**Australian Functional Genomics Network**

**Functional Genomics Platform EOI**

**Gene List**

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# High level summary

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE SYMBOL** | **GENE NAME** | **DISEASE ASSOCIATION** | **CLINVAR**  ***# of VUS***  ***(% of VUS)*** |
| **MYH7** | Myosin Heavy Chain 7 | Cardiomyopathy & Myopathy | 2184(60%) |
| **MYBPC3** | Myosin Binding Protein C, Cardiac | Cardiomyopathy | 1941(50%) |
| **RP1L1** | Retinitis Pigmentosa 1-Like 1 | Retinitis pigmentosa & Macular dystrophy | 690(61%) |
| **DNAH11** | Dynein Axonemal Heavy Chain 11 | Primary ciliary dyskinesia (Ciliopathy) | 1308(24%) |
| **CDH23** | Cadherin-Related 23 | Usher syndrome (deafness, reduced vestibular function, retinal degeneration), Deafness (AR) & Pituitary adenoma | 1692(35%) |
| **MYO7A** | Myosin VIIA | Deafness (AD & AR), Usher syndrome | 1432(34%) |
| **DSP** | Desmoplakin | Arrhythmogenic cardiomyopathy with wooly hair and keratoderma & Arrhythmogenic right ventricular dysplasia | 2688(56%) |
| **KMT2D** | Lysine Methyltransferase 2D | Kabuki syndrome (multisystem disorder including facial, neurological & cardiac malformations) | 1893(37%) |
| **COL4A4** | Collagen Type IV Alpha 4 Chain | Kidney disease (Alport syndrome & Hematuria) | 759(27%) |
| **LDLR** | Low-Density Lipoprotein Receptor | Familial hypercholesterolemia | 1075(33%) |
| **SMAD4** | SMAD Family Member 4 | Juvenile polyposis, hereditary hemorrhagic telangiectasia syndrome (blood vessel malformations) & Myhre syndrome (connective tissue disorder) | 1085(52%) |
| **ENG** | Endoglin | Hereditary hemorrhagic telangiectasia syndrome (blood vessel malformations) | 344(33%) |
| **ACVRL1** | Activin A Receptor Like Type 1 | Hereditary hemorrhagic telangiectasia syndrome | 257(27%) |
| **FBN1** | Fibrillin-1 | Connective tissue disorders including Marfan syndrome | 2685(39%) |
| **CFH** | Complement Factor H | Blood disorders including hemolytic-uremic syndrome (HUS) and chronic hypocomplementemic nephropathy | 411(53%) |
| **IDH2** | Isocitrate Dehydrogenase 2 | Neurometabolic disorder (D-2-hydroxyglutaric aciduria) | 97(50%) |
| **COL6A3** | Collagen Type VI Alpha 3 Chain | Bethlem Myopathy, Dystonia &Ullrich Congenital Muscular Dystrophy | 1893(59%) |
| **SQSTM1** | Sequestosome 1 | Frontotemporal dementia and/or amyotrophic lateral sclerosis, distal myopathy, childhood-onset neurodegeneration & Paget disease of bone | 355(53%) |
| **ARID1B** | AT-Rich Interaction Domain 1B | Coffin-Siris Syndrome (Multiple malformation syndrome) | 615(36%) |
| **ARID1A** | AT-Rich Interaction Domain 1A | Coffin-Siris Syndrome | 468(44%) |
| **GCK** | Glucokinase | Diabetes mellitius including Maturity onset diabetes of the young (MODY) type 2,late onset noninsulin-dependent, permanent neonatal & familial hyperinsulinemic hypoglycemia | 416(48%) |
| **HNF1A** | Hepatocyte Nuclear Factor 1 Alpha | Insulin-dependent diabetes mellitus, MODY type 3 & renal cell carcinoma | 285(42%) |

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## MYH7 | Myosin Heavy Chain 7

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **MYH7  Myosin Heavy Chain 7** | Hexameric protein containing 2 heavy chain subunits, 2 alkali light chain subunits, 2 regulatory light chain subunits. Encodes the beta (or slow) heavy chain subunit of cardiac myosin.  Predominantly expressed in normal human ventricle and skeletal muscle tissues rich in slow-twitch type I muscle fibers. Changes in relative abundance of this protein and the alpha (or fast) heavy subunit of cardiac myosin correlate with the contractile velocity of cardiac muscle. Expression is also altered during thyroid hormone depletion and hemodynamic overloading.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Myosins are actin-based motor molecules with ATPase activity essential for muscle contraction. Forms regular bipolar thick filaments that, together with actin thin filaments, constitute the fundamental contractile unit of skeletal and cardiac muscle.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Cardiomyopathy & Myopathy | Hypertrophic cardiomyopathy, AD, DD;  Dilated cardiomyopathy, AD;Myosin storage myopathy, AD, AR;Laing distal myopathy, AD  (source: OMIM) | 2184(60%) |
| **PROTEIN SIZE** |
| 1935 AA |

