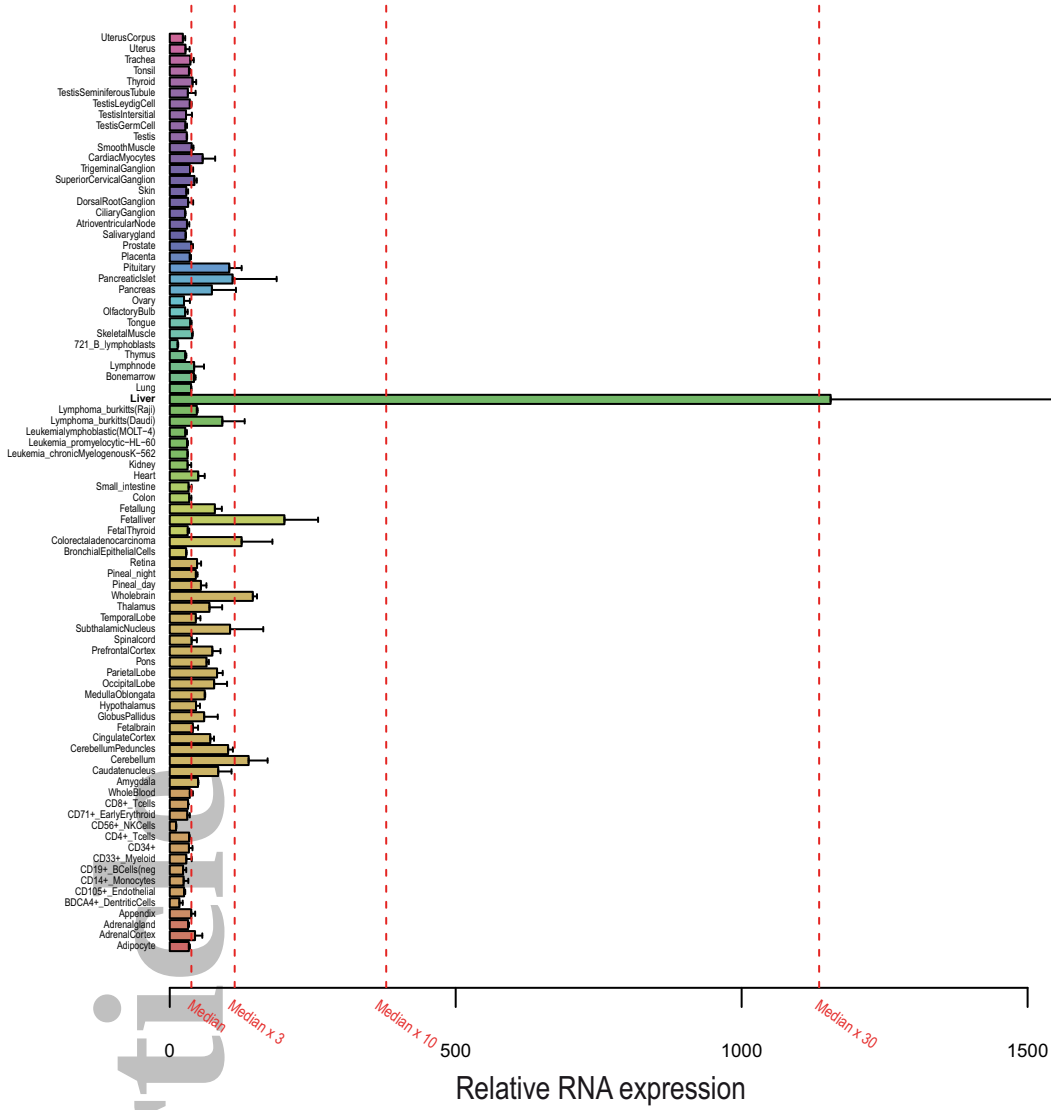




