Review Article

Received on 31.10.2016, **Accepted on** 26.11.2016

Indian Journal of Genetics and Molecular Research
Volume 5 Number 2, July - December 2016
DOI: http://dx.doi.org/10.21088/ijgmr.2319.4782.5216.3

Varying Manifestations of Ring Chromosome 18

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Abstract

Chromosome 18 represents approximately 2.5% of the total DNA in cells and contains 200 to 300 genes that code for proteins essential for a variety of functions in the body. Partial deletions of the p and q arms can result in ring formation. Ring chromosome 18 is one of the rare structural chromosome abnormalities. This aberration can cause varied phenotypic manifestations ultimately leading to a suboptimal loss of body function. Structural abnormalities affect genes of the defunct part of the chromosome. Subsequent loss of protein translation leads to various genetic abnormalities, depending on the location and extent of the genes deleted during formation of the ring. Hence, there are various manifestations of this disorder. Most of the children with ring chromosomes show a failure to thrive beyond the extent expected from their chromosomal imbalances. The phenotypic diversity observed in Ring 18 is described. Chromosome abnormalities including ring 18 detected in our laboratory in a child with metabolic leukodystrophy are illustrated. The availability of preimplantation genetic diagnosis (PGD) in India and its benefits are highlighted.

Keywords: Ring Chromosome 18; Telomeres; Leukodystrophy; Microarray; NGS; FISH; PGD.

Introduction

Chromosome aberrations resulting in deletions or duplications cause abnormal phenotypic presentations. The clinical manifestation and severity varies, depending on which regions of the genes are affected. There are over 57000 genomic copy number changes between 100 bp and 3 Mb in size, half of which include known genes comprising 30% of the reference genome [1, 2]. As broken chromosomes have sticky ends which tend to rejoin, one of the manifestations of deletions is the formation of a ring chromosome, which is the result of terminal deletions on both arms of a single chromosome. Ring chromosomes were first described by Lilian Vaughan Morgan in 1926 [3] and were later denoted by the symbol "r" in cytogenetic nomenclature. In rare cases, the telomeres at the ends of a chromosome fuse without any disappearance of genetic material [4]. There are genes that are not dosage sensitive meaning that they can be duplicated or deleted with no ill effect. Dosage sensitive genes are linked with phenotypic alterations and out of all the genes only 5-10% will be dosage sensitive [5]. The phenotypic variation depends on the extent of homozygosity, ring chromosome instability and somatic mosaicism [6-10]. Diseases are manifested according to the chromosome that is involved in ring formation. A few examples are ring 20 syndrome which results in epilepsy, ring 13 and 14 which manifest with intellectual disability and dysmorphic facial features, ring 15 associated with intellectual disability, dwarfism and microcephaly and ring X which leads to Turner syndrome.

The different symptomatic presentations depend on the location and amount of deletion of the telomere ends and not solely due to ring formation [11]. However, ring syndrome patients not only display diverse symptoms resulting from deletions or duplications, but most of them have some features in

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common. In a meta-study including more than two hundred patients with congenital ring chromosomes it was demonstrated that the majority of children with rings showed a failure to thrive beyond the extent expected from their chromosomal imbalances. It has been suggested that this is due to the mitotic instability of rings, preventing somatic cells to proliferate normally. The hypothesis is supported by the fact that growth failure is more common among patients with large ring chromosomes, than among those with small ones [12]. The determinant factor in the phenotypic makeup is the genes which code for numerous proteins. Thus, when a part of the chromosome is lost, it results in the loss of genes and the coding proteins and hence manifests as a phenotypic abnormality.

Chromosome 18 Deletion

Chromosome 18 deletion is of 2 types, one with distal deletion where the deletion can occur at the terminal ends of the chromosome at the telomere regions referred to as distal 18p- and 18q- resulting in ring chromosomes, while the other is a proximal deletion where the insult happens closer to the centromeric region. Because of genetic diversity very few people with chromosome 18 deletion will have similar abnormalities. A child with sub-optimal growth and development, delayed milestones, presence of birth defects, subtle facial dysmorphism or any other family member with a chromosomal abnormality should be subjected to genetic evaluation such as karyotyping, followed by microarray [13]. A chromosome microarray (CMA or arrayCGH) report gives genomic coordinates, which are long numbers indicating base pairs that point to the exact location where the deletion or duplication has occurred on a chromosome. This helps in determining the extent of the deletion and the genes involved. The website of the Chromosome 18 Registry and Research Society has given a detailed description of phenotypes associated with altered genes and critical regions on chromosome 18 together with the base pairs and breakpoints as given below [14-16].