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## MYBPC3 | Myosin Binding Protein C, Cardiac

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **MYBPC3  Myosin Binding Protein C, Cardiac** | MYBPC3 encodes the cardiac isoform of myosin-binding protein C. Myosin-binding protein C is a myosin-associated protein found in the cross-bridge-bearing zone (C region) of A bands in striated muscle. MYBPC3 is expressed exclusively in heart muscle and is a key regulator of cardiac contraction. Mutations in this gene are a frequent cause of familial hypertrophic cardiomyopathy.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Thick filament-associated protein located in the crossbridge region of vertebrate striated muscle a bands. In vitro it binds MHC, F-actin and native thin filaments, and modifies the activity of actin-activated myosin ATPase. It may modulate muscle contraction or may play a more structural role.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Cardiomyopathy | Cardiomyopathy, dilated, 1MM, AD; Cardiomyopathy, hypertrophic, 4, AD, AR; Left ventricular noncompaction 10, AD  (source: OMIM) | 1941 (50%) |
| **PROTEIN SIZE** |
| 1274 AA |

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## RP1L1 | Retinitis Pigmentosa 1-Like 1

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **RP1L1**  **Retinitis Pigmentosa 1-Like 1** | This gene encodes a member of the doublecortin family. The protein encoded by this gene contains two N-terminal doublecortin domains, which bind microtubules and regulate microtubule polymerization, and two C-terminal large repetitive regions, both of which contain a high percentage of glutamine and glutamic acid residues. This protein is a retinal-specific protein. Its exact length varies among individuals due to the presence of a 16aa repeat in the first C-terminal repetitive region. The 16aa repeat is encoded by the highly polymorphic 48-bp repeat, and 1-6 copies of the 16aa repeat have been identified in normal individuals. The current reference sequence shown here has a single copy of the 16aa repeat. This protein and the RP1 protein, another retinal-specific protein, play essential and synergistic roles in affecting photosensitivity and outer segment morphogenesis of rod photoreceptors. Mutations in this gene cause occult macular dystrophy (OMD).  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Required for the differentiation of photoreceptor cells. Plays a role in the organization of outer segment of rod and cone photoreceptors (By similarity).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Retinitis pigmentosa & Macular dystrophy | Occult macular dystrophy, AD;Retinitis pigmentosa 88, AR  (source: OMIM) | 690(61%) |
| **PROTEIN SIZE** |
| 2400 AA |

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## DNAH11 | Dynein Axonemal Heavy Chain 11

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **DNAH11**  **Dynein Axonemal Heavy Chain 11** | This gene encodes a ciliary outer dynein arm protein and is a member of the dynein heavy chain family. It is a microtubule-dependent motor ATPase and has been reported to be involved in the movement of respiratory cilia. Mutations in this gene have been implicated in causing Kartagener Syndrome (a combination of situs inversus totalis and Primary Ciliary Dyskinesia (PCD), also called Immotile Cilia Syndrome 1 (ICS1)) and male sterility.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Force generating protein of respiratory cilia. Produces force towards the minus ends of microtubules. Dynein has ATPase activity; the force-producing power stroke is thought to occur on release of ADP.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Primary ciliary dyskinesia (Ciliopathy) | Primary ciliary dyskinesia, with or without situs inversus, AR  (source: OMIM) | 1308(24%) |
| **PROTEIN SIZE** |
| 4516 AA |

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## CDH23 | Cadherin-Related 23

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| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **CDH23**  **Cadherin-Related 23** | This gene is a member of the cadherin superfamily, whose genes encode calcium dependent cell-cell adhesion glycoproteins. The encoded protein is thought to be involved in stereocilia organization and hair bundle formation. The gene is located in a region containing the human deafness loci DFNB12 and USH1D. Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of this cadherin-like gene. Upregulation of this gene may also be associated with breast cancer. Alternative splice variants encoding different isoforms have been described.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Cadherins are calcium-dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells. CDH23 is required for establishing and/or maintaining the proper organization of the stereocilia bundle of hair cells in the cochlea and the vestibule during late embryonic/early postnatal development. It is part of the functional network formed by USH1C, USH1G, CDH23 and MYO7A that mediates mechanotransduction in cochlear hair cells. Required for normal hearing.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Vision and hearing loss syndrome & pituitary adenoma | Autosomal recessive deafness; Usher syndrome, type 1D, AR; Usher syndrome, type 1D/F digenic, AR, DR; Pituitary adenoma, AR, DR;  (source: OMIM) | 1692 (35%) |
| **PROTEIN SIZE** |
| 2215 AA |

