

A Rare Case of Duplication of Chromosome 2 (q31.3q36.3) in a 4.5-year-old Boy and Review of the Literature

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Abstract

De novo duplication of 2q is very rare. Most cases of 2q duplications result from familial translocations, and are associated with simultaneous monosomy of another chromosome segment. To our knowledge and search in English literature there are less than 20 reported cases of isolated 2q duplication. Hereby we introduce a 4.5-year-old Iranian boy of a non-consanguineous marriage who was referred for cytogenetic study due to developmental delay and intellectual disability.

He also had short stature and dysmorphic facial features. He had depressed broad nasal bridge and broad nasal tip, long philtrum and thin upper lip. His hands were edematous and the first phalanxes were broad and the thumbs were larger than normal. The chromosomal analysis revealed isolated 2q31.3q36.3 duplication, and array comparative genomic hybridisation (CGH) confirmed the diagnosis. After six months follow-up, could not walk or speak despite occupational therapy. We also, describe the common morphological characteristics of isolated 2q duplication.

Key Words: Array CGH, Karyotype, Developmental delay, 2q duplication.

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1- INTRODUCTION

Chromosome 2q duplication is a rare chromosomal abnormality which indicates that there is an extra copy of genetic material on the long arm (q) of chromosome 2. Most of the reported cases in literature result from familial translocations (1), and are accompanied by monosomy of another segment of chromosome (2-5) that obscures the association of the 2q duplication to the phenotype (6). The majority of cases involve the distal segment, 2q3 (6). The isolated cases of 2q duplication are very rare. The size and location of the duplication and the involved genes are associated with signs and symptoms and their severity. Most cases are de novo, but people can pass the abnormality to their children. Some common features of this abnormality are developmental delay, intellectual disability, behavioral problems, and distinctive facial features. This abnormality is not associated with advanced parental age and may arise from unequal crossing over during gametogenesis (7).

2- CASE REPORTS

The patient was a 4.5-year-old boy and the second child of a non-consanguineous marriage of Iranian parents who was referred by his endocrinologist to Children's Medical Center, a referral center for pediatric diseases in Tehran, Iran, for karyotype analysis. The first child of the family was a healthy girl aged 11 with normal developmental milestones and intellectual abilities. The mother and father were 36 and 40 years old at the time of the birth of the affected child. The mother had no history of infertility. She had history of 4 pregnancies, 2 of which were terminated by induced abortions. There was no pertinent family history. Also, there was no history of exposure to mutagens or teratogens before or during the pregnancy in parents. The mother had

no drug history in the antenatal period and during pregnancy. The pregnancy was uncomplicated and the baby was born by repeat caesarian section at term at 38 weeks. The patient birth weight, height, and head circumference were 3,500 gr, 49 cm, and 36.5 cm, respectively (about 50th percentile). No complication of the cesarean section including hypoxia or cyanosis was reported in the medical file. Physical exam at birth showed no abnormal finding and the newborn was discharged from hospital one day after cesarean section. The patient had developmental delay from birth. The infant was hypotonic. He could strengthen his neck muscles at 5 months with occupational therapy, sit up on his own without support at 19 months and crawl at 4 years. The patient could not walk and had no speech at the age of 4.5 years. He had a history of bilateral undescended testes and had orchiopexy surgery at age of 26 months. He also had intellectual disability. He had no history of convulsion.

The laboratory exams showed normal thyroid and metabolic panels. The ultrasound study of abdomen and pelvis was normal except for undescended testes at inguinal canals at age one year. The electroencephalogram (EEG) showed no abnormality. Brain MRI appeared normal. On physical examination at 4.5 years of age, his weight was 9 kg and his height was 95 cm (below the 5th percentile). His skull was slightly microcephal (44 cm) and his face was also mildly dysmorphic. He had a depressed broad nasal bridge and broad nasal tip, long philtrum and thin upper lip (**Figure.1**). His hands were edematous and the first phalanxes were broad and the thumbs were larger than normal (**Figure.2**). Chromosomal analysis by G-banding of cultured lymphocytes from peripheral blood showed an abnormal male chromosomal complement with duplication of distal part of the long arm of

chromosome 2 probably between bands q31.3 and q36.3 in all the 50 analyzed cells [46, XY, dup (2)(q31.3q36.3)] (**Figure 3**). The parents were apparently normal looking and their karyotypes were also normal (46, XX and 46, XY, 21 ps+). Whole genome oligonucleotide array CGH was performed using SurePrint G3 ISCA V2 8X60K whole genome oligo array version 2 and was analyzed using Agilent CytoGenomics software version 4.0. The

array consists of 60,000 spots with overall median probe spacing of 60 kb and higher in close to 500 targeted disease regions. The sample was twice analyzed against the male reference. The imbalance was detected as a male with 49.2 Mb pathogenic gain of 2q31.3q36.3 from nucleotide 181045202 to 230254104, compatible with partial trisomy of 2q31.3q36.3 (**Figure 4**).



