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Address for correspondence and reprints: Dr. Wendy P. Robinson, BC Research Institute for Children's and Women's Health, 3086 – 950 West 28th Avenue, Vancouver, B.C., Canada V5Z 4H4. E-mail: wendyr@interchange.ubc.ca

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Demonstration of the Recurrence of Marfan-like Skeletal and Cardiovascular Manifestations Due to Germline Mosaicism for an *FBN1* Mutation

To the Editor:

Marfan syndrome (MFS [MIM 154700]) is a dominantly inherited disease of connective tissue. Cardinal manifestations involve the eye (lens dislocation and myopia), skeleton (dolichostenomelia, arachnodactyly, anterior chest deformity, spinal curvature, and joint laxity) and cardiovascular system (aortic root dilation and dissection, mitral valve prolapse, and mitral and aortic valve regurgitation). Striae distensae and inguinal hernia are frequent findings in the integument, and pneumothorax and dural ectasia occur in some patients (Pyeritz and McKusick 1979; First International Symposium on the Marfan Syndrome 1989). If untreated, the syndrome shortens life expectancy mainly because of cardiovascular complications. The disorder is characterized by considerable variation in the distribution and severity of organ system involvement between families, leading to the definition of diagnostic criteria listed first in the Berlin nosology (Beighton et al. 1988) and subsequently revised in the Ghent nosology (de Paepe et al. 1996). In 1986, Sakai and colleagues identified a 350-kD glycoprotein called "fibrillin," which represents the major structural component of connective tissue microfibrils. By using an anti-fibrillin antibody, Godfrey, Hollister, and their colleagues demonstrated a reduction of microfibrils in immunofluorescence studies of cultured dermal fibroblasts in patients with MFS (Godfrey et al. 1990; Hollister et al. 1990). Subsequent studies of fibrillin synthesis, secretion, and incorporation into the extracellular matrix showed abnormalities in most but not all MFS fibroblast strains (Milewicz et al 1992; Collod et al. 1994). Finally, mutations in the *FBN1* gene, encoding fibrillin, have been demonstrated to result in MFS or associated phenotypes (Dietz et al. 1991; Hayward et al. 1994; Kainulainen et al. 1994; Lonnqvist et al. 1994; Sood et al. 1996). The *FBN1* gene is ~200 kb in size, with a coding sequence fragmented into 65 exons (Corson et al. 1993; Pereira et al. 1993; Biery et al. 1999) located on chromosome 15q21.1 (Magenis et al. 1991).

It encodes a large glycoprotein composed of repeated modules, 47 of which are homologous to human epidermal growth factor (EGF) ("EGF-like modules") and are interspersed by seven modules displaying high homology to transforming growth factor β1–binding protein (TGFβ1-bp), ("8-cysteine modules") (Corson et al. 1993; Pereira et al. 1993). To date, >160 *FBN1* mutations in patients with MFS or associated phenotypes have been reported or submitted in the Marfan Database (Collod et al. 1996; Collod-Béroud et al. 1997, 1998). However, hardly any predictions of the resulting phenotype can yet be made on the basis of the nature of a specific mutation.

The prevalence of MFS has been estimated at 1/5,000, and $\geqslant$25% of patients represent sporadic cases. This high mutation rate should be associated with cases of germline mosaicism, as has been reported in other connective-tissue disorders or other genetic disorders with a high mutation rate. Therefore, it was surprising that, until recently (Montgomery et al. 1998; Rantamaki et al. 1999), no instance of somatic or germline mosaicism had been reported in MFS. Furthermore, since *FBN1* mutations are also associated with phenotypes overlapping MFS, mosaicism could also be identified in these subtypes. In this report, we demonstrate somatic mosaicism of a *FBN1* genomic mutation in the father of two siblings who presented with the typical skeletal and cardiovascular features observed in the Marfan syndrome.

