Review

Characteristics and Vascular Complications of Familial Hypercholesterolemia in Korea

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Familial hypercholesterolemia (FH) is presently an important health issue worldwide. This condition shows phenotypic and genetic variations among affected people, and clinical and genetic data on FH are critical for effective diagnosis and management. Korean FH patients have relatively low levels of cholesterol and prevalence of xanthoma than patients from other countries, as determined by previous studies. The best predictive value of low-density lipoprotein cholesterol (LDL-C) for pathogenic mutations is suggested as 225 mg/dL. Many known and novel mutations on *LDLR* and some on *APOB* or *PCSK9* have been identified in one-third of clinically diagnosed probands, and their locations on genes varied. Coronary artery disease was reported in 28% Korean FH patients, and traditional cardiovascular risk factors were associated with this complication. Aortic valve changes were also prevalent. However, the achievement rate of LDL-C target using lipid-lowering therapy is not satisfactory and is only 21%−44%. A further expanded registry and additional analysis may provide a more useful clinical tool for the diagnosis and treatment of Korean FH patients.

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Key words: Cholesterol, Genetics, Korea, Coronary artery disease, Aortic valve

Introduction

Familial hypercholesterolemia (FH), the most common autosomal dominant disorder, is presently an important health issue worldwide[1]. Particularly, because it causes premature atherosclerotic cardiovascular disease, proper screening, diagnosis, and treatment should be emphasized[2]. However, because of phenotypic and genetic variations among affected individuals, it is often difficult to diagnose and manage FH patients effectively. Furthermore, useful clinical and genetic data are not sufficiently available in many countries including Korea. Although clinical characteristics of FH can differ between ethnicities, these data are indispensable for clinical diagnosis. In addition, information regarding genetic characteristics is critical for FH screening in populations as well as in families. Lipid-lowering therapy in these patients prevents vascular complications predictably and to a large extent[3, 4]. Nevertheless, FH patients are frequently undertreated[2]. Moreover, in many countries, basic data regarding the present status of treatment have not yet been reported.

This article covers the clinical and genetic characteristics of heterozygous FH patients in Korea. Vascular complications and preventive measures are also comprehensively described. Particularly, data for Korean patients and those from Western and other Asian countries are simultaneously reviewed.

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Clinical Characteristics

A recent study supported by the Korean Society of Lipidology and Atherosclerosis (KSLA) reported that patients clinically diagnosed with heterozygous FH had a mean total cholesterol level of 313 mg/dL and low-density lipoprotein cholesterol (LDL-C) level of 226 mg/dL. Mutation-positive patients had a mean LDL-C level of 249 mg/dL[5]. In a prior Korean

Table 1. Clinical characteristics of FH patients enrolled in the KSLA-supported study (from reference with permission)

	Total (n=97)	Mutation (+) (n=31)	Mutation (−) (n=66)	p-value
Age, years	54.1±11.4	50.8±13.2	55.6±10.2	0.06
Female	59 (60)	13 (42)	46 (70)	0.01
Medical history				
Diabetes mellitus	7 (7)	2 (7)	5 (8)	1.00
Hypertension	37 (38)	12 (39)	25 (38)	0.94
CAD	27 (28)	11 (36)	16 (24)	0.25
Smoking	15 (16)	5 (17)	10 (16)	1.00
Family history				
Hypercholesterolemia	54 (58)	20 (65)	34 (55)	0.37
Premature CAD	50 (54)	20 (67)	30 (48)	0.10
Body mass index	25.0±3.5	25.4±4.0	24.8±3.2	0.50
Tendon xanthomas	19 (20)	7 (23)	12 (18)	0.61
Laboratory values, mg/dL				
Total cholesterol	313±43	332±44	303±39	0.002
Triglycerides	169±81	155±62	176±88	0.18
HDL-cholesterol	49.9±14.7	45.0±10.8	52.3±15.7	0.02
LDL-cholesterol	226±38	249±42	216±31	<0.001

