

## Case Report

# An Indian diagnostic laboratory case report on mosaic chromosome 18

Prachi Sinkar, Minakshi Pandita, Sandhya Iyer\*

Department of Genetics, Thyrocare Technologies Limited, Turbhe, Navi Mumbai, Maharashtra, India

**Received:** 18 October 2020

**Accepted:** 10 January 2021

**\*Correspondence:**

Dr. Sandhya Iyer,

E-mail: [sandhya.iyer@thyrocare.com](mailto:sandhya.iyer@thyrocare.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

Distal 18q deletion syndrome, and ring chromosome 18 are structural abnormalities involving chromosome 18. Distal or terminal deletion event is characterized by deletion of a region from the terminal end of a chromosome, while in ring chromosome, the telomeric ends of both the arms of homologous chromosomes are lost, causing the sticky ends to fuse together to form a ring. Clinical findings vary in each case depending on the type of abnormality, and the region of chromosome affected. This case report focuses on the chromosome 18 abnormality detected in the proband tested with the clinical indication of cleft lip, congenital anomaly, and feeding difficulty. Parental karyotyping to rule out de-novo or abnormality due to inheritance, clinical correlation, genetic counseling and high resolution microarray was recommended.

**Keywords:** Karyotyping, Mosaic, Ring chromosome 18, 18q deletion

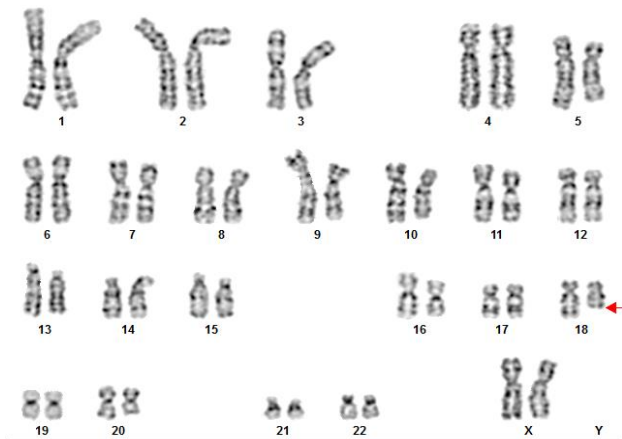
### INTRODUCTION

Abnormalities associated with chromosome 18 include; 18q deletion syndrome, 18p deletion, and ring 18 chromosomes, and the documented occurrence of 18q deletion is approximately 1 in 40,000 live births.<sup>1,2</sup> Distal 18q deletion syndrome, and ring 18 chromosomes are structural abnormalities which occur mostly as a sporadic event, and can be occasionally transferred from parents to off-spring in 1% of the cases, of which 90% bear maternal origin.<sup>3-5</sup> Chromosomal abnormalities can occur either in meiosis or in early post zygotic division.<sup>3</sup> 18q deletion is a syndrome caused by deletion of the long arm of chromosome 18.<sup>1,2</sup> The clinical findings may vary from case-to-case, depending on the percentage of abnormality and the genes affected.<sup>6</sup> Genes present on the long arm of chromosome 18 are postulated to be involved in the production of growth hormone, and hence individuals with deletion in 18q arm exhibit growth hormone deficiency as reported by studies.<sup>2</sup> Evidences of growth failure in each aneuploidy have been found to be unique.<sup>7</sup> Ring chromosome abnormality has been reported in all human chromosomes with variations in clinical

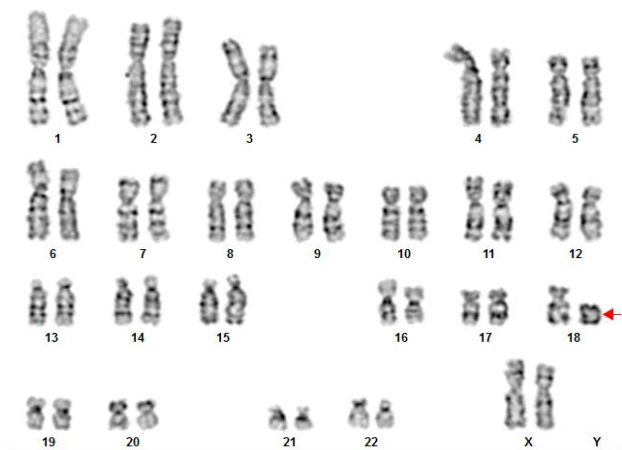
findings.<sup>3,5,8</sup> Formation of ring chromosome involves break in the terminal region of both the chromosome arms, with fusion of the broken arms resulting in the classical form of a ring pattern, or can also occur without the loss of terminal region, wherein the opposite arms fuse together resulting in a complete ring pattern.<sup>3,4,9</sup> During the process of replication, the ring chromosomes need to break open in each of the successive cell cycle, and the event around breaking open, and rejoining may not succeed appropriately, leading to generation of mosaic forms with some cells having ring chromosome, and some cells with loss of the ring chromosome altogether giving rise to monosomy of the affected chromosome.<sup>3,8</sup> Due to the unstable nature of ring chromosomes the genetic material can be modified during each phase of cell division leading to mosaicism.<sup>3,5</sup>

