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Review

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Individualized Treatment for Patients With Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia (FH) is one of the most common and, therefore, important inherited disorders in preventive cardiology. This disease is mainly caused by a single pathogenic mutation in the low-density lipoprotein receptor or its associated genes. Moreover, it is correlated with a high risk of cardiovascular disease. However, the phenotype severity even in this monogenic disease significantly varies. Thus, the current study aimed to describe FH and its importance and the factors (inherited and acquired) contributing to differences in phenotype severity. Different lipid-modification therapies according to these factors can lead to individualized treatments, which are also essential in the general populations.

Keywords: Hyperlipoproteinemia type II; LDL receptors; Cardiovascular diseases

INTRODUCTION

Familial hypercholesterolemia (FH) is characterized by the clinical triad of primary low-density lipoprotein (LDL) hypercholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD).[1] This disease is mainly caused by pathogenic mutations in genes. These include the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and LDL receptor adaptor protein 1 (*LDLRAP1*), which are associated with LDL metabolism.[2] Based on the number of pathogenic FH mutation, FH is classified into heterozygous FH (HeFH) with a single FH mutation and homozygous FH (HoFH) caused by mutations of both copies of FH genes.[3] The LDL cholesterol level in HeFH is about two times higher, and that in HoFH is four times higher than that of the general population.[1] Thus, patients with HoFH exhibit more severe phenotypes than those with HeFH. However, the phenotype severity is significantly diverse even among patients with HeFH.[4-7] This difference is attributed to several factors, which include inherited and acquired ones. The risk for CAD must be determined because of their extremely high risk at the first place. Now that there are different lipid-modification therapies, including the use of statins, ezetimibe, PCSK9 inhibitor, bempedoic acid, lomitapide, and evinacumab,[8-15] the risk for CAD on top of FH should be determined in this personalized medicine era.[16] Therefore, the current understanding of the different types of FH and the importance of genetic analysis for not only their diagnosis but also further risk stratification were discussed.

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FH AND DEVELOPMENT OF CORONARY ATHEROSCLEROSIS

FH was initially described as xanthomatous disease and first documented approximately 100 years ago.[17] In the 1903s, physicians and researchers discovered that it is an inherited disease.[18] Since then, it was characterized by the clinical triad of primary LDL hypercholesterolemia, tendon xanthomas, and premature CAD. Further, in the 1970s, Brown and Goldstein discovered that it was primarily caused by genetic abnormalities in *LDLR*.[1] More recently, studies have found that it was correlated with *LDLR*-associated genes including *APOB*, *LDLRAP1*, and *PCSK9*.[2,19-22] Its prevalence in the general population is approximately 1 per 500 persons.[23] However, another study showed that its prevalence was as high as 1 per 208 person based on genetic studies conducted in Hokuriku district in Japan.[24] Based on reports published after ours, the prevalence of FH in the general population in the United States and Europe is similar.[25,26] Recent meta-analyses have revealed that its prevalence rates are around 1 per 300 person in the general population, 1 per 31 among patients with CAD, and 1 per 15 among patients with premature CAD.[27,28]

Interestingly, this disorder uniquely exemplifies the causal association between LDL cholesterol and CAD because of the following facts: 1) patients with FH who have hypercholesterolemia since birth have a significantly higher risk for CAD than the general populations and their siblings who do not have mutations,[29] 2) the use of LDL cholesterol-lowering method can reduce the risk of CAD,[30] 3) The most frequent cause of death at earlier ages compared with non-FH among patients with untreated FH is CAD (**Fig. 1**),[1] and 4) FH accounts for 3%–8% of all patients with acute coronary syndrome.[31-33]

In 1970, Brown and Goldstein described the role of *LDLR* in LDL metabolism, and results showed that FH could be caused by a defect in this gene. Since its discovery, along with the development and standardization of genetic analysis, several different pathogenic mutations have been identified,[34-36] which include those in the *APOB* and *PCSK9* genes. Based on this concept, only one monogenic mutation causes the critical phenotype. Thus, both cascade screening and the assessment of segregation pattern are important. However, in a substantial proportion of patients with FH, no deleterious mutation in such genes has been found.[37,38] Therefore, researchers have been assessing one or more novel genes associated with this disorder via comprehensive genetic analyses, including exome sequencing.[39] However, there was no novel gene compatible with the concept of the monogenic type of FH, which

