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Enhancing Familial Hypercholesterolemia Detection in South Korea: A Targeted Screening Approach Integrating National Program and Genetic Cascade Screening

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AUTHOR'S SUMMARY

Our study introduces an approach to screening familial hypercholesterolemia (FH), integrating the General Health Screening Program (GHSP) with cascade genetic screening to manage FH more effectively. By analyzing individuals with high low-density lipoprotein levels from the GHSP and confirming pathogenic mutations through genetic testing, we identified a significant proportion of undiagnosed FH cases (8.4%). Sixty-one point one percentage of their screened relatives carry pathogenic FH mutations—highlighting the potential efficiency for this targeted screening strategy. This approach promises to significantly lower the risk of cardiovascular diseases associated with FH, showcasing a model for efficient, large-scale FH detection and intervention.

ABSTRACT

Background and Objectives: Familial hypercholesterolemia (FH) increases the risk of premature cardiovascular disease through disrupted low-density lipoprotein cholesterol (LDL-C) metabolism. Although FH is a severe condition, it remains widely underdiagnosed, which can be attributed to barriers in genetic testing and a lack of awareness. This study aims to propose and evaluate a targeted screening program for FH in South Korea by integrating the General Health Screening Program (GHSP) with cascade genetic screening.
Methods: The study included individuals with LDL-C levels ≥190 mg/dL identified during the 2021 GHSP (primary participants). Data on demographics, lifestyle, medical history, and family history were collected through questionnaires. Targeted next-generation sequencing was used to identify pathogenic mutations in the *PCSK9*, *APOB*, *LDLRAP1*, and *LDLR* genes associated with FH. Pathogenic mutations found in primary participants were confirmed in their relatives (secondary participants) using Sanger sequencing. Participant characteristics were analyzed based on the presence of pathogenic mutations.
Results: Among 83 individuals with severe hypercholesterolemia identified through the

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Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions
Conceptualization: Kim HY, Shin MH; Formal analysis: Yang JH, Shin MH; Investigation: Yang JH, Shin MH; Methodology: Shin MH; Supervision: Shin MH; Writing - original draft: Yang JH, Kim HY, Shin MH; Writing - review & editing: Yang JH, Cho KH, Hong YJ, Kim JH, Kim HY, Shin MH.

GHSP, 7 primary participants (8.4%) carried pathogenic mutations in the *LDLR* and *PCSK9* genes. In secondary participants, pathogenic mutations were identified in 61.1% of the relatives of 4 patients with pathogenic mutations. The prevalence of pathogenic mutations was significantly higher in primary participants compared to secondary participants.
Conclusions: Integrating community resources with FH screening can enhance the early detection and treatment of FH. By utilizing GHSP data and adding genetic screening, the proposed model provides a strategy to reduce the cardiovascular risks associated with FH, supporting its wider adoption at the national level.

Keywords: Mass screening; Hypercholesterolemia; Heredity; Sequence analysis

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder primarily caused by mutations in the *LDLR*, *APOB*, and *PCSK9* genes. These mutations impair the normal metabolism of low-density lipoprotein cholesterol (LDL-C), leading to its accumulation in the bloodstream and significantly elevated cholesterol levels. This disruption sharply increases the risk of premature atherosclerotic heart disease, with individuals with FH facing a cardiovascular risk more than ten times that of the general population.[1)2)] Early detection and intensive lipid-lowering treatments can markedly decrease the risk of cardiovascular disease (CVD), underscoring the critical need for early diagnosis.[1)2)]

Despite its genetic basis, the clinical presentation of FH can vary widely. There are significant differences in LDL-C levels and treatment responses, even among individuals with the same mutation. FH is typically diagnosed clinically based on various criteria, such as the Simon Broome[3)] or Dutch Lipid Clinic Network (DLCN) criteria.[4)] The clinical criteria for FH often include a history of premature coronary heart disease (CHD) or elevated LDL-C levels in the patient or their family members, as well as physical signs like tendinous xanthomata (**Supplementary Tables 1** and **2**). Although the phenotype often guides the clinical management and diagnosis, genetic testing is recommended due to the variable therapeutic responses and the higher risks associated with FH mutations.[5)] Diagnosing FH through genetic evidence not only supports cascade screening among relatives but also enhances the patient's understanding of their condition and improves adherence to lipid-lowering medications.[6)]

Several guidelines about the management of hypercholesterolemia address the screening for FH. The National Institute for Health and Care Excellence suggests that FH should be suspected in cases where total cholesterol exceeds 7.5 mmol/L (290 mg/dL) or when there is a family history of premature CHD. For primary care, clinical diagnosis is recommended using either the Simon Broome or DLCN criteria. If the Simon Broome criteria indicate a possible FH diagnosis, or if the DLCN criteria score exceeds 5, DNA testing is advised. The guidelines also recommend cascade screening for first-, second-, and third-degree relatives of individuals diagnosed with FH.[7)] The European Society of Cardiology/European Atherosclerosis Society guidelines recommend genetic testing and cascade screening if total cholesterol is greater than 8 mmol/L (310 mg/dL), or in the presence of a personal or family history of premature CHD/cardiac death, or tendon xanthoma. They also endorse using the DLCN or Simon Broome criteria for clinical diagnosis.[8)] Furthermore, the American College of Cardiology/American Heart Association recommends early diagnosis of FH through lipid

