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Software and database for the analysis of mutations in the human LDL receptor gene

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ABSTRACT

The low-density lipoprotein receptor (LDLr) plays a pivotal role in cholesterol homeostasis. Mutations in the LDLr gene (LDLR), which is located on chromosome 19, cause familial hypercholesterolemia (FH), an autosomal dominant disorder characterized by severe hypercholesterolemia associated with premature coronary atherosclerosis. To date almost 300 mutations have been identified in the LDLR gene. To facilitate the mutational analysis of the LDLR gene, and promote the analysis of the relationship between genotype and phenotype, a software package along with a computerized database (currently listing 210 entries) have been created.

INTRODUCTION

The low-density lipoprotein receptor (LDLr) is an ubiquitous transmembrane glycoprotein of 839 amino acids that mediates the transport of LDL into cells, via receptor-mediated endocytosis, and is pivotal in cholesterol homeostasis (1). Defects in the LDLr result in familial hypercholesterolemia (FH). FH is characterized clinically by raised plasma LDL–cholesterol concentrations, xanthomas and early coronary heart disease (2). FH is an autosomal dominant trait, homozygotes being more severely affected than heterozygotes. FH is also one of the most common inherited disorders with a frequency of heterozygotes estimated to be 1:500 and a frequency of homozygotes being ~1:10^6 in most populations. FH frequency is higher in certain communities in which a small number of mutations predominate due to founder effects. These communities include French Canadians (3), Christian Lebanese (4), Druze (5), Finns (6), Afrikaners (7) and Ashkenazi Jews of Lithuanian descent (8).

The gene for the LDL receptor (LDLR) located at chromosome 19p13.1–13.3 (9), spans 45 kb, and is divided into 18 exons (10). The correspondence between gene exons and functional domains of the mature protein is well established (10). *Exon 1* encodes the 21 amino acids of the signal sequence which is cleaved from the protein during translocation into the endoplasmic reticulum (ER). *Exons 2–6* encode the ligand-binding domain, which is made up of seven repeats of 40 amino acids each. These repeats are homologous to sequences of the protein C9 of the complement cascade (10). Each repeat contains six cysteine residues that form three disulfide bonds. The C-terminal end of each repeat contains a negatively charged triplet, SDE, important for ligand binding. *Exons 7–14* encode a 400 amino acids sequence that is 33% identical to a portion of the human epidermal growth factor (EGF) precursor gene. This region includes three growth factor repeats which are 40 amino acid cysteine-rich sequences that differ from the cysteine-rich sequences in the ligand-binding domain. The two first repeats are contiguous and separated from the third by a 28 amino acids sequence that contains five copies of a conserved motif (YWTD) repeated once each 40–60 amino acids (10). This domain is required for the dissociation of lipoproteins from the receptor in the endosome during receptor recycling. It also serves to position the ligand binding domain so that it can bind LDL on the cell surface (11). *Exon 15* encodes 58 amino acids that are enriched in serine and threonine residues, which serve as attachment sites for O-linked sugar chains. Absence of this exon has no significant functional consequence in cultured hamster fibroblasts (12). *The 3′ end of exon 16 and the 5′ end of exon 17* encode the 22 hydrophobic amino acids of the membrane-spanning domain. *The remainder of exon 17 and the 5′ end of exon 18* encode the 50 amino acids that make up the cytoplasmic domain. This domain is important for the localization of the receptor in coated pits on the cell surface (12–14). *The remainder of exon 18* specifies the 2.6 kb 3′ untranslated region of the mRNA.

In normal fibroblasts, an LDLr precursor protein (120 kDa) is produced in the ER. Within 30 min the protein (160 kDa) is transported to the Golgi complex. From the Golgi complex, the receptor is transported then to the cell surface where it binds its ligand, LDL, and is internalized by endocytosis (1). Mutations in the LDLR gene have been classified into five functional groups based on the characteristics of the LDLr produced (15). *Class 1* mutations disrupt the receptor's synthesis in the ER. *Class 2* mutations block transport to the Golgi complex: *class 2A* mutations completely block receptor transport, while *class 2B* mutations produce proteins that are transported at a detectable,

