



Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome (sSMC) inherited from her mosaic sSMC(15) mother and a literature review

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ABSTRACT

Objective: We characterized a maternally inherited small supernumerary marker chromosome (sSMC) derived from chromosome 15 according to prenatal detection and made a review on the prenatal sSMC(15) cases with mosaic maternal inheritance.

Case report: A 29-year-old woman underwent amniocentesis at 19 weeks of gestation due to the high risk of Down syndrome in maternal serum screening. No abnormalities were observed in prenatal ultrasound findings. G-banding analysis revealed a karyotype of 47,XX,+mar. Subsequently, we recalled the couple back for chromosomal analysis. The father's karyotype was normal while the mother's karyotype was 47,XX,+mar[15]/46,XX[35]. Molecular genetic analysis was utilized to identify the marker chromosome. The chromosomal microarray analysis (CMA) results of the mother showed there existed microduplications in the locus of 14q32.33, 15q21.1, 19p12 and Xq26.2, respectively. Then Fluorescence in situ hybridization (FISH) using specific probes for chromosomes 13/21, 14/22, and 15 was applied on the mother and the fetus. And the marker chromosomes for the mother and the fetus were all finally identified as inv dup(15) (D15Z1++, SNRPN-, PML-), which illustrated that the fetus inherited the sSMC(15) from her mother. Finally, a healthy female infant was delivered with no phenotypic abnormalities at 39 weeks.

Conclusion: The combined utilization of the molecular genetic technologies, such as FISH and CMA, plays a critical role in the identification of the origins and genetic constitutions of sSMC, which would make a significant contribution to genetic counseling and prenatal diagnosis.

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Introduction

Small supernumerary marker chromosomes (sSMCs) were extra chromosomes which occurred in addition to the 46 human chromosomes and could not be identified by traditional cytogenetic technology. They were structurally aberrations and equal in size to or smaller than a chromosome 20 [1,2]. The detecting incidence of sSMC was about 0.075% in prenatal diagnosis. However, the frequency rate decreased to 0.044% in newborns probably because of

the spontaneous abortion and selective termination of pregnancies resulting from sSMC [3,4].

The clinic phenotypes of the sSMC carriers were associated with multiple factors, such as chromosomal mosaicism, origins, inheritance, and genetic materials, which would lead to variable manifestations, ranging from normal to severe abnormalities [5]. In previous reported sSMC carriers, approximately 30% were inherited and 70% were *de novo* [6]. Among all the sSMC, 70% resulted from the acrocentric chromosomes. Compared with sSMC derived from non-acrocentric chromosomes, acrocentric sSMC carriers had fewer phenotypic abnormalities (28% vs. 7%) [2,6]. According to the literature review, the sSMC(15) accounted for up to 35% in all sSMC, and they could cause abnormal phenotypes especially when the Prader-Willi/Angelman syndrome critical region (PWACR) was

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included [5,7]. The common clinic manifestations of sSMC(15) contained inv dup (15) syndrome, isodicentric chromosome 15 syndrome or tetrasomy 15q syndrome, which were usually associated with hypotonia, developmental delay and intellectual disability [8].

Here, we presented a rare prenatal case who inherited the sSMC(15) from her mother, whose karyotype was 47,XX,+mar/46,XX. The cytogenetic and molecular genetic analysis were applied to confirm the origins and constitutions of the sSMC.

