

Novel Gene with Pathogenic Mutation Associated with Dilated Cardiomyopathy, Hydrocephalus and Developmental Delay in Saudi Patient

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Abstract

Case Report

Dilated cardiomyopathy (DCM) often has a genetic pathogenesis. Because of the large number of genes and alleles attributed to DCM, comprehensive genetic testing encompasses ever-increasing gene panels. Genetic diagnosis can help predict prognosis, especially with regard to arrhythmia risk for certain subtypes. Moreover, cascade genetic testing in family members can identify those who are at risk or with early stage disease, offering the opportunity for early intervention. Determining genetic variants is emerging as an additional adjunct to help further refine subtypes of DCM. We report a rare new pathogenic missense mutation in *CFAP 58* in patient with cardiomyopathy disease not previously associated with DCM, developmental delay and dysmorphic features. Our patient had a rapidly progressing course, despite maximal medical management. To the best of our knowledge, it is the first report of mutation in *CFAP 58* in Saudi patients associated with dilated cardiomyopathy and developmental delay.

Keywords: Dilated cardiomyopathy (DCM), Echocardiography, CFAP58 (Cilia and Flagella Associated Protein 58) is a Protein Coding gene. Whole - exome sequencing (WES).

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INTRODUCTION

Cardiomyopathy (CM) remains one of the leading cardiac causes of death in children, although in the majority of cases, the cause is unknown. To have an impact on morbidity and mortality, attention must shift to etiology-specific treatments. The diagnostic evaluation of children with CM of genetic origin is complicated by the large number of rare genetic causes, the broad range of clinical presentations, and the array of specialized diagnostic tests and biochemical.

CASE PRESENTATION

A 17 months old boy presented at age of ten months old to emergency room complaining of shortness of breath, cough, fever, decreased activity, oral feeding with poor feeding since age of three months. He has a history of recurrent visits to emergency room with similar illness treated a chest infection.

Patient looks ill, lethargic, on respiratory distress. He appeared small for age with current body weight of 6 kg (below fifth centile). Vital sign showed

of heart rate of 170 bpm, blood pressure 88/59 mmHg, and respiratory rate 35-45 breath per minute.

Cardiovascular examination revealed cold extremities, poor perfusion, apex beat shifted downward and outward. Audible first and second heart sound with third heart sound. Abdomen examination suggestive hepatomegaly, palpable liver 5 cm below costal margin.

Central nervous system, examination showed large head, anterior fontanelle was open and flat with dilated veins and sunken eyes. Both pupils were reactive to light. Patient is hypotonic; power was 3/5 with absent reflexes.

He was investigated and showed

Electrocardiogram showed sinus tachycardia with inverted T-waves and maximum voltage in V4, V5 and V6 and no arrhythmias (Figure 1). Chest X-ray was suggestive of cardiomegaly with congested lung (Figure 2).

Echocardiography: Two dimensional long parasternal view echo revealed severely dilated LV,

severely depressed LV function, LV ejection fraction of 18% (Figure 3). Color doppler of apical four chamber echo showed severely dilated LV with moderate mitral regurgitation (figure 4).

CT brain showed of prominent of sub convexity CSF spaces with prominent ventricular system consisting with communicating hydrocephalus. Whole exome analysis for the patient was send and result showed that a homozygous variant of CFAP58 was identified.

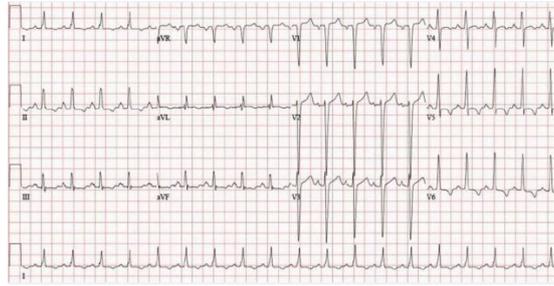


Fig-1: ECG showing sinus tachycardia, left atrial enlargement, T wave inversions in the lateral limb (I and aVL) and precordial (V5 – V6) leads and deep S waves in V1, V2, V3

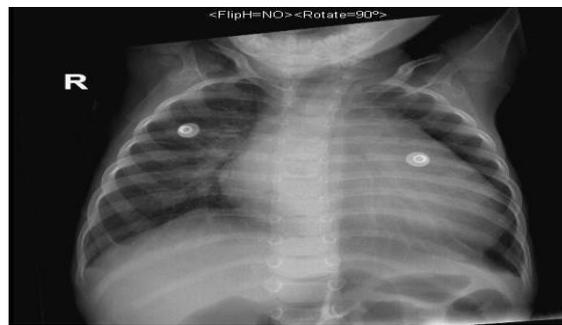


Fig-2: Chest X-ray showed of cardiomegaly with congested lung



Fig-3: Twodimensional long parasternal view echocardiogram revealed severely dilated LV, severely depressed LV function, LV ejection fraction of 18%