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## MYO7A | Myosin VIIA

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| **GENE** | **GENE SUMMARY** | | |
| **MYO7A**  **Myosin VIIA** | This gene is a member of the myosin gene family. Myosins are mechanochemical proteins characterized by the presence of a motor domain, an actin-binding domain, a neck domain that interacts with other proteins, and a tail domain that serves as an anchor. This gene encodes an unconventional myosin with a very short tail. Defects in this gene are associated with the mouse shaker-1 phenotype and the human Usher syndrome 1B which are characterized by deafness, reduced vestibular function, and (in human) retinal degeneration. Alternative splicing results in multiple transcript variants.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Myosins are actin-based motor molecules with ATPase activity. Unconventional myosins serve in intracellular movements. Their highly divergent tails bind to membranous compartments, which are then moved relative to actin filaments. In the retina, plays an important role in the renewal of the outer photoreceptor disks. Plays an important role in the distribution and migration of retinal pigment epithelial (RPE) melanosomes and phagosomes, and in the regulation of opsin transport in retinal photoreceptors. In the inner ear, plays an important role in differentiation, morphogenesis and organization of cochlear hair cell bundles. Involved in hair-cell vesicle trafficking of aminoglycosides, which are known to induce ototoxicity (By similarity). Motor protein that is a part of the functional network formed by USH1C, USH1G, CDH23 and MYO7A that mediates mechanotransduction in cochlear hair cells. Required for normal hearing  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Deafness (AD & AR), Syndromic hearing & vision loss | Deafness, autosomal dominant 11, AD;Deafness, autosomal recessive 2, AR;Usher syndrome, type 1B, AR  (source: OMIM) | 1432 (34%) |
| **PROTEIN SIZE** |
| 2215 AA |

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## DSP | Desmoplakin

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| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **DSP**  **Desmoplakin** | This gene encodes a protein that anchors intermediate filaments to desmosomal plaques and forms an obligate component of functional desmosomes. Mutations in this gene are the cause of several cardiomyopathies and keratodermas, including skin fragility-woolly hair syndrome. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jan 2016]  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Major high molecular weight protein of desmosomes. Regulates profibrotic gene expression in cardiomyocytes via activation of the MAPK14/p38 MAPK signaling cascade and increase in TGFB1 protein abundance (By similarity).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Syndromic cardiomyopathy & ventricular dysplasia | Arrhythmogenic right ventricular dysplasia 8, AD;  Dilated cardiomyopathy with woolly hair and keratoderma, AR;  Dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis, AD;  Lethal acantholytic epidermolysis bullosa, AR;  Keratosis palmoplantaris striata II, AD;  (source: OMIM) | 2688(56%) |
| **PROTEIN SIZE** |
| 2871 AA |

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## KMT2D | Lysine Methyltransferase 2D

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **KMT2D**  **Lysine Methyltransferase 2D** | The protein encoded by this gene is a histone methyltransferase that methylates the Lys-4 position of histone H3. The encoded protein is part of a large protein complex called ASCOM, which has been shown to be a transcriptional regulator of the beta-globin and estrogen receptor genes. Mutations in this gene have been shown to be a cause of Kabuki syndrome.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Histone methyltransferase that catalyzes methyl group transfer from S-adenosyl-L-methionine to the epsilon-amino group of 'Lys-4' of histone H3 (H3K4) (PubMed:25561738). Part of chromatin remodeling machinery predominantly forms H3K4me1 methylation marks at active chromatin sites where transcription and DNA repair take place (PubMed:25561738, PubMed:17500065). Acts as a coactivator for estrogen receptor by being recruited by ESR1, thereby activating transcription (PubMed:16603732).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Multisystem disorder including facial, neurological & cardiac malformations | Branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome, AD;  Kabuki syndrome 1, AD  (source: OMIM) | 1893(37%) |
| **PROTEIN SIZE** |
| 5537 AA |

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## COL4A4 | Collagen Type IV Alpha 4 Chain

