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IV.　研究成果の刊行物・別冊

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Original Articles

Mutations in Japanese Subjects with Primary Hyperlipidemia — Results from the Research Committee of the Ministry of Health and Welfare of Japan since 1996 —

Takao Maruyama[1], Shizuya Yamashita[1], Yuji Matsuzawa[2], Hideaki Bujo[3], Kazuo Takahashi[4], Yasushi Saito[4], Shun Ishibashi[5], Ken Ohashi[6], Futoshi Shionoiri[7], Takanari Gotoda[8], Nobuhiro Yamada[9], and Toru Kita[10], on behalf of the Research Committee on Primary Hyperlipidemia of the Ministry of Health and Welfare of Japan

[1] *Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan.*
[2] *Sumitomo Hospital, Osaka, Japan.*
[3] *Department of Genome Research and Clinical Application,*
[4] *Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.*
[5] *Department of Metabolic Diseases, Jichi Medical School of Medicine, Tochigi, Japan.*
[6] *Department of Metabolic Diseases, Faculty of Medicine, University of Tokyo, Tokyo, Japan.*
[7] *Yokosuka Hokubu Kyosai Hospital, Kanagawa, Japan.*
[8] *Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan.*
[9] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.*
[10] *Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.*

Primary hyperlipidemia is caused by various molecular defects in lipid metabolism. The Research Committee on Primary Hyperlipidemia organized by the Ministry of Health and Welfare of Japan (present: the Ministry of Health, Labour and Welfare) has investigated reported mutations in Japanese patients with primary hyperlipidemia and related disorders (including hypolipidemia), and has created a database based on the questionnaire sent to the members of council board of the Japan Atherosclerosis Society. Mutations in the following genes were investigated: low density lipoprotein receptor, lecithin: cholesteryl acyltransferase, lipoprotein lipase (LPL), hepatic lipase, apolipoproteins A-I, A-II, A-IV, B, C-II, C-III and E, microsomal triglyceride transfer protein, and cholesterol ester transfer protein (CETP). Until 1998, 922 patients with primary hyperlipidemia and related disorders has been registered with the Research Committee, and 190 mutations in 15 genes had been reported, showing a marked variation in Japanese patients with primary hyperlipidemia and related disorders. So-called "common mutations" have been described in Japanese patients with familial hypercholesterolemia, LPL deficiency and CETP deficiency. The genetic defect of familial combined hyperlipidemia (FCHL) is still unknown although FCHL is speculated to be the most prevalent genetic hyperlipidemia, and further investigations should be performed to elucidate the molecular mechanisms of FCHL. *J Atheroscler Thromb, 2004; 11: 131–145.*

Key word: Apolipoprotein, Hyperlipoproteinemia, Mutational spectrum, Receptor

Address for correspondence: Shizuya Yamashita, Department of Internal Medicine and Molecular Science, B5, Graduate School of Medicine, Osaka University, 2–2, Yamadaoka, Suita, Osaka 565–0871, Japan.
E-mail: shizu@imed2.med.osaka-u.ac.jp
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Introduction

Hyperlipidemia is one of the important bases for atherosclerotic cardiovascular diseases, and it is crucial to clarify the molecular mechanism of its pathophysiology and establish treatments of hyperlipidemia. Primary hy-

perlipidemia, caused by various molecular deficits of enzymes, receptors, transfer proteins or apolipoproteins (apo) involved in lipid metabolism, is generally hard to treat and causes various complications, such as coronary artery disease in patients with familial hypercholesterolemia (FH) due to mutations in the low-density lipoprotein receptor (LDLR) gene (1). To clarify the molecular mechanism of primary hyperlipidemia, the Ministry of Health and Welfare of Japan (present: the Ministry of Health, Labour and Welfare) organized the Research Committee in 1983. In the present study, in order to evaluate the current status of mutational analysis for primary hyperlipidemia in Japan, we investigated the reported mutations for primary hyperlipidemia and related disorders and created a database for mutations in Japanese patients based on the work of the Research Committee on Primary Hyperlipidemia of the Ministry of Health and Welfare of Japan (Chairman: Professor Toru Kita, Kyoto University).

Methods

Registered mutations

Reported mutations in the following genes were registered with the Research Committee: LDLR, lecithin: cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL), hepatic lipase (HL), apo A-I, apo A-II, apo A-IV, apo B, apo C-II, apo C-III, apo E, microsomal triglyceride transfer protein (MTP) and cholesteryl ester transfer protein (CETP). Some of these molecular defects, which cause hypolipidemia, were also registered with the Research Committee. Furthermore, mutations in genes recently identified as causes of primary hyperlipidemia and related disorders were also investigated in this report.

Registration of the mutations

A questionnaire was sent to the members of the council board of the Japan Atherosclerosis Society and the related institutes and/or hospitals of the councilors, and the database was built up based on the returned questionnaires until 1998. In this questionnaire, the following items were investigated: clinical diagnosis, age, sex, height, weight, blood pressure, corneal ring and/or opacification, xanthoma, history of smoking, hypertension, diabetes mellitus, coronary artery disease, cerebral vessel disease, carotid artery stenosis, peripheral artery disease and pancreatitis, serum levels of total cholesterol, triglycerides, high density lipoprotein (HDL)-cholesterol, apo A-I, A-II, A-IV, B, C-II, C-III and E, activities of CETP, LPL, HL, LCAT and LDLR, phenotype of apo E, phenotype of hyperlipidemia, and mutation (if identified). Furthermore, mutations reported in the academic meetings including the Annual Meetings of the Japan Atherosclerosis Society, as well as the published mutations in the journals until 2003, were added to the database as thoroughly as possible.