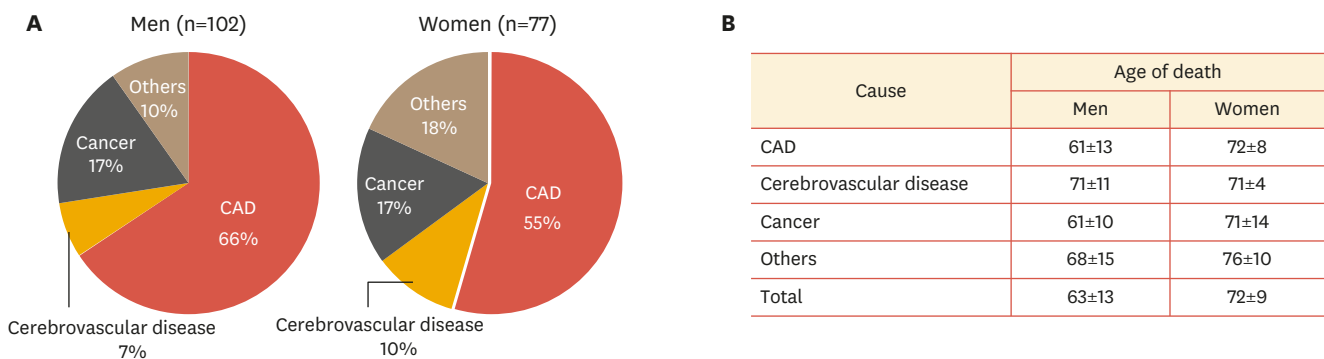| Cause	Age of death	
	Men	Women
CAD	61±13	72±8
Cerebrovascular disease	71±11	71±4
Cancer	61±10	71±14
Others	68±15	76±10
Total	63±13	72±9

Fig. 1. Cause of death and average life span of patients with HeFH.
(A) Cause of death. (B) Average life span.
HeFH, heterozygous familial hypercholesterolemia; CAD, coronary artery disease.

is the standard type of FH, and the presence of pathogenic mutation in FH-gene has been associated with a higher risk of CAD, independent of LDL cholesterol level.[40] Moreover, the presence of pathogenic mutation in FH-gene increased the risk of developing CAD in people other than those with FH, which include those with a family history of premature CAD/FH and Achilles tendon thickness.[41] Collectively, these data indicate that the identification of monogenic FH could be quite useful for not only diagnosis but also further risk stratification.

PHENOTYPIC VARIATIONS OF FH AND SEVERE FH

FH is associated with an extremely high risk for CAD. However, there are substantial phenotypic variations in this simple familiar disorder. Some patients with FH present with severe CAD during early life. Meanwhile, other patients do not. In fact, there are several different types of clinical criteria for FH worldwide, which include the Dutch Lipid Clinic Network,[42] Simon Broome,[43] and Japan Atherosclerosis Society.[44] However, none of these specifically defined severe FH. Under these circumstances, the International Atherosclerosis Society defines severe familial hypercholesterolemia and the implications for clinical management in 2016.[45] Several factors can contribute to such phenotypic variations, or severity. These include the classical risk factors of coronary atherosclerosis, such as hypertension, diabetes, and smoking, which are not specific to FH. By contrast, the factors specific to FH associated with a more severe phenotype, such as Achilles tendon thickness and the presence of pathogenic mutation in FH-gene, should be identified.

PHENOTYPIC VARIATIONS OF FH

1. Achilles tendon thickness

There are several clinical factors correlated with the phenotypic severity of FH. For example, Achilles tendon thickness, which is quite a specific physical finding of FH, is associated with worse clinical outcomes among patients with extremely elevated LDL cholesterol levels.[46] This phenomenon may be attributed to the fact that Achilles tendon thickness reflects not only the state of FH but also exposure to more elevated LDL cholesterol levels with inflammatory properties. Moreover, it is positively associated with aging only among patients with FH,[47,48] and the association between Achilles tendon thickness and cholesterol year score is stronger than that of Achilles tendon thickness and simple aging.[49] Collectively, these data indicate that patients with FH should be diagnosed before the occurrence of Achilles tendon thicken, even though this is one of the major diagnostic criteria of the disease. In addition to these specific physical findings, we showed that the presence of pathogenic mutation in FH-gene (e.g., *LDLR* and *PCSK9*) was significantly associated with a higher risk for CAD, independent of other conventional risk factors (**Fig. 2**). This likely reflects the fact that patients with FH mutation have true FH, and their LDL cholesterol level have been elevated since the fetal period.[50]

