A Missense Mutation in PRKAG2 as a Novel Cause of Familial Atrial Cardiomyopathy with Features of Glycogen Deposition

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**Introduction**: Atrial cardiomyopathy (ACM) is a novel subtype of cardiomyopathy characterized by atrial lesions which are associated with significant atrial arrhythmias. Rarely, heritable forms of ACM have been reported, and underlying mechanisms remain unknown. Herein, a 3-generation family affected by ACM with histories of syncope, atrial tachycardia, embolic events and pace maker implantations were enrolled.

**Methods**: We carried out whole genome sequencing with linkage analysis in 3 affected members. The atrium samples were obtained from the proband via surgical intervention. Control atrium biopsies came from a patient with congenital heart disease. Comparative histology, transmission electron microscopy and western blot analyses were carried out to explore the pathogenesis in this ACM pedigree. Human induced pluripotent stem cell-derived atrial cardiomyocytes were transfected with adenovirus carrying the same mutation. Quantitative structural analyses were used to define the functional disturbances of the mutation.

**Result**: Exome sequencing identified a missense mutation c.905G > A (R302Q) in the gene that encodes the gamma2 regulatory subunit of AMP-activated protein kinase (PRKAG2). Compared to control, PRKAG2-R302Q atria displayed disordered myofibrils, profound fibrosis and extensive glycogen deposition. Overexpressing PRKAG2-R302Q mutation in hiPSC-derived atrial cardiomyocytes resulted in significantly increased glycogen deposition and apoptosis ratio. Investigation of the protein expression levels revealed that PRKAG2-R302Q mutation led to increased AMPK activities.

**Conclusion**: We have identified a variant in PRKAG2 as pathogenic variant for familial ACM. It demonstrated that PRKAG2-R302Q mutation could lead to glycogen deposition and further atrial lesions via AMPK pathway. These results improved our understanding of the molecular basis of ACM. Pedigrees considered to be relevant for ACM can be identified by the approach presented here.