Case presentation

A 29-year-old, gravida 1, para 0, woman underwent amniocentesis at 19 weeks of gestation because of the increased Down syndrome risk of 1/209. No prenatal ultrasound findings were observed. The pregnancy woman and her husband were nonconsanguineous and healthy. The medical history of the woman was normal, and there was no family history of diabetes mellitus or congenital anomalies. The mother denied teratogenic exposure and no signs of symptoms during this pregnancy. Amniocentesis revealed the karyotype of the fetus was 47,XX,+mar (Fig. 1). We recalled the couple back for karyotypic analysis. The father's karyotype was normal while the mother's was 47,XX,+mar [15]/46,XX[35]. Chromosomal microarray analysis (CMA) was applied on the mother through CytoScan 750K array (Affymetrix, Santa Clara, CA), and the results were shown as arr[hg19]14q32.33(106,251,069–106,950,412) × 3; arr[hg19]15q21.1(45,533,504–45,724,020) × 3; arr[hg19]19p12(20,771,374–21,015,105) × 3; arr[hg19]Xq26.2(130,725,733–130,997,111) × 3. Fluorescence in situ hybridization (FISH) analysis using probes of chromosome 15 and centromere probes of chromosomes 13/21 and 14/22 were applied on the metaphase of the mother and the fetus for further identification. The 13/21 and 14/22 probes were as follows: D13Z1/D21Z1 (13p11.1-q11.1, spectrum green; 21p11.1-q11.1, spectrum green) and D14Z1/D22Z1 (14p11.1-q11.1, spectrum red; 22p11.1-q11.1, spectrum red)

(CytoCell Technologies, Cambridge, UK). Probes for chromosome 15 were as follows: SNRPN (15q11.2, spectrum orange), PML (15q24, spectrum orange) and D15Z1 (15p11.2, spectrum green). The FISH results revealed that the marker chromosomes in the mother and the fetus were both sSMC(15) and were finally identified as inv dup(15) (D15Z1++, SNRPN-, PML-) (Fig. 2). The pregnancy woman chose to continue the pregnancy and gave birth to a healthy female infant with no phenotypic abnormalities at 39 weeks. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University (2016-433), and written informed consents were obtained from the couple.

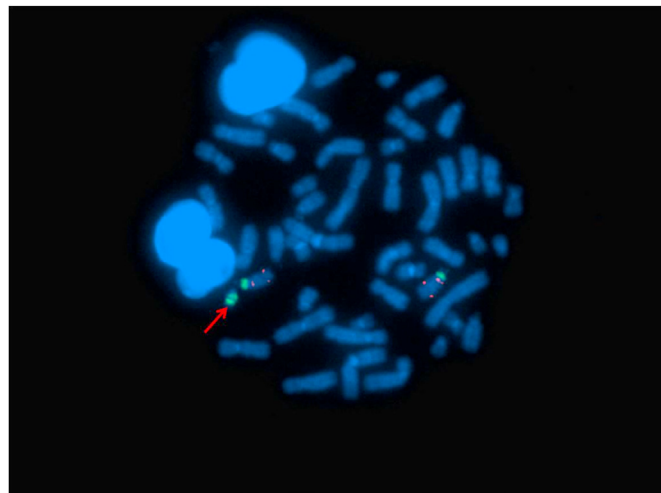


Fig. 2. FISH results showed the sSMC was positive for D15Z1 (the arrow), the marker chromosome was finally identified as inv dup(15) (D15Z1++, SNRPN-, PML-).