2. Assessment of coronary and carotid plaque in FH

Currently, we can assess the plaque burden of coronary artery invasively and less invasively. For example, intravascular ultrasonography (IVUS) has been a useful tool for assessing coronary artery plaque burden for not only patients with FH but also the non-FH general populations.[51] A larger plaque burden has been associated with worse clinical outcomes.[52] Thus, the assessment of plaque burden quantitatively may be a useful marker for risk stratification in
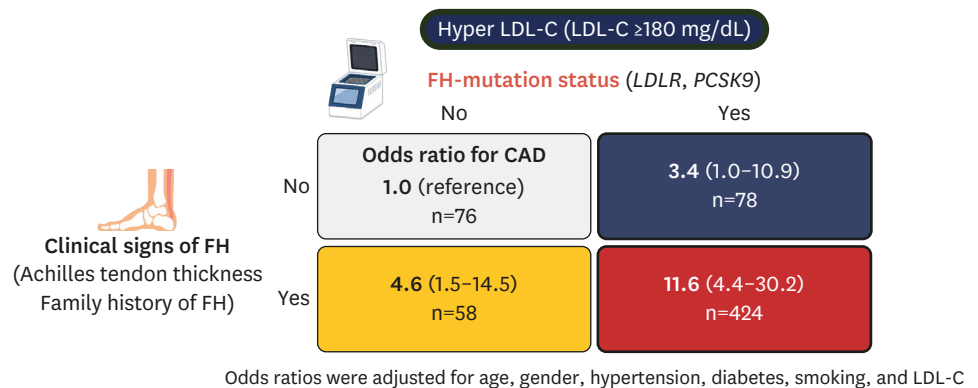
Fig. 2. Odds ratio for CAD.
Patients with hyper-LDL cholesterol levels (≥180 mg/dL) were divided into four groups based on the presence of pathogenic mutation in FH-gene and the clinical signs of FH.
CAD, coronary artery disease; LDL, low-density lipoprotein; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; *LDLR*, LDL receptor; *PCSK9*, proprotein convertase subtilisin/kexin type 9.

patients with FH. Moreover, we can assess coronary plaque burden via computed tomography (CT) scan, which is a less invasive procedure. Coronary plaque burden assessed with CT scan were significantly associated with future cardiovascular events in FH.[53] In addition to the assessments or coronary plaque burden, CT scan can be performed to assess coronary and aortic calcification quantitatively, which is also associated with future cardiovascular events.[54-56] Moreover, we can now assess other important characteristics of coronary plaque, such as the presence of lipid-rich plaque and thin-cap fibroatheroma, using optical coherence tomography.[57,58] Both of them have been associated with worse clinical outcomes.

By contrast, we can assess their state of atherosclerosis non-invasively via carotid ultrasonography. It is quite helpful for this purpose because 1) it can be used to assess plaque burden in pediatric patients with FH, 2) plaque burden can be evaluated quantitatively, and 3) carotid plaque burden is associated with future cardiovascular events in patients with FH.[59] Using these modalities, we showed that carotid plaque may start to develop at the age of 17 years in men and 26 years in women.[59] Moreover, coronary plaque is commonly observed at an average age of 23 years in men and 34 years in women.[60] Hence, individuals with FH must be diagnosed before those ages.

FACTORS CONTRIBUTING TO THE PHENOTYPIC VARIATIONS OF FH

1. Conventional and FH-specific factors associated with atherosclerosis

Other studies and ours have revealed that conventional risk factors for coronary atherosclerosis, such as hypertension, diabetes, and smoking, are also associated with disease severity even among patients with FH.[61-63] Some reports have shown that lipoprotein (a) (Lp[a]) can exacerbate the phenotype.[64,65] Notably, patients with FH have elevated Lp(a) levels,[66] indicating that LDLR may be involved in the catabolism of Lp(a). All these factors are not specific to FH but are applicable to the general populations.

2. Timing of the initial therapy (cascade vs. proband)

With consideration of FH phenotype severity, the timing of diagnosis is quite important, and this might also be applicable in other cardio metabolic inherited diseases. For example,

almost all patients with pediatric HeFH are asymptomatic, except for those with hyper-LDL cholesterolemia.[67] Meanwhile, adult patients with HeFH are gradually developing carotid and coronary atherosclerosis (**Fig. 3**).[59,60] Moreover, early diagnosis and LDL-lowering therapy at childhood can prevent atherosclerotic cardiovascular disease (ASCVD) events.[68] In addition, in our study, we managed brothers with compound heterozygous FH. That is, the older brother who was initially treated at the age of 23 years exhibited repeated coronary events. Meanwhile, the younger brother who has been receiving treatment since the age of 15 years had been event-free for a long period, despite having similar LDL cholesterol levels caused by the same mutations (NM_000527.4 [LDLR]:c.2054C>T [p.Pro685Leu]/ NM_000527.4[LDLR]:c.2431A>T [p.Lys811Ter]) (**Fig. 4**).[69] The phenotypic difference between them clearly indicate that early intervention for LDL cholesterol can be quite beneficial even for extremely worse cases. In fact, we have shown that Achilles tendon thickness in HeFH was significantly associated with age.[41] In addition, it is correlated with phenotypic severity.[41] Accordingly, diagnosing patients with FH prior to Achilles tendon thickening may be quite beneficial to prevent ASCVD events.

