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LETTER TO THE EDITOR

DELETION 2q37.3→qter AND DUPLICATION 15q24.3→qter CHARACTERIZED BY ARRAY CGH IN A GIRL WITH EPILEPSY AND DYSMORPHIC FEATURES

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The girl was the second child of a 28-year-old mother and a 28-year-old father. The parents were healthy and non-consanguineous. The family history was unremarkable. The girl was delivered uneventfully at 38 weeks of gestation with a birth weight of 3,300 g. She was referred to the hospital at one month of age because of weak cry, stridor and hypotonia. Cytogenetic analysis revealed a derivative chromosome 2 with additional material attached to the terminal part of the long arm of a chromosome 2. Subsequent cytogenetic analysis of the family members showed a karyotype of 46,XX in the mother, a karyotype of 46,XY,t(2;15)(q37;q24) in the father and a karyotype of 46,XX,t(2;15)(q37;q24) in her elder sister. She suffered from seizures since one year of age and needed medical treatment to control seizures. Electroencephalography (EEG) showed sharp waves from the right frontal area following seizures. At age 16 months, her weight was 10 kg (50th centile), length 82 cm (75th centile), and head circumference (HC) 44 cm (10th centile). Ultrasound findings of the heart and kidneys were normal. Computed tomography (CT) scans of the brain revealed mild widening of both lateral ventricles and third ventricle. At age 2 years, she underwent supraglottoplasty to treat laryngomalasia, and partial small bowel resection to treat intestinal obstruction and stenosis. At age 4 years, her weight was 17 kg (25th centile), and HC 47.9 cm (25-50th centile). She manifested severe mental retardation, unstable gait, learning difficulties, speech disorders and delayed psychomotor development but no autistic disorders. She presented a long thin face, a high anterior hairline, upturned nares, a prominent nasal bridge, hypertelorism, epicanthic folds, downslanting palpebral fissures, a long philtrum, a pointed chin, low-set ears and elongated digits (Figs 1 and 2). At age 7 years, her weight was 21 kg (50-75th centile), and HC 48.5 cm (50th centile). At age 8 years, she manifested tall stature. Her weight was 24 kg (50-75th centile), and length 132 cm (>

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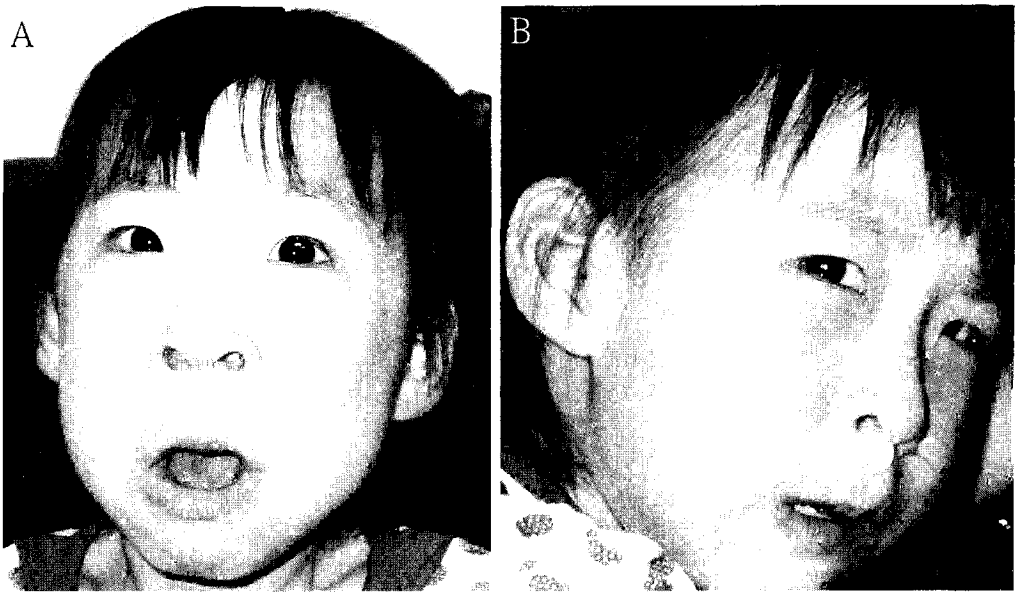

Figure 1: (A) Anterior view and *(B)* lateral view of the proband at age 4 years shows a long thin face, a high anterior hairline, epicanthic folds, a prominent nasal bridge, a pointed chin, a long philtrum and low-set ears.

