The genetics of hypertrophic cardiomyopathy

The discovery that two families with hypertrophic cardiomyopathy have mutations in the cardiac myosin heavy chain genes may be the most important advance since the recognition of this condition in 1958. It provides an opportunity to reassess our understanding of the genetics of hypertrophic cardiomyopathy and to examine the challenges posed for future study.

Clinical studies

MODE OF INHERITANCE

In an addendum to Teare's original description of eight cases of asymmetrical hypertrophy one was reported to be familial. This family was subsequently investigated and found to have an autosomal dominant pattern of inheritance. Several reports of single pedigrees followed and confirmed this observation. The first large scale family screening study of hypertrophic cardiomyopathy was reported by Emanuel et al in 1971. These investigators used clinical examination, electrocardiography, and chest x ray plus the results of haemodynamic investigation, operation, and necropsy, when available, to screen relatives of 76 index cases. The familial incidence was estimated to be between 30 and 50% and the data suggested that both autosomal dominant and autosomal recessive transmission occurred. We now realise that clinical examination and electrocardiography alone may be normal in up to 20% of relatives who show left ventricular hypertrophy on cross sectional echocardiography. The introduction of echocardiography had a major impact on the assessment of hypertrophic cardiomyopathy and remains the cornerstone of diagnosis and therefore of family screening. Early M mode echocardiograms almost certainly over-diagnosed asymmetrical septal hypertrophy by placing the ultrasound beam off axis. Thus two M mode family studies in the early 1970s suggested that hypertrophic cardiomyopathy was familial in over 90% of cases. Cross sectional echocardiography has increased the accuracy of wall thickness measurements. Two large family screening studies with cross sectional echocardiography were performed in the 1980s. Both studies used the same echocardiographic criteria for the diagnosis of left ventricular hypertrophy, namely the thickness of the intraventricular septum alone or septum and posterior wall thickness > 14 mm in adults or wall thickness above the normal 95% confidence interval in children. Maron et al at the National Institutes of Health in the United States screened three or more first degree relatives of 70 index cases. In 39 (56%) of the 70 families two or more members (including the proband) were found to be affected. In 30 (77%) of these 39 pedigrees inheritance was consistent with an autosomal dominant trait. Greaves et al screened 193 first degree relatives of 50 index cases in New Zealand and, coincidentally, found the same familial frequency as Maron et al, namely 56%. In 15 (54%) of the 28 affected families transmission was autosomal dominant. In the remaining families in both studies, cases were detected in one generation only; therefore the pattern of inheritance could not be assigned. In summary, family studies to date suggest that hypertrophic cardiomyopathy is an inherited disorder in over 50% of cases. The transmission in most families is autosomal dominant. X linked inheritance has been discounted because of the many instances of father to son transmission. Autosomal recessive transmission may be the mode of transmission in some families but this remains controversial.

PENETRATION

Family studies have shown that the phenotype of hypertrophic cardiomyopathy may vary between affected members of the same family. Emanuel et al found that isolated asymmetrical septal hypertrophy, without any other feature of hypertrophic cardiomyopathy, was compatible with a pattern of variable expression and autosomal dominant gene. Family studies also show that a proportion of relatives have electrocardiographic abnormalities only. Such cases may represent incomplete penetrance of a hypertrophic cardiomyopathy gene. Epstein et al have recently identified four adults in three families who, because of their position in the pedigree, must have been obligate carriers of the gene. These individuals had normal electrocardiograms and echocardiograms, although three of the four showed late potentials on signal averaged electrocardiography. It is unlikely that the presence of late potentials could reliably detect gene carriers in large studies but this report illustrates the potential for non-penetration of a hypertrophic cardiomyopathy gene by standard electrocardiographic criteria. Variable penetrance poses problems for genetic linkage studies because misclassification of individuals as unaffected leads to erroneous results. What factors influence the degree of gene penetrance in hypertrophic cardiomyopathy? Age is undoubtedly important. Previously normal teenagers can develop cardiomyopathy over several years and in family screening studies higher proportions of positive cases were detected in parents than siblings and in siblings than children. Gender may be important as males seem to be affected more often than females. Factors which cause secondary hypertrophy in their own right may promote the development of hypertrophic cardiomyopathy in a genetically predisposed individual (and cause diagnostic difficulty). There is some evidence that systemic hypertension may have such an effect and, although unproven, our clinical impression is that there is an excess of athletically active individuals among young people presenting with hypertrophic cardiomyopathy. There are also many neurohormonal mechanisms and tissue growth factors that could be important in the development of myocardial hypertrophy when a gene for hypertrophic cardiomyopathy is present. Detailed comparative studies of siblings who show different degrees of morphological disease may identify relevant factors. Serial clinical screening of the young and of equivocal cases is also necessary.
SPORADIC CASES AND CLINICAL HETEROGENEITY
All family studies report a substantial proportion, approximately 45%, of cases showing no evidence of familial transmission. These cases are termed "sporadic." The only study that compared sporadic and familial cases found no significant differences in terms of age, sex, or echocardiographic appearances. There are several potential explanations for apparently sporadic cases of hypertrophic cardiomyopathy. Other affected family members may not be identified either because they are not screened or because they have incomplete penetrance of the gene. In the New Zealand study the chance of finding an affected relative increased directly with the number of relatives screened: where six or more relatives were screened the condition was always found to be familial. In some sporadic cases a new mutation may have occurred (but offspring could be affected). Sporadic cases may also be due to somatic mutations during embryonic development which affect the same genes as in the familial form but spare the germ cell line. Alternatively, sporadic cases of hypertrophic cardiomyopathy may have a polygenic or "environmental" basis or both. This becomes increasingly likely in view of the clinical heterogeneity of the condition with variants such as apical hypertrophic cardiomyopathy and "hypertrophic cardiomyopathy of the elderly" in which sporadic occurrence seems common.

