Editorial

# Significance of Genetic Diagnosis of Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is a common genetic hyperlipidemia and has been recognized as a cause of premature coronary artery disease (CAD). FH is caused by mutations in one or more genes involving cholesterol metabolism. The most common cause of FH is the mutations or defects of low-density lipoprotein (LDL) receptor gene, and the specific mutations in the ligand of LDL receptor; apolipoprotein B-100 or gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9), which enhances LDL receptor degradation, are also known to cause FH. The LDL receptor adapter protein 1 causes a genetically different type of FH, namely autosomal recessive hypercholesterolemia[1]. Recent advances in gene analysis reveal that the frequency of Japanese heterozygous FH estimated from that of homozygous is as much as 1 in 208 people[2]. Moreover, double heterozygosity of different FH genes could be found in clinically diagnosed heterozygous or homozygous FH[3, 4].

Four major different diagnostic criteria of heterozygous FH have been proposed so far: the Make Early Diagnosis to Prevent Early Death (MedPed) program from the US, the Simon Broome Register Group from the UK, the Dutch Lipid Clinic Network, and the Japan Atherosclerosis Society. Very recently, the American Heart Association proposed a new diagnostic criterion of FH[5]. Of those, the UK, Dutch, and US criteria adopted the genetic testing as one of the components for the diagnosis of FH. Although genetic diagnosis of a disease with multiple causal genes is sometimes difficult, expensive, and time consuming, the detection of a variant makes the diagnosis definitive.

It could be speculated that coronary atherosclerosis predominantly develops with the cumulative exposure burden of LDL cholesterol, and CAD will be clinically overt when it will reach the threshold. Coronary risk factors such as sex, diabetes, hypertension, smoking, and other lipid abnormalities are believed to be just the modifiers of the threshold (**Fig. 1**)[6]. The early initiation of statin treatment reduces the cumulative LDL cholesterol burden in subjects with FH and is consequently believed to retard the development of CAD. Because the exposure to LDL cholesterol starts from the embryonic stage, the early diagnosis or differential diagnosis of FH is significant in the clinical setting. Once the causal variant has been identified, cascade screening in the patient's relatives is simplified, and statin therapy can be promptly initiated.

In this issue of the journal, Galaska et al. report that the thoracic calcium score of the ascending aorta detected by computed tomography (CT) of genetically diagnosed FH patients was greater than that of patients with severe hypercholesterolemia without FH gene mutations[7]. Moreover, after adjusting for the risk factors such as the levels of LDL-cholesterol themselves, a positive result for FH gene mutation was a significant predictor of higher coronary and ascending aorta calcium score[7]. Their results demonstrated that the positive for FH gene mutation, which is the reflection of the higher cumulative exposure burden of LDL cholesterol, is superior in predicting the existence of subclinical atherosclerosis and possibly future cardiovascular events compared with onetime measurement of blood LDL cholesterol.

However, the following questions arise: there are a significant number of subjects with mild-hyperlipidemia or even normo-lipidemia who are positive for FH gene variants. The most extreme case is the common PCSK9 gene mutation (E32K) carrier in Japan, who are mild-hypercholesterolemia and their LDL-cholesterol levels distribute between those of LDL receptor gene mutation carriers and normal subjects[3]. Do these gene carriers with normo-lipidemia have a high risk of CAD ? Contrastingly, there are a significant number of patients, who are clinically diagnosed

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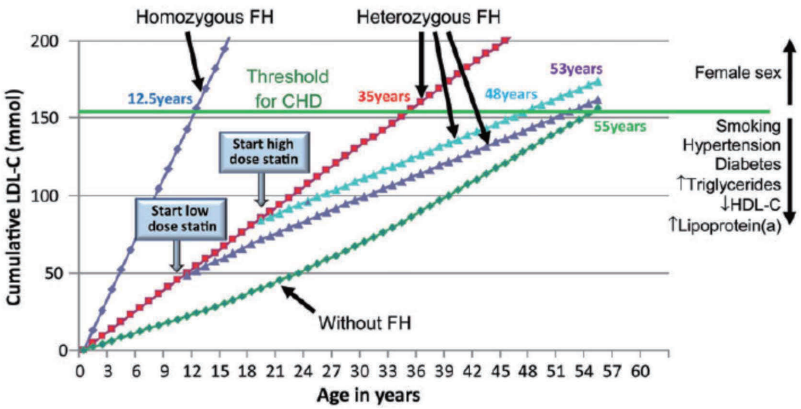


**Fig. 1.** The cumulative exposure burden of LDL cholesterol and the onset of CAD with or without FH (quoted from 6).

with FH due to hypercholesterolemia accompanied with typical physical findings such as tendon xanthoma, despite the absence of FH gene variants. Do they have low risk of CAD ? Recent exome sequencing of subjects with suspected Mendelian inheritance of extreme hyper-LDL-cholesterolemia with unknown FH gene variants failed to identify the genetic etiologies[8].

Presently, there are three different types of FH based on genetic background: a) monogenic FH, b) polygenic FH, and c) mutation unknown (possibly affected by environmental factors). Galaska et al. demonstrated that patients with monogenic FH have increased burden of subclinical atherosclerosis compared with extreme hypercholesterolemia without FH gene variants. Further studies that compare major adverse cardiac events between these groups are needed to fully elucidate the importance of determining the genetic backgrounds of patients suspected to have FH.

Subclinical atherosclerosis imaging, including cardiac CT angiography, can detect asymptomatic atherosclerosis burden and possibly detect individual patients needing intensive cholesterol-lowering therapy. For example, higher plaque scores as detected using CT angiography are reported to be a significant predictor of major adverse cardiac events in heterozygous FH[9]. Genetic diagnosis is not always a panacea of FH; thus, the combined use of genetic testing and subclinical imaging could help in determining a prompt strategy for patients suspected to have FH.

## Conflicts of Interest

None.

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