

Frequency and clinical expression of cardiac troponin I mutations in 748 consecutive families with hypertrophic cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant cardiac condition with a prevalence of 1 in 500. Clinical diagnosis depends upon the demonstration of unexplained myocardial hypertrophy.

Disease causing mutations have been identified in 11 different sarcomeric proteins (including troponin I (TNNI3)) therefore it is possible to provide a genetic diagnosis in the majority of HCM cases. The use of genetic diagnosis in clinical management of affected HCM families is dependant upon detailed information about genotype-phenotype correlation. Previous studies have suggested a genotype-phenotype correlation in the case of some mutations but these have been small scale studies and information has been from individuals and has not addressed disease presentation within families.

Issue addressed in paper

This study performed a detailed analysis of the genotype-phenotype relationship in families with mutations in the TNNI3 gene. The potential value of genetic diagnosis for management, counselling and follow up of HCM families with TNNI3 mutations was investigated.

Summary of findings

Mutation analysis of the TNNI3 gene was performed in 748 HCM probands from a cardiomyopathy clinic. Relatives of probands with TNNI3 mutations were then invited for cardiac and genetic assessment.

- TNNI3 mutations were found in 3.1% of cases. In total 100 mutation carriers were identified in 23 families with 12 different mutations (6 novel).
- Mutations were all clustered to exons 7 and 8.
- Disease penetrance was 48%.
- The morphological spectrum observed represented a wide range of HCM.

Conclusions

- Clinical expression of TNNI3 mutations is very heterogeneous within and between families – there is no apparent mutation or gene specific disease pattern.
- Therefore the severity or timing of HCM disease development in genotype positive offspring cannot be predicted by the severity of disease in HCM probands with a TNNI3 mutation.
- Clinically unaffected mutation carriers are present at all ages and comprise 52% of all genotype positive individuals. Life long clinical follow up is important and warranted in these patients due to the unpredictable expression of TNNI3 mutations.
- Relatives who do not carry the identified TNNI3 mutation can be informed that they have no risk of developing the disease or passing it on to their offspring.
- **Therefore genetic diagnosis identifies relatives who require follow up and allows the termination of cardiac evaluation in individuals without the mutation. This is both beneficial to patients and facilitates the cost effective use of resources for clinical screening.**
- Previous studies have suggested that mutations in different HCM genes may be associated with specific clinical phenotypes. The heterogeneity and relatively low penetrance observed with TNNI3 mutations from this study of a larger number of genotype positive families show the importance of large scale studies to make firm conclusions about genotype-phenotype relations in HCM.

The study concluded that genetic diagnosis of individuals with a TNNI3 mutation is technically feasible and that there are data to support its potential clinical utility in HCM.