The proband, MS48MA307, was identified at the Centre Hospitalier in Amiens (by M.M. and Y.M.), and his family was investigated at the Marfan Clinic at Ambroise Paré Hospital, Boulogne (by G.J.). The diagnostic criteria used were those reported by Beighton et al. (1988). The parents of MS48MA307 and his brother, MS48MA308, were unaffected. Patient MS48MA307, a 16-year-old boy, presented dilation of the ascending aorta (46 mm at the sinuses of Valsalva, 8 SD above the mean when standardized to age and body surface area), mitral valve prolapse with regurgitation, highly arched palate, arachnodactyly (positive wrist and thumb signs), tall stature (199 cm, +4 SD, 76 kg), and scoliosis. His 9-year-old brother (MS48MA308) displayed dilation of the ascending aorta (32 mm at the sinuses of Valsalva, 6 SD above the mean when standardized to age and body surface area), arachnodactyly (positive wrist and thumb signs), dolichostenomelia (arm span–to-height ratio 1.05), tall stature (144 cm, +3 SD, 31 kg), highly arched palate, and joint hypermobility. No other typical anomaly of MFS (including ectopia lentis) was found in either subject. Both parents were examined thoroughly, and the diagnosis of MFS was excluded for both. Blood samples were collected from the four family members and from 150 unrelated French subjects. DNA was extracted from white blood cells (Henry et al. 1984). Informed consent was obtained for all individuals. Sense and antisense primers designed from flanking intron sequences were used for PCR amplification of exons 1–65 of *FBN1* and were described, along with PCR amplification conditions, in Nijbroek et al. (1995). SSCP analysis of the *FBN1* gene from white blood cells revealed an abnormal pattern for the 419-bp fragment of exon 24 for patient MS48MA307. This abnormal pattern was also identified in his brother, MS48MA308, but was absent in the mother. However, the father presented a very slight abnormal pattern (fig. 1*a*). Paternity and maternity had been tested previously and indirectly by analysis of highly polymorphic markers on chromosomes 3, 5, and 15 (data not shown). The abnormal fragment from the SSCP gel was cut out of the gel, and DNA was eluted in water and reamplified by PCR. The PCR product was purified with the Promega Wizard Prep kit and was directly sequenced on both strands by means of a cycle-sequencing kit (Pharmacia). Sequencing revealed that the two boys carried the identical heterozygous 2954 G→A transition that results in a Gly→Glu change at codon 985 (G985E) (fig. 1*d*). There is a compelling body of evidence to suggest that G985E is indeed a disease-producing mutation. First, this alteration was not observed during screening of 306 chromosomes. Second, the mutation substitutes an uncharged for a negatively charged amino acid of much higher molecular weight. Finally, the mutational event occurs in the 8-cysteine module 3 at a position conserved in the bovine, murine, and porcine sequences.

Since MFS is characterized by a high mutation rate, the recurrence of the disease in the sibs could have been due to two unrelated de novo mutations. However, since mutations in the *FBN1* gene are essentially private, the presence of an identical mutation in the brothers suggested that the most likely hypothesis was that the mutation had been inherited from one of the parents. Since the mutation creates a new *Taq*I restriction site resulting in two fragments of 202 and 217 bp, it could easily be looked for in the family (fig. 1*b*). After transfer on Hybond N+ membrane (Amersham) and hybridization with the sense primer, the 217-bp fragment resulting from digestion was found in the father's white blood cell DNA (MS48MA305), at a very low level, but was not found in that from the mother (MS48MA306) or in three controls (fig. 1*c*). The finding of the alteration in the father's white blood cells and the recurrence of the disease in his children implied somatic and germline mosaicism in the father. Careful reassessment of clinical examination of the father (performed systematically before the identification of the mosaicism) revealed no skeletal or ocular sign but minor findings: discreet dilation of the ascending aorta (43 mm, +2 SD when standardized to age and body surface area [193 cm, 75 kg, at age 41 years]) and minimal aortic regurgitation. This

