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ONLINE CASE REPORT

De Novo Duplication of 7p21.1p22.2 in a Child with Autism Spectrum Disorder and Craniofacial Dysmorphism

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وجود طفرة جينية للتضاعف الصبغي في 7p21.1p22.2 في طفل لديه اضطراب طيف التوحد واختلافات خلقية

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ABSTRACT: The duplication of the short arm of chromosome 7 as *de novo* is extremely rare. The phenotype spectrum varies depending on the region of duplication. We report a case of *de novo* duplication of chromosomal region 7p21.1p22.2 in a three-year-old male child with autism who presented to the Sultan Qaboos University Hospital in Muscat, Oman, in January 2012. The patient was diagnosed with craniofacial dysmorphism, global developmental delay, hypotonia and bilateral cryptorchidism. The duplication was detected by conventional G-banded karyotype analysis/fluorescence *in situ* hybridisation and confirmed by array comparative genomic hybridisation. To the best of the authors' knowledge, this is the first report of chromosomal region 7p21.1 involvement in an autistic patient showing features of a 7p duplication phenotype. Identifying genes in the duplicated region using molecular techniques is recommended to promote characterisation of the phenotype and associated condition. It may also reveal the possible role of these genes in autism spectrum disorder.

Keywords: Autism Spectrum Disorder; Array Comparative Genomic Hybridization; Craniofacial Abnormalities; Chromosome 7; Duplication 7p; Case Report; Oman.

الملخص: يعد التضاعف الصبغي للذراع الأقصر لكروموسوم 7 حالة نادرة جداً. ويعتمد النمط الظاهري للحالة على المنطقة المتضاعفة للكروموسوم. ونعرض في هذا البحث وجود تضاعف صبغي في الذراع الأقصر للكروموسوم 7 في المنطقة 7p21.1p22.2 في طفل قد تم تشخيصه باضطراب طيف التوحد في مستشفى جامعة السلطان قابوس في يناير 2012م. ويشمل النمط الظاهري للحالة الآتي: اختلافات خلقية في الوجه، وتأخر نمائي عام، وارتخاء في العضلات واختلاف خلقي في الخصيتين. وتم تشخيص هذا الاختلاف الصبغي عن طريق دراسة النمط الكروموسومي وتم تأكيده بتقنية الميكرو أريه. ومبلغ علمنا تعتبر هذه الحالة هي الأولى التي تؤشر إلى وجود ارتباط بين الاختلافات الصبغية في 7p21.1 وتشخيص اضطراب طيف التوحد. نستنتج من هذه الحالة وجود جينات في المنطقة الصبغية 7p مرتبطة باضطراب طيف التوحد و تحث على عمل دراسة دقيقة للجينات الموجودة في هذه المنطقة الصبغية ودراسة مدى أهميتها لفهم الأسباب الجينية لمرض اضطراب طيف التوحد.

مفتاح الكلمات: اضطراب طيف التوحد؛ ميكرو اري؛ اختلافات خلقية في الوجه؛ كروموسوم 7؛ التضاعف الصبغي في 7p؛ تقرير الحالة؛ عمان.

Although there are approximately 60 published reports on chromosome 7p duplication, the *de novo* duplication of the short arm of chromosome 7—without involving any rearrangements with other chromosomes in the form of unbalanced translocations—is extremely rare.[1–3] The size of the duplicated segment varies from patient to patient.[2,3] The phenotype spectrum also varies accordingly, but its association with a clinical manifestation of autism spectrum disorder (ASD) is rarely documented. Wolpert *et al.* reported a duplication of the 7p11.2p14 region in a 25-year-old male patient with autism.[4] The current report presents an autistic child with unique features and duplication of chromosome 7p21.1p22.2. To the best of the authors' knowledge, this is the first report of a patient with 7p duplication associated with ASD involving region 7p21.1.

Case Report

A three-year-old male child presented to the Sultan Qaboos University Hospital in Muscat, Oman, in January 2012. He was diagnosed with global developmental delay, hypotonia and abnormal repetitive social interactions. He was the first child born to a healthy Omani consanguineous couple (first cousins); the mother was 24 years old and the father was 25 years old. The child had a birth weight of 2.11 kg.

