



The β -Catenin Pathway is Activated in Focal Nodular Hyperplasia but not in Cirrhotic FNH-like Nodules

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Key Words:	Focal nodular hyperplasia, zonation, glutamine synthetase, benign tumor, diagnostic markers, beta-catenin
Abstract:	<p>Background & Aims: Focal nodular hyperplasias (FNHs) are benign liver lesions considered to be a hyperplastic response to increased blood flow in normal liver. In contrast, FNH-like occur in cirrhotic liver but share similar histopathological features. To identify biological pathways deregulated in FNH, we conducted a transcriptome analysis. Methods: Gene expression profiles obtained in FNH and normal livers were compared. Differentially-expressed genes were validated using quantitative-RT-PCR in 70 benign liver tumors including FNH-like lesions. Results: Among the deregulated genes in FNHs, 19 displayed physiological restricted distribution in the normal liver. All six perivenous genes were up-regulated in FNH, whereas 13 periportal genes were down-regulated. Almost all these genes are known to be regulated by β-catenin. Glutamine synthetase was markedly overexpressed in anastomosed areas usually centered on visible veins. Moreover, activated hypophosphorylated β-catenin protein accumulated in FNH in the absence of activating mutations. These results suggest the zoned activation of the β-catenin pathway in FNH, whereas the other benign hepatocellular tumors, including FNH-like lesions, demonstrated an entirely different pattern of β-catenin expression. Conclusions: In FNH, increased activation of the β-catenin pathway</p>

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The β -Catenin Pathway is Activated in Focal Nodular Hyperplasia but not in Cirrhotic FNH-like Nodules

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Short title: β -catenin activation in focal nodular hyperplasia

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Keywords: Focal nodular hyperplasia; zonation; β -catenin; glutamine synthetase; benign tumor; diagnostic markers; transcriptome; microarray.

Abbreviations: FNH (Focal Nodular Hyperplasia), HCA (hepatocellular adenoma), RT-PCR (Reverse Transcriptase Polymerase Chain Reaction), GLUL (gene coding for glutamine synthetase), GS (Glutamine Synthetase), AAT1 (alpha-1 antitrypsin deficiency), APC (adenomatosis polyposis coli), CTNNB1 (gene coding for beta-catenin), ANGPT1 and ANGPT2 (genes coding for angiopoietin 1 and 2, respectively), HNF1 α (hepatocyte nuclear factor 1 alpha), TCF1, transcription factor 1 (gene coding for HNF1alpha), HGDN (high-grade dysplastic nodules), LGDN (low-grade dysplastic nodules), MRN (macroregenerative nodules), GSK3beta (glycogen synthase kinase 3 beta)

Abstract

Background & Aims: Focal nodular hyperplasias (FNHs) are benign liver lesions considered to be a hyperplastic response to increased blood flow in normal liver. In contrast, FNH-like occur in cirrhotic liver but share similar histopathological features. To identify biological pathways deregulated in FNH, we conducted a transcriptome analysis.

Methods: Gene expression profiles obtained in FNH and normal livers were compared. Differentially-expressed genes were validated using quantitative-RT-PCR in 70 benign liver tumors including FNH-like lesions.

Results: Among the deregulated genes in FNHs, 19 displayed physiological restricted distribution in the normal liver. All six perivenous genes were up-regulated in FNH, whereas 13 periportal genes were down-regulated. Almost all these genes are known to be regulated by β -catenin. Glutamine synthetase was markedly overexpressed in anastomosed areas usually centered on visible veins. Moreover, activated hypophosphorylated β -catenin protein accumulated in FNH in the absence of activating mutations. These results suggest the zonated activation of the β -catenin pathway in FNH, whereas the other benign hepatocellular tumors, including FNH-like lesions, demonstrated an entirely different pattern of β -catenin expression.

Conclusions: In FNH, increased activation of the β -catenin pathway was found restricted to enlarged perivenous areas. FNH-like nodules may have a different pathogenetic origin.

Introduction

Focal nodular hyperplasia (FNH), first described by Edmondson (1), is the second most common benign liver tumor, outnumbered only by hemangioma. FNH usually occurs in women 20–50 years old. A relation between FNH and oral contraceptive use has been reported but is disputed (2). Classical FNH is characterized by a central stellate fibrous region containing malformed vascular structures (3). The solitary central artery with high flow and the absent portal vein give the lesions a characteristic radiological appearance (4) in more than 80% of FNH cases. However, some classical FNHs, mainly those smaller than 3 cm, have no central scar at pathological examination (5). In all cases, the treatment of FNH is conservative because there is very low risk of complications such as bleeding, and malignant transformation has not yet been proven (6).

FNH typically occurs in normal or almost normal liver. The lesion is multinodular, composed of nearly normal hepatocytes arranged in 1–2–cell-thick plates. Bile ductules are usually found at the interface between hepatocytes and fibrous regions (7, 8). It is thought that increased arterial flow hyperperfusion the local parenchyma, leading to secondary hepatocellular hyperplasia. FNH is therefore considered a hyperplastic response to increased blood flow, rather than a neoplastic process (3, 9, 10). Various vascular abnormalities such as telangiectases, hereditary hemorrhagic telangiectasia, arteriovenous malformation, and anomalous venous drainage may be present, especially in patients with multiple FNHs.

Clonal analysis demonstrated the reactive polyclonal nature of liver cells in FNH in 60–100% of cases, depending on the series (11–15). Other studies analyzing chromosome gains and losses by comparative genomic hybridization, allelotyping, or karyotyping identified chromosome alterations indicating a clonal origin of the FNH nodules in 14–50% of cases (2, 15, 16). However, genetic analysis of FNH did not demonstrate somatic gene mutations in *CTNNB1*, *TP53*, *TCF1* or *APC* (15, 17, 18). Recently, it was shown that two angiopoietin genes (*ANGPT1* and *ANGPT2*) involved in vessel maturation have altered mRNA expression levels, with a consistently increased *ANGPT1/ANGPT2* ratio in FNH.(14, 15)

Focal nodular hyperplasia-like (FNH-like) nodules are lesions arising in cirrhotic liver that closely resemble FNH at both the morphological and radiological levels (19, 20). It has been hypothesized that FNH-like nodules arise as a local hyperplastic response to vascular alterations (20, 21) known to occur in liver cirrhosis (3). However, the exact pathogenesis of FNH-like nodules remains to be elucidated.

β -catenin in focal nodular hyperplasia

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To better understand the pathophysiology of FNH, we searched for genes deregulated in FNH by conducting a combined cDNA and oligonucleotide transcriptomic analysis exploring expression of more than 15,000 different genes. In this experiment, transcriptome profiles of eight FNHs were compared to six non-tumor liver samples. After the analysis, selected genes belonging to the most strongly activated or inactivated pathways were validated using quantitative RT-PCR in a larger series of 70 benign liver tumors including FNH, hepatocellular adenomas (HCA), macroregenerative and dysplastic cirrhotic nodules, and FNH-like lesions.

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Material and Methods

Patients and Samples

A series of 11 FNHs, 15 HCAs, 6 normal liver tissues [including samples taken at a distance from HCAs (3), FNHs (1), and hemangiomas (2)], 8 cirrhotic nodules [including 3 high-grade dysplastic nodules (HGDN), 1 low-grade dysplastic nodules (LGDN), and 4 macroregenerative nodules (MRN)], 11 FNH-like nodules, and 19 samples of random cirrhotic liver [including samples taken at a distance from hepatocellular carcinoma (8), FNH-like nodules (7), and dysplastic nodules (4)] were collected at the University Hospital of Bordeaux and Leuven. HCAs were classified as described previously;(22, 23) five cases were HNF1 α -inactivated, five were β -catenin-mutated, and the remaining five HCAs were non-mutated and inflammatory. For all cases included in this study, full clinical and morphological data were available and are summarized in Table 1. Frozen tissue samples were available for all cases, and the prerequisite to include samples in the study was an adequate sampling of fresh and fixed liver tissue. This study was conducted with the authorization of our local ethics committees (CCPPRB Paris Saint-Louis, France, and Committee from the University Hospitals, Leuven).

For each case, tissue from surgical samples including the nodules and corresponding non-tumor tissue was cut into thin slices. A representative portion of the nodule, as well as of the non-tumor liver, was immediately frozen in liquid nitrogen and stored at -80°C until used for molecular studies. Paraffin tissue sections were routinely stained with H&E and Masson's trichrome for diagnostic purposes. Pathological diagnosis of FNH and HCA was made on the basis of classical criteria (7, 8).

DNA and RNA were extracted as described previously.(15) DNA was quantified by fluorometry (Fluoroskan Thermo Labssystem, Cergy-Pontoise, France). The quality of DNA and RNA was assessed by gel electrophoresis followed by staining with ethidium bromide, and degraded samples were excluded. RNA was accepted for quantitative RT-PCR if the 28S/18S ratio was greater than 1. For microarray analysis, RNA was analyzed by Agilent Bioanalyzer profiling, and RNA was qualified if the 28S/18S ratio was greater than 1.5 and if the RNA was not degraded.

Microarray Analysis

Transcriptional profiling of FNH lesions and non-tumor liver tissues was performed using two different microarray approaches (Affymetrix oligonucleotide GeneChips U133 and a cDNA microarray). Minimum Information about a Microarray Experiment (MIAME)-compliant data were deposited in Gene Expression Omnibus (GEO) at NCBI (<http://www.ncbi.nlm.nih.gov/geo/>) and are accessible through GEO series accession number GSE9536. The characteristics of the in-house

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3 manufactured cDNA array are described in Graudens et al. 2006 Additional data file 2 (24). The
4 detailed procedure for the gene array analysis is provided in the supplementary material and
5 methods. Gene ontology (GO) categories that were significantly over-represented in FNH were
6 determined by the hypergeometric test using the web-based tool GOTree Machine (GOTM)
7 (<http://bioinfo.vanderbilt.edu/gotm/>). Distribution in GO categories of genes significantly up-
8 regulated and down-regulated in FNH were compared to the distribution of the overall genes
9 included in the HG-U133A Affymetrix array. GO categories were considered significantly enriched
10 when the *P*-value was less than 0.01.
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20 **Quantitative RT-PCR**

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22 Quantitative RT-PCR was performed as described previously (25) using pre-designed primers
23 and probe sets from Applied Biosystems for the detection of *R18S*, *NTS*, *HAL*, *ANGPT1*, *ANGPT2*,
24 *GLUL*, *GPR49* (*LGR5*), *SDS* and *CTNNB1*. Ribosomal 18S RNA (*R18S*) was used for the
25 normalization of expression data. The relative amount of mRNA in samples was determined using
26 the $2^{-\Delta\Delta CT}$ method, where $\Delta\Delta CT = (CT_{\text{target}} - CT_{R18S})_{\text{sample}} - (CT_{\text{target}} - CT_{R18S})_{\text{calibrator}}$.
27 Final results were expressed as the *n*-fold differences in target gene expression in tested samples
28 compared with the mean expression value of non-tumor tissues.
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35 **Immunohistochemistry**

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37 Immunostaining was performed on 5- μ m sections of formalin-fixed, paraffin-embedded liver
38 samples using a Dako autostainer. A monoclonal antibody against β -catenin (1:200, BD
39 Biosciences 610153) and a biotinylated mouse antibody against glutamine synthetase (1:400, BD
40 Biosciences) were used for immunostaining. Prior to immunostaining, endogenous peroxidase was
41 blocked, and antigen retrieval was performed in a bain-marie with 0.001 M citrate buffer, pH 6, at
42 98°C. Detection was amplified by the Dako Envision system.
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49 **Western Blotting**

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51 Total protein extracts were obtained after tissue homogenization in RIPA lysis buffer (Santa
52 Cruz Biotechnology), and protein concentration was determined using a Pierce BCA protein assay
53 kit. A mouse monoclonal antibody specific for the dephosphorylated, active form of β -catenin
54 (Upstate Biotechnology, 05-665) was used at a 1:500 dilution. Rabbit polyclonal antibodies were
55 used at a 1:500 dilution for the detection of GSK3 β and phospho GSK3 β ser9 (Cell Signalling).
56 Ponceau Red staining was used to evaluate protein loading and to normalize the signals. Detection
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β -catenin in focal nodular hyperplasia

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was performed using the ECL SuperSignal West Pico Chemiluminescent Substrate (Pierce) and horseradish peroxidase-conjugated anti-mouse IgG (1:4000, Amersham) as the secondary antibody.

Statistical Analysis

All reported values are mean \pm SD. Statistical analysis was performed using GraphPad Prism version 4 software, and significance was determined using the nonparametric Mann-Whitney test for unpaired data. A difference was considered significant at $P < 0.05$.

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β-catenin in focal nodular hyperplasia

Results

Identification of Overexpressed Genes Encoding Proteins of the Extracellular Matrix

Analysis of the Affymetrix and cDNA microarray results revealed 240 and 284 genes that were respectively significantly up- and down-regulated in FNH compared to control non-tumor liver samples (Supplementary Table 1). We analyzed these sets of genes to identify biological pathways that were specifically altered. Using a gene ontology-based analysis, we identified several GO categories that were significantly over-represented in FNH (Supplementary Table 2). Among the up-regulated genes in FNH, the extracellular matrix and cell adhesion terms achieved the highest degree of significance ($P=6.10^{-22}$ and $P=8.10^{-12}$ respectively) (Table 2). The overexpression of the genes encoding proteins of the extracellular matrix is consistent with the presence of fibrosis in most cases of typical FNH, particularly in the fibrous scar area. In FNH, fibrosis appears as a blue area as revealed using trichrome staining (Fig. 1A and B) or is also immunostained using anti-collagen IV antibodies (Fig. 1C-E). This profile of expression is characteristic of the TGF-β-dependent pathways. Accordingly, we identified a two-fold overexpression of the TGF-β1 gene in FNH, as well as overexpression of other key genes involved in fibrogenesis such as *PDGFA* and *PDGFRB*. A smooth muscle actin (SMA) staining was observed in myofibroblasts present at the periphery and within the fibrotic area (Fig. 1G-H). These results are consequently consistent with an activation of the TGFβ pathway in cells located around the central fibrous scar.

Expression of Zonated Genes is altered in FNH

Nineteen regulated genes were identified whose expression is physiologically zonated in the hepatic lobule. In addition, the expression of these genes is known or was previously suggested to be regulated by β-catenin (Table 3) (26, 27). Among these, the expression of 13 genes physiologically expressed in the periportal area was down-regulated in FNH. Moreover, the expression of six genes normally expressed in the perivenous area was up-regulated in FNH nodules, suggesting altered zonation in FNH. To further explore this phenomenon, we analyzed the architectural distribution of glutamine synthetase (GS), a well characterized overexpressed protein in FNH that is physiologically expressed in only one or two plates of hepatocytes immediately adjacent to the central veins in normal liver (Fig. 1I). In FNH, we observed the overexpression of GS in hepatocytes that were heterogeneously distributed in the nodules. A systematic analysis of the staining architecture showed a non-random distribution of the highly stained hepatocytes over relatively large areas, often anastomosed in “map-like” patterns centered on central veins, whereas they remained at a distance from fibrous bands (Fig. 1J and 1K). This zonal distribution pattern of

GS expression in FNH strongly differs from the homogeneous staining usually observed in β -catenin–mutated adenomas (22).

The expression of *GLUL*, the gene encoding GS, is known to be up-regulated by β -catenin (28). Accordingly, we found that *GLUL* mRNA overexpression significantly correlated with a slight but significant *CTNNB1* (the gene encoding β -catenin) mRNA overexpression in FNH compared with normal liver tissues ($r^2 = 0.33$, $P = 0.016$, Fig. 1L). However, immunohistochemical analysis of FNH nodules using a β -catenin antibody did not show any abnormal β -catenin localization. β -catenin was membranous in all hepatocytes, without significant cytoplasmic or nuclear accumulation, even in hepatocytes that overexpressed GS (Fig. 1M-O). Despite no detectable variation of the total β -catenin expression in hepatocytes of FNH, we observed the overexpression of the active, unphosphorylated β -catenin protein in FNH compared to normal liver samples (Fig. 1P). Consistent with β -catenin activation in FNH, our transcriptomic analysis revealed at least seven additional genes known to be regulated by the β -catenin pathway but whose physiological localization in the lobule was unknown (Table 3). Taken together, these results suggest the up-regulation of the β -catenin signaling pathway in areas surrounding the veins of FNH nodules. This up-regulation is related to overexpression of the active form of β -catenin in the absence of *CTNNB1*-activating mutations, as evidenced in 11 screened FNH samples. As activated β -catenin signaling is a known readout of Wnt signaling, we compared the expression levels of Wnt regulators in FNH and normal liver tissues. We did not find any significant differences in GSK3 β and phospho-GSK3 β ser9 expression using western blotting (Supplementary Fig. 1). Similarly, no significant difference was observed regarding the expression levels of *AXIN1*, *WNT* (14 genes analyzed), *FZD* (Frizzled receptors) (9 genes analyzed), *DVL* (3 genes analyzed), *LRP5* and *LRP6* mRNA (Supplementary Fig.2). Surprisingly, against the hypothesis of a β -catenin activation through APC silencing, we found a mild but significant overexpression of the *APC* transcript in FNH (2-fold) when compared to non-tumor livers (Supplementary Fig. 2).

Expression of the FNH-deregulated Genes in Other Types of Benign Hepatocellular Tumors

In a series of 70 liver samples including cirrhotic and normal tissues, different subtypes of adenomas, typical FNH nodules, and FNH-like, dysplastic, and macroregenerative nodules developed in cirrhosis, we examined the specificity of FNH-deregulated genes as identified in our microarray analysis or as described previously in the literature (all the data are provided in the

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3 supplementary Table 3). The ratio of expression of two angiopoietin genes, *ANGPT1/ANGPT2*,
4 which was previously shown to be increased in FNH, (29) demonstrated a significantly increased
5 mean -fold change of expression (9.5 ± 6.5) in FNH compared with non-tumor liver tissues.
6 However, in our series, the *ANGPT1/ANGPT2* ratio also increased significantly, although at a lower
7 level, in cirrhosis-related samples including random cirrhosis (3.9 ± 0.4), regenerative and
8 dysplastic nodules (7.5 ± 0.9), and FNH-like nodules (4 ± 0.6) (Fig. 2). In contrast, the
9 overexpression of the *NTS* transcript, which encodes neurotensin, was observed specifically in FNH
10 (Fig. 2). The ratio of expression of *NTS/HAL* was fully specific and sensitive to discriminate FNH
11 from the other benign tumors (Fig. 2).
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20 The microarray results indicating significant overexpression in FNH of the β -catenin target
21 genes *GLUL*, *GPR49*, and *TBX3* were confirmed using quantitative RT-PCR (Fig. 2 and data not
22 shown). Interestingly, overexpression was lower than that observed in β -catenin–mutated
23 adenomas. The other subtypes of lesions demonstrated normal or significantly decreased expression
24 levels of the β -catenin target genes compared to FNH (Fig. 2). Similarly, two periportal genes, *SDS*
25 and *HAL*, which encode the serine dehydratase and histidine amomnia lyase, respectively, were
26 down-regulated specifically in FNH and β -catenin–mutated adenomas (Fig. 2).
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33 Interestingly, FNH-like nodules demonstrated an expression profile similar to those of other
34 cirrhotic samples but different from the profile observed in typical FNH. In particular, in FNH-like
35 nodules, the β -catenin–induced perivenous genes encoding GS and GPR49 were significantly
36 down-regulated compared with non-tumor liver and FNH nodules (Fig. 2). Consistent with this
37 result, very little parenchymal GS staining was observed in FNH-like nodules (Fig. 3). Some
38 parenchymal staining was observed around venous structures, in addition to the ductular reaction, of
39 FNH-like nodules. Because ductules occupy only a small area of FNH-like nodules and no
40 parenchymal GS staining was detectable, no GS over-expression was observed at the RT-PCR
41 level. However, the immunohistochemical pattern of GS expression was distinct from that of FNH,
42 thus confirming that FNH-like nodules represent a separate entity. Moreover, in FNH-like nodules,
43 neurotensin and the selected genes displaying periportal localization were not found differentially
44 expressed when compared to non-tumor liver tissues by quantitative RT-PCR (Fig. 2). In fact,
45 FNH-like nodules showed similar expression patterns as other cirrhotic lesions. Consequently, our
46 results support the idea that FNH-like nodules have a pathophysiological origin different from that
47 of typical FNH.
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Discussion

In the present work, we carried out a transcriptomic analysis which revealed the molecular pathways altered in FNH. For the first time, activation of the β -catenin pathway was demonstrated in these tumors. Recently, β -catenin was identified as a master actor of hepatocyte proliferation, liver regeneration, hepatocyte metabolism, and liver development and as a master regulator of liver zonation (26, 30-34). In normal hepatocytes, β -catenin and its known target genes, such as GS, are expressed exclusively in the immediate perivenous areas (28, 35). This zoned defined pattern of expression differs from that observed in β -catenin-activated HCA or carcinoma, which usually shows more diffuse cytoplasmic GS staining and nuclear β -catenin staining, in accordance with the monoclonal origin of the β -catenin-activating mutations in these tumors (8, 30).

