ACMG Variant Classification Report

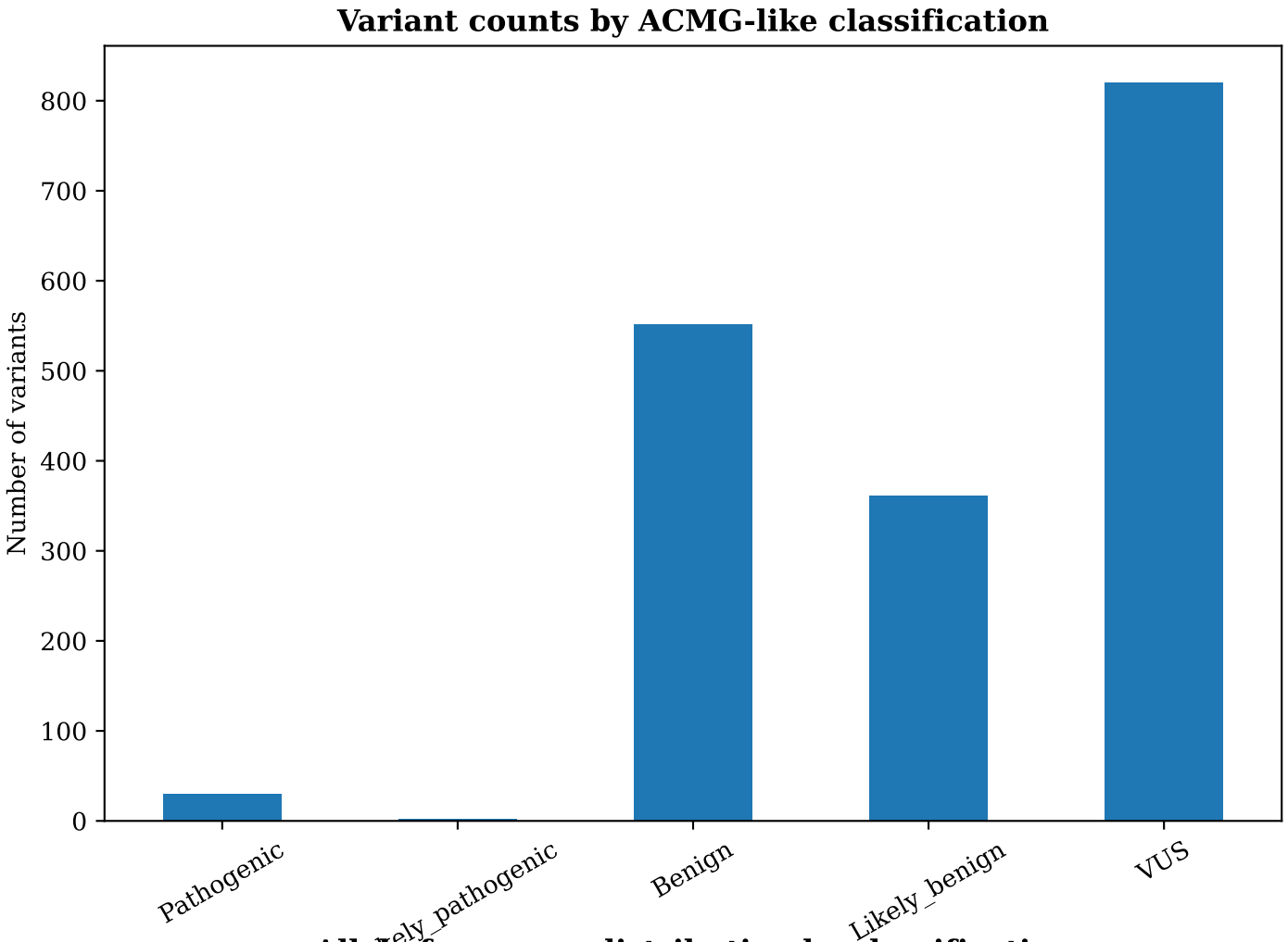
Created by: Seyed Ahmad Mousavi

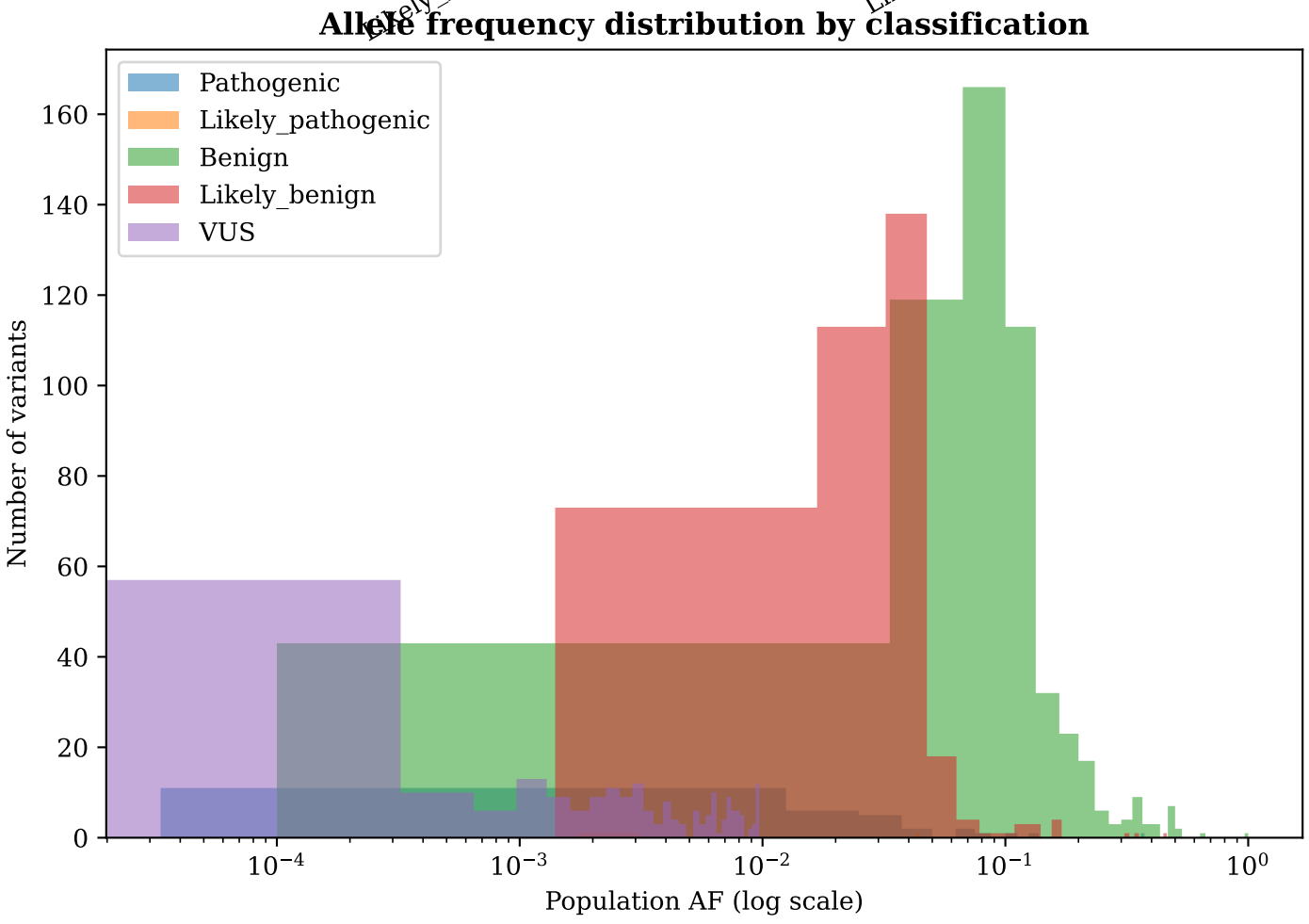
Sample name: Sample_Exome

Date: 2025-11-29

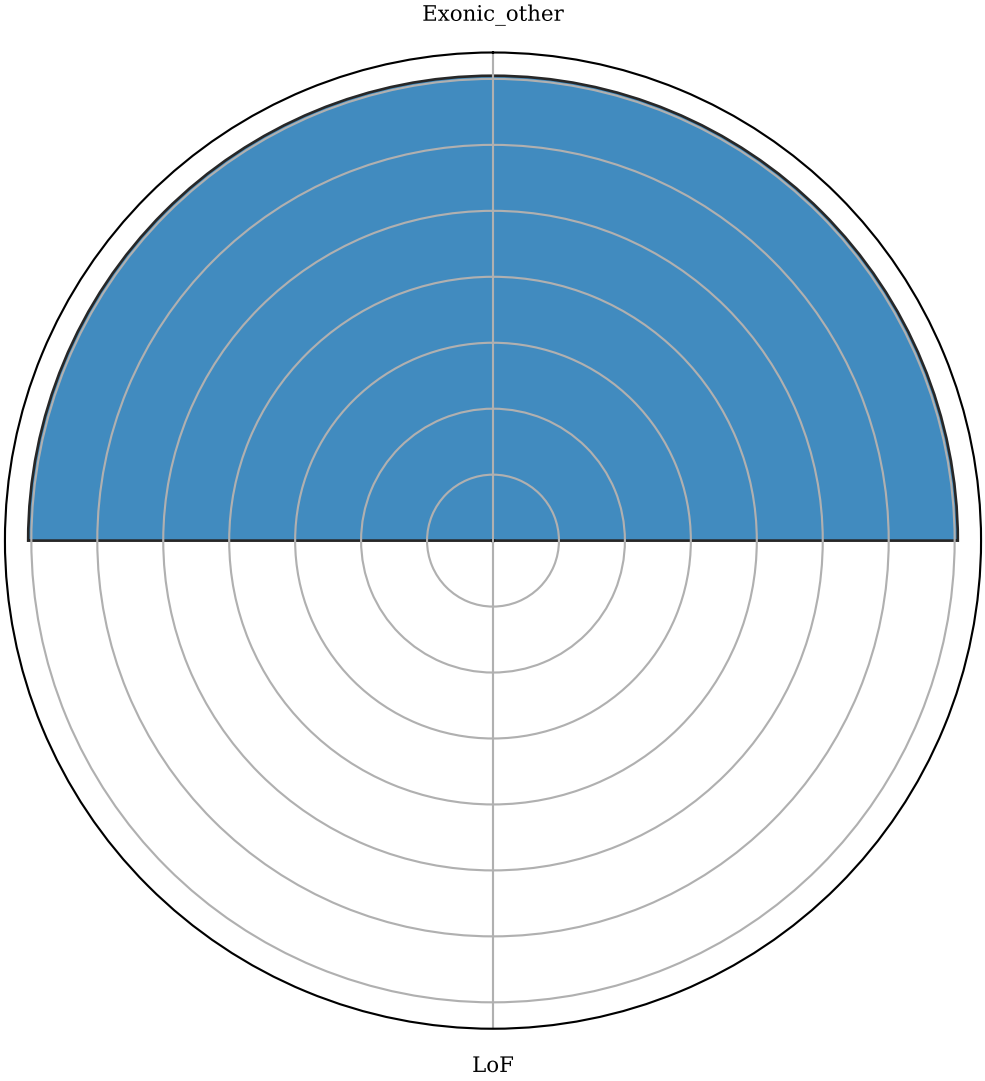
Input file: sample.tsv

Total variants analyzed: 1765 Counts by ACMG-like classification: • Pathogenic: 30 • Likely_pathogenic: 2 • Benign: 552 • Likely_benign: 361 • VUS: 820 This report applies a heuristic ACMG-like scoring pipeline that integrates: • ClinVar CLNSIG (when available) • Population allele frequencies (ExAC / gnomAD) • Loss-of-function annotation (ANNOVAR / SnpEff) • In silico prediction tools (SIFT, LRT, MutationTaster, ClinPred) WARNING: This tool is intended for RESEARCH USE ONLY and does not replace formal clinical ACMG/AMP interpretation by qualified molecular geneticists.

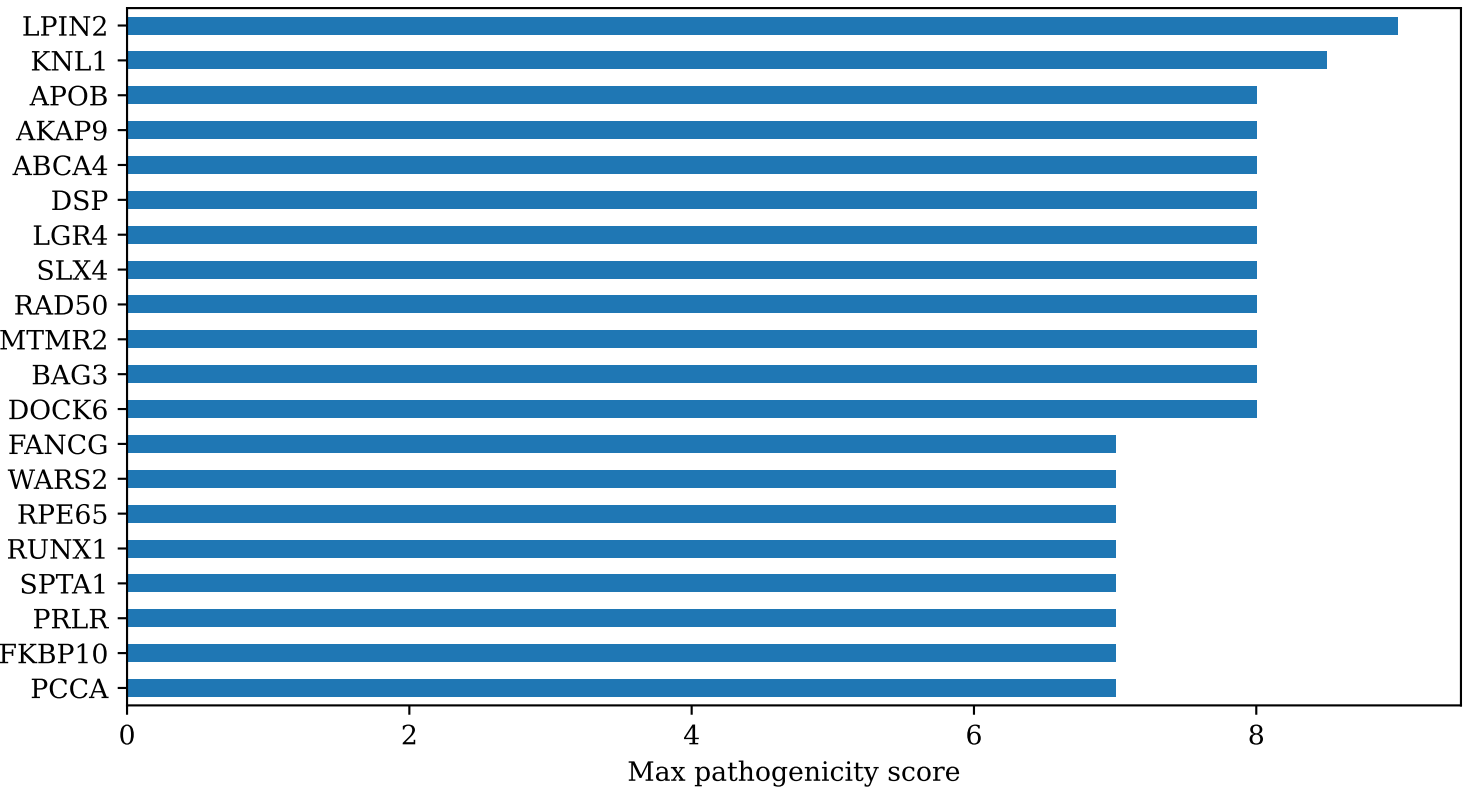

Variant counts by ACMG-like classification
Number of variants
0
100
200
300
400
500
600
700
800
Pathogenic
Likely_pathogenic
Benign
Likely_benign
VUS