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A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
44	1	7	-19	CCC	del1a	del	7delC - DALLAS 1	Pro	Fr.	Signal peptide	1	Hmz	ab	?		American	16
45	1	11	-18	TGG	TAG	G->A	W-18X - COLUMBIA 1	Trp	Stop	Signal peptide	1	Hmz	aa			Columbian	16
46	1	12	-18	TGG	TGA	G->A	W-18X - NANJING 1	Trp	Stop	Signal peptide	1	Hmz	ab	109		Chinese	16
47	2	81	6	TGT	TGG	T->G	C6W - SAN FRANCISCO	Cys	Trp	Ligand binding #1	2B	Hmz	aa			American	16
48	2	97	12	CAG	del1a	Stop at 204	97delC - ALGERIA 4	Gln	Fr.	Ligand binding #1	1	Hmz	ab	95		Algerian	16
17	2	97	12	CAG	TAG	C->T	Q12X - TURKEY	Gln	Stop	Ligand binding #1	1		aa		R	Turkish	15
150	2	97	12	CAG	TAG	C->T	Q12X	Gln	Stop	Ligand binding #1	1	Hmz	aa		R	French	49
49	2	131	23	TGG	TAG	G->A	W23X - CINCINNATI 5	Trp	Stop	Ligand binding #1	1	Hmz	ab	?	R	American	16
201	2	131	23	TGG	TAG	G->A	W23X	Trp	Stop	Ligand binding #1	1				R	German-Canadian	16
1	2	139	26	GAT	del6a	del	139del6 - CAPE TOWN-1	Asp	Fr.	Ligand binding #1	2B	Hmz	aa			Black Sud Africains	39
50	2	155	31	TGC	TAC	G->A	C31Y - PARIS 4	Cys	Tyr	Ligand binding #1	2B	Hmz	ab	?		French	16
51	2	172	37	GAG	del1a	Stop at 204	172delG - PEDI 1	Glu	Fr.	Ligand binding #1	1	Hmz	ab	del3 prom		Pedi tribe	16
188	3	211	50	GGG	del1a	Stop at 204	211delG	Gly	Fr.	Ligand binding #2						Irish	67
156	3	253	64	CAG	TAG	C->T	Q64X	Gln	Stop	Ligand binding #2			Wa			German	58
3	3	259	66	TGG	GGG	T->G	W66G - FRENCH CANADIAN-4	Trp	Gly	Ligand binding #2	3/5	Hmz	aa		F	French-Canadian	3
52	3	269	69	GAT	GGT	A->G	D69G - LONDON 4	Asp	Gly	Ligand binding #2	2B	Hmz	ab	79		British	16
123	3	268	69	GAT	TAT	G->T	D69Y - DURBAN 1	Asp	Tyr	Ligand binding #2	2B	Hmz	ab	124		South Afr-Indian	55
140	3	296	78	TCA	TGA	C->G	S78X - SVARTOR	Ser	Stop	Ligand binding #2	1		Wa		F	Norvegian	44
53	3	301	80	GAG	AAG	G->A	E80K - LANCASHIRE	Glu	Lys	Ligand binding #2	2B	Htz	Wa		F	English	68
151	3	301	80	GAG	AAG	G->A	E80K	Glu	Lys	Ligand binding #2	2B	Htz	Wa		?	French	49
36	3	301	80	GAG	TAG	G->T	E80X - FINN-1	Glu	Stop	Ligand binding #2			Wa			Finnish	34
54	3	304	81	CAA	TAA	C->T	Q80X -RAPONI	Gln	Stop	Ligand binding #2	1	Hmz	aa			Italian-American	16
55	4	325	88	TGC	CGC	T->C	C88R - MUNSTER 1	Cys	Arg	Ligand binding #3	2B	Hmz	ab	89		German	16
37	4	325	88	TGC	del13a	Stop at 200	325del13 - FINN-2	Cys	Fr.	Ligand binding #3			Wa			Finnish	34
56	4	337	92	GAG	TAG	G->T	E92X - PARIS 5	Glu	Stop	Ligand binding #3	1	Hmz	ab	4		French	16
57	4	382	107	TGT	del4a	Stop at 203	382del4 - DALLAS 2	Cys	Fr.	Ligand binding #3	1	Htz	Wa			African-American	16
121	4	406	115	GAC	del12c	del	408del12	Asp	Fr.	Ligand binding #3	2B	Hmz	aa			American	71
59	4	418	119	GAG	AAG	G->A	E119K - PHILIPPINES	Glu	Lys	Ligand binding #3	2B	Hmz	ab	?	?	Philippine-Canadian	16
124	4	418	119	GAG	AAG	G->A	E119K - DURBAN 2	Glu	Lys	Ligand binding #3	2B	Hmz	ab	123	?	South Afr-Indian	55
145	4	418	119	GAG	AAG	G->A	E119K	Glu	Lys	Ligand binding #3	2B	Htz	Wa		F	Danish	31
154	4	418	119	GAG	AAG	G->A	E119K	Glu	Lys	Ligand binding #3		Hmz	ab	153	F	Japanese	40
58	4	418	119	GAG	TAG	G->T	E119X - VENEZUELA	Glu	Stop	Ligand binding #3	1	Hmz	ab	?		Italian-Venezuelan	16
60	4	463	134	TGC	GGC	T->G	C134G - GERMANY	Cys	Gly	Ligand binding #4	2B	Hmz	ab	3		Polish	16
163	4	481	140	ATC	ins19c	Stop at 178	483ins19	Ile	Fr.	Ligand binding #4		Htz	Wa			Belgian	53
165	4	501	146	TGC	TGA	C->A	C146X	Cys	Stop	Ligand binding #4		Htz				Dutch	47
61	4	502	147	GAC	CAC	G->C	D147H - SEPHARDIC	Asp	His	Ligand binding #4	2B		aa		F	Sephardic Jewish	41
197	4	502	147	GAC	TAC	G->T	D147Y	Asp	Tyr	Ligand binding #4		Htz			F	Norvegian	29
62	4	517	152	TGC	CGC	T->C	C152R - GREECE 1	Cys	Arg	Ligand binding #4	2B	Hmz	ab	78		Greek	16
157	4	517	152	TGC	GGC	T->G	C152G	Cys	Gly	Ligand binding #4			Wa		F	German	58
26	4	523	154	GAT	AAT	G->A	D154N - AFRIKANER 3	Asp	Asn	Ligand binding #4	3		Wa		F	Afrikaner	36
5	4	530	156	TCG	TTG	C->T	S156L - PUERTO RICO	Ser	Leu	Ligand binding #4	2B+3	Hmz	aa		R	Puerto Rico	30
142	4	530	156	TCG	TTG	C->T	S156L	Ser	Leu	Ligand binding #4	2B+3				R	German	57