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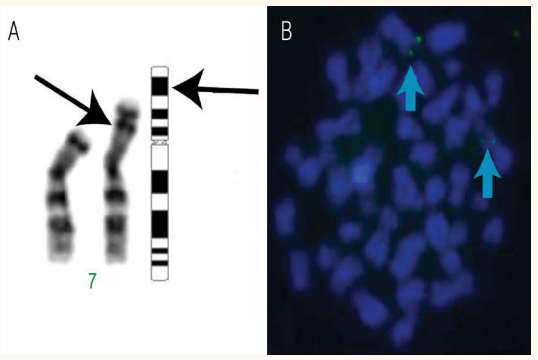

Figure 1A & B: A: Partial karyotype showing the G-banded pairs of chromosome 7 and the duplicated segment 7p21-22 (arrows) in an autistic child with craniofacial dysmorphism. **B:** Fluorescence *in situ* hybridisation showing telomeres (arrows) on the 7p region.

Upon examination, the patient would not speak spontaneously and rarely vocalised directly to either the examiners or his parents. Non-verbal communications (including gestures, smiling, pointing or using other body parts) and the range of distinct facial expressions were very limited. Methods of communication were not coordinated with eye contact and the child showed limited enjoyment during interactions. The patient did not request objects and was not interested in showing objects to others. He showed no interest in symbolic/pretend play but demonstrated unusual sensory interest in materials (e.g. licking objects). The patient showed stereotypical motor repetitive behaviour (repetitive hand flicking) and persistent odd hand positioning in the form of bilateral wrist flexion. No disruptive, aggressive or self-injurious behaviours were noted. His communication and reciprocal social interaction scores fell within the range of ASD. Based on the above clinical and multidisciplinary evaluations, the patient was diagnosed with ASD.

The patient had delayed developmental milestones, demonstrating head control at the age of 12 months old, sitting with support by 14 months old, standing with support by two years old and walking by the time he was three years old. His hearing test results were normal, although an eye examination showed hypermetropic astigmatism. During a follow-up ophthalmological appointment, a slightly enlarged cup-to-disc ratio was noticed, indicating glaucoma.

Features of craniofacial dysmorphism were observed, including a high forehead with a prominent metopic ridge; brachycephalic and plagiocephalic closed anterior fontanelle; a low v-shaped posterior hairline; well-arched thin eyebrows; hypoplastic *alae naris*; narrow anteverted nares; a bulbous nasal tip; ears with prominent *crus* and overfolded helices; a

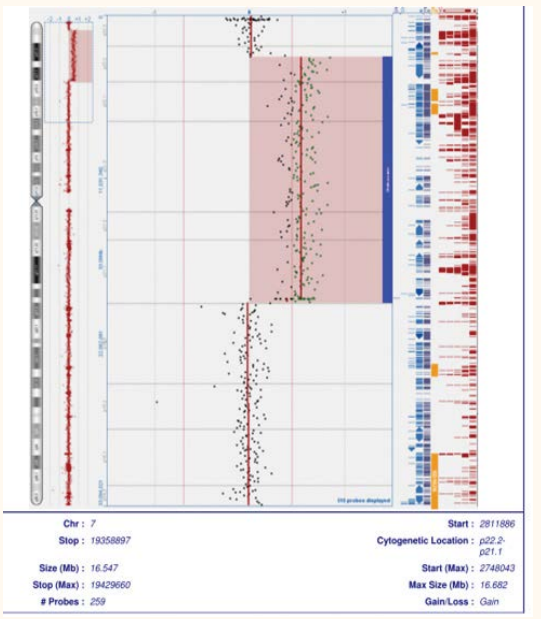

Figure 2: Array comparative genomic hybridisation of an autistic child with craniofacial dysmorphism showing a duplication interval of ~16.5 million bases within the breakpoints at chromosome 7p22.2 and 7p21.

short *philtrum*; a prominent lower lip; micrognathia; and bilateral cryptorchidism. The patient had undergone an operation for the cryptorchidism. The coronal sutures were open but appeared narrow. The height and weight of the patient were both at the 50–75th centile, with head circumference at the 25th centile. Magnetic resonance imaging of the brain, echocardiography and abdominal ultrasonography findings were unremarkable. The parents refused permission for photographs of the child to be published.

Peripheral blood chromosomal G-band karyotyping analysis was performed with 400–550 band resolution, which showed a 46, XY, dir dup(7) (p21p22) karyotype [Figure 1A]. Fluorescence *in situ* hybridisation using a subtelomeric probe (Cytocell Ltd., Cambridge, UK) showed the presence of telomeres on both short arms of chromosome 7 [Figure 1B]. The parental karyotypes were normal, indicating the 7q duplication in the child to be a *de novo* occurrence.