Results

Until 1998, 922 patients with primary hyperlipidemia had been registered with the Research Committee (2). Patients with FH were the largest in number, followed by those with apo E abnormality (deficiency/variant), CETP deficiency, LPL deficiency and apo A-I abnormality (deficiency/variant) (Table 1).

Disorders in cholesterol metabolism

LDLR is the most intensively analyzed gene in patients with primary hyperlipidemia. To date, approximately 80 mutations have been reported in Japanese patients with FH (Table 2), including large rearrangements, small deletions and/or insertions and point mutations throughout the gene, and a marked variation was observed in the mutations in the LDLR gene. Some of these mutations have been reported to be common among Japanese patients with FH (3, 4), such as C317S in exon 7 (5), P664L in exon 14 (6) and K790X in exon 17 (3).

Familial defective apo B-100 (FDB), of which the clinical characteristics are similar to those of FH, have been reported to be common in the Western population (7). FDB is caused by mutations in the binding domain of apo B-100 to LDLR, and to date, 3 mutations have been identified as responsible for FDB, R3,500Q (8), R3,500W (9) and R3,531C (10). However, no patients have been diagnosed with FDB in hundreds of clinically diagnosed Japanese FH patients (11).

Recently, mutations have been identified in patients with autosomal recessive hypercholesterolemia (ARH), characterized by severe hypercholesterolemia, xanthoma and premature atherosclerosis without any impairment of LDLR, in a gene encoding a putative adaptor protein, and a novel insertion mutation was discovered in the ARH gene (insertion of an extra C at positions 599–606 in exon 6, creating a permature stop codon at 657–659) in Japanese siblings with ARH (12).

FCHL is characterized by increased levels of apo B-100 and elevated levels of very low density lipoprotein (VLDL), LDL, or both, in plasma, and is speculated to be the most prevalent disorder of primary hyperlipidemia with an increased risk of atherosclerotic diseases (7), however, the molecular basis of FCHL is still unknown. Fourteen patients have been registered (2) with the Research Committee according to the diagnostic criteria published by the committee in 1987 (13).

On the other hand, hypobetalipoproteinemia and abetalipoproteinemia have been known to cause genetic hypocholesterolemia. The molecular basis of familial hypobetalipoproteinemia is the truncated form of apo B-100, and various mutations causing a premature stop codon have been identified in the Western population

(7). In Japanese patients, 3 mutations, apo B-38.7, B-54.4 and B-54.8 (Table 3) have been reported (14), each of which results in the appearance of a premature stop codon.

Abetalipoproteinemia, which is characterized by the absence of VLDL and LDL in plasma, fat malabsorption and acanthocytosis, is caused by a functional deficit of MTP (7). To date, 4 mutations have been reported as causes of abetalipoproteinemia in Japanese patients (Table 4) (15).

Disorders in triglyceride metabolism

LPL is a lipolytic enzyme and is essential for the hydrolysis of chylomicron and VLDL triglycerides, and a functional defect of LPL causes marked hyperchylomicronemia and hypertriglyceridemia (type I or type V hyperlipidemia) (16). To date, 25 mutations have been identified in Japanese patients with LPL deficiency (Table 5). Among these mutations, S447X (17) in exon 9 and 916delG (LPL-Arita) (18) have been reported to be common in Japanese patients with LPL deficiency.

Apo C-II is a coenzyme of LPL, and its genetic defect causes hyperchylomicronemia and hypertriglyceridemia, similar to LPL deficiency (16). Three mutations have been identified in Japanese patients with apo C-II deficiency (Table 6). In these patients, serum levels of triglycerides were not so high as those in LPL deficiency, and some patients had no history of pancreatitis, suggesting that the clinical features of apo C-II deficiency are mild compared with those of LPL deficiency.

Familial HL deficiency is a rare autosomal recessive disorder characterized by moderate hypertriglyceridemia and premature atherosclerotic cardiovascular diseases (15). One mutation (C53G) in the HL gene has been reported to be responsible for HL deficiency in a Japanese subject (Table 7) (19)

Type III hyperlipidemia (dysbetalipoproteinemia) is characterized by elevated concentrations of both plasma cholesterol and triglycerides, the presence of β-migrating VLDL, and accumulation of atherogenic cholesterol-enriched remnants, such as intermediate density lipoprotein and chylomicron remnants (20). The genetically determined polymorphism of apo E has a significant impact on lipid metabolism: the wild type of apo E is E3, and there are the common variants E2 (Arg158Cys) and E4 (Cys112Arg). The primary molecular defect in most patients with type III hyperlipidemia is homozygous ε2/ε2 (20). Other than the common variants E2 and E4, there have been some mutations causing apo E deficiency/variants (Table 8) in Japanese patients. Some of these mutations are responsible for type III hyperlipidemia with autosomal dominant inheritance. Apo E5 (21) and apo E7 (22) have been reported to be relatively common in Japanese patients. Patients with apo E7 have been re-

Table 1. Resistered numbers of patients with primary hyperlipidemia.

	Clinical Diagnosis				Genetic Diagnosis		
	Total	Homozygote	Heterozygote	Undetermined	Homozygote	Compound Heterozygote	Heterozygote
FH	636	17	617	2	12	3	28
ApoE abnormality	103	32	71	0	32	6	65
CETP deficiency	77	26	45	6	22	30	6
LPL deficiency	23	16	7	0	5	3	0
ApoA-I abnormality	18	3	15	0	3	12	2
FCHL	14	0	0	14	0	0	0
FH-like syndrome	12	0	0	12	0	0	0
LCAT deficiency	6	6	0	0	4	0	0
ApoC-II deficiency	6	4	2	0	3	2	0
LPG	5	0	5	0	0	0	5
Abetalipoproteinemia	3	3	0	0	3	0	0
Hypobetalipoproteinemia	1	1	0	0	1	0	0
HL deficiency	1	0	0	0	0	0	0
Others	17	8	3	6	1	0	0

Apo: apolipoprotein, CETP: cholesteryl ester transfer protein, FCHL: familial combined hyperlipidemia, FH: familial hypercholesterolemia, HL: hepatic lipase, LCAT: lecithin cholesterol acyltransferase, LPG: lipoprotein glomerulopathy, LPL: lipoprotein lipase.