Patients with ring chromosome 18 exhibit telomeric deletion in both the arms and thus express clinical features of 18p minus, and 18q minus syndrome, or can exhibit a combination of both the syndromes.<sup>4</sup> Ring chromosome 18, and distal 18q deletion syndrome are

mostly associated with growth retardation, mental retardation, short stature, congenital aural atresia (CAA), foot deformities, microcephaly, midface hypoplasia, and other non-specific abnormalities.<sup>3,4,9,10</sup> The incidence and the type of congenital anomalies in patients with ring, and deletion in chromosome 18 are similar.<sup>7</sup> In our case, the mosaicism involved chromosomal abnormalities with combination of 18q deletion, and ring 18 which we believe have occurred mostly due to the instability of the ring chromosome.<sup>5</sup> However the exact mechanism of the abnormality continues to be unknown.



**Figure 1: GTG-banded karyotype image derived from patient's peripheral blood sample showing terminal deletion of one of the chromosome 18 at region q21.3 (highlighted by red arrow).**



**Figure 2: GTG-banded karyotype image derived from patient's peripheral blood sample showing ring 18 chromosome at region p11.3q23 (highlighted by red arrow).**

In this study, a conventional karyotyping analysis of the proband detected the karyotype as mos 46, XX, del(18)(q21.3)[34]/46, XX, r(18)(p11.3q23)[16] (Figure 1, 2). No chromosomal abnormality was detected in both the parents tested. For further clarification of breakpoints high resolution microarray was recommended.

## CASE REPORT

Karyotyping was performed on lymphocytes from peripheral blood sample collected in sodium heparin vacutainer, and transported to the College of American Pathologists (CAP) accredited laboratory within 24 hours of collection under ambient conditions. Culture in peripheral blood was initiated in RPMI-1640 with L-Glutamine medium (Roswell Park Memorial Institute - Gibco) supplemented with Pen-strep (Penicillin-streptomycin antibiotic-Gibco), along with phytohemagglutinin (PHA-Gibco), and fetal bovine serum (FBS - Gibco). The tubes were incubated for 48 hours, and 72 hours at 37°C followed by harvesting, and GTG banding which were performed using standard protocol as described in AGT Cytogenetics laboratory manual (fourth edition). Chromosomes were analyzed using Applied Spectral Imaging (ASI) Olympus Microscope (Olympus Corporation, Japan). Karyotype designation was described according to the International System for Cytogenetics Nomenclature (ISCN 2016).

FISH testing was performed on metaphase culture obtained from the lymphocytes of the proband's peripheral blood sample using standard protocol as described in AGT Cytogenetics laboratory manual followed by pre-hybridization, hybridization and post hybridization. Signals were analyzed using fluorescence microscope (Olympus Corporation, Japan). Centromere specific probe kit (X/Y/18) (MetaSystems Probes GmbH) was used to confirm the presence of, and study chromosome 18.

Here we report a case with complex chromosome anomaly involving mosaicism for chromosome 18. The referred patient was a female baby born full term by cesarean section to a healthy, young, and non-consanguineous couple without any complications in the pregnancy period. The elder sister of the proband was documented to be healthy and phenotypically normal. For the proband, cleft lip was observed during ultrasonography on 32-33 weeks of gestational age with mild polyhydramnios.

Proband has a history of paternal grandfather with mild mental retardation, and rest all the family members have no history of physical anomalies. Proband was referred to the cytogenetics laboratory for karyotyping testing at the age of 15 days with clinical indication of cleft lip, congenital heart defect, and feeding difficulty. Chromosomal analysis was performed on GTG banded slides by standard protocol.

A total of 50 cells were analyzed which revealed a mosaic karyotype pattern involving 34 cells with deletion of chromosome 18 at region q21.3 (Figure 1) and 16 cells with ring formation of chromosome 18 at region p11.3q23 (Figure 2). To rule out the origin of occurrence, parents were also recommended for the cytogenetics evaluation, and were found to be normal. Additional

FISH test was performed, and the result revealed the presence of 18 centromeric regions in all the 200 metaphases scanned.