Allele frequency distribution by classification
Pathogenic
Likely_pathogenic
Benign
Likely_benign
VUS
Number of variants
0
20
40
60
80
100
120
140
160
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
Population AF (log scale)

Variant type distribution (circos-style)



Top genes (ranked by most critical variant)



Variant 1: Pathogenic (score 9.00)

Gene: LPIN2

Genomic position: chr18:2920363 C>A

Variant type: Exonic_other

Population AF (max): 0.0087

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 2

ACMG-like rationale:

Popmax AF=0.0087; 2 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

Mouse studies suggest that this gene functions during normal adipose tissue development and may play a role in human triglyceride metabolism. This gene represents a candidate gene for human lipodystrophy, characterized by loss of body fat, fatty liver, hypertriglyceridemia, and insulin resistance. [provided by RefSeq, Jul 2008]

Variant 2: Pathogenic (score 8.50)

Gene: KNL1

Genomic position: chr15:40652024 G>A

Variant type: Exonic_other

Population AF (max): 3.321e-05

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=3.321e-05; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene is a component of the multiprotein assembly that is required for creation of kinetochore-microtubule attachments and chromosome segregation. The encoded protein functions as a scaffold for proteins that influence the spindle assembly checkpoint during the eukaryotic cell cycle and it interacts with at least five different kinetochore proteins and two checkpoint kinases. This gene was originally identified as a fusion partner with the mixed-lineage leukemia (MLL) gene in t(11;15)(q23;q14). Mutations in this gene cause autosomal recessive primary microcephaly-4 (MCPH4). Alternative splicing results in multiple transcript variants encoding different isoforms. Additional splice variants have been described but their biological validity has not been confirmed. [provided by RefSeq, Jan 2013]

Expression information (NCBI):

In adults, this gene is predominantly expressed in normal testes, various cancer cell lines and primary tumors from other tissues and is ubiquitously expressed in fetal tissues.

Variant 3: Pathogenic (score 8.00)

Gene: ABCA4

Genomic position: chr1:94077712 C>T

Variant type: Exonic_other

Population AF (max): 0.0033

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0033; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the ABC1 subfamily. Members of the ABC1 subfamily comprise the only major ABC subfamily found exclusively in multicellular eukaryotes. This protein is a retina-specific ABC transporter with N-retinylidene-PE as a substrate. Mutations in this gene are found in patients diagnosed with Stargardt disease, a form of juvenile-onset macular degeneration. Mutations in this gene are also associated with retinitis pigmentosa-19, cone-rod dystrophy type 3, early-onset severe retinal dystrophy, fundus flavimaculatus, and macular degeneration age-related 2. [provided by RefSeq, Sep 2019]

Expression information (NCBI):

It is expressed exclusively in retina photoreceptor cells, and the gene product mediates transport of an essental molecule, all-trans-retinal aldehyde (atRAL), across the photoreceptor cell membrane.

Variant 4: Pathogenic (score 8.00)

Gene: ABCA4

Genomic position: chr1:94008251 C>T

Variant type: Exonic_other

Population AF (max): 0.0239

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 3

ACMG-like rationale:

Popmax AF=0.0239; 3 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the ABC1 subfamily. Members of the ABC1 subfamily comprise the only major ABC subfamily found exclusively in multicellular eukaryotes. This protein is a retina-specific ABC transporter with N-retinylidene-PE as a substrate. Mutations in this gene are found in patients diagnosed with Stargardt disease, a form of juvenile-onset macular degeneration. Mutations in this gene are also associated with retinitis pigmentosa-19, cone-rod dystrophy type 3, early-onset severe retinal dystrophy, fundus flavimaculatus, and macular degeneration age-related 2. [provided by RefSeq, Sep 2019]

Expression information (NCBI):

It is expressed exclusively in retina photoreceptor cells, and the gene product mediates transport of an essental molecule, all-trans-retinal aldehyde (atRAL), across the photoreceptor cell membrane.