In order to identify patients with FH at early phase of this disorder, there are two major methods that can effectively identify patients with FH. First is the universal screening at a certain age, which is a proposed screening method for FH.[70,71] Second is the cascade screening for FH, which has been recommended by several organizations worldwide.[72,73] In countries
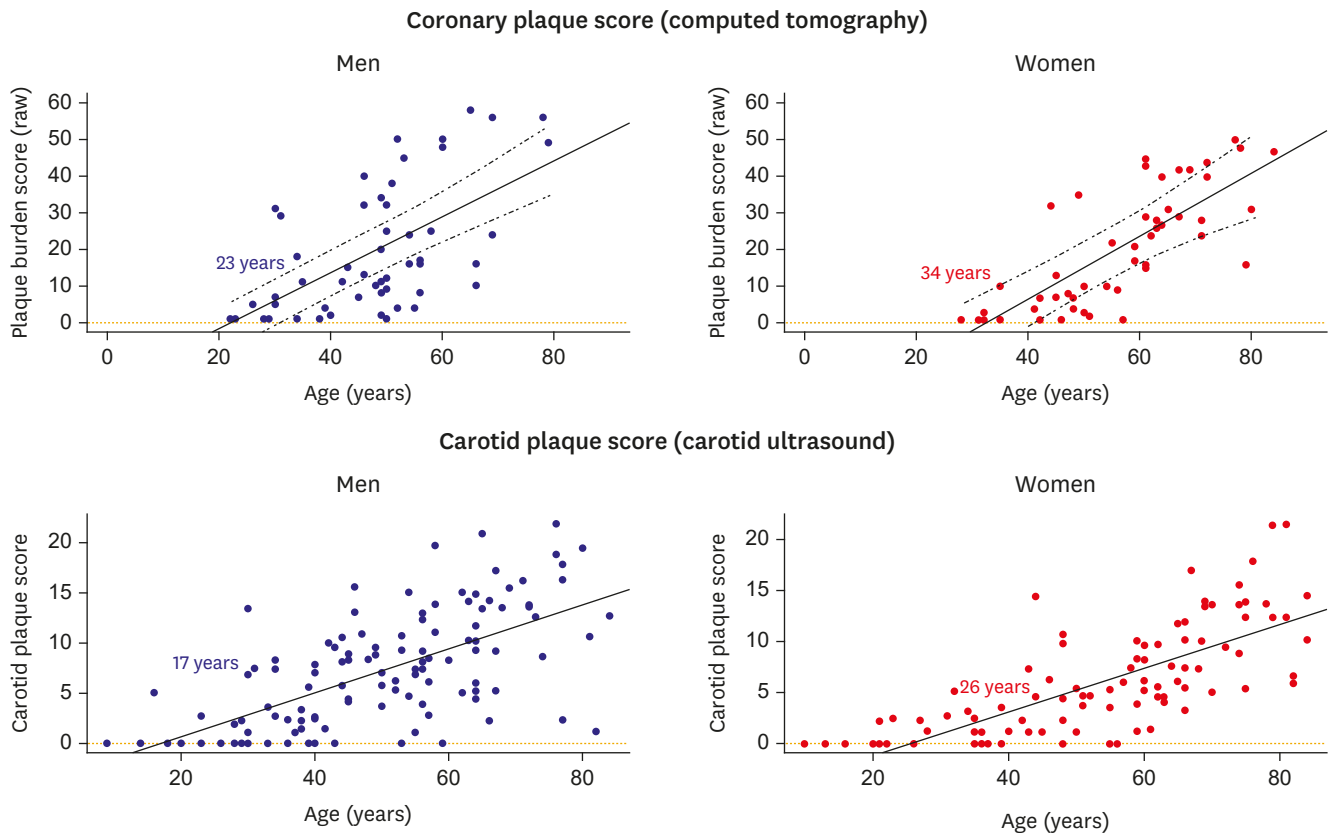

