Review Article

Small supernumerary marker chromosomes and their correlation with specific syndromes

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Abstract

A small supernumerary marker chromosome (sSMC) is a structurally abnormal chromosome. It is an additional chromosome smaller than one chromosome most often lacking a distinct banding pattern and is rarely identifiable by conventional banding cytogenetic analysis. The origin and composition of an sSMC is recognizable by molecular cytogenetic analysis. These sSMCs are seen in different shapes, including the ring, centric minute, and inverted duplication shapes. The effects of sSMCs on the phenotype depend on factors such as size, genetic content, and the level of the mosaicism. The presence of an sSMC causes partial tris- or tetrasomy, and 70% of the sSMC carriers are clinically normal, while 30% are abnormal in some way. In 70% of the cases the sSMC is *de novo*, in 20% it is inherited from the mother, and in 10% it is inherited from the father. An sSMC can be causative for specific syndromes such as Emanuel, Pallister-Killian, or cat eye syndromes. There may be more specific sSMC-related syndromes, which may be identified by further investigation. These 10 syndromes can be useful for genetic counseling after further study.

Key Words: Banding cytogenetic, fluorescence *in situ* hybridization, small supernumerary marker chromosome, syndromes

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INTRODUCTION

A marker chromosome, abbreviated as mar by ISCN 2013, is a structurally abnormal chromosome. Such marker chromosomes are mainly detected by conventional banding cytogenetics.[1] They are usually present in addition to the normal cytogenetic content of 46 chromosomes, are considered as an extra chromosome or an sSMC, and are usually equal to or smaller in size than a chromosome 20 of the same metaphase spread. Also, the sSMC may replace one of the 46 normal chromosomes, either an X or a Y chromosome.[2] Around 3 million humans in a population of 7 billion are sSMC carriers, and sSMCs can originate from any human chromosomes (22 pairs of autosomes and 2 sex chromosomes).[3] The origin of an sSMC can only be diagnosed by molecular cytogenetic methods such as the fluorescence *in situ* hybridization (FISH) technique.[4] The first sSMC was observed in 1961 by Ilberry *et al*. Karyotype patient was 47, XY,+mar/46, XY and the origin of the sSMC was never determined.[5]

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The sSMC frequency in newborn cases is 0.044%, in prenatal cases 0.075%, in mentally retarded cases 0.288%, and in subfertile cases 0.125%.

The effects of an sSMC depend on its size, genetic content, and degree of mosaicism.[2] Uniparental disomy of the sSMC's sister chromosomes could be effective as well.[6]

Studies by Buckton *et al*. indicated that about 86% of the SMCs were derived from the acrocentric chromosomes. The majority of sSMCs (65%) originated from chromosome 15, while sSMCs derived from chromosomes 13, 14, 21, and 22 constitute only 7%.[5]

About 70% of the cases are new mutations (*de novo*), and 30% segregate within a family. Familial sSMCs in general have little or no effect on the phenotype.[3] If one parent has the same marker as the fetus does, there are usually no problems. The parent's normal development suggests that the extra genetic material is silent. If neither of the parents has the sSMC, there could be some extra active genetic information present.[3,5] Considering that the frequency of sSMCs is very low and they mainly produce *de novo* mutations, sSMCs already seen more frequently and associated with specific syndromes are reviewed in this paper to help further clear up doubts concerning markers in genome patients with these signs of phenotypic syndromes and to do complementary tests in this area.

SYNDROMES

Turner syndrome

Female patients with Turner syndrome that have a marker chromosome originating from X or Y chromosome

Turner syndrome patient with 45, X/46, X,+mar (X)

If the so-called XIST gene (X-inactive specific transcript) is present in the sSMC, the latter X chromosome is most likely genetically inactive. If the XIST gene is absent but other euchromatin is present in addition to Turner syndrome characteristics, these patients may have mental retardation, soft tissue syndactyly, or abnormal faces.[3,6] These patients have a variable phenotype, ranging from the moderate "classic" Turner syndrome to anencephaly, complex heart deformity, agenesis of the corpus callosum, and syndactyly of the toes.[7]

Turner syndrome patient with 45, X/46, X,+mar (Y)

In case Turner syndrome is due to an erroneous rescue event of an original 46, XY karyotype, it is important to counsel the patient on the risk of gonadoblastoma.[6]

