Top 10 Genes Ranked by Potency of Perturbation, Sorted by Benchmark Dose Mediana

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| Gene Symbol | Entrez Gene IDs | Probe IDs | BMD1Std (BMDL1Std–BMDU1Std) in mg/kg | Maximum Fold Change | Direction of Expression Change |
| ***Ddit4*** | 140942 | 1368025\_at | <20.3b (NR) | 2.8 | UP |
| ***Ugt2b17*** | 286954 | 1370698\_at | <20.3 (NR) | 2.4 | UP |
| ***Ces2c*** | 171118 | 1368905\_at | <20.3 (NR) | 13.0 | UP |
| ***Gstt3*** | 499422 | 1371942\_at | <20.3 (NR) | 2.3 | UP |
| ***Aldh1a1*** | 24188 | 1387022\_at | 21.0 (12.8–41.1) | 2.5 | UP |
| ***Cryl1*** | 290277 | 1376051\_at | 23.0 (14.0–45.2) | 3.0 | UP |
| ***Me1*** | 24552 | 1370870\_at | 23.6 (14.5–45.6) | 3.1 | UP |
| ***Slc34a2*** | 84395 | 1368168\_at | 25.8 (14.9–61.5) | 3.4 | DOWN |
| ***App*** | 54226 | 1371572\_at | 28.8 (18.4–52.8) | 2.4 | UP |
| ***Slc6a6*** | 29464 | 1368778\_at,1374531\_at | 30.7 (20.2–53.8) | 13.2 | DOWN |

Benchmark response set at 1 standard deviation from the mean.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMDU = benchmark dose upper confidence limit; NR = the BMDL-BMDU range is not reportable because the BMD median is below the lower limit of extrapolation (<1/3 the lowest nonzero dose tested).

aDescriptions of orthologous human genes are shown due to the increased detail available in public resources such as UniprotKB[23](#_ENREF_23" \o "UniProt, 2020 #1281) and Entrez Gene.[24](#_ENREF_24) Human UniprotKB was used as the primary resource due to the greater breadth of annotation and depth of functional detail provided. Rat UniprotKB was used as the secondary resource if the primary source did not provide a detailed description of function. Human Entrez Gene Summary was used as the third resource. Rat Entrez Gene Summary was used as the fourth resource.

b<20.3 = a best-fit model was identified and a BMD was estimated that was <1/3 the lowest nonzero dose tested.

**Gene definition version:** <https://doi.org/10.22427/NTP-DATA-002-00600-0002-000-0>.

***Ddit4*:** Human Uniprot function (Human *DDIT4*): Regulates cell growth, proliferation, and survival via inhibition of the activity of the mammalian target of rapamycin complex 1 (mTORC1). Inhibition of mTORC1 is mediated by a pathway that involves DDIT4/REDD1, AKT1, the TSC1-TSC2 complex, and the GTPase RHEB. Plays an important role in responses to cellular energy levels and cellular stress, including responses to hypoxia and DNA damage. Regulates p53/TP53-mediated apoptosis in response to DNA damage via its effect on mTORC1 activity. Its role in the response to hypoxia depends on the cell type; it mediates mTORC1 inhibition in fibroblasts and thymocytes but not in hepatocytes (by similarity). Required for mTORC1-mediated defense against viral protein synthesis and virus replication (by similarity). Inhibits neuronal differentiation and neurite outgrowth mediated by NGF via its effect on mTORC1 activity. Required for normal neuron migration during embryonic brain development. Plays a role in neuronal cell death. {ECO0000250, ECO0000269|PubMed15545625, ECO0000269|PubMed15632201, ECO0000269|PubMed15988001, ECO0000269|PubMed17005863, ECO0000269|PubMed17379067, ECO0000269|PubMed19557001, ECO0000269|PubMed20166753, ECO0000269|PubMed21460850}.

***Ugt2b17*:** Human Uniprot function (Human *UGT2B17*): 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 (PubMed8798464, PubMed16595710, PubMed18719240, PubMed19022937, PubMed23288867). Catalyzes the glucuronidation of endogenous steroid hormones such as androgens (epitestosterone, androsterone) and estrogens (estradiol, epiestradiol) (PubMed8798464, PubMed16595710, PubMed18719240, PubMed19022937, PubMed23288867). {ECO0000269|PubMed16595710, ECO0000269|PubMed18719240, ECO0000269|PubMed19022937, ECO0000269|PubMed23288867, ECO0000269|PubMed8798464}.

***Ces2c*:** Human Uniprot function (Human *CES2*): Involved in the detoxification of xenobiotics and in the activation of ester and amide prodrugs (PubMed9169443). Shows high catalytic efficiency for hydrolysis of cocaine, 4-methylumbelliferyl acetate, heroin and 6-monoacetylmorphine (PubMed9169443). Hydrolyzes aspirin, substrates with large alcohol group and small acyl group and endogenous lipids such as triacylglycerol (PubMed28677105). Converts monoacylglycerides to free fatty acids and glycerol. Hydrolyzes 2-arachidonoylglycerol and prostaglandins (PubMed21049984). {ECO0000269|PubMed21049984, ECO0000269|PubMed9169443, ECO0000303|PubMed28677105}.

