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Advances in Brief

A Large Deletion Disrupts the Exon 3 Transcription Activation Domain of the *BRCA2* Gene in a Breast/Ovarian Cancer Family[1]

Margareta Nordling, Per Karlsson, Jan Wahlström, Yvonne Engwall, Arne Wallgren, and Tommy Martinsson[2]

Departments of Clinical Genetics [M. N., J. W., Y. E., T. M.] and Oncology [P. K., A. W.], Sahlgrenska University Hospital, Gothenburg University, S-41685 Gothenburg, Sweden

Abstract

We describe the identification of a large deletion in the *BRCA2* gene as the disease-causing mutation in a Swedish breast/ovarian cancer family. The 5068-bp deletion encompassed the 3′ region of exon 3, including the 3′ splice site and most of intron 3, and it resulted on the mRNA level in an inframe exon 3 skipping. The junction site also included an insertion of 4 bp (CCAT). The mutation (nt504del5068insCCAT) resulted in a genotype absent of the two transcription activation regions localized to exon 3. The breast cancer phenotype associated with the described mutation resembled the phenotype of breast cancer found in both *BRCA1* and *BRCA2* mutation carriers. This is the first report of a large deletion as the disease-causing mutation in the *BRCA2* gene.

Introduction

Two genes associated with familial breast and ovarian cancer have been cloned and characterized, *i.e.*, the *BRCA1* gene located in chromosome region 17q21 (1) and the *BRCA2* gene located in 13q12.3 (2). Together, germ-line mutations in these two genes are considered to constitute the major cause of hereditary breast/ovarian cancer. The biological functions of *BRCA1* and *BRCA2* are still unknown, and, due to their large size, the proteins probably have many functional domains. Similarities between these two proteins that can lead to clues of their functions have, however, recently been reported. Both proteins contain a transcriptional-activation domain (3, 4), and they both also show binding to Rad51 (an eukaryotic homologue of the *Escherichia coli* RecA protein; Ref. 5), which is involved in maintaining the integrity of the genome (6, 7). To elucidate the importance and functions and also the clinical significance of these domains, genotype-phenotype studies of deletion mutations in breast/ovarian cancer patients are crucial.

The reported mutation spectra of the *BRCA1* and *BRCA2* genes mainly involve small bp changes *i.e.*, deletions/insertions of one or a few bp or base substitutions (8, 9). The bias for detection of small bp alterations is likely to be partly due to the methods used in mutation detection. Recently, it has also been shown that three large deletions in *BRCA1* are major founder mutations in Dutch breast cancer patients (10). We here describe the first case of a large deletion in the *BRCA2* gene.

Materials and Methods

Family. The analyzed family (Fig. 1) was referred to the Genetic Counseling Clinic for Hereditary Cancer at the Sahlgrenska University Hospital in Gothenburg, Sweden. The four affected individuals examined for germ-line mutations in the *BRCA1* and *BRCA2* genes are two sisters, their mother, and a cousin (Fig. 1). The youngest sister (III:5) was treated at ages 40 and 42 for bilateral breast cancer. Her first tumor was a tubulolobular carcinoma with DCIS[3] in the surrounding area, and the second tumor was a high-grade ductal carcinoma of no special type but with lymphocytic infiltration. The second sister (III:4) was treated at age 38 for a small intraductal cancer of comedo type in the left breast. Three years later, she had an invasive cancer of the same breast and multiple axillary and supraclavicular node metastases. The tumor was estrogen receptor positive and progesterone receptor negative. They have an unaffected sister (III:3) 49 years of age who has been subjected to oophorectomy. Their mother (II:5) had a bilateral ovarian seropapillary cystadenocarcinoma with omental metastases at age 70. She had one sister (II:4), who is reported to have died from cancer in the breast region at age 43. Of two brothers, one died (II:2) of an abdominal cancer at age 75. He was an obligate carrier, given that one of his two daughters (III:1) carried the mutation. She had been treated for a tubuloductal breast cancer at age 41 with some DCIS in the surrounding area.

