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 |
| ***Hsd17b2*** | 79243 | 1387156\_at | <21.7b (NR) | 6.0 | UP |
| ***Nr1d2*** | 259241 | 1370541\_at,1390430\_at | <21.7 (NR) | 3.8 | UP |
| ***Jade1*** | 310352 | 1374636\_at | <21.7 (NR) | 2.1 | UP |
| ***Lgalsl*** | 360983 | 1376867\_at | <21.7 (NR) | 3.0 | DOWN |
| ***Sdr42e1*** | 307897 | 1394960\_at | <21.7 (NR) | 2.1 | UP |
| ***Tef*** | 29362 | 1385374\_at | <21.7 (NR) | 2.1 | UP |
| ***Per3*** | 78962 | 1378745\_at | <21.7 (NR) | 5.5 | UP |
| ***Bcar3*** | 310838 | 1374947\_at | <21.7 (NR) | 2.2 | UP |
| ***Nfil3*** | 114519 | 1368488\_at | <21.7 (NR) | 3.3 | DOWN |
| ***Akr7a3*** | 26760 | 1368121\_at | <21.7 (NR) | 4.5 | UP |

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<21.7 = 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>.

***Hsd17b2*:** Human Uniprot function (Human *HSD17B2*): Capable of catalyzing the interconversion of testosterone and androstenedione, as well as estradiol and estrone. Also has 20-alpha-HSD activity. Uses NADH, whereas EDH17B3 uses NADPH. {ECO0000269|PubMed8099587}.

***Nr1d2:*** Human Uniprot function (Human *NR1D2*): Transcriptional repressor that 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 nucleotides (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}.

***Jade1:*** Human Uniprot function (Human *JADE1*): Scaffold subunit of some HBO1 complexes, which have a histone H4 acetyltransferase activity (PubMed16387653, PubMed19187766, PubMed20129055, PubMed24065767). Plays a key role in HBO1 complex by directing KAT7/HBO1 specificity towards histone H4 acetylation (H4K5ac, H4K8ac and H4K12ac), regulating DNA replication initiation, regulating DNA replication initiation (PubMed20129055, PubMed24065767). May also promote acetylation of nucleosomal histone H4 by KAT5 (PubMed15502158). Promotes apoptosis (PubMed16046545). May act as a renal tumor suppressor (PubMed16046545). Negatively regulates canonical Wnt signaling; at least in part, cooperates with NPHP4 in this function (PubMed22654112). {ECO:0000269|PubMed15502158, ECO:0000269|PubMed16046545, ECO:0000269|PubMed16387653, ECO:0000269|PubMed19187766, ECO:0000269|PubMed20129055, ECO:0000269|PubMed22654112, ECO:0000269|PubMed24065767}.

***Lgalsl:*** Human Uniprot function (Human *LGALSL*): Does not bind lactose and may not bind carbohydrates. {ECO0000269|PubMed18320588, ECO0000269|PubMed18433051}.

***Sdr42e1:*** No description available.

***Tef:*** Human Uniprot function (Human *TEF*): Transcription factor that binds to and transactivates the TSHB promoter. Binds to a minimal DNA-binding sequence 5'-[TC][AG][AG]TTA[TC][AG]-3'.

