### 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 |
| **Tbx3** | 353305 | 1393160\_at | <25.7 (NR) | 2.2 | UP |
| **Gck** | 24385 | 1387312\_a\_at | <25.7 (NR) | 6.1 | DOWN |
| **Nr1d1** | 252917 | 1370816\_at | <25.7 (NR) | 10.0 | UP |
| **Nr1d2** | 259241 | 1370541\_at,1390430\_at | <25.7 (NR) | 4.1 | UP |
| **Sik2** | 315649 | 1376649\_at | <25.7 (NR) | 2.1 | UP |
| **Syne1** | 499010 | 1370264\_at | <25.7 (NR) | 2.3 | DOWN |
| **Oaf** | 315594 | 1388425\_at | <25.7 (NR) | 2.2 | UP |
| **Dbp** | 24309 | 1387874\_at | <25.7 (NR) | 18.4 | UP |
| **Cdkn1a** | 114851 | 1388674\_at | <25.7 (NR) | 6.5 | DOWN |
| **Cldn1** | 65129 | 1383946\_at | <25.7 (NR) | 3.0 | DOWN |

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.

<25.7 = 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

**Tbx3:** *Human Uniprot function (Human TBX3):* Transcriptional repressor involved in developmental processes. Probably plays a role in limb pattern formation. Acts as a negative regulator of PML function in cellular senescence. {ECO0000269|PubMed10468588, ECO0000269|PubMed22002537}.

**Gck:** *Human Uniprot function (Human GCK):* Catalyzes the phosphorylation of hexose, such as D-glucose, D-fructose and D-mannose, to hexose 6-phosphate (D-glucose 6-phosphate, D-fructose 6-phosphate and D-mannose 6-phosphate, respectively) (PubMed7742312, PubMed11916951, PubMed15277402, PubMed17082186, PubMed18322640, PubMed19146401, PubMed25015100, PubMed8325892). Compared to other hexokinases, has a weak affinity for D-glucose, and is effective only when glucose is abundant (By similarity). Mainly expressed in pancreatic beta cells and the liver and constitutes a rate-limiting step in glucose metabolism in these tissues (PubMed18322640, PubMed25015100, PubMed8325892, PubMed11916951, PubMed15277402). Since insulin secretion parallels glucose metabolism and the low glucose affinity of GCK ensures that it can change its enzymatic activity within the physiological range of glucose concentrations, GCK acts as a glucose sensor in the pancreatic beta cell (By similarity). In pancreas, plays an important role in modulating insulin secretion (By similarity). In liver, helps to facilitate the uptake and conversion of glucose by acting as an insulin-sensitive determinant of hepatic glucose usage (By similarity). Required to provide D-glucose 6-phosphate for the synthesis of glycogen (PubMed8878425). Mediates the initial step of glycolysis by catalyzing phosphorylation of D-glucose to D-glucose 6-phosphate (PubMed7742312). {ECO0000250|UniProtKBP17712, ECO0000250|UniProtKBP52792, ECO0000269|PubMed11916951, ECO0000269|PubMed15277402, ECO0000269|PubMed17082186, ECO0000269|PubMed18322640, ECO0000269|PubMed19146401, ECO0000269|PubMed25015100, ECO0000269|PubMed7742312, ECO0000269|PubMed8325892, ECO0000269|PubMed8878425}.

