### 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 |
| **nefh** | 24587 | NEFH\_33218 | <0.050 (NR) | 2.4 | DOWN |
| **top2a** | 360243 | TOP2A\_10059 | 12.334 (3.464-46.527) | 2.8 | DOWN |
| **ect2** | 361921 | ECT2\_8523 | 31.232 (16.473-67.195) | 2.2 | DOWN |
| **nqo1** | 24314 | NQO1\_33055 | 40.551 (21.583-79.355) | 2.6 | UP |
| **cyp1a1** | 24296 | CYP1A1\_8415 | 49.045 (39.236-64.853) | 8.8 | UP |
| **hmgcs2** | 24450 | HMGCS2\_8812 | 106.351 (59.870-208.329) | 2.6 | DOWN |
| **nfil3** | 114519 | NFIL3\_9304 | 121.321 (82.552-229.790) | 2.2 | DOWN |
| **mt1** | 24567 | MT1A\_9255 | 168.588 (103.554-1208.950) | 2.1 | DOWN |
| **cyp2c11** | 29277 | CYP2C11\_32593 | 216.743 (139.563-368.944) | 8.4 | DOWN |
| **rassf1** | 363140 | RASSF1\_32475 | 903.848 (608.514-1171.720) | 2.7 | 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.

<0.050 = 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

**Nefh:** *Human Uniprot function (Human NEFH):* Neurofilaments usually contain three intermediate filament proteins NEFL, NEFM, and NEFH which are involved in the maintenance of neuronal caliber. NEFH has an important function in mature axons that is not subserved by the two smaller NF proteins. May additionally cooperate with the neuronal intermediate filament proteins PRPH and INA to form neuronal filamentous networks (By similarity). {ECO0000250|UniProtKBP19246}.

**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}.

**Ect2:** *Human Uniprot function (Human ECT2):* Guanine nucleotide exchange factor (GEF) that catalyzes the exchange of GDP for GTP. Promotes guanine nucleotide exchange on the Rho family members of small GTPases, like RHOA, RHOC, RAC1 and CDC42. Required for signal transduction pathways involved in the regulation of cytokinesis. Component of the centralspindlin complex that serves as a microtubule-dependent and Rho-mediated signaling required for the myosin contractile ring formation during the cell cycle cytokinesis. Regulates the translocation of RHOA from the central spindle to the equatorial region. Plays a role in the control of mitotic spindle assembly; regulates the activation of CDC42 in metaphase for the process of spindle fibers attachment to kinetochores before chromosome congression. Involved in the regulation of epithelial cell polarity; participates in the formation of epithelial tight junctions in a polarity complex PARD3-PARD6-protein kinase PRKCQ-dependent manner. Plays a role in the regulation of neurite outgrowth. Inhibits phenobarbital (PB)-induced NR1I3 nuclear translocation. Stimulates the activity of RAC1 through its association with the oncogenic PARD6A-PRKCI complex in cancer cells, thereby acting to coordinately drive tumor cell proliferation and invasion. Also stimulates genotoxic stress-induced RHOB activity in breast cancer cells leading to their cell death. {ECO0000269|PubMed10579713, ECO0000269|PubMed14645260, ECO0000269|PubMed15254234, ECO0000269|PubMed15545273, ECO0000269|PubMed15642749, ECO0000269|PubMed16103226, ECO0000269|PubMed16170345, ECO0000269|PubMed16236794, ECO0000269|PubMed16495035, ECO0000269|PubMed19129481, ECO0000269|PubMed19468300, ECO0000269|PubMed19617897, ECO0000269|PubMed21189248, ECO0000269|PubMed21373644, ECO0000269|PubMed25068414, ECO0000269|PubMed31888991}.

**Nqo1:** *Human Uniprot function (Human NQO1):* The enzyme apparently serves as a quinone reductase in connection with conjugation reactions of hydroquinons involved in detoxification pathways as well as in biosynthetic processes such as the vitamin K-dependent gamma-carboxylation of glutamate residues in prothrombin synthesis.