Genetic studies
GENETIC LINKAGE STUDIES
Genetic linkage studies produce a statistical probability known as a LOD score (logarithm of the odds) that a disease is or is not associated with a specific chromosomal location (a LOD score > 3.0 is considered evidence of positive linkage). In 1989 a group in Boston reported the first positive linkage study in hypertrophic cardiomyopathy. They found strong linkage (LOD 9-4) to an area of chromosome 14 in a large French-Canadian family that had been the subject of one of the early reports. Subsequently this group reported that a second family showed linkage to chromosome 14 and recently, investigators in Boston reported linkage to chromosome 14 in a further nine families (LOD 5-6). However, there is also evidence from linkage studies that familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. The Boston group reported that two families were definitely not linked to chromosome 14, and a report has suggested linkage to chromosome 18 in 11 Japanese families (LOD 3-1) and a further report, linkage to chromosome 2 in another North American families (LOD 3-0).

MUTATIONS IN CARDIAC MYOSIN HEAVY CHAIN GENES
The contractile unit or sarcomere is a regular assembly of thick filaments composed primarily of myosin heavy and light chains and thin filaments composed primarily of actin. In the human myocardium there are two isoforms of myosin heavy chains—an α and a β chain. The genes coding for the human α and β cardiac myosin heavy chains have been localised to chromosome 14. The Boston group noted that the linkage site on chromosome 14 was close to these loci. The group and their collaborators have proceeded to identify mutations in the myosin heavy chain genes in the affected members of both these families. In a family of North European descent an abnormal α-β chain hybrid gene was present and in the second family (the French-Canadian family of the original linkage report) a point mutation was identified. This mutation would change an arginine to a glutamine residue in the functional region of the protein that binds to actin. This arginine residue is highly conserved throughout many species, suggesting that it is a site of functional importance. These reports of mutations in human myosin genes shed a completely new light on the pathogenesis of hypertrophic cardiomyopathy. The preservation of systolic function in hypertrophic cardiomyopathy meant that the contractile apparatus was not a prime suspect in the search for a cause of this condition. How do these genetic defects produce hypertrophic cardiomyopathy? Two existing experimental models may help to answer this question. First, mutations in the myosin heavy chain genes of the flight muscles of Drosophila melanogaster result in an imbalance between the amounts of actin and myosin produced and subsequent derangement of the myofilament assembly. Secondly, mutations in the unc-54 gene which codes for myosin heavy chain in the body wall muscle of the nematode Caenorhabditis elegans produce dominant phenotypes of varying severity with impaired mobility and disorganised assembly of thick myofilibrillar lattice. These effects are due to production of an abnormal myosin heavy chain which "poisons" the assembly process. Likewise, the mutations in myosin heavy chain genes found in patients with hypertrophic cardiomyopathy may produce a disruptive protein, and indeed myofilament structure is known to be disorganised in hypertrophic cardiomyopathy. Detailed correlation of myocyte ultrastructure and myosin heavy chain content with genetic defects may confirm this hypothesis. Presumably, sufficient intracellular disruption of myofilaments may interfere with normal intercellular connections and thus produce myocardial disarray and hypertrophy. These genetic discoveries raise many questions about the clinical features of the disease. Why does a defect in the myosin gene in all cells often result in asymmetrical left ventricular hypertrophy? Why does hypertrophy develop typically in the teenage years? Why is there variable penetrance in individuals in the same family carrying the same mutation? The answers may lie with the control of expression of the actin and myosin gene isoforms. For instance, the relative proportions of α and β myosin heavy chains in human myocardium change from fetal to adult life and may vary regionally within the ventricle. β myosin heavy chain is the predominant form expressed in the normal adult ventricle but the α/β ratio is affected by factors such as thyroid hormone, pressure overload, athletic training, and sex hormones. Such factors may also influence the expression of an abnormal myosin gene and thus the morphological pattern of hypertrophic cardiomyopathy in an individual.