Numbers in parentheses are percentages; FH: familial hypercholesterolemia; KSLA: Korean Society of Lipidology and Atherosclerosis; CAD: coronary artery disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein

study[6], the mean LDL-C level was higher than the levels in the abovementioned study[5]. Stricter inclusion criteria and enrollment of affected family members could be the reason for the differences in cholesterol levels between the studies. The phenotypical severity of FH such as cholesterol levels or xanthoma can be partly influenced by ethnic background or diet. For instance, elevated cholesterol levels and xanthoma are more obvious in Chinese populations who have migrated to Canada compared to those who live in China[7]. The LDL-C levels in pretreatment FH patients was 274−302 mg/dL in Western countries[8-10] and 248−292 mg/dL in Asian countries[11-13]. In Korea, the LDL-C value that could best predict putative pathogenic mutations is 225 mg/dL[5]. The US Make Early Diagnosis to Prevent Early Deaths criteria indicated that an LDL-C cutoff value of 240 mg/dL shows 98% specificity at the age of 30 years[14]. In Japan, conversely, a cutoff value of 250 mg/dL shows very high specificity, whereas 180 mg/dL is the recommended cutoff value in patients with xanthoma or a family history[15].

A previous Korean study has shown that Achilles tendon thickness in FH patients was 14.2 mm, which was higher than that in controls (Han *et al*, data presented at the Korean Society of Lipidology Scientific Session, 1991). However, the incidence of xanthoma in individuals clinically diagnosed with FH was as low as 20% (**Table 1**). Although the incidence of xanthoma varies with inclusion criteria, the incidence in Korean patients is lower than that in patients from the UK[16], Hong Kong[13], and Japan[11] (47%, 50%, and 87%, respectively).

Genetic Characteristics

It is well known that only some patients with clinically diagnosed FH have pathogenic mutations in *LDLR*, *APOB*, or *PCSK9*[10, 12, 17]. In the KSLA-supported study, the largest Korean FH study to date, putative mutations in these 3 genes were found in 32% of the enrolled patients. In the study, *LDLR* point mutations were most frequent on exons 4 and 14 (**Fig. 1**)[5, 18]. Point mutations of *LDLR* have been previously reported in a variety of gene locations in Koreans[19]. Large deletions[20-23] and copy number variation[18] in *LDLR* associated with FH have also been identified. Although not common, mutations in *APOB* and *PCSK9* are reported in Korean FH patients[5, 18]. On the basis of the data reported thus far, it is difficult to determine whether there are any hot spots of mutations in Koreans. *LDLR* mutations reported in Koreans have shown little similarities with those reported in other Asian countries such as Japan[24] or Taiwan[25, 26].

