### 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 |
| **zfp354a** | 24522 | ZFP354A\_10203 | 3.267 (1.720-6.668) | 6.5 | DOWN |
| **g0s2** | 289388 | G0S2\_32729 | 3.451 (1.074-14.322) | 2.1 | UP |
| **tsku** | 308843 | TSKU\_10094 | 6.126 (1.466-41.334) | 2.4 | DOWN |
| **egr1** | 24330 | EGR1\_8533 | 8.263 (1.517-45.905) | 5.3 | DOWN |
| **c7** | 117517 | C7\_8179 | 13.843 (5.329-41.896) | 2.5 | DOWN |
| **trib3** | 246273 | TRIB3\_10079 | 16.895 (6.465-58.991) | 2.3 | UP |
| **akr7a3** | 26760 | AKR7A3\_8015 | 19.850 (12.797-32.354) | 4.1 | UP |
| **nqo1** | 24314 | NQO1\_33055 | 24.112 (16.415-37.043) | 4.8 | UP |
| **ephx1** | 25315 | EPHX1\_8567 | 24.878 (15.487-41.380) | 2.6 | UP |
| **loc100911558** | 100911558 | SPINK1\_32461 | 26.630 (12.428-61.587) | 2.0 | DOWN |

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

**Zfp354a:** *Rat Uniprot Function (Human ZNF354A):* It may play a role in renal development and may also be involved in the repair of the kidney after ischemia-reperfusion or folic acid administration.

**G0s2:** *Human Uniprot function (Human G0S2):* Promotes apoptosis by binding to BCL2, hence preventing the formation of protective BCL2-BAX heterodimers. {ECO0000269|PubMed19706769}.

**Tsku:** *Human Uniprot function (Human TSKU):* Contributes to various developmental events and other processes such as wound healing and cholesterol homeostasis through its interactions with multiple signaling pathways. Wnt signaling inhibitor which competes with WNT2B for binding to Wnt receptor FZD4 and represses WNT2B-dependent development of the peripheral eye. Plays a role in regulating the hair cycle by controlling TGFB1 signaling. Required for the development of the anterior commissure in the brain by inhibiting neurite outgrowth. Essential for terminal differentiation of hippocampal neural stem cells. Plays a role in regulating bone elongation and bone mass by modulating growth plate chondrocyte function and overall body size. Required for development of the inner ear through its involvement in stereocilia formation in inner hair cells. Facilitates wound healing by inhibiting secretion of TGFB1 from macrophages which prevents myofibroblast differentiation, maintaining inflammatory cell quiescence. Plays a role in cholesterol homeostasis by reducing circulating high-density lipoprotein cholesterol, lowering cholesterol efflux capacity and decreasing cholesterol-to-bile acid conversion in the liver. In one study, shown to negatively regulate sympathetic innervation in brown fat, leading to reduced energy expenditure. In another study, shown not to affect brown fat thermogenic capacity, body weight gain or glucose homeostasis.

**Egr1:** *Human Uniprot function (Human EGR1):* Transcriptional regulator (PubMed20121949). Recognizes and binds to the DNA sequence 5'-GCG(T/G)GGGCG-3'(EGR-site) in the promoter region of target genes (By similarity). Binds double-stranded target DNA, irrespective of the cytosine methylation status (PubMed25258363, PubMed25999311). Regulates the transcription of numerous target genes, and thereby plays an important role in regulating the response to growth factors, DNA damage, and ischemia. Plays a role in the regulation of cell survival, proliferation and cell death. Activates expression of p53/TP53 and TGFB1, and thereby helps prevent tumor formation. Required for normal progress through mitosis and normal proliferation of hepatocytes after partial hepatectomy. Mediates responses to ischemia and hypoxia; regulates the expression of proteins such as IL1B and CXCL2 that are involved in inflammatory processes and development of tissue damage after ischemia. Regulates biosynthesis of luteinizing hormone (LHB) in the pituitary (By similarity). Regulates the amplitude of the expression rhythms of clock genes ARNTL/BMAL1, PER2 and NR1D1 in the liver via the activation of PER1 (clock repressor) transcription. Regulates the rhythmic expression of core-clock gene ARNTL/BMAL1 in the suprachiasmatic nucleus (SCN) (By similarity). {ECO0000250|UniProtKBP08046, ECO0000269|PubMed20121949, ECO0000269|PubMed25258363, ECO0000269|PubMed25999311}.

**C7:** *Human Uniprot function (Human C7):* Constituent of the membrane attack complex (MAC) that plays a key role in the innate and adaptive immune response by forming pores in the plasma membrane of target cells. C7 serves as a membrane anchor.

