

FIBROBLAST GROWTH FACTOR RECEPTOR 4: A PUTATIVE KEY DRIVER FOR THE AGGRESSIVE PHENOTYPE OF HEPATOCELLULAR CARCINOMA

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4 **FIBROBLAST GROWTH FACTOR RECEPTOR 4: A PUTATIVE KEY**
5 **DRIVER FOR THE AGGRESSIVE PHENOTYPE OF**
6 **HEPATOCELLULAR CARCINOMA**
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ABSTRACT

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7 Recently, we found upregulation of fibroblast growth factor receptor 4 (FGFR4) in a subset of
8 hepatocellular carcinoma (HCC). Here, we provide mechanistic insight into the role of FGFR4-
9 mediated signaling for the aggressive behaviour of HCC cells.

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11 To overexpress FGFR4, hepatoma/hepatocarcinoma cells were transfected with a construct coding
12 for FGFR4. For down-modulation of endogenous FGFR4 we used siRNA or adenoviral infection
13 with dominant-negative FGFR4 constructs being either kinase dead (kdFGFR4) or coding for the
14 auto-inhibitory soluble domain (solFGFR4).
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18 FGFR4 overexpression in non-tumourigenic hepatocarcinoma cells significantly reduced cell-matrix
19 adhesion, enabled cells to grow anchorage-independently in soft agar, to disintegrate the lymph-
20 /blood-endothelial barrier for intra-/extravasation of tumour cells, and to form tumours in SCID mice.
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22 Transcriptome analysis revealed altered expression of genes involved in cell-matrix interactions.
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24 Conversely, in highly tumourigenic cell lines kdFGFR4 or solFGFR4 lowered the proportion of cells
25 in S-phase of the cell cycle, enhanced the G0/G1 and G2/M-phase proportions, reduced anchorage-
26 independent growth in vitro, and attenuated disintegration of the lymph-/blood-endothelium and
27 tumour formation in vivo. These findings were confirmed by altered expression profiles of genes
28 being important for late stages of cell division.
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32 Deregulated FGFR4 expression appears to be one of the key drivers of the malignant phenotype of
33 HCC cells. Accordingly, blockade of FGFR4-mediated signaling by soluble dominant-negative
34 constructs, like solFGFR4, may be a feasible and promising therapeutic approach to antagonize
35 aggressive behaviour of hepatoma/hepatocarcinoma cells.
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42 **Summary:** Here, we found that deregulated FGFR4 expression appears to be one of the key drivers
43 of the malignant phenotype of hepatoma/hepatocarcinoma cells. Accordingly, blockade of FGFR4-
44 mediated signalling may be a promising therapeutic approach to antagonize aggressive behaviour of
45 the cells.
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INTRODUCTION

Hepatocellular carcinoma (HCC) is among the five most common cancer entities worldwide, with about half a million new cases diagnosed annually, and an almost equal number of deaths, mostly due to early metastatic spread. About 15% of HCC patients only are candidates for surgical resection or liver transplantation. Standard chemotherapy is not applicable due to the intrinsically high chemoresistance of this tumour type. New strategies offering improvements in therapeutic efficacy and disease outcome are eagerly sought (1-3).

Upregulation of growth and survival factors is an important hallmark of hepatocarcinogenesis and a major driving force for tumour progression and dissemination (1-4). We have recently found overexpression of fibroblast growth factor receptor 4 (FGFR4) in almost 50% of HCC cases investigated, which agrees with observations of another group (5,6). Also, FGFR4-ligands, like FGF2 and FGF8-subfamily members were found to be upregulated in many HCC cases investigated (5-10). FGFR4 belongs to a RTK family of genes with similar protein structures (*FGFR1-4*) (7-11). Upon ligand binding the phosphorylated and dimerized form of FGFR4 recruits several adapter proteins, like FRS2 α , and activates several signaling pathways including mitogen-activated protein kinase and phosphoinositide 3-kinase cascades. In dependence on the ligand, a great variety of cell-biological and biochemical processes may be affected, like cell cycle regulation, survival, differentiation, migration, adhesion, and/or bile acid metabolism (8-12). There is some evidence that FGFR4 may contribute to the development and progression of HCC, e.g., siRNA against FGF19 or antibodies targeting the FGF19-FGFR4 axis impaired the tumourigenicity of Huh7-cells, while this approach lacked significant effects in HepG2, SNU182 and SNU423 hepatoma/hepatocarcinoma cells (13-16). Different FGFR ligands may impact in a specific way on one and the same receptor, as shown by the highly divergent molecular and biological effects of FGF7 and FGF10 on FGFR2b-mediated signaling (17). Also FGF19 exerts unique features with regard to FGFR4-activation and metabolic effects in hepatocytes, which are not shared by other FGFR4-ligands (8,11,12). We therefore used several hepatoma and recently established hepatocarcinoma cell lines which show inherent overexpression of FGF8-subfamily members, like 59% of the HCC cases studied (5,18). Since many FGFR4 ligands are upregulated in HCC, we targeted the receptor and applied not only siRNA and kinase-dead FGFR4-construct but also a soluble FGFR4-protein, which may be applicable in the near future, as exemplified by soluble decoy FGFR1c receptor being currently tested in a phase-1 clinical trial to treat solid tumours (19). In addition a novel, 3-dimensional bulk invasion assay was used to analyse the mechanism of tumour cell-mediated disruption of blood or lymphatic vessels (20). For the first time we show that FGFR4 over-expression reduced cell adhesion and enhanced anchorage-

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3 independent growth, and disintegration of the lymph/blood-endothelial barrier. The boosted
4 aggressive phenotype was confirmed by accelerated tumour formation of the HCC cells in SCID
5 mice. In contrast, transfection with FGFR4-targeting siRNA or with kinase-deficient or soluble forms
6 of FGFR4 impaired the malignant cell phenotype in vitro and tumour formation in vivo. Thus, use of
7 soluble FGFR4-protein appeared as promising therapeutic option. In-depth investigations revealed
8 that deregulations in FGFR4-mediated signaling affect genes involved in cell-matrix interactions,
9 chromosome segregation, and/or cytokinesis. These findings together provide mechanistic insight
10 into the role of FGFR4 as one of the key drivers of the malignant phenotype of HCC cells.
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20 EXPERIMENTAL PROCEDURES

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22 **Cells.** HepG2 and CCL-13 were obtained from ATCC (Rockville, MD). HCC-1.2. and HCC-3 lines,
23 and telomerase-immortalised human lymphendothelial cells (LEC) and blood endothelial cells (BEC)
24 were recently established and characterized (18,21). Authentication of the lines was performed by
25 short-tandem-repeat-analyses, parallel to in-vitro studies. Determination of cell proliferation and cell
26 death followed previous descriptions (5).
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30 **siRNA.** Silencer®Select siRNA, targeting human FGFR4 and nonsilencing Silencer®Select
31 scrambled siRNA (No AM4390843) were obtained from LifeTechnologies (Vienna/Austria). Further
32 details see (5).
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36 **Vectors and adenoviral constructs.** pcDNA3.1-vectors with(out) human VSV-tagged FGFR4 were
37 kindly provided by Axel Ullrich (Max Planck Institute, Martinsried/FRG). The constructs were
38 introduced into HCC-1.2 cells via FuGene® (Roche, Graz/Austria). Neomycin (PAA Laboratories,
39 Cölbe/FRG; 0.5mg/ml medium) served to generate clones.
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43 Adenoviral expression vectors for FGFRs have been described previously (22). Plasmids coding for
44 human FGFR4 and solFGFR4 were kindly provided by Shereen Ezzat (Ontario Cancer Institute,
45 Canada) (23). The open reading frame was subcloned into pENTR1A (Invitrogen, Carlsbad/CA) with
46 KpnI/XhoI. To generate a kinase-deficient variant (kdFGFR4), the kinase domain was removed by
47 digestion with BglIII/NotI and replaced by the BglIII/NotI-digested sequence of cyan fluorescent
48 protein (CFP). The resulting FGFR4-CFP chimera and the solFGFR4 were transferred into
49 pAd/CMV/V5-Dest by Gateway recombination (Invitrogen). Virus amplification was done as
50 described and an adenovirus expressing GFP was used as control (24). Virus titers were determined
51 with the Adeno-X Rapid Titer Kit (Clontech, Mountain View/CA). Cells were exposed to the
52 constructs at the lowest multiplicity of infection (MOI) leading to 100% cell infection (titrated by a
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3 GFP-adenovirus).

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5 **Clonogenicity.** 48hrs after transfection cells were plated in medium containing 10% FCS. At clone
6 appearance in controls, cells were fixed in acetone/methanol (v50:50) and stained with 0.01% of
7 crystal violet.
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10 **Soft agar assay.** 48hrs after transfection cells were suspended in 20% FCS-RPMI containing 0.3%
11 agar (Sigma) and were seeded onto 20% FCS-RPMI with 0.6% agar. Three-four weeks later the
12 number of colonies (>10 cells) was determined.
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15 **Cell adhesion assay.** 96-well plates were coated with type 1 collagen or fibronectin (Sigma,
16 St.Louis/MO). Cells were plated at a density of 5×10^3 per well. After incubation for 60, 90, or
17 120min at 37°C, medium was removed and wells were washed twice with 1xPBS to eliminate non-
18 adherent cells. The number of adherent cells was determined by the EZ4U assay.
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21 **CCID (circular chemorepellent-induced defects) assay.** 1×10^3 cells were incubated in 150 μ l
22 EGM2-MV medium (Lonza, Walkersville/MD) containing 20% methylcellulose (M-0512, Sigma) in
23 round bottom microtitre plates (BD-Biosciences) to allow spheroid formation within 48hrs.
24 Spheroids were washed in PBS and transferred to confluent LEC/BEC monolayers, kept in EGM2-
25 MV medium and stained by cytotracker green (2 μ g/ml for 1hr, Invitrogen); 4hrs later, the spheroid
26 and the CCID area in the LEC/BEC monolayer underneath were photographed. For each condition,
27 the size of ≥ 10 spheroids and appendant CCIDs was measured by Image-J-software. For details see
28 suppl.figs.1 and 2.
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31 **Gene expression analyses.** For qRT-PCR, the extracted RNA was processed and measured by the
32 ABI-Prism/7500 Sequence Detection System (Applied-Biosystems, Foster City/CA) using TaqMan-
33 based assays (Applied-Biosystems), as described (5).
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36 For whole genome expression analyses, the extracted RNA was subjected to quality control (2100
37 Bioanalyzer-System, Agilent, StClara/CA) and prepared by “Low RNA Input Linear Amplification
38 Kit Plus”, the “RNA Spike-In Kit” and the “Gene Expression Hybridization Kit” according to the
39 manufacturer’s instructions (Agilent). The 4x44k microarray (Agilent) was used as a two-color array
40 and was analysed by the G2505B-Microarray-Scanner (Agilent). Samples were analysed in triplicate
41 in each individual experiment. Per run, data were processed by a combination of “Feature Extraction
42 Software” and “GeneSpring-GX” (Agilent). Fold-change cutoffs ($\geq 2/\leq 0.5$) were used to select
43 upregulated and downregulated genes, respectively. Differential gene expression was detected by t-
44 test and Benjamini-Hochberg correction for multiple testing to ensure a false discovery rate less than
45 0.05. The functional annotation analysis on the selected lists was carried out using (i) gene set
46 enrichment analysis (GSEA) to identify significantly enriched curated gene sets (version 3.0) among
47 those included in the MSigDB database (<http://www.broadinstitute.org/gsea/msigdb/index.jsp>) and
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3 (ii) Ingenuity Pathway Analysis (IPA, version 8.8; Ingenuity Systems, Redwood City, CA;
4 www.ingenuity.com) (24). Further details see suppl.tab.5 and 6.

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6 **Immunoblotting.** Protein purification, separation, and detection followed published protocols (5,18).
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8 Antibodies used: anti-VSV tag (eBioscience, San Diego/CA); anti-FGFR4 (sc-124 and sc-9006;
9 Santa-Cruz Inc/CA), anti- β -actin (Sigma, St Louis, MO), anti-phospho-PLC γ 1(Tyr783) (Cell
10 Signaling, Danvers, MA), anti-PLC γ 1 (Cell Signaling), anti-phospho-p44/42 MAPK (ERK 1/2)
11 (Thr202/Tyr204) (Cell Signaling), anti-ERK1/2 (Sigma), anti-phospho-AKT (Ser437) (Cell
12 Signaling), anti-AKT (Cell Signaling). Band intensities were quantified by densitometry
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14 (ImageQuant 5.0-software; GE-Healthcare).
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18 **Animal study.** 1×10^6 cells were injected subcutaneously into both flanks of SCID/BALBc mice by
19 standard procedures. HCC-1.2, HCC-3, and HepG2 cells were applied in serum-free medium
20 containing 50% matrigel (Becton-Dickinson). The number and diameter of palpable tumours were
21 determined thrice a week. When the local tumour affected the status of the host, the animal was
22 sacrificed for necropsy. The experiments were performed according to the Austrian guidelines for
23 animal care and protection.
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RESULTS

Upregulation of FGFR4 enhances the aggressive phenotype of hepatocarcinoma cells. We recently found upregulation of FGFR4 in a subset of HCC (5). We therefore asked whether FGFR4 expression levels affect growth and aggressive phenotype of malignant hepatocytes. The hepatoma/hepatocarcinoma cell-lines used differ greatly in clonogenicity, anchorage-dependency in vitro, and tumorigenicity in vivo. Thus, CCI-13 cells are highly clonogenic in two different assays and tumorigenic in SCID mice, while HCC-1.2 cells are (almost) incapable of forming clones and tumours. HCC-3 and HepG2 cells rank in between these two extremes (fig.1). Spheroids of these hepatoma/hepatocarcinoma cells, attached to LEC or BEC monolayers, were used to simulate a critical step of metastasis, i.e., the gaps/CCID formed in the monolayer mimic entry gates for intravasating tumour emboli. The cell lines also vary in their capacity to disintegrate these lymph-/blood-endothelial barriers and to form CCID, with CCI-13 being most aggressive in this respect and HCC-1.2 forming only moderate CCID in LEC/BEC monolayers (fig.1D, E, and F; suppl.figs.1 and 2).

We generated HCC-1.2 clones with stable overexpression of FGFR4 (C11-C14). The resulting cells showed considerably elevated levels of FGFR4 mRNA and protein and enhanced levels of phosphorylated ERK and phosphorylated phospholipase-C γ 1 (PLCG1), which indicates activation of the major FGFR-mediated pathways under our experimental conditions (suppl.fig.3) (8). When analysing the transcriptome profiles of clones 1 and 3, we found significant, ≥ 2 -fold downregulations of 1295 and ≥ 2 -fold upregulations of 1119 genes (suppl.tab.2). Gene set enrichment or Ingenuity showed that many of the deregulated genes are involved in bile acid- and phase I&II-metabolism as well as in lipid and carbohydrate metabolism, confirming that our cells show known, hepatocyte-specific reaction patterns towards FGFR4-mediated signaling (suppl.tab.5 and 6) (11,12). Furthermore, many deregulations affected pathways being directly or indirectly involved in PLCG- and MAPK-mediated signaling. Similar alterations in the expression level of critical genes became evident in human HCC samples with high FGFR4 expression providing evidence that the hepatocarcinoma cells used are a relevant tool to study FGFR4-driven alterations in hepatocarcinogenesis (suppl.tab.7).

In contrast to vector controls, FGFR4-overexpressing cells became capable to form tumours in SCID mice (fig.2C). Studies on the mechanisms conferring tumorigenicity to HCC-1.2 cells revealed that FGFR4 upregulation had little effect on viability, cell-cycle, or apoptotic activity of the cells (data not shown), but enhanced dramatically the clone forming capacity of the cells at low density (fig.2A). Transcriptome analysis showed that many of the affected genes are involved in cell adhesion, e.g.,

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3 several members of the collagen, integrin, laminin, lectin, cadherin or protocadherin family were
4 found to be deregulated (tab.1). In line with this observation, adherence of most of the clones to
5 polystyrene, collagen and to some extent also to fibronectin was significantly reduced and growth in
6 soft-agar was greatly increased (fig.2B,E). We also found upregulation of genes involved in
7 metastasis (suppl.tab.2 and 5). Accordingly, the capacity of clones to induce CCID in BEC
8 monolayers was greatly increased (fig.2D). This may indicate that overexpressed FGFR4 confers the
9 ability for anchorage-independent growth and for invasiveness into blood-/lymph-endothelium, one
10 of the hallmarks of a malignant cell phenotype.
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18 **Knock-down of FGFR4 reduces clone forming capacity of hepatocarcinoma cell lines.** Next, we
19 down-modulated the expression of FGFR4 by siRNA, which significantly reduced mRNA and
20 protein levels in the cells investigated (fig. 3A and 3B). Viability (fig.3C) as well as cell cycle and
21 apoptotic activity of the cells (not shown) was not altered, but the formation of clones at low density
22 and in soft agar was significantly reduced (fig.3D and E). Scrambled siRNA (siSCR) did not impact
23 on any of the test end points (not shown). These results provide further evidence that endogenous
24 FGFR4 is essential for the pro-tumourigenic phenotype of hepatocarcinoma cells.
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31 **Blockade of FGFR4-induced signaling antagonizes tumour formation.** To further study the
32 relevance of FGFR4 in malignant transformation we interfered with FGFR4-mediated signaling.
33 Cells were infected with adenoviral constructs coding for (i) dominant negative FGFR4, in which the
34 kinase domain had been replaced by CFP (kdFGFR4), or (ii) the soluble part of FGFR4 (solFGFR4)
35 which is also considered to act dominant-negatively by interfering with receptor-ligand interactions
36 (23). This resulted in high expression of the constructs at the protein level and lowered
37 phosphorylation of the FGFR binding adaptor protein FRS2 α (supplementary figs.4 and 5). Impaired
38 FGFR4 signaling resulted in dramatic reduction of clonogenicity and anchorage-independent growth
39 in all 4 cell lines (fig.4A, B) and lowered the cells' capacity to induce gaps in LEC/BEC monolayers
40 (fig.4G). Correspondingly, tumour forming capacity tested with the 2 most tumourigenic lines,
41 HepG2 and CCI-13, was significantly attenuated (fig.4C). These findings suggest that blockade of
42 FGFR4-mediated signaling is a promising approach to antagonize tumour formation by hepatoma
43 /hepatocarcinoma cells.
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55 **Blockade of FGFR4-mediated signaling may affect late stages of cell proliferation.** Studies on
56 the mechanisms underlying the reduced tumourigenicity of cell lines revealed that solFGFR4, and
57 more strongly kdFGFR4, reduced the viability of the cells and increased the apoptotic activity
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(fig.4D,E). Coincidentally a considerable percentage of cells was shifted from the S to the G0/G1 and G2/M phase of the cell cycle (fig.4F). Transcriptome profiles revealed that FGFR4 blockade affected mostly genes involved in the formation and/or function of the spindle apparatus or kinetochore complex, as outlined in detail in the discussion (tab.1, supplementary tabs.3 and 4). Furthermore, the transcripts of genes, which are involved in the initiation and propagation of DNA replication (e.g. CDC7, NOL8) were reduced, while negative regulators of cell cycle (e.g. C13ORF15) tended to be expressed at an enhanced level. Many of these alterations occurred in both, kdFGFR4 or solFGFR4-transfected cells, indicating a similar consequence being more or less independent of the mode of FGFR4 blockade.

To conclude, these findings strongly suggest that expression and function of FGFR4 is an important determinant of the aggressive phenotype of the hepatoma/hepatocarcinoma cell lines tested.

Discussion

Here we show that FGFR4 appears to be a key driver of the aggressive phenotype of hepatoma/hepatocarcinoma cells, as outlined in the following.

For our mechanistic studies, we chose a panel of cell-lines, e.g. in barely aggressive HCC-1.2 cells upregulated FGFR4 expression elevated considerably clone formation, anchorage-independent and invasive growth and tumourigenicity. For proof of principle we chose the opposite approach and interfered in aggressive hepatoma/hepatocarcinoma cells with FGFR4 by (i) siRNA-mediated knock-down, (ii) kinase-dead kdFGFR4 for non-functional dimers with endogenous FGFR4, and (iii) solFGFR4 which consists of the IgI-loop/acidic box, lacks ligand-binding domains, and nevertheless neutralizes the mitogenic effects of FGFR4 ligands (23). The IgI-IgII linker region of FGFR1-3 serves as hinge allowing the IgI-loop/acidic box to auto-inhibit the ligand-binding domain (26). Since FGFR4 harbours the shortest IgI-IgII linker, solFGFR4 may compensate for this lack and compete with FGFs for binding (23,27). Here, solFGFR4 lowered phosphorylated FRS2 α and altered the expression profiles to a similar extent as kdFGFR4 (suppl.fig.5). When compared to siRNA, solFGFR4 and kdFGFR4 caused more pronounced effects. The dominant-negative constructs decreased viability, anchorage-independent and invasive growth, and tumour formation in vivo. Thus, our data provide strong evidence that up- or downregulation of FGFR4 increases or decreases the aggressive phenotype of malignant hepatocytes, respectively. Furthermore, soluble FGFR4-protein appears as a very promising approach in the therapy of HCC, similar to FP-1039, a soluble decoy FGFR1c receptor being currently applied in a phase-1 clinical trial to treat solid tumours (19; <http://www.fiveprime.com/pipeline/fp-1039>).

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3 An important hallmark of aggressive tumour cells is their capability to intravasate into the blood or
4 lymphatic vasculature and to extravasate for metastasis formation. Since hepatocarcinoma cells
5 preferably metastasize within the liver, which is hard to simulate in vivo, we established a 3-
6 dimensional co-culture model of hepatoma/hepatocarcinoma cells with LEC/BEC-monolayers. LEC
7 or BEC retracted and generated CCID, which resembles entry gates for tumour emboli through the
8 lymphatic/blood cell wall. CCID formation could be impaired by inhibitors of I- κ B α
9 phosphorylation, matrix-metalloproteases, and lipoxygenases 12/15-1 (suppl.tab.1). Thus, the activity
10 of NF- κ B and secretion of metalloproteases and 12/15-HETE appear to be critical for the
11 disintegration of the lymph/hemangioendothelial barrier by hepatoma/hepatocarcinoma cells, as
12 reported for MCF-7 cells (20). The CCID formation could be greatly enhanced by overexpressing
13 FGFR4 and impaired by interfering with FGFR4-mediated signaling. Transcriptome analyses
14 revealed upregulation of NF κ B-dependent genes by FGFR4 overexpression, such as phospholipase
15 A2, which releases arachidonic acid from the membranes to provide substrate for lipoxygenases-
16 12/15-1 (suppl.tab.2).

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18 The aggressive phenotype is also characterized by altered cell-cell and cell-matrix interactions to
19 enable evasion from organized tissue structures. The increased cloning efficacy of cells
20 overexpressing FGFR4 may indicate a reduced dependency on cell-cell contacts, while the reduced
21 matrix adhesion and the enhanced growth in soft-agar reflect lower requirements on anchorage for
22 survival and proliferation.

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24 In contrast to FGFR1-3 and mutant FGFR4, wildtype FGFR4 seems not to interact with NCAM (28-
25 30). Upregulated FGFR4 reduced the expression of several cadherins, proto-cadherins, and integrins,
26 which serve as docking sites for collagens, vitronectin and/or thrombospondins (31,32). Furthermore,
27 transcript encoding for several collagens, vitronectin and thrombospondins were lowered as well
28 (tab.1). These alterations altogether may explain the reduced adhesion of FGFR4-overexpressing
29 hepatocarcinoma cells to collagen, fibronectin, and polystyrene.

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31 It is becoming increasingly evident that cell-matrix interactions impact profoundly on several steps of
32 cell division (33). At start of mitosis, cells loose attachments, disassemble focal adhesions, and adopt
33 a round morphology. Cell-adhesion molecules, like β -integrins, regulate centrosome function, spindle
34 formation and orientation, and cytokinesis (34-36). In line with these findings is our observation that
35 dominant negative FGFR4 constructs reduced the proportion of hepatoma/hepatocarcinoma cells in
36 S-phase of the cell cycle and increased the proportion in G2/M. This was accompanied by changed
37 transcription of genes involved in the formation and/or function of cohesins, chromosomal
38 condensation, kinetochores, centrosome separation, the formation, stabilization and function of the
39 spindles, and cytokinesis. Furthermore, impaired FGFR4-activity increased anchorage-dependency,
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3 induced apoptosis and impaired disintegration of the LEC/BEC barrier. On the other hand,
4 overexpressed FGFR4 reduced anchorage-dependency and cell adhesion, facilitated proliferation and
5 probably mitosis in the emerging clones, and affected also indirectly the interaction with LEC/BEC.
6 Thus, disruption of FGFR4-mediated signaling seems to interfere with mechanisms linking cell
7 matrix interactions with late stages of cell division and to impact on several important components of
8 the malignant phenotype of hepatoma/hepatocarcinoma cells.
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14 To conclude, our mechanistic studies demonstrate the oncogenic impact of FGFR4 on the aggressive
15 behaviour of HCC cells. Thus, great potential might lie in FGFR4 as a target for the treatment of this
16 cancer entity and in the application of solFGFR4-protein as therapeutic tool.
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21 **Abbreviations:** FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HCC,
22 hepatocellular carcinoma; solFGFR4, soluble fibroblast growth factor receptor 4; kdFGFR4,
23 dominant negative fibroblast growth factor receptor 4.
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27

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18 regulated kinase (MEK/ERK) signaling. *J. Biol. Chem.*, **287**, 2520-2530.
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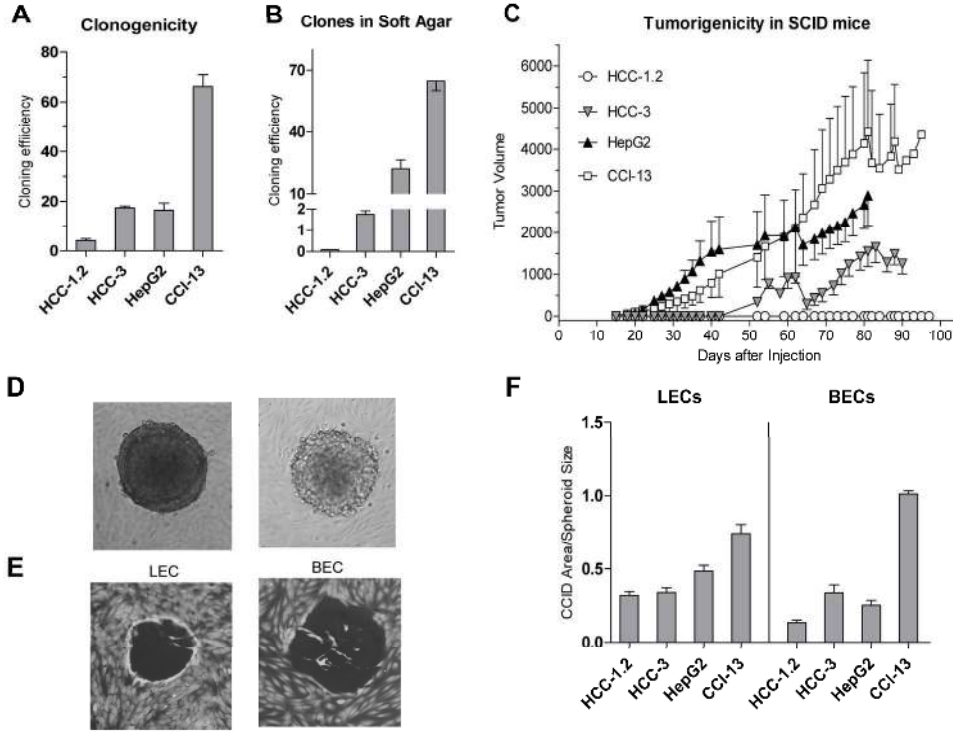
Figure 1. Cloning efficiency, invasive growth and tumourigenicity differ between hepatoma/hepatocarcinoma cell lines. In (A) cell lines were plated at a low density of 240 cells/cm² (HCC-1.2), 100 cells/cm² (HepG2, HCC-3), and of 60 cells/cm² (CCI-13). Clone numbers were determined after 3 weeks (HCC-1.2, HCC-3, HepG2) or 7 days (CCI-13). In (B) cells were seeded in soft agar at a density of 540 cells/cm² (HCC-1.2, HCC-3) or 180 cells/cm² (HepG2, CCI-13). Clones were counted after 4 weeks. In (A) and (B) the cloning efficiency was determined as the percentage of the cells seeded that form a clone. In (C) 1x10⁶ cells/100µl serum-free medium were injected into flanks of SCID/BALBc mice. In (D,E) 3x10³ cells were used for spheroid formation (for details see Methods). 48hrs later the spheroids formed were placed on confluent monolayers of LEC or BEC and were incubated for 4hrs. Pictures of spheroids and gap areas underneath were taken and areas were measured by ImageJ software. (D), representative spheroids of untreated HCC-1.2 cells and (E) CCID formed beneath in LEC or BEC. (F) gives the ratio between CCID area and spheroid size. All data are given as mean +/- SD of 3 independent experiments in (A,B,F) or of 4 animals in (C).