In FNH, β -catenin activation showed a heterogeneous distribution along the hepatocellular nodules, with a characteristic architectural distribution over relatively large areas, sometimes centered on visible veins and usually remaining at a distance from fibrous bands. This specific β -catenin expression pattern may be interpreted as the result of an altered hepatocyte zonation in FNH leading to increased β -catenin gradient starting from the veins. Because FNHs are most frequently polyclonal tumors, it is not surprising to find a heterogeneous distribution of β -catenin pathway activation in the absence of gene mutation (11, 13-16).

In FNH, sinusoidal blood flow is modified by arteriohepatic hyperperfusion, and sinusoids are directly irrigated by inlet arterioles coming from fibrous septa (3, 10). The abnormal arteries drain indirectly into sinusoids via capillaries in the fibrous septa, leading to a modified sinusoidal endothelial cell phenotype (9, 36-38). This situation is entirely different from the normal lobulation of the liver (Fig. 4). Because the fibrous septa with arteries are the location of blood inflow, they can be considered “portal tract equivalents,” i.e., they have the artery and the ductular reaction but not that of the bile duct and vein (39). In FNH, we observed an extension from the centrolobular equivalent area toward the portal tract equivalent. The blood composition may likely participate in zonal/restricted β -catenin activation. One could therefore hypothesize that the almost completely arterial inflow in FNH, without portal venous blood inflow, may cause β -catenin activation to extend much farther toward the inflow area than in normal liver or in cirrhotic liver, where there is still some portal venous inflow. The mechanism of β -catenin activation in FNH remains to be elucidated since we did not identify any alteration of the main known regulators of the Wnt pathway. As such, we did not observe any variations in the expression level of negative regulators such as GSK3 β , AXIN1 and APC and positive regulators such as WNT, FZD (Frizzled), DVL and LRP (Supplementary Fig. 1 and 2). Moreover, in FNH we did not identify any activating mutations

of β -catenin. Furthermore a previous work showed the lack of *AXIN1* and *APC* inactivating mutations in those tumors (17).

Activation of the β -catenin pathway in FNH could consequently contribute to tumor formation as β -catenin may promote hepatocyte proliferation and regeneration. However, in contrast to an activating mutation, hepatocytes in FNH remain sensitive to repression of the β -catenin pathway in regions surrounding fibrosis. The present study also shows that fibrosis in FNH is related to the overexpression of several genes encoding extracellular matrix proteins, in addition to increased TGF- β expression. This result is in agreement with *in situ* hybridization experiments in which a high expression level of TGF- β 1 was detected in mesenchymal cells in FNHs (40). TGF- β 1 is a multifunctional cytokine that is involved in development and tissue differentiation through its effects on cell proliferation, migration, differentiation, and apoptosis. TGF β -1 is also important in the pathological process of fibrosis. Interestingly, TGF- β and Wnt/ β -catenin pathways regulate a number of common processes during embryonic development, such as the patterning of imaginal discs in *Drosophila* and tissue specification and organogenesis in vertebrate embryos (41). Several recent reports have highlighted the complex, intertwined nature of the two signaling pathways (42). Zhang and collaborators supported the hypothesis that β -catenin in renal epithelial cells, rather than in mesenchymal cells, may suppress TGF- β 1-dependent signaling (43). Furthermore, analysis of TGF- β 1 transgenic mice showed reduced GS expression resulting from apoptosis of GS-positive hepatocytes (44). However, Lotz and collaborators showed that in FNH, TGF- β activation was not related to increased hepatocyte apoptosis (40). Consequently, additional functional analyses of the interplay between TGF- β and β -catenin pathways in hepatocytes are required to better understand the pathogenesis of FNH. One hypothesis could be proposed in which TGF β overexpression in FNH may occur to counteract the proliferative effect of β -catenin activation. In another hypothesis, β -catenin activation could represent a response to an abnormal TGF β -activation in FNH. Considering that most frequent FNH remain stable, activation of these pathways is probably tightly controlled to balance cell proliferation rate.

Another important finding of our study was that FNH-like nodules gene expression profile significantly differs from that of typical FNH nodules. In particular, FNH-like nodules did not show β -catenin activation. Moreover, they did not exhibit increased *NTS/HAL* expression ratio as did typical FNH. None of the genes tested in FNH-like nodules demonstrated a significantly different level of expression from that of random cirrhotic samples or cirrhotic dysplastic nodules. Our results demonstrate that, despite an enhancement of the signal during the arterial phase in MR/CT imaging of both types of nodules, typical FNH and FNH-like nodules derive from different

pathophysiological processes. The specific markers identified in the present study will be useful tools to correctly diagnose and classify benign lesions of the liver, including the different molecular subtypes of HCA (22).

In conclusion, abnormally zoned β -catenin activation is a particular feature of typical FNH that may explain the slight polyclonal over-proliferation of hepatocytes at the origins of the lesions. In contrast, FNH-like nodules, as random cirrhosis, do not share the same molecular defect, indicating a different pathogenesis. Finally, molecular and immunohistochemical markers will be useful tools in clinical practice to diagnose and classify benign hepatocellular tumors.

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Figure 1. Expression of the TGF β and β -catenin pathways in FNH.

(A, B) Two serial sections of FNH stained with Masson's trichrome (TC) showing fibrous bands stained in blue. (C, D, E) Immunostaining of collagen IV (Col IV) in NTL (C) and FNH (D, E). In NTL, some Co IV fibrils are found around vessels and biliary channels in portal tract; in FNH, immunostaining showed a diffuse pattern with more intense expression in and around fibrous bands (black arrows), also found along sinusoids. (F, G, H) Immunostaining of smooth muscle actin (SMA) in NTL (F) and FNH (G, H). In NTL, SMA is expressed only by myofibroblasts of vascular walls (black arrow): artery (right), central vein (left); in lobules, only a few hepatic stellate cells (HSC) express faintly SMA (red arrow); in FNH, SMA is overexpressed by myofibroblasts in and around fibrous bands (black arrow) and veins (red arrow). (I, J, K) Immunohistochemistry using GS antibody in non-tumor liver (NTL) (I) and FNH (J, K). In NTL, GS is expressed only by hepatocytes of 1 or 2 centrilobular plates (arrow); in FNH, typical aspect of GS staining in a "map-like" pattern (J); this large GS+ area is centered on a central vein and remains at a distance from the fibrous band (K). (L) Correlation between *GLUL* and *CTNNB1* mRNA overexpression in FNH and in NTL. Expression of *GLUL* (encoding GS) and *CTNNB1* (encoding β -catenin) was measured in FNH ($n = 11$) and in NTL ($n = 6$) with quantitative RT-PCR. (M, N, O) Immunohistochemistry using a total β -catenin antibody in NTL (M) and FNH (N, O). In NTL, β -catenin immunostaining showed a normal membranous staining in hepatocytes and an obvious cytoplasmic staining in biliary cells (arrows); in FNH, no cytoplasmic nor nuclear β -catenin staining was observed in hepatocytes that overexpressed GS, but there was normal membranous expression. In fibrotic areas, biliary cells of the ductular reaction showed normal strong cytoplasmic expression of β -catenin (arrows). (P) Overexpression of active, unphosphorylated β -catenin in FNH ($n = 4$) compared with NTL tissues ($n = 4$).

Figure 2. Validation of deregulated genes in well-defined subtypes of benign liver tumors.

Gene expression was examined by quantitative RT-PCR in different subgroups of samples: N, normal liver samples ($n = 6$); FNH-like nodules ($n = 11$); Cirr N, dysplastic or macroregenerative nodules in cirrhosis ($n = 8$); Cirr, cirrhotic nodules ($n = 19$); FNH ($n = 11$); Inflamm. Ad, inflammatory adenomas ($n = 5$); HNF1 Ad, HNF1 α -mutated adenomas ($n = 5$); β -cat. Ad, β -catenin-mutated adenomas ($n = 5$). All results were normalized to the mean expression level of normal liver samples. When box-and-whiskers graphs are used, the line in the middle is the median, the box extends from the 25th to 75th percentile, and the whiskers extend to the lowest and highest values. Significant results of the Mann-Whitney test comparing expression of each subgroup of tumors with normal liver samples are indicated as follows: ** $P < 0.01$, * $P < 0.05$.

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3 **Figure 3.** Expression of glutamine synthetase (GS) in FNH-like nodule and cirrhosis. (A) FNH-like
4 nodule with a diameter of 9 mm (left side) and some surrounding regenerative cirrhotic nodules (S).
5 The FNH-like nodule contains several septa that are surrounded by reactive ductules (arrows). (B)
6 GS-staining of the FNH-like nodule and surrounding regenerative cirrhotic nodules. In the FNH-
7 like nodules, there is staining of the reactive ductules (arrows), but parenchymal staining is very
8 limited, in contrast to focal nodular hyperplasia. In the surrounding cirrhotic nodules, there is some
9 patchy parenchymal staining, mostly related to venous structures (arrowheads).
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18 **Figure 4.** Schematization of glutamine synthetase staining in normal liver (A) and in FNH (B). GS
19 staining is indicated in brown. CV, central vein; PT, portal tract; V, vein; DV, dystrophic vessels;
20 fib, fibrosis (in grey); DR, ductular reaction; hep GS +, glutamine synthetase-positive hepatocytes;
21 hep GS -, glutamine synthetase-negative hepatocytes.
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Table 1. Clinical Features of Included Samples and Patients

	Number of analyzed samples	Number of patients	Age (mean \pm SD)	Gender (F/M)	Tumor diameter (mean \pm SD, cm)	Number of nodules (mean)	Risk factor of cirrhosis
Normal liver	6	6	48 \pm 14	6/0			-
FNH	11	8	41 \pm 7	8/0	5.1 \pm 1.8	2	-
FNH-like	11	6	62 \pm 7	2/4	1.2 \pm 0.5	2	HCV = 3 Alcohol = 2 AAT1 = 1
Dysplastic and macroregenerative cirrhotic nodules	8	6	55 \pm 4	3/3	1.1 \pm 0.5	4	HCV = 3 Alcohol = 3
Cirrhosis	19	16	60 \pm 7	2/14			HCV = 9 HBV = 3 Alcohol = 5* AAT1 = 1
Inflammatory HCA	5	5	39 \pm 7	5/0	5 \pm 3	3	-
HNF1α-mutated HCA	5	5	36 \pm 12	4/1	2.8 \pm 2.9	3	-
β-catenin-mutated HCA	5	5	47 \pm 14	4/1	3.3 \pm 2.2	2	-

*Two patients presented simultaneously with alcohol intake and hepatitis B viral (HBV) or hepatitis C viral (HCV) infection. AAT1: alpha-1 antitrypsin deficiency.

β -catenin in focal nodular hyperplasia

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Table 2. Genes Encoding Extracellular Matrix Proteins Up-regulated in FNH

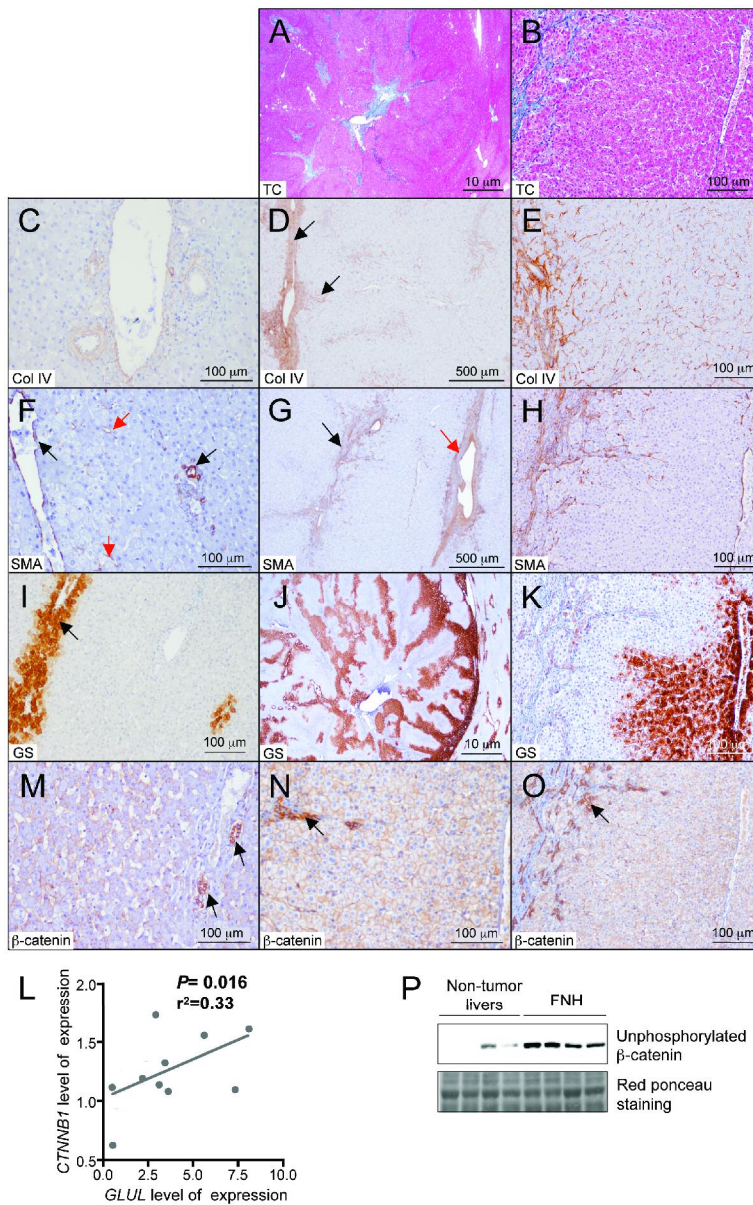
Gene Symbol	Gene Name	Affymetrix Ratio 4FNH/4NTL	cDNA array Ratio 7FNH/8NTL
Extracellular matrix			
COL1A1	Collagen. type I. alpha 1	19.8	<i>nd</i>
COL1A2	Collagen. type I. alpha 2	9.3	<i>nd</i>
COL3A1	Collagen. type III. alpha 1	9.8	<i>nd</i>
COL4A1	Collagen. type IV. alpha 1	3.3	<i>nd</i>
COL4A2	Collagen. type IV. alpha 2	5	<i>nd</i>
COL5A1	Collagen. type V. alpha 1	4.3	2.4
COL5A2	Collagen. type V. alpha 2	3.8	<i>nd</i>
COL6A1	Collagen. type VI. alpha 1	2.5	<i>nd</i>
COL6A2	Collagen. type VI. alpha 2	2	1.4
COL15A1	Collagen. type XV. alpha 1	3.1	1.7
CSPG2	Chondroitin sulfate proteoglycan 2 (versican)	5.8	1.7
DCN	Decorin	1.9	<i>na</i>
EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	9.5	<i>nd</i>
FBLN2	Fibulin 2	2.6	<i>nd</i>
FBLN5	Fibulin 5	4	<i>nd</i>
FBN1	Fibrillin 1 (Marfan syndrome)	3.2	<i>nd</i>
FLRT2	Fibronectin leucine-rich transmembrane protein 2	2.1	<i>nd</i>
HSPG2	Heparan sulfate proteoglycan 2 (perlecan)	2.9	<i>ns</i>
IBSP	Integrin-binding sialoprotein (bone sialoprotein II)	2.4	<i>nd</i>
LAMA2	Laminin. alpha 2 (merosin)	2.2	2.5
LAMB2	Laminin. beta 2 (laminin S)	1.8	<i>nd</i>
LOXL4	Lysyl oxidase-like 4	<i>nd</i>	2.9
LUM	Lumican	5.7	1.8
MGP	Matrix Gla protein	3.4	1.5
MMP11	Matrix metalloproteinase 11 (stromelysin 3)	3.1	2.5
MMP2	Matrix metalloproteinase 2	2.1	<i>ns</i>
PRG4	Proteoglycan 4	-2.2	<i>nd</i>
SPARC	Secreted protein. acidic. cysteine-rich (osteonectin)	1.9	1.4
SPON2	Spondin 2	2.8	<i>ns</i>
TFPI2	Tissue factor pathway inhibitor 2	6.1	<i>na</i>
TGFBI	Transforming growth factor, beta-induced, 68 kDa	2.3	1.5
THBS2	Thrombospondin 2	5.3	<i>nd</i>
TIMP1	Tissue inhibitor of metalloproteinase 1	3.4	<i>ns</i>
TNC	Tenascin C (hexabrachion)	11.2	<i>ns</i>
TNXB	Tenascin XB	2.1	<i>nd</i>
VWF	Von Willebrand factor	23.2	<i>nd</i>
Cell matrix adhesion			
ADAM15	A disintegrin and metalloproteinase domain 15 (metargidin)	<i>ns</i>	2.3
EMCN	Endomucin	7.3	<i>nd</i>
GPLD1	Glycosylphosphatidylinositol specific phospholipase D1	-2.4	-1.8
ITGA6	Integrin, alpha 6	2.1	1.5
ITGAV	Integrin, alpha V (vitronectin receptor, antigen CD51)	2	<i>ns</i>
ITGBL1	Integrin, beta-like 1 (with EGF-like repeat domains)	18.8	<i>nd</i>
SGCE	Sarcoglycan, epsilon	-2	<i>nd</i>
XLKD1	Extracellular link domain containing 1	-6.6	<i>nd</i>
Fibrogenesis pathway			
TGFB1	Transforming growth factor. beta 1	2.2	-1.2
ENG	Endoglin (Osler-Rendu-Weber syndrome 1)	2.7	1.4
TGIF2	TGFB-induced factor 2 (TALE family homeobox)	<i>ns</i>	-2.2
PDGFA	Platelet-derived growth factor alpha polypeptide	2.3	<i>nd</i>
PDGFRB	Platelet-derived growth factor receptor, beta polypeptide	2.2	1.9
TGFB111	Transforming growth factor beta 1 induced transcript 1	<i>ns</i>	1.9