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
178	4	532	157	GAT	ins8b	Stop at 178	533ins8	Asp	Fr.	Ligand binding #4						German	26
27	4	564	167	TAC	TAG	C->G	Y167X - DRUZE	Tyr	Stop		1		aa		F	Druze (Israel)	5
164	4	568	169	TTC	del23a	Stop at 170	568del23	Phe	Fr.			Htz	Wa			Belgian	53
187	4	580	173	AGT	del7c	Stop at 202	582del7	Ser	Fr.	Ligand binding #5			Wa			New Zeland	64
190	4	589	176	TGC	CGC	T->C	C176R	Cys	Arg	Ligand binding #5		Hmz	ab	12-118		British	69
64	4	590	176	TGC	TAC	G->A	C176Y - SALVADOR 1	Cys	Tyr	Ligand binding #5	2B	Hmz	ab	111		El Salvadorian	16
63	4	590	176	TGC	TTC	G->T	C176F - SHREVEPORT	Cys	Phe	Ligand binding #5	2B	Hmz	ab	21		African American	16
65	4	622	187	GAG	AAG	G->A	E187K - JERUSALEM	Glu	Lys	Ligand binding #5	2B	Hmz	ab	?		Moslem	16
138	4	631	190	CAC	del3b	Stop at 189	632delACT	His	Fr.	Ligand binding #5	3	Htz	Wa			Chinese	62
166	4	646	195	TGT	del2a	Stop at 215	646delTG	Cys	Fr.	Ligand binding #5		Htz				Dutch	47
181	4	649	196	GAT	del37c	Stop at 251	651del37	Asp	Fr.	Ligand binding #5						German	26
180	4	652	197	GGT	del1a	Stop at 204	652delG	Gly	Fr.	Ligand binding #5						German	26
18	4	652	197	GGT	del3a	del	652delGGT - LITHUANIA	Gly	Fr.	Ligand binding #5	2B		aa		F	Jewish Ashkenazi	8
9	4	661	200	GAC	del21a	del	661del21	Asp	Fr.	Ligand binding #5	2					African American	71
38	4	661	200	GAC	TAC	G->T	D200Y - FINN-3	Asp	Tyr	Ligand binding #5			Wa		?	Finnish	34
176	4	661	200	GAC	TAC	G->T	D200Y	Asp	Tyr	Ligand binding #5					?	German	26
66	4	662	200	GAC	GGC	A->G	D200G - PADOVA	Asp	Gly	Ligand binding #5	2B	Htz	Wa			British	28
39	4	665	201	TGC	TAC	G->A	C201Y - FINN-4	Cys	Tyr	Ligand binding #5			Wa			Finnish	34
25	4	670	203	GAC	AAC	G->A	D203N - PORTUGAL	Asp	Asn	Ligand binding #5	2B	Hmz	aa			Portugese	16
68	4	671	203	GAC	GGC	A->G	D203G - ITALY 2	Asp	Gly	Ligand binding #5	2B	Hmz	ab	?		Italian-American	16
177	4	671	203	GAC	GTC	A->T	D203V	Asp	Val	Ligand binding #5						German	26
69	4	676	205	TCT	CCT	T->C	S205P - MIAMI 1	Ser	Pro	Ligand binding #5	2B	Hmz	aa			Seminole Indian	16
32	4	676	205	TCT	ins18c	Stop at 216	679ins18 - AFRIKANER 4	Ser	Fr.	Ligand binding #5			Wa		DN	Afrikaner	37
30	4	679	206	GAC	del2b	Stop at 215	680delAC - LONDON 5	Asp	Fr.	Ligand binding #5			Wa			British	27
6	4	681	206	GAC	GAG	C->G	D206E - AFRIKANER-1	Asp	Glu	Ligand binding #5	2B	Hmz	aa		F	Afrikaner	40
202	4	681	206	GAC	GAG	C->G	D206E	Asp	Glu	Ligand binding #5	2B				R	English	16
179	4	679	206	GAC	ins18c	Stop at 216	681ins18	Asp	Fr.	Ligand binding #5						German	26
4	4	682	207	GAG	AAG	G->A	E207K - FRENCH CANADIAN-3	Glu	Lys	Ligand binding #5	2B	Hmz	aa		F	French-Canadian	3
119	4	682	207	GAG	AAG	G->A	E207K - MEXICO	Glu	Lys	Ligand binding #5	2B		aa		R	Mexican	3
203	4	682	207	GAG	AAG	G->A	E207K	Glu	Lys	Ligand binding #5	2B				R	French	16
204	4	682	207	GAG	AAG	G->A	E207K	Glu	Lys	Ligand binding #5	2B				R	Italian	16
71	4	682	207	GAG	CAG	G->C	E207Q - TULSA 2	Glu	Gln	Ligand binding #5	2B	Hmz	ab	67		African American	16
67	4	682	207	GAG	ins21c	Stop at 216	684ins21 - TULSA 1	Glu	Fr.	Ligand binding #5	2B	Hmz	ab	71		African American	16
70	4	682	207	GAG	TAG	G->T	E207X - MOROCCO	Glu	Stop	Ligand binding #5	1	Hmz	aa			Moroccan-American	16
195	4	691	210	TGC	GGC	T->G	C210G	Cys	Gly	Ligand binding #5		Htz	Wa		F	Norvegian	63
29	4	693	210	TGC	TGA	C->A	C210X - LONDON 3	Cys	Stop	Ligand binding #5			Wa			British	27
131	5	703	214	ACC	del87b	del	704del87	Thr	Fr.	Ligand binding #6	2A	Htz				German	56
72	5	718	219	GAA	AAA	G->A	E219K - CHARLOTTE	Glu	Lys	Ligand binding #6	2B	Hmz	ab	114		American	16
73	5	724	221	CAG	TAG	C->T	Q221X - CORSICA	Gln	Stop	Ligand binding #6	1	Hmz	aa			French	16
193	5	743	227	TGC	TAC	G->A	C227Y	Cys	Tyr	Ligand binding #6		Hmz	ab	192		British	69
74	5	743	227	TGC	TTC	G->T	C227F - BRETAGNE 1	Cys	Phe	Ligand binding #6	2B	Hmz	ab	84		French	16
75	5	767	235	GAC	GGC	A->G	D235G - NEVERS	Asp	Gly	Ligand binding #6	2B	Hmz	ab	?		French	16

