Journal of Assisted Reproduction and Genetics (2018) 35:721–725
https://doi.org/10.1007/s10815-018-1117-5

GENETICS

Characterization of a complex chromosomal rearrangement involving chromosomes 1, 3, and 4 in a slightly affected male with bad obstetrics history

Pritti K. Priya[1] · Vineet V. Mishra[2] · Thomas Liehr[3] · Monika Ziegler[3] · Stuti Tiwari[4] · Alpesh Patel[5] · Shiva Shankar Chettiar[5] · Hetvi Patel[2]

Received: 10 July 2017 / Accepted: 4 January 2018 / Published online: 23 January 2018

Background

Complex chromosomal rearrangements (CCRs) are rare structural chromosomal aberrations characterized by more than two breakpoints in one or more chromosomes, with inter- as well as intra-chromosomal insertions of single segments [1, 2]. These abnormalities may involve distal segments causing mainly reciprocal translocations and/or interstitial segments leading predominantly to insertions, inversions, deletions, or duplications [3, 4].

Notably, CCRs are rare structural rearrangements which can be balanced or unbalanced.

The phenotype of CCR carriers varies from normal to mild to severely affected with congenital abnormalities and/or intellectual disability. The likelihood of an abnormal phenotype increases with the number of breakpoints associated with an apparently balanced CCR [5–7]. Till date, more than 250 CCR cases involving three or more chromosomes have been reported, and most of them were de novo.

While almost all unbalanced CCRs lead to serious clinical problems for the carrier, balanced CCRs may go unrecognized until the affected carriers is diagnosed with a severe reproductive impairment. The latter is due to meiotic disturbance and/or chromosomal imbalances in the resulting gametes [8–10]. Thus, there is a high risk of miscarriage or having live born children with unbalanced chromosomal rearrangements due to the CCR.

Often, it is not possible to distinguish balanced from unbalanced CCRs only by banding cytogenetics. Advanced techniques like fluorescence in situ hybridization (FISH) may also not be conclusive in all cases [11–14]. However, array comparative genomic hybridization (aCGH) studies have been shown to be suited to identify cryptic CCRs [1, 15, 16].

Here, we present an adult male with minor facial dysmorphism, speech impairment, and a history of previous unsuccessful pregnancy in the partnership. A CCR with cryptic imbalances of about 1.5 megabase pairs (Mbp) was identified.

Material and methods

Case presentation

A 32-year-old male and his 26-year-old wife contacted a genetic counselor due to medical issues in the previous conception, which was terminated after sonographic detection of not nearer specified brain anomaly in eighth week of gestation. A mild facial dysmorphism with

✉ Pritti K. Priya
preeti.ikdrc@gmail.com

[1] Genetic Division, Department of Obstetrics and Gynaecology, Institute of Kidney Diseases and Research Centre (IKDRC-ITS), Ahmedabad 380016, India

[2] Department of Obstetrics and Gynaecology, IKDRC, Ahmedabad, Gujarat, India

[3] Jena University Hospital, Institute of Human Genetics, Friedrich Schiller University, Kollegiengasse 10, 07743 Jena, Germany

[4] All India Child Development and Genetic Centre, Lawyers Colony, Agra 282005, India