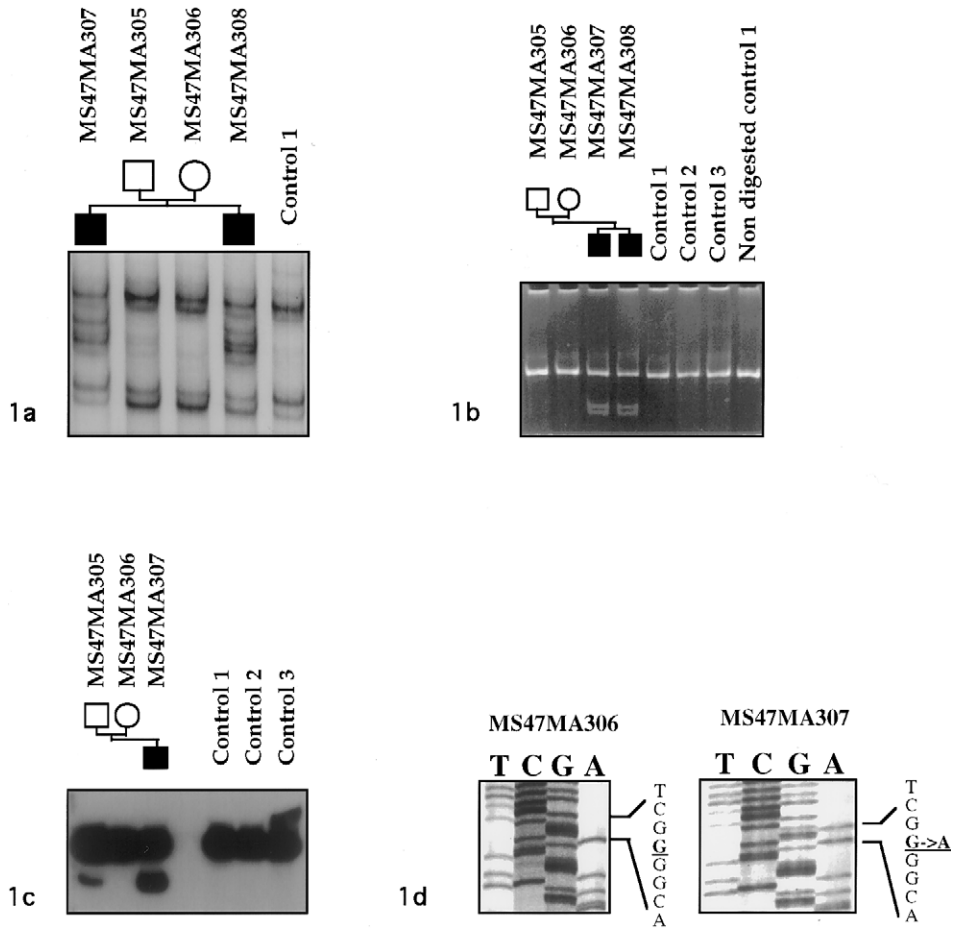

Figure 1 *a,* DNA single-strand analysis by nondenaturing PAGE (SSCP) of a 419-bp PCR product including exon 24. Aberrant migration of PCR product is found in subjects MS47MA307 and MS47MA308 compared with their parents and the normal control. *b,* The G→A transition creates a *Taq*I site within the 419-bp PCR product of exon 24, resulting in two fragments of 202 and 217 bp. *Taq*I digestion confirmed the G985E mutation in the two brothers MS47MA307 and MS47MA308. *c,* The digestion products were migrated and then were hybridized with the sense primer. Only the PCR product resistant to digestion can be found for normal controls 1, 2, and 3 and for the mother (MS47MA306). The heterozygous three-banded restriction enzyme pattern after *Taq*I digestion is present for MS47MA307 and the father MS47MA305, after overexposure. *d,* The normal (for MS47MA306) and abnormal (for MS47MA307) fragments from the SSCP gel (in *a,* above) were cut, eluted in water, and reamplified by PCR. Sequencing for MS47MA307 compared with normal sequence (MS47MA306) revealed a G→A transition at nucleotide position 2954, resulting in a Gly→Glu change at codon 985 (G985E).

mutation probably arose at an early mitotic stage in embryonic development, as reflected by distribution in somatic and germ cell tissues.

The MFS-like phenotype associated with the G985E mutation in exon 24 is not associated with ocular anomalies. Of interest, the Marfan Database (Collod-Béroud et al. 1998), when sorted for mutations in MFS patients who have no ocular anomaly, indicates that half (9/19) of these mutations are located in exons 23–29. This contrasts with mutations associated with the complete classic MFS, which are widely distributed throughout the gene. Furthermore, study of the distribution of mutations identified in 8-cysteine modules after their alignment by their consensus sequence indicates that the G985E mutation affects a residue close to three consecutive cysteines. This region harbors three other mutations (5137ins4 [Dietz et al. 1993], C1721Y [Collod-Béroud et al. 1998], and V984I [Collod-Béroud et al. 1998]) identified in probands that do not have ectopia lentis. The 8-cysteine modules are found only in fibrillins and latent TGFβ1-bp, and their function in fibrillins is still unclear. The absence of ectopia lentis and, therefore, the probable absence of major zonular alteration in subjects carrying mutations in this region of the 8-cysteine modules would tend to indicate the absence of a specific function of this module in the zonule.

Our observation shows that somatic and germline mosaicism are associated with MFS-like features and should be looked for in parents of sporadic cases presenting with these MFS-like features. In effect, if mild or isolated

features of the disease are found in one of the parents, genetic counseling should take into account the possible presence of the disease in another child. Somatic mosaicism could also explain the mild and incomplete features often seen in patients referred to MFS clinics for diagnosis. Again, caution is warranted in the follow-up of these patients and in evaluation of the risk of transmission.