Phenotypic Manifestations with Altered Genes on 18p

TGIF1 (*3,451,591-3,458,406):Holoprosencephaly.* This gene is located on chromosome band 18p11.31. Holoprosencephaly is a type of birth defect in which the brain fails to divide into two separate halves during early embryonic development. The patients also have developmental delays, hydrocephalus and seizures.

GNAL (*11,689,014-11,885,683*): *Dystonia.* This gene is located on chromosome band 18p11.21. This condition is most often identified in the teens or early adulthood and manifests as acute dystonia with abnormal movements. Muscles fail to contract and relax appropriately and results in abnormal posture and movement.

Critical regions on 18p require special mention and are associated with a lot of medical and developmental issues when deleted. Some of the recognized disorders associated with critical region deletions are:

Sensorineural Hearing Loss, Strabismus (1-1,192,031)

Ptosis, scoliosis, kyphosis, conductive hearing loss (1-2,931,532)

Sacral agenesis (1-5,520,172)

White matter abnormalities causing leukodystrophy (1-5,389,025)

Tetralogy of Fallot, pectus excavatum (1-9,148,020)

Pituitary anomalies (1-9,849,184)

Seizures (1-10,952,107)

Autoimmune disorders (1-12,317,830)

Hip dysplasia, congenital cataracts (1-13,325,333)

Phenotypic Manifestations with Altered Genes on 18q

SMAD4 (48,556,583-48,611,411): This 18q region deletion results in 2 conditions, juvenile polyposis and hereditary hemorrhagic telangiectasia. The incidence of colonic cancer increases with colonic polyps and hereditary telangiectasias lead to bleeding diathesis.

TCF4 (52,889,562-53,303,188): Pitt Hopkins Syndrome. This includes developmental delay, cognitive impairment, breathing abnormalities and seizures.

TSHZ1 (72,997,498-73,000,596): Aural atresia and stenosis. This gene is located in chromosome band 18q22.3. It manifests as absent ear canal with hearing loss, rocker bottom feet, and cleft lip and palate.

Some recognized disorders associated with critical region deletions in 18q are Atopic disorders (70,220,470-71,304,427)

IgA deficiency *(62,548,985-76,923,991)*

Nystagmus (72,632,502-75,158,616)

Congenital heart disease (69,799,020-78,016,181)

Growth Hormone Deficiency (73,540,560-

75,158,616)

Kidney Abnormalities (73,10,7903-75,158,616)

Delayed Myelination (72,980,819-75,485,284)

Mood Disorders (72,854,624-73,497,405)

Cleft palate (72,379,769-76,526,497)

Once diagnosed with chromosome 18 deletions, appropriate evaluation needs to be done according to the guidelines of the Chromosome 18 Clinical Research Centre [16] such as

- Pedigree analysis, further genetic evaluation and counseling
- Parental chromosome evaluation to check for transmission
- Periodic ophthalmology evaluation
- Periodic hearing evaluations with consideration of hearing aids
- Thyroid testing on annual basis
- Monitoring of growth and referral to endocrinologist if needed
- Renal ultrasound to rule out kidney defects
- Cardiology evaluation to rule out a heart defect
- Orthopedic evaluation for management of foot abnormalities
- Neurologic evaluation if seizures occur
- Referral for developmental services and therapies
- Consideration of a communication device if non-verbal
- Screening for mood disorders; referral to psychiatry if needed

Ring 18 in Leukodystrophies

Leukoencephalopathies are disorders, which selectively involve the cerebral white matter. The term "leukodystrophies" refer to the disorders with primary white matter involvement with a demonstrable biochemical or molecular defect [17]. They are a group of rare, progressive, metabolic, genetic diseases that affect the brain, spinal cord and often the peripheral nerves. Non-development or destruction of white mater of the brain and myelin sheath which is the protective covering of the nerves is the hallmark of this disease pathogenesis [18, 19]. Abnormal myelination has also been reported in cases of 18q deletion [20] and ring 18 [21]. During childhood, they represent an important cause of progressive neurological disability. The presenting symptoms of leukodsytrophy are neurological. With an insidious clinical onset, the symptoms usually progress slowly with possible periods of stagnation. Neurological symptoms of leukodsytrophy are in the form of spasticity and changes in cognition and language. Defective peripheral myelination presents with spasticity and decreased muscle stretch reflexes. MRI is the gold standard to detect the abnormal myelination. Childhood leukodystrophies are classified according to neuroimaging patterns such as confluent MRI lesions, cavitating MRI lesions, hypomyelination and calcification.

