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Meiotic Microdeletion Breakpoints in the BRCA1 Gene Are Significantly Associated with Symmetric DNA-Sequence Elements

To the Editor:

Mutation screening by SSCP, protein-truncation test, and subsequent sequencing revealed an 11-bp deletion in exon 11 of the BRCA1 gene segregating in a German breast-cancer family with four affected females and an obligate male carrier manifesting prostate cancer. The deletion, which starts at either nucleotide 3599 or 3600 (GenBank U14680 [http://www.ncbi.nlm.nih.gov/]) and causes premature termination at codon 1166, has been described before and was shown to be disease causing (Struewing et al. 1995). Interestingly, inspection of the DNA-sequence context of 3599/3600del11 led to the identification of two symmetric sequence elements, TAGAT and GAAATAAAG, located immediately upstream of the proximal breakpoint and separated from each other by 6 bp (fig. 1).

Evidence for the involvement of symmetric elements in meiotic microdeletions, on the basis of seven deletional hotspots in five human genes, has been reported elsewhere by one of us (Krawczak and Cooper 1991). Each hotspot either consisted of or was flanked by a symmetric element (GAGAG at codon 245 of the AT3 gene; AATAA and GAAGAAG at codons 340/341 of the F8 gene; TGGAGAGGT and CTCCCTC at codon 31 of the HBA2 gene; GAGGAG at codon 7, TGAGT at codon 41, and ATCACTA at codon 141 of the HBB gene; and GTTTG at codon 178 of the HPRT gene). However, whether symmetric elements play a role in small-deletion mutagenesis in general has remained contentious. Although symmetric elements of $\geqslant 5$ bp were observed in 50 of 60 microdeletions analyzed, this was not found to represent a significant excess over random expectation, and it was concluded that symmetric elements are not a major cause of microdeletions (Krawczak and Cooper 1991). However, reanalysis of a threefold-larger sample (Cooper and Krawczak 1993) indicated that symmetric elements might be overrepresented, by a factor of 1.3, in the vicinity of microdeletion breakpoints.

Review of the sequences surrounding the 108 small deletions in the BRCA1 gene that have been published so far or that have been submitted to the mutation database of the Breast Cancer Information Core (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic) suggests that breakpoints in the BRCA1 gene are associated with symmetric elements. To assess the statistical significance of this outcome, the distance to the nearest symmetric element of a given length was deter-

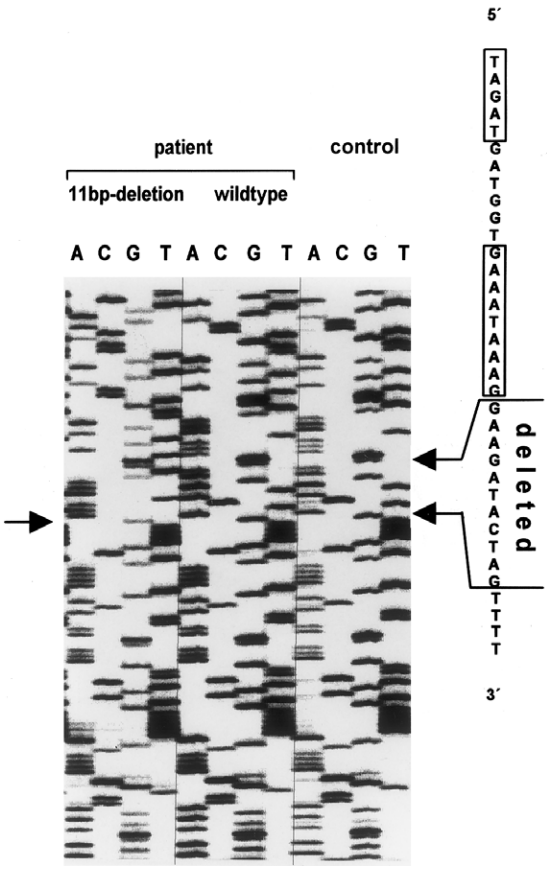

Figure 1 Partial BRCA1 exon 11 sequence of a 3599/3600del11 carrier and of a control. The deletion junctions are indicated by arrows. Symmetric elements upstream of the proximal breakpoint are boxed. The mutation was detected in a male obligate carrier manifesting prostate cancer and in four first-degree female relatives with breast cancer.