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
76	5	798	245	GAT	GAA	T->A	D245E - CINCINATI 1	Asp	Glu	Ligand binding #6	2B	Hmz	aa			American	16
77	5	809	249	TGC	TAC	G->A	C249Y - MIAMI 2	Cys	Tyr	Ligand binding #6	2B	Hmz	ab	?		American	16
174	6	829	256	GAG	AAG	G->A	E256K	Glu	Lys	Ligand binding #7			ab	175	?	Swedish	23
182	6	829	256	GAG	AAG	G->A	E256K	Glu	Lys	Ligand binding #7		Htz			?	Spanish	54
78	6	858	265	AGC	AGA	C->A	S265R - GREECE 2	Ser	Arg	Ligand binding #7	2B	Hmz	ab	62		Greek	16
167	6	877	272	GAC	del1a	Stop at 272	877delG	Asp	Fr.	Ligand binding #7		Htz				Dutch	47
194	6	902	280	GAC	GCC	A->C	D280A	Asp	Ala	Ligand binding #7		Hmz	ab	78		Greek	69
189	6	906	281	TGC	TGG	C->G	C281W	Cys	Trp	Ligand binding #7		Hmz	aa			Iraqi	69
21	6	910	283	GAC	AAC	G->A	D283N - DENVER 2	Asp	Asn	Ligand binding #7	2B		aa			African-American	15
79	6	912	283	GAC	GAG	C->G	D283E - BALTIMORE 1	Asp	Glu	Ligand binding #7	2B	Hmz	ab	delex17/18	R	American	16
205	6	912	283	GAC	GAG	C->G	D283E	Asp	Glu	Ligand binding #7	2B				R	English	16
206	6	912	283	GAC	GAG	C->G	D283E	Asp	Glu	Ligand binding #7	2B				R	French	16
147	6	910	283	GAC	TAC	G->T	D283Y	Asp	Tyr	Ligand binding #7	3	Htz	Wa			French	49
40	6	915	284	TGG	TGA	G->A	W284X - FINN-5	Trp	Stop	Ligand binding #7			Wa			Finnish	34
80	6	917	285	TCA	TTA	C->T	S285L - AMSTERDAM	Ser	Leu	Ligand binding #7	2B	Hmz	ab	?		Dutch	16
28	6	922	287	GAA	del7c	Stop at 366	924del7 - KARELIA	Glu	Fr.	Ligand binding #7	1	Htz	Wa		F	Finnish	6
146	6	932	290	AAA	AGA	A->G	K290R	Lys	Arg	Ligand binding #7	3	Htz	Wa			French	49
81	6	939	292	TGC	TGA	C->A	C292X - CYPRUS	Cys	Stop	Ligand binding #7	1	Hmz	aa			Greek Cypriot	16
82	7	953	297	TGC	TAC	G->A	C297Y - MEXICO 1	Cys	Tyr	EGF precursor A	2B	Hmz	ab	?		Mexican-American	16
127	7	953	297	TGC	TTC	G->T	C297F - TRIESTE	Cys	Phe	EGF precursor A	2A	Htz	Wa		F	Italian	42
158	7	970	303	GGC	del1a	Stop at 368	970delG	Gly	Fr.	EGF precursor A			Wa			German	58
83	7	1003	314	GGC	AGC	G->A	G314S - PARIS 6	Gly	Ser	EGF precursor A	5	Htz	Wa			French	16
84	7	1008	315	TAC	TAA	C->A	Y315X - BRETAGNE 2	Tyr	Stop	EGF precursor A	1	Hmz	ab	74		French	16
152	7	1012	317	TGC	AGC	T->A	C317S - WAKAYAMA	Cys	Ser	EGF precursor A	2	Hmz	aa		F	Japanese	40
85	7	1026	321	GAC	GAG	C->G	D321E - NEW-YORK 1	Asp	Glu	EGF precursor A	2B/5	Hmz	ab	99		African-American	16
86	7	1027	322	GGC	AGC	G->A	G322S - PICARDIE	Gly	Ser	EGF precursor A	2B/5	Hmz	ab	79		French	16
192	7	1049	329	CGA	CCA	G->C	R329P	Arg	Pro	EGF precursor A		Hmz	ab	193		British	69
139	7	1048	329	CGA	TGA	C->T	R329X - FOSSUM	Arg	Stop	EGF precursor A	1	Htz	Wa		?	Norvegian	60
168	7	1048	329	CGA	TGA	C->T	R329X	Arg	Stop	EGF precursor A		Htz			?	Dutch	47
87	7	1055	331	TGC	TAC	G->A	C331Y - MEXICO 2	Cys	Tyr	EGF precursor A	2B/5	Hmz	ab	92		Mexican	16
89	7-8	1061	333	GAT	GGT	A->G	D333G - MUNSTER 2	Asp	Gly	EGF precursor A	2B/5	Hmz	ab	55		German	16
88	7-8	1061	333	GAT	GTT	A->T	D333V - OKLAHOMA	Asp	Val	EGF precursor A	5	Hmz	ab	?		American-Indian	16
90	8	1069	336	GAG	AAG	G->A	E336K - PARIS 7	Glu	Lys	EGF precursor B	2B/5	Hmz	ab	5		French	16
91	8	1075	338	CAG	TAG	C->T	Q338X - BRUSSELS	Gln	Stop	EGF precursor B	1	Hmz	ab	?		Belgian	16
92	8	1090	343	TGC	CGC	T->C	C343R - MEXICO 3	Cys	Arg	EGF precursor B	2B/5	Hmz	ab	87		Mexican-American	16
198	8	1097	345	CAG	CGG	A->G	Q345R	Gln	Arg	EGF precursor B		Htz			F	Norvegian	29
148	8	1103	347	TGC	TAC	G->A	C347Y	Cys	Tyr	EGF precursor B	2	Htz	Wa			French	49
24	8	1117	352	GGT	ins4c	Stop at 356	1119ins4 - NASHVILLE	Gly	Fr.	EGF precursor B	1		aa			American	15
93	8	1135	358	TGT	CGT	T->C	C358R - NAPLES 1	Cys	Arg	EGF precursor B	5	Hmz	aa			Italian	16
170	8	1168	369	AAG	TAG	A->T	K369X	Lys	Stop	EGF precursor B		Htz	Wa			Irish	66
120	8	1171	370	GCC	ACC	G->A	A370T	Ala	Thr	EGF precursor B						Afrikaner	36
41	8-9	1186	375	GGC	AGC	G->A	G375S - FINN-6	Gly	Ser	EGF Precursor like			Wa			Finnish	34

