

CASE REPORT

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First case of two supernumerary markers derived from chromosome 5 and chromosome 8

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Abstract

Background: Small supernumerary marker chromosomes (sSMC) are additional centric chromosome fragments too small to be identified by banding cytogenetics alone. A sSMC can originate from any chromosome and it is estimated that 70% of sSMC are de novo, while 30% are inherited. Cases of sSMC derived from chromosome 5 (sSMC5) are rare, accounting for 1.4% of all reported sSMC cases. In these patients, the most common reported features are macrocephaly, dysmorphic facial features, heart defects, growth retardation, hypotonia, and intellectual disability. Also sSMC derived from chromosome 8 are very rare and the phenotype of patients with sSMC8 is very variable. Common clinical features of the patients include developmental delay, mental retardation, intellectual disability, hypotonia, hypospadias, attention deficit hyperactivity disorders (ADHD), skeletal anomalies, dysmorphic facial features, and renal dysplasia. To the best of our knowledge, in literature there are no cases with coexistence of sSMC5 and sSMC8, so we reviewed the literature to compare cases with sSMC5 and those with sSMC8 separately. This study is aimed to highlight the unique findings of a patient with the coexistence of sSMC5 and sSMC8.

Case presentation: We describe a female patient with two supernumerary markers derived from chromosome 5 (sSMC5) and chromosome 8 (sSMC8). The patient was born prematurely at 30 weeks with respiratory distress and bronchodysplasia. On physical examination she presented dysmorphic features, respiratory issues, congenital heart defect, developmental delay, and intellectual disability. The G-banded chromosome analysis on cultured lymphocytes revealed in all the analyzed cells a female karyotype with the presence of two supernumerary chromosomal markers and the array-CGH highlighted the region and the size of these two duplications. We also used the fluorescent in situ hybridization analysis (FISH) using painting of chromosomes 5 and 8 to confirm the origin of the two sSMC. So, the karyotype of the patient was: 48, XX, +mar1, +mar2.

Conclusions: This is the first case with two markers: one from chromosome 5 and one from chromosome 8. Based on the data reported, we can affirm that the phenotype of our patient is probably caused mainly by the presence of the sSMC.

Keywords: Supernumerary marker chromosome, Chromosome 5, Chromosome 8, In situ hybridization, Dysmorphic facial features

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Background

Small supernumerary marker chromosomes (sSMC) are defined as structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone and are equal



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in size or smaller than a chromosome 20 of the same metaphase.

sSMC are reported in 0.043% of newborn infants, 0.077% of prenatal cases, 0.433% of patients with intellectual disability and 0.171% of subfertile people. About 70% of the cases are de novo, while 30% segregate within a family.

sSMC are a morphologically heterogeneous group of structurally abnormal chromosomes: different type of inverted duplicated chromosomes (inv dup), minute chromosomes (min) or ring chromosomes (r) [1].

In general, little is known about the exact mechanism of sSMC formation. Mainly, when, why, and how during gametogenesis or embryogenesis an sSMC evolves is unclear. Nonetheless, for all kinds of sSMC shapes there are models for how they could be formed. These ideas are based in part on the finding that uniparental disomy and sSMC can show up together and on the observation that sSMC can evolve by incomplete trisomic rescue. Overall, sSMC is formed by the combination of one or more rare events happening during gametogenesis or embryogenesis [2].

Apart from the correlation of about one third of the sSMC cases with specific clinical picture i.e., the *isochromosome-18p* (=i(18p)), *derivative chromosome 22* (der(22)t(11;22)(q23;q11.2) and the *cat-eye syndrome* (inv dup(22)), most of the remaining sSMC have not yet been correlated with clinical syndromes. Of this group, half of sSMC have derived from chromosome 15, although 50% of the carriers of sSMC(15) are healthy. However, only 8% of the carriers of sSMC derived from all other chromosomes, showed no clinical symptoms [3].

Cases of sSMC derived from chromosome 5 (SMC5) are rare and make up 1.4% of all reported and characterized SMC cases. In these patients, the most common features reported are macrocephaly, dysmorphic facial features, heart defects, growth retardation, hypotonia, and intellectual disability [4].

Cases of sSMC derived from chromosome 8 are rare. The phenotype of patients with sSMC(8) ranges from almost normal to variable degrees of abnormalities. Common clinical features of the patient included developmental delay, mental retardation, intellectual disability, hypotonia, hypospadias, attention deficit hyperactivity disorder (ADHD), skeletal anomalies, dysmorphic facial features, and renal dysplasia [5].

