Coarctation of the aorta and mild developmental delay in a child with a *de novo* deletion of 15(q21.2q22.1)

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Abstract

Background
Deletion of 15q2 appears to be a rare chromosomal anomaly. To date, there have been eight reports describing nine individuals with 15q2 deletion. Most of these individuals have moderate to severe mental retardation. We report a child with a de novo deletion of 15q21.2q22.1, and coarctation of the aorta, with mild developmental delay.

Methods
We used high-resolution chromosome 15-specific BAC array and employed Comparative Genomic Hybridization (CGH) to map the chromosomal breakpoints in this patient.

Results and conclusions
This is the first description of mapping of 15q2 breakpoints using the genomic array-based CGH. The report also expands the spectrum of clinical phenotype of this chromosomal abnormality and shows association of mild developmental delay with deletion of 15q21.2q22.1.
Background

Distal interstitial deletion of chromosome 15q is rare. To date, there have been only nine patients reported, six with distal deletion involving 15q2 [1-5] and three with larger deletion encompassing 15q15-2 [6-8]. All patients described have moderate to severe mental retardation. The four patients described by Yip et al.[1], Fryns et al.[2], Martin et al.[3] and Liehr et al. [4] have comparable cytogenetic breakpoints and share common features, including beaked nose, thin upper lip, and mental retardation. Congenital heart disease was described in one patient with 15q21q24 deletion [5] and two patients with larger interstitial deletion of chromosome 15q15q2 [6, 7]. Here, we describe a child with deletion of 15q21.2q22.1 and coarctation of the aorta, with mild developmental delay and minimal, if any dysmorphic features. We also refine the extent of the deletion by using chromosome 15 specific BAC array, and exclude the deletion of α-tropomyosin gene as the underlying cause of the cardiac phenotype in this patient.

Case Report

The proband was a 36-week product of a twin pregnancy, born to a 39-year old female. Pregnancy was achieved by in vitro fertilization secondary to mother’s history of endometriosis. His birth weight was 2.44 kg, (25th percentile), length was 47 cm (10th percentile), and head circumference was 34.5 cm (75th percentile). A cardiac murmur was noted soon after birth. An echocardiogram revealed severe juxtaductal aortic coarctation with near aortic arch interruption. He had a moderately dilated main pulmonary artery and branch arteries, severe septal hypertrophy, moderately depressed biventricular
systolic function, biventricular hypertrophy, and bicommissural aortic valve. He was also noted to have high arched palate, micrognathia, and ears with thickened helices. He had fair suck, normal muscle tone and strength. Renal ultrasound showed decreased corticomedullary differentiation, bifid right renal pelvis and moderate peliectasis. Head ultrasound showed partial agenesis of corpus callosum. He underwent surgery for juxtaductal aortic coarctation with end-to-end anastomosis and PDA ligation.

The child was seen again at 20 months (Figure 1), having been enrolled in infant stimulation program for 17 months. He started walking independently at 16 months. He continues to thrive well and is at the 80th percentile for weight and height. His renal ultrasound was repeated and was subsequently normal. Although developing well, he had a brief seizure episode at 16 months of age. Since then, he has been treated with Valproic acid and the seizures have not recurred. MRI scan of the brain following the seizure episode showed diffuse delay in myelination and partial agenesis of corpus callosum. EEG showed generalized paroxysmal activity with high voltage slow waves and some short spikes.

Methods

Cytogenetics, Comparative genomic hybridization and FISH analyses

Giemsa-banded chromosome analysis was performed according to standard procedures on peripheral blood lymphocytes. Twenty metaphases were examined at the 550-band level and the interstitial deletion of 15q was seen in all the cells, with loss of bands
15q21.1-q22.1. Further delineation of the size and boundaries of the deletion was carried out by genomic array-based comparative genomic hybridization (CGH) and FISH. For CGH, we utilized a high-resolution chromosome 15- specific BAC array developed in our laboratory that included 106 BAC clones across 15q providing a genome scanning resolution of greater than one clone per megabase. A single normal male DNA was used as reference control. Standard protocols for DNA preparation, labeling and hybridization were followed as described previously [9]. BAC clones chosen for FISH analysis were those that mapped within, proximal and distal to the deletion boundaries predicted by CGH. These included RP11-69G7 (GenBank accession number AC087612), RP11-23N2 (GenBank accession number AC025917), RP11-430B1 (GenBank accession number AC010674), and RP11-756K9 (GenBank accession number AC023890). FISH analyses were carried out as previously described [10]. Ten metaphase preparations were scored for each hybridization.
Results