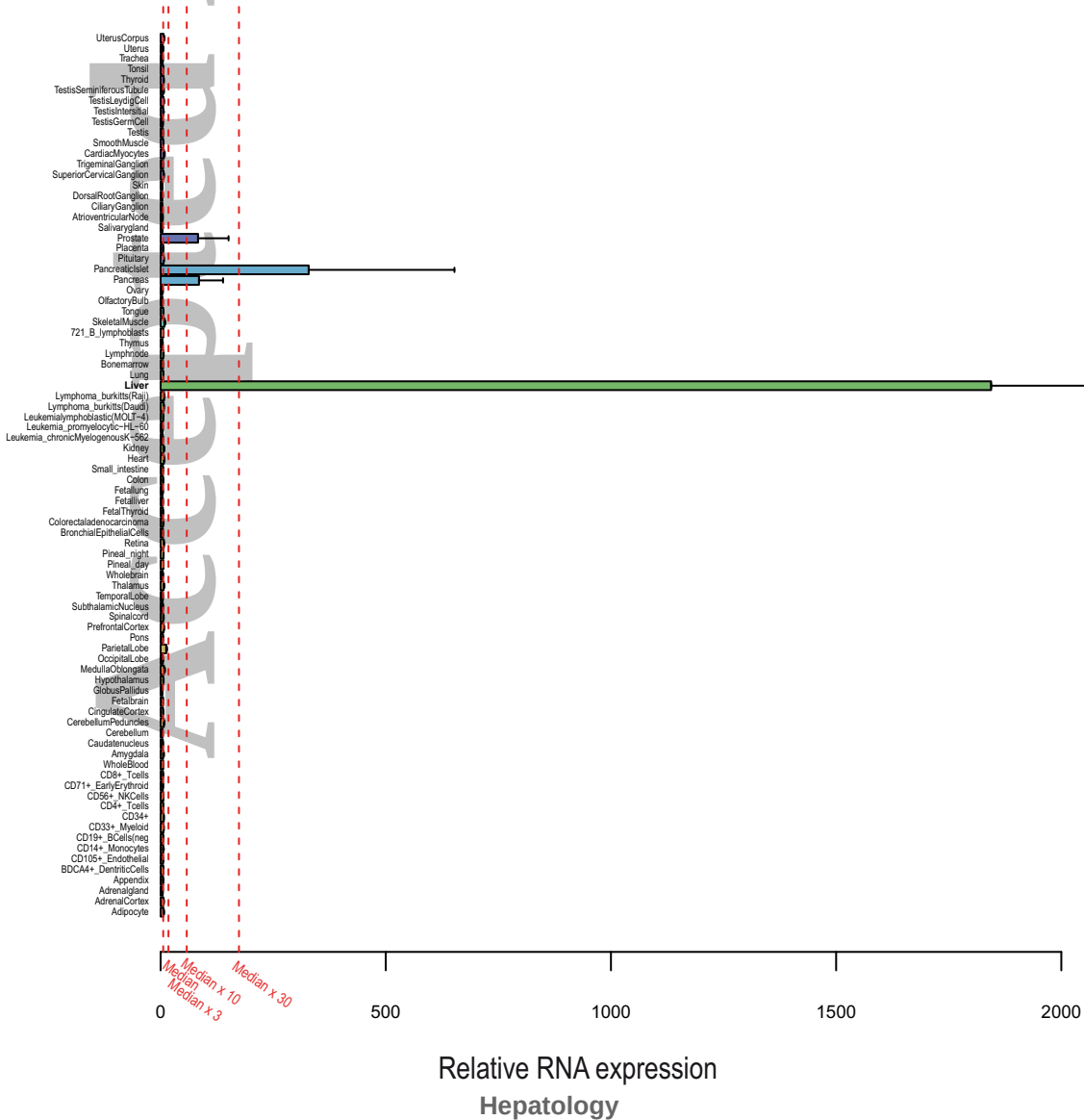


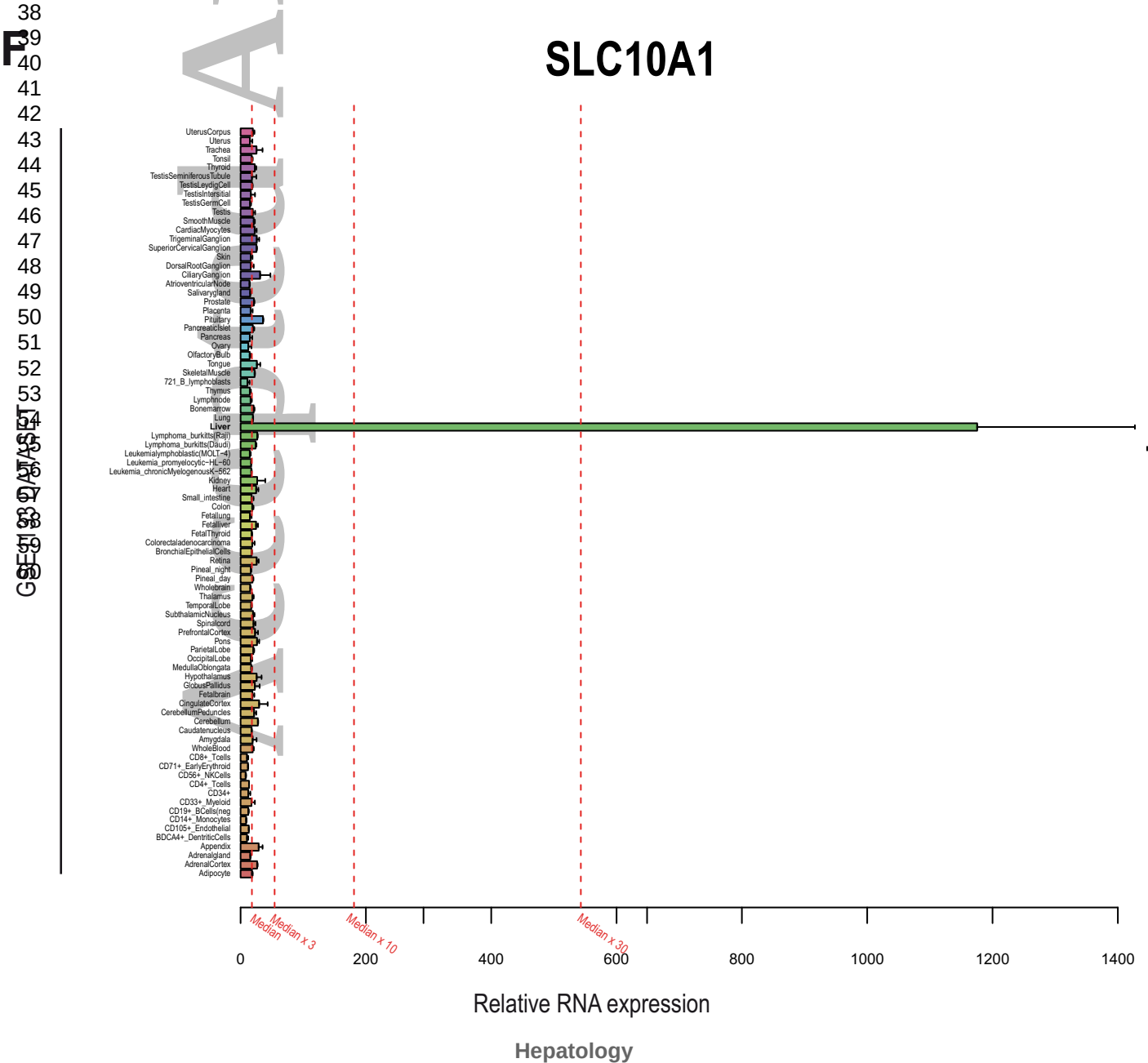
