

# The Roles of Genetic Analysis in the Diagnosis of Pediatric Patients with Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is a genetic disease characterized by high LDL-C levels, cutaneous and/or tendon xanthomas, and coronary artery disease (CAD) due to premature atherosclerosis<sup>1)</sup>. The development of CAD is related to accumulation of cholesterol that is LDL-C levels times year. For prevention of atherosclerotic disease in FH, the accumulation of cholesterol needs to be decreased since childhood. Therefore, FH needs to be diagnosed as early as possible to begin lipid lowering therapy.

Diagnosis of FH in children is made by the diagnosis criteria for pediatric FH (JAS 2017 version) in Japan, that is (1) LDL-C levels higher than 140 mg/dl and (2) family history of FH or premature CAD<sup>2)</sup>. However, Matsunaga K *et al.* reported that 68% of the genetically confirmed patients with FH did not meet the diagnosis criteria in their universal screening in Kagawa<sup>3)</sup>. Therefore, in order to give accurate diagnosis of FH in children, the Japanese criteria may be insufficient. First, most of the parents who have FH are not old enough to have CAD, the average age of which was approximately 59.5 years in patients with FH in the real world reported in the Explore J Study<sup>4)</sup>. This is due to the spread of statin therapy, which may delay the onset of events. Second, increase of divorce rate in Japan may make it difficult to have accurate family history. Third, the diagnosis criteria do not contain genetic diagnosis. In order to give them higher sensitivity, the diagnosis criteria need to be amended.

Cascade screening has been the main strategy to find patients with FH, which showed successful outcome especially in Netherland<sup>5)</sup>. Cascade screening is a cost effective and a useful strategy, on the other

hand, it is impossible to find all the patients. Recently, universal screening has been performed to find FH in children. Universal screening of FH has been implemented in preschool children in Slovenia and 2/3 of hypercholesterolemia patients had genetic analysis, showing 44.7% had FH-disease causing variant<sup>6)</sup>. In Japan, Matsunaga *et al.* performed universal screening of FH in Kagawa and 61% of hypercholesterolemia patients were diagnosed as having FH by genetic analysis<sup>3)</sup>. Almost all the patients with FH can be found by universal screening in the certain area, which shows that it is a useful tool to find patients with FH. There has been discussion related to the cost effectiveness of universal screening. If patients with FH can be diagnosed and start appropriate therapy in their childhood, they can control their LDL-C levels without having ASCVD. Therefore, several recent papers reported that universal screening is cost effective.

In the present paper, 33 patients who were clinically diagnosed as FH were subjected to genetic analysis and 48.5% were shown to have FH-disease causing variant; 45.5% had variants in *LDLR* and 3.0% had one in *PCSK9*<sup>7)</sup>. The percent of *LDLR* variants were almost the same as that of Japanese adult patients with FH reported by Tada<sup>8)</sup>. Futema M *et al.* reported the mutation spectrum of pediatric patients of FH in European countries<sup>9)</sup>. While the variants in *LDLR* are the main cause in all the countries studied, the rate of the variants in *PCSK9* and *APOB* varies in each country. In the present paper, the variants in *APOB* were not found. Actually, there have been no *APOB* variant in Japan until several years ago when we reported the first case in Japan<sup>10)</sup>. The variant spectrum in pediatric patients with FH is almost the same as that in adults except for mild variations, which may not show the phenotype of FH during

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childhood.

In the present cohort, the patients who were subjected to genetic analysis were only clinically diagnosed with FH. However, there may be significant amounts of pediatric patients with FH who do not meet the diagnosis criteria of FH as Matsunaga reported. Therefore, when we diagnose FH, we need to be very careful to this kind of underdiagnosis. Genetic analysis plays significant roles in giving accurate diagnosis of FH and needs to be implemented in the health care system.

### COI

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