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
34	9	1202	380	CTC	CAC	T->A	L380H -PORI	Leu	His	EGF Precursor like	5		Wa		F	Finnish	34
94	9	1222	387	GAG	AAG	G->A	E387K - ALGERIA 1	Glu	Lys	EGF Precursor like	5	Hmz	aa		R	Algerian	16
207	9	1222	387	GAG	AAG	G->A	E387K	Glu	Lys	EGF Precursor like	5				R	French	16
208	9	1222	387	GAG	AAG	G->A	E387K	Glu	Lys	EGF Precursor like	5				R	American	16
143	9	1246	395	CGG	ins5a	Stop at 439	1246ins5	Arg	Fr.	EGF Precursor like	4	Htz	Wa			Japanese	70
175	9	1268	402	ATC	ACC	T->C	I402T	Ile	Thr	EGF Precursor like			ab	174		Swedish	23
7	9	1285	408	GTG	ATG	G->A	V408M - AFRIKANER 2	Val	Met	EGF Precursor like	5	Hmz	aa		F	Afrikaner	40
125	9	1285	408	GTG	ATG	G->A	V408M	Val	Met	EGF Precursor like					R	Dutch	22
19	9	1291	410	GCT	ACT	G->A	A410T - ALGERIA 2	Ala	Thr	EGF Precursor like	5		aa			Algerian	15
31	9	1297	412	GAC	CAC	G->C	D412H - OSAKA 3	Asp	His	EGF Precursor like	2A	Hmz	aa			Japanese	51
95	9	1301	413	ACG	AAG	C->A	T413K - ALGERIA 3	Thr	Lys	EGF Precursor like	5	Hmz	ab	48		Algerian	16
96	9	1322	420	ATC	AAC	T->A	I420N - RUSSIA 1	Ile	Asn	EGF Precursor like	2A	Hmz	ab	116		Russian	16
97	9	1323	420	ATC	ATG	C->G	I420M - ROUEN	Ile	Met	EGF Precursor like	5	Hmz	ab	?		French	16
98	9	1329	422	TGG	TGC	G->C	W422C - NORTH-PLATT	Trp	Cys	EGF Precursor like	2B/5	Hmz	ab	12		American-French	16
141	9	1333	424	GAC	del1c	Stop at 425	1335delC - ODENSE	Asp	Fr.	EGF Precursor like	4					Danish	52
42	9	1335	424	GAC	GAA	C->A	D424E - FINN-8	Asp	Glu	EGF Precursor like			Wa			Finnish	34
129	10	1372	437	AGA	ins4b	Stop at 439	1373ins4 - SYDNEY 1	Arg	Fr.	EGF Precursor like			Wa			European	19
99	10	1432	457	GGG	AGG	G->A	G457R - NEW-YORK 2	Gly	Arg	EGF Precursor like	2B/5	Hmz	ab	85	?	African American	16
43	10	1432	457	GGG	AGG	G->A	G457R - FINN-9	Gly	Arg	EGF Precursor like			Wa		?	Finnish	34
200	10	1438	459	GCT	del11b	Stop at 461	1439del11 - REGGIO EMILIA	Ala	Fr.	EGF Precursor like		Htz	Wa			Italian	25
171	10	1444	461	GAC	AAC	G->A	D461N	Asp	Asn	EGF Precursor like	2B/5	Htz	Wa		?	Irish	66
191	10	1444	461	GAC	AAC	G->A	D461N	Asp	Asn	EGF Precursor like		Hmz	ab	9	?	British	69
172	10	1447	462	TGG	CGG	T->C	W462R	Trp	Arg	EGF Precursor like	2B/5	Htz	Wa			Irish	66
133	10	1448	462	TGG	TAG	G->A	W462X	Trp	Stop	EGF Precursor like		Hmz	aa			Chinese	62
100	10	1454	464	CAC	CGC	A->G	H464R - MILAN	His	Arg	EGF Precursor like	5	Hmz	ab	?		Italian	16
185	10	1459	466	AAC	del3b	del	1460delACA	Asn	Fr.	EGF Precursor like						Norvegian	45
128	10	1467	468	TAC	TAG	C->G	Y468X	Tyr	Stop	EGF Precursor like	1	Htz	Wa		F	French-Canadian	59
101	10	1469	469	TGG	TAG	G->A	W469X - CINCINNATI 2	Trp	Stop	EGF Precursor like	1	Hmz	ab	24	?	American	16
126	10	1469	469	TGG	TAG	G->A	W469X	Trp	Stop	EGF Precursor like	1	Htz	Wa		?	Norvegian	43
196	10	1474	471	GAC	del2c	Stop at 533	1476delCT - YRMEIH	Asp	Fr.	EGF Precursor like		Hmz				Iranian-Armenian	32
130	10	1477	472	TCT	del2b	Stop at 533	1478delCT - SYDNEY 2	Ser	Fr.	EGF Precursor like			aa		?	Armenian	19
160	10	1477	472	TCT	del2b	Stop at 533	1478delCT	Ser	Fr.	EGF Precursor like			aa		F	German	58
20	10	1567	502	GTG	ATG	G->A	V502M - KUWAIT	Val	Met	EGF Precursor like	5		aa			Kuwaiti	15
102	10	1576	505	CCT	TCT	C->T	P505S - CINCINNATI 3	Pro	Ser	EGF Precursor like	5	Hmz	ab	?		American	16
169	11	1603	514	GAC	TAC	G->T	D514Y	Asp	Tyr	EGF Precursor like		Htz				Dutch	47
103	11	1606	515	TGG	del1b	Stop at 546	1607delG - PITTSBURGH	Trp	Fr.	EGF Precursor like	1	Hmz	ab	?		American	16
22	11	1637	525	GGC	GAC	G->A	G525E - SAINT OMER	Gly	Asp	EGF Precursor like	2A		aa			French	15
23	11	1646	528	GGT	GAT	G->A	G528D - GENOA	Gly	Asp	EGF Precursor like	2A		aa			Italian	15
149	11	1646	528	GGT	GTT	G->T	G528V	Gly	Val	EGF Precursor like		Htz	Wa			French	49
144	11	1654	531	ATC	del1c	Stop at 546	1656delC	Ile	Fr.	EGF Precursor like	4	Htz				Japanese	70
135	11	1664	534	CTG	CCG	T->C	L534P	Leu	Pro	EGF Precursor like	2A	Htz	Wa			Chinese	62
122	11	1681	540	CAG	TAG	C->T	Q540X	Gln	Stop	EGF Precursor like	1	Hmz	aa			West-Indian	24