Case presentation

We present the case of a girl born prematurely at 30 weeks with hospitalization in Neonatal Intensive Care Unit due to respiratory distress and bronchodysplasia. We have little anamnestic data at the time of

birth because today the child is entrusted to an educational community. The presence of a small FOP and an iron-deficiency microcytic anemia under treatment was immediately found. At the age of 21 months on physical examination the patient had a height of 80 cm (at the 15th percentile) and a weight of 11.5 kg (between the 50 and 75th percentile). The dysmorphic features include macrocephaly, up-slanted palpebral fissures, hypertelorism, depressed nasal bridge, midfacial hypoplasia and heart-shaped mouth.

She also presented obesity and disproportion between the trunk and limbs length.

The G-banded chromosome analysis (450–500 band level) on cultured lymphocytes of the proband revealed in all the analyzed cells a female karyotype with the presence of two supernumerary chromosomal markers.

The array-CGH was carried out using the 300 Kb resolution 4 × 180 k CytoSure Oligo OGT (Oxford Gene Technology) according to the recommendations of the manufacturer. The analysis highlighted the region and the size of these duplications:

1. 1.53 Mb duplication on chromosome 5p14.2p14.1, of uncertain significance,
2. Small supernumerary marker chromosome (sSMC) **5p13.2q11.2-5q11.1q11.2** which determines the presence of an 11.87 Mb duplication of this chromosomal region, of pathological significance (Fig. 1),
3. Small supernumerary chromosome (sSMC) **8p11.21p11.1-8q11.1q11.21** which determines the duplication of about 5.55 Mb of this chromosomal region, also of pathological significance (Fig. 2).

The fluorescent in situ hybridization analysis (FISH), using painting of chromosomes 5 and 8 (*Kreatech, Resnova, Rome, Italy*), according to the manufacturer's instructions, confirmed the origin of the two sSMC to be from chromosome 5 and chromosome 8. So, the karyotype of the patient was as the following: 48, XX,+mar1 dn,+mar2 dn.ish r(5)(p13.2q11.2)(wcp5+), r(8)(p11.21q11.21)(wcp8+).arr[GRCh37] 5p14.2p14.1(23,788,614–25,320,290)×3,5p13.2p11-5q11.1q11.2(36,967,000–52,194,364)×3, 8p11.21p11.1-8q11.1q11.21(39,963,778–48,649,507)×3 (Fig. 3).

Parental karyotypes were normal.

The patient underwent further diagnostic tests:

Thyroid function, vitD and parathyroid hormone levels and screening for celiac disease were also evaluated, all of which were normal.

The abdominal ultrasound did not reveal any abnormalities in the abdominal organs.

