GLYCOGENIN-1 (GYG1) DEFICIENCY CARDIOMYOPATHY: REVISING DIAGNOSIS THROUGH GENETIC TESTING

Background: Cardiomyopathies are clinically and genetically heterogeneous disorders that often present with overlapping phenotypes, complicating their diagnosis. Hypertrophic cardiomyopathy (HCM) is diagnosed on finding unexplained left ventricular hypertrophy (wall thickness ≥15 mm); however, this may also occur with other structural and metabolic diseases.

Aim: Genetically diagnose a patient with suspected HCM and progressive heart failure, who remained genetically undiagnosed following standard testing.

Methods: Clinical evaluations included electrocardiography, echocardiography, and cardiac MRI. Exome sequencing analysed 185 cardiac disease genes, followed by an expanded metabolic and phenocopy gene panel. Periodic Acid Schiff (PAS) staining of explanted heart tissue was performed. A multidisciplinary team reviewed variant classification.

Results: A European male was clinically diagnosed with HCM at age 32 years, progressing to a dilated phenotype and heart failure requiring transplantation at age 40. Initial cardiac genetic testing was inconclusive. An expanded gene panel identified a homozygous *GYG1* NM_004130.4:c.304G>C p.Asp102His variant, with a European allele frequency of 0.0017 in gnomAD v3.1.2. The variant was previously reported in three unrelated families with isolated cardiomyopathy and cardiac transplantation. Digenic *GYG1* variants cause glycogen storage disease XV, and PAS staining of our patient's explanted heart tissue revealed glycogen accumulation and myocardial remodelling. The variant was classified as likely pathogenic, and segregation testing was offered to family members.

Conclusion: Comprehensive genetic testing can correct a clinical misdiagnosis of HCM, particularly when the clinical course is atypical. *GYG1* should be considered in the differential diagnosis of genetically elusive or atypical HCM, particularly given the relatively high European allele frequency.