Letters to the Editor

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Haploinsufficiency of the *HOXA* Gene Cluster, in a Patient with Hand-Foot-Genital Syndrome, Velopharyngeal Insufficiency, and Persistent Patent Ductus Botalli

To the Editor:

The homeobox-containing *HOX* genes constitute a highly conserved gene family, with a role in specifying the body plan. In humans and in mice, four clusters (A–D) of *HOX* genes are located on different chromosomes. The precise function of the individual *HOX* genes, in humans, can be deduced from their expression pattern during mouse development and from the phenotype of mice with a targeted disruption or overexpression of a specific *HOX* gene. In humans, mutations have only been described in *HOXD-13* and *HOXA-13,* causing synpolydactyly and the hand-foot-genital (HFG) syndrome, respectively (Muragaki et al. 1996; Mortlock and Innis 1997). The mechanisms by which mutations in *HOXA-13* lead to the phenotype—that is, whether through haploinsufficiency or through a dominant negative effect—are currently unknown. Here we report on a patient with HFG syndrome who carries a chromosome 7p14 deletion involving the entire *HOXA* cluster, indicating that haploinsufficiency of *HOXA-13* may cause the phenotype.

The patient is the second child of healthy, unrelated parents. Pregnancy and delivery were uneventful. Facial dysmorphism was evident from birth, with retrognathia, low-set malformed ears, upturned nostrils, large mouth, and upslanted eyes. There were mild anomalies of the hands and feet, with shortened and laterally deviated first toes and clinodactyly of the fifth fingers with short terminal phalanges. Radiographs revealed hand and foot anomalies characteristic of HFG syndrome (fig. 1 and 2) (Stern et al. 1970; Halal 1988). There was left-sided cryptorchidism and a ventral-bowed penis. An intravenous pyelogram was normal. In addition, he presented with severe feeding difficulties during infancy, caused by velopharyngeal insufficiency with a shortened soft palate and very small uvula. On a barium swallow, massive nasal reflux was visible. A persistent patent ductus Botalli was surgically corrected at age 4 years. Growth was normal. Full-scale IQ at age 7 years was 85. Presently, at age 21 years, he is healthy and functions at a borderline intelligence level.

Karyotype analysis of blood lymphocytes showed a de novo deletion in the short arm of chromosome 7, with karyotype 46,XY,del7(p14). FISH done with probe DO832 did not reveal a microdeletion in chromosome 22q11. FISH and microsatellite analysis were performed for the fine mapping of the deletion on 7p, as described by Devriendt et al. (1997). Informed consent was obtained from the patient and his parents. The physical-map data were from Van Laer et al. (1997). With use of YACs Y915D12 and 920C6 (located telomeric from the *HOXA* cluster) and YAC 961E5 (containing the *HOXA* cluster), no signal was seen on the deleted chromosome 7p. Microsatellites D8S529 and D8S2496 map telomeric and centromeric, respectively, from the *HOXA* cluster (Van Laer et al. 1997). Both markers were informative in this family and their analysis revealed that the patient missed a maternal allele for both markers. These data demonstrated that the entire *HOXA* cluster was deleted on this chromosome.

This patient with multiple congenital malformations carries a de novo interstitial deletion of chromosome 7p14, involving the entire *HOXA* gene cluster. Retrospectively, the hand and foot anomalies present in this patient are typical of HFG syndrome (Stern et al. 1970; Halal 1988). This autosomal dominant disorder is caused by mutations in the *HOXA-13* gene, which is the most centromeric *HOX* gene of the *HOXA* cluster on chromosome 7p (Mortlock and Innis 1997). Mutations in *HOXA-13* have so far been described in three families with HFG syndrome. In two of the families the mutations are predicted to lead to a truncated protein, whereas in one family a polyalanine tract expansion was observed (Mortlock and Innis 1997; Goodman et al. 1998*a*). The different mutations in *HOXA-13* do not result in clear phenotypic differences, although the presence of urinary-tract anomalies in certain male patients seems to be restricted to polyalanine-tract expansion (Goodman et al. 1998*a*).

At the present time, it is unclear whether these mutations result in haploinsufficiency of *HOXA-13* or in a dominant negative effect (Mortlock and Innis 1997;

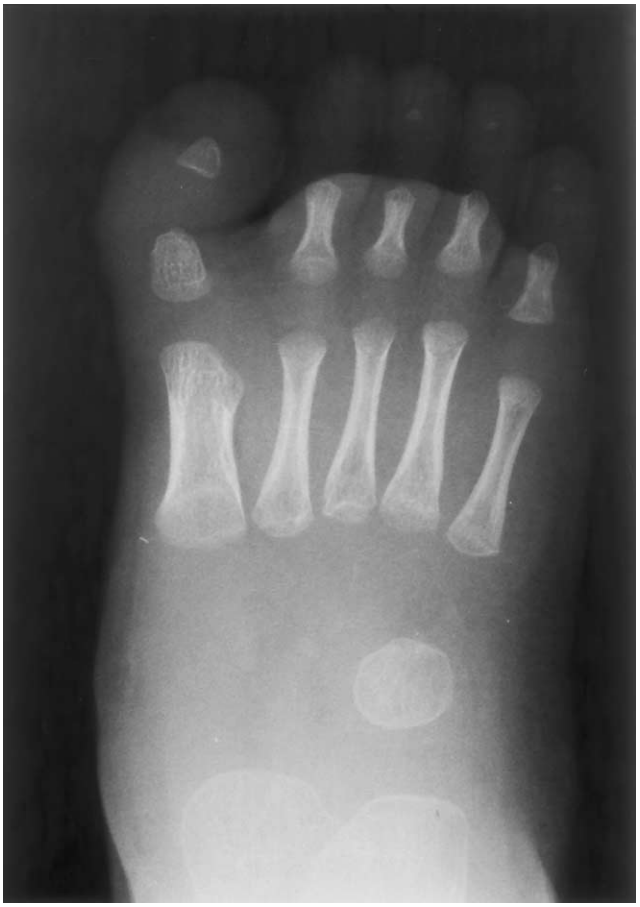

Figure 1 X-ray of the patient's left foot, at age 2 years 10 mo. The first toe is laterally deviated, with a triangular distal phalanx and shortened proximal phalanx. There is absence of calcification of the middle phalanges of toes II–V and distal phalanx of toe II.

