CASE REPORT

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.1 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
Pedigree; results from familial genotyping support the recessive mode of inheritance for MYL2 C-terminal variants in infantile-onset cardiomyopathy. D for the presented case and her elder sister indicates death, while parents and the eldest sister had no associated symptoms.

Distribution of MYL2 mutations; the location of dominant missense mutations in hypertrophic cardiomyopathy is indicated by blue arrows (A-F, K; A13T, F18L, E22K, N47K, R58Q, P95A, D166V).3) reported recessive mutations by red arrows (H-J; IVS6-1, P144LfsX2, N145TfsX2)3) and DCM associated mutations by green arrow (G; D94A).3) The patient’s recessive mutations by stars; one is I and the novel one is indicated as L.

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.4)
Discussion

Cardiac morphological phenotypes of recessive MYL2 myopathy have shown no clear correlation with the genotype.\textsuperscript{1,5} 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.\textsuperscript{1} Another sibling, homozygous of the P144Rfs\textsuperscript{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

We thank the patients and their family for participating in the study.

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