### 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 |
| **ugt2b7** | 286989 | UGT2B7\_33032 | 4.139 (1.398-16.569) | 3.6 | UP |
| **ephx1** | 25315 | EPHX1\_8567 | 12.509 (3.282-61.397) | 2.1 | UP |
| **adgre1** | 316137 | EMR1\_8558 | 119.065 (89.170-178.281) | 3.1 | UP |
| **map2** | 25595 | MAP2\_32650 | 145.437 (104.718-237.081) | 2.1 | UP |
| **slc6a1** | 79212 | SLC6A1\_32594 | 145.445 (104.722-237.101) | 2.0 | UP |
| **naaa** | 497009 | NAAA\_32484 | 151.002 (107.821-250.969) | 2.2 | UP |
| **il1b** | 24494 | IL1B\_8892 | 153.991 (109.464-258.668) | 2.9 | UP |
| **cyp24a1** | 25279 | CYP24A1\_32574 | 189.111 (127.579-364.247) | 2.2 | UP |
| **top2a** | 360243 | TOP2A\_10059 | 203.468 (108.442-572.253) | 2.1 | DOWN |
| **nsg1** | 25247 | NSG1\_32675 | 216.472 (166.237-342.576) | 3.4 | 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

**Ugt2b7:** *Human Uniprot function (Human UGT2B7):* UDP-glucuronosyltransferase (UGT) that catalyzes phase II biotransformation reactions in which lipophilic substrates are conjugated with glucuronic acid to increase the metabolite's water solubility, thereby facilitating excretion into either the urine or bile (PubMed10702251, PubMed15472229, PubMed15470161, PubMed18674515, PubMed18719240, PubMed19022937, PubMed23288867, PubMed23756265, PubMed26220143, PubMed17442341). Essential for the elimination and detoxification of drugs, xenobiotics and endogenous compounds (PubMed15470161, PubMed18674515, PubMed23756265). Catalyzes the glucuronidation of endogenous steroid hormones such as androgens (epitestosterone, androsterone) and estrogens (estradiol, epiestradiol, estriol, catechol estrogens) (PubMed2159463, PubMed15472229, PubMed18719240, PubMed19022937, PubMed23288867, PubMed26220143, PubMed17442341). Also regulates the levels of retinoic acid, a major metabolite of vitamin A involved in apoptosis, cellular growth and differentiation, and embryonic development (PubMed10702251). Contributes to bile acid (BA) detoxification by catalyzing the glucuronidation of BA substrates, which are natural detergents for dietary lipids absorption (PubMed23756265). Involved in the glucuronidation of the AGTR1 angiotensin receptor antagonist losartan, caderastan and zolarsatan, drugs which can inhibit the effect of angiotensin II (PubMed18674515). Also metabolizes mycophenolate, an immunosuppressive agent (PubMed15470161). {ECO0000269|PubMed10702251, ECO0000269|PubMed15470161, ECO0000269|PubMed15472229, ECO0000269|PubMed17442341, ECO0000269|PubMed18674515, ECO0000269|PubMed18719240, ECO0000269|PubMed19022937, ECO0000269|PubMed2159463, ECO0000269|PubMed23288867, ECO0000269|PubMed23756265, ECO0000269|PubMed26220143}.

**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}.

**Adgre1:** *Human Uniprot function (Human ADGRE1):* Orphan receptor involved in cell adhesion and probably in cell-cell interactions specifically involving cells of the immune system. May play a role in regulatory T-cells (Treg) development. {ECO0000250|UniProtKBQ61549}.

**Map2:** *Human Uniprot function (Human MAP2):* The exact function of MAP2 is unknown but MAPs may stabilize the microtubules against depolymerization. They also seem to have a stiffening effect on microtubules.

**Slc6a1:** *Human Uniprot function (Human SLC6A1):* Terminates the action of GABA by its high affinity sodium-dependent reuptake into presynaptic terminals.

