



## Resources for Genetics Professionals – Genes with Highly Homologous Gene Family Members or a Pseudogene(s)

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Gene families are genes of similar sequence and function that arose through duplication of an ancestral gene.

A pseudogene is a sequence of DNA that has some homology with a coding gene. Although most pseudogenes have the same structural elements (promoters, splice sites, and introns) found in coding genes, they do not encode proteins as they are often disrupted by multiple pathogenic variants. Processed pseudogenes are mRNA sequences copied and inserted into the genome and do not contain promoters or introns. The human genome contains approximately 20,000 pseudogenes.

The presence of non-unique sequence within the genome interferes with molecular genetic testing for many genetic disorders. The genes listed in the table below are common examples of genes with non-unique sequence and their associated disorders. Target enrichment (by PCR amplification or pull-down methods) can simultaneously amplify or capture sequence from a gene and other homologous regions. In addition, presence of homologous next-generation sequence reads can lead to loss of data (reads mapping to more than one location are discarded), false negative, or false positive results. In some cases, the length and degree of homology do not interfere with sequence analysis.

Although specific assays have been developed to distinguish the sequence of medically important genes from homologous sequences, these complex techniques are not easily implemented across the entire exome. Therefore, laboratories performing exome sequencing often exclude the analysis of highly homologous exons to avoid errors.

Many additional homologous sequences that may or may not (depending on specific assay design) interfere with sequence analysis are known. Assay performance must be assessed by laboratories performing testing.

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**Table.** Genes with Highly Homologous Gene Family Members or a Pseudogene(s)

Gene <sup>1</sup>	Homologous Genes and Pseudogenes	Disorder Caused by Pathogenic Variants in this Gene <sup>2</sup>	Proportion of Affected Individuals with Pathogenic Variants in This Gene
<i>ABCC6</i> <sup>3</sup>	<i>ABCC6P1</i> <i>ABCC6P2</i>	Pseudoxanthoma elasticum	100%
<i>ABCD1</i>	≥5 pseudogenes	X-linked adrenoleukodystrophy	100%
<i>ACTB</i>	≥18 pseudogenes	Baraitser-Winter syndrome cerebrofrontofacial syndrome	>60%
<i>AK2</i>	<i>AK2P1</i> <i>AK2P2</i>	Reticular dysgenesis (See X-Linked Severe Combined Immunodeficiency.)	100%
<i>ALG1</i>	≥8 pseudogenes	<i>ALG1</i> -CDG (CDG-type Ik) (See Congenital Disorders of N-linked Glycosylation & Multiple Pathway Overview.)	100%
<i>ANKRD11</i>	<i>LOC100419906</i> <i>LOC100287912</i>	KBG syndrome	100%
<i>ASL</i>	<i>ASLP1</i>	Argininosuccinate lyase deficiency	100%
<i>ASS1</i>	≥14 pseudogenes	Citrullinemia type I	100%
<i>BANF1</i>	≥5 pseudogenes	Nestor-Guillermo progeria syndrome (OMIM 614008)	100%
<i>BMPR1A</i>	<i>BMPR1APS1</i> <i>BMPR1APS2</i>	Juvenile polyposis syndrome	20%-25%
<i>C4A</i>	<i>CYP21A</i>	C4A deficiency (OMIM 614380)	100%
<i>C4B</i>	<i>CYP21A</i>	C4B deficiency (OMIM 614379)	100%
<i>CA5A</i>	<i>CA5AP1</i>	Carbonic anhydrase VA deficiency	100%
<i>CDC42</i>	≥9 pseudogenes	Takenouchi-Kosaki syndrome (OMIM 616737)	2 individuals
<i>CEL</i>	<i>CELP</i>	Diabetes-pancreatic exocrine dysfunction syndrome (OMIM 609812)	2 families
<i>CFH</i>	<i>CFHR1</i> <i>CFHR2</i> <i>CFHR3</i> <i>CFHR4</i>	Genetic atypical hemolytic-uremic syndrome	~50%
<i>CFH</i>	<i>CFHR5</i>	C3 glomerulopathy	~10%
<i>CFTR</i> <sup>4</sup>	<i>CFTRP1</i> <i>CFTRP3</i>	Cystic fibrosis & congenital absence of the vas deferens	100%
<i>CHEK2</i>	≥5 pseudogenes	Breast cancer susceptibility (OMIM 114480) Prostate cancer susceptibility (OMIM 176807)	<5%
<i>CORO1A</i>	<i>LOC606724</i>	Immunodeficiency 8 (OMIM 615401)	100%
<i>CRIPTO (TDGF1)</i>	≥7 pseudogenes	Holoprosencephaly	2 individuals
<i>CRYBB2</i> <sup>5</sup>	<i>CRYBB2P1</i>	Cataract 3, multiple types (OMIM 601547)	100%
<i>CYCS</i>	≥37 pseudogenes	Thrombocytopenia, AD, nonsyndromic, type IV (OMIM 612004)	100%

