Chromosomal imbalance letter

A de novo 7.9 Mb deletion in 22q13.2→qter in a boy with autistic features, epilepsy, developmental delay, atopic dermatitis and abnormal immunological findings

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Abstract

We report a 5-year-old boy with mental retardation, autistic features, epilepsy, developmental delay, atopic dermatitis and abnormal immunological findings, carrying a 7.9 Mb de novo deletion of chromosome 22q13.2→qter. This region contains the SHANK3, NCAPH2 and CYP2D6 genes which are associated with T-cell immune response. The present case provides evidence that 22q13 deletion syndrome may be associated with immune system dysfunction in addition to neuropsychiatric disorders.

1. Methods of detection

Karyotyping by GTG banding of the proband and the parents at 550 bands of resolution and high-resolution comparative genomic hybridization (HR-CGH) analysis of DNA by high-density fine-tiling oligonucleotide array (NimbleGen, Madison, WI, USA) were made. The fine-tiling array-CGH has a manufacture-specified resolution of 2 kb.

2. Chromosomal anomaly

Conventional karyotyping on 20 metaphase cells was performed and revealed a karyotype of 46,XY,del(22)(q13.2) (Fig. 1). Array-CGH analysis identified a deletion of 22q13.2→qter with the first clone locating at 41,675,914 bp on distal 22q13.2 and the last clone locating at 49,589,250 bp on 22q13.33 according to UCSC Genome Browser on Human Mar. 2006 Assembly (Fig. 2).

3. Method of confirmation

FISH experiments were performed using BAC clones on metaphase cells. The deletion was confirmed by using probes RP11-91O6 (22q11.21) and RP11-232E17 (22q13.33) (Fig. 3). Polymorphic DNA marker analysis was made to determine parental origin of the deletion.

4. Causative of the phenotype

The parental karyotypes were normal. Polymorphic DNA marker analysis revealed that the deletion was de novo and of paternal origin.

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5. Clinical description

The 5-year-old boy presented with mental retardation, autistic features, epilepsy, developmental delay and atopic dermatitis. He was born at term with a birth weight of 3497 g as the only child of healthy unrelated parents. The mother was 23 years of age and the father was 32 years of age at the time of his birth. There was no family history of autism, epilepsy and immunological or mental disorders. He was found to have hypotonia and gross motor delay postnatally. When examined at 1 year of age, the brain ultrasound showed lenticulostriatal vasculopathy, and magnetic resonance imaging (MRI) revealed delayed and immature myelination in the periventricular white matter of bilateral parietal lobes. The corpus callosum was normal (Fig. 4). When examined at 16 months of age, his body weight was 10.8 kg (50th centile), body length was 83 cm (75th–90th centile) and head circumference was 48.5 cm (75th–90th centile). He had right side auditory dysfunction. At 2 years of age, he underwent herniorrhaphy to treat inguinal hernia. Intermittent seizures had occurred since 3 years of age when electroencephalogram (EEG) revealed focal epileptogenicity with chaotic spikes and polyspikes arising from the left frontal region. Atopic dermatitis was noted at 4 years of age. Immunological examinations revealed a high IgE level of 448 IU/mL (normal: 10–180 IU/mL), a low CD8 level of 24.5% (normal: 30–40%), a low CD16 + CD56 level of 2.6% (normal: 5–15%), a low active T-cell level of 6.4% (normal: 8–15%), and normal levels of IgG, IgA, IgM, complement hemolysis 50%, CD3, CD4 and CD19. When examined at 5 years and 4 months of age, he was confirmed to have autistic features with speech disorders, language impairment, poor eye contact, stereotypic movements and mental retardation. His body weight was 19.7 kg (50th centile), and body height was 111.5 cm (50th centile). He manifested unstable gaits, ptosis of right eye, large dysplastic ears, dolichocephaly, a flat midface, a bulbous nose, a pointed chin, full cheeks, a wide nasal bridge, large hands and clinodactyly of fifth fingers (Fig. 5).

6. Discussion

We have described a patient with autistic features, developmental delay, epilepsy, language impairment, mental retardation, abnormal immunological findings and atopic dermatitis, carrying a 7.9 Mb de novo deletion of chromosome 22q13.2–qter. The patient manifested characteristic features of chromosome 22q13 deletion syndrome or Phelan-McDermid syndrome (OMIM

![Fig. 1. Karyotype of the proband. The arrow indicating the breakpoint.](image1)

![Fig. 2. Comparative genomic hybridization analysis of DNA by high-density fine-tiling oligonucleotide array showing a deletion of 22q13.2–qter.](image2)
which has clinical characteristics including large or unusual ears, relatively large hands, full brow, dolichocephaly, ptosis, full cheeks, a bulbous nose, a pointed chin, autistic behavior, neonatal hypotonia, global developmental delay, normal or accelerated growth and absent to severely delayed speech [9]. A comparison of the clinical features seen in this patient and the previously published report is presented on Table 1. Previous brain imaging study of the 22q13.3 deletion syndrome in childhood had shown normal or a thin or morphologically atypical corpus callosum on MRI [10]. The present case manifested immature myelination in the periventricular white matter of bilateral parietal lobes and focal epileptogenicity in the frontal region.

