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Editorial

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Targeted Panel Sequencing will Boost Detection of Genetic Backgrounds of Familial Hypercholesterolemia in the World's Most Populous Country

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Prevalence of Familial Hypercholesterolemia

Familial hypercholesterolemia (FH; OMIM #143890) is characterized by a clinical triad of primary hyper-LDL-cholesterolemia, tendon xanthomas, and premature atherosclerotic cardiovascular disease (ASCVD)[1]. Recently, researchers around the world, including ourselves, have shown that the prevalence of patients with FH among the general population is estimated to be around 1 in 250–300[2-4]. The prevalence of FH among patients under specific situations is estimated to be much higher, such as 1 in 31 among patients with ischemic heart disease, 1 in 15 among patients with premature ischemic heart disease, and 1 in 14 among patients with severe hypercholesterolemia. Accordingly, it is roughly estimated that there are approximately 500,000 patients with FH in Japan and 5,800,000 patients with FH in China. Currently, the awareness for FH in both countries, which contain some of the most populous areas in the world, is not adequate.

Clinical Diagnosis of FH

There are several different types of clinical diagnostic criteria for FH in the world, including Dutch Lipid Clinical Network (DLCN), Simon Broome Diagnostic Criteria, Make Early Diagnosis to Prevent Early Deaths diagnostic criteria, and Japan Atherosclerosis Society (JAS) FH diagnostic criteria[5]. JAS FH criteria adopts three major clinical characteristics of FH: 1) hyper-LDL-cholesterolemia (≥ 180 mg/dl); 2) xanthomas (Achilles tendon thickness ≥ 9.0 mm or xanthoma tuberosum are confirmed on X-rays); and 3) family history. These simple clinical criteria have great advantages, raising specificity through assessing xanthomas and family history and simultaneously controlling sensitivity by LDL cholesterol level. Conversely, DLCN FH criteria, which is currently most widely used around the world, adopts a scoring system of multiple clinical elements. However, both clinical criteria use family history (of FH and/or premature ASVCD); thus, it is sometimes difficult to clinically diagnose FH where family history information is obscure. Moreover, specific physical signs of FH, including tendon xanthomas, do not always exist, thereby leading to underdiagnosis. In that sense, genetic diagnosis of FH can be definitive, especially where a reliable reference of pathogenic genetic mutation information is available.

Genetic Diagnosis of FH

We understand that there are several types of FH in terms of genetic backgrounds: 1) monogenic FH caused by a deleterious mutation in LDL receptor or its associated genes; 2) polygenic FH caused by a significant accumulation of LDL-raising common genetic variations; and 3) oligogenic FH where rare and deleterious LDL-raising generic variations are exacerbating the phenotype of monogenic FH[6]. Determining their genetic backgrounds not only leads their definite diagnosis as FH but also provides risk stratification for ASCVDs[7]. In this regard, a detailed dataset of pathogenic mutations causing FH in particular ethnicities is quite useful. In this manuscript, Wang *et al.* provided the largest catalog of pathogenic

