

**ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1**

This version specified for the following genes: *LDLR*

Expert Panel Page: <https://www.clinicalgenome.org/affiliation/50004>

Gene	Disease	Transcript
<i>LDLR</i>	<i>hypercholesterolemia, familial (MONDO:0007750)</i>	<i>NM_000527.5</i>
<b>PATHOGENIC CRITERIA</b>		
Criteria	Criteria Description	<i>LDLR</i> Specification
<b>VERY STRONG CRITERIA</b>		
PVS1	See main text for specific variant types.	Disease specific / strength
<b>STRONG CRITERIA</b>		
PS1	Missense variant at the same codon as a variant classified pathogenic (by these guidelines), and leads to the same amino acid change. <b>Caveat:</b> there is no <i>in silico</i> predicted splicing impact for either variant.	Clarification
PS2	Variant is <i>de novo</i> in a patient with the disease and no family history. Follow SVI guidance for <i>de novo</i> occurrences: <a href="https://clinicalgenome.org/working-groups/sequence-variant-interpretation/">https://clinicalgenome.org/working-groups/sequence-variant-interpretation/</a>	Clarification
PS3	Variant meets Level 1 pathogenic functional study criteria. See below for specifics.	Disease specific / strength
PS4	Variant is found in $\geq 10$ unrelated FH cases (FH diagnosis met by any validated clinical criteria). <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF $< 0.02\%$ ).	Disease specific / strength
PVS1_Strong	See main text for specific variant types.	Disease specific / strength
PM5_Strong	Missense variant at a codon with $\geq 2$ missense variants classified pathogenic (by these guidelines), and leads to a different amino acid change.	Strength
PP1_Strong	Variant segregates with phenotype in $\geq 6$ informative meioses in $\geq 1$ family. Must include $\geq 2$ affected relatives (LDL-C $> 75$ th percentile) with the variant.	Disease specific / strength
<b>MODERATE CRITERIA</b>		
PM1	Missense variant is located in exon 4, or is a missense change in one of 60 highly conserved cysteine residues (listed below). <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF $< 0.02\%$ ).	Disease specific
PM2	Variant has a PopMax MAF $< 0.0002$ (0.02%) in gnomAD. Structural variants to be assessed in gnomAD SV dataset	Disease specific
PM3	This criterion can be used for a candidate <i>LDLR</i> variant observed in an individual with a homozygous FH phenotype when there is only one other pathogenic variant (by these guidelines) in <i>LDLR</i> (must be in trans), <i>APOB</i> or <i>PCSK9</i> (2-star in ClinVar). <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF $< 0.02\%$ ).	Disease specific
PM4	In-frame deletion/insertions smaller than one whole exon, or in-frame whole-exon duplications not considered in any PVS1 criteria. <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF $< 0.02\%$ ).	Disease specific

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PM5	Missense variant at the same codon as a variant classified pathogenic (by these guidelines), and leads to a different amino acid change.	Clarification
PM6	See PS2 above.	Clarification
PS3_Moderate	Variant meets Level 2 pathogenic functional study criteria. See below for specifics.	Disease specific / strength
PS4_Moderate	Variant is found in 6-9 unrelated FH cases (FH diagnosis made by any validated clinical criteria). <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF <0.02%).	Disease specific / strength
PP1_Moderate	Variant segregates with phenotype in 4-5 informative meioses in $\geq 1$ family. Must include $\geq 2$ affected relatives (LDL-C >75 <sup>th</sup> percentile) with the variant.	Disease specific / strength
PVS1_Moderate	See main text for specific variant types.	Disease specific / strength
<b>SUPPORTING CRITERIA</b>		
PP1	Variant segregates with phenotype in 2-3 informative meioses in $\geq 1$ family. Must include $\geq 1$ affected relative (LDL-C >75 <sup>th</sup> percentile) with the variant.	Disease specific / strength
PP2	<i>Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.</i>	N/A
PP3	Computational evidence supports a deleterious effect on the gene or gene product. See FH VCEP suggestions for missense/splicing predictors in main text.	Disease specific
PP4	Any <i>LDLR</i> variant identified in an FH patient [diagnosis based on any validated clinical criteria, ex. Dutch Lipid Clinic Network ( $\geq 6$ ), Simon Broome (possible/definite), MEDPED], <b>after alternative causes of high cholesterol are excluded</b> . <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF <0.02%).	Disease specific
PP5	<i>Reputable source recently reports variant as pathogenic but the evidence is not available to the laboratory to perform an independent evaluation</i>	N/A
PS3_Supporting	Variant meets Level 3 pathogenic functional study criteria. See below for specifics.	Disease specific / strength
PS4_Supporting	Variant is found in 2-5 unrelated FH cases (FH diagnosis made by any validated clinical criteria). <b>Caveat:</b> variant must also be rare (i.e. PopMax MAF <0.02%).	Disease specific / strength
<b>BENIGN CRITERIA</b>		
<b>STAND ALONE CRITERIA</b>		
BA1	Variant has a PopMax FAF >0.005 (0.5%) in gnomAD. Consider exceptions for founder variants.	Disease specific
<b>STRONG CRITERIA</b>		
BS1	Variant has a PopMax FAF >0.002 (0.2%) in gnomAD. Consider exceptions for founder variants.	Disease specific
BS2	Variant is identified in $\geq 3$ heterozygous or $\geq 1$ homozygous <b>well-phenotyped normolipidemic</b> adults (unrelated).	Disease specific

