Evolution of Diagnosis with Evolving Technology: A Story of 10q Duplication Syndrome

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Abstract

Complete or partial trisomy 10q involves a duplication of the long arm of chromosome 10. Distal 10q trisomy is a well-recognized but rare genetic syndrome in which duplication of distal segments of 10q results in a pattern of malformations. Molecular cytogenetic techniques are advantageous not only in identifying submicroscopic chromosomal imbalances, but also in identifying the exact origin of the extra chromosomal material. Many a times, the phenotype of patients also evolves with age. We report a 17-year-old boy, suspected to have Trisomy 21 during infancy, but who on re-evaluation and follow up, was identified by cytogenetic microarray (CMA) to have partial 10q duplication. In this short report, we discuss the overlapping features of 10q duplication with trisomy 21 and utility of CMA in evaluation of chromosomal imbalances.

Introduction

Duplication of 10q was first reported by Klep-de Pater et al. (1979) as a recognizable syndrome. It is characterized by a high and large forehead, round and flat face with flat nasal bridge, epicanthic folds, hypertelorism, fine eyebrows, antimongoloid slant of eyes, low-set ears, cleft palate, micrognathia, short nose, bow-shaped mouth, microcephaly, hypotonia, joint laxity, clinodactyly, scoliosis, short neck, growth retardation, psychomotor disorders, and cardiac, ocular and renal abnormalities (Roux et al., 1974; Berger et al., 1976; Tomkins et al., 1983; Klep-de Pater et al., 1979; Davies et al., 1998). The evidence for a distal 10q duplication syndrome is limited by the fact that out of well over 50 cases reported, no more than a handful have only 10q duplication without involvement of any other chromosome arm (Sarri et al., 2011; Carter et al., 2010; Xiao et al., 2012). With the advent of molecular cytogenetic techniques, it is possible to better delineate the region involved in the 10q duplication and also to detect other co-existing chromosomal imbalances.

Here we report a 17-years-old propositus with dysmorphic features and developmental delay with 10q duplication.

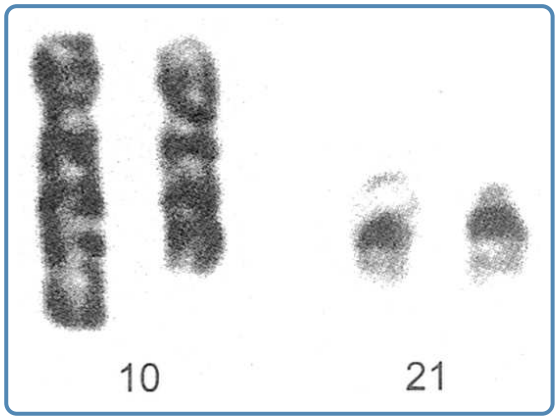

Figure 1 Partial karyotype of the patient showing extra material at the end of q arm of chromosome 10 (10q+).

Case report

A 17-year-old boy, born to healthy and non-consanguineous parents was first evaluated at 14 days of life for dysmorphic features. His facial features at that time were suggestive of Down syndrome and a karyotype was performed, which showed extra material on the q arm of chromosome 10 (Figure 1). Due to phenotypic resemblance to Down syndrome, a diagnosis of trisomy 21 was given and it was concluded that the extra material on chromosome 10q was a translocated long arm of chromosome 21 (21q). Parents' karyotypes were normal. The family was accordingly counseled and thereafter the child was lost to follow up.

Table 1 Comparison of the clinical features of the present patient with those of other previously reported patients.