[5] Geneexplore Diagnostics and Research Centre Pvt. Ltd., Ahmedabad, India

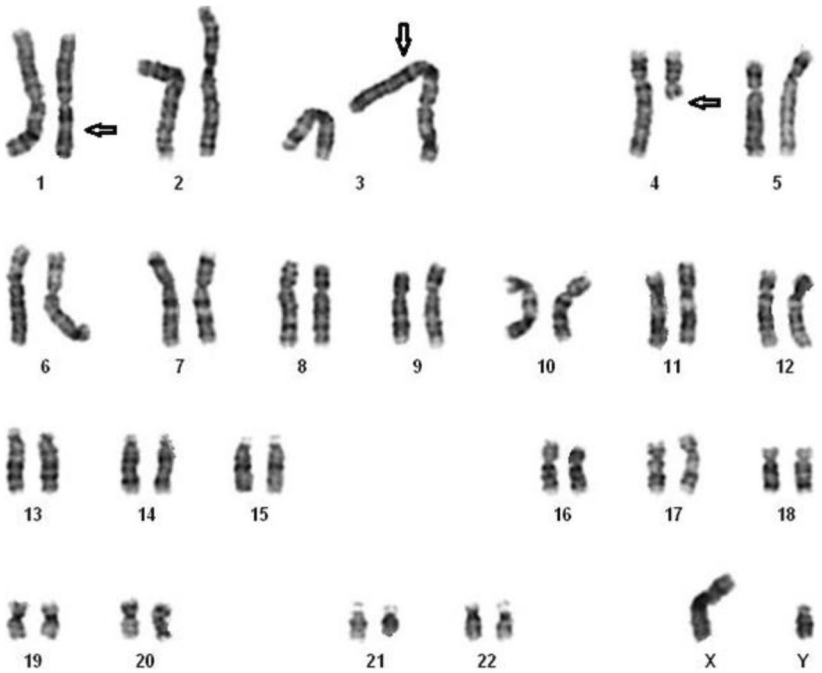

Fig. 1 GTG-banded karyotype of the patient showing three derivative chromosomes involved in the CCR

speech impairment was recognized in the male partner. As his semen analysis report was normal, the couple insisted on getting a karyotype done. Sample collection and written informed consent was obtained as per the institutional ethics committee.

Banding cytogenetics

Cytogenetic analysis was performed according to standard procedures. Analysis of the GTG-banded metaphase chromosomes at the resolution level of 400 bands was done in the couple, and as parents of the male were not alive, his brother's karyotype was performed instead.

Molecular cytogenetics

FISH was performed using whole-chromosome painting (WCP) probes for chromosome 1, 3, and 4; a BAC probe RP11-95E11 in 3p26.3 (home-made probes); and a subtelomeric probe for 3pter (Abbott Molecular, VYSIS, Mannheim, Germany). High-resolution molecular cytogenetic analysis was carried out applying a multicolor banding (MCB) probe set for chromosome 1 [17].

Molecular karyotyping

Molecular karyotyping was done based on the aCGH platform of Agilent Technologies and a custom-designed 8 × 60 K oligonucleotide microarray with a genomic coverage for interrogation of over 250 genetic disorders, giving an average genome-wide resolution of 30 kb. Experimental procedures were performed according to the manufacturer's description. Microarray images were processed with Feature Extraction v.11.1 (Agilent Technologies,

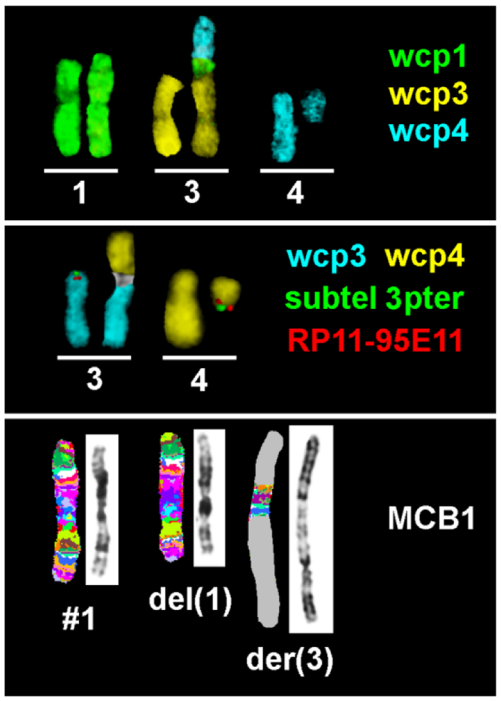

Fig. 2 FISH results with whole-chromosome painting (WCP) for chromosomes 1, 3, and 4, and subtelomeric probes 4pter and 3pter along with RP11-95E11 in 3p26.3. Multicolor banding (MCB) images show the deletion of the particular segment from chromosome 1 and its insertion into derivative chromosome 3

