Supplemental Content

eTable 1. Frequency of suspected pathogenic variants of *LDLR* in mutation-positive* subjects (N=120)†

rs number	Protein Alteration	cDNA Alteration	Location	MAF (gnomAD)	Number (%) of Mutations‡	Evidence of pathogenicity (ClinVar/LOVD)
	p.W4Gfs*202	c.6delG	Exon 1	NA	1 (0.8)	Pathogenic***
rs2228671	p.C27W	c.81C>G	Exon 2	$1.5x10^{-5}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs121908024	p.Q33*	c.97C>T	Exon 2	$7.9x10^{-6}$	1 (0.8)	Pathogenic
	p.K38*	**c.112A>T**	**Exon 2**	**NA**	**1 (0.8)**	**Not reported**
rs146675823	p.R78H	c.233G>A	Exon 3	$5.3x10^{-5}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs875989893	p.Q85*	c.253C>T	Exon 3	NA	2 (1.6)	Pathogenic
rs121908025	p.W87G	c.259T>G	Exon 3	$2.8x10^{-5}$	10 (8.2)	Pathogenic
rs8759254456	p.C95R	c.283T>C	Exon 3	NA	1 (0.8)	Pathogenic
rs144172724	p.E101K	c.301G>A	Exon 3	$1.7x10^{-5}$	1 (0.8)	Pathogenic/likely pathogenic
rs769383881	p.E113*	c.337G>T	Exon 4	$3.9x10^{-6}$	1 (0.8)	Pathogenic/likely pathogenic
	p.C116S	**c.347G>C**	**Exon 4**		**1 (0.8)**	
	p.I122_I210del	**c.367_631del**	**Exon 4**		**1 (0.8)**	
rs777321035	p.D168E	c.504C>A	Exon 4	$7.9x10^{-6}$	1 (0.8)	Likely pathogenic
rs76931835	p.C173W	c.519C>G	Exon 4	$7.9x10^{-6}$	1 (0.8)	Pathogenic/likely pathogenic
	p.G218del	c.652_654delGGT	Exon 4	NA	4 (3.3)	Not reported
	p.G219Pfs*8	**c.653delGT**	**Exon 4**		**1 (0.8)**	
rs121908027	p.G219del	c.654_656delTGG	Exon 4		1 (0.8)	Pathogenic/likely pathogenic
rs121908029	p.E228*	c.682G>T	Exon 4	$1.1x10^{-5}$	3 (2.5)	Pathogenic/likely pathogenic

	p.D304Gfs*5	**c.910insG**	**Exon 6**		**1 (0.8)**	
rs879254739	p.C318F	c.953G>T	Exon 7	NA	1 (0.8)	Likely pathogenic
rs72658860	p.G324S	c.970G>A	Exon 7	$1.2x10^{-3}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs755757866	p.C340Y	c.1019G>A	Exon 7	$7.9x10^{-6}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs879254791	p.C368R	c.1102T>C	Exon 8	$3.9x10^{-6}$	2 (1.6)	Pathogenic/Likely pathogenic
	p.K393E	c.1177A>G	Exon 8	NA	1 (0.8)	Not reported
rs137943601	p.E408K	c.1222G>A	Exon 9	$7.6x10^{-6}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs879254838	p.E408V	c.1223A>T	Exon 9	NA	1 (0.8)	Likely pathogenic
rs879254839	p.R410S§	c.1230G>C	Exon 9	NA	1 (0.8)	Conflicting interpretations of pathogenicity
rs368562025	p.T413M	c.1238C>T	Exon 9	$2.7x10^{-5}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs879254867	p.W443C	c.1329G>C	Exon 9	NA	1 (0.8)	Pathogenic/Likely pathogenic
rs370777955	p.Y489*	c.1467C>G	Exon 10	$3.9x10^{-6}$	4 (3.3)	Pathogenic/Likely pathogenic
rs373646964	p.D492H	c.1474G>C	Exon 10	$7.1x10^{-6}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs769370816	p.A540T	c.1618G>A	Exon 11	$7.9x10^{-6}$	1 (0.8)	Pathogenic/Likely pathogenic
rs28941776	p.G549D	c.1646G>A	Exon 11	$2.4x10^{-5}$	1 (0.8)	Pathogenic/Likely pathogenic
rs137929307	p.G592E§	c.1775G>A	Exon 12	$5.7x10^{-5}$	1 (0.8)	Pathogenic/Likely pathogenic
rs201102492	p.R595Q‖	c.1784G>A	Exon 12	$3.9x10^{-5}$	2 (1.6)	Conflicting interpretations of pathogenicity
	p.A643_L647del	**c.1927_1941del**	**Exon 13**		**1 (0.8)**	
rs875989936	p.M652T	c.1955T>C	Exon 13	$3.9x10^{-6}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs28942083	p.C667Y	c.2000G>A	Exon 14	$3.9x10^{-6}$	5 (4.1)	Pathogenic/Likely pathogenic
rs775092314	p.C677R	c.2029T>C	Exon 14	$3.9x10^{-6}$	1 (0.8)	Pathogenic/Likely pathogenic
rs121908031	p.C681*	c.2043C>A	Exon 14	$7.9x10^{-6}$	5 (4.1)	Pathogenic/Likely pathogenic
rs28942084	p.P685L	c.2054C>T	Exon 14	$3.2x10^{-5}$	1 (0.8)	Pathogenic/Likely pathogenic
rs201573863	p.P699L	c.2096C>T	Exon 14	$3.8x10^{-5}$	1 (0.8)	Conflicting interpretations of pathogenicity
rs1057516127	p.E723*	c.2167G>T	Exon 15	$3.2x10^{-5}$	1 (0.8)	Pathogenic/Likely pathogenic
rs200793488	p.R744*	c.2230C>T	Exon 15	$3.9x10^{-6}$	1 (0.8)	Pathogenic