Fig. 3. Coronary and carotid plaque score assessed via computed tomography scan or carotid ultrasonography.
Upper panel indicates coronary plaque score. The X-axis represents age and the Y-axis represents coronary plaque score. The blue section indicates men; the red section, women. Lower panel indicates carotid plaque score. The X-axis represents age and the Y-axis represents carotid plaque score. The blue section indicates men, the red section, women.
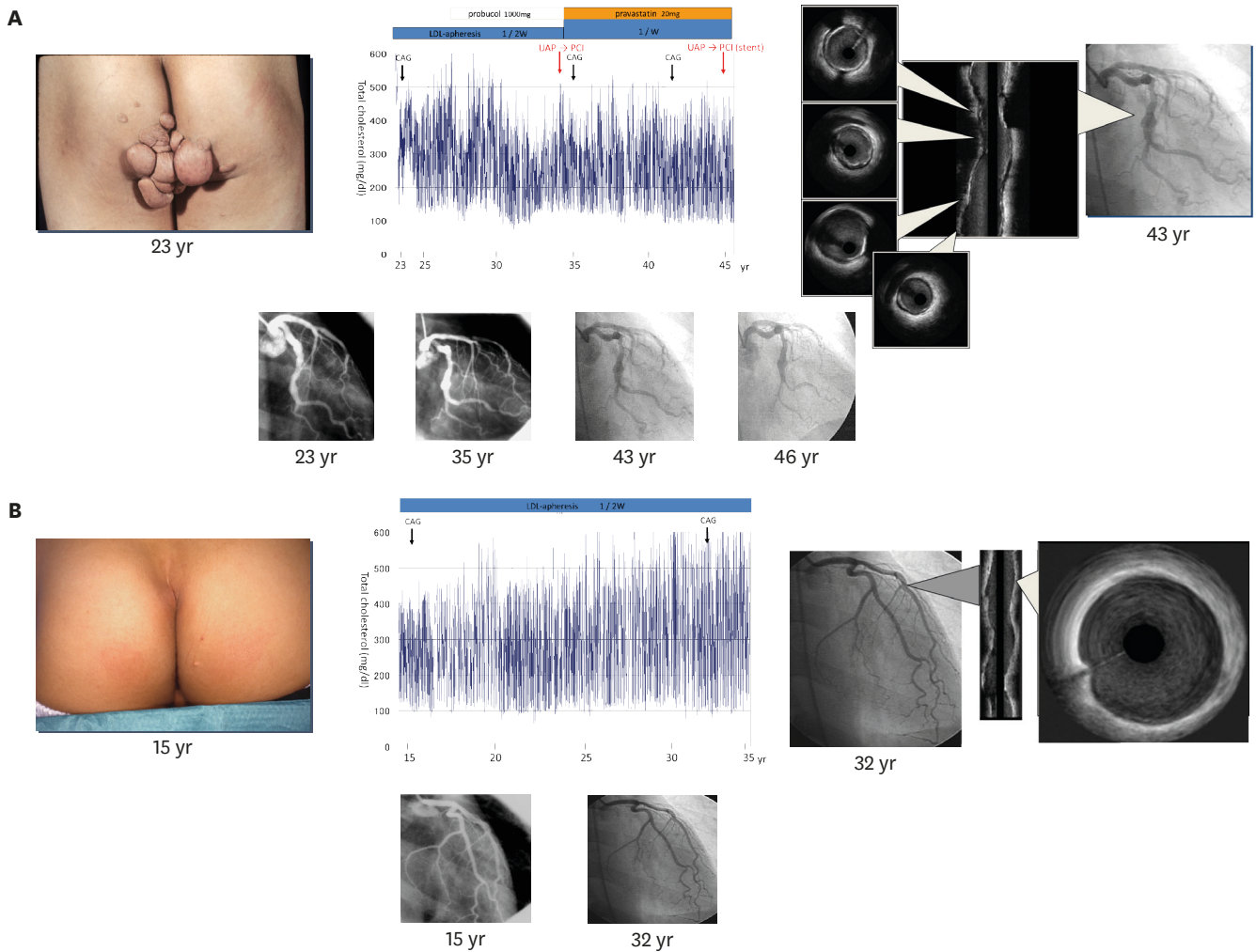
Fig. 4. Clinical course of brothers with compound heterozygous FH.
(A) Clinical course of the older brother: Image of the buttocks with a large xanthoma is shown in the left image. The clinical course is depicted in the middle image. The blue section indicates total cholesterol levels (mg/dL). Images obtained via intravascular ultrasonography are shown in the right images. (B) Clinical course of the younger brother: Image of the buttocks with a small xanthoma is shown in the left image. The clinical course is depicted in the middle image. The blue section indicates total cholesterol levels (mg/dL). Images obtained via intravascular ultrasonography are shown in the right images.
UAP, unstable angina pectoris; CAG, coronary angiogram; PCI, percutaneous coronary intervention.

where dedicated cascade screening programs have been implemented, the number of patients with FH is significantly higher. For example, about 71% and 43% of patients were diagnosed with FH in the Netherlands and Norway, respectively.[74] In any case, we strongly recommend to identify as many patients with FH. Then, early treatment should be started if possible.

3. Cholesterol year score

In recent years, the accumulation of exposure to cholesterol for a long period has been proposed to contribute the development of coronary atherosclerosis, and this considered an important concept.[74] This is an idea based on the fact that LDL cholesterol is the causal factor for coronary atherosclerosis, and this concept is likely to explain the development of coronary atherosclerosis in HeFH and HoFH, including attenuation by LDL-lowering therapies. Typically, cholesterol-year-score is calculated as: LDL Cholesterol Max × (Age at Diagnosis/Statin Initiation) + LDL Cholesterol at Inclusion × (Age at Inclusion − Age at

Diagnosis/Statin Initiation). In fact, we have shown that a cholesterol year score representing the accumulation of exposure to LDL cholesterol in HeFH is significantly associated with major cardiovascular events beyond their cross-sectional LDL cholesterol levels.[49] In addition, it was significantly correlated with Achilles tendon thickness in HeFH, which was one of the established clinical signs of severe FH.[49] Collectively, these data indicated that we need to the degree and duration of exposure to elevated LDL cholesterol.