Table 2. Mutations in the low-density lipoprotein receptor gene in Japanese patients with familial hypercholesterolemia.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
intron 1	68-1 G→C		G→C at 68-1	3' splice signal	class 1	Maruyama T	Hum Mutat 11: 480–481, 1998
exon 2	W23X	Nanao	G→A at 132	Trp→Stop at 23	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 2	C25Y†		G→A at 137	Cys→Tyr at 25	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 2	D26N		G→A at 139	Asp→Asn at 26	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exons 2–3	In1-In3 del		deletion of 4 kb	deletion of exons 2,3	class 3	Yamakawa K	Hum Genet 82: 317–321, 1989
exons 2–3	In1-In3 del		deletion of 5 kb	deletion of exons 2,3	NR	Kigawa K	J Biochem (Tokyo) 113: 372–376, 1993
exons 2–3	In1-In3 del	Tonami-2	deletion of 10 kb	deletion of exons 2,3	class 3	Kajinami K	Circulation (Suppl) 80: II278, 1989
exons 2–4	In1-In4 del	Kanazawa-1	deletion of 12 kb	deletion of exons 2-4	NR	Kajinami K	J Intern Med 227: 247–251, 1990
exon 3	C54S		T→A at 223	Cys→Tyr at 54	class 2	Emi M	Jpn Heart J 39: 785–789, 1998
exon 3	230delG†		deletion of G at 230	frame shift	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 3	C61F†		G→T at 244	Cys→Phe at 61	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 3	C74X		C→A at 285	Cys→Stop at 74	class 1	Hirayama T	J Hum Genet 43: 250–254, 1998
exon 3	C74F†		G→T at 288	Cys→Phe at 74	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	327insC†		insertion of C at 327	premature stop at codon 158	NR	Hirota R	Ann Clin Biochem 39 (Pt 5): 526–530, 2002
exon 4	R94H	Fukuoka	G→A at 344	Arg→His at 94	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 4	355del7bp†		deletion of GGGAAGT at 355	premature stop at codon 183	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 4	C100G†		T→G at 361	Cys→Gly at 100	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	S109T†		T→A at 388	Ser→Thr at 109	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	389insC†		insertion of C at 389	frame shift	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	E119K	Phillipines	G→A at 418	Glu→Lys at 119	class 2B	Hobbs HH	Hum Mutat 1: 445–466, 1992
exon 4	C134R†		T→C at 463	Cys→Arg at 134	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	C139R†		T→C at 478	Cys→Arg at 139	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	C163R†		T→C at 550	Cys→Arg at 163	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	V168M†		G→A at 565	Val→Met at 168	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 4	C183S†		G→C at 611	Cys→Ser at 183	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 5	D245N†	Naha	G→A at 796	Asp→Asn at 245	NR	Yu W	Atherosclerosis 165: 335–342, 2002

Table 2. Mutations in the low-density lipoprotein receptor gene in Japanese patients with familial hypercholesterolemia (continued).

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
exon 5	D245G[†]		A→G at 797	Asp→Gly at 245	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 6	D280Y	Tsuruga	G→T at 901	Asp→Tyr at 280	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 7	C317S	Wakayama	T→A at 1012	Cys→Ser at 317	class 2	Funahashi T	J Intern Med 239: 187–190, 1996
exon 7	C317R	Gifu	T→C at 1012	Cys→Arg at 317	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 7	R329X[†]		C→T at 1048	Arg→Stop at 329	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exons 7–14	In6–In14 del	Osaka-2	deletion of 12 kb	deletion of exons 8-14	class 5	Miyake Y	J Biol Chem 364: 16584–16590, 1989
exons 7–14	Ex7–In14 del	Okayama	deletion of 13 kb	deletion of exons 8-14	NR	Kajinami K	J Intern Med 227: 247–251, 1990
exon 8	1061insT[†]		insertion of T at 1061	frame shift	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 8	D335H	Kanagawa	G→C at 1066	Asp→His at 335	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 8	1115del9bp, ins6bp		deletion of 9 bp, insertion of 6 bp from 1115	GlyGlyGlyTyr→ AlaLeuAsn from 351	NR	Yamakawa K	Hum Genet 93: 625–628, 1994
exon 8	C358Y		G→A at 1136	Cys→Tyr at 358	class 5	Hirayama T	J Hum Genet 43: 250–254, 1998
exon 9	F382L		T→A at 1207	Phe→Leu at 382	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 9	1246ins5bp		insertion of 5 bp at 1246	frame shift after Arg395	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 9	R395W[§]	Morioka	C→T at 1246	Arg→Trp at 395	defective	Yagi K	J Jpn Atheroscler Soc 22: 100, 1994
exon 9	E397K[†]		G→A at 1252	Glu→Lys at 397	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 9	V408M	Afrikaner-2	G→A at 1285	Val→Met at 408	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 9	A410T[†]		G→A at 1291	Ala→Thr at 410	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 9	D412H	Osaka-3	G→C at 1297	Asp→His at 412	class 2	Miyake Y	Eur J Biochem 210: 1–7, 1992
exon 10	A480E[§]		C→A at 1502	Ala→Glu at 480	class 2B	Miyake Y	J Jpn Atheroscler Soc 24: 733, 1997
exon 10	V502M[†]		G→A at 1567	Val→Met at 502	class 2A	Yu W	Atherosclerosis 165: 335–342, 2002
intron 10	1587 – 1 G→A[†]		G→A at 1587 – 1	3' splice signal	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 11	W512X[†]		G→A at 1599	Trp→Stop at 512	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 11	1687insC[†]		insertion of C at 1687	premature stop at codon 559	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 11	L547V[†]		C→G at 1702	Leu→Val at 547	NR	Hattori H	Hum Mutat 14: 87, 1999
intron 11	1705 + 1 G→C		G→C at 1705+1	5' splice signal	class 1	Miyake Y	Int Symp on Lipoprotein Metabolism & Atherogenesis, Kyoto