Variant 5: Pathogenic (score 8.00)

Gene: DSP

Genomic position: chr6:7583470 G>A

Variant type: Exonic_other

Population AF (max): 0.0164

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 3

ACMG-like rationale:

Popmax AF=0.0164; 3 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

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]

Variant 6: Pathogenic (score 8.00)

Gene: AKAP9

Genomic position: chr7:92014296 G>A

Variant type: Exonic_other

Population AF (max): 0.0052

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0052; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The A-kinase anchor proteins (AKAPs) are a group of structurally diverse proteins which have the common function of binding to the regulatory subunit of protein kinase A (PKA) and confining the holoenzyme to discrete locations within the cell. This gene encodes a member of the AKAP family. Alternate splicing of this gene results in at least two isoforms that localize to the centrosome and the Golgi apparatus, and interact with numerous signaling proteins from multiple signal transduction pathways. These signaling proteins include type II protein kinase A, serine/threonine kinase protein kinase N, protein phosphatase 1, protein phosphatase 2a, protein kinase C-epsilon and phosphodiesterase 4D3. [provided by RefSeq, Aug 2008]

Variant 7: Pathogenic (score 8.00)

Gene: RAD50

Genomic position: chr5:132588018 G>A

Variant type: Exonic_other

Population AF (max): 0.019

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 2

ACMG-like rationale:

Popmax AF=0.019; 2 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene is highly similar to Saccharomyces cerevisiae Rad50, a protein involved in DNA double-strand break repair. This protein forms a complex with MRE11 and NBS1. The protein complex binds to DNA and displays numerous enzymatic activities that are required for nonhomologous joining of DNA ends. This protein, cooperating with its partners, is important for DNA double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiotic recombination. Knockout studies of the mouse homolog suggest this gene is essential for cell growth and viability. Mutations in this gene are the cause of Nijmegen breakage syndrome-like disorder.[provided by RefSeq, Apr 2010]

Variant 8: Pathogenic (score 8.00)

Gene: APOB

Genomic position: chr2:21015495 C>T

Variant type: Exonic_other

Population AF (max): 0.0077

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0077; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

This gene product is the main apolipoprotein of chylomicrons and low density lipoproteins (LDL), and is the ligand for the LDL receptor. It occurs in plasma as two main isoforms, apoB-48 and apoB-100: the former is synthesized exclusively in the gut and the latter in the liver. The intestinal and the hepatic forms of apoB are encoded by a single gene from a single, very long mRNA. The two isoforms share a common N-terminal sequence. The shorter apoB-48 protein is produced after RNA editing of the apoB-100 transcript at residue 2180 (CAA->UAA), resulting in the creation of a stop codon, and early translation termination. Mutations in this gene or its regulatory region cause hypobetalipoproteinemia, normotriglyceridemic hypobetalipoproteinemia, and hypercholesterolemia due to ligand-defective apoB, diseases affecting plasma cholesterol and apoB levels. [provided by RefSeq, Dec 2019]

Variant 9: Pathogenic (score 8.00)

Gene: BAG3

Genomic position: chr10:119676794 G>A

Variant type: Exonic_other

Population AF (max): 0.0084

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0084; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

BAG proteins compete with Hip for binding to the Hsc70/Hsp70 ATPase domain and promote substrate release. All the BAG proteins have an approximately 45-amino acid BAG domain near the C terminus but differ markedly in their N-terminal regions. The protein encoded by this gene contains a WW domain in the N-terminal region and a BAG domain in the C-terminal region. The BAG domains of BAG1, BAG2, and BAG3 interact specifically with the Hsc70 ATPase domain in vitro and in mammalian cells. All 3 proteins bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity in a Hip-repressible manner. [provided by RefSeq, Jul 2008]

Variant 10: Pathogenic (score 8.00)

Gene: LGR4

Genomic position: chr11:27368192 T>C

Variant type: Exonic_other

Population AF (max): 0.0241

ClinVar CLNSIG (raw): Pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 3

ACMG-like rationale:

Popmax AF=0.0241; 3 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene is a G-protein coupled receptor that binds R-spondins and activates the Wnt signaling pathway. This Wnt signaling pathway activation is necessary for proper development of many organs of the body. [provided by RefSeq, Oct 2016]

Variant 11: Pathogenic (score 8.00)

Gene: DOCK6

Genomic position: chr19:11221884 G>A

Variant type: Exonic_other

Population AF (max): 0.0095

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0095; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a member of the dedicator of cytokinesis (DOCK) family of atypical guanine nucleotide exchange factors. Guanine nucleotide exchange factors interact with small GTPases and are components of intracellular signaling networks. The encoded protein is a group C DOCK protein and plays a role in actin cytoskeletal reorganization by activating the Rho GTPases Cdc42 and Rac1. Mutations in this gene are associated with Adams-Oliver syndrome 2. [provided by RefSeq, Dec 2011]

Variant 12: Pathogenic (score 8.00)

Gene: SLX4

Genomic position: chr16:3589581 G>T

Variant type: Exonic_other

Population AF (max): 0.0008

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0008; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a protein that functions as an assembly component of multiple structure-specific endonucleases. These endonuclease complexes are required for repair of specific types of DNA lesions and critical for cellular responses to replication fork failure. Mutations in this gene were found in patients with Fanconi anemia. [provided by RefSeq, Sep 2016]

Variant 13: Pathogenic (score 8.00)

Gene: MTMR2

Genomic position: chr11:95835367 A>G

Variant type: Exonic_other

Population AF (max): 0.013

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 2

ACMG-like rationale:

Popmax AF=0.013; 2 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

This gene is a member of the myotubularin family of phosphoinositide lipid phosphatases. The encoded protein possesses phosphatase activity towards phosphatidylinositol-3-phosphate and phosphatidylinositol-3,5-bisphosphate. Mutations in this gene are a cause of Charcot-Marie-Tooth disease type 4B, an autosomal recessive demyelinating neuropathy. Alternatively spliced transcript variants encoding multiple isoforms have been found for this gene. [provided by RefSeq, Aug 2011]