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **COL4A4**  **Collagen Type IV Alpha 4 Chain** | This gene encodes one of the six subunits of type IV collagen, the major structural component of basement membranes. This particular collagen IV subunit, however, is only found in a subset of basement membranes. Like the other members of the type IV collagen gene family, this gene is organized in a head-to-head conformation with another type IV collagen gene so that each gene pair shares a common promoter. Mutations in this gene are associated with type II autosomal recessive Alport syndrome (hereditary glomerulonephropathy) and with familial benign hematuria (thin basement membrane disease). Two transcripts, differing only in their transcription start sites, have been identified for this gene and, as is common for collagen genes, multiple polyadenylation sites are found in the 3' UTR.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Type IV collagen is the major structural component of glomerular basement membranes (GBM), forming a 'chicken-wire' meshwork together with laminins, proteoglycans and entactin/nidogen.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Kidney disease | Alport syndrome 2, AR;Hematuria, familial benign, 1, AD  (source: OMIM) | 759(27%) |
| **PROTEIN SIZE** |
| 1690 AA |

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## LDLR | Low-Density Lipoprotein Receptor

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **LDLR**  **Low-Density Lipoprotein Receptor** | The low density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. The encoded protein is normally bound at the cell membrane, where it binds low density lipoprotein/cholesterol and is taken into the cell. Lysosomes release the cholesterol, which is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. At the same time, a reciprocal stimulation of cholesterol ester synthesis takes place. Mutations in this gene cause the autosomal dominant disorder, familial hypercholesterolemia. Alternate splicing results in multiple transcript variants.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Binds low density lipoprotein /LDL, the major cholesterol-carrying lipoprotein of plasma, and transports it into cells by endocytosis. In order to be internalized, the receptor-ligand complexes must first cluster into clathrin-coated pits. Forms a ternary complex with PGRMC1 and TMEM97 receptors which increases LDLR-mediated LDL internalization (PubMed:30443021).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Familial hypercholesterolemia | Hypercholesterolemia, familial, 1, AD, AR; LDL cholesterol level QTL2, AD, AR  (source: OMIM) | 1075 (33%) |
| **PROTEIN SIZE** |
| 860 AA |

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## SMAD4 | SMAD Family Member 4

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **SMAD4**  **SMAD Family Member 4** | This gene encodes a member of the Smad family of signal transduction proteins. Smad proteins are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to transforming growth factor (TGF)-beta signaling. The product of this gene forms homomeric complexes and heteromeric complexes with other activated Smad proteins, which then accumulate in the nucleus and regulate the transcription of target genes. This protein binds to DNA and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad-binding element (SBE). The protein acts as a tumor suppressor and inhibits epithelial cell proliferation. It may also have an inhibitory effect on tumors by reducing angiogenesis and increasing blood vessel hyperpermeability. The encoded protein is a crucial component of the bone morphogenetic protein signaling pathway. The Smad proteins are subject to complex regulation by post-translational modifications. Mutations or deletions in this gene have been shown to result in pancreatic cancer, juvenile polyposis syndrome, and hereditary hemorrhagic telangiectasia syndrome. (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| In muscle physiology, plays a central role in the balance between atrophy and hypertrophy. When recruited by MSTN, promotes atrophy response via phosphorylated SMAD2/4. MSTN decrease causes SMAD4 release and subsequent recruitment by the BMP pathway to promote hypertrophy via phosphorylated SMAD1/5/8. Acts synergistically with SMAD1 and YY1 in bone morphogenetic protein (BMP)-mediated cardiac-specific gene expression. Binds to SMAD binding elements (SBEs) (5'-GTCT/AGAC-3') within BMP response element (BMPRE) of cardiac activating regions (By similarity). Common SMAD (co-SMAD) is the coactivator and mediator of signal transduction by TGF-beta (transforming growth factor). Component of the heterotrimeric SMAD2/SMAD3-SMAD4 complex that forms in the nucleus and is required for the TGF-mediated signaling (PubMed:25514493). Promotes binding of the SMAD2/SMAD4/FAST-1 complex to DNA and provides an activation function required for SMAD1 or SMAD2 to stimulate transcription. Component of the multimeric SMAD3/SMAD4/JUN/ FOS complex which forms at the AP1 promoter site; required for synergistic transcriptional activity in response to TGF-beta. May act as a tumor suppressor. Positively regulates PDPK1 kinase activity by stimulating its dissociation from the 14-3-3 protein YWHAQ which acts as a negative regulator. (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Juvenile polyposis, blood vessel malformations & connective tissue disorder | Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, AD;Myhre syndrome, AD;Pancreatic cancer, somatic, AD;Polyposis, juvenile intestinal, AD  (source: OMIM) | 1085(52%) |
| **PROTEIN SIZE** |
| 552 AA |