Fig.1: (*The dysmorphic face*): Face of the patient at age 4.5 year revealing brachycephaly and depressed broad nasal bridge.



Fig.2: (*The abnormalities of hands*): The patient's hands were edematous and showed rather broad first phalanges. The thumbs were also larger than normal.

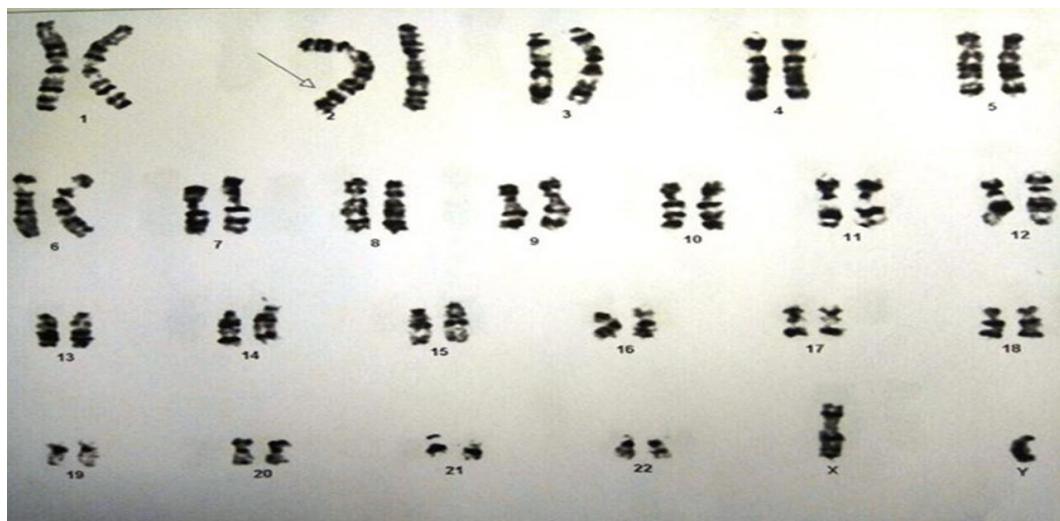


Fig.3: (*The peripheral blood karyotype*): The karyotype of patient showing an extra genetic material resembling distal part of long arm of chromosome 2 probably between bands q31.3 and q36.3.

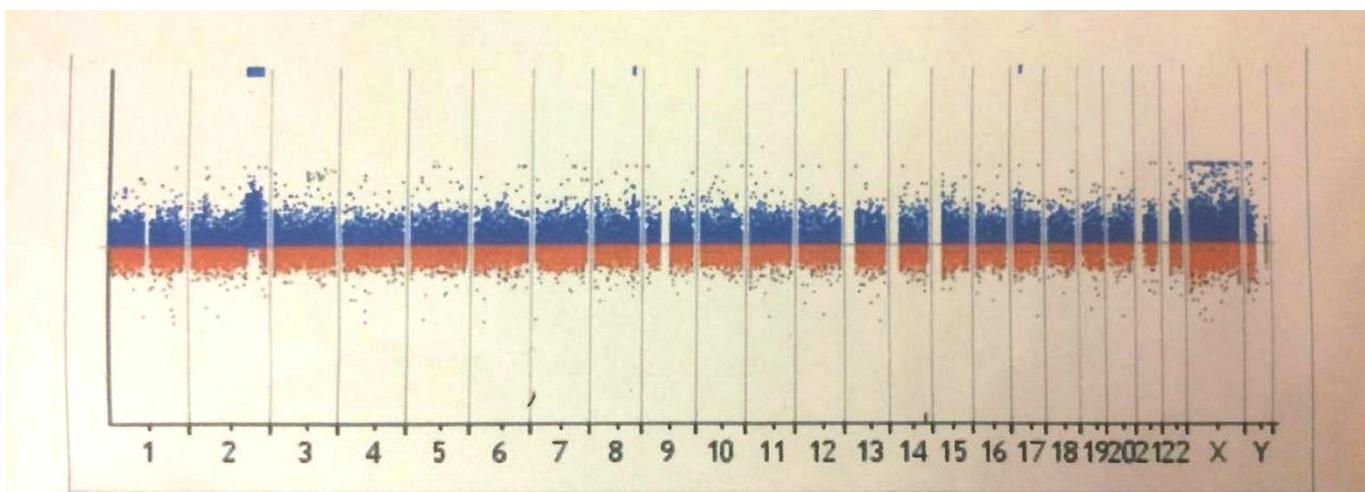


Fig.4: (*The array CGH study*): The whole genome oligo array CGH study of the patient showed arr [GRCh37] 2q31.3q36.3 (181045202 _ 230254104) x3 which is interpreted as gain of 49.2 Mb on 2q31.3q36.3. This imbalance is considered pathogenic (ACMG classification). The region contains several OMIM genes.

