ELECTRONIC LETTER

Detection of large rearrangements of exons 13 and 22 in the *BRCA1* gene in German families

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The breast and ovarian cancer susceptibility gene *BRCA1* contains an unusually high density (41.5%) of Alu elements.[1] The homology between these repetitive Alu sequences can promote ectopic or homotopic homologous recombination. Ectopic homologous recombination, such as that reported in the *BRCA1* gene, leads to large genomic rearrangements, which subsequently may cause disease phenotypes. In the *BRCA1* gene, a number of different Alu mediated rearrangements, ranging from 510 bp to 23.8 kb, have been found to date.[2–13] Two of them, a 510 bp deletion of exon 22 (IVS21-36del510) and a 3835 bp deletion of exon 13 (IVS12-1643del3835), are founder mutations in Dutch breast cancer patients and represent 36% of all *BRCA1* mutations in this population.[7] An additional recurrent founder mutation, a 6 kb duplication of exon 13 (ins6kbEx13), was detected mainly in English speaking countries.[9 14]

We tested German families with a strong history of breast and ovarian cancer for mutations in the *BRCA1* and *BRCA2* genes by direct sequencing and DHPLC.[15] In 270 investigated families, we detected 48 families carrying *BRCA1* and 22 families carrying *BRCA2* mutations (25.9 %). Forty-seven families showed an unclassified variation (UV) in either of these genes and 153 families tested negative.

In order to assess the possibility that the families, previously tested negative for both *BRCA1* and *BRCA2* coding region mutations (153 families) and for *BRCA*-UV (47 families), could carry large DNA rearrangements in the *BRCA1* gene, we screened them (total 200) for known founder mutations IVS21-36del510 and ins6kbEx13 by a mutation specific PCR based assay.[7 14] This assay was applied to all probands in Berlin and Bonn. In case of a potential deletion of exon 13 (IVS12-1643del3835), analysis using a mutation specific PCR based assay was restricted to affected subjects in Berlin (37 index patients) who are homozygous for polymorphism 4427T>C in exon 13.[7] Patients determined to be heterozygous for this polymorphism by direct sequencing carry both alleles and thus, a deletion of exon 13 can be excluded.

Whereas mutations IVS21-36del510 and ins6kbEx13 were found, the deletion IVS12-1643del3835 was not identified in the families investigated. In family B19 we detected deletion IVS21-36del510. Another family, BN8, was found to carry duplication ins6kbEx13. The pedigrees of both families strongly suggest a *BRCA1* mutation, because in BN8 three cases of breast cancer and two cases of ovarian cancer have been reported and B19 included three cases of breast cancer, two of them diagnosed at age <50 years (fig 1).

Haplotype analysis comparing genotypes of index cases of family BN8 with a positive control DNA as well as the sequencing of the exon 13 duplication junction indicated that family BN8 has the same common ancestor as reported duplication carriers (S Mazoyer, personal communication).

Thus, this is the first report of large rearrangements in the *BRCA1* gene in German breast and ovarian cancer families. All families investigated participate in a study of the "German Consortium for Hereditary Breast and Ovarian Cancer" to establish a *BRCA1/2* mutation profile and to determine family types with high frequencies of particular mutations.[15] The included families are grouped into six categories depending on the family history. In fact, the families described here with a rearrangement in the *BRCA1* gene are in the most severe categories with respect to their family history (B19, group A1 and BN8, group B). Up to now the deletion IVS21-36del510 comprising exon 22 has exclusively been detected in Dutch breast cancer patients.[16] The duplication ins6kbEx13 was mainly found in English speaking countries, except two reported cases from countries that have trading or other historical links with Britain, Belgium and Portugal.[2 9 14] Consequently, family BN8 is the third family carrying the ins6kbEx13 duplication from a non-English speaking country. These newly described German cases support a recommendation to *BRCA1/2* diagnostic laboratories to more generally implement tests for these specific rearrangements as well as other conceivable rearrangements within the *BRCA* genes.

