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Polygenic Risk Scores in Sarcomeric Cardiomyopathies: A New Era?

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Introduction

Sarcomeric cardiomyopathies encompass a myriad of heart muscle disorders. Two major subtypes are Dilated Cardiomyopathy (DCM) and Hypertrophic Cardiomyopathy (HCM). Damage to the integrity of the sarcomere affects its role in myocardial contractility, leading to cardiomyopathy. (1) HCM and DCM are considered to be monogenic diseases caused by rare, genetic variants with large effect sizes sufficient to cause a disease phenotype.(2) However, there are a proportion of patients who do not have pathogenic (P) or likely pathogenic (LP) mutations in their genetic panel. This has raised questions about the genetic architecture of these conditions and prompted consideration that combinations of "low-level" common variants may be at play, indicating a polygenic phenomenon. (3)

Take Home Messages

- Sarcomeric Cardiomyopathies such as HCM and DCM have historically been considered to be monogenic disorders, adhering to Mendelian inheritance. However, this does not explain the significant proportion of patients in whom a pathogenic variant is not identified.
- Genome Wide Association Studies (GWAS) have identified Single Nucleotide Polymorphisms (SNPs), combinations of which may contribute to certain cardiomyopathic phenotypes.
- This has led to the creation of Polygenic Risk Scores, with early evidence suggesting that a higher PRS may correlate with more severe phenotypes of HCM.
- Although this may help us risk stratify patients, it is unlikely to replace the comprehensive assessment afforded by ECG, imaging modalities, detailed pedigree assessment and the clinical experience of the reviewing physician.

One versus many – what do we mean?

Monogenic risk variants have long been known to be associated with sarcomeric cardiomyopathies, typically adopting a Mendelian pattern of inheritance. These variants confer a high risk of disease. (4) They have been grouped by the National Institutes of Health (NIH) Clinical Genome Resource, depending on the level of evidence supporting their role as a monogenic cause for a specific condition. (5-7) (**Table 1**)

Table 1: Classification of variants	
Pathogenic (P)	Established disease gene
Likely Pathogenic (LP)	As per pathogenic, albeit with less compelling evidence (with regards to familial segregation or functional impact)
Variants with unknown significance (VUS)	Insufficient experimental or segregation data for clinical use

However, only a proportion of individuals with sarcomeric cardiomyopathies have one of these rare variants that can be directly attributed to their condition. This led to the hypothesis that common variants play a more important role than originally considered, and that the summation of these variants may eventually lead to phenotypic manifestation. Multiple Genome-Wide Association Studies (GWAS) have facilitated in-depth evaluation of sarcomeric conditions, comparing entire genomes of these individuals with healthy controls. This has resulted in the identification of Single Nucleotide Polymorphisms (SNPs). SNPs are DNA sequence variations occurring when a single nucleotide of a gene varies between individuals.(8) Although highly prevalent in the general population, various combinations of certain SNPs may lead to the development of a disease.(9) The creation of Polygenic Risk Scores (PRS) have increased the clinical utility of this data by assessing the weighted summation of these SNPs, thus improving the prediction of cardiovascular conditions.(10)

