Case Report

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# Molecular Delineation of Partial Trisomy 14q and Partial Trisomy 12p in a Patient with Dysmorphic Features, Heart Defect and Developmental Delay

Divya Bose[a] Venkatesh Krishnamurthy[c] K.S. Venkatesh[b] Mohamed Aiyaz[c]
Mitesh Shetty[a] Sudha N. Rao[c] A.V.M. Kutty[a]

[a]Division of Genomics, Department of Cell Biology and Molecular Genetics, Sri Devaraj Urs Academy of Higher Education and Research, and [b]Department of Pediatrics, R.L. Jalappa Hospital and Research Center, Kolar, and [c]Genotypic Technology Pvt. Ltd., Bangalore, India

**Key Words**
Array CGH · Balanced translocation · Partial trisomy 12p · Partial trisomy 14q

**Abstract**
This study describes a molecular analysis of partial trisomy 14q and partial trisomy 12p in a 5-year-old male child presenting with dysmorphic features, congenital heart disease and global developmental delay. Chromosomal analysis of the patient with GTG bands revealed a 47,XY,+der(14)t(12;14)(p13;q22)mat karyotype; the mother's karyotype was 46,XX,t(12;14)(p13;q22). Further, oligonucleotide array-CGH studies revealed an amplification of 32.3 Mb in the 14q11.1q22.1 region, substantiating partial trisomy 14q and additionally displaying an amplification of ~1 Mb in the 12p13.3pter region for partial trisomy 12p. This is the first study to demonstrate a novel association of partial trisomies of 14q and 12p due to a 3:1 segregation of a maternal balanced translocation involving chromosomes 12 and 14. Gene ontology studies indicated 5 potential candidate genes in the amplified regions for the observed congenital anomalies.


Congenital malformations due to various types of chromosomal aberrations have been described extensively in the literature [Schinzel, 2001]. Complete trisomy of chromosome 14, a rare chromosomal disorder, is frequently associated with spontaneous abortions, and on the other hand, in the presence of a normal cell line, it appears to be compatible with live birth [Kajii et al., 1972]. The life expectancy of patients with partial trisomy 14 depends upon the chromosomal segment involved in the structural abnormality [Smith et al., 1980; Dundar et al., 2011]. Similarly, trisomy 12p is also a rare chromosomal disorder with the incidence of 1:50,000 births. Little is known in the literature about the clinical features or the life expectancy of children affected by trisomy 12p aberrations [Stengel-Rutkowski et al., 1981; Segel et al., 2006]. Generally, these types of partial chromosomal aberrations present with multiple congenital and dysmorphic anomalies besides developmental delay with or without mental retardation [Liu et al., 2012; Salas-Labadía et al., 2014].

Traditional methods of chromosome analysis can identify abnormalities up to a limit of 5 Mb and have a limited scope to identify submicroscopic deletions and amplifications, particularly in nonsyndromic malforma-

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E-Mail karger@karger.com
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Dr. A.V.M. Kutty
Faculty of Allied Health Sciences
Sri Devaraj Urs Academy of Higher Education and Research
Kolar 563101 (India)
E-Mail kuttyavm@gmail.com

tions. Array CGH as a tool for molecular genetic analysis to understand the basis of congenital malformations is a rapidly developing trend, as evidenced by a large number of reports from several countries [Aradhya et al., 2007; Baris et al., 2007; Almal and Padh, 2012]. Here, we report a case of a 5-year-old male child with partial trisomy 14q, as shown by conventional karyotyping and array-CGH studies, confirming the results and further revealing an additional partial trisomy 12p.

## Case Report

*Patient Details*

A 5-year-old male child was presented with fever, cough and dysmorphic features. He is the second child born to a nonconsanguineous couple. His medical records indicated the following: birth weight ~2.5 kg, the presence of meconium-stained liquor and that he cried after resuscitation. At the age of 4 years, he was diagnosed with atrial septal defect and pulmonary stenosis with a history of respiratory as well as feeding difficulties with global developmental delay.