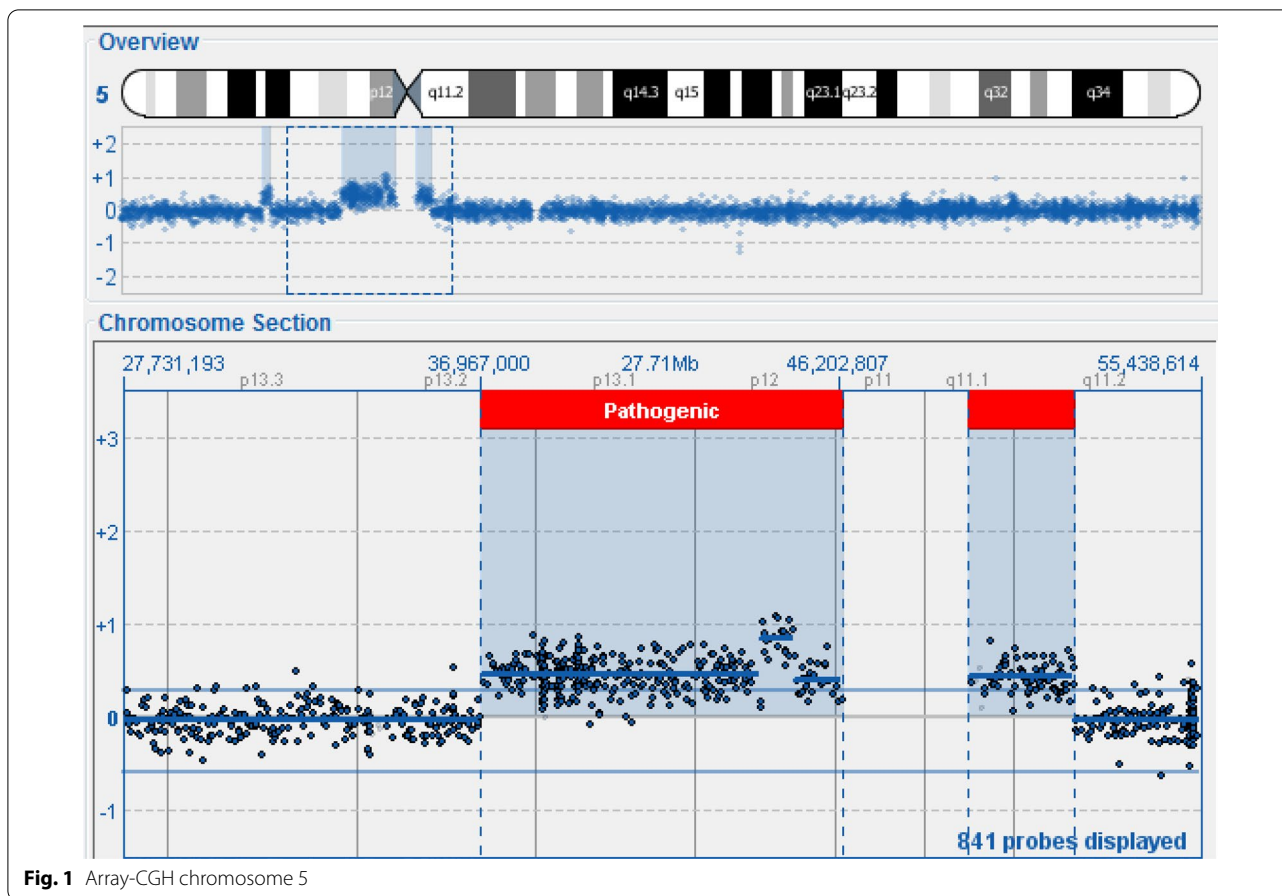


Fig. 1 Array-CGH chromosome 5

The electroencephalography (EEG) in the predominantly agitated waking phase recorded a background activity of 5–6 c/s, structured for age, symmetrical on both hemispheres. No graph elements of certain pathological significance were recorded.

Brain magnetic resonance imaging (MRI) revealed a signal accentuation in the white matter adjacent to the left ventricular trigon, slightly wider than the contralateral, in relation to non-specific leukopathy.

An echocardiogram showed the absence of the FOP present at birth and overall, the echocardiographic findings are normal.

The neuropsychiatric evaluation revealed that the average age of development is about 15 months versus 25 months of chronological age (QS=60).

In conclusion, the patient has a global developmental delay with an important speech delay.

Patient has recurrent respiratory infections (IRRs), and she performed the sweat chloride testing for diagnosis of cystic fibrosis (CF) which resulted negative. The

otolaryngology visit highlighted the presence of adenotonsillar gigantism with severe Apnoic Respiratory Obstructive Syndrome and bilateral endothympenic effusion with flat tympanogram (type B).

The patient underwent antibiotic and cortisone therapy which improved her respiratory condition.

Discussion

The peculiarity of our case is the coexistence of two supernumerary chromosomal markers derived from chromosome 5 and 8.

We use the online database Liehr T. [6] “Small supernumerary marker chromosomes” [6] where we found all the sSMCs present in literature, divided by chromosome. Thank to this database, we can find out two cases with multiple supernumerary markers, one case with 3 sSMCs and one case with 4 sSMCs.

The first case is characterized by the presence of three supernumerary markers derived from chromosome 5, 8 and 9. The patient is a 4-year-old male, and the clinical

