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Cardiomyopathy diagnosed in the eldest child harboring p.S24X mutation in *JUP*

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CONFLICT OF INTEREST

The authors state no conflict of interest.

TO THE EDITOR,

In 2010 we reported two separate homozygous mutations in the 5' region of *JUP* which segregated with skin fragility and normal heart development in children from four separate families(1). At the time, only 3 mutations in this gene had been previously reported and each of the earlier identified mutations segregated with an inherited progressive disease of the heart, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)(2-4). Five years on and as a result of close monitoring in each patient we report here that the eldest individual harboring homozygous mutations p.S24X has been diagnosed with left dilated cardiomyopathy (also considered ARVD/C) at age 17 years. All other patients examined report normal heart function.

The *JUP* gene encodes the protein plakoglobin (PG), also known as γ-catenin, which is abundant in cell cell junction complexes of adherens junctions and desmosomes. As well as this structural role PG can also influence cellular signaling where it's homology to and interaction with, β-catenin is crucial (for review see(5)). Mutations in *JUP* leading to Naxos disease(3), a so-called cardio-cutaneous syndrome affecting both skin and heart, identified PG as a protein important in these tissues, and confirmed earlier observations that mutation in genes encoding desmosomal components are a major cause of this type of cardiomyopathy(6). While originally termed ARVD/C, it has been shown that both right and left ventricles are often affected and as such, a

descriptive change to Arrhythmogenic Cardiomyopathy (AC) has been proposed to better reflect the pathology(7). Nearly half of all diagnosed AC patients harbor mutation in at least one of the genes encoding desmosomal proteins expressed in the heart: PG (*JUP*), plakophilin2 (*PKP2*), desmoplakin (*DSP*), desmocollin2 (*DSC2*), and desmoglein2 (*DSG2*). Thus, AC is classified as a disease of the desmosome. The majority of desmosomal gene mutations (48.1%) have been identified in PKP2(8) while *JUP* represents the least affected, contributing to 3.8% of all mutations(9) (see Table 1 and Fig. 1 for a summary of pathogenic *JUP* mutations).

Prompted by the observation that since our publication 10 further mutations have been reported in *JUP* and that all of these mutations, with the except of p.Q539X which resulted in early lethality due to severe skin involvement (10), are associated with AC(9), we re-visited the hospital records of patients harboring p.S24X and the splice site mutation, c.468G>A. Informed consent and ethical approval to study molecular and skin pathology in these children were obtained for the original study(1), while here we report clinical follow-up. These five patients are monitored regularly (every 2-3 years) and records showed that the eldest patient harboring p.S24X presented with slight dilation of the left ventricle with normal systolic function as determined by Doppler echocardiography at age 17 (Table 2). The cardiac involvement progressed to diagnosis of left dilated cardiomyopathy 20 months later, age 19, at which point the patient was prescribed angiotensin-converting enzyme inhibitors and β-blockers. Further monitoring will determine whether an implantable cardioverter-defibrillator (ICD) is necessary (11). Given the development of heart involvement we propose to reclassify patients harboring p.S24X mutation in *JUP* as a cardio-cutaneous syndrome.

Since our original report the two patients harboring c.468G>A mutation in *JUP* have two new siblings affected by the same disorder. All four individuals share phenotypic characteristics which include: diffuse hypotrichosis, diffuse palmoplantar keratoderma (observed to worsen with advancing age), recurrent paronychia followed by nail-dystrophy; skin fragility; eczematoid skin rashes affecting mainly the scalp, face & extremities; poor dentition; and recurrent skin infections. As previously reported the most notable difference with patients harboring p.S24X *JUP* mutation is the presence of hypotrichosis (1) (Figure 2). Given the structural and ultrastructural similarities we previously reported between patients harboring homozygous p.S24X and c.468G>A mutations(1), we predict that patients with c.468G>A will likely develop similar cardiac abnormalities. All patients will continue to be monitored on a regular basis.

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Table 1: Spectrum of *JUP* mutations, phenotype, mode of inheritance, and allele frequency identified in the Exome Aggregation Consortium (ExAC) database (accessed January 1st 2016). The ExAC database reports exome sequencing data from >60,000 unrelated individuals and indicates the prevalence of previously reported pathogenic *JUP* mutations. D = dominant, R = recessive. * - homozygous mutation, p.Q529X resulted in post-natal lethality due to massive transcutaneous fluid loss with apparent normal heart development (10). ** - p.V603L identified in one family with incomplete penetrance (14).

Mutation	Reference	Phenotype	Inheritance	Allele Count	Allele Frequency
p.T19I	12	Heart	D	13	0.0001139
p.S24X	1	Skin and Heart	R	-	-
p.S39_K40insS	2	Heart	D	-	-
p.I131del	13	Heart	D	-	-
c.468G>A	1	Skin (eldest 9 yrs)	R	-	-
p.V159L	4, 13	Heart	D	5	0.00004237
p.S225L	14	Heart	D	1	0.000008256
p.R265H	15	Skin and Heart	R	1	0.000008252
p.E301G	9	Skin and Heart	R	1	0.000008256
p.V407I	14	Heart	D	3	0.00002472
p.T427M	14, 16	Heart	D	6	0.0000494
p.Q529X	10	Skin (lethal)*	R	-	-
p.V603L	14	Heart	D**	76	0.0006604
p.G680fsX690	3	Skin and Heart	R	-	-
p.Y693C	16	Heart	D	3	0.00002563

Table 2: Cardiac investigations in patients with homozygous *JUP* mutations, p.S24X or c.468G>A.

Patient	Mutation	Age of cardiac investigation and result
1	p.S24X	16 years, normal
2	p.S24X	17 years, Left Dilated Cardiomyopathy
3	p.S24X	9 years, normal
4	c.468G>A	9 years, normal
5	c.468G>A	7 years, normal

FIGURE LEGEND

Fig. 1: 15 pathogenic variants have been identified in *JUP* encoding plakoglobin. Cartoon shows plakoglobin protein and the relative locations of pathogenic mutations identified to date. Blue text indicates mutations resulting in cardiomyopathy only while red text indicates skin involvement, with lighter red indicating no reported cardiomyopathy. Boxes represent Armadillo repeat domains.

Fig. 2: Patients harboring homozygous p.S24X *JUP* mutations do not exhibit hypotrichosis as observed in c.468G>A homozygous patients.

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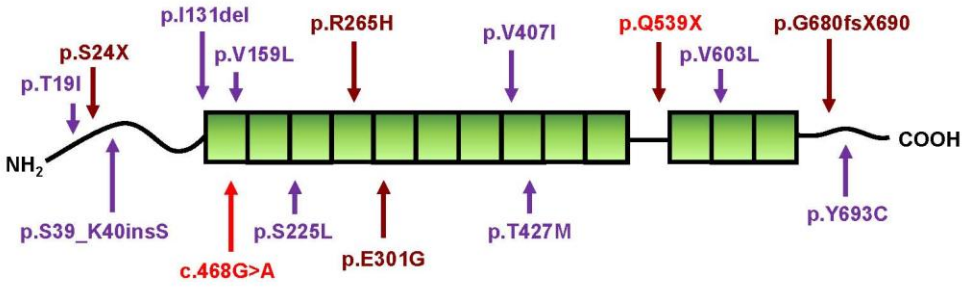

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