Mutation Analyses. Genomic DNA and RNA were purified from blood lymphocytes. Total RNA was prepared from lymphocytes enriched by Histopaque (Sigma Chemical Co.) fractionation and purified using RNA-STAT (Ambion), and cDNA was reverse transcribed from mRNA using hexamers and Superscript II (both from Promega). PTT primers for screening the *BRCA1* gene for truncating mutations were as described by Hogervorst *et al.* (11). The *BRCA2* gene was amplified on seven partly overlapping fragments. Exons 2–9 were amplified on one fragment with the following primer pair: LP, 5′-T7-GCTTATTTACCAAGCATTGGA-3′, and RP, 5′-TCTCTGTGTCTAATAG-GTCT-3′. Primers for amplification of exons 10 (one fragment) and 11 (four fragments) were as described by Håkansson *et al.* (12). The primer pairs used for amplification of exons 12–27 (three fragments) comprised the following: for exons 12–17, LP, 5′-T7-GTGGGAAAAGAACAGGCTTCA-3′, and RP, 5′-GCTGTGTCATCCCTTTCCAT-3′; for exons 17–23, LP, 5′-T7-GGA-ATACAGTTGGCTGATGGT-3′, and RP, 5′-AATCCTATTAGGTCCACCTC-3′; and for exons 23–27, LP, 5′-T7-GGGAAGTTGCGTATTGTAAGC-3′, and RP, 5′-CTGGAAAGGTTAAGCGTCAA-3′.[4] The T7 sequence used was 5′-GCTAATACGACTCACTATAGGAACAGACCACCATG-3′. Genomic DNA was used for amplification of exon 11 in the *BRCA1* gene and exons 10 and 11 in the *BRCA2* gene, whereas the surrounding exons were amplified by RT-PCR. The TnT T7 coupled reticulocyte lysate system (Promega) was used for the *in vitro* transcription/translation reactions. The synthesized protein products were analyzed by SDS-PAGE using the Protean II electrophoretic separation cell (Bio-Rad). Homogenous 12.5% polyacrylamide Ready-Made gels (Bio-Rad) were used as gel matrix. For DNA sequence determinations, the standard ALF DNA sequencer (Pharmacia) was used. Cycle sequencing using Thermo Sequenase (Amersham) was performed directly on the PCR fragments. For sequence determination of the aberrant PTT fragment, the T7 promoter sequence at the 5′ end of the PTT L-primer enabled fluorescein-labeled T7-sequencing primer to be used in the sequencing reactions. Exons 2, 3, and 4 in the *BRCA2* gene were amplified separately and in different combinations from genomic DNA with the following intronic primer pairs: exon 2, LP, 5′-CCAGGAGATGGGACTGAATTAG-3′, and RP, 5′-CTGTGACGTACTGGGTTTTTAGC-3′; exon 3, LP, 5′-GATCTT-TAACTGTTCTGGGTCACA-3′, and RP, 5′-CCCAGCATGACACAATTA-ATGA-3′; and exon 4, LP, 5′-AGAATGCAAATTTATAATCCAGAGTA-3′, and RP, 5′-AATCAGATTCATCTTTATAGAACAAA-3′. All L primers where synthesized with a 5′-M13 sequence (5′-CGACGTTGTAAAACGACGGC-

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[2] To whom requests for reprints should be addressed, at Department of Clinical Genetics, Sahlgrenska University Hospital, S-416 85 Gothenburg, Sweden. E-mail: tommy.martinsson@clingen.gu.se.

[3] The abbreviations used are: DCIS, ductal carcinoma *in situ;* PTT, protein truncation test; RT, reverse transcription.

[4] Å. Borg, personal communication.

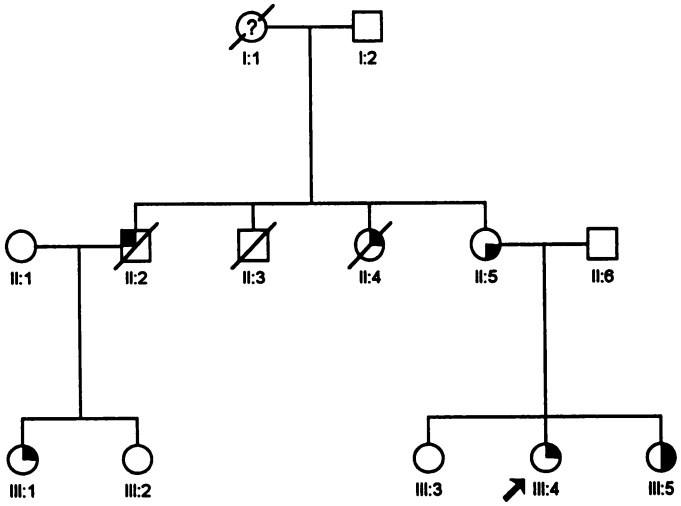

Fig. 1. Pedigree of the family analyzed indicating the positions of affected individuals (○, females; □, males). *Arrow,* index case. *Upper right-filled symbols,* breast cancer; *lower right-filled symbols,* ovarian cancer; *upper left-filled symbols,* abdominal cancer.

