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CASE REPORT

Role of comprehensive cytogenomic investigation in successful reproductive outcome of parental small neocentromeric supernumerary ring chromosome: A case report

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Abstract

Small supernumerary marker chromosomes (sSMC) can form small supernumerary ring chromosomes (sSRC). Loss of parentally inherited sSRC containing vital gene content may cause an "unbalanced" karyotype and fetal microdeletion syndromes. Rarely, sSRC with neocentromere can be inherited, leading to a "balanced" karyotype, which can be diagnosed with preimplantation genetic testing.

KEYWORDS

microdeletion, neocentromere, preimplantation genetic testing, small supernumerary ring chromosome

Small supernumerary marker chromosomes (sSMC) are structurally abnormal chromosomes that cannot be classified unambiguously by conventional banding technology alone and are found in 0.075% of unselected prenatal cases and in 0.044% of consecutively studied postnatal ones.[1] Rarely, the sSMC can form small supernumerary ring chromosomes (sSRC) with or without neocentromeres.[1] The neocentromeres are newly derived centromeres with no detectable alpha-satellite DNA and play a role in stabilizing the sSMC during mitosis and meiosis.[2] While the loss of sSRC may lead to congenital malformations in the fetus, familial inheritance of sSRC was rarely documented.[3,4] To the best of our knowledge, there were no studies in the literature utilizing PGT-SR (Preimplantation Genetic Testing for Structural Rearrangements) as a reproductive option for familial sSRC ascertained by a previously affected pregnancy.

We present a unique case of the successful application of PGT in mitigating the risk of unbalanced transmission of an sSRC with a neocentromere at a tertiary care hospital. The proband was a 36-year-old woman, and the father of the pregnancy was of the same age. The couple was non-consanguineous. The father was healthy, and the mother was born with bilateral cataracts and iris coloboma. She also had hypothyroidism and was developmentally normal.

In her first pregnancy, she was seen at 19 weeks gestation with fetal ultrasound findings of multiple anomalies, including absence of cavum septum pellucidum, query agenesis of the corpus callosum, colpocephaly, bilateral parietal foramina, prominent stomach, and loops of dilated bowel. The couple was counseled and chose to interrupt the pregnancy and consented to fetal autopsy. The fetal autopsy showed dysmorphic facies with micrognathia and posteriorly rotated low-set left ear, bilateral cataracts, multiple contractures, axillary and elbow pterygia, and partial syndactyly of digits 2–3 and 3–4 on both hands (Figure 1A). The bowel showed multiple areas of atresia and non-rotation. The skull and brain showed bilateral parietal foramina, agenesis of the corpus callosum, and periventricular nodular heterotopia (Figure 1A). Fetal SNP microarray and karyotype analysis revealed an interstitial deletion of 26.9 Mb in the short arm of chromosome 11 from 11p11.2 to 11p14.3, including the genes *EXT2*, *ALX4*, *WT1*, and *PAX6* (Figure 1A). G-banding analysis of maternal peripheral blood revealed similar chromosome 11 deletion with a mosaic small supernumerary marker chromosome in the form of a small ring (sSRC). SNP microarray confirmed that the sSRC originated from interstitial material of the short arm of chromosome 11 and, therefore, formed a neocentromere. The maternal karyotype reads as: mos 47,XX,del(11)(p14.3p11.2),+r(11)(::p14.3->neo->11.12::)[16]/46,XX,del(11)(p.14.3p11.2)[4] (Figure 1B).

In their second pregnancy, the couple chose to have IVF/ICSI following preconception counseling. PGT-SR was completed with microarray analysis (BlueGnome 24sure+) on trophectoderm cells biopsied from five Day 5 blastocysts (Table 1). Of the five embryos tested, two were "euploid/balanced" and found to have no deletion on the microarray. The other two were "unbalanced" with a single copy number loss of chromosome 11 from cytoband p11.2 to p14.3 (Figure 1C). Incidentally, one of the

