# Letters to the Editor

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## Recurrent Williams-Beuren Syndrome in a Sibship Suggestive of Maternal Germ-Line Mosaicism

*To the Editor:*

Williams syndrome (WS; MIM 194050) is a multisystem disorder characterized by mental retardation and an outgoing personality, distinctive facial features, infantile hypercalcemia, and supravalvular aortic stenosis (Williams et al. 1961; Beuren et al. 1962). A deletion encompassing the elastin (Ewart et al. 1993), replication factor subunit 2 (Peoples et al. 1996), LIM kinase-1 (Frangiskakis et al. 1996; Tassabehji et al. 1996), wnt receptor *Drosophila* frizzled homologue FZD3 (Wang et al. 1997), WBSCR1 (Osborne et al. 1996), and syntaxin 1A (Osborne et al. 1997*b*) genes at the 7q11.23 locus almost always is found in patients with WS. Earlier reports have indicated that a high frequency of deletions associated with WS result from unequal meiotic recombination, as shown by the common concurrence of these deletions with recombination between markers proximal and distal to the deletion (Dutly and Schinzel 1996; Baumer et al. 1998). Several independent studies that demonstrated duplicated genes flanking the deleted region in WS have provided a structural basis for the high frequency of unequal crossover events (Robinson et al. 1996; Osborne et al. 1997*a*; Perez Jurado et al. 1998). The recurrence risk of an interchromosomal rearrangement in the sibship of a proband with WS is usually negligible and thus is likely to account for the sporadic occurrence of almost all cases of WS. A minority of interstitial 7q11.23 deletions could, however, result from an intrachromosomal rearrangement, occurring during or before parental meiosis. In case of a premeiotic intrachromosomal recombination, the theoretical possibility of gonadal mosaicism for the WS deletion has been suggested recently by Dutly and Schinzel (1996). In agreement with this hypothesis, we report here the recurrence of a 7q11.23 deletion in two siblings with WS whose parents did not carry this rearrangement in their somatic cells.

The first affected proband, a male, was the third offspring of unrelated parents aged 26 years (mother) and 32 years (father) at the time of delivery. Both elder sisters and parents were healthy. Unilateral kidney agenesis and growth retardation were detected in the fetus during the third trimester of pregnancy. The child was delivered at 40 wk of gestation by cesarean section. Birth weight, length, and head circumference were 2,020 g (<10th percentile), 43 cm (<10th percentile), and 31 cm (<10th percentile), respectively. No hypercalcemia was noted. Supravalvular aortic stenosis and peripheral pulmonary arterial stenosis were detected at age 3 mo. Psychomotor development was markedly delayed, walking started by age 25 mo, and language developed by age 4 years. At the current age of 8 years, the proband's facies is characteristic of WS, with a narrowed forehead, strabismus with hypermetropia, periorbital fullness, malar hypoplasia, and a large open mouth with an everted lower lip (fig. 1). IQ is markedly reduced, and behavior is characteristic of WS, with attention deficit, loquaciousness, and hypersensitivity to sound. The second affected child, a boy currently aged 3 years, has a clinical picture similar to the one reported in the first affected proband, except for the absence of supravalvular aortic stenosis (fig.1).

Informed consent was obtained from the probands' parents prior to implementation of the genetic studies reported here. FISH was done with biotin-labeled DNA kits (Oncor), according to the protocols provided by the manufacturer. ELN and D7S427 (7q36) probes (Oncor) were used for testing the 7q11.23 locus and for chromosome 7 identification, respectively. The 7q11.23 deletion was found in both affected siblings, whereas it was not detected in either parent (data not shown). To our knowledge, this is the first report of the recurrence of full-blown WS secondary to a 7q11.23 deletion in nontwin sibs whose parents are unaffected. The familial cases of WS with the typical 7q deletion reported so far have involved either offspring of an affected individual (Ewart et al. 1993, 1994; Morris et al. 1993*a,* 1993*b*) or MZ twins (Castorina et al. 1997). Recurrence of WS in nontwin sibs with unaffected parents has earlier been reported (Burn 1986), but has never been established in cases with proven elastin deletion.

Both affected siblings, their healthy sisters, and their parents were genotyped with DNA $(CA)_n$ polymorphisms, from centromere to telomere, as follows: D7S645-D7S2415-D7S672-D7S653-D7S489B-ELN

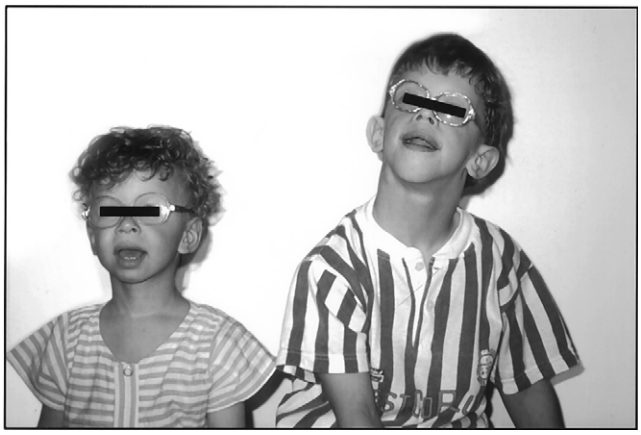

**Figure 1** Photograph of the affected siblings

(intron 18 of the elastin gene)-D7S1870-D7S2470-D7S675-D7S669-D7S634-D7S660 (Généthon; Foster et al. 1993; Gyapay et al. 1994; Gilbert-Dussardier et al. 1995; Dib et al. 1996; Robinson et al. 1996). DNA samples from peripheral leukocytes were analyzed according to procedures published elsewhere (Gilbert-Dussardier et al. 1995). Both probands failed to inherit a maternal allele at the elastin and D7S1870 loci, thus indicating that the 7q11.23 deletion was maternal in origin (fig. 2). Moreover, they shared a single maternal haplotype, outside the deletion, with their eldest sister, who did not carry the WS deletion in her leukocytes, as indicated by microsatellite analysis. These data were highly suggestive of maternal mosaicism. In the probands' mother, heterozygosity at both elastin and D7S1870 loci, consistent with the absence of deletion of chromosome 7 in her leukocytes, by FISH, indicated that mosaicism was likely to be restricted to germ cells.