Figure 2. Overexpression of FGFR4 enhances anchorage-independency, invasiveness, and tumourigenicity of HCC-1.2 cells. Experiments in (A)–(D) have been performed as described in fig.1. (D), CCID formation of FGFR4-overexpressing clones. For further details on clones see suppl.fig.3. In (E) cells were seeded to petri dishes (made of polystyrene), being uncoated or coated with collagen or fibronectin; 60, 90, or 120min later the number of attached cells was determined. Data are expressed as fold vector control (pcDNA3.1) in (A,B,E) and are given as mean ± SD of ≥3 independent experiments in (A,B,D,E). (C) shows tumour formation in individual animals for each treatment group. Statistics by t-test in (A,B,D) and by Kruskal-Wallis test in (C,E): a) p < 0.05; b) p < 0.01; c) p < 0.001.

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4 **Figure 3. FGFR4 knockdown in hepatocarcinoma/hepatoma cell lines lowers clonogenicity**
5 **and colony formation in soft agar.** Cells were transiently transfected with scrambled siRNA
6 (siSCR) or siRNA targeting FGFR4 (siFGFR4) applying 20nM (HCC-1.2, HepG2) or 10nM
7 (HCC-3, CCI-13) of each. (A), the FGFR4 expression level was determined by qRT-PCR. The
8 level of FGFR4 protein was determined 48hrs after transfection by immunoblotting and bands
9 obtained were subjected to densitometry in (B). In (C) cell viability was determined by the
10 EZ4U assay (see Experimental Procedures). In (D) cells were allowed to grow for up to 48hrs
11 after transfection, were re-seeded and cultivated until the formation of colonies. Further details
12 see fig.1. In (E) 48 hrs after transfection cells were replated in soft agar and were cultivated
13 until the appearance of colonies. Further details are given in fig.1. Abbreviation: n.d., not
14 determined. Data in (A-E) are means \pm SD of fold siSCR of 3 independent experiments.
15 Statistical analyses were performed with the t-test for siFGFR4 vs. siSCR: a) $p < 0.05$; b) $p <$
16 0.01 ; c) $p < 0.001$; d) $p < 0.0001$.

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28 **Figure 4. Blockade of FGFR4-mediated signaling impairs growth of**
29 **hepatoma/hepatocarcinoma cells.** Adenoviral constructs were used to transfect cells with
30 kdFGFR4 or solFGFR4 (see experimental procedures). Untransfected cells (Co) and cells
31 transfected with the adenoviral construct expressing GFP only (Vector) served as controls. (A)
32 gives the clonogenicity and (B) the clone forming capacity in soft agar of untreated and infected
33 cells. In (C) cells were implanted subcutaneously into the flanks of SCID/BALBc mice. In (D)
34 the viability was determined by the EZ4U assay (see Experimental Procedures). FACS analyses
35 served to determine the frequency of apoptosis in (E) and of the relative cell cycle distribution of
36 asynchronous cultures in (F). In (G), 24hrs after transfection, 3×10^3 cells were used for spheroid
37 formation and were placed on BEC/LEC monolayers for CCID formation. In (A), (B), (D)-(G)
38 the mean \pm SD of ≥ 3 independent experiments are given. (C) shows the means of 2
39 independent experiments each with 4 animals per treatment group. Statistics by t-test in (A,B,D-
40 G) and by Kruskal-Wallis test in (C) for solFGFR4 or kdFGFR4 vs. vector: a) $p < 0.05$; b) $p <$
41 0.01 ; c) $p < 0.001$; d) $p < 0.0001$.

FIGURE 1



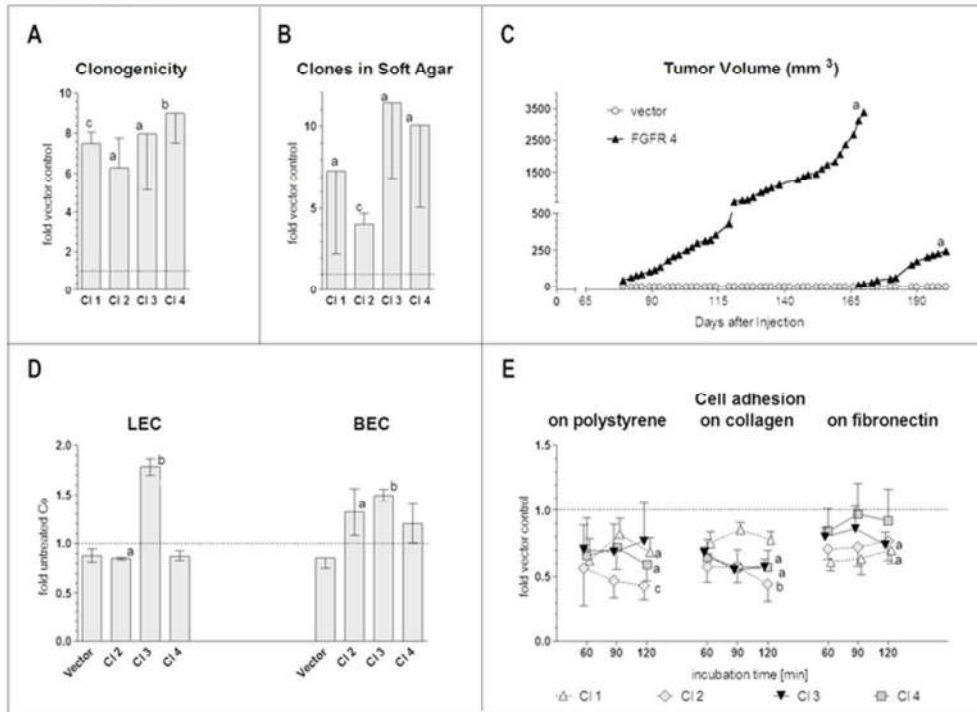
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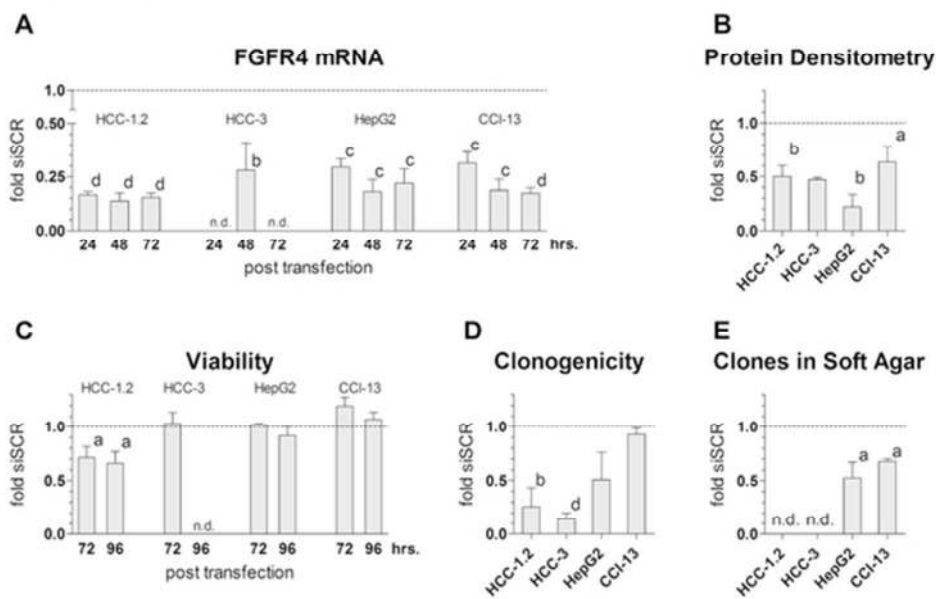
FIGURE 2



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review

FIGURE 3

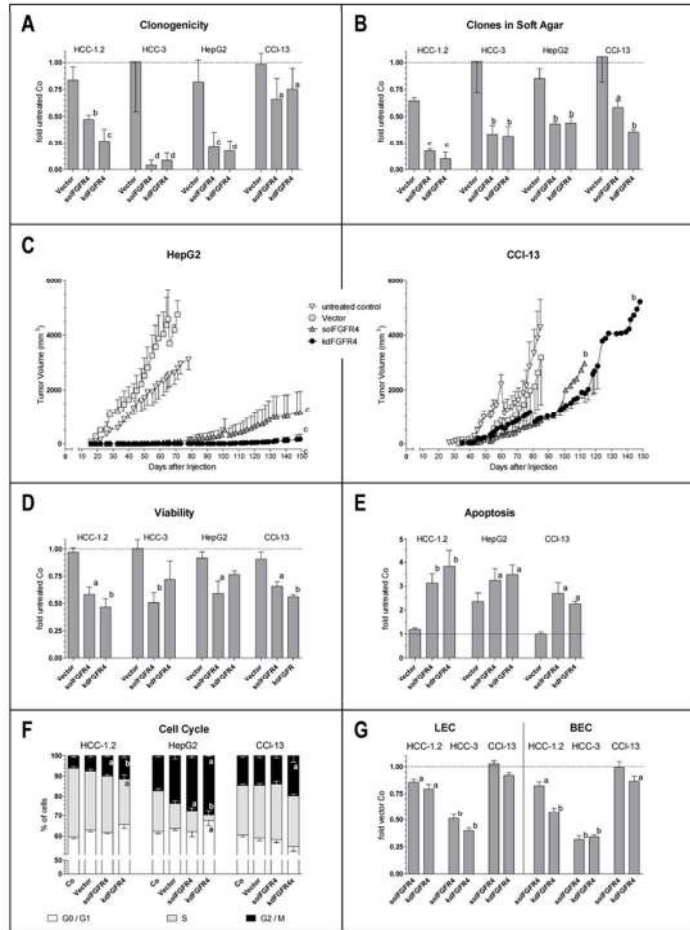


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FIGURE 4



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Table 1. Selected genes being deregulated at least 2-fold by FGFR4 overexpression or dominant negative FGFR4-constructs. Further information is given in Experimental Procedures. For the significance of gene deregulation see supplementary tabs. 2-4. Gene set enrichment analyses are given in suppl.tab.5.

Type of Reg.	HCC-1.2 expressing FGFR4	HepG2 expressing solFGFR4	HepG2 expressing kdFGFR4
Cell Cycle/Division			
↓	<i>Genes involved in the function of: G1/S and/or G2/M (CCAR1,CCNB3, CDKN1A, CLSPN), M-phase: MPHOSPH10, cohesins (SMC1A), spindles (NEK1), kinetochore (CENPF,CENPJ), centrosome (CEP290, KIF15)</i>	<i>Genes involved in the function of: cohesins (SGOL2), kinetochore (CENPC1, CENPE, NDC80), centrosome (CEP290,TTK), spindles (HMMR, DLGAP5)</i>	<i>Genes involved in the function of: G1/S-Phase (CDC7, DNA2, RB1CC1), M-phase (C14ORF106, MPHOSPH10, CUZD1,CDC40, NCAPG), cohesins (ESCO1,SGOL2, SMC2/6), kinetochore (CCDC99, CENPE, CENPK, CENPQ,CENPC1, MAD2L1, NDC80,NUF2,PLK4, ZWILCH), centrosome (KIF15), spindles (HMMR,DLGAP5,NEK7), cytokinesis (ANLN,SEPT7), Other: G2E3,NOL8, MORC3</i>
↑	<i>G1/S and/or G2/M: CDKN1C, PPP2R1B, CCRK, Spindles (FEZ1, NEK6), cytokinesis (NEK6, SEPT4/5/6)</i>	<i>G0/G1: G0S2, G1/S and G2/M: RRAD, C13ORF15</i>	<i>G1/S and G2/M: RRAD</i>
Cell Adhesion/Extracellular Matrix			
↓	<i>AHR, cadherins (CDH11/12 PCDH1), CADM4, CEACAM1/3,CLDN4, collagens (COL4A5/6, COL5A2/3,COL8A2,COL9A3,COL21A1), CTHRC1,DST,DTNA,FAT1,FLNC,FLRT3,GJA1, GULP1,HPSE, ICAM5, integrins (ITGA1/2/V), KIRREL, laminins (LAMA4/B1), LGALS1, LPP, LUM, MMP15, MUC4/15,NRCAM,PARD6A, PECAM1, PPFIBP1,PLXND1,PNN,PRPH2, RELN,ROBO1,ROCK1/2,SSX2IP,STEAP1, thrombospondins(receptor) (THBS1/4, THSD4, CD36), TRPM7, TSPAN8/13, UNC5B</i>	<i>HMMR</i>	<i>CUZD1,HMMR,SEPP1, TMEM87A,</i>
↑	<i>cadherins (CDH16/17,PCDHA1, PCDH24, PCDHB2/5/12), CADM1,CLDN14, CLEC10A, COL4A2,FBLN7,FBN1,FLRT1,GJA3,GPC1/4/5 integrins (ITGA3, ITGAM,ITGB2,ITGB1BP2), LAMB3,LOXL2,MPP1/7,NFASC,NPNT, PARVA,PRG4,SDCBP2,TNC,TNN,TNS1/3, TRO,VTN, TPBG</i>	<i>PLXND1,PSG2, RASD1,ROBO3, UNC5B</i>	<i>RASD1</i>

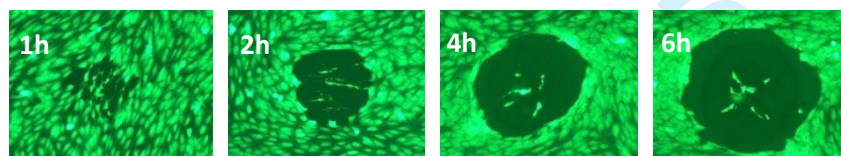
Online Supplement

Studies on interactions of hepatoma/hepatocarcinoma cells with blood and lymphatic endothelium.

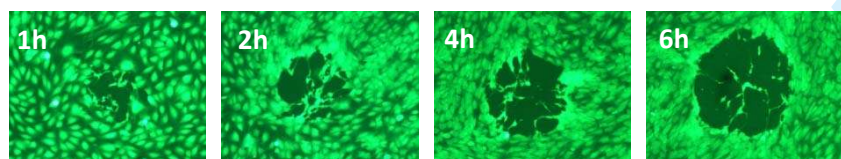
Metastasis is one of the primary causes for human mortality by cancer, as is true also for hepatocellular carcinoma (HCC). In particular, HCC most frequently show intrahepatic colonization due to the dense hepatic vasculature in the liver microenvironment (Van Zijl et al., 2011). Blood circulation is considered the main route of metastatic spread of HCC cells although invasion into the lymphatic system is often observed as well (Mitsunobu et al., 1996). In epithelial cancer entities, cells spontaneously form cohesive groups, which directly penetrate lymphatic vessel walls through large discontinuities (Kerjaschki et al., 2004; Christiansen et al., 2006; Friedl et al., 2010).

To gain insight into the mechanisms underlying lymphatic bulk invasion, an in vitro assay was established mimicking some features of the in vivo situation (Kerjaschki et al., 2011). MCF-7 cells were used to form spheroids, which were placed on telomerase immortalized human lymphendothelial cells (LEC) grown to confluent monolayers. Co-cultivation of spheroids on LEC resulted in the formation of circular discontinuities in the monolayers precisely beneath the spheroids, termed as circular chemorepellent-induced defects (CCID).

BEC



LEC


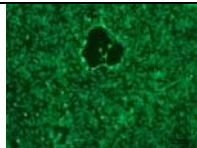
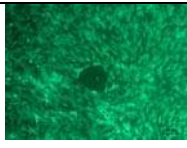

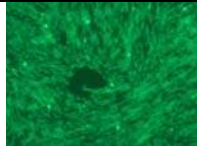


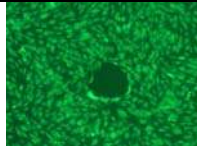
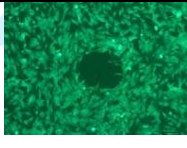

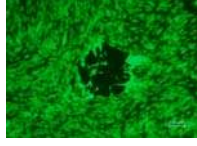
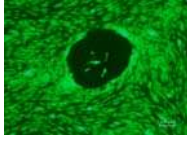


Supplementary Figure 1. Interaction of hepatoma/hepatocarcinoma cell lines with endothelial cells. 1×10^3 CCl-13 cells were incubated in $150 \mu\text{l}$ EGM2-MV medium (Lonza, Walkersville, MD) containing 20% methyl cellulose (M-0512, Sigma Aldrich) in round bottom microtitre plates (BD Biosciences) to allow spheroid formation within 48hrs. Spheroids were washed in PBS and transferred to confluent LEC/BEC monolayers, kept in 24-well plates and EGM2-MV medium and stained by cytotracker green ($2 \mu\text{g}/\text{ml}$ for 1hr, Invitrogen). After 4hrs of incubation, the spheroid size and the CCID area in the LEC/BEC monolayer underneath were photographed at the time points indicated. Magnification ($\times 100$).

Further, centrifugal migration (retraction) of LEC instead of apoptosis was defined as the mechanism for gap formation (Kerjaschki et al., 2011).

We applied this assay to study the interaction of hepatoma/hepatocarcinoma cells with monolayers of telomerase immortalized LEC and blood endothelial cells (BEC) (Schoppmann et al., 2004). Generally, all cell lines used were able to form spheroids and CCID in endothelial cell monolayers. Pictures, taken at regular intervals, revealed centrifugal retraction of LEC and BEC beneath the spheroids, as has been shown before (suppl.fig.1).

CCI-13 cells had the highest capacity to disintegrate the LEC/BEC barrier, followed by HepG2, HCC-3 and HCC-1.2 cells, which agrees with the highly differing aggressive phenotype of the cell lines (suppl.fig.2 and fig.1 in manuscript). HepG2 spheroids were larger and less compact than those of CCI-13, HCC-1.2, or HCC-3 cells, and tended to fall apart when being transferred to LEC/BEC monolayers. Consequently, we used CCI-13, HCC-1.2, and HCC-3 cells for further experimentation.

A						
	<i>Spheroid</i>	<i>Mean spheroid size (mm²)</i>	<i>CCID in LEC</i>	<i>Mean area of CCID in LEC (mm²)</i>	<i>CCID in BEC</i>	<i>Mean area of CCID in BEC (mm²)</i>
HCC-1.2		0.108 ± 0.019		0.041 ± 0.01		0.017 ± 0.005
HCC-3		0.127 ± 0.015		0.035 ± 0.009		0.036 ± 0.016
HepG2		0.170 ± 0.034		0.081 ± 0.01		0.044 ± 0.021
CCI-13		0.098 ± 0.012		0.073 ± 0.015		0.099 ± 0.016

Supplementary Figure 2. Interaction of HCC model cell lines with endothelial cells. Methodical details see suppl.fig.1. After 4hrs of co-culture pictures of spheroids and CCID underneath were taken and the size of spheroids and the area of CCID underneath were measured by ImageJ software. Data are means ± SD of four independent experiments. Magnification x100.

As shown by Honn et al. (1994) and Kerjaschki et al. (2011), the hypoxia-inducible enzymes lipooxygenases 12 (ALOX12) and ALOX15-1, which metabolize arachidonic acid to 12-hydroxyeicosatetraenoic acid (12(S)-HETE), were identified as mediators of CCID formation by MCF-7 cells. LEC exposed to 12(S)-HETE transiently destabilize VE-cadherin resulting in focal disruption of inter-endothelial adhesions and induction of migration of these cells. NFκB activation and matrix-metalloproteases (MMP) were also found to enhance the process of CCID formation (Vonach et al., 2011). Flister et al. (2010) suggested that activation of NF-κB enhances the motility of LEC which is required for the retraction of the cells. MMP degrade components of the extracellular matrix, modulate cell-cell and cell-matrix interactions, and therefore assist tumour cell metastasis (Deryugina et al., 2006). Accordingly, gap formation by MCF-7 spheroids was decreased by inhibition of MMP, which was assigned to impaired degradation of the VE-cadherin meshwork at inter-endothelial junctions and matrix attachments (Kerjaschki et al., 2011; Deryugina et al., 2006).

To investigate the mechanisms underlying the effects of hepatoma/hepatocarcinoma spheroids on endothelial cells, we applied inhibitors of I-κBα phosphorylation (BAY11-7082, Merck, Darmstadt, FRG), MMP (GM6001, Merck), or ALOX12/15-1 (baicalein, Merck) 1hr before spheroids were transferred to LEC or BEC (suppl.tab.1). These pretreatments of spheroids reduced the size of CCID in LEC and BEC, with the exception of baicalein-treated CCL13 cells. Thus, the activity of NF-κB, MMP, and 12/15-HETE appear to be critical for the disintegration of the lymph/hemangi endothelial barrier by hepatoma/hepatocarcinoma cells.

		HCC-1.2.		HCC-3		CCL13	
		LEC	BEC	LEC	BEC	LEC	BEC
BAY	5 μM	99 ± 2	100 ± 11	90 ± 5	80 ± 8	97 ± 7	96 ± 15
BAY	10 μM	73 ± 3 ^b	84 ± 15	73 ± 16	75 ± 8 ^a	89 ± 1 ^b	95 ± 2 ^a
GM6001	10 μM	83 ± 9	82 ± 8	98 ± 7	75 ± 3 ^b	97 ± 11	94 ± 1 ^a
GM6001	20 μM	86 ± 7	83 ± 6 ^a	93 ± 6	82 ± 5 ^a	87 ± 5 ^a	81 ± 8
GM6001	50 μM	83 ± 5 ^a	62 ± 6 ^b	85 ± 7	80 ± 2 ^b	58 ± 5 ^b	77 ± 2 ^b
Baicalein	10 μM	90 ± 9	78 ± 17	93 ± 5	87 ± 5	104 ± 15	99 ± 9
Baicalein	20 μM	83 ± 3 ^a	73 ± 10 ^a	87 ± 5 ^a	78 ± 6 ^a	100 ± 12	100 ± 4
Baicalein	50 μM	76 ± 7 ^a	65 ± 12 ^a	75 ± 6 ^a	67 ± 4 ^b	97 ± 5	104 ± 13

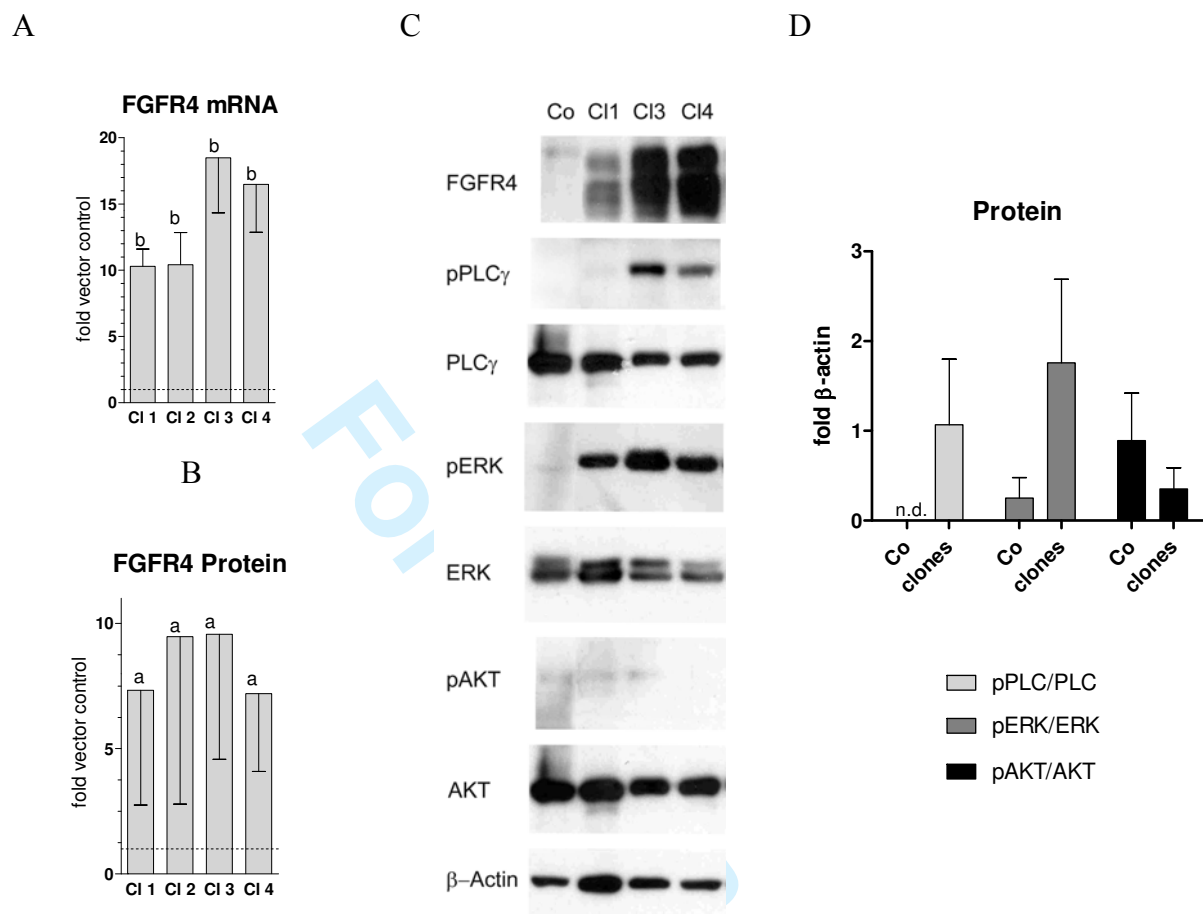
Supplementary Table 1. BAY 11-7082, GM6001, and baicalein impair spheroid-induced gap formation in BEC and LEC monolayers. Methodical details see suppl.fig.1. Spheroids were treated with different concentrations of BAY11-7082, GM6001 and baicalein for 1h and were placed on confluent LEC or BEC monolayers for 4hrs. Pictures of spheroids and gap areas underneath were taken and areas were measured by ImageJ software. Results are shown as % of untreated control and

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3 are expressed as mean \pm SD of 3 independent experiments. Significant differences to untreated
4 controls were determined by t-test: a), $p < 0.05$; b), $p < 0.01$.
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7 8 **References**

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HCC-1.2. clones overexpress FGFR4 at the transcript and protein level and show enhanced phosphorylation of ERK and phospholipase C γ (PLC γ).

