### Male Liver Top 10 Genes Ranked by Potency of Perturbation (Sorted by BMD Median)

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| --- | --- | --- | --- | --- | --- |
| **Gene Symbol** | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1std-BMDU1std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| **myc** | 24577 | MYC\_9271 | 0.186 (0.103-0.478) | 3.3 | DOWN |
| **zfp36** | 79426 | ZFP36\_10204 | 0.368 (0.097-1.817) | 2.1 | DOWN |
| **acot2** | 192272 | ACOT2\_7969 | 1.012 (0.809-1.377) | 19.9 | UP |
| **eci1** | 29740 | ECI1\_8520 | 1.013 (0.769-1.465) | 23.5 | UP |
| **loc100911558** | 100911558 | SPINK1\_32461 | 1.270 (0.542-3.173) | 2.0 | UP |
| **spink1** | 266602 | SPINK1\_32461 | 1.270 (0.542-3.173) | 2.0 | UP |
| **ehhadh** | 171142 | EHHADH\_8534 | 1.280 (1.047-1.879) | 95.2 | UP |
| **crot** | 83842 | CROT\_8384 | 1.411 (1.092-1.919) | 7.5 | UP |
| **acaa1a** | 24157 | ACAA1A\_7954 | 1.874 (1.524-2.760) | 39.0 | UP |
| **acaa1b** | 501072 | ACAA1A\_7954 | 1.874 (1.524-2.760) | 39.0 | UP |

Descriptions of orthologous human genes are shown due to the increased detail that is available in public resources such as UniprotKB (<https://www.uniprot.org/uniprot/>) and Entrez Gene (<https://www.ncbi.nlm.nih.gov/gene/>). Human UniprotKB was used as primary resource due to the greater breadth of annotation and depth of functional detail that is provided. Rat UniprotKB was used as the second resource if the primary source did not provide a detailed description of function. Human Entrez gene summary was used as third resource.  Rat Entrez gene summary was used as the fourth resource.

**Gene definition version:**https://cebs.niehs.nih.gov/cebs/study/002-00600-0002-000-0 V05282021

**Myc:** *Human Uniprot function (Human MYC):* Transcription factor that binds DNA in a non-specific manner, yet also specifically recognizes the core sequence 5'-CAC[GA]TG-3'. Activates the transcription of growth-related genes. Binds to the VEGFA promoter, promoting VEGFA production and subsequent sprouting angiogenesis (PubMed24940000). Regulator of somatic reprogramming, controls self-renewal of embryonic stem cells. Functions with TAF6L to activate target gene expression through RNA polymerase II pause release (By similarity). {ECO0000250|UniProtKBP01108, ECO0000269|PubMed24940000, ECO0000269|PubMed25956029}.