mined for all 5,711 nucleotide positions in the BRCA1 cDNA sequence. Only symmetrical elements that were fully included in the same exon were considered. The distance then was divided into five intervals of approximately the same overall frequency, and the distance distribution of the breakpoints was determined (fig. 2). Ambiguous breakpoint positions were scored according to their posterior probability of involvement, on the assumption that there was an even prior distribution among deletion localizations. For element lengths of 5–7 bp, deletion breakpoints were significantly associated with very short distances to a nearby symmetric element (χ^2 values were 23.7 for 5 bp, 30.4 for 6 bp, and 22.0 for 7 bp). No such relationship was found for element lengths >7 bp (a threshold of 15.1 was adopted for the χ^2 values; this yielded an overall $P < .05$, 4 df, allowing for the 11 multiple tests performed).

Thus, our findings suggest that relatively short symmetric elements indeed may predispose DNA sequences to meiotic microdeletion. This may happen either by promotion of unstable secondary structures due to the symmetric elements or by the symmetric elements functioning as binding sites for critical DNA-replication/-repair enzymes. In this context it is interesting to note that, together with some intervening sequence, the two symmetric elements immediately upstream of 3599/

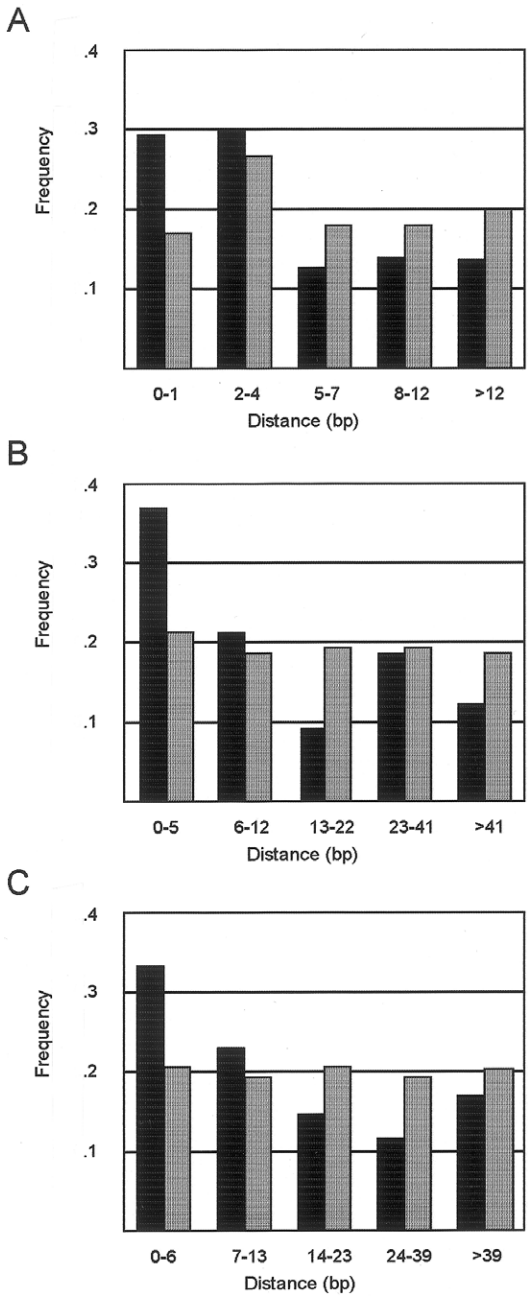

Figure 2 Distribution of the minimum distance between a deletion breakpoint and a nearby symmetric element of a given length. Observed (*blackened boxes*) and expected (*shaded boxes*) frequencies of distance intervals are shown for element lengths of 5 (*A*), 6 (*B*), and 7 (*C*) nucleotides.

