

# Clinical and Molecular Delineation of a Novel *De Novo* 4q28.3–31.21 Interstitial Deletion in a Patient with Developmental Delay

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The 4q deletion syndrome is a rare disorder, with an estimated incidence of 1 in 100000<sup>1</sup> and approximately 150 patients have been reported globally.<sup>2</sup> With common clinical presentations with craniofacial dysmorphism, cardiac and skeletal defects, growth failure and developmental delay, wide spectrum of phenotypes in 4q deletion syndrome patients have been described in correlations with deletion size, genes and genomic environment of the affected region.<sup>2</sup> Array-comparative genomic hybridization (aCGH) has advocated this approach by detecting various small genetic aberrations that were neglected by the conventional chromosomal analysis.<sup>3</sup> Herein, we report a case of 4q deletion syndrome confirmed by aCGH which detected a novel *de novo* interstitial deletion of 4q28.3–31.21 in a 6-year-old boy with mild developmental delay.

The proband, a Korean male, was born at 39 weeks of gestation by normal vaginal delivery with birth weight of 2460 g, as the second son of the parents. Both parents and his brother were healthy without any remarkable family history. Even though no medical or surgical event occurred, the patient could only speak single words, such as mother, at 30 months. Bailey scales of infant development revealed no specific developmen-

tal delay in the areas of motor, social function and cognition, except language, for 20 months delay. On physical examination, no specific abnormality was found. With little suspicion for chromosomal abnormalities, genetic studies were ordered to rule out congenital chromosomal disorders for mild language delay.

Chromosome analysis performed with peripheral blood by conventional G-banding technique at 550-band resolution revealed the karyotype of 46,XY,inv(9)(p12q13)[20] (Fig. 1A), which is generally considered as normal variant karyotype.<sup>4</sup> However, when aCGH with NimbleGen CGX-3 whole-genome array (Roche NimbleGen, Inc., Madison, WI, USA) was performed with Genoglyphix software (Signature Genomics, Spokane, WA, USA) for further evaluation, 6 Mb deletion (chr4: 139151789-145163068) within the region 4q28.3–31.21 was detected (Fig. 1B). Consequent chromosome and aCGH studies in both parents were normal, implying a *de novo* microdeletion in the patient.

During follow-up outpatient clinics, he had no additional symptoms or signs associated with neurologic dysfunction or cardiac problem. Until the day of publication, the patient was treated with supportive speech therapies and tolerated well in public childcare facilities.

The 4q deletion syndrome is a good example of genetic disorders that have well-established genotype-phenotype correlations. Two recent studies have proposed that 4q35.1 region is critical for the 4q syndrome, and that 4q32.2–q34.3 region is critical for cardiovascular phenotypes.<sup>2,5</sup> Another case report presented various clinical features of hypertonia, respiratory distress syndrome, and developmental delay with the small deletion (4q31.2–31.22, 1 Mb) described until today.<sup>6</sup>

In this perspective, our case is important for relatively large deletion with only single phenotype (i.e., mild language delay), when compared with two previous cases who presented simi-

