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Clinical Characteristics of Homozygous Familial Hypercholesterolemia in Japan

A Survey Using a National Database

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ABSTRACT

BACKGROUND The studies evaluating patients' characteristics and lipid-lowering therapy for patients with homozygous familial hypercholesterolemia (HoFH) are scarce.

OBJECTIVES This study aims to evaluate the characteristics of and treatments for patients with HoFH.

METHODS This study included 201 patients who were diagnosed with definite or probable HoFH from the National Database of the Japanese Ministry of Health, Labour, and Welfare.

RESULTS The patients' median age at diagnosis was 27 years and exhibited a bimodal distribution. Approximately 70% of patients had coronary artery disease. Regarding genetic backgrounds, mutations in the low-density lipoprotein (LDL) receptor (*LDLR*) were identified in most of the patients, followed by proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and double heterozygotes of *LDLR*. High-intensity statins were introduced to 74% of the patients, lipoprotein apheresis was performed in 21%, and PCSK9 inhibitors were administered to 50%. The mean of LDL cholesterol before and after treatment were 10.1 mmol/L and 3.9 mmol/L, respectively. Patients with coronary artery disease had significantly decreased LDL cholesterol. A quarter of the patients (n = 49, 24%) exhibited valvular diseases, particularly aortic valvular disease (n = 34, 61%).

CONCLUSIONS The national epidemiological study of patients with HoFH showed patient's clinical and genetic characteristics and LDL-lowering therapy in Japan. There was considerable diversity in the severity of phenotypes, including LDL cholesterol levels, among patients with HoFH. In Japan, the management of LDL cholesterol in HoFH is still inadequate despite the availability of intensive lipid-lowering therapies. (JACC: Asia 2023;■:■-■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

APOB = apolipoprotein B

CABG = coronary artery bypass grafting

CAD = coronary artery disease

FH = familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDLR = low-density lipoprotein receptor

LDLRAP1 = low-density lipoprotein receptor adaptor protein 1

PCI = percutaneous coronary intervention

PCSK9 = proprotein convertase subtilisin/kexin type 9

Mutations in genes connected to the low-density lipoprotein (LDL) receptor (LDLR) system cause an inherited condition known as familial hypercholesterolemia (FH), including apolipoprotein B (*APOB*), low-density lipoprotein receptor adapter protein 1 (*LDLRAP1*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and LDL receptor (*LDLR*).[1] Particularly, patients with homozygous familial hypercholesterolemia (HoFH) possessing homozygotes of identical mutations or compound or double heterozygotes of mutations in the related genes have an extremely high risk of premature atherosclerotic cardiovascular disease and a poor prognosis without early intervention with lipid-lowering therapy.[1-5] HoFH is a very rare disease, and clinical data on patients' characteristics and on lipid-lowering therapy in a real-world clinical setting are insufficient.[6-9] In Japan, HoFH is registered as one of the designated intractable diseases. For these diseases, the government pays for the patients' medical costs, and such cases are registered in the National Database (operated by the Ministry of Health, Labour, and Welfare of Japan). Considering this situation, this study aimed to analyze the characteristics of and lipid-lowering therapies for patients with HoFH using a national epidemiological survey by the Japanese Ministry of Health, Labour, and Welfare.

METHODS

STUDY POPULATION. Based on the clinical personal records of HoFH patients in the National Database of Rare and Intractable Disease of the Ministry of Health, Labour, and Welfare of Japan, this cross-sectional study was conducted using the national epidemiological survey about HoFH in 2019. From 230 patients, 201 were identified as diagnosed with definite or probable HoFH.

The study protocol was approved by the Institutional Review Board of Kanazawa University (approval no. 2021-058). Because of the retrospective nature of the study, written informed consent was waived in both registries; however, patients who refused to participate in the study when reached out during follow-up were excluded. This approach complies with the recommendations from the Japanese Ministry of Health, Labour, and Welfare.

DEFINITIONS AND DIAGNOSIS OF HoFH. Patients with definite HoFH were those in whom LDLR pathway gene mutations were found or LDLR activity was used to identify HoFH. Patients with probable HoFH were those having total cholesterol levels greater than 450 mg/dL (11.64 mmol/L) or LDL cholesterol levels greater than 370 mg/dL (9.57 mmol/L) in the fasting steady state or the presence of clinical manifestations suggesting severe hypercholesterolemia, such as the presence of percutaneous xanthoma from their childhood and being refractory to medications.[10]

DATA COLLECTION. The attending physician obtained patients' medical records by reviewing hospital charts or conducting interviews. Generally, medical records are submitted to the government to register patients for designated intractable diseases. The collected variables described in this study were age, sex, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, family history, age at diagnosis, cutaneous xanthoma, tendon xanthoma, Achilles tendon thickness, valvular disease, intervention for valvular disease, prior coronary artery bypass grafting (CABG), coronary artery disease, prior percutaneous coronary intervention (PCI), aortic aneurysm, arteriosclerosis obliterans, carotid arteriosclerosis, arcus corneae, total cholesterol before medication, triglycerides before medication, high-density lipoprotein cholesterol before medication, LDL cholesterol before medication, genetic testing, lipoprotein apheresis, and lipid-lowering medication (statin, resin, probucol, ezetimibe, and PCSK9 inhibitors).