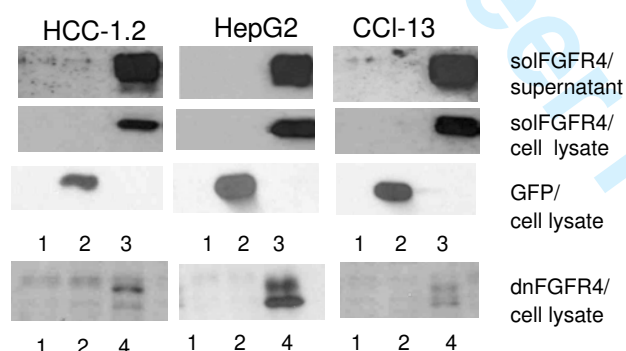


Supplementary Figure 3. We generated HCC-1.2 clones with stable overexpression of FGFR4 (Cl1-Cl4). In (A) FGFR4 mRNA levels of clones 1-4 (Cl1-Cl4) were determined by qRT-PCR. In (B)- (D) cell lysates of the clones were subjected to immunoblotting to detect proteins. Antibodies used: anti-FGFR4 (sc-124 and sc-9006; Santa-Cruz Inc/CA), anti- β -actin (Sigma, St Louis, MO), anti-phospho-PLC γ 1(Tyr783) (Cell Signaling, Danvers, MA), anti-PLC γ 1 (Cell Signaling), anti-phospho-p44/42 MAPK (ERK 1/2) (Thr202/Tyr204) (Cell Signaling), anti-ERK1/2 (Sigma), anti-phospho-AKT (Ser437) (Cell Signaling), anti-AKT (Cell Signaling). Band intensities were quantified by densitometry (ImageQuant 5.0-software; GE-Healthcare). Band intensities were quantified by densitometry and normalized to the β -actin level. Abbreviation: n.d., not detectable. Data are means \pm SD of ≥ 3 independent (in A, B) and of ≥ 2 experiments in (D). Statistics by t-test: a) $p < 0.05$; b) $p < 0.001$.

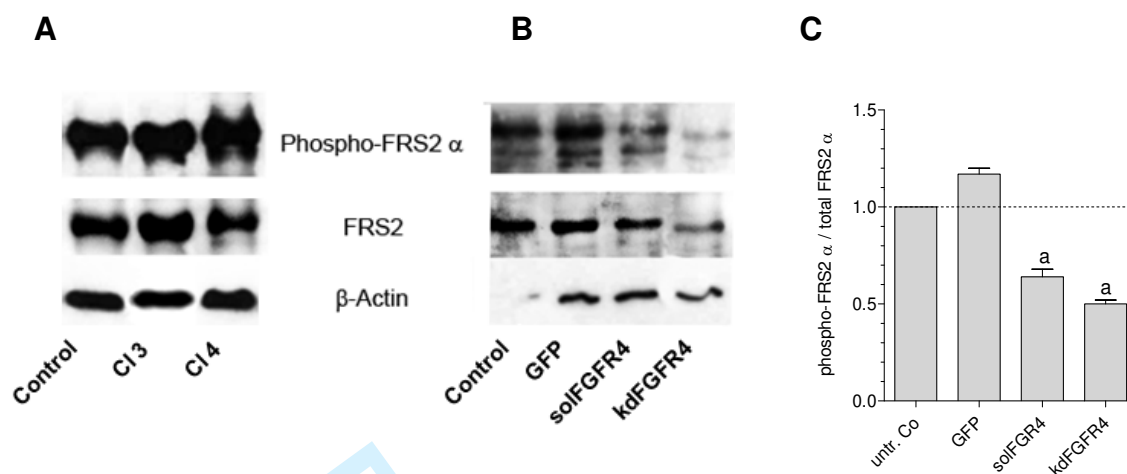
Expression of dominant negative FGFR4 constructs and interference with downstream signaling.

Hepatoma/hepatocarcinoma cell lines were infected with dominant-negative FGFR4 constructs. The high expression of the constructs is shown in suppl.fig.4.

To investigate interference with FGFR4-mediated signaling, phosphorylation of the FGFR binding adaptor protein Frs2 α was determined. On immunoblots signals were obtained at 60-75kDa which conforms to the molecular weights known for Frs2 proteins (suppl.fig.5). The impact of stable FGFR4 overexpression on the amount of phosphorylated Frs2 α is shown in suppl.fig.5A. In all three HCC cell lines, the expression of dominant-negative FGFR4 constructs interfered with downstream signaling, as indicated by a reduced amount of phosphorylated Frs2 α relative to total Frs2 protein (suppl.fig.5B and 5C).



Supplementary Figure 4. Expression of dominant-negative FGFR4-constructs in hepatoma/hepatocarcinoma cell lines. Cells were infected with adenoviruses encoding for dn-FGFR4 or sol-FGFR4. Untreated cells and cells infected with a GFP-adenovirus served as controls. Proteins were isolated 24 hrs after infection and determined by immunoblotting. Proteins in the cell supernatants were isolated by EtOH precipitation, as described by Gaughhofer et al (*Hepatology*, 2011;53:854-864). For further details see *Experimental Procedures*. Lane 1, untreated; lane 2, GFP; lane 3, solFGFR4; lane 4, kdFGFR4.



Supplementary Figure 5. Effect of FGFR4 blockade on downstream signaling. (A), cell lysates of clones overexpressing the vector (control) or FGFR4 (C1). (B), cell lysates of untreated HCC-1.2 cells (control) or 48hrs after infection with vector (GFP), solFGFR4, or kdFGFR4). Lysates were subjected to immunoblotting to detect total FRS2 and the phosphorylated form of FRS2 α . Antibodies: anti-FRS2 (Santa Cruz Biotechnology, St. Cruz, CA) anti-FRS2 α (Tyr196) Cell Signaling Technology (Danvers, MA). (C), band intensities were quantified by densitometry and normalized to the β -actin level. The values, obtained in untreated controls, were arbitrarily set 1. Means and SD of fold control values are given. Statistics by t-test for solFGFR4 or kdFGFR4 vs. GFP: a) $p < 0.05$.

Impact of FGFR4 overexpression and of interference with FGFR4-mediated signaling on transcriptome profiles of hepatoma/hepatocarcinoma cells.

Supplementary Table 2. Genes being deregulated in FGFR4-overexpressing HCC-1.2. cells. Data were processed as described in Experimental Procedures and are means of fold-vector control values of two different clones (clone 1 and 3). Fold-change cutoffs of ≥ 2 and ≤ 0.5 were used to select upregulated and downregulated genes, respectively.

Gene	reg.	Mean x Control	S.D.	p-value					
A1BG	up	8,3	6,7	0,1842	ADH1C	up	2,6	0,6	0,0906
A2BP1	down	-2,8	0,1	0,0128	ADH4	up	15,7	16,0	0,2089
A2M	down	-7,1	6,7	0,2091	ADORA1	up	2,9	1,3	0,1445
AADAC	down	-2,3	1,6	0,2313	ADPRHL1	up	2,1	0,1	0,0253
AASDH	down	-2,2	0,1	0,0269	ADRB2	up	6,3	3,7	0,1464
ABCA3	up	8,3	5,1	0,1454	ADRBK2	up	4,5	3,2	0,1849
ABCC3	down	-2,2	0,2	0,0420	AFAP1L1	up	2,1	0,4	0,0784
ABCD3	up	2,7	0,7	0,0934	AFF1	down	-2,0	0,4	0,0891
ABCE1	down	-2,1	0,2	0,0466	AFM	up	8,9	7,3	0,1857
ABCG5	up	9,3	0,8	0,0209	AFP	up	29,8	35,3	0,2274
ABCG8	up	3,8	0,3	0,0248	AGAP2	up	2,9	0,4	0,0420
ABHD12	up	2,4	0,2	0,0334	AGBL2	up	2,7	1,0	0,1271
ABHD2	up	2,0	0,8	0,1548	AGGF1	down	-2,4	0,4	0,0667
ACMSD	up	23,9	20,8	0,1817	AGK	down	-2,4	0,4	0,0646
ACPP	down	-6,3	2,1	0,0862	AGPAT2	up	2,9	0,4	0,0485
ACSL3	down	-3,2	0,3	0,0326	AGPAT4	up	4,1	0,0	0,0013
ACSL5	up	3,0	0,3	0,0363	AGPS	down	-2,3	0,6	0,1111
ACSL6	down	-9,5	7,6	0,1803	AGR2	down	-7,0	1,6	0,0608
ACSM1	down	-5,3	4,8	0,2126	AGTR1	down	-2,2	0,5	0,0951
ACSM3	up	2,5	0,8	0,1201	AGXT	up	2,2	0,5	0,0862
ACSS1	up	6,7	0,1	0,0043	AHCTF1	down	-3,2	0,4	0,0452
ACSS2	up	2,5	0,1	0,0211	AHCY	up	2,2	0,1	0,0182
ACSS3	down	-3,4	1,7	0,1487	AHR	down	-3,2	1,3	0,1302
ACTG2	down	-3,2	2,2	0,1974	AHRR	up	2,3	0,0	0,0035
ACVR1C	up	3,1	0,9	0,0923	AHSA2	down	-2,0	0,3	0,0680
ACYPI	down	-2,1	0,3	0,0571	AIF1	down	-3,9	3,1	0,2076
ADAM21	up	2,0	0,8	0,1655	AIF1L	up	12,0	4,1	0,0816
ADAM23	down	-2,9	0,6	0,0736	AIFM3	down	-2,6	0,5	0,0707
ADAM6	down	-2,6	0,8	0,1101	AIMP1	down	-2,0	0,4	0,0795
ADAM8	up	2,8	0,1	0,0074	AKAP11	down	-2,3	0,6	0,0961
ADAM9	down	-2,2	0,0	0,0075	AKAP12	up	3,2	2,6	0,2201
ADAMTS2	down	-12,4	4,6	0,0882	AKAP14	up	9,6	3,4	0,0880
ADAMTS9	up	2,8	1,2	0,1441	AKAP9	down	-3,8	1,0	0,0777
ADARB1	up	2,3	0,4	0,0679	AKD1	up	3,2	0,9	0,0871
ADC	up	2,7	0,4	0,0525	AKR1B10	down	-2,4	1,3	0,1802
ADCY5	up	5,1	0,5	0,0277	AKR1C1	up	4,7	2,5	0,1417
ADCY9	up	2,0	0,7	0,1364	AKR1C3	up	2,1	0,1	0,0210
ADH1A	up	14,7	14,2	0,2019	AKR1D1	up	5,6	0,6	0,0280
					AKT1S1	up	2,0	0,1	0,0319
					ALAD	up	2,2	0,0	0,0079

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ALB	up	3,9	3,9	0,2442	APOL4	up	2,2	0,6	0,1007
ALDH8A1	up	2,5	1,2	0,1660	APOLD1	up	2,5	0,6	0,0885
ALDOB	down	-2,4	0,6	0,0961	AQP3	up	3,0	0,7	0,0795
ALKBH8	down	-2,2	0,8	0,1495	ARAP1	up	2,1	0,2	0,0431
ALMS1	down	-2,7	0,8	0,1005	ARAP2	down	-10,0	5,2	0,1221
ALMS1P	down	-2,2	0,5	0,0980	ARG2	down	-2,5	0,4	0,0655
ALOX5AP	up	7,1	0,5	0,0186	ARGLU1	down	-2,1	0,2	0,0415
ALPK1	down	-2,6	1,4	0,1773	ARHGAP12	down	-2,7	0,7	0,0868
ALX4	down	-2,3	0,2	0,0391	ARHGAP18	down	-5,2	3,2	0,1587
AMMECR1	down	-2,1	0,0	0,0028	ARHGAP20	up	3,6	2,1	0,1641
AMOTL1	up	7,8	0,1	0,0031	ARHGAP21	down	-2,1	0,1	0,0118
AMPD3	up	10,6	0,2	0,0042	ARHGAP22	down	-6,0	2,3	0,1011
ANG	up	2,2	0,7	0,1265	ARHGAP29	down	-2,6	0,2	0,0310
ANGPT1	down	-4,9	0,0	0,0007	ARHGAP5	down	-2,0	0,4	0,0892
ANGPTL1	down	-3,5	1,0	0,0895	ARHGEF10	down	-2,5	1,0	0,1369
ANK3	down	-2,2	1,0	0,1770	ARHGEF16	down	-3,1	1,7	0,1643
ANKRD10	down	-2,3	0,3	0,0570	ARID4B	down	-2,5	0,1	0,0166
ANKRD12	down	-3,7	0,6	0,0506	ARID5B	down	-2,8	0,1	0,0184
ANKRD18B	up	7,2	1,7	0,0594	ARL10	up	3,0	0,1	0,0093
ANKRD20A2	up	5,1	0,8	0,0424	ARL17	down	-2,1	0,2	0,0464
ANKRD26	down	-3,2	0,7	0,0715	ARL17P1	down	-2,5	0,7	0,1025
ANKRD32	down	-2,4	0,4	0,0680	ARL4C	up	8,0	2,9	0,0921
ANKRD36	down	-2,4	0,4	0,0728	ARMC2	up	3,4	1,2	0,1098
ANKRD36B	down	-2,6	0,5	0,0722	ARMC9	up	2,5	0,4	0,0653
ANKRD58	up	7,2	2,0	0,0729	ARMCX1	down	-4,7	2,1	0,1206
ANKRD6	up	16,8	7,3	0,1004	ARMCX3	down	-3,5	0,3	0,0314
ANKRD62	down	-6,7	4,9	0,1751	ARNTL2	down	-3,6	1,1	0,0890
ANTXR1	up	3,7	1,2	0,0993	ARRDC4	up	2,4	0,5	0,0790
ANTXR2	down	-2,3	0,9	0,1366	ARSJ	down	-39,8	46,0	0,2218
ANXA1	down	-7,8	0,6	0,0196	ART5	up	3,2	0,4	0,0420
ANXA13	up	12,6	0,5	0,0088	ASB2	up	2,9	0,5	0,0558
ANXA3	down	-2,8	1,5	0,1678	ASB9	down	-2,3	1,2	0,1811
AP1AR	down	-2,3	0,2	0,0281	ASHIL	down	-3,6	1,4	0,1126
APBA2	up	9,1	3,1	0,0842	ASMT	down	-3,5	0,3	0,0308
APBB1IP	up	5,6	0,7	0,0321	ASPA	up	5,0	0,1	0,0043
APBB2	down	-2,2	0,2	0,0325	ASPG	up	2,9	0,3	0,0345
APLF	down	-6,5	2,4	0,0951	ASPH	down	-2,9	0,4	0,0431
APLN	up	4,7	1,0	0,0619	ASPHD1	down	-3,8	0,3	0,0219
APOA2	down	-2,0	0,3	0,0711	ASPM	down	-2,6	0,1	0,0209
APOA4	up	3,2	0,0	0,0046	ASS1	up	3,1	0,3	0,0320
APOA5	up	7,4	1,3	0,0468	ATAD2	down	-2,2	0,2	0,0280
APOB	down	-3,4	0,6	0,0593	ATAD4	up	2,2	0,6	0,1000
APOBEC3C	down	-3,3	2,6	0,2139	ATAD5	down	-3,8	1,1	0,0838
APOBEC3G	up	6,4	2,8	0,1127	ATG16L2	down	-2,5	0,4	0,0627
APOC1	up	2,3	0,1	0,0144	ATOH7	up	2,5	1,0	0,1356
APOC3	up	6,6	2,4	0,0948	ATOH8	down	-5,1	1,1	0,0625
APOL2	up	2,2	0,5	0,0811	ATP10D	up	2,6	0,7	0,0928

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ATP13A3	down	-2,1	0,3	0,0556	C10orf10	down	-5,5	0,7	0,0368
ATP2B1	down	-2,4	0,4	0,0597	C10orf116	down	-3,7	0,9	0,0756
ATP7A	down	-2,1	0,6	0,1223	C10orf118	down	-2,8	0,8	0,0996
ATR	down	-2,4	0,6	0,0876	C10orf82	up	10,4	10,3	0,2102
ATRNL1	up	5,0	4,0	0,1943	C10orf90	down	-2,3	0,0	0,0043
ATRX	down	-2,9	0,2	0,0292	C10orf93	up	8,3	6,9	0,1864
AUTS2	up	23,9	1,5	0,0150	C11orf60	up	3,2	0,5	0,0508
AVIL	up	4,3	3,3	0,1950	C11orf63	up	7,2	6,7	0,2073
AZGP1	up	3,9	1,8	0,1325	C11orf82	down	-2,0	0,2	0,0361
AZI2	down	-3,1	0,0	0,0034	C11orf86	up	2,6	1,0	0,1366
B3GALNT1	down	-4,0	2,5	0,1676	C11orf92	down	-2,3	0,9	0,1454
B4GALNT3	up	5,3	1,1	0,0546	C11orf93	down	-2,2	0,9	0,1499
BACE1	down	-2,4	0,7	0,1136	C12orf34	up	2,2	0,5	0,0831
BAGE	down	-3,4	0,5	0,0429	C12orf35	down	-2,8	0,0	0,0003
BAT2D1	down	-2,1	0,2	0,0334	C12orf39	down	-6,9	0,7	0,0257
BATF	down	-10,6	9,1	0,1875	C12orf42	up	2,2	0,1	0,0122
BAZ1A	down	-2,5	1,0	0,1349	C12orf70	down	-3,0	0,0	0,0028
BAZ2B	down	-2,8	0,9	0,1141	C13orf15	down	-7,5	0,6	0,0217
BBOX1	up	3,8	0,2	0,0151	C13orf29	down	-2,9	0,5	0,0617
BBS7	down	-2,4	0,3	0,0404	C13orf31	down	-2,6	0,9	0,1173
BCL2A1	up	2,0	0,3	0,0665	C14orf106	down	-2,3	0,7	0,1221
BCL2L11	up	2,2	0,2	0,0373	C14orf132	up	7,8	1,9	0,0613
BCLAF1	down	-2,1	0,8	0,1539	C14orf145	down	-2,3	0,0	0,0076
BDKRB1	down	-14,0	3,8	0,0655	C15orf27	up	9,1	2,2	0,0605
BDP1	down	-2,5	0,4	0,0600	C15orf41	down	-2,8	0,6	0,0730
BEND5	up	10,6	1,6	0,0384	C15orf48	up	15,3	6,0	0,0920
BEST1	down	-3,2	0,7	0,0686	C15orf59	up	4,7	1,9	0,1114
BEX5	up	2,5	0,6	0,0893	C16orf45	up	8,4	1,9	0,0578
BICC1	down	-4,5	3,4	0,1936	C16orf74	up	5,3	2,4	0,1188
BIN3	up	2,4	0,0	0,0009	C17orf108	up	2,1	0,3	0,0626
BIRC3	down	-6,5	0,4	0,0155	C17orf97	up	6,1	0,7	0,0295
BIVM	down	-2,1	0,6	0,1137	C18orf1	up	79,6	2,4	0,0070
BMF	up	4,7	1,4	0,0821	C19orf18	up	4,1	1,5	0,1062
BMP8B	up	2,2	0,3	0,0665	C19orf69	down	-11,4	10,3	0,1949
BNIP3L	up	2,0	0,3	0,0706	C1orf114	down	-3,9	0,7	0,0529
BOD1L	down	-5,3	1,6	0,0833	C1orf115	up	2,2	0,4	0,0698
BPI	up	9,7	0,8	0,0210	C1orf161	down	-2,8	0,5	0,0659
BRCA2	down	-4,5	1,1	0,0716	C1orf162	down	-2,1	0,2	0,0328
BRCC3	down	-2,9	0,6	0,0673	C1orf21	up	6,7	2,2	0,0837
BRF1	down	-2,3	0,7	0,1181	C1orf210	up	3,7	2,0	0,1546
BRIP1	down	-2,4	0,5	0,0875	C1orf226	up	2,5	0,3	0,0486
BRUNOL4	down	-3,5	0,5	0,0436	C1orf27	down	-3,3	0,6	0,0581
BRWD1	down	-4,5	0,8	0,0511	C1orf89	down	-2,2	0,3	0,0620
BRWD3	down	-2,3	0,1	0,0153	C1orf9	down	-3,8	0,7	0,0528
BTBD9	up	2,8	0,2	0,0276	C1R	up	2,3	0,2	0,0337
BTD	up	2,3	0,3	0,0487	C20orf132	up	2,8	0,4	0,0472
BTG1	up	2,3	0,2	0,0345	C20orf29	up	2,3	0,0	0,0013

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3	C20orf3	up	2,2	0,4	0,0720	C9orf123	up	2,2	0,5	0,0996
4	C20orf94	down	-100,9	102,1	0,1991	C9orf125	down	-3,5	1,4	0,1190
5	C21orf122	up	2,6	0,8	0,1091	C9orf130	up	2,2	0,3	0,0639
6	C21orf129	down	-2,3	1,3	0,1962	C9orf150	down	-4,9	0,5	0,0261
7	C21orf34	down	-11,6	0,0	0,0001	C9orf167	up	2,8	0,8	0,1022
8	C22orf41	up	2,6	0,1	0,0124	C9orf3	up	2,0	0,0	0,0003
9	C2CD2	down	-2,2	0,0	0,0002	C9orf43	up	2,9	0,4	0,0443
10	C2orf60	down	-2,1	0,5	0,1025	C9orf5	up	2,3	0,2	0,0259
11	C2orf63	down	-2,1	0,7	0,1285	C9orf57	down	-7,4	0,5	0,0167
12	C2orf77	down	-5,5	0,9	0,0428	C9orf9	up	3,0	0,2	0,0265
13	C2orf88	up	2,0	0,4	0,0805	CA13	up	16,2	10,3	0,1431
14	C3	up	2,4	0,4	0,0626	CA14	down	-2,0	0,1	0,0317
15	C3orf14	down	-2,5	0,8	0,1143	CA5A	up	2,2	0,4	0,0669
16	C3orf15	down	-6,9	0,0	0,0015	CA9	down	-2,9	0,5	0,0575
17	C3orf32	down	-2,6	0,9	0,1125	CACHD1	up	4,8	2,3	0,1281
18	C3orf57	down	-4,1	2,6	0,1704	CACNA1D	down	-2,7	0,2	0,0223
19	C3orf63	down	-2,4	0,4	0,0675	CACNG1	down	-4,1	0,2	0,0166
20	C4B	up	5,5	2,6	0,1240	CACNG4	down	-3,0	0,7	0,0759
21	C4orf21	down	-4,2	1,5	0,0978	CADM1	up	2,3	0,7	0,1235
22	C4orf41	down	-2,1	0,0	0,0003	CADM4	down	-2,6	0,3	0,0361
23	C4orf49	down	-2,5	0,3	0,0407	CADPS2	down	-3,2	1,1	0,1055
24	C5orf24	up	2,5	0,0	0,0013	CALR3	up	2,0	0,5	0,1053
25	C5orf32	down	-13,5	12,4	0,1950	CAMK2D	down	-2,1	0,5	0,0995
26	C5orf42	down	-3,2	0,1	0,0075	CAMKK1	up	2,9	1,2	0,1366
27	C6	down	-5,0	3,9	0,1927	CAMSAP1L1	down	-2,3	0,2	0,0311
28	C6orf114	up	2,1	0,3	0,0684	CAMTA1	down	-2,8	0,1	0,0158
29	C6orf132	up	4,9	0,1	0,0073	CAMTA2	down	-2,1	0,1	0,0127
30	C6orf134	down	-4,7	0,0	0,0006	CAPN2	up	4,6	3,0	0,1672
31	C6orf141	down	-11,4	10,5	0,1971	CASC5	down	-2,2	0,6	0,1095
32	C6orf145	up	2,0	0,3	0,0691	CASK	down	-2,2	0,1	0,0273
33	C6orf154	up	2,3	0,1	0,0181	CASP8	down	-3,3	0,7	0,0637
34	C6orf168	up	3,1	1,7	0,1618	CASP8AP2	down	-2,6	0,6	0,0868
35	C6orf208	up	2,5	0,6	0,0842	CCAR1	down	-2,1	0,5	0,1032
36	C6orf225	up	2,9	0,8	0,0922	CCBL2	down	-2,1	0,2	0,0367
37	C6orf26	down	-2,5	0,0	0,0075	CCDC11	down	-8,0	1,9	0,0611
38	C6orf59	up	4,2	0,5	0,0344	CCDC116	up	2,1	0,2	0,0501
39	C7orf10	up	2,5	0,6	0,0932	CCDC122	down	-2,0	0,3	0,0604
40	C7orf53	down	-2,9	1,3	0,1444	CCDC125	down	-2,2	0,3	0,0595
41	C7orf58	down	-7,3	1,2	0,0417	CCDC132	down	-2,0	0,1	0,0201
42	C8B	up	4,1	2,0	0,1320	CCDC135	up	3,6	1,1	0,0891
43	C8orf38	down	-2,0	0,1	0,0134	CCDC144A	up	2,3	0,6	0,0964
44	C8orf4	down	-20,8	0,3	0,0031	CCDC150	down	-2,9	0,4	0,0423
45	C8orf47	up	2,7	0,7	0,0930	CCDC151	up	2,9	0,1	0,0102
46	C8orf58	up	2,1	0,2	0,0512	CCDC155	up	5,7	2,8	0,1279
47	C9orf109	up	3,0	0,0	0,0006	CCDC28B	down	-2,1	0,5	0,1042
48	C9orf114	up	2,0	0,1	0,0141	CCDC34	down	-2,2	0,2	0,0370
49	C9orf122	up	3,6	1,3	0,1086	CCDC36	up	4,8	0,0	0,0007