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BS3	Variant meets Level 1 benign functional study criteria. See below for specifics.	Disease specific / strength
BS4	Lack of segregation in $\geq 2$ index case families (unrelated), when data is available for $\geq 2$ informative meioses in each family. <b>Caveat:</b> must be $\geq 1$ affected relative (LDL-C >75th percentile) who does not carry the variant.	Disease specific
<b>SUPPORTING CRITERIA</b>		
<i>BP1</i>	<i>Missense variant in gene where only LOF causes disease</i>	N/A
BP2	If a FH patient with a heterozygous phenotype carries a proven pathogenic variant (by these guidelines) in <i>LDLR</i> , <i>APOB</i> or <i>PCSK9</i> , BP2 is applicable to any additional <i>LDLR</i> variants.	Disease specific
<i>BP3</i>	<i>In-frame deletions/insertions in a repetitive region without a known function</i>	N/A
BP4	Computational evidence supports no impact on gene or gene product. See FH VCEP suggestions for missense/splicing predictors in main text.	Disease specific
<i>BP5</i>	<i>Variant found in a case with an alternate molecular basis for disease</i>	N/A
<i>BP6</i>	<i>Reputable source recently reports variant as benign but the evidence is not available to the laboratory to perform an independent evaluation</i>	N/A
BP7	Variant is synonymous. <b>Caveat:</b> variant must also meet BP4 (i.e., no predicted impact on splicing).	Disease specific
BS3_Supporting	Variant meets Level 3 benign functional study criteria. See below for specifics.	Disease specific / strength

<b>PATHOGENIC</b>		
1 Very Strong AND	1 or more Strong	
	2 or more Moderate	
	1 Moderate AND	1 Supporting
	2 or more Supporting	
$\geq 2$ Strong		
1 Strong AND	3 or more Moderate	
	2 Moderate AND	2 or more Supporting
	1 Moderate AND	4 or more Supporting
<b>LIKELY PATHOGENIC</b>		
1 Very Strong AND	1 Moderate	
1 Strong AND	1-2 Moderate	
	2 or more Supporting	
3 or more Moderate		
2 Moderate AND	2 or more Supporting	

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1 Moderate AND	4 or more Supporting
<b>BENIGN</b>	
1 Stand-Alone	
2 or more Strong	
<b>LIKELY BENIGN</b>	
1 Strong AND	1 Supporting
2 or more Supporting	
<b>VUS</b>	
Other criteria shown above are not met OR	
the criteria for benign and pathogenic are contradictory	