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GWENAËLLE COLLOD-BÉROUD,[1] MARILYN LACKMY-PORT-LYS,[1] GUILLAUME JONDEAU,[2] MICHÈLE MATHIEU,[4] YVES MAINGOURD,[5] MONIQUE COULON,[1] MICHEL GUILLOTEL,[1] CLAUDINE JUNIEN,[1,3] AND CATHERINE BOILEAU[1,3]

[1]*INSERM U383, Hôpital Necker-Enfants Malades, Université René Descartes, Paris;* [2]*Service de Cardiologie et* [3]*Laboratoire Central de Biochimie, d'Hormonologie et de Génétique Moléculaire, Hôpital Ambroise Paré, Boulogne; and* [4]*Centre de Génétique Clinique and* [5]*Unité de Cardiologie Pédiatrique, CHU d'Amiens, Hôpital Nord, Amiens, France*

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Marfan Database, http://www.umd.necker.fr/ (for *FBN1* mutations)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for MFS [MIM 154700)

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Address for correspondence and reprints: Dr. C. Boileau, INSERM U383, Hôpital Necker-Enfants Malades, Clinique Maurice Lamy, 149-161, rue de Svres, 75743 Paris Cedex 15, France. E-mail: boileau@ceylan.necker.fr

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The Jewish Ashkenazi Founder Mutations in the BRCA1/BRCA2 Genes Are Not Found at an Increased Frequency in Ashkenazi Patients with Prostate Cancer

To the Editor:

BRCA1 and BRCA2, the predisposing genes for breast cancer (BC) and ovarian cancer (OC), have been suggested to increase the risk of prostate cancer (PrC) in male carriers (Ford et al. 1994; Thorlacius et al. 1996; Struewing et al. 1997); however, no direct evidence exists to confirm this hypothesis. A population with a high carrier frequency of BRCA1 and BRCA2 germinal mutations allows a direct approach to studying the role BRCA1 and BRCA2 play in the development of PrC; if germinal mutations in BRCA1 and BRCA2 increase the risk of PrC in carriers, it is to be expected that the carrier frequency in PrC patients will be higher than in the general population, as was demonstrated in female patients diagnosed with BC and OC (Ford et al. 1995; Claus et al. 1996, Abeliovich et al. 1997).

In the Ashkenazi Jewish population, three founder mutations, 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene, exist at a high frequency (2.5%) (Struewing et al. 1995; Oddoux et al. 1996; Roa et al. 1996; Fodor et al. 1998). To assess the contribution of the BRCA1/BRCA2 germinal mutations to PrC morbidity, we analyzed the Ashkenazi founder mutations in two groups (with the same age distribution) of Ashkenazi men, a group of unselected PrC patients, and a control group of men with no history of cancer. The study was designed around the fact that, in families known to segregate BRCA1/BRCA2 mutations, men with PrC were noted sporadically. It was thus assumed that, if BRCA1 and BRCA2 play a role in the development of PrC, they do so as risk modifiers rather than as major dominant genes, and therefore will not be confined to familial cases.

Patients diagnosed with adenocarcinoma of the prostate (n = 87) were recruited from the oncology outpatient clinic at Sharett Institute, Hadassah Hebrew University Hospital, with no preselection. The patients signed an informed-consent form approved by the hospital's ethics committee. Each patient was interviewed regarding his family history. Clinical and pathological records were the sources of the clinical data.

The control group included 87 healthy men with no history of cancer. These men were approached in Jerusalem-area homes for the elderly and were asked to participate in the study; if they agreed, they signed an informed-consent form. Their blood samples were kept anonymous, labeled only with the patients' ages and origins (table 1). The median age was 71 years at the time of diagnosis for the patients with PrC and 72 years at the time of blood sampling for the control group (table 2). The mutations were analyzed as described elsewhere (Abeliovich et al. 1997).

The risk of developing PrC is age-dependent and is determined by differential exposure to environmental factors. In addition, positive family history is a major risk factor for developing PrC at an early age (Steinberg et al. 1990; Spitz et al. 1991; Whittemore et al. 1995). It is assumed that ~10% of all cases of PrC and half of the cases diagnosed at an early age (<60 years) are dominantly inherited. Linkage analyses in families with multiple cases of PrC pointed to a PrC-susceptibility gene (or group of genes) on chromosome 1 (Smith et al. 1996; Grönberg et al. 1997*a*; Berthon et al. 1998; Schaid et al. 1998), and, recently, an X-linked gene was suggested (Xu et al. 1998). It can be argued that BRCA1 and BRCA2 markedly reduce the age at onset of PrC and that therefore the effect of BRCA1/BRCA2 will be shown only in patients diagnosed with PrC at age <60 years, whereas in our study only five patients were ascertained in this age group. However, since 2.5% of Ashkenazi males are BRCA1/BRCA2 carriers, it would be expected that an excess of Ashkenazi men will develop PrC at age <60 years. The stratification of the ages