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3	CCDC41	down	-2,1	0,4	0,0747	CECR2	up	2,9	0,1	0,0094
4	CCDC46	down	-2,9	1,5	0,1612	CECR6	up	4,5	0,3	0,0167
5	CCDC47	down	-2,0	0,3	0,0706	CENPC1	down	-2,7	0,8	0,0983
6	CCDC50	down	-2,0	0,1	0,0188	CENPE	down	-4,8	1,7	0,0999
7	CCDC55	down	-2,4	0,7	0,1039	CENPF	down	-3,2	0,3	0,0356
8	CCDC66	down	-3,1	0,0	0,0006	CENPJ	down	-2,7	0,7	0,0905
9	CCDC68	down	-3,8	1,0	0,0784	CEP110	down	-2,3	0,2	0,0318
10	CCDC69	up	5,6	1,3	0,0612	CEP120	down	-2,1	0,0	0,0029
11	CCDC74B	down	-2,9	0,2	0,0248	CEP135	down	-2,3	0,5	0,0881
12	CCDC82	down	-2,9	0,2	0,0213	CEP152	down	-2,4	0,3	0,0481
13	CCDC88A	down	-3,6	1,3	0,1085	CEP170	down	-3,5	0,4	0,0328
14	CCL20	down	-3,1	0,8	0,0854	CEP192	down	-2,1	0,4	0,0784
15	CCL27	up	2,9	0,2	0,0199	CEP290	down	-4,6	1,6	0,0995
16	CCL28	down	-4,2	1,2	0,0838	CEP350	down	-2,6	0,1	0,0193
17	CCNB3	down	-2,9	0,1	0,0122	CEP63	down	-2,1	0,3	0,0645
18	CCNJL	down	-2,4	1,5	0,2001	CES4	down	-4,6	2,9	0,1632
19	CCNL1	down	-2,7	0,0	0,0053	CFB	up	6,4	3,8	0,1473
20	CCNT2	down	-2,0	0,6	0,1196	CHAC2	down	-2,0	0,5	0,1034
21	CCPG1	down	-2,5	0,2	0,0260	CHADL	up	2,4	0,4	0,0620
22	CCR6	down	-2,6	0,7	0,0986	CHD1	down	-3,3	0,4	0,0418
23	CCRK	up	3,0	0,1	0,0096	CHD2	down	-2,6	0,6	0,0797
24	CD163	down	-10,4	7,8	0,1696	CHD9	down	-3,0	0,9	0,0950
25	CD163L1	down	-3,8	0,3	0,0247	CHIC1	down	-2,6	0,4	0,0559
26	CD2	up	3,0	1,8	0,1773	CHM	down	-2,2	0,3	0,0477
27	CD244	up	3,8	2,8	0,1920	CHML	down	-3,1	1,1	0,1125
28	CD36	down	-21,4	19,2	0,1866	CHMP7	up	2,2	0,0	0,0063
29	CD72	up	3,3	0,5	0,0440	CHN1	up	2,1	0,6	0,1083
30	CD83	down	-2,1	0,1	0,0206	CHP2	up	2,2	0,6	0,1039
31	CD86	up	4,0	0,8	0,0621	CHPT1	up	2,2	0,4	0,0786
32	CD8A	up	7,0	3,3	0,1190	CHRDL2	down	-2,2	0,2	0,0279
33	CD9	up	5,1	2,1	0,1081	CHRM3	up	10,2	1,3	0,0307
34	CD99L2	up	3,6	0,9	0,0746	CHST14	up	2,1	0,2	0,0440
35	CDC42BPA	down	-2,7	0,7	0,0954	CHST7	up	2,3	1,5	0,2193
36	CDCA7L	up	8,2	3,6	0,1101	CIDEB	up	2,0	0,1	0,0231
37	CDH11	down	-3,6	0,0	0,0005	CIDEC	up	2,1	0,6	0,1218
38	CDH12	down	-6,9	0,3	0,0114	CIZ1	up	2,1	0,1	0,0260
39	CDH16	up	3,0	1,9	0,1881	CKMT1A	up	2,3	0,4	0,0709
40	CDH17	up	23,5	8,8	0,0861	CLDN14	up	2,2	0,4	0,0649
41	CDKN1A	down	-2,1	0,6	0,1205	CLDN4	down	-3,7	2,0	0,1585
42	CDKN1C	up	4,2	1,2	0,0849	CLEC10A	up	2,3	0,4	0,0761
43	CDS1	down	-6,7	2,4	0,0904	CLK1	up	3,7	0,0	0,0024
44	CDYL2	up	4,6	0,7	0,0437	CLMN	up	4,0	0,8	0,0612
45	CEACAM1	down	-3,1	0,2	0,0208	CLOCK	down	-2,3	0,7	0,1105
46	CEACAM3	down	-2,5	0,2	0,0314	CLRN3	up	2,1	0,1	0,0198
47	CEBPB	up	2,0	0,3	0,0571	CLSPN	down	-2,6	0,4	0,0581
48	CEBPE	up	2,3	0,2	0,0296	CMAH	down	-2,1	0,6	0,1183
49	CEBPZ	down	-2,3	0,5	0,0836	CNNM2	up	3,3	0,2	0,0165

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DENND2C	up	2,2	0,5	0,0893	DPF3	up	2,6	0,4	0,0578
DENND4A	down	-2,8	0,0	0,0040	DPY19L1P1	down	-2,6	0,4	0,0582
DES	down	-2,9	0,9	0,1028	DPY19L2P4	down	-2,7	0,1	0,0119
DFNB59	down	-2,5	0,5	0,0662	DPYD	up	2,1	0,3	0,0537
DGCR8	down	-2,8	0,2	0,0281	DPYS	down	-8,6	8,5	0,2133
DGKB	down	-14,5	1,1	0,0182	DPYSL2	up	2,3	0,1	0,0110
DGKG	down	-8,7	4,5	0,1255	DPYSL5	up	13,4	12,4	0,1957
DHCR24	up	2,0	0,2	0,0426	DQX1	down	-5,2	1,3	0,0699
DHDPSL	up	5,4	1,4	0,0696	DSE	up	2,9	1,2	0,1383
DHRS2	up	3,3	0,1	0,0088	DST	down	-2,3	0,0	0,0053
DIAPH2	down	-2,4	0,1	0,0110	DTNA	down	-3,8	0,5	0,0396
DIAPH3	down	-3,1	0,0	0,0039	DUSP26	up	16,8	5,9	0,0819
DICER1	down	-2,3	0,1	0,0250	DUSP6	down	-3,8	1,9	0,1405
DIO1	up	2,9	0,4	0,0512	DYDC2	up	2,8	0,2	0,0241
DIP2C	up	57,2	22,4	0,0875	DYNLT3	down	-2,6	0,2	0,0257
DIS3	down	-2,6	0,1	0,0164	DZIP1L	up	7,7	1,3	0,0425
DISC1	down	-6,7	4,1	0,1510	EBF3	down	-3,2	2,7	0,2300
DISP2	up	6,5	1,7	0,0674	ECE1	up	2,2	0,2	0,0371
DKFZP434L187	up	6,2	0,4	0,0168	ECHDC3	down	-4,0	2,0	0,1409
DKFZP547L112	up	14,3	7,3	0,1170	EDEM3	down	-2,0	0,3	0,0720
DKFZP564C152	down	-2,6	0,5	0,0703	EDNRB	down	-4,0	3,0	0,1974
DKFZp667E0512	down	-3,0	0,4	0,0438	EEA1	down	-2,2	0,2	0,0283
DKK4	down	-10,6	0,1	0,0015	EEF1E1	down	-2,0	0,1	0,0307
DLC1	up	2,2	0,2	0,0396	EFEMP1	down	-35,6	47,7	0,2461
DLG3	up	6,3	0,5	0,0231	EFHD1	up	2,5	0,6	0,0919
DLK2	up	3,1	0,4	0,0475	EFR3B	up	13,9	6,5	0,1084
DLX1	down	-6,6	3,9	0,1432	EFTUD1	down	-2,7	0,3	0,0435
DLX2	down	-2,6	0,7	0,0916	EGFL7	up	2,0	0,1	0,0204
DMKN	up	3,0	1,5	0,1523	EGR1	down	-2,3	0,6	0,1006
DMTF1	down	-2,2	0,6	0,1151	EHBP1	down	-2,2	0,1	0,0222
DNA2	down	-2,3	0,4	0,0691	EHD3	up	4,2	2,0	0,1310
DNAH14	down	-2,2	0,2	0,0474	EIF3A	down	-2,3	0,7	0,1200
DNAJA4	up	5,3	4,7	0,2101	EIF4EBP2	up	2,0	0,2	0,0409
DNAJB14	down	-2,3	0,5	0,0803	EIF5	down	-2,9	0,9	0,1093
DNAJB2	up	2,1	0,3	0,0726	EIF5B	down	-2,5	0,8	0,1213
DNAJC2	down	-3,0	0,6	0,0660	ELOVL6	down	-3,1	1,3	0,1290
DNAJC25	up	2,1	0,3	0,0526	ELOVL7	up	2,8	1,3	0,1476
DNAJC3	down	-2,1	0,3	0,0710	EMID1	up	3,0	0,2	0,0269
DNM1L	down	-2,4	0,5	0,0835	EMILIN2	up	2,2	1,3	0,2078
DNMBP	up	2,2	0,1	0,0245	EML1	up	2,7	1,2	0,1453
DNMT3B	up	3,1	0,3	0,0300	EML4	down	-4,2	0,2	0,0174
DNMT3L	up	3,6	2,3	0,1772	EMP2	up	9,2	4,9	0,1285
DNTTIP2	down	-2,5	0,5	0,0721	EMR1	up	10,4	7,5	0,1649
DOCK7	down	-2,3	0,1	0,0152	ENAH	down	-2,5	0,2	0,0241
DOK1	up	3,0	0,7	0,0760	ENC1	down	-6,5	2,8	0,1091
DOK3	up	2,9	0,5	0,0594	ENDOD1	up	6,5	4,7	0,1734
DOLPP1	up	2,2	0,3	0,0615	ENPP4	down	-3,5	2,8	0,2116

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3	ENPP6	down	-9,5	0,0	0,0008	FAM153A	down	-2,4	0,1	0,0183
4	ENTPD8	up	2,9	0,2	0,0192	FAM153B	down	-2,9	0,1	0,0114
5	EP400	up	2,2	0,3	0,0567	FAM155B	down	-2,3	0,7	0,1126
6	EPB41L1	up	5,1	1,6	0,0868	FAM167A	up	5,1	1,1	0,0590
7	EPB41L3	up	19,2	16,6	0,1819	FAM171A1	up	7,3	4,2	0,1412
8	EPB41L4B	up	2,1	0,4	0,0870	FAM171B	down	-5,4	3,8	0,1761
9	EPCAM	down	-8,1	8,8	0,2286	FAM174B	down	-3,4	1,8	0,1594
10	EPHA10	up	4,0	0,4	0,0279	FAM178A	down	-2,1	0,8	0,1485
11	EPM2AIP1	down	-2,5	1,1	0,1567	FAM183A	up	3,5	1,5	0,1225
12	EPN3	down	-2,8	0,8	0,1017	FAM184A	down	-2,0	0,6	0,1251
13	EPRS	down	-2,0	0,2	0,0524	FAM188B	down	-8,9	8,3	0,2030
14	EPS8	down	-3,1	0,1	0,0131	FAM189A1	up	8,7	5,3	0,1435
15	EPSTI1	up	4,4	1,2	0,0784	FAM20A	up	7,9	2,0	0,0654
16	ERAP1	down	-4,9	0,0	0,0005	FAM20C	up	8,5	1,6	0,0479
17	ERAP2	down	-3,4	0,0	0,0019	FAM22A	up	2,2	0,5	0,0940
18	EREG	down	-2,2	0,0	0,0038	FAM22D	up	5,0	1,5	0,0804
19	ERMAP	up	2,8	0,1	0,0185	FAM38B	down	-9,5	5,5	0,1365
20	ESPN	up	2,4	0,3	0,0419	FAM3B	down	-3,1	2,7	0,2392
21	ESPNL	up	2,4	0,2	0,0243	FAM40B	down	-2,3	0,1	0,0231
22	ETAA1	down	-2,4	0,5	0,0731	FAM50B	up	2,3	0,3	0,0427
23	ETNK2	up	2,5	0,5	0,0681	FAM60A	down	-2,1	0,2	0,0380
24	ETS1	down	-2,9	0,3	0,0338	FAM78A	up	4,1	0,4	0,0290
25	ETS2	down	-2,2	0,1	0,0190	FAM81A	down	-2,2	0,2	0,0365
26	ETV1	down	-3,7	0,8	0,0622	FAM9B	down	-186,7	108,2	0,1244
27	ETV4	down	-4,3	0,3	0,0220	FAM9C	down	-31,3	0,5	0,0041
28	ETV5	down	-3,2	0,2	0,0206	FANCB	down	-2,9	0,4	0,0493
29	EVC2	down	-3,1	0,3	0,0280	FANCD2	down	-2,3	0,3	0,0520
30	EVI5	down	-2,0	0,2	0,0418	FANCI	down	-2,0	0,4	0,0822
31	EXOC5	down	-2,0	0,5	0,1114	FANCL	down	-3,0	0,6	0,0711
32	EXPH5	up	2,8	0,2	0,0285	FANCM	down	-2,7	0,4	0,0573
33	EXT1	down	-2,4	0,1	0,0201	FAR1	down	-2,0	0,2	0,0545
34	EYA3	down	-2,7	0,0	0,0046	FAR2	up	3,2	1,6	0,1491
35	EYA4	down	-10,5	0,7	0,0158	FASTKD1	down	-2,5	0,2	0,0258
36	F9	up	89,3	105,2	0,2229	FAT1	down	-2,6	0,1	0,0167
37	FAAH	up	2,4	0,4	0,0673	FBLN7	up	3,7	2,3	0,1717
38	FABP6	up	2,3	0,6	0,1112	FBN1	up	2,3	0,4	0,0630
39	FADS1	up	2,6	0,1	0,0128	FBP1	up	5,8	1,0	0,0470
40	FADS6	up	3,5	1,1	0,0951	FBXL17	up	2,3	0,5	0,0893
41	FAM105A	down	-10,0	10,0	0,2115	FBXL21	up	11,2	1,3	0,0293
42	FAM111B	down	-3,7	1,5	0,1161	FBXL7	up	9,5	4,0	0,1021
43	FAM129A	down	-2,6	0,1	0,0193	FBXO38	down	-2,2	0,6	0,1077
44	FAM133A	down	-68,5	26,6	0,0865	FBXO4	down	-2,8	1,3	0,1459
45	FAM133B	down	-2,0	0,1	0,0274	FBXW10	down	-2,8	1,0	0,1199
46	FAM135A	down	-3,9	0,1	0,0106	FBXW2	up	2,9	0,0	0,0057
47	FAM13A	down	-2,5	0,8	0,1124	FCGBP	up	2,5	1,1	0,1553
48	FAM13AOS	down	-3,1	0,0	0,0016	FCGR2A	up	2,4	0,3	0,0401
49	FAM150A	down	-2,9	0,0	0,0044	FCGR3A	up	22,6	14,5	0,1409

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FCRLA	up	7,1	2,1	0,0758	FRY	down	-2,1	0,5	0,1007
FCRLB	up	4,4	1,5	0,0937	FRYL	down	-2,5	0,6	0,0829
FER	down	-2,0	0,7	0,1391	FST	down	-3,6	0,7	0,0593
FER1L4	up	4,3	2,5	0,1547	FSTL5	down	-18,0	13,6	0,1639
FES	up	5,8	1,0	0,0474	FUT8	down	-2,3	0,3	0,0444
FEZ1	up	8,0	3,7	0,1126	FUZ	down	-3,8	0,2	0,0166
FGD5	up	3,8	0,9	0,0709	FZD2	up	2,0	0,2	0,0330
FGF13	down	-7,3	6,3	0,1967	FZD3	down	-2,4	0,8	0,1155
FGF19	down	-10,7	7,8	0,1645	FZD4	down	-2,1	1,4	0,2316
FGF2	up	11,0	4,8	0,1044	FZD7	up	2,6	0,8	0,1084
FGF9	down	-4,5	1,8	0,1117	G0S2	up	2,1	0,8	0,1559
FGFR4	up	7,7	7,1	0,2050	G6PC	up	3,6	1,2	0,0981
FGR	up	3,6	0,2	0,0163	GABARAPL1	up	2,0	0,8	0,1633
FHL1	up	10,6	8,6	0,1793	GABRA5	up	4,6	2,8	0,1603
FHOD3	up	5,4	2,1	0,1037	GABRE	down	-3,5	0,4	0,0367
FILIP1	down	-4,0	0,3	0,0255	GABRG2	down	-2,2	0,9	0,1577
FLI1	down	-59,3	31,6	0,1166	GAD1	up	2,4	0,3	0,0498
FLJ11235	up	2,0	0,3	0,0584	GADD45B	up	2,5	0,0	0,0061
FLJ13744	down	-2,2	0,1	0,0285	GAF3	down	-4,7	0,1	0,0079
FLJ23834	down	-3,5	0,1	0,0132	GALNS	up	5,5	1,9	0,0913
FLJ36031	up	2,2	0,1	0,0219	GALNT6	up	6,7	3,0	0,1128
FLJ37644	down	-4,0	0,1	0,0108	GALNTL1	up	13,8	6,6	0,1121
FLJ40330	down	-6,6	0,9	0,0365	GARNL3	up	5,7	0,3	0,0142
FLJ40852	up	3,4	0,5	0,0493	GAS5	down	-2,1	0,1	0,0258
FLJ42875	up	3,0	1,2	0,1261	GATA3	down	-3,3	1,5	0,1355
FLJ45244	down	-2,4	0,2	0,0303	GATM	up	3,8	2,0	0,1510
FLNC	down	-13,8	13,1	0,1996	GBA3	up	6,2	5,0	0,1907
FLRT1	up	2,5	0,2	0,0242	GBP2	down	-2,7	0,7	0,0829
FLRT3	down	-8,1	6,9	0,1900	GBP3	down	-2,8	0,5	0,0591
FLYWCH2	up	2,0	0,6	0,1274	GCNT4	down	-3,3	2,3	0,1940
FMNL1	down	-4,2	2,5	0,1575	GCOM1	up	5,6	1,3	0,0644
FMO1	up	15,7	10,7	0,1511	GDA	down	-3,3	0,1	0,0062
FMO3	down	-20,5	2,6	0,0301	GDF1	up	2,5	0,8	0,1184
FMO4	up	3,4	1,0	0,0919	GDF10	up	20,0	8,0	0,0923
FMO5	down	-3,9	0,3	0,0224	GDF15	down	-2,5	0,3	0,0381
FNBP1L	down	-2,8	0,5	0,0644	GDPD3	down	-2,2	0,7	0,1261
FNIP2	down	-2,7	0,5	0,0646	GEM	up	2,6	0,0	0,0061
FOLR1	up	3,6	1,7	0,1381	GEN1	down	-2,1	0,2	0,0465
FOXC1	down	-2,1	0,3	0,0520	GGT8P	down	-2,2	0,2	0,0355
FOXG1	down	-2,3	0,0	0,0067	GHR	down	-2,1	0,4	0,0812
FOXN4	up	4,8	0,1	0,0053	GIGYF2	down	-2,1	0,4	0,0892
FOXO1	down	-2,1	0,4	0,0782	GIMAP7	up	3,4	0,6	0,0596
FOXO3	up	2,0	0,4	0,0896	GIPC2	down	-2,2	1,2	0,1915
FRAS1	down	-2,1	0,8	0,1488	GJA1	down	-7,4	0,1	0,0047
FRMD3	down	-3,7	2,0	0,1549	GJA3	up	8,9	4,8	0,1298
FRMD6	down	-3,1	0,1	0,0116	GLA	down	-2,2	0,1	0,0268
FRRS1	down	-2,7	0,1	0,0082	GLE1	up	2,1	0,0	0,0063

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3	GLI1	up	5,2	2,1	0,1097	GPX7	down	-8,8	0,1	0,0017
4	GLIPR1	down	-2,1	0,0	0,0027	GPX8	up	3,5	0,8	0,0702
5	GLIPR2	down	-4,0	3,9	0,2368	GRAMD3	down	-2,1	0,1	0,0268
6	GLS	down	-3,8	0,1	0,0117	GRB14	down	-3,3	1,3	0,1175
7	GLT1D1	up	6,7	5,7	0,1971	GREM1	down	-4,5	2,8	0,1597
8	GLT8D3	down	-2,4	0,6	0,0994	GSN	up	6,7	0,3	0,0109
9	GLT8D4	up	2,7	0,0	0,0028	GSTA1	up	16,0	6,4	0,0932
10	GLUD1	up	2,0	0,3	0,0639	GSTA2	up	14,2	4,1	0,0696
11	GLUD2	up	2,4	0,4	0,0695	GSTA3	up	12,8	4,2	0,0787
12	GM2A	up	2,1	0,1	0,0239	GSTA5	up	13,2	4,6	0,0826
13	GNB4	up	9,2	0,2	0,0049	GSTO2	up	2,7	0,5	0,0718
14	GNGT1	down	-5,2	0,3	0,0168	GTDC1	up	2,7	1,7	0,1997
15	GNPDA2	down	-2,2	0,3	0,0524	GTF2H5	down	-2,1	0,5	0,0925
16	GNRH1	down	-2,3	0,6	0,1054	GTF2IRD2	up	5,5	1,3	0,0659
17	GNS	up	2,7	0,0	0,0043	GUCA1B	down	-2,2	0,1	0,0148
18	GOLGA2LY1	down	-2,3	0,7	0,1164	GUCY2C	up	2,8	2,1	0,2219
19	GOLGA4	down	-4,7	0,8	0,0491	GULP1	down	-4,1	0,0	0,0005
20	GOLGA6A	down	-2,3	0,1	0,0120	H2AFY2	up	6,5	2,7	0,1074
21	GOLGA6L10	down	-2,2	0,7	0,1359	HAO2	up	7,9	6,5	0,1855
22	GOLGA6L9	down	-2,2	0,5	0,0866	HAUS6	down	-2,1	0,2	0,0415
23	GOLGA8A	down	-2,4	0,0	0,0067	HAVCR2	down	-5,6	1,9	0,0889
24	GOLGA8F	down	-2,1	0,8	0,1515	HBE1	down	-4,9	2,1	0,1140
25	GOLGB1	down	-2,4	0,6	0,0958	HBG1	down	-5,0	2,0	0,1089
26	GOLM1	down	-8,8	9,2	0,2217	hCG_1817306	down	-2,1	0,0	0,0041
27	GON4L	down	-2,1	0,0	0,0081	hCG_1993592	down	-2,0	0,1	0,0209
28	GOT1	down	-2,2	0,0	0,0055	HCG27	down	-2,5	1,3	0,1651
29	GPATCH4	down	-2,3	0,3	0,0548	HCP5	up	2,7	0,1	0,0116
30	GPBP1	down	-2,1	0,3	0,0658	HDAC6	down	-2,3	0,4	0,0661
31	GPC1	up	3,4	0,1	0,0140	HDGFRP3	up	36,9	22,7	0,1342
32	GPC4	up	5,1	1,9	0,1022	HDHD3	up	2,3	0,3	0,0468
33	GPC5	up	8,3	6,9	0,1863	HEATR1	down	-2,1	0,4	0,0830
34	GPD1	up	2,4	0,5	0,0709	HECA	up	3,5	0,6	0,0537
35	GPD1L	down	-2,5	0,8	0,1171	HERC2P2	down	-2,1	0,3	0,0637
36	GPR109B	down	-2,7	1,4	0,1681	HERC6	up	3,2	0,8	0,0783
37	GPR110	down	-5,4	2,7	0,1310	HERV-FRD	down	-2,5	0,0	0,0018
38	GPR126	down	-3,4	0,3	0,0243	HEY1	up	2,7	0,9	0,1161
39	GPR128	up	2,2	0,6	0,1007	HEY2	down	-4,0	2,9	0,1922
40	GPR133	up	2,3	0,4	0,0636	HEYL	up	7,0	1,2	0,0461
41	GPR146	up	2,1	0,3	0,0530	HHAT	up	3,7	0,1	0,0119
42	GPR158	down	-2,4	0,5	0,0858	HIBCH	down	-2,1	0,1	0,0297
43	GPR176	up	2,8	0,1	0,0071	HIST2H2BE	up	2,6	0,2	0,0332
44	GPR177	down	-3,1	0,6	0,0610	HK2	down	-2,6	0,7	0,0907
45	GPR68	up	6,8	0,0	0,0008	HLA-DQB1	up	8,7	4,1	0,1145
46	GPR81	down	-2,7	0,5	0,0695	HLTF	down	-3,0	0,8	0,0845
47	GPRC5B	up	2,8	1,6	0,1767	HMGCS2	up	3,0	1,0	0,1074
48	GPRIN1	up	2,0	0,1	0,0172	HMGN1	down	-3,8	0,8	0,0642
49	GPSM1	up	3,7	1,8	0,1374	HMGN5	down	-3,3	0,2	0,0212

