The aim of this study was to identify mutations in the cardiac heavy-chain beta-myosin gene (MYH7b) in a group of Spanish patients with hypertrophic cardiomyopathy. The study included 36 families with at least one member who had hypertrophic cardiomyopathy. DNA from exons 3 to 24 of the MYH7b gene was sequenced. Two mutations were identified: Arg858Cys and Met515Val. They occurred in 2 families, one of which was of Moroccan origin. This corresponds to a MYH7b gene mutation frequency of less than 5%. In contrast to findings in other Caucasian populations, MYH7b gene mutation occurred infrequently in this group of Spanish families with hypertrophic cardiomyopathy.

Key words: Hypertrophy cardiomyopathy. MYH7b gene mutation.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a heart disease characterized by ventricular hypertrophy, generally of the left ventricle. Usually, the interventricular septum is strongly affected. No cause of such hypertrophy is immediately apparent. The prevalence of this disease is 1:500-600,1,2 depending on the population. Inherited in the Mendelian fashion (autosomal dominant), the severity of the problem depends upon the mutation carried.

Twelve genes associated with this disease have been identified, of which nine code for proteins of the cardiac sarcomere.3-10 In total, more than 150 different mutations are thought to lie at the root of the problem. Studies of large numbers of patients of European and North American origin show mutations of the cardiac beta-myosin heavy-chain gene (MYH7b) to be that most commonly associated with HCM; some 20%-30% of all patients with this disease have a mutation of this gene.

The aim of the present study was to analyze the sequence of MYH7b in a number of Spanish patients
with HCM to establish the frequency and the types of mutation shown by this gene in Spain.

METHODS

Patients

The study subjects were 144 patients belonging to 36 families, each with at least one member who suffered HCM. The diagnostic criteria for inclusion in the study were: a left ventricular wall or interventricular septum of thickness ≥13 mm (in adults) with no immediately apparent cause of such hypertrophy; in the direct family members of affected patients, mild ventricular hypertrophy (thickness ≤13 mm) associated with an abnormal electrocardiogram (ECG; abnormal Q wave or marked inversion of the T wave) was deemed sufficient for a positive diagnosis to be made. The patients analyzed (24 males and 12 females aged 3-79 years) were recruited at the cardiology units of hospitals in Madrid. Thirty three of the corresponding families were Spanish, 3 were Moroccan of Arabic origin. All patients had undergone at least one ECG at some time. All patients gave their informed consent to be included, in keeping with the demands of the ethics committee of the Hospital Universitario La Paz.

Genetic Analyses

The MYH7b gene was sequenced in one member of each family. Exons 3-24 (both inclusive) and the adjacent intronic regions were amplified separately by the polymerase chain reaction (PCR). Both DNA strands were sequenced following the Sanger method. The resulting sequences were compared with those for MYH7b stored in NCBI database (http://www.ncbi.nlm.nih.gov/entrez) (ref. NT_026437).

In those families in which more than 1 member could be studied, 2 MYH7b intragenic microsatellite markers, MYO I and MYO II, were analyzed to determine whether a mutation of this gene was the cause of disease in each patient.

RESULTS

Eighteen of the patients had a family history of HCM and 18 showed sporadic presentation. Analysis of the polymorphic markers MYO I and MYO II showed that the mutation of MYH7b was not the cause of the disease in 6 families. In the remaining 30 patients the disease either appeared sporadically or the number of individuals in each family was too small to allow the segregation of alleles to be analyzed and correlated to clinical manifestations. In these 30 patients, the regions of the gene where the mutations that most commonly cause HCM were analyzed.

DISCUSSION

Hypertrophic cardiomyopathy is frequently associated with mutations of MYH7b, a gene that codes for the heavy chain of cardiac beta-myosin. Sequencing of more than 80% of this gene, including the regions where mutations most commonly occur, identified 2 mutations in 36 families (5.5%). One of these mutations, Arg858Cys, has been described by van Driest et al., although these authors provide no clinical data for the patient involved. Aminoacid Arg858 has been conserved throughout evolution, reflecting its functional importance (Figure 2B). The
other mutation detected was Met515Val. The strict conservation of methionine 515 (Figure 2A) indicates that this mutation may affect the function of the protein.

The present results show that mutations of MYH7b in the Spanish population of patients with HCM is uncommon compared to that seen in other Caucasian groups. As in other studies of patients with HCM, the present population was recruited at hospital clinics, therefore a selection bias with respect to the general population of patients with HCM (many of whom are undiagnosed) cannot be ruled out. The results of this study are of importance with respect to diagnostic strategies and in the genetic counseling of families affected by this disease.

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