A previously undescribed de novo insertion-deletion mutation in the β myosin heavy chain gene in a kindred with familial hypertrophic cardiomyopathy

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Abstract

A previously undescribed de novo insertion-deletion mutation in the β myosin heavy chain gene was found in a kindred with familial hypertrophic cardiomyopathy. In the mutated allele there is an inserted-deleted guanine at nucleotides 8823 and 8850 of the β myosin heavy chain gene, resulting in a dramatic change of the aminoacid sequence (AA 395–404). Such a mutation, detected in the proband and in his son but not in the proband’s parents, is likely to produce major impairment of myosin function.

Keywords: hypertrophic cardiomyopathy; myosin; mutation.

Familial hypertrophic cardiomyopathy is an autosomal dominant inherited cardiac disorder characterised by unexplained thickening of the interventricular septum and the free wall of the left ventricle. It is the most common cause of sudden cardiac death in otherwise healthy young individuals. The genetic heterogeneity of familial hypertrophic cardiomyopathy has been confirmed by several groups. Four genes (on chromosomes 1, 11, 14, and 15) encoding for sarcomeric proteins (cardiac troponin T, cardiac myosin binding protein-C, β myosin heavy chain (β-MHC), and α tropomyosin, respectively), have been associated to the disease.1–4 We have recently shown that β myosin purified from soleus muscle biopsies of individuals with two distinct missense mutations in the β-MHC gene (Arg403Gln and Leu908Val) translocates phallolidin-labelled actin filaments at a slower velocity than that of normal controls in an in vitro motility assay,5 suggesting that cardiac hypertrophy may be a compensatory mechanism.

Comparison of nucleotide and amino acid sequences of β-MHC

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<th>Nucleotide sequence</th>
<th>Wild type</th>
<th>Mutant</th>
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<tbody>
<tr>
<td>8819 GAC GTG GCT CAC CTT GAG CTC</td>
<td></td>
<td>8819 GAC GTG GCT CAC CTT GAG CTC</td>
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<tr>
<td>8854 AAA</td>
<td>8854 AAA</td>
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<table>
<thead>
<tr>
<th>Aminoacid sequence</th>
<th>Wild type</th>
<th>Mutant</th>
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<tr>
<td>394 D L K G L N P P</td>
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<td>394 D R A Q G A V P P</td>
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<tr>
<td>395</td>
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<td>8854 G K 405</td>
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Order of appearance of the mutation in each of the four genes and the possible sequence of events leading to the clinical manifestation of the disease. Paternity and the parental origin of the chromosome bearing the de novo mutation were assessed by a demonstration of the inheritance of appropriate alleles at eight polymorphic dimeric short tandem repeats sequences (STRs) and by haplotype analysis of the β-MHC gene,7 (data not shown). The mutation was not detected in 100 chromosomes from unrelated, unaffected individuals.
Discussion

This study provides the first description of a de novo insertion-deletion mutation in the \( \beta \)-MHC gene in familial hypertrophic cardiomyopathy. Our finding is particularly interesting because the nature of this mutation is quite different from the missense mutations reported by us and others in patients with \( \beta \)-MHC-linked hypertrophic cardiomyopathy. The site of the mutation, near the actin-binding interface of myosin S-1, as demonstrated by the amino acid and the three-dimensional structural similarities between chicken skeletal muscle and human \( \beta \)-cardiac myosin, may be causing a dramatic impairment of the protein function, and it could be responsible for the development of cardiac hypertrophy in the affected individuals. The genetic background may play a major part in the appearance of this mutation. Calabria, a region of south Italy where the study was performed, has a very homogeneous genetic background for historic and geographic reasons. As shown by others, \( \beta \) ethnic origin can be responsible for particular forms of this disease arising and it should be taken in account when genetic screening is done.

We thank Dr. Angelo Lamberti for the valuable technical assistance.

This study was supported by the Italian Telethon Foundation (grant 474).

6. Epstein ND, Cola GM, Cyran F, Fananapazir L. Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the \( \beta \)-myosin heavy chain gene: a 906
\( \rightarrow \) mutation and a 403