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
184	11	1686	541	TGG	TGA	G->A	W541X - SKJETTEN	Trp	Stop	EGF Precursor like					F	Norvegian	46
186	11	1690	543	AAT	CAT	A->C	N543H	Asn	His	EGF Precursor like			Wa			French	66
8	11	1694	544	GGC	GTC	G->T	G544V - NAPLES 2	Gly	Val	EGF Precursor like	2A	Hmz	aa			Italian	18
104	12	1731	556	TGG	TGA	G->A	W556X - MOSCOW	Trp	Stop	EGF Precursor like	1	Hmz	aa			Russian	16
105	12	1735	558	GAC	AAC	G->A	D558N - CINCINNATI 4	Asp	Asn	EGF Precursor like	2B	Hmz	ab	?		American	16
106	12	1735	558	GAC	ins3c	Stop at 578	1737insGTC - PARIS 8	Asp	Fr.	EGF Precursor like	2A	Hmz	ab	del ex 5		French	16
173	12	1744	561	CTT	del2b	Stop at 577	1745delTT	Leu	Fr.	EGF Precursor like			Wa			Swedish	23
132	12	1747	562	CAC	TAC	C->T	H562Y	His	Tyr	EGF Precursor like	2B	Htz	Wa			Chinese	62
107	12	1775	571	GGG	GAG	G->A	G571E - SICILY	Gly	Glu	EGF Precursor like	5	Hmz	ab	?		Italian-German	16
161	12	1783	574	CGG	del7a	Stop at 661	1783del7	Arg	Fr.	EGF Precursor like			Wa		F	German	58
108	12	1796	578	TTG	TCG	T->C	L578S - LONDON 5	Leu	Ser	EGF Precursor like	2B	Hmz	ab	?		British	16
136	13	1879	606	GCC	ACC	G->A	A606T	Ala	Thr	EGF Precursor like	2B	Htz	Wa			Chinese	62
199	13	1963	634	TTC	CTC	T->C	F634L	Phe	Leu	EGF Precursor like						Spanish	20
10	14	2000	646	TGT	TAT	G->A	C646Y - FRENCH CANADIAN-2	Cys	Tyr	EGF precursor C		Hmz	aa		F	French-Canadian	3
109	14	2011	650	ACC	del1b	Stop at 663	2012delC - NANJING 2	Thr	Fr.	EGF precursor C	1	Hmz	ab	46		Chinese	16
137	14	2014	651	CTG	del1b	Stop at 663	2015delT	Leu	Fr.	EGF precursor C	3	Hmz	ab	46		Chinese	62
110	14	2029	656	TGC	CGC	T->C	C656R - NEW-YORK 3	Cys	Arg	EGF precursor C	2B	Hmz	ab	76		American	16
111	14	2032	657	CAG	TAG	C->T	Q657X - EL SALVADOR 2	Gln	Stop	EGF precursor C	1	Hmz	ab	64		El Salvadorian	16
162	14	2042	660	TGC	TAC	G->A	C660Y	Cys	Tyr	EGF precursor C			Wa			German	58
11	14	2043	660	TGC	TGA	C->A	C660X - LEBANESE	Cys	Stop	EGF precursor C	2A		aa		F	Lebanese	4
112	14	2045	661	CTC	CCC	T->C	L661P - ISSOIRE	Leu	Pro	EGF precursor C	2B	Hmz	ab	?		French	16
12	14	2054	664	CCG	CTG	C->T	P664L - GUJERAT	Pro	Leu	EGF precursor C	2B+3	Hmz	aa		R	Asian-Indian	61
209	14	2054	664	CCG	CTG	C->T	P664L	Pro	Leu	EGF precursor C	2B+3				R	Italian	16
210	14	2054	664	CCG	CTG	C->T	P664L	Pro	Leu	EGF precursor C	2B+3				R	Norvegian	16
118	14	2054	664	CCG	CTG	C->T	P664L - ZAMBIA	Pro	Leu	EGF precursor C	2B/3	Htz	Wa		F	British	33
155	14	2054	664	CCG	CTG	C->T	P664L	Pro	Leu	EGF precursor C		Hmz			F	Japanese	40
113	14	2092	677	TGC	del1a	Stop at 707	2092delT - NEW-YORK 4	Cys	Fr.	EGF precursor C	1	Htz	Wa			American	16
159	14	2096	678	CCG	CTG	C->T	P678L	Pro	Leu	EGF precursor C			Wa		F	German	58
114	15	2177	705	ACC	ATC	C->T	T705I - PARIS 9	Thr	Ile	O-linked sugars	2B	Htz	Wa			French	49
115	15	2290	743	ATA	del1a	Stop at 763	2290delA - TYRONE	Ile	Fr.	O-linked sugars	1	Htz	Wa			Irish	68
116	16	2374	771	ATT	TTT	A->T	I771F - RUSSIA 2	Ile	Phe	Transmembrane	2A	Hmz	ab	96		Russian	16
183	16-17	2389	776	GTG	ATG	G->A	V776M	Val	Met	Transmembrane		Htz				Spanish	54
153	17	2431	790	AAG	TAG	A->T	K790X - TOKYO	Lys	Stop	Cytoplasmic		Hmz	ab	154	F	Japanese	40
14	17	2439	792	TGG	TGA	G->A	W792X	Trp	Stop	Cytoplasmic	4A		aa		R	French	48
13	17	2439	792	TGG	TGA	G->A	W792X - BAHRAIN	Trp	Stop	Cytoplasmic	4A		aa		R	Saudi Arabia	38
15	17	2452	797	ATC	ins4c	Stop at 815	2454ins4 - PARIS 3	Ile	Fr.	Cytoplasmic	4A		aa		?	French	17
35	17	2452	797	ATC	ins4c	Stop at 815	2454ins4	Ile	Fr.	Cytoplasmic	4A	Hmz	aa		?	American	38
134	17	2476	805	CCC	del1b	del	2477delC	Pro	Fr.	Cytoplasmic	3	Htz	Wa			Chinese	62
117	17	2479	806	GTC	ATC	G->A	V806I - NEW-YORK 5	Val	Ile	Cytoplasmic	4A	Hmz	ab	18		American	16
16	17	2483	807	TAT	TGT	A->G	Y807C - BARI	Tyr	Cys	Cytoplasmic	4A	Htz	Wa		R	Italian	21
211	17	2483	807	TAT	TGT	A->G	Y807C	Tyr	Cys	Cytoplasmic	4A				R	Syrian	16
33	17	2531	823	GGC	GAC	G->A	G823D - TURKU (FINN-10)	Gly	Asp	Cytoplasmic			Wa		F	Finnish	34