4. Genetic backgrounds of FH (LDLR, PCSK9 E32K)

About 2,000 different types of mutations causes FH in *LDLR* alone.[75] Even in Japan, we have shown that at least 132 different pathogenic mutations exist, and it is likely that there are several region-specific and/or private mutations across the country (**Fig. 5**) and worldwide.[76,77] Based on the abovementioned information, the presence of pathogenic mutation in FH-gene (*LDLR* or *PCSK9*) is associated with a higher risk for CAD.[41] However, accumulating evidence has shown differences in the effect of mutations (and their phenotypes) on LDL cholesterol levels among the different types of FH mutations. For example, the LDL cholesterol level of patients with HeFH caused by E32K (*PCSK9*) was lower than that in patients with HeFH caused by K811X (*LDLR*) (**Fig. 6**). Moreover, some studies have shown that there are significant differences in phenotypes (LDL cholesterol and coronary atherosclerosis) among the different types of mutations in *LDLR*, such as missense mutations and loss-of function mutations, including nonsense, frameshift, splice cite, and large insertion/deletion mutations.[78] Thus, information regarding the pathogenicity of the genetic variations in FH must be further collected, and they can be classified according to their effects on LDL cholesterol and CAD.
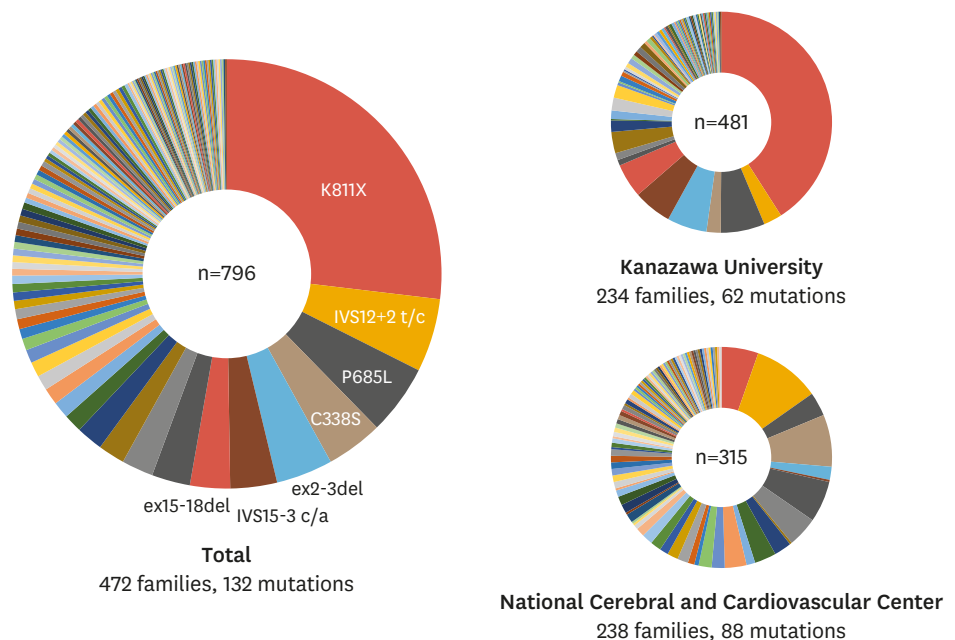

Fig. 5. Pathogenic mutations in the *LDLR* gene found in Japanese patients with familial hypercholesterolemia. The left pie chart shows the total mutation distribution. The right upper pie chart indicates the mutation distribution found in Kanazawa University. The right lower pie chart depicts the mutation distribution found in the National Cerebral and Cardiovascular Center.
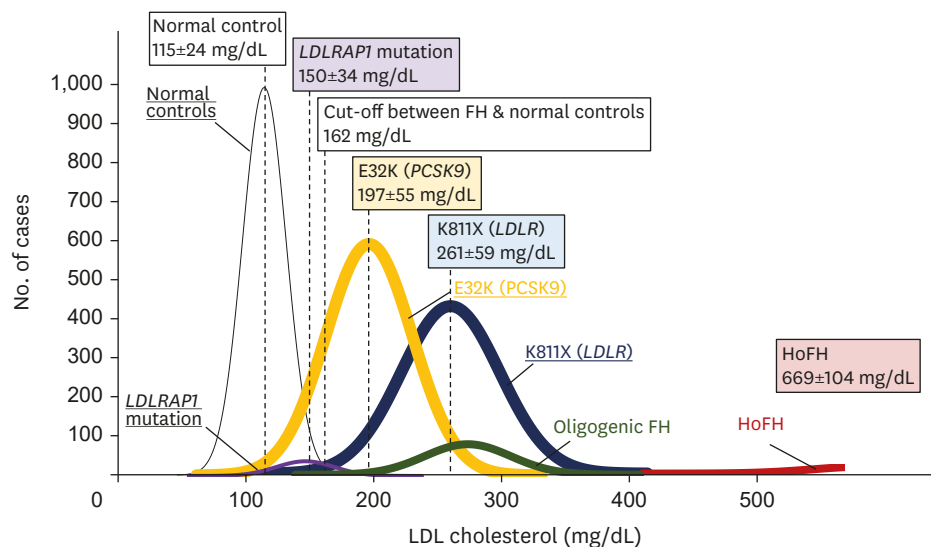*LDLR*, low-density lipoprotein receptor