We could not rule out conclusively that the deletion in the present cases had occurred as a result of unequal crossover between homologous chromosomes 7 during maternal meiosis, because DNA of the maternal grandparents was not available. However, our comparison of haplotypes, using markers centromeric and telomeric to the deletion region, failed to suggest any recombination event within this region in any of the four siblings (fig. 2), making the possibility of a meiotic crossover very unlikely. On the basis of a female recombination distance of 6 cM between the first informative markers centromeric (D7S653) and telomeric (D7S675) to the deletion (Dib et al. 1996), the probability of a double recombination event in both affected sibs was very low (~$1/7.5 \times 10^4$). Thus, the 7q11.23 deletion observed in both probands most likely resulted from a premeiotic intrachromosomal event responsible for a gonadal mosaicism in the probands' mother.

Apart from a gonadal mosaicism, the presence of a constitutive structural defect of the maternal chromosome 7 could theoretically account for the recurrence of the elastin deletion in sibs. A cryptic 7q11.23 rearrangement in a maternal homologue, such as an inversion or an insertion, could indeed interfere with meiotic pairing, thus leading to recurrence of unequal crossover in distinct meiosis and greatly enhancing the possibility of a deletion. However, high-resolution chromosome banding at the 500–850 bands level failed to detect any chromosomal abnormality in maternal leukocytes, and DNA haplotyping data were irrelevant to an interchromosomal crossover, thus arguing against this hypothesis. Whereas germ-line mosaicism in this particular family clearly results in an increased risk of WS in subsequent pregnancies, it would be necessary to determine the frequency of gonadal mosaicism in a large cohort of families with WS to assess the potential impact of this phenomenon on the overall recurrence risk of WS.

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## Electronic-Database Information

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

Généthon, ftp://ftp.genethon.fr/pub/Gmap/Nature-1995/data/data_chrom7 (for sequence-tagged site used for chromosome 7 genotyping)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for WS [MIM194050])

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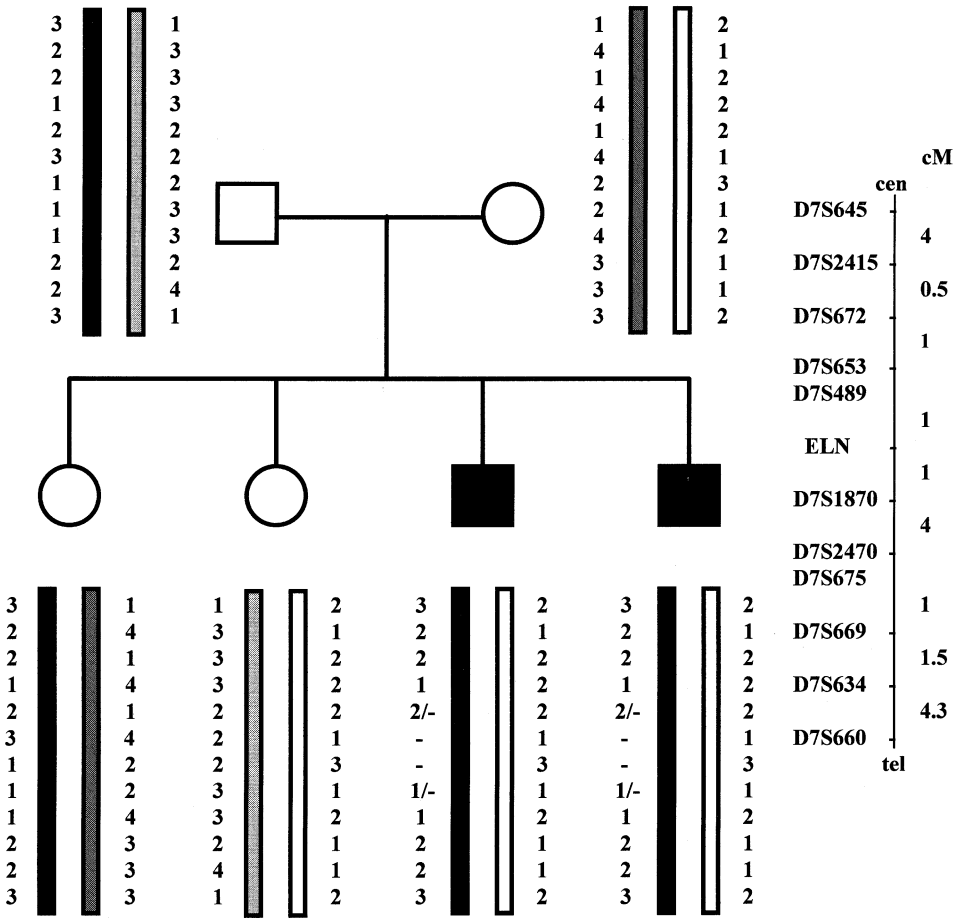


**Figure 2** Segregation of microsatellite polymorphic markers within and surrounding the elastin gene on chromosome 7q in the nuclear family. The markers used and approximate genetic distances are given in the inset (sex average). The $(CA)_n$ repeat, which occurs in the elastin gene intron 18; marker D7S489B; and marker D7S1870 are known to be deleted in typical WS.

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