Table 2. Mutations in the low-density lipoprotein receptor gene in Japanese patients with familial hypercholesterolemia (continued).

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
exon 12	1773insG		insertion of G at 1773	frame shift	class 1	Hirayama T	J Hum Genet 43: 250–254, 1998
exon 12	R574Q		G→A at 1784	Arg→Gln at 574	NR	Varret M	Nucl Acid Res 26: 248–252, 1998
exon 12	P587S		C→T at 1822	Pro→Ser at 587	class 2	Hirayama T	J Hum Genet 43: 250–254, 1998
intron 12	1845 + 2T→C	Niigata	T→C at 1845 + 2	5' splice signal	class 1	Maruyama T	Eur J Biochem 232: 700–705, 1995
exon 13	1963delT		deletion of T at 1963	frame shift	class 1	Hirayama T	J Hum Genet 43: 250–254, 1998
exon 13	1867delATC[†]		deletion of ATC at 1867–1869	deletion of Ile at 602	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 13	L621S[†]		T→G at 1925	Leu→Ser at 621	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 14	G655S[†]		G→A at 2026	Gly→Ser at 655	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 14	2035insT[†]		insertion of T at 2035	premature stop at codon 696	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 14	P664L	Kanazawa-2	C→T at 2054	Pro→Leu at 664	class 2B	Soutar AK	Proc Natl Acad Sci USA 86: 4166–4170, 1989
exon 14	2055delG[†]		deletion of G at 2055	frame shift	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 14	E693K[†]		G→A at 2140	Glu→Lys at 693	NR	Hattori H	Hum Mutat 14: 87, 1999
exon 15	In14–In15 del	Tonami-1	deletion of 6 kb	deletion of exon 15	NR	Kajinami K	Arteriosclerosis 8: 187–192, 1988
exon 15	2199delCA	Mishima	deletion of CA at 2199 or 2201	frame shift after Thr 713	NR	Tashiro J	Eur J Clin Invest 28: 712–719, 1998
exon 15	Q718X[§]	Yokote	C→T at 2215	Gln→Stop at 718	NR	Higashikata T	J Jpn Atheroscler Soc 23: 847, 1996
exons 15–16	In14–In16 del		deletion of 5.5 kb	deletion of exons 15, 16	NR	Yamakawa K	Hum Genet 82: 317–321, 1989
intron 15	2312–3 C→A[†]		C→A at 2312–3	3' splice signal	NR	Yu W	Atherosclerosis 165: 335–342, 2002
exon 16	1655delT		deletion of T at 1655	frame shift after Asp 530	NR	—	—
exons 16–17	In15–In17 del		deletion of 4 kb	deletion of exons 16, 17	NR	Yamakawa K	Hum Genet 82: 317–321, 1989
exons 16–18	In15–In18 del	Osaka-1	deletion of 7.8 kb	deletion of exons 16-18	class 4B	Miyake Y	Proc Natl Acad Sci USA 78: 5151–5155, 1981
exon 17	2412insG[§]		insertion of G after 2412	frame shift after Gly 784	NR	Miyake Y	J Jpn Atheroscler Soc 22: 646, 1995
exon 17	K790X		A→T at 2431	Lys→Stop at 790	class 1, 4	Maruyama T	Arterioscler Thromb Vasc Biol 15: 1713–1718, 1995

[†]: Mutation reported after the closing of registration to the Research Committee in 1998.
[§]: Mutation reported in an abstract form in Japanese.

ported to be susceptible to coronary artery disease.

Lipoprotein glomerulopathy (LPG) is a newly recognized renal disease characterized by abnormal lipoprotein deposition in the glomeruli, dysbetalipoproteinemia, and a high level of plasma apo E, and is caused by mutations in the apo E gene (23). Some mutations in the apo E gene have been described in Japanese Patients with LPG (Table 8) (24).

Disorders in HDL metabolism

Hyperalphalipoproteinemia (HALP) is a common disorder in the Japanese population, and approximately 60% of marked HALP with serum HDL-cholesterol levels of 100 mg/dl or over is caused by CETP deficiency (25). CETP is a key protein in the reverse cholesterol transport system, which transfers cholesteryl ester from HDL particles to apo B-containing lipoproteins, and its genetic defect results in marked HALP (26). Nine mutations have been described in Japanese patients with CETP deficiency (Table 9), and two mutations, 1451 + 1G > A in intron 14 (27) and D442G in exon 15 (28), are known to be common in patients with CETP deficiency.