Fig. 6. LDL cholesterol level distribution according to mutation status.
The X-axis represents LDL cholesterol levels (mg/dL); the Y-axis, the number of cases. The black section indicates normal controls (without FH mutation); purple, patients with a *LDLRAP1* mutation; yellow, patients with E32K (*PCSK9*) mutation; blue, patients with K811X (*LDLR*) mutation; green, patients with oligogenic FH; and red, HoFH.
LDL, low-density lipoprotein; FH, familial hypercholesterolemia; *LDLRAP1*, LDL receptor adapter protein 1; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *LDLR*, LDL receptor; HoFH, homozygous FH.

5. Monogenic, polygenic, and oligogenic FH

In addition to the so-called FH mutation, there are other classifications among patients with FH according to genetic backgrounds. One is monogenic FH, which is a conventional concept in which one rare deleterious pathogenic mutation causes an FH phenotype. However, Talmud et al. have discussed about polygenic FH, which is another interesting concept in which multiple common genetic variations can mimic FH phenotype.[79] There may be substantial proportions of such patients[80] simply because some individuals have millions of common genetic variations. However, their phenotypes are milder than those of the typical monogenic FH.[81,82] By contrast, at least a portion of patients with monogenic FH also have rare and deleterious mutation(s) in the LDL-related genes, such as ATP-binding cassette sub-family G member 5 (*ABCG5*) and ATP-binding cassette sub-family G member 8 (*ABCG8*), leading to the exacerbation of their phenotype (**Fig. 7**).[83] This is referred to as oligogenic FH. In fact, oligogenic FH is an unique status accompanied by mutations in related genes along with conventional FH gene mutations. *ABCG5* and *ABCG8* are cause sitosterolemia, which is a recessive disorder.[84] The effect size of *ABCG5* mutation may be smaller than that of *LDLR* mutation. Moreover, a single rare mutation in both genes can increase LDL cholesterol levels and the risk of CAD.[85] Notably, the development of CAD can be explained by the high LDL cholesterol levels as they are linearly correlated.

6. Homozygous FH and its phenocopies

Homozygous FH is the most severe FH phenotype. Further, it is characterized by an extremely elevated LDL cholesterol level (>500 mg/dL), cutaneous xanthomas since childhood, premature CAD during childhood, and supravalvular aortic stenosis.[3] Typically, homozygous FH refers to double pathogenic mutations in the FH genes (*LDLR*, *PCSK9*, *APOB*, or *LDLRAP1*). The severity of this condition can be assessed based on genes and/or mutation types. For example, the phenotypes of homozygous FH caused by loss-of-function mutations in *LDLR* are more severe than those caused by missense mutations in *LDLR*, *PCSK9*, or *APOB*. In
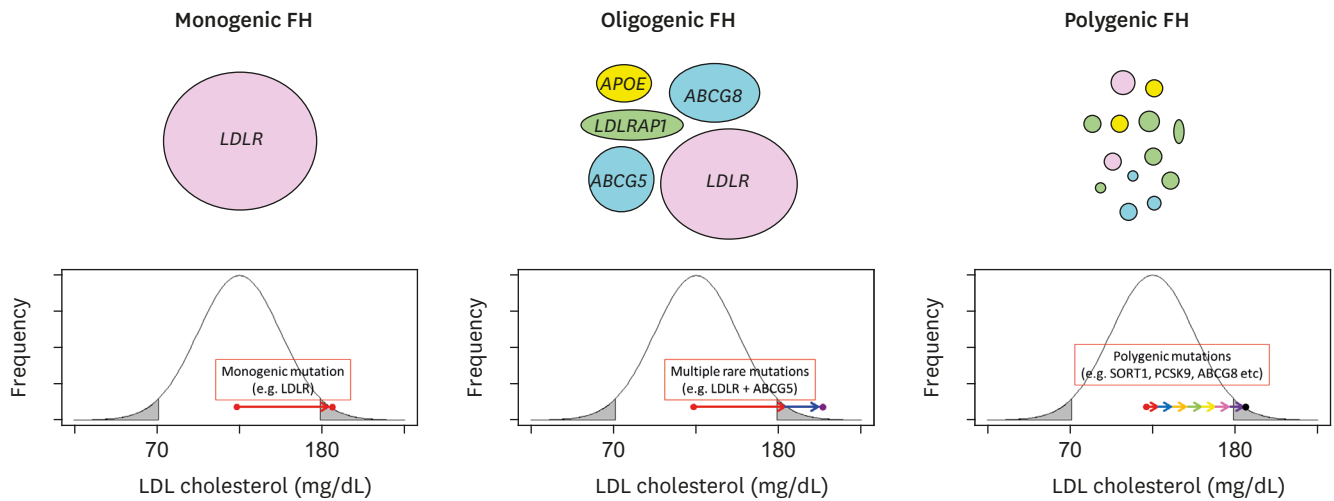
Fig. 7. Concept of monogenic, polygenic, and oligogenic FH.
Upper panel: The circles indicate the effect on the phenotype. Lower panel: The X-axis represents LDL cholesterol level; the Y-axis, the incidence of FH in the general population. Typically, the frequency distribution is normal. However, monogenic, oligogenic, or polygenic mutations could cause an increase in the LDL cholesterol level above the threshold for FH.
FH, familial hypercholesterolemia; LDL, low-density lipoprotein; *ABCG5* and *ABCG8*, adenosine triphosphate (ATP)–binding cassette sub-family G, members 5 and 8; *APOE*, apolipoprotein E; *LDLR*, LDL receptor; *LDLRAP1*, LDL receptor adapter protein 1; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *SORT1*, sortilin 1.

