Dilated Cardiomyopathy and the Desmin Gene

To the Editor:

Li et al report a mutation screening study of actin and desmin genes in 44 probands with familial dilated cardiomyopathy (DCM) and conclude that a mutation of the desmin gene can cause DCM. We believe that the genetic data are not yet sufficient to justify this conclusion.

Attempts to find genes for autosomal dominant DCM by linkage analysis have been frustrating; although 6 chromosomal loci have been mapped, none of these linkages have yet led to disease-gene identification. Not surprisingly, investigators have turned to direct candidate gene analysis. However, in forgoing linkage analysis, one of the pillars of evidence supporting a real association is removed.

Other criteria for assessing a causal effect are that the DNA variant in the affected individuals is not present in a large number of normal controls, that the predicted change in the encoded protein is significant, and that mutations in the same gene are found in more than 1 affected family. Such observations have been sufficient to propose a causal role for missense mutations in cardiac actin in DCM. However, without evidence of cosegregation (linkage) or an observed biological effect, some uncertainty remains, and actin mutations have not yet been found in other DCM series. Demonstration of de novo mutation confirms the role of a disease gene, but this has not been achieved for DCM.

The second candidate gene to reveal a mutation in DCM is that encoding desmin. Li et al describe a missense mutation, Ile451Met, in the desmin gene in a single proband with DCM. The variant was not present in normal controls, but this alone does not indicate a disease-causing role. Three relatives carried the mutation, but only 1 of these was clinically affected. The presence of the mutation in equal numbers of affected and unaffected individuals raises concern about the statement that the mutation segregates with DCM in this family. One risks false-positive findings in studies of plausible candidate genes (such as desmin in DCM) by assuming incomplete penetrance rather than postulating nonsegregation of the mutation with the disease, ie, the null hypothesis.

However, the family was large enough (4 generations) to have used linkage analysis to test the role of the desmin variant. With only the data presented, 2 interpretations remain: the variant may be disease causing, albeit partially penetrant, or it may be incidental and therefore not likely to be transmitted from the deceased ancestor to the 2 living affected and 3 deceased, presumed-affected cousins. Three simple tests can and should be applied to resolve these alternatives. First, if tissue blocks are available on any deceased, presumed-affected relative, then demonstration of the mutation would support linkage. Second, analysis of relatives of the mother of the proband (II:4) would check that the variant was not inherited from her (indicating an incidental role). Third, haplotype analysis of the desmin gene region in the 5 surviving siblings of the deceased (III:4–8), who do not themselves have the mutation, would test whether 4 copies of the desmin gene are present, revealing that the mutation was not present on that side of the family and could not have caused the disease. If there is no linkage to desmin, there is a high chance that haplotype analysis will reveal it, because there are sufficient individuals to reconstruct genotypes of deceased parents. It would be very helpful to know what can be learned by a more comprehensive genetic analysis in this pedigree.

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Response

We appreciate the comments of Mayosi, Blair, and Watkins concerning our desmin missense mutation causing dilated cardiomyopathy. In contrast to the authors’ statement, the family was inadequate to obtain a significant LOD (log of the odds) score with linkage analysis. In fact, a major reason for the candidate gene approach in this family was that an inadequate number of affected individuals were available with whom we could perform linkage analysis. This will be a common problem in the future, since more genes are likely to be identified by the candidate gene approach.

In answer to your first question, unfortunately we do not have tissue from any of the deceased individuals. In response to your second suggestion, extensive genotyping and haplotype analyses were conducted on this family before submission of the manuscript (results removed in revision). Forty-two relatives of the proband’s mother (II:4) were examined and genotyped. We were able to determine unequivocally the haplotypes of her 2 parents and concluded that the chromosome carrying the mutation had to have originated with the proband’s father (II:3). In response to your third comment, we were able to show that none of the normal living siblings (III:4–8) had the disease-associated chromosome. Haplotype analysis of this sibship identified 2 chromosomes from their father (II:1) and 1 from their mother (II:2). This maternal chromosome was identical to the paternal chromosome in normal individual III:12. The 3 deceased individuals (III:1–3), who died between the ages of 15 and 37 years, had heart failure. It is reasonable to assume that they had the missing maternal chromosome, since statistically this chromosome should appear several times in a sibship of 8. It is only an assumption that the missing chromosome carries the mutation.

In conclusion, the presence of the mutation in all living affected relatives, the absence of the mutation in a large normal population, and the highly conserved nature of the mutated region, along with the observation that desmin knockout mice exhibit a phenotype similar to that of dilated cardiomyopathy in humans indicate this mutation is responsible for the disease in our family. These facts together with the haplotype information all point to the strong probability of this mutation being causative of the disease in this family. In a recent publication by other investigators, our mutation has been confirmed to be responsible for disease in other families. In addition, mutations in other regions of desmin are associated with cardiac and muscular disease. In preliminary experiments, MCF-7 cells transfected with our mutant desmin exhibited filament discontinuity and asymmetrical perinuclear localization. Further studies are ongoing in which we have successfully developed a transgenic mouse, and phenotypic characterization will begin soon.


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