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Gene <sup>1</sup>	Homologous Genes and Pseudogenes	Disorder Caused by Pathogenic Variants in this Gene <sup>2</sup>	Proportion of Affected Individuals with Pathogenic Variants in This Gene
<i>CYP21A2</i> <sup>6</sup>	<i>CYP21A1P</i>	21-hydroxylase-deficient congenital adrenal hyperplasia	100%
<i>DCLRE1C</i> <sup>7</sup>	<i>DCLRE1CP1</i>	Omenn syndrome (OMIM 603554)	>70 individuals
		SCID Athabaskan (OMIM 602450)	100%
<i>DDX11</i>	≥6 pseudogenes	Warsaw breakage syndrome	100%
<i>DHFR</i>	≥4 pseudogenes	Megaloblastic anemia due to dihydrofolate reductase deficiency (OMIM 613839)	100%
<i>DIS3L2</i>	<i>DIS3L2P1</i>	Perlman syndrome (OMIM 267000)	100%
<i>DPY19L2</i>	≥5 pseudogenes	Globozoospermia, spermatogenic failure (OMIM 613958)	100%
<i>EIF4E</i>	≥5 pseudogenes	Autism (OMIM 615091)	3 families
<i>FANCD2</i>	<i>FANCD2P1</i>	Fanconi anemia	~3%
<i>FLNC</i>	<i>LOC392787</i>	Hypertrophic cardiomyopathy (OMIM 102565)	8 families
		Restrictive cardiomyopathy (OMIM 617047)	2 families
		Distal ABD-filaminopathy	100%
		Myofibrillar myopathy (OMIM 609524)	3%
<i>GBA1</i> ( <i>GBA</i> ) <sup>8</sup>	<i>GBA1LP</i> ( <i>GBAP</i> )	Gaucher disease	100%
<i>GCSH</i>	≥8 pseudogenes	Nonketotic hyperglycinemia	<1%
<i>GJA1</i>	<i>GJA6P</i> <i>GJA1P1</i>	Oculodentodigital dysplasia (OMIM 164200)	100%
		Craniometaphyseal dysplasia, AR (OMIM 218400)	100%
		Palmoplantar keratoderma and congenital alopecia type 1 (OMIM 104100)	100%
		Hypoplastic left heart syndrome (OMIM 241550)	8 individuals
<i>GK</i>	<i>GK3P</i> <i>GK6P</i> <i>GK4P</i>	Glycerol kinase deficiency (OMIM 307030)	100%
<i>GLDC</i> <sup>9</sup>	<i>GLDCP1</i>	Nonketotic hyperglycinemia	70%-75%
<i>GLUD1</i>	≥6 pseudogenes	Familial hyperinsulinism	5%
<i>GNAQ</i>	<i>GNAQP1</i>	Sturge-Weber syndrome (OMIM 185300)	88%
<i>HBA1</i> <sup>10</sup> <i>HBA2</i>	<i>HBAP1</i> <i>HBZP</i>	Alpha-thalassemia	100%
<i>HBB</i>	<i>HBBP1</i>	Sickle cell disease	100%
		Beta-thalassemia	
<i>HCN4</i>	≥2 pseudogenes	Brugada syndrome	<1%