CAGT-3′) and all R primers with a 5′-M13rev sequence (5′-CAGGAAACAGC-TATGAC-3′) to enable subsequent DNA sequence determinations from both directions using M13 and M13rev sequencing primers. All PCR fragments were analyzed on 1% agarose gels.

Results and Discussion

The family, with a high incidence of breast and ovarian cancer (Fig. 1), was referred to the Genetic Counseling Clinic for Hereditary Cancer in Gothenburg, Sweden, and was subjected to DNA analyses for mutations in the breast/ovarian cancer susceptibility genes *BRCA1* and *BRCA2*. The affected family member III:4 (Fig. 1) was analyzed for truncating mutations in *BRCA1* using the PTT (13). Genomic DNA was used to analyze exon 11, and the rest of the coding region was analyzed on cDNA using RT-PCR (11). This investigation did not reveal any truncating mutation in *BRCA1*. Thereafter, we analyzed *BRCA2* sequences with the same technique as for *BRCA1*. *BRCA2* exons 10 and 11 were subjected to PTT analysis from genomic DNA (12), and RT-PCR and PTT were used to analyze the rest of the coding regions in four partly overlapping fragments.

Agarose gel analysis of the RT-PCR product for exons 2–9 revealed an aberrant fragment, approximately 300 bp shorter, in addition to the normal one (Fig. 2*a*). It was noted that the aberrant fragment was significantly more intense on gel than was the normal fragment (Fig. 2*a*). As this analysis was based on RT-PCR amplification, the amount of amplified product reflects the amount of mRNA present in the sample. Genes harboring mutations can be differently expressed, although their expression is usually down-regulated (14, 15). Alternatively, the low expression of the normal allele could be due to some epigenetic factor such as partial methylation of the normal-sized product (16). Subsequent PTT analysis of the PCR fragments revealed a protein product with a molecular mass approximately 12 kDa smaller than that of the normal product (53 kDa; Fig. 2*b*). The combined data indicated to us that there could be an inframe deletion of a complete exon. The only exon in *BRCA2* fulfilling the criteria, *i.e.,* size divisible by 3 and approximate size 300 bp, was exon 3. To analyze this further, we sequenced the PCR fragment generated for the PTT analysis. The sequencing revealed in fact a fragment that lacked exon 3; *i.e.,* exon 4 was situated directly adjacent to exon 2 (Fig. 2*c*). The aberration was further analyzed on genomic DNA.

We reasoned that the exon 3 skipping could be due to a small mutation in one of the splice sites flanking exon 3, or alternatively, it could be due to a large deletion involving a part of exon 3, including one of its splice sites or possibly even the complete exon 3. PCR amplification of exon 3 was thus performed on genomic DNA using primers flanking this exon (3L-3R; Fig. 3*a*). The fragment was se-