## ENG | Endoglin

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **ENG**  **Endoglin** | This gene encodes a homodimeric transmembrane protein which is a major glycoprotein of the vascular endothelium. This protein is a component of the transforming growth factor beta receptor complex and it binds to the beta1 and beta3 peptides with high affinity. Mutations in this gene cause hereditary hemorrhagic telangiectasia, also known as Osler-Rendu-Weber syndrome 1, an autosomal dominant multisystemic vascular dysplasia. This gene may also be involved in preeclampsia and several types of cancer. Alternatively spliced transcript variants encoding different isoforms have been found for this gene.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Vascular endothelium glycoprotein that plays an important role in the regulation of angiogenesis (PubMed:21737454, PubMed:23300529). Required for normal structure and integrity of adult vasculature (PubMed:7894484). Regulates the migration of vascular endothelial cells (PubMed:17540773). Required for normal extraembryonic angiogenesis and for embryonic heart development (By similarity). May regulate endothelial cell shape changes in response to blood flow, which drive vascular remodeling and establishment of normal vascular morphology during angiogenesis (By similarity). May play a critical role in the binding of endothelial cells to integrins and/or other RGD receptors (PubMed:1692830). Acts as a TGF-beta coreceptor and is involved in the TGF-beta/BMP signaling cascade that ultimately leads to the activation of SMAD transcription factors (PubMed:8370410, PubMed:21737454, PubMed:22347366, PubMed:23300529). Required for GDF2/BMP9 signaling through SMAD1 in endothelial cells and modulates TGFB1 signaling through SMAD3 (PubMed:21737454, PubMed:22347366, PubMed:23300529).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Blood vessel malformations | Hereditary Hemorrhagic Telangiectasia, Type 1, AD  (source: OMIM) | 344(33%) |
| **PROTEIN SIZE** |
| 658 AA |

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## ACVRL1 | Activin A Receptor Like Type 1

|  |  |  |  |
| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **ACVRL1**  **Activin A Receptor Like Type 1** | This gene encodes a type I cell-surface receptor for the TGF-beta superfamily of ligands. It shares with other type I receptors a high degree of similarity in serine-threonine kinase subdomains, a glycine- and serine-rich region (called the GS domain) preceding the kinase domain, and a short C-terminal tail. The encoded protein, sometimes termed ALK1, shares similar domain structures with other closely related ALK or activin receptor-like kinase proteins that form a subfamily of receptor serine/threonine kinases. Mutations in this gene are associated with hemorrhagic telangiectasia type 2, also known as Rendu-Osler-Weber syndrome 2.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Type I receptor for TGF-beta family ligands BMP9/GDF2 and BMP10 and important regulator of normal blood vessel development. On ligand binding, forms a receptor complex consisting of two type II and two type I transmembrane serine/threonine kinases. Type II receptors phosphorylate and activate type I receptors which autophosphorylate, then bind and activate SMAD transcriptional regulators. May bind activin as well.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Blood vessel malformations | Hereditary hemorrhagic telangiectasia, type 2, AD  (source: OMIM) | 257(27%) |
| **PROTEIN SIZE** |
| 503 AA |

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## FBN1 | Fibrillin-1

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| --- | --- | --- | --- |
| **GENE** | **GENE SUMMARY** | | |
| **FBN1**  **Fibrillin-1** | This gene encodes a member of the fibrillin family of proteins. The encoded preproprotein is proteolytically processed to generate two proteins including the extracellular matrix component fibrillin-1 and the protein hormone asprosin. Fibrillin-1 is an extracellular matrix glycoprotein that serves as a structural component of calcium-binding microfibrils. These microfibrils provide force-bearing structural support in elastic and nonelastic connective tissue throughout the body. Asprosin, secreted by white adipose tissue, has been shown to regulate glucose homeostasis. Mutations in this gene are associated with Marfan syndrome and the related MASS phenotype, as well as ectopia lentis syndrome, Weill-Marchesani syndrome, Shprintzen-Goldberg syndrome and neonatal progeroid syndrome.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues (PubMed:1860873, PubMed:15062093).  Fibrillin-1-containing microfibrils provide long-term force bearing structural support (PubMed:27026396).  In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin (PubMed:27026396).  Microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles (PubMed:27026396).  Plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (PubMed:27026396).  Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11(PubMed:24039232).  This leads to disruption of TNFSF11-induced Ca2+ signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232).  Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1 (PubMed:12807887, PubMed:17158881).  Binds heparin and this interaction has an important role in the assembly of microfibrils (PubMed:11461921).Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:27087445, PubMed:30853600).  Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:27087445).  Binds the olfactory receptor OR4M1 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:27087445, PubMed:31230984).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Connective tissue disorders | Marfan syndrome, AD;Acromicric dysplasia, AD;Ectopia lentis, familial, AD;Geleophysic dysplasia 2, AD;Marfan lipodystrophy syndrome, AD;MASS syndrome, AD;Stiff skin syndrome, AD;Weill-Marchesani syndrome 2,  AD  (source: OMIM) | 2685(39%) |
| **PROTEIN SIZE** |
| 2871 AA |

