We describe a 9-year-old male patient with a 15q14 microdeletion including MEIS2. The patient was born with a ventricular septal defect and submucosal cleft. His parents were referred to our institute because of his birth缺陷 and developmental delay. From these findings, MEIS2 was determined to be the gene responsible for chromosome 15q14 deletion syndrome (MIM #616898). We report here an additional patient with a 15q14 microdeletion that involves MEIS2.

The patient is a 9-year-old boy who was born at term, measuring 51 cm in length (+1.0 s.d.), 2,976 g in weight (−0.2 s.d.) and 31 cm in occipitofrontal circumference (OFC) (−1.7 s.d.). Ventricular septal defect (VSD), which was detected through auscultation of heart murmur, later spontaneously closed. Otitis media with effusion was recurrently observed. He did not walk until 20 months, and his language development was delayed. Because of his language delay, he received special education for children with disabilities.

At present, his height is 126.4 cm (−0.6 s.d.), weight is 22.6 kg (−1.0 s.d.) and OFC is 53.5 cm (+0.7 s.d.). His intelligence quotient (IQ) was evaluated by the Kyoto Scale of Psychological Development. Although there was no abnormality in his motor development, his language development score was 63, indicating mild developmental delay. VSD was also identified, indicating the low penetrance of this gene.

This study was approved by the ethics committee at our institution. After obtaining written informed consent, a blood sample was acquired and genomic DNA was extracted from the patient’s blood. Target resequencing using the TruSight One Sequencing panel (Illumina, San Diego, CA, USA) was performed to detect disease-causing mutations; however, there were no possible disease-causing variants. Subsequently, eXome Hidden Markov Model analysis using a BAM file extracted through next-generation sequencing identified a possible microdeletion in the 15q14 region (Figure 1a,b). Microarray chromosomal testing was performed for reconfirmation of the identified finding. For this purpose, an Agilent Technologies Catalog 60 K microarray system (Agilent Technologies, Santa Clara, CA, USA) was used. The result showed a 3.17 Mb deletion in the 15q14 region (15q14:34,105,933-37,270,012) [hg19], which is depicted in Figure 1c. The genes involved in the 3.2 Mb deletion region are summarized in Supplementary Table S1. Because parental samples were also analyzed and they did not contain any abnormalities, a de novo origin was considered, although a rare segmental translocation of 15q14 in the parents cannot be excluded.

The deletion regions identified in the previously reported patients are depicted in the genome map (Figure 1d,e). The clinical features of this patient are summarized in Table 1 and are compared with those of the previously reported patients with 15q14 deletions and MEIS2 mutations. As shown, various degrees of developmental delay are commonly observed in the patients with MEIS2 haploinsufficiency. VSD and cleft palate are also reported in many patients. The present patient showed mild developmental delay. VSD was also identified, although it spontaneously closed later. A submucosal cleft (rather than an open cleft palate) was diagnosed in this patient, and was also reported in the previous patients. On the basis of these findings, most of the clinical features observed in the present patient were considered to be due to MEIS2 haploinsufficiency.

The present patient did not show any symptoms of gastroesophageal reflux, which is reported in patients with nucleotide alterations in MEIS2 (Table 1). The developmental delay in the present patient is milder than the delay commonly reported in patients with MEIS2 mutations. This difference might be due to phenotypic variability.

The relatively mild developmental delay and lack of additional phenotypic features in this patient indicate that the neighboring genes involved in the deletion region do not play important roles in the observed phenotypic features in the heterozygous state. Defects in the actin alpha cardiac muscle 1 gene (ACTC1; MIM #102540) have been associated with idiopathic dilated cardiomyopathy and familial hypertrophic cardiomyopathy in an autosomal dominant trait. However, the present patient did not show any related finding, indicating the low penetrance of this gene.
The present patient showed behavior abnormalities related to autism spectrum disorder. Because some patients with MEIS2 haploinsufficiency showed similar features to this disorder (Table 1), our findings might contribute to investigations of this condition.

**Table 1. Summary of the clinical features of patients**

| Submicroscopic deletions involving MEIS2 | Nucleotide alterations in MEIS2 | Present patient |
|----------------------------------------|--------------------------------|-----------------|
| Number of the patients                 | 12                             | 2               |
| Developmental delay                    | 10/12                          | 2/2             | +               |
| Verbal developmental delay             | 2/12                           | 2/2             | +               |
| Motor developmental delay              | 9/12                           | 2/2             | +               |
| Autism spectrum disorder               | 1/12                           | 1/2             | +               |
| Congenital heart defects               | 6/12                           | 2/2             | +               |
| Cleft palate                           | 10/12                          | 2/2             | +               |
| Gastroesophageal reflux                | 0/12                           | 2/2             | −               |

Abbreviation MEIS2, Meis homeobox 2.

*Table 1 reported by Fujita et al. is modified.*

**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.1376.
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COMPETING INTERESTS
The authors declare no conflict of interest.

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