**Cyp1a1:** *Human Uniprot function (Human CYP1A1):* A cytochrome P450 monooxygenase involved in the metabolism of various endogenous substrates, including fatty acids, steroid hormones and vitamins (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301, PubMed15041462, PubMed18577768, PubMed19965576, PubMed20972997, PubMed10681376). 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 (NADPH--hemoprotein reductase) (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301, PubMed15041462, PubMed18577768, PubMed19965576, PubMed20972997, PubMed10681376). Catalyzes the hydroxylation of carbon-hydrogen bonds. Exhibits high catalytic activity for the formation of hydroxyestrogens from estrone (E1) and 17beta-estradiol (E2), namely 2-hydroxy E1 and E2, as well as D-ring hydroxylated E1 and E2 at the C15-alpha and C16-alpha positions (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301). Displays different regioselectivities for polyunsaturated fatty acids (PUFA) hydroxylation (PubMed15041462, PubMed18577768). Catalyzes the epoxidation of double bonds of certain PUFA (PubMed15041462, PubMed19965576, PubMed20972997). Converts arachidonic acid toward epoxyeicosatrienoic acid (EET) regioisomers, 8,9-, 11,12-, and 14,15-EET, that function as lipid mediators in the vascular system (PubMed20972997). Displays an absolute stereoselectivity in the epoxidation of eicosapentaenoic acid (EPA) producing the 17(R),18(S) enantiomer (PubMed15041462). May play an important role in all-trans retinoic acid biosynthesis in extrahepatic tissues. Catalyzes two successive oxidative transformation of all-trans retinol to all-trans retinal and then to the active form all-trans retinoic acid (PubMed10681376). May also participate in eicosanoids metabolism by converting hydroperoxide species into oxo metabolites (lipoxygenase-like reaction, NADPH-independent) (PubMed21068195). {ECO0000269|PubMed10681376, ECO0000269|PubMed11555828, ECO0000269|PubMed12865317, ECO0000269|PubMed14559847, ECO0000269|PubMed15041462, ECO0000269|PubMed15805301, ECO0000269|PubMed18577768, ECO0000269|PubMed19965576, ECO0000269|PubMed20972997, ECO0000269|PubMed21068195}.

**Hmgcs2:** *Human Uniprot function (Human HMGCS2):* Catalyzes the first irreversible step in ketogenesis, condensing acetyl-CoA to acetoacetyl-CoA to form HMG-CoA, which is converted by HMG-CoA reductase (HMGCR) into mevalonate. {ECO0000269|PubMed11228257, ECO0000269|PubMed23751782, ECO0000269|PubMed29597274}.

**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}.

**Mt1:** *Human Uniprot function (Human MT1A):* Metallothioneins have a high content of cysteine residues that bind various heavy metals; these proteins are transcriptionally regulated by both heavy metals and glucocorticoids.

**Cyp2c11:** *Human Uniprot function (Human CYP2C9):* A cytochrome P450 monooxygenase involved in the metabolism of various endogenous substrates, including fatty acids and steroids (PubMed7574697, PubMed9866708, PubMed9435160, PubMed12865317, PubMed15766564, PubMed19965576, PubMed21576599). 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 (NADPH--hemoprotein reductase) (PubMed7574697, PubMed9866708, PubMed9435160, PubMed12865317, PubMed15766564, PubMed19965576, PubMed21576599). Catalyzes the epoxidation of double bonds of polyunsaturated fatty acids (PUFA) (PubMed7574697, PubMed15766564, PubMed19965576, PubMed9866708). Catalyzes the hydroxylation of carbon-hydrogen bonds. Metabolizes cholesterol toward 25-hydroxycholesterol, a physiological regulator of cellular cholesterol homeostasis (PubMed21576599). Exhibits low catalytic activity for the formation of catechol estrogens from 17beta-estradiol (E2) and estrone (E1), namely 2-hydroxy E1 and E2 (PubMed12865317). Catalyzes bisallylic hydroxylation and hydroxylation with double-bond migration of polyunsaturated fatty acids (PUFA) (PubMed9866708, PubMed9435160). Also metabolizes plant monoterpenes such as limonene. Oxygenates (R)- and (S)-limonene to produce carveol and perillyl alcohol (PubMed11950794). Contributes to the wide pharmacokinetics variability of the metabolism of drugs such as S-warfarin, diclofenac, phenytoin, tolbutamide and losartan (PubMed25994031). {ECO0000269|PubMed11950794, ECO0000269|PubMed12865317, ECO0000269|PubMed15766564, ECO0000269|PubMed19965576, ECO0000269|PubMed21576599, ECO0000269|PubMed25994031, ECO0000269|PubMed7574697, ECO0000269|PubMed9435160, ECO0000269|PubMed9866708}.

