

DATA REPORT

A 15q14 microdeletion involving *MEIS2* identified in a patient with autism spectrum disorder

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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. Mild developmental disability and autism spectrum disorder diagnosed in childhood were also considered to be consequences of *MEIS2* haploinsufficiency. The relatively mild developmental delay and lack of additional phenotypic features in this patient indicate that only *MEIS2* plays an important role in the observed phenotypic features in the heterozygous state.

Human Genome Variation (2017) **4**, 17029; doi:10.1038/hgv.2017.29; published online 20 July 2017

Meis homeobox 2 (*MEIS2*) is known to contribute to developmental programs. Recently, two patients with *de novo* *MEIS2* mutations have been reported.^{1,2} Both patients presented cleft palate, congenital heart septal defects 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 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. His speech has a nasal sound caused by a submucosal cleft. Echolalia is frequently observed. Although he can write characters and numbers, he cannot read properly. When he cannot perform tasks according to his expectations, he exhibits behavior such as tantrums, irritability and self-injury. He does not have many friends at school, which might be due to his impaired communication skills. These behaviors suggest characteristics of autism spectrum disorder.

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).³ Microarray chromosomal testing was performed for reconfirmation of the identified finding.³ 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 deletions⁴⁻⁸ and *MEIS2* mutations.^{1,2} As shown, various degrees of developmental delay are commonly observed in the patients with *MEIS2* haploinsufficiency.² 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.⁹ However, the present patient did not show any related finding, indicating the low penetrance of this gene.

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Received 4 April 2017; revised 12 May 2017; accepted 12 May 2017

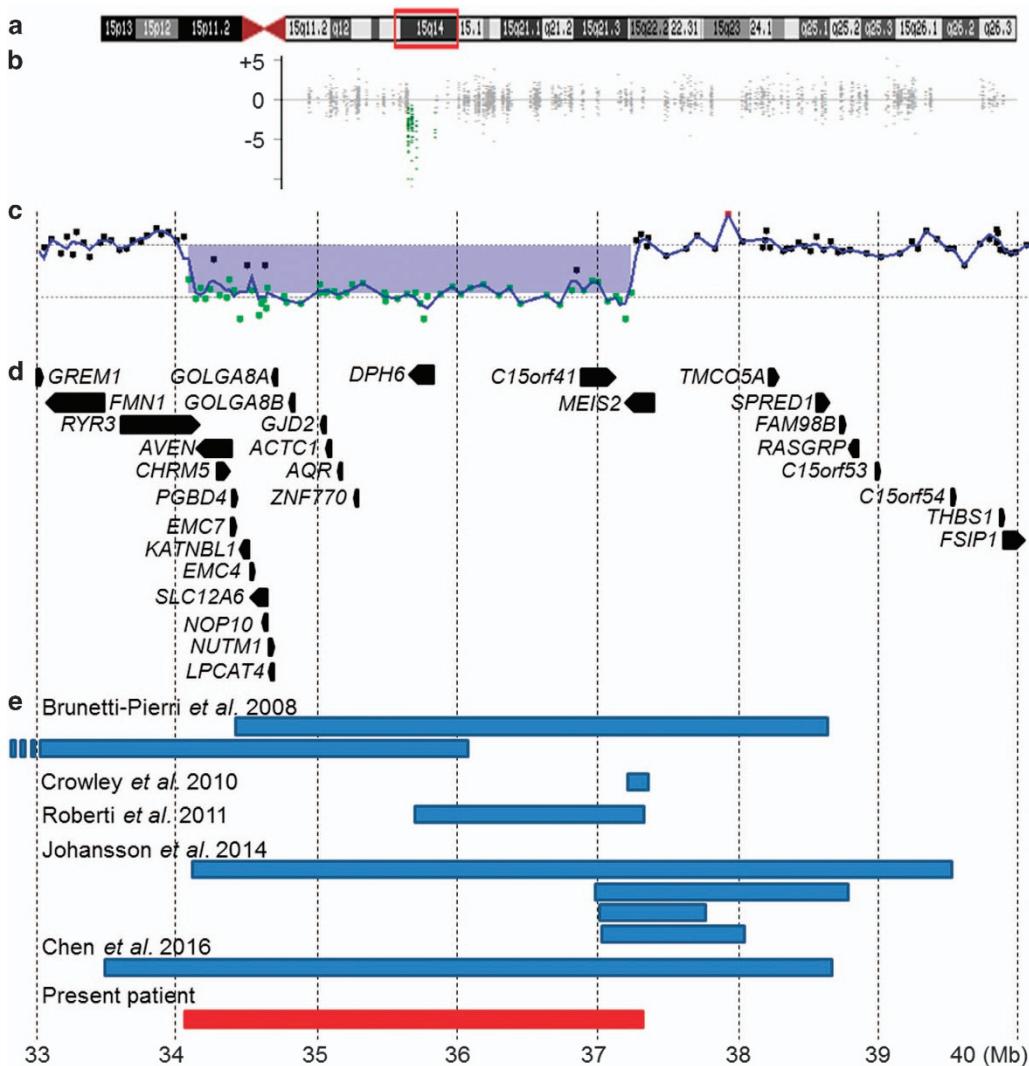


Figure 1. Genome map around 15q14 with the deletion regions in the reported patients. (a) Region of interest around 15q14 is shown by a red rectangle on the image of chromosome 15, captured from the UCSC genome browser (<https://genome.ucsc.edu/>). (b) XHMM shows a possible microdeletion in the 15q14 region. The x and y axes indicate the z-scores and genomic positions, respectively. (c) Data were extracted through chromosomal microarray testing. A GeneView created by Agilent Genomic Workbench (Agilent Technologies) is shown. The aberrant region is indicated by a blue transparent rectangle. (d) The locations, regions and directions of the genes are shown. (e) Previously reported deletions are shown with blue rectangles. *MEIS2* is partially involved in the deletion region identified in the present patient, which is shown with a red rectangle. XHMM, eXome Hidden Markov Model.

Table 1. Summary of the clinical features of patients^a

	Submicroscopic deletions involving <i>MEIS2</i>	Nucleotide alterations in <i>MEIS2</i>	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.

^aTable 1 reported by Fujita et al.² is modified.

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.

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>.

ACKNOWLEDGEMENTS

We are grateful to the patients and their families for their cooperation. This research was supported by the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) and the Japan Society for the Promotion of Science (JSPS) KAKENHI grant number 15K09631 (TY).

COMPETING INTERESTS

The authors declare no conflict of interest.

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