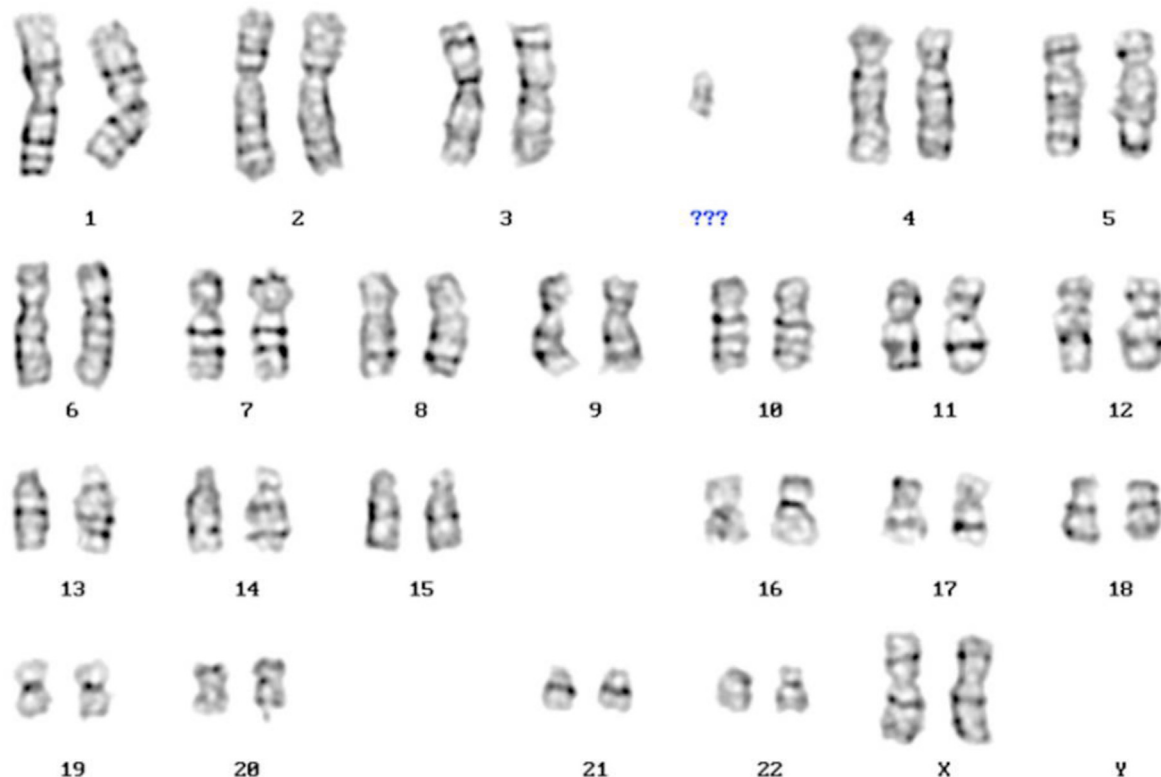


Fig. 1. G-banding revealed the female infant with chromosomal karyotype 47,XX,+mar.

Table 1
The common sSMC and their clinical phenotypes.

Origination of sSMC	sSMC by chromosome	Clinical manifestations
acrocentric chromosomes	sSMC(15)	Marker chromosome 15 syndrome
	sSMC(22)	Tetrasomy 15qter syndrome
	sSMC(13/21)	Emanuel syndrome
	sSMC(14/22)	Cat eye syndrome
nonacrocentric chromosomes	sSMC(13/21)	Der(22)t(8; 22) (q24.1; q11.1) syndrome
	sSMC(14/22)	Dysmorphic features; mental retardation
	sSMC(5)	Dysmorphic features; mental retardation
	sSMC(9)	Isochromosome i(5p)
	sSMC(12)	9p isochromosome
	sSMC(18)	Pallister-Killian syndrome
	mar(X)	Isochromosome 18p syndrome
	mar(Y)	Turner syndrome: mental retardation, soft tissue syndactyly, or abnormal faces
		Risk of gonadoblastoma

Discussion

The present study described a prenatal sSMC(15) case with mosaic maternal inheritance, who presented no abnormal ultrasound findings. The sSMC was finally described as inv dup(15) (D15Z1++, SNRPN-, PML-).

It was recognized that majority of sSMC originated from acrocentric chromosomes(13/21, 14/22, 15). Approximately 70% of the

sSMC carriers were healthy and 30% were correlated with clinical syndromes [9]. The common sSMC and their related clinical phenotypes were summarized in Table 1 [9–11]. In addition, the infertility symptoms were also involved in sSMC derived from almost all human chromosomes, except chromosomes 10, 19 and X [12]. Currently, the isodicentric chromosomes 15 [idic(15)] or inv dup (15) were the most common manifestations of sSMC(15) [8]. Based upon the constitutions, the inv dup (15) could be further divided into two categories. One group with 15q euchromatin, involving the Prader–Willi/Angelman critical region (PWACR) (15q11–q13), was generally considered to be associated with abnormal brain function [13,14]. The other group, including the heterochromatin only, was the most common aberration accounting for 70% in all sSMC, with no evident phenotypic abnormalities [14]. The fetuses with parentally inherited sSMC usually would not lead to severe abnormalities when the sSMC existed in the parents with normal phenotypes [15,16]. The sSMC in our prenatal case was identified as inv dup(15) (D15Z1++, SNRPN-, PML-), which was inherited from her mother, and the normal phenotypes of the fetus might be attributed to the presence of heterochromatin in sSMC.