**Naaa:** *Human Uniprot function (Human NAAA):* Degrades bioactive fatty acid amides to their corresponding acids, with the following preference N-palmitoylethanolamine > N-myristoylethanolamine > N-lauroylethanolamine = N-stearoylethanolamine > N-arachidonoylethanolamine > N-oleoylethanolamine (PubMed15655246, PubMed17980170, PubMed18793752, PubMed30301806, PubMed22825852). Also exhibits weak hydrolytic activity against the ceramides N-lauroylsphingosine and N-palmitoylsphingosine (PubMed15655246). {ECO0000269|PubMed15655246, ECO0000269|PubMed17980170, ECO0000269|PubMed18793752, ECO0000269|PubMed22825852, ECO0000269|PubMed30301806}.

**Il1b:** *Human Uniprot function (Human IL1B):* Potent proinflammatory cytokine. Initially discovered as the major endogenous pyrogen, induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production. Promotes Th17 differentiation of T-cells. Synergizes with IL12/interleukin-12 to induce IFNG synthesis from T-helper 1 (Th1) cells (PubMed10653850). Plays a role in angiogenesis by inducing VEGF production synergistically with TNF and IL6 (PubMed12794819). {ECO0000269|PubMed10653850, ECO0000269|PubMed12794819, ECO0000269|PubMed3920526}.

**Cyp24a1:** *Human Uniprot function (Human CYP24A1):* A cytochrome P450 monooxygenase with a key role in vitamin D catabolism and calcium homeostasis. Via C24- and C23-oxidation pathways, catalyzes the inactivation of both the vitamin D precursor calcidiol (25-hydroxyvitamin D(3)) and the active hormone calcitriol (1-alpha,25-dihydroxyvitamin D(3)) (PubMed24893882, PubMed15574355, PubMed8679605, PubMed11012668, PubMed16617161). With initial hydroxylation at C-24 (via C24-oxidation pathway), performs a sequential 6-step oxidation of calcitriol leading to the formation of the biliary metabolite calcitroic acid (PubMed24893882, PubMed15574355). With initial hydroxylation at C-23 (via C23-oxidation pathway), catalyzes sequential oxidation of calcidiol leading to the formation of 25(OH)D3-26,23-lactone as end product (PubMed11012668, PubMed8679605). Preferentially hydroxylates at C-25 other vitamin D active metabolites, such as CYP11A1-derived secosteroids 20S-hydroxycholecalciferol and 20S,23-dihydroxycholecalciferol (PubMed25727742). 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 FDXR/adrenodoxin reductase and FDX1/adrenodoxin (PubMed8679605). {ECO0000269|PubMed11012668, ECO0000269|PubMed15574355, ECO0000269|PubMed16617161, ECO0000269|PubMed24893882, ECO0000269|PubMed25727742, ECO0000269|PubMed8679605}.

**Top2a:** *Human Uniprot function (Human TOP2A):* Key decatenating enzyme that alters DNA topology by binding to two double-stranded DNA molecules, generating a double-stranded break in one of the strands, passing the intact strand through the broken strand, and religating the broken strand (PubMed17567603, PubMed18790802, PubMed22013166, PubMed22323612). May play a role in regulating the period length of ARNTL/BMAL1 transcriptional oscillation (By similarity). {ECO0000250|UniProtKBQ01320, ECO0000269|PubMed17567603, ECO0000269|PubMed18790802, ECO0000269|PubMed22013166, ECO0000269|PubMed22323612}.

**Nsg1:** *Human Uniprot function (Human NSG1):* Plays a role in the recycling mechanism in neurons of multiple receptors, including AMPAR, APP and L1CAM and acts at the level of early endosomes to promote sorting of receptors toward a recycling pathway. Regulates sorting and recycling of GRIA2 through interaction with GRIP1 and then contributes to the regulation of synaptic transmission and plasticity by affecting the recycling and targeting of AMPA receptors to the synapse (By similarity). Is required for faithful sorting of L1CAM to axons by facilitating trafficking from somatodendritic early endosome or the recycling endosome (By similarity). In an other hand, induces apoptosis via the activation of CASP3 in response to DNA damage (PubMed20599942, PubMed20878061). {ECO0000250|UniProtKBP02683, ECO0000250|UniProtKBQ62092, ECO0000269|PubMed20599942, ECO0000269|PubMed20878061}.

