



Contents lists available at ScienceDirect

## Taiwanese Journal of Obstetrics &amp; Gynecology

journal homepage: [www.tjog-online.com](http://www.tjog-online.com)

## Case Report

## Clinical, cytogenetic and molecular analyses of a rare case with ring chromosome 15 and review of the literature



Hui-Yuan Shao, Hong-Ling Wang, Hong Wu, Xiao-Yan Liu, Zong-Yu Miao\*

Medical Laboratory Center, Yantai Yu Huang Ding Hospital, Shandong, China

## ARTICLE INFO

## Article history:

Accepted 5 May 2020

## Keywords:

SNP array

Cytogenetic

Ring chromosome 15

Micro-duplication

## ABSTRACT

**Objective:** Ring chromosome 15 [r (15)], accompanied by a series of clinical symptoms, is a rare genetic disease. The genotype and phenotypic diversity of patients with r (15) still needed further enrichment. In this study we present a rare case of mosaic ring chromosome 15 with facial anomalies and extremities slenderness.

**Case report:** This case involves a 30-year-old woman, unpregnancy within 6 years. Clinical examination of the patient only revealed facial anomalies and extremities slenderness. The result of routine G-band karyotyping was 46,XX,r(15)(p12q26.3)[53]/46,XX,r(15;15)(p11.2q26.3;p11.2q11.2)[28]/45,XX,-15[10]/46,XX,r(15;15)(p11q26.3;p11q26.3)[4]. SNP array was employed to investigate the genome copy number variations (CNVs). The result revealed that there was a micro-duplication of 2.0 Mb at 15q26.3(arr[ph19]15q26.3 (100,400,214–102,429,112)×3). The duplicated chromosomal section encompassed genes including CHSY1, ALDHIA3, LRRK1, and INS1. We further compared to the cytogenetic characteristics and clinical symptoms of the patient with those already reported by reviewing the literature.

**Conclusion:** This report is especially helpful to supplement the phenotypic diversity of patients with r (15).

© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Ring chromosome 15 [r (15)] is a rare genetic abnormality. Clinical examination of the patients with r (15) revealed a series of clinical symptoms, such as intellectual disability, congenital heart disease, severe growth retardation, hypertelorism, microcephalus, special face, multiple hyperpigmented or café-au-lait spots, short stature, clinodactyly and so on [1–4]. Though about 100 patients with r (15) have been reported in the literature, the genotype and phenotypic diversity of patients with r (15) still needed further enrichment. Here, we presented a rare case of mosaic ring chromosome 15 which had a micro-duplication of 2.0 Mb at 15q26.3. At the same time, we further analyzed the clinical symptoms of the patients with 15q duplication by reviewing the literature.

## Case report

This case involves a 30-year-old woman, unpregnancy within 6 years. Clinical examination of the patient revealed facial anomalies (a