STATISTICAL ANALYSIS. Continuous variables were expressed as mean, standard deviation, and median with interquartile ranges. These variables were analyzed using the Student's *t* test or the Wilcoxon rank-sum test based on their distributions. On the other hand, categorical variables were expressed as frequencies and percentages and evaluated using the chi square test. We conducted a subgroup analysis on the patient features stratified by age, definite or probable HoFH, and the presence or absence of coronary artery disease (CAD).

Statistical analyses were conducted using R version 3.6.1 (R Foundation for Statistical Computing). *P* values less than 0.05 were considered as statistically significant, and all the stated *P* values were 2-tailed.

RESULTS

PATIENTS' CHARACTERISTICS. The mean age of the patients was 54 years, and 43% of them were men (Table 1). The median age at diagnosis was 27 years and exhibited a bimodal distribution (Figure 1). Cutaneous xanthoma was observed in 56% of the patients, tendon xanthoma in 80%, and Achilles tendon thickening in majority of them (Table 1). Regarding concomitant valvular disease, 24% of the patients had valvular disease, the majority of whom had aortic valvular disease (Table 1). Furthermore, 70% of the patients had CAD; according to the data, 28% had a previous CABG and 57% had a previous PCI (Table 1).

MUTATIONS IN GENES. Genetic testing was conducted on 65 (32.3%) patients with HoFH. Regarding genes, mutations in *LDLR* were identified in 52% of the patients and mutations in *LDLR* and *PCSK9* in 26%. Other types of double heterozygotes, such as *LDLR*+*LDLRAP1*+*PCSK9*, *LDLR*+*PCSK9*+Others, and *LDLR*+*PCSK9*+*LDLRAP1*+Others, were identified in 1.5%, 1.5%, and 6.2% of the patients, respectively. Moreover, 1.5% of patients had mutations in *LDLRAP1* and *PCSK9* (Figure 2).

Among patients with 143 probable HoFH, 15 patients (10.5%) of patients were conducted genetic testing. Among these 15 patients, mutations in *LDLR* were identified in 8 of 15 (53%) of patients, other than *LDLR*, *PCSK9*, and *LDLRAP1* mutations were identified in 3 of15 (20%) of patients, and others were identified in 1 of 15 (6.7%) patients.

LDL MEASUREMENTS AND LIPID-LOWERING THERAPIES. In terms of lipid-lowering therapies, 96% of the patients took statins, 70% took ezetimibe, and 50% used PCSK9 inhibitors. High-intensity statins were used by 74% of the patients. Furthermore, lipoprotein apheresis was performed in 21% of the patients (Table 1). The mean of LDL cholesterol before and after treatment were 10.1 mmol/L and 3.9 mmol/L, respectively, indicating a significant reduction ($P < 0.001$) (Figure 3). Stratifying according to the presence of CAD, a more significant reduction in LDL cholesterol was achieved in patients with CAD than in those without CAD ($P = 0.009$) (Figure 3).

SUBGROUP ANALYSIS. In the subgroup whose age at diagnosis was below 15 years, most of the patients were diagnosed at 0 years old. Tendon xanthoma was more frequently observed in patients <15 years of age (at diagnosis) than in those ≥15 years of age (at diagnosis). The prevalence of CAD was higher in patients ≥15 years of age (at diagnosis), but the difference was not statistically significant; also, prior PCI was more frequently observed in patients ≥15 years of age (at diagnosis) than in those <15 years of age (at diagnosis).

LDL cholesterol before treatment was not different between patients <15 years of age (at diagnosis) and those ≥15 years of age (at diagnosis). Genetic testing was more frequently conducted in patients <15 years of age (at diagnosis) than in those ≥15 years of age (at diagnosis) (61% and 20%, $P < 0.001$); of those <15 years of age (at diagnosis), 51% were diagnosed with definite HoFH.

In terms of lipid-lowering therapies, there was no significant difference between the 2 groups regarding

