### Male Kidney 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 |
| **decr1** | 117543 | DECR1\_8458 | 0.680 (0.505-1.264) | 3.1 | UP |
| **vnn1** | 29142 | VNN1\_10157 | 0.705 (0.488-1.353) | 6.0 | UP |
| **acmsd** | 171385 | ACMSD\_32377 | 0.775 (0.183-4.177) | 2.3 | DOWN |
| **hmgcs2** | 24450 | HMGCS2\_8812 | 0.804 (0.541-1.442) | 11.8 | UP |
| **ehhadh** | 171142 | EHHADH\_8534 | 0.953 (0.671-1.585) | 8.7 | UP |
| **eci2** | 291075 | ECI2\_8521 | 0.989 (0.643-1.915) | 2.1 | UP |
| **acaa2** | 170465 | ACAA2\_7955 | 1.346 (0.539-4.058) | 2.8 | UP |
| **acot1** | 50559 | ACOT1\_7968 | 1.363 (0.938-2.405) | 2.2 | UP |
| **cyp4a1** | 50549 | CYP4A1\_33111 | 1.593 (1.021-3.028) | 4.5 | UP |
| **ech1** | 64526 | ECH1\_8516 | 2.055 (1.124-4.620) | 2.2 | 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

**Decr1:** *Human Uniprot function (Human DECR1):* Auxiliary enzyme of beta-oxidation. It participates in the metabolism of unsaturated fatty enoyl-CoA esters having double bonds in both even- and odd-numbered positions in mitochondria. Catalyzes the NADP-dependent reduction of 2,4-dienoyl-CoA to yield trans-3-enoyl-CoA. {ECO0000269|PubMed15531764}.

**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}.

**Acmsd:** *Human Uniprot function (Human ACMSD):* Converts alpha-amino-beta-carboxymuconate-epsilon-semialdehyde (ACMS) to alpha-aminomuconate semialdehyde (AMS). ACMS can be converted non-enzymatically to quinolate (QA), a key precursor of NAD, and a potent endogenous excitotoxin of neuronal cells which is implicated in the pathogenesis of various neurodegenerative disorders. In the presence of ACMSD, ACMS is converted to AMS, a benign catabolite. ACMSD ultimately controls the metabolic fate of tryptophan catabolism along the kynurenine pathway. {ECO0000269|PubMed19843166}.

**Hmgcs2:** *Human Uniprot function (Human HMGCS2):* Catalyzes the first irreversible step in ketogenesis, condensing acetyl-CoA to acetoacetyl-CoA to form HMG-CoA, which is converted by HMG-CoA reductase (HMGCR) into mevalonate. {ECO0000269|PubMed11228257, ECO0000269|PubMed23751782, ECO0000269|PubMed29597274}.

**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}.

**Eci2:** *Human Uniprot function (Human ECI2):* Able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species. Has a preference for 3-trans substrates. {ECO0000269|PubMed10419495}.

**Acaa2:** *Human Uniprot function (Human ACAA2):* In the production of energy from fats, this is one of the enzymes that catalyzes the last step of the mitochondrial beta-oxidation pathway, an aerobic process breaking down fatty acids into acetyl-CoA (Probable). Using free coenzyme A/CoA, catalyzes the thiolytic cleavage of medium- to long-chain unbranched 3-oxoacyl-CoAs into acetyl-CoA and a fatty acyl-CoA shortened by two carbon atoms (Probable). Also catalyzes the condensation of two acetyl-CoA molecules into acetoacetyl-CoA and could be involved in the production of ketone bodies (Probable). Also displays hydrolase activity on various fatty acyl-CoAs (PubMed25478839). Thereby, could be responsible for the production of acetate in a side reaction to beta-oxidation (Probable). Abolishes BNIP3-mediated apoptosis and mitochondrial damage (PubMed18371312). {ECO0000269|PubMed18371312, ECO0000269|PubMed25478839, ECO0000305|PubMed25478839}.

**Acot1:** *Human Uniprot function (Human ACOT1):* Acyl-CoA thioesterases are a group of enzymes that catalyze the hydrolysis of acyl-CoAs into free fatty acids and coenzyme A (CoASH), regulating intracellular levels of acyl-CoAs, free fatty acids and CoASH. More active towards saturated and unsaturated long chain fatty acyl-CoAs (C12-C20). {ECO0000269|PubMed16940157}.