Array-based comparative genomic hybridisation (aCGH) using 8x60k oligoarray platforms (Oxford Gene Technology, Begbroke, Oxfordshire, UK) confirmed the presence of a cytogenetically visible duplication within the short arm of one chromosome 7. Analysis using CytoSure™ Interpret software, Version 3.4.8 (Oxford Gene Technology), showed that this duplication was ~16.5 million bases (Mb) in size. The breakpoints were also refined. The duplication involving the region 7p22.2 to 7p21.1 thus showed arr 7p22.2p21.1(2,811,886-19,358,897)x3, with a minimum size of ~16.5 Mb and a maximum size of ~16.7 Mb

Table 1: Comparative analysis of cases of *de novo* 7p duplication in the literature

Characteristic/clinical finding	Author and year of case report				
	Wolpert *et al.*[4] 2001	Papadopoulou *et al.*[1] 2006	Zahed *et al.*[11] 2007	Chui *et al.*[10] 2011	Present case
Region	7p11.2p14.1	7p13p22.1	7p22.1p22.3	7p22.1	7p21.1p22.2
Size	N/A	N/A	5 Mb	1.7 Mb	16.5 Mb
Confirmatory test	WCP FISH	Multicolour FISH	Array CGH	Array CGH	Array CGH
Origin	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Karyotype	46.XY,?dup(7) (p14.1p11.2)	46,XX,dup(7).ish.dup(7) (p-ter>p13::p22.1>qter)	46,XY,add(7) (p22).arr cgh 7p22.3p22.1x3	46,XY.ish. subtle (41x2) .arr7p22.1x3	46,XY,dup(7) (p21p22). arr7p22.2p21.2x3
Patient age/gender	25 years/male	9 months/female	1.6 years/male	2.4 years/male	3 years/male
Nationality or ethnicity	Caucasian	Greek	Lebanese	Peruvian	Omani
Dysmorphism	No	Yes	Yes	Yes	Yes
Developmental delay	No	Yes	N/A	Yes	Yes
Consanguineous parents	N/A	No	Yes	No	Yes
Hypotonia	N/A	No	Yes	No	Yes
High forehead	Yes	N/A	N/A	Yes	Yes
Low nasal bridge	Yes	N/A	N/A	Yes	Yes
Low-set ears	N/A	N/A	Yes	Yes	No
Cardiovascular abnormalities	Yes	N/A	N/A	Yes	No
Abnormal palmar creases	No	N/A	N/A	Yes	No
Skeletal anomalies	No	N/A	N/A	No	No
Autism spectrum disorder	Yes	No	No	No	Yes
Cryptorchidism	No	No	Bilateral	Yes	Bilateral
Ocular hypertelorism	No	N/A	No	Yes	Yes

N/A = not available; WCP = whole chromosome painting; FISH = fluorescence in situ hybridisation; CGH = comparative genomic hybridisation.

[Figure 2]. This analysis was done commercially. No other imbalances were detected. The duplication interval contained 67 annotated genes, of which six had morbid entries in the Online Mendelian Inheritance in Man® (OMIM) catalogue. However, the genes in this region were not directly disrupted by the breakpoints.

Discussion

Duplication of 7p has been reported previously and the region/size varies among patients.[1–13] Common features include craniofacial anomalies, a large fontanelle, dysmorphism and psychomotor delay, with hypotonia being the most common complication observed.[1–8,10,11,13] In their review of the literature, Cai *et al.* found that 50% of 7p duplications were the result of balanced reciprocal translocation carriers.[3] Reish *et al.* suggested that these could be an entire duplication of 7p in a few cases or smaller terminal 7p segments in others.[2] Arens *et al.* reported complete 7p trisomy (without the involvement of any other chromosomes) in two patients.[6] Similar diagnoses have been made in five other patients.[4,7] Many phenotypic features common to 7p duplication syndrome were present in the patient in the current report [Table1];[1,4,10,11] these have also been described in earlier case reports.[3,6,8] Notably, the patient described in the current report did not have any cardiovascular abnormalities and thus had a better prognosis compared to patients in previous reports who died early as a result of these abnormalities.[3,6,8]

Evidence suggests that most 7p duplications occur due to malsegregation of parental balanced translocations or abnormal recombination of parental chromosome inversions and that these duplications rarely result from *de novo* partial 7p direct

duplication.[2,3] The critical region for physical and mental abnormalities is 7p15-pter;[2] for craniofacial dysmorphism, it is 7p21.[2,3,9] Both these patient groups, *viz*. those with physical and mental abnormalities, have many specific features in common. The range of severity may depend on the size and genes involved.

