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LETTER TO THE EDITOR

A 5.3-MB DUPLICATION OF 9p12→p13.1 CHARACTERIZED BY ARRAY CGH IN A FEMALE INFANT WITH DEVELOPMENTAL DELAY

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The female infant was the first child of a 28-year-old mother and a 32-year-old father. The parents were healthy and non-consanguineous. The family history was unremarkable. The infant was delivered uneventfully at 38 weeks of gestation with a birth weight of 2,835 g. When examined at 8 months of age, the infant manifested developmental delay, a long face, low-set ears, hypopigmentation, trichiasis, entropion, astigmatism and mild edema of the lower part of the legs. Her body weight was 8.2 kg (50th centile), body length 68.2 cm (25-50th centile) and head circumference 43 cm (25-50th centile). When examined at 2 years and 4 months of age, she had speech delay, unstable gait, a body weight of 12 kg (25-50th centile), a body length of 89 cm (50th centile), a head circumference 46.8 cm (25-50th centile) and mild facial dysmorphism (Fig. 1). The cytogenetic analysis revealed a karyotype of 46,XX. Array CGH analysis identified a 5.3-Mb duplication of 9p12→p13.1 with the first abnormal clone located at 38,815,000 bp and the last abnormal clone at 44,135,000 bp (Fig. 2). The parents did not have such a duplication. Increase in length of the bands 9p12 and 9p13.1 could be observed on G-banding karyogram of the proband's lymphocytes (Fig. 3).

The previously reported regions of extra G-band-positive, C-band-negative euchromatic variants include 8p23.1, 9p12, 9q12, 15q11.2-q13, 16p11 and 16p11.2 (1-5,8). The additional euchromatic bands are due to an amplified DNA cassette, and the additional material comprises pseudogenes (3, 7).

Di Giacomo *et al*. (6) first reported duplication of 9p11.2-p13.1 involving 5~5.2 Mb segment spanning from band 9p11.2 to the middle of band 9p13.1 in two fetuses and their phenotypically normal mothers, and in one 33-year-old female with a normal phenotype and reproductive failure. Di Giacomo *et al*. (6) accordingly suggested that dup(9)(p11.2p13.1) has no phenotypic or reproductive consequences

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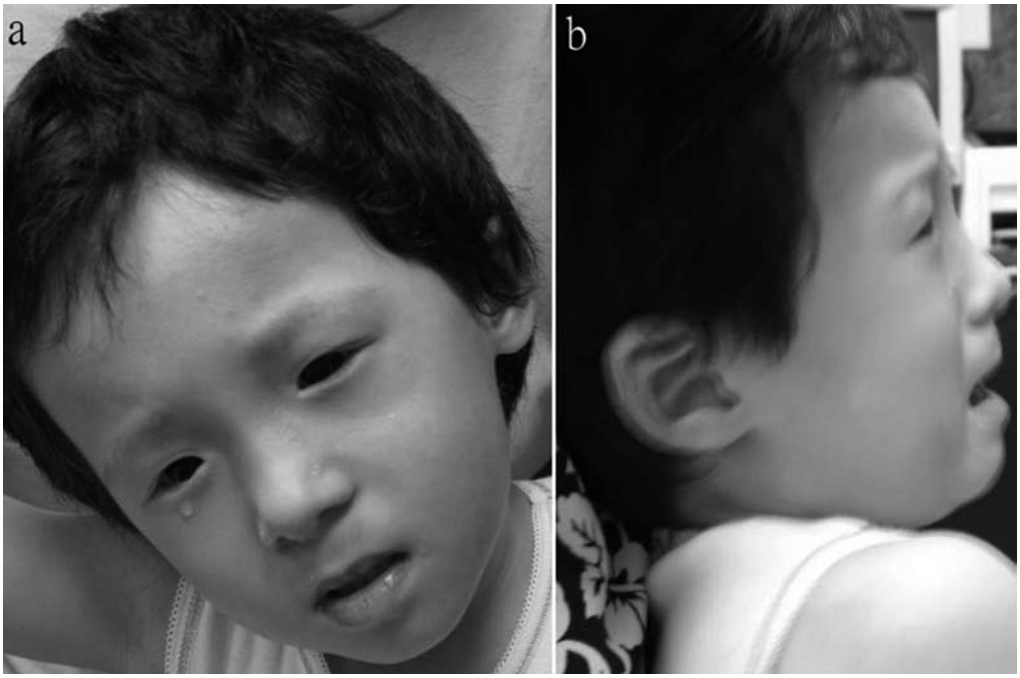

Figure 1: (a) Anterior view and (b) lateral view of the proband at age 2 years and 4 months.