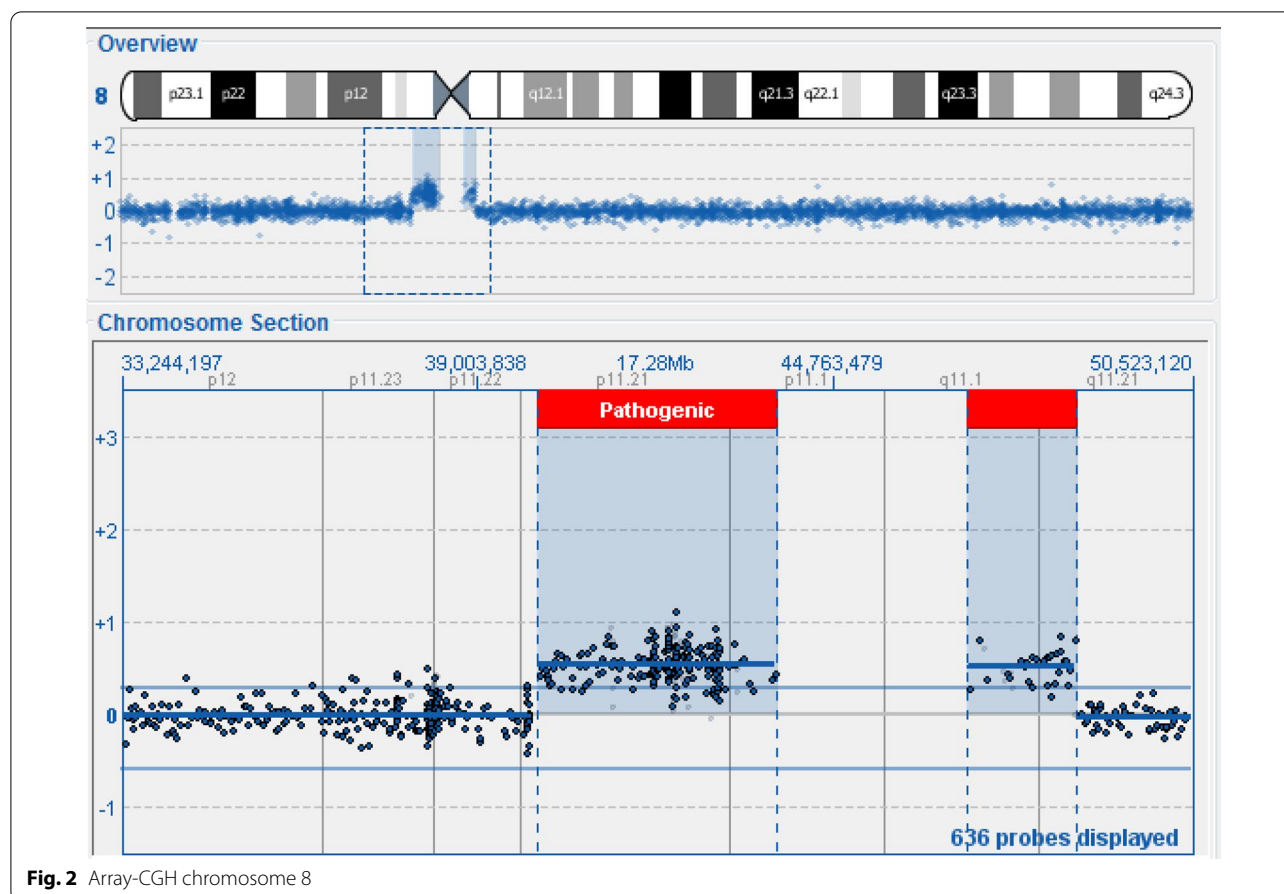


Fig. 2 Array-CGH chromosome 8

presentation is characterized by: mental retardation, hypertelorism, up-slanting palpebral fissures, large ears, bifid uvula, hypospadias, right testicular ectopia, syndactyly of 2–3 toes and obesity. His karyotype is the following: 49,XY,+3mar[9]/48,XY,+2mar[25]/47,XY,+mar1[13]/47,XY,+mar2[14]/46,XY[3].

The second case is characterized by the presence of four supernumerary markers derived from chromosomes 4,5, 8 e 13. The patient is a 7-years-old female, with mental retardation, developmental delay, facial abnormalities, abnormal placed anus and ASD. Her karyotype is the following: 47,XY,+mar1[4] 48,XY,+mar1,+mar2[13]/49,XY,+mar1,+mar2,+mar3[27]/50,XY,+mar1,+mar2,+mar3,+mar4[4].

Besides these two cases, there are no other cases with supernumerary markers derived from chromosome 5 and chromosome 8, so the markers of our case are examined individually and compared with some of the reported cases in literature.

We reviewed the literature for additional cases of SMCs involving overlapping chromosomes 5 material. The individuals in these cases possess features that vary widely (Table 1).

We excluded the case reported by T. Liehr et al. [6] because the analysis was performed prenatally.

The phenotype of trisomy 5p usually includes psychomotor retardation and a characteristic facies, and the pregnancy is often complicated by polyhydramnios. The latter was present in the two cases published by D'amato Sizonenko et al. [9], in the case reported by Avansino et al. [7] and in the case reported by Armstrong et al. [4]. The pregnancy of our patient wasn't complicated by polyhydramnios.