In a review of the sSMC database [10], the clinic findings of sSMC(15) cases inherited from their mosaic sSMC(15) mothers with normal phenotypes were summarized in Table 2. Almost all mothers presented normal phenotypes and various degrees of mosaic sSMC(15), while the phenotypes and the mosaicism for all

Table 2
Summary of cases with sSMC(15) inherited from the normal mother with mosaic sSMC(15) according to the sSMC database [11].

Case no.	Gender/age at diagnosis	De novo/inherited	GTG-banding result grade of mosaicism	Descriptions of the sSMC	Clinical symptoms	sSMC no. according to Ref. [13]
1	Female/adult	n.a.	47,XX,+mar[28%]/46,XX[72%]	inv dup(15) (q11.1)	normal female, child with sSMC abnormal but no AS ^a or PWS ^b .	15-O-q11.1/1-16
2	Female/26y	n.a.	47,XX, +mar[35%]/46,XX[65%]	inv dup(15) (q11.1)	normal female; sSMC detected in unborn child with 48,XX,+21,+mar.	15-O-q11.2/1-18
3	Female/39y	n.a.	47,XX, +mar[87%]/46,XX[13%]	inv dup(15) (q11.2–q12)	normal female, mar detected in unborn child; in child no ultrasound abnormalities and no UPD ^c 15. Normal child born.	15-O-q11.2–12/1-2
4	Female/adul	n.a.	47,XX, +mar[56%]/46,XX[44%]	inv dup(15) (q13)	normal female; son with same sSMC but in 100% of blood cells abnormal.	15-O-q13/1-1
5	Female/at birth	maternal	47,XX,-14,+t(14; 21) (p11; p11), +mar[100%]	inv dup(15) (q11.2or q12)	Down-Syndrome	15-U-2
6	Female/postnatal	n.a.	mos 47,XX,+mar/46,XX	inv dup(15) (q13.1)	normal woman; female daughter 32m with same sSMC in 100% of cells and DD ^d .	15-O-q13.1/2-1
7	Male/5y	maternal	47,XY,+mar[100%]	r(15) (::p13-12→q13:)	unspecific phenotype with moderate to severe mental retardation. At 5 years IQ of 37. The parents are also mild mentally retarded, mosaic in mother	15-W-q13/3-3
8	Male/15y	maternal	47,XY,+mar[98%]/46,XY[2%]	inv dup(15) (q11.1)	No symptoms in mother and child, the mother with marker in mosaic	15-O-q11.1/1-11
9	Female/prenatal	maternal	47,XX,+mar[79%]/46,XX[21%]	r(15) (::p11.2→q13.1:)	Advanced maternal age-sonography normal, normal child born, mother with mar in 10% of PBL ^e .	15-O-q13.1/1-1
10	Female/prenatal	maternal	47,XX,+mar[65%]/46,XX[35%]	mar(15)	mother normal with sSMC in 10% of PBL. Child normal at 3y	15-CO-21
11	Female/at birth	maternal	47, XX, +mar	inv dup(15) (D15Z1++, SNRPN-, PML-)	No symptoms in child; normal mother with sSMC in 30% of PBL	Our case

^a Angelman syndrome.^b Prader–Willi syndrome.^c Uniparental disomy.^d Developmental delay.^e Peripheral blood.