Genetic hypoalphalipoproteinemia results from mutations in the apo A-I/C-III/A-IV gene complex, the LCAT gene the ATP-binding cassette transporter 1 (ABCA1) gene, and other unknown molecules (26). LCAT is a plasma enzyme that esterifies free cholesterol in serum lipoproteins, and LCAT deficiency leads to marked reduction in serum HDL-cholesterol levels (29). To date, 13 mutations have been reported in Japanese patients with LCAT deficiency (Table 10). Patients with the M293I mutation, with partially residual LCAT activity, have been reported to show mild renal dysfunction (30). The R99C and T123I mutations have been identified in patients with fish eye disease (partial deficiency of LCAT activity).

Eighteen mutations have been described in the apo A-I gene (Table 11), including apo A-I variants and deficiency. Patients with apo A-I deficiency show marked hypoalphalipoproteinemia and susceptibility to premature atherosclerosis (26). In contrast, in patients with an apo A-I variant, hypoalphalipoproteinemia is relatively rare.

Apo A-II deficiency is a rare disorder caused by mutations in the apo A-II gene (31), and only 1 mutation (Apo A-II Hiroshima) has been reported in a Japanese patient with apo A-II deficiency (Table 12). In these patients, the apo A-II level was undetectable. Although the serum apo A-I level was slightly decreased, hypoalphalipoproteinemia was not observed in a patient with apo A-II deficiency (31).

So far, no mutations have been identified in the apo A-IV gene or the apo C-III gene in Japanese subjects.

Mutations in the ABCA1 gene have recently been identified as causes of Tangier disease and familial HDL deficiency (FHD) (32). Some mutations in the ABCA1 gene have been described in Japanese patients with Tangier disease and FHD (Table 13).

Table 3. Mutations in the apolipoprotein B gene in Japanese patients with hypobetalipoproteinemia.

Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Author	References
Q1755X	ApoB-38.7	C→T at 5472	Gln→Stop at 1755	Ohashi K	Arterioscler Thromb Vasc Biol 18: 1330–1334, 1998
7612insA[†§]	ApoB-54.4	insertion of A at 7612	Trp→Stop at 2468	Ohashi K	J Jpn Atheroscler Soc 29: 259, 2001
R2486X[†§]	ApoB-54.8	C→T at 7665	Arg→Stop at 2486	Ohashi K	J Jpn Atheroscler Soc 24: 142, 1998

†: Mutation reported after the closing of registration to the Research Committee in 1998.
§: Mutation reported in an abstract form in Japanese.

Table 4. Mutations in the microsomal triglyceride transfer protein gene in Japanese patients with abetalipoproteinemia.

Position	Mutation	Nucleotide Change	Effect on Coding Sequence	Author	References
intron 2	G1237A[§]	G→A at 1237	3' splice signal	Ohashi K	—
intron 9	(-1) G→A[§]	G→A at (-1)	3' splice signal	Yo S	J Jpn Atheroscler Soc 24: 734, 1997
exon 11	1389delA	deletion of A at 1389	frame shift after Glu462	Ohashi K	J Lipid Res 41: 1199–1204, 2000
exon 16	N780Y	A→T at 2338	Asn→Tyr at 780	Ohashi K	J Lipid Res 41: 1199–1204, 2000

§: Mutation reported in an abstract form in Japanese.

Table 5. Mutations in the lipoprotein lipase gene in Japanese subjects.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
exon 1	W(-14)X		G→A at 216	Trp→Stop at (-14)		Nakaura T	J Atheroscler Thromb 3: 17-24, 1996
exon 2	N43S		A→G at 383	Asn→Ser at 43		Kobayashi J	Biochem Biophys Res Commun 205: 506-515, 1994
intron 2	423 + 1 G→A		G→A at 423+1	5' splice signal	class 1	Gotoda T	J Biol Chem 226: 24757-24762, 1991
exon 3	Y61X		T→A at 432	Tyr→Stop at 61	class 1	Gotoda T	Biochim Biophys Acta 1138: 353-356, 1992
exon 3	G105R[†]		G→A at 568	Gly→Arg at 105	class 2	Ikeda Y	Clin Sci (Lond) 99: 569-578, 2000
exon 5	G154V[†]		G→T at 716	Gly→Val at 154	class 1	Ikeda Y	J Lipid Res 42: 1072-1081, 2001
exon 5	G188E		G→A at 818	Gly→Glu at 188	class 1	Emi M	J Biol Chem 265: 5910, 1990
exon 5	I194T[§]		T→C at 836	Ile→Thr at 194		Kobayashi J	Domyakukoka 25: 131, 1997
exon 5	K198R		A→G at 848	Lys→Arg at 198		—	—
exon 5	V200A		T→C at 854	Val→Ala at 200		Takagi A	Athrosclerosis 134: 27-28, 1997
exon 5	D204E		C→G at 867	Asp→Glu at 204	class 2	Gotoda T	J Clin Invest 88: 1856-1864, 1991
exon 5	916delG	Arita	delection of G at 916	frame shift after Glu220		Takagi A	J Clin Invest 89: 581-591, 1992
exon 6	C239X[§]	Obama	C→A at 972	Cys→Stop at 239		Ikeda Y	J Jpn Atheroscler Soc 25: 141, 1998
exon 6	R243C[§]		G→T at 983	Arg→Cys at 243		Ikeda Y	J Jpn Atheroscler Soc 25: 141, 1998
exon 6	R243H		G→A at 983	Arg→His at 243	class 2	Gotoda T	J Clin Invest 88: 1856-1864, 1991
exon 6	A261T[§]		C→A at 1036	Ala→Thr at 261		Takagi A	J Jpn Atheroscler Soc 23: 872, 1996
exon 6	F270L	Mima	T→G at 1065	Phe→Leu at 270	class 2	Takagi A	Biochim Biophys Acta 1502: 433-446, 2000
exon 6	C278R		T→C at 1087	Cys→Arg at 278		Takagi A	Atherosclerosis 134: 27-28, 1997
exon 6	L303F[†]		G→C at 1069	Leu→Phe at 303	class 1	Saika Y	Eur J Clin Invest 33: 216-222, 2003
exon 7	del A[§]		deletion of A at codon 291	frame shift after codon 303		Kobayashi J	J Jpn Atheroscler Soc 25: 131, 1997
exon 7	A334T		G→A at 1255	Ala→Thr at 334		Kobayashi J	Biochem Biophys Res Commun 191: 1046-1054, 1993
exon 8	1400delG		deletion of G at 1400	frame shift after Trp 382	class 2 or 3	Gotoda T	J Clin Invest 88: 1856-1864, 1991
exon 8	W382X[†]		G→A at 1401	Trp→Stop at 382	class 1	Takagi A	Clin Chim Acta 285: 143-154, 1999
intron 8	1496 + 2 T→C[†]		T→C at 1496+2	5' splice signal	class 1	Ikeda Y	J Lipid Res 42: 1072-1081, 2001
exon 9	S447X		C→G at 1595	Ser→Stop at 447		Kobayashi J	Biochem Biophys Res Commun 182: 70-77, 1992