Whereas congenital heart defects have been reported in only three cases [7, 10, 11], respiratory issues and recurrent respiratory infections have been a consistent problem for approximately 50% of the patients [4, 7, 9, 11]. In fact, as in the case of our patient, both of

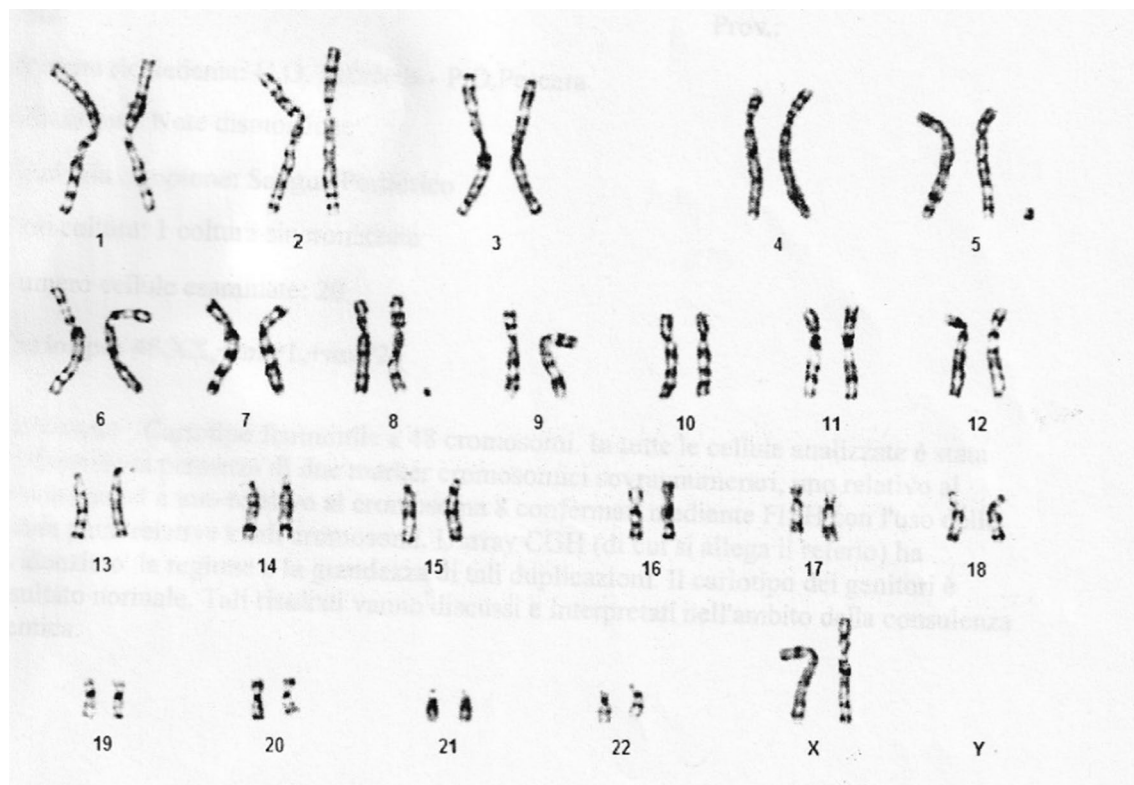


Fig. 3 Karyotype 48, XX, +mar1 dn, +mar2 dn.ish r(5)(p13.2q11.2)(wcp5+), r(8)(8p11.21q11.21)(wcp8+).arr[GRCh37] 5p14.2p14.1(23,788,614–25,320,290)×3,5p13.2p11–5q11.1q11.2(36,967,000–52,194,364)×3,8p11.1–8q11.1q11.21(39,963,778–48,649,507)×3

the patients mentioned by D'Amato Sizonenko et al. [9], were born with respiratory distress and during the first years of life they were hospitalized several times due to recurrent respiratory infections. The patient 1 [9] died at the age of 3 years 3 months as a result of respiratory failures. The patient mentioned by Armstrong et al. (2018) [4] at birth, before being discharged, spent 5 weeks in the hospital because of respiratory problems. The patient of Loscalzo et al. (2008) [11] in her additional medical complications have included multiple hospital admissions related to respiratory issues including laryngomalacia.

73% of patients have developmental delay [4, 7, 9, 11–13], while 63% have intellectual disability [4, 8–10, 12, 13].

82% of patients presented macrocephaly [4, 7, 9–11, 13, 14], 91% have hypertelorism [7–14], 63% have upslanted palpebral fissures [7–9, 11, 14], 54% have midface hypoplasia [4, 7, 9, 13] and 73% have depressed nasal bridge [7–9, 11, 13, 14].