**Trib3:** *Human Uniprot function (Human TRIB3):* Inactive protein kinase which acts as a regulator of the integrated stress response (ISR), a process for adaptation to various stress (PubMed15781252, PubMed15775988). Inhibits the transcriptional activity of DDIT3/CHOP and is involved in DDIT3/CHOP-dependent cell death during ER stress (PubMed15781252, PubMed15775988). May play a role in programmed neuronal cell death but does not appear to affect non-neuronal cells (PubMed15781252, PubMed15775988). Acts as a negative feedback regulator of the ATF4-dependent transcription during the ISR while TRIB3 expression is promoted by ATF4, TRIB3 protein interacts with ATF4 and inhibits ATF4 transcription activity (By similarity). Disrupts insulin signaling by binding directly to Akt kinases and blocking their activation (By similarity). May bind directly to and mask the 'Thr-308' phosphorylation site in AKT1 (By similarity). Interacts with the NF-kappa-B transactivator p65 RELA and inhibits its phosphorylation and thus its transcriptional activation activity (PubMed12736262). Interacts with MAPK kinases and regulates activation of MAP kinases (PubMed15299019). Can inhibit APOBEC3A editing of nuclear DNA (PubMed22977230). {ECO0000250|UniProtKBQ8K4K2, ECO0000269|PubMed12736262, ECO0000269|PubMed15299019, ECO0000269|PubMed15775988, ECO0000269|PubMed15781252, ECO0000269|PubMed22977230}.

**Akr7a3:** *Human Uniprot function (Human AKR7A3):* Can reduce the dialdehyde protein-binding form of aflatoxin B1 (AFB1) to the non-binding AFB1 dialcohol. May be involved in protection of liver against the toxic and carcinogenic effects of AFB1, a potent hepatocarcinogen. {ECO0000269|PubMed18416522}.

**Nqo1:** *Human Uniprot function (Human NQO1):* The enzyme apparently serves as a quinone reductase in connection with conjugation reactions of hydroquinons involved in detoxification pathways as well as in biosynthetic processes such as the vitamin K-dependent gamma-carboxylation of glutamate residues in prothrombin synthesis.

**Ephx1:** *Human Uniprot function (Human EPHX1):* Biotransformation enzyme that catalyzes the hydrolysis of arene and aliphatic epoxides to less reactive and more water soluble dihydrodiols by the trans addition of water (By similarity). Plays a role in the metabolism of endogenous lipids such as epoxide-containing fatty acids (PubMed22798687). Metabolizes the abundant endocannabinoid 2-arachidonoylglycerol (2-AG) to free arachidonic acid (AA) and glycerol (PubMed24958911). {ECO0000250|UniProtKBP07687, ECO0000269|PubMed22798687, ECO0000269|PubMed24958911}.

**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}.

### 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 |
| **kif22** | 293502 | KIF22\_8963 | 0.962 (0.282-4.473) | 2.1 | UP |
| **anln** | 363031 | ANLN\_32599 | 3.325 (1.105-12.281) | 2.1 | UP |
| **anlnl1** | 307056 | ANLN\_32599 | 3.325 (1.105-12.281) | 2.1 | UP |
| **car3** | 54232 | CAR3\_8196 | 3.449 (2.131-6.021) | 6.8 | DOWN |
| **aass** | 296925 | AASS\_7936 | 5.811 (2.605-14.079) | 2.3 | DOWN |
| **asns** | 25612 | ASNS\_8091 | 6.056 (2.744-14.335) | 3.5 | UP |
| **a2m** | 24153 | A2M\_7932 | 8.459 (1.870-42.023) | 2.8 | DOWN |
| **loc100911545** | 100911545 | A2M\_7932 | 8.459 (1.870-42.023) | 2.8 | DOWN |
| **nr1d2** | 259241 | NR1D2\_9358 | 9.460 (2.213-49.422) | 2.2 | UP |
| **sez6** | 192247 | SEZ6\_9819 | 10.639 (3.960-29.500) | 3.7 | DOWN |

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**Kif22:** *Human Uniprot function (Human KIF22):* Kinesin family member that is involved in spindle formation and the movements of chromosomes during mitosis and meiosis. Binds to microtubules and to DNA (By similarity). Plays a role in congression of laterally attached chromosomes in NDC80-depleted cells (PubMed25743205). {ECO0000250|UniProtKBQ9I869, ECO0000269|PubMed25743205}.

**Anln:** *Human Uniprot function (Human ANLN):* Required for cytokinesis (PubMed16040610). Essential for the structural integrity of the cleavage furrow and for completion of cleavage furrow ingression. Plays a role in bleb assembly during metaphase and anaphase of mitosis (PubMed23870127). May play a significant role in podocyte cell migration (PubMed24676636). {ECO0000269|PubMed10931866, ECO0000269|PubMed12479805, ECO0000269|PubMed15496454, ECO0000269|PubMed16040610, ECO0000269|PubMed16357138, ECO0000269|PubMed23870127, ECO0000269|PubMed24676636}.