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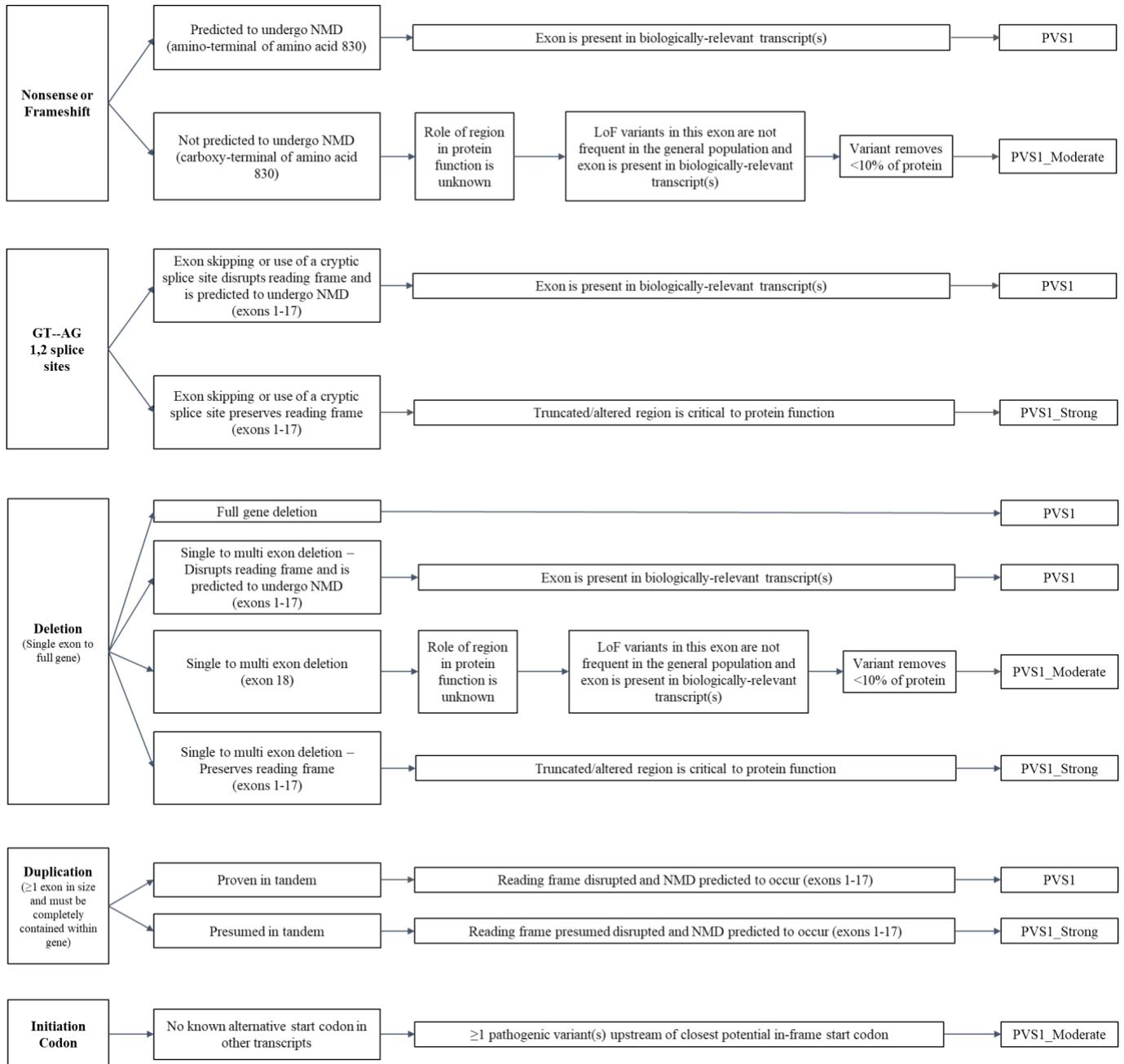
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## PVS1