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profiling before the age of 2 if there is a family history of early CVD or if total cholesterol is ≥240 mg/dL (≥6.2 mmol/L), LDL-C ≥190 mg/dL (≥4.9 mmol/L), or non-high density lipoprotein cholesterol (HDL-C) ≥220 mg/dL (≥5.7 mmol/L).[9]

Globally, the prevalence of FH varies, estimated at approximately 1 in 200 to 1 in 500 individuals in the general population.[10] However, barriers such as high costs of genetic testing, and low awareness of FH significantly contribute to its underdiagnosis, particularly in countries like South Korea. This underdiagnosis underscores the urgent need for screening strategies that target the identification of undiagnosed individuals, thereby reducing the preventable burden of CVD associated with FH.[11]

In South Korea, the diagnosis of FH is guided by the DLCN and Simon Broome criteria, which incorporate a combination of clinical features such as medical history, physical examinations, LDL-C levels, and genetic markers.[2] The nationwide General Health Screening Program (GHSP) mandates LDL-C testing every 4 years for individuals aged 20 and older.[12] This program likely improves the detection of patients with severe hypercholesterolemia, characterized by LDL-C levels of 190 mg/dL or higher, a group that exhibits a 23-fold increase in FH prevalence compared to unaffected individuals.[13] With a participation rate of 70–80%,[12] the program serves as a robust platform for identifying high-risk individuals, thereby enabling targeted genetic and physical assessments to optimize FH screening.

Cascade screening, a family-based approach, systematically tests relatives of diagnosed individuals, beginning with first-degree relatives. This method has proven to be cost-effective and efficient in identifying undiagnosed cases of FH, facilitating early intervention.[14] Given the low rates of FH diagnosis in countries like South Korea, the implementation of a cascade screening program could significantly enhance the early detection and management of FH. Therefore, this study proposes a program in collaboration with the National Health Insurance Service, targeting patients with severe hypercholesterolemia identified through GHSP for genetic testing of key FH genes, including *APOB*, *LDLR*, and *PCSK9*. By using identified monogenic FH patients as probands for cascade screening, this initiative aims to improve the detection and management of FH, ultimately reducing its associated health burden.

METHODS

Ethical statement

This study was approved by the Institutional Review Board of Chonnam National University Hospital (approval No. CNUH-2022-312), and informed consent was obtained from all participants, ensuring compliance with ethical standards and the Helsinki declaration of 2013.

Subjects

In the 2021 GHSP, lipid profiles were tested in 161,692 individuals residing in Gwangju. Of these, 4,789 exhibited LDL-C levels of 190 mg/dL or higher. For this study, 84 of these individuals who volunteered for a screening program were initially recruited. However, one participant (participant number: F44) withdrew, and was thus excluded from the analysis. The study proceeded with the remaining 83 individuals; hereafter referred to as primary participants. Genetic testing identified 7 probands among them. Four of these probands agreed to participate in cascade screening, which led to the recruitment of 18 additional relatives as secondary participants (**Figure 1**).

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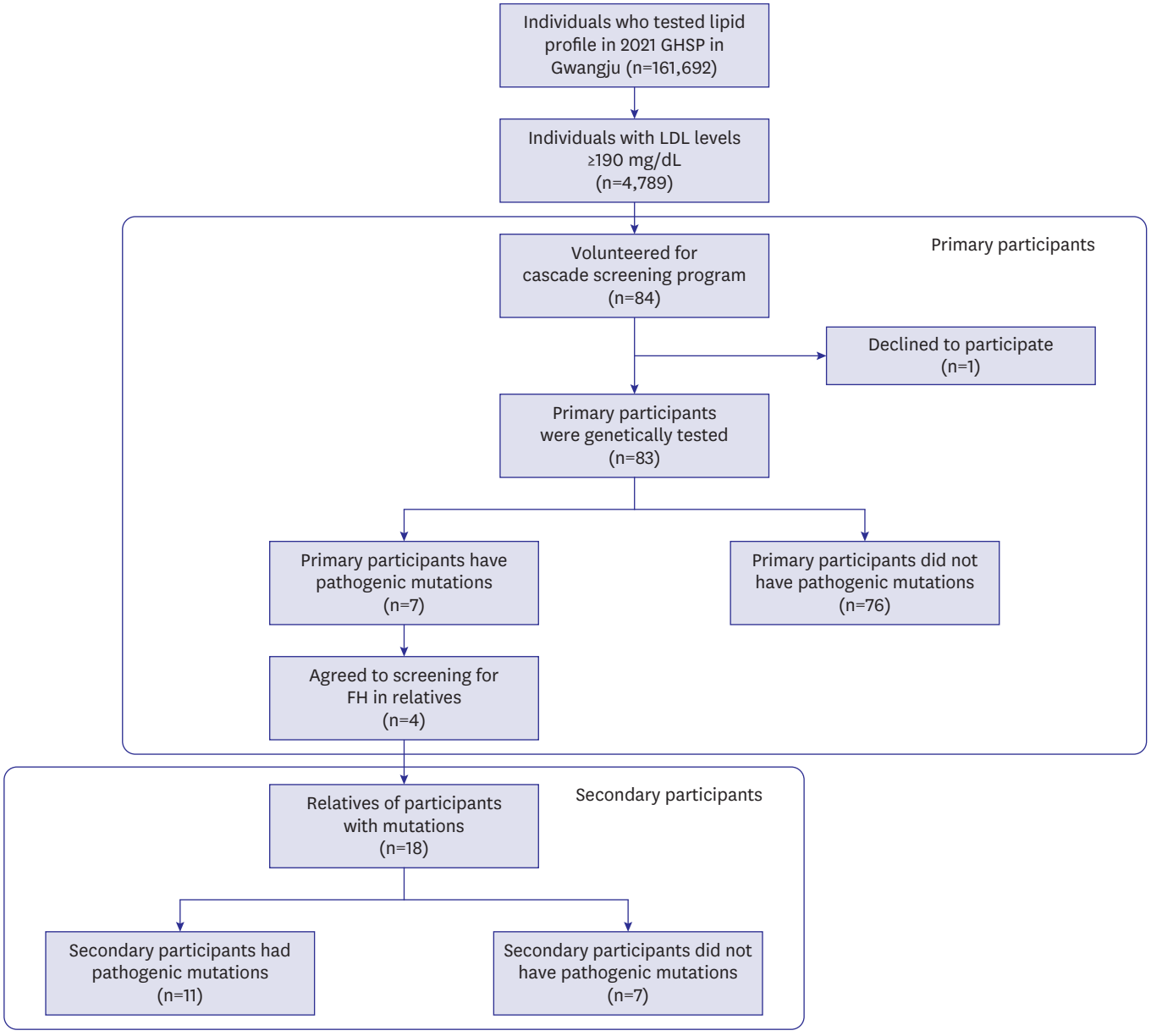