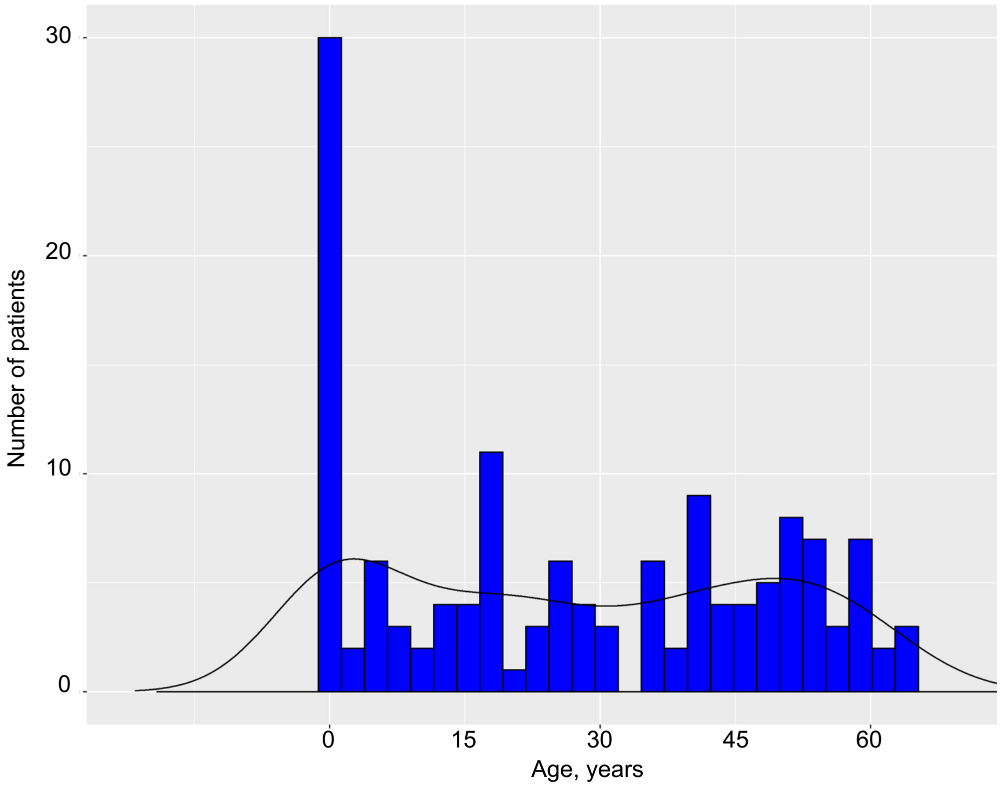
TABLE 1 Characteristics of Patients With Definite or Probable HoFH

	Definite or Probable HoFH (N = 201)	No. Patients Evaluated
Male	86 (43)	201
Age at assessments, y	54 ± 15	201
Body mass index, kg/m^2	24.4 ± 4.5	193
Systolic blood pressure, mm Hg	125 ± 16	192
Diastolic blood pressure, mm Hg	70 ± 13	192
Heart rate, beats/min	72 ± 11	177
Family history	163 (93)	175
Age at diagnosis	27 (4.5 - 47.5)	140
Cutaneous xanthoma	112 (56)	199
Tendon xanthoma	159 (80)	200
Achilles tendon thickness, mm	17.53 ± 9.72	144
Achilles tendon thickness ≥9 mm	140 (97)	144
Valvular disease	49 (24)	201
Aortic valvular disease	34 (69)	
Other valvular disease	21 (43)	
Intervention for valvular disease	19 (27)	70
Coronary artery disease	139 (70)	198
Prior PCI	85 (57)	149
Prior CABG	39 (28)	139
Aortic aneurysm	12 (6.0)	201
Arteriosclerosis obliterans	12 (6.0)	199
Carotid arteriosclerosis	105 (55)	192
Arcus corneae	60 (32)	190
Total cholesterol before medication, mmol/L	12.36 ± 2.52	137
Triglycerides before medication, mmol/L	1.92 ± 1.35	133
HDL cholesterol before medication, mmol/L	1.40 ± 1.02	131
LDL cholesterol before medication, mmol/L	10.15 ± 2.32	139
Genetic testing	65 (33)	198
Diagnosis		201
Definite	58 (29)	
Probable	143 (71)	
Lipoprotein apheresis	42 (21)	198
Statin	192 (96)	200
High-intensity statin[a]	148 (74)	200
Resin	18 (9.7)	185
Probucol	24 (12)	193
Ezetimibe	139 (70)	199
PCSK9 inhibitors	100 (50)	201

Values are n (%), mean ± SD, or mean (IQR) unless otherwise indicated. [a]In this study, statin doses greater than or equal to 20 mg atorvastatin, 4 mg pitavastatin, or 10 mg rosuvastatin were considered as high-intensity statin therapy.

CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; HoFH = homozygous familial hypercholesterolemia; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin kexin 9.

FIGURE 1 **Age Distribution at Diagnosis**



Histogram showing distribution of age at diagnosis as homozygous familial hypercholesterolemia.

the intake of statins, ezetimibe, and PCSK9 inhibitors. However, a higher percentage of patients <15 years of age (at diagnosis) received lipoprotein apheresis than those ≥15 years of age (at diagnosis) (40% and 13%, respectively, $P = 0.001$) (Table 2).

