Validation of clinical diagnostic criteria of familial hypercholesterolemia in Japan: evidence from a comprehensive genetic analysis

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Background: Although awareness of familial hypercholesterolemia (FH) is increasing, this common, potentially fatal, treatable condition remains underdiagnosed. Japanese clinical diagnostic criteria of FH include LDL cholesterol level = 180 mg/dl, Achilles tendon thickness (ATT) = 9.0 mm, and family history of FH or premature coronary disease. Despite FH being a genetic disorder, genetic testing is rarely used, few data exist regarding the validation of those criteria, especially, by studies using comprehensive genetic analyses.

Methods: This study included 680 subjects (344 men, mean LDL cholesterol = 175 mg/dl) who underwent the full assessments for FH, including LDL cholesterol measurement, Achilles tendon X-ray, investigations for family history, and comprehensive genetic analyses on FH-associated genes (LDL receptor, PCSK9, APOB, and LDLRAP1) in our University Hospital since 2006 to 2018. The area under curve (AUCs) of receiver-operating characteristic (ROC) curve analyses predicting FH-mutation positive were compared among those determined by each component.

Results: ROC analyses revealed the optimal cutoff LDL cholesterol value for predicting the presence of FH-mutation was 181 mg/dl, and that of ATT was = 7.0 mm. AUCs of each component (ATT, LDL cholesterol, and family history) were 0.827, 0.889, and 0.906, respectively, and the combination of all components increased it to 0.975. When adopting ATT = 7.0 mm as one of the clinical diagnostic criteria, 13 individuals (2 %) were newly classified as true-FH, whereas, 27 (4 %) individuals were newly misclassified as FH.

Conclusion: The current Japanese clinical diagnostic criteria of FH were pretty well validated in our independent cohort. However, the threshold of ATT could be lowered to 7.0 mm to raise the sensitivity of its criteria.