Figure 1. Flow diagram for study participants. Primary participants are individuals directly recruited from the GHSP due to high LDL cholesterol levels. Secondary participants are relatives who were cascade-screened because they are related to a primary participant with a pathogenic mutation.
FH = familial hypercholesterolemia; GHSP = General Health Screening Program; LDL = low density lipoprotein.

Variables

Data collection was conducted by trained physicians who used questionnaires to gather information on demographics, lifestyle factors such as smoking and alcohol consumption, medical history including hypertension, diabetes, dyslipidemia treatment, and CHD, and family history of CHD and stroke. Drinking status was classified into 3 categories: never drinker, former drinker, and current drinker. Similarly, smoking status was divided into never smoker, former smoker, and current smoker. Family history assessments included CHD occurrences in first-degree relatives of each participant. Participants were required to fast overnight and refrain from taking morning medication before sample collection.

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Venous blood samples were drawn between 8 AM and 10 AM and centrifuged 30 minutes post-collection. Venous samples were centrifuged at 30 minutes after collection. Analytical measurements included liver enzyme tests (aspartate transaminase, alanine transaminase, gamma-glutamyl transferase), creatinine, glucose, and lipid profiles (total cholesterol, triglyceride, HDL-C, LDL-C), which were performed using enzymatic methods on an automated chemical analyzer (model 7600; Hitachi Ltd., Tokyo, Japan). Participants also self-reported on the presence of xanthomas or xanthelasma, specifically noting any nodules on their elbows and heels, while physicians directly examined the face and hands. The clinical diagnosis of FH was based on the DLCN criteria. In cases where primary participants from the GHSP confirmed an LDL-C level of 190 mg/dL or higher, LDL-C values recorded below 190 mg/dL in the current study were adjusted to 190 mg/dL to maintain consistency in evaluation. The 95th percentile of low density lipoprotein (LDL) values in the general population was estimated from the 2021 Korea National Health and Nutrition Examination Survey, which is a representative nationwide dataset[15] (**Supplementary Table 3**).

Mutation detection and analysis

Genomic DNA was isolated from a peripheral blood sample using the QIAamp DNA Blood Mini Kit (Qiagen Inc., Chatsworth, CA, USA), following the manufacturer's instructions. The extracted DNA was measured using the Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA), and the DNA was subsequently diluted to a specific concentration of 10 ng/μL. The library preparation process was performed according to the CleanPlex® FH Panel (Paragon genomics, Fremont, CA, USA) Guide. The genes included in the panel are *PCSK9*, *APOB*, *LDLRAP1*, and *LDLR*, which are associated with FH. Polymerase chain reaction-based and purified indexed samples were diluted with PhiX control, pooled, and sequenced on the iseq100 sequencer (Illumina, Hayward, CA, USA).

Data analysis was performed using the DNA Amplicon workflow on the iSeq100 Reporter Software version 3.0.0.769 (Illumina), which incorporates the Burrows-Wheeler Aligner for read alignment against the GRCh37/hg19 reference genomes specified in the sample sheet. The Integrative Genomics Viewer version 2.13.2 was employed to assess the quality and variability of BAM and VCF files. Mutations were classified according to the 2015 the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines.[16] Additionally, the ClinGen Expert Panel consensus guidelines were used for classifying mutations in the *LDLR* gene.[17] Tools such as PolyPhen-2, SIFT, and MutationTaster were utilized to predict amino acid variations.[18-20] For secondary participants, variants in the probands' family trees were identified and analyzed using the Sanger method (ABI 3730XL DNA Analyzer) and confirmed through bioinformatics approaches including vector screening, BLASTN/X, and quality trimming with chromas.

Statistical analysis

In both primary and secondary participants, we compared characteristics based on the presence of pathogenic mutations. We employed the Mann-Whitney U test to assess differences in continuous variables, and Fisher's exact test to evaluate the distribution of categorical variables associated with pathogenic mutation status. We stratified medication status for dyslipidemia when analyzing the lipid profiles.