The clinical features described in our patient are concordant with many of the features presented by the

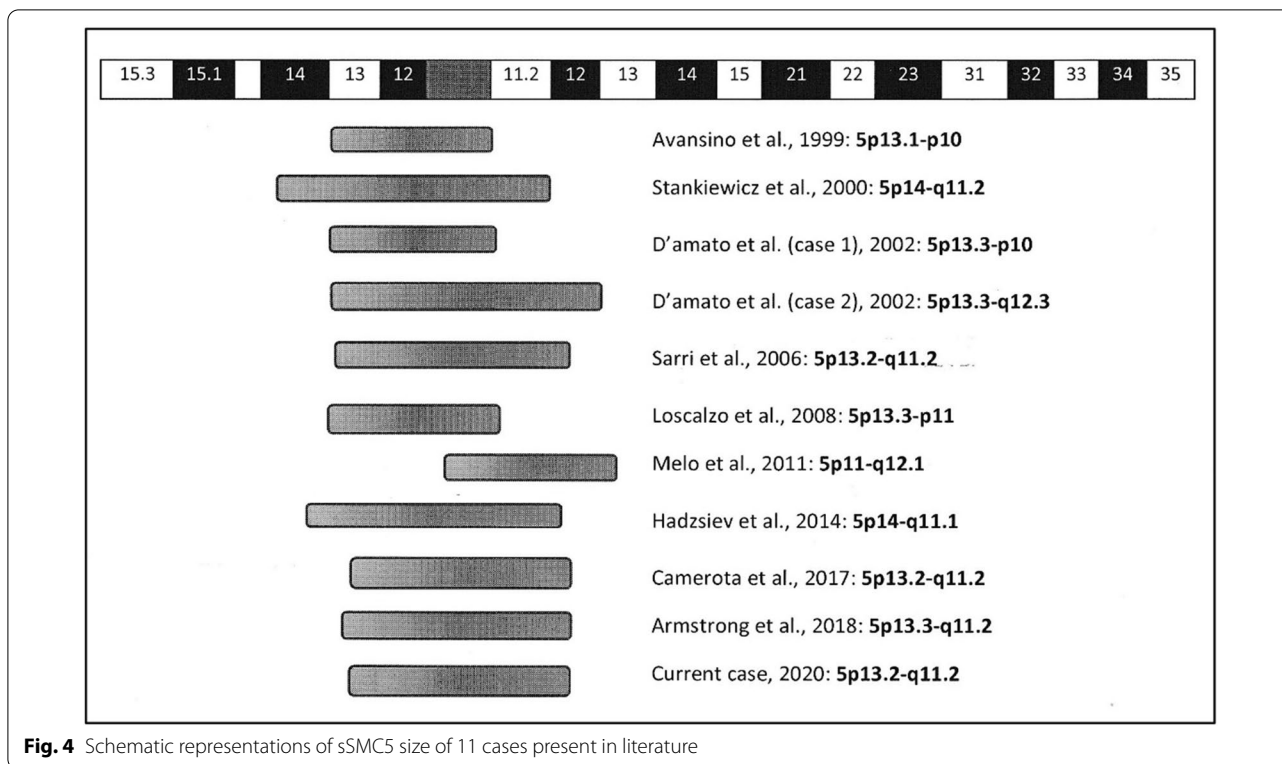
patients of the ten cases collected in Table 1, especially the ID, macrocephaly, and the dysmorphic features.

The approximative breakpoints/genetic content of the sSMC5 documented with or without clinical findings and with an adequate cytogenetic characterization are shown in Fig. 4.

All the cases reported involved partial trisomy of 5p-arm. A critical region has been proposed for 5p13, which, in trisomy, is associated with pregnancy complicated by polyhydramnios, psychomotor delay and characteristic facial features. Of the ten reported cases with a molecular cytogenetic content overlapping our case, six involve 5p-arm euchromatic content, namely, the critical region proposed for 5p13, and euchromatic material from 5q-arm (Stankiewicz et al. [5] (case 1); D'Amato Sizonenko et al. [9] (case 2); Sarri et al. [10]; Hadzsiev et al. [13]; Camerota et al. [14] and Armstrong et al. [4]). The dysmorphic features of these cases are concordant with the ones described for trisomy involving 5p13 (Avansino et al. [7]; D'Amato Sizonenko et al. [9] (case 1)).

