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CASE REPORT

A case report of *de novo* 11q triplication, duplication, and segmental area of absence of heterozygosity in an infant with dysmorphic features, failure to thrive, and developmental delay

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ABSTRACT

Background: With recent advances in array comparative genomic hybridization (aCGH) methods, several, previously unrecognized pathogenic copy number variants have been recognized. Intrachromosomal triplications are rare and have been reported in few genomic regions. In this report, we describe an infant with complex chromosomal rearrangement involving the long arm of chromosome 11 with concomitant triplication, duplication, and segmental area of absence of heterozygosity (AOH).

Case Presentation: We report an infant who presented dysmorphic features, severe failure to thrive, developmental delay, dysgenesis of the corpus callosum, and intestinal malrotation. aCGH showed 19,930 megabases (Mb) triplication at 11q13.3q14.3, 346 kilobases (kb) duplication at 11q14.3, and an area of AOH at 11q14.3-qter.

Conclusion: The occurrence of triplication along with AOH [most likely as a result of segmental uniparental isodisomy (UPD)] is a rare, complex genomic rearrangement. It is suggested that these complex genomic rearrangements coupled with segmental UPD arise as a result of one-ended DNA break repair coupled with microhomology-mediated break-induced replication.

Keywords: Tetrasomy, triplication, dysmorphic features.

Background

With recent advances in array comparative genomic hybridization (aCGH) methods, several, previously unrecognized pathogenic copy number variants have been recognized in individuals presenting with variable manifestations (1). The number of identified microdeletion and microduplication syndromes increased significantly over the past decade (2). While microdeletion and microduplication syndromes are relatively common, intrachromosomal triplications are rare and have been reported in few genomic regions, including 1q42.12-qter (3), 5q33.3q34 (4), 7q36.1q36.2 (5), 9q21.1q21.33 (6), 16p11.2 (7), and Xp22.31 (8). Two previous reports of triplication on the long arm of chromosome 11 have be published (9,10). Kekis et al. (9) described a female child with dysmorphic features and mild speech delay who was found to have tetrasomy of 11q14.1–q22.1 due to an intrachromosomal triplication. Xiao et al. (10) also reported a *de novo* triplication at 11q13.4–q14.3 in a child who presented with developmental delay, facial dysmorphism, microcephaly, and brain malformations (absence of cerebellar vermis and partial absence of corpus callosum). This subject also had uniparental isodisomy (UPD) for 11q14.3-qter.

In this report, we describe an infant with complex chromosomal rearrangement involving the long arm of

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chromosome 11 with~ 20 megabases (Mb) triplication at 11q13.3q14.3, 346 kilobases (kb) duplication at 11q14.3, and an area of absence of heterozygosity (AOH) at 11q14.3-qter of 45 Mb.

Case Presentation

The proband is a 7-month-old girl who was born to healthy non-consanguineous parents. Pregnancy was uncomplicated apart from intrauterine growth restriction (IUGR) with birth weight of 1.8 kilograms (kg) (<third centile), whereas birth length and head circumference are not available. Family history is not significant with previous two healthy children. The proband had delayed passage of meconium and hospitalized in the neonatal intensive care unit (NICU) for 1 month due to abdominal distention and poor feeding requiring orogastric tube feeding.

Following discharge from NICU, she continued to have abdominal distention and poor feeding. She was evaluated at our facility for the first time at 5 months of age. By that time, she was cachectic with all growth parameters below the third centile (weight 2.8 kg, length 50 centimeters (cm), and head circumference of 35 cm). On the exam, she was dysmorphic with frontal bossing, hypertelorism, depressed nasal bridge, low-set, malformed ears, micrognathia, and rocker bottom feet. She had significant abdominal distention. Developmentally, she was globally delayed in all domains. She was not rolling over, not supporting her neck, and not vocalizing. She only had a social smile at that time. Brain magnetic resonance imaging (MRI) revealed corpus callosum dysgenesis (Figure 1). Workup for abdominal distention revealed normal-caliber proximal small bowel with significantly distended distal small bowel loops with no evidence of complete bowel obstruction suggesting incomplete small-bowel obstruction Subsequently, she had laparotomy and was found to have intestinal malrotation that was repaired with Ladd procedure. The subject was also evaluated by immunology because of transient lymphopenia Other evaluations included normal echocardiography and normal abdominal ultrasound.

