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CASE REPORT

Dilated cardiomyopathy in a child with truncating mutation in *NRAP* gene

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ABSTRACT

Background: Dilated cardiomyopathy (DCM) is a progressive disorder that has a heterogeneous genetic background. It has been linked to mutations in nebulin-related-anchoring protein (*NRAP*) gene. NRAP expressed mainly in striated and cardiac muscles, and it plays a substantial role in the sarcomeric contraction cycle and myofibrillogenesis.

Case Presentation: A 17-month-old baby girl presented at the age of 13 months with symptoms of heart failure. She was diagnosed as a case of DCM. Using whole exome sequencing, diagnosis is confirmed due to homozygous nonsense *NRAP* variant (c.400-407del; p.Cys134 Serfs*12), which creates premature stop codon.

Conclusion: This case report supports preceding reports that biallelic nonsense mutations in *NRAP* gene cause an autosomal recessive DCM with low penetrance genetic risk factor. However, the age of presentation can vary from early infancy up to adulthood.

Keywords: NRAP, dilated cardiomyopathy, nebulin, whole exome sequencing.

Introduction

Dilated cardiomyopathy (DCM) is the predominant type of cardiomyopathy in the pediatric population with a higher incidence in the first year of life (1,2). Majority of the cases of DCM are idiopathic. Nevertheless, genetic causes account for 40% of cases, and it is inherited commonly as an autosomal recessive pattern with incomplete, age-related penetrance, and variable expression (3,4). Clinical phenotypes are variable among different families and within family members as well. Most patients remain asymptomatic for many years prior to the development of manifestations, which include different symptoms such as arrhythmias, DCM, and sudden death (5,6).

Although DCM genetic nature is still poorly characterized, yet many genes were linked to DCM (7). such as the genes that encode cytoskeleton, sarcomere, nuclear envelope, ion channels, and intercellular junctions proteins (3,8). One of the recent discoveries on the genetic basis of DCM is nebulin-related-anchoring protein (*NRAP*) gene (OMIM #602873), which is involved in the sarcomeric contraction cycle (9).

NRAP belongs to nebulin family, which acts as integral cytoskeleton proteins that predominantly present in skeletal muscle thin filaments. It plays a significant role in myofibrillogenesis during cardiomyocyte development, and in the adult heart (10–12). It has a good expression in myofibril precursors but has limited one in the terminal bundles of actin filaments of the skeletal muscles and in the intercalated disk of the heart muscle (13–15). NRAP is consisting of a LIM domain followed by 46 nebulin repeats. The N-terminal LIM domain interacts with α-actinin and talin and the C-terminal super repeats interact with filamin C and vinculin (12,15,16). Experimentally, upregulation of NRAP expression was observed in DCM mice models and DCM human patients (17).

In spite of existing evidence that *NRAP* is crucial in the fetal heart, as well as in the adult heart, few variants in this gene were linked to cardiac disease. Herein, we report a child presented in her infancy period with a picture of DCM.

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Case Report

The proband is a 17-month-old baby girl presented to Emergency at age of 13 months with symptoms of heart failure, with easy fatigability, weakness, irritability, and shortness of breath. She was diagnosed as a case of DCM. Echocardiography showed severely depressed function with Ejection Fraction 22% and started on a regular dose of Carvedilol and Furosemide. She is a product of consanguineous marriage with unremarkable perinatal history. Development history was normal prior to her illness. Family history showed that she had a brother who was diagnosed at age of 12 months with cardiomyopathy, died at 17 months (Figure 1) with no molecular diagnosis. On physical examination, she appeared in vegetative neurological status post cardiac arrest with intact brainstem reflexes and normal eye examination, with no dysmorphic feature. Growth parameter showed height is 84 cm (75th–90th percentile), weight is 9.6 kg (10th–25th percentile), and head circumference is 46.5 cm (25th–50th percentile). Cardiovascular examination showed displaced apex beat with normal first and second heart sound and pansystolic murmur. No hepatomegaly and no clinical signs of skeletal myopathy noticed.