### PVS1 flowchart FH VCEP adaptation



Adapted from Tayoun et al., 2018

### ***LDLR* exon information.**

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Exon No.	Start (g.)	Stop (g.)	Start (c.)	Stop (c.)	Length	Start Phase	End Phase
1	11089463	11089615	-86	67	153	-	1
2	11100223	11100345	68	190	123	1	1
3	11102664	11102786	191	313	123	1	1
4	11105220	11105600	314	694	381	1	1
5	11106565	11106687	695	817	123	1	1
6	11107392	11107514	818	940	123	1	1
7	11110652	11110771	941	1060	120	1	1
8	11111514	11111639	1061	1186	126	1	1
9	11113278	11113449	1187	1358	172	1	2
10	11113535	11113762	1359	1586	228	2	2
11	11116094	11116212	1587	1705	119	2	1
12	11116859	11116998	1706	1845	140	1	0
13	11120092	11120233	1846	1987	142	0	1
14	11120370	11120522	1988	2140	153	1	1
15	11123174	11123344	2141	2311	171	1	1
16	11128008	11128085	2312	2389	78	1	1
17	11129513	11129670	2390	2547	158	1	0
18	11131281	11133820	2548	2583	35	0	-

LDLR transcript: NM\_000527.5.

Phase: the position of an exon/intron boundary within a codon. A phase of zero means the boundary falls between codons, one means between the first and second base and two means between the second and third base.

## PS3, BS3

### Functional study criteria specifications for *LDLR*.

Pathogenic	
PS3 (Level 1)	(1) Study of the <i>whole</i> LDLR cycle (LDLR expression/biosynthesis, LDL binding, and LDL internalization) performed in heterologous cells (with no endogenous LDLR) transfected with mutant plasmid. Assay result of <70% of wild-type activity in either expression/biosynthesis, binding OR internalization.

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<p>PS3_Moderate (Level 2)</p>	<p>(1) Study of a) only <i>part</i> of the LDLR cycle following Level 1 methodology, or b) <i>whole or part</i> of LDLR cycle in true homozygous patient cells. A variant with assay results of &lt;70% of wild type activity in either LDLR expression/biosynthesis, LDL binding OR internalization.</p> <p>(2) RNA studies, using RNA extracted from heterozygous or homozygous patient cells, where aberrant transcript is confirmed by sequencing and is quantified as &gt;25% of total transcript from heterozygous cells or 50% of total transcript from homozygous cells.</p> <p>(3) Variants with two or more Level 3 functional studies (must be different assays); or any Level 3 functional study #1-4 performed by two or more independent labs with concordant results.</p>
<p>PS3_Supporting (Level 3)</p>	<p>(1) Study of LDLR cycle (part or whole) in heterozygous patient cells, with assay results of &lt;85% of wild-type activity in either LDLR expression/biosynthesis, LDL binding OR internalization.</p> <p>(2) Luciferase studies with transcription levels of &lt;50% compared to wild-type (applicable to 5'UTR/promoter variants).</p> <p>(3) Minigene splicing assays with &lt;10% wild-type transcript present where an aberrant transcript from the candidate variant is confirmed by sequencing.</p> <p>(4) High-throughput assays, which include alternative microscopy assays (Thormaehlen et al., 2015), Multiplex Assays of Variant Effect (MAVE) (Weile &amp; Roth, 2018) and deep mutational scanning assays, can be considered here, only if assay has been validated with a minimum of four pathogenic and four benign variant controls in LDLR. *Note: % activity thresholds will be defined by the FH VCEP as more data becomes available.</p> <p>(5) RNA studies, using RNA extracted from heterozygous or homozygous patient cells, with aberrant transcript confirmed by sequencing (but without transcript quantification).</p>
<p><b>Benign</b></p>	
<p>BS3 (Level 1)</p>	<p>(1) Study of the <i>whole</i> LDLR cycle (LDLR expression/biosynthesis, LDL binding, and LDL internalization) performed in heterologous cells (with no endogenous LDLR) transfected with mutant plasmid. Assay result of &gt;90% of wild-type activity in expression/biosynthesis, binding AND internalization.</p> <p>Note: studies of only part of the LDLR cycle are not eligible for BS3 or BS3_Supporting.</p>