offsprings were varied. In these sSMC(15) cases, two newborns (case 2 and 5) presented Down syndrome in clinic. Compared with the sSMC(15), the entire gain of chromosome 21 was expected to have a more pronounced effect on the clinical outcome [17]. The newborns (case 1, 4 and 6) showed abnormal manifestations, which suggested that their abnormalities might be due to the existence of the sSMC(15). For case 7, the boy presented more severe mental retardation compared with his mild retarded parents. Case 8, 9 and 10 were mosaic sSMC(15) with normal phenotypes, but the mosaic proportions were different from their mothers with normal phenotypes. The case in our report was a female infant with non-mosaic sSMC(15) inherited from her mosaic sSMC(15) mother with normal phenotypes, which was similar to case 3. All these clinic findings suggested that there existed phenotypic diversity in the offsprings of the mosaic sSMC(15) carriers, which would bring a challenging in genetic counseling.

In our study, we failed to confirm the mosaic sSMC of the mother was *de novo* or inherited. *De novo* inv dup (15) might be caused by crossover error, such as U-type, between homologous chromosomes during meiosis [18]. After the error program of meiosis, the anaphase lagging in the zygote would lead to the trisomy rescue of sSMC, which accounted for the emergence of mosaicism [19].

It was worth mentioning that the effects of inherited sSMC on fertility problems in offspring should not be ignored. It was speculated that sons with maternal inherited and daughters with paternal inherited sSMC are more inclined to infertility [12]. For the infertile sSMC cases, assisted reproductive techniques (ART) was an effective way to get pregnant. Many couples could get their offsprings through intracytoplasmic sperm injection (ICSI), but the risk of transmitting the sSMC must be considered [20]. With application of preimplantation genetic diagnosis (PGD), embryos without sSMC could be further selected for transfer [12]. Our female newborn inherited the sSMC(15) from her mosaic sSMC(15) mother, so it was speculated that her fertility might not be negatively affected but long-term follow-up should be guaranteed till her adulthood.

In addition, CMA results inferred that the mother had several microduplications: a 0.70 Mb microduplication at 14q32.33, a 0.19 Mb microduplication at 15q21.1, a 0.24 Mb microduplication at 19p12, and a 0.27 Mb microduplication at Xq26.2. The 14q32.33 duplication, encompassing the gene *KIAA0125*, encoding a long noncoding RNA which was expressed aberrantly in different cancers and diseases. The overexpression of *KIAA0125* suppressed cell proliferation, migration, and invasion in colorectal cancer (CRC). The *KIAA0125*, acting as a tumor suppressor gene, might be considered as a diagnosis biomarker in CRC [21]. However, whether the carriers with *KIAA0125* duplication should accept colonoscopy or lower GI X-ray examination or not still needs further investigation. The region 15q21.1 included the gene *GATM*, *SLC28A2*, and *C15orf48*. The homozygotic mutation of *GATM* (OMIM: 612718) had been associated with cerebral creatine deficiency syndrome-3 (CCDS3) characterized by developmental delay, mental retardation, severe disturbance of expressive [22]. In addition, no OMIM genes were found in the regions of 19p12 and Xq26.2. Currently, There is no available evidence for the triplosensitivity in association with these genes, which catered for her normal phenotypes to some extent.

In summary, we presented a female sSMC(15) case with mosaic maternal inheritance, which was identified as inv dup(15) (D15Z1++, SNRPN-, PML-). The normal mother presented mosaicism of inv dup(15) while the healthy child showed non-mosaic inv dup(15), which was rarely reported in clinic. In our study, the application of the molecular genetic technologies, such as FISH and CMA, played critical roles in the identification of the origins and genetic components of sSMC, especially for the genetic counseling of prenatal sSMC cases.

Availability of data and materials

The data and materials during the study are available from the corresponding author on a reasonable request.

Ethics approval and consent to participate

The study was approved by Medical Ethics Committee of First Hospital of Jilin University. The parents of the patient provided written informed consent to participate in this study.

Consent for publication

The parents of the patient provided written informed consent for the publication of the present case report.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Not applicable.

Abbreviations

sSMCs	Small supernumerary marker chromosomes
OMIM	Online Mendelian Inheritance in Man
CMA	Chromosome microarray analysis
FISH	Fluorescence in situ hybridization

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