addition, homozygous FH caused by *LDLRAP1* mutations (so-called ARH) is characterized by a milder phenotype, probably because the function of their *LDLR*, particularly in the clearance of remnant lipoproteins, is not completely impaired.[86,87] Thus, based on these findings, the genotypes of homozygous FH is helpful for not only diagnosis but also risk stratification.

Moreover, sitosterolemia is an important differential diagnosis of homozygous FH. This condition is caused by double pathogenic mutations in *ABCG5* or *ABCG8* and is extremely rare. However, the prevalence of sitosterolemia has been significantly higher than previously expected based on the prevalence of loss-of-function mutation in the general population in public database (gnomAD).[88] Occasionally, HoFH is challenging to differentiate from sitosterolemia because both conditions have similar symptoms. These include elevated LDL cholesterol levels, cutaneous xanthomas since childhood, and premature CAD in childhood.[89-91] We have managed worse cases of sitosterolemia with premature CAD, a case of a young lady (aged 25 years old) with myocardial infarction,[89] and a boy (aged 15 years old) with ischemic heart failure.[91] Both patients had cutaneous xanthomas and Achilles tendon thickness similar to HoFH. Notably, the prognosis and standard therapy for sitosterolemia differ from those of HoFH. For example, ezetimibe, rather than statins, are strongly recommended. Meanwhile, statins are less effective against HoFH because of their reduced LDLR activity. Moreover, dietary counseling is quite effective in reducing LDL cholesterol levels in sitosterolemia. Meanwhile, dietary counseling has almost no beneficial effect on HoFH.[92] Accordingly, an accurate diagnosis which include differentiating HoFH from sitosterolemia, is important.

7. Common genetic variations associated with coronary atherosclerosis

Do common genetic variations have any effects on their phenotypes in FH? The answer is probably yes. Common genetic variations are associated with coronary atherosclerosis in the general populations.[93] In particular, polygenic risk score (PRS) comprising multiple common genetic variations are attracting significant attention to date. Fahed et al.[94] have shown that

independent of other traditional risk factors, such PRS is also associated with CAD among patients with FH. Notably, the most common genetic variations included in this score are associated with hypertension, diabetes, inflammation, and other unknown factors, but not with lipid levels.[94] Accordingly, assessing such risk caused by common genetic variations are useful for not only the general populations but also patients with FH regardless of genetic status.

PRINCIPLES OF INDIVIDUALIZED TREATMENT FOR PATIENTS WITH FH

As stated above, we need to identify patients with FH very early, ideally, before their Achilles tendon becomes thick, and then start to treat them. Secondly, we need to clarify the genetic backgrounds not only for FH-gene, but also other genes associated with CAD and lipids, including common genetic variations. These information can tell us clear diagnosis of them as well as responsiveness to lipid-lowering therapy.[76] Thirdly, we need to assess phenotypic severity, including coronary and carotid atherosclerosis. Finally, we need to decide the intensity of therapies based on all information. The most intensive therapies, including LDL apheresis and PCSK9 inhibitor would be needed when patients diagnosed late who have high risk genetic variants and exhibit coronary and carotid artery stenoses.

CONCLUSION

FH should be diagnosed as early as possible. Then, patients must receive individualized treatment based on other clinical risk factors (FH-specific or not) and genetic backgrounds (rare and common). As FH is one of the most common cardio metabolic disorders, a full understanding of its associated factors will help improve prognosis, thereby reducing the burden of cardiovascular disease worldwide.

ACKNOWLEDGEMENTS

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