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## CFH | Complement Factor H

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| **GENE** | **GENE SUMMARY** | | |
| **CFH**  **Complement Factor H** | This gene is a member of the Regulator of Complement Activation (RCA) gene cluster and encodes a protein with twenty short consensus repeat (SCR) domains. This protein is secreted into the bloodstream and has an essential role in the regulation of complement activation, restricting this innate defense mechanism to microbial infections. Mutations in this gene have been associated with hemolytic-uremic syndrome (HUS) and chronic hypocomplementemic nephropathy. Alternate transcriptional splice variants, encoding different isoforms, have been characterized.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Glycoprotein that plays an essential role in maintaining a well-balanced immune response by modulating complement activation. Acts as a soluble inhibitor of complement, where its binding to self markers such as glycan structures prevents complement activation and amplification on cell surfaces (PubMed:21285368, PubMed:25402769).Accelerates the decay of the complement alternative pathway (AP) C3 convertase C3bBb, thus preventing local formation of more C3b, the central player of the complement amplification loop (PubMed:19503104, PubMed:26700768).As a cofactor of the serine protease factor I, CFH also regulates proteolytic degradation of already-deposited C3b (PubMed:23332154, PubMed:18252712, PubMed:28671664).In addition, mediates several cellular responses through interaction with specific receptors. For example, interacts with CR3/ITGAM receptor and thereby mediates the adhesion of human neutrophils to different pathogens. In turn, these pathogens are phagocytosed and destroyed (PubMed:9558116, PubMed:20008295).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Blood disorders | Susceptibility to Hemolytic uremic syndrome, atypical, AD, AR; Susceptibility to age-related macular degeneration, AD; Basal laminar drusen, AD; Complement factor H deficiency, AD, AR  (source: OMIM) | 411(53%) |
| **PROTEIN SIZE** |
| 1231 AA |

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## IDH2 | Isocitrate Dehydrogenase 2

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| **GENE** | **GENE SUMMARY** | | |
| **IDH2**  **Isocitrate Dehydrogenase 2** | Isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate. These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the mitochondria. It plays a role in intermediary metabolism and energy production. This protein may tightly associate or interact with the pyruvate dehydrogenase complex. Alternative splicing results in multiple transcript variants.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Plays a role in intermediary metabolism and energy production (PubMed:22416140, PubMed:19228619).It may tightly associate or interact with the pyruvate dehydrogenase complex (PubMed:22416140, PubMed:19228619).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Neurometabolic disorder | D-2-hydroxyglutaric aciduria 2  (source: OMIM) | 97(50%) |
| **PROTEIN SIZE** |
| 452 AA |

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## COL6A3 | Collagen Type VI Alpha 3 Chain

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| **GENE** | **GENE SUMMARY** | | |
| **COL6A3**  **Collagen Type VI Alpha 3 Chain** | This gene encodes the alpha-3 chain, one of the three alpha chains of type VI collagen, a beaded filament collagen found in most connective tissues. The alpha-3 chain of type VI collagen is much larger than the alpha-1 and -2 chains. This difference in size is largely due to an increase in the number of subdomains, similar to von Willebrand Factor type A domains, that are found in the amino terminal globular domain of all the alpha chains. These domains have been shown to bind extracellular matrix proteins, an interaction that explains the importance of this collagen in organizing matrix components. Mutations in the type VI collagen genes are associated with Bethlem myopathy, a rare autosomal dominant proximal myopathy with early childhood onset. Mutations in this gene are also a cause of Ullrich congenital muscular dystrophy, also referred to as Ullrich scleroatonic muscular dystrophy, an autosomal recessive congenital myopathy that is more severe than Bethlem myopathy. Multiple transcript variants have been identified, but the full-length nature of only some of these variants has been described.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Collagen VI acts as a cell-binding protein.  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Neuromuscular disorders | Bethlem Myopathy 1C, AD;  Dystonia 27, AR;  Ullrich Congenital Muscular Dystrophy 1C, AD, AR  (source: OMIM) | 1893 (59%) |
| **PROTEIN SIZE** |
| 3177 AA |