Last evaluation at 7 months of age was significant for persistent failure to thrive (weight 3.6 kg, length 56 cm, head circumference 37 cm; all below third centile). Developmentally, she started to roll over and coo only.

Chromosomes karyotype analysis performed in-house and showed 46,XX,dup(11)(q13.3q23.3); a female karyotype with interstitial duplication of the segment on

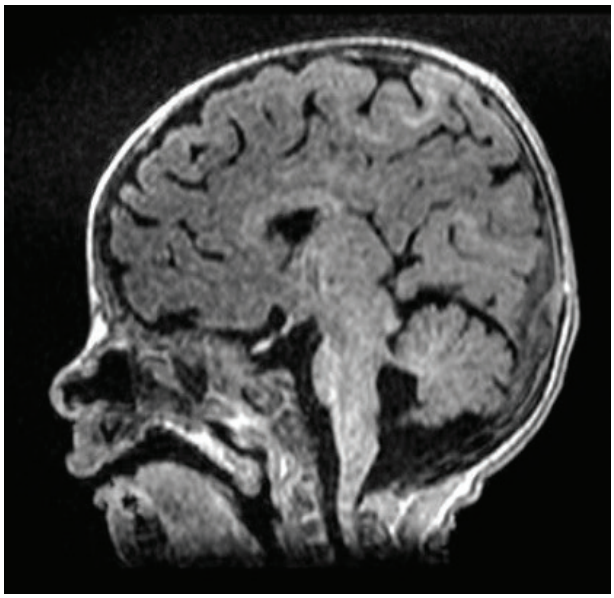

Figure 1. *Sagittal T1 weighted MRI image shows dysplastic corpus callosum.*

chromosome 11 long arm from band 11q13.3 to possible band 11q23.3, at banding resolution between 450 and 525. Array CGH, using the Cytoscan HD platform (Applied Biosystems), was performed revealing a 19,930 Mb triplication at 11q13.3q14.3 (69,542,815–89,472,531, hg19), 346 kb duplication at 11q14.3 (89,472,590–89,818, AOH (most likely representing UPD) at 11q14.3-qter of 45 Mb (Figure 2). Testing both parents ruled out balanced chromosomal rearrangements in the same region.

Discussion and Conclusions

In this report, we described an infant with an apparently *de novo* complex chromosomal rearrangement involving the long arm of chromosome 11 with concomitant triplication, duplication, and segmental area of AOH most likely representing UPD. The infant presented with dysmorphic features, severe failure to thrive (FTT), developmental delay, dysgenesis of the corpus callosum, and intestinal malrotation.

Partial trisomy 11q, caused by interstitial duplications, is a relatively rare copy number variant with variable manifestations reported including dysmorphic features and developmental delay/intellectual disability (11–14). Partial tetrasomy 11q, caused by triplications, is even much rarer and we are aware of only two previously

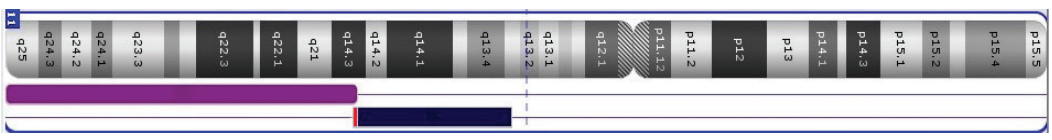

Figure 2. *Ideogram of chromosome 11 showing the areas of triplication (blue bar), duplication (red bar), and AOH (purple bar).*

