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Hereditary Transmitted Heart Disease: Hypertrophic Cardiomyopathy (HCM)

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Definition and epidemiology

HCM is a genetic disorder which effects the cardiac myocytes due to which cardiac hypertrophy condition observed where abnormal thickening of cardiac muscles makes difficult in pumping of blood. HCM usually goes unknown as most of the people with the disease have lack of symptoms.

Cardiac hypertrophy is usually asymmetric which frequently occurs at the basal inter ventricular septum subjacent to aortic valves, less occurs at myocardial regions like mid portion and the posterior wall of the left ventricle.

HCM is a genetic disorder without geographical, cultural, sex distinction of distribution. Usually Cardiomyopathy diagnosed by the thickness of left ventricular diastolic wall > 15 mm which was suggested by European society of cardiology guidelines.

Cardiac hypertrophy not only caused through genetic disorder it might effect of environment also result in phenocopy condition in clinically diagnosed children's approximately 5 - 10% of individuals. Moreover due to other effects such as atrial hypertension or aortic stenosis these conditions may also results in HCM which differentiate primary HCM from secondary HCM.

Molecular genetic basis

Hypertrophic cardiomyopathy is a typically autosomal dominant inheritance with single point gene disorder where single mutation is usually sufficient to cause disease though with variable penetrance and expression. Most of the patients with HCM unambiguously known as familial disease. In some rare cases HCM also shows autosomal recessive and X linked type of inheritance.

Great efforts by Christine and Jonathan Seidman have led to study and elucidate of the molecular genetic of Hypertrophic cardiomyopathy. By finding the mutation p.Arg403Glu in MYH7 gene, which encodes sarcomere protein MYH7 leads to the important findings. By the discovery of different mutations in the fundamental causal genes, and in sarcomere proteins, HCM is corroborated as genetically heterogeneous disease. In mutated genes, Myosin heavy chain 7 and myosin binding protein C 3 are the two genes together are reasonable for most of the patients with familial Hypertrophic cardiomyopathy. Other Mutations in TPM1, TNNI3 and TNNT2 unusually causes HCM albeit those Mutated TNNI3, TPM1, TNNT2 responsible to < 10% of cases. Mutations in α-cardiac actin 1, myosin light chain 2 and 3 and in CSRP3 are not common but causes hypertrophic cardiomyopathy. Findings regarding role of the above 9 genes in Hypertrophic cardiomyopathy are stronger.

Some pairs of pathogenic variants that shows large phenotypic effects, results in more penetrance and co-segregate with the phenotype in Big HCM family's are considered as the causal mutations. Reasons for causing such mutations is strongly explained by co-segregation

and linkage analysis. This is the reason for the common Hypertrophic cardiomyopathy genes, such as Myosin heavy chain 7 and MYBPC3, whose effecting role in HCM is well determined. Albeit genetic variants responsible for cardiomyopathy disease but not all not genetic variants are responsible to cause HCM. Some variants are not very tolerant to missense and LOF (loss of function) of genetic variants. This explains that missense and LoF variants in those genes are merely rare in the common population but not completely absent. Hence not all missense and Loss of function (LOF) variants in the genes responsible for HCM. In contrast some genes causes HCM which are intolerant to missense and LoF variants like ACTC1 gene was observed in approximately 60,000 unrelated individuals which is extremely not tolerant to missense and Loss of function variants.

Possible digenic/oligogenic origin or cause of HCM disease

A subset of HCM patients, approximately 5%, exhibits digenic or oligogenic effecting mutations in the same gene or effecting mutation in different genes. The intensity of ventricular hypertrophy well explanatory with such kind of mutations. As Digenic mutations are primarily limited to variants in well-known Hypertrophic cardiomyopathy genes identified in individuals of small families. Because of that it became harder to show co-segregation and to know particularly the effecting role of each variant. With this findings it raise the interesting possible outcomes regarding the missing causal genes may be explained, due to the digenic and oligogenic nature in few patients with cardiomyopathy. Because of this few patients with Hypertrophic cardiomyopathy may not into the fundamental definition of a single point (gene) disorder. More over these findings changes the focus from genetic causal of a single dominant mutation to identification of the pathogenic mutations in sporadic HCM and HCM occurring in small families. There is no sufficient data to find the differences in the phenotypic expression of hypertrophic cardiomyopathy caused by 2 mutations on a single gene and one mutation on each of two effecting genes [1-3].

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