

Case Report:

Clinical Manifestation of de novo Duplication at the distal end of Chromosome 7p

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Abstract: *In this communication, we report the case of a one and a half month old baby boy with de novo duplication at the distal end of chromosome 7p who visited our facility at SSKM Hospital. The clinical manifestations associated with duplication at the end of 7p are mostly delineated and in most cases result from inheritance of parental chromosome harbouring a balanced translocation. In this study, we describe de novo duplication and review the previously published literature from other parts of the world dissecting the genotype-phenotype correlation in such cases.*

Keywords: *Extra chromosomal material, duplication, partial Trisomy, chromosome 7, karyotype, dysmorphism.*

Introduction: The phenotype for duplication at the distal arm of chromosome 7p is well described. The clinical features associated with such chromosome anomaly comprises of large fontanelles and sutures, hypertelorism, large, apparently low set ears, high arched palate, hip joint dislocation or contractures, a high frequency of cardiac septal defect, and mental retardation (1). The infant who was brought in our facility was similarly diagnosed of with developmental, cardiovascular, pigmentation problems. However, in most cases such partial trisomy or segmental duplication occurs because of mis-segregation of the chromosome or mis-alignment of the chromosomes and are inherited from parents in form of balanced translocations. In this article, we present the case of possible partial *de novo* 7p duplication depicting the same clinical features and are of utmost importance as it indicates pure segmental imbalances which reflect genotype-phenotype correlations accurately.

Case Presentation: A new born infant boy was referred to the NICU of our department with suspected congenital heart disease and dysmorphism. The infant was born at 35 weeks gestation by normal spontaneous vaginal delivery after an uncomplicated pregnancy; birth weight was 1600gms (10–25th centile), head circumference was 29.5 cm (<10th centile), and length was 42 cm (10–25th centile). His mother had an uneventful pregnancy. At his birth the mother was 28 old and the father was 32 years of age. The family history is unremarkable and the couple has a healthy seven year old male child. The baby was unable to breast feed due to dysmorphic features and assisted feeding was practiced.

Physical examination revealed presence of bilateral complete cleft lip and palate, low set ears, deformed ear, right hand thumb deformity, micrognathia, nasal bridge broad with angular tip, hypertelorism, bilateral un-descended testis, and flexion deformity of wrist, knee and elbow. Further the infant had skin hypopigmentation over the dorsum of right hand. (Figure 1)

Echocardiogram shows D-TGA with 7.8 mm perimembranous VSD, 5.6 mm ostium secundum ASD, pulmonary atresia, PDA, right to left shunt. Ultrasound and MRI study of the brain was normal. Ultrasound abdomen revealed both kidneys are echogenic with few cysts noted at the cortex. Right testes could not be visualized. He was enrolled for corrective cardiac surgery. He was treated conservatively and was discharged from NICU at two months of age.

He was followed up at Neurodevelopment clinics at three months of age. Physical examination revealed failure to thrive. He has subnormal visual development and developmental delay. The patient has lost follow up after that.

Further molecular cytogenetic investigations were carried out by high resolution GTG banding on peripheral blood lymphocyte cultures according to usual procedures. PHA stimulated 72 hours whole blood culture followed by banding was performed. About 30 metaphase plates were analyzed by Olympus BX53 and 10 representative plates were karyotyped by GenASIs software. Analysis of the metaphase chromosomes of the child revealed additional chromosomal material at 22.1 distal end of the short arm of chromosome 7. (Figure 1) The chromosomes of the parents and the siblings were normal. The chromosomes were classified according to the international nomenclature (ISCN, 1995).

Discussion: The above phenotypic observations were in corroboration to other reports on duplication at the distal 7p end. Several reports suggest a set of recognizable phenotypes that involve severe/profound psychomotor retardation, dolichocephaly or microbrachycephaly, gaping fontanel and wide sagittal and metopic sutures, hypertelorism, large apparently low-set ears, micrognathia, choanal atresia/stenosis, hyperextensible joints subject to dislocation, joint contractures, and a high rate of cardiac septal defects (1). Sometimes in cases of parental inheritance of balanced translocations resulting in partial 7p trisomy or segmental duplication would involve additional features (1). However, as in our case a pure 7p would involve craniofacial and cardiac deformities. E. Papadopoulou et. al (2006) and Cox ,Butler (2015) represented their cases which had some similarities with our patient case such as low set ears, malformed ear, micrognathia, nasal bridge broad with angular tip, hypertelorism, developmental delay and growth retardation (3,4). On other hand our presented case with some other deformities like skin hypopigmentation, bilateral complete cleft lip and palate, right hand thumb deformity, bilateral undescended testis, flexion deformity of wrist, knee and elbow, visual and hearing impairments, congenital heart disease(D-TGA ,VSD, ASD, pulmonary atresia, PDA). The presences of cardiovascular abnormalities are possibly less frequent in pure 7p duplication syndrome, but our presented case had a severe congenital heart disease (1).

Extra chromosomal material on 7p can arise de novo, may be due to non allelic homologous recombination. The distal end around the 7p 21.2 region

seems to be important with respect to development and reports on molecular analysis of this region reveal three genes that are very important with respect to development of the embryo viz. TWIST, GLI-3 and HOXA.

TWIST is a gene encoding a transcription factor involved in craniofacial development. TWIST has been previously associated with Saethre-Chotzen syndrome which clinically is characterized by craniosynostosis, a flat face with a thin, long, pointed nose, shallow orbits, plagiocephaly, small, posterior rotated ears with long and prominent crus, cleft palate, and often subtle abnormalities of the hands such as mild syndactyly of digits 2 and 3 and bifid terminal phalanges of the hallux, congenital heart defects, and contractures of the elbow and knee (2). There are also reports that the autosomal dominant disorder Greig cephalopolysyndactyly syndrome (GCPS) that affects limb and craniofacial development in humans is caused by a translocation within the GLI3 gene (2). *HOXA* homeodomain cluster has been reported in the hand-foot-genital syndrome (2). Thus, all these genes have contributions that would help to explain the phenotype of the disease.

The various reports present indicate that *TWIST* gene in triple dosage at the distal end of chromosome 7 may be causally related to the presence of a large anterior fontanelle with delayed closure, which is the more characteristic clinical feature of the 7p duplication syndrome (2) as also represented in our case study. The presence of cardiovascular problems in our case is unique to other such case representation.

Declaration:

Contribution of authors: All authors participated in the analysis of the presented case report.

Dr. Dinesh Munian clinically investigated the case and under the guidance of Dr. Dipanjana Datta (Scientist); Jayita Dey Mondal and Manali Singha cytogenetically analysed the patient's sample and contributed in the preparation of manuscript. Acknowledgement and appreciation are expressed to all the authors for the evaluation and management of the patient.

Conflict Of Interest:

There is no conflict of interest.

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Figure 1: a) Physical characteristics of the baby depicting complete cleft lip and palate, low set ears, deformed ear, right hand thumb deformity, micrognathia, nasal bridge broad with angular tip, hypertelorism, bilateral undescended testis, and flexion deformity of wrist, knee and elbow and hyperpigmentation of skin b) Pedigree depicting the family and no previous history of such manifestation. c) Representative karyotype of the baby by GTG banding on peripheral blood lymphocyte cultures revealed 46 XY (7p ter dup).

The chromosomes of the parents and the siblings were normal

Figure 1