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HNRNPA3	down	-2,2	0,3	0,0646	IGSF11	up	6,9	0,1	0,0028
HNRNPU	down	-2,5	0,1	0,0210	IGSF9	up	6,4	2,1	0,0873
HOMER2	up	5,0	0,5	0,0251	IKBKAP	up	3,2	1,2	0,1148
HOOK1	down	-3,2	0,2	0,0167	IL11RA	up	2,2	0,1	0,0159
HOXA13	up	2,6	2,1	0,2436	IL13RA2	down	-8,0	0,1	0,0023
HOXB5	down	-12,0	2,0	0,0402	IL18	down	-13,3	16,0	0,2369
HOXC13	down	-7,5	2,7	0,0914	IL18R1	up	21,4	5,6	0,0615
HOXD10	down	-2,4	0,0	0,0058	IL1F7	up	2,4	0,7	0,1101
HOXD8	down	-2,4	0,6	0,0966	IL1R2	up	2,4	0,0	0,0027
HP	up	2,8	1,1	0,1307	IL1RAP	down	-2,3	0,1	0,0236
HPGD	down	-3,5	0,9	0,0825	IL1RN	up	6,0	0,7	0,0317
HPR	up	3,9	1,9	0,1354	IL22RA1	up	2,2	0,6	0,1058
HPSE	down	-5,2	0,5	0,0265	IL23R	down	-10,2	6,4	0,1449
HRASLS	up	8,3	3,1	0,0923	IL2RB	down	-5,2	4,0	0,1864
HRC	down	-4,4	0,9	0,0592	IL2RG	down	-5,2	1,1	0,0591
HRCT1	down	-2,2	0,4	0,0767	IL6ST	down	-2,4	0,4	0,0723
HRG	up	2,5	0,7	0,0998	IL8	down	-6,1	4,4	0,1734
HSD17B11	down	-2,4	0,1	0,0231	IMPA2	up	2,3	1,0	0,1568
HSD17B12	down	-2,0	0,2	0,0389	INHBE	up	5,4	0,7	0,0377
HSD17B6	up	3,5	2,2	0,1727	INPP1	down	-2,9	0,5	0,0518
HSD3B1	up	4,6	3,5	0,1892	INPP5D	up	17,9	5,7	0,0747
HSP90AA1	down	-2,2	0,1	0,0253	INPP5K	up	2,1	0,3	0,0546
HSP90B1	down	-2,4	0,4	0,0723	INTS6	down	-2,2	0,1	0,0127
HSPA12A	up	9,2	7,4	0,1802	IPO7	down	-2,0	0,5	0,1042
HSPA12B	up	24,1	14,3	0,1318	IPW	down	-3,1	1,5	0,1474
HSPA4L	down	-3,3	0,5	0,0517	IQCA1	up	30,2	5,7	0,0438
HSPA6	up	2,5	1,1	0,1481	IQCK	up	2,8	0,2	0,0289
HSPH1	down	-2,0	0,6	0,1279	IQGAP2	down	-2,8	1,5	0,1672
HTRA1	up	7,3	0,9	0,0328	IQSEC2	up	2,2	0,6	0,1055
HYAL4	down	-5,6	3,7	0,1657	IRF8	up	3,6	2,1	0,1609
HYLS1	up	2,6	0,1	0,0099	IRF9	up	2,6	0,3	0,0471
ICA1	up	2,0	0,3	0,0576	IRS2	up	2,2	0,8	0,1313
ICA1L	down	-2,2	1,2	0,1896	IRX3	up	5,2	3,8	0,1807
ICAM5	down	-2,4	0,0	0,0032	ISCA1	up	2,1	0,3	0,0555
IDS	down	-2,3	0,0	0,0046	ISX	up	4,1	0,7	0,0525
IER3	down	-4,2	0,5	0,0358	ITGA1	down	-2,3	0,1	0,0119
IER5L	down	-2,3	0,4	0,0656	ITGA2	down	-6,7	0,1	0,0023
IFI16	up	2,4	1,0	0,1425	ITGA3	up	4,0	2,7	0,1779
IFRD1	down	-2,7	0,2	0,0303	ITGAM	up	4,0	3,5	0,2212
IFT80	down	-2,4	0,2	0,0331	ITGAV	down	-2,7	0,2	0,0301
IFT81	down	-2,3	0,5	0,0758	ITGB1BP2	up	2,2	0,7	0,1278
IFT88	down	-2,3	0,3	0,0477	ITGB2	up	9,0	9,5	0,2220
IGFBP2	up	6,2	6,5	0,2298	ITIH1	up	7,5	4,5	0,1463
IGFBP3	up	2,5	0,2	0,0377	ITIH3	up	3,4	2,6	0,2069
IGFBP4	up	5,9	1,7	0,0766	ITIH4	up	3,3	1,9	0,1675
IGFBPL1	down	-2,1	0,3	0,0610	ITLN1	up	2,0	0,4	0,0861
IGSF1	up	2,1	0,8	0,1530	ITPR3	up	6,1	2,0	0,0841

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3	ITPRIPL1	down	-2,2	0,5	0,0957	KIAA1804	down	-2,6	0,5	0,0737
4	ITSN2	down	-2,5	0,9	0,1255	KIAA1908	up	2,4	0,0	0,0045
5	IYD	up	8,7	1,3	0,0373	KIAA1967	up	2,5	0,3	0,0498
6	JAG1	down	-5,0	4,2	0,2041	KIF14	down	-3,1	0,5	0,0533
7	JAZF1	up	5,4	0,3	0,0163	KIF15	down	-3,8	0,1	0,0115
8	JMJD1C	down	-2,7	0,4	0,0573	KIF20B	down	-2,6	0,6	0,0822
9	JUN	down	-3,0	0,7	0,0749	KIF21A	down	-2,1	0,5	0,0973
10	KALRN	down	-8,4	2,2	0,0674	KIF3A	down	-2,5	0,8	0,1081
11	KANK1	up	2,1	0,4	0,0773	KIF6	up	2,5	1,0	0,1370
12	KANK3	up	2,0	0,5	0,1087	KIRREL	down	-2,2	1,0	0,1668
13	KANK4	up	54,9	26,3	0,1059	KLC4	up	2,4	0,0	0,0038
14	KBTBD11	up	40,0	24,9	0,1347	KLF2	up	2,8	0,6	0,0701
15	KCNC1	up	6,1	0,5	0,0237	KLHL24	up	3,0	1,5	0,1606
16	KCNC3	up	3,4	0,3	0,0247	KLHL3	up	2,2	0,3	0,0661
17	KCNE1L	down	-3,1	1,2	0,1165	KLHL34	down	-5,7	2,0	0,0947
18	KCNE3	up	10,6	5,8	0,1293	KLHL5	down	-2,3	0,6	0,1067
19	KCNJ15	down	-2,7	0,1	0,0171	KNG1	up	10,5	0,0	0,0001
20	KCNJ16	up	187,5	13,2	0,0159	KRAS	down	-2,1	0,0	0,0097
21	KCNJ8	up	2,4	0,7	0,1014	KRCC1	down	-3,3	0,9	0,0852
22	KCNK10	up	6,3	2,9	0,1163	KREMEN1	up	3,3	0,0	0,0035
23	KCNK5	up	7,4	2,0	0,0681	KRT222	down	-2,3	0,9	0,1489
24	KCNQ1OT1	down	-2,4	0,4	0,0621	KRT23	down	-15,1	13,6	0,1897
25	KCTD5	up	2,1	0,1	0,0136	KRT6A	up	10,9	3,9	0,0871
26	KCTD7	down	-2,1	0,5	0,0926	KRT86	down	-2,0	0,1	0,0283
27	KDM4D	up	2,1	0,2	0,0432	KRTAP19-1	down	-3,1	1,2	0,1215
28	KHDC1	up	2,7	0,3	0,0354	KRTCAP3	down	-2,0	0,3	0,0601
29	KIAA0040	up	5,6	2,8	0,1290	KRTDAP	up	4,9	2,2	0,1232
30	KIAA0125	up	2,6	0,5	0,0708	KTN1	down	-3,2	0,9	0,0882
31	KIAA0232	down	-2,3	0,8	0,1303	KYNU	down	-2,9	0,3	0,0324
32	KIAA0319	up	5,3	4,2	0,1909	L3MBTL3	up	3,5	0,8	0,0739
33	KIAA0564	down	-2,2	0,1	0,0161	LAMA4	down	-19,9	22,9	0,2255
34	KIAA0802	down	-2,8	1,6	0,1804	LAMB1	down	-4,9	2,1	0,1174
35	KIAA0907	down	-2,2	0,1	0,0135	LAMB3	up	2,3	0,1	0,0234
36	KIAA0947	down	-2,7	0,4	0,0510	LANCL2	up	2,7	0,3	0,0431
37	KIAA1009	down	-2,8	0,6	0,0725	LARGE	up	10,3	1,9	0,0457
38	KIAA1107	down	-2,3	1,0	0,1632	LARP1B	down	-2,5	0,6	0,0846
39	KIAA1109	down	-4,1	0,4	0,0261	LARP7	down	-3,0	0,8	0,0826
40	KIAA1147	down	-2,4	0,3	0,0550	LARS	down	-2,3	0,7	0,1161
41	KIAA1161	up	3,8	0,6	0,0498	LAT2	up	2,1	0,4	0,0737
42	KIAA1199	up	18,8	23,2	0,2366	LBP	up	9,0	6,7	0,1695
43	KIAA1377	up	5,5	3,1	0,1443	LCA5	down	-4,1	2,6	0,1745
44	KIAA1430	down	-2,3	0,0	0,0023	LCAT	up	2,9	0,2	0,0256
45	KIAA1549	down	-3,0	0,4	0,0479	LCORL	down	-2,5	0,5	0,0782
46	KIAA1656	up	3,7	0,6	0,0482	LCP1	down	-10,3	3,0	0,0707
47	KIAA1683	down	-2,1	0,0	0,0052	LDHD	up	2,0	0,0	0,0079
48	KIAA1712	down	-2,6	0,0	0,0008	LDLRAD1	up	8,7	3,2	0,0894
49	KIAA1731	down	-3,4	0,5	0,0449	LDOC1L	up	2,1	0,2	0,0456

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LEF1	up	20,9	14,2	0,1490	LOC100288846	up	3,2	0,3	0,0275
LEFTY1	up	5,2	3,5	0,1710	LOC100289058	down	-2,5	0,3	0,0395
LEO1	down	-2,2	0,3	0,0564	LOC100289169	down	-2,7	0,9	0,1074
LEPR	up	2,9	0,5	0,0620	LOC100289490	up	2,9	0,3	0,0360
LFNG	down	-6,5	2,7	0,1075	LOC100289574	down	-2,0	0,7	0,1378
LGALS1	down	-2,2	0,0	0,0083	LOC100292427	up	2,3	0,3	0,0434
LGALS2	up	2,8	0,1	0,0100	LOC100293208	down	-2,4	0,0	0,0037
LHPP	up	2,4	0,0	0,0077	LOC134466	down	-2,6	1,0	0,1350
LHX1	down	-4,9	0,9	0,0529	LOC145783	down	-4,0	0,1	0,0068
LHX2	up	4,7	2,4	0,1353	LOC150759	down	-4,2	1,8	0,1201
LHX6	up	5,4	1,6	0,0794	LOC151438	up	4,9	1,6	0,0883
LIFR	up	13,7	7,1	0,1207	LOC157562	down	-2,2	0,5	0,0897
LIG4	down	-2,2	0,0	0,0009	LOC221442	down	-7,8	4,9	0,1492
LILRB3	down	-2,3	0,2	0,0294	LOC283352	up	2,9	0,8	0,0944
LIMA1	down	-3,8	1,8	0,1345	LOC283663	down	-2,6	0,2	0,0262
LIMCH1	down	-2,1	0,1	0,0232	LOC283788	down	-3,0	0,3	0,0320
LIMD2	up	2,2	0,4	0,0700	LOC284232	up	2,9	0,0	0,0009
LIN54	down	-2,5	0,2	0,0252	LOC284542	down	-2,2	1,1	0,1804
LINGO1	down	-40,6	11,1	0,0620	LOC284561	up	2,1	0,6	0,1104
LIPG	down	-2,1	1,1	0,1970	LOC285216	down	-2,6	0,7	0,0900
LITAF	up	23,3	9,9	0,0967	LOC285441	down	-2,9	0,0	0,0040
LMBRD2	down	-2,1	0,4	0,0812	LOC338620	down	-3,3	1,2	0,1089
LNPEP	down	-2,4	0,6	0,0997	LOC339240	down	-2,9	0,3	0,0353
LNX1	down	-2,0	0,2	0,0349	LOC339524	down	-4,2	1,6	0,1088
LOC100127983	down	-3,5	1,4	0,1205	LOC340888	down	-2,4	1,2	0,1752
LOC100128164	up	10,8	9,4	0,1893	LOC344887	down	-6,7	0,9	0,0359
LOC100128842	down	-2,1	0,6	0,1158	LOC346887	down	-3,1	1,2	0,1200
LOC100129104	down	-2,5	0,4	0,0570	LOC348751	up	4,5	0,0	0,0031
LOC100129291	down	-4,5	1,5	0,0940	LOC374491	down	-2,2	0,5	0,0822
LOC100129488	down	-3,4	0,3	0,0253	LOC387895	down	-3,3	1,7	0,1506
LOC100130506	down	-2,1	0,2	0,0513	LOC388242	down	-2,1	0,5	0,0958
LOC100130967	up	3,2	1,0	0,1008	LOC388630	down	-2,8	1,8	0,1990
LOC100131067	up	2,5	0,2	0,0246	LOC389634	up	4,8	0,7	0,0405
LOC100131504	up	4,4	2,5	0,1524	LOC389831	down	-2,1	0,1	0,0300
LOC100131564	down	-2,1	0,5	0,1070	LOC399815	down	-2,6	0,5	0,0642
LOC100131646	up	2,3	0,4	0,0741	LOC400027	up	2,2	0,2	0,0375
LOC100131929	down	-2,4	0,3	0,0488	LOC400987	down	-2,1	0,2	0,0387
LOC100132247	down	-2,4	0,1	0,0138	LOC439949	up	7,7	0,7	0,0243
LOC100134228	down	-2,0	0,3	0,0747	LOC440173	up	2,0	0,2	0,0402
LOC100134229	up	2,1	0,6	0,1265	LOC441208	up	3,5	0,1	0,0066
LOC100170939	down	-2,2	0,7	0,1243	LOC441601	down	-2,1	0,0	0,0074
LOC100286895	down	-2,1	0,7	0,1346	LOC441666	down	-4,5	0,8	0,0514
LOC100286909	down	-2,4	0,7	0,1100	LOC552889	up	12,1	3,4	0,0687
LOC100287412	up	2,0	0,0	0,0037	LOC642413	up	2,1	0,2	0,0313
LOC100287869	up	2,2	0,6	0,1102	LOC644662	up	3,0	0,1	0,0081
LOC100288367	down	-3,0	0,6	0,0713	LOC646509	up	2,1	0,1	0,0160
LOC100288671	down	-2,1	0,1	0,0149	LOC646936	down	-4,6	2,3	0,1333

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3	LOC646976	up	2,1	0,4	0,0717	LYPD1	up	8,2	4,4	0,1297
4	LOC650226	up	2,1	0,6	0,1160	LYSMD3	down	-2,9	0,6	0,0649
5	LOC723809	down	-17,9	0,3	0,0035	LYST	down	-3,2	0,1	0,0129
6	LOC727758	down	-2,2	0,0	0,0093	LYZ	down	-4,8	0,3	0,0182
7	LOC727916	up	2,4	0,3	0,0502	MACF1	down	-2,2	0,5	0,0981
8	LOC729683	up	2,3	0,1	0,0136	MACROD2	down	-12,1	0,4	0,0078
9	LOC729806	down	-3,9	1,9	0,1347	MAF	up	2,7	0,4	0,0536
10	LOC729817	down	-2,4	0,1	0,0226	MAFB	up	3,6	0,2	0,0207
11	LOC730098	up	3,0	0,7	0,0744	MAFF	down	-2,9	0,8	0,0987
12	LOC84740	down	-4,1	3,9	0,2298	MAG	up	2,1	0,5	0,0971
13	LOH3CR2A	down	-2,1	0,5	0,0984	MAGEA10	up	9,6	0,8	0,0204
14	LONRF1	down	-2,0	0,1	0,0110	MAGEA9	up	12,1	4,4	0,0863
15	LOXL1	up	9,5	7,7	0,1805	MAGEB2	up	17,7	2,4	0,0325
16	LOXL2	up	27,6	15,6	0,1252	MAGEC1	up	20,7	10,3	0,1130
17	LOXL4	up	5,4	1,4	0,0689	MAGEC2	up	6,1	0,6	0,0272
18	LPA	up	3,1	0,8	0,0787	MALAT1	down	-4,4	1,7	0,1125
19	LPAL2	up	3,4	0,3	0,0283	MAN1C1	up	5,6	3,0	0,1386
20	LPCAT3	up	2,7	0,3	0,0420	MANBA	down	-2,1	0,2	0,0472
21	LPGAT1	down	-2,2	0,4	0,0718	MAP3K8	down	-2,1	0,9	0,1711
22	LPP	down	-2,0	0,0	0,0057	MAP4K3	down	-2,2	0,2	0,0396
23	LRFN5	down	-4,2	0,0	0,0013	MAPK13	up	3,4	0,2	0,0175
24	LRMP	up	4,1	2,0	0,1369	MAPKAP1	up	2,1	0,1	0,0226
25	LRP11	up	2,5	0,4	0,0655	MAPT	down	-2,8	0,6	0,0681
26	LRP12	down	-3,9	0,0	0,0031	MARCO	up	8,5	7,7	0,1986
27	LRP4	up	2,3	1,3	0,1911	MARK1	up	2,6	0,5	0,0639
28	LRRC16A	up	7,0	4,4	0,1503	MARVELD1	up	12,6	0,9	0,0172
29	LRRC27	up	4,5	2,3	0,1362	MASP2	up	2,6	0,8	0,1032
30	LRRC31	up	4,5	0,6	0,0355	MAT2A	down	-2,5	0,3	0,0429
31	LRRC39	down	-3,7	1,2	0,0933	MATN2	up	2,0	0,6	0,1319
32	LRRC4	down	-2,1	0,5	0,0900	MBD2	up	2,7	0,2	0,0288
33	LRRC47	up	2,5	0,0	0,0031	MBL2	up	2,1	0,1	0,0232
34	LRRC48	up	2,3	0,1	0,0114	MBNL1	down	-2,5	0,1	0,0128
35	LRRC6	up	12,0	1,1	0,0231	MBNL2	down	-2,8	1,4	0,1644
36	LRRC1	down	-3,5	0,6	0,0560	MBOAT2	up	4,7	2,0	0,1182
37	LRRFIP1	down	-2,2	0,6	0,1083	MBP	down	-15,3	12,8	0,1799
38	LSAMP	down	-2,1	0,0	0,0057	MBTPS1	up	2,0	0,1	0,0111
39	LTB	down	-2,8	2,1	0,2203	MCC	down	-10,5	1,4	0,0330
40	LTBP1	up	137,0	2,8	0,0047	MCM3APAS	down	-2,8	0,1	0,0128
41	LUC7L3	down	-3,6	0,8	0,0652	MCTS1	down	-3,3	1,7	0,1547
42	LUM	down	-6,8	3,5	0,1296	ME3	down	-2,1	0,9	0,1747
43	LUZP4	up	8,5	1,2	0,0371	MEG3	down	-2,0	0,1	0,0126
44	LY6G5C	up	3,1	0,6	0,0641	MEIS2	down	-2,1	0,3	0,0676
45	LY6K	up	2,1	0,2	0,0313	MESP1	up	3,3	0,2	0,0211
46	LY75	down	-8,2	4,3	0,1274	MET	down	-2,4	0,4	0,0646
47	LY96	down	-6,2	0,7	0,0307	METTL7A	up	3,5	2,0	0,1626
48	LYG1	down	-2,4	0,5	0,0791	MFAP2	up	3,2	1,0	0,0994
49	LYNX1	down	-2,8	0,6	0,0713	MFG8	up	2,4	0,0	0,0002

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MFNG	up	2,4	0,9	0,1276	MTMR11	up	2,4	1,4	0,1976
MFSD8	down	-2,4	0,7	0,1013	MTMR6	down	-2,0	0,1	0,0290
MGC23270	up	2,3	0,2	0,0290	MTMR8	down	-3,8	0,5	0,0419
MGC24125	down	-2,7	0,9	0,1097	MTMR9L	down	-4,4	0,9	0,0575
MGC70870	down	-3,2	0,8	0,0808	MUC15	down	-2,1	0,1	0,0122
MIB2	up	3,3	0,2	0,0191	MUC4	down	-2,0	0,2	0,0440
MID2	down	-2,6	0,4	0,0512	MVK	up	2,3	0,2	0,0387
MIPOL1	down	-2,0	0,7	0,1391	MVP	up	3,7	0,1	0,0105
MIR17HG	down	-2,6	1,1	0,1459	MXRA8	down	-2,8	1,3	0,1485
MKKS	down	-2,0	0,2	0,0335	MYCBP2	down	-3,8	1,3	0,0971
MKLN1	down	-3,2	0,7	0,0720	MYCN	down	-95,7	112,8	0,2228
MLF1	down	-2,1	0,4	0,0867	MYH10	down	-2,0	0,3	0,0547
MLH3	down	-3,1	0,7	0,0744	MYH3	down	-2,0	0,4	0,0843
MLLT11	down	-2,8	0,6	0,0796	MYL5	up	2,6	0,6	0,0865
MLLT3	down	-2,0	0,3	0,0631	MYO10	down	-2,2	0,1	0,0151
MLXIP	up	2,8	0,5	0,0674	MYO1D	up	4,9	0,9	0,0485
MMD	down	-2,1	0,6	0,1175	MYO5A	down	-2,4	1,2	0,1683
MMP11	up	2,1	0,3	0,0511	MYO5C	down	-2,2	0,3	0,0511
MMP15	down	-2,9	1,3	0,1402	MYO6	down	-2,6	0,3	0,0415
MMP23B	down	-2,1	0,6	0,1172	MYO9A	down	-2,9	0,3	0,0350
MNS1	down	-2,2	0,7	0,1271	MYOM2	up	6,3	3,9	0,1526
MOBKL1A	down	-2,2	0,6	0,1082	MYSM1	down	-3,1	0,9	0,0943
MOBKL2B	up	3,0	1,1	0,1207	N4BP2	down	-2,7	0,5	0,0610
MOGAT2	down	-3,2	0,0	0,0018	N4BP2L2	down	-2,5	0,1	0,0181
MORC3	down	-2,4	0,4	0,0732	NAAA	down	-2,2	0,7	0,1357
MORC4	down	-2,3	0,3	0,0438	NARG1	down	-2,5	0,2	0,0241
MOSPD2	down	-2,2	0,8	0,1405	NARG1L	down	-2,2	0,7	0,1253
MOXD1	up	5,1	2,0	0,1061	NAT8	down	-2,7	1,0	0,1276
MPDZ	down	-2,2	0,4	0,0704	NAT8L	up	2,1	0,8	0,1597
MPHOSPH10	down	-2,7	0,5	0,0691	NBN	down	-2,1	0,1	0,0285
MPP1	up	3,2	1,4	0,1294	NCALD	up	3,2	1,7	0,1548
MPP7	up	6,0	1,7	0,0764	NCAPG	down	-2,2	0,5	0,0951
MPV17L	up	2,5	1,1	0,1550	NCOA7	down	-3,9	1,4	0,1052
MRC1L1	down	-3,5	0,4	0,0368	NCRNA00087	up	2,0	0,2	0,0409
MRPL30	up	2,3	0,3	0,0567	NCRNA00164	down	-2,5	1,6	0,2062
MRPL42P5	up	2,0	0,3	0,0733	NDRG1	up	4,4	0,3	0,0221
MSH2	down	-2,0	0,2	0,0416	NDRG4	up	3,5	1,1	0,0997
MSH3	down	-2,0	0,2	0,0391	NEAT1	down	-2,2	0,7	0,1263
MSRA	up	2,7	0,2	0,0227	NEBL	up	3,5	0,5	0,0408
MST1R	down	-5,3	2,7	0,1318	NECAB1	down	-5,0	3,3	0,1700
MT1B	up	2,1	0,1	0,0214	NEK1	down	-2,5	0,5	0,0761
MT1F	up	4,1	0,1	0,0048	NEK6	up	2,2	0,3	0,0560
MT1G	up	2,2	0,0	0,0031	NES	down	-4,4	0,3	0,0225
MT1H	up	2,1	0,0	0,0067	NETO2	up	3,8	0,4	0,0351
MT1X	up	2,2	0,1	0,0107	NEURL1B	up	3,0	0,1	0,0150
MTBP	down	-2,5	0,1	0,0181	NEXN	down	-2,7	0,4	0,0566
MTHFD2	down	-2,6	0,5	0,0634	NFASC	up	6,4	5,9	0,2091

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3	NFATC4	up	2,1	0,5	0,1082	ODF2L	down	-2,8	1,1	0,1309
4	NFIB	down	-2,4	0,1	0,0103	OFD1	down	-2,2	0,6	0,1121
5	NFKBIE	down	-2,3	0,8	0,1347	ONECUT1	up	2,1	0,6	0,1177
6	NHS	down	-16,3	5,4	0,0773	ONECUT2	down	-3,1	0,8	0,0811
7	NIN	down	-2,1	0,6	0,1283	OPHN1	down	-3,5	0,3	0,0251
8	NIPBL	down	-2,3	0,3	0,0495	OPN3	down	-4,1	1,6	0,1145
9	NKTR	down	-3,2	0,7	0,0688	OR2A9P	down	-2,0	0,2	0,0463
10	NKX2-1	up	2,2	0,2	0,0413	OR51B4	down	-4,0	2,8	0,1847
11	NLGN2	up	3,1	0,6	0,0632	ORM2	up	2,4	0,2	0,0333
12	NLRC5	up	2,6	0,1	0,0144	OSBPL10	down	-3,6	3,2	0,2273
13	NLRP2	up	2,1	0,1	0,0111	OSBPL3	down	-2,2	0,7	0,1287
14	NLRP5	down	-5,2	3,7	0,1783	OSBPL6	up	2,6	1,2	0,1530
15	NNMT	down	-2,4	0,7	0,1091	OSCAR	up	3,3	1,5	0,1394
16	NOC3L	down	-2,4	0,6	0,0930	OTC	down	-2,1	0,2	0,0317
17	NOL8	down	-2,1	0,7	0,1322	OTUD4	down	-2,2	0,5	0,0825
18	NOM1	down	-2,2	0,1	0,0136	OTUD7B	down	-2,9	0,3	0,0312
19	NOSTRIN	down	-3,1	0,8	0,0846	OXCT1	up	3,7	0,2	0,0167
20	NOTCH1	up	2,6	1,5	0,1912	OXT	up	7,2	1,4	0,0495
21	NPAS1	down	-2,2	0,5	0,0876	OXTR	down	-2,5	0,6	0,0940
22	NPEPPS	down	-2,0	0,2	0,0468	P2RX5	down	-2,6	1,1	0,1469
23	NPHP1	up	3,2	1,7	0,1532	P2RY2	up	2,0	0,2	0,0350
24	NPM2	down	-2,7	1,0	0,1273	PABPC1L	down	-7,3	0,5	0,0180
25	NPNT	up	16,7	11,6	0,1529	PABPC4L	down	-4,1	1,3	0,0919
26	NR0B2	down	-8,9	5,5	0,1455	PAGE4	up	3,4	1,8	0,1561
27	NR1I3	up	3,8	0,7	0,0591	PAICS	down	-2,3	0,2	0,0273
28	NR2E3	down	-3,0	0,2	0,0229	PAIP2B	up	3,7	1,4	0,1090
29	NRCAM	down	-2,0	0,5	0,1049	PAK6	up	5,7	0,2	0,0117
30	NRG4	up	4,4	1,0	0,0651	PALLD	down	-2,1	0,6	0,1203
31	NRIP1	down	-2,4	0,0	0,0053	PALMD	down	-6,1	3,8	0,1542
32	NRXN3	up	21,4	15,8	0,1597	PAM	down	-2,0	0,6	0,1282
33	NSD1	up	2,5	0,1	0,0131	PAQR8	down	-3,1	1,3	0,1285
34	NT5E	down	-2,9	1,4	0,1545	PARD3B	down	-3,8	3,5	0,2267
35	NTN5	up	4,6	2,4	0,1430	PARD6A	down	-2,3	0,3	0,0507
36	NUAK2	down	-2,9	1,7	0,1778	PARP11	up	2,5	0,7	0,0987
37	NUDT13	down	-3,4	0,0	0,0003	PARP14	down	-2,1	0,6	0,1183
38	NUDT9	down	-2,7	0,1	0,0150	PARVA	up	4,7	1,9	0,1101
39	NUFIP2	down	-2,6	0,7	0,0946	PAX3	down	-2,0	0,2	0,0451
40	NUP205	down	-2,2	0,4	0,0842	PBRM1	down	-2,0	0,5	0,1127
41	NXF2	up	6,0	2,9	0,1232	PBX3	up	2,0	0,3	0,0635
42	NXF5	up	6,0	2,8	0,1215	PBX4	down	-3,0	1,9	0,1836
43	NXN	up	2,2	0,0	0,0017	PC	up	2,0	0,1	0,0218
44	NYNRIN	up	2,3	0,7	0,1210	PCDH1	down	-3,6	0,1	0,0110
45	OASL	up	3,6	1,6	0,1353	PCDH24	up	4,5	0,9	0,0548
46	OAT	up	2,1	0,2	0,0518	PCDHA1	up	2,5	0,1	0,0092
47	OBFC1	up	2,3	0,3	0,0582	PCDHB12	up	2,8	0,2	0,0229
48	OBSCN	up	2,2	0,4	0,0801	PCDHB2	up	2,1	0,1	0,0179
49	OCA2	up	2,8	0,4	0,0518	PCDHB5	up	3,2	0,7	0,0679