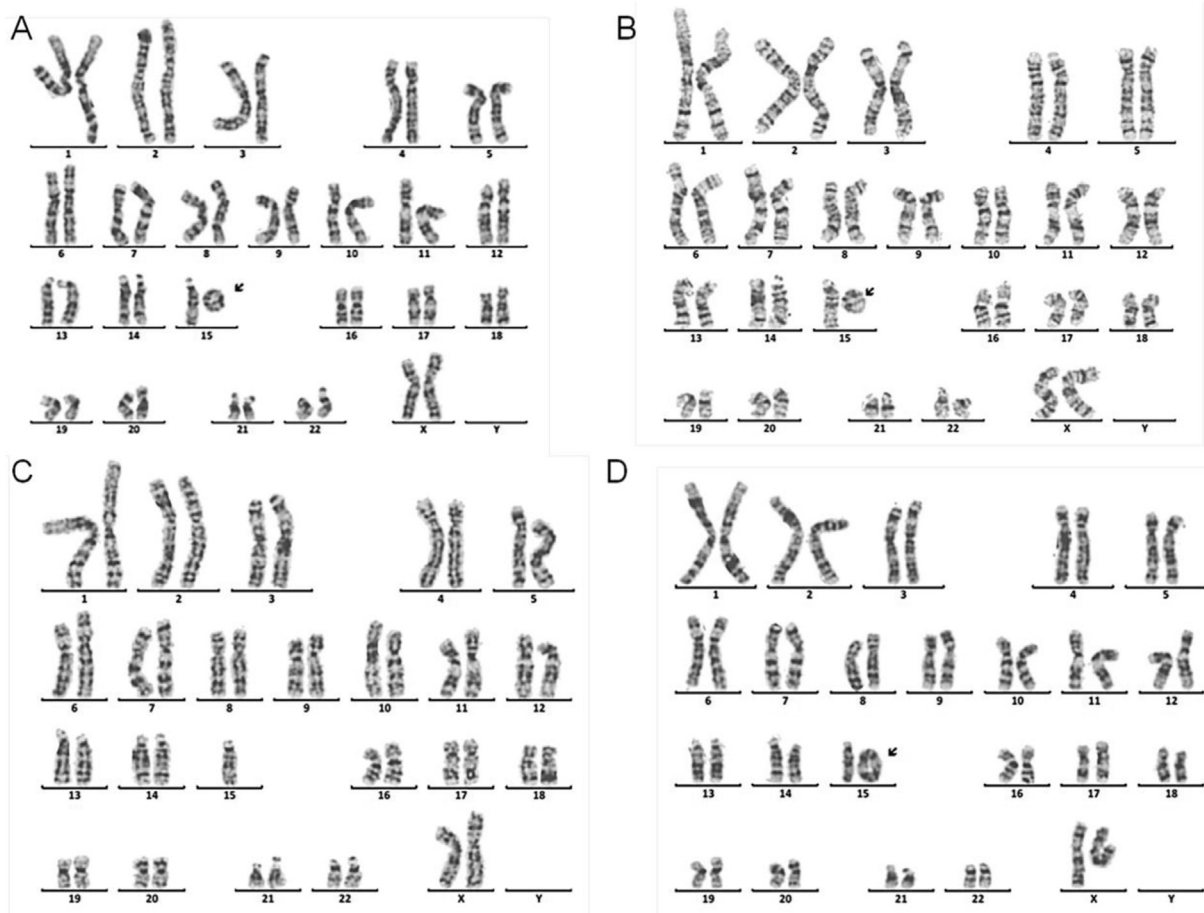
long thin face and micromandible), extremities slenderness, normal intelligence, normal height (170 cm) and weight (58 kg). In order to find out the cause of infertility, the patient underwent a series of tests. Sex hormone, fallopian tube, endometrium, menstrual cycle and other results were normal. The result of routine G-band karyotyping was 46,XX,r(15)(p12q26.3)[53]/46,XX,r(15;15)(p11.2q26.3;p11.2q11.2)[28]/45,XX,-15[10]/46,XX,r(15;15)(p11q26.3;p11q26.3)[4] (Fig. 1). SNP array revealed that there was a micro-duplication of 2.0 Mb at 15q26.3(arr[ph19]15q26.3(100,400,214–102,429,112)×3) (Fig. 2). The duplicated chromosomal section encompassed the genes CHSY1, ALDHIA3, LRRK1, and INS1.

The patient is free from harmful substances and radiation exposure history as well as family history of chromosome disease. This study was approved by the Medicine Ethics Committee of Yantai Yu Huang Ding Hospital. Informed consent was obtained from participant.

## Discussion

As is known, r (15) is an uncommon chromosomal abnormality which results from the loss of the distal ends of both the p and q chromosome arms, followed by fusion of the broken ends [5]. A genotype–phenotype correlation is determined by the extent of

\* Corresponding author. Medical Laboratory Center, Yantai Yu Huang Ding Hospital, 20#, the East Road of Yu Huang Ding, Zhifu District, Yantai, 264000, Shandong, China.  
E-mail address: [miaozongyu313@163.com](mailto:miaozongyu313@163.com) (Z.-Y. Miao).



