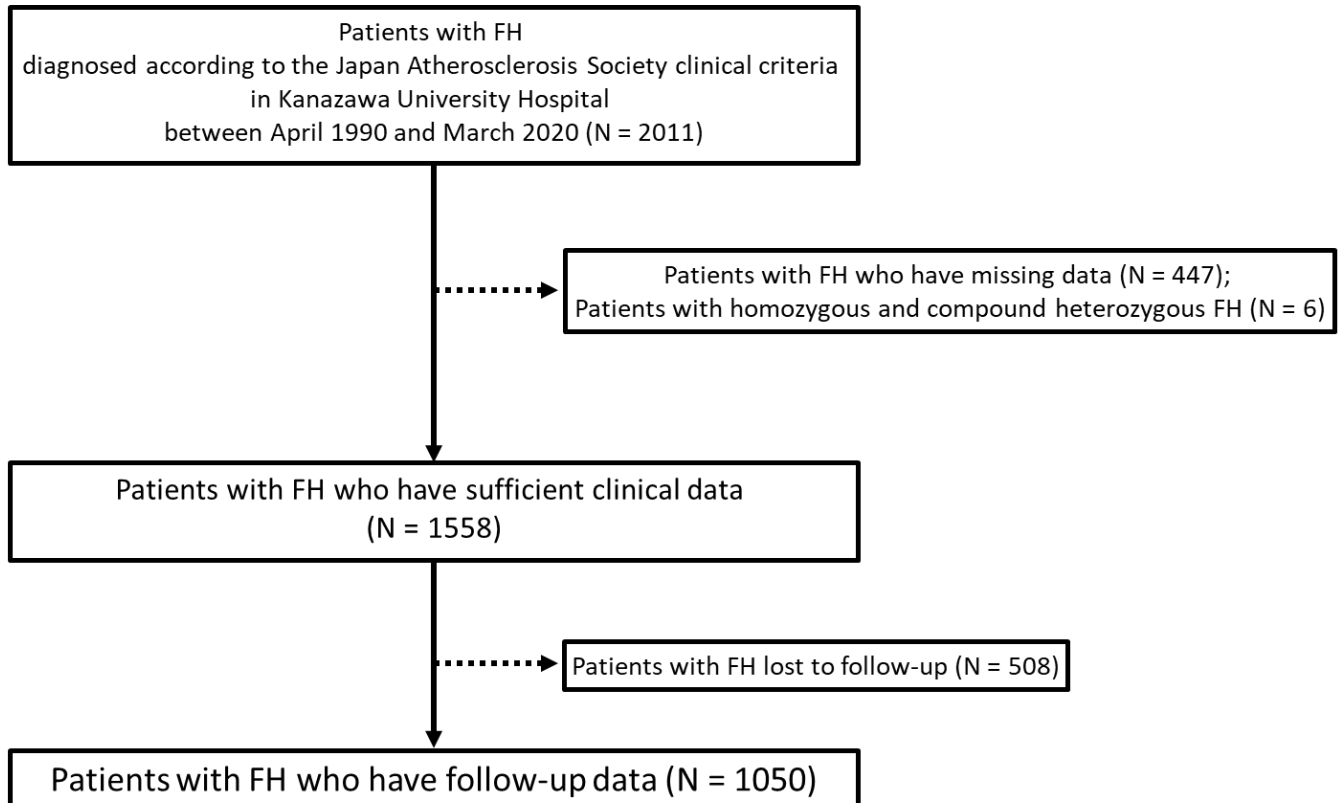


Supplementary Material

Supplemental Figure 1. STROBE flow diagram of patient selection



The flow diagram shows the process of patient selection.

Supplemental Table 1. Baseline characteristics according to genotype

	All (N = 1050)	without pathogenic variants (N = 385)	with missense variants (N = 277)	with PTVs (N = 388)
Age (years)	49 ± 16	52 ± 16	48 ± 17	46 ± 17
Male gender (%)	490 (46.7%)	200 (51.9%)	127 (45.8%)	163 (42.0%)
Hypertension (%)	250 (23.8%)	99 (25.7%)	66 (23.8%)	85 (21.9%)
Diabetes (%)	83 (7.9%)	53 (13.8%)	14 (5.1%)	16 (4.1%)
Smoking (%)	224 (21.3%)	90 (23.4%)	56 (20.2%)	78 (20.1%)
Total cholesterol level (mg/dL)	326 [268–365]	318 [244–344]	328 [279–377]	348 [290–392]
Triglyceride level (mg/dL)	113 [76–177]	142 [90–190]	125 [80–175]	104 [78–170]
HDL cholesterol level (mg/dL)	47 [43–51]	49 [44–52]	48 [43–50]	45 [41–49]
LDL cholesterol level (at baseline, mg/dL)	244 [208–279]	216 [196–248]	236 [219–285]	256 [218–295]
LDL cholesterol level (at follow-up, mg/dL)	110 [96–120]	112 [98–1120]	114 [94–122]	106 [90–118]
Family history of FH and/or premature CVD (%)	776 (73.9%)	277 (71.9%)	193 (69.7%)	306 (78.9%)
History of CVD (%)	290 (27.6%)	97 (25.2%)	69 (24.9%)	124 (32.0%)