**Nr1d1:** *Human Uniprot function (Human NR1D1):* Transcriptional repressor which coordinates circadian rhythm and metabolic pathways in a heme-dependent manner. Integral component of the complex transcription machinery that governs circadian rhythmicity and forms a critical negative limb of the circadian clock by directly repressing the expression of core clock components ARTNL/BMAL1, CLOCK and CRY1. Also regulates genes involved in metabolic functions, including lipid and bile acid metabolism, adipogenesis, gluconeogenesis and the macrophage inflammatory response. Acts as a receptor for heme which stimulates its interaction with the NCOR1/HDAC3 corepressor complex, enhancing transcriptional repression. Recognizes two classes of DNA response elements within the promoter of its target genes and can bind to DNA as either monomers or homodimers, depending on the nature of the response element. Binds as a monomer to a response element composed of the consensus half-site motif 5'-[A/G]GGTCA-3' preceded by an A/T-rich 5' sequence (RevRE), or as a homodimer to a direct repeat of the core motif spaced by two nucleotides (RevDR-2). Acts as a potent competitive repressor of ROR alpha (RORA) function and regulates the levels of its ligand heme by repressing the expression of PPARGC1A, a potent inducer of heme synthesis. Regulates lipid metabolism by repressing the expression of APOC3 and by influencing the activity of sterol response element binding proteins (SREBPs); represses INSIG2 which interferes with the proteolytic activation of SREBPs which in turn govern the rhythmic expression of enzymes with key functions in sterol and fatty acid synthesis. Regulates gluconeogenesis via repression of G6PC and PEPCK and adipocyte differentiation via repression of PPARG. Regulates glucagon release in pancreatic alpha-cells via the AMPK-NAMPT-SIRT1 pathway and the proliferation, glucose-induced insulin secretion and expression of key lipogenic genes in pancreatic-beta cells. Positively regulates bile acid synthesis by increasing hepatic expression of CYP7A1 via repression of NR0B2 and NFIL3 which are negative regulators of CYP7A1. Modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy; controls mitochondrial biogenesis and respiration by interfering with the STK11-PRKAA1/2-SIRT1-PPARGC1A signaling pathway. Represses the expression of SERPINE1/PAI1, an important modulator of cardiovascular disease and the expression of inflammatory cytokines and chemokines in macrophages. Represses gene expression at a distance in macrophages by inhibiting the transcription of enhancer-derived RNAs (eRNAs). Plays a role in the circadian regulation of body temperature and negatively regulates thermogenic transcriptional programs in brown adipose tissue (BAT); imposes a circadian oscillation in BAT activity, increasing body temperature when awake and depressing thermogenesis during sleep. In concert with NR2E3, regulates transcriptional networks critical for photoreceptor development and function. In addition to its activity as a repressor, can also act as a transcriptional activator. In the ovarian granulosa cells acts as a transcriptional activator of STAR which plays a role in steroid biosynthesis. In collaboration with SP1, activates GJA1 transcription in a heme-independent manner. Represses the transcription of CYP2B10, CYP4A10 and CYP4A14 (By similarity). Represses the transcription of CES2 (By similarity). Represses and regulates the circadian expression of TSHB in a NCOR1-dependent manner (By similarity). Negatively regulates the protein stability of NR3C1 and influences the time-dependent subcellular distribution of NR3C1, thereby affecting its transcriptional regulatory activity (By similarity). Plays a critical role in the circadian control of neutrophilic inflammation in the lung; under resting, non-stress conditions, acts as a rhythmic repressor to limit inflammatory activity whereas in the presence of inflammatory triggers undergoes ubiquitin-mediated degradation thereby relieving inhibition of the inflammatory response (By similarity). Plays a key role in the circadian regulation of microglial activation and neuroinflammation; suppresses microglial activation through the NF-kappaB pathway in the central nervous system (By similarity). Plays a role in the regulation of the diurnal rhythms of lipid and protein metabolism in the skeletal muscle via transcriptional repression of genes controlling lipid and amino acid metabolism in the muscle (By similarity). {ECO0000250|UniProtKBQ3UV55, ECO0000269|PubMed12021280, ECO0000269|PubMed15761026, ECO0000269|PubMed16968709, ECO0000269|PubMed18006707, ECO0000269|PubMed19710360, ECO0000269|PubMed1971514, ECO0000269|PubMed21479263, ECO0000269|PubMed22184247, ECO0000269|PubMed23398316, ECO0000269|PubMed2539258}.

**Nr1d2:** *Human Uniprot function (Human NR1D2):* Transcriptional repressor which coordinates circadian rhythm and metabolic pathways in a heme-dependent manner. Integral component of the complex transcription machinery that governs circadian rhythmicity and forms a critical negative limb of the circadian clock by directly repressing the expression of core clock components ARNTL/BMAL1 and CLOCK. Also regulates genes involved in metabolic functions, including lipid metabolism and the inflammatory response. Acts as a receptor for heme which stimulates its interaction with the NCOR1/HDAC3 corepressor complex, enhancing transcriptional repression. Recognizes two classes of DNA response elements within the promoter of its target genes and can bind to DNA as either monomers or homodimers, depending on the nature of the response element. Binds as a monomer to a response element composed of the consensus half-site motif 5'-[A/G]GGTCA-3' preceded by an A/T-rich 5' sequence (RevRE), or as a homodimer to a direct repeat of the core motif spaced by two nuclegotides (RevDR-2). Acts as a potent competitive repressor of ROR alpha (RORA) function and also negatively regulates the expression of NR1D1. Regulates lipid and energy homeostasis in the skeletal muscle via repression of genes involved in lipid metabolism and myogenesis including CD36, FABP3, FABP4, UCP3, SCD1 and MSTN. Regulates hepatic lipid metabolism via the repression of APOC3. Represses gene expression at a distance in macrophages by inhibiting the transcription of enhancer-derived RNAs (eRNAs). In addition to its activity as a repressor, can also act as a transcriptional activator. Acts as a transcriptional activator of the sterol regulatory element-binding protein 1 (SREBF1) and the inflammatory mediator interleukin-6 (IL6) in the skeletal muscle (By similarity). Plays a role in the regulation of circadian sleep/wake cycle; essential for maintaining wakefulness during the dark phase or active period (By similarity). Key regulator of skeletal muscle mitochondrial function; negatively regulates the skeletal muscle expression of core clock genes and genes involved in mitochondrial biogenesis, fatty acid beta-oxidation and lipid metabolism (By similarity). May play a role in the circadian control of neutrophilic inflammation in the lung (By similarity). {ECO0000250|UniProtKBQ60674, ECO0000269|PubMed17892483, ECO0000269|PubMed17996965}.