Table 1. Each line represents a single LDLR mutation. The columns contain the following information and abbreviations

A: File number.
B: Exon number in which the mutation occurred. Exons are numbered according to Südhof *et al*. (10) with respect to the translational initiation site given by Yamamoto *et al*. (80).
C: Nucleotide position in which the mutation occurred.
D: Codon number in which the mutation occurred. Codons are numbered according to Yamamoto *et al*. (80). Therefore, the 21 amino acids of the signal peptide (exon 1) are numbered in negative (from –21 to –1). Codon number 1 is the last codon of exon 1 and encodes the first amino acid (Ala) of the mature LDLr protein. If the mutation spans more than one codon, e.g. there is a deletion of several bases, only the first (5′) deleted codon is entered.
E: Normal base sequence of the codon in which the mutation occurred.
F: Mutated base sequence of the codon in which the mutation occurred. If the mutation is a base pair deletion or insertion, this is indicated by « del »or « ins » followed by the number of bases deleted or inserted and the position of this deletion or insertion in the codon (a, b or c). The nucleotide position is the first that is deleted or the one preceding the insertion. For example, « del12c » is a deletion of 12 bases including the third base of the codon, « ins8b » is an insertion of eight bases occurring between the second and the third base of the codon.
G: Concerns base substitutions. It gives the base change, by convention, read from the coding strand. If the mutation predicts a premature protein termination, the novel stop codon position is given, e.g. « stop at 204 ».
H: Mutation name according to Beaudet *et al*. (81). Missense mutations are designated by the codon number flanked by the single letter code of the normal amino acid prior and of the mutant amino acid after (e.g. Val to Met at codon 408 is designated « V408M »). Nonsense mutations are designated similarly except that X is used to indicate any termination codon (e.g. Tyr to stop at codon 167 is designated « Y167X »). Frameshift, insertion and deletion mutations are designated by the nucleotide number followed by 'ins' for insertion or 'del' for deletion. The nucleotide position is the first that is deleted or the one preceding it in the case of insertions. Exact nucleotides are indicated for two or less bases (e.g. 7delG). For three or more bases, the insertion or deletion is specified by the size of the change (e.g. 661del21 indicates a 21 pb deletion starting from nucleotide 661). For many of the mutations that have been reported this nomenclature has not been used. Therefore, the original name also appears in this column. These names were given according to the population or the city in which the mutation was reported first, e.g. AFRIKANER 4.
I: Wild-type amino acid.
J: Mutant amino acid. Deletion and insertion mutations which result in a frameshift are designated by « Fr. ». Nonsense mutations are designated by « Stop ».
K: Protein domain in which the mutation occurs. In the ligand-binding domain, each of the seven repeats are numbered separately and according to their position with respect to the amino-terminal end of the protein.
L: Functional class as defined by Hobbs *et al*. (16).
M: Clinical status according to Goldstein *et al*. (2): Hmz indicates homozygotes and Htz indicates heterozygotes.
N: Genotype: aa indicates homozygotes, ab indicates compound heterozygotes, and Wa indicates heterozygotes. Empty cases appear when no information is available.
O: Number of the file in which the second mutation identified in a compound heterozygote is described. When the second mutation is one of those omitted in the database, this mutation is briefly described with respect to the coding sequence. Finally, « ? » indicates that the second mutation has not been identified.
P: Recurrence of the mutation. « F » designates a founder effect, « DN » designates a *de novo* mutation found in a proband, but not carried by the proband's parents, « R » designates recurrent mutations, and « ? » mutations that have been identified in at least two unrelated probands of different ethnic backgrounds but for which LDLR gene haplotypes are not described. Empty cases designate mutations identified in a single proband.
Q: Ethnic background of the proband.
R: Reference number indicating the publication in which the mutation is described. Full citations (authors, year, title, journal, volume, pages) are provided with the database. If the same mutation has been reported for the same patient in different papers, only one entry is made. If the same mutation has been reported for unrelated patients (recurrent mutations), a separate entry is made for each patient.

