Familial hypertrophic cardiomyopathy (FHC) is a genetic disorder arising from mutations in sarcomeric protein genes. Human genetic studies have implicated at least 9 different genes in FHC, emphasizing the enormous genetic and allelic heterogeneity associated with FHC.1 β-Myosin heavy chain (βMyHC, MYH7) is the most commonly mutated gene in FHC, and at least 60 different MYH7 gene mutations have been described in human FHC subjects.2 The vast majority of these are single base pair mutations that produce missense amino acid substitutions. Myosin is a highly asymmetric protein with a long rod domain and 2 globular heads. The globular domain of myosin, heavy meromyosin (HMM), can be proteolyzed into subfragment 1 (S1) and subfragment 2 (S2). The S1 head is the enzymatic “business” end of the molecule in that it possesses actin-activated ATPase activity and is capable of directing the sliding of actin filaments in vitro. The crystal structure of S1 has been determined, shedding light on the potential conformational changes that occur in response to ATP hydrolysis and that ultimately are responsible for myocyte shortening, skeletal muscle movement, and the beating of our hearts.3 Myosin was one of the first proteins to be purified and proteolytically separated into distinct functional domains contributing to the domain theory of proteins. Similarly for human genetic studies, the domain structure of myosin has proved useful because all the reported missense mutations in βMyHC map to the head and neck region, a region of the rod most proximal to the globular head. Within the S1 head, FHC mutations cluster to regions implicated in ATP hydrolysis, actin binding, or myosin light chain binding.4

In this issue, Blair et al5 describe mutations in the MYH7 gene associated with familial hypertrophic cardiomyopathy. The unusual feature about these mutations is their locale. Two missense mutations, A1379T and S1776G, were identified that map within the light meromyosin (LMM) domain. LMM is an α-helical coiled-coil and possesses properties of self-assembly under low ionic strength conditions. LMM assembles into paracrystals with characteristic 43-nm periodicity, identical to those seen in native thick filaments isolated from muscle. The myosin rod has a heptad repeat motif that is responsible for the coiled-coil configuration. Both the A1379T and S1776G missense changes may disrupt the heptad motif, although the position of the second mutation, S1776G, is more likely to result in disruption because it alters one of the d positions critical to forming a coiled-coil (see Figure 5 of Blair et al5). The positioning of these mutations may compromise thick filament assembly. Alternatively, these mutations may affect proteins that bind thick filaments such as myosin binding protein C, titin, or myomesin.6,7

Studies of in vitro assembly of thick filaments suggest that the first portion of LMM is important for self-assembly into dimers, but regions more distal have also been suggested to be relevant for macromolecular thick filament assembly.8,9 Further studies on the in vitro assembly properties of these mutant LMM molecules will likely shed light on the mechanism by which these mutations alter myosin function.

Because FHC is inherited in an autosomal dominant fashion, most mutations are likely to exert a dominant negative effect to produce the hypertrophic phenotype. The hallmark of FHC is marked thickening of the ventricle that leads to congestive heart failure and cardiac arrhythmias. FHC has variable expressivity that can only partially be explained by specific mutations. The fact that most missense mutations map to functional domains within the myosin head has lead to the hypothesis that FHC is a disorder of force production. Supporting this idea, in vitro motility properties of mutant myosin molecules demonstrate a reduced velocity of actin filament sliding, but in a few instances an increased velocity has been noted.10,11 Taken together, missense mutations that change myosin’s enzymatic function, force production, or efficiency of energy utilization appear to produce a hypertrophic phenotype. Because the A1379T and S1776G LMM mutations are more consistent with a disruption of thick filament assembly or stability, this indicates that disorders of force transmission may also be associated with a hypertrophic phenotype.

These findings complicate our understanding of the molecular pathology of cardiomyopathy and have critical implications for molecular genetic diagnostics. First, it appears that, in the strict sense, not all hypertrophic cardiomyopathy is associated with abnormalities of force production. Mutations that alter LMM assembly or stability, as would be predicted by the position and type of mutation reported by Blair et al, are unlikely to alter the enzymatic properties of...
myosin. Second, it could be argued that a disorganized thick filament may, in fact, alter the transmission of force within the cardiomyocyte. Although this hypothesis requires in vitro and in vivo modeling, the distinct nature of these LMM missense mutations raises this possibility. It has been suggested that disrupted force transmission within the cardiomyocytes may lead to a dilated cardiomyopathy phenotype. Yet for these LMM mutations, it is intriguing to speculate that the hypertrophic phenotype is the result of defective force transmission. Moreover, it may yet be proved that LMM mutations associate with dilated cardiomyopathy.

An additional implication of these FHC LMM mutations is that the entire MYH7 gene should be examined when assessing FHC subjects. The A1379T and S1776G mutations fall into regions of the MYH7 gene that are often not included in mutational analysis. The large size of the MYH7 gene, 40 exons spanning over 25 kb (GenBank accession No. AJ238393), has lead to a refined approach for mutation screening where it is common to screen only exons 3 to 23 because it is these exons that encode the S1 and proximal neck region of βMHC. Blair et al studied a selected population of FHC subjects where MYH7 exons 3 to 23 as well as the other sarcomeric genes were already excluded. Overall, LMM mutations are a rare finding because only 4 of 82 probands screened had LMM mutations. Although LMM mutations are not a common cause of FHC, it seems prudent to study the entire MYH7 gene when evaluating FHC subjects.

Certainly, these findings do little to simplify mutation screening in FHC. Determining mutations associated with FHC, like those associated with the Long-QT syndrome, remains a troublesome issue given the heterozygous nature of mutations coupled with the large number of private mutations found in many different genes. To complicate matters more, FHC genes span significant intervals, further expanding the sequences to be screened. Mutational analysis frequently relies on direct sequencing, a methodology that requires considerable time and effort. Alternative strategies detect conformational changes that arise from substitutions, deletions, and insertions within segments of DNA. Blair et al utilized denaturing high-pressure liquid chromatography in which abnormal conformers have unique migration patterns. The increasing use of this technology may improve mutation screening for FHC and other disorders both for research and clinical uses.

Understanding the pathological mechanisms that underlie FHC, including the progression to congestive heart failure and the incidence of arrhythmias, remains an active area of research. The documentation of mutations within the LMM region of myosin muddies the waters a bit for those who hope that a single pathological mechanism can account for pathology, but nonetheless opens up a fascinating new avenue for the role of the myosin rod and thick filament formation in the role of FHC.

References

Key Words: hypertrophic cardiomyopathy  myosin  light meromyosin  thick filament  mutation

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**References**


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