**Fig. 1.** The chromosome karyotype of lymphocytes in peripheral blood. The abnormal Chromosome 15 was marked by arrow. A:46,XX,r(15;15)(p11.2q26.3;p11.2q11.2).B: 46,XX,r(15)(p12q26.3).C: 45,XX, -15.D: r(15;15)(p11q26.3;p11q26.3).

euchromatic loss, the level of mosaicism, the mitotic instability of ring chromosome and the variation of tissue-specific mosaicism [6,7].

r (15) syndrome is a complex genetic disease with diverse clinical symptoms. The main clinical manifestations of r (15) syndrome are severe growth retardation (76.53%), low weight (42.86%), microcephalus (39.8%), clinodactyly (33.67%), and special face (32.65%) [3]. Patients with a breakpoint on 15q26 are often accompanied by some common clinical manifestations, such as musculoskeletal abnormalities and growth retardation [3]. In this report, G-band karyotyping revealed a karyotype of 46,XX,r(15)(p12q26.3)[53]/46,XX, r(15;15) (p11.2q26.3;p11.2q11.2) [28]/45,XX,-15[10]/46,XX,r(15;15)(p11q26.3; p11q26.3)[4]. This karyotype is very complex and rare, and the patient only implicated with facial anomalies and extremities slenderness. Therefore, this report could be played an important role to improve the genotype and phenotypic diversity of patients with r (15).

CNVs include important and functional DNA sequences and are one of the most common causes of human disease. In this report, SNP array was employed to investigate the CNVs. The result revealed that there was a micro-duplication of 2.0 Mb at 15q26.3(arr[ph19] 15q26.3(100,400,214- 102,429,112)×3). It has been reported that the duplication of 15q26 was associated with a range of clinical manifestations [8–16] (Table 1). In our study, the patient presented with facial anomalies and extremities slenderness. Among the clinical

symptoms of patients with duplication of 15q26 which have been reported, facial anomalies (75.00%, 9/12) are the most common symptoms and extremities slenderness is rarely mentioned. Overgrowth (58.33%, 7/12) and psychomotor retardation (50.00%, 6/12) are the other two most common symptoms of patients with the duplication of 15q26. However, the patient in this study had normal height (170 cm) and intelligence.

The duplications of 15q24→qter and 15q25→qter are the other two common structural abnormality of chromosome 15. The simple retrospective analysis of chromosome karyotypes and clinical symptoms of patients with the duplication of 15q24→qter and 15q25→qter was done (Table 2). The results showed that facial anomalies, which is mainly manifested as a narrow asymmetric face with down-slanting palpebral fissures, a Large, prominent nose, and micrognathia (64.29%; 9/14), developmental delay (57.14%,8/14) and overgrowth (35.71%, 5/14) are three common clinical symptoms, which was consistent with the patients with the duplication of 15q26. Furthermore, compared with the duplication of 15q26, congenital heart disease (35.71%, 5/14) and renal disease (28.57%, 4/14) had a higher incidence in patients with the duplications of 15q24→qter and 15q25→qter.

In addition, SNP array also detected that the duplicated chromosomal section encompassed genes, including CHSY1, ALDHIA3, LRRK1, and INS1. Studies have shown that CHSY1 mutation was associated with Temtamy preaxial brachydactyly syndrome [31],