Note: The present version of the database cannot accommodate two mutational events in a given allele, therefore the compound insertion–deletions reported by Yamakawa-Kobayashi *et al*. (82) (i.e. 1115del9;1115ins6) and by Geisel *et al*. (26) (i.e. 654ins6;657del5) have been omitted.

but markedly reduced rate. *Class 3* mutations produce proteins that are transported to the cell surface, but fail to bind LDL normally. *Class 4* mutations affect the cytoplasmic domain alone (4A) or also the membrane-spanning region (4B). They produce proteins that cannot internalize bound LDL into the cell. Finally, *Class 5* mutations block the acid-dependent dissociation of receptor and ligand in the endosome, an essential event for receptor recycling (16).

Through an extensive survey of the literature we found that 302 mutations have been reported in the LDLR gene. Among these, only 72 (~25%) are major rearrangements. Therefore the majority of FH-causing mutations are either small deletions/insertions/duplications or point mutations. With the exception of « founder » gene mutations, many mutations are extremely rare and have been identified in single families only. In effect, true recurrence has only been conclusively demonstrated in a few cases. While much effort has been put into the identification of molecular defects in the LDLR gene, few teams (except Hobbs and coworkers) (16) have explored their functional implication and hardly no effort has been made to investigate genotype/phenotype relationships. In this perspective, and to facilitate the mutational analysis of the LDLR gene, we have compiled a database and created a software package for its analysis.

DATABASE AND SOFTWARE

In an effort to standardize the information regarding LDLr mutations, we have created a computerized database that currently contains information about the published mutations of the LDLr gene. The current version of the database contains 210 entries (3–6,8,15–71). Major rearrangements, as well as the six mutations in the promoter sequence (16,72–74), the 14 splice mutations (16,44,46,47,75–78) and polymorphisms were omitted as they cannot be accommodated in the present version of the software. For each mutation, information is provided at several levels: at the gene level (exon and codon number, wild type and mutant codon, mutational event, mutation name), at the mRNA level (size, processing), at the protein level (wild type and mutant amino acid, affected domain, activity, mutation class), and at the personal level (ethnic background, age, sex, body mass index and familial history of coronary heart disease). Table 1 gives part of the database in Excel spreadsheet format.

The software package contains routines for the analysis of the LDLR database that were developed with the 4th dimension^{R} (4D) package from ACI. The use of the 4D SGDB gives access to optimized multicriteria research and sorting tools to select records from any field. Moreover, six routines were specifically developed: (i) 'Position' studies the distribution of mutations at the nucleotide level to identify preferential mutation sites; (ii) 'Statistical evaluation of mutational events' is comparable with (i) but also indicates the type of mutational event. The result can either be displayed as a table or in a graphic representation; (iii) 'Frequency of mutation' allows one to study the relative distribution of mutations at all sites and to sort them according to their frequency. A graphic representation is also available and displays a cumulative chart of mutation distribution; (iv) 'Stat exons' studies the distribution of mutations in the different exons. It enables detection of a statistically significant difference between observed and expected mutations. (v) 'Protein' studies the distribution of mutational events in various protein domains (ligand-binding and EGF-precursor-like motifs), and aligns the amino acids of the consensus sequence for each domain type. (vi) 'Insertions and deletions analysis' searches for repeated sequences surrounding the mutation and possibly involved in the mutational mechanism.

The present version of the database contains no clinical data as these are incompletely given in almost all mutation reports that have been published. However, as the purpose of this database is to promote not only the molecular analysis of mutational events within the LDLR gene, but also genotype/phenotype relationships, the database will be expanded in the future to include clinical data (symptomatic coronary artery disease, xanthomas) and biological data (total plasma cholesterol and LDL–cholesterol before or without treatment), as well as the ages at which they were assessed and, when appropriate, the age of death. Furthermore, data should also be available concerning therapy. Finally, the software will be expanded as the database grows and according to the requirements of its users. New functions could be implemented comparable with those already available in the APC gene mutations database (79).

AVAILABILITY

The current database and subsequent updated versions are (will be) available on request from M.V. and C. Bo. on floppy disc using Apple format and Microsoft Excel^{R}. Notification of omissions and errors in the current version as well as specific phenotypic data would be gratefully received by the corresponding authors. The software package is available on a collaborative basis.

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