CASE REPORT

Siblings With Deletion 22q13.3 and Trisomy 15q26 Inherited From a Maternally Balanced Translocation

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We describe two siblings with generalized hypotonia, expressive language delay, developmental delay, mild facial dysmorphism, and accelerated growth. In addition, the male sibling had testis dysgenesis. Cytogenetic evaluation revealed an unbalanced maternally inherited translocation t(15;22)(q26;q13.3) resulting in partial monosomy 22q and trisomy 15q. The combination of deletion 22q and duplication 15q has not been described previously.

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1. Introduction

Chromosome 22 is associated with several clinically relevant cytogenetic anomalies. Cat-eye syndrome is usually associated with a chromosome 22–derived bisatellited supernumerary chromosome.1 DiGeorge syndrome or velocardiofacial syndrome is associated with a deletion or microdeletion of chromosome 22q11.2,3 Although chromosome abnormalities involving band 22q11 have been well studied, little is known about chromosome abnormalities of 22q13, the most distal band. In the literature, only seven cases with cytogenetically visible and two cryptic terminal deletions of 22q13.3 have been described. These patients demonstrated a generalized developmental delay, abnormal or accelerated growth, hypotonia, severe delays in expressive speech, and mildly dysmorphic facial features.4,5

To date, only one case of trisomy 15q26.1 has been described in the literature. The 35-year-old and profoundly mentally retarded male demonstrated multiple dysmorphic stigmata, including large dysplastic ears, short neck, mandibular prognathism, large bulbous deviated nose, large thick lips, severe kyphoscoliosis, pectus excavatum, horseshoe kidney, and cryptorchidism.6

Here, we describe two siblings with an unbalanced maternally inherited translocation t(15;22)(q26.1;q13.3) resulting in partial monosomy 22q and partial trisomy 15q. This translocation has not been previously described, and

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some obvious differences in growth rate between the genders in these cases were observed.

2. Case Report

Case 1 (Proband 1) presented at 30 days of age for evaluation of hypotonia. He had a birth weight of 2750 g (10th percentile); birth length of 51 cm (50th percentile); head circumference (HC) of 34 cm (10th–25th percentile); and was born after 36 weeks of gestation to a 30-year-old gravida 2, para 2 woman. His Apgar scores were 9 at 1 minute and 10 at 5 minutes. During the newborn period, he was noted to have a down-slanting palpebral fissure, bulbous nasal bridge, long philtrum, retro- and micrognathia, crumpled ears, a persistent foramen ovale, and feeding difficulties. The patient received hernioplasty because of an incarcerated inguinal hernia and testis dysgenesis. He presented with sensorineural hearing loss and developmental delay, and was rolling at 13 months, sitting at 15 months, crawling at 21 months, pulled to a stand at 24 months, and walked alone at 30 months. On physical examination at 30 months of age, his length was 92 cm (25th–50th percentile), weight was 14 kg (50th percentile), and HC was 52 cm (>97th percentile). A brain magnetic resonance imaging showed a mild delay in myelination and a thin appearance of the corpus callosum. Bone age was mildly advanced to 3 years at 2 years and 7 months of age. The body height of this patient’s father was 160 cm and that of his mother was 158 cm.

Case 2 (Proband 2) is the elder sister of Case 1 and presented at 2 years and 9 months of age for evaluation of developmental delay. She was born weighing 3250 g (10th percentile); birth length of 51 cm (50th percentile); head circumference (HC) of 34 cm (10th–25th percentile); and was born after 36 weeks of gestation to a 30-year-old gravida 2, para 2 woman. His Apgar scores were 9 at 1 minute and 10 at 5 minutes. During the newborn period, he was noted to have a down-slanting palpebral fissure, bulbous nasal bridge, long philtrum, retro- and micrognathia, crumpled ears, a persistent foramen ovale, and feeding difficulties. The patient received hernioplasty because of an incarcerated inguinal hernia and testis dysgenesis. He presented with sensorineural hearing loss and developmental delay, and was rolling at 13 months, sitting at 15 months, crawling at 21 months, pulled to a stand at 24 months, and walked alone at 30 months. On physical examination at 30 months of age, his length was 92 cm (25th–50th percentile), weight was 14 kg (50th percentile), and HC was 52 cm (>97th percentile). A brain magnetic resonance imaging showed a mild delay in myelination and a thin appearance of the corpus callosum. Bone age was mildly advanced to 3 years at 2 years and 7 months of age. The body height of this patient’s father was 160 cm and that of his mother was 158 cm.