	Devriendt et al. (1999)	Hou (2003)	Migliori et al. (2002)	Petek et al. (2001)	Al-Sarraj et al. 2014	Wong et al. 2015	Carter et al. 2010	Sarri et al. 2011	Xiao et al. 2012	Present study
Cytogenetic technique	FISH	FISH	FISH	FISH	CMA	CMA	CMA	CMA	CMA	CMA
Segment										
Duplication	10q26-qter	10q26.1-qter	10q25.3-qter	10q24.33-qter	10q24.31-10qter	10q23.1-10q25.1	10q25.1-26.3	10q26.11-q26.2	10q25.3-26.2	10q25.1-26.3
Deletion	-	-	-	-	-	-	10q26.3-qter	10q26.22-q26.3	10q26.2-26.3	10q26.3
Development										
Mental retardation/ Developmental delay	+	+	+	+	+	+	+	+	+	+
Short stature	-	-	-	+	+	+	+	+	-	-
Facial dysmorphisms										
Blepharophimosis	+	+	+	+	+	-	+	-	+	-
Hypertelorism/ epicanthus	-	-	+	+	+	+	+	+	+	-
Ptosis	-	-	+	-	-	+	+	-	-	-
Low-set/ malformed ears	-	-	+	+	-	-	+	-	+	+
Strabismus	-	-	-	-	+	-	-	+	+	-
Short neck	-	+	+	-	-	+	+	+	+	+
Long philtrum	-	+	-	+	+	-	-	-	+	-
Skeletal anomalies										
Camptodactyly/ sandal gap	+	+	+	-	+	+	+	+	-	-
Lordosis/scoliosis	+	+	-	-	+	+	+	-	-	-
Hypermobility	+	+	+	+	-	-	+	-	-	-
Hip dysplasia	-	-	-	+	-	-	+	-	-	+
Hypotonia	+	-	+	+	-	-	+	+	+	-
Others	-	Hearing loss; ventricular septal defect	-	-	Facial asymmetry, marfanoid habitus, autism	Left-sided inguinal hernia, cardiac, renal, ocular and brain abnormalities, autism	Hearing loss	Behavioral anomalies	-	Bilateral simian crease, difficulty in squatting, delayed puberty, Down syndrome like features in early infancy

('+' and '-' symbols denote presence and absence respectively)

Figure 2 Clinical photograph of the patient showing oval face, midface hypoplasia, short nose, short neck, low posterior hair line and protruding thick lower lip.

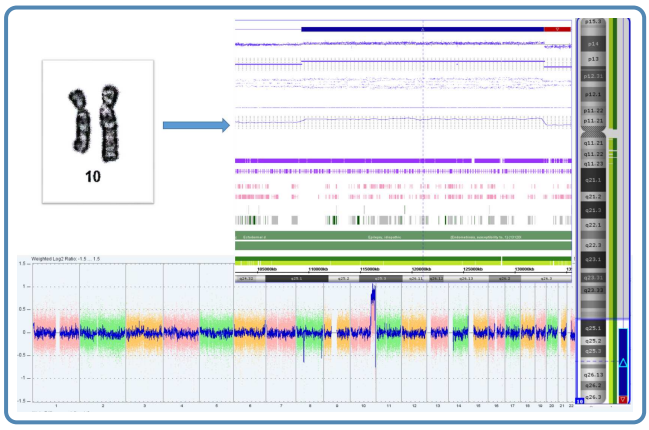

Figure 3 Cytogenetic microarray showing 23.5Mb duplication (blue colour) on 10q25.1-26.3 and 2.5Mb deletion (red colour) on 10q26.3 along with the whole genomic view (bottom).

He was brought to the Genetics OPD again, after 17 years, for evaluation of global developmental delay, delayed puberty and facial dysmorphism. On examination his height was 172 cm (+1.5 to +2 SD), weight was 75 kg (+1.5 to +2 SD) and head circumference was 53.5cm (-2 SD). He had an oval, flat face with a protruding thick lower lip, mid face hypoplasia, short nose, a short neck, low posterior hair line, small ears, micropenis and delayed puberty (SMR stage 2) and this time his facial features were not suggestive of Down syndrome (Figure 2). He had bilateral simian crease and difficulty in squatting. He did not have ptosis but had puffy upper eyelids bilaterally. He was found to have slipped epiphyses of head of femur. There was no history of seizures, gastrointestinal symptoms, cardiac symptoms or frequent infections. He was studying in the 9th standard and had learning difficulties. Formal evaluation showed IQ to be 65 (by Malin's intelligence scale for Indian children). Cytogenetic microarray was performed to ascertain the origin of extra material on chromosome 10.

Cytogenetic Microarray done using Affymetrix CytoScan™ 750K Array revealed a 23.5Mb duplication of 10q25.1 (arr[hg19] 10q25.1q26.3(109,292,821-132,860,709)x3) and a terminal 2.5Mb deletion of 10q26.3 (arr[hg19] 10q26.3(132,861,927-135,426,386)x1) (Figure 3).