**Rassf1:** *Human Uniprot function (Human RASSF1):* Potential tumor suppressor. Required for death receptor-dependent apoptosis. Mediates activation of STK3/MST2 and STK4/MST1 during Fas-induced apoptosis by preventing their dephosphorylation. When associated with MOAP1, promotes BAX conformational change and translocation to mitochondrial membranes in response to TNF and TNFSF10 stimulation. Isoform A interacts with CDC20, an activator of the anaphase-promoting complex, APC, resulting in the inhibition of APC activity and mitotic progression. Inhibits proliferation by negatively regulating cell cycle progression at the level of G1/S-phase transition by regulating accumulation of cyclin D1 protein. Isoform C has been shown not to perform these roles, no function has been identified for this isoform. Isoform A disrupts interactions among MDM2, DAXX and USP7, thus contributing to the efficient activation of TP53 by promoting MDM2 self-ubiquitination in cell-cycle checkpoint control in response to DNA damage. {ECO0000269|PubMed10888881, ECO0000269|PubMed11333291, ECO0000269|PubMed12024041, ECO0000269|PubMed14743218, ECO0000269|PubMed15109305, ECO0000269|PubMed15949439, ECO0000269|PubMed16510573, ECO0000269|PubMed18566590, ECO0000269|PubMed21199877}.

### 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 |
| **cyp1a1** | 24296 | CYP1A1\_8415 | 12.886 (9.131-19.323) | 15.5 | UP |
| **gstp1** | 24426 | GSTP1\_8762 | 14.763 (9.430-25.720) | 3.5 | UP |
| **cyp26b1** | 312495 | CYP26B1\_8418 | 18.187 (10.018-36.727) | 2.1 | UP |
| **vwf** | 116669 | VWF\_32396 | 19.676 (4.116-94.078) | 2.1 | DOWN |
| **abcb1b** | 24646 | ABCB1B\_7939 | 20.794 (8.254-57.212) | 6.2 | DOWN |
| **npas2** | 316351 | NPAS2\_9350 | 21.088 (11.331-43.562) | 3.1 | DOWN |
| **arntl** | 29657 | ARNTL\_8086 | 22.913 (11.412-50.159) | 3.4 | DOWN |
| **c4a** | 24233 | C4A\_8176 | 24.209 (8.100-89.537) | 2.3 | DOWN |
| **loc103689965** | 103689965 | C4A\_8176 | 24.209 (8.100-89.537) | 2.3 | DOWN |
| **nqo1** | 24314 | NQO1\_33055 | 25.681 (7.739-86.121) | 2.2 | UP |

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**Cyp1a1:** *Human Uniprot function (Human CYP1A1):* A cytochrome P450 monooxygenase involved in the metabolism of various endogenous substrates, including fatty acids, steroid hormones and vitamins (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301, PubMed15041462, PubMed18577768, PubMed19965576, PubMed20972997, PubMed10681376). 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 (NADPH--hemoprotein reductase) (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301, PubMed15041462, PubMed18577768, PubMed19965576, PubMed20972997, PubMed10681376). Catalyzes the hydroxylation of carbon-hydrogen bonds. Exhibits high catalytic activity for the formation of hydroxyestrogens from estrone (E1) and 17beta-estradiol (E2), namely 2-hydroxy E1 and E2, as well as D-ring hydroxylated E1 and E2 at the C15-alpha and C16-alpha positions (PubMed11555828, PubMed14559847, PubMed12865317, PubMed15805301). Displays different regioselectivities for polyunsaturated fatty acids (PUFA) hydroxylation (PubMed15041462, PubMed18577768). Catalyzes the epoxidation of double bonds of certain PUFA (PubMed15041462, PubMed19965576, PubMed20972997). Converts arachidonic acid toward epoxyeicosatrienoic acid (EET) regioisomers, 8,9-, 11,12-, and 14,15-EET, that function as lipid mediators in the vascular system (PubMed20972997). Displays an absolute stereoselectivity in the epoxidation of eicosapentaenoic acid (EPA) producing the 17(R),18(S) enantiomer (PubMed15041462). May play an important role in all-trans retinoic acid biosynthesis in extrahepatic tissues. Catalyzes two successive oxidative transformation of all-trans retinol to all-trans retinal and then to the active form all-trans retinoic acid (PubMed10681376). May also participate in eicosanoids metabolism by converting hydroperoxide species into oxo metabolites (lipoxygenase-like reaction, NADPH-independent) (PubMed21068195). {ECO0000269|PubMed10681376, ECO0000269|PubMed11555828, ECO0000269|PubMed12865317, ECO0000269|PubMed14559847, ECO0000269|PubMed15041462, ECO0000269|PubMed15805301, ECO0000269|PubMed18577768, ECO0000269|PubMed19965576, ECO0000269|PubMed20972997, ECO0000269|PubMed21068195}.