Variant 14: Pathogenic (score 7.00)

Gene: SPTA1

Genomic position: chr1:158685339 C>G

Variant type: Exonic_other

Population AF (max): 0.0077

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0077; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a member of a family of molecular scaffold proteins that link the plasma membrane to the actin cytoskeleton and functions in the determination of cell shape, arrangement of transmembrane proteins, and organization of organelles. The encoded protein is primarily composed of 22 spectrin repeats which are involved in dimer formation. It forms a component of the erythrocyte plasma membrane. Mutations in this gene result in a variety of hereditary red blood cell disorders, including elliptocytosis-2, pyropoikilocytosis, and spherocytosis, type 3. [provided by RefSeq, Aug 2017]

Variant 15: Pathogenic (score 7.00)

Gene: RPE65

Genomic position: chr1:68438977 A>C

Variant type: Exonic_other

Population AF (max): 0.0276

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0276; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene is a component of the vitamin A visual cycle of the retina which supplies the 11-cis retinal chromophore of the photoreceptors opsin visual pigments. It is a member of the carotenoid cleavage oxygenase superfamily. All members of this superfamily are non-heme iron oxygenases with a seven-bladed propeller fold and oxidatively cleave carotenoid carbon:carbon double bonds. However, the protein encoded by this gene has acquired a divergent function that involves the concerted O-alkyl ester cleavage of its all-trans retinyl ester substrate and all-trans to 11-cis double bond isomerization of the retinyl moiety. As such, it performs the essential enzymatic isomerization step in the synthesis of 11-cis retinal. Mutations in this gene are associated with early-onset severe blinding disorders such as Leber congenital. [provided by RefSeq, Oct 2017]

Variant 16: Pathogenic (score 7.00)

Gene: WARS2

Genomic position: chr1:119140608 A>C

Variant type: Exonic_other

Population AF (max): 0.0063

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0063; ClinVar=Pathogenic

NCBI Gene summary:

Aminoacyl-tRNA synthetases catalyze the aminoacylation of tRNA by their cognate amino acid. Because of their central role in linking amino acids with nucleotide triplets contained in tRNAs, aminoacyl-tRNA synthetases are thought to be among the first proteins that appeared in evolution. Two forms of tryptophanyl-tRNA synthetase exist, a cytoplasmic form, named WARS, and a mitochondrial form, named WARS2. This gene encodes the mitochondrial tryptophanyl-tRNA synthetase. Two alternative transcripts encoding different isoforms have been described. [provided by RefSeq, Jul 2008]

Variant 17: Likely_pathogenic (score 7.00)

Gene: RUNX1

Genomic position: chr21:34792308 A>C

Variant type: Exonic_other

Population AF (max): 0.0017

ClinVar CLNSIG (raw): Likely_pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 4

ACMG-like rationale:

Popmax AF=0.0017; 4 in silico tools support deleterious effect; ClinVar=Likely_pathogenic

NCBI Gene summary:

Core binding factor (CBF) is a heterodimeric transcription factor that binds to the core element of many enhancers and promoters. The protein encoded by this gene represents the alpha subunit of CBF and is thought to be involved in the development of normal hematopoiesis. Chromosomal translocations involving this gene are well-documented and have been associated with several types of leukemia. Three transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]

Variant 18: Pathogenic (score 7.00)

Gene: FKBP10

Genomic position: chr17:41819332 G>A

Variant type: Exonic_other

Population AF (max): 0.0023

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0023; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene belongs to the FKBP-type peptidyl-prolyl cis/trans isomerase (PPIase) family. This protein localizes to the endoplasmic reticulum and acts as a molecular chaperone. Alternatively spliced variants encoding different isoforms have been reported, but their biological validity has not been determined.[provided by RefSeq, Nov 2009]

Variant 19: Pathogenic (score 7.00)

Gene: PCCA

Genomic position: chr13:100368479 G>T

Variant type: Exonic_other

Population AF (max): 0.0446

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0446; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The protein encoded by this gene is the alpha subunit of the heterodimeric mitochondrial enzyme Propionyl-CoA carboxylase. PCCA encodes the biotin-binding region of this enzyme. Mutations in either PCCA or PCCB (encoding the beta subunit) lead to an enzyme deficiency resulting in propionic acidemia. Multiple transcript variants encoding different isoforms have been found for this gene.[provided by RefSeq, May 2010]

Variant 20: Pathogenic (score 7.00)

Gene: FANCG

Genomic position: chr9:35079505 G>A

Variant type: Exonic_other

Population AF (max): 0.0337

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0337; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

The Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2). The previously defined group FANCH is the same as FANCA. Fanconi anemia is a genetically heterogeneous recessive disorder characterized by cytogenetic instability, hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair. The members of the Fanconi anemia complementation group do not share sequence similarity; they are related by their assembly into a common nuclear protein complex. This gene encodes the protein for complementation group G. [provided by RefSeq, Jul 2008]

Variant 21: Pathogenic (score 7.00)

Gene: PRLR

Genomic position: chr5:35072610 T>G

Variant type: Exonic_other

Population AF (max): 0.0285

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0285; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a member of the protein-tyrosine phosphatase family. Protein tyrosine phosphatases are cell signaling molecules that play regulatory roles in a variety of cellular processes. Studies of this class of protein tyrosine phosphatase in mice demonstrates that they are prenylated in vivo, suggesting their association with cell plasma membrane. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2013]

Expression information (NCBI):

The encoded protein may enhance cell proliferation, and overexpression of this gene has been implicated in tumor metastasis.