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RESULTS

Table 1 presents the characteristics of the primary participants, stratified by the presence or absence of pathogenic mutations. Of these, 7 participants (8.4%) have pathogenic mutations in the *PCSK9* and *LDLR* genes. Those with mutations exhibited higher total cholesterol and LDL-C levels compared to those without mutations, independent of dyslipidemia medication use. Additionally, the prevalence of a medical or family history of CHD was more common among participants with mutations. However, statistical differences in

Table 1. Characteristics of primary participants* according to pathogenic mutation status

Variables	Without pathogenic mutations	With pathogenic mutations	p value†
Participants	76 (91.6)	7 (8.4)	
Age (years)	50.6±6.8	49.0±6.3	0.470
Sex			0.254
Male	41 (53.9)	2 (28.6)	
Female	35 (46.1)	5 (71.4)	
Drinking status			0.471
Never drinker	25 (32.9)	4 (57.1)	
Former drinker	7 (9.2)	0 (0.0)	
Current drinker	44 (57.9)	3 (42.9)	
Smoking status			0.386
Never smoker	53 (69.7)	7 (100.0)	
Former smoker	17 (22.4)	0 (0.0)	
Current smoker	6 (7.9)	0 (0.0)	
Medical history of hypertension	7 (9.2)	1 (14.3)	0.522
Medical history of diabetes	4 (5.3)	0 (0.0)	1.000
Medication for dyslipidemia	38 (50.0)	2 (28.6)	0.435
Medical history of CHD	3 (3.9)	1 (14.3)	0.302
Family history of CHD‡	17 (22.4)	3 (42.9)	0.351
AST (U/L)	27.7±12.3	27.0±17.0	0.302
ALT (U/L)	29.6±22.1	21.3±11.1	0.342
GGT (U/L)	43.1±87.4	31.5±25.4	0.793
Creatinine (mg/dL)	1.2±1.5	0.9±0.1	0.082
Glucose(mg/dL)	99.2±11.4	96.7±6.8	0.876
Dyslipidemia medication naïve (n=43)			
Total cholesterol (mg/dL)	266±40	288±58	0.191
Triglyceride (mg/dL)	131±58	141±90	0.783
HDL (mg/dL)	54.6±13.7	50.0±7.8	0.663
LDL (mg/dL)§	183±36	209±41	0.085
Dyslipidemia medication use (n=40)			
Total cholesterol (mg/dL)	187±39	256±12	0.041
Triglyceride (mg/dL)	125±58	126±6	0.577
HDL (mg/dL)	56.2±10.4	59.9±7.9	0.555
LDL (mg/dL)§	113±33	176±20	0.051
Tendon/skin xanthoma	2 (2.6)	0 (0.0)	1.000
DLCN criteria			<0.001
Definite FH	-	7 (100)	
Probable FH	-	-	
Possible FH	76 (100)	-	
Unlikely FH	-	-	

Values are presented as mean±standard deviation or number (%).
ALT = alanine transaminase; AST = aspartate transaminase; CHD = coronary heart diseases; DLCN = Dutch lipid clinic network; FH = familial hypercholesterolemia; GGT = gamma-glutamyl transferase; HDL = high density lipoprotein; LDL = low density lipoprotein.
*Primary participants are individuals directly recruited from the GHSP due to high LDL-C levels (LDL-C≥190 mg/dL).
†The characteristics according to pathogenic mutation status were compared using Mann-Whitney U test and Fisher's exact test.
‡Family history of CHD included the medical history of first-degree relatives.
§LDL levels were significantly lower in participants on dyslipidemia medication compared to those not on the medication (p value<0.001).

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these characteristics were not significant, except for total cholesterol levels in participants treated for dyslipidemia. According to the DLCN criteria, participants without mutations were classified as "possible FH," whereas those with mutations were categorized as "definite FH.". In addition, LDL levels were significantly lower in participants receiving dyslipidemia medication compared to those not receiving the treatment (p value<0.001).

Table 2 outlines the characteristics of secondary participants, also divided by pathogenic mutation status. 11 secondary participants (61.1%) have pathogenic mutations. Creatinine and glucose were significantly lower in participants with mutations than without mutations. As with the primary participants, total cholesterol and LDL-C levels generally were higher

Table 2. Characteristics of secondary participants* according to pathogenic mutation status