reported cases (Table 1) (9,10). Kekis et al. (9) described a female child with dysmorphic features and mild speech delay who had tetrasomy of 11q14.1–q22.1 due to an intrachromosomal triplication. Xiao et al. (10) also reported a *de novo* triplication at 11q13.4–q14.3 in a child who presented with developmental delay, facial dysmorphism, microcephaly, and brain malformations (absence of cerebellar vermis and partial absence of corpus callosum). This subject also had UPD for 11q14. 3-qter.The triplication size and the breakpoints in the case reported here (19.9 Mb; chr11:69,542,815–89,472,513, hg19) are very close to the case reported by Xiao et al. (10) (18.7Mb; chr11:71,002,347–89,725,167, hg19). There is also a similar area of AOH at 11q14.3qter. In the case we are presenting here, there is an additional small duplicated area at 11q14.3. This case share similar clinical features with the case reported by Xiao et al. (10) including dysmorphic facial features (hypertelorism, depressed nasal bridge, and micrognathia), developmental delay, and abnormalities of the corpus callosum. This case has additional findings of intestinal malrotation and lymphopenia. The triplication reported by Kekis et al. (9) is more distally located compared to the case we report here and the one reported by Xiao et al. (10) and it lacks the area of AOH. The location of the triplication and the lack of AOH may count for the less severe presentation in the case reported by Kekis et al. (9). There are183 genes located in the triplicated region in the case we reported here. This large number of genes, in addition to the rarity of cases and the nonspecific phenotype associated with them, make it difficult to pinpoint specific genes as the culprit for the phenotype.

The occurrence of triplication along with segmental UPD is a rare, complex genomic rearrangement reported in several cases (3,4,6,10,15). It is suggested that these complex genomic rearrangements coupled with segmental UPD arise as a result of one-ended DNA break repair coupled with microhomology-mediated break-induced replication (MMBIR) (3,6,15). Kohmoto et al. (15) reported a case with interstitial duplication at 1q42. 12–q42.2 and triplication at 1q42.2–q43 followed by UPD at1q43-qter. Detailed mapping of breakpoint junctions suggested that the complex genomic rearrangement found in association with UPD was triplication with flanking duplications. Microhomology was observed in both junctions between the triplicated region and the flanking duplicated regions, supporting evidence for replication-based mechanisms, such as MMBIR, in chromosomal disorders.

In summary, here, we present the second case of partial tertarsomy 11q along with segmental AOH (most likely due to UPD). Our case share similar features to the previously reported case with dysmorphic features, developmental delay, and corpus callosum abnormalities.

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Table 1. *Summary of our case and two additional cases reported with partial 11q tetrasomy.*

	This case	Kekis et al.	Xiao et al.
Triplicated segment*	19.93 Mb at 11q13.3q14.3 (69,542,815–89,472,531)	22.37 Mb at 11q14.1q22.1 (77,671,586–100,181,135)	18.7 Mb at 11q13.4q14.3 (71,002,347–89,725,167)
AOH	11q14.3-qter	No UPD	45 Mb at11q14.3-qter (89,843,477–134,930,689)
Dysmorphic features	frontal bossing, hypertelorism, depressed nasal bridge, low-set, malformed ears, micrognathia, and rocker bottom feet	Widely spaced nipples, telecanthus, flat facial profile, deep spaced eyes, prognathism	Sparse hair and eye brows, round face, hypertelorism, depressed nasal bridge, thick upper and lower lip, irregular teeth, retrognathia.
Growth	Severe FTT	IUGR, short stature	Microcephaly
Developmental delay	+	+	+
Brain malformations	corpus callosum dysgenesis		Absence of the cerebellar vermis and partial absence of corpus callosum
Others	• Additional area of duplication (346 kb at 11q14.3) • Intestinal malrotation • Lymphopenia • Normal echocardiogram and renal ultrasound	• Multiple allergic complaints and loose stools • Intermittent exotropia • Normal renal ultrasound	• Normal echocardiogram

*Break points are according to hg19.
AOH: absence of heterozygosity; FTT: failure to thrive, IUGR: intrauterine growth restriction.

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Declaration of conflicting interests
PR is an employee of CGC genetics. The authors declare that there are no conflicts of interest in the subject matter or materials discussed in this manuscript.

Ethical approval
The study was approved by the research center at King Fahad medical city (IRB registration number H-01-R-012).

Consent for publication
Informed consent was obtained for publication.

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