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PCID2	down	-5,1	1,6	0,0865	PKIG	up	2,2	0,2	0,0425
PCK1	up	2,5	0,6	0,0827	PKN2	down	-2,1	0,9	0,1680
PCM1	down	-2,3	1,2	0,1804	PLA2G1B	up	4,5	0,1	0,0041
PCP4L1	up	2,4	0,6	0,0974	PLAC2	up	3,8	1,0	0,0768
PCSK1N	up	2,3	0,7	0,1213	PLAC8	down	-6,4	3,0	0,1200
PCSK7	up	2,0	0,3	0,0741	PLAGL1	up	3,5	0,1	0,0115
PDCD7	down	-2,1	0,0	0,0023	PLCB1	down	-2,7	0,6	0,0747
PDE4D	down	-12,5	9,4	0,1668	PLCD1	up	2,1	0,1	0,0199
PDE4DIP	down	-2,2	0,3	0,0594	PLCG2	up	25,8	11,7	0,1024
PDE5A	down	-6,1	4,3	0,1716	PLCH1	down	-3,1	0,0	0,0013
PDE6A	up	11,9	0,0	0,0008	PLD1	down	-2,9	0,0	0,0050
PDE6B	up	43,4	5,1	0,0268	PLD6	down	-2,1	0,3	0,0569
PDGFRL	up	2,1	0,6	0,1114	PLEKHA1	down	-2,1	0,3	0,0662
PDK4	up	9,6	2,2	0,0566	PLEKHA6	down	-2,1	0,6	0,1116
PDLIM3	down	-3,1	1,2	0,1213	PLEKHG1	up	4,3	3,4	0,2015
PDLIM4	up	3,3	0,4	0,0366	PLEKHG6	up	2,3	0,4	0,0741
PDS5B	down	-2,4	0,1	0,0226	PLEKHN1	down	-2,2	0,4	0,0639
PDZD3	up	3,9	0,2	0,0127	PLG	up	3,5	1,2	0,1001
PDZRN3	up	11,9	6,4	0,1254	PLGLB1	up	2,7	1,4	0,1642
PECAM1	down	-4,7	0,2	0,0141	PLIN1	up	6,2	2,1	0,0871
PFKFB2	down	-2,7	0,5	0,0676	PLK3	down	-3,4	0,4	0,0337
PFN3	up	2,6	0,3	0,0444	PLOD2	down	-2,7	0,1	0,0194
PGC	down	-4,0	1,8	0,1241	PLXND1	down	-2,9	1,6	0,1690
PGLYRP2	up	3,6	1,3	0,1046	PMFBP1	down	-2,2	0,1	0,0164
PGRMC1	up	2,9	0,0	0,0010	PML	up	2,1	0,0	0,0005
PHF11	down	-2,4	0,7	0,1120	PMS1	down	-2,5	0,4	0,0600
PHF6	down	-2,4	0,6	0,0959	PNMA2	up	2,9	0,2	0,0264
PHIP	down	-4,9	0,7	0,0389	PNMAL1	up	2,8	1,4	0,1662
PHLDA1	down	-2,6	0,8	0,1061	PNN	down	-4,1	0,6	0,0445
PHLDA2	down	-2,8	0,3	0,0341	PNPLA7	up	3,5	0,4	0,0345
PHTF2	down	-2,6	0,3	0,0383	PNPLA8	down	-2,4	1,0	0,1524
PI4K2A	up	2,0	0,1	0,0273	PODXL	down	-2,4	0,9	0,1349
PI4K2B	down	-2,1	0,6	0,1205	POF1B	down	-2,1	0,0	0,0020
PIBF1	down	-2,5	0,4	0,0551	POLK	down	-2,8	0,6	0,0799
PIGA	down	-2,3	0,2	0,0255	POLQ	down	-2,3	0,7	0,1145
PIK3C2A	down	-2,3	0,1	0,0225	POP1	down	-2,0	0,0	0,0106
PIK3CA	down	-2,1	0,1	0,0144	POU2AF1	down	-3,8	1,6	0,1258
PIK3IP1	up	2,2	0,3	0,0657	POU6F1	up	2,7	0,7	0,0880
PINK1	up	2,1	0,4	0,0892	PPARGC1A	up	7,1	7,6	0,2302
PION	down	-2,3	0,4	0,0612	PPFIBP1	down	-2,5	0,0	0,0058
PIPOX	up	2,2	0,5	0,0996	PPIG	down	-2,2	0,2	0,0358
PITPNC1	up	4,2	0,9	0,0644	PPIL6	up	3,9	1,2	0,0923
PITX2	down	-4,5	3,4	0,1929	PPM1E	up	11,4	6,9	0,1396
PIWIL4	down	-89,0	102,3	0,2191	PPM1K	down	-2,7	0,2	0,0228
PKD2	up	4,7	2,4	0,1339	PPM1L	down	-6,0	0,7	0,0313
PKHD1L1	down	-2,4	1,1	0,1609	PPP1R14A	up	7,4	2,9	0,0994
PKIB	down	-4,5	1,7	0,1029	PPP1R1A	up	2,1	0,9	0,1752

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3	PPP1R3B	down	-2,8	0,5	0,0634	QKI	up	2,0	0,0	0,0090
4	PPP1R3C	up	3,2	0,6	0,0629	QSER1	down	-2,2	0,2	0,0297
5	PPP1R3F	up	3,3	0,2	0,0195	R3HCC1	up	2,2	0,2	0,0419
6	PPP1R9A	down	-2,9	0,0	0,0022	RAB11FIP2	down	-2,1	0,8	0,1528
7	PPP2R1B	up	3,7	1,3	0,1074	RAB11FIP4	up	3,1	1,8	0,1792
8	PPP2R2B	down	-2,6	0,6	0,0787	RAB26	down	-2,0	0,3	0,0697
9	PPP2R2C	down	-3,7	0,1	0,0078	RAB27B	down	-7,7	1,6	0,0549
10	PPP4R2	down	-2,1	0,1	0,0132	RAB28	down	-2,0	0,6	0,1207
11	PPWD1	down	-2,2	0,2	0,0326	RAB31	down	-4,6	3,9	0,2078
12	PQLC3	down	-2,0	0,6	0,1245	RAB37	up	5,1	0,8	0,0428
13	PRAGMIN	down	-2,5	1,1	0,1584	RAB3B	down	-3,9	0,2	0,0157
14	PRAME	up	2,2	0,1	0,0143	RAB3D	down	-7,6	1,5	0,0517
15	PRAP1	up	3,0	0,4	0,0417	RAB7B	down	-2,4	0,1	0,0094
16	PRDM13	up	2,6	0,3	0,0421	RAB8B	down	-3,0	0,9	0,1004
17	PRDM6	up	13,2	3,1	0,0560	RABEP1	down	-2,3	1,0	0,1552
18	PRDXDD1P	down	-3,1	1,0	0,1012	RAC2	up	2,1	0,6	0,1233
19	PRELID2	down	-2,5	0,1	0,0083	RAD50	down	-2,4	0,2	0,0364
20	PREX1	down	-5,6	3,6	0,1604	RAD54B	down	-2,6	0,4	0,0555
21	PRG4	up	3,4	0,5	0,0436	RADIL	up	3,4	0,6	0,0560
22	PRKAA1	down	-2,2	0,1	0,0244	RAG1	up	3,8	1,9	0,1427
23	PRKAB1	up	2,1	0,2	0,0314	RALGPS1	up	22,6	1,5	0,0158
24	PRKAB2	down	-2,6	0,5	0,0692	RAMP1	down	-2,3	1,0	0,1588
25	PRKAG2	up	3,6	1,7	0,1383	RANBP2	down	-2,2	0,5	0,0994
26	PRKD1	up	3,9	1,8	0,1328	RAPGEF5	down	-3,0	1,6	0,1641
27	PROM1	down	-9,2	9,2	0,2139	RAPGEF6	down	-2,5	0,3	0,0479
28	PRPF39	down	-3,1	0,2	0,0200	RAPH1	up	2,2	0,1	0,0230
29	PRPF4B	down	-3,1	1,2	0,1220	RASA2	down	-3,0	0,6	0,0698
30	PRPH	up	2,2	1,0	0,1726	RASD1	down	-4,2	1,3	0,0929
31	PRPH2	down	-6,5	2,9	0,1118	RASD2	down	-4,0	1,4	0,1055
32	PRR13	up	2,1	0,0	0,0081	RASEF	up	6,2	1,0	0,0443
33	PRR15	up	18,1	0,2	0,0027	RASGEF1B	down	-3,4	0,1	0,0064
34	PRR22	up	2,1	0,0	0,0072	RASL11A	up	3,2	1,5	0,1414
35	PRR5-ARHGAP8	up	3,3	1,1	0,1040	RASL12	down	-13,0	9,9	0,1675
36	PRSS16	up	3,9	0,1	0,0076	RASSF5	up	2,9	0,1	0,0089
37	PRSS23	down	-2,7	1,9	0,2131	RASSF8	down	-2,4	0,7	0,1103
38	PRSS7	down	-10,6	2,2	0,0504	RAVER2	up	17,3	2,9	0,0403
39	PRTG	up	3,1	0,0	0,0050	RB1CC1	down	-2,1	0,7	0,1367
40	PSKH2	up	3,1	0,4	0,0442	RBBP6	down	-2,4	0,7	0,1028
41	PSMD9	up	2,4	0,4	0,0593	RBBP8	down	-2,0	0,3	0,0645
42	PTGIS	up	4,9	1,2	0,0697	RBM25	down	-2,1	0,3	0,0559
43	PTK6	up	5,0	1,6	0,0878	RBM27	down	-2,1	0,4	0,0722
44	PTK7	up	4,5	1,0	0,0637	RBM41	down	-3,1	0,1	0,0094
45	PTPN22	down	-2,7	0,1	0,0184	RBMS1	up	6,6	0,4	0,0164
46	PTPN4	down	-6,0	0,5	0,0222	RBP1	up	4,7	1,6	0,0969
47	PVRL1	up	5,7	2,8	0,1259	RBP2	up	6,7	0,2	0,0071
48	PYGO1	up	15,4	5,5	0,0835	RBP5	up	2,9	0,7	0,0759
49	PYY2	up	2,1	0,2	0,0458	RCN1	down	-2,6	1,4	0,1771

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3	SEMA3D	down	-3,9	3,8	0,2365	SLC13A3	up	10,2	0,2	0,0037
4	SEMA3G	down	-2,1	0,2	0,0419	SLC13A4	down	-14,7	0,5	0,0086
5	SEMA6A	down	-3,4	2,6	0,2066	SLC13A5	up	2,0	0,4	0,0793
6	SENP3	down	-2,1	0,4	0,0804	SLC16A10	up	3,8	0,7	0,0523
7	SENP7	down	-2,7	0,3	0,0388	SLC16A12	up	6,6	4,3	0,1590
8	SEPP1	down	-2,4	0,0	0,0001	SLC16A2	up	9,4	1,7	0,0454
9	SEPT4	up	4,2	2,9	0,1807	SLC16A3	down	-3,9	1,6	0,1180
10	SEPT5	up	2,5	0,0	0,0058	SLC17A1	up	6,2	1,8	0,0763
11	SEPT6	up	2,6	0,2	0,0326	SLC17A2	up	7,5	1,3	0,0453
12	SERINC2	up	2,0	0,0	0,0054	SLC1A2	up	32,5	29,2	0,1849
13	SERINC5	up	2,5	0,9	0,1193	SLC1A3	up	8,0	0,2	0,0068
14	SERPINA10	up	2,5	0,5	0,0749	SLC1A7	up	2,4	1,2	0,1754
15	SERPINA11	up	2,0	0,8	0,1617	SLC22A15	down	-2,1	0,2	0,0320
16	SERPINA4	up	2,7	0,0	0,0053	SLC22A4	up	2,5	1,0	0,1419
17	SERPINA5	up	2,1	0,4	0,0745	SLC22A7	up	5,0	2,7	0,1409
18	SERPINA6	up	2,0	0,3	0,0557	SLC22A9	up	2,4	0,2	0,0262
19	SERPINA7	up	3,9	2,6	0,1821	SLC23A3	up	7,6	2,4	0,0799
20	SERPINB9	up	8,6	4,4	0,1242	SLC25A12	down	-2,8	0,5	0,0633
21	SERPING1	up	3,7	1,3	0,1045	SLC25A18	up	2,7	0,4	0,0544
22	SERPINI1	up	2,0	0,8	0,1617	SLC25A36	down	-2,1	0,3	0,0534
23	SESN1	up	2,7	0,2	0,0314	SLC25A42	up	2,1	0,6	0,1087
24	SETBP1	down	-5,3	4,0	0,1861	SLC2A10	up	2,1	0,8	0,1613
25	SETD8	up	2,0	0,0	0,0002	SLC2A13	down	-2,4	0,8	0,1192
26	SETX	down	-2,1	0,6	0,1229	SLC2A2	up	2,8	0,2	0,0218
27	SF1	down	-2,3	0,1	0,0111	SLC2A3	up	2,4	0,5	0,0731
28	SFMBT2	up	6,7	1,0	0,0400	SLC30A1	up	2,4	0,5	0,0811
29	SFN	down	-2,5	0,5	0,0726	SLC30A3	up	2,3	1,3	0,1985
30	SFRP4	up	2,2	0,3	0,0522	SLC30A4	up	22,2	0,1	0,0011
31	SFRS11	down	-2,2	0,3	0,0582	SLC30A8	up	2,8	1,0	0,1221
32	SFRS12	down	-2,9	0,4	0,0498	SLC35F2	up	3,8	1,2	0,0899
33	SFRS18	down	-2,6	0,3	0,0462	SLC38A1	up	2,1	0,2	0,0437
34	SGK2	up	2,0	0,4	0,0895	SLC38A11	down	-3,5	2,1	0,1713
35	SGMS1	up	2,1	0,4	0,0802	SLC38A2	down	-2,7	0,7	0,0911
36	SGOL1	down	-2,0	0,3	0,0575	SLC38A5	down	-3,3	1,2	0,1133
37	SGOL2	down	-2,4	0,4	0,0647	SLC39A14	up	2,3	0,1	0,0138
38	SGSM1	down	-3,6	2,8	0,2071	SLC39A5	up	2,2	0,5	0,0957
39	SH3BGRL	down	-2,4	0,5	0,0703	SLC41A1	up	2,5	0,8	0,1159
40	SH3GLB1	down	-2,3	1,0	0,1622	SLC44A3	down	-2,1	0,7	0,1324
41	SH3RF1	down	-2,6	0,9	0,1173	SLC44A5	down	-3,6	0,4	0,0320
42	SH3TC1	down	-2,5	0,0	0,0009	SLC45A4	down	-4,0	0,9	0,0660
43	SHPRH	down	-2,2	0,6	0,1060	SLC4A4	down	-5,9	2,3	0,1034
44	SHROOM2	up	12,6	6,0	0,1116	SLC4A7	down	-6,3	0,3	0,0147
45	SIK2	up	2,2	0,2	0,0290	SLC5A11	down	-2,6	0,8	0,1090
46	SIX2	up	2,4	0,6	0,0996	SLC5A3	down	-2,5	0,7	0,1065
47	SKAP1	up	4,1	2,2	0,1457	SLC6A11	down	-2,5	0,1	0,0211
48	SLC10A1	up	4,2	1,5	0,0999	SLC6A13	up	2,1	0,2	0,0382
49	SLC12A2	down	-2,2	0,1	0,0208	SLC6A20	down	-3,5	0,8	0,0697

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SLC6A6	down	-3,3	1,5	0,1398	SPINK5L3	down	-3,7	0,6	0,0523
SLC7A11	down	-4,0	0,1	0,0040	SPINT1	up	2,2	1,4	0,2106
SLCO2B1	up	2,8	0,2	0,0272	SPINT2	up	2,1	0,4	0,0859
SLCO4C1	up	2,1	0,3	0,0558	SPOCK2	up	2,2	0,8	0,1369
SLFN11	down	-22,3	17,2	0,1656	SPP2	up	36,8	42,4	0,2218
SLK	down	-2,0	0,6	0,1242	SPRED1	down	-2,0	0,5	0,1102
SLPI	up	7,8	3,3	0,1036	SPRY1	down	-3,5	2,1	0,1682
SLTM	down	-2,5	0,5	0,0746	SPRY2	down	-3,1	2,0	0,1937
SMAD9	down	-2,1	1,0	0,1875	SPRY4	down	-6,9	1,9	0,0727
SMARCA1	down	-2,5	0,9	0,1239	SPTBN5	up	2,7	0,0	0,0037
SMARCAD1	down	-2,4	0,9	0,1398	SRC	up	2,4	0,0	0,0032
SMC1A	down	-3,5	0,1	0,0097	SRCRB4D	up	3,7	2,4	0,1794
SMC2	down	-2,1	0,3	0,0676	SRGN	down	-11,9	6,5	0,1263
SMC4	down	-2,5	0,5	0,0749	SRP72	down	-2,2	0,5	0,0861
SMC5	down	-2,3	0,2	0,0306	SRPX	up	9,1	3,2	0,0876
SMC6	down	-3,3	0,9	0,0821	SSB	down	-2,0	0,4	0,0873
SMCHD1	down	-2,2	0,4	0,0746	SSBP2	up	8,4	1,4	0,0418
SMG1	down	-2,3	0,5	0,0871	SSFA2	down	-2,8	0,1	0,0080
SMO	down	-2,6	0,6	0,0783	SSTR1	up	5,7	2,1	0,0959
SMS	down	-2,1	0,6	0,1159	SSTR2	down	-25,2	2,9	0,0268
SMYD1	up	3,9	0,2	0,0190	SSTR5	down	-6,3	0,1	0,0046
SNAP25	down	-2,4	1,0	0,1518	SSX1	down	-9,6	8,9	0,2006
SNHG1	down	-3,1	0,6	0,0571	SSX2IP	down	-2,6	0,4	0,0623
SNORD123	up	2,2	0,2	0,0292	SSX8	down	-6,8	3,0	0,1122
SNRK	down	-2,2	0,1	0,0166	ST6GAL1	up	2,4	0,6	0,0924
SNRPN	down	-3,0	2,3	0,2130	STAG2	down	-3,3	0,8	0,0724
SNURF	down	-2,2	0,4	0,0692	STARD6	up	3,7	2,5	0,1815
SNX13	down	-2,6	0,7	0,0969	STAT3	up	2,0	0,5	0,1080
SNX25	down	-2,2	0,5	0,0964	STEAP1	down	-2,0	0,2	0,0484
SOCS1	down	-3,1	1,4	0,1429	STEAP2	down	-2,6	0,3	0,0385
SOCS3	up	2,0	0,2	0,0361	STEAP3	up	2,2	0,4	0,0710
SOHLH2	down	-2,2	0,4	0,0684	STH	down	-2,6	0,6	0,0792
SORBS2	down	-2,1	0,8	0,1517	STK39	down	-8,4	1,3	0,0399
SORCS3	up	4,5	1,4	0,0866	STOM	up	2,7	0,3	0,0407
SORD	up	2,2	0,1	0,0143	STRN	down	-2,4	1,0	0,1450
SOX2	up	11,4	0,1	0,0012	STX11	up	2,0	0,8	0,1542
SOX4	down	-2,2	0,9	0,1540	STXBP1	up	18,9	6,2	0,0768
SOX5	down	-3,5	1,2	0,1042	STXBP4	down	-2,1	0,1	0,0150
SOX6	down	-15,4	16,9	0,2199	STXBP5	down	-2,2	0,2	0,0360
SOX9	down	-6,6	3,2	0,1208	STXBP5L	down	-2,7	0,0	0,0064
SP4	down	-2,1	0,1	0,0128	SUCLA2	down	-2,2	0,4	0,0792
SP5	up	18,2	0,2	0,0020	SUGT1L1	down	-2,6	0,1	0,0104
SPAG8	down	-2,4	0,1	0,0132	SULF2	up	209,5	121,3	0,1243
SPARC	up	8,9	1,8	0,0520	SULT2A1	up	3,6	0,1	0,0078
SPG20	down	-3,6	0,8	0,0717	SUOX	up	2,0	0,0	0,0073
SPINK4	down	-6,9	2,4	0,0886	SUZ12	down	-2,5	0,1	0,0143
SPINK5	down	-2,1	0,9	0,1651	SUZ12P	down	-2,1	0,2	0,0458

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3	SV2B	up	6,0	1,0	0,0435	TFR2	up	2,3	0,4	0,0621
4	SVOP	up	5,4	1,4	0,0718	TGFB3	down	-3,0	1,4	0,1436
5	SVOPL	up	2,3	0,4	0,0638	TGM2	up	2,2	0,4	0,0661
6	SYDE2	down	-2,6	0,2	0,0248	TH1L	up	2,1	0,2	0,0318
7	SYNC	down	-2,0	0,2	0,0525	THAP5	down	-2,3	0,3	0,0450
8	SYNM	down	-2,9	0,1	0,0153	THBS1	down	-3,9	0,8	0,0586
9	SYT1	down	-3,4	1,3	0,1172	THBS4	down	-2,1	0,8	0,1472
10	SYT13	up	13,8	6,9	0,1162	THG1L	up	2,2	0,2	0,0293
11	SYT15	up	2,2	0,0	0,0065	THOC2	down	-3,7	0,9	0,0721
12	SYT7	up	2,9	0,3	0,0401	THSD4	down	-4,2	1,6	0,1058
13	SYTL1	down	-2,6	1,3	0,1679	THUMPD2	down	-2,3	0,4	0,0752
14	SYTL3	up	3,2	0,5	0,0539	TIA1	down	-2,2	0,6	0,1112
15	SYTL5	down	-2,6	1,4	0,1759	TIMD4	down	-3,4	0,8	0,0788
16	TACC1	down	-3,0	0,0	0,0003	TLE2	up	3,9	2,4	0,1682
17	TAF15	down	-2,1	0,3	0,0690	TLE4	down	-5,1	3,6	0,1794
18	TAF1A	down	-2,2	0,5	0,0913	TLL2	up	3,9	1,3	0,0993
19	TAF2	down	-2,7	0,4	0,0459	TLR2	up	3,4	1,7	0,1498
20	TAF5L	down	-2,0	0,8	0,1601	TLR4	down	-2,2	0,9	0,1524
21	TAF7	up	2,5	0,7	0,0981	TM4SF1	down	-7,9	7,0	0,1992
22	TANC2	up	5,6	4,4	0,1887	TM4SF4	up	2,4	0,5	0,0763
23	TANK	down	-2,1	0,2	0,0413	TMBIM1	up	2,2	0,4	0,0691
24	TAS2R14	down	-2,9	0,9	0,0999	TMC6	down	-5,2	0,8	0,0414
25	TBC1D12	down	-2,9	0,8	0,0907	TMCC3	up	8,2	1,1	0,0338
26	TBC1D2	up	3,3	0,9	0,0825	TMEM108	up	4,4	1,8	0,1134
27	TBC1D4	down	-6,2	3,5	0,1409	TMEM127	up	2,1	0,2	0,0429
28	TBC1D8B	down	-3,0	0,5	0,0543	TMEM150C	up	9,5	4,6	0,1161
29	TBX18	down	-3,9	0,4	0,0350	TMEM159	up	8,8	4,9	0,1325
30	tcag7.1307	up	10,5	3,3	0,0763	TMEM19	up	2,1	0,5	0,1100
31	TCEA2	up	5,4	1,0	0,0521	TMEM2	down	-2,7	0,1	0,0180
32	TCEAL3	down	-3,5	0,6	0,0528	TMEM200A	up	2,8	0,0	0,0051
33	TCEAL5	down	-2,4	1,3	0,1852	TMEM217	up	2,6	0,4	0,0504
34	TCEAL6	down	-3,8	0,7	0,0559	TMEM220	down	-15,1	8,9	0,1341
35	TCF12	down	-2,3	0,1	0,0114	TMEM30B	down	-2,1	0,5	0,0936
36	TCF25	up	2,0	0,5	0,0997	TMEM42	down	-5,7	1,8	0,0862
37	TCIRG1	down	-2,1	1,0	0,1864	TMEM45A	up	11,1	0,2	0,0053
38	CTEX1D2	up	2,3	0,3	0,0578	TMEM45B	up	6,1	6,3	0,2291
39	TDH	up	8,2	6,2	0,1736	TMEM47	down	-19,1	18,3	0,1978
40	TDO2	down	-3,9	0,3	0,0237	TMEM55A	down	-2,9	0,1	0,0169
41	TDRD10	up	3,9	1,9	0,1378	TMEM8B	up	4,6	0,3	0,0174
42	TERF1	down	-2,2	0,1	0,0277	TMF1	down	-2,3	0,1	0,0196
43	TESC	down	-5,6	3,5	0,1590	TMOD1	up	2,5	0,3	0,0469
44	TEX11	down	-15,7	7,3	0,1082	TMPRSS2	up	5,1	0,9	0,0470
45	TEX15	down	-6,5	0,0	0,0019	TMPRSS6	up	4,8	0,3	0,0204
46	TEX19	up	3,0	1,8	0,1833	TMSB4X	down	-5,1	2,1	0,1099
47	TFCP2	down	-52,9	0,9	0,0037	TMSL3	down	-8,3	8,4	0,2163
48	TFEB	down	-4,1	0,1	0,0056	TMX3	down	-2,0	0,4	0,0925
49	TFPI	down	-14,5	3,1	0,0519	TNC	up	3,5	1,4	0,1239