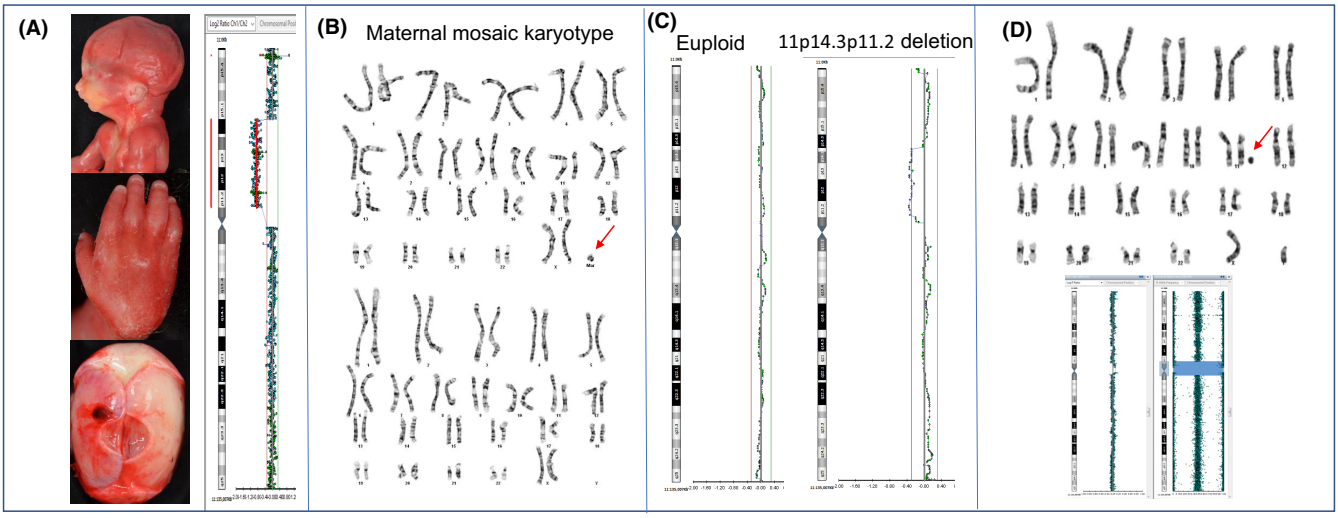

FIGURE 1 Small supernumerary ring chromosomes. (A) Fetal autopsy anomalies. SNP microarray (right panel) revealed chromosome 11 deletion at 11p14.3p11.2. (B) Maternal mosaic karyotype. Note the presence of the sSRC in one population of lymphocytes from the mother. (C) Results of PGT-SR, the left panel is euploid (profile for chromosome 11 is shown only), the right panel is abnormal with the deletion in the short arm of chromosome 11. (D) Prenatal microarray (only chromosome 11 is shown) and karyotype following transfer of the euploid embryo. Red arrows indicate the sSRC.

TABLE 1 PGT-SR by SNP microarray

ID	Array result	CNV (gain/loss)
1	Unbalanced	Loss(11)(p14.3→p11.2)
2	Unbalanced/?aneuploid	Loss(11)(p14.3→p11.2), ? mos +22
3	Euploid	
4	Aneuploid	−21
5	Euploid	

two unbalanced embryos was also found to be mosaic for trisomy 22. The fifth embryo was aneuploid with a loss of chromosome 21.

Transfer of one of the euploid/balanced embryos resulted in a successful pregnancy and the fetal anatomy ultrasounds at 16 weeks and 19 weeks gestation were normal. Amniocentesis was completed at 16 weeks gestation, and prenatal microarray analysis was consistent with a normal male chromosomal microarray result. However, fetal chromosome analysis revealed an apparently balanced male karyotype with non-mosaic maternally inherited chromosome 11 deletion and maternally inherited sSRC, showing 47,XY,del(11)(p14.3p11.2),+r(11)(::p14.3- > neo- > p11.2::)mat. (Figure 1D). No UPD for chromosome 11 was detected. Following genetic counseling, the mother decided to continue the pregnancy. The rest of the pregnancy was uneventful. A baby boy was delivered at 38 + 5/7 weeks via elective C-section due to breech position and the birth weight was 4.17 kg (90-97th centile). A detailed newborn examination did not reveal any anomalies, and at the 6-month follow-up, he had no abnormalities with normal growth and development.

