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Thomas Liehr,
Leon B. Liehr

An update on small supernumerary marker chromosomes (sSMC)

Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics,
Friedrich-Schiller-Universität Jena, Jena, 07737, Germany

Corresponding author: Thomas Liehr (Thomas.Liehr@med.uni-jena.de)

Abstract

Background: Small supernumerary marker chromosomes (sSMCs) are a clinical problem in prenatal and postnatal diagnostic cases. They include few well-defined clinical syndromes, like cat eye syndrome or Emanuel syndrome. However, they are also a unique model to do research on numerical as well as structural aberrations in the human karyotype. **Aim of the study:** Here we provide an update on the present knowledge on sSMC formation, shape, content and clinical consequences. **Materials and methods:** All relevant underlying data was taken from a free data-collection on sSMCs set up by Thomas Liehr (<http://ssmc-tl.com/sSMC.html> or <http://markerchromosomes.wg.am/>). **Results:** A comprehensive genotype-phenotype correlation for sSMCs is still not available and has been recently complicated by the detection of so-called discontinuous sSMCs, most likely based on formation by chromothripsis. Factors like presence of uniparental disomy of sSMC's sister chromosomes, the latter also influenced by the shape of the sSMC, mosaicism, genetic content (they may be formed by material derived from one or more chromosomes), and if they are parentally derived or de novo may have influence on the phenotype of its carrier. **Conclusions:** Here we summarize the present knowledge on sSMCs, and stress that for reasonable genetic counselling sSMCs must be comprehensively characterized for their potential parental and chromosomal origin, genetic content, potential influence of imprinting and mosaicism. **Keywords:** small supernumerary marker chromosomes (sSMCs); chromothripsis; infertile; prenatal diagnostics; uniparental disomy

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Introduction. Small supernumerary marker chromosomes (sSMCs) are observed in an otherwise normal (or numerically abnormal) karyotype as extra structurally abnormal chromosomes. In a world population of about 8 billion people there are ~3.2 million carriers of an sSMC. ~70% of these sSMC carriers are without any clinical symptoms while the remainder ~30% has mild to severe clinical abnormalities. Only a small subset of those sSMC patients can be attributed to a clear clinical syndrome, e.g.

cat eye syndrome, Emanuel syndrome or Pallister Killian syndrome. For the vast majority of sSMCs associated with clinical problems a well elaborated genotype phenotype correlation is still pending [1-4].

The aim of the study. Here we intend to summarize the present knowledge on sSMCs, discuss how they may be best characterized and how they may be formed.

Material and methods. Besides the (molecular) cytogenetic study of >1500 sSMC cas-

es in my lab and the references mentioned in this paper, the database accessible at <http://ssmc-tl.com/sSMC.html> or <http://markerchromosomes.wg.am/> is the main source for all data provided here [3].

Results and discussion

Basic knowledge:

sSMCs were first reported in 1961 [1]. Since then >6,100 cases were published in [3] and for sure 10-50 times more cases characterized in pre- or postnatal diagnostics without publishing or including in any databases. sSMCs may have 3 different shapes – they can have a ring shape, a centric-minute shape and an inverted duplication shape (<https://www.youtube.com/watch?v=H2kNU8zyKbc>)¹ and may include hetero- and euchromatic material. The vast majority of sSMCs include centromeric material and are derived from the pericentric region of any of the 24 human chromosomes; less than 2.5% of sSMCs have a so-called neocentromere. The chromosomal origin is unequally distributed among the human chromosomes. A reason therefore is not known and sSMCs derived from chromosome 15 are most frequently observed [1-3].

How to characterize an sSMC:

sSMCs may be characterized for their frequency per tissue of a patient – up to 50% of sSMC cases are mosaic – this can just be done by banding cytogenetics; however cryptic mosaics may only be identified by molecular cytogenetic approaches. In most cases mosaic status is not important for clinical outcome – however, there are few exceptions, which also spoil seemingly clear genotype-phenotype correlations even for established sSMC-related syndromes in individual cases [1, 5].

Also, parental cytogenetic studies are indicated to clarify if and sSMC is inherited or de novo. Furthermore, it is necessary to find out the chromosomal origin and content of an sSMC. This can be done by microdissection of the sSMC and reverse FISH (= fluorescence in

situ hybridization), multicolor-FISH either based in whole chromosome painting or centromeric probes. To find out about the presence or absence of small parts of centromere-near euchromatin locus specific probes may be used [1]. Molecular karyotyping (= array comparative genomic hybridization, aCGH) is nowadays used a lot for characterization of euchromatic sSMC-content – as recently shown, this approach is not really suited to study sSMCs, especially if they are not found in infertile patients [6]. aCGH is perfect to determine an exact euchromatic size of an sSMC, however, one can only get to a full picture how an sSMC really looks like when combining with (molecular) cytogenetic results.

Another important aspect in de novo sSMC is to check if a uniparental disomy (UPD) of the sSMC's sister chromosomes is present. This is the case in up to 5% of the cases and may be accompanied by clinical problems due to imprinting or activation of a recessive gene in case of isodisomy. The underlying mechanism here is trisomic rescue, which may be accompanied by formation of an sSMC of any of the three shapes mentioned above [1, 7].

How about a genotype phenotype correlation for sSMC?

The main thing to be considered for a genotype phenotype correlation is the genetic content of the sSMC and the thus induced genetic imbalance [1, 3]. Here it matters especially if the involved regions contain dosage-dependent genes or not. The second most important thing is if there is a UPD of the sSMC's sister chromosomes [1, 7]. Finally, mosaicism may have some influence [1, 3].

However, due to the recent finding that trisomic rescue and sSMC formation may be achieved by chromothripsis, the genetic content-based genotype-phenotype correlation for sSMC became more complicated [8-10]. At present, it seems that most sSMCs are the so-called continuous derivatives – however, a systematic study in sSMC is still lacking, which would clarify the real percentage of discontinuous, chromothripsis-derived sSMCs [9]. Additionally, the potential influence of epigenetic factors driven by altered nuclear architecture due to sSMC-presence is far from being understood [11-12].

¹ Film summarizing the content of this paper; it was first shown on 27 March 2019 on a congress in St. Petersburg dedicated to the memory of Prof. Yuri Yurov, (Moscow, Russia, 26-29 March 2019; “Medical genomics: multidisciplinary aspects”).

Conclusion. A genotype-phenotype correlation for sSMCs was never simple. Due to the recent detection of continuous versus discontinuous sSMCs this correlation became more difficult once again. Nonetheless, for genetic counselling it is imperative to do the best possible molecular cytogenetic characterization of each sSMC.

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Information about the authors

Thomas Liehr, PhD, PD, Head of Lab, Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Jena, Germany, E-mail: Thomas.Liehr@med.uni-jena.de, ORCID: 0000-0003-1672-3054.

Leon B. Liehr, academic degree/titles: none, Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Jena, Germany, E-mail: lxeohl@gmail.com.

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