Physical examination revealed that his head circumference was 46 cm (<5th centile), weight 13 kg (<5th centile) and his height 98 cm (<5th centile). Clinical examination revealed dysmorphic features such as microcephaly, low-set ears with prominent pinnae, a prominent nose with a broad nasal bridge, and a high-arched palate besides retrognathia with mental retardation. The child also had tachycardia, tachypnea and nutritional anemia. Neurological examination revealed hypertonia and increased deep tendon reflexes. Unfortunately, the child passed away 2 days after hospital admission due to aspiration pneumonia. No further clinical information was available regarding this patient.

*Cytogenetic and Molecular Analysis*

A peripheral blood sample was taken from the patient and referred to our laboratory for chromosomal analysis. Metaphase chromosomes were obtained from a PHA-stimulated lymphocyte culture by standard technique [Seabright, 1971]. Chromosomal analysis was carried out by GTG banding at 400–450 band-level resolution in the patient and parents. The G-banded chromosomes were analyzed and interpreted according to the International System for Human Cytogenetic Nomenclature 2013 [ISCN, 2013]. Further, array CGH was also performed.

Genomic DNA was extracted from peripheral blood using the standard salting-out procedure [Miller et al., 1988]. The DNA concentration was determined using Nanodrop spectrophotometer (ND-1000, Thermo Fisher Scientific, Waltham, Mass., USA). Array CGH was performed by using Agilent Human 1×1M Oligonucleotide CGH array (AMAMDID 21529, Agilent Technologies Inc., Santa Clara, Calif., USA) containing about 962,029 probes with an overall median probe spacing of 2.1 kb. Analysis was performed in accordance with the manufacturer's protocol. The microarray slide was scanned using Agilent scanner (design G4900DA, Agilent Technologies), and the data were processed and analyzed by means of Agilent CytoGenomics 2.7 version software with the statistical algorithm ADM-1, with the threshold of 6.0 and a 2-probe minimum aberration call with an average log ratio of 0.25 to identify chromosome aberrations.

## Results

GTG banding revealed 47 chromosomes with a marker chromosome in all the analyzed metaphases of the proband. This marker chromosome appeared to be acrocentric, which was smaller than the D-group and larger than the G-group chromosomes. QFQ banding was performed to identify the marker chromosome, and it demonstrated the presence of a single normal Y chromosome. Parental chromosomal analyses revealed that the mother was a carrier of a balanced translocation 46,XX,t(12;14)(p13;q22) and the father had a normal 46,XY karyotype. The analyses also confirmed the maternal origin of marker chromosome (14q–) in the patient. The child's karyotype was 47,XY,+der(14)t(12;14)(p13;q22)mat and the mother's karyotype was 46,XX,t(12;14)(p13;q22) (fig. 1).

In our patient, array-CGH analysis confirmed the partial trisomy 14q with the amplification of 32,313,772 bases (18,505,611–50,819,383) in the q11.1q22.1 region of chromosome 14 represented by 10,312 probes on the arrays. Chromosome 12 also showed amplification of 1,000,846 bases (59,822–1,060,668) in the terminal region (12p13.3pter) represented by 436 probes, suggesting partial trisomy of 12p (fig. 2). This partial trisomy 12p segment was undetectable by conventional karyotyping as the amplified segment was ~1 Mb. Array CGH of the mother revealed that there was no major loss or gain of genetic material indicating that the net genomic content has remained intact in the mother, which supports the clinically normal phenotype of mother, despite being a carrier of balanced translocation.

## Discussion

The advent of the chromosomal microarray technique has facilitated the identification of an increasing number of submicroscopic chromosomal deletions and duplications which have been associated with a variety of congenital anomalies. To the best of our knowledge, this is the first study to report the combined presence of partial trisomy 14q and partial trisomy 12p in a child consequential to maternal-balanced translocations involving chromosomes 12 and 14 by employing the array-CGH technology. The molecular mechanism of the formation of partial trisomy14q is suggested to be due to suppression of chiasma formation at the centromere region; the unstable bivalent formed between the normal and the abnormal chromosome 14 predisposes to premature desynapsis or asynapsis and the subsequent segregation of the 2 chromosomes 14