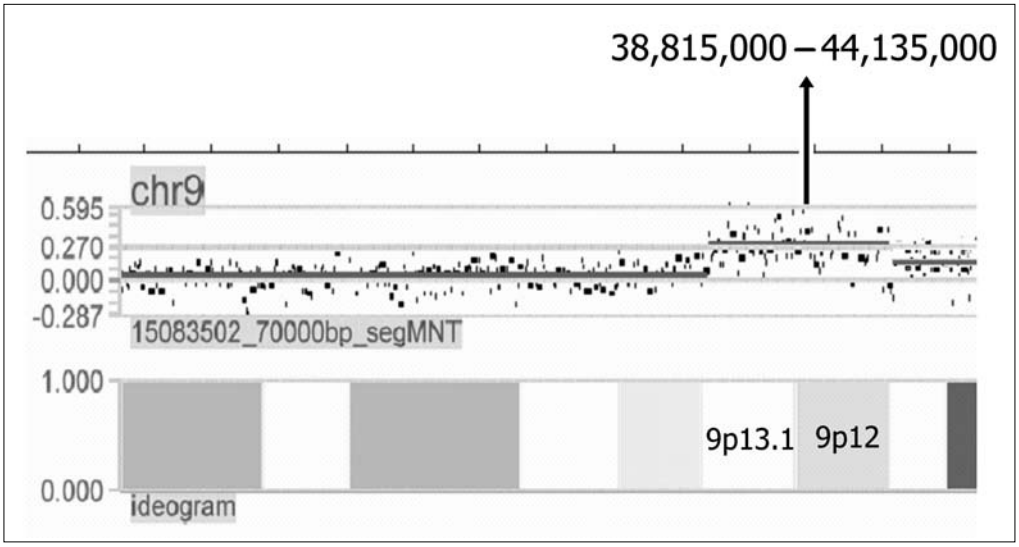

Figure 2: High-resolution comparative genomic hybridization (HR-CGH) analysis of proband's DNA using NimbleGen's high-density tiling oligonucleotide arrays (Madison, WI, USA) shows a duplication of 9p12→p13.1 encompassing a region from 38,815,000 bp to 44,135,000 bp.

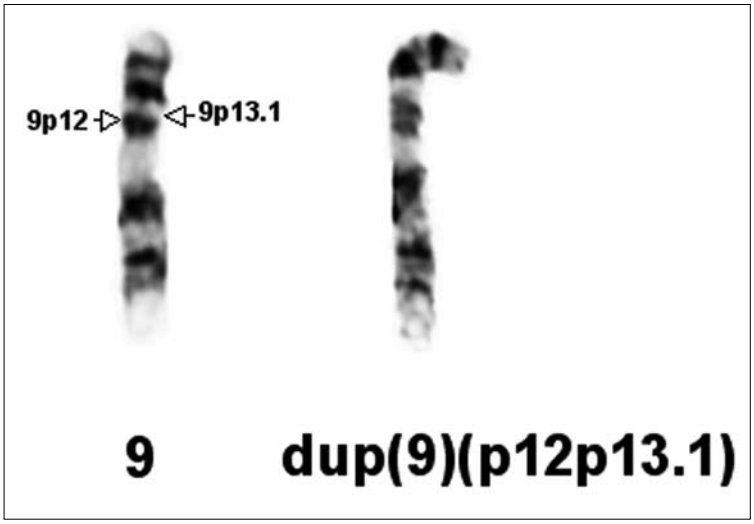

Figure 3: Partial G-banded karyogram shows increase in length of the bands 9p12 and 9p13.1 in the aberrant chromosome 9. Arrows indicate the bands 9p12 and 9p13.1 in the normal chromosome 9.

in both sexes and is a benign cytogenetic variant. Lecce *et al.* (8) subsequently reported three additional cases of a similar polymorphism in a healthy 33-year-old woman and in two unrelated fetuses, both of whom had received the rearrangement from their healthy fathers, but found that it was a locus-specific amplification caused by repeated copies of a small DNA segment mapping within 9p12 rather than a simple duplication. The present case was associated with *de novo* dup(9)(p12p13.1) and phenotypic consequences. The duplication has spanned the whole band of 9p13.1 with gene dosage increase in the pseudogenes and the functional genes on 9p13.1 such as *VN2R3P*, *CNTNAP3*, *FAM75A1*, *FAM75A2*, *FAM74A1*, *LOC647069* and *LOC727745*. *VN2R3P* is a vomeronasal 2 receptor 3 pseudogene. *FAM75A1* and *FAM75A2* are associated with hypothetical proteins LOC647060 and LOC642265, respectively. *LOC647069* is similar to *FKBP52* that encodes 52 kD FK506 binding protein which is a critical determinant of uterine progesterone actions in preparing the uterus for blastocyst implantation. *LOC727745* is a hypothetical gene. *CNTNAP3* (OMIM 610517) encodes contactin-associated protein 3 which belongs to the neurexin family of multidomain transmembrane proteins that are involved in cell adhesion and intercellular communication, and are expressed in brain tissues and in other organs during fetal development and in the adult stage (9).

As shown in this presentation, a duplication of 9p13.1 can be associated with phenotypic consequences. Although the extra G-band-positive material on 9p12 has been well known to be a euchromatic variant, we think that the genetic consequences of a chromosome duplication

spanning from band 9p12 to band 9p13.1 should be interpreted with caution during genetic counseling, especially in the *de novo* cases.

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