

# Hypertrophic Cardiomyopathy: Never-Ending Complexity

Francesc Navarro-López

Servicio de Cardiología, Hospital Clínic, Barcelona, Spain.

The year 1990 saw a decisive step forward in the understanding of hypertrophic cardiomyopathy (HCM)—one of the most common hereditary diseases (prevalence 1/500 families)—when it was discovered that the associated left ventricular wall hypertrophy was due to a mutation in the gene coding for the beta-myosin heavy chain (*MYH7*),<sup>1</sup> the main contractile protein of the sarcomere and that which forms the thick filament. Since then, more than 270 causal mutations have been described in at least 13 genes coding for sarcomere proteins; this highlights the unusual genetic complexity of this disease (<http://genetics.med.harvard.edu/seidman/cg3/index.html>). Despite this genetic heterogeneity, HCM has a common, basic manifestation: hypertrophy of the myocardium and the risk of sudden death. The severity of the disease, however, is very variable (phenotype heterogeneity), and this can seriously hinder the establishment of a prognosis and therefore make it difficult to select patients who require aggressive treatment.<sup>2-4</sup>

Genotype determination—which as yet is a technique only available to a few laboratories that undertake research—has, however, opened up the possibility of studying the relationship between mutations and their clinical manifestations. There is hope that precise knowledge of a causal mutation will help physicians predict the severity of its associated cardiac lesions and thus help establish a prognosis. In recent years, systematic genotype-phenotype correlation studies have awakened much interest, although the information available is still scant. The work published in this issue of the REC by Laredo et al (Hospital Universitario Juan Canalejo, A Coruña) discusses this and examines whether HCM caused by mutations in the *MYH7* gene are more severe than those

caused by other genes, and investigates the prevalence of *MYH7*-associated HCM in a Spanish population.<sup>5</sup>

## Prevalence of *MYH7* Mutations Associated With HCM

The first research in this area to use an exhaustive methodology (complete sequencing of nine genes) in a large group of non-related patients (n=197)—the EUROGENE project—was performed in France, and confirmed the estimates of previous studies. A mutation in *MYH7* was detected in 25% of patients with HCM, in the gene *MYBPC3* (myosin-binding protein C, a structural protein) in 26%, and in *TNNT2* (troponin T) in 4%. In 38% of patients, no causal gene could be identified.<sup>6</sup>

Van Driest had already reported, however, that the frequency of *MYH7* mutations might be smaller than that previously indicated. The prevalence observed in the largest cohort studied until then, which involved 389 outpatients who attended a tertiary reference center (the Mayo Clinic, Minnesota, USA), was 15%, while that of *MYBPC3* mutations was 18%.<sup>7</sup> In Finland a prevalence of 3% was reported (although only 35 families were studied).<sup>8</sup> In contrast, in a study of 100 families in China, Song et al<sup>9</sup> reported the frequency of *MYH7* mutations to reach 41% (the frequencies for *MYBPC3* and *TNNT2* mutations were 18% and 2% respectively). It therefore came to be understood that the spectrum of causal HCM mutations did not follow the regular distribution, but varied considerably depending on the region studied. To arrive at this conclusion, it has to be assumed that these studies are comparable in terms of: *a*) the sensitivity of the mutation detection technique; *b*) the age of the population (the percentage of patients with a recognizable phenotype [penetrance] depends on the age of the subjects; prevalence can be underestimated if the age of the population is low, on the other hand it may be higher if patients carrying the more severe mutations have already died); or *c*) the patient selection bias (if the population is selected from tertiary reference hospitals, serious mutations are more likely to be seen).

With these precedents, the low prevalence of 10.2% described in the paper by Laredo et al<sup>5</sup> in 128 families can be considered an argument in favor of the

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Correspondence: Dr. F. Navarro-López.  
Servicio de Cardiología. Instituto del Tórax. Hospital Clínic. Universidad de Barcelona.  
Villarroel, 170. 08036 Barcelona. España.  
E-mail: fnavarro@ub.edu

variability of the mutation profile in different regions since the methodology used is similar to that employed in other studies in terms of its sensitivity (84%-89%). The mean age of the population is also similar (44 years compared to 41 in the study by van Driest), as is the outpatient origin of the patients (in the Laredo paper these patients were considered representative of a little selected-population from Galicia, northwestern Spain). In this context, the prevalence of 6.7% described in Asturias (30 cases)<sup>10</sup> lends support to the idea that the mutation frequency of *MYH7* in northwestern Spain is low.

## Genotype-Phenotype Correlations

### *Is There Any Distinctive Clinical Pattern Associated With MYH7 Gene?*

Early reports indicated that mutations in the *MYH7* gene were associated with important left ventricular wall hypertrophy and a high risk of sudden death. Mutations in the *MYBPC3* gene, the most benign, were thought to be related to a very mild hypertrophy and a very small risk of sudden death, and those of *TNNT2* to be associated with minimum hypertrophy but a high risk of sudden death. This simplification now seems somewhat excessive, and the most recent studies have started to question whether there is any substantial difference between the phenotypes associated with the mutations of these three genes. The results of van Driest et al on *MYBPC3*-associated HCM,<sup>11</sup> for example, suggest that the phenotypes of patients with mutations in this gene are virtually the same as those with beta-myosin mutations; only those patients with multiple mutations showed more severe phenotypes.

