

Ring chromosome 21: A Case Report

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KEYWORDS Male Child. Mental Retardation. Ring 21. Genotype-Phenotype Correlation. Counseling

ABSTRACT In this article is reported, the phenotype of the male proband, with the ring configuration in chromosome 21. A 3½-year-old male child was referred for karyotyping, with the chief complaint of mental retardation. The manifested features were the delayed milestones, long face, large and low set ears, slight epicanthic folds, short little finger, clinodactyly, simian crease, flat feet and hypogonadism. The chromosomal analysis was obtained from the peripheral lymphocyte culture. The karyotype of the male proband was 46,XY,r(21)(p11q21). Chromosome 21 was present from region 11 in the short arm to the region 21 in the long arm. Or the regions lost in 21, were distal to the break points in the short arm: 21p11 to 21pter and long arm: 21q22 to 21qter. The phenotype and the genotype were correlated. In effect, proband has had partial monosomy for the distal segments of the short and long arm of 21. The loss of the chromatin material from the short arm of 21, one of the acrocentric chromosomes, is not of any significance, since, the genes are involved in the formation of the nucleoli; whereas, the loss of the long arm may have resulted in the clinical picture of dysmorphogenesis and mental retardation. The parents were counseled.

INTRODUCTION

Chromosomal abnormality (CA), one of the major genetic disorders is divided into numerical (NCA) and structural (SCA), which are also known as genomic and chromosomal mutations. Structural chromosomal abnormality results from chromosomal breakage and reunion in a different configuration. One of the structural chromosomal abnormalities is the ring formation. The frequency reported for the ring chromosomes is one in 25,000 recognized conceptions; almost all human chromosomes are involved in the formation of the ring and 50% are supposed to be derived from acrocentric chromosomes, the D and G group, 13 to 15 and 21 and 22 (Wong et al. 1989).

A ring chromosome is formed when a break occurs in each arm of the chromosome, leaving two 'sticky' ends and subsequent end-to-end fusion. Mostly, ring chromosomes are *de novo* in origin. The concept has been proved or not; it is opined, that somehow, ring formation is related to or derived from translocation.

A complex mechanism in the formation of ring

21 has been described. The first step in the ring 21 configuration is the formation of the rearranged intermediate with duplication of the centromere and the long arm of the chromosome 21. The second step is the chromosomal breaks, in the telomeric region of one of the long arms and a break in the proximal region of the other long arm in the rearranged chromosome. Thus, the preceding event is the rearranged chromosome containing two long arms predisposing the chromosome to the ring formation (Wong et al. 1989).

There seemed to be the mechanical disruption in the cell divisions, throughout the postnatal life of the individual with ring chromosome, because the ring arrangements become entangled or broken or doubled or otherwise disturbed. At the mitotic cell divisions, the daughter cells may have partial or total aneuploidy of the involved chromosome in the ring formation, resulting in 'dynamic mosaicism'. The process of the continuous loss and regeneration of the cells, seriously undermine the growth. Finally, the ring associated syndrome and features pertaining to the involved chromosome may occur with mental and growth retardation and dysmorphogenesis or occasionally to normal phenotype (Gardner and Sutherland 1996).

In the present article, is reported the phenotype and genotype correlation in the male proband, with the ring formation for the chromosome 21.

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MATERIAL AND METHODS

Case Report (Figure 1)

A 3½-year-old male child of 3rd birth order, born to non-consanguineous couple was referred to the chief complaint of mental retardation for karyotyping and counseling. The birth weight was 3.402kgs. He was born with breech and forceps delivery. The proband was kept in incubator. Clinical findings include delayed mile stones, long face, large and low set ears, slight epicanthic folds, short little finger, clinodactyly, simian crease, flat feet and hypogonadism.

At the time of conception, father was 22 years and mother 19. There was family history of

spontaneous abortions. The elder brother was 10 years old and had hot water epilepsy and mild mental retardation. Proband had 2 normal female siblings.

Chromosomal preparations and karyotype were obtained from GTG (G-banding with Trypsin and Giemsa) banded preparation of the peripheral lymphocyte microculture (Schaffer and Tommerup 2005).

RESULTS

50 metaphase spreads were checked and the total number of chromosomes was 46. Among the examined cells, one of the 21s was missing and in its place the ring arrangement was detected.