Tufano et al. [12] recently reported fulminant autoimmune hepatitis in a girl with 22q13 deletion syndrome and suggested a possible relationship between immune system dysfunction and 22q13 deletion syndrome. Our patient was also associated with abnormal immunological findings in addition to neuropsychiatric abnormalities. The present case had haploinsufficiency of the SHANK3, NCAPH2 and CYP2D6 genes. SHANK3 gene (OMIM 606230) encodes proline-rich synapse-associated protein 2, which is a structural protein of postsynaptic density. Haploinsufficiency of

Fig. 3. FISH using BAC clones RP11-91O6 (22q11.21) (red signal) and RP11-232E17 (22q13.33) (green signal) showing absence of the green signal on the aberrant chromosome 22.

Fig. 4. Axial T2-weighted images on magnetic resonance imaging scans showing delayed and immature myelination in the periventricular white matter of bilateral parietal lobes (arrows).

Fig. 5. Frontal view of the patient at age 5 years.
the SHANK3 gene has been shown to be a major causative factor in the neurological symptoms of chromosome 22q13 deletion syndrome [13]. Durand et al. [4] and Moessner et al. [8] reported that abnormal gene dosage of SHANK3 and mutations in the SHANK3 gene are associated with autism spectrum disorders. SHANK3 has also been detected in thymus in addition to cerebral cortex and cerebellum [11]. Redecker et al. [11] found SHANK as a constituent of the cell cortex of thymocytes and hypothesized that SHANK proteins serve as a platform for the coordination of membrane receptor-dependent signal transduction in immune cells. A lack of SHANK3 may result in a deficient immunological synapse and decreased natural thymic regulatory T-cells [11]. NCAPH2 gene (OMIM 611230) encodes a chromosome condensin II subunit, kleisin-β, which plays an essential role in mitotic chromosome assembly and segregation. Gosling et al. [5] identified nessy mutant mice with a mutation in the Ncap2 gene and a defect in T-lymphocyte development. The nessy mutant mice exhibited a decrease in circulation T-cell numbers, a loss of naïve CD8 cells, reduced CD4⁺ mutant mice exhibited a decrease in circulation T-cell numbers, Ncaph2-kleisin- were healthy, viable and fertile. Gosling et al. [5,6] concluded that kleisin-β is required for a normal T-cell immune response. CYP2D6 gene (OMIM 124030) encodes hepatic cytochrome P450, which is a drug-metabolizing enzyme. Cytochrome P450 2D6 has been shown to be a large antigen of liver-specific autoimmunity [12], and CYP2D6-specific CD8 T-cell immune response has been associated with autoimmune hepatitis type 2 [7].

In conclusion, the present case provides evidence that 22q13 deletion syndrome may be associated with immune system dysfunction, although the abnormal immunological findings in our patient can be coincidental. We suggest that further reports are required to prove the correlation between immunological imbalance and chromosome 22q13 deletion syndrome.

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References


Table 1

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Present case</th>
<th>Cusmano-Ozog et al. [3] (n = 107)</th>
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<tbody>
<tr>
<td>Normal/accelerated growth</td>
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<td>95</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>+</td>
<td>105</td>
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<tr>
<td>Delayed/absent speech</td>
<td>+</td>
<td>103</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td>92</td>
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<tr>
<td>Autistic behavior</td>
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<td>47</td>
</tr>
<tr>
<td>Seizures</td>
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<td>25</td>
</tr>
<tr>
<td>Epicanthal folds</td>
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<td>32</td>
</tr>
<tr>
<td>Dolichocephaly</td>
<td>+</td>
<td>32</td>
</tr>
<tr>
<td>Large/dysplastic ears</td>
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<td>58</td>
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<tr>
<td>Prolis</td>
<td>+</td>
<td>25</td>
</tr>
<tr>
<td>2–3 toe syndactyl</td>
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</tr>
<tr>
<td>Large hands</td>
<td>+</td>
<td>35</td>
</tr>
<tr>
<td>Abnormal nails</td>
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