### 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 |
| **pck1** | 362282 | PCK1\_9439 | 1.149 (0.548-2.562) | 2.7 | DOWN |
| **a2m** | 24153 | A2M\_7932 | 1.733 (0.972-3.497) | 3.0 | DOWN |
| **loc100911545** | 100911545 | A2M\_7932 | 1.733 (0.972-3.497) | 3.0 | DOWN |
| **zfp354a** | 24522 | ZFP354A\_10203 | 1.785 (0.579-5.737) | 3.6 | DOWN |
| **akr7a3** | 26760 | AKR7A3\_8015 | 2.192 (1.593-3.715) | 9.5 | UP |
| **ephx1** | 25315 | EPHX1\_8567 | 2.467 (1.828-4.041) | 5.6 | UP |
| **me1** | 24552 | ME1\_9215 | 3.531 (2.076-6.794) | 3.4 | UP |
| **cyp4a1** | 50549 | CYP4A1\_33111 | 4.588 (2.345-9.587) | 2.6 | UP |
| **anxa7** | 155423 | ANXA7\_8051 | 4.660 (2.970-7.797) | 3.8 | UP |
| **slc17a3** | 266730 | SLC17A3\_9840 | 5.147 (3.485-8.103) | 3.1 | 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

**Pck1:** *Human Uniprot function (Human PCK1):* Cytosolic phosphoenolpyruvate carboxykinase that catalyzes the reversible decarboxylation and phosphorylation of oxaloacetate (OAA) and acts as the rate-limiting enzyme in gluconeogenesis (PubMed30193097, PubMed24863970, PubMed26971250, PubMed28216384). Regulates cataplerosis and anaplerosis, the processes that control the levels of metabolic intermediates in the citric acid cycle (PubMed30193097, PubMed24863970, PubMed26971250, PubMed28216384). At low glucose levels, it catalyzes the cataplerotic conversion of oxaloacetate to phosphoenolpyruvate (PEP), the rate-limiting step in the metabolic pathway that produces glucose from lactate and other precursors derived from the citric acid cycle (PubMed30193097). At high glucose levels, it catalyzes the anaplerotic conversion of phosphoenolpyruvate to oxaloacetate (PubMed30193097). Acts as a regulator of formation and maintenance of memory CD8(+) T-cells up-regulated in these cells, where it generates phosphoenolpyruvate, via gluconeogenesis (By similarity). The resultant phosphoenolpyruvate flows to glycogen and pentose phosphate pathway, which is essential for memory CD8(+) T-cells homeostasis (By similarity). In addition to the phosphoenolpyruvate carboxykinase activity, also acts as a protein kinase when phosphorylated at Ser-90 phosphorylation at Ser-90 by AKT1 reduces the binding affinity to oxaloacetate and promotes an atypical serine protein kinase activity using GTP as donor (PubMed32322062). The protein kinase activity regulates lipogenesis upon phosphorylation at Ser-90, translocates to the endoplasmic reticulum and catalyzes phosphorylation of INSIG proteins (INSIG1 and INSIG2), thereby disrupting the interaction between INSIG proteins and SCAP and promoting nuclear translocation of SREBP proteins (SREBF1/SREBP1 or SREBF2/SREBP2) and subsequent transcription of downstream lipogenesis-related genes (PubMed32322062). {ECO0000250|UniProtKBQ9Z2V4, ECO0000269|PubMed24863970, ECO0000269|PubMed26971250, ECO0000269|PubMed28216384, ECO0000269|PubMed30193097, ECO0000269|PubMed32322062}.

**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

**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.

**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}.

**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}.

**Me1:** *Human Entrez Gene Summary (Human ME1):* This gene encodes a cytosolic, NADP-dependent enzyme that generates NADPH for fatty acid biosynthesis. The activity of this enzyme, the reversible oxidative decarboxylation of malate, links the glycolytic and citric acid cycles. The regulation of expression for this gene is complex. Increased expression can result from elevated levels of thyroid hormones or by higher proportions of carbohydrates in the diet. [provided by RefSeq, Jul 2008]

**Cyp4a1:** *Human Uniprot function (Human CYP4A22):* Catalyzes the omega- and (omega-1)-hydroxylation of various fatty acids such as laurate and palmitate. Shows no activity towards arachidonic acid and prostaglandin A1. Lacks functional activity in the kidney and does not contribute to renal 20-hydroxyeicosatetraenoic acid (20-HETE) biosynthesis. {ECO0000269|PubMed10860550, ECO0000269|PubMed15611369}.