Although abnormal rearrangement of proximal chromosome 15q is commonly seen in cases of inv dup(15), trisomy of the distal region of chromosome 15q is rare. Duplication 15q syndrome was initially described by Fujimoto et al.7 Duplication of distal 15q has now been described in at least 28 additional cases.8 The breakpoints are all mapped between bands 15q21 and 15q23, except for two families with breakpoints at 15q25 and two families with breakpoints at 15q15. The clinical phenotype includes postnatal growth deficiency and severe to profound mental retardation. However, two patients with duplication of 15q25—qter presented with only mild retardation. Most of the duplication 15q cases result from unbalanced translocations, all but one of which were the offsprings of a balanced carrier parent. Despite the fact that the second chromosome involved in the reciprocal translocation has varied, the clinical phenotype is consistent. A summary and comparison of the anomalies of patients with isolated trisomy 15q and monosomy 22q, as well as our sibling cases, are listed in Table 1.

### Table 1 Summary of findings.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trisomy 15q26</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Deletion 22q13.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down-slanting palpebral fissure</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Bulbous nose</td>
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<tr>
<td>Broad nasal bridge</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Long philtrum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>High-arch palate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heart defects</td>
<td>±</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>Developmental delay/mental retardation</td>
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<td>Joint defects</td>
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<td>–</td>
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<td>Sensorineural hearing loss</td>
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<td>Slender fingers and toes</td>
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<td>Hypotonia</td>
<td>+</td>
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<td>+</td>
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<td>Macrocephaly</td>
<td>–</td>
<td>+</td>
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</tr>
</tbody>
</table>

+ = condition present; – = condition not present; ± = condition present or absent.
Patients with terminal 22q13 deletion syndrome share a number of clinical features, including severe expressive language delay, generalized hypotonia, developmental delay, and mild facial dysmorphism.4 Cytogenetically visible deletions of 22q13.3 are associated with the aforementioned common phenotypes and have the additional phenotype of abnormal or accelerated growth. Nesslinger et al.5 documented seven patients who displayed abnormal or accelerated growth, three having macrocephaly, one being greater than the 95th percentile in height and one having large hands and feet. This was also seen in some of the cases published previously.9–11 This is unusual because most deletion syndromes and most duplication syndromes described are noted for growth retardation.12 These previously reported cases were all younger than 5 years, and no significant difference between genders was noted. It is interesting that in our cases, the female patient had accelerated growth with macrocephaly and had been greater than the 97th percentile for weight and the 90th percentile for height since the age of 2 years, and her bone age was significantly advanced by the age of 3 years. On the other hand, the male patient had normal growth for HC, height, and weight, and his bone age was only mildly advanced by the age of 2 years and 6 months. Because previous cases are rare and little is known about gender differences, differences in phenotype may become clearer over time. Overall, most patients with 22q13.3 deletion syndrome have a pure 22q deletion, either terminal or interstitial, with about 25% having deletions resulting from an unbalanced translocation or other structural rearrangement.13

SHANK 3 is the best candidate gene that might be responsible for the neurological deficits, developmental delay, and absence of speech seen in cases of 22q13.3 syndrome, because it is located in the critical region, encodes a structural protein located in the postsynaptic density, and is involved in spine maintenance of hippocampal neurons.14,15 Therefore, it may play a role in neonatal hypotonia, delayed speech, and global developmental delay, but may or may not be involved in the observed accelerated growth.

In summary, we have described two unbalanced sibling patients with monosomy 22q (deletion 22q13.3 syndrome) and trisomy 15q (distal 15q trisomy) inherited from their mother who has a balanced translocation. Over the 8 years of follow-up, they demonstrated a shared combined phenotype resulting from the unbalanced translocation but displayed a difference in accelerated growth rates.

References