rs750518671	p.V797M	c.2389G>A	Exon 16	$7.9x10^{-6}$	1 (0.8)	Conflicting interpretations of pathogenicity
	p.V806Gfs*11	c.2416_2417insG	Exon 17	NA	1 (0.8)	Pathogenic***
	p.N817Kfs*9	c.2447_2450dup	Exon 17	NA	1 (0.8)	Pathogenic***
rs137853964	p.V827I	c.2479G>A	Exon 17	$9.2x10^{-4}$	1 (0.8)	Conflicting interpretations of pathogenicity
	p.0?	c.?_-187_67+1_68-1del	Exon 1		29 (23.8)	Pathogenic***
	p.Val23_Pro105delinsAla	c.67+1_68-1_313+1_314-1del	Exon 2, 3		1 (0.8)	Pathogenic***
	p.Val23_Cys313del	c.67+1_68-1_940+1_941-1del	Exon 2, 3, 4, 5, 6		1 (0.8)	Pathogenic***
	p.Leu64_Ala232delinsSer	c.190+1_191-1_694+1_695-1del	Exon 3, 4		1 (0.8)	Pathogenic***
	p.Leu64Trp;Ser65_Gly314del	c.191-512_940+631del	Exon 3, 4, 5, 6		3 (2.5)	Pathogenic***
		Exons 4-10 dup	**Exons 4-10**		1 (0.8)	
		Exon 6 dup	**Exon 6**		1 (0.8)	
	p.Gly314Alafs*19	c.940+1_941-1_1586+1_1587-1del	Exon 7, 8, 9, 10		1 (0.8)	Pathogenic***
	p.?	c.2140+1_2141-1_*2514_?del	Exons 15-18		1 (0.8)	Pathogenic***
	p.?	c.2389+1_2390-1_*2514_?del	Exon 17, 18		1 (0.8)	Pathogenic***

Del, deletion; dup, duplication; fs, frameshift; het, heterozygous; hom, homozygous; ins, insertion.
LDLR mRNA Accession Number NM_000527.4; *LDLR* Protein Accession Number NP_000518.1
*Excludes subjects carrying only the p.A391T or p.T726I variants of *LDLR*.
†All missense, frameshift, and truncation mutations suspected to be disease causing are shown. Novel *LDLR* variants (N=12) are shown in **bold** font.