Variables	Without pathogenic mutations	With pathogenic mutations	p value†
Participants	7 (38.9)	11 (61.1)	
Age (years)	55.3±29.3	35.5±21.4	0.191
Sex			0.145
Male	5 (71.4)	3 (27.3)	
Female	2 (28.6)	8 (72.7)	
Drinking status			0.751
Never drinker	2 (28.6)	3 (27.3)	
Former drinker	1 (14.3)	0 (0.0)	
Current drinker	4 (57.1)	8 (72.7)	
Smoking status			0.263
Never smoker	5 (71.4)	9 (81.8)	
Former smoker	2 (28.6)	0 (0.0)	
Current smoker	0 (0.0)	2 (18.2)	
Medical history of hypertension	1 (14.3)	0 (0.0)	0.389
Medical history of diabetes	1 (14.3)	1 (9.1)	>0.999
Medication for dyslipidemia	2 (28.6)	1 (9.1)	0.528
Medical history of CHD	2 (28.6)	0 (0.0)	0.137
Family history of CHD‡	0 (0.0)	4 (36.4)	0.119
AST (U/L)	25.3±4.8	23.1±10.4	0.103
ALT (U/L)	22.5±16.1	20.0±12.6	0.724
GGT (U/L)	22.9±8.7	20.3±19.9	0.211
Creatinine (mg/dL)	2.0±2.4	0.8±0.2	0.026
Glucose(mg/dL)	124.6±76.6	85.5±8.5	0.027
Dyslipidemia medication naïve (n=15)			
Total cholesterol (mg/dL)	120±8	153§	0.667
Triglyceride (mg/dL)	155±72	122§	1.000
HDL (mg/dL)	34.4±9.5	44.1§	0.667
LDL (mg/dL)‖	63±14	96§	0.667
Dyslipidemia medication use (n=3)			
Total cholesterol (mg/dL)	215±19	235±47	0.310
Triglyceride (mg/dL)	108±42	90±52	0.310
HDL (mg/dL)	60.1±12.3	61.3±12.3	0.768
LDL (mg/dL)‖	142±31	164±46	0.440
Tendon/skin xanthoma	0 (0.0)	0 (0.0)	1.000
DLCN criteria			<0.001
Definite FH	-	9 (81.8)	
Probable FH	-	2 (18.2)	
Possible FH	3 (42.9)	-	
Unlikely FH	4 (57.1)	-	

Values are presented as mean±standard deviation or number (%).
ALT = alanine transaminase; AST = aspartate transaminase; CHD = coronary heart diseases; DLCN = Dutch lipid clinic network; FH = familial hypercholesterolemia; GGT = gamma-glutamyl transferase; HDL = high density lipoprotein; LDL = low density lipoprotein.
*Secondary participants are relatives who were cascade-screened because they are related to a primary participant with a pathogenic mutation.
†The characteristics according to pathogenic mutation status were compared using Mann-Whitney U test and Fisher's exact test.
‡Family history of CHD included the medical history of first-degree relatives.
§Since only one subject with a pathogenic mutation was treated with DL medication, it was not possible to calculate the standard deviation.
‖LDL levels were significantly lower in participants on dyslipidemia medication compared to those not on the medication (p value=0.002).

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Table 3. The distribution of variants in *LDLR*, *PCSK9* in primary participants

Novel or known status	Sample No.	Gene	Nucleotide change	Amino acid change	PolyPhen-2	SIFT prediction	Mutation t@ster	Database
Known	F25	*LDLR*	c.1702C>G	Leu568Val	Probably damaging	Damaging	Deleterious	rs746959386
Known	F28	*LDLR*	c.1747C>T	His583Tyr	Probably damaging	Damaging	Deleterious	rs730882109
Known	F37	*LDLR*	c.190+1G>A	Splicing site donor			Deleterious	rs879254428
Known	F74	*LDLR*	c.361T>G	Cys121Gly	Probably damaging	Damaging	Deleterious	rs879254492
Known	F49, F51, F75	*PCSK9*	c.94G>A	Glu32Lys	Benign	Tolerated	Deleterious	rs564427867

in participants with mutations, irrespective of dyslipidemia medication status. Based on DLCN criteria, only 3 participants (42.9%) without mutations reached the threshold for a classification of "possible FH," whereas those with mutations were classified as either "probable FH" or "definite FH." In addition, LDL levels were significantly lower in participants receiving dyslipidemia medication compared to those not receiving the treatment (p value=0.002).

Supplementary Table 4 presents diagnoses established based on the DLCN criteria without DNA test confirmation for the 11 secondary participants identified with FH-associated pathogenic mutations. Among them, 7 participants (63.6%) were categorized as unlikely to have FH. The diagnostic classification according to the DLCN criteria for secondary participants was significantly different according to the usage of DNA test results (p<0.001).

Table 3 details the 5 variants in the *LDLR* and *PCSK9* genes identified in 7 primary participants. The variants identified as pathogenic and associated with FH according to the ClinGen database include 4 mutations in the *LDLR* gene (c.1702C>G, c.1747C>T, c.190+1G>A, c.361T>G) and one in the *PCSK9* gene (c.94G>A). All identified pathogenic variants had been previously reported to be associated with FH.

Figure 2 depicts the pedigree charts of 4 primary participants with mutations (F37, F51, F75, F74). Of the 25 relatives of probands contacted, 18 (72%) underwent genetic testing.

DISCUSSION

In this study, we introduced a screening system to identify FH among participants. We discovered that 8.4% of participants with severe hypercholesterolemia possessed 5 pathogenic mutations indicative of FH, which were found in the *PCSK9* and *LDLR* genes. Individuals with these mutations exhibited significantly higher levels of total cholesterol and LDL-C compared to those without the mutations. Moreover, the prevalence of FH mutations was significantly greater in participants undergoing cascade screening than in severe hypercholesterolemia patients identified in primary screening.

