Cardiology in the Young (2014), **24**, 953–954
doi:10.1017/S1047951113002035

Brief Report

Dilated cardiomyopathy due to a phospholamban duplication

Teresa M. Lee,[1] Linda J. Addonizio,[1] Wendy K. Chung[2]

[1]*Department of Pediatrics, Division of Cardiology;* [2]*Department of Pediatrics, Division of Molecular Genetics, Columbia University Medical Center, New York, New York, United States of America*

Abstract Dilated cardiomyopathy is characterised by dilation and impaired systolic function. We present the case of a child with dilated cardiomyopathy caused by a 624 kb duplication of 6q22.31, which includes the phospholamban gene. The patient also has failure to thrive and developmental delay due to complex cytogenetic abnormalities including a 5p15 deletion associated with Cri du Chat and an 11p15 duplication associated with Russell–Silver syndrome.

Keywords: Cardiomyopathy; dilated; phospholamban; 6q22.31

Received: 15 August 2013; Accepted: 20 October 2013; First published online: 22 January 2014

DILATED CARDIOMYOPATHY IS CHARACTERISED BY dilation and impaired systolic function of one or both ventricles. It is a major cause of heart failure worldwide with a prevalence of 1 in 2500 individuals.[1] Approximately 20–48% of cases are considered familial,[1] and the majority of cases follow an autosomal-dominant mode of inheritance with variable expressivity and penetrance.

Currently, over 30 genes have been implicated in dilated cardiomyopathy, with most of these genes being sarcomere genes.[2] The gene phospholamban encodes a sarcoplasmic reticulum calcium ATPase inhibitor. Mutations in this gene have been associated with dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Mutation carriers present with a spectrum of clinical severity ranging from sudden cardiac death to asymptomatic adults.[3–5] We report the first case of dilated cardiomyopathy due to a cytogenetic duplication of phospholamban.

Case report

The patient is a 2.5-year-old female with a history of failure to thrive, developmental delay, and dilated cardiomyopathy who was first referred to our centre at 18 months of age. She was born premature at 29 weeks of gestation to a 30-year-old G4P1 woman. Her prenatal course was complicated by cystic hygroma and intrauterine growth restriction noted at 24 weeks of gestation. Amniocentesis was performed and revealed a normal karyotype. Her birth weight was 672 g, length 28 cm, and head circumference 23.7 cm (all less than the third percentile).

An echocardiogram at 4 months showed a structurally normal heart with normal function. At 14 months of age, she was admitted with respiratory symptoms. A chest film at that time showed cardiomegaly, and an echocardiogram revealed severe biventricular dilation, poor systolic function, and an ejection fraction of 28% (normal 56–78%). She was started on intravenous inotropic medications and diuretics, which were eventually transitioned to oral anti-congestive medications. Her current electrocardiogram demonstrates normal sinus rhythm, left ventricular hypertrophy, and non-specific T-wave changes in the lateral leads. Serial echocardiograms have demonstrated an ejection fraction ranging from 40.7% to 52.6% with a moderately dilated left ventricle. She is currently on digoxin, carvedilol, enalapril, furosemide, spironolactone, aspirin, and ferrous sulfate.

The patient has dysmorphic features including a triangular face with hypertelorism, downslanting palpebral fissures, and is severely hypotonic. She has

Correspondence to: W. K. Chung, Department of Pediatrics, Division of Cardiology, Columbia University Medical Center, 1150 St. Nicholas Avenue, Room 620, New York, New York 10032, United States of America. Tel: 212-851-5315; E-mail: wkc15@columbia.edu

consistently grown parallel to the normal growth curves, but remains less than the third percentile for weight and height. The patient's development has been delayed. She began cruising at ~30 months of age. Currently, she can walk with assistance. She does not yet have any speech. Her family history is notable for her mother's three first trimester miscarriages.

Prior genetic testing at another institution, including methylation studies of chromosome 11, confirmed a diagnosis of Russell–Silver syndrome. However, given the complex nature of her findings, we performed additional molecular genetic testing.

Chromosome microarray demonstrated a 2 Mb deletion of 5p15.33 to pter (113,576–2,044,935; all coordinates based on Human Genome version 19), a 624 kb duplication of 6q22.31 (118,593,133–119, 217,162) including phospholamban, and a 5.1 Mb duplication of 11p15.4 to pter (230,615–5,139,027). This complex abnormality is associated with Cri du Chat (5p15 deletion) and Russell–Silver syndrome (11p15 duplication), neither of which are associated with cardiomyopathy. The 624 kb duplication of 6q22.31 includes the genes Minichromosome Maintenance Deficient Domain Containing 1, Anti-Silencing Function 1, and phospholamban, which has previously been associated with hereditary cardiomyopathy. Sequence-based genetic testing of 27 dilated cardiomyopathy genes, including phospholamban, was normal.

Initial karyotype testing of both parents was normal. However, florescence in situ hybridisation for chromosomes 5 and 11 identified the mother as a balanced translocation carrier (46,XX.ish t(5;11)(p15.3-,p15.5+;p15.5-,p15.3+).

The father's testing was normal. The phospholamban duplication was de novo with normal florescence in situ hybridisation for phospholamban in both parents.

Discussion

This case represents a unique case of syndromic cardiomyopathy due to a complex cytogenetic rearrangement. Sequence-based genetic testing for dilated cardiomyopathy identifies mutations in 17% of patients.[6] However, large deletions or duplications are not routinely identified by sequencing methods.

Phospholamban plays a primary role in cardiac contractility and relaxation through inhibition of the sarcoplasmic reticulum calcium ATPase. Animal studies have shown that mutations that cause gain of function or overexpression of phospholamban are associated with cardiomyopathy, and there is a report of a woman with hypertrophic cardiomyopathy with a sequence change in the phospholamban promoter, which increases activity.[7]

In syndromic cases with multiple extracardiac abnormalities, cytogenetic abnormalities including copy number variations should be considered and interrogated with a chromosome microarray. Identifying a genetic cause of non-isolated cardiomyopathy is particularly important in children to assist with appropriate comprehensive medical care and may include early intervention referrals for children at high risk of developmental delay. Appropriate expectations for growth are also necessary as growth is used as a primary outcome measure for adequacy of heart failure management. Furthermore, in this case, identifying the genetic aetiology clarified the recurrence risk for both cardiomyopathy and for other children with unbalanced cytogenetic rearrangements.

Acknowledgement

This publication was made possible by grant number T32-GM082771. The authors thank the family for their valuable contribution.

Financial Support

None.

Conflicts of Interest

None.

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