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TNF	down	-8,7	7,1	0,1846	TRNP1	down	-2,0	0,0	0,0030
TNFAIP8	down	-2,3	0,4	0,0617	TRNT1	down	-2,1	0,1	0,0133
TNFRSF11A	up	3,9	0,3	0,0256	TRO	up	17,0	5,7	0,0792
TNFRSF11B	down	-15,1	0,4	0,0066	TRPM7	down	-2,4	0,1	0,0174
TNFRSF25	up	5,7	0,6	0,0290	TRPV2	down	-7,1	3,5	0,1210
TNFSF11	down	-21,5	5,4	0,0581	TSNARE1	up	2,3	0,2	0,0424
TNFSF13B	down	-4,1	1,1	0,0747	TSPAN13	down	-2,4	0,2	0,0385
TNFSF4	down	-2,2	1,1	0,1862	TSPAN3	up	2,4	0,1	0,0172
TNIK	down	-2,8	1,7	0,1827	TSPAN8	down	-2,2	0,7	0,1314
TNK1	down	-2,2	0,1	0,0157	TSPAN9	up	2,0	0,1	0,0325
TNN	up	2,7	0,2	0,0222	TSPYL1	up	2,1	0,1	0,0186
TNNC1	down	-5,7	3,4	0,1493	TSPYL4	up	2,8	0,3	0,0421
TNPO1	down	-2,7	0,8	0,1089	TTC13	down	-2,6	0,4	0,0616
TNPO2	down	-5,7	0,3	0,0128	TTC14	down	-2,1	0,4	0,0781
TNS1	up	3,9	0,1	0,0109	TTC21B	down	-2,1	0,4	0,0874
TNS3	up	2,0	0,4	0,0852	TTC22	down	-12,1	13,1	0,2210
TOX2	up	4,6	0,7	0,0426	TTC3	down	-3,2	1,0	0,0978
TP53I3	up	2,2	0,5	0,0999	TTC37	down	-2,6	0,8	0,1051
TP53INP2	up	2,9	0,2	0,0235	TTC39C	up	2,0	0,1	0,0285
TP53TG3	up	2,0	0,6	0,1240	TTC7B	up	3,5	0,4	0,0317
TP73	up	3,2	0,1	0,0105	TTC9	up	3,1	0,9	0,0931
TPBG	up	2,1	0,6	0,1209	TTLL11	up	2,3	0,3	0,0481
TPD52L1	up	11,9	8,5	0,1603	TTLL2	down	-5,6	1,1	0,0508
TPK1	down	-2,8	1,9	0,2034	TTR	down	-2,4	1,5	0,2091
TPP2	down	-2,1	0,3	0,0634	TUB	up	2,9	0,5	0,0544
TPR	down	-2,6	0,5	0,0747	TUBAL3	down	-11,8	11,7	0,2071
TPTE	down	-2,3	0,3	0,0521	TUBB2B	up	3,7	1,5	0,1197
TRAF3IP2	up	3,1	0,4	0,0456	TUBB4	up	2,0	0,1	0,0240
TRAF5	down	-3,0	0,3	0,0309	TUSC3	up	4,8	0,8	0,0490
TRANK1	up	2,3	0,4	0,0678	TWISTNB	down	-2,1	0,4	0,0756
TRAPPC2L	up	2,3	0,6	0,0966	TXLNA	up	2,0	0,0	0,0080
TRAPPC6A	up	2,6	0,2	0,0220	TXNDC11	up	2,1	0,1	0,0279
TRIB2	up	6,0	0,7	0,0304	TXNL4B	up	2,0	0,3	0,0644
TRIM13	down	-2,9	0,2	0,0189	TYMP	up	3,9	0,8	0,0598
TRIM14	up	2,3	0,1	0,0213	TYW3	down	-2,1	0,6	0,1194
TRIM2	down	-2,1	0,3	0,0491	UAP1L1	up	2,1	0,4	0,0788
TRIM31	up	2,1	0,4	0,0753	UBA6	down	-3,6	0,7	0,0610
TRIM32	up	2,2	0,1	0,0162	UBR1	down	-2,1	0,5	0,1045
TRIM34	down	-2,6	1,2	0,1540	UCHL5	down	-2,2	0,4	0,0715
TRIM35	up	2,1	0,2	0,0485	UCP2	up	2,0	0,4	0,0924
TRIM36	up	2,4	0,1	0,0133	UGGT2	down	-3,1	0,9	0,0985
TRIM5	down	-2,7	1,7	0,1887	UGT1A6	down	-4,7	3,2	0,1735
TRIM59	up	3,3	1,0	0,0997	UGT2B11	down	-3,0	0,8	0,0905
TRIM60	up	6,2	0,5	0,0226	UGT2B4	down	-3,4	0,7	0,0645
TRIM74	up	2,5	0,4	0,0584	UGT2B7	down	-3,6	2,0	0,1571
TRIM9	down	-3,8	2,2	0,1610	ULK1	up	2,5	0,8	0,1067
TRIP11	down	-2,5	0,3	0,0474	ULK2	up	17,0	4,5	0,0620

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3	UNC13C	down	-3,7	0,1	0,0058	WNK4	down	-2,5	0,2	0,0321
4	UNC5B	down	-8,3	9,6	0,2374	WNT5A	up	5,5	0,1	0,0035
5	UNC93A	up	2,9	0,5	0,0650	WRN	down	-2,2	0,1	0,0268
6	UNG	up	2,2	0,1	0,0226	WSCD1	up	2,1	0,1	0,0272
7	UPF2	down	-3,0	0,4	0,0412	WWOX	up	2,2	0,0	0,0084
8	UPF3B	down	-4,1	0,9	0,0641	XAF1	down	-2,9	2,0	0,2002
9	USHBP1	down	-4,0	2,3	0,1606	XBP1	down	-2,3	0,6	0,1046
10	USO1	down	-2,1	0,7	0,1450	XIAP	down	-2,3	0,2	0,0420
11	USP16	down	-2,4	0,7	0,0996	XIST	down	-55,6	22,7	0,0911
12	USP25	down	-2,5	0,1	0,0187	XK	up	4,9	0,2	0,0140
13	USP46	down	-2,0	0,4	0,0938	XKR6	up	7,8	2,2	0,0722
14	USP47	down	-2,3	0,3	0,0515	XPR1	down	-2,3	0,1	0,0171
15	USP48	down	-2,4	0,0	0,0052	XRCC2	down	-2,4	0,0	0,0039
16	USP53	down	-3,1	1,2	0,1203	XYLB	up	3,1	0,4	0,0411
17	USP6NL	down	-2,3	0,6	0,0975	YIF1B	up	5,2	2,2	0,1136
18	UTP14A	down	-2,0	0,0	0,0012	YPEL1	up	2,6	0,7	0,0937
19	UTP15	down	-2,0	0,3	0,0615	YPEL2	up	2,2	0,0	0,0044
20	UTP20	down	-2,2	0,7	0,1277	YTHDC2	down	-3,0	0,7	0,0764
21	UTRN	down	-2,0	0,2	0,0512	ZADH2	down	-2,0	0,4	0,0936
22	UTS2	down	-5,9	6,1	0,2308	ZBTB20	down	-2,8	0,2	0,0216
23	VAMP4	down	-2,6	0,5	0,0754	ZBTB41	down	-2,6	0,3	0,0422
24	VASH1	up	3,5	0,4	0,0313	ZC3H10	up	2,1	0,0	0,0004
25	VAV2	up	2,0	0,1	0,0227	ZC3H11A	down	-2,0	0,0	0,0043
26	VCX	up	8,4	3,1	0,0910	ZC3H12C	up	35,9	0,1	0,0006
27	VCX2	up	5,4	1,7	0,0848	ZC3H13	down	-3,9	1,0	0,0747
28	VCX3A	up	10,0	4,1	0,1007	ZC3H6	down	-3,9	0,0	0,0007
29	VCY	up	5,8	2,0	0,0902	ZCCHC3	up	2,4	0,6	0,0922
30	VDR	up	10,5	3,0	0,0696	ZDHHC2	up	5,8	0,1	0,0036
31	VPS13A	down	-5,3	0,5	0,0276	ZDHHC8P	up	2,1	0,5	0,0946
32	VPS13B	down	-2,1	0,7	0,1267	ZEB1	down	-2,9	1,3	0,1390
33	VPS13C	down	-2,6	1,0	0,1312	ZER1	up	2,7	0,3	0,0441
34	VPS54	down	-2,3	0,2	0,0410	ZFAND2A	up	2,0	0,2	0,0522
35	VSNL1	down	-2,2	0,1	0,0267	ZFC3H1	down	-2,1	0,4	0,0832
36	VTN	up	2,3	0,3	0,0435	ZFHX4	down	-2,2	0,1	0,0178
37	VWCE	up	2,1	0,2	0,0399	ZFYVE16	down	-2,1	0,0	0,0016
38	VWF	up	2,2	0,7	0,1317	ZIC5	down	-2,6	1,3	0,1683
39	WBP5	down	-2,0	0,6	0,1306	ZIM2	up	2,0	1,2	0,2154
40	WDHD1	down	-2,4	0,3	0,0495	ZMYM5	down	-2,2	0,1	0,0180
41	WDR66	up	5,0	1,5	0,0827	ZMYM6	down	-2,1	0,3	0,0667
42	WDR67	down	-2,2	0,3	0,0606	ZMYND12	up	2,2	0,1	0,0195
43	WDR72	down	-3,0	0,2	0,0208	ZNF100	down	-2,6	1,1	0,1500
44	WFIKKN1	up	2,4	0,6	0,0983	ZNF107	down	-3,6	0,4	0,0326
45	WFS1	down	-2,0	0,2	0,0434	ZNF138	down	-2,5	0,3	0,0395
46	WHSC1	down	-2,5	0,1	0,0220	ZNF146	down	-2,2	0,1	0,0138
47	WIPF1	up	2,8	0,0	0,0005	ZNF148	down	-2,2	0,3	0,0519
48	WNK2	down	-9,2	0,0	0,0000	ZNF177	up	2,4	1,0	0,1421
49	WNK3	up	10,5	1,4	0,0341	ZNF182	down	-2,1	0,3	0,0680

Supplementary Table 3. Genes being deregulated in HepG2-cells expressing solFGFR4. Data were processed as described in Experimental Procedures and are means of fold-vector control values of 2 different experiments. Fold-change cutoffs of ≥ 2 and ≤ 0.5 were used to select upregulated and downregulated genes, respectively.

Gene	reg.	Mean x Control	S.D.	p-value					
ABLIM3	up	2,24	0,39	0,070	FUT1	up	3,79	2,11	0,157
ABTB1	up	2,80	0,19	0,024	GNPDA2	down	-2,02	0,40	0,086
ACAD10	up	20,14	2,21	0,026	G0S2	up	4,76	0,80	0,048
ADC	up	5,34	2,91	0,141	GPAM	down	-2,00	0,70	0,146
ADH4	down	-2,03	0,22	0,047	HLTF	down	-2,52	0,24	0,036
AKAP9	down	-2,02	0,72	0,147	HMMR	down	-2,10	0,46	0,092
ALB	down	-2,34	0,97	0,150	HSPA6	down	-2,29	0,14	0,024
ALG10B	down	-2,07	0,32	0,066	IER3IP1	down	-2,13	0,17	0,034
ANGPTL1	down	-2,51	0,64	0,093	IFIT1	down	-2,56	0,89	0,121
ANGPT2	up	3,81	2,95	0,203	IGF2	up	2,97	1,36	0,145
ANKRD32	down	-2,33	0,12	0,020	IGFBP1	up	2,04	0,19	0,041
AQP3	up	2,37	0,84	0,130	IGFBP3	up	2,24	0,21	0,039
BRCA2	down	-2,19	0,66	0,119	INHBE	up	2,41	0,51	0,079
C12orf60	down	-2,02	0,63	0,132	IQCG	up	2,44	0,53	0,082
C6orf167	down	-2,03	0,00	0,000	ITGB3BP	down	-2,05	0,89	0,171
C13orf15	up	2,07	0,89	0,169	KLHDC7B	up	2,18	0,56	0,103
C14orf72	up	2,13	0,49	0,095	KLHL29	up	4,56	0,41	0,026
C7orf58	down	-2,20	0,56	0,101	LARP6	up	4,13	2,46	0,162
CASP8AP2	down	-2,11	0,49	0,096	LENG8	up	9,72	1,11	0,029
CCDC150	down	-2,05	0,48	0,098	LOC100129113	up	4,12	1,77	0,121
CCDC41	down	-2,06	0,35	0,073	LOC401397	down	-2,11	0,68	0,130
CENPC1	down	-2,36	0,21	0,035	LRRC47	up	2,09	0,13	0,026
CENPE	down	-2,39	1,03	0,154	MANEA	down	-2,34	0,22	0,037
CEP290	down	-2,01	0,63	0,131	MEI1	up	2,41	0,09	0,014
CHMP4B	up	2,43	1,17	0,167	NDC80	down	-2,04	0,47	0,098
COG6	down	-2,31	0,21	0,035	NUP107	down	-2,04	0,72	0,145
CUL5	down	-2,21	0,09	0,017	NXT2	down	-2,07	0,39	0,081
CYB561	up	2,03	0,21	0,046	OSCAR	up	2,25	0,06	0,011
CYTH4	up	2,08	0,00	0,000	PAEP	up	2,00	0,01	0,002
DLEU2	down	-2,09	1,11	0,199	PHIP	down	-2,00	0,64	0,136
DLGAP5	down	-2,01	0,30	0,066	PI4K2B	down	-2,04	0,08	0,018
DNAJB4	down	-2,08	0,45	0,091	PIGK	down	-2,28	0,45	0,078
EGR2	up	2,91	1,70	0,179	PLXND1	up	2,38	0,61	0,097
EIF4A2	down	-2,01	0,23	0,051	PSG2	up	4,06	2,40	0,161
FANCM	down	-2,04	0,50	0,104	RAB39B	up	10,47	1,26	0,030
FLNB	up	2,00	0,71	0,148	RAC2	up	2,08	0,14	0,029
FPGT	down	-2,09	0,66	0,129	RAD54B	down	-2,09	0,22	0,046
					RASD1	up	2,04	0,04	0,008

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4	RNF160	down	-2,40	0,17	0,028	SSTR3	up	12,74	2,33	0,044
5	ROBO3	up	3,62	0,23	0,020	TBL1XR1	down	-2,01	0,21	0,047
6	RRAD	up	2,55	0,96	0,131	TNFRSF10D	up	2,05	0,51	0,105
7	SERPINE1	up	2,01	0,03	0,007	TNPO1	down	-2,08	0,42	0,086
8	SFRS12IP1	down	-2,14	0,47	0,089	TTK	down	-2,13	0,11	0,021
9	SGOL2	down	-2,40	0,38	0,060	UNC5B	up	4,25	0,49	0,034
10	SLC25A36	down	-2,05	0,46	0,096	USP15	down	-2,29	0,43	0,074
11	SLCO4C1	down	-2,25	0,48	0,085	ZDHHC14	up	2,64	1,67	0,199
12	SNORD22	down	-2,26	0,09	0,015	ZNF267	down	-2,02	0,08	0,018
13	SPRR2C	up	3,57	1,23	0,104	ZNF292	down	-2,09	0,67	0,130
14	SPRR2D	up	6,51	4,20	0,157	ZNF418	up	2,25	0,11	0,020
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Supplementary Table 4. Genes being deregulated in HepG2-cells expressing kdFGFR4. Data were processed as described in Experimental Procedures and are means of fold-vector control values of 2 different experiments. Fold-change cutoffs of ≥ 2 and ≤ 0.5 were used to select upregulated and downregulated genes, respectively.

Gene	reg.	mean x Control	S.D.	p-value					
ACADM	down	-2.02	0.16	0.035	DLGAP5	down	-2.39	0.20	0.033
AIMP1	down	-2.02	0.36	0.078	DNA2	down	-2.51	0.37	0.054
AKAP9	down	-2.75	1.48	0.171	DNTTIP2	down	-2.38	0.35	0.056
ANKRD12	down	-3.03	1.63	0.164	DOPEY1	down	-2.17	0.64	0.117
ANKRD32	down	-2.67	0.34	0.045	EEA1	down	-2.13	0.31	0.060
ANLN	down	-2.15	0.48	0.092	EIF2A	down	-2.08	0.38	0.077
ARHGAP18	down	-2.04	0.16	0.035	EIF3E	down	-2.21	0.95	0.161
ARL6IP1	down	-2.17	0.43	0.081	EIF4A2	down	-2.52	0.12	0.018
ASNSD1	down	-2.13	0.28	0.055	ELMOD2	down	-2.14	0.14	0.027
BDP1	down	-2.51	1.17	0.159	ERBB2IP	down	-2.04	0.53	0.111
BLZF1	down	-2.18	0.20	0.039	ERGIC2	down	-2.19	0.33	0.062
BRIX1	down	-2.06	0.05	0.011	ESCO1	down	-2.26	0.02	0.004
C12orf4	down	-2.15	0.67	0.125	ESF1	down	-2.13	0.74	0.139
C12orf60	down	-2.07	0.69	0.137	EXOC6	down	-2.05	0.23	0.048
C14orf106	down	-2.36	0.85	0.132	FAM133B	down	-2.49	0.10	0.015
C1orf156	down	-2.10	0.22	0.045	FAM35A	down	-2.06	0.13	0.027
C5	down	-2.17	0.92	0.161	FASTKD1	down	-2.00	0.07	0.015
C6orf211	down	-2.10	0.26	0.052	FASTKD3	down	-2.03	0.04	0.008
CASP8AP2	down	-2.61	0.85	0.113	G2E3	down	-2.32	0.04	0.007
CCDC41	down	-2.36	0.41	0.066	GFM2	down	-2.03	0.47	0.099
CCDC77	down	-2.13	0.08	0.016	GNPDA2	down	-2.10	0.19	0.039
CCDC99	down	-2.06	0.57	0.115	GOLGA4	down	-2.53	1.09	0.149
CCNL1	down	-2.99	2.43	0.227	HLTF	down	-2.35	0.35	0.058
CCPG1	down	-2.08	0.06	0.012	HMMR	down	-2.48	0.50	0.075
CDC40	down	-2.14	0.36	0.071	HOOK1	down	-2.63	0.54	0.073
CDC7	down	-2.06	0.24	0.051	HSP90AA1	down	-2.48	0.94	0.134
CDC73	down	-2.04	0.22	0.048	IER3IP1	down	-2.10	0.10	0.021
CEBPZ	down	-2.39	0.34	0.054	IFIT1	down	-2.59	0.46	0.064
CENPC1	down	-3.29	0.55	0.054	IL6ST	down	-2.24	0.22	0.040
CENPE	down	-3.86	2.55	0.179	ITGB3BP	down	-2.12	0.84	0.155
CENPK	down	-2.36	0.62	0.100	KIAA0528	down	-2.53	0.11	0.016
CENPQ	down	-2.14	0.47	0.089	KIAA0776	down	-2.43	0.14	0.022
CFI	down	-2.16	0.02	0.003	KIAA1033	down	-2.05	0.14	0.031
CHD9	down	-2.15	0.57	0.107	KIAA1524	down	-2.18	0.22	0.041
COG6	down	-3.03	0.07	0.007	KIF15	down	-2.09	1.01	0.184
COMMD8	down	-2.03	0.37	0.079	KPNA5	down	-2.32	0.65	0.106
CUL5	down	-2.63	0.02	0.002	KRR1	down	-2.05	0.07	0.014
CUZD1	down	-2.33	0.10	0.017	KRT37	up	2.53	0.03	0.005
DCUN1D4	down	-2.13	0.53	0.102	KTN1	down	-2.20	0.55	0.099
DDX18	down	-2.13	0.59	0.112	LARP7	down	-2.52	0.21	0.031
DDX6	down	-2.05	0.97	0.184	LOC401397	down	-2.39	0.81	0.125
					LPAR6	down	-2.32	0.71	0.115
					LRRC58	down	-2.45	0.17	0.027

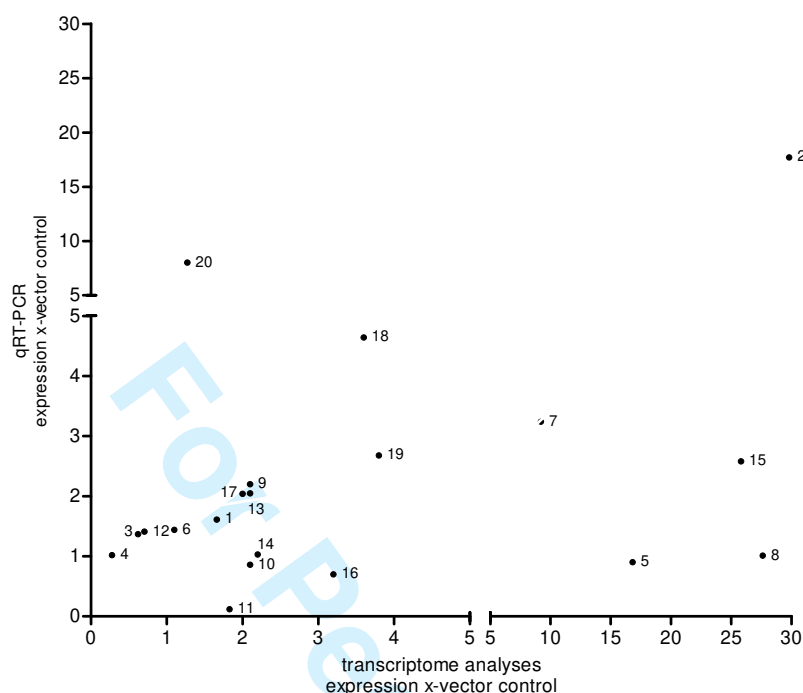
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LTV1	down	-2,06	0,17	0,036	RRAD	up	2,86	2,05	0,211
LUC7L3	down	-2,00	0,02	0,005	SAMD9	down	-3,93	0,12	0,009
MAD2L1	down	-2,19	0,24	0,044	SCOC	down	-2,08	0,73	0,142
MANEA	down	-2,68	0,05	0,006	SDCCAG1	down	-2,29	0,40	0,069
MBNL3	down	-2,25	0,71	0,122	SEPP1	down	-2,22	0,17	0,030
MORC3	down	-2,11	0,02	0,003	SEPT7	down	-2,05	0,05	0,011
MPHOSPH10	down	-2,39	0,73	0,114	SFRS12IP1	down	-3,18	0,65	0,066
MRPL50	down	-2,07	0,59	0,119	SGOL2	down	-3,56	0,71	0,062
MTERF	down	-2,42	0,10	0,016	SHOC2	down	-2,08	0,58	0,116
MTTP	down	-2,18	0,04	0,008	SLC25A36	down	-2,13	0,15	0,030
NARG2	down	-2,32	0,33	0,056	SMC2	down	-2,34	0,10	0,017
NBEAL1	down	-2,05	0,48	0,099	SMC6	down	-2,38	0,05	0,008
NCAPG	down	-2,08	0,49	0,099	SPP1	down	-2,02	0,14	0,031
NDC80	down	-2,33	0,40	0,066	SSX2IP	down	-2,22	0,34	0,062
NEK7	down	-2,45	0,15	0,023	STXBP4	down	-2,03	0,04	0,008
NOC3L	down	-2,29	0,47	0,081	TAF1B	down	-2,29	0,09	0,016
NOL11	down	-2,46	0,47	0,072	TANK	down	-2,13	0,62	0,119
NOL8	down	-2,25	0,46	0,081	TAX1BP1	down	-2,09	0,56	0,110
NOP58	down	-2,07	0,10	0,021	TBC1D23	down	-2,29	0,71	0,118
NUDCD1	down	-2,00	0,36	0,080	TBC1D8B	down	-2,21	0,13	0,024
NUF2	down	-2,14	0,53	0,100	TBK1	down	-2,50	0,03	0,005
NUP107	down	-2,24	0,70	0,122	TBL1XR1	down	-2,08	0,08	0,016
NXT2	down	-2,21	0,55	0,099	TGDS	down	-2,15	0,27	0,052
PAK1IP1	down	-2,01	0,05	0,012	THUMPD2	down	-2,01	0,14	0,030
PBK	down	-2,12	0,08	0,016	TMEM161B	down	-2,20	0,07	0,013
PGM3	down	-2,05	0,62	0,126	TMEM87A	down	-2,02	0,60	0,125
PIBF1	down	-2,81	0,68	0,083	TMTC3	down	-2,10	0,55	0,109
PIK3C3	down	-2,09	0,59	0,115	TNFAIP2	up	2,11	0,59	0,114
PION	down	-2,08	0,53	0,107	TNFRSF10D	up	2,04	0,16	0,035
PLK4	down	-2,30	0,31	0,053	TNPO1	down	-2,44	0,39	0,059
PLS1	down	-2,25	0,52	0,091	TTC37	down	-2,26	0,17	0,030
PMS1	down	-2,46	0,52	0,079	TXNDC9	down	-2,04	0,60	0,123
PPIG	down	-2,22	0,04	0,008	UBA3	down	-2,07	0,54	0,109
PPWD1	down	-2,04	0,01	0,003	UPF3B	down	-2,02	0,36	0,077
PRKRIR	down	-2,05	0,39	0,082	USP15	down	-2,58	0,80	0,110
PTAR1	down	-2,04	0,09	0,019	WDR36	down	-2,17	0,56	0,104
RAC2	up	2,14	0,66	0,123	ZC3H11A	down	-2,00	0,83	0,169
RAD51AP1	down	-2,35	0,11	0,018	ZNF146	down	-2,82	0,55	0,066
RAD54B	down	-2,29	0,07	0,012	ZNF195	down	-2,05	0,01	0,003
RARS	down	-2,06	0,87	0,168	ZNF24	down	-2,29	0,92	0,148
RASD1	up	2,32	0,88	0,140	ZNF267	down	-2,87	0,52	0,062
RB1CC1	down	-2,07	0,17	0,035	ZNF292	down	-2,58	0,85	0,116
RBM41	down	-2,72	1,18	0,143	ZNF600	down	-2,01	0,05	0,011
RECQL	down	-2,00	0,27	0,060	ZNF644	down	-2,53	0,91	0,127
RIF1	down	-2,76	0,91	0,112	ZNF823	down	-2,05	0,37	0,077
RNMT	down	-2,12	0,63	0,121	ZRANB2	down	-2,20	0,09	0,016
RPAP3	down	-2,36	0,09	0,015	ZRANB3	down	-2,21	0,56	0,100

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Supplementary Figure 6. Validation of transcriptome data by quantitative RT-PCR (qRT-PCR). Correlation of the relative expression of selected genes determined by transcriptome analysis and qRT-PCR. FGFR4-overexpressing clones and vector controls were subjected to the analysis. Each data point represents the expression level of a given gene, expressed as fold vector control, and is the mean of ≥ 2 independent determinations per method applied. Symbols: 1, ACAD10; 2, AFP; 3, CDC7; 4, CENPE; 5, DUSP26; 6, GAPDH; 7, GNB4; 8, LOXL2; 9, MAPKAP1; 10, MMP11; 11, MMP14; 12, NDC80; 13, PI4K2A; 14, PIK3IP1; 15, PLCG2; 16, PPP1R3C; 17, PRKAB1; 18, PRKAG2; 19, RPS6KA5; 20, ZNF14. Statistics by GraphPad Prism (Version 5.0): $r^2 = 0.7818$; $p < 0.01$.