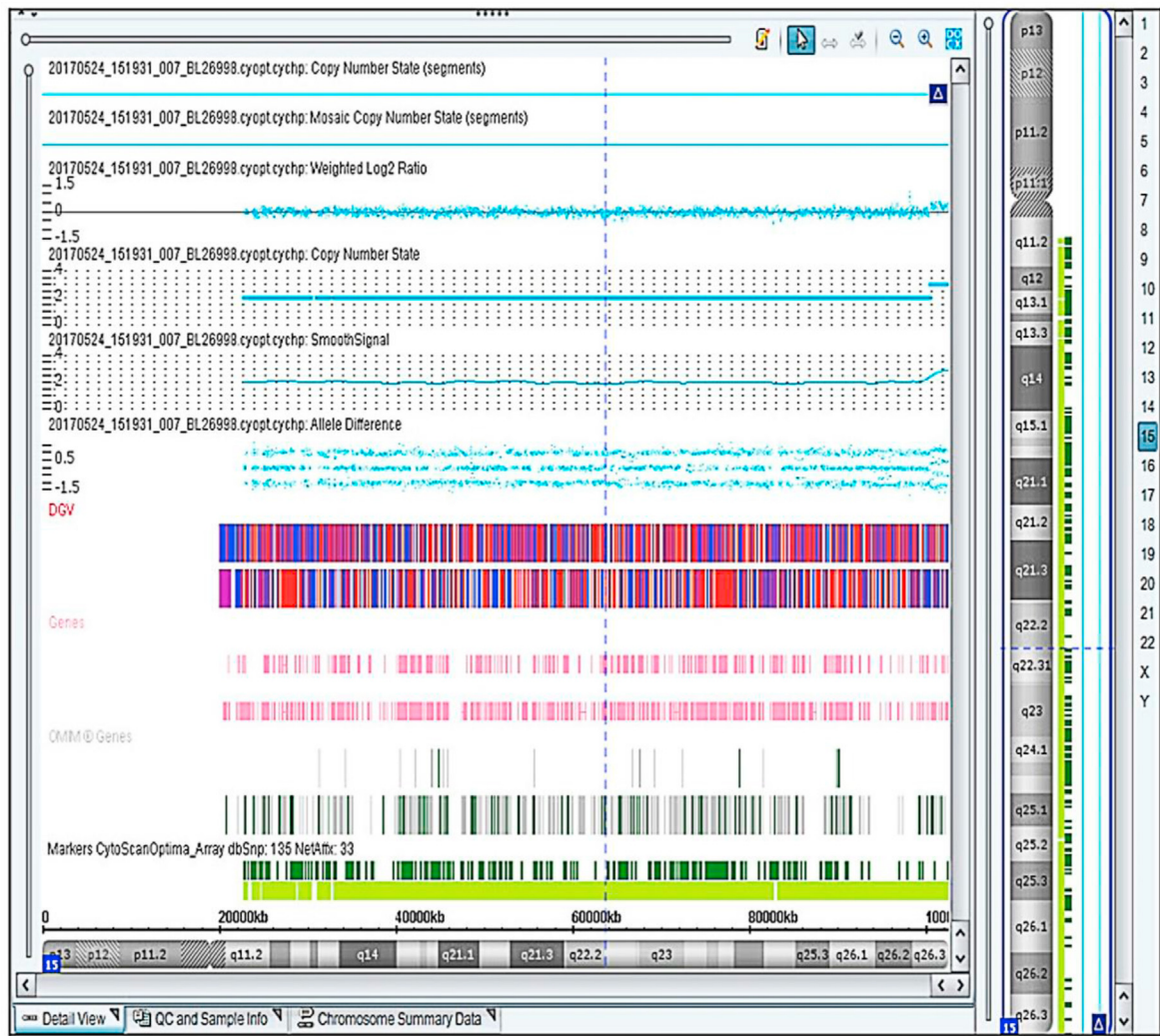


Fig. 2. The genome copy number variations was detected by SNP array.

ALDHIA3 was a cancer stem cell-related gene, LRRK1 mutation was associated with osteosclerotic metaphyseal dysplasia [32], and LINS1 mutation was associated with mental retardation [33], but the patient did not have these symptoms. So the further follow-up is necessary for this patient.

In summary, we present a rare case of r (15) accompanied by facial anomalies and extremities slenderness. This report is especially helpful to supplement the genotype and phenotype diversity of patients with r (15). In addition, we analyzed the clinical symptoms of patients with 15q duplication.

