Letters to the Editor

Am. J. Hum. Genet. 54:553–554, 1994

Marfan Syndrome or Marfan-like Connective-Tissue Disorder

To the Editor:

Boileau et al. (1993) describe a finding of great significance in their paper, namely, genetic heterogeneity in Marfan syndrome. Unfortunately, instead of describing their results in a clear and succinct manner, they have obscured and confused them.

The authors have gone to great pains to describe their family as "Marfan-like." However, they have previously (Boileau et al. 1990) described this family as having Marfan syndrome. Why have they changed their minds?

By the Berlin criteria (Beighton et al. 1988), the diagnosis of Marfan syndrome can be made in an individual if there is a positive family history and involvement of at least two systems with at least one major manifestation. The family, as currently and previously described, meets the criteria for diagnosis for Marfan syndrome—family history of autosomal dominance, skeletal manifestations, and major manifestation of the heart. The Berlin criteria do not require that such a family also have major manifestation of the eye to qualify for the diagnosis of Marfan syndrome. Nor has the diagnosis of Marfan syndrome come to depend on known linkage to the Fib15 gene.

It should not surprise us that Marfan syndrome may be genetically heterogeneous. Other dominant syndromes are known to have genetic heterogeneity, such as Charcot-Marie-Tooth, myotonic dystrophy, autosomal dominant polycystic kidney disease, to name but a few. The basic diagnosis for these disorders remains the same, on the basis of clinical criteria, with subgroup definition aided by molecular differences.

The current diagnosis of Marfan syndrome is by clinical criteria. To refine our clinical classification of Marfan syndrome into subtypes based on phenotypic-genotypic correlations, in a systematic and formal manner, may well be appropriate. To create new syndromes based on linkage alone is not.

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Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, et al (1988) International nosology of heritable disorders of connective tissue. Am J Med Genet 29:581–594

Boileau C, Jondeau G, Babron M-C, Coulon M, Alexandre J-A, Sakai L, Melki J, et al (1993) Autosomal dominant Marfan-like connective-tissue disorder with aortic dilation and skeletal anomalies not linked to the fibrillin genes. Am J Hum Genet 53:46–54

Boileau C, Jondeau G, Bonaïti C, Coulon M, Delorme G, Dubourg O, Bourdarias J-P, et al (1990) Linkage analysis of five fibrillar collagen loci in a large French Marfan syndrome family. J Med Genet 27:78–81

EDITOR'S NOTE: *During the review process, the authors of the manuscript by Boileau et al. were asked to change the title of the paper and the references within the paper,*

from "Marfan syndrome" to "a Marfan-like disorder." This request was made by the editor because none of the reviewers felt that all the designated "affected" family members had Marfan syndrome, and, indeed, they thought that many did not. Thus, the reporting of the family in different contexts could raise the concerns indicated by Dr. Gilchrist. As she points out, the diagnosis of Marfan syndrome remains, despite enormous advances in mutation detection in fibrillin, a diagnosis made on the basis of clinical criteria.

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Reply to Gilchrist

To the Editor:

Diagnosis of Marfan syndrome is clinical and, in some cases, difficult. Therefore, guidelines were set forth in the Berlin nosology (Beighton et al. 1988). This diagnosis was made, in the family we reported (Boileau et al. 1990), repeatedly and independently by different clinicians since 1970. Furthermore, some affected members do fulfill the criteria recommended in 1986. The same diagnosis is again suggested by Dr. Gilchrist; however, other specialists, using the same criteria with the same clinical data, do not agree with this diagnosis (see accompanying note from the Editor), and the family phenotype was coined as "Marfan-like" (Boileau et al. 1993). This controversy underlines the fact that diagnosis of Marfan syndrome is highly susceptible to personal divergent interpretation of the Berlin criteria. Therefore the first issue raised by our article is that these criteria should be reconsidered, and clear recommendations should be given for diagnosis of variant forms of the syndrome.

Clinical diagnosis of Marfan syndrome will be made in other probands presenting with manifestations comparable to those observed in our family. Although this has little effect on recommended follow-up and genetic counseling, it has a major impact on presymptomatic molecular testing in related individuals. Indeed, cloning of the fibrillin gene on chromosome 15 (Fib15) and identification of polymorphic markers have permitted molecular-based linkage analysis for presymptomatic and prenatal diagnosis in informative families (Godfrey et al. 1993). However, in practice, most pedigree structures do not comply with the requirements of linkage analysis, and true linkage (lod score ≥ 3) is rarely obtained. Therefore, even if no recombinants are observed (a highly likely event in small families), geneticists should be aware that the family referred as having Marfan syndrome may be truly unlinked to the Fib15 gene, and the segregating haplotype unrelated to the molecular defect. Therefore the second issue raised by our report is that caution is warranted in the interpretation of molecular analyses, if immunochemical analysis of skin and fibroblast culture with antibodies to fibrillin is unavailable or if linkage to the fibrillin gene has not been demonstrated conclusively in a given family.

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Beighton P, DePaepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, et al (1988) International nosology of heritable disorders of connective tissue, Berlin, 1986. Am J Med Genet 29:581–594

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Godfrey M, Vandemark N, Wang M, Velinov M, Wargowski D, Tsipouras P, Han J, et al (1993) Prenatal diagnosis and a donor splice site mutation in fibrillin in a family with Marfan syndrome. Am J Hum Genet 53:472–480

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Linkage and Association

To the Editor:

The recent paper by Hodge (1993) argues that neither the family-based association test of Parsian et al. (1991)