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Submicroscopic familial chromosomal translocation between 7q and 12p mimicking an autosomal dominant holoprosencephaly syndrome

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To the Editor:

In 1977, Martin et al. (1) described a novel autosomal dominant midline cleft syndrome resembling familial holoprosencephaly in this journal. At the time, the genetic etiology of this syndrome was unknown. We recently reevaluated this family and identified an unbalanced chromosomal translocation between 7q and 12p involving *Sonic Hedgehog* (*SHH*).

The proband (III-10 in the original study) was a 54-year-old man with moderate mental retardation and congenital scoliosis. He showed delayed development and had an intelligence quotient of 49. He had a broad nasal root and tip and a long prominent chin (Fig. 1a), but no physical features suggestive of holoprosencephaly. Complete absence of the sacrum and coccyx below S3 was identified during the evaluation. Proband IV-5, a first cousin once removed of the proband III-10, was 34 years old and had global developmental delay/mental retardation. Proband IV-5 had downslanting palpebral fissures, a broad nasal tip, and a long prominent chin (Fig. 1b). He had microforms of holoprosencephaly, including a single maxillary central incisor, cleft uvula, and absence of the superior labial frenulum (Fig. 1c,d). X-ray study identified partial vertebral agenesis below S1. The family history was remarkable for the typical facial characteristics associated with holoprosencephaly in several relatives, all of whom died shortly after birth as described in the original article.

To elucidate the underlying mechanism of this syndrome, we performed microarray comparative genomic hybridization (CGH) analysis on III-10 and IV-5 with Signature Select OS 105K v1.1, using an Agilent 105K platform (Signature Genomics, Spokane, WA). This

revealed a deletion of the chromosomal region 7q36.2–7q36.3 (153,236,516–158,767,841) and duplication of 12p13.33–12p13.31 (85,117–7,316,329) in both probands; both have the same unbalanced chromosomal translocations. The 5.53 Mb deletion at 7q36 included *SHH* and *HLXB9* genes. Within this interval, more than 20 genes were located. The size of the duplication at 12p13.3 was 7.24 Mb, and more than 80 genes were located within the duplicated segment. In addition to the unbalanced chromosomal translocation between 7q and 12p, proband IV-5 was identified to have an approximately 270 kb microduplication of chromosomal region 20q11.21 (29,341,538–29,611,708). This microduplication includes about 10 genes within the duplicated region; however, a similar duplication has never been reported. Therefore, the significance of this duplication is unknown. An apparently balanced chromosomal translocation between 7q36 and 12p13 was identified in proband IV-5's mother.

Terminal deletion of 7q was identified as one of the causes of holoprosencephaly, leading to the identification of *SHH* as a causative gene for holoprosencephaly (2, 3). However, patients with 7q terminal deletion have a wide phenotypic spectrum (4). Similarly, we observed a highly variable expression in this family from a full and severe holoprosencephaly phenotype to the absence of microform findings. The analysis of a large family in which a chromosomal anomaly segregates provides a unique opportunity to eliminate the effect of gene dosage because we can assume that the size of the deletion is the same in all affected family members. Therefore, we conclude that the occurrence of holoprosencephaly was not determined solely by the size of the deletion at 7q36. Further studies are required to identify the factors that influence the occurrence of holoprosencephaly that result from 7q36 deletions. Terminal deletions of 7q also lead to the identification of *HLXB9* gene as a causative gene for autosomal dominant sacral agenesis (5). Sacral agenesis found in both probands probably represents the consequence of the haploinsufficiency of *HLXB9*.

The phenotypes of our probands were also likely to be influenced by the duplication of chromosome 12p13. Our patients shared characteristic facial features of 12p trisomy including a prominent nose and a pointed chin, which became more prominent in adulthood (6). The findings of our study reinforce the view that there is a specific dysmorphism associated with 12p duplication, which is particularly apparent in adulthood. Therefore, we hypothesize that the critical genomic region responsible for facial dysmorphism associated with 12p trisomy is located at 12p13.31–13.33, although co-occurrence of 7q deletion impedes a clear conclusion. Three family members died in their infancy, presumably because of holoprosencephaly. Because our probands lived to adulthood, our findings confirmed those of Segel et al. (6): 12p trisomy does not usually cause significant early mortality.

Our findings underscore the importance of reevaluation of previously described unique cases. With advances in genetic testing modalities, for example the routine use of array CGH in clinical practice, such a strategy could identify genetic basis of other rare syndromes.

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Fig. 1.
(a) Facial appearances of proband III-10, (b) facial appearances of proband IV-5, (c, d) oral phenotypes of the proband IV-5, (c) single maxillary central incisor and absence of the superior labial frenulum, and (d) cleft uvula.