Poor Myocardial Compaction in a Patient with Recessive MYL2 Myopathy

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Summary
Recessive mutations in the Myosin regulatory light chain 2 (MYL2) gene are the cause of an infantile-onset myopathy, associated with fatal myocardial disease of variable macromorphology. We here present the first Japanese family affected with recessive MYL2 myopathy. Affected siblings manifested typical features and the proband’s autopsy findings were compatible with the diagnosis of noncompaction cardiomyopathy. The rapidly progressive clinical course of this recessive MYL2 cardiomyopathy highlights the crucial role of c-terminal tails in MYL2 protein in maintaining cardiac morphology and function.

Key words: Cardiomyopathy, Noncompaction, Congenital heart disease, Heart failure, Skeletal myopathy, Pediatrics, Familial heart disease, Cardiomyocyte, Muscle fiber, Histopathology

Recessive mutations in the Myosin regulatory light chain 2 (MYL2) gene, expressed specifically in type I skeletal muscle fibers and ventricular cardiomyocytes, cause a rare infantile-onset myopathy with severe myocardial involvement. We here present the first report from Japan on this extremely rare myopathy, and provide a description of the patient’s cardiac histopathology.

Case Report

A 4-month-old girl was referred for assessment of suspected myopathy. No signs of prenatal muscle involvement had been noted, such as diminished fetal movement or polyhydramnios. Jerky involuntary movements of the limbs had been present since the age of one month. Positive scarf and heel-to-ear signs suggested generalized hypotonia with predominant involvement of the proximal extremities. Facial muscles were uninvolved at presentation. Deep tendon reflexes were attenuated, and abnormal reflexes were absent. She failed to achieve head control and exhibited progressive muscle weakness. Laboratory testing, including normal level blood creatine kinase (69 units/L) and blood/urine metabolic profiling, imaging analyses of the nervous system, and nerve conduction studies all failed in reaching an etiological diagnosis. At 5 months of age, elevated plasma BNP level (149.2 pg/mL) prompted an echocardiogram, which revealed dilated heart chambers with mild attenuation of left ventricular ejection fraction (49.0%) and restrictive physiology. Conduction abnormalities (right bundle branch block) emerged, reflecting the progressive nature of myocardial degeneration. At 11 months of age, her left ventricular ejection fraction and BNP level had worsened to 27% and 5186 pg/mL, respectively. Despite aggressive heart failure therapy, she deceased within one month of admission to the intensive care unit.

In order to elucidate the genetic cause of her phenotype, whole exome sequencing was performed. The capture library was constructed from peripheral blood cell-derived total DNA using Agilent SureSelect Human All Exon V6 (Agilent Technologies) and was sequenced with the Hiseq 2000 platform (Illumina). Variant detection was conducted through the Genomon pipeline (Laboratory of DNA Information Analysis, Human Genome Center, The Institute of Medical Science, The University of Tokyo). Overall coverage of the target exome was 99.59%, 99.19%, and 98.16% for a minimum depth of 2X, 10X, and 20X, respectively, and the average sequencing depth was 89-fold. Compound heterozygous variants in the
MYL2 gene were identified; c.431_432del:p.P144Rfs*57 and c.T499C:p.*167Qext*? (Figure 1). The former, dbSNP ID rs1566147422, causing a frameshift within the last exon of the MYL2 gene, had previously been identified in the homozygous state in two siblings. They both presented with infantile-onset hypertrophic cardiomyopathy that led to death before one year of age. Functional analysis of the variant showed destabilization of the mutated protein due to elongation of the C-terminus (Figure 2). Detected in trans was a novel stop-loss variant absent from the gnomAD and ClinVar databases, which also extended the C-terminus of the MYL2 protein beyond the 3’ UTR. Moreover, recurrence of the variants in her elder sister, who also had shown muscle weakness and experienced death in her infancy due to dilated cardiomyopathy, supports the pathogenicity of the identified variants. Her parents and another sibling showed no associated symptoms and targeted Sanger sequencing of the parents revealed that they were unaffected heterozygous carriers of each variant (Figure 1).

At autopsy, the proband’s skeletal muscles showed atrophic changes compatible with the MYL2 myopathy diagnosis (Figure 3A). Cardiac examination showed enlargement of the chambers. Hypertrabeculation along the posterior wall blurred the distinction between papillary muscle structure and abnormally prominent trabeculae. The non-compacted to compacted layer ratio reached 1.6 at the left ventricular free wall (Figure 3B, C). These together fulfilled the histological criteria for noncompaction cardiomyopathy diagnosis.
**Discussion**

Cardiac morphological phenotypes of recessive MYL2 myopathy have shown no clear correlation with the genotype. Reported patients from two Italian families and 8 Dutch families, all harboring mutations affecting the last exon, have invariably experienced premature death, although cardiac morphology ranged from hypertrophic, dilated to noncompaction cardiomyopathy. Another sibling, homozygous of the P144Rfs*57 variant, showed the hypertrophic phenotype, well contrasting with the noncompaction morphology of the presented case. Detailed histopathological examination has so far been missing and may elucidate the structural determinant of cardiac deterioration behind the diverse macromorphological expression.

**Acknowledgment**

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**Disclosure**

**Ethical standards:** This study was approved by the institutional ethics committee (#G3565). Written consent for publication has been obtained from the patient’s parents.

**Conflicts of interest:** None.

**References**

1. Weterman MA, Barth PG, van Spaendonck-Zwarts KY, et al. Recessive MYL2 mutations cause infantile type 1 muscle fibre disease and cardiomyopathy. Brain 2013; 136: 282-93.
2. Huan W, Liang J, Yuan CC, et al. Novel familial dilated cardiomyopathy in MYL2 affects the structure and function of myosin regulatory light chain. FEBS J 2015; 282: 2379-93.
3. Manivannan SN, Darouich S, Masmoudi A, et al. Novel frameshift variant in MYL2 reveals molecular differences between dominant and recessive forms of hypertrophic cardiomyopathy. PLoS Genet 2020; 16: e1008639.
4. Burke A, Mont E, Kutys R, Virmani R. Left ventricular non-compaction: a pathological study of 14 cases. Hum Pathol 2005; 36: 403-11.
5. Yadav S, Sitobon YH, Kazmierczak K, Danuta Szczesna-Cordary. Hereditary heart disease: pathophysiology, clinical presentation, and animal models of HCM, RCM and DCM associated with mutations in cardiac myosin light chains. Pflugers Arch 2019; 471: 683-99.