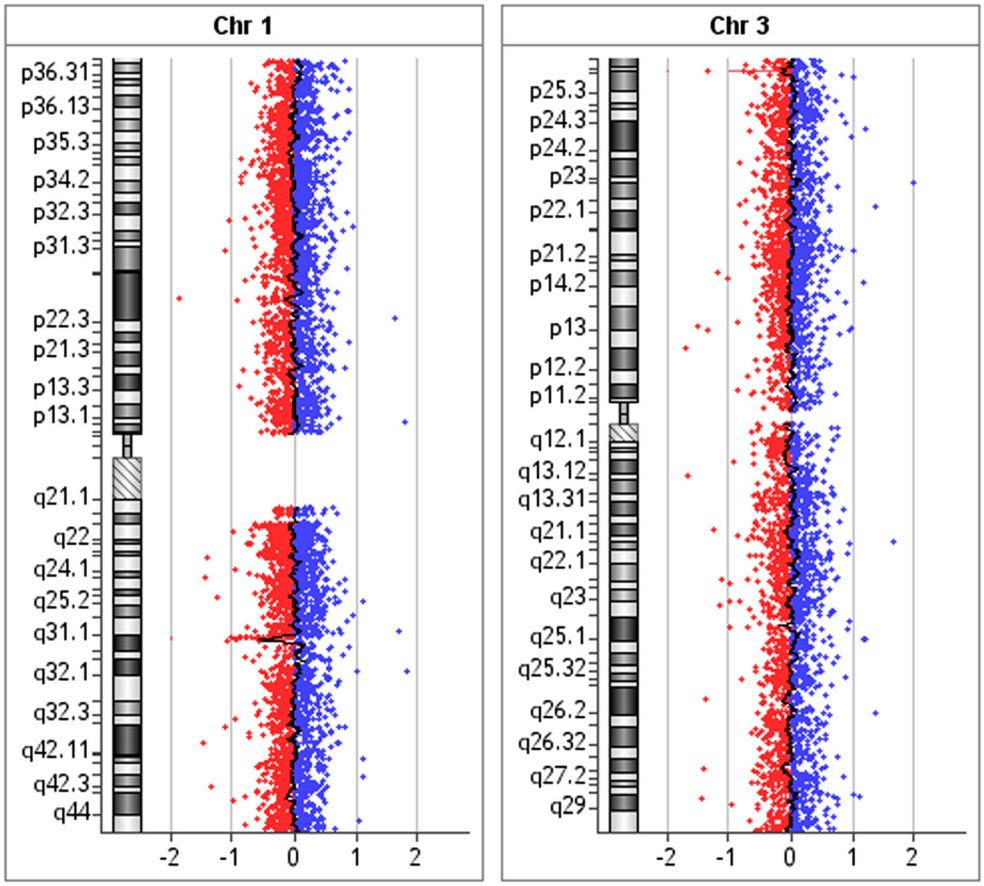

Fig. 3 Array-CGH results for chromosome 1 (**a**) and chromosome 3 (**b**) The log2 ratio, weighted log2 ratio, and copy number state indicate the deleted regions for both chromosomes 1 and 3 and one segment of loss of heterozygosity for chromosome 1

USA) and imported to Agilent Cyto Genomic Workbench 3.0.6.6 for analysis. Copy number variations (CNVs) were identified and evaluated to minimize false-positive calls. CNVs were considered pathogenic if they overlapped with the critical regions of well-characterized duplication/deletion syndromes or pathogenic regions as reported in ISCA or Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) database or were relatively large and encompassing many genes.