**Zfp36:** *Human Uniprot function (Human ZFP36):* Zinc-finger RNA-binding protein that destabilizes several cytoplasmic AU-rich element (ARE)-containing mRNA transcripts by promoting their poly(A) tail removal or deadenylation, and hence provide a mechanism for attenuating protein synthesis (PubMed9703499, PubMed10330172, PubMed10751406, PubMed11279239, PubMed12115244, PubMed12748283, PubMed15187101, PubMed15634918, PubMed17030620, PubMed16702957, PubMed20702587, PubMed20221403, PubMed21775632, PubMed27193233, PubMed23644599, PubMed25815583). Acts as an 3'-untranslated region (UTR) ARE mRNA-binding adapter protein to communicate signaling events to the mRNA decay machinery (PubMed15687258, PubMed23644599). Recruits deadenylase CNOT7 (and probably the CCR4-NOT complex) via association with CNOT1, and hence promotes ARE-mediated mRNA deadenylation (PubMed23644599). Functions also by recruiting components of the cytoplasmic RNA decay machinery to the bound ARE-containing mRNAs (PubMed11719186, PubMed12748283, PubMed15687258, PubMed16364915). Self regulates by destabilizing its own mRNA (PubMed15187101). Binds to 3'-UTR ARE of numerous mRNAs and of its own mRNA (PubMed10330172, PubMed10751406, PubMed12115244, PubMed15187101, PubMed15634918, PubMed17030620, PubMed16702957, PubMed19188452, PubMed20702587, PubMed20221403, PubMed21775632, PubMed25815583). Plays a role in anti-inflammatory responses; suppresses tumor necrosis factor (TNF)-alpha production by stimulating ARE-mediated TNF-alpha mRNA decay and several other inflammatory ARE-containing mRNAs in interferon (IFN)- and/or lipopolysaccharide (LPS)-induced macrophages (By similarity). Plays also a role in the regulation of dendritic cell maturation at the post-transcriptional level, and hence operates as part of a negative feedback loop to limit the inflammatory response (PubMed18367721). Promotes ARE-mediated mRNA decay of hypoxia-inducible factor HIF1A mRNA during the response of endothelial cells to hypoxia (PubMed21775632). Positively regulates early adipogenesis of preadipocytes by promoting ARE-mediated mRNA decay of immediate early genes (IEGs) (By similarity). Negatively regulates hematopoietic/erythroid cell differentiation by promoting ARE-mediated mRNA decay of the transcription factor STAT5B mRNA (PubMed20702587). Plays a role in maintaining skeletal muscle satellite cell quiescence by promoting ARE-mediated mRNA decay of the myogenic determination factor MYOD1 mRNA (By similarity). Associates also with and regulates the expression of non-ARE-containing target mRNAs at the post-transcriptional level, such as MHC class I mRNAs (PubMed18367721). Participates in association with argonaute RISC catalytic components in the ARE-mediated mRNA decay mechanism; assists microRNA (miRNA) targeting ARE-containing mRNAs (PubMed15766526). May also play a role in the regulation of cytoplasmic mRNA decapping; enhances decapping of ARE-containing RNAs, in vitro (PubMed16364915). Involved in the delivery of target ARE-mRNAs to processing bodies (PBs) (PubMed17369404). In addition to its cytosolic mRNA-decay function, affects nuclear pre-mRNA processing (By similarity). Negatively regulates nuclear poly(A)-binding protein PABPN1-stimulated polyadenylation activity on ARE-containing pre-mRNA during LPS-stimulated macrophages (By similarity). Also involved in the regulation of stress granule (SG) and P-body (PB) formation and fusion (By similarity). Plays a role in the regulation of keratinocyte proliferation, differentiation and apoptosis (PubMed27182009). Plays a role as a tumor suppressor by inhibiting cell proliferation in breast cancer cells (PubMed26926077). {ECO0000250|UniProtKBP22893, ECO0000269|PubMed10330172, ECO0000269|PubMed10751406, ECO0000269|PubMed11279239, ECO0000269|PubMed11719186, ECO0000269|PubMed12115244, ECO0000269|PubMed12748283, ECO0000269|PubMed15187101, ECO0000269|PubMed15634918, ECO0000269|PubMed15687258, ECO0000269|PubMed15766526, ECO0000269|PubMed16364915, ECO0000269|PubMed16702957, ECO0000269|PubMed17030620, ECO0000269|PubMed17369404, ECO0000269|PubMed18367721, ECO0000269|PubMed19188452, ECO0000269|PubMed20221403, ECO0000269|PubMed20702587, ECO0000269|PubMed21775632, ECO0000269|PubMed23644599, ECO0000269|PubMed25815583, ECO0000269|PubMed26926077, ECO0000269|PubMed27182009, ECO0000269|PubMed27193233, ECO0000269|PubMed9703499}.; FUNCTION (Microbial infection) Negatively regulates HTLV-1 TAX-dependent transactivation of viral long terminal repeat (LTR) promoter. {ECO0000269|PubMed14679154}.

**Acot2:** *Human Uniprot function (Human ACOT2):* Acyl-CoA thioesterases are a group of enzymes that catalyze the hydrolysis of acyl-CoAs to the free fatty acid and coenzyme A (CoASH), providing the potential to regulate intracellular levels of acyl-CoAs, free fatty acids and CoASH (PubMed16940157). Acyl-coenzyme A thioesterase 2/ACOT2 displays higher activity toward long chain acyl CoAs (C14-C20) (PubMed16940157, PubMed10944470). The enzyme is involved in enhancing the hepatic fatty acid oxidation in mitochondria (By similarity). {ECO0000250|UniProtKBQ9QYR9, ECO0000269|PubMed10944470, ECO0000269|PubMed16940157, ECO0000303|PubMed16940157}.

**Eci1:** *Human Uniprot function (Human ECI1):* Able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species. {ECO0000269|PubMed7818490}.

**LOC100911558:** *Human Uniprot function (Human SPINK1):* Serine protease inhibitor which exhibits anti-trypsin activity (PubMed7142173). In the pancreas, protects against trypsin-catalyzed premature activation of zymogens (By similarity). {ECO0000250|UniProtKBP09036, ECO0000269|PubMed7142173}.; FUNCTION In the male reproductive tract, binds to sperm heads where it modulates sperm capacitance by inhibiting calcium uptake and nitrogen oxide (NO) production. {ECO0000250|UniProtKBP09036}.

**Spink1:** *Human Uniprot function (Human SPINK1):* Serine protease inhibitor which exhibits anti-trypsin activity (PubMed7142173). In the pancreas, protects against trypsin-catalyzed premature activation of zymogens (By similarity). {ECO:0000250|UniProtKB:P09036, ECO:0000269|PubMed7142173}.; FUNCTION: In the male reproductive tract, binds to sperm heads where it modulates sperm capacitance by inhibiting calcium uptake and nitrogen oxide (NO) production. {ECO:0000250|UniProtKB:P09036}.