Electrocardiogram showed normal sinus rhythm, right axis deviation, and left ventricular hypertrophy, with inverted T-wave in lateral leads. On follow-up, echocardiography showed deterioration of left ventricular systolic function, estimated left ventricle ejection fraction was 15%, and moderate to severe mitral valve regurgitation, with no pericardial effusion. Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein were normal. Metabolic investigations were unremarkable, including lactic acid 1.03 (0.50–2.20 mmol/l), creatine phosphokinase 163 (26–168 U/l), as well as plasma amino acid, total carnitine 91 (34–84 µmol/l), free carnitine 71 (23–63 µmol/l), and acylcarnitine 19.2 (4–28 µmol/l). Brain MRI demonstrates severe recent hypoxic ischemic insult consist with cardiac arrest, no structural abnormality. By whole exome sequencing, a variant in *NRAP* gene NM_001261463, (c.400-407 del, p.Cys134 Serfs*12), creates a shift in the reading frame starting at codon 134 was detected. The new reading frame ends in a stop codon 11 positions downstream. This variant was detected in the mother in the heterozygous state; where the father is homozygous for the same mutation although he is asymptomatic. This mutation we detect in our patient has been previously described as a potential disease causing mutation for in a Saudi patient presented with cardiomyopathy (18).

Discussion

To date, no OMIM phenotype has been associated with the pathogenic variants in the *NRAP* gene. Our case report supports the recent report, which links the homozygous mutation in *NRAP* gene to DCM (19). The early presentation of our case at the age of 12-month infant supports that *NRAP* plays an important role in myofibrillogenesis in early childhood. Previous reports link *NRAP* with DCM in a 26-years-old patient, who was completely healthy until he rapidly progressed to biventricular heart failure. A homozygous truncated LoF variant in NRAP was the genetic risk factor for DCM in that case. Homozygosity of the same mutation was also found in the proband's asymptomatic brother (36 years old), which indicates that LoF of *NRAP* in humans can be tolerated, has limited penetrance, and/or requires other factors to express the manifestation (9,19). The

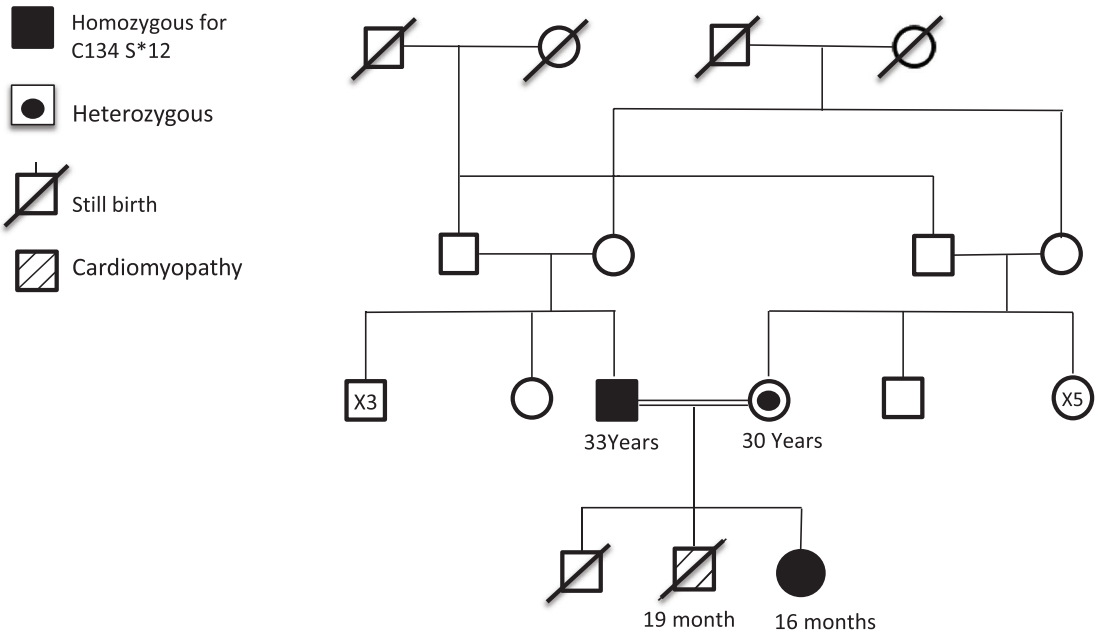

Figure 1. *Family pedigree showing family members genotype.*

same finding as in this case report. We postulate that a biallelic nonsense *NRAP* mutation could have led to cardiac dysfunction in this patient and previous cases, perhaps in conjunction with other genetic/non-genetic factors (9,20).

Conclusion

In conclusion, we report the second patient with DCM with a homozygous nonsense variant in the *NRAP* gene, as well as her healthy father with the same genotype. Our findings suggest that biallelic nonsense mutations in *NRAP* could have a wide range of age at presentation and a low penetrance genetic risk factor for DCM.

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Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication
Informed consent was obtained from the parents.

Ethical Approval:
Ethical approval is not required at our institution to publish an anonymous case report.

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