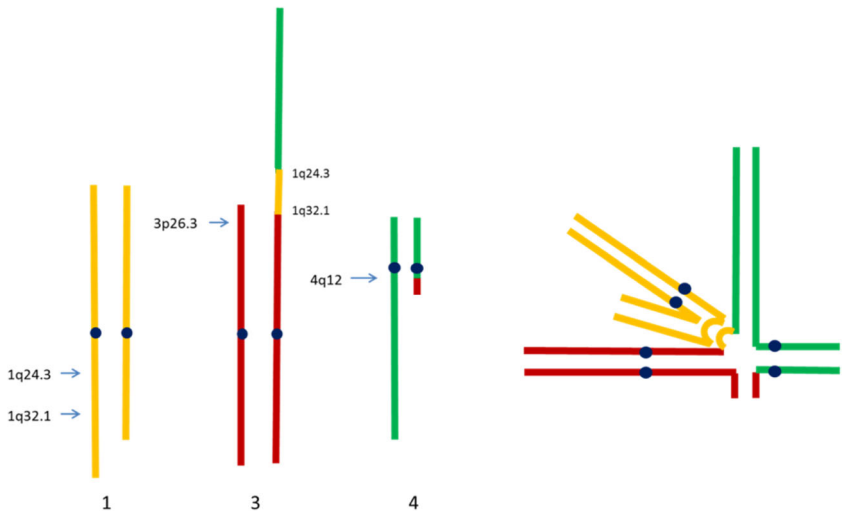

Fig. 4 Schematic presentation of the partial karyogram showing the CCR (left). Pachytene diagram of the patient (right)

Results

GTG-banding revealed a normal karyotype in the female partner of the studied couple, while a complex rearrangement involving chromosomes 1, 3, and 4 was seen in the male (Fig. 1). Also, a normal karyotype was found in the patient's brother, making a de novo CCR-event somewhat likely. Subsequently, FISH was done in the male patient and revealed a final karyotype as 46,XY,del(1)(q24.3q31.1),der(3)(4qter->4q12::1q24.3->1q31.1::3p26.2->3qter),der(4)t(3;4)(p26.2;q12) (Fig. 2). Array-CGH carried out surprisingly identified a 1132 kb microdeletion in chromosome 1q31.1 from position 186,549,764 to 187,681,865 (UCSC genome Browser; http://genome.ucsc.edu/; GRCh37/hg19 release), which encompassed two genes: *PTGS2* and *PLA2G4A* extended (Fig. 3). Also, there was another microdeletion of only 337 kb in size in 3p26.2 (positions 3,316,827 to 3,653,405) but encompassing no genes.

According to ISCN 2016, the aCGH result can be summarized as arr[GRCh37] 1q31.1(186549764_187681865) × 1,3p26.2(3316827_3653405) × 1.

Discussion

CCRs are rarely found in general populations but frequently associated with congenital abnormalities, mental retardation, and/or recurrent spontaneous abortions and infertility [6, 9, 18]. The application of FISH and aCGH is crucial for further delineation of chromosomal breakpoints and possible imbalances in CCRs [9, 19].

The present cryptically imbalanced CCR-case is the first one involving breakpoints in 1q24.3, 1q31.1, 3p26.2, and 4q12. According to the categorization of CCRs proposed by Madan [20], it can be considered as variant of type III CCR; also, it is most likely de novo. Even though two microdeletions of overall ~ 1.5 Mbp in size were detected, affecting the genes *PTGS2* and *PLA2G4A* in 1q31.1, the significance of this deletion is not clear, and as of now, they have only been associated with schizophrenia [21]. Thus, unfortunately, the genetic reasons for speech impairment and facial dysmorphism in the present patient remained unresolved here.

Another interesting feature of the present case is that the CCR did not lead to infertility, as the sperm count and sperm morphology were normal. Thus, this case belongs to the minority of male CCR cases, which presented with repeated abortions in the partnership and not because of infertility [22].

