

## **The devil's in the details: progress in familial hypertrophic cardiomyopathy.**

M Keating

*J Clin Invest.* 1994;**93**(1):2-3. <https://doi.org/10.1172/JCI116946>.

Research Article

**Find the latest version:**

<https://jci.me/116946/pdf>



Nobody said it would be easy. The field of molecular genetics promised that molecular understanding of human disease would lead to better prediction, prevention, and treatment. Although I am confident this promise will be realized, during certain stages of every great journey the goal may appear more elusive than it did at the start. This is the case with the molecular genetics of familial hypertrophic cardiomyopathy, a journey that began more than 5 years ago.

The field got off to a rapid start in 1989 when Jarcho et al. (1) used the technique of genetic linkage analysis to identify the chromosomal location (chromosome 14) of a gene causing familial hypertrophic cardiomyopathy. A candidate gene, the  $\beta$  cardiac myosin heavy chain gene, was located nearby, and when disease-associated mutations were identified (2), hope that hypertrophic cardiomyopathy would relinquish many of its secrets in one burst of enlightenment seemed promising.

Now, however, the journey has taken a challenging turn. Over the past few years it has become clear that not all cases of familial hypertrophic cardiomyopathy are caused by mutations in the  $\beta$  cardiac myosin heavy chain gene; about 40% of cases appear to be linked to chromosome 14. Genetic linkage analysis has been used to identify three additional hypertrophic cardiomyopathy loci (chromosomes 1, 11, and 15), and at least one (and possibly several) additional loci must exist since many families still remain unlinked (3–5). From a clinical perspective, this degree of locus heterogeneity is a significant problem, making genetic testing for this disorder currently impractical in many cases.

Investigators have also identified allelic heterogeneity among affected individuals with  $\beta$  cardiac myosin missense mutations. At least 15 different point mutations in the myosin heavy chain gene have now been associated with hypertrophic cardiomyopathy, and the list continues to grow (for a list and brief review, see reference 6). In this issue of *The Journal*, for example, Anan et al. (7) identify three new  $\beta$  cardiac myosin missense mutations in DNA from hypertrophic cardiomyopathy patients (7). One of these mutations is nonconservative (Arg 719 Trp) and is associated with significant morbidity and mortality, while a second, more conservative mutation (Phe 513 Cys) appears to be relatively benign with no significant effect on life expectancy.

Although genetic heterogeneity for hypertrophic cardiomyopathy complicates genetic testing and risk stratification, each mutation sheds new light on the molecular mechanisms underlying this disorder and a genotype/phenotype catalogue has begun to emerge. Most myosin mutations are located in the portion of the gene encoding the head or head-rod junction; mutations involving the rod are infrequent and seem to cause mild disease. Although some mutations associated with more severe disease are known to affect actin binding domains, the effect of most mutations is still hidden in the structure of the

myosin protein, a structure that is just now being examined. One hopeful finding in Anan's study is that mutations leading to a change in charge seem to have a more malignant effect than conservative amino acid substitutions. Charge, however, is not the whole answer; Anan's study (7) demonstrates that some charge-altering mutations lead to a low risk phenotype, while a recent study by Fananapazir and Epstein (8) shows that a conservative substitution that is benign in some families can be malignant in others (8).

Should we be discouraged by the complexity of hypertrophic cardiomyopathy? I think not. A comparison of what we know now and what we knew in 1988 shows impressive progress (Table I). The dramatic discoveries that occurred in the 80s have led to a series of steady discoveries in the 90s. With time we will uncover all of the genes that cause hypertrophic cardiomyopathy and amass a body of information that correlates mutation with risk. New, more efficient methods for identifying genotypes will be developed, helping to make disease prediction for complex disorders feasible. Eventually, we hope to discover new ways for preventing and treating deadly cardiovascular disorders such as hypertrophic cardiomyopathy.

The mutational events that led to the introduction of hypertrophic cardiomyopathy into the human phenotype evolved over many, many years. If a molecular understanding of hypertrophic cardiomyopathy and the ability to predict its occurrence are accomplished within a decade of the first linkage finding, the journey will have been quite rapid. The scientific community can then focus on the most exciting promises of molecular genetics: prevention and treatment of disease.

Mark Keating

Department of Medicine and Human Genetics  
University of Utah

## References

1. Jarcho, J. A., W. McKenna, P. Pare, S. D. Solomon, R. F. Holcombe, S. Dickie, T. Levi, H. Donis-Keller, J. G. Seidman, and C. E. Seidman. 1989. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N. Engl. J. Med.* 321:1372–1378.
2. Geisterfer-Lowence, A. A. T., S. Kass, G. Tanigawa, H. P. Vosberg, W. McKenna, C. E. Seidman, and J. G. Seidman. 1990. A molecular basis for famil-

Table I. Genetics of Hypertrophic Cardiomyopathy

Year	Mode of inheritance	Chromosome location	Gene	Malignant genotype
1988	AD	?	?	
1993	AD	1	?	
		11	?	
		14	$\beta$ Cardiac Myosin Heavy chain	Arg403Gln Arg453Cys Arg719Trp
		15	?	
		?	?	

J. Clin. Invest.

© The American Society for Clinical Investigation, Inc.

0021-9738/94/01/0002/02 \$2.00

Volume 93, January 1994, 2–3

ial hypertrophic cardiomyopathy: A  $\beta$  cardiac myosin heavy chain gene missense mutation. *Cell*. 62:999–1006.

3. Watkins, H., C. MacRae, L. Thierfelder, Y. H. Chou, M. Frenneaux, W. McKenna, J. G. Seidman, and C. E. Seidman. 1993. A disease locus for familial hypertrophic cardiomyopathy maps to chromosome 1q3. *Nature Genetics*. 3:333–337.

4. Carrier, L., C. Hengstenberg, J. S. Beckmann, P. Guicheney, C. Dufour, J. Bercovici, E. Dausse, I. Berebby-Bertrand, C. Wisnewsky, D. Pulvenis, et al. 1993. Mapping a novel gene for familial hypertrophic cardiomyopathy to chromosome 11. *Nature Genetics*. 4:311–313.

5. Thierfelder, L., C. MacRae, H. Watkins, J. Tomfohrde, W. McKenna, K. Bohm, G. Noeske, M. Schlepper, J. Just, A. Bowcock, H. P. Vosberg, C. E. Seidman, and J. G. Seidman. 1993. A disease locus for familial hypertrophic

cardiomyopathy maps to chromosome 15q2. *Proc. Natl. Acad. Sci. USA*. 90:6270–6274.

6. Hengstenberg, C., M. Komajda, and K. Schwartz. 1993. Genetics of familial hypertrophic cardiomyopathy: results and strategies. *Trends in Cardiovascular Medicine* 3:115–119.

7. Anan, R., G. Greve, L. Thierfelder, H. Watkins, W. J. McKenna, S. Solomon, C. Vecchio, H. Shono, S. Nakao, H. Tanaka, et al. 1994. Prognostic implications of novel  $\beta$  cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. *J. Clin. Invest.* 93:280–285.

8. Fananapazir, L., and N. Epstein. 1993. Genotype-phenotype correlations in hypertrophic cardiomyopathy: insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation*. In press.