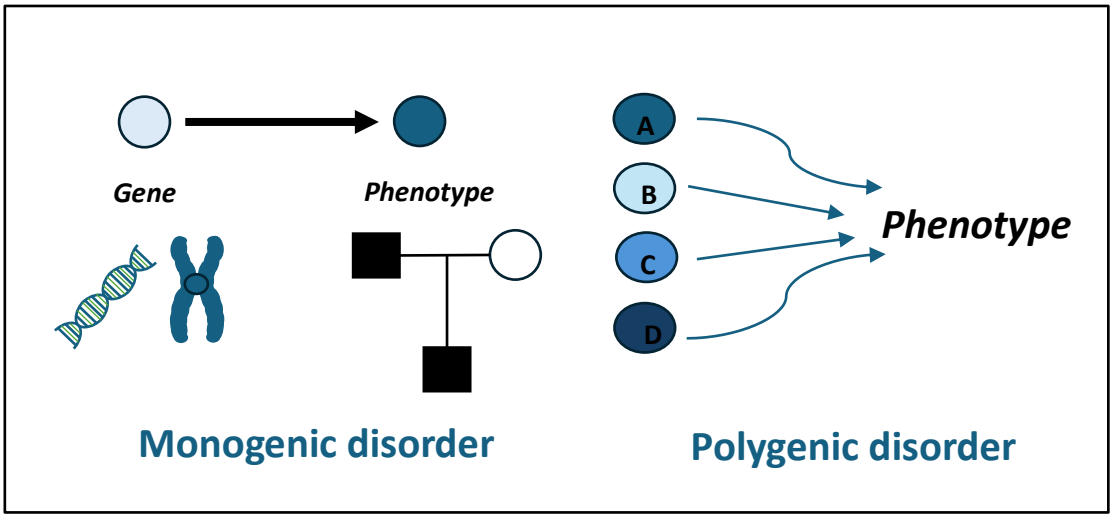

Figure 1: Monogenic versus Polygenic Disorder
Image created by Yande Kasolo

Hypertrophic Cardiomyopathy

Hypertrophic Cardiomyopathy is a primary myocardial condition, characterised by asymmetrical left ventricular hypertrophy that is unexplained by loading conditions. In 30-60% of cases it has a sarcomeric basis, with P/LP variants in MYH7 and MYBPC3 being the most common(6) (**Table 2**). Higher detection rates of up to 52% are observed in those with a familial basis of the condition, in comparison to 32% of probands without a family history. (11)

Table 2: Causative genes of hypertrophic cardiomyopathy (12)		
Functional Group	Gene	Protein
Sarcomere (thick filament)	MYBPC3 MYH7 MYL2 MYL3 TTN	Myosin-binding protein C β-Myosin heavy chain Myosin light chain 2 Myosin light chain 3 Titin
Sarcomere (thin filament)	TNNC1 TNNT2 TNNI3 TPM1 ACTC1	Cardiac troponin C Cardiac troponin T Cardiac troponin I Tropomyosin α-1 α-Cardiac actin

In those without a causative variant, GWAS analysis has helped establish the polygenic hypothesis. Retrospective analysis of 2780 HCM patients and 47000 UK Biobank controls led to the identification of 12 genome-wide significant susceptibility loci for HCM (13). This has led to creation of HCM-specific PRS, which have retrospectively been observed to play a significant role in predicting event-free survival in those with rare, disease causing variants (14)

Dilated Cardiomyopathy

Dilated Cardiomyopathy is characterised by LV cavity dilatation and impairment of systolic function. Its genetic basis is less well defined than in HCM, however pathogenic variants (both sarcomeric and non-sarcomeric) can be seen in 40-50% of patients. (15, 16) (**Table 3**)

In an attempt to explore potential polygenicity of this condition, GWAS initially highlighted 2 DCM-associated SNPs, one of which was a non-synonymous variant in BAG-3, which is a traditional DCM-associated gene.(17) Subsequent GWAS analysis (most recently in 2020) has led to the identification

of 28 SNPs which corelate with left ventricular end-systolic volume indexed values, and have subsequently been found to be strongly associated with the development of DCM.(18)

Table 3: Representative causative genes for dilated cardiomyopathy (12)		
Functional Group	Gene	Protein
Sarcomere	TTN	Titin
	ACTC1	α-Cardiac actin
	MYH7	β-Myosin heavy chain
	TNNC1	Cardiac troponin C
	TNNT2	Cardiac troponin T
	TNNI3	Cardiac troponin I

Future directions

Although exploring polygenic causes for sarcomeric cardiomyopathies and other inherited cardiac conditions has galvanised interest, it is important to consider whether this can translate into the real-world management of these patients.

Evolving research suggests that Polygenic Risk Scores may have a place in risk stratification. Evaluation of one cohort ,comprised of 214 relatives of 184 index HCM cases, found that those with a high PGS risk had a higher left ventricular wall thickness (+3.5mm, 95% CI 1.26 to 6.41, p 0.0035) and importantly, a higher incidence of major adverse cardiovascular events (HR 1.74 per PGS, 95% CI 1.03 to 2.91, p 0.036).(19) All of these patients were carriers of pathogenic sarcomeric variants, hence suggesting that PRS may be transferable to a clinical setting in terms of risk stratification and service planning. Similar risk scores have been explored in DCM; in those with rare pathogenic variants, PRS stratified disease penetrance (top quintile: 7.3%, bottom quintile: 1.7%, P 0.005). (20) Overall, what will be important to determine is whether polygenic profile can modulate risk for sudden cardiac death in this cohort of patients; unlike scar, PRS currently has no role in cardiomyopathy risk scores.

Conclusion

Exploring the polygenic basis for sarcomeric cardiomyopathies has facilitated greater understanding of these conditions. Evolving evidence suggests that Polygenic Risk Scores may have a role in the risk stratification of the relatives of those with pathogenic variants, a cohort which represents a significant proportion of our clinic volume in the inherited cardiac conditions service. Implementation of such scores in the future may therefore help us refine our follow up pathways for these patients and potentially reduce follow up duration for lower risk individuals. However, such scores are unlikely to replace the validity of an integrated, multifaceted assessment from an experienced clinician.

Disclosures

No relevant disclosures.

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