**Table 1**  
The karyotypic characteristics and clinical feature of patients with duplication of 15q26.

Reference	Karyotypic characteristics	Clinical feature
[8]	46,XY,-2,+der(2),t(2;15)(q37;q26)pat	multiple congenital anomalies including complex craniosynostosis
[9]	trisomy 15q26.1 → qter	overgrowth, craniosynostosis, facial anomalies, finger joint contractures
[9]	trisomy 15q26.1 → qter	craniosynostosis, facial anomalies, and finger joint contractures
[10]	trisomy 15q26.1 → qter	overgrowth, macrocephaly and mild developmental delay (four cases)
[11]	trisomy of 15q26 → qter	overgrowth
[12]	46,XX,dup (15)(pter → q26.3::q24 → qter)	developmental delay, scoliosis, mild dysmorphism
[13]	inverted duplication of 15q26.1 → qter	Additional folds of skin were present behind the neck, and feet, fingers and toes were abnormally long, renal failure
[14]	trisomy 15q26 → qter	overgrowth, psychomotor retardation, a cranio-facial dysmorphism
[15]	trisomy 15q26 → qter	micro-dolichocephaly, palpebral fissures slightly oriented downwards and outwards, a large nose, pronounced micrognathia, prominent aural helices, ligament abnormalities, osseous malformations evocative of diastrophic dwarfism, severe congenital heart defect, and profound encephalopathy.

**Table 2**

The karyotypic characteristics and clinical feature of patients with duplication of 15q24→qter and 15q25→qter.

Reference	Karyotypic characteristics	Clinical feature
[16]	duplication of 15q24→qter	Ebstein anomaly of the tricuspid valve
[17]	inverted triplication of 15q24→q26	Overgrowth
[18]	tetrasomy 15q24.3→qter	body asymmetry, facial dysmorphism, arachnodactyly, severe scoliosis, and mental
[19]	inv dup(15) (qter→q24::q24→qter)	low-set dysplastic ears, micrognathia, high-arched palate, antimongoloid slant of palpebral fissures, epicanthal folds, bulbous nose, long philtrum, down-turned corners of the mouth, ulnar-deviated hands, and arachnodactyly of fingers and toes, skeletal dysplasia, mental retardation, overgrowth
[20]	tetrasomy 15q24→qter	heart defect, bilateral hydronephrosis
[21]	duplication of chromosome 15q24q26.3	overgrowth, mental retardation
[22]	duplication of chromosome 15q24→q26.3	ptosis, small size, developmental delay(two cases)
[23]	46,XX,inv(9)(p12q13),dup(15)(q24q26.3)	intrauterine overgrowth, a narrow asymmetric face with down-slanting palpebral fissures, a large, prominent nose, and micrognathia, arachnodactyly, camptodactyly, congenital heart disease, hydronephrosis, hydroureter
[24]	inverted duplication of 15q25→qter	severe hypotonia, cardiovascular defects, hearing loss, central nervous system anomalies, and facial anomalies
[25]	inverted duplication of 15q25→qter	mental retardation, absent speech, hypotonia, minor facial anomalies, unusual digits, pigmentation anomalies
[26]	tetrasomy 15q25.3→qter	macrosomia, long fingers and toes, and craniosynostosis, bilateral called nephroblastoma
[27]	15q25→qter trisomy	overgrowth
[28]	tetrasomy 15q25.2→qter	heart defect, pleural effusion, clubbed feet, absent right kidney, distinct facial features
[29]	tetrasomy 15q25.2→qter	development delay, arachnodactyly, joint contractures and typical facial dysmorphism including frontal bossing, short palpebral fissures, long philtrum, low-set ears, high-arched palate and retrognathia
[30]	ish der(15)(qte→q25::q25 [neocen]→qter)	overgrowth, partial deafness

## Authors' contributions

Hui-Yuan Shao and Hong-Ling Wang contributed equally to this work.

## Declaration of competing interest

The authors declare no conflict of interest.

## Acknowledgements

We thank the patient for her kind cooperation in this study.

