**A novel desmin gene variant as an important cause of biventricular arrhythmogenic cardiomyopathy**

Alexandros Protonotarios, Ellie Quinn, Chrysoula Dalageorgou, Marta Futema, Mohammed Akhtar, Angeliki Asimaki, Michael Ashworth, Konstantinos Savvatis, Petros Syrris, Perry Elliott, Luis R Lopes

**Introduction**: Arrhythmogenic Cardiomyopathy (AC) is typically caused by mutations in the desmosomal genes, however non-desmosomal genes have been increasingly implicated. Desmin gene *(DES*) mutations have been previously reported in AC, but in many cases there are insufficient data to support their pathogenicity.

**Purpose**: We assessed our AC cohort for *DES* gene mutations and describe the clinical phenotype associated with a recurring variant present in 3 unrelated families.

**Methods**: Genetic testing was performed using next-generation sequencing for 41 genes in a total of 138 AC probands with a definite diagnosis of AC based on the revised 2010 Task Force diagnostic criteria. All candidate variants were confirmed using Sanger sequencing. Clinical and genetic cascade screening were expanded to the first-degree relatives of the probands. Retained tissue from deceased individuals was used for genetic testing. All living mutation carriers underwent clinical assessment including physical examination, 12-lead ECG, signal-averaged ECG, echocardiography, cardiac magnetic resonance imaging (MRI) and 24h Holter-monitoring.

**Results**: Two *DES* gene variants, p.Ser298Leu (n=1) and p.Leu115Ile (n=3), were identified in 4 out of the 138 probands (3%). The former coexisted with a pathogenic DSP gene mutation and has not been further evaluated. The latter is a novel variant, absent in control databases (gnomAD) and was the only variant present in 3 unrelated families (see figure). One carrier required heart transplant (A-II-1), two died suddenly (A-III-1, B-II-1) and one died of non-cardiac causes (B-I-2). Detailed clinical information was present in 8 mutation carriers (2 male, age 45 ± 19 years). Seven (88%) had a definite diagnosis and one had a borderline diagnosis of AC. All cases (100%) had right ventricular (RV) wall motion abnormalities, 6 (75%) had a dilated RV, 6 (75%) a dilated LV and 6 (75%) had LV dysfunction (mild in 5 and severe in 1). LV late gadolinium enhancement (LGE) was present in all 6 carriers that had a cardiac MRI with a circumferential sub-epicardial distribution (see figure, case A-III-2). Non-sustained ventricular tachycardia (VT) was present in 7 (88%) and sustained VT in 2 cases (25%). The ventricular ectopic burden per 24h ranged from 426 to 10583 with a median value of 820.

**Conclusion**: Variants of the *DES* gene are rare causes of AC. The novel p.Leu115Ile variant seems to be prevalent in a large UK-based cohort and it causes a biventricular form of AC, with a characteristic scar pattern on MRI and severe outcomes.