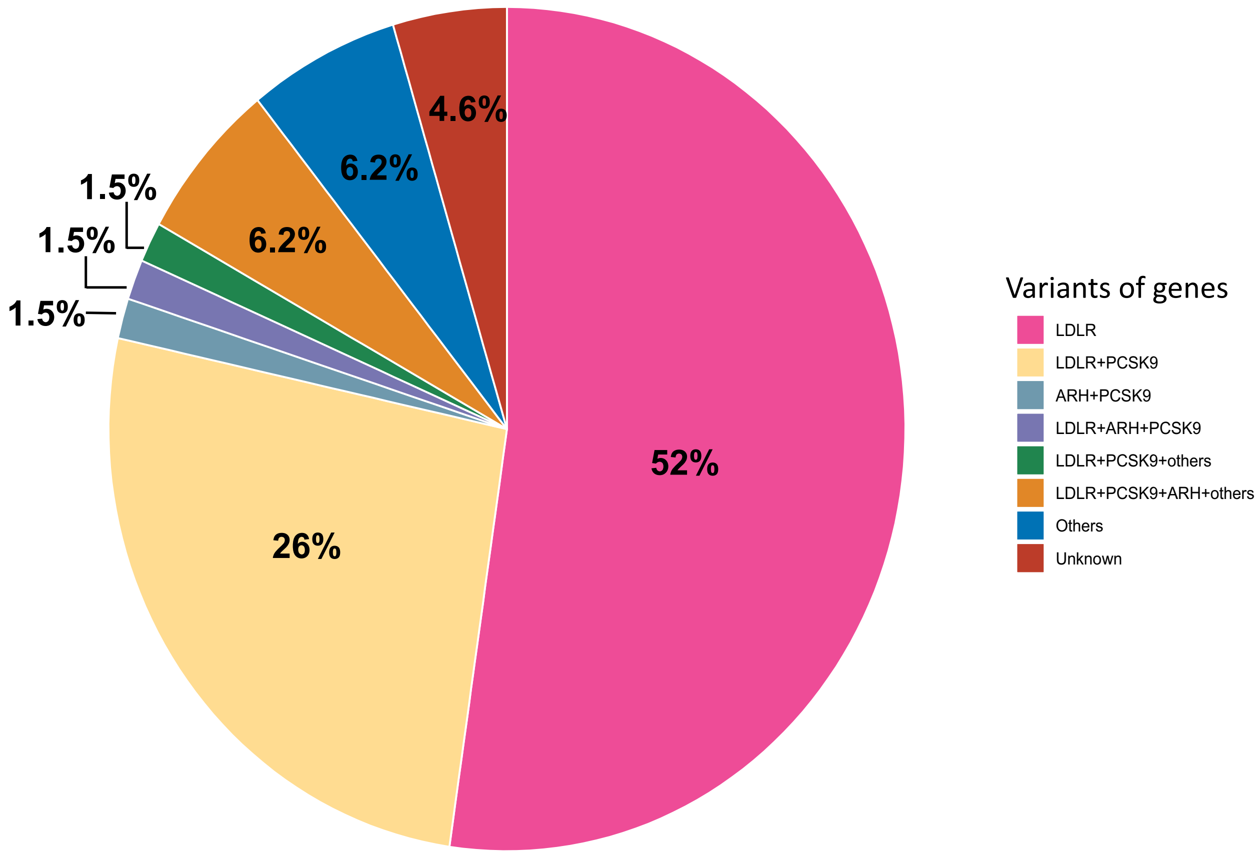
Similar baseline characteristics were obtained between definite HoFH and probable HoFH, except for age at diagnosis, valvular disease, carotid arteriosclerosis, arcus corneae, genetic testing, and lipoprotein apheresis. Age at diagnosis was younger in definite HoFH, and genetic testing and lipoprotein apheresis were more frequent in definite HoFH than in probable HoFH (Table 3).

In the subgroup analysis stratified based on the presence or absence of CAD, patients without CAD were predominantly female, younger in age, and diagnosed at a younger age compared to those with CAD (Table 4). They also exhibited a higher prevalence of family history, lower occurrence of cutaneous xanthoma, and reduced incidence of carotid arteriosclerosis. However, there was no significant difference in LDL cholesterol levels before medication between the 2 groups.

DISCUSSION

The major findings of this study evaluating the characteristics of patients and the treatment of HoFH from a national epidemiological survey were as follows (Central Illustration): (1) The median age at diagnosis was 27 years and exhibited a bimodal distribution. (2) Approximately 70% of the patients had CAD. (3) The primary cause of this situation was *LDLR*, followed by double heterozygotes of *LDLR* and *PCSK9*. (4) The mean of LDL cholesterol before and after treatment were 10.1 mmol/L and 3.9 mmol/L, respectively, indicating a significant reduction due to the use of intensive lipid-lowering

FIGURE 2 Variants of Mutated Genes in Patients With HoFH



Pie chart showing the frequency of mutated gene variants in patients with homozygous familial hypercholesterolemia (HoFH). ARH = autosomal recessive hypercholesterolemia; LDLR = low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin kexin 9.