Goodman et al. 1998*a*). The deletion of *HOXA-13* in the present patient leads to haploinsufficiency of this gene and demonstrates that this can result in the HFG phenotype. A polyalanine-tract expansion has also been observed in *HOXD-13* and causes synpolydactyly, probably through a dominant negative effect (Goodman et al. 1997). On the other hand, deletions in this gene that probably result in a null allele also result in a slightly different phenotype (Goodman et al. 1997, 1998*b*).

Interestingly, the patient presented with additional malformations, including persistent patent ductus Botalli, velopharyngeal insufficiency, and a distinct but nonspecific facial dysmorphism. These features have not been reported in HFG syndrome and probably result from the haploinsufficiency associated with one or more of the deleted genes on chromosome 7p14. There is a striking resemblance to the features found in the homozygous *Hoxa-3* knock-out mice (formerly termed *Hox-1.5*) (Chisaka and Capecchi 1991). These mice also display a disorganized musculature in the throat, with a shortened, malfunctioning soft palate. Patent ductus arteriosus was also observed in three *Hoxa-3* knock-out mice. Although we cannot exclude the possibility that the cardiac and velopharyngeal malformations in the present patient are caused by the deletion of another adjacent gene, outside the *HOXA* cluster, the similarity with the *Hoxa-3* knock-out mouse phenotype is very striking and suggests that these anomalies might be related to haploinsufficiency of this gene.

In conclusion, the congenital malformations in the present patient result from the deletion of contiguous developmental genes on chromosome 7p14. The HFG syndrome is caused by haploinsufficiency of *HOXA-13*, whereas the velopharyngeal insufficiency and patent ductus arteriosus are possibly related to haploinsufficiency of *HOXA-3*.

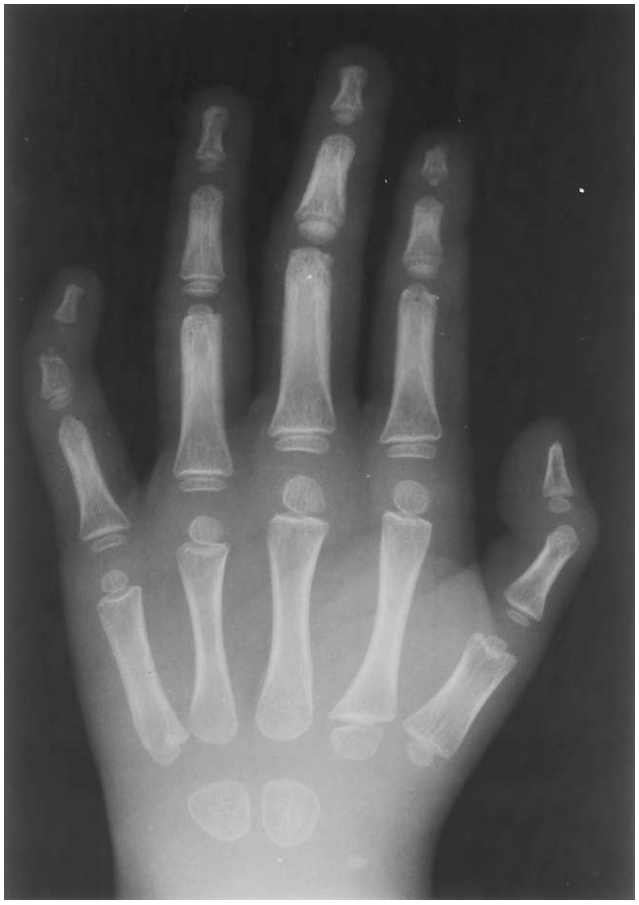

Figure 2 X-ray of the patient's left hand at age 7.5 years. Note the thumb anomalies: shortened metacarpal, pointed distal phalanx, and pseudoepiphysis of the metacarpal. There is a brachymesophalanx V causing clinodactyly and associated with a pseudoepiphysis. There is shortening of the distal phalanx of finger II. Pseudoepiphyses are present at metacarpal II and V. Bone age was 4.1 years.

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KOENRAAD DEVRIENDT,[1] JAAK JAEKEN,[2] GERT MATTHIJS,[1] HILDE VAN ESCH,[1] PHILIPPE DEBEER,[1] MARC GEWILLIG,[3] AND JEAN-PIERRE FRYNS[1]

[1]*Centre for Human Genetics,* [2]*Department of Pediatrics, and* [3]*Pediatric Cardiology Unit, University Hospital Leuven, Leuven, Belgium*

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Address for correspondence and reprints: Dr. K. Devriendt, Centre for Human Genetics, Herestraat 49, B-3000 Leuven, Belgium. E-mail: koen.devriendt@med.kuleuven.ac.be

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