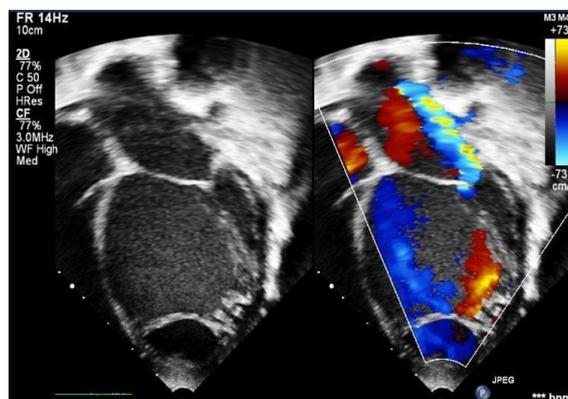


Fig-4: Color doppler of apical four chamber echo showed severely dilated LV with moderate mitral valve regurgitation

DISCUSSION

Dilated cardiomyopathy (DCM) is a heart muscle disorder characterized by left ventricular (LV) dilation and systolic dysfunction, often resulting in low cardiac output secondary to heart failure. It is the most common cardiomyopathy in children [1].

Epidemiology

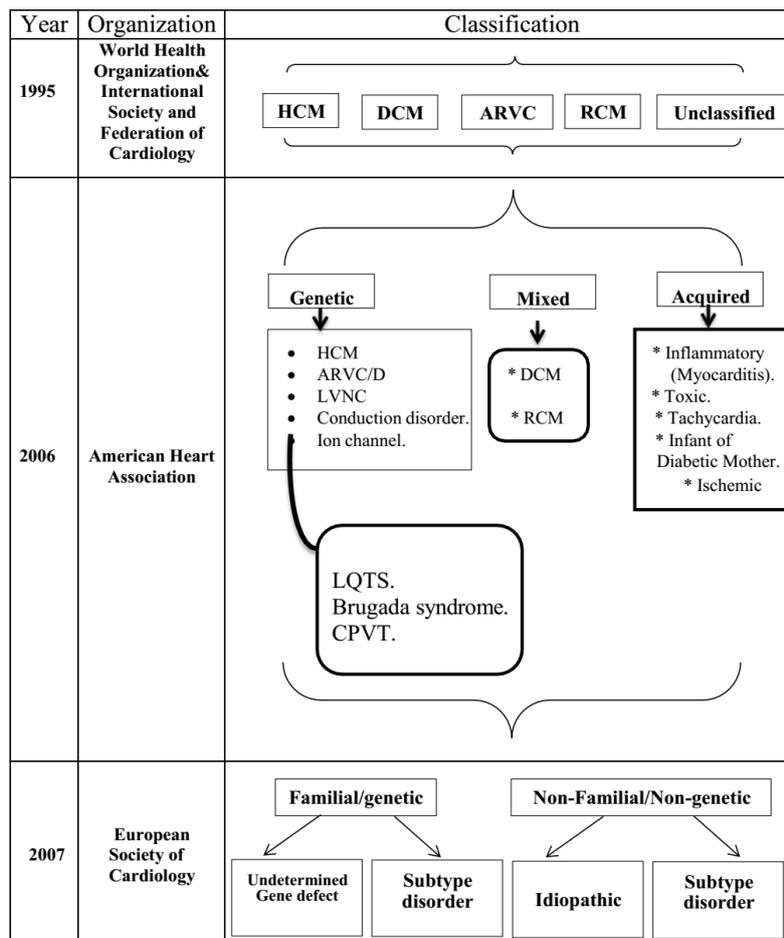
DCM is a rare, but debilitating disease of the heart that can lead to heart failure in both children and adults. The annual incidence of DCM in children younger than 18 years was 0.57 cases per 100 000 per year overall. The annual incidence was higher in boys than in girls (0.66 vs 0.47 cases per 100 000; $P < .001$), in blacks than in whites (0.98 vs 0.46 cases per 100 000; $P < .001$), and in infants (<1 year) than in children (4.40 vs 0.34 cases per 100 000; $P < .001$). The majority of children (66%) had idiopathic disease. The most common known causes were myocarditis (46%) and neuromuscular disease (26%). The 1- and 5-year rates of death or transplantation were 31% and 46%, respectively [2].

Classification of pediatric cardiomyopathies

Cardiomyopathies are defined as abnormalities of the ventricular myocardium unexplained by abnormal loading conditions or congenital heart disease. The 1995 World Health Organization classifications were based on a combination of morphological (dilated and hypertrophic), physiological (restrictive), and etiologic (causes extrinsic to the myocardium, such as infection, were excluded) characteristics [3]. The identification of genetic mutations has led to controversies on the classification criteria.

In 2006, the American Heart Association updated the definition and classification by defining them as a heterogeneous group of myocardial diseases with mechanical and (or) electrical dysfunction which were categorized into primary and acquired types [4].

In 2007, cardiomyopathy was classified into familial/genetic and non-familial/non-genetic (Table 1). However, the classifications of cardiomyopathies are very complex, because cases can actually be classified as more than one type or change from one type to another [5].



