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Molecular cytogenetics characterization of seven small supernumerary marker chromosomes derived from chromosome 19: Genotype-phenotype correlation and review of the literature

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ABSTRACT

Only a few subjects carrying supernumerary marker chromosomes derived from 19 chromosome (sSMC(19)) have been described to date and for a small portion of them the genic content has been defined at the molecular level.

We present seven new different sSMCs(19) identified in eight individuals, seven of whom unrelated. The presence of the sSMC is associated with a clinical phenotype in five subjects, while the other three carriers, two of whom related, are normal. All sSMCs(19) have been characterized by means of conventional and molecular cytogenetics. We compare the sSMCs(19) carriers with a clinical phenotype to already described patients with gains (sSMCs or microduplications) of overlapping genomic regions with the aim to deepen the pathogenicity of the encountered imbalances and to assess the role of the involved genes on the phenotype. The present work supports the correlation between the gain of some chromosome 19 critical regions and specific phenotypes.

1. Introduction

Small supernumerary marker chromosomes (sSMCs) are small additional structurally abnormal chromosomes that cannot be unambiguously identified or characterized by conventional banding cytogenetics. They may derive from any of the human chromosomes, are often present in a mosaic condition (Liehr et al., 2010), have different size and may have a ring shape (small supernumerary ring chromosomes, sSRCs) or not. It has been estimated that sSMCs are encountered in 0.075% of prenatal cases and in 0.044% of newborn cases, with a rate increased to 0.288% in patients with intellectual disability (Liehr and Weise, 2007).

An sSMC can be associated or not to an abnormal phenotype depending on its size, gene content, mosaicism percentage and tissue distribution. All these information can be obtained by integrating conventional and molecular cytogenomics techniques such as fluorescence in situ hybridization (FISH) and array based comparative genomic hybridization (array-CGH).

sSMCs derived from chromosome 19 (sSMCs(19)) are rare. Fiftytwo sSMCs(19) are listed in the online database of sSMCs (Liehr, 2017; http://ssmc-tl.com/sSMC.html, sSMC -chromosome 19 page) which records the sSMCs in the two categories: cases without clinical findings and cases with clinical findings. Within the latter group including 36 cases, 16 sSMC cases are reported in the literature (reference available

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Table 1
Main clinical features of sSMC(19) patients from 1 to 5 (blue bars in Fig. 3).

Involved region/ cells with sSMC(19) (%)	Patients				
	1	2	3 (fetal autopsy)	4	5
Clinical signs	q12q13.2 (11.62 Mb) /40	p13.2q12 (17.33 Mb) /55	p12q12 (10.43 Mb) /80-87	p12 (2.62 Mb) /100	p13.2p11 (12.45 Mb) /19
Hypotonia		+			+
Microcephaly					+
Macrocephaly	+				
High forehead					+
Up-slanting palpebral fissure					+
Down-slanting palpebral fissure	+				
Strabismus	+				+
Ears anomalies	+				
High palate					+
Smooth philtrum	+				
Short neck	+				+
Fingers anomalies		+	+		+
Skin pigmentation anomalies	+				
MRI anomalies				+	+
EEG anomalies/Seizures					+
Short stature		+			+
Obesity/high BMI					
ID/DD	+	+	n.a.	+	+
Language absence/impairment	+	+	n.a.	+	+
Behavioral disorder/SCD			n.a.	+	+

+ = present; +/− = borderline; BMI = body mass index; ID = intellectual disability; DD = developmental delay; SCD = social communication disorder; n.a. = not assessed.
The table shows the main clinical features of our patients from 1 to 5.

in the above mentioned database). Further restricted is the number of sSMCs(19) for which the gene content has been precisely defined by molecular techniques.

Chromosome 19 is a gene-rich chromosome and several pathogenic microdeletions have been reported suggesting dosage sensitivity for the haploinsufficient genes, but the association to abnormal phenotypes is not clear in case of gains (Nevado et al., 2015; Dong et al., 2016).

In the present work we describe by conventional karyotyping, FISH and array-CGH seven new different sSMCs(19) identified in eight individuals, two related, five of whom expressing a clinical phenotype. We compare our patients to already described ones carrying gains (sSMCs or microduplications) of overlapping genomic regions with the aim to deepen the pathogenicity of the encountered gains and to establish the role of the involved genes on the phenotype. The overall results support the link of four critical over-represented regions from 19p13.2 to 19q13.2 to specific clinical signs and suggest actionable candidate genes.

2. Patients data

Out of eight subjects five present clinical signs (patients from 1 to 5; Table 1).

Patient 1 is a 6 years old girl, first of two siblings of healthy non-consanguineous parents. She was born at 40 weeks gestation; birth weight was 3450 g (50°p), length 48.9 cm (25°p) and head circumference 35 cm (10–25°p). Apgar scores were 9 (1′) and 10 (5′). She pronounced her first words at 12 months and walked independently at 16 months. Until 3 years of age she presented drooling. At clinical evaluation (age 6) she displayed the following dimorphisms: macrocephaly, depressed nasal bridge, ptosis, epicanthus, down-slanting palpebral fissures, strabismus on right eye, short nose, anteverted nostrils, smooth philtrum, low ears, short neck, squat chest, genu valgum, and flat feet. Language delay on the phonetic-phonological and morphosyntactic aspects, with poor narrative skills was recorded. Dermatological evaluation evidenced dermatitis and a peculiar cutaneous mosaicism, consistent of hypo- and hyperpigmented areas observable on the whole body (no pictures available). Noonan syndrome diagnosis was excluded since no mutation has been identified in the major *PTPN11*, *SOS1*, *KRAS* and *RAF1* genes.

Patient 2 is a 3 years old boy with developmental and language delay, hypotonia and short stature. His weight is between 3° and 10° p. He presents also pre-axial polydactyly at the right hand, clubfeet, gastroesophageal reflux (GERD) and right pneumothorax. Laryngomalacia was present at birth as well as Patent Ductus Arteriosus (PDA) that was then corrected.

Patient 3 is a male fetus of a woman who underwent chromosome prenatal test for advanced maternal age by both chorionic villi and amniotic fluid analyses which were respectively conducted at the 12th and the 17th gestation weeks. Fetal autopsy after interruption of pregnancy at 20th week showed triangular face, small nose with anteverted nostrils, modest micrognathia and bilateral camptodactyly of the 5th finger. Pictures are not available.

Patient 4 is a 26 old man, third of three siblings of healthy non-consanguineous parents. Auxological parameters at birth were: weight 3600 g (75–90°p) and length 52 cm (50–75°p). The child manifested at 6 months a weight loss associated with recurrent vomiting. Celiac disease was excluded. He presented language delay: at 3 years his vocabulary consisted of about ten words: some language improvement was noted by the parents at age 4 after adenoids removal. Indeed an important adenoids problem was encountered at age 3 and thought to be the reason of vomit and hearing loss causing the language delay. During the school time he manifested attention deficit, learning delay, dysgraphia and dyslalia. In the adult time the intellectual disability persists (QI = 47) also with anxiety, impulsivity and irritability. From the social point of view, the patient manifests difficulties in social relationships outside his family and adaptive difficulty setting according to Vineland Adaptive Behavior Scales (VABS). X fragile syndrome test was negative.

Patient 5 is the only daughter of healthy non-consanguineous parents. She was born small for gestational age at 37th week of gestation. At 10 months, because of persistent antibiotic resistant urinary tract infections, she had an abdomen ultrasound scan which revealed