Our results indicated that 8.4% of primary participants with severe hypercholesterolemia, as confirmed through GHSP, were diagnosed with FH. This prevalence aligns with the global prevalence observed in populations with severe hypercholesterolemia (7.2%).[13] On the other hand, 11 (61.1%) secondary participants have pathogenic mutation, and the proportion of participants with FH associated mutation is higher in cascade screening than primary genetic screening in high-risk group (p value<0.001). Clinical diagnoses of FH, when not supported by cascade DNA testing, could lead to a significant underdiagnosis of pathogenic mutations. Among 11 secondary participants with pathogenic mutation, 7 participants (63.6%) were categorized according to DLCN as unlikely to have FH without DNA test result. Notably, 5

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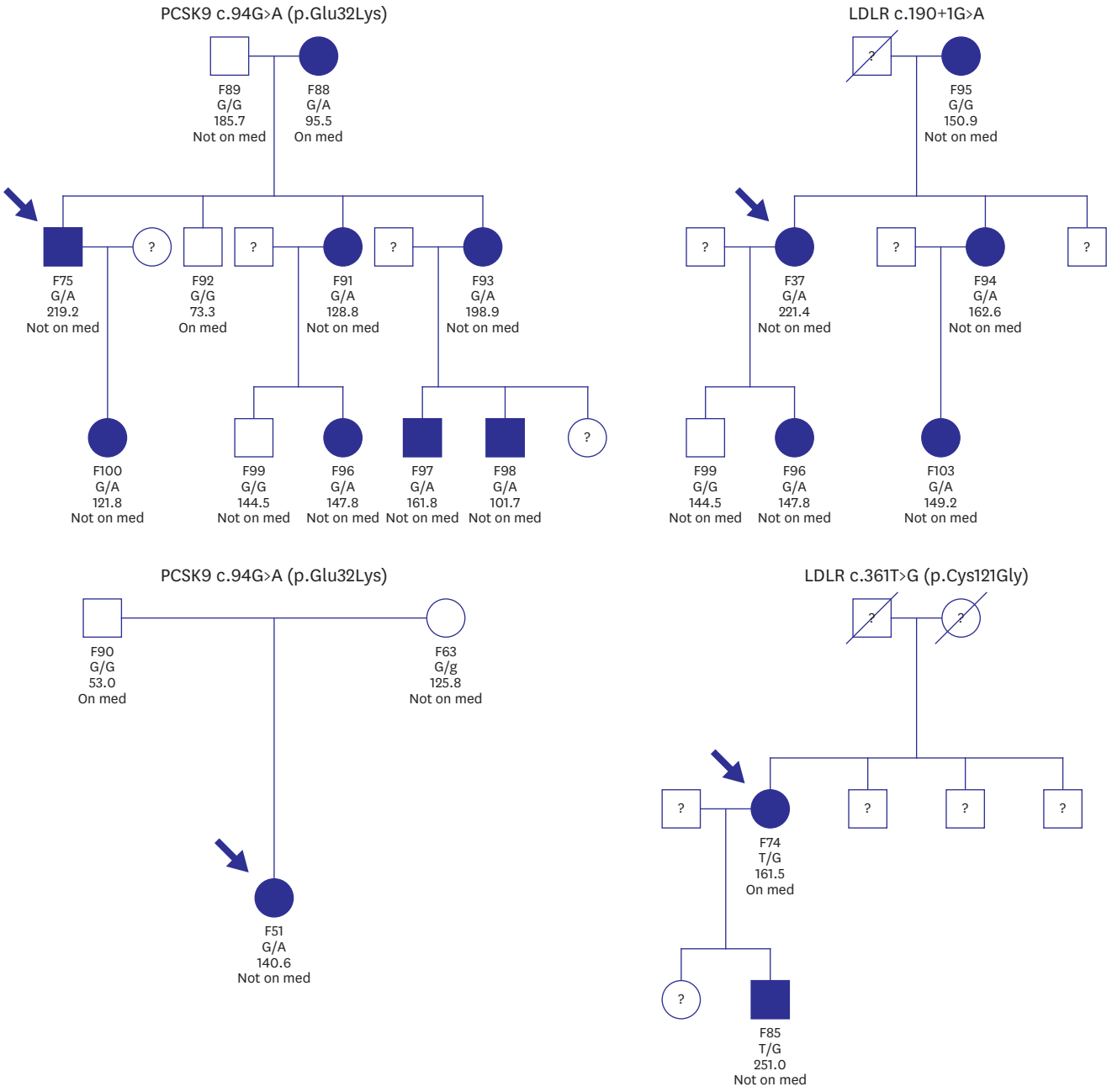

Figure 2. Pedigree chart of the family of 4 proband. The probands are indicated by arrowheads. Individuals with pathogenic mutation are indicated by filled symbols (square, male; circle, female). Individuals who did not conduct genetic testing are indicated by symbols with question mark. Genetic mutation of probands is indicated by title of each pedigree. Participants ID, genotypes and LDL levels, medication status for dyslipidemia are listed beside each symbol. LDL = low density lipoprotein.

of these were under the age of 30, which aligns with the fact that phenotypic expression in heterozygous FH is usually not apparent before the ages of 25 to 30.[21] Among the participants with pathogenic mutations, none had been previously diagnosed with FH or had undergone genetic mutation testing. Several studies reported the proportion of diagnosed FH as less than 1% to 10%.[4][22] Unfortunately, there was no study about the diagnosis rate of FH in Korea.

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Treatment rate for dyslipidemia in primary participants was quite low in the present analysis. 47.0% of primary participants was treated for dyslipidemia, and the rate is similar to the treatment rate of dyslipidemia in Korean general population reported in previous study.[23] This underscores the need for strategies to enhance the treatment rate for dyslipidemia. In addition, primary participants with pathogenic mutations tended to have lower treatment rates compared to participants without pathogenic mutations. Participants with pathogenic mutations tend to have higher LDL levels compared to those without such mutations. Consequently, these individuals may be more stringently managed by clinicians. Additionally, the rate of volunteering may be lower among participants with pathogenic mutations who are already undergoing dyslipidemia treatment.