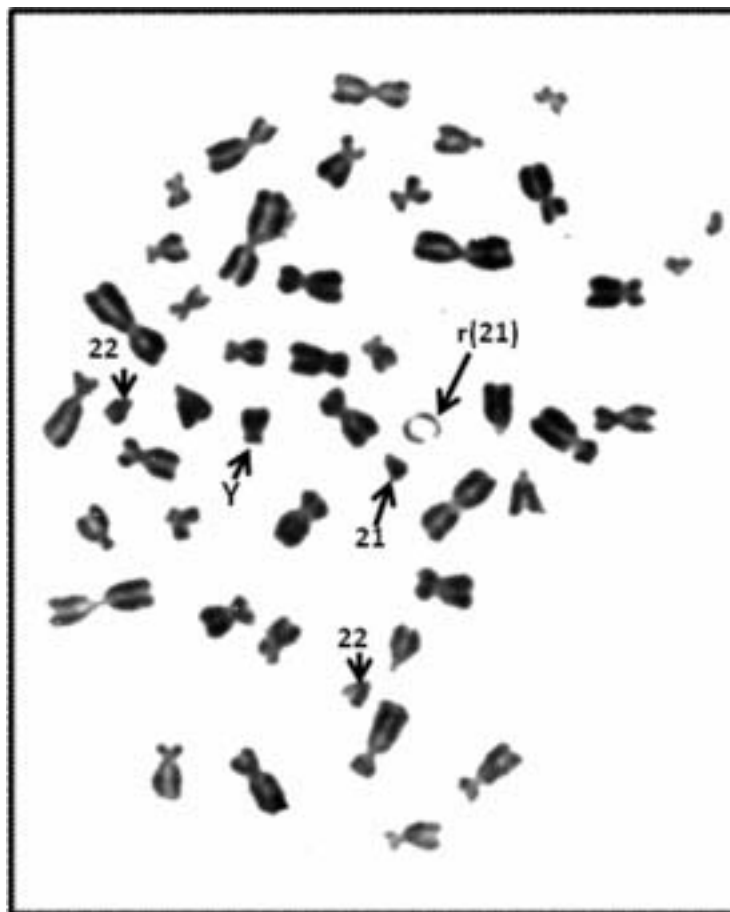


Fig. 1. Metaphase spread: 46,XY,r(21)
Arrows indicate ring 21 and normal 21; chromosomes 22 and Y

Hence, the karyotype was found to be 46,XY,r(21)(p11q21). The break points in 21 were at the p11 region in the short arm (p arm) and q22 region in the long arm (q arm): 46,XY,r(21)(:p11'!q21::) i.e. breakage and reunion at band 21p11 and 21q21. The segments distal to the break points have been deleted.

Chromosome 21 is present from region 11 in short arm (p arm) to the region 21 in the long arm (q arm). Or the regions lost in chromosome 21 are distal to the break points in the short arm: 21p11 to 21pter and long: 21q22 to 21qter. Proband's elder brother had normal karyotype. Parental karyotype could not be confirmed.

DISCUSSION

Ring chromosomes are found as constitutional aberrations associated with developmental abnormalities. Ring formations in the chromosomes may be associated with multiple congenital anomaly (MCA), mental retardation (MR), dysmorphic features, dwarfism, infertility, amenorrhea, bad obstetric history (BOH), epilepsy and tumors. The involved chromosome is an autosome, then, the phenotypic effects are usually serious (Wang et al. 1962; Spinner et al. 2007)

In spite of the presence of the genetically imbalanced karyotype, in individuals with ring chromosomes, the genotype may not be accurately correlated. There are reports, that the carriers with stable ring chromosomes are affected; whereas those with unstable ring chromosomes have manifested normal phenotype (Kennerknecht et al. 1990). For example, a family with ring 21 has been reported. Mother was the carrier for the ring 21. She had dizygotic twin pregnancy and the karyotypes of the twins were 46,XY and 46,XX,r(21). The carriers for ring 21 were normal, both in appearance and intelligence. There seemed to be preponderance for the maternal origin of the ring chromosomes (Melnik et al. 1995).

Nearly, 61 features have been attributed to the ring 21 (de Grouchy and Turleau 1984). The observed features in the ring chromosome 21 syndrome: dysmorphic features, developmental delays, growth retardation, predisposition to the congenital malformations involving neurologic, craniofacial, digestive, genitourinary, skeletal and hematological systems. The presence of ectopia lentis, abdominal hernia, dilated ascending aorta

indicates that the disorders are associated to connective tissue (Rope et al. 2004). In the present case, nearly, 12 (19.67%) of the listed features were noticed. In addition, 4 specific features were noticed in the proband, due to the ring chromosome 21: cleft lip, clinodactyly, short little finger and hypogonadism. These specific features also could be correlated to the lost genes that were situated on chromosome 21.

Chromosome 21, belonging to G group considered to be the smallest chromosome, spans about 47 billion base pairs, and represents 1.5% of the total DNA. 200 to 400 genes have been localized to 21. In its long arm are the 2 major regions and 3 sub-regions; 49 genes and 29 products and 27 disorders are assigned (McKusick and Amberger 2002). The short arm of 21 includes the stalk and the satellite, involved in the organization of the nucleoli, because of the presence of rRNA genes. Hence, in the present study, the loss of regions in 21p may not play any significant functional role in the phenotype. Due to ring configuration, in the present study, nearly 40 genes may have been lost from 21q. The breaks and the lost genes in the deleted segments in 21 may be having the direct and or the indirect effects in the genetic pathway involved in the development of the various systems in the proband, thereby manifested as mental retardation and the clinical findings.

Due to the deletion in the autosomes (1,4,7,8,9,10,11,13,15,18,21,22), partial or total autosomal monosomy results in developmental anomalies of the reproductive system. The critical region in 21 is from 21q22'!qter. In addition to the somatic abnormalities (down slanting palpebral fissures, broad nose, low set ears, cleft palate, cardiac and renal anomalies), micropenis, cryptorchidism, clitoromegaly and frank genital ambiguity have also been noticed (Pinsky et al. 1999). In the present study was the presence of hypogonadism, in the male proband. The variations in the phenotype in ring 21, may be because of the differences in the break points as well as the deleted genetic material.

Genetic Counseling

Counseling Includes the Diagnosis and Prognosis

It has been opined that 99% of the ring formation is of sporadic occurrence and hence,

the recurrence in the family may not occur. However, proband with the ring 21 may have a low risk to get an offspring with Down syndrome, due to Robertsonian translocation or the tandem duplication of the 21 (Kosztolanyi et al. 1987).

The medical management to the proband and the follow up were emphasized. Proband has hypogonadism and the chance to become sub fertile was also explained (Dallapiccola et al. 1986).

CONCLUSION

Male proband with mental retardation and dysmorphic features referred for karyotyping, showed the presence of non-mosaic ring formation in one of the chromosome 21s. The correlated genotype and phenotype provided the information that 21 may also be involved in the development and growth of the primary gonadal tissue in male.

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