**Anxa7:** *Human Uniprot function (Human ANXA7):* Calcium/phospholipid-binding protein which promotes membrane fusion and is involved in exocytosis.

**Slc17a3:** *Human Uniprot function (Human SLC17A3):* [Isoform 2] voltage-driven, multispecific, organic anion transporter able to transport para-aminohippurate (PAH), estrone sulfate, estradiol-17-beta-glucuronide, bumetanide, and ochratoxin A. Isoform 2 functions as urate efflux transporter on the apical side of renal proximal tubule and is likely to act as an exit path for organic anionic drugs as well as urate in vivo. May be involved in actively transporting phosphate into cells via Na(+) cotransport.

### 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 |
| **abcc3** | 140668 | ABCC3\_7941 | 5.019 (2.945-9.451) | 3.5 | UP |
| **gsta2** | 24422 | GSTA2\_8756 | 5.153 (2.796-10.815) | 2.8 | UP |
| **gsta5** | 494499 | GSTA2\_8756 | 5.153 (2.796-10.815) | 2.8 | UP |
| **ephx1** | 25315 | EPHX1\_8567 | 5.233 (3.072-9.586) | 3.8 | UP |
| **akr7a3** | 26760 | AKR7A3\_8015 | 5.348 (3.082-10.631) | 5.7 | UP |
| **ehhadh** | 171142 | EHHADH\_8534 | 5.355 (3.108-9.861) | 2.2 | UP |
| **pir** | 363465 | PIR\_9487 | 6.124 (2.642-15.294) | 2.8 | UP |
| **gclm** | 29739 | GCLM\_8700 | 8.034 (3.552-19.773) | 2.1 | UP |
| **dao** | 114027 | DAO\_8437 | 8.071 (2.669-26.141) | 2.1 | UP |
| **me1** | 24552 | ME1\_9215 | 8.192 (2.618-30.949) | 2.3 | UP |

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**Abcc3:** *Human Uniprot function (Human ABCC3):* May act as an inducible transporter in the biliary and intestinal excretion of organic anions. Acts as an alternative route for the export of bile acids and glucuronides from cholestatic hepatocytes (By similarity). {ECO0000250}.

**Gsta2:** *Human Uniprot function (Human GSTA2):* Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

**Gsta5:** *Rat Uniprot Function (Human GSTA5):* Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

**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}.

**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}.

**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}.

**Pir:** *Human Uniprot function (Human PIR):* Transcriptional coregulator of NF-kappa-B which facilitates binding of NF-kappa-B proteins to target kappa-B genes in a redox-state-dependent manner. May be required for efficient terminal myeloid maturation of hematopoietic cells. Has quercetin 2,3-dioxygenase activity (in vitro). {ECO0000269|PubMed17288615, ECO0000269|PubMed20010624, ECO0000269|PubMed20711196, ECO0000269|PubMed23716661}.

**Gclm:** *Human Entrez Gene Summary (Human GCLM):* Glutamate-cysteine ligase, also known as gamma-glutamylcysteine synthetase, is the first rate limiting enzyme of glutathione synthesis. The enzyme consists of two subunits, a heavy catalytic subunit and a light regulatory subunit. Gamma glutamylcysteine synthetase deficiency has been implicated in some forms of hemolytic anemia. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Apr 2015]

**Dao:** *Human Uniprot function (Human DAO):* Regulates the level of the neuromodulator D-serine in the brain. Has high activity towards D-DOPA and contributes to dopamine synthesis. Could act as a detoxifying agent which removes D-amino acids accumulated during aging. Acts on a variety of D-amino acids with a preference for those having small hydrophobic side chains followed by those bearing polar, aromatic, and basic groups. Does not act on acidic amino acids. {ECO0000269|PubMed17303072}.

**Me1:** *Human Entrez Gene Summary (Human ME1):* This gene encodes a cytosolic, NADP-dependent enzyme that generates NADPH for fatty acid biosynthesis. The activity of this enzyme, the reversible oxidative decarboxylation of malate, links the glycolytic and citric acid cycles. The regulation of expression for this gene is complex. Increased expression can result from elevated levels of thyroid hormones or by higher proportions of carbohydrates in the diet. [provided by RefSeq, Jul 2008]