In their extensive study of patients at the Mayo Clinic, van Driest et al<sup>7</sup>—and now Laredo et al<sup>5</sup> in Galicia—tried to define the clinical pattern of *MYH7*-associated HCM, comparing their patients with those who suffered HCM but who had no mutation of this gene. The conclusions reached by both groups of authors are the same. In the Laredo study, which involved an outpatient population attending a tertiary hospital, the clinical presentation of the index case patients of 13 families with *MYH7*-associated HCM was quite different to those belonging to other families with HCM caused by mutations in other genes (n=115): hypertrophy was more intense, the ejection was fraction larger, the cavity of the left ventricle was smaller, penetrance was greater, and a family history of HCM was much more common. A finding of particular importance, which the van Driest et al study did not report, is the higher frequency of a family history of sudden death in *MYH7*-associated HCM than in HCM of other causes (31% vs 7% of cases). This supports the controversial concept that mutations

of this gene are associated with a greater risk of sudden death.

The group of patients who did not have *MYH7* mutations, used as control group in both the above studies, appears to be quite heterogeneous. Both include a large proportion of patients without detectable mutations. These patients represent between 40% and 60% of all cases of HCM in both series, and with all probability they have a more benign clinical expression, especially if it is assumed that there are no differences between *MYH7*- and *MYBPC3*-associated HCM.<sup>11</sup>

### *Malignant Mutations of MYH7*

It is possible that the clinical characteristics of HCM do not depend so much on the gene involved but on the type of mutation they carry since mutations with benign, malignant and intermediate prognoses have all been described for *MYH7*, *MYBPC3*, and *TNNT2*.<sup>2</sup> The confirmation of the benign or malignant nature of a mutation, however, is fraught with difficulty since the frequency of rare mutations rarely exceeds 1%-2%, and the number of families studied in the literature is still very small (and these have insufficient numbers of affected members to corroborate the consistency of a clinical pattern).

Among the malignant mutations in *MYH7* (according to the classification of Roberts et al)<sup>2</sup> Arg719Trp and Arg723Gly (the “Barcelona mutation” described by the present author’s group) stand out.<sup>12,13</sup> These are localized in the converter domain (codons 711-781), the neck which joins the head of the myosin with the lever arm (an alpha-helix) and functions as a hinge that transmits movement from the head, promoting the sliding of the thick filament over the thin filament. These mutations are associated with an increased frequency of sudden death, the implantation of automatic defibrillators, terminal heart failure, the progression to the dilated phase, and the need for heart transplant before the age of 60.<sup>12</sup>

It is also interesting to note that the I736T mutation, which stands out for its malignancy in the study of Laredo et al, is also localized in the converter domain. Six of the 9 carriers of this mutation in the 3 affected families suffered a malignant outcome (1 died of heart failure, 4 died suddenly, and 1 progressed to the dilated phase). This indicates that malignancy is related to the strategic localization of the mutation to the converter domain, a critical region of the myosin molecule; the result is serious functional disease. This unifying explanation could, however, be somewhat premature since we do not understand the details of the molecular and cellular dysfunction mechanisms. At the laboratory of Kraft and Brenner, in Hanover (Germany), the present author’s group studied the effect of the mutations Ile376 Thr, Arg719Trp, and

Arg723Gly on the contractile function of muscle fibers isolated from the calf muscle, and it was confirmed that the contractility and relaxation of the myocytes are impaired (as determined from the “force/Ca concentration” relationship). These alterations were different in different myocytes from the same patient, and the dispersion of the mechanical characteristics of the myocytes contributed to a loss of contractile efficiency.<sup>13</sup> The confirmation that mutations affecting the converter domain lead to serious, complex modifications of myocyte contractibility does not mean that other factors cannot be involved, for example the quantity of mutated myosin present in cells. Myocytes can coexpress wild type and mutated myosin, but in proportions that vary considerably depending on the mutations involved.<sup>13</sup>

Apart from the determining role of the gene and casual mutation, there are many other genetic and environmental factors (which are being given ever greater importance) that can modify the clinical expression of the mutation, e.g., the presence of multiple mutations of the same gene (6% of cases), or other genes (mitochondrial second hit), modifying polymorphisms, sex, exercise and blood pressure, may all confound genotype-phenotype relationships. These could explain the differences seen between carriers of the same family.

Only through large-scale registries recording genotype-phenotype correlations, with exhaustive studies of the genotype and the modulator factors, along with the natural history of mutation carriers in sufficiently large families, can we achieve a more subtle, more clear vision of the predictive value of knowing a patient’s genotype. We may also one day know the molecular and cellular basis of the genotype-phenotype correlations. For the time being, however, molecular genetics falls short of facilitating the prediction of risk, although we now better understand the size and complexity of the problem.

### Addendum

Mora et al<sup>14</sup> have just published a short communication that once again reports the low frequency of *MYH7* mutation in Spain.<sup>14</sup>

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