Marker chromosome 15 syndrome

Chromosome region 15q11q13, known for its instability, is susceptible to genomic rearrangements, such as supernumerary marker chromosomes (SMCs) created by the inverted duplication of proximal chromosome15. Inv dup (30) results in tetrasomy 15p and partial tetrasomy 15q.[8] Marker chromosome 15 syndrome was explained for the first time in England in 1974 by Watson and Gordon.[9] Two types of inv dup (15) marker chromosomes have been identified, with different phenotypic features.[10,11] The first type is a metacentric or submetacentric and heterochromatic chromosome, not including the Prader-Willi Syndrome/Angelman Syndrome (PWS/AS) critical region (PWS/ASCR), and the cytogenetic description is dic (15)(q11). The second type of inv dup (15) includes PWS/ASCR and has 15q euchromatin, and the cytogenetic description is dic (15)(q12 or q13). The majority of dic (15)(q12 or q13) arises from the two homologous maternal chromosomes at meiosis and is associated with increased average maternal age at gestation.[12,13] The inv dup (15) or isodicentric (15) syndrome shows clinical findings demonstrated by early central hypotonia, developmental delay and intellectual disability, epilepsy, and autistic behavior. Autistic behavior is determined by the absence of community interaction, the earliest type of recognition, stereotypies, missing or very bad echolalic language, limited conception, and poor attempt to speak. Developmental delay and intellectual disability affect all individuals with inv dup (15) and are usually moderate to profound.[10,14]

Emanuel syndrome

Emanuel syndrome (ES), which is also known as derivative 22 syndrome, derivative 11;22 syndrome, partial trisomy 11;22, or supernumerary der (22) t (11;22) syndrome is an inherited chromosomal abnormality syndrome that usually results from a 3:1 meiotic segregation of a parental balanced translocation between chromosomes 11 and 22. This translocation is the most common recurrent reciprocal translocation in humans.[15,16] Nine percent of SMCs are derived from chromosome 22.[17] This chromosome abnormality consists of a derivative chromosome 22 [der (22)] as a supernumerary chromosome with the following karyotype: 47, XX,+der (22) t (11;22) (q23;q11) in females or 47, XY,+der (22) t (11;22) (q23;q11) in males.[18] The breakpoints of the t (11;22) translocation are within palindromic AT-rich repeats on chromosomes 11 and 22 and makes hairpin/cruciform structures mediate double-strand breaks in meiosis. As a result of these breaks, recombination between 11q23 and 22q11 results in recurrent translocation.[19] This syndrome is rare with reported cases of around 100. Male and female balanced carriers have 0.7% and 3.7% risk, respectively, of having children with supernumerary der (22).[20] Carriers are usually determined to follow examination for multiple miscarriages, infertility, or after the

birth of an infant with ES.[18] Patients with ES have a specific phenotype comprising characteristic facial dysmorphism including prominent forehead, epicanthal folds, downslanting palpebral fissures, broad and flat nasal bridge, long and pronounced philtrum, abnormal auricles ranging from microtia to large ears often associated with a preauricular ear pit and/or skin tags, microcephaly, severe mental retardation, developmental delay, renal anomalies, congenital cardiac defects, and genital anomalies in boys. Oral findings are generally micrognathia, cleft, or high-arched palate.[18] The vast majority of children with ES have global developmental delay and intellectual disability. While most children do not independently ambulate, over 70% of the subjects eventually learn to walk with support. Expressive language is significantly impaired, with rudimentary speech acquisition in only 20%.[21] The most important differential diagnosis of ES is cat eye syndrome (CES). CES generally derives from partial tetrasomy 22. Iris coloboma, however, which is a cardinal feature of CES, is not reported in ES. Unlike with ES, the majority of individuals with CES have mild or no intellectual impairment.[22] Clinical tests such as chromosomal analysis, FISH technique, whole chromosome paint (WCP), array genomic hybridization (AGH), or multiplex ligation-dependent probe amplification (MLPA) assay can be performed for the ES diagnosis.[23] The highest mortality is within the first few months of life. While the exact mortality rate in ES is unknown, if the patient survives the infancy period long-term, survival is possible.[21] In terms of genetic counseling for affected families, the following two issues are important. First, when one parent is a carrier of t (11;22), future pregnancies are at an increased risk for ES, balanced t (11;22), therefore prenatal cytogenetic testing should be performed in future pregnancies. Second, carrier testing of the unaffected siblings should be performed when they have reached adulthood and are able to understand the reproductive implications of being a carrier.[16]