ns: not significant; na: not analyzed; nd: not done; NTL: non tumor-livers

Table 3. Known Zonated and β -Catenin Target Genes Deregulated in FNH

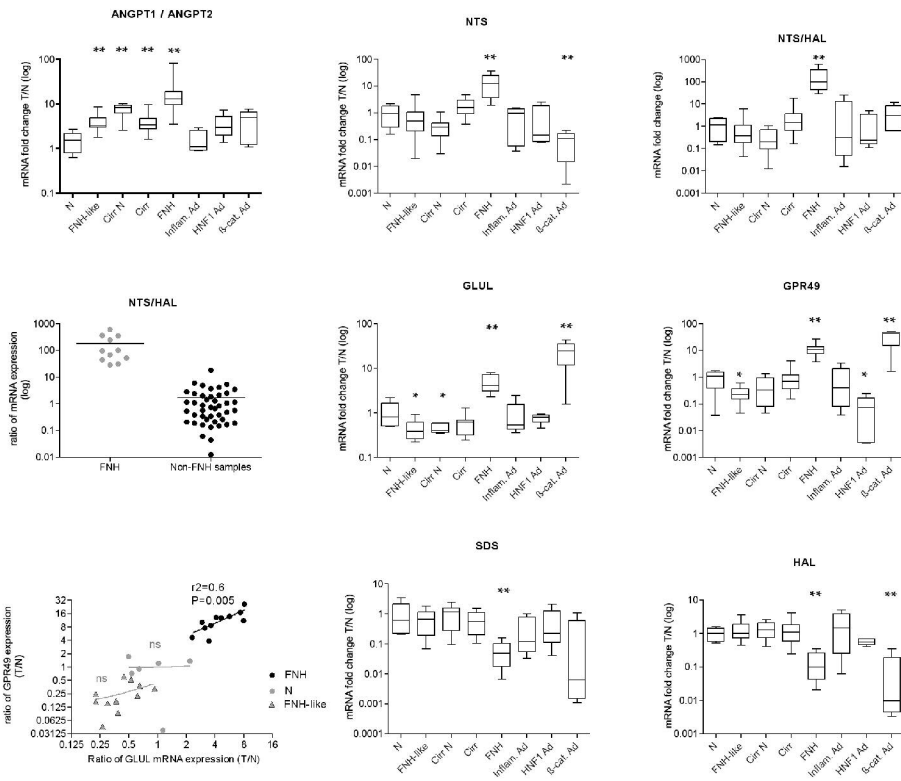
Gene Symbol	Gene Name	Affymetrix Ratio 4FNH/4NTL	cDNA array Ratio 7FNH/8NTL	Function	Known effect of β -catenin activation
Periportal genes					
SDS	Serine dehydratase	-20.2	<i>nd</i>	amino acid catabolism	Repressed
GLS2	Glutaminase 2 (mitochondrial)	-18.9	<i>nd</i>	amino acid catabolism	Repressed
HAL	Histidine ammonia-lyase	-5.9	<i>nd</i>	amino acid catabolism	Repressed
SDSL	Serine dehydratase-like	<i>nd</i>	-2.2	amino acid catabolism	
ASS	Argininosuccinate synthetase	-2.4	-2.1	amino acid catabolism	Repressed
CPS1	Carbamoyl-phosphate synthetase 1 mitochondrial	-2.2	-1.6	amino acid catabolism	
GLDC	Glycine dehydrogenase	-2.3	<i>nd</i>	amino acid catabolism	Repressed
GNMT	Glycine N-methyltransferase	-6.5	<i>nd</i>	amino acid metabolism	Repressed
SLC7A2	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	-2.2	<i>nd</i>	amino acid transporter	Repressed
IGF1	Insulin-like growth factor 1 (somatomedin C)	-2.7	-3.5	growth factor	Repressed
ALDOB	Aldolase B. fructose-bisphosphate	-2.3	<i>ns</i>	glycolysis	Repressed
HES1	Hairy and enhancer of split 1	-2.7	-2.2	transcriptional regulator	Repressed
CYP1A1	Cytochrome P450, family 1, subfamily A, polypeptide 1	<i>na</i>	-1.9	xenobiotic metabolism	
Pericentral genes					
GLUL	Glutamate-ammonia ligase (glutamine synthase)	3.7	2.3	glutamine synthesis	Induced
RHBG	Rhesus blood group. B glycoprotein	6.1	<i>nd</i>	ammonium transporter	Induced
LGR5	Leucine-rich repeat-containing G protein-coupled receptor 5	2	<i>nd</i>	receptor	Induced
TBX3	T-box 3 (ulnar mammary syndrome)	3.1	<i>ns</i>	transcriptional regulator	Induced
SLC13A3	Solute carrier family 13 (sodium-dependent dicarboxylate transporter) member 3	2.6	<i>nd</i>	dicarboxylic acid transporter	Induced
SERPINE2	Serine (or cysteine) proteinase inhibitor member 2	2.2	<i>nd</i>	regulation of proteolysis	
Other genes regulated by β-catenin					
LAMA3	Laminin, alpha 3	4.9	1.7	extracellular matrix	Induced
CCND1	Cyclin D1 (PRAD1: parathyroid adenomatosis 1)	3.1	1.6	cell cycle	Induced
SOX9	SRY (sex determining region Y)-box 9	4.1	<i>nd</i>	transcriptional regulator	Induced
SOX4	SRY (sex determining region Y)-box 4	2.2	<i>ns</i>	transcriptional regulator	Induced
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	2	<i>na</i>	ABC transporter	Induced
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	-4.3	-2.2	transcriptional regulator	Repressed
FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	<i>na</i>	-4.6	transcriptional regulator	Repressed

ns: not significant; na: not analyzed; nd: not done; NTL: non tumor-livers



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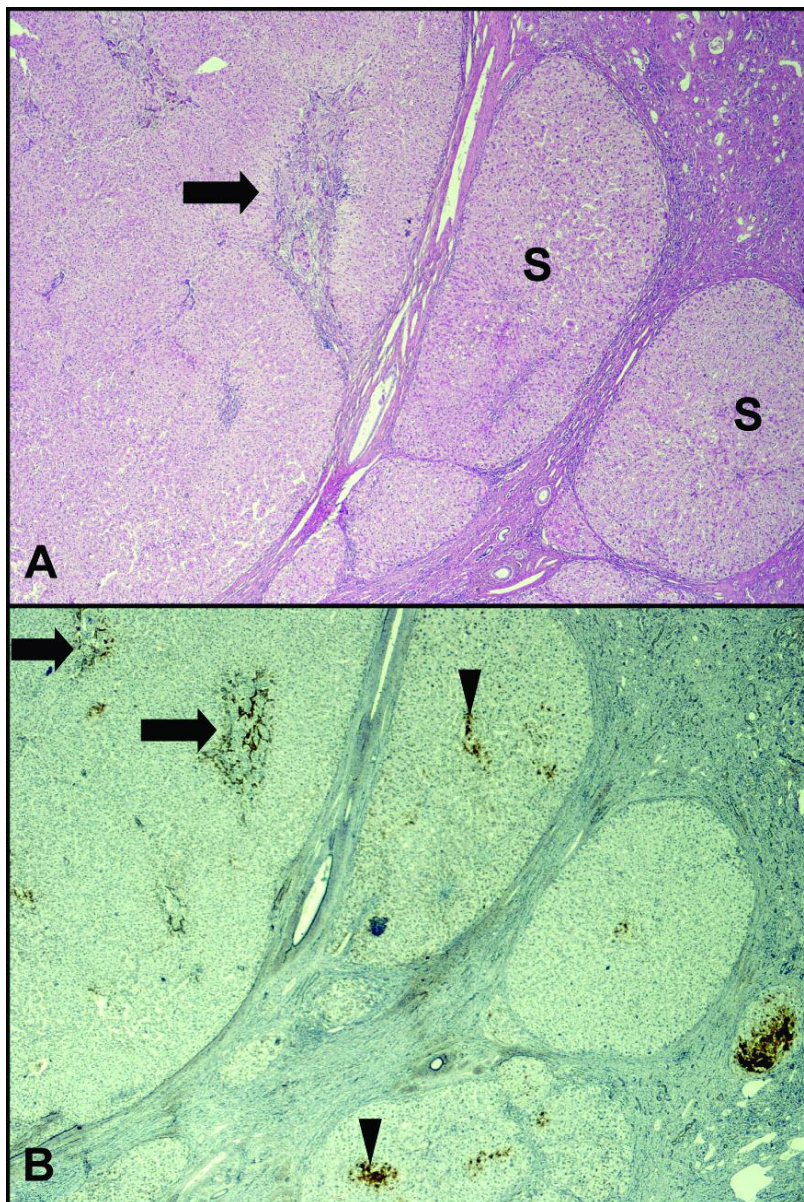
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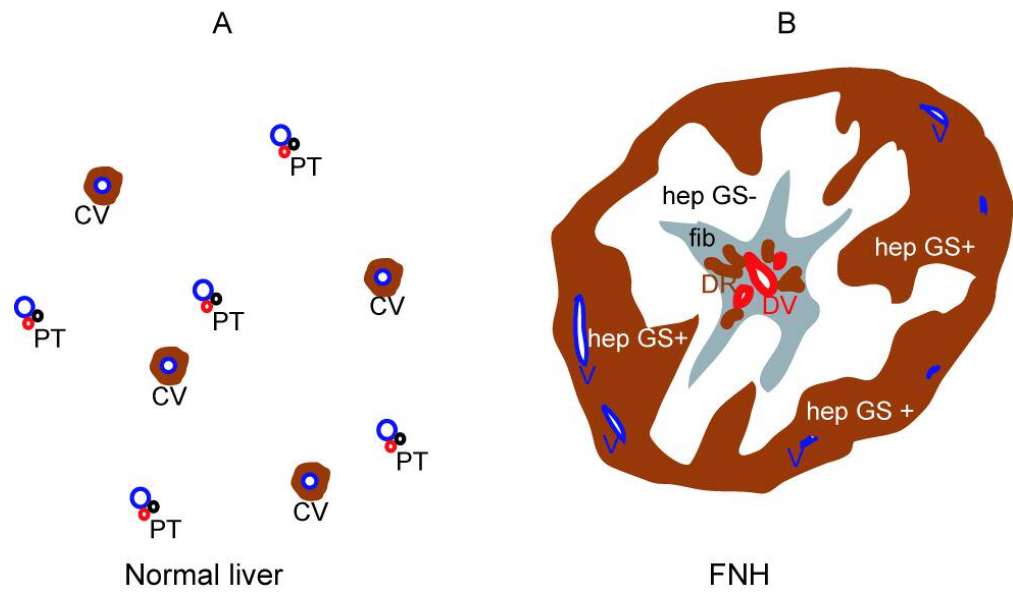
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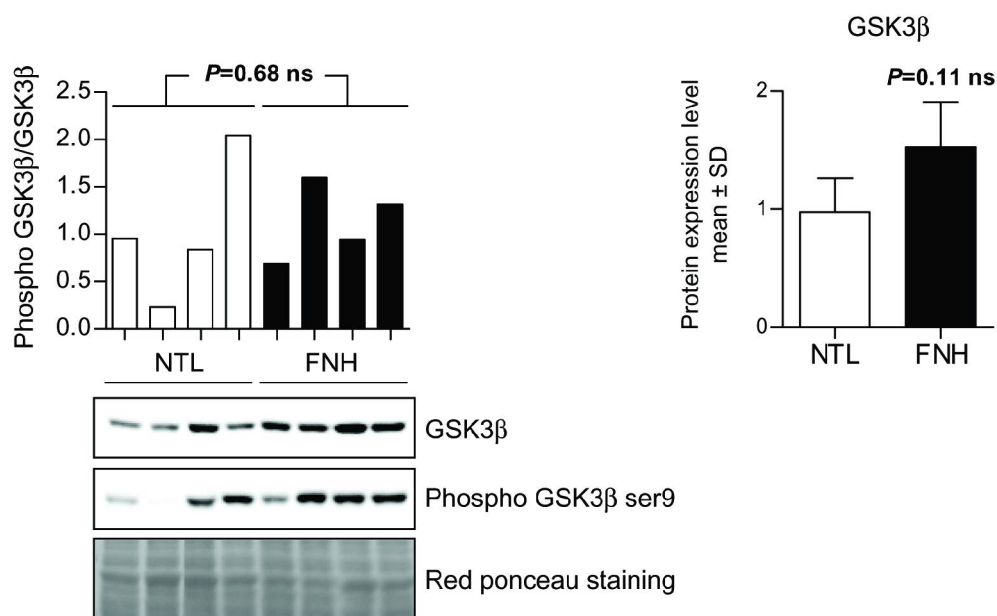
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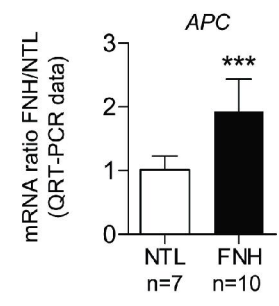
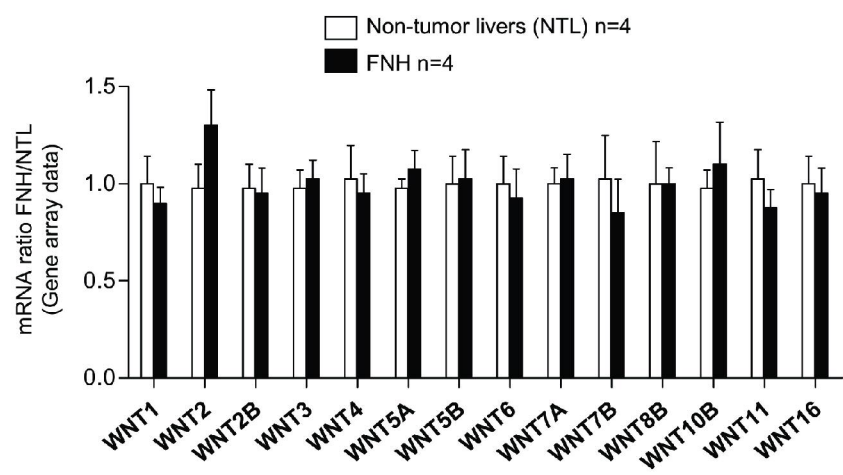
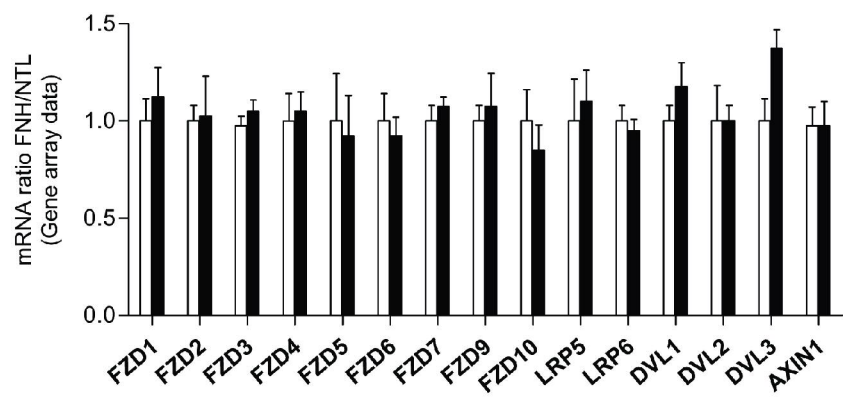
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Supplementary Figures

Supplementary Figure 1. Quantification of protein expression of GSK3 β and phospho GSK3 β by western blotting in FNH. Immunoblots were quantitated densitometrically using the ChemiDoc (BioRad) and the Quantity One software (Bio-Rad). Protein expression levels were compared between 4 non-tumor livers (NTL) and 4 FNH. Data are expressed as the n-fold differences in tested samples compared to the mean expression value of non-tumor liver tissues.

Supplementary Figure 2. Gene array (Affymetrix) and QRT-PCR data showing the transcriptional level of expression of the main genes related to the Wnt/ β -catenin signalling pathway in FNH compared to non tumor-livers (NTL). Results are mean \pm SD and are expressed as the n-fold differences in tested samples compared to the mean expression value of non-tumor liver tissues.

For Review Only

Supplementary material and methods

cDNA microarray

In a first experiment, microarray analyses were applied to 7 Focal nodular hyperplasias (FNHs) and 8 non related non-tumor livers using cDNA in-house manufactured arrays following a randomized and blinded unbalanced design.

RNA labelling, hybridization and analysis of fluorescence (including quality controls) were carried out, as described in [Graudens et al., Genome Biol 2006, 7: R19; PMID: 16542501], considering that uneven numbers of samples were randomly allocated to each of the engineers who were not aware of sample phenotypes. To assess data reproducibility and minimize dye bias effects, each of the samples was measured four times, twice with Cy3 and twice with Cy5. To ensure robustness and flexibility in data analysis, a reference design was used with a universal reference sample (Stratagene, USA) serving as a baseline for the comparisons of tumor samples.

Labeling protocol: one-round of RNA amplification was performed on total RNA as described in [Van Gelder et al., 1990; Eberwine et al., 1992] with some modifications. Amplified RNA products were air dried, resuspended in 10 μ l RNase-free water and then stored at -80°C; 1 μ l of the reaction (1/10) was stored to perform quality assessment (Purity, size, yield).

aRNA Targets were synthesized using 1.0 μ g amplified RNA, 1 μ l anchored oligo-(dT) and 2 μ l random nonamers (GE Healthcare, USA) for priming (total volume 11 μ l, 10 min, 70°C) in presence of 1 μ l spike RNA from Lucidea™ Microarray Human Scorecard v1.1 (GE Healthcare, USA). cDNA products were generated using 1 mM of either Cy3- or Cy5-dCTP (GE Healthcare, USA) and 200 units MMLV RNase H- reverse transcriptase (Promega, USA) at 42°C for 2 to 3 hr. After reverse transcription, the RNA was degraded by adding 2 μ l of 2.5 N NaOH and incubating at 37°C for 10 min. The reaction was then neutralized by adding 10 μ l of 2 M MOPS (free acid) and Cy3- and Cy5-containing targets were purified twice onto QIAquick PCR columns (Qiagen, Germany) according the manufacturer's instructions with minor modifications. The Cy-dye targets were controlled during quality assessment (purity, size, yield). Adjusted Cy-dye target yield was calculated to reflect carryover of unlabeled aRNA. Thus, certified targets were air-dried in a vacuum centrifuge for 1.5 hr and resuspended in RNase-free water to reach a 10 pmol/ μ l concentration.

Hybridization protocol: Hybridizations were performed onto an 11K human array (11K_VJF-ARRAY, GPL3282), which provides a genome-wide coverage of functional pathways.

A mixture of equimolar aliquots (20 pmol) of each labeled target (DATA and REF) was incubated at 95°C for 4 min in the presence of 1.5 μ g Oligo-A80 (Eurogentec, USA) and 1 μ g human Cot-I DNA® (Invitrogen, USA). Fragmented labeled cDNA was then placed onto 11K_VJF-ARRAY slides in a 30 μ l hybridization solution (50% formamide, GE Healthcare, USA) and covered by a coverslip. The slides were subsequently hybridized in a humid hybridization cabinet (GE Healthcare, USA) for 16 hr at 42°C. Then the hybridized slides were washed in 1xSSC, 0.2% SDS for 10 min at 55°C, twice in 0.1x SSC, 0.2% SDS for 10 min at 55°C and twice in 0.1x SSC for 1 min at room temperature.

Scanning protocol: After washing and drying, the arrays were scanned at 532 nm (PMT 600 V) and 635 nm (PMT 650 V) using a 3rd generation array scanner (GE Healthcare, USA) and independent grayscale images (8 bits, Tiff) were generated for each pair of samples to be compared.

Data extraction: Foreground (raw) data - ARMDens - were local background-subtracted (corners between spots - median value) and normalized using a Lowess (locally weighted linear regression) transformation. The following selection criteria were applied: all spots having a mean signal (after background subtraction) less than that of the background and below that of the negative controls in both Cy3 and Cy5 channels were systematically excluded; the data were also filtered to exclude spots flagged as missing or corrupted in one array. We next calculated the expression ratios (DATA/REF) in all analyses; the provided VALUE corresponds to the log, base 2 ratios. Replicate spots on the array (n=2) are considered separately.

Affymetrix chip

In a second experiment, HG-U133A Affymetrix GeneChip™ arrays were used to compare the expression profiles of 4 Focal nodular hyperplasias (FNHs) and 4 non related non-tumor livers.

