Editorial

Genetic factors in familial hypertrophic cardiomyopathy: does molecular cardiology offer new perspectives?

The fact that hypertrophic cardiomyopathy is often familial has been known for a long time, and seven years ago the era of molecular cardiology opened up when hypertrophic cardiomyopathy in a large family was first linked to a locus on chromosome 14.[1] Since this first report, major breakthroughs have been made in the understanding of the genetic background of this autosomal dominant disease. However, nobody anticipated the high degree of genetic heterogeneity observed in familial hypertrophic cardiomyopathy (FHC), which is also seen in other familial cardiovascular disorders such as the long QT syndrome. Does the development of molecular biology offer the clinician an important new perspective on FHC ?

A high degree of genetic heterogeneity

After the identification of the first locus on chromosome 14 q11-q12 (CMH1), three other loci have been reported on chromosome 1q3 (CMH2), 15q2 (CMH3), and 11p13- q 3 (CMH4). Furthermore, in some families there is no evidence of a link with any of these loci, which suggests the existence of at least a fifth locus. In addition, in a particular form of FHC associated with a Wolff-Parkinson-White syndrome, another locus has been identified on chromosome 7q3.[2]

The morbid genes involved in FHC that have been identified encode proteins of the contractile apparatus: B myosin heavy chain (CMH1), cardiac troponin T (CMH2), α tropomyosin (CMH3), and the cardiac myosin binding protein C (CMH4).[3–5] This finding was recently reinforced by the identification of mutations in the essential (chromosome 5) and the regulatory (chromosome 3) light chains of myosin associated with a rare variant of cardiac hypertrophy and abnormal skeletal muscle.[6]

It is striking that all the morbid genes identified encode proteins of the sarcomere or proteins involved in the regulation of contraction. This observation suggests that FHC is a disease of the sarcomere and that ventricular hypertrophy, a major clinical characteristic of the disease, is a mechanism that compensates for depressed contractility. Indeed, some in vitro studies indicate that mutations in the B myosin heavy chain gene decrease the actin activated ATPase of myosin fragments and the actin translocation rate on the mutated myosin.[7 8] These in vitro experiments are preliminary, however, and much additional work is needed to assess the functional consequences of the abnormal genes at the molecular and cellular levels.

More than 30 mutations have been identified in the B myosin heavy chain gene and several have also been reported in the genes encoding cardiac troponin T and α tropomyosin (see review in reference 9). This indicates considerable intragenic heterogeneity. In most instances, the molecular mechanism involved is a missense mutation with a nucleotide substitution changing one amino acid residue in the protein. Other types of mutations have also been reported in the genes for cardiac troponin T and cardiac myosin binding protein C.

Prognosis stratification

Because the prognosis varies greatly from one family to another, it is important to determine whether or not the genetic heterogeneity accounts for the clinical diversity and to assess the relation between phenotype and genotype.

Various mutations of the B myosin heavy chain gene have been associated with a poor prognosis (malignant mutations rather than benign mutations). More generally, it has been proposed that mutations that change the electric charge of the amino acid residue are likely be malignant whereas neutral mutations are likely to be benign: conflicting results have been reported, however. This underlines the fact that large kindreds are needed for risk stratification and the need to create an international data base.

Left ventricular hypertrophy and penetrance

The extent and pattern of left ventricular hypertrophy can vary considerably from one family to another. However, there are several reasons why it is difficult to try to establish a relation between left ventricular hypertrophy and the type of genes or mutations involved. Firstly, the number of affected individuals in a given family is often too small to give conclusive data; secondly, parent mutations occurring within the same codon may result in different clinical presentations; and thirdly, other factors, including the environment and modifier genes, are likely to modulate the phenotype of the disease. Genes coding for proteins involved in the modulation of cardiac hypertrophy such as the renin angiotensin system in particular may play a key part in the clinical expressivity. For example, it has been shown that the presence of the D/D genotype of the insertion/deletion polymorphism of the angiotensin I converting enzyme is associated with a greater extent of hypertrophy in FHC.[10] The search for other modifier genes is therefore of paramount importance to an understanding of the high variability of clinical expression of FHC.

Genetic analysis has revealed the high frequency of healthy adult carriers in FHC pedigrees. The identification of healthy carriers raises many clinical and ethical questions particularly in young adults in families with the malignant gene. Children can develop clinical symptoms during adolescence and FHC may be associated with no hypertrophy. A careful follow up will be necessary to determine whether or not healthy carriers develop the disease.

Clinical perspectives

Though there are obvious limitations related to the genetic complexity of the disease, the development of molecular biology in FHC has increased enthusiasm for potential clinical applications.

- The diagnostic criteria based on the genotype should be re-examined becaue such an analysis may lead to more accurate and refined criteria for the clinical diagnosis of FHC.
- Identification and long term follow up of healthy carriers will throw light on the course of FHC
- The analysis of the course of FHC diagnosed on the basis of the genotype can be used to stratify risk. Here again, long term follow up of patients will be required to give a better assessment of the prognosis asociated with each mutation and to identfy affected individuals at risk of disease-rélated death: the question of how to treat them remains open.
- Ultimately, is routine genotyping warranted? The scientific information available is too scarce to allow a positive answer at present. The only clinical implication of this strategy would be to advise a change in life style (for example, avoiding competitive sports) in young individuals carrying a malignant mutation, because currently no preventive treatment is available. Moreover, because of the many ethical problems concerning its social and psychological consequences, widespread testing cannot be recommended at present.

To improve understanding of FHC and achieve the major clinical goals detailed above, it is necessary to develop collaboration between cardiologists and moleculoar biologists and to establish a large international data base on the clinical characteristics and the prognosis of known mutations.

Remarkable efforts are currently being made in Europe to create this data base and initiate a network with the specific objective of improving our understanding of the relations between the phenotype and the genotype of familial hypertrophic cardiomyopathy. Much more information should therefore become available.

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