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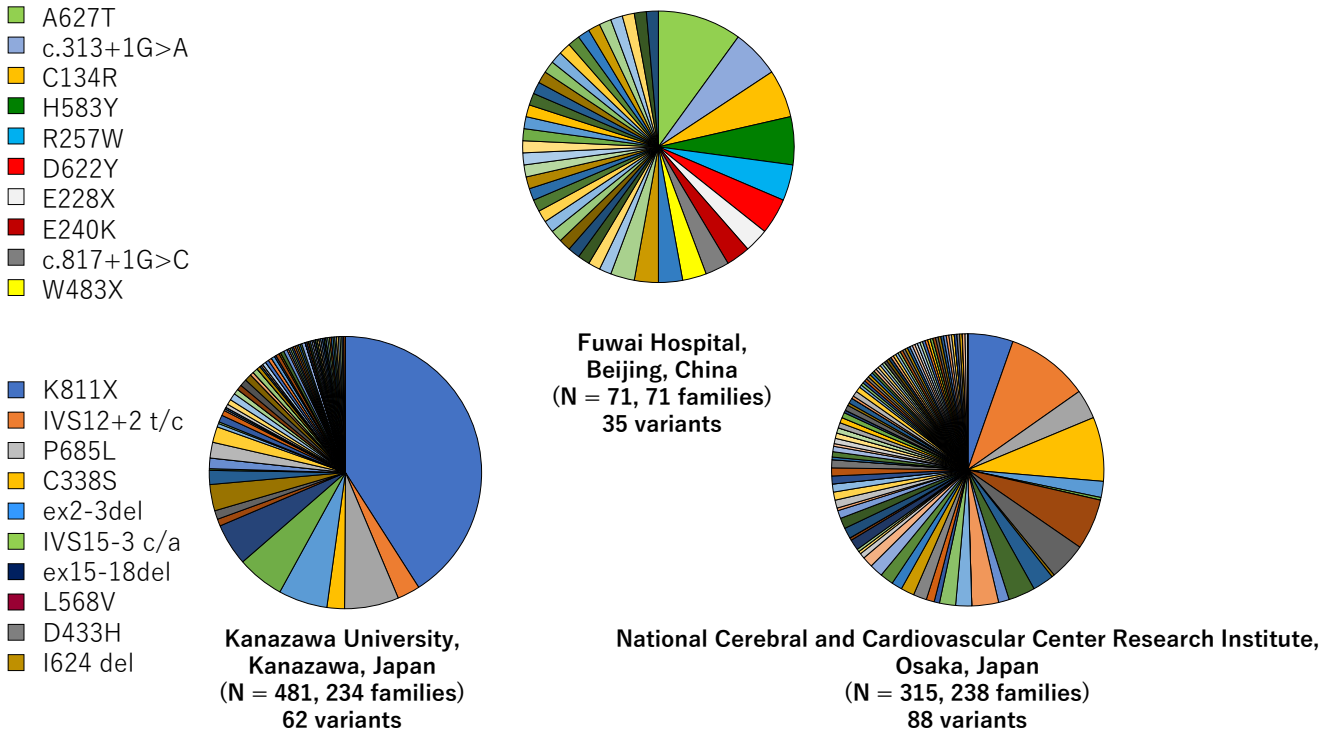

Fig. 1. Pathogenic mutation distribution in Chinese, and Japanese major FH-care centers

A. Fuwai Hospital, Beijing, China
B. Kanazawa University, Kanazawa, Japan
C. National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

mutations among Chinese patients with FH[8]. When compared with pathogenic mutations in LDL receptor gene among the Japanese[9], only 7 among 35 (20%) mutations overlapped **(Fig. 1)**. Further, there were large variations of pathogenic mutations in Fuwai Hospital, Beijing, a metropolitan area in China, and National Cerebral and Cardiovascular Center Research Institute, Osaka, a metropolitan area in Japan, whereas only a few pathogenic mutations account for a significant proportion in Kanazawa University, Kanazawa, a rural area in Japan. These observations suggest that distributions of pathogenic mutations of FH appear to be different according to regions and that we need much more data across all regions of the world for referral of pathogenic mutations of FH.

Conclusion

Presently, we have various therapeutic strategies, including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, to effectively reduce the LDL cholesterol levels of individuals with FH. Furthermore, it has been proposed that timely diagnosis and treatment could prevent ASCVD events in patients with FH[10]. It is essential to identify patients with FH at a young age to initiate treatment and prevent premature ASCVD. However, it is somewhat difficult to diagnose FH in younger individuals because they typically do not exhibit increased Achilles tendon thickness, which is used worldwide as one of the major diagnostic criteria for FH. In this regard, genetic analyses can be particularly useful for younger patients as well as for patients with an unclear family history. We are anticipating that the targeted panel sequencing used in this study will increase the detection of the genetic backgrounds of FH in the world's most populous country.

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Conflict of Interest

None.

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