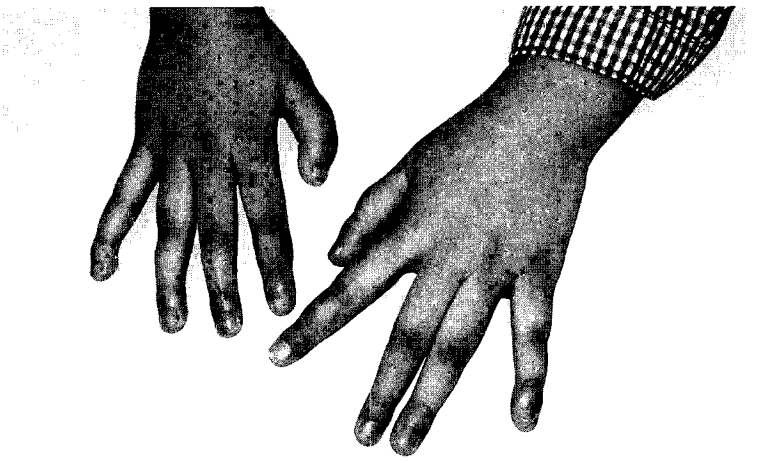

Figure 2: Long hands with elongated fingers at age 7 years.

97th centile). Molecular cytogenetic analyses were performed. High-resolution comparative genomic hybridization (HR-CGH) analysis of proband's DNA using NimbleGen's high-density tiling oligonucleotide arrays (Madison, WI, USA) showed a 2.5-Mb deletion of 2q37.3→qter and a 24.7-Mb duplication of 15q24.3→qter (Fig. 3). The karyotype of the proband was 46,XX,der(2)t(2;15) (q37.3;q24.3)pat.

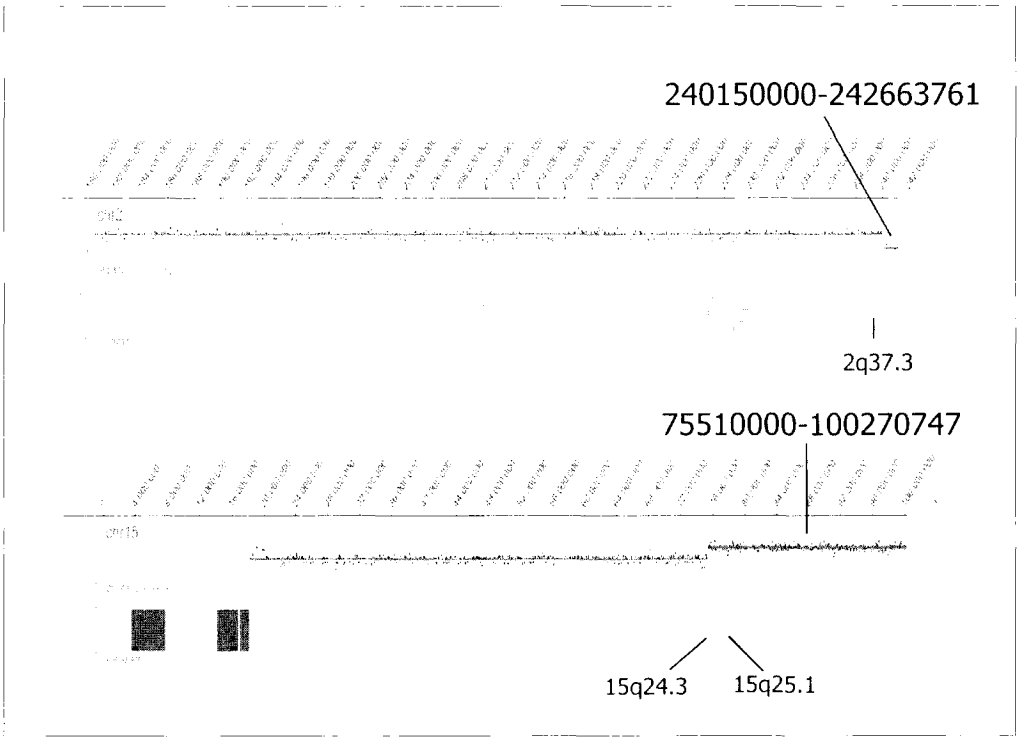

Figure 3: High-resolution comparative genomic hybridization (HR-CGH) analysis of proband's DNA using NimbleGen's high-density tiling oligonucleotide arrays (Madison, WI, USA) shows a deletion of 2q37.3→qter (240,150,000 bp – 242,663,761 bp) and duplication of 15q24.3→qter (75,510,000 bp – 100,270,747 bp).