**Anlnl1:** *Human Uniprot function (Human ANLN):* Required for cytokinesis (PubMed16040610). Essential for the structural integrity of the cleavage furrow and for completion of cleavage furrow ingression. Plays a role in bleb assembly during metaphase and anaphase of mitosis (PubMed23870127). May play a significant role in podocyte cell migration (PubMed24676636). {ECO0000269|PubMed10931866, ECO0000269|PubMed12479805, ECO0000269|PubMed15496454, ECO0000269|PubMed16040610, ECO0000269|PubMed16357138, ECO0000269|PubMed23870127, ECO0000269|PubMed24676636}.

**car3:** *Human Uniprot function (Human CA3):* Reversible hydration of carbon dioxide.

**Aass:** *Human Uniprot function (Human AASS):* Bifunctional enzyme that catalyzes the first two steps in lysine degradation. The N-terminal and the C-terminal contain lysine-ketoglutarate reductase and saccharopine dehydrogenase activity, respectively.

**Asns:** *Human Entrez Gene Summary (Human ASNS):* The protein encoded by this gene is involved in the synthesis of asparagine. This gene complements a mutation in the temperature-sensitive hamster mutant ts11, which blocks progression through the G1 phase of the cell cycle at nonpermissive temperature. Alternatively spliced transcript variants have been described for this gene. [provided by RefSeq, May 2010]

**A2m:** *Human Uniprot function (Human A2M):* Is able to inhibit all four classes of proteinases by a unique 'trapping' mechanism. This protein has a peptide stretch, called the 'bait region' which contains specific cleavage sites for different proteinases. When a proteinase cleaves the bait region, a conformational change is induced in the protein which traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity against high molecular weight substrates is greatly reduced). Following cleavage in the bait region, a thioester bond is hydrolyzed and mediates the covalent binding of the protein to the proteinase.

**LOC100911545:** *Human Uniprot function (Human A2M):* Is able to inhibit all four classes of proteinases by a unique 'trapping' mechanism. This protein has a peptide stretch, called the 'bait region' which contains specific cleavage sites for different proteinases. When a proteinase cleaves the bait region, a conformational change is induced in the protein which traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity against high molecular weight substrates is greatly reduced). Following cleavage in the bait region, a thioester bond is hydrolyzed and mediates the covalent binding of the protein to the proteinase. A2MG\_HUMAN,P01023

**Nr1d2:** *Human Uniprot function (Human NR1D2):* Transcriptional repressor which coordinates circadian rhythm and metabolic pathways in a heme-dependent manner. Integral component of the complex transcription machinery that governs circadian rhythmicity and forms a critical negative limb of the circadian clock by directly repressing the expression of core clock components ARNTL/BMAL1 and CLOCK. Also regulates genes involved in metabolic functions, including lipid metabolism and the inflammatory response. Acts as a receptor for heme which stimulates its interaction with the NCOR1/HDAC3 corepressor complex, enhancing transcriptional repression. Recognizes two classes of DNA response elements within the promoter of its target genes and can bind to DNA as either monomers or homodimers, depending on the nature of the response element. Binds as a monomer to a response element composed of the consensus half-site motif 5'-[A/G]GGTCA-3' preceded by an A/T-rich 5' sequence (RevRE), or as a homodimer to a direct repeat of the core motif spaced by two nuclegotides (RevDR-2). Acts as a potent competitive repressor of ROR alpha (RORA) function and also negatively regulates the expression of NR1D1. Regulates lipid and energy homeostasis in the skeletal muscle via repression of genes involved in lipid metabolism and myogenesis including CD36, FABP3, FABP4, UCP3, SCD1 and MSTN. Regulates hepatic lipid metabolism via the repression of APOC3. Represses gene expression at a distance in macrophages by inhibiting the transcription of enhancer-derived RNAs (eRNAs). In addition to its activity as a repressor, can also act as a transcriptional activator. Acts as a transcriptional activator of the sterol regulatory element-binding protein 1 (SREBF1) and the inflammatory mediator interleukin-6 (IL6) in the skeletal muscle (By similarity). Plays a role in the regulation of circadian sleep/wake cycle; essential for maintaining wakefulness during the dark phase or active period (By similarity). Key regulator of skeletal muscle mitochondrial function; negatively regulates the skeletal muscle expression of core clock genes and genes involved in mitochondrial biogenesis, fatty acid beta-oxidation and lipid metabolism (By similarity). May play a role in the circadian control of neutrophilic inflammation in the lung (By similarity). {ECO0000250|UniProtKBQ60674, ECO0000269|PubMed17892483, ECO0000269|PubMed17996965}.

**Sez6:** *Human Uniprot function (Human SEZ6):* May play a role in cell-cell recognition and in neuronal membrane signaling. Seems to be important for the achievement of the necessary balance between dendrite elongation and branching during the elaboration of a complex dendritic arbor. Involved in the development of appropriate excitatory synaptic connectivity (By similarity). {ECO0000250}.