Labeling protocol: RNA labelling, hybridization and analysis were carried out following the manufacturer's instructions (Affymetrix, Santa Clara, CA). For each case, 5 µg of total RNA were labeled according to the protocols provided by the manufacturer (Affymetrix, Santa Clara, CA).

Hybridization protocol: Hybridization was performed using 20 µg of cRNA per hybridization (GeneChip Fluidics Station 400), following the manufacturer's protocols (Affymetrix, Santa Clara, CA).

Scanning protocol: Array images were digitized by using Microarray Suite 5.0 (MAS5) software, embedded in the Affymetrix GeneChip Operating Software (Affymetrix, Santa Clara, USA).

Data extraction: Gene intensity derivation was carried out from the raw numerical data (CEL files) by using the R package affy [Gautier et al., Bioinformatics 2004, 20: 307-15], available as part of the Bioconductor project [Gentleman et al., Genome Biol 2004, 5: R80], and the DNA-Chip analyzer (dChip) program [Li & Wong, PNAS 2001, 98: 31-6]. Probe sets corresponding to control genes or having a “_x_” annotation were masked yielding a total of 19,787 probe sets available for further analyses. Background subtraction, normalization and expression summaries for every probe set were calculated with the log-scale robust multi-array analysis (RMA) algorithm using a background adjusted PM intensities model [Irizarry et al., Nucleic Acids Research 2003, 31: e15], and with the model-based expression indexes (MBEI) calculation following a PM/MM difference model [Li & Wong, PNAS 2001, 98: 31-6].

Differential Analysis of the gene expression data

A platform-dependant statistical comparison was performed considering Focal nodular hyperplasias (FNHs) versus non tumor liver tissues, using multiple testing procedures to evaluate statistical significance for differentially expressed genes, as described in [Graudens et al., Genome Biol 2006, 7: R19; PMID: 16542501] and in the supplemental experimental procedures in [Rebouissou et al., J Biol Chem 2007, 282(19):14437-46, PMID: 17379603].

Statistical analysis of both cDNA and Affymetrix GeneChip arrays data was performed using multiple testing procedures to evaluate statistical significance for differentially expressed genes, as described in [Graudens et al., Genome Biol 2006, 7: R19; PMID: 16542501].

Two gene selection methods were applied (i) significance analysis of microarrays [SAM; Tusher et al. 2001], and (ii) *p*-value ranking using *z*-statistics in ArrayStat 1.0 software (Imaging Research Inc.), *t*-statistics via the dChip program and the class comparison tools available in BRB-ArrayTools v3.2.3 package, an Excel Add-in (Korn et al. 2002).

A pooled curve-fit error method was used for random error estimation; a range of 3.0 median absolute deviations (MADs) to 4.0 MAD established outlier-detection thresholds automatically. Then, groups were compared as independent conditions ($\alpha = 0.001$). In this step, data were subjected to iterative normalization by centering to the median across groups. Statistical tests were computed for each probe set using the log-transformed data and a probe set was declared to be significant when the *p*-value was less than the α -level=0.001. For multiple testing corrections, the false discovery rate (FDR) procedure was used (Benjamini et al. 1995). Univariate and multivariate permutation tests ($n > 1000$) were computed to control the proportion of false discoveries (i.e. false positives, > 90% confidence). Only genes whose expression significantly differed between Focal nodular hyperplasias (FNHs) versus non tumor liver tissues (*p*-values < 0.01) were selected.

To assess the classification accuracy, a variety of methods were used in BRB-ArrayTools v3.2.3 package, including unsupervised compound covariate, diagonal linear discriminant analysis, *k*-nearest-neighbor (*k*=1 and 3), nearest centroid, and support vector machine predictors. For all of those class

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3 prediction methods, the cross-validated misclassification rate was calculated using the one-leave-one-
4 out voting classifier validation (α -level=0.001).
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7 A cross-platform comparison was done considering the UGCluster Identifiants as a common primary
8 key (Unigene Build184-June05).
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For Review Only

Supplementary Table 1. Results from cDNA and Affymetrix microarray experiments comparing the expression profiles of non-tumor livers with those of FNH. Data are expressed as the n-fold difference in gene expression in FNH relative to non-tumor livers (NTL).

Min and Max P-values correspond respectively to the lower and upper bound of the *P*-value considering the different statistical analyses carried out. The gene is considered significantly differentially expressed when the Min *P*-value is ≤ 0.01 .

ns: not significant

na: not analyzed, indicate that the corresponding gene is represented on the corresponding gene array but was not analyzed (data not interpretable)

nd: not done, indicate that the corresponding gene is not represented on the corresponding gene array

Unigene ID	Gene Symbol	Name	Affymetrix array			cDNA array		
			Ratio 4FNH/4NTL	MIN-P-value	MAX-P-value	Ratio 7FNH/8NTL	MIN-P-value	MAX-P-value
Hs.524672	ASCL1	Achaete-scute complex-like 1 (Drosophila)	-66.7	2.7E-07	2.7E-07	-1.3	ns	ns
Hs.421437	CD209L	C-type lectin domain family 4, member M	-35.4	0.0E+00	3.4E-05	nd	nd	nd
Hs.439023	SDS	Serine dehydratase	-20.3	3.0E-06	2.8E-05	nd	nd	nd
Hs.212606	GLS2	Glutaminase 2 (liver, mitochondrial)	-18.9	0.0E+00	1.1E-05	nd	nd	nd
Hs.54517	FCN2	Ficolin (collagen/fibrinogen domain containing lectin) 2 (hucolin)	-13.0	0.0E+00	7.2E-04	nd	nd	nd
Hs.284310		MRNA full length insert cDNA clone EUROIMAGE 254679	-10.1	3.3E-06	3.3E-06	nd	nd	nd
Hs.307734	MME	Membrane metallo-endopeptidase (neutral endopeptidase, enkephalinase, CALLA, CD10)	-7.5	0.0E+00	3.9E-05	nd	nd	nd
Hs.326579	LRRC3	Leucine rich repeat containing 3	-7.0	2.1E-07	2.1E-07	nd	nd	nd
Hs.246769	XLKD1	Extracellular link domain containing 1	-6.6	0.0E+00	2.4E-06	nd	nd	nd
Hs.144914	GNMT	Glycine N-methyltransferase	-6.5	0.0E+00	1.0E-06	nd	nd	nd
Hs.170053	GPR88	G-protein coupled receptor 88	-6.4	4.0E-15	6.2E-05	nd	nd	nd
Hs.190783	HAL	Histidine ammonia-lyase	-5.9	0.0E+00	5.3E-04	nd	nd	nd
Hs.150595	CYP26A1	Cytochrome P450, family 26, subfamily A, polypeptide 1	-5.8	9.9E-05	8.8E-04	nd	nd	nd
Hs.272499	DHRS2	Dehydrogenase/reductase (SDR family) member 2	-5.4	3.8E-09	3.8E-09	-2.0	1.1E-05	5.0E-03
Hs.534364	VIL1	Villin 1	-5.3	0.0E+00	5.9E-05	nd	nd	nd
Hs.98280	KCNN2	Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	-4.8	0.0E+00	2.5E-04	nd	nd	nd
Hs.144845	BBOX1	Butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1	-4.8	6.5E-04	6.5E-04	-4.2	0.0E+00	7.0E-06
Hs.523443	HBB	Hemoglobin, beta	-4.7	0.0E+00	0.0E+00	1.2	ns	ns
Hs.9914	FST	Follistatin	-4.4	0.0E+00	2.9E-13	1.1	ns	ns

Hs.75678	FOSB	FBJ murine osteosarcoma viral oncogene homolog B	-4.4	0.0E+00	0.0E+00	-2.2	8.9E-11	8.9E-11
Hs.144795	KCNMA1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1	-4.1	0.0E+00	3.2E-04	nd	nd	nd
Hs.446077	SLC38A4	Solute carrier family 38, member 4	-4.0	0.0E+00	1.3E-05	nd	nd	nd
Hs.224171	ENO3	Enolase 3 (beta, muscle)	-4.0	0.0E+00	0.0E+00	-1.8	0.0E+00	2.8E-01
Hs.370666	FOXO1A	Forkhead box O1A (rhabdomyosarcoma)	-3.9	0.0E+00	6.2E-06	1.1	ns	ns
Hs.143261	CAPN3	Calpain 3, (p94)	-3.9	0.0E+00	8.3E-12	-2.2	0.0E+00	2.0E-04
Hs.485572	SOCS2	Suppressor of cytokine signaling 2	-3.9	0.0E+00	5.3E-04	-3.2	0.0E+00	1.7E-05
Hs.489615	PBEF1	Pre-B-cell colony enhancing factor 1	-3.9	0.0E+00	4.0E-05	nd	nd	nd
Hs.478673	IL1RAP	Interleukin 1 receptor accessory protein	-3.9	0.0E+00	5.1E-04	nd	nd	nd
Hs.497822	DUSP10	Dual specificity phosphatase 10	-3.5	0.0E+00	9.0E-05	na	na	na
Hs.180919	ID2	Inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	-3.5	0.0E+00	2.8E-08	-1.7	9.2E-06	3.0E-03
Hs.192221	ELL2	Elongation factor, RNA polymerase II, 2	-3.5	0.0E+00	7.2E-05	nd	nd	nd
Hs.491308	RAB25	RAB25, member RAS oncogene family	-3.4	3.2E-10	3.2E-10	nd	nd	nd
Hs.439074	LPAL2	Lipoprotein, Lp(a)-like 2	-3.3	1.7E-10	2.1E-04	nd	nd	nd
Hs.364544	TM4SF13	Tetraspanin 13	-3.3	0.0E+00	1.6E-04	nd	nd	nd
Hs.213289	LDLR	Low density lipoprotein receptor (familial hypercholesterolemia)	-3.3	0.0E+00	9.1E-05	na	na	na
Hs.520819	INSIG1	Insulin induced gene 1	-3.3	0.0E+00	2.9E-04	-2.1	3.9E-11	8.0E-04
Hs.416073	S100A8	S100 calcium binding protein A8 (calgranulin A)	-3.2	0.0E+00	7.1E-11	-1.3	ns	ns
Hs.223858	DBH	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	-3.2	3.5E-12	1.1E-04	-4.0	0.0E+00	1.8E-05
Hs.368641	SCD	Stearoyl-CoA desaturase (delta-9-desaturase)	-3.2	1.9E-14	1.5E-05	-1.1	ns	ns
Hs.155097	CA2	Carbonic anhydrase II	-3.1	0.0E+00	4.0E-06	nd	nd	nd
Hs.53155	PFC	Properdin P factor, complement	-3.1	5.0E-13	2.9E-06	nd	nd	nd
Hs.503911	NNMT	Nicotinamide N-methyltransferase	-3.1	0.0E+00	2.7E-15	-3.3	0.0E+00	2.0E-04
Hs.436298	EMP1	Epithelial membrane protein 1	-3.1	0.0E+00	3.6E-11	nd	nd	nd
Hs.99195	GPR125	G protein-coupled receptor 125	-3.0	0.0E+00	5.8E-05	na	na	na
Hs.82071	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	-3.0	0.0E+00	9.2E-05	nd	nd	nd
Hs.442781	SLC25A15	Hypothetical protein LOC283507	-2.9	7.7E-14	6.7E-05	na	na	na
Hs.446050	ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	-2.8	6.1E-08	2.6E-03	nd	nd	nd
Hs.407190	FKBP5	FK506 binding protein 5	-2.8	8.2E-15	8.0E-04	1.0	ns	ns
Hs.369042	FLJ20605	Hypothetical protein FLJ20605	-2.8	9.3E-15	2.0E-04	-1.8	4.1E-05	2.0E-04

Hs.23581	LEPR	Leptin receptor	-2.8	3.1E-14	5.9E-07	nd	nd	nd
Hs.102788	MAN1A1	Mannosidase, alpha, class 1A, member 1	-2.8	0.0E+00	2.4E-06	nd	nd	nd
Hs.106576	AGXT2L1	Alanine-glyoxylate aminotransferase 2-like 1	-2.8	0.0E+00	1.0E-03	nd	nd	nd
Hs.200250	CREM	CAMP responsive element modulator	-2.7	1.1E-14	7.2E-04	-1.7	5.6E-09	1.6E-03
Hs.250666	HES1	Hairy and enhancer of split 1, (Drosophila)	-2.7	1.8E-15	6.1E-07	-2.2	0.0E+00	4.0E-04
Hs.427055	NR0B2	Nuclear receptor subfamily 0, group B, member 2	-2.7	2.3E-13	5.2E-04	nd	nd	nd
Hs.86724	GCH1	GTP cyclohydrolase 1 (dopa-responsive dystonia)	-2.7	0.0E+00	8.1E-05	nd	nd	nd
Hs.390738	FLJ20366	Hypothetical protein FLJ20366	-2.7	0.0E+00	5.6E-05	nd	nd	nd
Hs.268581	LPIN2	Lipin 2	-2.7	0.0E+00	5.6E-04	nd	nd	nd
Hs.160562	IGF1	Insulin-like growth factor 1 (somatomedin C)	-2.7	1.4E-11	8.1E-09	-3.5	0.0E+00	4.0E-03
Hs.145442	MAP2K1	Mitogen-activated protein kinase kinase 1	-2.7	0.0E+00	1.1E-05	nd	nd	nd
Hs.371763	GBA3	Glucosidase, beta, acid 3 (cytosolic)	-2.7	0.0E+00	6.5E-05	nd	nd	nd
Hs.444915	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	-2.6	2.4E-15	4.8E-07	nd	nd	nd
Hs.409352	FLJ20701	Hypothetical protein FLJ20701	-2.6	0.0E+00	4.3E-04	nd	nd	nd
Hs.81073	FETUB	Fetuin B	-2.6	3.2E-12	8.7E-04	nd	nd	nd
Hs.165258	NR4A2	Nuclear receptor subfamily 4, group A, member 2	-2.6	2.6E-05	9.2E-04	na	na	na
Hs.839	IGFALS	Insulin-like growth factor binding protein, acid labile subunit	-2.5	5.8E-11	6.8E-04	nd	nd	nd
Hs.272493	CCL15	Chemokine (C-C motif) ligand 14	-2.5	4.2E-13	3.1E-04	na	na	na
Hs.502745	FADS2	Fatty acid desaturase 2	-2.5	6.4E-09	5.9E-04	nd	nd	nd
Hs.409794	CLEC2	C-type lectin domain family 1, member B	-2.5	0.0E+00	4.3E-10	nd	nd	nd
Hs.439056	CYP2A6	Cytochrome P450, family 2, subfamily A, polypeptide 6	-2.5	0.0E+00	4.3E-04	nd	nd	nd
Hs.477440	OSBPL11	Oxysterol binding protein-like 11	-2.5	2.2E-16	9.4E-04	-1.9	0.0E+00	4.0E-04
Hs.552	SRD5A1	Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	-2.5	0.0E+00	9.5E-05	-1.8	6.1E-07	6.0E-04
Hs.161640	TAT	Tyrosine aminotransferase	-2.5	0.0E+00	1.4E-05	nd	nd	nd
Hs.49688	ABLIM3	Actin binding LIM protein family, member 3	-2.5	9.4E-10	1.5E-08	-1.4	2.1E-03	2.1E-03
Hs.500047	P4HA1	Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide I	-2.5	0.0E+00	5.5E-10	nd	nd	nd
Hs.525704	JUN	V-jun sarcoma virus 17 oncogene homolog (avian)	-2.5	0.0E+00	5.4E-07	1.1	ns	ns
Hs.160786	ASS	Argininosuccinate synthetase	-2.4	0.0E+00	8.0E-04	-2.1	0.0E+00	1.0E-06
Hs.197043	MAN1C1	Mannosidase, alpha, class 1C, member 1	-2.4	0.0E+00	7.1E-09	nd	nd	nd
Hs.19904	CTH	Cystathionase (cystathionine gamma-lyase)	-2.4	1.5E-14	8.9E-04	nd	nd	nd
Hs.497469	ETNK2	Ethanolamine kinase 2	-2.4	4.4E-11	9.9E-05	nd	nd	nd

Hs.335034	DPYD	Dihydropyrimidine dehydrogenase	-2.4	0.0E+00	2.3E-04	-1.6	2.7E-04	2.7E-04
Hs.512001	GPLD1	Glycosylphosphatidylinositol specific phospholipase D1	-2.4	1.7E-06	2.3E-03	-1.8	0.0E+00	6.0E-04
Hs.156540	SGNE1	Secretory granule, neuroendocrine protein 1 (7B2 protein)	-2.4	0.0E+00	1.9E-04	na	na	na
Hs.407966	GALK1	Galactokinase 1	-2.4	1.5E-10	2.4E-04	-1.3	ns	ns
Hs.274402	HSPA1B	Heat shock 70kDa protein 1B	-2.4	0.0E+00	2.5E-07	-1.3	ns	ns
Hs.444870	ORC2L	Origin recognition complex, subunit 2-like (yeast)	-2.3	6.2E-04	6.4E-03	nd	nd	nd
Hs.80756	BHMT	Betaine-homocysteine methyltransferase	-2.3	0.0E+00	5.4E-14	-2.1	0.0E+00	2.0E-04
Hs.125180	GHR	Growth hormone receptor	-2.3	1.2E-14	2.6E-09	1.4	ns	ns
Hs.485527	MUT	Methylmalonyl Coenzyme A mutase	-2.3	0.0E+00	1.0E-06	nd	nd	nd
Hs.269180	EPB41L4B	Erythrocyte membrane protein band 4.1 like 4B	-2.3	0.0E+00	3.2E-04	-2.0	0.0E+00	4.0E-04
Hs.406678	ACSL1	Acyl-CoA synthetase long-chain family member 1	-2.3	0.0E+00	2.5E-04	nd	nd	nd
Hs.530274	ALDOB	Aldolase B, fructose-bisphosphate	-2.3	4.4E-16	2.9E-04	-1.3	ns	ns
Hs.534348	SLC5A3	Solute carrier family 5 (inositol transporters), member 3	-2.3	6.7E-08	8.9E-05	nd	nd	nd
Hs.149156	GLDC	Glycine dehydrogenase (decarboxylating; glycine decarboxylase, glycine cleavage system protein P)	-2.3	2.4E-11	4.3E-04	nd	nd	nd
Hs.462323	NCOR1	Nuclear receptor co-repressor 1	-2.3	1.1E-15	2.6E-03	-1.0	ns	ns
Hs.149032	PIK3R4	Phosphoinositide-3-kinase, regulatory subunit 4, p150	-2.3	0.0E+00	1.9E-04	-1.7	0.0E+00	3.0E-03
Hs.483067	C5orf13	Chromosome 5 open reading frame 13	-2.3	4.2E-11	4.9E-08	nd	nd	nd
Hs.497816	FLJ22390	Hypothetical protein FLJ22390	-2.3	9.0E-08	8.8E-04	nd	nd	nd
Hs.161220	CG018	Hypothetical gene CG018	-2.2	0.0E+00	6.9E-04	-1.1	ns	ns
Hs.249441	WEE1	WEE1 homolog (S. pombe)	-2.2	3.5E-08	2.9E-06	nd	nd	nd
Hs.443150	ESR2	Estrogen receptor 2 (ER beta)	-2.2	9.2E-04	4.0E-02	nd	nd	nd
Hs.432458	PRG4	Proteoglycan 4	-2.2	5.2E-06	1.7E-04	nd	nd	nd
Hs.198003	SARDH	Sarcosine dehydrogenase	-2.2	3.8E-07	9.2E-05	nd	nd	nd
Hs.481704	FLJ20152	Hypothetical protein FLJ20152	-2.2	6.3E-14	1.2E-04	nd	nd	nd
Hs.148716	SIAT10	ST3 beta-galactoside alpha-2,3-sialyltransferase 6	-2.2	8.9E-15	5.5E-04	nd	nd	nd
Hs.435001	KLF10	Kruppel-like factor 10	-2.2	2.4E-10	6.1E-04	nd	nd	nd
Hs.435765	ENPEP	Glutamyl aminopeptidase (aminopeptidase A)	-2.2	0.0E+00	1.0E-05	nd	nd	nd
Hs.98206	GREM2	Gremlin 2 homolog, cysteine knot superfamily (Xenopus laevis)	-2.2	8.0E-10	7.9E-03	nd	nd	nd
Hs.192374	TRA1	Tumor rejection antigen (gp96) 1	-2.2	2.5E-13	5.1E-06	1.0	ns	ns
Hs.118651	HHEX	Hematopoietically expressed homeobox	-2.2	2.2E-16	1.7E-04	nd	nd	nd