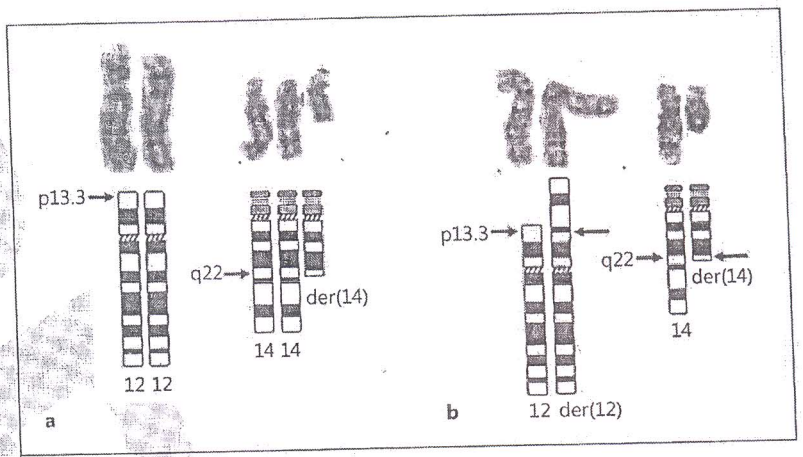


**Fig. 1.** **a** GTG banding showing partial trisomy 14q, 46,XY,+der(14)t(12;14)(p13;q22)mat, of the patient. Arrows indicate translocation breakpoints. **b** The mother's partial karyotype showing a balanced translocation 46,XX,t(12;14)(p13;q22). Arrows indicate translocation breakpoints and break-reunion junction.

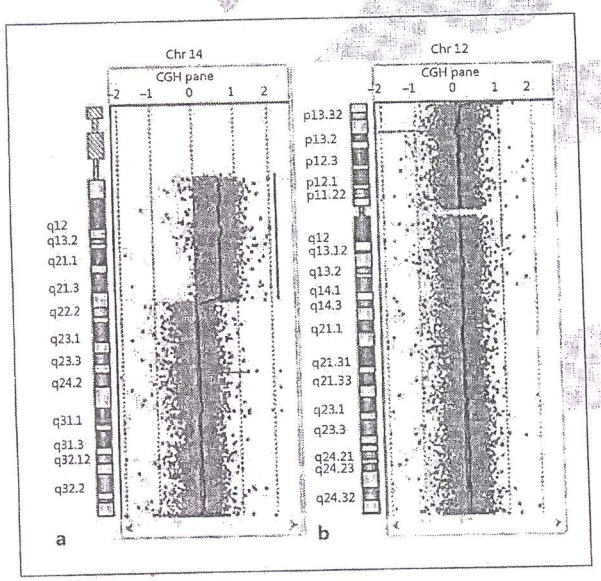


**Fig. 2.** Array-CGH profile revealing partial trisomy 14q with amplification in the 14q11.1q22.1 region (**a**) and partial trisomy 12p with amplification in the 12p13.3pter region (**b**).

**Table 1.** Clinical manifestations in the present case correlated with common features in both partial trisomy 14q and partial trisomy 12p

| Clinical features | Partial trisomy | | Present case |
|---|---|---|---|
| | 12p[a] | 14q[b] | |
| Birth weight | normal/high | low | normal |
| Developmental delay | + | + | + |
| Microcephaly | – | + | + |
| Macrocephaly | + | – | – |
| Low-set/malformed ears | + | + | + |
| Prominent nose or broad nasal bridge | + | + | + |
| Micrognathia/retrognathia | – | + | + |
| Cardiac defect | + | + | + |
| Mental retardation | + | + | + |

[a] Allen et al., 1996; Rauch et al., 1996; Chen et al., 1997; Tekin et al., 2001; Shashidhar Pai et al., 2003; Tsai et al., 2005, Liu et al., 2012.

[b] Allderdice et al., 1971; Fryns et al., 1974; Cohen et al., 1975; Simpson and Zellweger, 1977; Smith et al., 1980; Angle et al., 1999; Shashidhar Pai et al., 2003.

to the same spindle [Cohen et al., 1975]. The probability of a 14q proximal partial trisomy zygote has been shown to be higher in female balanced translocation carriers than in male carriers [Valkova and Stefanova, 1993]. The results of the present study also indicate that the origin of the derivative chromosome is due to a 3:1 segregation during meiosis resulting in an unbalanced aneuploidy [Angle et al., 1999].

Comparing cases of partial trisomy 14q and 12p previously reported in literature with the present case revealed a combination of the clinical features found in our patient which are depicted in table 1.