FAMILIES WITH NO CHROMOSOME 14 LINK
Although evidence is accumulating that a substantial proportion of familial hypertrophic cardiomyopathy is associated with genetic defects on chromosome 14, there is also clear evidence of genetic heterogeneity. The proportion of cases mapped to chromosome 14 may decrease when sporadic cases and atypical forms of hypertrophic cardiomyopathy, such as apical hypertrophy cardiomyopathy and the "hypertrophic cardiomyopathy of the elderly," are studied. We already know that hypertrophic cardiomyopathy occurs as part of the clinical spectrum of many inherited conditions which have quite different genetic causes. Burrows has listed 36 such disorders. A large Italian family has been reported to have a fragile site on chromosome 16 suggesting that a gene in this region may also cause hypertrophic cardiomyopathy. Previous theories of pathogenesis based on defective regulation of cytosolic calcium and abnormal responsiveness of developing cardiac cells to sympathetic stimulation are worthy of further study. Finally, the discovery that defects in myosin can produce hypertrophic cardiomyopathy will focus attention on the other proteins involved in the contractile apparatus.
CLINICAL IMPLICATIONS OF GENETIC STUDIES

These rapid advances in unravelling the genetic basis of hypertrophic cardiomyopathy have implications for clinical practice in the coming years. First, different mutations in the myosin heavy chain genes may result in differences in disease severity and prognosis. Similarly, families in which the disease is not linked to chromosome 14 may differ from those in which it is, in terms of clinical disease and its treatment. Detailed documentation and presentation of the clinical features of all families studied will be necessary to identify such differences. Second, genetic analysis may become valuable when diagnosis is difficult. For instance in athletes or hypertensive patients with apparently excessive hypertrophy, genetic analysis may give a positive diagnosis of hypertrophic cardiomyopathy. Third, the ability to detect carriers of the disease gene either in utero or in childhood will now be possible in some families. This raises important ethical and practical questions about screening for and management of gene carriers. Knowledge of the natural history and penetrance of a given mutation will assist in management. To date, in both families with myosin heavy chain abnormalities all individuals with mutations in the gene who have had clinical disease 2 but there was considerable variability in severity within the French-Canadian families. Studies of further families are needed. In hypertrophic cardiomyopathy there may be time to intervene before the development of morphological disease, because many individuals do not develop hypertrophy until their teenage years. 20 Elucidation of the mechanisms by which mutations in the myosin genes lead to the phenotypic abnormality combined with prospective follow up of young carriers should lead to trials of therapy to prevent hypertrophy. Finally, the discovery that mutations in the genes which code for the heavy chains of cardiac myosin may cause hypertrophic cardiomyopathy focuses attention on the role of myosin in secondary hypertrophy. The current discoveries suggest that the degree of hypertrophy for a given stimulus might reflect variations in myosin genotype.

Conclusion

The discovery that mutations in the genes that code for cardiac myosin heavy chains are the cause of hypertrophic cardiomyopathy in some families is the most important advance since the original description of the condition. Future work will identify to what extent familial hypertrophic cardiomyopathy is due to mutations in the myosin heavy chain genes and will determine how these mutations produce the condition of hypertrophic cardiomyopathy. Some families will not show defects in myosin and further studies are required to identify the genetic abnormalities in these families. Eventually we may understand how myocardiopathy and disarray can be prevented.

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