arrhythmias including SVT, AF, flutter, and AV block. Cardiac MRI was available for 21,222 of the WES individuals. We extracted the LV ejection fraction (LVEF), end-systolic (LVESV) and end-diastolic volumes (LVEDV). We removed outliers > 7 SD from the mean and normalized volumes (LVEDV, LVESV) by body surface area (BSA), age and sex. For each of the gene groups, we compared those with rare variants to the rest. 

**Results:** We validated that nonsense variants in genes of the definitive and strong evidence group were associated with both adverse cardiovascular outcomes, LV dilation and ventricular/SV arrhythmia. Importantly, we found that genes in the “moderate” evidence group (ACTC1, ACTN2, JPH2, TNNI3, TPM1, VCL) with ClinVar annotations were associated with increased cardiac morbidity (OR 3.6, 95% CI 1.7-7.6), and variants with SIFT or nonsynonymous annotations were associated with increased LVESV (+3.94 ml vs control, p = 0.01) and LVEDV (+4.45 ml vs control, p = 0.03), and decreased LVEF (-0.65% vs control, p = 0.03), as well as with SV arrhythmia (OR 5.1, 95% CI 2.2-11.6).

**Conclusion:** We provide evidence to support the interaction of genes previously classified as “moderate” with DCM, arrhythmia and adverse cardiovascular outcomes.

**HF-566-02**

**PREDICTED RISK OF VENTRICULAR ARRHYTHMIA IN INDIVIDUALS WITH DESMOSOME GENE VARIANTS IDENTIFIED VIA POPULATION GENOMIC SCREENING**

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**Background:** Population genomic screening for desmosomal variants associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) may help facilitate early detection of disease and protective intervention. However, early studies have shown that disease penetrance in this setting is low. The ARVC risk calculator offers a novel means to risk stratify individuals who present with variants identified via population genomic screening.

**Objective:** Quantify the risk of arrhythmic events in individuals with ARVC-associated variants ascertained “genome first” from a general population.

**Methods:** Individuals harboring a pathogenic/likely pathogenic (P/LP) variant in a desmosome gene (PKP2, DSP, DSG2, or DSC2) were identified through the Geisinger MyCode Genomic Screening and Counseling program. The ARVC risk calculator was applied to all patients with a subsequent evaluation of RV function. Missing 24-hour PVC counts (i.e. no rhythm monitoring study or PVC count not quantified), were imputed with the group median.

**Results:** Of 184 individuals with a clinically confirmed P/LP desmosome variant, 80 (median age 57 [IQR 44-68]; 71% female) had cardiac imaging in follow-up. Fifty-eight (72%) had no ARVC task force criteria (TFC) besides the P/LP variant (possible diagnosis), 11 (14%) had a single minor criterion (borderline diagnosis), and 11 (14%) met criteria for definite diagnosis. The overall median 5-year predicted VA risk was 5.2% (risk of fast VA 2.0%), notably much lower than median risk in the calculator’s derivation cohort (20.6%). The predicted risk was modestly higher in individuals with any TFC (10.1 [4.5-17.0%]) versus those with none (4.5 [2.8-7.1%], p = 0.01). The risk was also higher in those with left ventricular dysfunction and arrhythmia (i.e. “ALVC” 13.7 [8.2-18.5]% vs. non-ALVC 4.9 [2.9-7.9]%).

**Conclusion:** The predicted 5-year risk of VA in individuals ascertained via population genomic screening with ARVC risk is relatively low (5.2%; 2% for “fast” VA) but may vary by gene, having any TFC, and affected ventricle.

**HF-566-03**

**EMD MISSENSE VARIANTS ARE ASSOCIATED WITH A DILATED CARDIOMYOPATHY AND CONDUCTION SYSTEM DISEASE/ATL**

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**Background:** Emerin (EMD) is an essential inner nuclear envelope protein encoded by EMD. Loss of function (LoF) variants in EMD result in Emery-Dreifuss muscular dystrophy type 1 (EMD1). Cardiac involvement in EMD1 is characterized by sinus node dysfunction (SND), atrial fibrillation (AF) and dilated cardiomyopathy (DCM). Recently a non-syndromic cardiac phenotype termed cardiac emerinopathy was recognized in patients with predominantly LoF variants in EMD. The contribution of EMD missense variants to cardiac disease is unknown.

**Objective:** To characterize the impact of EMD missense variants and delineate the associated cardiac phenotypes.

**Methods:** We surveyed exome sequencing data in the Penn Medicine Biobank (PMBB) for all coding variants identified in EMD. The medical record of male individuals with non-synonymous EMD variants (given an X-linked inheritance pattern) were reviewed to characterize cardiac and musculoskeletal pathology. Male individuals with synonymous EMD variants with no predicted effect on mRNA splicing were used as a reference group.

**Results:** A total of 28 EMD missense variants and a single frameshift insertion were identified in 68 male individuals (mean age 68±14). Seventy-seven patients with synonymous variants
(age 63±16) were used as reference group. Non-synonymous EMD variants were associated with non-ischemic cardiomyopathy, cardiac conduction disease and atrial fibrillation (OR: 7.2, 95% CI 3.3-15). Forty-two patients had a cardiac phenotype, 14 individuals had symptomatic SND and/or advanced AV block, 8 patients had DCM, 6 patients had LV dysfunction, 2 patients had ARVC, 2 patients had HCM, 9 patients had isolated AF and a patient with an EMD frameshift variant who had EDMD1. Overall 32% had AF; 22% had a cardiac implantable electronic device. Interestingly, individuals with non-synonymous variants had a higher incidence of tendon rupture and tendinopathy when compared to reference group (OR 3.4, 95% CI 1.3 to 9.2). Among patients in the PMBB, EMD related cardiac disease was detected in 1 out of every 520 male patients.

**Conclusion:** Missense EMD variants contribute to a cardiac emerinopathy in male patients. The disease spectrum includes LV dysfunction, cardiac conduction disease and atrial arrhythmias.

**Cardiac Emerinopathy Phenotype Spectrum**

**Presentation Based on Variant Effect**

**ABSTRACT HP-573:**


Saturday, April 30, 2022
9:15 AM - 10:15 AM

**HP-573-01**

**Lesion Quality and Safety Maintained as Trainees Develop Catheter Handling Skills and Progress to Independence: Cloud-Based Analysis**

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