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Translocation Affecting Sonic Hedgehog Genes in Basal-Cell Carcinoma

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To the Editor

The sonic hedgehog (SHH) signaling pathway plays an essential role during human development, and its dysregulation causes developmental defects such as holoprosencephaly and a variety of human cancers, including basal-cell carcinomas.¹ Although mutations in patched homologue 1 (*PTCH1*) and smoothed homologue (*SMO*) encoding the receptors *PTCH1* and *SMO*, respectively, are known to predispose to inherited and sporadic basal-cell carcinomas, up-regulation of hedgehog ligands such as sonic hedgehog have been associated with lethal tumors such as pancreatic or lung cancer. Here, we describe a person with overexpression of *SHH* and widespread and aggressive basal-cell carcinomas.

A 41-year-old man presented with several advanced basal-cell carcinomas on his head, trunk, and all four extremities. He had microcephaly, hypotelorism, a flat nasal bridge (Fig. 1A), and T-shaped incisors (Fig. 1B); these characteristics were suggestive of mild holoprosencephaly. His skin was normal at birth, and the onset of tumors occurred at about 9 years of age (Fig. 1C).

Testing was negative for mutations in *PTCH1* and *SMO* associated with Gorlin's syndrome. A previous karyotype analysis showed a balanced translocation between chromosomes 7 and Y,² and this was confirmed. To characterize the molecular characteristics of the translocation breakpoint, we sequenced DNA purified from whole blood with the use of paired-end sequencing (with the Illumina Genome Analyzer II or HiSeq), generating 77 million reads (more than twice the physical coverage of the haplotype). This analysis revealed products indicating a translocation between chromosomes 7 and Y. (The products contained three instances of either a 7–Y junction or a Y–7 junction.)

Using the hg19 human genome reference sequence, we determined that the translocation resulted in the juxtaposition of position 19466894 on the Y chromosome and position 155747671 (the *SHH* locus) on chromosome 7 (Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The translocation fused the middle of the *SHH* promoter with Y-chromosome sequences, leaving intact 140 kb of regulatory sequences upstream of the *SHH* transcriptional start site.³ Juxtaposed Y-chromosome sequences derived from the “gene desert” between the azoospermia factor (AZF) regions AZFa and ZAFb, regions thought to contribute to sperm maturation.⁴ Analysis by means of polymerase chain reaction confirmed the predicted junctions (Fig. 1D, and Fig. 2 in the Supplementary Appendix).

The translocation explains the mild holoprosencephaly; we suggest that aberrant control of *SHH* expression resulted in partial loss of *SHH* expression during development. It also explains the basal-cell carcinomas; we suggest that the mutant promoter drives SHH expression in the skin (Fig. 1E). Indeed, the patient's tumors expressed higher levels of SHH protein (not shown) and in 5-azacytidine-treated, tumor-derived keratinocytes, significantly higher levels of SHH messenger RNA (Fig. 1F). SHH overexpression in this patient contrasts with the absence of SHH expression in common basal-cell carcinomas described in other patients with *PTCH1* or *SMO* mutations.¹ Given his large and aggressive tumor burden, the patient was enrolled in a phase 2 clinical trial (NCT00833417) that is described by Sekulic et al. in this issue of the *Journal*.⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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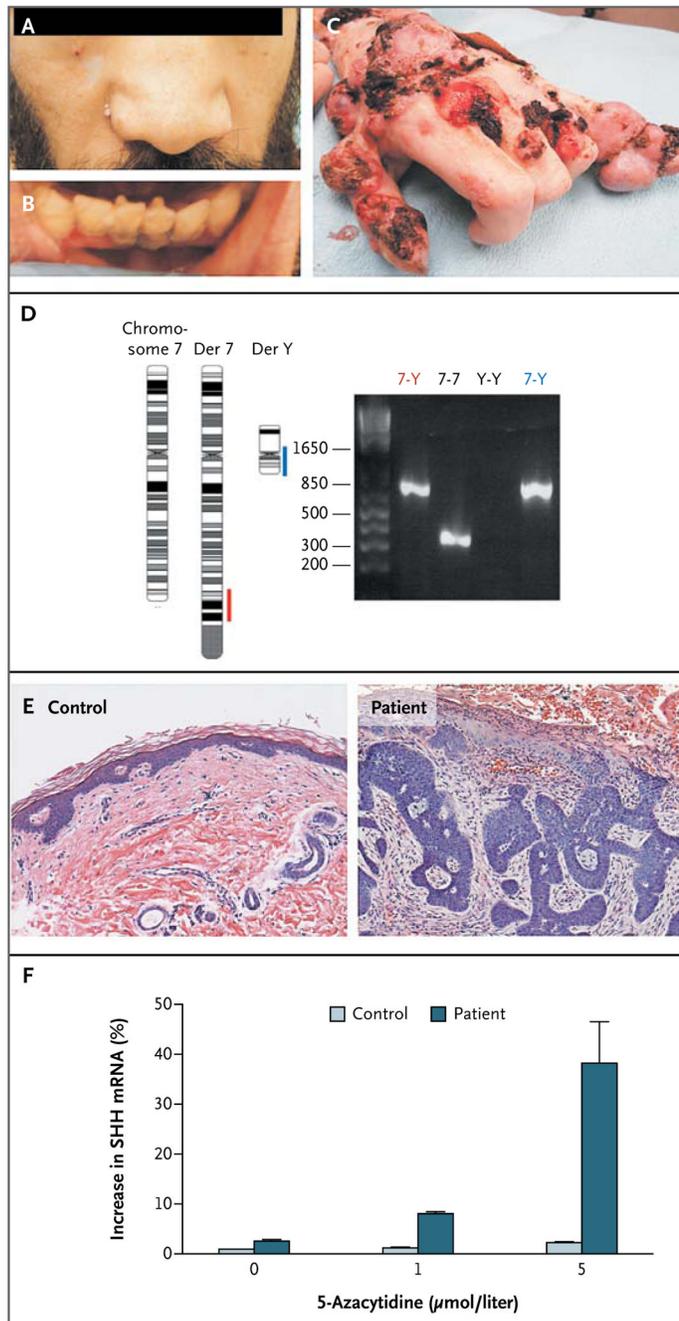


Figure 1. Clinical, Molecular, and Histologic Findings in a 41-Year-Old Man with Overexpression of the Sonic Hedgehog (SHH) Gene

Panel A shows a flat nasal bridge, and Panel B shows T-shaped midline teeth in a man with hypotelorism; these findings are characteristic of mild holoprosencephaly. Panel C shows a hand with widespread invasive and erosive basal-cell carcinomas. Panel D shows polymerase-chain-reaction (PCR) confirmation of translocation between chromosome 7 (red bar) and chromosome Y (blue bar) with the use of primers that span parental wild-type 7-7 and Y-Y sequences; this shows that 7-7, 7-Y, and Y-7, but not Y-Y sequences are present in the patient's chromosomes. Der denotes derivative chromosome. Panel E shows histologic characteristics of tissue from a control patient and the patient with a basal-cell

carcinoma tumor. Panel F shows real-time PCR of sonic hedgehog (SHH) messenger RNA (mRNA) from keratinocytes obtained from a control patient and from the patient with a basal-cell carcinoma after treatment with various levels of the demethylating agent 5-azacytine, which inhibits the DNA methylation that commonly occurs when cells and tumors are placed in cell culture. The level of mRNA was 40 times as high in the patient as in the control patient.