[†]: Mutation reported after the closing of registration to the Research Committee in 1998.
[§]: Mutation reported in an abstract form in Japanese.

Table 6. Mutations in the apoC-II gene in Japanese patients with apoC-II deficiency.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Author	References
intron 2	93+1 G→C	Tokyo	G→C at 93+1	5' splice signal	Okubo M	Atherosclerosis 130: 153–160, 1997
exon 3	108delC	Japan	deletion of C at 108	frame shift	Xiong WJ	Am J Hum Genet 48: 383–389, 1991
exon 3	W26R	Wakayama	T→C at 180	Trp→Arg at 26	Inadera H	Biochem Biophys Res Commun 193: 1174–1183, 1993

Table 7. Mutation in the hepatic lipase gene in a Japanese subject.

Position	Mutation	Nucleotide Change	Effect on Coding Sequence	Author	Reference
exon 2	C53G	T→G at 230	Cys→Gly at 53	Ikeda Y	Atherosclerosis XI: 777–788, 1998

Table 8. Mutations in the apolipoprotein E gene in Japanese subjects.

Exon	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
3	E3K	E-5	G→A at 28	Glu→Lys at 3	E-5	Tajima S	J Biochem (Tokyo) 104: 48–52, 1988
3	R25C	E2 Kyoto	C→T at 94	Arg→Cys at 25	LPG	Moriyama K	Kidney Int 56: 421–427, 1999
3	Q46H[§]		G→C at 159	Gln→His at 46	NR	Hisaki M	Domyakokuka 23: 891, 1996
4	135-142 ins[†]	E-5	insertion of 24 bp from codon 135	duplication of 135-142	E-5	Yamanouchi Y	J Hum Genet 46: 633–639, 2001
4	141-143 del[†]	E-Tokyo	deletion of 9 bp from codon 141	deletion of 141-143	LPG	Konishi K	Nephron 83: 214–218, 1999
4	141-146 del[†]	E-Maebashi	deletion of 18 bp from codon 141	deletion of 141-146	LPG	Ogawa T	Pediatr Nephrol 14: 149–151, 2000
4	R142S[†§]	E-1		Arg→Ser at 142	type III (d)	Sakuma N	Domyakokuka 29:252, 2001
4	K146E	E-1	A→G at 457	Lys→Glu at 146	type III (d)	Moriyama K	Biochim Biophys Acta 1128: 58-64, 1992
4	R145H	E-2 Kochi	G→A at 465	Arg→His at 145	type III (d)	Suehiro	—
4	156-173 del[†]	E-1	deletion of 54 bp from codon 156	deletion of Q156-G173	LPG	Ando M	Kidney Int 56: 1317–1323, 1999
4	Q187E	E2 Toranomon	C→G at codon 187	Gln→Glu at 187	type III (d)	Okubo M	Atherosclerosis 140: 187–190, 1998
4	A216V[§]	E3 Nananuma	C→T at 668	Ala→Val at 216	type III (d)	Matsunaga A	Domyakukoka 23: 846, 1996
4	R224Q	E2 Fukuoka	C→A at 692	Arg→Gln at 224	type III (d)	Moriyama K	Biochim Biophys Acta 1301: 185–190, 1989
4	E244K, E245K	E7 Suita	G→A at 751, 754	Glu→Lys at 244, 245	E-7	Tajima S	J Biochem (Tokyo) 105: 249–253, 1989
4	R145P	E2 Sendai	G→C at 445	Arg→Pro at 145	LPG	Oikawa S	J Am Soc Nephrol 8: 820–823, 1997

(d): dominant, LPG: lipoprotein glomerulopathy.
†: Mutation reported after the closing of registration to the Research Committee in 1998.
§: Mutation reported in an abstract form in Japanese.

Sterol storage disorders (cerebrotendinous xanthomatosis and sitosterolemia)

Sterol storage disorders are characterized by accumulation of plant sterols and massive xanthoma similar to those in homozygous FH, such as cerebrotendinous xanthomatosis (CTX, accumulation of cholestanol) and sitosterolemia (accumulation of sitosterol) (33). These disorders do not belong to primary hyperlipidemia but are recognized as related disorders, and one such patient has been registered with the Research Committee (2). CTX is caused by mutations in sterol 27 hydroxylase (Cyp27) (33), and sitosterolemia by mutations in the ATP-binding cassette transporter G5 or G8 (34). Some mutations have been identified in Japanese patients with sterol storage disorders (Table 14).