## References

- Britto IS, Regina Silva Herbest S, Tedesco GD, Drummond CL, Bussamra LC, Araujo Júnior E, et al. Prenatal diagnosis of a fetus with ring chromosomal 15 by two- and three-dimensional ultrasonography. *Case Rep Obstet Gynecol* 2014;2014:495702.
- Szabó A, Czakó M, Hadzsiev K, Duga B, Bánfai Z, Komlósi K, et al. Small supernumerary marker chromosome 15 and a ring chromosome 15 associated with a 15q26.3 deletion excluding the IGF1R gene. *Am J Med Genet A* 2018;176(2):443–9.
- Paz-Y-Miño C, Guevara-Aguirre J, Paz-Y-Miño A, Velarde F, Armendáriz-Castillo I, Yumiceba V, et al. Ring chromosome 15—cytogenetics and mapping arrays: a case report and review of the literature. *J Med Case Rep* 2018;16:12(1):340.
- Ribeiro Dias Barroso C, Silveira Gomes L, Abrantes Silvestre V, Yamada Utigawa C. Cutis tricolor parvumaculata in ring chromosome 15 syndrome: a case report. *Pediatr Dermatol* 2018;35(3):e204–5.
- Tan SJ, Chen CH, Chen CP, Chen CW, Chen CY, Hwang KS. Prenatal diagnosis of mosaic ring chromosome 15 with abnormal maternal serum Down syndrome screening and Dandy-Walker malformation. *Taiwan J Obstet Gynecol* 2012;51(1):109–11.
- Guilherme RS, Meloni V de F, Takeno SS, Pellegrino R, Brunoni D, Kulikowski LD, et al. Twenty-year cytogenetic and molecular follow-up of a patient with ring chromosome 15: a case report. *J Med Case Rep* 2012;6:283.
- Guilherme RS, Meloni VF, 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.
- Van Allen MI, Siegel-Bartelt J, Feigenbaum A, Teshima IE. Craniosynostosis associated with partial duplication of 15q and deletion of 2q. *Am J Med Genet* 1992;43(4):688–92.
- Nagai Toshiro, Shimokawa Osamu, Harada Naoki, Sakazume Satoru, Ohashi Hirofumi, Matsumoto Naomichi, et al. Postnatal overgrowth by 15q-trisomy and intrauterine growth retardation by 15q-monosomy due to familial translocation t(13;15): dosage effect of IGF1R? *Am J Med Genet* 2002;113(2):173–7.
- Faivre Laurence, Gosset Philippe, Cormier-Daire Valérie, Odent Sylvie, Jeanne Amiel, Giurgea Irina, et al. Overgrowth and trisomy 15q261-qter including the IGF1 receptor gene: report of two families and review of the literature. *Eur J Hum Genet* 2002;10(11):699–706.
- Kant SG, Kriek M, Walenkamp MJ, Hansson KB, van Rhijn A, Clayton-Smith J, et al. Tall stature and duplication of the insulin-like growth factor I receptor gene. *Eur J Med Genet* 2007;50(1):1–10.
- Chandler K, Schrander-Stumpel CT, Engelen J, Theunissen P, Fryns JP. Partial trisomy 15q: report of a patient and literature review. *Genet Couns* 1997;8(2):91–7.
- Mahjoubi F, Peters GB, Malafiej P, Shalhoub C, Turner A, Daniel A, et al. An analphoid marker chromosome inv dup(15)(q261qter), detected during prenatal diagnosis and characterized via chromosome microdissection. *Cytogenet Genome Res* 2005;109(4):485–90.
- Zabel B, Baumann W. Partial trisomy for the distal part of the long arm of chromosome 15 due to a balanced maternal X/15 translocation. *Ann Genet* 1977;20(4):285–9.
- Turleau C, de Grouchy J, Chavin-Colin F, Roubin M. Distal trisomy 15q. *Ann Genet* 1977;20(3):214–6.
- Miller MS, Rao PN, Dudovitz RN, Falk RE. Ebstein anomaly and duplication of the distal arm of chromosome 15: report of two patients. *Am J Med Genet A* 2005;139A(2):141–5.
- James PA, Aftimos S, Oei P. Partial tetrasomy 15 due to a unique inverted triplication of chromosome 15q24–q26. *Am J Med Genet A* 2004;130A(2):208–10.
- Schluth C, Mattei MG, Mignon-Ravix C, Salman S, Alembik Y, Willig J, et al. Intrachromosomal triplication for the distal part of chromosome 15q. *Am J Med Genet A* 2005;136(2):179–84.
- Blennow E, Telenius H, de Vos D, Larsson C, Henriksson P, Johansson O, et al. Tetrasomy 15q: two marker chromosomes with no detectable alpha-satellite DNA. *Am J Hum Genet* 1994;54(5):877–83.
- Spiegel M, Hickmann G, Senger G, Kozłowski P, Bartsch O. Two new cases of analphoid marker chromosomes. *Am J Med Genet A* 2003;116A(3):284–9.
- Gutiérrez-Franco Mde L, Madariaga-Campos Mde L, Vásquez-Velásquez AI, Matute E, Guevara-Yáñez R, Rivera H. A girl with 15q overgrowth syndrome and dup(15)(q24q263) that included telomeric sequences. *Korean J Lab Med* 2010;30(3):318–24.
- Roggenbuck JA, Mendelsohn NJ, Tenenholz B, Ladda RL, Fink JM. Duplication of the distal long arm of chromosome 15: report of three new patients and review of the literature. *Am J Med Genet A* 2004;126A(4):398–402.
- Abe Y, Tanaka D, Soga T, Takeuchi T, Iikura Y. A case of de novo distal duplication of chromosome 15. *Clin Genet* 2003;63(1):76–8.
- Huang B, Ning Y, Lamb AN, Sandlin CJ, Jamehdor M, Ried T, et al. Identification of an unusual marker chromosome by spectral karyotyping. *Am J Med Genet* 1998;80(4):368–72.
- Rowe AG, Abrams L, Qu Y, Chen E, Cotter PD. Tetrasomy 15q25→qter: cytogenetic and molecular characterization of an analphoid supernumerary marker chromosome. *Am J Med Genet* 2000;93(5):393–8.
- Hu J, McPherson E, Surti U, Hasegawa SL, Gunawardena S, Gollin SM. Tetrasomy 15q253→qter resulting from an analphoid supernumerary marker chromosome in a patient with multiple anomalies and bilateral Wilms tumors. *Am J Med Genet* 2002;113(1):82–8.