Discussion

This case illustrates the utility of CMA in delineating imbalances detected by traditional karyotyping. The case also stresses the need to re-evaluate patients with undiagnosed dysmorphic syndromes using newer diagnostic tests. Table 1 summarizes clinical features of cases with duplication of terminal part of q arm of chromosome 10. Majority of the reported cases have occurred in association with partial monosomy of other chromosomes, complicating the delineation of clinical features.

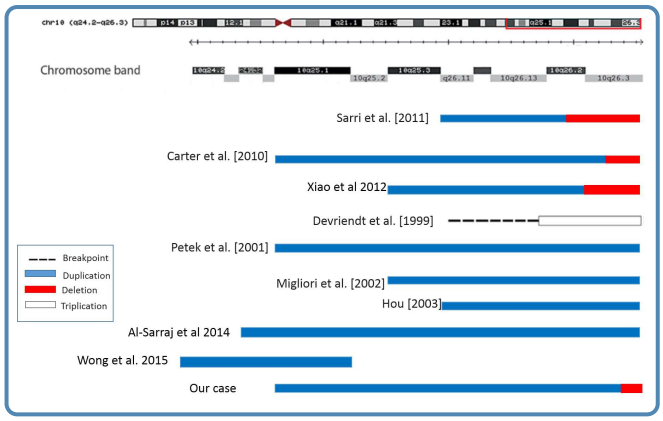

Figure 4 The affected region of 10q in present case and its comparison with other reported patients.

Our literature search yielded nine case reports with sufficient clinical data to attempt a comparison of features by size of duplicated segment (Figure 4 and Table 1). The comparison is limited by the resolution of the breakpoint mapping in older reports, as only few of them were subjected to microarray analysis. Four cases were evaluated by traditional karyotyping and FISH and five were evaluated by CMA. Only three cases are reported where duplication of 10q is associated with deletion (Sarri et al 2011, Carter et al 2011, Xiao et al 2012). In our study, the patient had

a de novo duplication of 10q25.1–q26.3 spanning 23.5Mb, arr[hg19] 10q25.1q26.3(109,292,821-132,860,709)x3 which contains approximately 84 known genes, as well as a 2.5Mb deletion of the terminal end of 10q26.3arr[hg19] 10q26.3(132,861,927-135,426,386)x1 including 16 OMIM genes.

Though the patient was clinically suspected to have Down syndrome in the neonatal period, on re-evaluation at 17 years of age his phenotype had evolved clearly and did not match the Down syndrome phenotype. Oval face, small nose, midface hypoplasia, protruding and thick lower lip, low posterior hair line and puffy eyelids were the conspicuous features of this patient. Similar facial phenotype has been described in other reports (Migliori et al., 2002; Al-Saraj et al., 2014). All the reported cases had a variable degree of intellectual disability; the reported patient had moderate intellectual disability. Most of the reported cases had blepharophimosis and ptosis, hypotonia, hypermobility, mild hand and foot anomalies, and absence of major congenital anomalies (Miglior et al., 2002; Carter et al., 2010). The smallest involved region was from 10q26.2-qter (Devriendt et al., 1999), suggesting that a dosage-sensitive locus responsible for blepharophimosis in these individuals resides within band 10q26.2 or 10q26.3. Two of the reported cases had conductive hearing loss (Hou et al., 2003; Carter et al., 2010) and two had autism (Al-Saraj et al., 2014, Wong et al., 2015). Phenotypic features of cases of 10q duplication (only) and cases with duplication followed by terminal deletion of 10q are given in Table 1. Blepharophimosis had once been considered as a characteristic feature for 10q duplication but it is not present in all the cases including the present case. Additional frequent features of 10q duplication are skeletal anomalies, which include camptodactyly, sandal gap, scoliosis or hypermobility as listed in Table 1. Our patient had no obviously abnormal skeletal feature but on radiological evaluation was found to have slipped epiphyses of head of the femur.

This case report clearly reinforces the fact that it is important to review patients with dysmorphic syndromes and keep them under regular follow-up, as both the clinical phenotype and diagnostic technologies evolve with time.

Acknowledgement

We sincerely thank the cooperation of the patient and his family and acknowledge Indian Council of Medical Research, New Delhi for funding (BMS-63/8/2010).

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