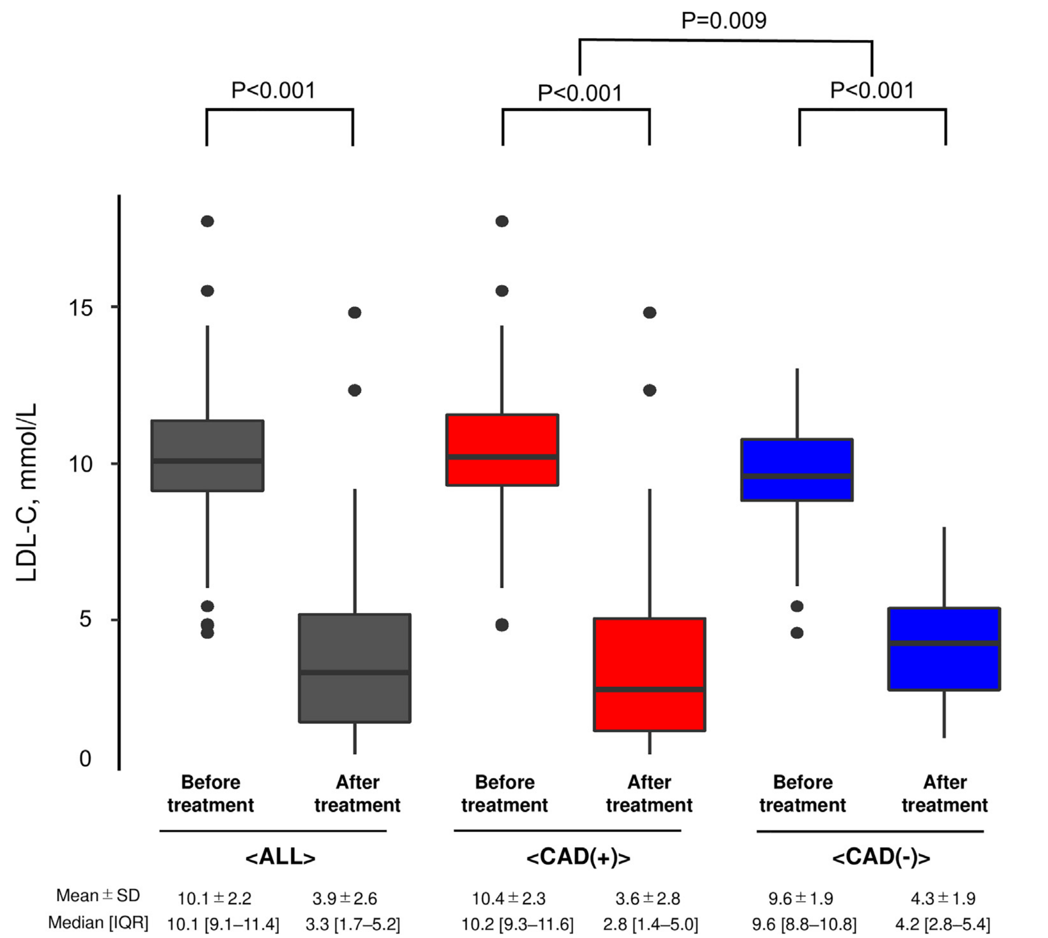
therapies. (5) Patients with CAD experienced a more notable decrease in LDL cholesterol than those without CAD.

HoFH is an inherited disease caused by mutations in genes connected to the LDLR pathway, and unless treatment is provided, atherosclerotic cardiovascular disease events start to occur even in the first decade.[1-5] Given that HoFH is a rare disease with prevalence estimated at 1:175,000 to 1:300,000, large-scale studies evaluating patient characteristics and management for patients with HoFH are scarce.[6-9,11-15] Therefore, this study evaluated the characteristics of and management for patients with genetically or clinically diagnosed HoFH using a national epidemiological survey from the Ministry of Health, Labour, and Welfare of Japan.

In this study, the median age of diagnosis exhibited a bimodal distribution. Most patients were diagnosed at 0 years old, and we presumed that these patients had manifestations specific to HoFH, such as cutaneous xanthomas from their childhood. Contrarily, some patients were diagnosed at approximately 40 years of age. We presumed that these patients (1) were overlooked in their childhood and were diagnosed later in their medical examinations or (2) were categorized as having severe heterogeneous FH whose phenotype was similar to HoFH because of additional factors, such as elevated Lp(a) and hypertension.

Previous studies from Europe had shown that more than 90% of patients with HoFH have pathogenic variants in both *LDLR* alleles.[6,8,16] However, as much

FIGURE 3 **LDL-C Change Before/After Treatment in Patients With and Without CAD**



Boxplots showing low-density lipoprotein cholesterol (LDL-C) levels. **Gray** indicates all patients. **Red** indicates patients with coronary artery disease (CAD). **Blue** indicates patients without CAD.

as a quarter of the HoFH cases were caused by double heterozygous mutations in *LDLR* and *PCSK9*. This was probably because a particular missense mutation in *PCSK9* ((NM_174936.4) : c.94G>A (p.Glu32Lys)) was common in Japan.[17-19] We have previously shown that a double heterozygous mutation in *LDLR* and this particular missense mutation in *PCSK9* led to the phenotype of typical HoFH.[10] However, there was no patient with HoFH caused by mutations in *APOB* in this database. A particular pathogenic mutation (c.10580 G>A: p.[Arg3527Gln] in *APOB*) has been shown as one of the most common pathogenic mutations as FH in some European countries, probably because of the founder effect.[20] However, it has been shown that the proportion of FH patients with this variant in *APOB* is low in Asian countries, including Japan.[21] In fact, the first FH case with this variant was identified very recently in Japan.[22]

In this study, LDL cholesterol before treatment was not different between patients with definite HoFH (molecularly defined) and those with probable HoFH (clinically defined). This fact adds justification to the criteria of probable FH (clinically defined) in terms of diagnostic criteria and risk stratification for this disease.

