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De Novo Titin Mutation In Familial Restrictive Cardiomyopathy

Arad, M[1]; Potashnik, Y[1]; Yoskovitz, G[2]; Pras, E[2]; Gramlich, M[3]; Gerull, B[3]; Thierfelder, L[3]; Feinberg, M[1]; Afek, A[4]; Freimark, D[1]
[1]Heart Institute, Tel Hashomer, Israel; [2]Sheba Hospital, Tel Hashomer, Israel; [3]Max Delbrueck Center for Molecular Medicine, Berlin, Germany; [4]Sheba Medical Center, Tel Hashomer, Israel

Familial restrictive cardiomyopathy (RCM) is the least common amongst inherited cardiomyopathies. We report a novel mutation in titin (TTN) in a family with RCM inherited as an autosomal dominant trait. Family members were screened by ECG, echo-doppler, serum creatine kinase and NTproBNP. DNA was extracted from peripheral venous blood. Linkage to candidate loci was examined with custom generated polymorphic repeat markers. The family comprised 5 affected individuals (2 males, 3 females) aged 12-35 years, and 12 healthy first degree relatives. Echo-doppler of the affected was characterized by restrictive left ventricular filling and miniature 'A' waves but normal wall thickness and preserved left ventricular function. Four had symptoms of heart failure and NTproBNP of 1016 to 4242 pg/µl. All had left axis deviation on ECG, 3 had RBBB but none had atrioventricular block or skeletal myopathy. Endomyocardial biopsy showed extensive fibrosis and disorganized sarcomeres but no storage or infiltration. The proband and her daughter had undergone heart transplantation while a 16 year old nephew expired. Linkage analysis to candidate loci excluded 18 genes of sarcomere proteins, desmin, etc. A common haplotype surrounding the TTN gene was shared by all the affected. Sequence analysis identified a Y7621C mutation, replacing a highly conserved hydrophobic tyrosine with a polar cystein within the fibronectin3 domain. The mother and 2 siblings of the proband carried the disease haplotype but not the mutation, suggestive of germ-line mosaicism. TTN mutations were previously reported to cause skeletal myopathy and dilated or hypertrophic cardiomyopathy. In this family, a missense mutation arose de novo resulting in malignant RCM. Titin is a giant protein responsible for sarcomere assembly and regulating resting tension. We propose that the change in protein structure impairs the "molecular spring" function, thereby leading to restriction and development of cardiomyopathy.