In the present case, there are several possibilities how unfavorable meiotic alignments may finally lead to an adverse pregnancy outcome. At pachytene stage, the CCR may, for example, form a hexavalent configuration, different from three-way translocation (Fig. 4). Generally, unbalanced 3:3, 4:2, 5:1, and 6:0 segregations produce severe genomic imbalances, thereby leading to early pregnancy loss. In addition, recombination involving the inserted segment can result in gametes with new unbalanced karyotypes. Also, live-born abnormal children with congenital anomalies are possible through 4:2 segregation. The der(3) consists of segments from three chromosomes. As the inserted segment 1q24.3-1q31.1 is inverted in this chromosome, any recombination in this segment would lead to non-viable dicentrics or acentric segments. The mode of meiotic segregation in the first fetus of this case remains unknown, as no genetic analysis was done. However, as the couple meanwhile conceived spontaneously and cytogenetic analysis and aCGH at 16th week of gestation was normal, there must have been an alternate segregation without any recombination possible.

Conclusion

According to the literature [6], CCR carriers have a 50% risk of spontaneous abortion and a 20% risk of having a child with an unbalanced karyotype. Albeit individual CCRs may have variant risk estimates, as the category of CCRs and the number of chromosomes involved can vary and also recombination hot spot clusters may play a role [23, 24]. Thus, although the reported couple was fortunate to have conceived a normal baby, future parents should always be counseled about the high possibility of miscarriages or live birth of a child with malformations due to an unbalanced karyotype and be advised on other options like pregestational diagnostics or pregnancy based on donor gametes [25, 26].

Acknowledgements We are very grateful to Dr. Kamlesh Madan for her advice.

Compliance with ethical standards

Informed consent Sample collection and written informed consent was obtained as per the institutional ethics committee.

Competing interests The authors declare that they have no competing interests.

References

1. Pai GS, Thomas GH, Mahoney W, Migeon BR. Complex chromosome rearrangements. Report of a new case and literature review. Clin Genet. 1980;18:436–44.
2. Madan K. What is a complex chromosome rearrangement? Am J Med Genet. 2013;Part A 161A:1181–4.
3. Gardner RJM, Sutherland GR. Chromosome abnormalities and genetic counseling. Oxford: Oxford University Press; 2004. p. 68.
4. Patsalis PC. Complex chromosomal rearrangements. Genet Couns. 2007;18(1):57–69.