Supplementary Table 5. Most significant gene sets in GSEA analysis of hepatoma/hepatocarcinoma cells showing FGFR4-overexpression or subjected to interference with FGFR-4 mediated signaling by solFGFR4 or kdFGFR4. For further details on GSEA see <http://www.broadinstitute.org/gsea/doc/GSEAUUserGuideFrame.html>. Gene sets were considered to be significantly deregulated in case of a FDR q-value of less than 0.25 and/or a p-value of less than 0.05.

TREATMENT	SOURCE ¹	GENESET ²	ES ³	NES ⁴	p-value ⁵	FDR q-value ⁶	up/dwn ⁷
METABOLISM							
FGFR4 Overexpr.	reactome	integration of energy metabolism	432	16443998	0,010	0,143	Up
Bile Acid & Phase I / II Metabolism							
FGFR4 Overexpr.	reactome	glutathione conjugation	762	20704389	0,000	0,003	Up
SolFGFR4	reactome	glutathione conjugation	-0,391	-16707102	0,000	0,004	down
kdFGFR4	reactome	glutathione conjugation	-391	-1551765	0,000	0,003	down
FGFR4 Overexpr.	reactome	xenobiotics	737	18618722	0,010	0,029	up
FGFR4 Overexpr.	reactome	phase1 functionalization of compounds	716	25428765	0,000	0,000	up
FGFR4 Overexpr.	reactome	phase ii conjugation	431	14801257	0,039	0,277	up
FGFR4 Overexpr.	kegg	drug metabolism cytochrome p450	604	20455685	0,000	0,003	up
FGFR4 Overexpr.	kegg	primary bile acid biosynthesis	756	19609323	0,000	0,009	up
FGFR4 Overexpr.	reactome	synthesis of bile acids and bile salts	729	19394598	0,000	0,012	up
Carbohydrate Metabolism							
FGFR4 Overexpr.	kegg	glycolysis gluconeogenesis	535	18168197	0,000	0,044	up
kdFGFR4	reactome	glycolysis	-340	-11867602	0,000	0,085	down
solFGFR4	reactome	regulation of glucokinase by glucokinase regulatory protein	-340	-18091897	0,000	0,002	down
kdFGFR4	reactome	regulation of glucokinase by glucokinase regulatory protein	-341	-15361433	0,000	0,004	down
kdFGFR4	kegg	pentose phosphate pathway	-246	-13278433	0,000	0,028	down
FGFR4 Overexpr.	reactome	regulation of insulin secretion	381	13782212	0,047	0,342	up
solFGFR4	signal transduction ke	g alpha s pathway	-408	-15892403	0,000	0,007	down
Lipid Metabolism							
FGFR4 Overexpr.	reactome	metabolism of lipids and lipoproteins	408	18155632	0,000	0,044	up
FGFR4 Overexpr.	kegg	ppar signaling pathway	479	16627568	0,006	0,143	up
FGFR4 Overexpr.	kegg	fatty acid metabolism	534	16547354	0,004	0,144	up
FGFR4 Overexpr.	reactome	fatty acid triacylglycerol and ketone body metabolism	374	14658921	0,014	0,276	up
kdFGFR4	reactome	activated ampk stimulates fatty acid oxidation in muscle	-445	-15405483	0,000	0,003	down
FGFR4 Overexpr.	reactome	lipoprotein metabolism	517	15096359	0,027	0,249	up
solFGFR4	reactome	cholesterol biosynthesis	-0,341	-1348732	0,000	0,045	down
kdFGFR4	reactome	cholesterol biosynthesis	-347	-19267347	0,000	0,000	down
solFGFR4	kegg	steroid biosynthesis	-409	-18535615	0,000	0,001	down
FGFR4 Overexpr.	kegg	steroid biosynthesis	758	19486688	0,000	0,010	up
kdFGFR4	kegg	steroid biosynthesis	-431	-1532288	0,000	0,004	down
FGFR4 Overexpr.	kegg	glycerophospholipid metabolism	422	1476495	0,021	0,279	up
kdFGFR4	reactome	peroxisomal lipid metabolism	-557	-29659848	0,000	0,000	down
solFGFR4	reactome	peroxisomal lipid metabolism	-359	-15086856	0,042	0,014	down

GROWTH FACTORS & SIGNALING							
FGFR4 Overexpr.	reactome	signaling by fgfr	372	13992958	0,026	0,328	up
FGFR4 Overexpr.	reactome	signaling by ngf	377	15654117	0,000	0,200	up
FGFR4 Overexpr.	kegg	neurotrophin signaling pathway	342	13113501	0,050	0,380	up
FGFR4 Overexpr.	pathway interaction db	hnf3b pathway	575	185707	0,000	0,030	up
FGFR4 Overexpr.	biocarta	wnt pathway	548	1544899	0,029	0,215	up
FGFR4 Overexpr.	signal transduction ke	wnt ca2 cyclic gmp pathway	677	18498185	0,002	0,030	up
FGFR4 Overexpr.	kegg	vegf signaling pathway	471	16928533	0,000	0,136	up
FGFR4 Overexpr.	kegg	insulin signaling pathway	421	16532453	0,004	0,143	up
FGFR4 Overexpr.	reactome	dag and ip3 signaling	542	16121129	0,006	0,166	up
FGFR4 Overexpr.	pathway interaction db	foxo pathway	455	14477632	0,038	0,283	up
FGFR4 Overexpr.	molecular signature db	neighbourhood of egfr	486	18112922	0,000	0,017	up
FGFR4 Overexpr.	kegg	erbbsignaling pathway	448	16314427	0,006	0,153	up
FGFR4 Overexpr.	pathway interaction db	erbbsignaling proximal pathway	535	16491752	0,014	0,139	up
FGFR4 Overexpr.	reactome	pi3k events in erbb2 signaling	473	1462234	0,045	0,277	up
FGFR4 Overexpr.	reactome	signaling by erbb2	457	16867846	0,002	0,134	up
FGFR4 Overexpr.	reactome	grb2 sos provides linkage to mapk signaling for integrins	619	15648876	0,032	0,198	up
FGFR4 Overexpr.	pathway interaction db	myc represspathway	416	14346324	0,041	0,290	up
FGFR4 Overexpr.	literature ^b	growth factors	291	15379304	0,000	0,051	up
FGFR4 Overexpr.	molecular signature db	neighbourhood of igfbp1	469	18355389	0,003	0,021	up
solFGFR4	pathway interaction db	smad2, 3 pathway	-445	-16881058	0,045	0,004	down
FGFR4 Overexpr.	reactome	regulation of insulin like growth factor igf activity by insulin like growth factor binding proteins igfbps	755	19594024	0,000	0,009	up
FGFR4 Overexpr.	molecular signature db	neighbourhood of igf1	615	22455778	0,000	0,000	up
FGFR4 Overexpr.	biocarta	igf1r pathway	512	14718565	0,043	0,277	up
FGFR4 Overexpr.	pathway interaction db	mtor 4pathway	499	17298361	0,004	0,110	up
kdFGFR4	biocarta	igf1 mtor pathway	-461	-16046475	0,000	0,002	down
solFGFR4	biocarta	mtor pathway	-387	-16303421	0,000	0,005	down
kdFGFR4	biocarta	mtor pathway	-562	-2946386	0,000	0,000	down
kdFGFR4	pathway interaction db	smad2, 3 pathway	-576	-21198254	0,000	0,000	down
kdFGFR4	reactome	pkb mediated events	-499	-21047058	0,000	0,000	down
solFGFR4	signal transduction ke	erk1 erk2 mapk pathway	-250	-13145965	0,000	0,058	down
kdFGFR4	signal transduction ke	erk1 erk2 mapk pathway	-389	-16336486	0,000	0,001	down
FGFR4 Overexpr.	biocarta	erk pathway	547	16009966	0,018	0,165	up
FGFR4 Overexpr.	reactome	p130cas linkage to mapk signaling for integrins	601	15549306	0,047	0,206	up
FGFR4 Overexpr.	pathway interaction db	p53 downstream pathway	364	1408855	0,016	0,314	up
DNA REPLICATION							
solFGFR4	kegg	dna replication	-355	-16250973	0,000	0,005	down
solFGFR4	reactome	scf skp2 mediated degradation of p27 p21	-328	-17479932	0,000	0,002	down
kdFGFR4	reactome	e2f mediated regulation of dna replication	-320	-12472445	0,000	0,054	down
kdFGFR4	biocarta	raccydc pathway	-248	-10537288	0,000	0,195	down
kdFGFR4	gene ontology	regulation of mitotic cell cycle	-326	-11982346	0,133	0,040	down
FGFR4 Overexpr.	reactome	deposition of new cenpa containing nucleosomes at the centromere	501	1692985	0,000	0,140	up

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FGFR4 Overexpr.	reactome	meiotic recombination	442	16039301	0,008	0,166	up
kdFGFR4	gene ontology	cytokinesis	-277	-14520413	0,000	0,009	down
CELL ADHESION							
FGFR4 Overexpr.	kegg	adherens junction	445	161398	0,004	0,166	up
FGFR4 Overexpr.	reactome	integrin alpha <i>ii</i> b beta3 signaling	536	15740358	0,033	0,192	up
FGFR4 Overexpr.	reactome	signal transduction by l1	532	1608842	0,016	0,167	up
FGFR4 Overexpr.	signal transduction ke	integrin signaling pathway	397	14292204	0,036	0,293	up
FGFR4 Overexpr.	kegg	n glycan biosynthesis	455	14559896	0,039	0,280	up
FGFR4 Overexpr.	reactome	formation of fibrin clot clotting cascade	487	14463629	0,046	0,277	up
FGFR4 Overexpr.	reactome	glycosaminoglycan metabolism	391	14483864	0,018	0,286	up
FGFR4 Overexpr.	kegg	cell adhesion molecules cams	334	16972758	0,000	0,031	up
FGFR4 Overexpr.	literature ⁹	cell adhesion	354	14507823	0,031	0,082	up
FGFR4 Overexpr.	reactome	hs gag biosynthesis	518	1536494	0,049	0,221	up
FGFR4 Overexpr.	geneontology	leukocyte cell-cell adhesion	464	16197507	0,013	0,040	up
FGFR4 Overexpr.	reactome	chondroitin sulfate dermatan sulfate metabolism	523	1618145	0,016	0,163	up
MALIGNANT PHENOTYPE							
FGFR4 Overexpr.	kegg	non small cell lung cancer	508	16354848	0,014	0,150	up
FGFR4 Overexpr.	kegg	endometrial cancer	487	15982684	0,014	0,166	up
FGFR4 Overexpr.	kegg	thyroid cancer	506	14910656	0,041	0,259	up
FGFR4 Overexpr.	pathway interaction db	upa upar pathway	527	16548454	0,006	0,147	up
solFGFR4	biocarta	ndkdynamin pathway	-326	-13396149	0,043	0,048	down
kdFGFR4	molecular signature db	breuhahn - growth factor signaling in liver cancer	-237	-0, 922641	0,750	0,195	down

- The source of the geneset.
- The name of the geneset listed in the molecular signature database or gene ontology.
- ES: **Enrichment score** for the gene set is the degree to which this gene set is overrepresented at the top or bottom of the ranked list of genes in the expression dataset.
- NES: **Normalized enrichment score** is the enrichment score for the gene set after it has been normalized across analyzed gene sets.
- p-value: the statistical significance of the enrichment score not adjusted for gene set size or multiple hypothesis testing.
- FDR q-value: the estimated probability that the normalized enrichment score represents a false positive finding.
- up/down: whether the geneset is enriched in the up-regulated or the down-regulated portion of the array
- This geneset was constructed from literature and encompasses: AGT, AMBN, AMELX, AMH, ANGPTL3, AREG, ARTN, BDNF, BMP1, BMP10, BMP15, BMP2, BMP3, BMP4, BMP5, BMP6, BMP7, BMP8A, BMP8B, BTC, CD320, CECR1, CLCF1, CLEC11A, CSF1, CSF2, CSF3, CSPG5, CTGF, CXCL1, CXCL12, DKK1, EFEMP1, EGF, EREG, ESM1, F2, FGF1, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF2, FGF20, FGF21, FGF22, FGF23, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FIGF, GDF1, GDF10, GDF11, GDF15, GDF2, GDF3, GDF5, GDF6, GDF9, GDNF, GFER, GH1, GKN1, GMFB, GMFG, GPI, GRN, HBEGF, HDGF, HDGFRP3, HGF, IGF1, IGF2, IL10, IL11, IL12A, IL12B, IL1B, IL2, IL3, IL4, IL5, IL6, IL7, IL9, INHA, INHBA, INHBB, INHBC, INHBE, JAG1, JAG2, KGFLP1, KITLG, LACRT, LEFTY1, LEFTY2, LEP, LIF, MDK, MIA, NDP, NENF, NODAL, NOV, NRG1, NRG2, NRG4, NRTN, NTF3, NUDT6, OGN, OSM, PDGFA, PDGFB, PDGFC, PDGFD, PGF, PPBP, PROK1, PSPN, PTN, RABEP1, RABEP2, REG1A, TDGF1, TFF1, TGFA, TGFB1, TGFB2, TGFB3, THPO, VEGFB, VEGFC, VGF and WISP3.
- This geneset was manually constructed from literature and consists of: CEACAM6, L1CAM, EFEMP1, NCAM1, CHL1, VCAM1, DSCAM, TCAM1, DSCAML1, ECM1, CEACAM4, CEACAM5, SDK1,

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3 OPCML, ECM2, CEACAM7, GLYCAM1, ALCAM, CEACAM8, MATN1, SPON1, MADCAM1,
4 CEACAM21, PECAM1, AMBN, NRCAM, COMP, CEACAM3, BSN, EFEMP2, MCAM, FREM1,
5 ESAM, CEACAM1, CEACAM20, CEACAM19, SPON.
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For Peer Review

Supplementary Table 6. Ingenuity Pathway Analysis of hepatoma/hepatocarcinoma cells showing FGFR4-overexpression or subjected to interference with FGFR4-mediated signaling by solFGFR4 or kdFGFR4. The functional significance of differentially expressed genes was evaluated using Ingenuity Pathway analysis software (Ingenuity Systems Version 8.8, Redwood City, CA; www.ingenuity.com). GenBank IDs of all genes with at least a two-fold change and $p < 0.05$ were imputed for network generation and pathway analyses and mapped to canonical pathways and functional networks available in the Ingenuity Pathway Knowledge Base. A score was determined for each network, reflecting the negative logarithm of the p -value based on the chance that the focus genes were grouped in the network by random chance. Abbreviations: TCP, top canonical pathway; TN, top networks.

TREATMENT	Cat.		p-value	Ratio	Score
METABOLISM					
solFGFR4	TCP	Superpathway of Methionine Degradation	4,47E-07	15/65 (0,231) ⁸⁾	
FGFR4 Overexpr.	TCP	Protein Ubiquitination Pathway	3,61E-06	99/270 (0,367)	
solFGFR4	TCP	Protein Ubiquitination Pathway	7,49E-11	67/270 (0,248)	
kdFGFR4	TCP	Protein Ubiquitination Pathway	3,67E-10	65/270 (0,241)	
solFGFR4	TN	Small Molecule Biochemistry ¹⁾			36 ⁹⁾
kdFGFR4	TN	Small Molecule Biochemistry ¹⁾			34
Bile Acid & Phase I / II Metabolism					
FGFR4 Overexpr.	TCP	LXR/RXR Activation	4,05E-08	60/123 (0,488)	
FGFR4 Overexpr.	TCP	CAR/RXR Activation	1,93E-04	17/29 (0,586)	
FGFR4 Overexpr.	TCP	PXR/RXR Activation	1,15E-05	34/67 (0,507)	
FGFR4 Overexpr.	TCP	LXR/RXR Activation	1,47E-07	58/139 (0,417)	
kdFGFR4	TN	Drug Metabolism ²⁾			34
Carbohydrate Metabolism					
solFGFR4	TN	Carbohydrate Metabolism ²⁾			36
kdFGFR4	TN	Carbohydrate Metabolism ²⁾			34
Lipid Metabolism					
solFGFR4	TCP	Superpathway of Methionine Degradation	4,47E-07	15/65 (0,231)	
FGFR4 Overexpr.	TN	Lipid Metabolism ³⁾			27
GROWTH FACTORS & SIGNALING					

solFGFR4	TCP	Role of BRCA1 in DNA Damage Response	5,82E-10	26/71 (0,366)	
kdFGFR4	TCP	Role of BRCA1 in DNA Damage Response	3,6E-07	22/71 (0,31)	
solFGFR4	TCP	Hereditary Breast Cancer Signaling	6,32E-08	35/134 (0,261)	
solFGFR4	TCP	p53 Signaling	3,34E-04	24/99 (0,242)	
kdFGFR4	TCP	p53 Signaling	3,92E-03	21/99 (0,212)	
kdFGFR4	TCP	ATM Signaling	1,6E-06	21/66 (0,318)	
solFGFR4	TCP	Hypoxia-Inducible Factor Signaling	9,56E-05	20/70 (0,286)	
FGFR4 Overexpr.	TCP	Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	9,12E-06	73/212 (0,344)	
FGFR4 Overexpr.	TN	Cell-To-Cell Signaling and Interaction ⁴⁾			27
DNA REPLICATION					
solFGFR4	TN	Cell Cycle, DNA Replication ⁵⁾			36
kdFGFR4	TN	Cell Cycle, DNA Replication ⁵⁾			34
FGFR4 Overexpr.	TN	Cell Cycle, DNA replication ⁵⁾			27
kdFGFR4	TCP	Mitotic Roles of Polo-Like Kinase	7,99E-09	26/74 (0,351)	
FGFR4 Overexpr.	TCP	Mitotic Roles of Polo-Like Kinase	3,68E-06	35/74 (0,473)	
solFGFR4	TCP	Cell Cycle: G1/S Checkpoint Regulation	7,66E-05	20/69 (0,29)	
kdFGFR4	TCP	Cell Cycle: G1/S Checkpoint Regulation	1,74E-03	17/69 (0,246)	
solFGFR4	TCP	Cell Cycle: G2/M DNA Damage Checkpoint Regulation	3,29E-06	18/48 (0,375)	
kdFGFR4	TCP	Cell Cycle: G2/M DNA Damage Checkpoint Regulation	5,48E-05	16/48 (0,333)	
kdFGFR4	TCP	Liver Necrosis/Cell Death	1,56E-03	48/271 (0,177)	
FGFR4 Overexpr.	TCP	Liver Necrosis/Cell Death	1,25E-05	102/271 (0,376)	
CELL ADHESION					

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FGFR4 Overexpr.	TN	Connective Tissue Development and Function ⁶⁾			27
solFGFR4	TCP	Remodeling of Epithelial Adherens Junctions	1,43E-08	26/70 (0,371)	
kdFGFR4	TCP	Remodeling of Epithelial Adherens Junctions	1,03E-06	23/70 (0,329)	
FGFR4 Overexpr.		Cellular Movement ⁷⁾			27
MALIGNANT PHENOTYPE					
solFGFR4	TCP	Hereditary Breast Cancer Signaling	6,32E-08	35/134 (0,261)	

- 1) Part of the TN: Carbohydrate Metabolism, Small Molecule Biochemistry, Nephrosis
- 2) Part of the TN: Carbohydrate Metabolism, Drug Metabolism, Small Molecule Biochemistry
- 3) Part of the TN: Developmental Disorder, Hereditary Disorder, Lipid Metabolism
- 4) Part of the TN: Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization, Cellular Function and Maintenance
- 5) Cell Cycle, Cellular Assembly and Organization, DNA Replication, Recombination, and Repair
- 6) Part of the TN: Organ Morphology, Skeletal and Muscular System Development and Function, Connective Tissue Development and Function
- 7) Part of the TN: Dermatological Diseases and Conditions, Cell Cycle, Cellular Movement.
- 8) indicates the ratio between deregulated genes to the total number of genes being grouped to a pathway given.
- 9) A score of 2 corresponds with a 1 in 100 chance that the focus genes are grouped together by random chance. As such, scores of 2 or higher indicate at least a 99% confidence that a true molecular relationship exists.

view

Human hepatocellular carcinoma and FGFR4-overexpressing hepatocarcinoma cells exhibit similar alterations in signaling cascades

Following ligand binding and FGFR4 dimerization, the kinase domains transphosphorylate each other. As a result, several downstream pathways may be activated: RAS–RAF–MAPK, PI3K–AKT, signal transducer and activator of transcription (STAT), and phospholipase C γ (PLCG) (Turner et al., Nat Rev Cancer 2010). FGFRs also phosphorylate ribosomal S6 kinase (Kang *et al.*, *Mol Cell Biol* 2009). Signaling can be negatively regulated at several levels, e.g., by receptor internalization or the induction of negative regulators, including sproutys or MAPK phosphatases, which may interfere through modulation of the MAPK pathway (Turner et al., Nat Rev Cancer 2010).

In FGFR4-overexpressing hepatocarcinoma cells enhanced phosphorylation of PLCG1 and ERK became evident, which indicates activation of the PLCG- and RAS-RAF-MAPK-pathways (suppl.fig.3C and 3D). Interestingly, AKT phosphorylation appeared to be somewhat reduced. Analyzing the transcriptome of these cells and the subsequent validation of the data by qRT-PCR revealed deregulations of several further genes, involved directly or indirectly in FGFR4-mediated signaling, which is outlined in the following.

In one of the clones we found elevated mRNA levels of 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2 (**PLCG2**). Like PLCG1, PLCG2 hydrolyzes phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂ or PIP₂) to form inositol 1,4,5-triphosphate and diacylglycerol. The former product promotes the intracellular mobilization of calcium, whereas the latter one activates protein kinase C isoforms. Generally, the functionality of PLCG isoenzymes is based on the products of phosphoinositide metabolism and phosphatidylinositol 4-kinase type 2-alpha (**PI4K2A**) phosphorylates PtdIns at the D-4 position, an essential step in the biosynthesis of PtdInsPs (Barylko et al., JBC 2001). This indicates that apart from the enhanced phosphorylation of PLCG1 further components of the PLCG-pathway were affected occasionally by FGFR4-overexpression.

With regard to the RAS-RAF-MAPK pathway, we found unchanged levels of the serine/threonine kinase, PDZ binding kinase (**PBK**), and enhanced expression of the target of rapamycin complex 2 subunit (**MAPKAP1**). PBK is related to the dual specific mitogen-activated protein kinase kinase (MAPKK) family. Evidence suggests that mitotic phosphorylation is required for its catalytic activity (Gaudet et al., PNAS 2000). MAPKAP1

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3 binds to both ATF-2 and p38, enhances ATF-2-dependent transcription in the MAPK-
4 pathway and inhibits RAS-mediated signaling (Makino et al., Genes Cells 2006; Schroder et
5 al., Cell Sign 2007).
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10 The activation of ribosomal S6 kinase by FGFR4 appeared to be active as well, since the
11 ribosomal protein S6 kinase polypeptide 5 (**RPS6KA5**) was found to be upregulated in two
12 of three FGFR4-overexpressing hepatocarcinoma cell clones. As members of the RSK family
13 of serine/threonine kinases it phosphorylates various substrates, including members of the
14 mitogen-activated kinase (MAPK) signaling pathway. The activity of these proteins has been
15 implicated in controlling cell growth and differentiation (Xing et al., Science 1996). In
16 response to growth factors or stress RPS6KA5 is activated by either ERK or SAPK2 proteins,
17 which in turn mediates activation of the CREB (cAMP response element-binding protein) and
18 ATF1 (Activating Transcription Factor-1). The growth-factor induced activation of RPS6KA5
19 can be blocked by inhibitors for the MAPK pathways. Dual specificity protein phosphatase 26
20 (**DUSP26**) inactivates MAPK1 and MAPK3 which leads to dephosphorylation of heat shock
21 factor protein 4 and a reduction in its DNA-binding activity. In dependence of the context,
22 DUSP26 can also induce activation of MAP kinase p38 and c-Jun N-terminal kinase (Yu et
23 al., Oncogene 2007). The level of this gene appeared to be altered by FGFR4-overexpression.
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36 Also counterregulations appear to be active. Li et al (Mol Cell Biochem 2008) show that zinc
37 finger protein 418 (**ZNF418**) is a transcriptional repressor with the KRAB motif as the basal
38 repressive domain. Overexpression of ZNF418 inhibits the transcriptional activity of SRE and
39 AP-1 and may act as a negative regulator in MAPK signaling pathway. Phosphoinositide-3-
40 kinase-interacting protein 1 (**PIK3IP1**) shares homology with the p85 regulatory PI3K
41 subunit. It directly binds to the p110 catalytic subunit and down modulates PI3K activity
42 (Zhu et al., Biochem Biophys Res Commun 2007). The upregulation in clone 4 may explain
43 the somewhat reduced phosphorylation of AKT (see suppl.fig. 3C and 3D).
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51 In samples of human hepatocellular carcinoma (HCC) we studied the expression of genes,
52 which were found to be deregulated in FGFR4-overexpressing clones. We discriminated
53 between HCC with low and high FGFR4-expression. In the latter group mRNA deregulations
54 of PLCG2, PI4K2A, MAPKAP1, DUSP26, ZNF418, and PIK3IP1 were evident. This may be
55 indirect evidence that in FGFR4-overexpressing HCC and FGFR4-overexpressing
56 hepatocarcinoma cells similar signaling cascades are activated.
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Supplementary Table 7. FGFR4-overexpressing hepatocarcinoma cells and human hepatocellular

82	f	HCC2, pT1, pNx, pMx	0,4	0,32	0,94	0,11	0,48	1,05	0,17	0,36	0,34	1,96
62	m	HCC2, pT1, pN0, pMx	0,6	0,36	0,09	11,23	0,41	0,29	3,42	0,17	2,13	0,55
56	m	HCC2, pT1, pNx, pMx	0,6	1,17	1,45	0,53	0,47	0,79	0,47	0,22	0,46	0,73
48	m	HCC2, pT2, pNx, pMx	0,7	0,6	1,01	1,56	0,78	1,56	0,27	0,09	0,52	0,4
59	m	HCC2, pT2, pN0, pMx	0,6	2,12	1,15	0,62	0,78	0,62	1,09	3,19	0,29	2,24

- a) The expression level in FGFR4-overexpressing clone, relative to that in the vector control, has been expressed as $2^{-\text{deltaCT}}$, which reflects deltaCT of the FGFR4-overexpressing clone minus deltaCT of the vector control (normalized to 1).
- b) The expression level in HCC, relative to that in the surrounding liver tissue, has been expressed as $2^{-\text{deltaCT}}$, which reflects deltaCT of the HCC minus deltaCT of the surrounding non-tumorous liver tissue (normalized to 1).