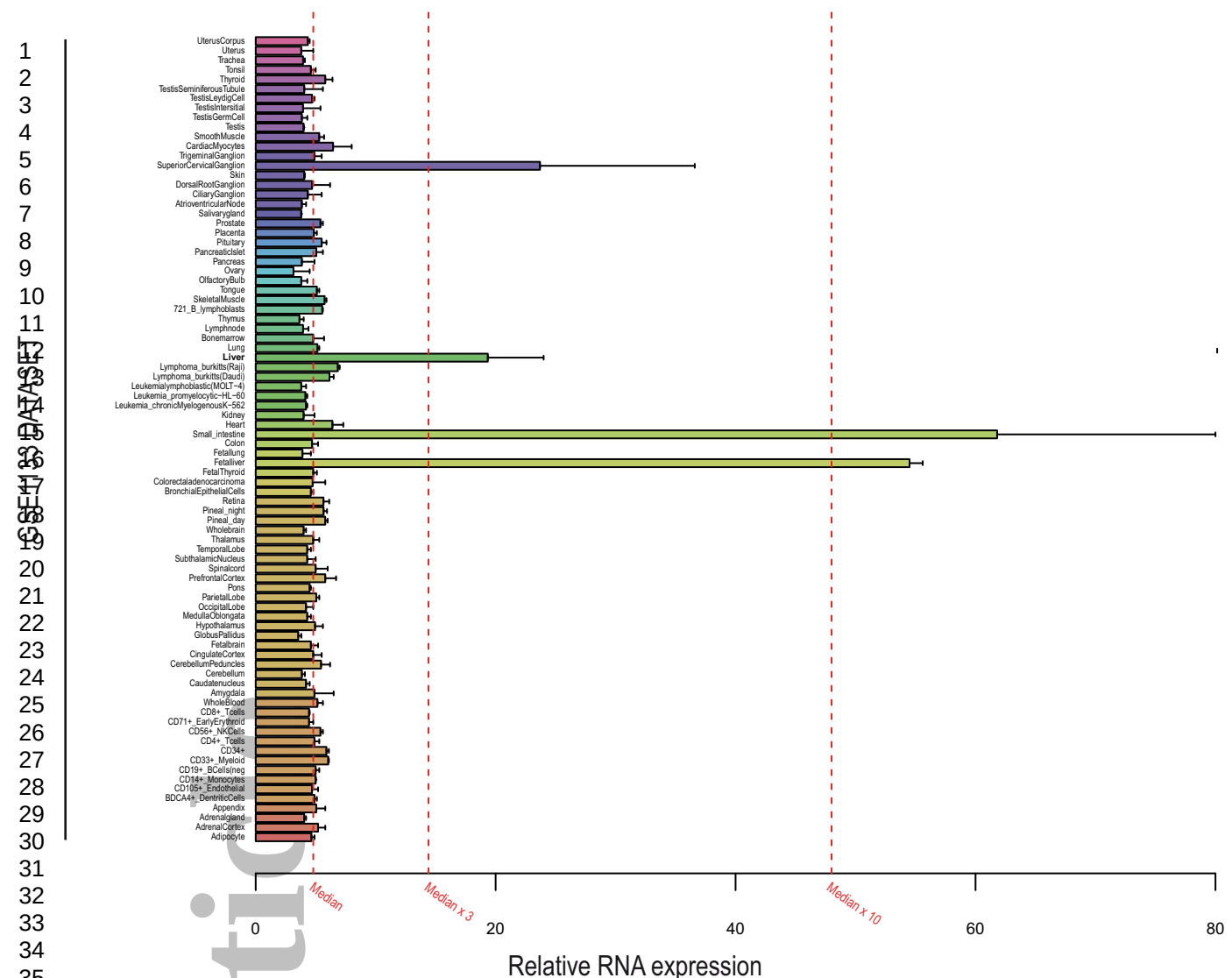