- [27] Faivre Laurence, Rousseau Thierry, Laurent Nicole, Gosset Philippe, Sanlaville Damien, Thauvin-Robinet Christel, et al. Prenatal overgrowth and mosaic trisomy 15q25-qter including the IGF1 receptor gene. *Prenat Diagn* 2004;24(5):393–5.
- [28] George-Abraham JK, Zimmerman SL, Hinton RB, Marino BS, Witte DP, Hopkin RJ. Tetrasomy 15q252→qter identified with SNP microarray in a patient with multiple anomalies including complex cardiovascular malformation. *Am J Med Genet A* 2012;158A(8):1971–6.
- [29] Xu H, Xiao B, Ji X, Hu Q, Chen Y, Qiu W. Nonmosaic tetrasomy 15q252→qter identified with SNP microarray in a patient with characteristic facial appearance and review of the literature. *Eur J Med Genet* 2014;57(7):329–33.
- [30] Huang XL, de Michelena MI, Mark H, Harston R, Benke PJ, Price SJ, et al. Characterization of an analphoid supernumerary marker chromosome derived from 15q25→qter using high-resolution CGH and multiplex FISH analyses. *Clin Genet* 2005;68(6):513–9.
- [31] Sher G, Naeem M. A novel CHSY1 gene mutation underlies Temtamy preaxial brachydactyly syndrome in a Pakistani family. *Eur J Med Genet* 2014;57(1):21–4.
- [32] Guo Long, Girisha Katta M, Iida Aritoshi, Hebbar Malavika, Shukla Anju, Shah Hitesh, et al. Identification of a novel LRRK1 mutation in a family with osteosclerotic metaphyseal dysplasia. *J Hum Genet* 2017;62(3):437–41.
- [33] Sheth J, Ranjan G, Shah K, Bhavsar R, Sheth F. Novel LINS1 missense mutation in a family with non-syndromic intellectual disability. *Am J Med Genet A* 2017;173(4):1041–6.