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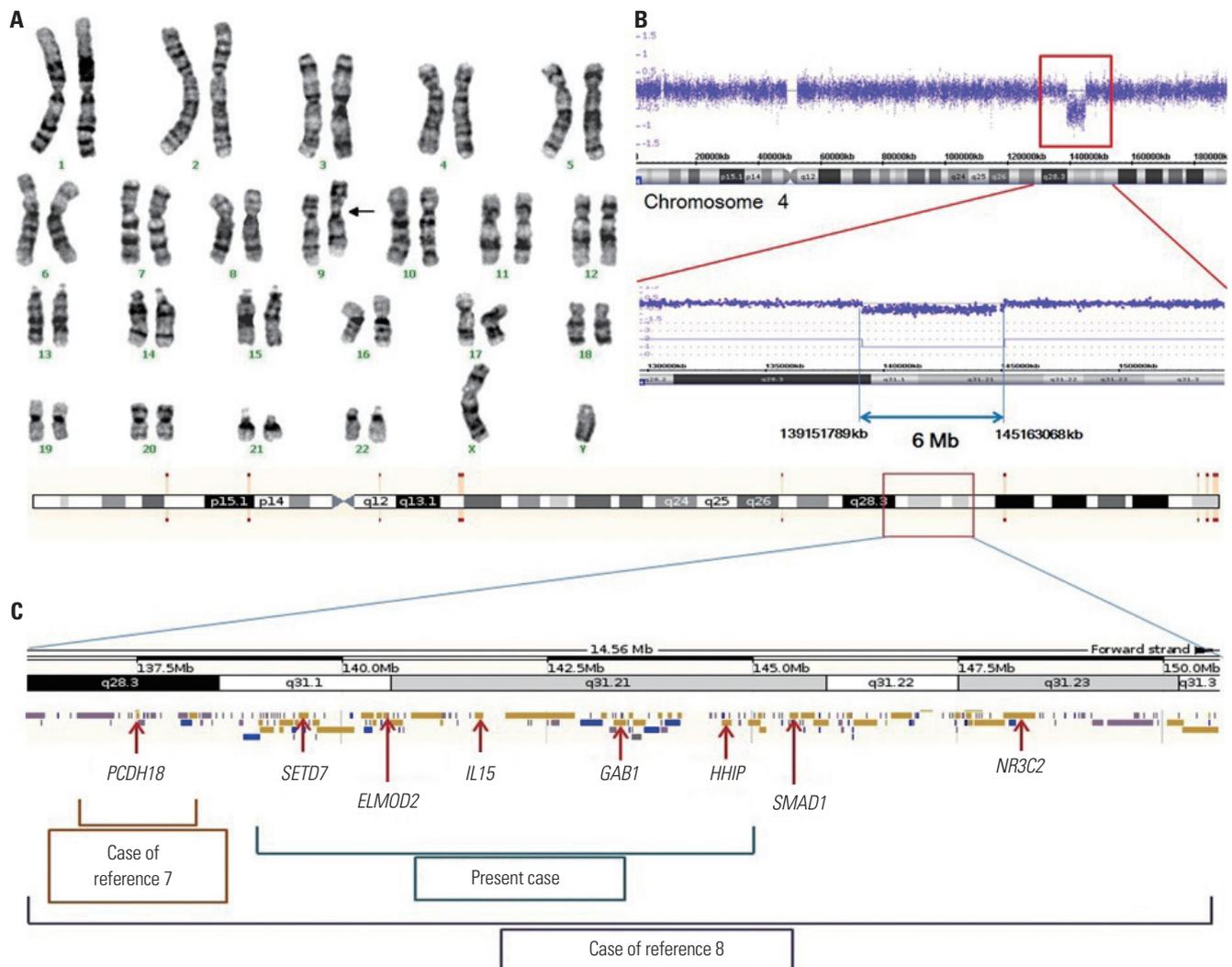
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**Fig. 1.** (A) The G-banded karyotype of the patient. Trypsin-Giemsa banded chromosome analysis at the 550-band level shows a pericentric inversion of chromosome 9 (arrow), which is considered as the normal variant commonly seen in normal population. Interestingly, microdeletion in the long arm of chromosome 4 was not noticed in the chromosome analysis. (B) The array-comparative genomic hybridization result of the patient. Deletion at the region from 4q28.3 to 4q31.21 is observed (red box). The size of deletion fragment was estimated to be 6 Mb (from 139151789 kb to 145163068 kb). (C) Comparison of deletion loci and sizes among three 4q deletion cases (present case, case of reference 7, and case of reference 8) within the region 4q28.3-31.23. There are 8 deleted genes within the region with possible effects on the phenotypes (i.e., *PCDH18*, *SETD7*, *ELMOD2*, *IL15*, *GAB1*, *HHIP*, *SMAD1*, and *NR3C2*). Considering the severities of three cases, *PCDH18*, *SMAD1*, and *NR3C2* are suggested to be major contributors to severe phenotypes in the 4q deletion syndrome including cardiac and neurologic defects.

lar deletion regions (Fig. 1C). A recent 4q deletion syndrome with single gene (*PCDH18*) deletion on 4q28.3 (1.5 Mb, chr4: 137417338-138947282) expressed severe developmental delay, seizures, microcephaly, hypoplastic corpus callosum, and craniofacial dysmorphism.<sup>7</sup> Another case of 4q deletion syndrome with deletion region on 4q28.3-31.23 (14 Mb, chr4: 136127048-150690325) expressed various clinical features; growth failure, developmental delay, ventricular septum defect, patent foramen ovale, vascular malformation of lung, corpus callosum dysgenesis and craniofacial dysmorphism.<sup>8</sup> In contrast to two earlier cases, our case revealed only mildly delayed language development until the day of publication. We could explain this wide gap of clinical phenotypes among three 4q syndrome patients with similar deleted regions by analyz-

ing the critical genes for severe phenotypes. Genes such as *PCDH18*, *SMAD1*, and *NR3C2* are located outside of the deleted region of our case, but within the encompassing region (i.e., chr4:136127048-139151789 and chr4:145163068-150690325), suggesting as possible major contributor for severe phenotypes in the 4q deletion syndrome including cardiac and neurologic defects. This finding is also in line with suggestion that 4q31.2-31.22 region (chr4:145963820-147044764) is essential for clinical features in the 4q deletion syndrome.<sup>6</sup>

Even though there was one previous Korean 4q deletion syndrome case with severe agenesis of corpus callosum and neonatal death, diagnosed by cytogenetic analysis,<sup>9</sup> our case is the first Korean 4q deletion syndrome case diagnosed by aCGH with clinical symptom. Among 150 previously reported 4q de-

letion syndrome reports, there were not many Asian patients. More cases of Korean 4q deletion syndrome with various clinical features are expected.

In conclusion, we reported a case of 4q deletion syndrome with a novel *de novo* interstitial deletion of 4q28.3–31.21, confirmed by aCGH, in a 6-year-old boy with mild developmental delay.

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