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Gene <sup>1</sup>	Homologous Genes and Pseudogenes	Disorder Caused by Pathogenic Variants in this Gene <sup>2</sup>	Proportion of Affected Individuals with Pathogenic Variants in This Gene
<i>HPS1</i> <sup>11</sup>	<i>LOC100500719</i>	<a href="#">Hermansky-Pudlak syndrome</a>	75% of Puerto Ricans; 44% of individuals not of Puerto Rican descent
<i>HSPD1</i>	≥23 pseudogenes	Hypomyelinating leukodystrophy (OMIM 612233)	2 individuals
		Hereditary spastic paraplegia (OMIM 605280)	1 family
<i>HYDIN</i>	<i>HYDIN2</i>	<a href="#">Primary ciliary dyskinesia</a>	Founder variant in Faroe Islands; 1 additional family
<i>IDS</i> <sup>12</sup>	<i>IDSP1</i>	<a href="#">Mucopolysaccharidosis type II</a>	100%
<i>IFT122</i>	<i>LOC653712</i>	<a href="#">Cranioectodermal dysplasia</a>	~10%
<i>IKBKG</i>	<i>IKBKGP1</i>	<a href="#">Incontinentia pigmenti</a>	~75%
<i>KAL1</i>	<i>KALP</i>	<a href="#">Kallmann syndrome (See Isolated Gonadotropin-Releasing Hormone Deficiency.)</a>	5%-10%
<i>KRT16</i>	≥5 pseudogenes	<a href="#">Pachyonychia congenita</a>	29%
		<a href="#">Palmoplantar keratoderma, nonepidermolytic (focal) (OMIM 613000)</a>	≥5 families
<i>KRT6A</i>	≥4 pseudogenes	<a href="#">Pachyonychia congenita</a>	42%
<i>KRT86</i>	<i>KRT87P</i> <i>KRT88P</i>	<a href="#">Monilethrix (OMIM 158000)</a>	≥4 families
<i>LEFTY2</i>	<i>LEFTY3</i>	<a href="#">Left-right axis malformations (OMIM 601877)</a>	2 individuals
<i>MATR3</i>	<i>LOC100499497</i> <i>LOC100499496</i> <i>LOC401957</i>	<a href="#">Amyotrophic lateral sclerosis type 21 (OMIM 606070)</a>	5 families
<i>NCF1</i>	<i>NCF1B</i> <i>NCF1C</i>	<a href="#">Chronic granulomatous disease</a>	20%
<i>NF1</i>	≥11 pseudogenes	<a href="#">Neurofibromatosis type 1</a>	100%
<i>NLRP7</i>	<i>LOC100421039</i>	<a href="#">Recurrent hydatidiform mole (OMIM 231090)</a>	~75%
<i>NOTCH2</i>	<i>NOTCH2P1</i>	<a href="#">Alagille syndrome</a>	1%-2%
		<a href="#">Hajdu-Cheney syndrome (OMIM 102500)</a>	100%
<i>OCLN</i>	<i>LOC647859</i>	<a href="#">Band-like calcification with simplified gyration and polymicrogyria (OMIM 251290)</a>	100%
<i>OPHN1</i>	<i>ARHGAP42P3</i>	<a href="#">X-linked intellectual disability with cerebellar hypoplasia and distinctive facial appearance (OMIM 300486)</a>	8 families
<i>OTOA</i>	<i>LOC653786</i>	<a href="#">Deafness, AR, type 22 (OMIM 607038)</a>	100%
<i>PHKA1</i>	<i>PHKA1P1</i>	<a href="#">Phosphorylase kinase deficiency</a>	~17%

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Gene <sup>1</sup>	Homologous Genes and Pseudogenes	Disorder Caused by Pathogenic Variants in this Gene <sup>2</sup>	Proportion of Affected Individuals with Pathogenic Variants in This Gene
<i>PIK3CA</i>	<i>LOC100422375</i>	<i>PIK3CA</i> -related segmental overgrowth	100%
<i>PKD1</i>	≥7 pseudogenes	Polycystic kidney disease, AD	85%
<i>PLEKHM1</i>	<i>PLEKHM1P1</i>	Osteopetrosis, AR type 6 (OMIM 611497)	100%
<i>PMM2</i>	<i>PMM2P1</i>	<i>PMM2</i> -CDG ( <i>CDG-Ia</i> )	100%
<i>PMS2</i> <sup>13</sup>	≥14 pseudogenes	Lynch syndrome	<5%
<i>PRODH</i>	<i>LOC440792</i>	Hyperprolinemia, type 1 (OMIM 239500)	100%
<i>PROS1</i>	<i>PROS2P</i>	Thrombophilia due to protein S deficiency (OMIM 176880)	100%
<i>PRSS1</i> <sup>14</sup>	<i>PRSS3P2</i> <i>PRSS3P1</i>	Hereditary pancreatitis (See <a href="#">Pancreatitis Overview</a> .)	60%-100%
<i>PTEN</i>	<i>PTENP1</i>	<i>PTEN</i> hamartoma tumor syndrome	100%
<i>RBM8A</i>	<i>RBM8B</i>	Thrombocytopenia absent radius syndrome	100%
<i>RPS17</i>	≥16 pseudogenes	Diamond-Blackfan anemia	~1%
<i>RPS19</i>	≥7 pseudogenes	Diamond-Blackfan anemia	25%
<i>SALL1</i>	<i>SALL1P1</i>	Townes-Brocks syndrome	75%
<i>SBDS</i> <sup>15</sup>	<i>SBDSP</i>	Shwachman-Diamond syndrome	100%
<i>SDHA</i>	≥4 pseudogenes	Hereditary paraganglioma-pheochromocytoma syndromes	1%-3%
<i>SDHC</i>	≥5 pseudogenes	Hereditary paraganglioma-pheochromocytoma syndromes	4%-8%
<i>SDHD</i>	≥7 pseudogenes	Hereditary paraganglioma-pheochromocytoma syndromes	~30%
<i>SFTPA2</i>	<i>SFTPA3P</i>	Idiopathic pulmonary fibrosis (See <a href="#">Familial Pulmonary Fibrosis</a> .)	2 families
<i>SLC25A15</i>	≥5 pseudogenes	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	100%
<i>SLC6A8</i>	<i>SCL6A10P</i> <i>SCL6A10PB</i>	Creatine deficiency syndromes	56%
<i>SMAD4</i> <sup>16</sup>	≥1 pseudogene (not named)	Juvenile polyposis syndrome ± Hereditary hemorrhagic telangiectasia	20%
<i>SMN1</i> <i>SMN2</i>	<i>SMNP</i> <i>LOC100132090</i>	Spinal muscular atrophy	100%
<i>STRC</i> <sup>17</sup>	<i>STRCP1</i>	<i>STRC</i> -related autosomal recessive hearing loss	6%-11%
<i>TARDBP</i>	<i>LOC643387</i> <i>TARDBPP1</i> <i>TARDBPP2</i>	<i>TARDBP</i> -related amyotrophic lateral sclerosis-frontotemporal dementia	100%
<i>TBX20</i>	<i>LOC100418730</i>	ASD type 4 (OMIM 611363)	3 families