Table 1 Genetic and clinical features of cases with sSMC 5

| | Avansino et al. [7] | Stankiewicz et al. (case 1) [8] | D'Amato Sizonenko et al. (case 1) [9] | D'Amato Sizonenko et al. (case 2) [9] | Sarri et al. [10] | Loscalzo et al. [11] | Melo et al. [12] | Hadzиеv et al. [13] | Camerota et al. [14] | Armstrong et al. [4] | Present case | Total |
|------------------------------|---------------------|---------------------------------|---------------------------------------|---------------------------------------|-------------------|----------------------|------------------|---------------------|----------------------|----------------------|-------------------|-------|
| SMC5 coordinates | 5p10 p13.1 | 5p14 q11.2 | 5p10 p13.3 | 5p13.3q12.3 | 5p13q11.2 | 5p11 p13.3 | 5p11q12.1 | 5p14 q11.1 | 5p13 q12.2 | 5p13.3 q11.2 | 5p13 q11.2 | |
| Karyotype | 47 XY+mar | 47,XX,+r/46,XX | 47,XX,+r/46,XX | 47,XY+r/46,XY | 47 XX,+r/46,XX | 46,XX,dup(5) | 47 XX,+r/46,XX | 47 XX,+mar | 47 XX+r/46 XX | 47 XY,+mar | 48, XX,+mar1,+mar | |
| Age at evaluation | 5 months | 7 y | 3 y | 9 months | 9 y | 5 y | 4 y | 10 y | 17 y | 18 y | 1 months | |
| Gestational age | 31 weeks | NR | 37 weeks | 37 weeks | 37 weeks | 33 weeks | NR | At term | At term | 30 weeks | 30 weeks | |
| Developmental delay | + | NR | + | + | - | + | + | + | - | + | + | 8/11 |
| Intellectual disability | NR | + | + | - | + | NR | + | + | - | + | + | 7/11 |
| Congenital heart defect | + | - | - | - | + | + | - | - | - | - | + | 4/11 |
| Respiratory issues | + | - | + | + | - | + | - | - | - | + | + | 6/11 |
| Macrocephaly | + | NR | + | + | + | + | NR | + | + | + | + | 9/11 |
| Upslanted palpebral fissures | + | + | + | + | - | + | NR | - | + | - | + | 7/11 |
| Hyper-telorism | + | + | + | + | + | + | + | + | + | - | + | 10/11 |
| Midface hypoplasia | + | - | + | + | - | - | NR | + | - | + | + | 6/11 |
| Depressed nasal bridge | + | + | + | + | - | + | - | + | + | - | + | 8/11 |



Therefore, even if the sSMC5's clinical phenotype is well-defined with ID, macrocephaly and characteristic dysmorphisms, a genotype/phenotype correlation is difficult due to breakpoint distribution heterogeneity and to different levels and distributions of mosaicism [12].

For chromosome 8 we compared 18 cases present in the literature with our clinical case, as reported in Table 2a, b.

Of all the cases present in the literature, we have considered only 18 and of these the 84% present intellectual disability [15–18, 20–26] and 58% have developmental delay [17–19, 21–24, 26].

Concerning the dysmorphic features, all patients have some, but these features are very widely and not in agreement with those that our patient present.

Only 26% of patients presented macrocephaly [15, 21, 23, 24] and have hypertelorism [15–17, 25], 21% have upslanted palpebral fissures [17, 18, 25]. No one have hypoplasia of the

midface and only 26% present depressed nasal bridge [17, 18, 23].

In 37% of the cases, we found some heart congenital deflections included VSD with coarctation of aorta [15], valvular pulmonary stenosis with a secundum ASD [17, case 1], VSD with persistent left superior vena cava [17, case 2], patent ductus arteriosus with pulmonary hypertension [19], coarctation of aorta [22] and anomalous pulmonary venous return [23].

In 32% of the cases, there are respiratory problems such as respiratory distress at the birth [17], recurrent respiratory infections [19], recurrent otitis [22, 23, 26], Osas [23] and asthma [26].

In conclusion, we report the first case with two markers: one from chromosome 5 and one from chromosome 8. Based on the data reported, we can affirm that the phenotype of our patient is probably caused mainly by the presence of the sSMC.