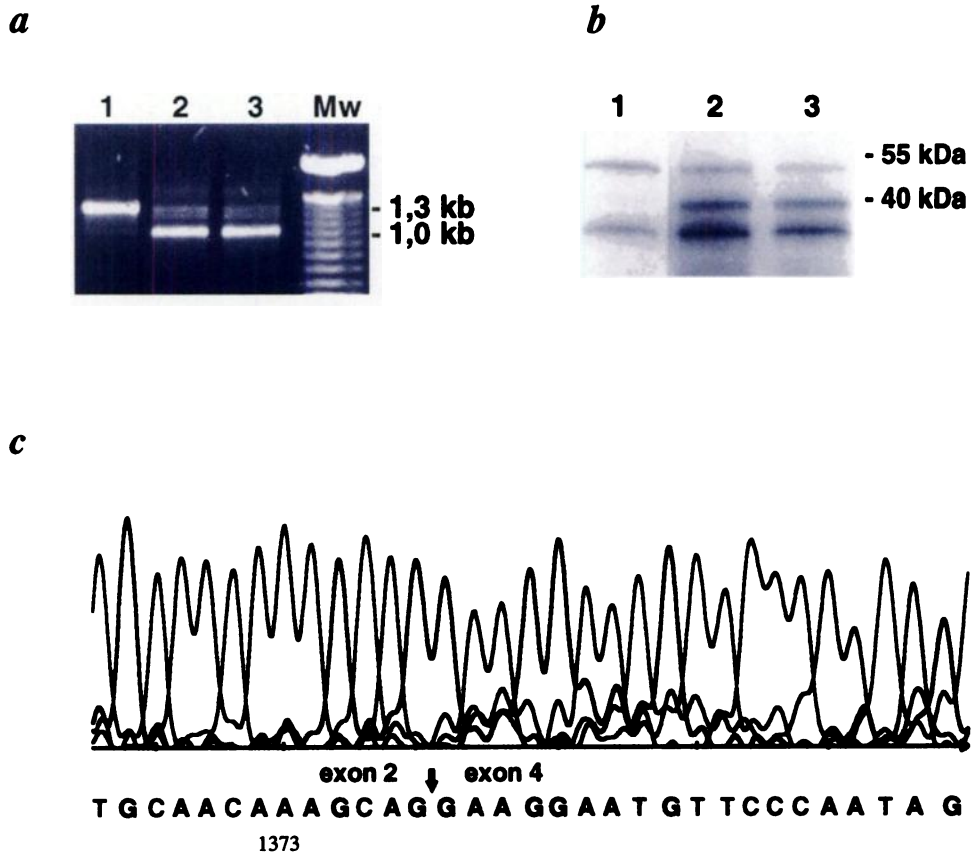

Fig. 2. Analysis of *BRCA2* exon 2–9 RT-PCR product; agarose gel analysis (*a*) and PTT analysis (*b*) of the fragment in control (*Lanes 1*) and family members III:5 (*Lanes 2*) and III:4 (*Lanes 3*). Molecular masses are indicated. *c,* DNA sequence determination of the same fragment (family member III:4). The exon 3 sequence from the normal allele can be observed as a low background in the exon 4 sequence.

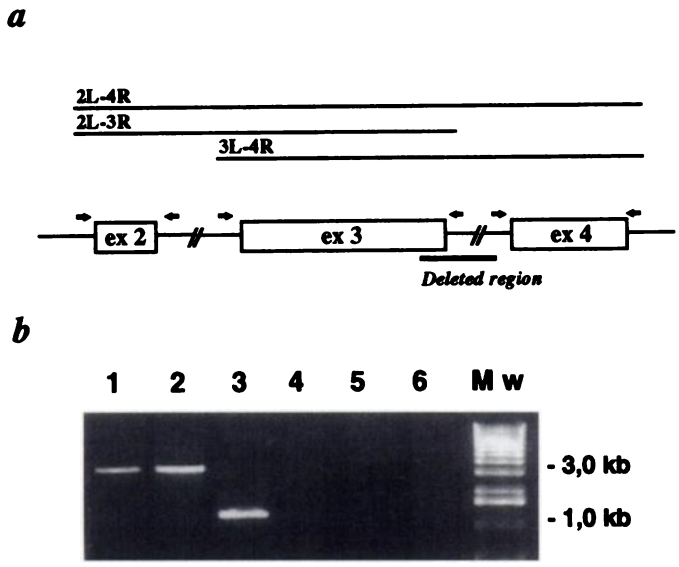

Fig. 3. Analysis of the large *BRCA2* deletion on genomic DNA in family member III:4. *a*, schematic map of *BRCA2* exons 2–4 and the primer combinations used. *Arrows*, primer positions. *Lines*, expected length of PCR fragments using different primer combinations. The approximate location of the deleted region is indicated by a *bar*. *b*, agarose gel analysis of the PCR amplification products using primer combination 2L-3R (*Lanes 1* and *2*), 3L-4R (*Lanes 3* and *4*), and 2L-4R (*Lanes 5* and *6*). *Lanes 1, 3,* and *5* represent family member III:4 and *Lanes 2, 4,* and *6* represent controls. Patient III:4 displays a PCR fragment for the 3L-4R primer combination, whereas the healthy control does not.

