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Hypertrophic Cardiomyopathy Molecular Diagnosis: At the Heart of Cardiac Disease

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Introduction

Hypertrophic cardiomyopathy is a genetic myocardial disease characterised by left ventricular hypertrophy. Even among members of the same family, the disease is characterised by high locus, allelic, and phenotypic heterogeneity. The list of confirmed and potentially relevant genes implicated in the disease is constantly growing, with new genes being discovered on a regular basis. More than half of confirmed cases are thought to be caused by heterozygous changes in the five main sarcomeric genes. Recent genetic discoveries have shed more light on the molecular pathogenic mechanisms of HCM, contributing to significant advances in disease diagnosis. Genetic testing using next-generation sequencing technologies, as well as early diagnosis prior to clinical manifestation of the disease among family members, show significant progress in the field.

Hypertrophic cardiomyopathy is a type of inherited cardiomyopathy characterised by the presence of left ventricular hypertrophy in the absence of any other disease that could cause secondary LVH. Individuals with HCM are more likely to develop atrial fibrillation, which can result in blood clots, stroke, and other heart-related complications. HCM can also cause heart failure and sudden cardiac death. The disease is caused by transcriptomic defects in sarcomere proteins caused by specific genomic alterations on thick and thin filaments and Z-disks. These mutations set off a chain of events that result in histological or morphological changes in the myocardial cell, causing it to become hypertrophic and fibrotic [1].

Description

HCM is still a clinical diagnosis, and despite the molecular identification of the previously mentioned genetic loci, molecular findings alone cannot be used to diagnose HCM. Clinical practise guidelines for assessing HCM in children and adults have been created. An individual's evaluation includes a detailed pedigree with emphasis on heart disease and early death in the family. Clinical signs of HCM are usually detected clinically by a physician cardiologist, depending on the examiner's skills. A rapid increase in carotid pulse rate, with a forceful presystolic hump of the apex beat followed by a prolonged upstroke, indicates disease. In the absence of severe mitral regurgitation and a significant septal defect and a severe obstruction, a bisferiens contour might be observed [2].

HCM prevalence has previously been reported to be as high as 0.2%. However, more recent research suggests a prevalence of 0.03% to 0.07%. According to a recent study conducted in Germany involving five million patients, the prevalence of the condition has been increasing in recent years. According to the same study, HCM is more common in male patients across all age groups studied, and the prevalence rises with age. It is worth noting that the reported prevalence in the literature can vary greatly depending on the population studied and the diagnostic tools used. The disease affects all races, and distinguishing between them would be difficult due to differences in disease prevalence, severity, and consequences.

The benefit of using gene panels for targeted sequencing is that the region of sequencing can be highly specific and covered in great depth with many samples analysed at the same time. Targeted sequencing is significantly less expensive than WES and WGS for diseases involving a small number of genes. Panels containing many genes relevant to the phenotype have become the standard of care for HCM because they are usually feasible and cost-effective. Due to the genetic heterogeneity of cardiomyopathies, multigene panel testing is preferred over Sanger-sequencing-based single-gene testing. RNA analysis is required to demonstrate the effects of potential splice-disrupting changes.

Through the analysis of RNA isolated from fresh venous blood, myectomy samples, or induced pluripotent stem-cell-derived cardiomyocytes from patients, recent studies have succeeded in reclassifying variants from uncertain significance to likely pathogenic. The discovery of disease-causing aberrantly spliced mRNA in HCM patients opens up new avenues for the development of RNA-targeted therapies, in addition to improving the precision of molecular diagnostics. Short interfering RNAs and splice-switching antisense oligonucleotides are promising strategies. RNA-targeting drugs have great potential for the treatment of HCM, but more research is needed to overcome major challenges related to safety and delivery [3-5].

Conclusion

Patients without a pathogenic variant are now thought to have HCM via a non-Mendelian mechanism, with a better prognosis than those with sarcomeric pathogenic alterations. Continuous research efforts are critical to expanding our knowledge of the full spectrum of HCM-related genes and facilitating variant interpretation and classification as comprehensive whole-exome and whole-genome sequencing approaches become more widely available. However, while such extensive molecular testing can identify new genes associated with HCM, it is also expected that a large number of variants of uncertain significance will be detected, potentially increasing overall uncertainty as a result of inconclusive results and causing psychological stress to patients and their families.

To precisely translate the massive amount of data obtained from comprehensive NGS-based genetic testing, a more sophisticated understanding of genetic variation and novel strategies for assessing the pathogenicity of variants are required. Larger patient cohorts, including longitudinal clinical phenotypes and genotyping, are required to provide further insights into the genetic aetiology and pathogenesis of HCM due to the disease's enormous heterogeneity and diverse clinical manifestations.

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Furthermore, multicenter collaborations and interdisciplinary collaboration of cardiologists, molecular biologists, clinical geneticists, bioinformaticians, and genetic counsellors are required to efficiently interpret and communicate the results of NGS-based genetic testing to patients and their families.

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Conflict of Interest

There are no conflicts of interest by author.

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