3- DISCUSSION

Most cases of partial trisomy of 2q resulted from unbalanced translocations that were also associated with monosomy of a segment of another chromosome (1-3). So the suggested phenotype in the first case reports might also be related to monosomy of another chromosomal segment. Some of these reported features include low birth weight, hypotonia, a characteristic facial dysmorphism, developmental delay, mental retardation, cardiac, genitourinary, gastrointestinal, central nervous malformations and

microcephaly (8). The morphological characteristics of partial trisomy of 2q without monosomy of another chromosomal segment also depend on size and location. Here we review the reported features of isolated 2q duplication cases in literature from proximal to distal 2q. Mu et al. (1984) reported a 3.5 year old girl with dup (2) (q11.2q14.2) presented with congenital glaucoma, developmental delay, low weight and height below the 5th percentile, microcephaly and brachycephaly (7). The developmental delay and short stature were features in common with our case. Ounap et al.

(2005) reported a boy with trisomy of 2q13q21. He had intrauterine asphyxia, low birth length and weight, features of Pierre Robin sequence, mild exophthalmos, epicanthic folds, convergent strabismus, upturned nose, broad nasal tip, long philtrum, thin upper lip, and undescended testes, dilated ventricles, feeding difficulties, failure to thrive, spastic quadripareisis and severe developmental delay (1). The similar abnormalities with our case were broad nasal tip, long philtrum, thin upper lip, and undescended testes. Knox et al. (2015) reported a girl with dup (2) (q23.3q31.2) who had neonatal epilepsy, upslanting palpebral fissures, bilateral epicanthic folds, esotropia, a broad nasal bridge, anteverted nasal tip, long smooth philtrum, and a thin upper lip, multiple congenital cardiac abnormalities, and horseshoe kidney (9). Our case also had broad nasal bridge, anteverted nasal tip, long smooth philtrum, and a thin upper lip and developmental delay. Vecchi et al. (2011) reported a boy with mosaic duplication of 2q23.3q24.3 showing atypical epilepsy, mild delayed psychomotor development, head nodding and obtundation and neurological regression without any significant facial dysmorphism.

The milder symptoms of the patient could be attributed to the mosaic pattern and presence of duplication in 51% of the cells (10). Delayed psychomotor development is the only abnormality in common with our case. Lim et al. (2014) reported a boy with dup (2) (q24.3q32.1) showing early-infantile-onset epilepsy, hypoplastic left heart syndrome, short stature, and global developmental delay (11). The short stature and developmental delay matched our case. Also, it seems that genes in 2q2 region might be responsible for epilepsy. Romain et al. (1994) reported a woman with dup (2) (q33.1q35) presented with short stature, positional talipes, developmental delay, hypertelorism, and

epicanthic folds (12). It seems that fascial dysmorphism, short stature and developmental delay are among the most common abnormalities noted in most of the reported cases. Sebold et al. (2005) described a girl with dup (2) (q33.1q35) who had intrauterine growth retardation resulted in preterm labor, otitis media, conductive hearing loss, developmental and gross motor delay, hypotonia, feeding difficulties, brachycephaly, upward slanting palpebral fissures, left esotropia, a small nose, micrognathia, and a cupid's bow lip, inverted and displaced nipples, short fifth fingers, clinodactyly, and small atrial septal defect (8).

Our case also had gross motor delay and hypotonia. Bird et al. (2001) described a boy with dup (2) (q37.1q33), who had an intrauterine breech presentation, oligohydramnios, and fetal distress resulting in cesarean section. He had tiny anterior fontanelle, overriding sutures, hypertelorism, short palpebral fissures, left inferior iris coloboma, malformed ears, low nasal bridge, short nose with anteverted nares, long philtrum, thin upper lip, micrognathia, excess nuchal skin, widely spaced nipple, undescended testes, micropenis, single, transverse palmar crease, hypoplastic distal interphalangeal creases, pes cavus and lateral deviation of the hallux, hyperconvex nails, hypotonia, pulmonary hypertension, congenital heart, and renal abnormalities, poor feeding, and eczema (6). Anteverted nares, long philtrum, thin the upper lip, undescended testicles and hypotonia were identical features with our case. The last case of 2q duplication reported by Usui D (2013) was a 5-year- and 9-month-old Japanese boy with duplication of 2q32.1-q33.3 presented with epilepsy, psychomotor developmental delay, and autistic behavior. The case was confirmed by microarray testing and FISH study (13). Two-color fluorescent in situ hybridization studies (FISH) (1, 4, 6-7, 9-10) or array CGH (8-9) are usually

recommended to confirm the above diagnosis and rule out addition of material of unknown origin to the long arm of chromosome 2. FISH probe for the suspected region was not available for diagnosis but fortunately the oligonucleotide array CGH showed gain of 2q31.3q36.3 from nucleotide 181045202 to 230254104 and confirmed the diagnosis. After six months follow up, the patient had mild improvement in his developmental milestones by occupational therapy but still he could not walk or speak.

4- CONCLUSION

As it is seen, the morphologic features of partial trisomy of 2q depends on the size and location of extra genetic material. Thinking about the range of abnormalities could help us in the interpretation of karyotype analysis.

5- CONFLICT OF INTEREST: None.

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