quenced from both directions, but no mutation that could explain the exon 3 skipping was found in the splicing regions flanking exon 3 (data not shown). To investigate the possible presence of large deletions or rearrangements, we performed PCR using different combinations of exon-flanking primers as described in Fig. 3*a*. Deletions between primers using specific primer combinations could give rise to a significantly shorter fragment, easily detectable by PCR. The combinations used were 2L-4R (expected to give a normal fragment of 8964 bp), 2L-3R (expected size, 3314 bp), and 3L-4R (expected size, 6323 bp). Fragments 2L-4R and 3L-4R were in their normal size so large that they would not be expected to give any bands under standard PCR conditions, whereas the normal 3314-bp fragment generated with primer combination 2L-3R was readily amplifiable and clearly visible on agarose gel (Fig. 3*b*).

Primer combination 3L-4R, expected to give a 6323-bp fragment in normal DNA, gave a fragment with an approximate size of 1200 bp in DNA from patient III:4 (Fig. 3*b*). This indicated an approximate deletion of 5000 bp between intron 2 (splice acceptor site) and intron 4 (splice donor site). No fragment was amplified in control samples. The 1200-bp fragment, likely to be the result of a simple deletion or some other kind of more complex rearrangement, was sequenced from both directions. Analysis of the fragment revealed a 5068-bp deletion at nucleotide 504 (codon 92 in exon 3) and an insertion of four bases, CCAT, at the junction site (nt504del5068insCCAT; Fig. 4*a*). The deletion included the 3′ part of exon 3 and most of the 5751-bp-long intron 3, including the 5′ splicing donor site of intron 3 (Fig. 4*b*). The deletion thus well explains the skipping of exon 3 in patient III:4. Furthermore, this large deletion explains why no mutation could be detected using primers flanking exon 3 only, *i.e.*, the 3L-3R combination (Fig. 3*b*). Because the target for primer 3R was missing on the mutated allele, only normal sequences were amplified and analyzed.

All four affected individuals (II:5, III:1, III:4, and III:5) in the family indicated in Fig. 1 have been analyzed for the mutation, and all

