### 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 |
| **Fer1l5** | 679806 | 1396729\_at | <20.7 (NR) | 2.2 | DOWN |
| **Gsta3** | 494500 | 1371089\_at | <20.7 (NR) | 3.3 | UP |
| **Ces2c** | 171118 | 1368905\_at | 27.7 (18.7-48.5) | 7.6 | UP |
| **Abcc3** | 140668 | 1369698\_at | 32.1 (22.0-52.8) | 7.3 | UP |
| **Orm1** | 24614 | 1368731\_at | 32.6 (10.4-123.2) | 2.2 | UP |
| **Mnd1** | 295160 | 1391626\_at | 33.8 (14.8-91.6) | 2.3 | UP |
| **App** | 54226 | 1371571\_at,1371572\_at,1380533\_at | 37.7 (20.8-91.8) | 3.3 | UP |
| **Cyp7a1** | 25428 | 1368458\_at | 39.4 (17.3-109.9) | 4.7 | UP |
| **Ddit4** | 140942 | 1368025\_at | 41.6 (9.5-185.5) | 3.7 | UP |
| **Gstt3** | 499422 | 1371942\_at | 66.0 (28.7-178.7) | 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.

<20.7 = 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

**Fer1l5:** *Human Uniprot function (Human FER1L5):* Plays a role in myoblast fusion; probable mediator of endocytic recycling for membrane trafficking events during myotube formation. {ECO0000250}.

**Gsta3:** *Human Uniprot function (Human GSTA1):* Glutathione S-transferase that catalyzes the nucleophilic attack of the sulfur atom of glutathione on the electrophilic groups of a wide range of exogenous and endogenous compounds (Probable). Involved in the formation of glutathione conjugates of both prostaglandin A2 (PGA2) and prostaglandin J2 (PGJ2) (PubMed9084911). It also catalyzes the isomerization of D5-androstene-3,17-dione (AD) into D4-androstene-3,17-dione and may therefore play an important role in hormone biosynthesis (PubMed11152686). Through its glutathione-dependent peroxidase activity toward the fatty acid hydroperoxide (13S)-hydroperoxy-(9Z,11E)-octadecadienoate/13-HPODE it is also involved in the metabolism of oxidized linoleic acid (PubMed16624487). {ECO0000269|PubMed11152686, ECO0000269|PubMed16624487, ECO0000269|PubMed9084911, ECO0000305|PubMed20606271}.

**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 of 2-arachidonoylglycerol and prostaglandins (PubMed21049984). {ECO0000269|PubMed21049984, ECO0000269|PubMed9169443, ECO0000303|PubMed28677105}.

**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}.

**Orm1:** *Human Uniprot function (Human ORM1):* Functions as transport protein in the blood stream. Binds various ligands in the interior of its beta-barrel domain. Also binds synthetic drugs and influences their distribution and availability in the body. Appears to function in modulating the activity of the immune system during the acute-phase reaction. {ECO0000269|PubMed17008009, ECO0000269|PubMed17321687}.

**Mnd1:** *Human Uniprot function (Human MND1):* Required for proper homologous chromosome pairing and efficient cross-over and intragenic recombination during meiosis (By similarity). Stimulates both DMC1- and RAD51-mediated homologous strand assimilation, which is required for the resolution of meiotic double-strand breaks. {ECO0000250|UniProtKBQ8K396, ECO0000269|PubMed16407260}.

**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 towards synapes in axons (PubMed17062754, PubMed23011729). Involved in copper homeostasis/oxidative stress through copper ion reduction. In vitro, copper-metallated 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 a 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. {ECO0000250, ECO0000250|UniProtKBP12023, ECO0000269|PubMed17062754, ECO0000269|PubMed23011729, ECO0000269|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. {ECO0000250}.; 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).

**Cyp7a1:** *Human Uniprot function (Human CYP7A1):* A cytochrome P450 monooxygenase involved in the metabolism of endogenous cholesterol and its oxygenated derivatives (oxysterols) (PubMed11013305, PubMed12077124, PubMed19965590, PubMed2384150, PubMed21813643). 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 cytochrome P450 reductase (CPR; NADPH-ferrihemoprotein reductase) (PubMed2384150, PubMed11013305, PubMed12077124, PubMed19965590, PubMed21813643). Functions as a critical regulatory enzyme of bile acid biosynthesis and cholesterol homeostasis. Catalyzes the hydroxylation of carbon hydrogen bond at 7-alpha position of cholesterol, a rate-limiting step in cholesterol catabolism and bile acid biosynthesis (PubMed12077124, PubMed19965590, PubMed2384150). 7-alpha hydroxylates several oxysterols, including 4beta-hydroxycholesterol and 24-hydroxycholesterol (PubMed11013305, PubMed12077124). Catalyzes the oxidation of the 7,8 double bond of 7-dehydrocholesterol and lathosterol with direct and predominant formation of the 7-keto derivatives (PubMed21813643). {ECO0000269|PubMed11013305, ECO0000269|PubMed12077124, ECO0000269|PubMed19965590, ECO0000269|PubMed21813643, ECO0000269|PubMed2384150}.

**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}.

**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. GSTT1\_HUMAN,P30711