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Reply to Callen

To the Editor:

In our recent article in the *Journal* (Yang et al. 1997), we showed that an interstitial deletion of 17p11.2 had arisen after meiotic recombination in a carrier of an apparently balanced paracentric inversion (PAI; with breakpoints at 17p11.2 and 17p13.3). Considering all the cytogenetic and molecular evidence, especially the facts that (*a*) the breakpoints of the proband's interstitial deletion "flanked" the proximal breakpoint of the paternal PAI (the proximal Smith-Magenis syndrome (SMS) markers were deleted in spite of not being inverted), (*b*) some markers involved in the PAI were not deleted (the *PMP22* locus), and (*c*) the position of the recombination in paternal meiosis was mapped within the immediate vicinity of the resulting deletion, we proposed a model of unequal crossing-over at the base of an inversion loop.

In response to our article, Callen has raised an interesting point. He proposes an alternate explanation, wherein pairing at meiosis, followed by recombination between an *insertion*-bearing and the normal chromosome 17 homologue could result in the interstitial chromosomal deletion observed in the proband. We agree that a within-arm direct or inverted *insertion* is an important differential diagnosis in cases of suspected paracentric inversions, given the significantly enhanced risk of chromosomal imbalance associated with the former. However, although within-arm insertions (direct or inverted) can result in deletion or duplication of the inserted sequence (Gardner and Sutherland 1996), they cannot result in a concurrent deletion of non*inserted* sequences (proximal SMS markers) and sparing of *inserted* sequences (*PMP22* markers).

Taken together, the data seem to favor our hypothesis of an unequal crossing-over at meiosis, as proposed in our article. However, it should be noted that we have yet to formally exclude Callen's proposal—or even the possibility that the deletion arose de novo as a result of a slightly more proximal (unequal) recombination in 17p11.2.

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Anticipation in Familial Hodgkin Lymphoma

To the Editor:

Anticipation in childhood malignancy has been described by several investigators (Horwitz et al. 1996; Plon 1997). On the basis of 21 parent-child pairs with acute myelogenous leukemia and 9 parent-child pairs with chronic lymphocytic leukemia identified from the literature, Horwitz et al. rejected the hypothesis that there was no age-at-onset difference between the two generations, in either data set. Several published data sets were pooled to test whether there is a difference in parent-child pairs affected with Hodgkin lymphoma (HL). Because the occurrence of HL parent-child pairs is a rare event, several published data sets were pooled to test whether there is a difference, in cancer age at onset, between parents and children who are affected with HL. Thirty parent-child pairs with confirmed di-

Table 1

Pooled Parent-Child Pairs with Hodgkin Lymphoma

Reference	Parent (Age at Diagnosis [years])	Child (Age at Diagnosis [years])
Devore and Doan (1957)	Father (33)	Son (27)
	Mother (59)	Son (28)
	Father (60)	Daughter (29)
	Father (50)	Daughter (23)
Razis et al. (1959)	Mother (38)	Son (20)
	Mother (52)	Son (14)
	Father (40)	Daughter (38)
	Mother (52)	Son (46)
	Mother (40)	Son (13)
	Mother (47)	Daughter (19)
	Father (53)	Daughter (16)
Vianna et al. (1974)	Father (65)	Son (43)
	Mother (40)	Son (21)
	Father (43)	Son (23)
	Father (45)	Daughter (18)
	Father (50)	Son (18)
	Mother (41)	Son (28)
	Mother (41)	Daughter (16)
Hors et al. (1980)	Mother (47)	Daughter (15)
	Father (50)	Son (18)
	Father (44)	Son (21)
	Mother (46)	Daughter (24)
Haim et al. (1982)	Mother (26)	Daughter (28)
	Father (44)	Daughter (19)
Hors and Dausset (1983)	Father (39)	Son (18)
		Son (12)
Cimino et al. (1988)	Father (67)	Daughter (30)
	Father (41)	Daughter (9)
	Father (34)	Daughter (9)
	Father (41)	Son (9)

agnosis and well-documented age at diagnosis were included in this study. Age at onset and data sources are listed in table 1. In all pairs except one, HL children reveal a younger age at onset. The mean age at onset is 46 years in parents and 22 years in children. This significant difference between the age at diagnosis of parents and that of children was detected by use of the Mann-Whitney test ($N = 30$, $U = 40.5$, $P < .0001$). One may argue that the smaller number of parents of relatively young age among the pairs reported in the 50s may be due to reduced fitness, as a consequence of poorer treatment. To address this issue, the analysis was repeated after removal of these pairs. The age-at-onset difference between the two generations remained significant (Mann-Whitney; $N = 12$, $U = 2.0$, $P < .0001$), and the mean age at onset was 43.2 years in parents and 17.7 years in children. Therefore, the results presented in this letter support the hypothesis of anticipation in familial HL. Nevertheless, as pointed out by Penrose (1948), false claims of genetic anticipation may be the result of various selection biases. A more optimal study design should be based on prospectively selected cases, as discussed by Horwitz et al. (1996). In addition, infectious agents such as the Epstein-Barr virus (EBV) have been implicated in the etiology of familial HL. The observed anticipation may also be related to simultaneous parent-child exposure to viral infection. To unfold this intriguing relation, further study should focus on cases who test negative for EBV.