**Ehhadh:** *Human Uniprot function (Human EHHADH):* Peroxisomal trifunctional enzyme possessing 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and delta 3, delta 2-enoyl-CoA isomerase activities. Catalyzes two of the four reactions of the long straight chain fatty acids peroxisomal beta-oxidation pathway. Optimal isomerase for 2,5 double bonds into 3,5 form isomerization in a range of enoyl-CoA species (Probable). Also able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species (By similarity). With HSD17B4, catalyzes the hydration of trans-2-enoyl-CoA and the dehydrogenation of 3-hydroxyacyl-CoA, but with opposite chiral specificity (PubMed15060085). Regulates the amount of medium-chain dicarboxylic fatty acids which are essential regulators of all fatty acid oxidation pathways (By similarity). Also involved in the degradation of long-chain dicarboxylic acids through peroxisomal beta-oxidation (PubMed15060085). {ECO0000250|UniProtKBP07896, ECO0000250|UniProtKBQ9DBM2, ECO0000269|PubMed15060085, ECO0000305|PubMed15060085}.

**Crot:** *Human Uniprot function (Human CROT):* Beta-oxidation of fatty acids. The highest activity concerns the C6 to C10 chain length substrate. Converts the end product of pristanic acid beta oxidation, 4,8-dimethylnonanoyl-CoA, to its corresponding carnitine ester. {ECO0000269|PubMed10486279}.

**Acaa1a:** *Human Entrez Gene Summary (Human ACAA1):* This gene encodes an enzyme operative in the beta-oxidation system of the peroxisomes. Deficiency of this enzyme leads to pseudo-Zellweger syndrome. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2008]

**Acaa1b:** *Human Entrez Gene Summary (Human ACAA1):* This gene encodes an enzyme operative in the beta-oxidation system of the peroxisomes. Deficiency of this enzyme leads to pseudo-Zellweger syndrome. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2008]

### Female Liver Top 10 Genes Ranked by Potency of Perturbation (Sorted by BMD Median)

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| --- | --- | --- | --- | --- | --- |
| **Gene Symbol** | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1std-BMDU1std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| **gdf15** | 29455 | GDF15\_33113 | 17.724 (8.696-37.098) | 5.8 | UP |
| **igfbp1** | 25685 | IGFBP1\_32306 | 18.792 (7.230-51.558) | 4.3 | UP |
| **eci1** | 29740 | ECI1\_8520 | 32.546 (27.162-40.287) | 9.6 | UP |
| **etfdh** | 295143 | ETFDH\_8575 | 34.846 (26.297-48.311) | 2.0 | UP |
| **cyp2b1** | 24300 | CYP2B1\_32451 | 35.483 (29.479-44.233) | 196.8 | UP |
| **loc108348266** | 108348266 | CYP2B1\_32451 | 35.483 (29.479-44.233) | 196.8 | UP |
| **dhrs7** | 299135 | DHRS7\_8469 | 35.986 (10.630-156.958) | 4.4 | UP |
| **dhrs7l1** | 299131 | DHRS7\_8469 | 35.986 (10.630-156.958) | 4.4 | UP |
| **slc27a2** | 65192 | SLC27A2\_9860 | 36.103 (26.571-51.373) | 2.3 | UP |
| **vnn1** | 29142 | VNN1\_10157 | 37.026 (30.688-46.324) | 15.8 | UP |

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**Gene definition version:**https://cebs.niehs.nih.gov/cebs/study/002-00600-0002-000-0 V05282021

**Gdf15:** *Human Uniprot function (Human GDF15):* Regulates food intake, energy expenditure and body weight in response to metabolic and toxin-induced stresses (PubMed28953886, PubMed28846097, PubMed28846098, PubMed28846099, PubMed23468844, PubMed29046435). Binds to its receptor, GFRAL, and activates GFRAL-expressing neurons localized in the area postrema and nucleus tractus solitarius of the brainstem (PubMed28953886, PubMed28846097, PubMed28846098, PubMed28846099). It then triggers the activation of neurons localized within the parabrachial nucleus and central amygdala, which contitutes part of the 'emergency circuit' that shapes feeding responses to stressful conditions (PubMed28953886). On hepatocytes, inhibits growth hormone signaling (By similarity). {ECO0000250|UniProtKBQ9Z0J7, ECO0000269|PubMed23468844, ECO0000269|PubMed28846097, ECO0000269|PubMed28846098, ECO0000269|PubMed28846099, ECO0000269|PubMed28953886, ECO0000269|PubMed29046435}.

**Igfbp1:** *Human Uniprot function (Human IGFBP1):* IGF-binding proteins prolong the half-life of the IGFs and have been shown to either inhibit or stimulate the growth promoting effects of the IGFs on cell culture. They alter the interaction of IGFs with their cell surface receptors. Promotes cell migration. {ECO0000269|PubMed15972819}.