DCM: Dilated cardiomyopathy, HCM: Hypertrophic cardiomyopathy, RCM: Restrictive cardiomyopathy, ARVC/D: Arrhythmogenic right ventricular cardiomyopathy

Genetics

Pediatric cardiomyopathies are genetically heterogeneous with many different causative genes and multiple mutations in each gene. Mutations in genes encoding components of the sarcomere or costamere and related binding proteins, Z-band, nuclear membrane, desmosome, mitochondrial, and calcium-handling proteins have all been found in children with cardiomyopathy [6]. Genetic variants causing cardiomyopathy in children can also have systemic features affecting noncardiac organs [7].

Between 35% and 40% of genetic DCM cases are thought to be caused by sarcomere gene mutations, with mutations in the giant protein titin estimated to be responsible for about 25% [8]. Gene mutations can also affect multiple Z-band proteins. Which connect the thin

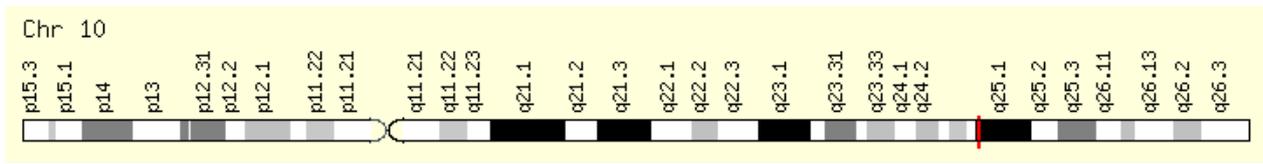
filaments and titin, thereby serving as an important nodal point of mechanosignaling[9,10].

Mutations in dystrophin and the sarcoglycans produce skeletal muscle disease and cardiomyopathy; as such, heart failure in these patients may be further compromised by hypoventilation from respiratory muscle weakness [11].

▼ Molecular Genetics in our case

Gene function

CFAP58 (Cilia and Flagella Associated Protein 58) is a Protein Coding gene in chromosome 10 [12, 13]. Cytogenetic Location (figure 5): figure 5.



Locus heterogeneity in cardiomyopathy and congenital hydrocephalus is strongly suggested by the identification of infants and children with a phenotype meeting the genotype but in whom no apparent pathogenic variant involving CFAP 58 or its locus have been identified[17,15].

Whole-exome sequencing showed a homozygous variant of CFAP58 (CFAP58:NM_001008723:exon18:c.2511-4A>C) was identified in this patient. Although no mutations have been reported in this gene, this variant is interesting because: a) the nature of the variant (novel, within ROH, predicted deleterious *in silico*) and b) the nature

of the gene (CFAP58 is cilia associated gene Cilia-associated genes are known to underlie congenital hydrocephalus)[13].

Our study identified a rare new pathogenic missense mutation in CFAP 58 in patient with cardiomyopathy disease and it is the first report of mutation in CFAP 58 in saudi patients with this disease. After doing segregation analysis for the blood sample from both parents and tow of the siblings the qPCR confirmed deleterious mutation of the CFAP 58 sequence in both unaffected parents, mom brother and two of the siblings (haploid, heterozygous) ,while other tested sibling is normal not having the variant (figure 6).

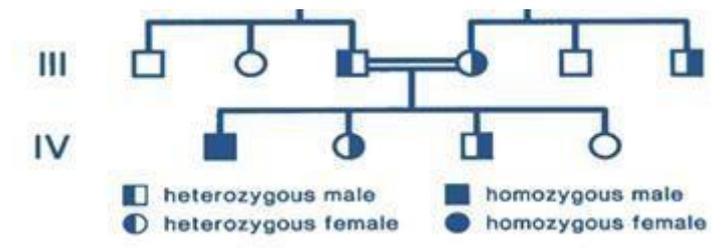


Fig-6

METHODS WES is performed on genomic DNA using the Agilent SureSelect Target Enrichment workflow to capture regions of interest from a DNA fragment library. The whole exome is sequenced on the Illumine HiSeq 2500 sequencing system with a minimum coverage of 30X of 95% of the target regions [16]. The proband's exome DNA sequences are mapped and compared to human genome build UCSC hg19 reference sequence. Saudi Diagnostic Laboratories uses an in-house pipeline to compare the proband's sequence to the reference sequence. Assessment of coverage and

quality for targeted coding exons of the known protein-coding RefSeq genes is performed. Exome analyses interrogate thousands of genetic variants in a proband using proprietary databases customized to Arab populations. A subset of these is characterized using the American College of Medical Genetics and Genomics (ACMG) guidelines to classify their clinical relevance. Sanger sequencing is performed to validate all variants included in the report unless otherwise stated [13, 14].

CONCLUSION

In this case we report novel gene with pathogenic mutation in Saudi patient who has dilated cardiomyopathy, large head, hypotonia and developmental delay.

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