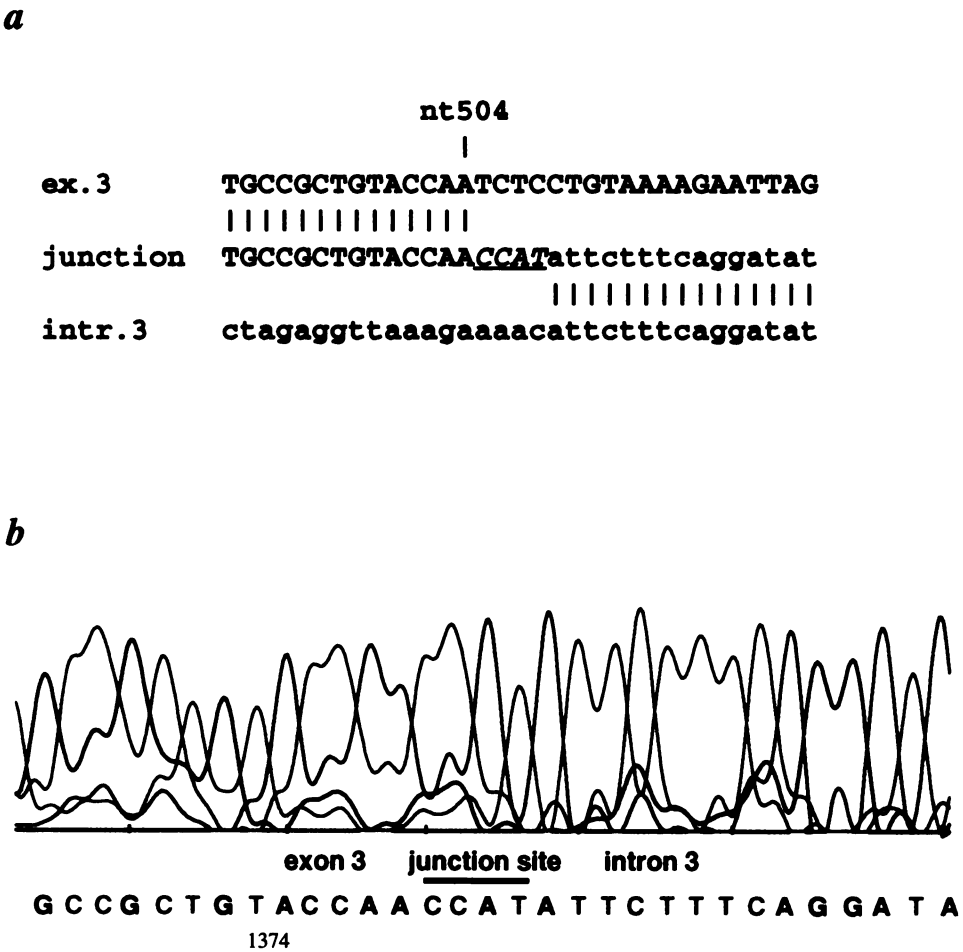

Fig. 4. *a*, overlapping DNA sequences to clarify the junction site of the deletion. The CCAT insertion is *underlined*. The indicated exon 3 cDNA sequence was obtained from the *BRCA2* cDNA sequence (GenBank accession no. U43746), and the intron 3 sequence was obtained from a *BRCA2* gene region sequence (GenBank accession no. Z74739). *nt*, nucleotide. *b*, DNA sequence analysis of the junction site.

have the same large deletion. Also, the male individual, II:2, must have been an obligate carrier of this mutation, given that his daughter, III:1, also was shown to carry it. It is noteworthy that this man later developed an abdominal cancer at the age of 75.

Milner and coworkers (4) found that *BRCA2* exon 3 harbors two transcription-activating regions (residues 18–60 represent a primary activating region, and residues 60–105 represent an auxiliary activating region) and that their activation potential is under negative control of inhibitory regions present immediately on either side of exon 3. A missense mutation detected in familial breast cancer in exon 3 (Tyr42Cys) was also shown to severely compromise the activation potential of the primary activating region (4). The large deletion detected in the family presented in this work, lacking the whole exon 3, presents a *BRCA2* genotype absent in both exon 3 transcription-activating regions but still remaining the Rad51 binding region in the 3′ region of *BRCA2*. A correlation between genotype and phenotype in this particular family could lead to insights into the influence of the different domains of BRCA2 on the phenotypic expression of the disease.

The studied family looked very much like a *BRCA1* family in that both breast and ovarian cancer occurred, and also one of four breast cancers in three individuals was at least partly a medullary cancer with lymphocytic infiltration. However, the other three breast cancers were tubuloductal or a mixture of ductal and lobular carcinomas, and one presented as a DCIS. Such features are considered less common in cancers from *BRCA1* families than in cancers from *BRCA2* families (17, 18). Thus, we found no specific characteristics that could be associated with the described mutation; however, there is a considerable overlap between the clinical findings in *BRCA1*- and *BRCA2*-mutation carriers and those in sporadic breast cancer cases. Investigation of pathological and clinical findings in more families carrying mutations in this region are needed to further delineate any specific phenotype connected with disruption of the transcription-activating potential of exon 3 in *BRCA2*.

The low number of large deletions or rearrangements in *BRCA1* and *BRCA2* reported could at least partly be a bias due to the methods used in mutation identification. They frequently involve PCR-based methods, such as single-strand conformational polymorphism, PTT, and direct sequencing using genomic DNA as source. It is noteworthy that methods involving single-exon amplification, *e.g.*, single-strand conformational polymorphism, or direct sequencing would not have detected the mutation presented here. A few single cases of large gene deletions in *BRCA1* have been reported (19, 20). In addition, Petrij-Bosch *et al.* (10) recently showed that three large *BRCA1* deletions comprise as much as 36% of all *BRCA1* mutations in the Dutch population. Also, this report on the first large deletion in the *BRCA2* gene further pronounces the importance of including mutation detection systems for large deletions in the *BRCA1* and *BRCA2* genes. In summary, we here present a breast/ovarian cancer family with a large deletion in the *BRCA2* gene giving rise to exon 3 skipping at the mRNA level. The mutation disrupted the transcription activation domain in exon 3 and is likely to be the cause of the phenotype in the described family.

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