Hs.30246	SLC19A2	Solute carrier family 19 (thiamine transporter), member 2	-2.2	0.0E+00	5.4E-04	nd	nd	nd
Hs.444049	BLNK	B-cell linker	-2.2	0.0E+00	0.0E+00	-1.7	1.8E-03	3.4E-03
Hs.130759	PLSCR1	Phospholipid scramblase 1	-2.2	3.3E-14	3.3E-14	-1.9	1.4E-02	1.2E-01
Hs.416735		KIAA1155 protein	-2.2	1.1E-06	3.1E-04	nd	nd	nd
Hs.443727	LHX1	LIM homeobox 1	-2.2	5.7E-07	5.7E-07	na	na	na
Hs.448520	SLC7A2	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	-2.2	0.0E+00	6.3E-05	nd	nd	nd
Hs.528295	AASS	Aminoacidpate-semialdehyde synthase	-2.2	6.9E-08	1.8E-07	nd	nd	nd
Hs.433732	CLK1	CDC-like kinase 1	-2.2	2.3E-07	5.8E-04	nd	nd	nd
Hs.149252	CPS1	Carbamoyl-phosphate synthetase 1, mitochondrial	-2.2	8.9E-16	5.1E-04	-1.6	7.3E-05	9.8E-03
Hs.292472	SEC24B	SEC24 related gene family, member B (S. cerevisiae)	-2.2	1.7E-09	7.8E-04	1.0	ns	ns
Hs.270570	DBT	Dihydrolipoamide branched chain transacylase E2	-2.2	8.1E-07	3.2E-03	nd	nd	nd
Hs.73793	VEGF	Vascular endothelial growth factor	-2.1	2.2E-10	4.3E-04	na	na	na
Hs.420106	ENDO G	Endonuclease G	-2.1	9.2E-07	9.2E-07	nd	nd	nd
Hs.213642	SLC35D1	Solute carrier family 35 (UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter), member D1	-2.1	3.5E-09	2.5E-03	nd	nd	nd
Hs.549037	HIVEP1	Human immunodeficiency virus type I enhancer binding protein 1	-2.1	1.8E-04	1.8E-04	nd	nd	nd
Hs.78944	RGS2	Regulator of G-protein signalling 2, 24kDa	-2.1	1.5E-06	1.5E-06	-1.7	1.3E-06	5.4E-02
Hs.211929	TXN2	Thioredoxin 2	-2.1	2.1E-06	1.0E-04	nd	nd	nd
Hs.408615	P2RX5	Purinergic receptor P2X, ligand-gated ion channel, 5	-2.1	2.1E-06	2.1E-06	-1.0	ns	ns
Hs.401316	IGFBP1	Insulin-like growth factor binding protein 1	-2.1	2.0E-09	7.3E-04	na	na	na
Hs.433902	DDT	D-dopachrome tautomerase	-2.1	9.7E-12	3.1E-08	nd	nd	nd
Hs.517581	HMOX1	Heme oxygenase (decycling) 1	-2.1	1.3E-10	3.3E-06	-1.5	3.7E-05	3.7E-05
Hs.551565	LONP	Peroxisomal lon protease	-2.1	8.1E-07	8.1E-07	-1.7	6.6E-05	4.4E-01
Hs.190977	ENPP2	Ectonucleotide pyrophosphatase/phosphodiesterase 2 (autotaxin)	-2.1	0.0E+00	6.5E-06	nd	nd	nd
Hs.522876	MGC12760	Hypothetical protein MGC12760	-2.1	4.1E-14	1.5E-04	-1.1	ns	ns
Hs.150276	CYP3A5	Cytochrome P450, family 3, subfamily A, polypeptide 43	-2.1	0.0E+00	7.2E-05	nd	nd	nd
Hs.496383	SOAT1	Sterol O-acyltransferase (acyl-Coenzyme A: cholesterol acyltransferase) 1	-2.1	2.3E-04	4.4E-02	nd	nd	nd
Hs.183671	TDO2	Tryptophan 2,3-dioxygenase	-2.1	4.6E-14	8.2E-04	-2.5	1.3E-07	1.1E-02
Hs.520120	LPA	Lipoprotein, Lp(a)	-2.1	0.0E+00	7.4E-04	nd	nd	nd

Hs.498494	PCSK6	Proprotein convertase subtilisin/kexin type 6	-2.1	1.3E-07	8.9E-05	nd	nd	nd
Hs.494261	PSAT1	Phosphoserine aminotransferase 1	-2.1	1.4E-12	3.9E-04	-1.5	6.1E-04	6.1E-04
Hs.386225	GYS1	Glycogen synthase 1 (muscle)	-2.1	5.9E-06	3.8E-04	1.1	ns	ns
Hs.520313	CD164	CD164 antigen, sialomucin	-2.1	0.0E+00	6.3E-04	nd	nd	nd
Hs.343911	EI24	Etoposide induced 2.4 mRNA	-2.1	1.9E-06	3.2E-06	-1.3	3.1E-03	3.7E-01
Hs.478230	PLD1	Phospholipase D1, phosphatidylcholine-specific	-2.1	2.9E-07	1.4E-02	nd	nd	nd
Hs.444314	C18orf11	Family with sequence similarity 59, member A	-2.0	1.9E-05	9.9E-04	nd	nd	nd
Hs.144567	AGXT	Alanine-glyoxylate aminotransferase (oxalosis I; hyperoxaluria I; glycolicaciduria; serine-pyruvate aminotransferase)	-2.0	1.5E-10	7.7E-04	nd	nd	nd
Hs.26403	GSTZ1	Glutathione transferase zeta 1 (maleylacetoacetate isomerase)	-2.0	1.1E-10	1.6E-06	-1.9	0.0E+00	4.0E-04
Hs.371199	SGCE	Sarcoglycan, epsilon	-2.0	2.8E-13	3.4E-04	nd	nd	nd
Hs.160976	SAH	SA hypertension-associated homolog (rat)	-2.0	5.5E-09	6.1E-04	-1.3	ns	ns
Hs.135087	IL6R	Interleukin 6 receptor	-2.0	5.0E-09	9.7E-04	nd	nd	nd
Hs.293811	C21orf91	Chromosome 21 open reading frame 91	-2.0	1.4E-07	4.3E-03	nd	nd	nd
Hs.488293	EGFR	Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	-2.0	6.3E-13	7.2E-03	-1.1	ns	ns
Hs.1011	PROZ	Protein Z, vitamin K-dependent plasma glycoprotein	-2.0	2.2E-07	7.4E-04	nd	nd	nd
Hs.387239	LCAT	Lecithin-cholesterol acyltransferase	-2.0	2.5E-09	2.7E-04	nd	nd	nd
Hs.509343	PLEKHC1	Pleckstrin homology domain containing, family C (with FERM domain) member 1	-2.0	0.0E+00	5.9E-04	na	na	na
Hs.62661	GBP1	Guanylate binding protein 1, interferon-inducible, 67kDa	-2.0	2.0E-09	1.0E-03	-1.2	ns	ns
Hs.516217	UGP2	UDP-glucose pyrophosphorylase 2	-2.0	2.7E-14	1.5E-05	-1.4	8.0E-04	3.4E-03
Hs.407709	DRE1	DRE1 protein	-2.0	1.2E-06	7.0E-06	nd	nd	nd
Hs.503546	FADS1	Fatty acid desaturase 1	-2.0	2.1E-10	6.5E-06	-1.0	ns	ns
Hs.194695	ARHI	DIRAS family, GTP-binding RAS-like 3	-2.0	4.4E-16	4.4E-16	-1.8	2.4E-06	7.8E-03
Hs.504398	SLC6A13	Solute carrier family 6 (neurotransmitter transporter, GABA), member 13	-2.0	1.4E-05	3.4E-04	nd	nd	nd
Hs.234898	ACACB	Acetyl-Coenzyme A carboxylase beta	-2.0	4.5E-14	2.3E-04	1.1	ns	ns
Hs.112955	SEC61A2	Sec61 alpha 2 subunit (S. cerevisiae)	-2.0	3.4E-06	8.2E-05	-1.1	ns	ns
Hs.135787	SALL1	Sal-like 1 (Drosophila)	-2.0	5.1E-06	6.9E-06	nd	nd	nd
Hs.282326	DSCR1	Down syndrome critical region gene 1	-2.0	2.4E-10	6.3E-04	-1.3	ns	ns
Hs.288034	SLC39A8	Solute carrier family 39 (zinc transporter), member 8	-2.0	1.5E-08	3.5E-04	nd	nd	nd
Hs.523789	TncRNA	Trophoblast-derived noncoding RNA	-2.0	5.3E-06	5.7E-06	nd	nd	nd
Hs.550470	CP	Ceruloplasmin (ferroxidase)	-2.0	8.5E-08	6.4E-04	nd	nd	nd

Hs.207459	SIAT1	ST6 beta-galactosamide alpha-2,6-sialyltransferase 1	-2.0	4.6E-07	6.2E-06	1.1	ns	ns
Hs.503074	TMEM16A	Transmembrane protein 16A	-2.0	6.5E-13	7.5E-04	nd	nd	nd
Hs.87159	CAB39L	Calcium binding protein 39-like	-2.0	7.0E-06	7.0E-06	-1.5	0.0E+00	3.3E-03
Hs.534302	APOF	Apolipoprotein F	-2.0	1.8E-12	1.5E-04	nd	nd	nd
Hs.89983	MASP1	Mannan-binding lectin serine protease 1 (C4/C2 activating component of Ra-reactive factor)	-2.0	3.8E-08	8.5E-04	nd	nd	nd
Hs.464166	ET	Hypothetical protein ET	-1.9	2.0E-05	9.5E-04	1.1	ns	ns
Hs.150557	KLF9	Kruppel-like factor 9	-1.9	7.3E-15	1.9E-04	nd	nd	nd
Hs.306220	CYP3A43	Cytochrome P450, family 3, subfamily A, polypeptide 43	-1.9	3.9E-14	2.1E-05	nd	nd	nd
Hs.519694	C5orf4	Chromosome 5 open reading frame 4	-1.9	2.2E-08	2.4E-04	-1.1	ns	ns
Hs.17483	CD4	CD4 antigen (p55)	-1.9	1.2E-07	1.0E-06	nd	nd	nd
Hs.18788	DHRS10	Dehydrogenase/reductase (SDR family) member 10	-1.9	4.5E-05	9.6E-04	-1.5	6.5E-05	1.1E-01
Hs.549067	SNTB1	Syntrophin, beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1)	-1.9	5.1E-09	3.3E-06	nd	nd	nd
Hs.444887	POLR2D	Polymerase (RNA) II (DNA directed) polypeptide D	-1.9	4.6E-04	6.3E-02	-1.1	ns	ns
Hs.304792	PROSC	Proline synthetase co-transcribed homolog (bacterial)	-1.9	3.4E-09	5.5E-04	-1.1	ns	ns
Hs.99886	C4BPB	Complement component 4 binding protein, beta	-1.9	6.0E-07	1.2E-06	-1.5	0.0E+00	2.2E-03
Hs.241431	GNAO1	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	-1.9	2.2E-09	1.7E-02	nd	nd	nd
Hs.136102	KIAA0853	KIAA0853	-1.9	2.4E-11	2.4E-11	-1.7	0.0E+00	1.5E-05
Hs.444612	SLC2A9	Solute carrier family 2 (facilitated glucose transporter), member 9	-1.9	4.6E-05	1.0E-03	-1.9	0.0E+00	4.4E-03
Hs.298651	RAB27A	RAB27A, member RAS oncogene family	-1.9	5.2E-08	7.9E-06	nd	nd	nd
Hs.94896	TMEM14A	Transmembrane protein 14A	-1.9	6.2E-07	1.6E-06	1.1	ns	ns
Hs.91747	PFN2	Profilin 2	-1.9	2.0E-08	7.1E-05	-1.7	4.2E-06	4.8E-03
Hs.284712	BAAT	Bile acid Coenzyme A: amino acid N-acyltransferase (glycine N-choloyltransferase)	-1.9	2.5E-08	5.9E-04	nd	nd	nd
Hs.437365	ASAH1	N-acylsphingosine amidohydrolase (acid ceramidase)-like	-1.9	8.1E-07	8.9E-04	1.1	ns	ns
Hs.12393	TGDS	TDP-glucose 4,6-dehydratase	-1.9	7.1E-06	5.3E-04	-1.7	3.4E-03	1.6E-01
Hs.109655	SCML1	Sex comb on midleg-like 1 (Drosophila)	-1.9	2.8E-05	8.4E-04	1.1	ns	ns
Hs.119983	MASP2	Mannan-binding lectin serine protease 2	-1.9	1.1E-06	8.3E-04	nd	nd	nd
Hs.17631	C2orf31	Chromosome 2 open reading frame 31	-1.9	3.0E-06	1.4E-04	nd	nd	nd
Hs.442498	FXYD1	FXYD domain containing ion transport regulator 1 (phospholemman)	-1.9	8.6E-07	8.4E-04	nd	nd	nd

Hs.236642	HIBCH	3-hydroxyisobutyryl-Coenzyme A hydrolase	-1.9	1.8E-12	1.8E-12	-1.5	3.6E-04	1.4E-03
Hs.525251	WDR23	WD repeat domain 23	-1.9	1.4E-07	4.6E-04	-1.5	0.0E+00	4.8E-03
Hs.904	AGL	Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III)	-1.9	4.4E-12	7.7E-05	nd	nd	nd
Hs.525205	NDRG2	NDRG family member 2	-1.9	4.2E-09	7.9E-04	nd	nd	nd
Hs.356190	UBB	Ubiquitin B	-1.9	7.9E-06	7.9E-06	-1.2	6.0E-04	2.0E-01
Hs.132225	PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (p85 alpha)	-1.9	1.8E-10	8.3E-04	nd	nd	nd
Hs.517070	SLPI	Secretory leukocyte protease inhibitor (antileukoproteinase)	-1.8	9.3E-06	9.2E-04	nd	nd	nd
Hs.134958	RODH-4	Microsomal NAD+-dependent retinol dehydrogenase 4	-1.8	8.5E-11	7.5E-04	nd	nd	nd
Hs.524513	RODH	Hydroxysteroid (17-beta) dehydrogenase 6	-1.8	3.2E-11	4.9E-05	nd	nd	nd
Hs.518727	FLJ20273	RNA-binding protein	-1.8	8.6E-11	7.0E-04	nd	nd	nd
Hs.227777	PTP4A1	Protein tyrosine phosphatase type IVA, member 1	-1.8	9.4E-14	4.5E-05	nd	nd	nd
Hs.259605	PIGV	Phosphatidylinositol glycan, class V	-1.8	1.6E-04	7.1E-04	nd	nd	nd
Hs.151573	CRY1	Cryptochrome 1 (photolyase-like)	-1.8	1.1E-03	1.1E-03	nd	nd	nd
Hs.500897	C10orf26	Chromosome 10 open reading frame 26	-1.8	5.4E-07	1.8E-04	nd	nd	nd
Hs.132760	SLC37A4	Solute carrier family 37 (glycerol-6-phosphate transporter), member 4	-1.8	4.6E-07	9.4E-04	-1.3	ns	ns
Hs.467097	SNRP70	Small nuclear ribonucleoprotein 70kDa polypeptide (RNP antigen)	-1.8	5.9E-04	5.5E-02	1.0	ns	ns
Hs.7644	HIST1H1C	Histone 1, H1c	-1.8	9.0E-06	1.3E-05	1.1	ns	ns
Hs.546387	FAHD2A	Fumarylacetoacetate hydrolase domain containing 2A	-1.8	2.4E-08	7.6E-04	-1.1	ns	ns
Hs.491232	SLC39A14	Solute carrier family 39 (zinc transporter), member 14	-1.7	2.3E-07	2.3E-07	-4.2	0.0E+00	9.0E-06
Hs.183109	MAOA	Monoamine oxidase A	-1.7	1.3E-08	2.6E-07	-1.8	3.3E-05	1.8E-03
Hs.7946	MTUS1	Mitochondrial tumor suppressor 1	-1.7	7.1E-08	1.1E-07	-2.0	0.0E+00	5.0E-06
Hs.15106	C14orf1	Chromosome 14 open reading frame 1	-1.5	1.1E-05	1.1E-05	-1.8	1.2E-03	4.2E-03
Hs.283869	C20orf121	Chromosome 20 open reading frame 121	-1.5	8.6E-06	8.6E-06	-2.2	0.0E+00	5.3E-05
Hs.171142	ASPA	Aspartoacylase (aminoacylase 2, Canavan disease)	-1.4	1.5E-05	1.5E-05	-2.1	3.5E-09	8.0E-04
Hs.252387	CELSR1	Cadherin, EGF LAG seven-pass G-type receptor 1 (flamingo homolog, Drosophila)	34.8	0.0E+00	0.0E+00	na	na	na
Hs.522334	C9orf13	Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1	34.5	0.0E+00	1.5E-04	na	na	na
Hs.440848	VWF	Von Willebrand factor	23.2	0.0E+00	2.0E-04	nd	nd	nd

