A *de novo* microdeletion in a patient with inner ear abnormalities suggests that the 10q26.13 region contains the responsible gene

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Microdeletions in the 10q26.1 region are related to intellectual disability, growth delay, microcephaly, distinctive craniofacial features, cardiac defects, genital abnormalities and inner ear abnormalities. The genes responsible for inner ear abnormalities have been narrowed to fibroblast growth factor receptor 2 gene (FGFR2), H6 family homeobox 2 gene (HMX2) and H6 family homeobox 3 gene (HMX3). An additional patient with distinctive craniofacial features, congenital deafness and balance dysfunctions showed a *de novo* microdeletion of 10q26.11q26.13, indicating the existence of a gene responsible for inner ear abnormalities in this region.

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Many patients have been reported to have 10q monosomies.1–4 The 10q26.1 region is proximal to the 10q telomere. Patients with interstitial microdeletions within this region show characteristic findings that differ from those of patients with terminal deletions of 10q. These characteristics include intellectual disability, growth delay, microcephaly, distinctive craniofacial features, cardiac defects, genital abnormalities and inner ear abnormalities, including deafness and balance dysfunction.5,6 By performing a genotype–phenotype correlational study, others have suggested critical regions related to each clinical finding.7 In this study, we identified an additional case of a patient with inner ear abnormalities associated with a 10q26.1 microdeletion. This finding provides further evidence supporting the existence of a gene responsible for deafness in this region.

A 22-month-old Japanese girl was born to healthy and non-consanguineous parents following *in vitro* fertilization and gestation. She was born with a standard stature. Her family history was not remarkable. Patent ductus arteriosus was identified in the patient, and, soon after, it was surgically repaired. She exhibited a mild motor developmental delay: crawling at 12 months and walking alone at 20 months. Congenital deafness at a level of 50–60 dB was confirmed, and a hearing aid was required. A computed tomography scan of the temporal bone was performed, and bilateral middle ear hypoplasia was identified (Figures 1a,b).

At present, the patient’s height is 79.2 cm (−1.2 s.d.), weight is 9.6 kg (−1.3 s.d.) and occipitofrontal circumference is 46 cm (−0.7 s.d.). She shows distinctive craniofacial features, including facial asymmetry, malformed ears associated with low-set and posteriorly rotated ears, epicanthic folds and a lateral cervical fistula. She can walk alone but with instability; she easily falls down and often suffers injuries. This may indicate difficulties in balance due to hypoplastic semicircular canals identified by computed tomography. Her intelligent quotient was evaluated as 92 according to the Kyoto Scale of Psychological Development.

The study was performed in accordance with the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Tokyo Women’s Medical University. Blood samples were obtained from the patient and her parents after receiving written informed consent. Chromosomal microarray testing using the Agilent 60 K Human Genome CGH Microarray platform (Agilent Technologies, Santa Clara, CA, USA) was performed in accordance with previous descriptions of the method.8 A genomic copy number loss of 10q26.11q26.13 was identified in the patient. The molecular karyotype was arr 10q26.11q26.13(120,807,022–126,581,953)×1 (Figure 1c), indicating a 5.8-Mb deletion. Fluorescence *in situ* hybridization (FISH) analysis, using the bacterial artificial chromosome 11p11–57J8 as a target probe, confirmed the deletion on the homologous chromosome 10q26.13 (Figure 1d). Parental FISH analysis showed no abnormality, determining a *de novo* occurrence in the patient.

In this study, genonic positions were referred to as GRCh37/hg19. We identified a *de novo* microdeletion of 10q26.11q26.13 in a patient with distinctive craniofacial features and congenital deafness. Using a genotype–phenotype correlational analysis, we constructed a genome map and depicted the deletions identified in this patient and in previously reported patients (Figure 2). All clinical manifestations of the present patient were common to the previously reported patients with microdeletions in this region. Facial asymmetry, which was observed in this patient, was common to the patient reported as Case 14 by Irving et al.4

Extra genital abnormality is one of the characteristic findings of male patients with 10q26.1 deletions.9,10 The critical region for genital abnormality was suggested to be in the 10q25.3-q26.11 region, where some of the possible candidate genes, such as the empty spiracles homeobox 2 gene (EMX2), are located.5,7,11 Because the present patient was female, there was no extra genital abnormality, and the critical region for genital abnormalities could not be discussed.

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Instead, we focused on the critical region for inner ear abnormalities. Miller et al.6 identified overlapping deletions of this region in patients with deafness and balance dysfunction; the commonly deleted region was suggested to be a critical region for such inner ear abnormalities (Figure 2). They suggested two contiguous genes, HMX2 and HMX3, as possible candidate genes because Hmx2/3 double knockout mice had altered vestibular dysfunction.12 Consequently, haploinsufficiency of HMX2 and HMX3 may be related to inner ear abnormalities, although mice with heterozygous mutations in the genes showed no such findings. Such a discrepancy is commonly observed and could be due to the difference in species.

FGFR2 was also considered a possible candidate. It is well known that gain-of-function mutations of this gene are responsible for craniosynostosis. Although the functional relevance of FGFR2 haploinsufficiency is unknown, it may be implicated in the development of distinctive craniofacial features in affected patients.7

As shown in Figure 2, three patients whose deletion regions were within the critical region did not show deafness. As a result, the genotype–phenotype correlation for inner ear abnormalities was unclear. The lack of deafness in these patients may be due to incomplete penetrance.

In conclusion, the present patient with inner ear abnormalities has a microdeletion in 10q26.11q26.13, suggesting that the gene responsible for these abnormalities may be located in the suggested critical region within 10q26.13.

HGV DATABASE
The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.790, http://dx.doi.org/10.6084/m9.figshare.hgv.793, http://dx.doi.org/10.6084/m9.figshare.hgv.796.
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COMPETING INTERESTS

The authors declare no conflict of interest.

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