Cat eye syndrome

Classical CES, also known as Schmid-Fraccaro syndrome, is a rare developmental disorder in humans and is associated with the presence of a bisatellite-dicentric small inv dup (22) SMC. Thus, patients with CES usually have a partial tetrasomy of a region that involves the entire short arm of chromosome 22 (p) plus part of its long arm (q), as far as band 11.[24,25] This band includes regions of low copy repeats (LCRs), which mediate meiotic unequal nonallelic homologous recombination events, resulting in rearrangements including the marker chromosome observed in CES.[26] A very large subset of SMCs is derived from the human chromosome 22 and usually confers tri- or tetrasomy for the proximal part of the long arm of chromosome 22 (the proximal 2Mb of chromosome 22q) that known as CES critical region (CESCR).[27] Different SMCs containing the CESCR have been identified, including the typical bisatellite small and larger CES chromosomes and small ring-like SMCs (22).[24,28] The CES chromosomes are classified into two types, according to the location of the required two breakpoints, to generate them within LCR22: (type I) small CES chromosomes that are symmetrical with both breakpoints located within the proximal interval and (type II) large CES chromosomes that are either asymmetrical (type IIa) with one breakpoint located in each of the two intervals, or symmetrical (type IIb) with both breakpoints located in the distal interval.[29] Clinically, the features of CES include ocular colobomata, anal atresia, congenital heart defects, renal malformations, craniofacial anomalies (e.g., preauricular skin tags and pits), male genital anomalies, skeletal defects, and borderline to moderate mental retardation.[30] The SMC derived from chromosome 22 can be different in molecular size, based on the LCRs in the q11 region where the rearrangement occurs.[9,10] The CES phenotype is variable and no correlation has yet been recognized between CES phenotypes and the supernumerary region.[31,32]

Der(22)t(8;22)(q24.1;q11.1) syndrome

One of the smallest subgroups of sSMC's is complex marker chromosomes.[33] This type of sSMC consists of chromosomal material derived from more than one chromosome.[34] The der (22) t (8;22)(q24.1;q11.1) chromosome was identified as a recurrent complex sSMC in 2010. As in ES, a 3:1 meiotic nondisjunction is causative for the creation of the related sSMC in the offspring of t (8;22)(q24.1;q11.1) carriers. Nondisjunction of the t (8;22) occurs during both male and female meiosis.[35] The breakpoints at 8q24.1 and 22q11.2 occur in palindromic AT-rich repeats (PATRRs) The PATRR on chromosome 22 has been identified as a hotspot for translocation breakpoints.[36] The 8q24 PATRR is flanked by two highly homologous Alu repeats that are in an inverted orientation with respect to one another. These Alu elements may also contribute to the formation of hairpin or cruciform structures.[35] Sheridan *et al.* described multiple individuals with balanced and unbalanced forms of the t (8;22) (q24.13;q11.2). The phenotype in patients with der (22) t (8;22) (q24.1;q11.1) syndrome is characterized by extremity anomalies, mild dysmorphia, and intellectual impairment. This phenotype is in contrast to the observed severe phenotype in patients with ES.[21] Thus, the incidence of t (8;22) may be determined to

be lower than the reasons of nonspecific phenotype in the affected offspring.

Isochromosome i (5p)

Tetrasomy of chromosome 5p is associated with clinical symptoms. In most reported cases, there has been mosaicism for an i (5)(p10) marker chromosome.[37-41] The significant phenotypic findings in all or most of the reported cases include hypotonia, developmental delay of varying severity, psychomotor retardation, seizures, and mosaic pigmentary changes of the skin. All had poor growth, with length or height between the 3rd and 5th centiles. Other findings include various dysmorphic facial features, clinodactyly, overlapping toes, and abnormal palmar creases. Other characteristics are variable among the patients and attributed as a result of variation in the presence and level of mosaicism of the marker chromosome in affected tissue.[41] In addition, i (5p) was identified as a novel abnormality in ovarian cancer.[42] Isochromosome i (5p) is also a frequent finding in bladder cancer and carcinomas of the cervix uteri, but it has been rarely described in breast cancer.[43,44]

9p isochromosome

9p isochromosome is a rare disorder. Duplication of the short arm of chromosome 9 is caused by meiosis II nondisjunction followed by rearrangements.[45] The first case of tetrasomy 9p was described by Ghymers *et al*. in 1973.[46] Up till now at least 30 cases have been reported.[47-52] Based on the nature of the isochromosome, tetrasomy 9p cases can be grouped into three types: [49] In the first type of case, breakpoint is at 10p without any portion of the long arm of chromosome 9. In the second type of case, the isochromosome includes a small amount of the heterochromatic region of 9q, extending to 9q12 or 9q13. In the third type of case, the isochromosome included a larger portion of the long arm of chromosome 9 extending to 9q21 or 9q22. Features of tetrasomy 9p were characteristic facial appearances with hypertelorism, broad nasal root or bulbous/beaked nose, cleft lip or palate, ear anomalies, and micrognathia. Other frequent clinical features include developmental delay, central nervous system anomaly, limb defects, postnatal growth failure, congenital heart disease, small gestational age, renal anomalies, wide sutures/large fontanel, and short neck/excess nuchal skin.[49] One third of the reported cases showed the mosaicism of tetrasomy 9p in a tissue-limiting manner, which is one cause of wide variety of phenotype.[53] Some cases with tetrasomy 9p mosaicism are mimicking Klinefelter syndrome phenotype.[54,55] These cases indicate the possibility of testicular hypofunction and urogenital anomalies induced by the overexpression of some genes on chromosome 9p.

