Genetics in the advanced heart failure population – University Hospital Centre Zagreb experience

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Background: Current guidelines recommend genetic counselling and testing in patients with familial non-ischemic idiopathic cardiomyopathies with hypertrophic, dilated, restrictive or arrhythmogenic phenotype.[1,2] We aimed to investigate genotype features of patients with non-ischemic cardiomyopathies in advanced stage of heart failure in University Hospital Centre Zagreb.

Methods: Genetic testing (single variant and multiple variant testing) was performed in part using the in-house genetics laboratory, and also in a collaborating genetics laboratory in Helsinki, Finland (Blueprint Genetics). Pathogenic and likely pathogenic variants that established a molecular diagnosis were confirmed by Sanger sequencing.

Results: From September 2016 to December 2020, we have performed genetic testing in 66 patients. Of this number, 14 patients (8 males, 41.5±14.3 years) had advanced heart failure as evidenced by either having undergone heart transplantation, mechanical circulatory support implantation, or were currently listed for heart transplantation. Before genetic testing, clinically observed phenotypes indicated dilated cardiomyopathy in 6 patients, restrictive cardiomyopathy in 6 patients, and arrhythmogenic cardiomyopathy in 2 patients. Diagnostic yield of the performed genetic tests was relatively high, only one test did not identify any mutations, and 4/14 identified mutations that can currently be classified only as variants of uncertain significance. Pathogenic and likely pathogenic mutations predominantly affected genes coding proteins of the sarcomere, cellular and nuclear membrane, or pathologic protein such as transthyretin (**Table 1**). Genetic testing lead to change in the clinically determined diagnosis in 4/14 patients. Results of genetic testing in this group of patients warranted further family clinical screening in all of the patients, and family genetic screening in 5 eligible patients.

Conclusion: Genetic testing in our advanced heart failure population yields important information on etiology of the diseases, and indicates further family screening.

TABLE 1. Genotypes associated with clinically observed phenotypes.

Clinical phenotype	DCM (N=6)	RCM (N=6)	ACM (N=2)
Gender (males)	3/6	4/6	1/2
Age (years)	34.6±11.9	49.9±14.4	36.9±12.7
Genotype			
- pathogenic	1/6	1/6	1/6
	TNNT2	FLNC	PKP2
- likely pathogenic	2/6	3/6	1/6
	FLNC	TTR	LMNA
	DSP	MYH7	
- VUS	3/6	1/6	0/6
	DMD, DES, DYSF, SGCB	KCNA5	
	MYH7, PRDM16		
	FLNC		
- negative	0/6	1/6	0/6

DCM: dilated cardiomyopathy, RCM: restrictive cardiomyopathy, ACM: arrhythmogenic cardiomyopathy, TNNT2: cardiac troponin T, FLNC: filamin C, PKP2: plakophilin 2, TTR: transthyretin, LMNA: lamin A/C, DSP: desmoplakin, MYH7: myosin heavy chain 7, DMD: dystrophin, DES: desmin, DYSF: dysferlin, SGCB: sarcoglycan beta, KCNA5: potassium voltage-gated channel subfamily A member 5, PRDM16: PR/SET Domain 16, VUS: variant of uncertain significance.

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LITERATURE

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