The present case had deletion of 2q37.3→qter and duplication of 15q24.3→qter associated with seizures, mental retardation, psychomotor delay, tall stature, learning difficulties and special facial appearance. It has been suggested that overgrowth, learning difficulties and characteristic facial appearance made of a long thin face with a prominent nose and chin constitute a distinctive phenotype of 15q overgrowth syndrome (5-6, 9).

Insulin-like growth factor 1 receptor (*IGF1R*) gene (OMIM 147370) is mapped to 15q26.3 and is involved in growth and insulin-related phenotypes and longevity. Faivre *et al.* (5) observed a specific phenotype related to trisomy 15q26.1-qter with macrosomia at birth, overgrowth, macrocephaly and mild developmental delay as the major features. Kant *et al.* (6) reported the frequent association of tall stature and mental retardation with trisomy 15q26-qter and a duplication of the *IGF1R* gene. Abuzzahab *et al.* (1) found mutations in the *IGF1R* gene in cases with unexplained intrauterine growth restriction and postnatal growth failure. Bonafè *et al.* (2) hypothesized that polymorphism of *IGF1R*

may play a role in synthetic IGF1 regulation, and down-regulation of the IGF1 pathway has been associated with human longevity. Increased gene dosage of *IGF1R* through duplication of the 15q26.3 region can lead to overgrowth and tall stature (5-7, 9).

The present case was associated with intermittent seizures since one year of age. Bonati *et al.* (3) reported a 4-year-9-month-old male with trisomy 15q25.2-qter and a phenotype including autistic disorders, postnatal overgrowth, a supratentorial widening of the ventricular system, a slight symmetry with irregular outline of lateral ventricles, and seizures. The region of 15q24.3→qter contains several genes involved in brain development and functioning such as *CHD2* (OMIM 602119) encoding chromodomain helicase DNA-binding protein 2, *AP3B2* (OMIM 602166) encoding adaptor-related protein complex 3, β2 subunit, *HOMER2* (OMIM 604799) encoding homer homolog 2 (Drosophila), *SH3GL3* (OMIM 603362) encoding SH3-domain GRB2-like 3, and *NMB* (OMIM 162340) encoding neuromedin B. Increased dosage of these genes may contribute to the phenotype of brain abnormalities and seizures in the patients with 15q overgrowth syndrome.

The present case had also a deletion of terminal 2q37.3→qter. Neurological effects of chromosome 2q terminal deletion include developmental delay, mental retardation, autistic-like behavior and hypotonia (4). Del(2)(q37.3→qter) has been also shown to be associated with seizures and intestinal atresia. Indeed, Reddy *et al.* (8) reported a 9-year-old female with del(2)(q37.3→qter) and dextrocardia, duodenal and jejunal atresia, an abdominal hernia, complete abnormal situs viscerum, seizures and mental retardation, and a 44-year-old male with del(2)(q37.3→qter) and diaphragmatic hypoplasia, intestinal malrotation, an abnormal kidney and mild mental retardation.

To date, only two cases with partial duplication of 15q and deletion of 2q have been reported (6, 10). Van Allen *et al.* (10) reported a 6-month-old male with a karyotype of 46,XY,der(2)t(2;15)(q37;q26)pat and phenotypic abnormalities including craniosynostosis, facial dysmorphism, left inguinal hernia, hypotonia, arachnodactyly, a horseshoe kidney and a right ureterocele. Kant *et al.* (6) reported a 7-year-9-month-old female with a karyotype of 46,XX,der(2)t(2;15)(q37.1;q22.3) and phenotypic abnormalities including hydronephrosis, ureteric reflux, a prominent nasal bridge, an elongated face, a high hairline, epicanthic folds, micrognathia, long narrow hands and feet with under-riding fifth toes, hypotonia, tall stature and macrocephaly. Our case complements the previous literature on partial duplication of distal 15q and deletion of terminal 2q with a characteristic phenotype made of epilepsy, facial dysmorphism, intestinal disorders, learning difficulties and tall stature.

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