***Per3:*** Human Uniprot function (Human *PER3*): Originally described as a core component of the circadian clock. The circadian clock, an internal time-keeping system, regulates various physiological processes through the generation of approximately 24‑hour circadian rhythms in gene expression, which are translated into rhythms in metabolism and behavior. It is derived from the Latin roots “circa” (about) and “diem” (day) and acts as an important regulator of a wide array of physiological functions including metabolism, sleep, body temperature, blood pressure, endocrine, immune, cardiovascular, and renal function. Consists of two major components: the central clock, residing in the suprachiasmatic nucleus (SCN) of the brain, and the peripheral clocks that are present in nearly every tissue and organ system. Both the central and peripheral clocks can be reset by environmental cues, also known as Zeitgebers (German for “time givers”). The predominant Zeitgeber for the central clock is light, which is sensed by the retina and signals directly to the SCN. The central clock entrains the peripheral clocks through neuronal and hormonal signals, body temperature, and feeding-related cues, aligning all clocks with the external light/dark cycle. Circadian rhythms allow an organism to achieve temporal homeostasis with its environment at the molecular level by regulating gene expression to create a peak of protein expression once every 24 hours to control when a particular physiological process is most active with respect to the solar day. Transcription and translation of core clock components (CLOCK, NPAS2, ARNTL/BMAL1, ARNTL2/BMAL2, PER1, PER2, PER3, CRY1, and CRY2) play a critical role in rhythm generation, whereas delays imposed by post-translational modifications (PTMs) are important for determining the period (tau) of the rhythms (tau refers to the period of a rhythm and is the length, in time, of one complete cycle). A diurnal rhythm is synchronized with the day/night cycle, whereas the ultradian and infradian rhythms have a period shorter and longer than 24 hours, respectively. Disruptions in the circadian rhythms contribute to the pathology of cardiovascular diseases, cancer, metabolic syndromes, and aging. A transcription/translation feedback loop (TTFL) forms the core of the molecular circadian clock mechanism. Transcription factors, CLOCK or NPAS2 and ARNTL/BMAL1 or ARNTL2/BMAL2, form the positive limb of the feedback loop, act in the form of a heterodimer, and activate the transcription of core clock genes and clock-controlled genes (involved in key metabolic processes), harboring E-box elements (5'-CACGTG-3') within their promoters. The core clock genes, PER1/2/3 and CRY1/2, which are transcriptional repressors, form the negative limb of the feedback loop and interact with the CLOCK|NPAS2-ARNTL/BMAL1|ARNTL2/BMAL2 heterodimer, inhibiting its activity and thereby negatively regulating their own expression. This heterodimer also activates nuclear receptors NR1D1, NR1D2, RORA, RORB, and RORG, which form a second feedback loop and which activate and repress ARNTL/BMAL1 transcription, respectively. Has a redundant role with the other PER proteins, PER1 and PER2, and is not essential for the circadian rhythms’ maintenance. In contrast, plays an important role in sleep-wake timing and sleep homeostasis, probably through the transcriptional regulation of sleep homeostasis-related genes, without influencing circadian parameters. Can bind heme. {ECO0000269|PubMed17346965, ECO0000269|PubMed19716732, ECO0000269|PubMed24439663, ECO0000269|PubMed24577121, ECO0000269|PubMed26903630}.

***Bcar3:*** Human Uniprot function (Human *BCAR3*): Acts as an adapter protein downstream of several growth factor receptors to promote cell proliferation, migration, and redistribution of actin fibers (PubMed24216110). Specifically involved in INS/insulin signaling pathway by mediating MAPK1/ERK2-MAPK3/ERK1 activation and DNA synthesis (PubMed24216110). Promotes insulin-mediated membrane ruffling (by similarity). In response to vasoconstrictor peptide EDN1, involved in the activation of RAP1 downstream of PTK2B via interaction with phosphorylated BCAR1 (PubMed19086031). Inhibits cell migration and invasion via regulation of TGFB-mediated matrix digestion, actin filament rearrangement, and inhibition of invadopodia activity (by similarity). May inhibit TGFB-SMAD signaling, via facilitating BCAR1 and SMAD2 and/or SMAD3 interaction (by similarity). Regulates EGF-induced DNA synthesis (PubMed18722344). Required for the maintenance of ocular lens morphology and structural integrity, potentially via regulation of focal adhesion complex signaling (by similarity). Acts upstream of PTPRA to regulate the localization of BCAR1 and PTPRA to focal adhesions, via regulation of SRC-mediated phosphorylation of PTPRA (by similarity). Positively regulates integrin-induced tyrosine phosphorylation of BCAR1 (by similarity). Acts as a guanine nucleotide exchange factor (GEF) for small GTPases RALA, RAP1A, and RRAS (by similarity). However, in a contrasting study, lacks GEF activity toward RAP1 (PubMed22081014).

***Nfil3:*** Human Uniprot function (Human *NFIL3*): Acts as a transcriptional regulator that recognizes and binds to the sequence 5' [GA]TTA[CT]GTAA[CT]-3', a sequence present in many cellular and viral promoters. Represses transcription from promoters with activating transcription factor (ATF) sites. Represses promoter activity in osteoblasts (by similarity). Represses transcriptional activity of PER1 (by similarity). Represses transcriptional activity of PER2 via the B-site on the promoter (by similarity). Activates transcription from the interleukin-3 promoter in T-cells. Competes for the same consensus-binding site with PAR DNA-binding factors (DBP, HLF, and TEF) (by similarity). Component of the circadian clock that acts as a negative regulator for the circadian expression of PER2 oscillation in the cell-autonomous core clock (by similarity). Protects pro-B cells from programmed cell death (by similarity). Represses the transcription of CYP2A5 (by similarity). Positively regulates the expression and activity of CES2 by antagonizing the repressive action of NR1D1 on CES2 (by similarity). {ECO0000250|UniProtKBO08750, ECO0000269|PubMed1620116, ECO0000269|PubMed7565758, ECO0000269|PubMed8836190}.

***Akr7a3:*** Human Uniprot function (Human *AKR7A3*): Can reduce the dialdehyde protein-binding form of aflatoxin B1 (AFB1) to the nonbinding AFB1 dialcohol. May be involved in protection of the liver against the toxic and carcinogenic effects of AFB1, a potent hepatocarcinogen. {ECO:0000269|PubMed18416522}.