G-band analysis of a peripheral blood sample revealed an abnormal male karyotype: 46,XY,del(15)(q21.2q22.1). Parental chromosomes were normal. Deletion at 22q11 (DiGeorge syndrome critical region) was excluded by FISH. Array CGH revealed an interstitial deletion with loss of 5 non-overlapping clones across 15q21.1-q22.2. The proximal boundary was telomeric to clone RP11 353B9 and distal boundary was centromeric to RP11 2312A23. This included the interval between 15q21.1 to 15q22.2 and spanned a genomic segment of about 10.25 Mb (Figure 2). FISH analysis using clones within and flanking the boundary confirmed the size and extent of the deletion (Figure 3). Each of RP11 430B1, RP11 756K9 and RP11 23N2 was deleted from one copy of the patient’s chromosome 15. FISH with RP11 69G7 that contains TPM1, the α-tropomyosin gene showed 2 hybridization signals, confirming the presence of both copies of the gene in this patient.

Discussion

Deletion of 15q2 is an infrequently described chromosomal abnormality. Of the nine reported cases, many have common features of beaked nose, small alae nasi, thin upper lip, truncal obesity, growth retardation, hypotonia and moderate to severe mental retardation [1, 2, 3]. In contrast, our patient has no significant dysmorphic features, has coarctation of the aorta, partial agenesis of corpus callosum, normal growth parameters and mild developmental delay. Two patients with larger interstitial deletion of 15q15q2 have also been described with craniosynostosis [6, 8]. Neurological problems including
hypotonia and seizures are also seen in many individuals with the deletion of this region of chromosome 15. Congenital heart defect with septal hypertrophy and dilatation of the aorta and pulmonary artery was described in one patient with the deletion of 15q21-15q24 [5], who died at 8 months of age. Another patient in the same report had deletion of 15q22-15q25 and frequent cyanosis of the extremities with no heart murmur, and died at 2 years of age with severe respiratory illness. Four other patients with comparable interstitial deletion had no evidence of congenital heart disease. Two additional cases with larger interstitial deletion of chromosome15q15-2 have been described with atrial and ventricular septal defects and Tetralogy of Fallot with septal hypertrophy, respectively [6, 7] [Table]. We explored probable hemizygous deletion of *TPM1*, the α-tropomyosin gene on 15q22.2 in our patient. Heterozygous mutation in *TPM1*, accounts for <5% cases of familial hypertrophic cardiomyopathy [11]. The phenotype ranges from a benign course to severe hypertrophy with progression to dilated cardiomyopathy [11, 12]. The possibility of *TPM1* deletion causing the cardiac phenotype of this patient was investigated by FISH with RP11 69G7 BAC, encompassing the α-tropomyosin gene. The normal FISH analysis at this locus makes *TPM1* gene an unlikely candidate for the left ventricular outflow tract obstruction observed in this patient.

The array CGH has refined the interstitial deletion in our patient to15q21.1-q22.2. This analysis validates hemizygous deletion of about 30 genes within this interval. Of these, few are known to be expressed in the heart, including *ARPP-19, RAB27A*, and *ADAM10*. Microarray-based Comparative genomic hybridization is a powerful method to detect and analyze genomic imbalances. Array CGH using large insert clones is a very useful tool
for detecting microdeletions or duplications that are well below the level of detection on high resolution banded karyotype analysis. Although cryptic cytogenetic abnormalities can be detected by fluorescent in situ hybridization (FISH), FISH is not easily multiplexed in contrast to CGH microarrays which can be used to assess hundreds or even thousands of loci in a single hybridization. We have used chromosome 15 specific microarray to define the 15q breakpoints in this case, thus providing a better opportunity for genotype/phenotype correlations in other similarly affected individuals.

Competing interest

The authors declare that they have no competing interests.

