Cardiomyopathies are disorders with primary abnormalities in the structure and function of the heart, and left ventricular hypertrophy (LVH) is a common presentation of the disease. Over the last 30 years, there has been tremendous progress in genetics research that has defined the molecular causes of cardiomyopathies.1,13

Fabry disease is caused by a deficiency of α-galactosidase A, and typically causes multi-organ dysfunction. Mutations in the α-galactosidase A gene cause the disease, and the disease shows X linked inheritance. Up to now more than 800 mutations have been reported to cause the disease, and most are family specific occurring only in single pedigrees.11 Patients with manifestations limited to the heart, mainly LVH, have been reported as a disease variation.5,7 A cardiac variant of Fabry disease was detected in 7 of 230 male individuals with LVH.9 Severe left ventricular dysfunction with associated conduction disturbances and ventricular arrhythmias occur in patients with terminal stage cardiac Fabry disease. In addition, LVH associated with thinning of the base of the left ventricular posterior wall is a characteristic of end stage cardiac Fabry disease.61

Hypertrophic cardiomyopathy (HCM) is a relatively common monogenic cardiovascular disease, and the prevalence in the general population is about 1 in 500. The pathological hallmark of the disease is unexplained LVH. Autosomal dominant inheritance is most commonly seen. More than 20 genes were reported to be associated with disease, and most of these genes encode proteins of the myofilaments or Z-disc of the sarcomeres. As such, HCM has been described as a ‘disease of the sarcomere’, and sarcomere genes definitively shown to have a pathogenic role in HCM. Since 1990, there has been extensive molecular screening of sarcomere genes. More than 1400 mutations have been described in association with HCM.1,13-11

In the current issue of International Heart Journal, Csányi, et al reported a novel Ile239Met mutation in α-galactosidase A gene in a family with a predominant cardiac phenotype of Fabry disease.12 The Ile239Met mutation is a previously unpublished mutation, and Ile239Thr mutation in the same codon was already reported in dialysis patients with the classical type of the disease.13 In the family reported by Csányi, et al, 6 individuals carried the Ile239Met mutation, and 5 individuals showed LVH. Interestingly, 4 of the 5 with LVH were female individuals. This finding is slightly unusual for cardiac Fabry disease since the disease shows X linked inheritance. Usually, heterozygous females have milder symptoms at a later age of onset than males, and some of them may develop the full phenotype of disease manifestations later in life.4,5

An issue of this paper seems to be whether the mutation is really the disease causing entity in this family as the authors discussed. It is still possible that another mutation that causes LVH is present in this family. Although the mutation in this family fulfills the criteria of a definite diagnosis of Fabry disease in the consensus recommendation on uncertain diagnosis of Fabry disease,14 and the rules of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guideline for combining criteria to classify sequence variants as ‘pathogenic’,15 it is possible another disease causing mutation with autosomal dominant inheritance was present depending on the pedigree and cardiac findings of the family.

Another issue in this family is that the histological findings of the heart and kidney of the index patient or other family members with LVH have not been shown, since histological demonstration of Fabry disease associated pathology is important for the diagnosis of the disease.

The pattern of hypertrophy might be useful to distinguish Fabry disease from HCM, but it is not an easy task. In HCM, the distribution of LVH is characteristically asymmetric and particularly heterogeneous, encompassing most possible patterns of wall thickening, from extensive and diffuse to mild and segmental, and with no single morphologic expression considered typical or classic.16-18 In Fabry disease, the typical pattern is a concentric thickening without LV outflow tract obstruction, and LVH associated with thinning of the base of the left ventricular posterior wall is a characteristics of end stage cardiac Fabry disease.5,7 The index patient shows marked LVH in the form of obstructive hypertrophic cardiomyopathy, and extent and distribution of LVH in this family is highly variable.12 Left ventricular outflow obstruction in the index patient and LVH in the inferior septum or infero-postero-lateral wall seen in the other members are not common findings in Fabry disease.

From the 1 Clinical Research Unit, National Miyakonojo Medical Center, Miyakonojo, Japan.
Address for correspondence: Ryuichiro Anan, MD, Clinical Research Unit, National Miyakonojo Medical Center, 5033-1 Iwayoshi, Miyakonojo, Miyazaki 885-0014, Japan. E-mail: louanan@m2.kufm.kagoshima-u.ac.jp
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disease. Pattern of hypertrophy in the family is not the definitive finding to establish the diagnosis of Fabry disease. Renal failure seen in the index patient in this family might be a suggestive finding for Fabry disease as a classical disease, but not for cardiac Fabry disease, and renal failure is a common finding in elderly individuals.

Recently, Oikawa, et al reported a family with the Glu66Gln mutation in the α-galactosidase A gene and zebra body. They initially diagnosed a female patient with LVH as cardiac Fabry disease based on the findings of zebra body. However, immunostaining showed little deposition of globotriaosylceramide in left ventricular myocardium, and gene mutations in the disease genes for HCM, Gly1009Val in cardiac myosin-binding protein C gene and Ser624del in α cardiac myosin heavy chain gene, were detected. Although the pathogenicity of the Glu66Gln mutation in the α-galactosidase A gene cannot be ruled out, mutations in the sarcomere proteins were more reasonable to explain the pathophysiology in the case. They concluded this case of hypertrophic obstructive cardiomyopathy with Fabry disease could be confused with that of α-galactosidase A gene Glu66Gln mutation. The possibility that some patients with the Glu66Gln mutation may have histological findings similar to those of Fabry disease should be taken into consideration, and such patients should be examined for the possibility for harboring gene mutations associated with HCM.

Other examples of multiple mutations found in families with LVH have been reported. A family with HCM with complex genetics has been reported. In the family, 3 different mutations in the cardiac myosin-binding protein C gene and β cardiac myosin heavy chain gene have been identified. A family with cardiomyopathy associated with Val606Met mutation in the β cardiac myosin heavy chain gene and Asp254Gly mutation in the lamin A/C gene has also been described. In the family reported by Csányi, et al, more extensive genetic screening and histological studies may further clarify the etiology of the LVH of the family members. Whole genome sequencing has recently become available. When we perform genetic analyses in cases with LVH, multiple mutations that may cause LVH could be identified in some families. The histological, biochemical, and functional impacts on the heart, and modes of inheritance of the detected mutations, should be taken into consideration when we interpret the results of genetic analyses.

**REFERENCES**