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Characterizing the genetic basis of Inherited Cardiomyopathies in families from the United Arab Emirates

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Background and aims: Rare pathogenic variants inherited in families contribute directly or indirectly to primary cardiomyopathy (CM), one of the most common clinical causes of heart failure worldwide. Numerous genes are now linked to primary CM. However, these conditions are characterized by reduced penetrance and variable expression, making it challenging to identify patients with incomplete, subclinical, or pre-symptomatic manifestations. This study aims to investigate rare genetic variants underlying primary CM in cases and families from the United Arab Emirates (UAE) using Whole exome sequencing.

Methods: A total of 29 individuals (16 symptomatic patients diagnosed with primary CM, such as hypertrophic or dialed CM, and 13 asymptomatic family members) were collected after informed consent. Untargeted whole exome sequencing was performed on the Illumina NovaSeq6000. VarSeq software was used for variant filtering, annotating, and interpretation. Patient-unique rare function-altering variation(s) in CM genes were identified, and best causative candidates were verified by Sanger sequencing.

Results: Potentially disease-causing variants altering CM genes were identified in 22 symptomatic and asymptomatic individuals. A heterozygous mutation in *MYBPC3*(NM_000256.3):c.1224-19G>A was identified in a symptomatic father of four. Three of his offspring were carrying the same genotype identifying them as high-risk individuals. Another pathogenic mutation in *MYH7*(NM_000257.4):c.4066G>A (p.Glu1356Lys) was identified in a mother of two, of whom one was found to carry the same genotype and at risk of developing CM in the future. A homozygous mutation in *TTNT2*(NM_001001430.3):c.817A>C (p.Lys273Gln) was found in a CM patient, yet parents carrying the heterozygous genotypes were asymptomatic. A homozygous variant of unknown significance (VUS) was detected in *NEXN* (NM_144573.4):c.1582_1584del(p.Glu528del) in

two sisters diagnosed with CM. All their asymptomatic offspring carried the heterozygous genotypes. Novel VUSs were detected in six independent cases and families.

Conclusions: This study provides for the first time an overview of the genetic aberrations in a cohort of patients with primary CM from the UAE and demonstrates the power of next-generation sequencing in identifying symptomatic and asymptomatic family members. Identification of CM-causing mutations is vital for accurate genetic counseling, therapy guidance, and early diagnosis in affected individuals and their family members.

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Key Words
Cardiomyopathy, Families, United Arab Emirates, Genetics