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Gene <sup>1</sup>	Homologous Genes and Pseudogenes	Disorder Caused by Pathogenic Variants in this Gene <sup>2</sup>	Proportion of Affected Individuals with Pathogenic Variants in This Gene
<i>TIMM8A</i>	<i>TIMM8AP1</i>	Deafness-dystonia-optic neuropathy syndrome	13 individuals
<i>TMEM231</i>	<i>LOC100420067</i>	Joubert syndrome	2 families & 2 individuals
<i>TNXB</i>	<i>TNXA</i>	<i>TNXB</i> -related classic-like Ehlers-Danlos syndrome	100%
<i>TPI1</i>	≥4 pseudogenes	Hemolytic anemia due to triosephosphate isomerase deficiency (OMIM 615512)	100%
<i>TUBA1A</i>	<i>TUBA3GP</i> <i>LOC100129818</i>	Lissencephaly and other complex cortical malformations (See <a href="#">Tubulinopathies Overview</a> .)	37% of classic lissencephaly
<i>TUBB2B</i>	<i>TUBB8P4</i> <i>TUBB4BP2</i> <i>TUBB2BP1</i>	Polymicrogyria-like cortical dysplasia (See <a href="#">Tubulinopathies Overview</a> .)	87.5%
<i>TYR</i>	<i>TYRL</i>	Oculocutaneous albinism type I (OMIM 203100, 606952)	100%
<i>UBE3A</i>	<i>UBE3AP2</i> <i>UBE3AP1</i>	Angelman syndrome	~11%
<i>VWF</i>	<i>VWFP1</i>	von Willebrand disease	100%

AD = autosomal dominant; AR = autosomal recessive; ASD = atrial septal defect

- Included in this table are genes that have: (1) one or more identified pseudogenes; and (2) pathogenic variants identified in more than one individual or family. Genes from the same gene family are listed together.
- For more information see hyperlinked *GeneReview*. An OMIM phenotype entry is provided if a *GeneReview* is not available.
- Two pseudogenes are almost identical to *ABCC6* [Pfundner et al 2008].
- Duplication of exon 10 [Rozmahel et al 1997]
- Gene conversion between *CRYBB2* and *CRYBB2P1* was reported by Vanita et al [2001].
- Testing the proband and parents may be required to clarify results [Hong et al 2015].
- The most common *DCLRE1C* pathogenic variant is a deletion resulting from homologous recombination of *DCLRE1C* and the pseudogene [Pannicke et al 2010].
- GBA1LP* is 96% homologous to *GBA1* [Basgalupp et al 2018].
- The processed pseudogene has 97.5% homology to the coding sequence of *GLDC* [Takayanagi et al 2000].
- HBA1* and *HBA2* have identical coding regions. This gene family also includes the embryonically expressed *HBZ*, *HBD*, and *HBQ1*.
- The pseudogene has 95% homology to *HPS1*; exon 6 is identical [Huizing et al 2000].
- 9% of pathogenic variants are complex rearrangements with the pseudogene. The pseudogene is 96% homologous to *IDS* [Bondeson et al 1995].
- Ongoing evolutionary sequence exchange between *PMS2* and one pseudogene (*PMS2CL*) has led to unreliable reference sequences and false positive and false negative results on sequencing [Hayward et al 2007] (see also Vaughn et al [2011]).
- Regardless of the sequencing method employed, primers must be carefully chosen and validated to amplify the fragment for the correct gene and transcript. Thus, a multistep method is required to verify the presence of a pathogenic variant in *PRSSI* [Masson et al 2008].
- Interpretations may be difficult as the extent of variation in *SBDSP* is not known. *SBDSP* is 97% homologous to *SBDS*.
- The presence of a processed pseudogene led to false positive MLPA results in some individuals [Millson et al 2015].
- STRCP1* is 99.6% homologous to *STRC* [Vona et al 2015].

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## Suggested Reading

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