### Female 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 |
| **mrc1** | 291327 | MRC1\_33067 | <0.023 (NR) | 2.1 | DOWN |
| **ckap2** | 306575 | CKAP2\_8324 | 2.608 (0.997-6.811) | 2.3 | UP |
| **ugt2b37** | 29623 | UGT2B15\_33121 | 32.501 (7.520-103.327) | 3.3 | UP |
| **slc51a** | 303879 | SLC51A\_33157 | 37.134 (11.007-108.745) | 2.2 | UP |
| **ugt2b7** | 286989 | UGT2B7\_33032 | 54.314 (15.595-186.641) | 4.8 | UP |
| **bbox1** | 64564 | BBOX1\_8133 | 61.319 (39.473-135.622) | 2.0 | UP |
| **adgre1** | 316137 | EMR1\_8558 | 61.524 (39.671-132.174) | 2.4 | UP |
| **clec4a** | 474143 | CLEC4A\_32636 | 82.466 (47.872-265.955) | 2.2 | UP |
| **cyp26b1** | 312495 | CYP26B1\_8418 | 238.250 (181.323-370.243) | 2.8 | UP |
| **lilrb4** | 292594 | LILRB4\_9000 | 350.991 (212.248-1011.690) | 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.

<0.023 = 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

**Mrc1:** *Human Uniprot function (Human MRC1):* Mediates the endocytosis of glycoproteins by macrophages. Binds both sulfated and non-sulfated polysaccharide chains.; FUNCTION (Microbial infection) Acts as phagocytic receptor for bacteria, fungi and other pathogens.; FUNCTION (Microbial infection) Acts as a receptor for Dengue virus envelope protein E. {ECO0000269|PubMed18266465}.; FUNCTION (Microbial infection) Interacts with Hepatitis B virus envelope protein. {ECO0000269|PubMed19683778}.

**Ckap2:** *Human Uniprot function (Human CKAP2):* Possesses microtubule stabilizing properties. Involved in regulating aneuploidy, cell cycling, and cell death in a p53/TP53-dependent manner (By similarity). {ECO0000250}.

**Ugt2b37:** *Human Uniprot function (Human UGT2B10):* UDPGT is of major importance in the conjugation and subsequent elimination of potentially toxic xenobiotics and endogenous compounds. UDB10\_HUMAN,P36537

**Slc51a:** *Human Uniprot function (Human SLC51A):* Essential component of the Ost-alpha/Ost-beta complex, a heterodimer that acts as the intestinal basolateral transporter responsible for bile acid export from enterocytes into portal blood. Efficiently transports the major species of bile acids. {ECO0000269|PubMed16317684}.

**Ugt2b7:** *Human Uniprot function (Human UGT2B7):* UDP-glucuronosyltransferase (UGT) that catalyzes phase II biotransformation reactions in which lipophilic substrates are conjugated with glucuronic acid to increase the metabolite's water solubility, thereby facilitating excretion into either the urine or bile (PubMed10702251, PubMed15472229, PubMed15470161, PubMed18674515, PubMed18719240, PubMed19022937, PubMed23288867, PubMed23756265, PubMed26220143, PubMed17442341). Essential for the elimination and detoxification of drugs, xenobiotics and endogenous compounds (PubMed15470161, PubMed18674515, PubMed23756265). Catalyzes the glucuronidation of endogenous steroid hormones such as androgens (epitestosterone, androsterone) and estrogens (estradiol, epiestradiol, estriol, catechol estrogens) (PubMed2159463, PubMed15472229, PubMed18719240, PubMed19022937, PubMed23288867, PubMed26220143, PubMed17442341). Also regulates the levels of retinoic acid, a major metabolite of vitamin A involved in apoptosis, cellular growth and differentiation, and embryonic development (PubMed10702251). Contributes to bile acid (BA) detoxification by catalyzing the glucuronidation of BA substrates, which are natural detergents for dietary lipids absorption (PubMed23756265). Involved in the glucuronidation of the AGTR1 angiotensin receptor antagonist losartan, caderastan and zolarsatan, drugs which can inhibit the effect of angiotensin II (PubMed18674515). Also metabolizes mycophenolate, an immunosuppressive agent (PubMed15470161). {ECO0000269|PubMed10702251, ECO0000269|PubMed15470161, ECO0000269|PubMed15472229, ECO0000269|PubMed17442341, ECO0000269|PubMed18674515, ECO0000269|PubMed18719240, ECO0000269|PubMed19022937, ECO0000269|PubMed2159463, ECO0000269|PubMed23288867, ECO0000269|PubMed23756265, ECO0000269|PubMed26220143}.