The array-CGH study showed an amplification of ~32.3 Mb in the 14q region and an amplification of somewhat more than 1 Mb in the 12p region, confirming partial trisomy 14q and partial trisomy 12p. These amplified

regions of the patient comprise of 237 genes on chromosome 14 and 11 genes on chromosome 12. Gene ontology studies indicate that several of these genes are involved in multiple signaling pathways (online suppl. table 1, see www.karger.com/doi/10.1159/000381294).

To establish the genotype-phenotype correlations, an extensive search in the OMIM database was performed for the amplified genes in the 14q region. This led us to consider the *MYH6* (OMIM 614089), *FOXG1* (OMIM 164874), *SUPT16H* (OMIM 613457), and *MGAT2* (OMIM 602616) genes, which are closely associated with abnormal phenotypes such as dysmorphic features, mental retardation and developmental delay.

*MYH6*, a cardiac muscle-specific myosin gene has been shown to be closely associated with atrial septal defect *(ASD3)* and familial hypertrophic cardiomyopathy. Unregulated expression of *MYH6* due to *TBX5* (a cardiac transcription factor) mutation leads to Holt-Oram syndrome [Ching et al., 2005].

*FOXG1* is a transcription factor closely associated with Rett syndrome, which regulates the development of the telencephalon from early embryonic to adult stages by multiple and diverse mechanisms. It has also been shown to have a role in brain development and has been recognized as a strong candidate gene to explain the developmental disorder associated with deletion in the 14q12 region [Kortüm et al., 2011].

*SUPT16H* encodes the large subunit of the conserved FACT complex. Haploinsufficiency of *SUPT16H* has been associated with congenital anomalies, developmental delay and mental retardation [Chelly et al., 2006; Zahir et al., 2007]. The *MGAT2* gene encodes UDP-N-acetyl glucosamine, a Golgi enzyme that catalyzes the conversion of oligomannose to complex N-glycans. Homozygous Lys237-to-Asn (K237N) mutation in the *MGAT2* gene has been associated with distinct dysmorphic features such as microcephaly, retrognathia, prominent columella, prominent nasal bridge, thin upper lip, diastema, and mental retardation [Alazami et al., 2012].

The amplified region of 12pter lies close to the 12p13.3p13.1 region, which has been implicated in 12p13.33 microdeletion syndrome and could be critical for the facial features [Rauch et al., 1996]. Among the 11 genes from this region, the *ERC1* gene encodes a protein that belongs to the family of RIM-binding proteins involved in the regulation of neurotransmitter release. *ERC1* has also been recognized to be responsible for speech sound disorder, childhood apraxia of speech and developmental verbal dyspraxia [Thevenon et al., 2013]. Further, *ERC1* has been found fused to the *RET* gene by rearrangement due to the translocation t(10;12)(q11;p13) in thyroid papillary carcinoma [Nakata et al., 2002].

Inherent duplications of some regions of the chromosomes involving strong candidate genes could present with multiple congenital anomalies [Patnala et al., 2013]. However, these conditions have been neither described succinctly nor compared with deletions in equivalent regions of the same chromosomes to decipher the roles of the deletion or amplification to the observed phenotypes. The phenotypic presentations in our patient could be attributed to the amplified genes but with the support of additional molecular events taking place in specific tissues or organs. Nonetheless, the emphasis on the candidate genes in the amplified region could not be ignored because of the functions detailed in the literature as discussed above.

Employing the array-CGH technique, we were able to establish the trisomies of 14q and 12p and to correlate the molecular underpinnings of the abnormal clinical presentations of the patient, either to the trisomies or to the genes located in the amplified regions. However, further epigenetic and gene expression studies need to be done to yield more definitive explanations to the etiopathogenesis of the congenital anomalies observed in our patient. The scope of such studies is limited at this stage; therefore, it is difficult to confirm or negate the roles the candidate genes play in causing the abnormal phenotypic features observed in our patient, who passed away shortly after hospital admission. Furthermore, this study highlights the relevance of array CGH in providing clinical and diagnostic results and cues for proper genetic counseling. The results of this study illustrate the possibility of having missed many submicroscopic chromosomal aberrations in several of the congenital anomalies already reported in the literature.

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