PTV: protein-truncating variant, CVD: cardiovascular disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein, FH: familial hypercholesterolemia

Supplemental Table 2. Mutations identified in FH genes

Gene	Nucleotide change	Mutation type	Effect on protein	Number of patients	ACMG
<i>LDLR</i>	c.14G>A	Missense	p.Gly5Asp	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.68-1G>C	Splice site	NA	2	PVS1/PM2/PM4/PP1/PP5 Pathogenic
<i>LDLR</i>	c.130T>G	Missense	p.Trp44Gly	3	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.137G>A	Missense	p.Cys46Tyr	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.191-2A>G	Splice site	NA	6	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.283T>G	Missense	p.Cys95Gly	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.284G>T	Missense	p.Cys95Phe	3	PM2/PM5/PP1/PP5 Likely pathogenic
<i>LDLR</i>	c.313+1G>A	Splice site	NA	2	PVS1/PM2/PM4 Pathogenic
<i>LDLR</i>	c.344G>A	Missense	p.Arg115His	3	PS1/PM2/PP3 Likely pathogenic
<i>LDLR</i>	c.361T>G	Missense	p.Cys121Gly	5	PM1/PM2/PP3/PP4/PP5 Likely pathogenic
<i>LDLR</i>	c.378del	Frameshift	p.Phe126LeufsTer80	4	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.389dupC	Frameshift	p.Asp131ArgfsTer49	5	PVS1/PM1/PM2/PM4/PP5 Pathogenic

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<i>LDLR</i>	c.413C>G	Nonsense	p.Ser138Ter	6	PVS1/PM2/PM4/PP1/PP5 Pathogenic
<i>LDLR</i>	c.418G>A	Missense	p.Glu140Lys	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.478T>C	Missense	p.Cys160Arg	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.489G>T	Missense	p.Gln163His	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.530C>T	Missense	p.Ser177Leu	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.532G>T	Missense	p.Asp178Tyr	5	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.611G>C	Missense	p.Cys204Ser	6	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.642G>C	Missense	p.Trp214Cys	7	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.682G>A	Missense	p.Glu228Gln	5	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.686_689del	Frameshift	p.Glu229AlafsTer35	4	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.694+1G>A	Splice site	NA	2	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.718G>A	Missense	p.Glu240Lys	3	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.718G>T	Nonsense	p.Glu240Ter	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.726G>C	Missense	p.Gln242His	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.796G>A	Missense	p.Asp266Asn	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.797A>G	Missense	p.Asp266Gly	3	PM1/PM2/PM5/PP1/PP3 Likely pathogenic
<i>LDLR</i>	c.829G>T	Nonsense	p.Glu277Ter	2	PVS1/PM2/PM4/PP1 Pathogenic

<i>LDLR</i>	c.874delC	Frameshift	p.Leu292TrpfsTer78	3	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.901G>T	Missense	p.Asp301Tyr	5	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.902A>T	Missense	p.Asp301Val	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.937T>G	Missense	p.Cys313Gly	3	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.939C>A	Missense	p.Cys313Ter	2	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.940+2T>C	Splice site	NA	2	PVS1/PM2/PM4/PP1 Pathogenic
<i>LDLR</i>	c.967G>A	Missense	p.Gly323Ser	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1007_1010delACGA	Frameshift	p.Tyr336CysfsTer33	2	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1012T>A	Missense	p.Cys338Ser	2	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1056C>A	Nonsense	p.Cys352Ter	4	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1062dupT	Frameshift	p.Ile355TyrfsTer3	5	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1067A>T	Missense	p.Asp356Val	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1069G>T	Nonsense	p.Glu357Ter	2	PVS1/PM2/PM4 Pathogenic
<i>LDLR</i>	c.1114_1115insC	Frameshift	p.Glu372AlafsTer9	4	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1123_1124insGA	Nonsense	p.Tyr375Ter	2	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1183_1184insC	Frameshift	p.Val395AlafsTer46	2	PVS1/PM2/PM4/PP5 Pathogenic
<i>LDLR</i>	c.1187-2A>G	Splice site	NA	3	PVS1/PM2/PM4/PP5 Pathogenic