**Sik2:** *Human Uniprot function (Human SIK2):* Phosphorylates 'Ser-794' of IRS1 in insulin-stimulated adipocytes, potentially modulating the efficiency of insulin signal transduction. Inhibits CREB activity by phosphorylating and repressing TORCs, the CREB-specific coactivators. SIK2\_HUMAN,Q9H0K1

**Syne1:** *Human Uniprot function (Human SYNE1):* Multi-isomeric modular protein which forms a linking network between organelles and the actin cytoskeleton to maintain the subcellular spatial organization. As a component of the LINC (LInker of Nucleoskeleton and Cytoskeleton) complex involved in the connection between the nuclear lamina and the cytoskeleton. The nucleocytoplasmic interactions established by the LINC complex play an important role in the transmission of mechanical forces across the nuclear envelope and in nuclear movement and positioning. May be involved in nucleus-centrosome attachment and nuclear migration in neural progenitors implicating LINC complex association with SUN1/2 and probably association with cytoplasmic dynein-dynactin motor complexes; SYNE1 and SYNE2 may act redundantly. Required for centrosome migration to the apical cell surface during early ciliogenesis. May be involved in nuclear remodeling during sperm head formation in spermatogenenis; a probable SUN3SYNE1/KASH1 LINC complex may tether spermatid nuclei to posterior cytoskeletal structures such as the manchette. {ECO0000250|UniProtKBQ6ZWR6, ECO0000269|PubMed11792814, ECO0000269|PubMed18396275}.

**Oaf:** No description available.

**Dbp:** *Human Uniprot function (Human DBP):* This transcriptional activator recognizes and binds to the sequence 5'-RTTAYGTAAY-3' found in the promoter of genes such as albumin, CYP2A4 and CYP2A5. It is not essential for circadian rhythm generation, but modulates important clock output genes. May be a direct target for regulation by the circadian pacemaker component clock. May affect circadian period and sleep regulation.

**Cdkn1a:** *Human Uniprot function (Human CDKN1A):* May be involved in p53/TP53 mediated inhibition of cellular proliferation in response to DNA damage. Binds to and inhibits cyclin-dependent kinase activity, preventing phosphorylation of critical cyclin-dependent kinase substrates and blocking cell cycle progression. Functions in the nuclear localization and assembly of cyclin D-CDK4 complex and promotes its kinase activity towards RB1. At higher stoichiometric ratios, inhibits the kinase activity of the cyclin D-CDK4 complex. Inhibits DNA synthesis by DNA polymerase delta by competing with POLD3 for PCNA binding (PubMed11595739). Plays an important role in controlling cell cycle progression and DNA damage-induced G2 arrest (PubMed9106657). {ECO0000269|PubMed11595739, ECO0000269|PubMed8242751, ECO0000269|PubMed9106657}.

**Cldn1:** *Human Uniprot function (Human CLDN1):* Claudins function as major constituents of the tight junction complexes that regulate the permeability of epithelia. While some claudin family members play essential roles in the formation of impermeable barriers, others mediate the permeability to ions and small molecules. Often, several claudin family members are coexpressed and interact with each other, and this determines the overall permeability. CLDN1 is required to prevent the paracellular diffusion of small molecules through tight junctions in the epidermis and is required for the normal barrier function of the skin. Required for normal water homeostasis and to prevent excessive water loss through the skin, probably via an indirect effect on the expression levels of other proteins, since CLDN1 itself seems to be dispensable for water barrier formation in keratinocyte tight junctions (PubMed23407391). {ECO0000269|PubMed23407391}.; FUNCTION (Microbial infection) Acts as a co-receptor for hepatitis C virus (HCV) in hepatocytes (PubMed17325668, PubMed20375010, PubMed24038151). Associates with CD81 and the CLDN1-CD81 receptor complex is essential for HCV entry into host cell (PubMed20375010). Acts as a receptor for dengue virus (PubMed24074594). {ECO0000269|PubMed17325668, ECO0000269|PubMed20375010, ECO0000269|PubMed24038151, ECO0000269|PubMed24074594}.