3600del11 show homology (6 of 8 bp) to the chi-recombination-stimulating element GCTGGTGG (Smith 1983; Steinmetz et al. 1987). Whether the deletion-promoting influence of symmetric elements is a gene-specific (i.e., regional) phenomenon or whether it applies to genomic DNA in general is at present unclear, but the increasing number of disease-associated inherited deletions, within gene-coding regions,that are being reported in the literature (Krawczak and Cooper 1997) will soon allow this question to be addressed.

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Goosecoid-Like Sequences and the Smallest Region of Deletion Overlap in DiGeorge and Velocardiofacial Syndromes

To the Editor:

In the May 1997 issue of the *Journal,* Gottlieb et al. (1997) reported the identification of a homeobox-coding gene named "*GSCL*" (*Goosecoid*-like) from a 22q11.2 region deleted in DiGeorge syndrome (DGS) and velocardiofacial syndrome (VCFS). The gene is located within the so-called minimal DiGeorge critical region (MDGCR), as defined by Lindsay et al. (1993) and Gong et al. (1996). Figure 3 of that article (Gottlieb et al. 1997, p. 1199) shows the *GSCL* gene as localized in the smallest region of deletion overlap (SRDO, a subsegment of the MDGCR), because *GSCL* was presumed to be deleted in patient G. Patient G is affected by DGS and has an interstitial deletion the proximal breakpoint of which defines the proximal boundary of the SRDO (Levy et al. 1995). However, chromosomes from patient G were not tested with *GSCL* sequences. We decided to perform experiments ourselves to test whether patient G is in fact deleted for *GSCL*.

From our bacterial-artificial-chromosome contig covering the homologous mouse region (Botta et al., in press), we have subcloned a 3.7-kb *Sma*I DNA fragment corresponding to nt 27970–31642 of the genomic sequence MMU70231 (Galili et al. 1997) and containing the three coding exons of the murine *Gscl*. We have used this fragment to screen our contig of the human DGS critical region (Lindsay et al. 1996). A 12.2-kb *Hin*dIII DNA fragment (pHgscl) was identified and subcloned from fosmid 39g9. Partial sequencing confirmed that this fragment contains *GSCL* sequences and corresponds to nt 129598–141800 of the genomic sequence HSU30597 (Gottlieb et al. 1997); thus it includes the entire *GSCL* gene, as characterized by Gottlieb et al. (1997), with the caveat that the transcription initiation of this gene has not yet been experimentally determined but has only been deduced on the basis of sequence features. FISH experiments on patient G's chromosomes showed that pHgscl is not deleted (fig. 1*A*); no detectable difference was seen in the hybridization-signal intensities in the two chromosomes. The *Not*I-*Hin*dIII 3.7-kb fragment (containing most of the coding sequences) was hybridized to restriction-digested genomic DNA from patient G and normal controls. *Bam*HI, *Hin*dIII, *Taq*I, and *Xho*I were tested. With none of these enzymes could we detect a rearranged genomic fragment in patient G. In particular, with *Hin*dIII the expected 12.2-kb band, corresponding to the fragment cloned, was detected apparently intact. Fosmid 39g9, from which pHgscl was subcloned, contains 5′ sequences of gene *ES2,* alias *DGS-I* (the clone was termed "Fos39" in the article by Lindsay et al. [1996]) and, by FISH analysis, is partially deleted in patient G (fig. 1*B*); hence, *GSCL* is located between *ES2* and the deletion breakpoint in patient G, within ~20–30 kb of DNA (fig. 2). Of course, even though *GSCL* is not deleted in patient G, the deletion may still affect its