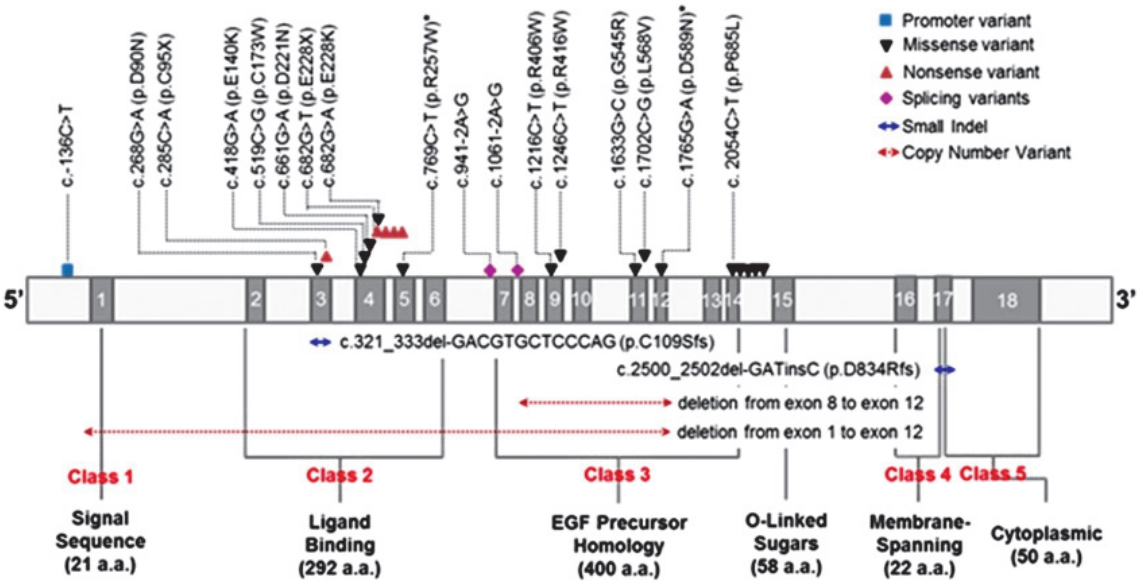

Fig. 1. Location and characteristics of mutations on *LDLR* in Korean FH patients (drawn by Soo Min Han)

Vascular Complications

In the KSLA-supported study, 28% heterozygous FH patients had a history of coronary artery disease (CAD) (45% in males and 17% in females: unpublished data)[5]. In the study population, 13% experienced acute coronary syndrome (21% in males and 7% in females: unpublished data). In the subgroup with CAD, majority of the patients had multivessel disease (**Table 2**). The prevalence of myocardial infarction in Japanese FH patients is 22% and 10% in males and females, respectively[27], and these data are similar to those in Koreans. A recent imaging study indicated that coronary atherosclerosis may begin in early twenties even in Asian FH patients[28].

Traditional cardiovascular risk factors including age and sex have been known to predispose FH patients to CAD in Western countries[29]. In Korea, independent predictors of CAD in FH patients were hypertension and low high-density lipoprotein cholesterol (HDL-C) levels[5]. These findings are similar to those in Japanese FH patients for whom classical risk factors were associated with CAD[11]. The relationship between Achilles tendon thickness and CAD has not been clarified in Koreans, although this has been reported as a significant factor in other countries[30].

Results from studies on the relationship between FH and cerebrovascular disease have been inconsistent. Although a study performed in Finland showed that FH increased the risk of stroke 20 times[31], stroke mortality in FH patients was not higher than that in the general population according to a study from the UK[32]. However, both studies had methodological limitations. The death rate from stroke was not increased by FH in Japanese people[33]. Interestingly, a recent meta-analysis revealed that the risk of cerebrovascular disease in FH populations was reduced after the introduction of statin therapy[34]. Meanwhile, the impact of FH on peripheral artery disease has been reported in several studies. In a study from the Netherlands, the prevalence of peripheral artery disease in FH patients was 31%, and it was about 8 times higher than that in the general population[35]. In other studies, the risk of this complication was 5 to 10 times greater than that in controls[36]. The prevalence of iliac artery disease (more than minimal) in FH patients in Japan was 56%[37]. Information on cerebrovascular or peripheral artery disease in Korean FH patients remains to be evaluated.

In the KSLA-supported study, 59 of 97 FH probands underwent echocardiographic examination, of whom 57% showed aortic valve changes, whereas 16% showed calcified or sclerocalcified changes (**Table 2**: data presented at the Satellite Symposium of the ISA 2015 in Tokyo, Japan). In a European study, computed tomography detected aortic valve calcification in 38% FH patients[38]. Conversely, the rate of aortic valve surgery was 24% in homozygous FH patients[39]. Groups of researchers have demonstrated that cholesterol levels and duration after diagnosis of FH are associated with aortic stenosis[40, 41]. However, the relation between cholesterol exposure and aortic stenosis

Table 2. Characteristics of CAD and aortic valve change in FH patients enrolled in the KSLA-supported study (from data presented at the Satellite Symposium of the ISA 2015 in Tokyo, Japan)