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## SQSTM1 | Sequestosome 1

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| **GENE** | **GENE SUMMARY** | | |
| **SQSTM1**  **Sequestosome 1** | This gene encodes a multifunctional protein that binds ubiquitin and regulates activation of the nuclear factor kappa-B (NF-kB) signaling pathway. The protein functions as a scaffolding/adaptor protein in concert with TNF receptor-associated factor 6 to mediate activation of NF-kB in response to upstream signals. Alternatively spliced transcript variants encoding either the same or different isoforms have been identified for this gene. Mutations in this gene result in sporadic and familial Paget disease of bone.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Molecular adapter required for selective macroautophagy (aggrephagy) by acting as a a bridge between polyubiquitinated proteins and autophagosomes (PubMed:16286508, PubMed:20168092, PubMed:24128730, PubMed:34471133, PubMed:22622177, PubMed:22017874, PubMed:15340068, PubMed:17580304, PubMed:28404643, PubMed:15953362, PubMed:29507397, PubMed:29343546, PubMed:31857589, PubMed:33509017, PubMed:37306101, PubMed:37802024).  Promotes the recruitment of ubiquitinated cargo proteins to autophagosomes via multiple domains that bridge proteins and organelles in different steps (PubMed:16286508, PubMed:20168092, PubMed:24128730, PubMed:22622177, PubMed:29507397, PubMed:29343546, PubMed:28404643, PubMed:37802024).  SQSTM1 first mediates the assembly and removal of ubiquitinated proteins by undergoing liquid-liquid phase separation upon binding to ubiquitinated proteins via its UBA domain, leading to the formation of insoluble cytoplasmic inclusions, known as p62 bodies (PubMed:15911346, PubMed:20168092, PubMed:24128730, PubMed:22017874, PubMed:29507397, PubMed:29343546, PubMed:31857589, PubMed:37802024).  SQSTM1 then interacts with ATG8 family proteins on autophagosomes via its LIR motif, leading to p62 body recruitment to autophagosomes, followed by autophagic clearance of ubiquitinated proteins (PubMed:16286508, PubMed:20168092, PubMed:24128730, PubMed:22622177, PubMed:28404643, PubMed:17580304, PubMed:37802024).  SQSTM1 is itself degraded along with its ubiquitinated cargos (PubMed:16286508, PubMed:17580304, PubMed:37802024). Also required to recruit ubiquitinated proteins to PML bodies in the nucleus (PubMed:20168092). Also involved in autophagy of peroxisomes (pexophagy) in response to reactive oxygen species (ROS) by acting as a bridge between ubiquitinated PEX5 receptor and autophagosomes (PubMed:26344566).  Acts as an activator of the NFE2L2/NRF2 pathway via interaction with KEAP1: interaction inactivates the BCR(KEAP1) complex by sequestering the complex in inclusion bodies, promoting nuclear accumulation of NFE2L2/NRF2 and subsequent expression of cytoprotective genes (PubMed:20452972, PubMed:28380357, PubMed:33393215, PubMed:37306101).  Promotes relocalization of 'Lys-63'-linked ubiquitinated STING1 to autophagosomes (PubMed:29496741).  Involved in endosome organization by retaining vesicles in the perinuclear cloud: following ubiquitination by RNF26, attracts specific vesicle-associated adapters, forming a molecular bridge that restrains cognate vesicles in the perinuclear region and organizes the endosomal pathway for efficient cargo transport (PubMed:27368102, PubMed:33472082).  Sequesters tensin TNS2 into cytoplasmic puncta, promoting TNS2 ubiquitination and proteasomal degradation (PubMed:25101860). May regulate the activation of NFKB1 by TNF-alpha, nerve growth factor (NGF) and interleukin-1 (PubMed:16079148, PubMed:10747026, PubMed:10356400, PubMed:11244088, PubMed:19931284, PubMed:12471037).  May play a role in titin/TTN downstream signaling in muscle cells (PubMed:15802564).  Adapter that mediates the interaction between TRAF6 and CYLD (By similarity).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Progressive neurodegenerative and neuromuscular conditions & bone disease | Frontotemporal dementia and/or amyotrophic lateral sclerosis 3, AD; Myopathy, distal, with rimmed vacuoles, AD; Neurodegeneration with ataxia, dystonia, and gaze palsy, childhood-onset, AR; Paget disease of bone 3, AD  (source: OMIM) | 355 (53%) |
| **PROTEIN SIZE** |
| 440 AA |

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## ARID1B | AT-Rich Interaction Domain 1B

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| **GENE** | **GENE SUMMARY** | | |
| **ARID1B**  **AT-Rich Interaction Domain 1B** | This locus encodes an AT-rich DNA interacting domain-containing protein. The encoded protein is a component of the SWI/SNF chromatin remodeling complex and may play a role in cell-cycle activation. The protein encoded by this locus is similar to AT-rich interactive domain-containing protein 1A. These two proteins function as alternative, mutually exclusive ARID-subunits of the SWI/SNF complex. The associated complexes play opposing roles. Alternative splicing results in multiple transcript variants.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (By similarity). Binds DNA non-specifically (PubMed:14982958, PubMed:15170388).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Multiple congenital malformations | Coffin-Siris Syndrome 1, AD  (source: OMIM) | 615 (36%) |
| **PROTEIN SIZE** |
| 2319 AA |