Variant 22: Likely_pathogenic (score 6.00)

Gene: BCHE

Genomic position: chr3:165830741 T>C

Variant type: Exonic_other

Population AF (max): 0.0443

ClinVar CLNSIG (raw): Pathogenic/Likely_pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 3

ACMG-like rationale:

Popmax AF=0.0443; 3 in silico tools support deleterious effect; ClinVar=Likely_pathogenic

NCBI Gene summary:

This gene encodes a cholinesterase enzyme and member of the type-B carboxylesterase/lipase family of proteins. The encoded enzyme exhibits broad substrate specificity and is involved in the detoxification of poisons including organophosphate nerve agents and pesticides, and the metabolism of drugs including cocaine, heroin and aspirin. Humans homozygous for certain mutations in this gene exhibit prolonged apnea after administration of the muscle relaxant succinylcholine. [provided by RefSeq, Jul 2016]

Variant 23: Pathogenic (score 6.00)

Gene: CYP27A1

Genomic position: chr2:218814154 C>T

Variant type: Exonic_other

Population AF (max): 0.0662

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 3

ACMG-like rationale:

Popmax AF=0.0662; 3 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This mitochondrial protein oxidizes cholesterol intermediates as part of the bile synthesis pathway. Since the conversion of cholesterol to bile acids is the major route for removing cholesterol from the body, this protein is important for overall cholesterol homeostasis. Mutations in this gene cause cerebrotendinous xanthomatosis, a rare autosomal recessive lipid storage disease. [provided by RefSeq, Jul 2008]

Variant 24: Pathogenic (score 6.00)

Gene: AMPD1

Genomic position: chr1:114679616 T>A

Variant type: Exonic_other

Population AF (max): 0.1297

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 4

ACMG-like rationale:

Popmax AF=0.1297; 4 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

Adenosine monophosphate deaminase 1 catalyzes the deamination of AMP to IMP in skeletal muscle and plays an important role in the purine nucleotide cycle. Two other genes have been identified, AMPD2 and AMPD3, for the liver- and erythocyte-specific isoforms, respectively. Deficiency of the muscle-specific enzyme is apparently a common cause of exercise-induced myopathy and probably the most common cause of metabolic myopathy in the human. Alternatively spliced transcript variants encoding different isoforms have been identified in this gene.[provided by RefSeq, Feb 2010]

Variant 25: Pathogenic (score 6.00)

Gene: FANCG

Genomic position: chr9:35075025 C>T

Variant type: Exonic_other

Population AF (max): 0.0316

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0316; ClinVar=Pathogenic

NCBI Gene summary:

The Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2). The previously defined group FANCH is the same as FANCA. Fanconi anemia is a genetically heterogeneous recessive disorder characterized by cytogenetic instability, hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair. The members of the Fanconi anemia complementation group do not share sequence similarity; they are related by their assembly into a common nuclear protein complex. This gene encodes the protein for complementation group G. [provided by RefSeq, Jul 2008]

Variant 26: Pathogenic (score 6.00)

Gene: BAG3

Genomic position: chr10:119670133 G>A

Variant type: Exonic_other

Population AF (max): 0.0179

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0179; ClinVar=Pathogenic

NCBI Gene summary:

BAG proteins compete with Hip for binding to the Hsc70/Hsp70 ATPase domain and promote substrate release. All the BAG proteins have an approximately 45-amino acid BAG domain near the C terminus but differ markedly in their N-terminal regions. The protein encoded by this gene contains a WW domain in the N-terminal region and a BAG domain in the C-terminal region. The BAG domains of BAG1, BAG2, and BAG3 interact specifically with the Hsc70 ATPase domain in vitro and in mammalian cells. All 3 proteins bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity in a Hip-repressible manner. [provided by RefSeq, Jul 2008]

Variant 27: Pathogenic (score 6.00)

Gene: SARS2

Genomic position: chr19:38930489 G>A

Variant type: Exonic_other

Population AF (max): 0.0258

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0258; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes the mitochondrial seryl-tRNA synthethase precursor, a member of the class II tRNA synthetase family. The mature enzyme catalyzes the ligation of Serine to tRNA(Ser) and participates in the biosynthesis of selenocysteinyl-tRNA(sec) in mitochondria. The enzyme contains an N-terminal tRNA binding domain and a core catalytic domain. It functions in a homodimeric form, which is stabilized by tRNA binding. Both genes are within the critical interval for the autosomal dominant deafness locus DFNA4 and might be linked to this disease. Multiple transcript variants encoding different isoforms have been identified for this gene. [provided by RefSeq, Mar 2009]

Expression information (NCBI):

This gene is regulated by a bidirectional promoter that also controls the expression of mitochondrial ribosomal protein S12.