Research has suggested that the *glioma-associated oncogene family zinc finger 3* (OMIM entry *165240; 7p13), *homeobox A13* (OMIM entry *142959; 7p15-7p14.2), *twist family basic helix-loop-helix transcription factor 1* (*TWIST1*; OMIM entry *601622; 7p21), *craniosynostosis type 1* (OMIM entry 123100; 7p21.3-7p21.2) and *mesenchyme homeobox 2* (OMIM entry *600535; 7p22.1-7p21.3) genes are associated with phenotypic 7p syndromes.[1] Chui *et al*. reported a patient with microduplication at 7p22.[1] (1.7 Mb) who showed all of the common craniofacial features and had cryptorchidism, but did not have global developmental delay or hypotonia.[10] Although the region 7p22.1 contains 27 genes, 13 of which are OMIM-annotated, only one gene (*β-actin* [*ACTB*]; OMIM entry *102630; 7p22.1) was commonly observed in both Chui *et al*.'s patient and the patient in the current report.[10] This would mean that *ACTB* is likely to be the causative factor for features like hypotonia, global developmental delay and cryptorchidism in the current patient.

The segmental size of the duplication in the current patient was larger than those reported elsewhere.[10,11] Furthermore, there was an association with ASD. Notably, two reports have associated 7p duplication with this disorder.[4,12] Wolpert *et al*. described an inverted duplication of 7p14.1p11.2 in an autistic adult, who lacked many of the characteristic features found in 7p duplication syndrome.[4] This may indicate that the critical region was distal. The patient was normocephalic, had normal developmental milestones, meatal stenosis, bilateral esotropia and mild scoliosis.[4] Cukier *et al*. reported a pair of autistic first cousins carrying two microduplications, one of whom had a tandem duplication on 7p21 replicating part of the *neurexophilin 1* (*NXPH1*; OMIM entry *604639) and *islet cell autoantigen 1* (*ICA1*; OMIM entry *147625) genes.[12] The patient in the current report was a child with direct duplication, clinical features of microcephaly and delayed milestones. None of the other features reported by Cukier *et al*. were present in the current patient.[12] However, both patients had common autistic phenotypes and behavioural features.[12] The duplication was more proximal in Cukier *et al*.'s case,[12] whereas it was distal in the current patient.

It has been suggested that the region within the duplication interval (7p21.1 to 7p22.2) observed in the current patient is the critical region for manifestations of the 7p duplication phenotype.[13] This region of 7p contains the OMIM morbid gene *TWIST1*, duplications of which are thought to be the cause of the large fontanelles in these patients;[13] it is hence likely to be the cause of the current patient's clinical phenotype. The duplication region of this patient encompassed the whole of the *TWIST1*, *ICA1* and *NXPH1* genes. These genes, however, were not directly disrupted by the breakpoints of the duplication. The aCGH analysis could not determine whether this duplication might have a position effect on the regulation of these genes.

Parental chromosomal studies confirmed that the duplication in the presently reported patient was *de novo* and did not occur from a balanced chromosomal rearrangement, which may sometimes occur as insertional translocations.[14] These translocations underlie 2.1% of apparently observed *de novo* interstitial copy number changes detected by aCGH.[14] Further molecular analysis is worth considering for genes of the duplicated region, particularly when they are associated with ASD phenotypes, for further delineation of genotype-phenotype correlations.

Conclusion

A *de novo* duplication of chromosomal region 7p21.1p-22.2 was identified in a three-year-old autistic child with craniofacial dysmorphism, global developmental delay, hypotonia and bilateral cryptorchidism. Characterising the genes involved in duplication regions may help in understanding the genotype-phenotype correlation in 7p duplication patients. It may also reveal the possible role of these genes in ASD. aCGH analysis is an important tool in revealing genetic abnormalities among children with intellectual disabilities and dysmorphic features, as these are usually not detected by conventional cytogenetics.

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