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<i>LDLR</i>	c.1207T>C	Missense	p.Phe403Leu	2	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1252G>A	Missense	p.Glu418Lys	6	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1285G>A	Missense	p.Val429Leu	3	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1297G>C	Missense	p.Asp433His	3	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1328G>C	Missense	p.Trp443Ser	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1339T>C	Missense	p.Ser447Pro	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1340C>G	Missense	p.Ser447Cys	2	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1432G>A	Missense	p.Gly478Arg	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1466A>G	Missense	p.Tyr489Cys	2	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1469G>A	Nonsense	p.Trp490Ter	1	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1474G>A	Missense	p.Asp492Asn	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1567G>A	Missense	p.Val523Met	3	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1573G>T	Missense	p.Asp525Tyr	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1586+1G>A	Splice site	NA	2	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1652_1662delACATCTACTCG	Frameshift	p.Asp551AlafsTer4	4	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1702C>G	Missense	p.Leu568Val	4	PM1/PM2/PP3/PP5 Likely pathogenic
<i>LDLR</i>	c.1705+1G>C	Splice site	NA	4	PVS1/PM2/PM4/PP4 Pathogenic

<i>LDLR</i>	c.1706A>G	Missense	p.Asp569Gly	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1727A>G	Missense	p.Tyr576Cys	6	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1731G>T	Missense	p.Trp577Cys	6	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1778dupG	Frameshift	p.Asn594GlnfsTer9	5	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1783C>T	Missense	p.Arg595Trp	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1845+2T>C	Splice site	NA	43	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1859G>C	Missense	p.Trp620Ser	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1868T>A	Missense	p.Ile623Asn	3	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1897C>T	Missense	p.Arg633Cys	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.1925T>C	Missense	p.Leu642Ser	3	PM1/PM2/PP3/PP4/PP5 Likely pathogenic
<i>LDLR</i>	c.1998G>C	Missense	p.Trp666Cys	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.2050G>T	Missense	p.Ala684Ser	2	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.2054C>T	Missense	p.Pro685Leu	34	PM1/PM2/PP3/PP4/PP5 Likely pathogenic
<i>LDLR</i>	c.2096C>T	Missense	p.Pro699Leu	4	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.2389G>A	Missense	p.Val797Met	13	PM1/PM2/PP3/PP4 Likely pathogenic
<i>LDLR</i>	c.2390-4_2393delACAGTGCT	Splice site	NA	3	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.2416delG	Frameshift	p.Val806SerfsTer123	4	PVS1/PM2/PM4/PP4 Pathogenic

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<i>LDLR</i>	c.2416dupG	Frameshift	p.Val806GlyfsTer11	4	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.2431A>T	Nonsense	p.Lys811Ter	185	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.2500G>A	Missense	p.Asp834Asn	4	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.2579C>T	Missense	p.Ala860Val	4	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.313-?_2311+?del	Large deletion	Truncated protein	21	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1186-?_1587+?dup	Large duplication	Truncated protein	17	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.1845-?_2141+?del	Large deletion	Truncated protein	16	PVS1/PM2/PM4/PP4 Pathogenic
<i>LDLR</i>	c.2141-?_2311+?del	Large deletion	Truncated protein	15	PVS1/PM2/PM4/PP4 Pathogenic
<i>PCSK9</i>	c.94G>A	Missense	p.Glu32Lys	42	PS1/PS3/PP3/PP4/PP5 Pathogenic

ACMG: American College of Medical Genetics, *LDLR*: low-density lipoprotein receptor, *PCSK9*: proprotein convertase subtilisin/kexin type 9, NA: not applicable, FH: familial hypercholesterolemia

Supplemental Table 2. Characteristics of the study subjects included and excluded

Variable	Study population (n = 1,050)	Individuals excluded* (n = 955)	p value
Age (years)	49 ± 16	44 ± 19	0.0034
Male gender (%)	490 (46.7%)	448 (46.9%)	0.95
LDL cholesterol level (at baseline, mg/dL)	244 [208–279]	240 [200–268]	0.14

*homozygous and compound heterozygous FH were excluded.