**Bbox1:** *Human Uniprot function (Human BBOX1):* Catalyzes the formation of L-carnitine from gamma-butyrobetaine.

**Adgre1:** *Human Uniprot function (Human ADGRE1):* Orphan receptor involved in cell adhesion and probably in cell-cell interactions specifically involving cells of the immune system. May play a role in regulatory T-cells (Treg) development. {ECO0000250|UniProtKBQ61549}.

**Clec4a:** *Human Uniprot function (Human CLEC6A):* Binds high-mannose carbohydrates in a Ca(2+)-dependent manner (PubMed28652405). Functional receptor for alpha-mannans on C.albicans hypheas. Plays an important role in the host defense against C.albicans infection by inducing TH17 cell differentiation. Recognizes also, in a mannose-dependent manner, allergens from house dust mite and fungi, by promoting cysteinyl leukotriene production. Recognizes soluble elements from the eggs of Shistosoma mansoni altering adaptive immune responses. Transduces signals through an Fc receptor gamma chain /FCER1G and Syk-CARD9-NF-kappa-B-dependent pathway (By similarity). {ECO0000250|UniProtKBQ9JKF4, ECO0000269|PubMed28652405}.

**Cyp26b1:** *Human Uniprot function (Human CYP26B1):* Involved in the metabolism of retinoic acid (RA), rendering this classical morphogen inactive through oxidation (PubMed10823918, PubMed22020119). Involved in the specific inactivation of all-trans-retinoic acid (all-trans-RA), with a preference for the following substrates all-trans-RA > 9-cis-RA > 13-cis-RA (PubMed10823918, PubMed22020119). Generates several hydroxylated forms of RA, including 4-OH-RA, 4-oxo-RA, and 18-OH-RA (PubMed10823918). Catalyzes the hydroxylation of carbon hydrogen bonds of atRA primarily at C-4 (PubMed10823918, PubMed22020119). Essential for postnatal survival (By similarity). Plays a central role in germ cell development acts by degrading RA in the developing testis, preventing STRA8 expression, thereby leading to delay of meiosis (By similarity). Required for the maintenance of the undifferentiated state of male germ cells during embryonic development in Sertoli cells, inducing arrest in G0 phase of the cell cycle and preventing meiotic entry (By similarity). Plays a role in skeletal development, both at the level of patterning and in the ossification of bone and the establishment of some synovial joints (PubMed22019272). {ECO0000250|UniProtKBQ811W2, ECO0000269|PubMed10823918, ECO0000269|PubMed22019272, ECO0000269|PubMed22020119}.; FUNCTION Has also a significant activity in oxidation of tazarotenic acid and may therefore metabolize that xenobiotic in vivo. {ECO0000269|PubMed26937021}.

**Lilrb4:** *Human Uniprot function (Human LILRB4):* Receptor for class I MHC antigens. Recognizes a broad spectrum of HLA-A, HLA-B, HLA-C and HLA-G alleles. Involved in the down-regulation of the immune response and the development of tolerance, e.g. towards transplants. Interferes with TNFRSF5-signaling and NF-kappa-B up-regulation. Inhibits receptor-mediated phosphorylation of cellular proteins and mobilization of intracellular calcium ions. {ECO0000269|PubMed11875462, ECO0000269|PubMed9151699}.