sSRC with neocentromere is a rare cytogenetic finding. Neocentromere formation can occur following interstitial deletions, providing stability to the broken chromosome fragments.[2] Neocentromere formation has been associated with most chromosomes, but only once previously reported with chromosome 11p, in which case a ring chromosome, formed from a deletion of 11p11.2p11.2, completely rescued a mother from the Potocki-Shafer Syndrome (PSS) phenotype but affected her three children in the absence of the ring chromosome.[5] Both WAGR syndrome and PSS are contiguous deletion syndromes involving 11p. WAGR syndrome, caused by haploinsufficiency of *WT1* and *PAX6* at 11p13, is characterized by aniridia, cataracts, Wilms tumor, genitourinary abnormalities, growth retardation, and intellectual disability. PSS, caused by haploinsufficiency of *EXT2* and *ALX4* at 11p11.2, is characterized by multiple exostoses, parietal foramina, intellectual disability, facial dysmorphism, and craniosynostosis. In our report, the mother and her son are, to our best knowledge, the first two cases of neocentromere formation in a ring chromosome formed following an interstitial deletion of 11p11.2p14.3, involving both the WAGR and PSS critical regions.

In our case, the maternal lymphocyte cytogenetics analysis revealed mosaicism and the loss of the ring chromosome in 20% of the cells, which explains the mother's bilateral congenital cataracts and iris coloboma. Her liveborn son had a prenatal diagnosis of the same maternally inherited sSRC in a non-mosaic state in the amniocytes and had normal physical exam features identified at birth and at 6 months of age. This is consistent with the sSMC case series reported by Crolla et al.,[6] in which only 60% of the patients with mosaic sSMC showed developmental delay and/or dysmorphic features. Understandably, the systemic involvement in these patients is independent of the proportion of the mosaicism detected in the lymphocyte cytogenetic studies, as the level of mosaicism can be different in other tissues. In contrast, a lower incidence of clinical anomalies (40%) was observed in patients with sSMC and no mosaic findings. It is possible that the absence of mosaicism in the tested tissue (e.g., lymphocytes or amniocytes) reflects the overall stability of sSMC or sSRC throughout postzygotic mitosis, resulting in a decreased karyotype imbalance in other tissues. However, clinically significant mosaicism developed through postzygotic mitosis cannot be completely ruled out. Thus, the son with sSRC will be followed longitudinally to monitor for symptoms associated with WAGR and PSS.

Our case is apparently the first report of the application of PGT as a reproductive option in parental sSRC with an affected fetus. The sSRC and other sSMC can be ascertained through work-up for infertility or a previously affected pregnancy. sSMC may be lost or gained during meiosis and is infrequently encountered in couples presented for infertility.[7] In this population, Cheng et al. reported successful PGT with a healthy pregnancy in the absence of the inheritance of either the paternal sSMC or the associated chromosome 8 deletion.[8] However, when the sSRC or sSMC are ascertained through a previously affected fetus, the risk for recurrence would be presumably higher. Although sporadic cases of familial sSRC have been reported,[3,4] it is unclear whether PGT could be utilized to reduce the risk of unbalanced karyotypes in the offspring of sSRC carriers. Here, we showed that sSRC ascertained through a previously affected pregnancy could be inherited in a fetus without clinical anomalies or significant mosaicism on amniocentesis. The formation of a neocentromere in the sSRC allowed its stable transmission through meiosis and mitosis. Although we cannot rule out the presence of mosaicism in other tissues of the liveborn son, the absence of WAGR and PSS-associated

abnormalities and the normal clinical assessment at 6 months of age are reassuring.

In summary, this is the first report of the successful application of PGT in sSRC to prevent the recurrence of major congenital anomalies in a subsequent pregnancy. Although further evidence is required to formulate a preimplantation practice guideline for sSRC and other sSMC carriers, PGT should be a tool of consideration to reduce the risk of recurrence for couples with previously affected pregnancies.

AUTHOR CONTRIBUTIONS

YW, JL, DMR, AN, DC, and EG contributed to conception and design, acquisition of data, and interpretation of data. YW, JL, DC, and EG wrote the manuscript. YW and EG prepared the revised version of the manuscript.

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CONFLICT OF INTEREST

The authors declare in conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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