Authors’ contributions

SRL carried out the clinical evaluation, the FISH analyses and drafted the manuscript. TS performed the CGH analysis and MES assisted in the FISH analyses. BAB participated in the clinical assessment of the patient, conceived the study design and coordinated the study progress. All authors read and approved the final manuscript.

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References


Figure 1
Proband at 20 months of age.

Figure 2
Chromosome 15 BAC Comparative genomic hybridization (CGH) analysis and partial karyotype of the case.

(A) CGH using chromosome 15 BAC microarray, shows deletion of 5 overlapping clones on 15q21.1q22.2; additionally clone 23N2 was shown to be deleted by FISH. The clones listed in blue are deleted; the adjacent clones listed in black are not deleted. (B) Partial karyotype, showing normal and derivative chromosome 15, with an apparent interstitial deletion of 15q21.2q22.1.

Figure 3
Fluorescence in situ hybridization (FISH) of 15q21.1q22.2 region using BAC probes.

(A) Hybridization of clones 231A23 (green) and 105D1 (red) showing deletion of one copy of 105D1. (B) FISH showing deletion of one copy of RP11 23N2 when hybridized against telomeric control probe. (C) Hybridization of 50C13 (green) with 485O10 (red) showing deletion of one copy of 50C13. (D) FISH with RP11 69G7 (red), encompassing α-tropomyosin gene, shows intact alleles on both chromosomes.
<table>
<thead>
<tr>
<th>References</th>
<th>Karyotype</th>
<th>Developmental delay</th>
<th>Failure to thrive</th>
<th>Hypoplastic alae nasi</th>
<th>Micrognathia</th>
<th>Thin upper lip</th>
<th>High arched palate</th>
<th>Eyes</th>
<th>Ears</th>
<th>Heart</th>
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<th>Brain imaging</th>
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<td>46,XY,del(15)(q21.2q22.1)</td>
<td>Mild</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Strabismus</td>
<td>Thickened helices</td>
<td>CoA</td>
<td>Hydronephrosis</td>
<td>Single episode of seizure</td>
<td>Hypotonia</td>
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<td>Martin [3]</td>
<td>46,XY,del(15)(q21.2q22.1)</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>NR</td>
<td>Strabismus</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Normal</td>
<td>Hypotonia, normal EEG</td>
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<td>Severe</td>
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<td>+</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>Hypopigmented iridis, microcornea</td>
<td>Low set, posteriorly rotated</td>
<td>NR</td>
<td>Genital hypoplasia</td>
<td>Spastic paraplegia, microcephaly</td>
<td>Hypotonia, seizures, abnormal EEG</td>
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<td>Formiga [5]</td>
<td>46,XX,del(15)(q22q25) (Case 1)</td>
<td>Severe</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Microphthalmia, hypopigmented iridis</td>
<td>Large with thickened helices</td>
<td>Nomal</td>
<td>Normal</td>
<td>Hypertonia, microcephaly</td>
<td>Hypotonia, abnormal EEG</td>
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<td>46,XX,del(15)(q21q24) (Case 2)</td>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Microphthalmia, coloboma of iris, hypopigmented iridis</td>
<td>Large with poorly defined helices</td>
<td>Septal hypertrophy</td>
<td>NR</td>
<td></td>
<td>Cortical atrophy</td>
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<tr>
<td>Fukushima [8]</td>
<td>46,XY,del(15)(q15q22.1)</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Low set and large left ear hypoplasia</td>
<td>ASD VSD TOF, septal hypertrophy</td>
<td>NR</td>
<td>Cryptorchidism</td>
<td>Hypotonia</td>
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<td>Koivisto [6]</td>
<td>46,XY,del(15)(q15.2q21.2)</td>
<td>Severe</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
<td>Ptosis</td>
<td>Left ear hypoplasia</td>
<td>ASD VSD TOF, septal hypertrophy</td>
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<tr>
<td>Shur [7]</td>
<td>46,XX,del(15)(q15q22.1)</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
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<td>Bilateral hydronephrosis</td>
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NR= not reported, CoA=coarctation of the aorta, ASD=atrial septal defect, VSD=ventricular septal defect, TOF=Tetralogy of Fallot, ACC=agenesis of corpus callosum, DLV=dilated lateral ventricles, HCC=hypoplastic corpus callosum
Additional files provided with this submission:

Additional file 1: cosent form final.tif : 176Kb
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