Regarding comorbidity, as many as 70% of the patients had a history of CAD, although their mean age was only 54 years. Importantly, more intensive lipid-lowering therapies had already been introduced for patients in secondary prevention than for those in primary prevention. However, LDL cholesterol after medication in each group was inadequate considering the targets (less than 2.6 mmol/L [100 mg/dL] for primary prevention and less than 1.8 mml/L [70 mg/dL] for secondary prevention).[5] More intensive lipid-lowering therapies are warranted for patients with high risks of arteriosclerotic events to reduce cardiovascular events and increase patients' life expectancy. Tromp et al[23] reported that use of more numbers of lipid-lowering therapies were associated with less LDL cholesterol level on treatment among patients with HoFH. In Japan, HoFH is registered as one of the designated intractable diseases where medical costs are fully covered by the government. So, several emerging new therapies, such as lomitapide and evinacumab that are rather expensive can be introduced for Japanese HoFH patients when indicated.[24,25] Alves et al[26] reported that phenotype was variable even among patients with HoFH. We also observed that the severity of their phenotypes, including LDL cholesterol were diverse, partly due to their genetic backgrounds (true homozygous or compound heterozygous).

As for the differential diagnosis of HoFH, to register HoFH patients in this Japanese National database, sitosterolemia, cerebrotendinous xanthomatosis, hypothyroidism and nephrotic syndrome should be ruled out as differential diagnoses of HoFH. Therefore, these conditions, including sitosterolemia were presumed to have been denied as potential differential diagnoses. Moreover, sitosterolemia is also defined as one of the designated intractable diseases in Japan by the Ministry of Health, Labour and Welfare of Japan.

TABLE 2 Characteristics of Patients With HoFH Dichotomized According to Age at Diagnosis

	Age <15 y (n = 47)	Age ≥15 y (n = 92)	*P*
Male	18 (38)	41 (45)	0.60
Age at assessments, y	46 ± 17	57 ± 13	<0.001
Body mass index, kg/m^2	23.8 ± 4.9	24.5 ± 4.1	0.37
Systolic blood pressure, mm Hg	119 ± 15	127 ± 16	0.009
Diastolic blood pressure, mm Hg	66 ± 13	71 ± 12	0.03
Heart rate, beats/min	70 ± 9	71 ± 10	0.94
Family history	44 (98)	75 (93)	0.42
Age at diagnosis, y	0.0 (0.0 - 4.5)	40.5 (25.0 - 52.0)	<0.001
Cutaneous xanthoma	32 (68)	48 (53)	0.14
Tendon xanthoma	43 (92)	66 (73)	0.02
Achilles tendon thickness, mm	19.05 (14.26)	16.81 (7.67)	0.31
Achilles tendon thickness ≥9 mm	38 (100)	58 (95)	0.43
Valvular disease	16 (34)	24 (26)	0.43
Aortic valvular disease	17 (71)	11 (69)	
Coronary artery disease	28 (61)	66 (73)	0.23
Prior PCI	12 (38)	44 (62)	0.04
Prior CABG	11 (36)	15 (23)	0.28
Carotid arteriosclerosis	30 (65)	47 (53)	0.26
Arcus corneae	19 (44)	28 (32)	0.23
Total cholesterol before medication, mmol/L	12.84 ± 3.27	12.16 ± 2.57	0.28
Triglycerides before medication, mmol/L	1.28 ± 0.60	1.97 ± 1.34	0.01
HDL cholesterol before medication, mmol/L	1.22 ± 0.41	1.53 ± 1.35	0.25
LDL cholesterol before medication, mmol/L	10.56 ± 2.84	9.89 ± 2.14	0.20
Genetic testing	28 (61)	18 (20)	<0.001
Diagnosis			0.001
Definite	24 (51)	19 (21)	
Probable	23 (49)	73 (79)	
Lipoprotein apheresis	19 (40)	12 (13)	0.001
Statin	44 (94)	90 (99)	0.22
High-intensity statin[a]	37 (79)	69 (75)	0.78
Ezetimibe	36 (78)	62 (68)	0.30
PCSK9 inhibitors	21 (45)	44 (48)	0.86

Values are n (%), mean ± SD, or mean (IQR) unless otherwise indicated. [a]In this study, statin doses ≥20 mg atorvastatin, 4 mg pitavastatin, or 10 mg rosuvastatin were considered as high-intensity statin therapy.
Abbreviations as in Table 1.