Variant 28: Pathogenic (score 6.00)

Gene: ATXN1

Genomic position: chr6:16327634 TGC>-

Variant type: Exonic_other

Population AF (max): 0.0482

ClinVar CLNSIG (raw): Pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0482; ClinVar=Pathogenic

NCBI Gene summary:

The autosomal dominant cerebellar ataxias (ADCA) are a heterogeneous group of neurodegenerative disorders characterized by progressive degeneration of the cerebellum, brain stem and spinal cord. Clinically, ADCA has been divided into three groups: ADCA types I-III. ADCAI is genetically heterogeneous, with five genetic loci, designated spinocerebellar ataxia (SCA) 1, 2, 3, 4 and 6, being assigned to five different chromosomes. ADCAII, which always presents with retinal degeneration (SCA7), and ADCAIII often referred to as the `pure' cerebellar syndrome (SCA5), are most likely homogeneous disorders. Several SCA genes have been cloned and shown to contain CAG repeats in their coding regions. ADCA is caused by the expansion of the CAG repeats, producing an elongated polyglutamine tract in the corresponding protein. The expanded repeats are variable in size and unstable, usually increasing in size when transmitted to successive generations. The function of the ataxins is not known. This locus has been mapped to chromosome 6, and it has been determined that the diseased allele contains 40-83 CAG repeats, compared to 6-39 in the normal allele, and is associated with spinocerebellar ataxia type 1 (SCA1). Alternative splicing results in multiple transcript variants, with one variant encoding multiple distinct proteins, ATXN1 and Alt-ATXN1, due to the use of overlapping alternate reading frames. [provided by RefSeq, Nov 2017]

Variant 29: Pathogenic (score 5.00)

Gene: COL6A3

Genomic position: chr2:237371833 C>T

Variant type: Exonic_other

Population AF (max): 0.0783

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 1

ACMG-like rationale:

Popmax AF=0.0783; 1 in silico tools support deleterious effect; ClinVar=Pathogenic

NCBI Gene summary:

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. [provided by RefSeq, Jun 2009]

Variant 30: Pathogenic (score 4.00)

Gene: NLRP3

Genomic position: chr1:247425556 C>A

Variant type: Exonic_other

Population AF (max): 0.0678

ClinVar CLNSIG (raw): Conflicting_interpretations_of_pathogenicity

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.0678; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a pyrin-like protein containing a pyrin domain, a nucleotide-binding site (NBS) domain, and a leucine-rich repeat (LRR) motif. This protein interacts with the apoptosis-associated speck-like protein PYCARD/ASC, which contains a caspase recruitment domain, and is a member of the NLRP3 inflammasome complex. This complex functions as an upstream activator of NF-kappaB signaling, and it plays a role in the regulation of inflammation, the immune response, and apoptosis. The SARS-CoV 3a protein, a transmembrane pore-forming viroporin, has been shown to activate the NLRP3 inflammasome via the formation of ion channels in macrophages. Mutations in this gene are associated with familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome, neonatal-onset multisystem inflammatory disease (NOMID), keratoendotheliitis fugax hereditarian, and deafness, autosomal dominant 34, with or without inflammation. Multiple alternatively spliced transcript variants encoding distinct isoforms have been identified for this gene. Alternative 5' UTR structures are suggested by available data; however, insufficient evidence is available to determine if all of the represented 5' UTR splice patterns are biologically valid. [provided by RefSeq, Aug 2020]

Variant 31: Pathogenic (score 4.00)

Gene: UBXN11

Genomic position: chr1:26282321 CCAGGACAGGGACTGGGGCCGGGACCGGGACCGGGACT

Variant type: Exonic_other

Population AF (max): 0.374

ClinVar CLNSIG (raw): Pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.374; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a protein with a divergent C-terminal UBX domain. The homologous protein in the rat interacts with members of the Rnd subfamily of Rho GTPases at the cell periphery through its C-terminal region. It also interacts with several heterotrimeric G proteins through their G-alpha subunits and promotes Rho GTPase activation. It is proposed to serve a bidirectional role in the promotion and inhibition of Rho activity through upstream signaling pathways. The 3' coding sequence of this gene contains a polymoprhic region of 24 nt tandem repeats. Several transcripts containing between 1.5 and five repeat units have been reported. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]

Variant 32: Pathogenic (score 4.00)

Gene: ZFHX3

Genomic position: chr16:72787694 ->GCCGCC

Variant type: Exonic_other

Population AF (max): 0.1026

ClinVar CLNSIG (raw): Pathogenic

Loss-of-function-like: False

damaging in-silico predictors: 0

ACMG-like rationale:

Popmax AF=0.1026; ClinVar=Pathogenic

NCBI Gene summary:

This gene encodes a transcription factor with multiple homeodomains and zinc finger motifs, and regulates myogenic and neuronal differentiation. The protein has also been shown to negatively regulate c-Myb, and transactivate the cell cycle inhibitor cyclin-dependent kinase inhibitor 1A (also known as p21CIP1). This gene is reported to function as a tumor suppressor in several cancers, and sequence variants of this gene are also associated with atrial fibrillation. [provided by RefSeq, Sep 2009]

Expression information (NCBI):

The encoded protein suppresses expression of the alpha-fetoprotein gene by binding to an AT-rich enhancer motif. Multiple transcript variants expressed from alternate promoters and encoding different isoforms have been found for this gene.