Literature search has its place in terms of retrieval of data for a metanalysis. However, in 36 publications, only 30 parent-child pairs were eligible for inclusion in this study, because pairs selected on the basis of certain age criteria were not suitable for the testing of anticipation. Another drawback to the use of published data is that the age at diagnosis of relatives is sometimes not reported, which results in a loss of information. Given the rarity and complexity of the disease, a large international collaboration is required, to fully demonstrate the anticipation effect as well as to elucidate the role of genetic factors in the etiology of familial HL.

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The 8765delAG Mutation in BRCA2 Is Common among Jews of Yemenite Extraction

To the Editor:

The proportion of high-risk families with BRCA2 mutations varies widely among populations. In Iceland, 8% of unselected breast cancer (BC) patients and 64% of patients with a definite family history of BC carry a founder mutation in BRCA2—995del5 (Thorlacius et al. 1997). In the Ashkenazi Jews, the 6174delT mutation is found in 24% of high-risk families and in 6% of unselected BC patients (Abeliovich et al. 1997; Levy-Lahad et al. 1997). Other ancient BRCA2 mutations have been summarized by Szabo and King (1997). Whereas some of the BRCA2 mutations were found in BC-only families, including the majority of families with male and female BC (Ford et al. 1998), other BRCA2 mutations, such as 6174delT, were found in BC/OC patients (i.e., those with BC and/or ovarian cancer [OC]).

In this letter, we describe the 8765delAG mutation in BRCA2, a founder mutation in Jews of Yemenite origin.

During the screening of BC/OC patients for mutations in the BRCA2 gene, PCR products of two patients (III-9 in family BC10 and III-6 in family BC149) of Yemenite extraction had mobility shifts, as determined by single-strand conformation polymorphism (SSCA) (fig. 1*a*). Sequencing of these fragments revealed a deletion of 2 bp (AG), one of three AGs starting at position 8761 (fig. 1*b*). The mutation was analyzed in genomic DNA of the patients and of their family members, by a *Bsm*AI restriction assay using a primer into which a mismatch was introduced (fig. 1*c*). Patient II-4 in family BC703 and patient III-2 in family BC703, who were referred to us because of their ethnic affiliation and positive family history, were analyzed directly for the mutation. The pedigrees of the three families are presented in figure 2. We could not find any relationship among the three families. In families BC10 and BC149, only BC was reported. In family BC703, one of the sisters had BC and

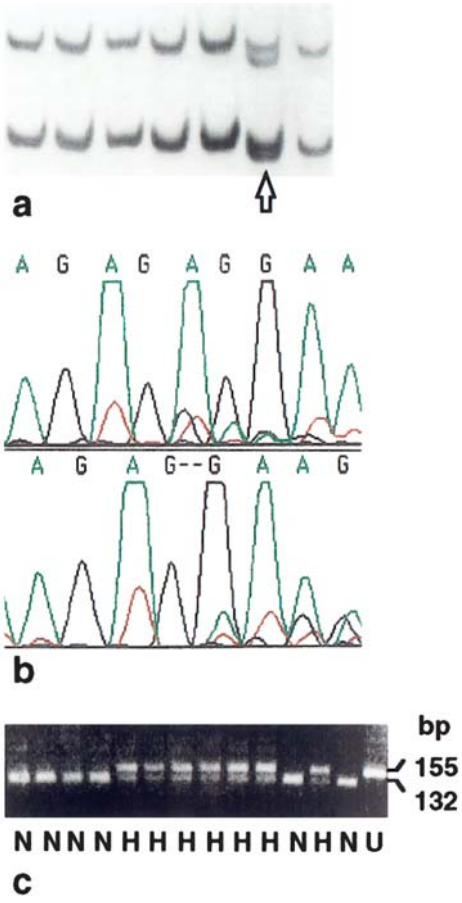

Figure 1 *a,* SSCA. The arrow indicates the fragment with mobility shift in patient III-1 of family BC10; and the other lanes contain DNA samples of unrelated BC/OC patients. PCR primers for amplification of exon 20 were retrieved from the Breast Cancer Information Core (1997); they are 20F, 5′-cactgtgcctggcctgatac-3′; and 20R, 5′-atgttaaattcaaagtctcta-3′. Amplification conditions were 35 cycles of 94°C for 30 s, 55°C for 1 min, and 72°C for 30 s; the size of the PCR product was 296 bp. SSCA was performed as described elsewhere (Zlotogora et al. 1995). *b,* Sequence of the 8765delAG mutation in exon 20 of BRCA2 The PCR fragments with mobility shift in SSCA were separated on 8% polyacrylamide gel, were excised from the gel, and were run on 1% low-melt-temperature agarose in tris-acetate/EDTA buffer. The DNA was cleaned with β-Agarase (NEB) and was precipitated with isopropanol. The purified PCR fragments were sequenced by the dideoxy terminator cycle–sequencing method with AmpliTaq DNA polymerase, FS (ABI Prism Ready Reaction Kit), and then were analyzed by use of an automatic DNA sequencer (ABI PRISM 310). The primers for sequencing were the same as those for SSCA. *c,* Restriction analysis (with *Bsm*AI) of the 8765delAG mutation in family members of the identified carriers. U = uncut; N = normal; and H = heterozygote. A mismatch was introduced into one of the primers, and, as a result, the normal allele acquired a *Bsm*AI restriction site. The PCR primers were 20F and misR (5′-gctgcttccttttcttcg*t-3′), and the size of the PCR product was 155 bp for the normal allele and 153 bp for the mutant allele. The PCR products were cut by *Bsm*AI (NEB) and were separated on NuSieve:agarose 3:1, were stained by ethidium bromide, and were visualized under a UV lamp. In the heterozygote, two bands—153 bp and 132 bp—were seen.