Discussion

In the present report, 190 mutations in 15 genes were described. The numbers of the described mutations were

Table 9. Mutations in the cholesteryl ester transfer protein gene in Japanese subjects.

Position	Mutation	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
promoter	(– 69)G→A[1]	G→A at (– 69)	promoter	deficiency	Nagano M	Arterioscler Thromb Vasc Biol 21: 985–990, 2001
exon 5	L151P[1]	T→C at codon 151	Leu→Pro at 151	deficiency	Nagano M	J Lipid Res 43: 1011–1018, 2002
exon 6	G181X	G→T at 722	Gly→Stop at 181	deficiency	Arai T	J Lipid Res 37: 2145–2154, 1996
exon 9	R282C[1]	C→T at codon 282	Arg→Cys at 282	deficiency	Nagano M	J Lipid Res 43: 1011–1018, 2002
exon 10	Q309X	C→T at 1106	Gln→Stop at 309	deficiency	Gotoda T	Biochem Biophys Res Commun 194: 519–524, 1993
intron 10	1111 + 2 T→G	T→G at 1111+2	5' splice signal	deficiency	Sakai N	J Lipid Res 37: 2065–2073, 1996
intron 14	1451 + 1 G→A	G→A at 1451+1	5' splice signal	deficiency	Brown ML	Nature 342: 448–451, 1989
intron 14	1451 + 3 ins T[b]	insertion of T at 1451+3	5' splice signal	deficiency	Inazu A	J Jpn Atheroscler Soc 21: 73, 1993
exon 15	D442G	A→G at 1506	Asp→Gly at 442	deficiency	Takahashi K	J Clin Invest 92: 2060–2064, 1993

[1]: Mutation reported after the closing of registration to the Research Committee in 1998.
[b]: Mutation reported in an abstract form in Japanese.

Table 10. Mutations in the lecithin:cholesterol acyltransferase gene in Japanese subjects.

Exon	Mutation	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
1	N5I	A→T at 15	Asn→Ile at 5	deficiency	Okubo M	Int J Clin Lab Res 26: 250–254, 1996
1	124insC	insertion of C at 124	frame shift after Pro 10	deficiency	Bujo H	Biochem Biophys Res Commun 181: 933–940, 1991
2	G30S[b]	G→T at 188	Gly→Ser at 30	deficiency	Yo S	J Jpn Atheroscler Soc 23: 179, 1995
3	R99C[1]	C→T at codon 99	Arg→Cys at 99	FED	Shinoda Y	J Jpn Atheroscler Soc 24: 690, 1997
4	T123I[b]	C→T at 418	Thr→Ile at 123	FED	Nishioka K	J Jpn Atheroscler Soc 23: 179, 1995
4	R140C[b]	C→T at 518	Arg→Cys at 140	deficiency	Aragane K	J Jpn Atheroscler Soc 23: 847, 1996
4	G141ins	insertion of GGC from 521	insertion of Gly 141	deficiency	Gotoda T	Lancet 388: 778–781, 1991
6	N228K	C→A at 784	Asn→Lys at 228	deficiency	Gotoda T	Lancet 388: 778–781, 1991
6	P250R[b]	C→G at 852	Pro→Arg at 250	deficiency	Aragane K	J Jpn Atheroscler Soc 23: 180, 1995
6	873delG	deletion of G at 873	frame shift after Val 264	deficiency	Moriyama K	J Lipid Res 36: 2329–2343, 1995
6	M293I	G→A at 979	Met→Ile at 293	deficiency	Maeda E	Biochem Biophys Res Commun 178: 460–466, 1991
6	T321M	C→T at 1065	Thr→Met at 321	deficiency	—	—
6	G334S	G→A at 1130	Gly→Ser at 344	deficiency	Moriyama K	J Lipid Res 36: 2329–2343, 1995

[1]: Mutation reported after the closing of registration to the Research Committee in 1998.
[b]: Mutation reported in an abstract form in Japanese.
FED : fish eye disease.

larger than those in the annual reports of the Research Committee published in 1996–1998 (2, 35, 36), because mutations reported in academic meetings and/or those published in journals until 2003 were added to the database of the Research Committee. Although some genetic polymorphisms might be included in these mutations, most mutations are thought to be responsible for the disorders.

Table 11. Mutations in the apolipoprotein A-I gene in Japanese subjects.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
promoter	−27A→C		A→C at (-27)	TATA box	deficiency	Matsunaga A	Arterioscler Thromb Vasc Biol 19: 348–355, 1999"
exon 3	78delA[§]		deletion of A at 693 (codon -5)	frame shift after Arg (−5)	deficiency	Itoh T	Domyakukoka 24: 287, 1996
exon 3	105insC	Tsukuba	insertion of C at 105	frame shift after Glu5	deficiency	Nakata K	Biochem Biophys Res Commun 196: 950–955, 1991
exon 3	W8X		G→A at 729	Trp→Stop at 8	deficiency	Takata K	Arterioscler Thromb Vasc Biol 15: 1866–1874,1995
exon 3	D13Y	Yame	G→T at 743	Asp→Tyr at 13		Takada Y	J Lipid Res 32: 275–280, 1991
exon 3	A37T		G→A at 815	Ala→Thr at 37		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	D51V	Kaho	A→T at 1447	Asp→Val at 51		Moriyama K	J Atheroscler Thromb 3: 12–16, 1996
exon 4	335ins23bp	Sasebo	insertion of 23 bp from 1779	frame shift after Gly 81	deficiency	Moriyama K	Arterioscler Thromb Vasc Biol 16: 1416–1423, 1996
exon 4	Q84X		C→T at 1545	Gln→Stop at 84	deficiency	Matsunaga T	Proc Natl Acad Sci USA 88: 2793–2797, 1991
exon 4	A95D	Hita	C→A at 1579	Ala→Asp at 95		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	Y100H	Karatsu	T→C at 1593	Tyr→His at 100		Moriyama K	Clin Genet 49: 79–84, 1996
exon 4	K106 del	Nanakuma	deletion of AAG at 1601–1606	deletion of Lys 106 or 107		Moriyama K	Atheroscler Thromb 3: 12–16, 1996
exon 4	W108R	Tsushima	T→C at 1617	Trp→Arg at 108		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	E110K	Fukuoka	G→A at 1623	Glu→Lys at 110		Takada Y	Biochim Biophys Acta 1043: 169–176, 1990
exon 4	V156E	Oita	T→A at 1762	Val→Glu at 156	deficiency	Huang W	Arterioscler Thromb Vasc Biol 18: 389–396, 1998
exon 4	H162Q	Kurume	T→G at 1781	His→Gln at 162		Moriyama K	Clin Genet 49: 79–84, 1996
exon 4	2100delC[†]		deletion of C at codon 184	frame shift after Glu 183		Yokota H	Atherosclerosis 162: 399–407, 2002
exon 4	E235 del	Nichinan	deletion of GAG at 1995–2000	deletion of Gln 235	low HDL	Han H	Arterioscler Thromb Vasc Biol 19: 1447–1455, 1999