	Percentages calculated in total patients (n=97)	Percentages calculated in patients with CAD or echocardiographic examination
CAD	27 (28)	27 (100)
Clinical presentation of CAD		
Acute coronary syndrome	13 (13)	13 (48)
Chronic ischemia	14 (14)	14 (52)
Number of diseased vessels		
1	5 (5)	5 (18)
2	8 (8)	8 (30)
3	14 (14)	14 (52)
Echocardiographic examinations		57 (100)
Normal aortic valve	--	23 (40)
Aortic valve change	--	34 (60)
Minimal thickening	--	11 (19)
Sclerotic	--	14 (25)
Calcified or sclerocalcified	--	9 (16)

Numbers in parentheses are percentages; FH: familial hypercholesterolemia; KSLA: Korean Society of Lipidology and Atherosclerosis; CAD: coronary artery disease

in FH is not consistent among studies[42].

Effect of Treatment

Although older generation statins have known to lower LDL-C levels by not more than 35%−40%[43, 44], treatment with stronger statins such as atorvastatin and rosuvastatin lowered LDL-C by 46% in Korean FH patients enrolled in the KSLA-supported study (data presented at the Satellite Symposium of the ISA 2015 in Tokyo, Japan). In the same population, the achievement rates of LDL-C target were 21% and 44% when targets of 100 mg/dL and 50% of the baseline level were set, respectively. In Western countries, statins are known to reduce LDL-C levels up to 55% in FH patients[45]. A study in FH patients in the UK showed that lipid-lowering therapy reduced cardiovascular risk by 24%−48%[3]. Furthermore, the relative risk reduction by lipid management was up to 76% in another study[4]. Although data regarding cardiovascular protection of lipid-lowering therapy in FH is insufficient in Asian countries, a retrospective study in Japan found that CAD onset was delayed in FH patients after the widespread use of statins[46].

In Korea, ezetimibe is known to reduce LDL-C levels by 10%−19%[47, 48] and is widely used in FH patients. According to data from the KSLA-supported study, statin−ezetimibe combination is used in about half of all registered patients (unpublished data). Although resins are also used as second-line agents, probucol is not actively prescribed in Korean FH patients. Meanwhile, probucol is more commonly used in Japanese FH patients[46], with supportive evidence of long-term cardiovascular benefits[49]. In addition, a combination of statins, ezetimibe, and resins showed further lowering of LDL-C levels without serious safety issues in Japan[50, 51].

In the future, novel therapeutic agents may improve prognosis in FH patients. Recently, clinical trials using emerging pharmacological agents, including a proprotein convertase subtilisin−kexin type 9 (PCSK9) inhibitors, were performed in FH patients. PCSK9 inhibitors have shown tremendous and consistent LDL-C-lowering efficacy with acceptable tolerability and seem to be the most promising among new therapeutic options. These agents, with or without ongoing statin therapy, reduced LDL-C levels by greater than 50% compared with the control group[52]. Although outcome studies remain to be completed, combined analyses support the reduction of cardiovascular risk with the use of PCSK9 inhibitors[53, 54]. Other new lipid-lowering agents have also shown effects on LDL-C lowering in homozygous FH patients: lomitapide inhibits microsomal triglyceride transfer protein that is involved in the assembly of very low-density lipoprotein and reduces LDL-C levels[55]. Mipomersen, which is based on an antisense oligonucleotide, inhibits apoB synthesis and results in a similar effect[56]. However, as both agents have limitations, including liver adverse events, the risks and benefits of their use

need to be considered when prescribing these drugs.

Conclusions

Phenotypical severity, such as cholesterol levels or xanthoma, is relatively mild in Korean FH patients. Mutations have been reported at various locations in classical FH-associated genes. Although CAD and aortic valve changes were prevalent in this population, the achievement rate of LDL-C target with current medical treatment was not satisfactory. An expanded registry and additional analysis may provide more useful clinical tools for the detection and management of FH patients in Korea.

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Conflict of Interest

There is no conflict of interest.

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