## DISCUSSION

A 15-days-old female child was reported as deletion and ring mosaicism involving chromosome 18 in a total of 50 metaphases analyzed from peripheral blood lymphocytes. Conventional cytogenetics screening (Figure 1, 2) was used, and the reported proband karyotype was described as 46,XX,del(18)(q21.3)[34]/ 46,XX,r(18)(p11.3q23)[16], with high-level mosaicism for 18q arm deletion at region q21.3 (Figure 1) and a low-level mosaicism for ring 18 at region p11.3q23 (Figure 2).

Chromosomes contain genetic information, and any alteration in the genetic makeup of the same can lead to an altered phenotype. The severity of the abnormality or alteration is directly proportional to the amount of genetic material lost or altered. Patients with chromosomal abnormality may exhibit variety of phenotype depending on the type of abnormality, and chromosome involved.<sup>8</sup>

Additional FISH test was performed to confirm the presence of centromeric region in chromosome 18. A total of 200 metaphases were analyzed, which showed two copies of chromosome X and two copies of chromosome 18. Parents were advised for karyotyping test to identify the inheritance of abnormality, and normal karyotype results were obtained; 46, XY in father and 46, XX in mother which concluded the cause of occurrence as de-novo.

## CONCLUSION

In conclusion, the mosaicism presents with the combination of chromosome 18 deletion and ring chromosome 18 has severe impact. This case report highlights the identification of a mosaic pattern involving chromosome 18 as a sporadic event. Further studies are required to describe the critical regions involving deletion and the phenotype-genotype relation in deletion 18q syndrome.

*Funding: No funding sources*

*Conflict of interest: All the contributing authors are employees of Thyrocare Technologies Limited. However, no remuneration has been received for this study and hence no aspect which can be construed as potential conflict of interest exists.*

*Ethical approval: Not required*

## REFERENCES

1. Feenstra I, Vissers LELM, Orsel M, van Kessel AG, Brunner HG, Veltman JA, et al. Genotype-phenotype mapping of chromosome 18q deletions by high-resolution array CGH: an update of the phenotypic map. *Am J Med Genet A*. 2007;143A(16):1858-67.
2. Hale DE, Cody JD, Baillargeon J, Schaub R, Danney MM, Leach RJ. The spectrum of growth abnormalities in children with 18q deletions. *J Clin Endocrinol Metab*. 2000;85(12):4450-4.
3. Caba L, Rusu C, Plăiașu V, Gug G, Grănescu M, Bujoran C, et al. Ring autosomes: Some unexpected findings. *Balkan J Med Genet*. 2012;15(2):35-46.
4. Heydari S, Hassanzadeh F, Nazarbadi MH. Ring chromosome 18: A case report. *Int J Mol Cel Med*. 2014;3(4):287-89.
5. Yip MY. Autosomal ring chromosomes in human genetic disorders. *Transl Pediatr*. 2015;4(2):164-74.
6. Budisteanu M, Arghir A, Chirieac SM, Tutulan-Cunita A, Lungeanu A. 18q deletion syndrome - A case report. *Maedica (Bucur)*. 2010;5(2):135-8.
7. Gereltzul E, Baba Y, Suda N, Shiga M, Inoue MS, Tsuji M, et al. Case report of de novo dup(18p)/del(18q) and r(18) mosaicism. *J Hum Genet*. 2008;53:941-46.
8. Guilherme RS, Meloni VFA, Kim CA, Pellegrino R, Takeno SS, Spinner NB, et al. Mechanisms of ring chromosome formation, ring instability and clinical consequences. *BMC Med Genet*. 2011;12:171.
9. Chen CP, Kuo YT, Lin SP, Su YN, Chen YJ, Hsueh RY, et al. Mosaic ring chromosome 18, ring chromosome 18 duplication/deletion and disomy 18: perinatal findings and molecular cytogenetic characterization by fluorescence in situ hybridization and array comparative genomic hybridization. *Taiwan J Obstet Gynecol*. 2010;49(3):327-32.
10. Knijnenburg J, van Haeringen A, Hansson KBM, Lankester A, Smit MJM, Belfroid RDM, et al. Ring chromosome formation as a novel escape mechanism in patients with inverted duplication and terminal deletion. *Eur J Hum Genet*. 2007;15(5):548-55.

**Cite this article as:** Sinkar P, Pandita M, Iyer S. An Indian diagnostic laboratory case report on mosaic chromosome 18. *Int J Sci Rep* 2021;7(2):137-9.