Cytogenetic Findings in a Case of Metabolic Leukodystrophy

A two year old boy with developmental delay and metabolic leukodystrophy was referred to our laboratory for cytogenetic analysis. Karyotyping was carried out on Giemsa banded (GTG) metaphases. A ring chromosome 18 was detected in 24 of 25 metaphases analyzed (96%) indicating low-grade mosaicism of the normal cell line (Fig. 1a). Hence the ring formation was likely to be a post-zygotic event. Ten metaphases were karyotyped. The ring was small with only one dark band, indicating a substantial deletion of 18q together with deletion 18p, hence the breakpoints of the ring were denoted as r(18)(p11.2q21.1).

In addition, deletion 1q25 was seen in one metaphase and translocation t(7;14)(q36;q12) was seen in another metaphase suggesting chromosome instability (Figures 1b, 1c). They were unwilling for a microarray and the patient was lost to follow-up.

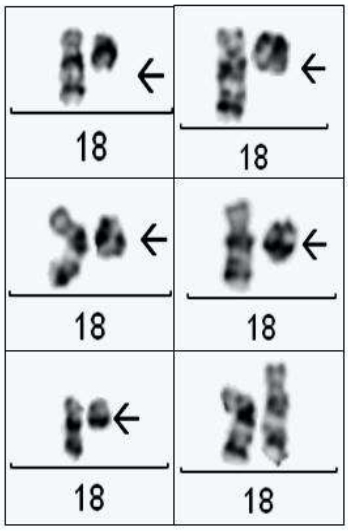

Fig. 1a: Composite showing Ring 18 in different metaphases. One Giemsa banded metaphase was normal.

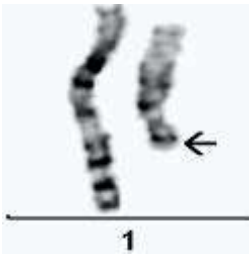

Fig. 1b: Deletion 1q25 in one metaphase

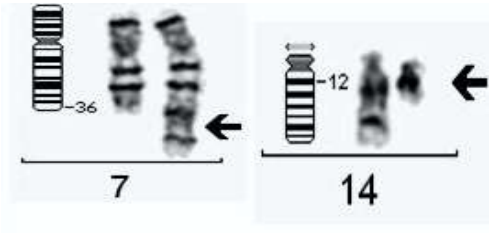

Fig. 1c: Translocation t(7;14)(q36;q12) in one metaphase

Discussion

Though ring chromosomes are very rare, a literature search picked up four published cases from India for constitutional rings 7, 13, 21 and 22 [22-25], though there are likely to be more unpublished cases. The present case is the first report of ring 18 associated with leukodystrophy from India. The diverse phenotypic presentation associated with ring 18 could be due to additional chromosome abnormalities or gene mutations. It also depends on the extent of the deletions during ring formation. Therefore, whole genome high resolution cytogenetic analysis by chromosome microarray and mutation detection by next generation sequencing (NGS) of the exome, though expensive, can provide additional information and will be indispensible for comprehensive diagnosis, accurate genetic counseling and clinical management of families [26].

Preimplantation genetic diagnosis (PGD) and screening (PGS) is possible in a few centres in India, to select unaffected embryos for transfer by opting for *in vitro* fertilization (IVF) if there is a history of chromosomal or single gene disorders in the family [27-32]. Embryos can be frozen while the trophectoderm biopsies are being analyzed, generally by the new techniques of NGS or CMA. However, FISH (fluorescence *in situ* hybridization) is currently the only method available for PGD worldwide, if the breakpoint of a familial translocation is at the tip or telomeric region of the chromosome. Unaffected embryos are thawed for transfer in a subsequent cycle. A pre-PGD workup is essential for accuracy in all PGD cases [33]. PGD and PGS have played a major role in improving the chances of success in IVF and eliminating the need for repeatedly aborting a pregnancy if prenatal diagnosis carried out during pregnancy after a natural conception shows that the fetus is affected.

Key Message

Ring chromosomes are caused by terminal deletions in both the arms of a chromosome. Depending on the extent of the deletion, the phenotype is variable. Ring 18 can occasionally be associated with leukodystrophy. Genetic counseling should include the availability in India of reproductive options such as preimplantation genetic diagnosis (PGD) for carriers of a known chromosomal or gene defect.

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