Polygenic risk score identifies disease burden for dilated cardiomyopathy in absence of monogenic cause

Background: Dilated cardiomyopathy (DCM) has long been considered as a single-gene (monogenic) condition, where one big effect rare variant a known DCM gene causes disease. But clinical genetic testing can find a pathogenic/likely pathogenic (P/LP) variant in only about 15–25% of unselected DCM cases. Among gene-positive cases, the titin gene (*TTN*) is most often involved, and its effects vary a lot between people. However, recent genome-wide association studies show the polygenic nature of DCM, with many common small-effect variants adding up the disease risk. We hypothesised that a high polygenic burden accounts for disease in patients without an identifiable monogenic variant and modifies the penetrance and expressivity of monogenic variants.

Methods: We studied 113 people of genetically determined European ancestry with a clinical diagnosis of DCM from the Australian Genomics Health Alliance (AGHA) Cardiovascular cohort. All went through clinical genetic testing and 34% had a P/LP variant in known DCM genes. To choose the best polygenic risk score (PRS) for DCM, we compared SBayesRC, SBayesR, LDpred2, LDpred-funct and PRScsx on 455,202 UK Biobank participants of European ancestry (including 1,456 DCM cases). We used these same UK Biobank European samples as our reference population to define PRS percentiles. We then investigated the proportion of AGHA patients having PRS in the top 10% of that reference PRS distribution.

Results: In UK Biobank, the SBayesRC-derived DCM PRS performed the best with odds ratio for 1 SD increase in the PRS as 1.67 (95% CI, 1.59–1.76). Relative to the reference population distribution, PRS values were statistically significantly higher in DCM cases without an identified P/LP variant and in cases with a *TTN* P/LP variant. Overall, 26% of patients without a P/LP variant and 25% of those with a *TTN* P/LP variant were in the top decile of the reference PRS distribution. By contrast, only 11% of patients carrying P/LP variants in non-TTN genes were in the top decile.

Conclusions: The SBayesRC PRS was the best performer and helped explain disease in a significant share of patients who do not have an identifiable monogenic variant. It also seems to modify risk in TTN-related DCM. Adding PRS to routine genetic testing may improve diagnosis and guide counselling and risk management for patients and their families.