**Eci1:** *Human Uniprot function (Human ECI1):* Able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species. {ECO0000269|PubMed7818490}.

**Etfdh:** *Human Uniprot function (Human ETFDH):* Accepts electrons from ETF and reduces ubiquinone.

**Cyp2b1:** *Human Uniprot function (Human CYP2B6):* A cytochrome P450 monooxygenase involved in the metabolism of endocannabinoids and steroids (PubMed21289075, PubMed12865317). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the epoxidation of double bonds of arachidonoylethanolamide (anandamide) to 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid ethanolamides (EpETrE-EAs), potentially modulating endocannabinoid system signaling (PubMed21289075). Hydroxylates steroid hormones, including testosterone at C-16 and estrogens at C-2 (PubMed21289075, PubMed12865317). Plays a role in the oxidative metabolism of xenobiotics, including plant lipids and drugs (PubMed11695850, PubMed22909231). Acts as a 1,4-cineole 2-exo-monooxygenase (PubMed11695850). {ECO0000269|PubMed11695850, ECO0000269|PubMed12865317, ECO0000269|PubMed21289075, ECO0000269|PubMed22909231}.; FUNCTION Allele 2B6\*9 Has low affinity for anandamide and can only produce 11,12 EpETrE-EAs. {ECO0000269|PubMed21289075}.

**LOC108348266:** *Human Uniprot function (Human CYP2B6):* A cytochrome P450 monooxygenase involved in the metabolism of endocannabinoids and steroids (PubMed21289075, PubMed12865317). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the epoxidation of double bonds of arachidonoylethanolamide (anandamide) to 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid ethanolamides (EpETrE-EAs), potentially modulating endocannabinoid system signaling (PubMed21289075). Hydroxylates steroid hormones, including testosterone at C-16 and estrogens at C-2 (PubMed21289075, PubMed12865317). Plays a role in the oxidative metabolism of xenobiotics, including plant lipids and drugs (PubMed11695850, PubMed22909231). Acts as a 1,4-cineole 2-exo-monooxygenase (PubMed11695850). CP2B6\_HUMAN,P20813

**Dhrs7:** *Human Entrez Gene Summary (Human DHRS7):* This gene encodes a member of the short-chain dehydrogenases/reductases (SDR) family, which has over 46,000 members. Members in this family are enzymes that metabolize many different compounds, such as steroid hormones, prostaglandins, retinoids, lipids and xenobiotics. [provided by RefSeq, Apr 2016]

**Dhrs7l1:** *Human Entrez Gene Summary (Human DHRS7):* This gene encodes a member of the short-chain dehydrogenases/reductases (SDR) family, which has over 46,000 members. Members in this family are enzymes that metabolize many different compounds, such as steroid hormones, prostaglandins, retinoids, lipids and xenobiotics. [provided by RefSeq, Apr 2016]

**Slc27a2:** *Human Uniprot function (Human SLC27A2):* Acyl CoA synthetase that activates long-chain and very long-chain fatty acids (VLCFAs) by catalyzing the formation of fatty acyl-CoA (PubMed10198260, PubMed10749848, PubMed11980911). Can also activate branched-chain fatty acids such as phytanic acid and pristanic acid (PubMed10198260). Does not activate C24 bile acids, cholate and chenodeoxycholate (PubMed11980911). In vitro, activates 3-alpha,7-alpha,12-alpha-trihydroxy-5-beta-cholestanate (THCA), the C27 precursor of cholic acid deriving from the de novo synthesis from cholesterol (PubMed11980911). Exhibits long-chain fatty acids (LCFA) transport activity and plays an important role in hepatic fatty acid uptake (PubMed20530735). {ECO0000269|PubMed10198260, ECO0000269|PubMed10749848, ECO0000269|PubMed11980911, ECO0000269|PubMed20530735}.; FUNCTION [Isoform 1] Exhibits both long-chain fatty acids (LCFA) transport activity and acyl CoA synthetase towards very long-chain fatty acids (PubMed21768100). Shows a preference for generating CoA derivatives of n-3 fatty acids, which are preferentially trafficked into phosphatidylinositol (PubMed21768100). {ECO0000269|PubMed21768100}.; FUNCTION [Isoform 2] Exhibits long-chain fatty acids (LCFA) transport activity but lacks acyl CoA synthetase towards very long-chain fatty acids. {ECO0000269|PubMed21768100}.

**Vnn1:** *Human Uniprot function (Human VNN1):* Amidohydrolase that hydrolyzes specifically one of the carboamide linkages in D-pantetheine thus recycling pantothenic acid (vitamin B5) and releasing cysteamine. {ECO0000269|PubMed10567687, ECO0000269|PubMed11491533, ECO0000269|PubMed25478849}.