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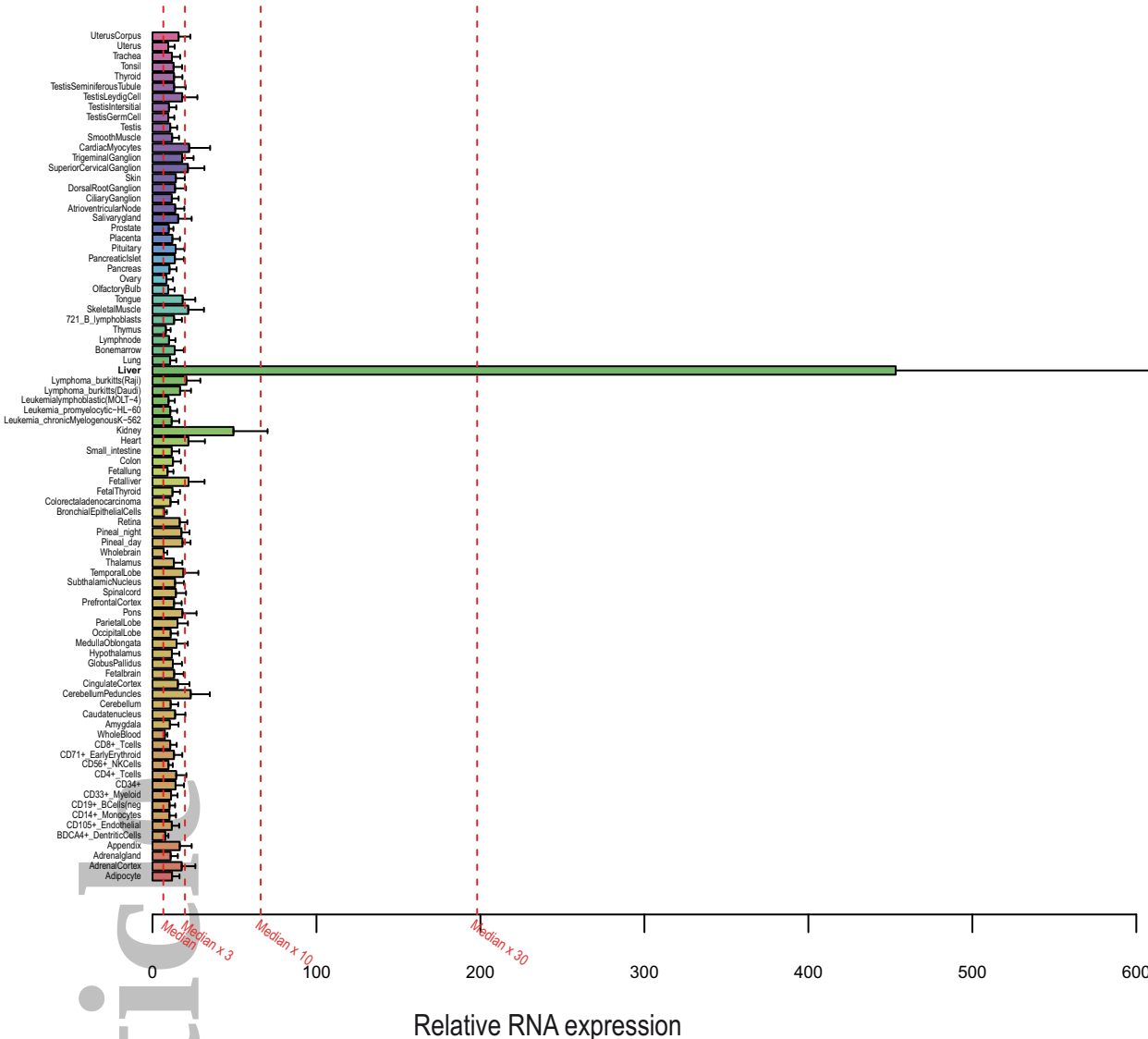


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