Hs.409034	COL15A1	Collagen, type XV, alpha 1	19.8	0.0E+00	3.3E-05	nd	nd	nd
Hs.508597	ITGBL1	Integrin, beta-like 1 (with EGF-like repeat domains)	18.8	0.0E+00	2.4E-05	nd	nd	nd
Hs.300772	TPM2	Tropomyosin 2 (beta)	17.4	0.0E+00	5.5E-04	nd	nd	nd
Hs.943	NK4	Interleukin 32	12.2	6.0E-06	2.0E-04	4.4	0.0E+00	1.0E-03
Hs.143250	TNC	Tenascin C (hexabrachion)	11.2	1.2E-11	8.8E-05	1.1	ns	ns
Hs.44532	UBD	Ubiquitin D	9.9	0.0E+00	3.0E-06	nd	nd	nd
Hs.489142	COL1A2	Collagen, type I, alpha 2	9.8	0.0E+00	7.6E-05	nd	nd	nd
Hs.76224	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	9.5	0.0E+00	6.0E-05	nd	nd	nd
Hs.22981	C18orf10	Chromosome 18 open reading frame 10	9.4	2.5E-09	4.5E-04	1.1	ns	ns
Hs.431099	MAP17	PDZK1 interacting protein 1	9.3	0.0E+00	1.6E-04	nd	nd	nd
Hs.172928	COL1A1	Collagen, type I, alpha 1	9.3	0.0E+00	7.5E-05	nd	nd	nd
Hs.80962	NTS	Neurotensin	7.7	0.0E+00	2.3E-06	2.8	0.0E+00	5.0E-06
Hs.152913	EMCN	Endomucin	7.3	0.0E+00	5.5E-04	nd	nd	nd
Hs.159428	BAX	BCL2-associated X protein	7.2	6.5E-10	2.2E-04	nd	nd	nd
Hs.130316	DBN1	Drebrin 1	7.0	7.6E-08	4.8E-03	1.3	4.0E-04	6.4E-01
Hs.522373	GSN	Gelsolin (amyloidosis, Finnish type)	7.0	0.0E+00	1.3E-05	-1.2	ns	ns
Hs.432329	PLXNA1	Plexin A1	6.9	2.5E-07	2.0E-02	nd	nd	nd
Hs.446192	CNTNAP2	Contactin associated protein-like 2	6.7	4.3E-10	6.3E-04	nd	nd	nd
Hs.472558	SDBCAG84	Serologically defined breast cancer antigen 84	6.7	2.3E-07	2.3E-07	1.7	8.0E-01	8.0E-01
Hs.390428	MAP3K4	Mitogen-activated protein kinase kinase kinase 4	6.5	2.8E-06	2.8E-06	nd	nd	nd
Hs.9029	KRT23	Keratin 23 (histone deacetylase inducible)	6.3	0.0E+00	1.1E-05	nd	nd	nd
Hs.438231	TFPI2	Tissue factor pathway inhibitor 2	6.1	8.3E-08	1.8E-04	na	na	na
Hs.131835	RHBG	Rhesus blood group, B glycoprotein	6.1	1.9E-11	2.0E-04	nd	nd	nd
Hs.497369	NAV1	Neuron navigator 1	5.9	9.3E-06	9.3E-06	1.4	1.6E-03	6.3E-03
Hs.443681	CSPG2	Chondroitin sulfate proteoglycan 2 (versican)	5.8	0.0E+00	6.7E-06	1.7	2.8E-03	8.1E-03
Hs.406475	LUM	Lumican	5.7	0.0E+00	9.2E-05	1.8	3.8E-11	1.5E-02
Hs.476402	ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3	5.6	6.9E-06	3.9E-04	nd	nd	nd
Hs.439463	AEBP1	AE binding protein 1	5.4	0.0E+00	4.9E-05	nd	nd	nd
Hs.371147	THBS2	Thrombospondin 2	5.3	0.0E+00	8.5E-06	nd	nd	nd
Hs.292156	DKK3	Dickkopf homolog 3 (Xenopus laevis)	5.2	0.0E+00	7.0E-06	nd	nd	nd
Hs.17441	COL4A1	Collagen, type IV, alpha 1	5.0	0.0E+00	8.2E-05	nd	nd	nd
Hs.436367	LAMA3	Laminin, alpha 3	4.9	1.3E-09	4.9E-06	1.7	6.9E-05	4.0E-04
Hs.546434	B7-H4	V-set domain containing T cell activation inhibitor 1	4.6	2.7E-09	2.5E-04	nd	nd	nd
Hs.78224	RNASE1	Ribonuclease, RNase A family, 1 (pancreatic)	4.5	0.0E+00	1.5E-04	2.0	3.0E-07	1.0E-03
Hs.2704	GPX2	Glutathione peroxidase 2 (gastrointestinal)	4.4	0.0E+00	2.4E-04	2.7	0.0E+00	7.8E-01
Hs.164021	CXCL6	Chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)	4.4	8.9E-16	2.0E-05	nd	nd	nd

Hs.508716	COL4A2	Collagen, type IV, alpha 2	4.3	0.0E+00	4.9E-05	2.4	0.0E+00	3.0E-06
Hs.411501	KRT7	Keratin 7	4.2	1.3E-09	2.3E-04	1.5	5.2E-04	1.2E-03
Hs.154299	F2RL1	Coagulation factor II (thrombin) receptor-like 1	4.2	2.6E-13	6.9E-06	nd	nd	nd
Hs.116471	CDH11	Cadherin 11, type 2, OB-cadherin (osteoblast)	4.1	7.1E-15	1.1E-04	nd	nd	nd
Hs.2316	SOX9	SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)	4.1	0.0E+00	1.6E-05	nd	nd	nd
Hs.332708	FBLN5	Fibulin 5	4.0	0.0E+00	6.1E-05	nd	nd	nd
Hs.57907	CCL21	Chemokine (C-C motif) ligand 21	3.8	8.4E-15	8.7E-04	nd	nd	nd
Hs.210283	COL5A1	Collagen, type V, alpha 1	3.8	0.0E+00	4.2E-05	nd	nd	nd
Hs.369762	TYMS	Thymidylate synthetase	3.7	0.0E+00	6.2E-05	1.6	2.2E-03	1.3E-02
Hs.517582	MCM5	MCM5 minichromosome maintenance deficient 5, cell division cycle 46 (<i>S. cerevisiae</i>)	3.7	1.1E-09	6.7E-05	nd	nd	nd
Hs.170499	XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound	3.7	0.0E+00	2.6E-14	nd	nd	nd
Hs.16426	PODXL	Podocalyxin-like	3.7	0.0E+00	2.2E-04	nd	nd	nd
Hs.518525	GLUL	Glutamate-ammonia ligase (glutamine synthase)	3.7	0.0E+00	1.0E-06	2.3	0.0E+00	8.6E-01
Hs.515258	GDF15	Growth differentiation factor 15	3.6	0.0E+00	4.1E-04	2.2	0.0E+00	2.0E-03
Hs.449585	IGLC2	Immunoglobulin lambda variable 3-21	3.6	0.0E+00	6.8E-13	nd	nd	nd
Hs.375108	CD24	CD24 antigen (small cell lung carcinoma cluster 4 antigen)	3.6	0.0E+00	5.2E-05	1.3	2.0E-04	2.5E-03
Hs.386726	RGS4	Regulator of G-protein signalling 4	3.5	0.0E+00	9.4E-05	nd	nd	nd
Hs.79170	TTC9	Tetratricopeptide repeat domain 9	3.5	1.5E-05	3.1E-04	nd	nd	nd
Hs.365706	MGP	Matrix Gla protein	3.4	2.8E-11	2.8E-11	1.5	3.9E-04	2.2E-03
Hs.522632	TIMP1	Tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)	3.4	0.0E+00	8.0E-05	-1.1	ns	ns
Hs.109438	KCTD12	Potassium channel tetramerisation domain containing 12	3.4	0.0E+00	7.7E-04	nd	nd	nd
Hs.78065	C7	Complement component 7	3.4	0.0E+00	2.0E-04	2.7	2.7E-12	4.2E-03
Hs.443625	COL3A1	Collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	3.3	0.0E+00	3.2E-05	nd	nd	nd
Hs.477420	HEG	HEG homolog 1 (zebrafish)	3.3	2.2E-16	9.5E-05	na	na	na
Hs.533287	WBP5	WW domain binding protein 5	3.3	4.6E-13	8.1E-10	1.1	ns	ns
Hs.519702	CYFIP2	Cytoplasmic FMR1 interacting protein 2	3.3	4.0E-14	5.0E-14	1.2	ns	ns
Hs.332847	CRIM1	Cysteine-rich motor neuron 1	3.3	0.0E+00	5.1E-06	nd	nd	nd
Hs.209983	STMN1	Stathmin 1/oncoprotein 18	3.2	4.6E-09	4.6E-09	1.3	2.0E-03	6.2E-01
Hs.12956	TAX1BP3	Tax1 (human T-cell leukemia virus type I) binding protein 3	3.2	0.0E+00	2.0E-06	nd	nd	nd
Hs.511605	ANXA2	Annexin A2	3.2	0.0E+00	8.6E-05	1.6	0.0E+00	3.0E-03

Hs.146447	FBN1	Fibrillin 1 (Marfan syndrome)	3.2	0.0E+00	1.3E-05	nd	nd	nd
Hs.129895	TBX3	T-box 3 (ulnar mammary syndrome)	3.1	1.3E-09	4.5E-04	-1.2	ns	ns
Hs.143751	MMP11	Matrix metalloproteinase 11 (stromelysin 3)	3.1	6.6E-06	8.3E-04	2.5	0.0E+00	2.0E-04
Hs.523852	CCND1	Cyclin D1 (PRAD1: parathyroid adenomatosis 1)	3.1	0.0E+00	2.9E-05	1.6	0.0E+00	3.8E-03
Hs.420269	COL6A2	Collagen, type VI, alpha 2	3.1	0.0E+00	2.9E-05	1.7	1.9E-06	8.4E-03
Hs.350899	CAPN2	Calpain 2, (m/II) large subunit	3.1	0.0E+00	4.0E-06	nd	nd	nd
Hs.100261		CDNA FLJ26539 fis, clone KDN09310	3.0	2.2E-16	3.0E-06	nd	nd	nd
Hs.481371	FAT	FAT tumor suppressor homolog 1 (Drosophila)	3.0	2.1E-12	7.7E-04	nd	nd	nd
Hs.471783	RAMP1	Receptor (calcitonin) activity modifying protein 1	2.9	0.0E+00	3.4E-04	1.9	0.0E+00	1.3E-05
Hs.479808	IGFBP7	Insulin-like growth factor binding protein 7	2.9	0.0E+00	6.4E-05	1.8	0.0E+00	2.2E-03
Hs.446352	ERBB2	V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	2.9	0.0E+00	1.2E-04	-1.1	ns	ns
Hs.116724	AKR1B10	Aldo-keto reductase family 1, member B10 (aldose reductase)	2.9	3.2E-10	8.9E-04	1.2	ns	ns
Hs.268557	PHLDA3	Pleckstrin homology-like domain, family A, member 3	2.9	8.1E-08	9.3E-03	-1.0	ns	ns
Hs.550478	HSPG2	Heparan sulfate proteoglycan 2 (perlecan)	2.9	0.0E+00	5.2E-04	1.0	ns	ns
Hs.516505	S100A13	S100 calcium binding protein A13	2.8	0.0E+00	1.5E-04	1.2	ns	ns
Hs.400095	HSPB8	Heat shock 22kDa protein 8	2.8	1.5E-05	2.5E-04	1.3	ns	ns
Hs.302963	SPON2	Spondin 2, extracellular matrix protein	2.8	0.0E+00	2.2E-04	1.4	ns	ns
Hs.386299	WIG1	P53 target zinc finger protein	2.8	8.6E-12	1.5E-04	1.0	ns	ns
Hs.468044	LBH	Likely ortholog of mouse limb-bud and heart gene	2.8	0.0E+00	6.7E-04	nd	nd	nd
Hs.503998	TAGLN	Transgelin	2.8	7.2E-12	7.0E-04	1.6	5.6E-05	5.4E-02
Hs.372331	SPTAN1	Spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)	2.7	2.5E-13	5.5E-05	nd	nd	nd
Hs.76753	ENG	Endoglin (Osler-Rendu-Weber syndrome 1)	2.7	5.6E-14	3.5E-13	1.4	ns	ns
Hs.283521	RHEB	Similar to family with sequence similarity 35, member A	2.7	5.9E-11	7.6E-04	nd	nd	nd
Hs.534392	KDEL3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	2.7	4.6E-14	8.2E-04	nd	nd	nd
Hs.76152	AQP1	Aquaporin 1 (channel-forming integral protein, 28kDa)	2.7	0.0E+00	6.9E-04	nd	nd	nd
Hs.529408	BACE2	Beta-site APP-cleaving enzyme 2	2.7	5.2E-07	2.4E-04	nd	nd	nd
Hs.34421	GALNT10	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 10 (GalNAc-T10)	2.7	8.4E-05	4.5E-03	-1.1	ns	ns
Hs.446574	TMSB10	Thymosin, beta 10	2.7	0.0E+00	4.5E-04	nd	nd	nd
Hs.502461	DGKZ	Diacylglycerol kinase, zeta 104kDa	2.7	2.3E-09	8.2E-04	nd	nd	nd

Hs.293907	FAM38B	Family with sequence similarity 38, member B	2.6	1.4E-11	4.8E-04	nd	nd	nd
Hs.198862	FBLN2	Fibulin 2	2.6	2.3E-07	2.3E-07	nd	nd	nd
Hs.511743	TUBB3	Tubulin, beta 3	2.6	7.2E-13	7.6E-04	1.6	0.0E+00	2.8E-01
Hs.250281	SLC13A3	Solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	2.6	4.1E-11	4.0E-04	nd	nd	nd
Hs.241579	SERPINH1	Serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)	2.5	1.8E-09	4.2E-04	1.2	1.4E-03	1.1E-01
Hs.486483	AKAP7	A kinase (PRKA) anchor protein 7	2.5	1.3E-04	3.6E-03	nd	nd	nd
Hs.413924	CXCL10	Chemokine (C-X-C motif) ligand 10	2.5	5.5E-10	3.6E-07	na	na	na
Hs.302085	PTGIS	Prostaglandin I2 (prostacyclin) synthase	2.5	4.4E-11	4.0E-04	nd	nd	nd
Hs.445827	COL5A2	Collagen, type V, alpha 2	2.5	1.7E-13	4.8E-04	nd	nd	nd
Hs.433529	RPS11	Ribosomal protein S11	2.4	0.0E+00	5.9E-04	-1.1	ns	ns
Hs.437191	PTRF	Polymerase I and transcript release factor	2.4	1.9E-11	3.3E-04	1.0	ns	ns
Hs.514821	CCL5	Chemokine (C-C motif) ligand 5	2.4	1.1E-08	3.0E-07	1.2	ns	ns
Hs.65436	LOXL1	Lysyl oxidase-like 1	2.4	4.1E-05	4.1E-05	nd	nd	nd
Hs.131704	NRP1	Neuropilin 1	2.4	1.1E-14	1.6E-10	1.1	ns	ns
Hs.518726	IBSP	Integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II)	2.4	3.8E-12	2.6E-04	nd	nd	nd
Hs.334587	RBPMS	RNA binding protein with multiple splicing	2.4	6.7E-13	1.2E-05	1.1	ns	ns
Hs.376032	PDGFA	Platelet-derived growth factor alpha polypeptide	2.3	7.3E-11	5.9E-04	nd	nd	nd
Hs.25338	PRSS23	Protease, serine, 23	2.3	4.4E-16	2.1E-04	nd	nd	nd
Hs.369397	TGFBI	Transforming growth factor, beta-induced, 68kDa	2.3	2.7E-15	2.4E-05	1.5	8.2E-05	6.5E-02
Hs.450000	GGTL4	Gamma-glutamyltransferase-like 4	2.3	3.3E-10	3.5E-09	nd	nd	nd
Hs.133892	TPM1	Tropomyosin 1 (alpha)	2.3	0.0E+00	4.4E-04	1.1	ns	ns
Hs.433615	TUBB2	Tubulin, beta, 2	2.3	2.2E-16	8.9E-04	1.2	ns	ns
Hs.471751	CMKOR1	Chemokine orphan receptor 1	2.3	1.1E-04	6.1E-03	nd	nd	nd
Hs.529244	NCK2	NCK adaptor protein 2	2.3	5.7E-14	8.0E-05	1.3	2.8E-03	2.4E-02
Hs.269512	FSTL1	Follistatin-like 1	2.3	1.4E-07	7.6E-04	1.1	ns	ns
Hs.76095	IER3	Immediate early response 3	2.3	0.0E+00	7.9E-04	na	na	na
Hs.494337	GOLPH2	Golgi phosphoprotein 2	2.3	0.0E+00	0.0E+00	1.3	0.0E+00	8.5E-03
Hs.376071	CCND2	Cyclin D2	2.3	6.9E-09	1.6E-06	-1.1	ns	ns
Hs.50649	TP53I3	Tumor protein p53 inducible protein 3	2.3	5.5E-12	5.3E-04	1.6	0.0E+00	7.1E-03
Hs.347270	HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1	2.3	2.4E-14	3.3E-07	-1.1	ns	ns
Hs.536275	PACS1	Phosphofurin acidic cluster sorting protein 1	2.3	4.0E-02	4.0E-02	1.5	0.0E+00	2.5E-04
Hs.509067	PDGFRB	Platelet-derived growth factor receptor, beta polypeptide	2.2	1.5E-09	9.4E-04	1.9	2.5E-03	4.6E-03

Hs.200841	LAMA2	Laminin, alpha 2 (merosin, congenital muscular dystrophy)	2.2	1.7E-09	8.8E-04	2.5	0.0E+00	0.0E+00
Hs.172684	VAMP5	Vesicle-associated membrane protein 5 (myobrevin)	2.2	1.8E-08	7.6E-04	nd	nd	nd
Hs.513488	MVP	Major vault protein	2.2	3.3E-08	3.3E-08	1.5	2.1E-04	2.9E-03
Hs.514412	PECAM1	Platelet/endothelial cell adhesion molecule (CD31 antigen)	2.2	2.6E-09	1.4E-04	-1.1	ns	ns
Hs.357901	SOX4	SRY (sex determining region Y)-box 4	2.2	0.0E+00	2.1E-04	1.0	ns	ns
Hs.195464	FLNA	Filamin A, alpha (actin binding protein 280)	2.2	1.1E-09	8.4E-04	nd	nd	nd
Hs.501928	MICAL2	Microtubule associated monooxygenase, calponin and LIM domain containing 2	2.2	1.3E-13	9.9E-04	1.2	ns	ns
Hs.1103	TGFB1	Transforming growth factor, beta 1 (Camurati-Engelmann disease)	2.2	1.1E-15	1.9E-09	-1.2	ns	ns
Hs.38449	SERPINE2	Serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	2.2	0.0E+00	7.0E-06	nd	nd	nd
Hs.501778	TRIM22	Tripartite motif-containing 22	2.2	2.2E-16	1.3E-07	nd	nd	nd
Hs.9999	EMP3	Epithelial membrane protein 3	2.2	6.2E-10	3.7E-07	nd	nd	nd
Hs.417004	S100A11	S100 calcium binding protein A11 (calgizzarin)	2.2	1.4E-10	1.1E-08	1.0	ns	ns
Hs.409934	HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	2.2	2.9E-15	2.5E-07	nd	nd	nd
Hs.133397	ITGA6	Integrin, alpha 6	2.1	3.3E-09	7.4E-04	1.5	5.5E-04	4.9E-01
Hs.512857	CD151	CD151 antigen	2.1	4.4E-16	2.8E-05	1.5	1.4E-05	1.0E-03
Hs.511397	MCAM	Melanoma cell adhesion molecule	2.1	3.0E-13	1.7E-04	nd	nd	nd
Hs.297343	CAMKK2	Calcium/calmodulin-dependent protein kinase kinase 2, beta	2.1	9.2E-10	2.3E-07	-1.1	ns	ns
Hs.515536	RRAS	Related RAS viral (r-ras) oncogene homolog	2.1	3.2E-08	3.2E-08	nd	nd	nd
Hs.439643	SLC16A7	Solute carrier family 16 (monocarboxylic acid transporters), member 7	2.1	1.1E-10	1.7E-06	1.3	ns	ns
Hs.520714	SNX10	Sorting nexin 10	2.1	1.6E-07	1.6E-07	nd	nd	nd
Hs.519909	MARCKS	Myristoylated alanine-rich protein kinase C substrate	2.1	5.5E-08	7.7E-06	1.4	7.3E-04	8.6E-03
Hs.485104	TNXB	Tenascin XB	2.1	2.0E-13	5.3E-04	nd	nd	nd
Hs.109590	GENX-3414	Genethonin 1	2.1	8.7E-09	6.4E-04	nd	nd	nd
Hs.550467	ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	2.1	4.7E-04	9.6E-03	nd	nd	nd
Hs.513617	MMP2	Matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	2.1	1.2E-14	3.0E-04	-1.1	ns	ns
Hs.309602	TRIM15	Tripartite motif-containing 15	2.1	4.6E-09	4.6E-09	nd	nd	nd
Hs.533710	FLRT2	Fibronectin leucine rich transmembrane protein 2	2.1	0.0E+00	4.4E-05	nd	nd	nd