STUDY LIMITATIONS. First, a cross-sectional survey was used in this study, and we could not evaluate clinical outcomes or estimate risk. The results of this study were different from the ones publicly announced by the Japanese Ministry of Health, Labour, and Welfare. Second, we did not have information about the accurate timing of LDL cholesterol measurement before and after treatment. Third, we did not have details about gene mutations in *LDLR* (true homozygous or compound heterozygous). Fourth, although this is the study with the largest National Database of HoFH in Japan, we acknowledge that this cohort does not include all of the patients with HoFH in Japan. However, when we consider the prevalence of patients with HoFH among general population (1 in 360,000) based on the assumption of the prevalence of HoFH (1 in 300), it is estimated that there are ~300 heterozygous FH patients in Japan (total population is 120 M).[27] Accordingly, as much as two-thirds of patients were included in this study; therefore, the current study can represent a landscape of the clinical features in Japanese HoFH patients. Fifth, only one-third of the patients with HoFH underwent genetic testing for FH, which can lead to an underestimation of the prevalence of definite HoFH. However, the cost of genetic testing for FH has been covered by national health insurance since 2022 in Japan. Accordingly, we anticipate that more patients will undergo genetic testing for FH, which would lead to

TABLE 3 Characteristics of Patients Stratified by Definite or Probable HoFH

	Definite (n = 58)	Probable (n = 143)	*P*
Male	24 (41)	62 (43)	0.92
Age at assessments, y	52 ± 15	55 ± 15	0.21
Body mass index, kg/m^2	23.8 ± 5.1	24.6 ± 4.2	0.24
Systolic blood pressure, mm Hg	120 ± 14	127 ± 17	0.01
Diastolic blood pressure, mm Hg	66 ± 12	72 ± 13	0.007
Heart rate, beats/min	71 ± 11	72 ± 12	0.46
Family history	50 (94)	113 (93)	0.93
Age at diagnosis	7.00 (0 - 35.5)	33.5 (15 - 51)	<0.001
Cutaneous xanthoma	35 (60)	77 (55)	0.56
Tendon xanthoma	51 (88)	108 (76)	0.09
Achilles tendon thickness, mm	19.3 ± 13.5	16.8 ± 7.5	0.15
Achilles tendon thickness ≥9 mm	42 (98)	98 (97)	1.00
Valvular disease	23 (40)	26 (18)	0.002
Intervention for valvular disease	11 (39)	8 (19)	0.11
Coronary artery disease	44 (77)	95 (67)	0.23
Prior PCI	23 (49)	62 (61)	0.24
Prior CABG	11 (25)	28 (30)	0.73
Carotid arteriosclerosis	41 (72)	64 (47)	0.003
Arcus corneae	27 (48)	33 (25)	0.003
Total cholesterol before medication, mmol/L	12.28 ± 2.99	12.40 ± 2.30	0.79
Triglycerides before medication, mmol/L	1.67 ± 1.05	2.01 ± 1.45	0.19
HDL cholesterol before medication mmol/L	1.20 ± 0.32	1.47 ± 1.17	0.19
LDL cholesterol before medication, mmol/L	10.41 ± 2.68	10.06 ± 2.17	0.43
Genetic testing	50 (88)	15 (11)	<0.001
Lipoprotein apheresis	18 (31)	24 (17)	0.047
Statin	55 (95)	137 (97)	0.89
High-intensity statin[a]	45 (78)	103 (72)	0.53
Ezetimibe	41 (71)	98 (70)	1.00
PCSK9 inhibitors	32 (55)	68 (48)	0.41

Values are n (%), mean ± SD, or mean (IQR) unless otherwise indicated. [a]In this study, statin doses greater than or equal to 20-mg atorvastatin, 4-mg pitavastatin, or 10-mg rosuvastatin were considered as high-intensity statin therapy.
Abbreviations as in Table 1.

the identification of more patients with definite HoFH in the near future. Sixth, information about causal gene(s) are available although there is no specific information on genetic variants in this database. So, it is rather unclear how pathogenicity of genetic variants was determined. However, it is common to use American College of Medical Genetics and/or Clinvar criteria in Japan as well.[28] Seventh, information about the supravalvular aortic stenosis, which is specific to HoFH, is lacking.[29] Eighth, Lp(a) level was not available in this database, although it has been described that Lp(a) levels in HoFH were higher than that in heterozygous FH, which should affect the phenotype of HoFH.[30] Ninth, we could not provide the information of when CAD occurred in this population. Finally, the phenotypes included in this database were limited; thus, some of their important clinical phenotypes might be missed. In this regard, another multicenter registry, the Committee on Primary Dyslipidemia of the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour, and Welfare of Japan, conducted a study on HoFH to thoroughly evaluate its genotypes and phenotypes. [31] This study will provide insights into the clinical management of HoFH in the future.

CONCLUSIONS

The national epidemiological study of patients with HoFH showed patient's clinical and genetic characteristics and LDL-lowering therapy in Japan. There was considerable diversity in the severity of phenotypes, including LDL cholesterol levels, among patients with HoFH. In Japan, the management of LDL cholesterol in HoFH is still inadequate despite the availability of intensive lipid-lowering therapies.