‡Number of mutations is larger than the number of subjects due to one subject with a homozygous mutation and one subject with compound heterozygous mutations in *LDLR*. Percentage was calculated using the total number of suspected disease-causing mutations identified (N=122) as the denominator.
§Subject was heterozygous for the *LDLR* p.R410S and p.G592E mutations.
‖The two subjects were heterozygous for the *LDLR* p.R595Q mutation and p.T726I variant, one of which was homozygous for p.T726I.
¶Subject was heterozygous for the *LDLR* p.V806Gfs mutation and p.T726I variant.
*** Information from https://www.ncbi.nlm.nih.gov/clinvar/ and https://databases.lovd.nl/shared/genes/LDLR accessed March 2019.

eTable 2. Demographic characteristics at screening visit* for the two mutation-positive subjects† with compound heterozygous and homozygous *LDLR* mutations

Characteristic	Subject 1	Subject 2
Protein alteration	W87G	R410S; G592E
cDNA alteration	259T>G	1230G>C; 1775G>A
Location	Exon 3	Exon 9; Exon 12
Genotype	Hom	Het; Het
Gender	Female	Male
Age (years)	56	22
Total cholesterol (mg/dL)	446	279
LDL-C (mg/dL)	376	208
Triglycerides (mg/dL)	172	199
HDL-C (mg/dL)	35	31
ApoAI (mg/dL)	82	98
ApoB (mg/dL)	281	165
PCSK9 (ng/mL)	84	86
Lipid-lowering medication	Atorvastatin; Ezetimibe; Fenofibrate; Estrogens	Rosuvastatin; Ezetimibe
CVD history	CHD	–

Clinical features of FH		
Bruits	No	No
Corneal arcus	No	No
Pulse		
Faint/slightly diminished[§]	No	No
Tendinous xanthomas	No	Yes
Tuberous xanthomas	No	No
Xanthelasma	Yes	No

ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; fs, frameshift; HDL-C, high-density lipoprotein cholesterol; het, heterozygous; hom, homozygous; ins, insertion; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

*The majority of subjects were receiving lipid-lowering therapy at screening.

[†]Excludes subjects carrying only the p.A391T or p.T726I variants of *LDLR*.

[‡]The category “Faint/slightly diminished” in any site includes subjects with ≥1 abnormal pulse.

eTable 3. Frequency of *PCSK9* variants in mutation-positive* (N=120) and mutation-negative† (N=80) subjects

rs number	Protein Alteration	cDNA Alteration	Location	MAF	Genotype	Number (%) of Mutations‡			Evidence of pathogenicity (ClinVar)
						Mutation Positive (N=120)	Mutation Negative (N=80)	Total (N=200)	
rs11591147	p.R46L	c.137G>T	Exon 1	0.01222	Het	3 (0.7)	0 (0.0)	3 (0.4)	Conflicting interpretations of pathogenicity, association
rs11583680	p.A53V	c.158C>T	Exon 1	0.1104	30 Het; 4 Hom	21 (4.7)	17 (5.5)	38 (5.1)	Benign/Likely benign
rs145886902	p.E57K	c.169G>A	Exon 1	2.614×10^{-4}	Het	0 (0.0)	2 (0.7)	2 (0.3)	Uncertain significance
rs372165281	p.R165Q	c.494G>A	Exon 3	3.184×10^{-5}	Het	1 (0.2)	0 (0.0)	1 (0.1)	Uncertain significance
rs148195424	p.R237W	c.709C>T	Exon 5	6.952×10^{-4}	Het	1 (0.2)	0 (0.0)	1 (0.1)	Conflicting interpretations of pathogenicity
rs562556	p.V474I	c.1420G>A	Exon 9	0.8539	48 Het; 145 Hom	202 (45.4)	136 (44.3)	338 (44.9)	Benign/ Likely Benign
rs149311926	p.Q554E	c.1660C>G	Exon 10	6.376×10^{-6}	Het	0 (0.0)	1 (0.3)	1 (0.1)	Uncertain significance

rs505151	p.E670G	c.2009A>G	Exon 12	0.0583	30 Het; 169 Hom	217 (48.8)	151 (49.2)	368 (48.9)	Benign/ Likely benign

PCSK9 mRNA Accession Number NM_174936.3; het, heterozygous; hom, homozygous.

*Excludes subjects carrying only the p.A391T or p.T726I variants of *LDLR*.

†Includes subjects carrying only the p.A391T or p.T726I variants of *LDLR*.

‡Number of mutations is larger than the number of subjects due to a number of subjects with homozygous and compound heterozygous mutations in *PCSK9*.

Percentage was calculated using the total number of mutations identified in each group (mutation-positive: N=445; mutation-negative: N=307; total: N=752) as the denominator.

*** Information from https://www.ncbi.nlm.nih.gov/clinvar/ accessed March 2019.