Hs.529038	FSTL3	Follistatin-like 3 (secreted glycoprotein)	2.1	8.5E-09	2.3E-04	nd	nd	nd
Hs.474053	COL6A1	Collagen, type VI, alpha 1	2.0	7.6E-13	1.6E-07	1.4	0.0E+00	4.2E-03
Hs.446429	PTGDS	Prostaglandin D2 synthase 21kDa (brain)	2.0	2.4E-07	6.3E-04	1.2	ns	ns
Hs.524390	K-ALPHA-1	Tubulin, alpha, ubiquitous	2.0	3.8E-15	4.8E-04	1.4	0.0E+00	2.5E-01
Hs.97199	C1QR1	Complement component 1, q subcomponent, receptor 1	2.0	8.9E-10	4.9E-04	nd	nd	nd
Hs.436035	TUBA6	Tubulin alpha 6	2.0	9.5E-13	9.2E-04	1.4	2.0E-04	4.6E-03
Hs.172176	LGR5	Leucine-rich repeat-containing G protein-coupled receptor 5	2.0	0.0E+00	1.5E-04	nd	nd	nd
Hs.46523	ELK3	ELK3, ETS-domain protein (SRF accessory protein 2)	2.0	1.8E-08	1.0E-06	na	na	na
Hs.275243	S100A6	S100 calcium binding protein A6 (calcyclin)	2.0	1.5E-09	2.2E-04	-1.1	ns	ns
Hs.436873	ITGAV	Integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	2.0	2.5E-14	3.1E-05	1.1	ns	ns
Hs.444118	MCM6	MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, S. pombe) (S. cerevisiae)	2.0	7.3E-10	7.1E-04	1.4	1.4E-03	4.8E-02
Hs.2030	THBD	Thrombomodulin	2.0	1.6E-08	6.3E-07	1.3	ns	ns
Hs.369201	GAS6	Growth arrest-specific 6	2.0	5.8E-08	6.6E-04	nd	nd	nd
Hs.132902	CAP2	CAP, adenylate cyclase-associated protein, 2 (yeast)	2.0	9.5E-09	9.4E-04	1.4	0.0E+00	1.1E-03
Hs.489033	ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	2.0	3.3E-11	3.1E-04	na	na	na
Hs.289092	COTL1	Coactosin-like 1 (Dictyostelium)	2.0	3.4E-06	4.8E-04	nd	nd	nd
Hs.524395	TUBA3	Tubulin, alpha 3	2.0	2.6E-12	1.4E-04	1.2	ns	ns
Hs.438720	MCM7	MCM7 minichromosome maintenance deficient 7 (S. cerevisiae)	2.0	3.1E-09	8.9E-04	1.1	ns	ns
Hs.66762	C10orf38	Chromosome 10 open reading frame 38	2.0	8.4E-07	7.9E-06	nd	nd	nd
Hs.25691	RAMP3	Receptor (calcitonin) activity modifying protein 3	1.9	4.7E-11	3.9E-06	nd	nd	nd
Hs.118400	FSCN1	Fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)	1.9	2.8E-12	4.1E-06	1.6	0.0E+00	1.4E-03
Hs.270291	ACTN4	Actinin, alpha 4	1.9	4.2E-06	5.0E-04	nd	nd	nd
Hs.111779	SPARC	Secreted protein, acidic, cysteine-rich (osteonectin)	1.9	8.2E-13	2.8E-06	1.4	3.4E-04	1.4E-01
Hs.50223	RBP4	Retinol binding protein 4, plasma	1.9	7.2E-12	8.0E-06	nd	nd	nd
Hs.173381	DPYSL2	Stromal cell-derived factor 2-like 1	1.9	1.5E-11	1.3E-05	1.2	ns	ns
Hs.202	BZRP	Benzodiazapine receptor (peripheral)	1.9	3.3E-07	8.1E-05	1.4	1.7E-03	3.1E-01
Hs.475353	LMCD1	LIM and cysteine-rich domains 1	1.9	4.1E-07	8.5E-07	1.8	1.3E-08	7.8E-03
Hs.156316	DCN	Decorin	1.9	1.1E-10	5.5E-04	na	na	na

Hs.134643	THY1	Thy-1 cell surface antigen	1.9	0.0E+00	1.0E-05	2.3	0.0E+00	1.0E-03
Hs.71465	SQLE	Squalene epoxidase	1.9	1.2E-11	3.2E-06	nd	nd	nd
Hs.520814	TENS1	Tensin-like SH2 domain containing 1	1.8	1.6E-10	1.4E-04	nd	nd	nd
Hs.517949	MAP4	Microtubule-associated protein 4	1.8	8.6E-11	1.8E-03	1.4	6.0E-04	3.9E-01
Hs.439726	LAMB2	Laminin, beta 2 (laminin S)	1.8	7.3E-12	2.9E-05	nd	nd	nd
Hs.522584	TMSB4X	Thymosin, beta 4, X-linked	1.8	5.0E-10	5.0E-10	1.2	1.4E-03	1.0E-01
Hs.76171	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	1.8	8.6E-06	1.8E-05	1.8	4.0E-04	1.8E-03
Hs.473109	C11orf9	Chromosome 11 open reading frame 9	1.8	1.2E-06	5.7E-04	nd	nd	nd
Hs.6764	HDAC6	Histone deacetylase 6	1.8	4.0E-08	2.4E-06	na	na	na
Hs.508343	AMACR	Alpha-methylacyl-CoA racemase	1.8	1.1E-08	1.1E-08	1.7	0.0E+00	5.4E-06
Hs.474833	CSNK1E	Casein kinase 1, epsilon	1.8	5.3E-06	5.3E-06	-1.0	ns	ns
Hs.132161	FOXK2	Forkhead box K2	-1.3	ns	ns	7.3	1.0E-06	7.0E-03
Hs.30743	PRAME	Preferentially expressed antigen in melanoma	-1.0	ns	ns	5.4	7.6E-04	9.6E-01
Hs.532968	DKFZp762E1312	Hypothetical protein DKFZp762E1312	1.0	ns	ns	3.8	0.0E+00	5.8E-02
Hs.502809	MARK2	MAP/microtubule affinity-regulating kinase 2	1.0	ns	ns	3.2	6.6E-02	6.6E-02
Hs.306814	LOXL4	Lysyl oxidase-like 4	nd	nd	nd	2.9	0.0E+00	4.0E-04
Hs.14333	FLJ10349	Hypothetical protein FLJ10349	1.2	ns	ns	2.7	0.0E+00	3.5E-01
Hs.145049	PLEKHM2	Pleckstrin homology domain containing, family M (with RUN domain) member 2	1.1	ns	ns	2.6	0.0E+00	2.0E-04
Hs.446554	RAD51	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)	-1.0	ns	ns	2.5	1.5E-08	1.4E-03
Hs.511367	CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1	-1.0	ns	ns	2.4	0.0E+00	3.3E-01
Hs.233160	STC2	Stanniocalcin 2	1.1	ns	ns	2.3	2.0E-05	4.1E-01
Hs.312098	ADAM15	A disintegrin and metalloproteinase domain 15 (metargidin)	1.3	ns	ns	2.3	2.0E-15	4.0E-04
Hs.329989	PLK1	Polo-like kinase 1 (Drosophila)	-1.0	ns	ns	2.2	3.7E-05	8.0E-03
Hs.524134	GATA3	GATA binding protein 3	1.0	ns	ns	2.2	0.0E+00	5.8E-05
Hs.531682	ALDH3A1	Aldehyde dehydrogenase 3 family, memberA1	1.3	ns	ns	2.2	0.0E+00	4.4E-03
Hs.491494	CCT3	Chaperonin containing TCP1, subunit 3 (gamma)	1.2	ns	ns	2.2	4.0E-04	5.4E-01
Hs.408488	MSLN	Mesothelin	-1.1	ns	ns	2.1	1.2E-08	1.2E-08
Hs.516933	NXT1	NTF2-like export factor 1	1.2	ns	ns	2.1	4.8E-04	6.1E-01
Hs.515835	SULT2A1	Sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1	-1.1	ns	ns	2.1	0.0E+00	1.0E-06
Hs.124015	HAGHL	Hydroxyacylglutathione hydrolase-like	nd	nd	nd	2.1	0.0E+00	8.2E-04
Hs.199487	RERG	RAS-like, estrogen-regulated, growth inhibitor	nd	nd	nd	2.1	1.5E-12	1.5E-12

Hs.515042	LMNB2	Lamin B2	1.1	ns	ns	2.0	0.0E+00	5.0E-01
Hs.402773	PTPN7	Protein tyrosine phosphatase, non-receptor type 7	1.1	ns	ns	2.0	4.8E-06	3.1E-03
Hs.356501	PHF6	PHD finger protein 6	nd	nd	nd	2.0	7.5E-10	7.5E-10
Hs.458332	PYCR1	Pyrroline-5-carboxylate reductase 1	1.0	ns	ns	2.0	0.0E+00	7.8E-04
Hs.58919	DTNA	Dystrobrevin, alpha	1.1	ns	ns	2.0	0.0E+00	2.8E-05
Hs.517972	TRIP	TRAF interacting protein	1.0	ns	ns	2.0	0.0E+00	4.1E-01
Hs.7962	FLJ30525	Hypothetical protein FLJ30525	nd	nd	nd	2.0	4.6E-08	3.7E-03
Hs.513530	TGFB111	Transforming growth factor beta 1 induced transcript 1	1.5	ns	ns	1.9	1.8E-09	1.0E-03
Hs.469116	SLC9A1	Solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter, Na+/H+, amiloride sensitive)	1.1	ns	ns	1.9	1.0E-09	1.0E-09
Hs.472716	C20orf129	Chromosome 20 open reading frame 129	nd	nd	nd	1.9	1.7E-08	1.7E-08
Hs.507080	APCS	Amyloid P component, serum	1.0	ns	ns	1.9	0.0E+00	2.0E-05
Hs.19193		Hypothetical gene supported by BC009385	nd	nd	nd	1.9	2.6E-08	3.8E-03
Hs.517168	TAGLN2	Transgelin 2	1.5	ns	ns	1.9	6.8E-10	2.5E-03
Hs.14559	C10orf3	Chromosome 10 open reading frame 3	1.0	ns	ns	1.9	0.0E+00	2.4E-04
Hs.169840	TTK	TTK protein kinase	1.1	ns	ns	1.9	0.0E+00	4.9E-04
Hs.84753	FLJ12442	Hypothetical protein FLJ12442	1.3	ns	ns	1.9	0.0E+00	8.8E-01
Hs.279766	KIF4A	Kinesin family member 4A	-1.1	ns	ns	1.9	4.4E-04	1.1E-01
Hs.155090	GNB5	Guanine nucleotide binding protein (G protein), beta 5	-1.2	ns	ns	1.9	4.9E-08	2.2E-01
Hs.524947	CDC20	CDC20 cell division cycle 20 homolog (S. cerevisiae)	1.1	ns	ns	1.8	0.0E+00	4.6E-01
Hs.69360	KIF2C	Kinesin family member 2C	-1.0	ns	ns	1.8	0.0E+00	8.3E-03
Hs.549075	XRCC3	X-ray repair complementing defective repair in Chinese hamster cells 3	-1.1	ns	ns	1.8	0.0E+00	2.8E-08
Hs.516155	CAPG	Capping protein (actin filament), gelsolin-like	1.5	ns	ns	1.8	0.0E+00	1.5E-03
Hs.466831	PAFAH1B3	Platelet-activating factor acetylhydrolase, isoform Ib, gamma subunit 29kDa	1.2	ns	ns	1.8	0.0E+00	5.6E-03
Hs.498248	EXO1	Exonuclease 1	1.0	ns	ns	1.8	7.8E-04	1.1E-02
Hs.99196	MGC11324	Hypothetical protein MGC11324	nd	nd	nd	-1.8	0.0E+00	6.8E-06
Hs.418241	MT2A	Metallothionein 2A	na	na	na	-1.8	6.6E-06	6.6E-06
Hs.530124	CTAGE4	CTAGE family, member 4	na	na	na	-1.8	4.6E-04	1.8E-03
Hs.42146	PAX3	Paired box gene 3 (Waardenburg syndrome 1)	-1.0	ns	ns	-1.8	0.0E+00	6.0E-04
Hs.510334	SERPINA5	Serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5	-1.1	ns	ns	-1.8	0.0E+00	2.7E-03

Hs.463059	STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	-1.3	ns	ns	-1.8	0.0E+00	3.7E-01
Hs.490510	ZNF212	Zinc finger protein 212	1.1	ns	ns	-1.8	0.0E+00	4.7E-03
Hs.512937	CPB2	Carboxypeptidase B2 (plasma, carboxypeptidase U)	-1.3	ns	ns	-1.8	0.0E+00	1.1E-04
Hs.32603	COLEC11	Collectin sub-family member 11	-1.4	ns	ns	-1.8	4.9E-06	9.3E-02
Hs.487447	FBXL18	F-box and leucine-rich repeat protein 18	1.0	ns	ns	-1.9	0.0E+00	0.0E+00
Hs.133527	TM4SF4	Transmembrane 4 L six family member 4	-1.0	ns	ns	-1.9	3.2E-05	1.0E-03
Hs.458312	MBD5	Methyl-CpG binding domain protein 5	-1.0	ns	ns	-1.9	8.3E-09	1.0E-03
Hs.506815	LOC89894	Hypothetical protein BC000282	nd	nd	nd	-1.9	4.3E-08	8.0E-04
Hs.516157	MAT2A	Methionine adenosyltransferase II, alpha	1.1	ns	ns	-1.9	0.0E+00	4.3E-01
Hs.272242	C20orf38	Chromosome 20 open reading frame 38	1.0	ns	ns	-1.9	4.7E-04	8.0E-03
Hs.274539	BDH	3-hydroxybutyrate dehydrogenase (heart, mitochondrial)	-1.1	ns	ns	-1.9	0.0E+00	3.7E-01
Hs.83758	CKS2	CDC28 protein kinase regulatory subunit 2	1.0	ns	ns	-1.9	0.0E+00	4.0E-04
Hs.72912	CYP1A1	Cytochrome P450, family 1, subfamily A, polypeptide 1	na	na	na	-1.9	0.0E+00	0.0E+00
Hs.9754	ATF5	Activating transcription factor 5	-1.1	ns	ns	-1.9	0.0E+00	6.0E-04
Hs.283109	COG1	Component of oligomeric golgi complex 1	nd	nd	nd	-1.9	0.0E+00	8.8E-04
Hs.302145	HBG2	Hemoglobin, gamma G	nd	nd	nd	-1.9	0.0E+00	1.4E-03
Hs.400613	CNDP1	Carnosine dipeptidase 1 (metallopeptidase M20 family)	nd	nd	nd	-1.9	0.0E+00	1.3E-05
Hs.26047	TNRC4	Trinucleotide repeat containing 4	1.1	ns	ns	-1.9	3.4E-09	5.0E-03
Hs.426485	HPX	Hemopexin	-1.1	ns	ns	-1.9	4.8E-04	3.9E-02
Hs.102696	MCTS1	Malignant T cell amplified sequence 1	1.1	ns	ns	-2.0	0.0E+00	3.3E-03
Hs.532091	AP3B1	Adaptor-related protein complex 3, beta 1 subunit	1.2	ns	ns	-2.0	2.2E-09	4.0E-04
Hs.471403	RNF25	Ring finger protein 25	1.1	ns	ns	-2.0	0.0E+00	1.8E-03
Hs.525629	MTA1	Metastasis associated 1	1.2	ns	ns	-2.0	0.0E+00	4.5E-02
Hs.213724	SUPT16H	Suppressor of Ty 16 homolog (S. cerevisiae)	1.1	ns	ns	-2.1	3.7E-13	1.0E-03
Hs.133044	raptor	Raptor	nd	nd	nd	-2.1	0.0E+00	1.0E-06
Hs.94107	GSTA2	Glutathione S-transferase A2	nd	nd	nd	-2.1	6.5E-06	1.4E-03
Hs.324250	NDUFB2	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	-1.0	ns	ns	-2.1	2.0E-04	3.3E-04
Hs.292281	TGIF2	TGFB-induced factor 2 (TALE family homeobox)	1.3	ns	ns	-2.2	0.0E+00	1.3E-03
Hs.75765	CXCL2	Chemokine (C-X-C motif) ligand 2	na	na	na	-2.2	2.0E-03	6.3E-02
Hs.503743	GRIA4	Glutamate receptor, ionotropic, AMPA 4	-1.1	ns	ns	-2.2	8.3E-05	2.0E-03
Hs.337594	SDSL	Serine dehydratase-like	nd	nd	nd	-2.2	0.0E+00	2.8E-01
Hs.547131	MGC4859	Hypothetical protein MGC4859 similar to HSPA8	-1.0	ns	ns	-2.2	0.0E+00	1.0E-06

Hs.504031	FXYD6	FXYD domain containing ion transport regulator 6	1.0	ns	ns	-2.2	0.0E+00	1.6E-03
Hs.487925	PDE4DIP	Phosphodiesterase 4D interacting protein (myomegalin)	-1.2	ns	ns	-2.2	0.0E+00	1.3E-01
Hs.391835	C8B	Complement component 8, beta polypeptide	-1.3	ns	ns	-2.2	0.0E+00	2.0E-05
Hs.60856	HCG4	HLA complex group 4	nd	nd	nd	-2.3	1.6E-03	1.4E-03
Hs.397609	RPS16	Ribosomal protein S16	1.1	ns	ns	-2.3	0.0E+00	8.6E-02
Hs.438994	ZNF544	Zinc finger protein 544	1.2	ns	ns	-2.3	1.1E-02	9.5E-01
Hs.2430	TCFL1	Transcription factor-like 1	1.3	ns	ns	-2.3	0.0E+00	0.0E+00
Hs.448456	FLJ35390	Hypothetical protein FLJ35390	nd	nd	nd	-2.4	0.0E+00	4.0E-06
Hs.434219	ANKHD1	Eukaryotic translation initiation factor 4E binding protein 3	-1.1	ns	ns	-2.4	0.0E+00	6.2E-01
Hs.12126	HCA112	Hepatocellular carcinoma-associated antigen 112	-1.1	ns	ns	-2.4	0.0E+00	1.2E-03
Hs.250181	GORASP1	Golgi reassembly stacking protein 1, 65kDa	1.1	ns	ns	-2.4	0.0E+00	1.8E-03
Hs.526920	GNAZ	Guanine nucleotide binding protein (G protein), alpha z polypeptide	-1.1	ns	ns	-2.4	1.6E-07	8.6E-03
Hs.433391	MT1G	Metallothionein 1G	1.2	ns	ns	-2.5	2.4E-09	2.4E-09
Hs.296949	CLDN9	Claudin 9	1.1	ns	ns	-2.5	1.1E-08	1.1E-08
Hs.497443	C1orf37	Chromosome 1 open reading frame 37	-1.2	ns	ns	-2.5	4.4E-05	2.0E-04
Hs.521295	LR8	LR8 protein	-1.0	ns	ns	-2.5	0.0E+00	5.7E-04
Hs.155396	NFE2L2	Nuclear factor (erythroid-derived 2)-like 2	-1.3	ns	ns	-2.5	1.6E-02	2.3E-02
Hs.202453	MYC	V-myc myelocytomatosis viral oncogene homolog (avian)	na	na	na	-2.7	6.8E-08	9.6E-02
Hs.517962	TCTA	T-cell leukemia translocation altered gene	1.0	ns	ns	-2.8	1.9E-04	5.3E-01
Hs.4	ADH1B	Alcohol dehydrogenase IB (class I), beta polypeptide	-1.2	ns	ns	-2.8	0.0E+00	1.3E-03
Hs.534085	TNNT1	Troponin T1, skeletal, slow	1.1	ns	ns	-2.8	3.7E-02	5.6E-02
Hs.119251	UQCRC1	Ubiquinol-cytochrome c reductase core protein I	1.1	ns	ns	-2.9	8.0E-04	8.6E-01
Hs.188401	ANXA10	Annexin A10	-1.3	ns	ns	-3.1	0.0E+00	4.8E-05
Hs.80409	GADD45A	Growth arrest and DNA-damage-inducible, alpha	-1.2	ns	ns	-3.1	8.4E-03	1.5E-02
Hs.25647	FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	na	na	na	-4.7	0.0E+00	3.3E-03
Hs.194686	SLC25A14	Solute carrier family 25 (mitochondrial carrier, brain), member 14	-1.0	ns	ns	-5.3	0.0E+00	6.6E-03
Hs.352253	MGC15885	Hypothetical protein MGC15885	nd	nd	nd	-6.1	2.8E-03	3.1E-03

Supplementary Table 2. Liste of Gene Ontology terms that were found significantly enriched in genes differentially expressed between FNH and non-tumor livers. In each branch of the GO term hierachy, only the most significant category is provided whatever its level.

