Type 1 Neurofibromatosis Gene: Correction

We would like to correct an error of interpretation in our report describing the cloning of a large transcript from the neurofibromatosis locus (denoted *NF1LT*) (*1*). Although the Southern blot presented in our figure 3 appears to indicate that the P5 partial cDNA clone extends across the t(17;22) translocation breakpoint in an NF1 patient, subsequent experiments have shown this to be incorrect; the entire P5 clone actually lies telomeric to this breakpoint. The apparent absence of the 4.0-kb Eco RI genomic fragment from the der(22) chromosome in our figure 3 (*1*) is due to the fact that the translocation falls within this 4.0-kb interval, and the resulting breakpoint fragment happens to be precisely the same size (15 kb) as the other human genomic band in this lane of the blot.

Our subsequent additional cDNA cloning efforts indicate that the t(17;22) break interrupts the *NF1LT* cDNA 681 bp 5′ to the end of P5 [between exons 4 and 5 in the numbering system of (*2*)], rather than within the P5 clone, as we had originally concluded. The evidence for this is presented in Fig. 1. This placement of the breakpoint now agrees precisely with the conclusions of R. M. Cawthon *et al.* (*2*), and we thank Ray White for independently pointing out the discrepancy to us.

The conclusion that *NF1LT* most likely represents the *NF1* gene remains unaltered by this revision, since functionally both the t(17;22) and t(1;17) translocations were shown to abolish *NF1LT* expression by RNA polymerase chain reaction (PCR) analysis of human-rodent hybrids bearing the translocation chromosomes (*1*). The weight of the genetic evidence supporting this identification, including an insertion in a new mutation NF1 patient (*1, 3*), deletions (*4*), and point mutations (*2*), is now overwhelming.

MARGARET R. WALLACE
DOUGLAS A. MARCHUK
LONE B. ANDERSEN
FRANCIS S. COLLINS
Howard Hughes Medical Institute,
University of Michigan,
4570 MSRB II,
Ann Arbor, MI 48109–0650

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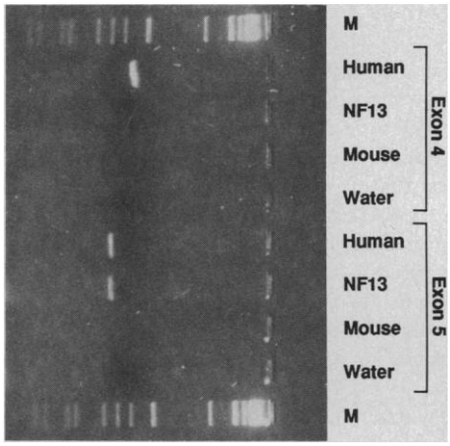

Fig. 1. Evidence that the t(17;22) breakpoint interrupts *NF1LT* between exons 4 and 5. Genomic DNA (0.2 μg) was amplified with PCR primers for exon 4 (lanes 2 to 5) and exon 5 (lanes 6 to 9). The PCR primer sequences are located in the introns adjacent to these exons and are given in (*2*). Source of DNA, normal human (lanes 2 and 6); NF13 mouse-human hybrid, containing the der(22) chromosome from the t(17;22) NF1 translocation (lanes 3 and 7); mouse (lanes 4 and 8); and water negative control (lanes 5 and 9). Lanes 1 and 10 are size markers (BRL, 1-kb ladder).

Wallace *et al.* (*1*) cite work done in our laboratory (*2*) to support their contention that analyses for loss of heterozygosity in neurofibromatosis (NF1) have not provided evidence to support a tumor suppressor function for the *NF1* locus. The cited work does in fact support such a tumor suppressor mechanism; we reported a loss of heterozygosity, using five probes for chromosome 17, in 7/14 malignancies studied. Five of those had losses only with markers from the long arm of chromosome 17 (where the *NF1* gene is located), one had a loss of all informative markers used from the long and the short arms of chromosome 17 and thus probably lost the whole chromosome, and one had a loss of one distal short arm marker. We interpreted these results to implicate the mutation of a tumor suppressor gene at the *NF1* locus in the genesis of malignant tumors in *NF1*.

Since submitting that paper we have extended our study by analyzing a total of 17 malignant tumors using seven probes from chromosome 17. We have observed a loss of heterozygosity in 13/17 of the tumors analyzed with no further losses on the short arm of chromosome 17. We have further demonstrated that in inherited cases the *NF1* allele remaining in the tumor was derived from the affected parent. This finding lends additional support for our conclusion that the *NF1* gene encodes a tumor suppressor.

GARY R. SKUSE
Division of Genetics,
University of Rochester,
Rochester, NY 14642

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Response: We appreciate the clarification provided by Skuse about his tumor analysis in neurofibromatosis (NF1). The data presented in their paper (*1*) are difficult to interpret because in most instances the 17p probes used were uninformative. In two tumors (57 and 8), however, maintenance of heterozygosity proximal to *NF1* on 17q, and loss of heterozygosity (LOH) distally on 17q, was described.

In general, other researchers (*2*) have not been able to document LOH specific to 17q in NF1 tumors, although LOH for 17p or for the entire chromosome is frequently seen, apparently reflecting the major role played by the P53 gene in tumor progression in this disorder (*3*). The additional data mentioned in Skuse's letter is interesting in this regard. Certainly, the observations that the NF1 mutations identified so far appear to inactivate the gene (*4*), and that the *NF1* gene has sequence and functional similarity to mammalian and yeast guanosine triphosphatase–activating proteins (*5*), are consistent with a tumor suppressor mechanism.

MARGARET R. WALLACE
DOUGLAS A. MARCHUK
LONE B. ANDERSEN
FRANCIS S. COLLINS
Howard Hughes Medical Institute,
University of Michigan,
4570 MSRB II,
Ann Arbor, MI 48109–0650

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