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<p>BS3_Supporting (Level 3)</p>	<p>(1) Study of <i>whole</i> LDLR cycle in a) true homozygous patient cells, with assay result of &gt;90% of wild-type activity in biosynthesis, binding AND internalization; or in b) heterozygous patient cells with assay result of &gt;95% of wild-type activity in biosynthesis, binding AND internalization.</p> <p>(2) Luciferase studies with transcription levels of &gt;90% when compared to wild-type (applicable to 5'UTR/promoter variants).</p> <p>(3) RNA studies, using RNA extracted from heterozygous or homozygous patient cells, with a) aberrant transcripts quantification, where aberrant transcript is &lt;10% of total transcript OR b) without transcript quantification where no aberrant transcript is confirmed by sequencing.</p> <p>(4) Minigene splicing assay where only wild-type transcript is present and confirmed by sequencing.</p> <p>(5) High-throughput assays as defined above; only applicable when assay can indicate the <i>whole</i> LDLR cycle (LDLR expression/biosynthesis, LDL binding AND internalization) is unaffected.</p>
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## PM1

### ***LDLR* cysteine residues involved in disulfide bond formation.**

Residue	Domain	Structure analysis	Potential impact on LDLR structure and/or function
CYS27	LDL-receptor class A 1	disulfide bond	folding defect
CYS34	LDL-receptor class A 1	disulfide bond	folding defect
CYS39	LDL-receptor class A 1	disulfide bond	folding defect
CYS46	LDL-receptor class A 1	disulfide bond	folding defect
CYS52	LDL-receptor class A 1	disulfide bond	folding defect
CYS63	LDL-receptor class A 1	disulfide bond	folding defect
CYS68	LDL-receptor class A 2	disulfide bond	folding defect
CYS75	LDL-receptor class A 2	disulfide bond	folding defect
CYS82	LDL-receptor class A 2	disulfide bond	folding defect
CYS89	LDL-receptor class A 2	disulfide bond	folding defect
CYS95	LDL-receptor class A 2	disulfide bond	folding defect
CYS104	LDL-receptor class A 2	disulfide bond	folding defect
CYS109	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect

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CYS116	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect
CYS121	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect
CYS128	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect
CYS134	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect
CYS143	LDL-receptor class A 3	disulfide bond	folding defect; LDL binding defect
CYS148	LDL-receptor class A 4	disulfide bond; acidic pH intramolecular binding interface	folding defect; receptor-recycling defect; LDL binding defect
CYS155	LDL-receptor class A 4	disulfide bond	folding defect; LDL binding defect
CYS160	LDL-receptor class A 4	disulfide bond; acidic pH intramolecular binding interface	folding defect; receptor-recycling defect; LDL binding defect
CYS167	LDL-receptor class A 4	disulfide bond	folding defect; LDL binding defect
CYS173	LDL-receptor class A 4	disulfide bond; acidic pH intramolecular binding interface	folding defect; receptor-recycling defect; LDL binding defect
CYS184	LDL-receptor class A 4	disulfide bond	folding defect; LDL binding defect
CYS197	LDL-receptor class A 5	disulfide bond	folding defect; LDL binding defect
CYS204	LDL-receptor class A 5	disulfide bond	folding defect; LDL binding defect
CYS209	LDL-receptor class A 5	disulfide bond	folding defect; LDL binding defect
CYS216	LDL-receptor class A 5	disulfide bond	folding defect; LDL binding defect
CYS222	LDL-receptor class A 5	disulfide bond; acidic pH intramolecular binding interface	folding defect; receptor-recycling defect; LDL binding defect
CYS231	LDL-receptor class A 5	disulfide bond	folding defect; LDL binding defect
CYS236	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS243	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS248	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS255	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS261	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS270	LDL-receptor class A 6	disulfide bond	folding defect; LDL binding defect
CYS276	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS284	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS289	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS296	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS302	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS313	LDL-receptor class A 7	disulfide bond	folding defect; LDL binding defect
CYS318	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS325	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS329	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS338	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS340	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS352	EGF-like 1	disulfide bond	folding defect; LDL binding defect
CYS358	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect

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CYS364	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect
CYS368	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect
CYS377	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect
CYS379	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect
CYS392	EGF-like 2; calcium-binding	disulfide bond	folding defect; receptor-recycling defect
CYS667	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect
CYS677	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect
CYS681	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect
CYS696	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect
CYS698	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect
CYS711	EGF-like 3	disulfide bond	folding defect; receptor-recycling defect

Adapted from Guo et al., 2019.