Eight primary participants without pathogenic mutations were found to carry variants of uncertain significance in the *APOB* gene (rs13306206). Studies from Korea and Japan have identified an association between this variant and increased risks of dyslipidemia and CVDs.[24][25]

In this study, cascade screening was completed only partially within 4 of the 7 identified proband families. Among the 3 remaining probands, one was hesitant to inform relatives about the potential for a genetic mutation, citing personal and familial sensitivities. The other 2 probands were willing to participate in the cascade screening program, but the geographical distance of their family members posed a challenge. Previous studies have highlighted several barriers to effective cascade screening for genetic conditions, including demographic factors, knowledge gaps, and attitudes.[26] In clinical settings, it is essential to address these barriers through targeted interventions such as patient and family education and the establishment of multicenter screening programs, which can mitigate the issues posed by geographical inaccessibility to genetic testing services.

We propose a 3-step FH cascade screening system, as implemented in our study. In the first step, the general population was screened under the GHSP, and individuals with severe hypercholesterolemia were identified. In the second step, these individuals underwent genetic testing. In the final step, relatives of patients carrying pathogenic mutations were tested through cascade screening. The overview of the screening system is depicted in **Figure 3**. This system

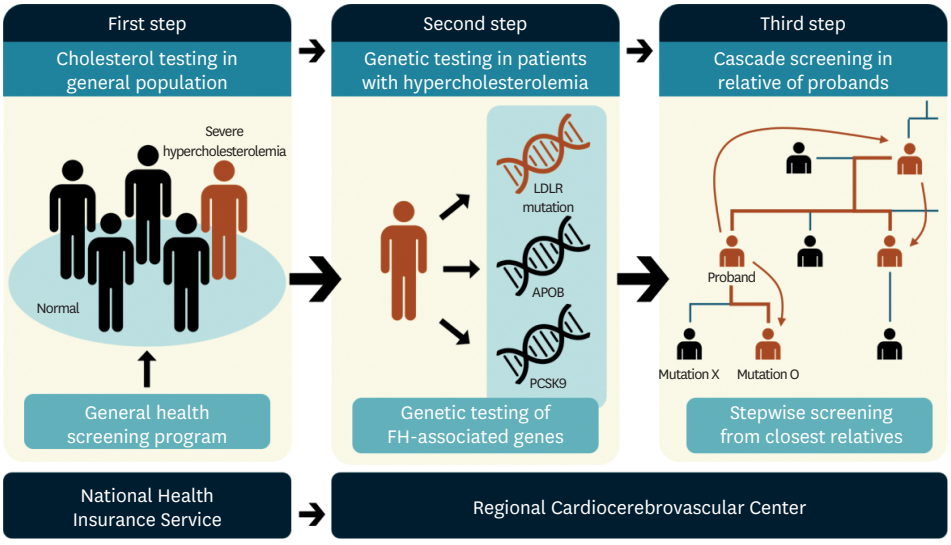

Figure 3. Three-step cascade screening system of familial hypercholesterolemia.
FH = familial hypercholesterolemia.

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was established in partnership with local healthcare resources. Recruitment of participants was facilitated through the regional National Health Insurance Service Center using data from the GHSP. Additionally, participant data collection, genetic testing, cascade screening, and patient education on dyslipidemia were supported by the Regional Cardiocerebrovascular Center. Leveraging regional resources to construct a screening approach, without the need for additional lipid profile screenings, enhances both the effectiveness and efficiency of the process.

The present study has several notable limitations. First, the enrollment criteria for primary participants might introduce selection bias, as they were volunteers with severe hypercholesterolemia diagnosed by GHSP. However, the high participation rate in GHSP in the general population potentially mitigated the bias. Second, the screening framework employed, which relies on detecting pathogenic mutations, may fail to identify cases of polygenic FH. Since polygenic FH does not exhibit a classic autosomal dominant inheritance pattern, our current cascade screening framework might be insufficient to detect such cases, suggesting the need for a new approach to effectively include polygenic FH cases.[22] Third, the LDL-C threshold (≥190 mg/dL) used for screening in this study was chosen and may exclude participants already undergoing dyslipidemia treatment who potentially have FH. This study does not claim that an LDL-C level of ≥190 mg/dL is the optimal criterion for screening participant selection. Future research should investigate the diagnostic yield and cost-effectiveness of early FH diagnosis using this or other criteria. Fourth, the observed difference in pathogenic mutation prevalence between primary and secondary participants provides only an indirect assessment of DNA test effectiveness in cascade screening. Further studies, such as community trials, are needed to evaluate the screening system's effectiveness. Given that FH clinical criteria include a family history of hypercholesterolemia and that diagnoses tend to be underreported due to less apparent clinical symptoms in younger individuals, the family history remains essential for diagnosis, underscoring the importance of cascade screening. Fifth, xanthoma assessment may not have been conducted adequately. In this study, xanthoma assessment may have been inadequate, as it relied on self-reported nodules on elbows and heels. The lower prevalence of xanthomas in this study compared to previous report (30% to 50% of heterozygous FH patients)[27] may result from a lack of awareness and the selection of asymptomatic patients. Further studies involving thorough examinations of xanthoma are necessary to refine the screening program for detecting polygenic FH using clinical criteria. Finally, clinical conditions associated with secondary hypercholesterolemia, such as kidney and liver diseases, were not assessed during recruitment.