**Gstp1:** *Human Uniprot function (Human GSTP1):* Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles. Involved in the formation of glutathione conjugates of both prostaglandin A2 (PGA2) and prostaglandin J2 (PGJ2) (PubMed9084911). Participates in the formation of novel hepoxilin regioisomers (PubMed21046276). Regulates negatively CDK5 activity via p25/p35 translocation to prevent neurodegeneration. {ECO0000269|PubMed21046276, ECO0000269|PubMed21668448, ECO0000269|PubMed9084911}.

**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}.

**Vwf:** *Human Uniprot function (Human VWF):* Important in the maintenance of hemostasis, it promotes adhesion of platelets to the sites of vascular injury by forming a molecular bridge between sub-endothelial collagen matrix and platelet-surface receptor complex GPIb-IX-V. Also acts as a chaperone for coagulation factor VIII, delivering it to the site of injury, stabilizing its heterodimeric structure and protecting it from premature clearance from plasma.

**Abcb1b:** *Human Uniprot function (Human ABCB1):* Translocates drugs and phospholipids across the membrane (PubMed8898203, PubMed2897240, PubMed9038218). Catalyzes the flop of phospholipids from the cytoplasmic to the exoplasmic leaflet of the apical membrane. Participates mainly to the flop of phosphatidylcholine, phosphatidylethanolamine, beta-D-glucosylceramides and sphingomyelins (PubMed8898203). Energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells (PubMed2897240, PubMed9038218). {ECO0000269|PubMed2897240, ECO0000269|PubMed8898203, ECO0000269|PubMed9038218}.

**Npas2:** *Human Uniprot function (Human NPAS2):* Transcriptional activator which forms 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 'timegivers'). The predominant Zeitgeber for the central clock is light, which is sensed by 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) plays 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, while 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 NR1D1/2 and RORA/B/G, which form a second feedback loop and which activate and repress ARNTL/BMAL1 transcription, respectively. The NPAS2-ARNTL/BMAL1 heterodimer positively regulates the expression of MAOA, F7 and LDHA and modulates the circadian rhythm of daytime contrast sensitivity by regulating the rhythmic expression of adenylate cyclase type 1 (ADCY1) in the retina. NPAS2 plays an important role in sleep homeostasis and in maintaining circadian behaviors in normal light/dark and feeding conditions and in the effective synchronization of feeding behavior with scheduled food availability. Regulates the gene transcription of key metabolic pathways in the liver and is involved in DNA damage response by regulating several cell cycle and DNA repair genes. Controls the circadian rhythm of NR0B2 expression by binding rhythmically to its promoter (By similarity). Mediates the diurnal variation in the expression of GABARA1 receptor in the brain and contributes to the regulation of anxiety-like behaviors and GABAergic neurotransmission in the ventral striatum (By similarity). {ECO0000250|UniProtKBP97460, ECO0000269|PubMed11441146, ECO0000269|PubMed11441147, ECO0000269|PubMed14645221, ECO0000269|PubMed18439826, ECO0000269|PubMed18819933}.