CYS, cysteine; EGF, epidermal growth factor

### BA1, BS1, PM2

#### *LDLR*-specific population data frequency thresholds.

	FAF/MAF	Prevalence	Penetrance	Allelic Het.	Genetic Het.
PM2	$\leq 0.0002$ (0.02%)	1/250	95%	0.1	0.9
BA1	$\geq 0.005$ (0.5%) <sup>a</sup>	1/250	50%	1.0	1.0
BS1	$\geq 0.002$ (0.2%) and $< 0.005$ (0.5%)	1/250	95%	1.0	0.9

FAF, filtering allele frequency; MAF, minor allele frequency; Het., heterogeneity.

<sup>a</sup>BA1 metrics were equal to 0.4%; however, we conservatively increased the BA1 threshold to 0.5%.

For BA1 and BS1 use PopMax FAF in gnomAD. For PM2 use PopMax MAF in gnomAD.

### PP1, BS4

#### Pedigree of a FH family.

Related publication(s):

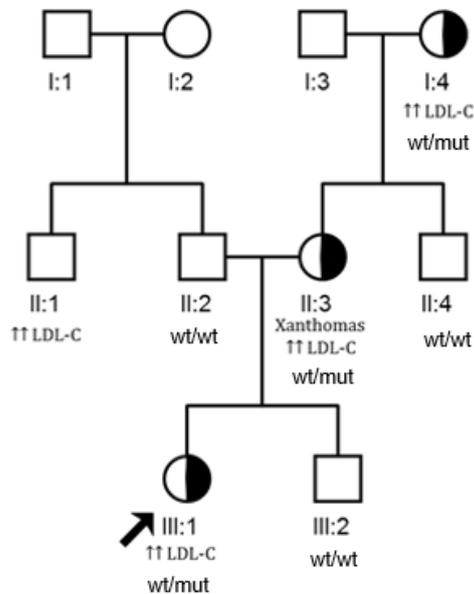
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Index case is identified with an arrow. Half-filled symbols represent heterozygous individuals. Index case III:1 inherited her LDLR variant from the maternal (II:3) side of the family. Her father (II:2) has normal cholesterol, no cardiovascular disease history, and is negative for the variant; therefore, her father (II:2) and paternal uncle (II:1) should not be considered in the co-segregation study. Similarly, the maternal grandfather (I:3) should not be considered.

In this family the individuals that can be considered informative meioses are the index case's brother (III:2), mother (II:3), maternal uncle (II:4) and maternal grandmother (I:4).

Index cases should not be counted as positive cases for co-segregation results.

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**PP3, BP4**

Do not apply if PVS1 (or modified strength) is met.

If both “missense” and splicing prediction are applicable, only 1 prediction of affecting function is necessary to apply PP3, but both need to predict a benign effect for BP4 to be given.

***In silico* classification of missense variants in *LDLR***

We recommend the use of REVEL,

- a) scores above 0.75 as supportive evidence of pathogenicity (PP3),
- b) scores below 0.50 as supportive evidence of benign (BP4).

***In silico* prediction of splicing effects in *LDLR***

Do not apply if *splicing* functional data is available.

Apply A, B or C based on variant location and use MaxEntScan (MES) for scores:

**Related publication(s):**

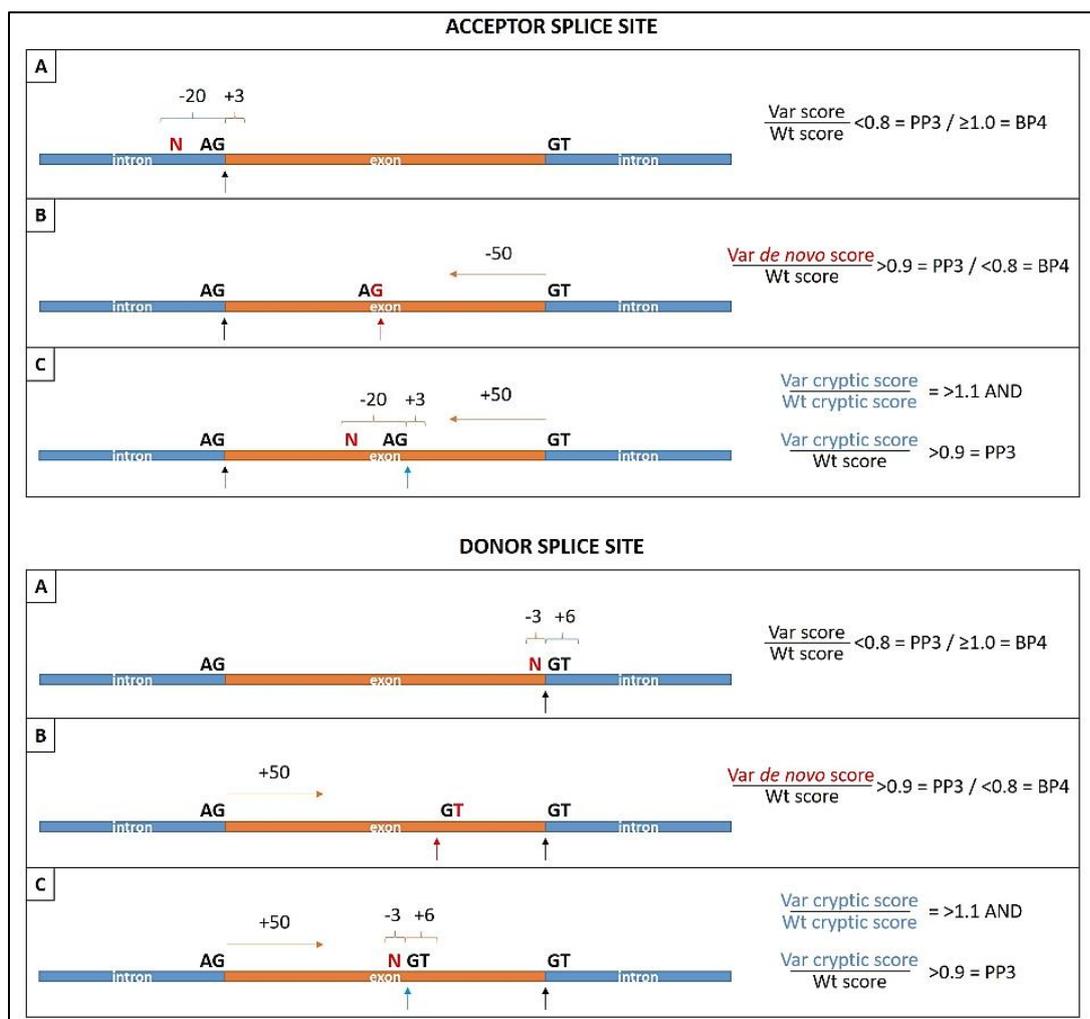
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(A) Variant is located at -20 to +3 bases related to the authentic acceptor splice site or at -3 to +6 related to the authentic donor splice site: A result of authentic splice site strength variant/wild-type score  $< 0.8$  is supportive evidence of pathogenicity (PP3), while a score  $\geq 1.0$  is supportive evidence of benign (BP4).

(B) Variant creates *de novo* acceptor splice site, which is at least 50 bases upstream of the authentic donor splice site, or *de novo* donor splice site, which is at least 50 bases downstream of the authentic acceptor splice site: A result of *de novo* splice site strength variant/authentic wild-type score in  $> 0.9$  is applicable to PP3, while a score  $< 0.8$  is applicable to BP4.

(C) Variant is located at -20 to +3 bases relative to an intra-exonic AG dinucleotide, which is at least 50 bases upstream of the authentic donor splice site, or at -3 to +6 bases relative to an intra-exonic GT dinucleotide, which is at least 50 bases downstream of the authentic acceptor splice site: Results of both variant cryptic/wild-type cryptic score in  $> 1.1$  and cryptic

**Related publication(s):**

**Date Approved: September 27, 2020**

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**ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1**

This version specified for the following genes: *LDLR*

Expert Panel Page: <https://www.clinicalgenome.org/affiliation/50004>

acceptor/authentic acceptor score or cryptic donor/authentic donor score in >0.9 is applicable to PP3.

Note: BP4 is applicable to exonic variants outside of the 50 base limits detailed above, given the unlikelihood of such variants to impact splicing in *LDLR*.

**Related publication(s):**

**Date Approved: September 27, 2020**

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