†: Mutation reported after the closing of registration to the Research Committee in 1998.
§: Mutation reported in an abstract form in Japanese.

Table 12. Mutation in the apolipoprotein A-II gene in a Japanese subject.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	Reference
intron 3	243 + 1 G→A	Hiroshima	G→A at 243 + 1	5' splice signal	deficiency	Deeb SS	Am J Hum Genet 46: 822–827, 1990

Table 13. Mutations in ATP-binding cassette transporter-1 gene in Japanese patients.

Disorder	Mutation	Nucleotide Change	Effect on Coding	Author Sequence	References
FHD	A255T	G→A at 1158	Ala→Thr at 255	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	N935H	A→C at 3198	Asn→His at 935	Guo Z	J Hum Genet 47: 325–329, 2002
TD	N935S	A→G at 3199	Asn→Ser at 935	Guo Z	J Hum Genet 47: 325–329, 2002
FHD	3787del4bp	deletion of CGCC from 3787	premature stop at 1224	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
TD	D1229N	G→A at 3805	Asp→Asn at 1229	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
FHD	N1611D	A→G at 5226	Asn→Asp at 1611	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	R1680W		Arg→Trp at 1680	Ishii J	J Hum Genet 47: 366–369, 2002
FHD	R1851X	C→T at 5946	Arg→Stop at 1851	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	R2021W	C→T at 6181	Arg→Trp at 2021	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
TD	In12-In14 del	deletion of 1221 bp	deletion of exons 13, 14	Guo Z	J Hum Genet 47: 325–329, 2002
TD	In16-In31 del	deletion of 19.9 kb	deletion of exons 17–31	Guo Z	J Hum Genet 47: 325–329, 2002

All mutations have been reported after the closing of registration to the Research Committee.
FHD: familial high-density lipoprotein deficiency, TD: Tangier disease.

Table 14. Mutations in Japanese patients with sterol strage disorders.

Disorder	Gene	Mutation	Nucleotide	Effect on Coding Change	Author Sequence	References
CTX	Cyp27	R104W†	C→T at codon 104	Arg→Trp at 104	Nakashima N	J Lipid Res 35: 663–668, 1994
CTX	Cyp27	E162X	G→T at codon 162	Glu→Stop at 162	Wakamatsu N	J Neurol Neurosurg Psychiatry 67: 195–198, 1999"
CTX	Cyp27	R362H	G→A at codon 362	Arg→His at 362	Chen W	Biochim Biophys Acta 1317: 119-126, 1996
CTX	Cyp27	P368R	G→C at codon 368	Pro→Arg at 368	Okuyama E	J Lipid Res 37: 631–639, 1996
CTX	Cyp27	R372Q	G→A at codon 372	Arg→Gln at 372	Chen W	J Lipid Res 38: 870–879, 1997
CTX	Cyp27	intron 7+1G→A	G→A at intron 7+1	5' splice signal	Shiga K	J Neurol Neurosurg Psychiatry 67: 675–677, 1999
CTX	Cyp27	R441W	C→T at codon 441	Arg→Trp at codon 441	Kim KS	J Lipid Res 35: 1031–1039, 1994
CTX	Cyp27	R441Q	G→A at codon 441	Arg→Gln at codon 441	Kim KS	J Lipid Res 35: 1031–1039, 1994
Sitosterolemia	ABCG5	R419H	G→A at 1396	Arg→His at 419	Lee MH	Nat Genet 27: 79–83, 2001
Sitosterolemia	ABCG5	exon 3 del	deletion of exon 3		Lu K	Am J Hum Genet 69: 278–290, 2001
Sitosterolemia	ABCG5	R408X	C→T at 1362	Arg→Stop at 408	Lu K	Am J Hum Genet 69: 278–290, 2001
Sitosterolemia	ABCG5	R389H	G→A at 1306	Arg→His at 389	Lu K	Am J Hum Genet 69:278–290, 2001
Sitosterolemia	ABCG5	R550S	A→C at 1791	Arg→Ser at 550	Lu K	Am J Hum Genet 69:278–290, 2001

ABCG5: ATP-binding cassette transporter subfamily G member 5, CTX: cerebrotendinous xanthomatosis, CYP27: sterol 27-hydroxylase.
†: Mutation resistered to the Research Committee