***Gstt3*:** Human Uniprot function (Human *GSTT1*): Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles. Acts on 1,2-epoxy-3-(4-nitrophenoxy)propane, phenethylisothiocyanate 4-nitrobenzyl chloride, and 4-nitrophenethyl bromide. Displays glutathione peroxidase activity with cumene hydroperoxide.

***Aldh1a1*:** Human Uniprot function (Human *ALDH1A1*): Can convert/oxidize retinaldehyde to retinoic acid. Binds free retinal and cellular retinol-binding protein-bound retinal (by similarity). May have a broader specificity and oxidize other aldehydes in vivo (PubMed19296407, PubMed26373694, PubMed25450233). {ECO0000250|UniProtKBP51647, ECO0000269|PubMed19296407, ECO0000269|PubMed25450233, ECO0000269|PubMed26373694}.

***Cryl1*:** Human Entrez Gene Summary (Human *CRYL1*): The uronate cycle functions as an alternative glucose metabolic pathway, accounting for about 5% of daily glucose catabolism. The product of this gene catalyzes the dehydrogenation of L-gulonate into dehydro-L-gulonate in the uronate cycle. The enzyme requires NAD(H) as a coenzyme and is inhibited by inorganic phosphate. A similar gene in the rabbit is thought to serve a structural role in the lens of the eye. [provided by RefSeq, Jul 2008]

***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]

***Slc34a2*:** Human Uniprot function (Human *SLC34A2*): May be involved in actively transporting phosphate into cells via Na(+) cotransport. It may be the main phosphate transport protein in the intestinal brush border membrane. May have a role in the synthesis of surfactant in lungs’ alveoli.

***App*:** Human Uniprot function (Human *APP*): Functions as a cell surface receptor and performs physiological functions on the surface of neurons relevant to neurite growth, neuronal adhesion, and axonogenesis. Interaction between APP molecules on neighboring cells promotes synaptogenesis (PubMed25122912). Involved in cell mobility and transcription regulation through protein-protein interactions. Can promote transcription activation through binding to APBB1-KAT5 and inhibits Notch signaling through interaction with Numb. Couples to apoptosis-inducing pathways such as those mediated by G(O) and JIP. Inhibits G(o) alpha ATPase activity (by similarity). Acts as a kinesin I membrane receptor, mediating the axonal transport of beta-secretase and presenilin 1 (by similarity). By acting as a kinesin I membrane receptor, plays a role in axonal anterograde transport of cargo toward synapes in axons (PubMed17062754, PubMed23011729). Involved in copper homeostasis/oxidative stress through copper ion reduction. In vitro, copper-metalated APP induces neuronal death directly or is potentiated through Cu(2+)-mediated low-density lipoprotein oxidation. Can regulate neurite outgrowth through binding to components of the extracellular matrix such as heparin and collagen I and IV. The splice isoforms that contain the BPTI domain possess protease inhibitor activity. Induces an AGER-dependent pathway that involves activation of p38 MAPK, resulting in internalization of amyloid-beta peptide and leading to mitochondrial dysfunction in cultured cortical neurons. Provides Cu(2+) ions for GPC1, which are required for release of nitric oxide (NO) and subsequent degradation of the heparan sulfate chains on GPC1. {ECO:0000250, ECO:0000250|UniProtKB:P12023, ECO:0000269|PubMed17062754, ECO:0000269|PubMed23011729, ECO:0000269|PubMed25122912}. FUNCTION: Amyloid-beta peptides are lipophilic metal chelators with metal-reducing activity. Bind transient metals such as copper, zinc, and iron. In vitro, can reduce Cu(2+) and Fe(3+) to Cu(+) and Fe(2+), respectively. Amyloid-beta protein 42 is a more effective reductant than amyloid-beta protein 40. Amyloid-beta peptides bind to lipoproteins and apolipoproteins E and J in the CSF and to HDL particles in plasma, inhibiting metal-catalyzed oxidation of lipoproteins. APP42-beta may activate mononuclear phagocytes in the brain and elicit inflammatory responses. Promotes both tau aggregation and TPK II-mediated phosphorylation. Interaction with overexpressed HADH2 leads to oxidative stress and neurotoxicity. Also binds GPC1 in lipid rafts. FUNCTION: Appicans elicit adhesion of neural cells to the extracellular matrix and may regulate neurite outgrowth in the brain. {ECO:0000250}. FUNCTION: The gamma-CTF peptides as well as the caspase-cleaved peptides, including C31, are potent enhancers of neuronal apoptosis. FUNCTION: N-APP binds TNFRSF21 triggering caspase activation and degeneration of both neuronal cell bodies (via caspase-3) and axons (via caspase-6).

***Slc6a6*:** Human Uniprot function (Human *SLC6A6*): Sodium-dependent taurine and beta-alanine transporter. Chloride ions are necessary for optimal uptake. {ECO0000269|PubMed31345061, ECO0000269|PubMed31903486, ECO0000269|PubMed8382624}.