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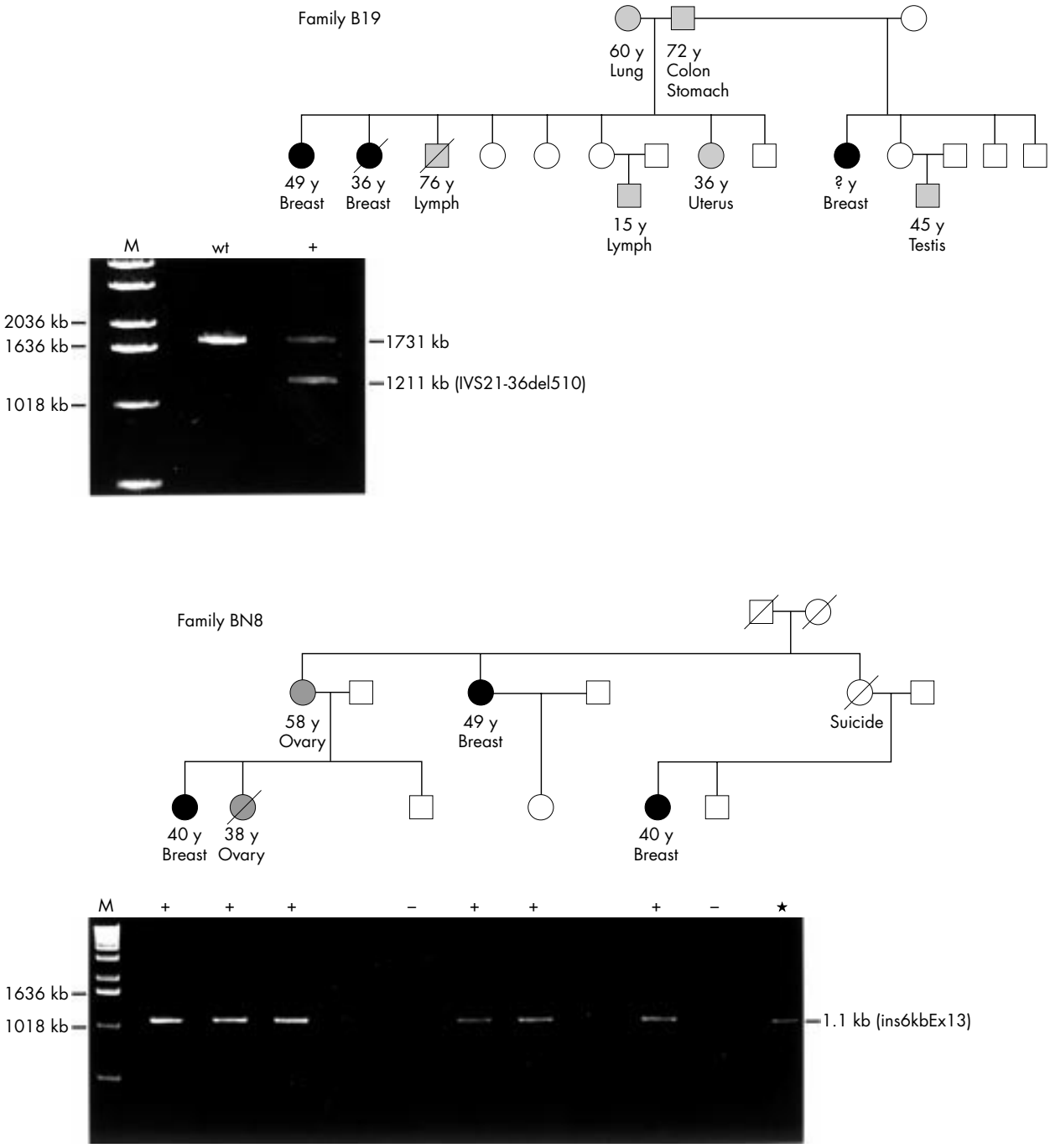

Figure 1 Pedigrees of German families B19 and BN8. Age at diagnosis, type of cancer, and mutation status (+ mutation found, – mutation not found, wt wild type, *control DNA sample) of the probands is given below the symbols.

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