Commentary

Too much sugar leaves a sour taste: A cardiac disease caused by excess glycogen deposit

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Unexplained cardiac hypertrophy is most commonly associated with hypertrophic cardiomyopathy, the number one monogenic cardiovascular disorder. Echocardiography-based epidemiological studies have shown a disease prevalence of 1 per 500 individuals, but a prevalence of 1 per 200 is estimated by clinical and genetic data including family members [1].

Hypertrophic cardiomyopathy is inherited in an autosomal dominant pattern, associated with mutations in the contractile components of the sarcomere or Z disk. A small subset with unexplained hypertrophy, however, have mutations in genes not related to the sarcomere. One of these is PRKAG2, which encodes the gamma2 subunit of the adenosine monophosphate activated protein kinase (AMPK) [2]. In contrast to hypertrophic cardiomyopathy, which is not characterized by a progressive disorder, PRKAG2 cardiomyopathy patients manifest progressive symptoms around the second decade of life. It is crucial to correctly differentiate those disorders because their management and prognosis are diverse.

In this issue of EBioMedicine Dan Hu and colleagues report on the identification, clinical manifestation and structural mechanisms of mutations in AMPK associated cardiac glycogen storage disease. They investigated 885 patients with unexplained hypertrophy and found 25 carriers (2.8%) from 12 independent families harboring 5 different variants of PRKAG2 gene mutations. The reported incidence could be twice as high (~5%), if the 22 family members who died from cardiac arrhythmia and its deleterious effect on cellular homeostasis pathways [3].

Abnormal lipid metabolism may occur with dysfunctional AMPK. Chronic AMPK activation in mice carrying y2 mutation, induces obesity and reduces β cell function, impairing insulin secretion in a murine model of PRKAG2 mutation. This involves augmentation of ghrelin signaling-dependent hyperphagia. Humans bearing the homologous y2 R302Q mutation show key aspects of the murine phenotype, particularly increased adiposity and reduced β cell function [5].

Through computational modeling, Hu et al. highlighted the mechanistic pathogenic role of a number of residues. They found that even remote mutations on the surface of the protein (such as N488I and L341S) can lead to a disruption in the nucleotide binding pocket and decrease the binding affinity for ligands. H401D and T400N, in addition to affecting the nucleotide binding pocket, also disrupt the intersubunit interface. This would explain the dysfunctional AMPK regulation and its deleterious effect on cellular homeostasis pathways [3].

Sudden cardiac death in PRKAG2 mutation carriers is frequent and occur early in life [8,9]. A timely pacemaker implantation will probably prevent sudden death as advanced atrioventricular block and severe sinus bradycardia is a common feature in patients already in the third decade. Another mechanism of sudden death is pre-excited atrial fibrillation and very fast ventricular rate. Ventricular pre-excitation is present in two-thirds of the most common mutation, R302Q, and may set the stage for fast ventricular rates. One unresolved issue is the occurrence of ventricular tachycardia and ventricular fibrillation as a mechanism of sudden death. Some patients receive an implantable cardiac defibrillator for primary prevention because of a mistaken diagnosis of hypertrophic cardiomyopathy. Most therapies were caused by episodes of fast atrial fibrillation [8]. Hu et al reported a sudden cardiac death incidence of 16.7%. However, they could not shed light on the mechanism of sudden cardiac death because they could not differentiate ventricular tachycardia from pre-excited atrial fibrillation. It seems that there is a lower risk of ventricular fibrillation in this condition. Sternick et al., reported no ventricular tachycardia induction during programmed ventricular stimulation [10]. Cardiac magnetic resonance shows late gadolinium enhancement in only one fourth of the patients [11]. Myocardial biopsy samples usually do not show fibrosis [12,13], except in patients with end-stage heart disease, like the one reported by Hu et al.

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Campuzano et al. also in this issue of *EBioMedicine*, re-analysed 104 patients with inherited arrhythmogenic syndromes and 17 post-mortem cases in which inherited arrhythmogenic syndrome was the likely cause of death, and found that two thirds of the rare genetic variants previously classified as likely pathogenic, were reclassified as of unknown significance ten years later [14].

In contrast, *PRKAG2* mutations have shown complete penetrance. Hu et al reported that 22 distinct heterozygous variants of *PRKAG2* mutation have been described, all of them located close to adenosine nucleotide binding CBS domains. However, reviewing cases reported in the literature and ClinVar, we compiled 34 distinct mutations. There are 21 variants, labeled as pathogenic (n = 14), likely pathogenic (n = 6), and with conflicting interpretations of pathogenicity (n = 1) at ClinVar. We also found an additional 13 variants in the literature. However, the total number of patients does not exceed 250 worldwide (excluding an equal number of family members who died due to heart failure or sudden death). Considering the incidence of 5% of *PRKAG2* mutation carriers in those with unexplained hypertrophy and deceased family members, as found by Hu et al, a prevalence of *PRKAG2* mutation of 1 per 10,000 adult individuals can be estimated in the general population. Similar work in 84 children (<15 years of age) with unexplained hypertrophy and deceased family members, as found by Hu et al, a prevalence of *PRKAG2* mutation (1%) and a sarcomeric gene mutation in 46 cases (54%) [15].

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In a different cohort of 24 patients with unexplained hypertrophy and ventricular pre-excitation, one third have a *PRKAG2* mutation, a yield of 46% for glycogen storage disease [16]. Hu and colleagues are to be commended for their contribution in increasing our understanding of the abnormal protein pathogenesis and increasing awareness of *PRKAG2* cardiomyopathy.

**Declaration of Competing Interest**

There is no conflict of interest to disclose.

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