**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}.

**Ech1:** *Human Uniprot function (Human ECH1):* Isomerization of 3-trans,5-cis-dienoyl-CoA to 2-trans,4-trans-dienoyl-CoA. {ECO0000250|UniProtKBQ62651}.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene Symbol** | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1std-BMDU1std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| **plod3** | 288583 | PLOD3\_9507 | <0.050 (NR) | 2.1 | UP |
| **eci1** | 29740 | ECI1\_8520 | 9.486 (7.353-12.810) | 4.4 | UP |
| **vnn1** | 29142 | VNN1\_10157 | 10.025 (7.993-13.110) | 7.8 | UP |
| **hmgcs2** | 24450 | HMGCS2\_8812 | 11.644 (9.266-15.267) | 37.7 | UP |
| **ehhadh** | 171142 | EHHADH\_8534 | 12.212 (9.437-16.563) | 6.7 | UP |
| **eci2** | 291075 | ECI2\_8521 | 12.789 (9.488-18.156) | 2.0 | UP |
| **acaa1a** | 24157 | ACAA1A\_7954 | 13.850 (11.009-18.172) | 5.2 | UP |
| **acaa1b** | 501072 | ACAA1A\_7954 | 13.850 (11.009-18.172) | 5.2 | UP |
| **ech1** | 64526 | ECH1\_8516 | 19.820 (14.141-29.396) | 2.1 | UP |
| **acaa2** | 170465 | ACAA2\_7955 | 22.339 (13.614-38.665) | 2.3 | 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.

<0.050 = A best-fit model as identified calculated a BMD that was less than 1/3 of the lowest tested dose in this study.

NR = The BMDL-BMDU range is not reportable because the BMD median is below the lower limit of extrapolation (less than 1/3 of the lowest tested dose in this study).

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

**Plod3:** *Human Uniprot function (Human PLOD3):* Multifunctional enzyme that catalyzes a series of essential post-translational modifications on Lys residues in procollagen (PubMed11956192, PubMed12475640, PubMed18298658, PubMed30089812, PubMed18834968). Plays a redundant role in catalyzing the formation of hydroxylysine residues in -Xaa-Lys-Gly- sequences in collagens (PubMed9582318, PubMed9724729, PubMed11956192, PubMed12475640, PubMed18298658, PubMed30089812, PubMed18834968). Plays a redundant role in catalyzing the transfer of galactose onto hydroxylysine groups, giving rise to galactosyl 5-hydroxylysine (PubMed12475640, PubMed18298658, PubMed30089812, PubMed18834968). Has an essential role by catalyzing the subsequent transfer of glucose moieties, giving rise to 1,2-glucosylgalactosyl-5-hydroxylysine residues (PubMed10934207, PubMed11896059, PubMed11956192, PubMed12475640, PubMed18298658, PubMed30089812, PubMed18834968). Catalyzes hydroxylation and glycosylation of Lys residues in the MBL1 collagen-like domain, giving rise to hydroxylysine and 1,2-glucosylgalactosyl-5-hydroxylysine residues (PubMed25419660). Essential for normal biosynthesis and secretion of type IV collagens (PubMed18834968) (Probable). Essential for normal formation of basement membranes (By similarity). {ECO0000250|UniProtKBQ9R0E1, ECO0000269|PubMed10934207, ECO0000269|PubMed11896059, ECO0000269|PubMed11956192, ECO0000269|PubMed12475640, ECO0000269|PubMed18298658, ECO0000269|PubMed18834968, ECO0000269|PubMed25419660, ECO0000269|PubMed30089812, ECO0000269|PubMed9582318, ECO0000269|PubMed9724729, ECO0000305}.

**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}.

**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}.

**Hmgcs2:** *Human Uniprot function (Human HMGCS2):* Catalyzes the first irreversible step in ketogenesis, condensing acetyl-CoA to acetoacetyl-CoA to form HMG-CoA, which is converted by HMG-CoA reductase (HMGCR) into mevalonate. {ECO0000269|PubMed11228257, ECO0000269|PubMed23751782, ECO0000269|PubMed29597274}.

**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}.

**Eci2:** *Human Uniprot function (Human ECI2):* Able to isomerize both 3-cis and 3-trans double bonds into the 2-trans form in a range of enoyl-CoA species. Has a preference for 3-trans substrates. {ECO0000269|PubMed10419495}.

**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]

**Ech1:** *Human Uniprot function (Human ECH1):* Isomerization of 3-trans,5-cis-dienoyl-CoA to 2-trans,4-trans-dienoyl-CoA. {ECO0000250|UniProtKBQ62651}.

**Acaa2:** *Human Uniprot function (Human ACAA2):* In the production of energy from fats, this is one of the enzymes that catalyzes the last step of the mitochondrial beta-oxidation pathway, an aerobic process breaking down fatty acids into acetyl-CoA (Probable). Using free coenzyme A/CoA, catalyzes the thiolytic cleavage of medium- to long-chain unbranched 3-oxoacyl-CoAs into acetyl-CoA and a fatty acyl-CoA shortened by two carbon atoms (Probable). Also catalyzes the condensation of two acetyl-CoA molecules into acetoacetyl-CoA and could be involved in the production of ketone bodies (Probable). Also displays hydrolase activity on various fatty acyl-CoAs (PubMed25478839). Thereby, could be responsible for the production of acetate in a side reaction to beta-oxidation (Probable). Abolishes BNIP3-mediated apoptosis and mitochondrial damage (PubMed18371312). {ECO0000269|PubMed18371312, ECO0000269|PubMed25478839, ECO0000305|PubMed25478839}.