Translocation Affecting Sonic Hedgehog Genes in Basal-Cell Carcinoma

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. Although mutations in patched homologue 1 (PTCH1) and smoothened 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

My Perspective article does not seek to criticize practitioners who promote integrative medicine as a useful adjunct to conventional therapy in selected patients. Rather, it is meant to raise the alarm about the growing spread of unscrupulous practitioners who comfortably prey on some of the sickest and most vulnerable patients in the community. In doing so, they cause not only financial but also physical and emotional harm. They also damage the reputation of their own colleagues who are interested in genuine means of alleviating the burden of suffering.

Ranjana Srivastava, F.R.A.C.P.
Monash Medical Centre
Melbourne, Vic, Australia

Since publication of her article, the author reports no further potential conflict of interest.

Translocation Affecting Sonic Hedgehog Genes in Basal-Cell Carcinoma

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 smoothened 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

Natalia Gomez-Ospina, M.D., Ph.D.
Anne Lynn S. Chang, M.D.
Kun Qu, Ph.D.
Anthony E. Oro, M.D., Ph.D.
Stanford University School of Medicine
Stanford, CA
oro@stanford.edu

Supported by a grant (R01AR046786) from the National Institutes of Health.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


Correspondence Copyright © 2012 Massachusetts Medical Society.