Table 2 Genetic and clinical features of cases with sSMC8

| | Allen and Hodgkin [15] | Biennow et al. [16] | Digilio et al. p2.1 [17] | Digilio et al. p2 [17] | Melnik and Dewald [18] | Ohashi et al. [19] | Butler et al. [20] | Spinner et al. [21] | Rothermund et al. II-1 [22] | Rothermund et al. III-1 [22] | Rothermund et al. III-2 [22] | Present case | Total |
|------------------------------|------------------------------------|---------------------|-------------------------------|-------------------------------|------------------------|--------------------|--------------------|------------------------|-----------------------------|------------------------------|------------------------------|--------------------|-------|
| sSMC coordinates | 8p21-pter | centromeric | Isodicentric 8p,8p | Isodicentric 8p,8p | 8p11.2-q11.2 | (8p23.1-pter) | pericentric | Pericentric p11-q11 | pericentric | pericentric | pericentric | 8p11.21q11.21 | |
| Karyotype | 46 XX -11+der (11)t(8;11)(p21;q25) | 46 XX /47XX+mar | 46XX/46XX-8+idic(8)(qter-p23) | 46XX/46XX-8+idic(8)(qter-p23) | 47 XX+mar | 47 XX+mar | 47 XY+mar | 46 XY(90)/47XY+mar(10) | 47 XX+mar | 47 XX+mar | 47 XX+mar | 48, XX,+mar1,+mar2 | |
| Age at evaluation | At birth | 1 year | 14 months | 2 months | 15 months | 2 years | At birth | 7 months | 4 years | XX at birth | XX at birth | XX, 21 months | |
| Gestational age | 34 weeks | 39 weeks | 28 weeks | At term | At term | 35 weeks | At term | At term | At term | At term | At term | 30 weeks | |
| Developmental delay | - | - | - | + | + | + | - | + | + | + | + | + | 11/19 |
| Intellectual disability | + | + | + | + | + | - | + | + | + | + | + | + | 16/19 |
| Congenital heart defect | + | - | + | + | - | + | - | - | - | + | + | + | 7/19 |
| Respiratory issues | - | - | + | - | - | + | - | - | + | + | - | + | 6/19 |
| Macrocephaly | + | - | - | - | - | - | - | + | - | - | - | + | 5/19 |
| Upslanted palpebral fissures | - | - | - | + | + | - | - | - | - | - | - | + | 4/19 |
| Hyper-telorism | + | + | + | + | - | - | - | - | - | - | - | + | 5/19 |
| Midface hypoplasia | - | - | - | - | - | - | - | - | - | - | - | + | 1/19 |
| Depressed nasal bridge | - | - | + | + | + | - | - | - | - | - | - | + | 5/19 |

Table 2 (continued)

| | Batanian et al. pz 1 [23] | Batanian et al. pz 2 [23] | Batanian et al. pz 3 [23] | Tonk et al. pz 1 [24] | Tonk et al. pz 2 [24] | Loeffle et al. [25] | Vander Pluym et al. [26] | Present case | Total |
|------------------------------|---------------------------|---------------------------|---------------------------|-----------------------|-----------------------|---------------------|--------------------------|--------------------|-------|
| (b) | | | | | | | | | |
| sSMC coordinates | 8cen-p12 | 8cen-p21 | Dup (8cen-p21) | pericentric | pericentric | 8p12-q12 | 8p11.21q11.21 | 8p11.21q11.21 | |
| Karyotype | 46 XY/47 XY +mar | 47 XX +mar | 46,XX /47,XX+mar | 47 XX+mar | 46,XY /47,XY+mar | 46 XX/47 XX +mar | 47 XX, +mar | 48, XX,+mar1,+mar2 | |
| Age at evaluation | 5 years | 10 years | At birth | 7 months | 6 months | 16 years | 3 years | 21 months | |
| Gestational age | At term | At term | 37 weeks | At term | At term | ? | At term | 30 weeks | |
| Developmental delay | + | + | - | - | + | - | + | + | 11/19 |
| Intellectual disability | + | + | - | + | + | + | + | + | 16/19 |
| Congenital heart defect | - | + | - | - | - | - | - | + | 7/19 |
| Respiratory issues | + | - | - | - | - | - | + | + | 6/19 |
| Macrocephaly | - | + | - | - | + | - | - | + | 5/19 |
| Upslanted palpebral fissures | - | - | - | - | - | + | - | + | 4/19 |
| Hyper-telorism | - | - | - | - | - | + | - | + | 5/19 |
| Midface hypoplasia | - | - | - | - | - | - | - | + | 1/19 |
| Depressed nasal bridge | - | - | + | - | - | - | - | + | 5/19 |

Abbreviations

sSMC: Small supernumerary marker chromosome; sSMC5: Small supernumerary marker chromosome 5; sSMC8: Small supernumerary marker chromosome 8; inv dup: Inverted duplicated chromosome; min: Minute chromosome; R: Ring chromosome; der: Derivative chromosome; ADHD: Attention deficit hyperactivity disorder; FISH: Fluorescent in situ hybridization analysis; EEG: Electroencephalography; MRI: Magnetic resonance imaging; IRRs: Recurrent respiratory infections; CF: Cystic fibrosis.

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Author contributions

RG and CPBDV visited the patient and required the genetic analysis contributing to the description of the case report and discussion. MA performed the karyotype, the FISH and the array-CGH. EM and PGF contributed to the discussion of the paper. All authors read and approved the final manuscript.

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Availability of data materials

The data that support the finding of this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report. The paper is exempt from ethical committee approval because this paper doesn't require any clinical experimentation.

Consent to publication

The family consented in publication.

Competing interests

The authors declare they have no financial relationship to this study and no competing interests.

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