Isochromosome 18p syndrome

Isochromosome 18p syndrome or tetrasomy 18p is a rare cytogenetic abnormality.[56] Froland *et al*. described a person with isochromosome 18p syndrome for the first time in 1963.[57] The presence of a supernumerary isochromosome 18p results in tetrasomy 18p. This type of isochromosome is one of the most common isochromosomes observed in humans.[58] Tetrasomy 18p occurs in one out of 180000 live-born children,[57] affecting males and females equally. Isochromosome 18p syndrome is often the result of *de novo* events, commonly an abnormal division of chromosome 18, during the formation of an egg or sperm cell, although familial cases have been also described.[59,60] For most of the familial cases of tetrasomy 18p, the origin of i (18p) is maternal.[61] Maternal age is considered a risk factor. Boyle *et al*. reported a family with two maternal half-sisters who had tetrasomy 18p. The karyotype result and FISH analysis for the mother revealed only normal diploid cells.[62] Clinical characteristics include moderate severe mental retardation, microcephaly, hypertonia, typical dysmorphic features, and other anomalies.

Tetrasomy 15qter syndrome (neocentric sSMC)

The neocentric marker chromosome constitutes the second smallest group of marker chromosome amongst reported patients with sSMC.[63]

Newly derived centromeres (or neocentromeres) are carried by neocentric (also called analphoid) markers. A neocentric sSMC is related with an adverse clinical outcome in 90% of patients.[33] Nonetheless, in 10% of the cases, mild symptoms can be present in a carrier of a neocentric sSMC.[63] Kuechler *et al*. reported on an 11-year-old girl. Clinical symptoms were muscular hypotonia, body asymmetry, a severe progressive idiopathic thoracolumbal scoliosis, slenderness, and mostly cold hands and feet, but no long fingers/toes. Chromosome analyses showed a mosaic karyotype with a SMC in one and a normal karyotype in the other cell line. Molecular cytogenetic studies could characterize the marker as an analphoid chromosome that derives from the distal part of chromosome 15q, including an inverted duplication of (15)(q24-qter). Array comparative genomic hybridization (CGH) analysis did not detect the imbalance marker, due to the low percentage of cells containing the sSMC. Tetrasomy 15qter was first described by Blennow *et al*.,[33] and it is a rare condition. To our knowledge, only 10 cases have been published up till now). In each of the cases, the tetrasomy caused by an analphoid SMC and nine out of 10 cases were mosaics. Although breakpoints (located between 15q23-qter and 15q26-qter) and mosaic status differed, all described

patients had the same features: Mental retardation, overgrowth, and body asymmetry craniofacial dysmorphism.[64]

Pallister-Killian syndrome

Pallister-Killian syndrome (PKS) is a multisystem sporadic genetic disorder usually characterized by mosaic tetrasomy of isochromosome 12p detected in cultured fibroblast cells. PKS is defined by hypotonia developmental delay facial anomalies and intellectual impairment, pigmentary skin differences, hearing loss, seizures, diaphragmatic hernia congenital heart defects, and other systemic abnormalities. PKS is commonly caused by the supernumerary isochromosome consisting of the short arms of chromosome 12 that result in tetrasomy 12p. Kosuke has identified a woman with PKS who has two small *de novo* interstitial duplications of 12p. This region defines a minimum critical region that, when duplicated, generates many of phenotypes of PKS. This PKS critical region contains the critical gene or genes responsible for this diagnosis when present in greater than two copies.[65,66] Cytogenetic analysis in a girl with multiple congenital anomalies showing PKS indicated a SMC in 34 out of 75 fibroblast metaphases and one out of 76 lymphocytes. GTG-banding pattern was revealed in the chromosomal region 12pter-12q11. While FISH, with a whole chromosome 12 painting probe resolute, a chromosome 12 specific a-satellite probe did not hybridize to it. A specific subtelomeric probe 12p indicated hybridization to both ends of the marker chromosome with FISH analysis.[67]

CONCLUSION AND OUTLOOK

Here, we showed that a subset of sSMC can be directly correlated with a specific syndrome. The phenotypes of patients are connected with the origin, composition, level of the mosaicism, and/or uniparental disomy arising in connection with sSMC presence. As der (13 or 21) t (13 or 21;18) syndrome was just recently identified, it is likely that more sSMC-related syndromes will be identified in near future. For the detection of these markers and their origin, karyotyping, FISH technique, and array CGH tests could be simultaneously performed.

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