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## ARID1A | AT-Rich Interaction Domain 1A

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| **GENE** | **GENE SUMMARY** | | |
| **ARID1A**  **AT-Rich Interaction Domain 1A** | This gene encodes a member of the SWI/SNF family, whose members have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. The encoded protein is part of the large ATP-dependent chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin. It possesses at least two conserved domains that could be important for its function. First, it has a DNA-binding domain that can specifically bind an AT-rich DNA sequence known to be recognized by a SNF/SWI complex at the beta-globin locus. Second, the C-terminus of the protein can stimulate glucocorticoid receptor-dependent transcriptional activation. It is thought that the protein encoded by this gene confers specificity to the SNF/SWI complex and may recruit the complex to its targets through either protein-DNA or protein-protein interactions. Two transcript variants encoding different isoforms have been found for this gene.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Binds DNA non-specifically. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (By similarity).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Multiple congenital malformations | Coffin-Siris Syndrome 2, AD  (source: OMIM) | 468 (44%) |
| **PROTEIN SIZE** |
| 2285 AA |

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## GCK | Glucokinase

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| **GENE** | **GENE SUMMARY** | | |
| **GCK**  **Glucokinase** | This gene encodes a member of the hexokinase family of proteins. Hexokinases phosphorylate glucose to produce glucose-6-phosphate, the first step in most glucose metabolism pathways. In contrast to other forms of hexokinase, this enzyme is not inhibited by its product glucose-6-phosphate but remains active while glucose is abundant. The use of multiple promoters and alternative splicing of this gene result in distinct protein isoforms that exhibit tissue-specific expression in the pancreas and liver. In the pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in the liver, this enzyme is important in glucose uptake and conversion to glycogen. Mutations in this gene that alter enzyme activity have been associated with multiple types of diabetes and hyperinsulinemic hypoglycemia. (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| 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) (PubMed:7742312, PubMed:11916951, PubMed:15277402, PubMed:17082186, PubMed:18322640, PubMed:19146401, PubMed:25015100, PubMed:8325892). 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 (PubMed:18322640, PubMed:25015100, PubMed:8325892, PubMed:11916951, PubMed:15277402). 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 (PubMed:8878425). Mediates the initial step of glycolysis by catalyzing phosphorylation of D-glucose to D-glucose 6-phosphate (PubMed:7742312). (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Diabetes mellitius | MODY, type II, AD; Diabetes mellitus, noninsulin-dependent, late onset, AR; Diabetes mellitus, permanent neonatal 1, AD; Hyperinsulinemic hypoglycemia, familial, 3, AD  (source: OMIM) | 416(48%) |
| **PROTEIN SIZE** |
| 465 AA |

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## HNF1A | Hepatocyte Nuclear Factor 1 Alpha

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| **GENE** | **GENE SUMMARY** | | |
| **HNF1A**  **Hepatocyte Nuclear Factor 1 Alpha** | The protein encoded by this gene is a transcription factor required for the expression of several liver-specific genes. The encoded protein functions as a homodimer and binds to the inverted palindrome 5'-GTTAATNATTAAC-3'. Defects in this gene are a cause of maturity onset diabetes of the young type 3 (MODY3) and also can result in the appearance of hepatic adenomas. Alternative splicing results in multiple transcript variants encoding different isoforms.  (Source: RefSeq) | | |
| **GENE FUNCTION** | | |
| Transcriptional activator that regulates the tissue specific expression of multiple genes, especially in pancreatic islet cells and in liver (By similarity). Binds to the inverted palindrome 5'-GTTAATNATTAAC-3' (PubMed:12453420, PubMed:10966642). Activates the transcription of CYP1A2, CYP2E1 and CYP3A11 (By similarity). (Microbial infection) Plays a crucial role for hepatitis B virus gene transcription and DNA replication. Mechanistically, synergistically cooperates with NR5A2 to up-regulate the activity of one of the critical cis-elements in the hepatitis B virus genome enhancer II (ENII).  (Source: UniProt) | | |
| **DISEASE ASSOCIATION** | | **# VUS IN CLINVAR** |
| Diabetes mellitus & kidney cancer | Diabetes mellitus, insulin-dependent, 20; Hepatic adenoma, somatic; MODY, type III, AD; Renal cell carcinoma  (source: OMIM) | 285(42%) |
| **PROTEIN SIZE** |
| 631 AA |

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