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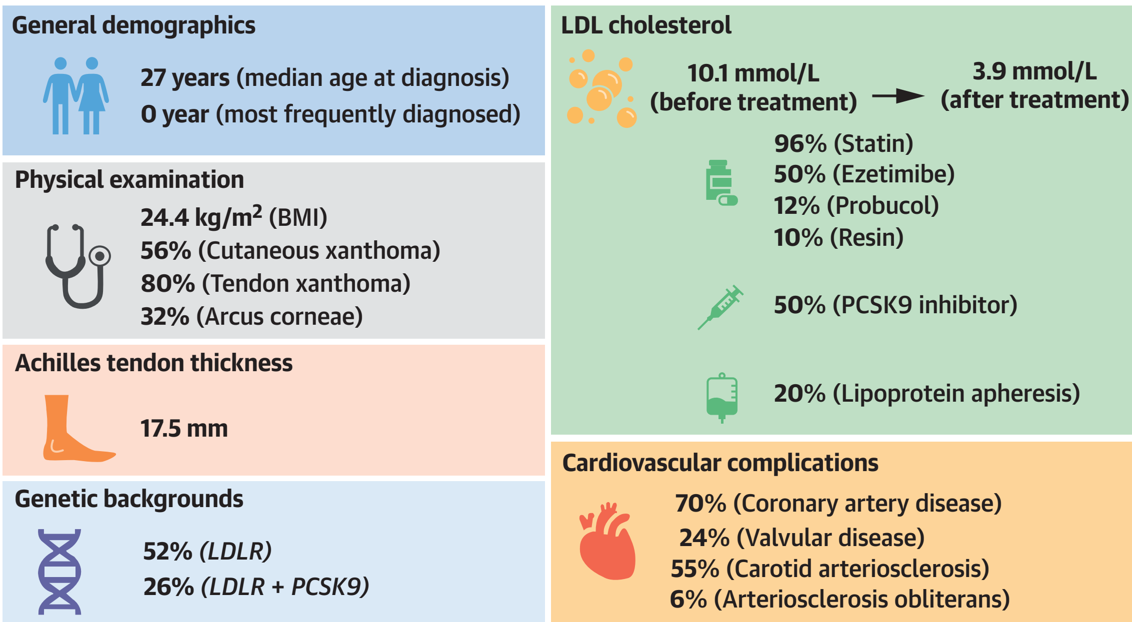
TABLE 4 Characteristics of Patients With HoFH Stratified Based on the Presence or Absence of CAD

	With CAD (n = 139)	Without CAD (n = 59)	*P*
Male	71 (51)	15 (25)	0.002
Age at assessments, y	58 ± 13	46 ± 15	<0.001
Body mass index, kg/m^2	24.5 ± 4.2	24.1 ± 5.2	0.62
Systolic blood pressure, mm Hg	126 ± 16	122 ± 16	0.19
Diastolic blood pressure, mm Hg	71 ± 13	69 ± 11	0.23
Heart rate, beats/min	71 ± 12	73 ± 10	0.40
Family history	107 (90)	54 (100)	0.04
Age at diagnosis	32.0 (5.8 - 49.0)	18.0 (4.5 - 37.0)	0.19
Cutaneous xanthoma	86 (62)	25 (44)	0.03
Tendon xanthoma	113 (81)	45 (78)	0.69
Achilles tendon thickness, mm	17.7 ± 7.7	17.4 ± 13.7	0.86
Achilles tendon thickness ≥9 mm	99 (99)	39 (93)	0.14
Valvular disease	40 (29)	9 (15)	0.07
Aortic valvular disease	29 (73)	5 (56)	
Prior PCI	84 (62)	0 (0)	<0.001
Prior CABG	39 (31)	0 (0)	0.07
Carotid arteriosclerosis	80 (61)	25 (43)	0.03
Arcus corneae	46 (36)	13 (22)	0.08
Total cholesterol before medication, mmol/L	12.51 ± 2.49	12.03 ± 2.60	0.31
Triglycerides before medication, mmol/L	2.14 ± 1.49	1.45 ± 0.78	0.008
HDL cholesterol before medication, mmol/L	1.25 ± 0.30	1.72 ± 1.77	0.02
LDL cholesterol before medication, mmol/L	10.34 ± 2.50	9.73 ± 1.86	0.16
Genetic testing	52 (38)	12 (21)	0.03
Diagnosis			0.23
Definite	44 (32)	13 (22)	
Probable	95 (68)	46 (78)	
Lipoprotein apheresis	31 (23)	11 (19)	0.71
Statin	132 (96)	57 (97)	1.00
High-intensity statin[a]	101 (73)	44 (75)	0.92
Ezetimibe	95 (68)	42 (74)	0.57
PCSK9 inhibitors	74 (53)	24 (41)	0.14

Values are n (%), mean ± SD, or mean (IQR) unless otherwise indicated. [a]In this study, statin doses greater than or equal to 20 mg atorvastatin, 4 mg pitavastatin, or 10 mg rosuvastatin were considered as high-intensity statin therapy.

Abbreviations as in Table 1.

CENTRAL ILLUSTRATION Clinical Characteristics of Homozygous Familial Hypercholesterolemia in Japan



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General demographics, physical examination, Achilles tendon thickness, genetic backgrounds, low-density lipoprotein (LDL) cholesterol, and cardiovascular complications of homozygous familial hypercholesterolemia in Japan are summarized. BMI = body mass index; LDLR = low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin kexin 9.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study has shown that at least a part of the patients with HoFH were undiagnosed during their childhood and that management of their LDL cholesterol level remains inadequate despite the availability of intensive lipid-lowering therapies.

TRANSLATIONAL OUTLOOK: Future studies are warranted to determine whether early diagnosis and treatment for patients with HoFH would lead to a better prognosis and to know how low their LDL cholesterol should be.

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