This paper highlights several strengths. Cascade screening for FH is widely acknowledged for its ability to detect the condition, yet no studies in Korea have previously investigated this method or evaluated its efficacy quantitatively. Unlike typical single-center studies, this research employed a national lipid screening program to identify individuals at high risk for genetic testing. This approach not only fills a significant research gap but also demonstrates an initiative to incorporate cascade screening into existing healthcare systems.

In conclusion, we advocate for the implementation of the FH screening system utilizing regional healthcare resources in Korea. This comprehensive strategy facilitates the assessment of familial risk and enhances the potential for early detection and intervention in affected families.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Simon Broome criteria for clinical diagnosis of familial hypercholesterolemia

Supplementary Table 2

DLCN criteria for clinical diagnosis of familial hypercholesterolemia

Supplementary Table 3

The 95 percentiles of LDL-C levels according to age and sex

Supplementary Table 4

Clinical diagnosis of FH in secondary participants* with pathogenic mutations (n=11) based on DLCN criteria, with and without incorporation of DNA test results

REFERENCES

1. Authors/Task Force MembersESC Committee for Practice Guidelines (CPG)ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis* 2019;290:140-205. PUBMED | CROSSREF
2. Lee CJ, Yoon M, Kang HJ, et al. 2022 Consensus statement on the management of familial hypercholesterolemia in Korea. *Korean J Med* 2022;97:339-52. CROSSREF
3. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;303:893-6. PUBMED | CROSSREF
4. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478-90. PUBMED | CROSSREF
5. Tandirerung FJ. The clinical importance of differentiating monogenic familial hypercholesterolemia from polygenic hypercholesterolemia. *Curr Cardiol Rep* 2022;24:1669-77. PUBMED | CROSSREF
6. Medeiros AM, Bourbon M. Genetic testing in familial hypercholesterolemia: is it for everyone? *Curr Atheroscler Rep* 2023;25:127-32. PUBMED | CROSSREF
7. National Institute for Health and Care Excellence. *Familial hypercholesterolaemia: identification and management*. London: National Institute for Health and Care Excellence; 2019.
8. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88. PUBMED | CROSSREF
9. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:3168-209. PUBMED | CROSSREF
10. Kim HN, Kweon SS, Shin MH. Detection of familial hypercholesterolemia using next generation sequencing in two population-based cohorts. *Chonnam Med J* 2018;54:31-5. PUBMED | CROSSREF
11. Alonso R, Perez de Isla L, Muñiz-Grijalvo O, Mata P. Barriers to early diagnosis and treatment of familial hypercholesterolemia: current perspectives on improving patient care. *Vasc Health Risk Manag* 2020;16:11-25. PUBMED | CROSSREF

12. Shin DW, Cho J, Park JH, Cho B. National general health screening program in Korea: history, current status, and future direction. *Precis Future Med* 2022;6:9-31. CROSSREF
13. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol* 2020;75:2553-66. PUBMED | CROSSREF
14. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA* 2017;318:381-2. PUBMED | CROSSREF
15. Oh K, Kim Y, Kweon S, et al. Korea National Health and Nutrition Examination Survey, 20th anniversary: accomplishments and future directions. *Epidemiol Health* 2021;43:e2021025. PUBMED | CROSSREF
16. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-24. PUBMED | CROSSREF
17. Chora JR, Iacocca MA, Tichý L, et al. The clinical genome resource (ClinGen) familial hypercholesterolemia variant curation expert panel consensus guidelines for LDLR variant classification. *Genet Med* 2022;24:293-306. PUBMED | CROSSREF
18. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods* 2010;7:248-9. PUBMED | CROSSREF
19. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc* 2009;4:1073-81. PUBMED | CROSSREF
20. Schwarz JM, Rödelsperger C, Schuelke M, Seelow D. MutationTaster evaluates disease-causing potential of sequence alterations. *Nat Methods* 2010;7:575-6. PUBMED | CROSSREF
21. Marais AD. Familial hypercholesterolaemia. *Clin Biochem Rev* 2004;25:49-68. PUBMED
22. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc* 2019;8:e013225. PUBMED | CROSSREF
23. Jin ES, Shim JS, Kim SE, et al. Dyslipidemia fact sheet in South Korea, 2022. *J Lipid Atheroscler* 2023;12:237-51. PUBMED | CROSSREF
24. Koyama S, Ito K, Terao C, et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. *Nat Genet* 2020;52:1169-77. PUBMED | CROSSREF
25. Moon S, Kim YJ, Han S, et al. The Korea biobank array: design and identification of coding variants associated with blood biochemical traits. *Sci Rep* 2019;9:1382. PUBMED | CROSSREF
26. Srinivasan S, Won NY, Dotson WD, Wright ST, Roberts MC. Barriers and facilitators for cascade testing in genetic conditions: a systematic review. *Eur J Hum Genet* 2020;28:1631-44. PUBMED | CROSSREF
27. Civeira F, Castillo S, Alonso R, et al. Tendon xanthomas in familial hypercholesterolemia are associated with cardiovascular risk independently of the low-density lipoprotein receptor gene mutation. *Arterioscler Thromb Vasc Biol* 2005;25:1960-5. PUBMED | CROSSREF