5. Batista DAS, Pai GS, Stetten G. Molecular analysis of a complex chromosomal rearrangement and a review of familial cases. Am J Med Genet. 1994;53(3):255–63.
6. Madan K, Nieuwint AWM, Van Bever Y. Recombination in a balanced complex translocation of a mother leading to a balanced reciprocal translocation in the child. Review of 60 cases of balanced complex translocations. Hum Genet. 1997;99:806–15.
7. De Vree PJ, Simon MEH, Van Dooren MF, et al. Application of molecular cytogenetic techniques to clarify apparently balanced complex chromosomal rearrangements in two patients with an abnormal phenotype: case report. Mol Cytogenet. 2009;2:15.
8. Ergul E, Liehr T, Mrasek K, Sazci A. A de novo complex chromosome rearrangement involving three chromosomes (2, 13, and 18) in an oligospermic male. Fertil Steril. 2009;92:391e9–391e12.
9. Pellestor F, Anahory T, Lefort G, Puechberty J, Liehr T, Hedon B, et al. *complex* Chromosomal rearrangements: origin and meiotic behaviour. Hum Reprod Update. 2011;17:476–94.
10. Shi Q, Martin RH. Aneuploidy in human sperm: a review of the frequency and distribution of aneuploidy, effects of donor age and lifestyle factors. Cytogenet Cell Genet. 2000;90:219–26.
11. Liao Y, Wang L, Zhang D, Liu C. Identification of a balanced complex chromosomal rearrangement involving chromosomes 3, 18 and 21 with recurrent abortion: case report. Mol Cytogenet. 2014;7:39.
12. Ngim CF, Keng WT, Ariffin R. Familial complex chromosomal rearrangement in a dysmorphic child with global developmental delay. Singap Med J. 2011;52:e206–9.
13. Lledó B, Ortiz JA, Morales R, Manchon I, Galan F, Bernabeu A, et al. Characterization of a balanced complex chromosomal rearrangement carrier ascertained through a fetus with dup15q26.3 and del5p15.33: case report. Hum Fertil (Camb). 2013;16:215–7.
14. De Gregori M, Ciccone R, Magini P, Pramparo T, Gimelli S, Messa J, et al. Cryptic deletions are a common finding in "balanced" reciprocal and complex chromosome rearrangements: a study of 59 patients. J Med Genet. 2007;44(12):750–62.
15. Griesi-Oliveira K, Moreira Dde P, Davis-Wright N, Sanders S, Mason C, Orabona GM, et al. A complex chromosomal rearrangement involving chromosomes 2, 5, and X in autism spectrum disorder. Am J Med Genet B Neuropsychiatr Genet. 2012;159 B(5):529–36.
16. Papadopoulou E, Sismani C, Christodoulou C, Ioannides M, Kalmanti M, Patsalis P. Phenotype-genotype correlation of a patient with a "balanced" translocation 9;15 and cryptic 9q34 duplication and 15q21q25 deletion. Am J Med Genet. 2010;152 A(6):1515–22.
17. Weise A, Mrasek K, Fickelscher I, Claussen U, Cheung SW, Cai WW, et al. Molecular definition of high-resolution multicolor banding probes: first within the human DNA sequence anchored FISH banding probe set. J Histochem Cytochem. 2008;56(5):487–93.
18. Parent P, Douet-Guilbert N, Le Bris MJ, Basinko A, Roche S, De Braekeleer M, et al. Balanced complex chromosome rearrangement in male infertility: case report and literature review. Andrologia. 2015;47(2):178–85.
19. Kausch K, Haaf T, Kohler J, Schmid M. Complex chromosomal rearrangement in a woman with multiple miscarriages. Am J Med Genet. 1988;31:415–20.
20. Loup V, Bernicot I, Janssens P, Hedon B, Hamamah S, Pellestor F, et al. Combined FISH and PRINS sperm analysis of complex chromosome rearrangement t(1;19;13): an approach facilitating PGD. Mol Hum Reprod. 2010;16:111–6.
21. Karadeniz N, Mrasek K, Weise A. Further delineation of complex chromosomal rearrangements in fertile male using multicolor banding. Mol Cytogenet. 2008;1:17.
22. Madan K. Balanced complex chromosome rearrangements: reproductive aspects. A review. Am J Med Genet. 2012;158A(4):947–63.
23. Wei J, Hemmings GPA. Study of a genetic association between the PTGS2/PLA2G4A locus and schizophrenia. Prostaglandins Leukot Essent Fat Acids. 2004;70(4):413–5.
24. Bhatt SS, Manvelyan M, Moradkhani K, Hunstig F, Mrasek K, Puechberty J, et al. Inverted segment size and the presence of recombination hot spot clusters matter in sperm segregation analysis. Cytogenet Genome Res. 2014;142(2):145–9.
25. Scriven PN, Bint SM, Davies AF, Ogilvie CM. Meiotic outcomes of three-way translocations ascertained in cleavage-stage embryos: refinement of reproductive risks and implications for PGD. Eur J Hum Genet. 2013;22(6):748–53.
26. Fischer J, Colls P, Escudero T, Munne S. Preimplantation genetic diagnosis (PGD) improves pregnancy outcome for translocation carriers with a history of recurrent losses. Fertil Steril. 2010;94:283–9.