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Editorial

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Can We Clarify the Causative Gene/Variants Underlying Familial Hypercholesterolemia and Improve Genetic Diagnosis Rate?

Mika Hori[1, 2]

[1]Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Aichi, Japan
[2]Department of Endocrinology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

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Familial hypercholesterolemia (FH) is characterized by high low-density lipoprotein-cholesterol (LDL-C) levels, skin and tendon xanthomas, and premature coronary artery disease. FH is caused by pathogenic gene variants of the low-density lipoprotein receptor (*LDLR*) and apolipoprotein B (*APOB*), an LDL ligand, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*), which degrades LDLR. Worldwide, > 95% of the variants that cause FH are in *LDLR*, 2%–11% are in *APOB*, and <1% are in *PCSK9* [1]. However, FH varies genetically across geography, so it is necessary to assess FH-causing variants in each population/country.

In the issue of the journal, Huang *et al.* investigated the spectrum of pathogenic variants of *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, *ABCG5*, and *ABCG8* in patients who were clinically diagnosed with FH in Taiwan[2]. Of the 750 index cases, 443 pathogenic variants of *LDLR* and *APOB* but not of *PCSK9* were identified in approximately 60% of the unrelated patients with FH. Of FH-causing variants, 86% were variants of *LDLR* and 13% were of *APOB*. This is consistent with the global rate of FH-causing variants. The most common variant was *APOB* c.10579C>T (p.Arg352Trp) (12.6%), which has been reported in Chinese patients with FH[3]. Huang *et al.* also discussed the regional difference in FH-related variants found in East Asia.

We reported that pathogenic variants of *LDLR* and *PCSK9* were found in 46% and 7.8% of unrelated Japanese patients with FH (n=650), respectively[4]. Of FH-causing variants, 85% were variants of *LDLR* and 15% were of *PCSK9*. The c.94G>A (p.Glu32Lys) variant comprised 88% of the pathogenic variants of *PCSK9*. Worldwide, this variant has only been reported in one patient with FH in Korea[5]. Mabuchi *et al.* and we have reported that patients with FH harboring the c.94G>A (p.Glu32Lys) variant have mild phenotypes compared with patients with FH harboring *LDLR* pathogenic variants[4, 6]. The c.94G>A (p.Glu32Lys) variant shows a mild FH phenotype compared with gain-of-function (GOF) variants of *PCSK9* detected in countries other than Japan. Thus, the c.94G>A (p.Glu32Lys) variant of *PCSK9* is unique to Japan. We recently found the first Japanese family with FH due to the c.10580G>A: p.(Arg3527Gln) variant of *APOB* although the frequency was low[7]. The phenotype of *APOB* pathogenic variant carriers has been reported to be mild compared with that of *LDLR* pathogenic variant carriers[8]. The *LDLR* pathogenic variants and *PCSK9* GOF variants are definite FH-causing variants, but the phenotype of FH caused by variants of *APOB* and *PCSK9* other than these variants is mild. Thus, the second type of FH-causing gene/variant varies by country and population.

Patients with FH harboring no pathogenic variants of *LDLR*, *APOB*, or *PCSK9* comprised approximately 40% of the total unrelated patients with FH[2, 4]. Recently, rare variants of *ABCG5* and *ABCG8* have been reported in patients with FH[9, 10]. Tada *et al.* reported that rare and deleterious mutations of *ABCG5* or *ABCG8* were found in 8% in the 487 patients who were clinically diagnosed with FH in Japan[9]. Reeskamp *et al.* reported that 2.4% of subjects in Netherlands's FH cohort carried putative pathogenic variants of *ABCG5* and *ABCG8* but had lower LDL-C levels compared with FH patients with an *LDLR* variant[10]. They concluded that these genes can partly explain the FH phenotype in some individuals but they might not cause FH inheritance

Address for correspondence: Mika Hori, Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan E-mail: mihori@riem.nagoya-u.ac.jp

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patterns. In recent years, whole-exome/genome sequencing has been increasingly implemented in genetic analysis for FH. It may be useful to search for novel FH-related genes/variants from LDL-C-associated single-nucleotide polymorphisms from genome-wide association studies in the FH cohort of each country[11]. The variants of *ABCG5*/*ABCG8* and other FH-related genes may reveal the FH phenotype by the presence of other genetic or environmental factors that affect cholesterol metabolism.

In conclusion, a cohort of larger size is needed to clarify the causative gene/variant underlying FH and improve genetic diagnosis rate. The regional or national FH registries, including genome information, could serve for detection and management of FH in each country/population.

Conflicts of Interest

None.

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