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The Phenotypic Variability of R249Q MYH7 Mutation in Familial Cardiomyopathy

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Aim:
Familial restrictive cardiomyopathy (RCM) is the least common among inherited cardiomyopathies. Only few RCM -causing mutations have been described, most of them are located to sarcomere protein genes. In the present study we describe a family with autosomal dominant inheritance expressed as restrictive cardiomyopathy caused by a mutation in myosin gene. The same mutation was previously implicated in hypertrophic cardiomyopathy and dilated cardiomyopathy.

Methods:
We identified a Muslim Arab family from the Galilee with familial cardiomyopathy inherited as an autosomal dominant trait. Family members underwent physical examination, ECG, Echo-Doppler studies. DNA was extracted from peripheral venous blood; candidate genes analysis was done using Next Generation Sequencing.

Results:
The proband, a 33-year-old women, presented with atrial fibrillation and thromboembolic phenomena followed by progressive heart failure and eventually heart transplantation. Echocardiography showed ventricles with normal wall thickness and systolic function, biatrial enlargement and diastolic dysfunction. Endomyocardial biopsy revealed hypertrophic changes, myocyte vacuolization and glycogen inclusions. The proband's mother was previously diagnosed with hypertrophic cardiomyopathy. Family screen identified 3 affected sisters exhibiting a restrictive phenotype and 15 years-old nephew with severe hypertrophic cardiomyopathy. Gene sequencing identified a point mutation within beta-myosin heavy chain gene, resulting in the replacement of arginine by glutamine (R249Q). This mutation affects the active ATP binding site of the beta-myosin head domain.

Conclusion:
R249Q mutation in MYH7 gene has been previously associated with hypertrophic and dilated cardiomyopathy, but for the first time we describe it in a family with restrictive cardiomyopathy. These findings demonstrate the remarkable phenotypic variability in families with cardiomyopathy. The genetic and environmental modifiers responsible for different modes of cardiac remodeling remain to be identified.