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Short Communication

Significance of Hypertrophic Cardiomyopathy

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DESCRIPTION

A single mutation is often enough to induce the illness, however its penetrance and expression might vary. Hypertrophic Cardiomyopathy is an archetypal single gene ailment with an autosomal dominant pattern of inheritance. The causative mutation working in conjunction with several other genetic and non-genetic effects is at least partially to blame for the phenotype's unpredictability. About 60% of HCM patients have a distinctly identifiable hereditary illness. Although rare, autosomal recessive and X-linked patterns of inheritance have been documented. Fabry disease, for example, is a phenocopy disorder that is frequently associated with an X-linked inheritance. Additionally, inherant illnesses like Anderson-Fabry disease and syndromic syndromes like the Noonan syndrome can have phenocopy conditions [1].

The causative mutations are subsets of pathogenic variations that have significant phenotypic consequences, have substantial penetrance, and co-segregate with the phenotype in large HCM families. Co-segregation and linkage analysis are used to firmly prove the causality of these mutations. This is true for the common HCM genes, including MYH7 and MYBPC3, whose clear causal connection to HCM. However, not all genetic variations in the recognized HCM causative genes really result in HCM. According to the ExAc, the genes are severely limited and not particularly tolerant to missense and Loss-of-Function (LoF) genetic variations. As a result, albeit highly uncommon in the general population, missense and LoF variations in these genes are not entirely absent [2].

Smaller phenotypic effects caused by genetic variations indicate inadequate penetrance. Such variations' penetration and phenotypic consequences rely on the existence of additional genetic and environmental variables. Patients with sporadic HCM and small families with HCM have a high prevalence of low- to moderate-penetrance genetic variations. It is extremely difficult to determine the causal function of such variations in HCM.

Human genetic variety, population-specific frequency of the variations, and the existence of thousands of pathogenic coding variants in each exome add to the challenge of determining causation, making it exceedingly difficult to distinguish between a causative and accidental variant [3].

Rare mutations lead to HCM. Genes that produce sarcomere and sarcomere-associated proteins generally have these mutations, which usually impact specific domains. Therefore, there is a very low incidence of certain mutations in an HCM population.

The MYBPC3 mutation p.Val762Asp, which has been found in 3.9% of the Japanese population, and the MYBPC3 mutation p.Arg502Trp, which has been reported to occur in between 1.5% and 3% of HCM patients, is two significant outliers. Nearly all other mutations are identified in just one proband or family and their incidence in the HCM population is less than 1%.

The high frequency is not a characteristic of mutations occurring in genetically distinct HCM groups and may only be present in the research populations that have been publicly disclosed. There is therefore no mutation in any of the known genes, with the hypothetical exception being two mutations [4].

In general, it is difficult to distinguish between the HCM phenotype and the site of the mutations in the encoded proteins. Although mutations in the MYH7 gene affect the rod domain, they exhibit a strong preference for the globular head and hinge region of the myosin heavy chain protein. Phenotypically, an earlier illness start has been linked to mutations in the converter domain and a flat surface area in the globular head of MYH7.

Overall, MYH7 and MYBPC3 are the two most frequent genes in apical HCM in addition to being the two most frequent causative genes in the typical type of HCM involving the basal septum.

Except for the mutations in MYBPC3, which have a tendency toward insertion/deletion and premature truncation mutations because of a frameshift, the bulk of the causative mutations in HCM are missense mutations.

By modifying the amino acid composition of the encoding protein, the missense mutation may change the structure and function of proteins. The Ubiquitin Proteasome System (UPS) then degrades the prematurely shortened proteins, causing haplo-insufficiency [5].

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CONCLUSION

There are several pathways connected to the pathogenesis of HCM, matching the variety of the causative genes and mutations. There are four groups of interlocking mechanisms that might be used to classify the mechanistic processes in HCM. The mutation is the main flaw. Initial or proximal phenotypes are those brought on by a mutation's direct impact on the sarcomere proteins' structure and function. The molecular alterations that follow alterations in the structure and function of the sarcomere protein are included in the intermediary (or secondary) phenotypes. Alterations in gene expression and the activation of signaling pathways like the TGFB1 and MAPK pathways are examples of the latter.

The secondary molecular processes that are perturbed in the heart, such as the activation of the hypertrophic signaling pathways, result in the subsequent histological and pathological phenotypes, which are the tertiary consequences. These histological and molecular alterations cause the clinical manifestations of HCM (quaternary). Since ventricular hypertrophy in the latter may result, at least in part, from storage of material, such as glycogen, and in part because of functional defects in myocytes, such as impaired contraction, it is crucial to note that there is a mechanistic distinction between cases of HCM caused by sarcomere protein mutation and the phenocopy conditions.

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