O: Observed gene number in the GO category (referred to genes differentially expressed between FNH and non-tumor livers)

E: Expected gene number in the GO category (referred to the content of the HG-U133A Affymetrix array)

R: Ratio of enrichment for the GO category (O/E)

P-value: Significance of enrichment for the GO category

List of over-represented Gene Ontology (GO) terms among genes overexpressed in FNH versus NTL					
	O	E	R	P-value	Gene symbol
<i>In biological process</i>					
cell adhesion	37	10.44	3.54	8.36E-12	CDH11; MSLN; SPON2; FBLN5; COL5A1; COL6A1; COL6A2; COL15A1; CSPG2; AEBP1; ENG; FAT; FLRT2; CNTNAP2; HSPG2; TNC; IBSP; ITGA6; ITGAV; LAMA2; LAMA3; LAMB2; MCAM; EMCN; PECAM1; CCL5; TGFB1; THBS2; THY1; TNXB; VWF; ADAM15; NRP1; ITGBL1; ENTPD1; CELSR1; CD151
anatomical structure development	51	24.3	2.1	1.10E-07	CDH11; SPON2; CAP2; CEBPA; VAMP5; COL1A1; COL1A2; COL3A1; COL15A1; DBN1; DCN; AEBP1; DPYSL2; MARK2; EMP3; ENG; ERBB2; FAT; FBN1; FLNA; PHLDA3; GAS6; GATA3; DKK3; ANXA2; IBSP; IGFBP7; CXCL10; LAMA2; LAMA3; MCAM; MGP; MMP11; PAFAH1B3; CRIM1; EMCN; SERPINE2; S100A6; SOX9; SPARC; TAGLN; TBX3; TGFB1; THY1; TIMP1; TAGLN2; RERG; NRP1; IER3; TRIM15; CELSR1
phosphate transport	10	1.25	8	3.38E-07	COL1A1; COL1A2; COL3A1; COL4A1; COL4A2; COL5A1; COL5A2; COL6A1; COL6A2; COL15A1
regulation of cell motility	5	0.63	7.94	3.64E-04	LAMA2; LAMA3; SERPINE2; THY1; ACTN4
protein depolymerization	5	0.66	7.58	4.32E-04	GSN; STMN1; MAP4; SPTAN1; CAPG
organismal physiological process	51	33.09	1.54	6.78E-04	CDH11; TRIM22; SPON2; CEBPA; FBLN5; UBD; COL1A1; COL1A2; COL3A1; DBN1; DTNA; ENG; F2RL1; FBN1; EFEMP1; CNTNAP2; GATA3; GLUL; HLA-DPA1; HLA-DQB1; APCS; IBSP; IGLC2; AQP1; CXCL10; LAMB2; LUM; MGP; NTS; AKR1B10; PTGDS; RBP4; CCL5; CCL21; CXCL6; SPARC; SULT2A1; TGFB1; TGFB1; THBD; THY1; TIMP1; TPM1; C7; VWF; TFPI2; NCK2; EXO1; CD24; ENTPD1; CD151
cell morphogenesis	13	4.76	2.73	9.42E-04	SPON2; CAP2; DBN1; MARK2; EMP3; GAS6; IGFBP7; CRIM1; S100A6; TGFB1; THY1; RERG; NRP1
positive regulation of cell proliferation	9	2.65	3.4	1.31E-03	ERBB2; CXCL10; PDGFA; S100A6; TGFB1; TIMP1; TTK; NCK2; NRP1
blood coagulation	7	1.77	3.95	1.86E-03	FBLN5; F2RL1; FBN1; THBD; VWF; TFPI2; ENTPD1

neurite development	5	1	5	3.00E-03	SPON2; DBN1; S100A6; THY1; NRP1
wound healing	7	1.93	3.63	3.05E-03	FBLN5; F2RL1; FBN1; THBD; VWF; TFPI2; ENTPD1
DNA-dependent DNA replication	6	1.59	3.77	4.92E-03	MCM5; MCM6; MCM7; RAD51; S100A11; EXO1
cell recognition	3	0.36	8.33	5.15E-03	CSPG2; CNTNAP2; PECAM1
negative regulation of protein metabolism	5	1.27	3.94	8.49E-03	GSN; MAP4; SPTAN1; TIMP1; CAPG
negative regulation of Wnt receptor signaling pathway	2	0.16	12.5	9.94E-03	DKK3; TAX1BP3
<i>In molecular function</i>					
calcium ion binding	31	12.92	2.4	4.11E-06	CDH11; FBLN5; CAMKK2; FSTL1; CSPG2; DTNA; FAT; FBLN2; FBN1; EFEMP1; GAS6; GSN; ANXA2; APCS; ITGA6; ITGAV; MGP; MMP2; MMP11; GALNT10; S100A6; S100A11; S100A13; SPARC; SPTAN1; THBD; THBS2; ACTN4; CAPN2; ENTPD1; CELSR1
actin binding	15	3.84	3.91	6.45E-06	HDAC6; DBN1; FLNA; COTL1; GSN; MARCKS; FSCN1; SPTAN1; TAGLN; TMSB4X; TPM1; TPM2; ACTN4; CAPG; TMSB10
DNA-dependent ATPase activity	5	0.65	7.69	4.30E-04	MCM5; MCM6; MCM7; RAD51; XRCC3
protein-lysine 6-oxidase activity	2	0.07	28.57	1.40E-03	LOXL1; LOXL4
glycosaminoglycan binding	6	1.64	3.66	5.78E-03	FSTL1; COL5A1; CSPG2; SERPINE2; CXCL6; THBS2
<i>In cellular component</i>					
extracellular matrix	36	4.85	7.42	6.20E-22	SPON2; FBLN5; COL1A1; COL1A2; COL3A1; COL4A1; COL4A2; COL5A1; COL5A2; COL6A1; COL6A2; COL15A1; CSPG2; DCN; FBLN2; FBN1; EFEMP1; FLRT2; HSPG2; TNC; LAMA2; LAMA3; LAMB2; LUM; MGP; MMP2; MMP11; SPARC; TGFB1; TGFB1; THBS2; TIMP1; TNXB; C7; VWF; TFPI2
cytoskeleton	28	13.48	2.08	1.60E-04	HDAC6; TUBB3; KIF2C; DBN1; FLNA; COTL1; KIF4A; C18orf10; KRT23; GSN; KRT7; STMN1; MARCKS; MAP4; PLK1; FSCN1; SPTAN1; TMSB4X; TPM1; TPM2; CCT3; TTK; CAPG; TUBA6; LMNB2; TMSB10; MICAL2; CDC20

List of over-represented Gene Ontology (GO) terms among genes underexpressed in FNH versus NTL					
	O	E	R	P-value	Gene symbol
<i>In biological process</i>					
amino acid and derivative metabolism	23	5.29	4.35	2.32E-09	AASS; SLC25A15; SDS; CPS1; CTH; DBH; DDT; SARDH; EGFR; GCH1; GLS2; GLDC; GSTZ1; PSAT1; HAL; MAOA; ASPA; BAAT; BHMT; SLC7A2; TAT; TDO2; BBOX1
fatty acid desaturation	3	0.1	30	6.08E-05	FADS1; SCD; FADS2
generation of precursor metabolites and energy	22	10.6	2.08	8.82E-04	AASS; DHRS2; SDS; CYP1A1; CYP2A6; CYP3A5; CYP26A1; SARDH; AGL; DPYD; ENO3; ALDOB; SLC37A4; TXN2; GYS1; LEPR; MAOA; NDUFB2; CYP3A43; UQCRC1; BBOX1; SLC25A14
transition metal ion homeostasis	4	0.5	8	1.35E-03	CP; HPX; MT2A; MYC
complement activation\, classical pathway	4	0.6	6.67	2.74E-03	MASP2; MASP1; C4BPB; C8B
<i>In molecular function</i>					
iron ion binding	16	4.63	3.46	1.51E-05	CYP1A1; CYP2A6; CYP3A5; CYP26A1; DPYD; HBB; HBG2; HMOX1; HPX; FADS1; P4HA1; SCD; CYP3A43; TDO2; BBOX1; FADS2
transcription factor activity	25	15.03	1.66	8.08E-03	CITED2; TNRC4; CREM; DSCR1; ESR2; ATF5; FOXO1A; FOS; FOSB; HHEX; JUN; LHX1; ASCL1; MYC; NFE2L2; NR4A2; PAX3; TGIF2; SALL1; SCML1; STAT3; KLF9; KLF10; NR0B2; MTA1
oxygen binding	6	0.64	9.38	3.25E-05	CYP1A1; CYP2A6; CYP3A5; CYP26A1; HBB; HBG2
protein dimerization activity	10	4.23	2.36	9.84E-03	CREM; AGXT; EGFR; ATF5; FOS; FOSB; JUN; NFE2L2; CNDP1; CD4
insulin-like growth factor receptor binding	3	0.19	15.79	6.77E-04	IGF1; PIK3R1; SOCS2
heme binding	9	1.45	6.21	1.20E-05	CYP1A1; CYP2A6; CYP3A5; CYP26A1; HBB; HBG2; FADS1; CYP3A43; FADS2
vitamin binding	8	1.45	5.52	8.83E-05	SLC19A2; DBH; AGXT; GNMT; ACACB; MUT; P4HA1; TAT
oxidoreductase activity\, acting on paired donors\, with incorporation or reduction of molecular oxygen	12	1.97	6.09	5.16E-07	CYP1A1; CYP2A6; CYP3A5; CYP26A1; DBH; HMOX1; FADS1; P4HA1; SCD; CYP3A43; BBOX1; FADS2
amino acid transporter activity	5	0.93	5.38	2.15E-03	SLC25A15; SLC38A4; SLC1A1; SLC6A13; SLC7A2

Supplementary Table 3. Quantitative RT-PCR data

Data are expressed as the n-fold differences in target gene expression in tested samples compared with the mean expression value of normal livers, using the 2^{-ΔΔCt} method, where ΔΔCt = (Ct_{target}-Ct_{R18S})_{Sample} - (Ct_{target}-Ct_{R18S})_{Normal livers}

		R18S	ANGPT1	ANGPT2	ANGPT1/ANGPT2	CTNNB1	GLUL	GPR49	NTS	SDS	HAL	NTS /HAL
	Sample ID	Ct	2^{-ΔΔCt}	2^{-ΔΔCt}		2^{-ΔΔCt}	2^{-ΔΔCt}	2^{-ΔΔCt}	2^{-ΔΔCt}	2^{-ΔΔCt}	2^{-ΔΔCt}	
Normal livers	CHC378N	9.5	2.0	0.7	2.7	0.9	1.1	0.04	1.4	0.2	0.6	2.2
	CHC469N	8.9	0.002	1.7	0.001	0.6	0.5	0.7	0.2	0.9	1.1	0.1
	CHC566N	9.1	1.2	0.8	1.6	1.2	2.2	1.4	2.2	0.5	1.2	1.8
	CHC591N	8.4	0.5	0.7	0.6	0.9	0.6	0.9	0.5	0.7	0.9	0.6
	CHC932N	8.1	0.8	0.5	1.7	1.1	0.5	1.7	0.4	3.5	1.6	0.3
	CHC934N	8.8	1.5	1.6	1.0	1.2	1.0	1.2	1.3	0.2	0.5	2.5
FNH	CHC767T	8.7	4.4	0.5	9.6	1.3	2.3	4.6	3.7	0.01	0.04	97.8
	CHC556T	8.3	10.0	0.4	23.3	1.4	7.9	11.1	10.9	0.02	0.3	31.6
	CHC561T	8.4	1.7	0.0	82.1	1.6	8.1	26.3	12.8	0.1	0.02	616.9
	CHC563T	8.3	3.1	0.2	19.1	1.1	3.1	7.7	1.9	0.1	0.1	29.1
	CHC564T	8.3	5.7	0.5	11.6	1.4	4.1	13.3	24.4	0.05	0.1	242.3
	CHC565T	8.2	2.4	0.2	11.5	1.1	3.6	8.6	16.0	0.01	0.04	369.5
	CHC595T	8.2	3.0	0.2	17.1	1.1	7.3	17.3	37.0	0.05	0.1	344.8
	CHC597T	8.6	5.4	0.4	12.9	1.6	5.6	13.7	10.7	0.1	0.2	45.0
	CHC600T	8.4	4.5	0.6	7.7	1.6	4.6	12.9	26.4	0.2	0.3	99.0
	CHC607T	8.6	4.7	0.3	16.5	1.3	3.4	3.8	14.3	0.1	0.3	51.2
CHC667T	8.5	2.3	0.6	3.5	1.7	2.9	10.2	3.2	0.02	0.05	68.5	
FNH-like	CHC1095T	8.6	1.4	0.4	3.2	1.5	0.9	0.3	0.4	1.8	1.1	0.4
	CHC1096T	8.8	1.3	0.4	3.1	1.4	0.6	0.2	0.5	1.7	1.0	0.5
	CHC1109T	8.8	2.4	0.8	3.0	1.1	0.7	0.4	0.3	0.7	2.1	0.2
	CHC1111T	9.1	5.2	0.6	8.6	1.0	0.2	0.2	0.9	0.6	0.7	1.3
	CHC1112T	8.9	0.5	0.3	1.8	0.4	0.2	0.2	1.1	0.4	0.9	1.1
	CHC1113T	7.8	1.9	0.5	3.8	1.0	0.4	0.6	0.6	1.0	1.9	0.3
	CHC1114T	9.0	1.1	0.6	1.8	0.7	0.4	0.1	4.9	1.1	0.8	6.0
	CHC1115T	10.4	3.0	0.4	6.6	0.4	0.5	0.5	0.2	0.2	1.1	0.2
	CHC1116T	8.7	1.9	0.6	3.2	0.7	0.4	0.2	1.3	1.2	3.6	0.3
	CHC708T	8.1	3.9	1.0	3.9	1.2	0.3	0.2	0.02	0.1	0.4	0.04
CHC709T	9.1	3.6	0.7	4.9	0.9	0.3	0.04	0.2	0.1	0.5	0.4	

		CHC1080T	8.5	1.6	0.6	2.5	1.0	0.4	0.1	0.03	2.4	2.3	0.01
		CHC1082T	8.4	2.2	0.2	10.0	1.2	0.4	1.0	0.3	1.9	0.5	0.6
		CHC1090T	8.9	2.6	0.3	7.7	0.7	0.6	0.05	0.5	0.2	2.6	0.2
		CHC1091T	8.7	1.7	0.2	9.4	0.7	0.4	0.1	0.1	0.3	1.9	0.1
		CHC1092T	8.2	0.9	0.1	6.3	1.3	0.4	0.6	1.1	1.2	1.0	1.1
		CHC1097T	8.2	2.6	0.3	9.2	1.1	0.6	0.9	0.2	1.2	1.2	0.1
		CHC1098T	8.3	4.3	0.5	8.9	1.3	0.6	1.4	0.3	1.1	1.4	0.2
		CHC1106T	8.5	1.9	0.3	6.3	1.0	0.4	0.1	0.4	0.1	0.4	0.9
		CHC099N	8.8	1.3	0.3	4.5	1.2	0.6	0.5	2.1	0.3	1.4	1.5
		CHC206N	8.6	2.2	0.6	3.4	1.2	1.1	2.6	1.2	0.3	1.1	1.1
		CHC233N	8.9	2.8	1.7	1.6	1.0	1.3	0.6	0.9	0.7	1.7	0.5
		CHC305N	8.3	1.1	0.3	3.2	1.2	1.0	2.3	2.2	0.6	0.6	3.7
		CHC306N	8.8	1.6	0.6	2.6	1.2	0.5	1.0	0.5	0.1	0.2	2.0
		CHC326N	8.4	2.6	0.4	6.7	1.1	0.2	1.0	3.5	0.2	0.7	5.2
		CHC327N	8.4	1.7	0.4	4.7	1.1	0.7	1.4	1.7	0.2	0.7	2.4
		CHC437N	8.8	2.5	0.9	2.8	1.4	0.9	4.0	4.8	0.5	0.3	18.2
		CHC1109N	8.6	2.6	0.8	3.4	1.3	0.6	0.4	0.4	1.1	2.3	0.2
		CHC1110N	9.0	4.1	1.1	3.6	1.7	0.6	0.9	0.5	1.1	2.6	0.2
		CHC1111N	9.0	2.9	0.3	9.6	1.2	0.3	0.7	0.9	0.8	0.8	1.1
		CHC1112N	8.1	2.1	1.1	1.9	0.8	0.3	0.4	3.9	0.6	0.9	4.2
		CHC1113N	8.0	1.3	0.5	2.5	0.6	0.3	0.2	0.9	0.6	1.1	0.8
		CHC1115N	8.9	2.1	0.7	3.1	0.9	0.6	0.3	1.1	1.5	4.1	0.3
		CHC1116N	8.6	2.7	0.5	5.2	0.8	0.6	0.4	2.1	1.3	3.1	0.7
		CHC1080N	8.3	2.0	0.7	2.9	1.3	0.4	0.6	1.6	1.3	1.8	0.9
		CHC1085N	8.6	4.2	0.8	5.4	1.3	0.6	1.2	2.9	0.2	0.6	5.0
		CHC1099N	8.5	1.5	0.3	4.7	1.0	0.3	0.8	1.6	0.1	0.5	3.4
		CHC1102N	8.4	1.5	0.6	2.8	1.1	0.3	0.3	3.8	0.2	1.3	2.9
		CHC344T	8.5	6.7	6.1	1.1	1.2	0.4	0.1	0.9	0.6	2.9	0.3
		CHC364T	7.7	2.0	2.2	0.9	1.2	2.4	3.3	1.5	0.1	0.1	24.6
		CHC377T	8.8	1.7	0.8	2.2	0.6	0.5	0.4	0.04	0.03	0.4	0.1
		CHC466T	7.9	2.2	2.4	0.9	1.0	0.7	0.9	1.3	0.1	1.5	0.9
		CHC471T	8.6	2.5	0.9	2.9	0.9	0.5	0.04	0.1	1.0	4.9	0.02
		CHC358T	8.7	2.1	0.8	2.7	2.0	0.8	0.004	0.1	0.2	0.7	0.2
		CHC383T	8.5	3.1	0.4	7.2	1.7	0.9	0.003	0.1	0.04	0.7	0.1
		CHC576T	7.6	1.0	0.7	1.4	2.0	1.0	0.1	2.6	0.2	0.5	5.1
		CHC633T	8.6	1.9	0.6	3.2	1.6	0.8	0.2	0.1	0.4	0.4	0.2
		CHC1117T	8.8	1.3	0.4	2.9	1.7	0.5	0.1	1.1	2.1	0.6	2.0

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β-catenin mutated HCA	CHC361Ta	8.6	2.5	0.4	5.7	1.5	24.6	28.8	0.1	0.1	0.04	3.0
	CHC372T	8.2	0.7	0.1	5.0	2.3	44.0	50.3	0.03	0.002	0.01	4.9
	CHC470T	8.6	1.3	0.9	1.4	1.7	22.1	47.5	0.1	0.001	0.01	12.1
	CHC786T	9.0	7.2	1.0	7.6	1.8	26.7	42.9	0.002	0.01	0.003	0.7
	CHC820T	8.5	3.1	2.9	1.1	1.5	1.6	1.7	0.2	1.1	0.4	0.6

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