**Arntl:** *Human Uniprot function (Human ARNTL):* Transcriptional activator which forms 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 'timegivers'). The predominant Zeitgeber for the central clock is light, which is sensed by 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) plays 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, while 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 NR1D1/2 and RORA/B/G, which form a second feedback loop and which activate and repress ARNTL/BMAL1 transcription, respectively. ARNTL/BMAL1 positively regulates myogenesis and negatively regulates adipogenesis via the transcriptional control of the genes of the canonical Wnt signaling pathway. Plays a role in normal pancreatic beta-cell function; regulates glucose-stimulated insulin secretion via the regulation of antioxidant genes NFE2L2/NRF2 and its targets SESN2, PRDX3, CCLC and CCLM. Negatively regulates the mTORC1 signaling pathway; regulates the expression of MTOR and DEPTOR. Controls diurnal oscillations of Ly6C inflammatory monocytes; rhythmic recruitment of the PRC2 complex imparts diurnal variation to chemokine expression that is necessary to sustain Ly6C monocyte rhythms. Regulates the expression of HSD3B2, STAR, PTGS2, CYP11A1, CYP19A1 and LHCGR in the ovary and also the genes involved in hair growth. Plays an important role in adult hippocampal neurogenesis by regulating the timely entry of neural stem/progenitor cells (NSPCs) into the cell cycle and the number of cell divisions that take place prior to cell-cycle exit. Regulates the circadian expression of CIART and KLF11. The CLOCK-ARNTL/BMAL1 heterodimer regulates the circadian expression of SERPINE1/PAI1, VWF, B3, CCRN4L/NOC, NAMPT, DBP, MYOD1, PPARGC1A, PPARGC1B, SIRT1, GYS2, F7, NGFR, GNRHR, BHLHE40/DEC1, ATF4, MTA1, KLF10 and also genes implicated in glucose and lipid metabolism. Promotes rhythmic chromatin opening, regulating the DNA accessibility of other transcription factors. The NPAS2-ARNTL/BMAL1 heterodimer positively regulates the expression of MAOA, F7 and LDHA and modulates the circadian rhythm of daytime contrast sensitivity by regulating the rhythmic expression of adenylate cyclase type 1 (ADCY1) in the retina. The preferred binding motif for the CLOCK-ARNTL/BMAL1 heterodimer is 5'-CACGTGA-3', which contains a flanking Ala residue in addition to the canonical 6-nucleotide E-box sequence (PubMed23229515). CLOCK specifically binds to the half-site 5'-CAC-3', while ARNTL binds to the half-site 5'-GTGA-3' (PubMed23229515). The CLOCK-ARNTL/BMAL1 heterodimer also recognizes the non-canonical E-box motifs 5'-AACGTGA-3' and 5'-CATGTGA-3' (PubMed23229515). Essential for the rhythmic interaction of CLOCK with ASS1 and plays a critical role in positively regulating CLOCK-mediated acetylation of ASS1 (PubMed28985504). Plays a role in protecting against lethal sepsis by limiting the expression of immune checkpoint protein CD274 in macrophages in a PKM2-dependent manner (By similarity). Regulates the diurnal rhythms of skeletal muscle metabolism via transcriptional activation of genes promoting triglyceride synthesis (DGAT2) and metabolic efficiency (COQ10B) (By similarity). {ECO0000250|UniProtKBQ9WTL8, ECO0000269|PubMed11441146, ECO0000269|PubMed12738229, ECO0000269|PubMed18587630, ECO0000269|PubMed23785138, ECO0000269|PubMed23955654, ECO0000269|PubMed24005054, ECO0000269|PubMed28985504}.

**C4a:** *Human Uniprot function (Human C4A):* Non-enzymatic component of C3 and C5 convertases and thus essential for the propagation of the classical complement pathway. Covalently binds to immunoglobulins and immune complexes and enhances the solubilization of immune aggregates and the clearance of IC through CR1 on erythrocytes. C4A isotype is responsible for effective binding to form amide bonds with immune aggregates or protein antigens, while C4B isotype catalyzes the transacylation of the thioester carbonyl group to form ester bonds with carbohydrate antigens. CO4A\_HUMAN,P0C0L4
Derived from proteolytic degradation of complement C4, C4a anaphylatoxin is a mediator of local inflammatory process. It induces the contraction of smooth muscle, increases vascular permeability and causes histamine release from mast cells and basophilic leukocytes. CO4A\_HUMAN,P0C0L4

**LOC103689965:** *Human Uniprot function (Human C4A):* Non-enzymatic component of C3 and C5 convertases and thus essential for the propagation of the classical complement pathway. Covalently binds to immunoglobulins and immune complexes and enhances the solubilization of immune aggregates and the clearance of IC through CR1 on erythrocytes. C4A isotype is responsible for effective binding to form amide bonds with immune aggregates or protein antigens, while C4B isotype catalyzes the transacylation of the thioester carbonyl group to form ester bonds with carbohydrate antigens. CO4A\_HUMAN,P0C0L4
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**Nqo1:** *Human Uniprot function (Human NQO1):* The enzyme apparently serves as a quinone reductase in connection with conjugation reactions of hydroquinons involved in detoxification pathways as well as in biosynthetic processes such as the vitamin K-dependent gamma-carboxylation of glutamate residues in prothrombin synthesis.