SMALL SUPERNUMERARY MARKER CHROMOSOMES (sSMC) — WHAT ABOUT THE GENOTYPE—PHENOTYPE CORRELATION?

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Genotype—phenotype correlations in patients with small supernumerary marker chromosomes (sSMC) are still difficult to asses. Here we review the presently known influence of chromosomal imbalance induced by sSMC size and origin, mosaicism of sSMC in different cells of the body and uniparental disomy (UPD) of sSMC's sister chromosomes on the clinical outcome.

Key words: genotype, phenotype, chromosomes, sSMC, mosaicism, uniparental disomy (UPD).

Small supernumerary marker chromosomes (sSMC) are a clinically heterogeneous group; the same holds true for their chromosomal origin and their shape (Liehr et al., 2006; Tsuchiya et al., 2008). sSMC can be derived from any of the 24 human chromosomes and appear as inverted duplicated-, ring-, or centric minute shaped derivative chromosomes. sSMC are defined as structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone, and are (in general) equal in size or smaller than a chromosome 20 of the same metaphase spread. According to present knowledge, in a world population of 7 billion human beings, ~3 million of them are carriers of an sSMC; ~2 million of them are clinically normal and the remainder show different kinds of clinical signs (Liehr et al., 2004; Liehr, 2012).

The finding of an sSMC during cytogenetic diagnostics is always unexpected. However, most often sSMC are found in mentally retarded, followed by infertility patients, and fetuses after invasive prenatal diagnostics (Liehr, Weise, 2007). In the latter the lack of reliable genotype-phenotype correlations led to induced termination in the majorities of those pregnancies, especially if the sSMC was *de novo* (Liehr et al., 2004; Liehr, 2012). Due to the progress made in multicolor molecular cytogenetic (Liehr et al., 2006) and array-based techniques (Tsuchiya et al., 2008) it became possible to characterize sSMC better and better during the last decade. Even a public web page is nowadays available, which enables alignment of actual with previously published cases (Liehr, 2012).

According to the present knowledge, the phenotype induced by an sSMC is mainly influenced by three major factors: 1) the size and origin of the euchromatin present on the sSMC; 2) the size of the cell population in which the sSMC is present (mosaicism); 3) the presence or absence of a uniparental disomy (UPD) of sSMC's sister chromosomes.

Besides, the situation may be complicated by the fact that a patient having a harmless sSMC shows (severe) clinical signs due to complications during birth (e. g. oxygen stress) (Liehr, 2012) or another genetic defect like fragile-X-syndrome (Nelle et al., 2010). The major influence on the clinical outcome is provided by size and origin of euchromatin present on the sSMC. Not surprisingly, additionally present heterochromatin is not deleterious for the phenotype. However, obviously there can be a major qualitative difference in euchromatin, one kind being and another kind not being associated with phenotypic consequences. The most likely explanation therefore are dosage sensitive genes distributed unevenly along the centromere-near euchromatin (Liehr 2011, 2012). Thus, the major challenge for sSMC genotype—phenotype correlation in next future is (1) to define the size of the gene-dosage insensitive genomic regions around each human centromere, and in a second step (2) to characterize the corresponding centromere-near gene-dosage sensitive genes and their respective clinical consequences.

Mosaicism in association with sSMC is a well-known fact; according to Liehr et al. (2010) ~ 50 % of sSMC cases are mosaic. Interestingly, acrocentric and non-acrocentric derived sSMC are differently susceptible to mosaicism; acrocentric derived ones are hereby the more stable ones. This holds true for centric and neocentric sSMC, and an explanation therefore is at present not available (Liehr et al., 2010).

Different kinds of mosaicism may be observed, as exemplified in the following. Most often seen are mosaics as 47, XX, +mar/46, XX. Here only rarely a harmful sSMC is present in such low percentages that no aberrant phenotype is observed, however, examples for these rare instances may be found (Liehr et al., 2010; Liehr, 2012; Papoulidis et al., 2012). Also there may be mosaics like 47, XX, + 16/47, XX, +mar(16)/46, XX; here, according to the size of the cell-population, trisomy 16 may have the most influence on the clinical outcome. In ~1 % of cases more than one sSMC may be found at the same time; example of a karyotype: 48, XX, +mar1, +mar2/47, XX, +mar1/47, XX, +mar2/46, XX. Here up to present the phenotypes were exclusively dependant on the size and origin of the sSMC. Also recently so-called cryptic mosaics were observed. Cryptic mosaicism appears as some sSMC tend to rearrange and/or be reduced in size during karyotypic evolution. This can lead to double ring

formation or inverted duplication starting from a centric minute-shaped chromosome and in the end to formation of different variants and a highly complex mosaic as some of the new variants can also be degraded in a subset of the studied cells. Here the influence on clinical outcome is not clear, yet.

Presence of an sSMC and UPD at the same time is rarely observed; however, normally both are causally correlated by their common origin a trisomic rescue process (Liehr et al., 2011). Interestingly, if the sSMC was present in mosaic with a normal cell line, acrocentric derived sSMC had three times higher chances of UPD-occurrence than in corresponding non-mosaic sSMC cases (Liehr et al., 2011). What has to be considered in connection with UPD and sSMC presence is that a disease can be caused if hetero-UPD or if iso-UPD affects a gene underlying genomic imprinting (= expression of a gene which depends on parental origin). Additionally, iso-UPD, independently of imprinting can result in a functional reduction to homozygosity and thus can cause a recessive disease to occur in the offspring of one carrier patient. Thus, UPD might have to be considered as a reason for a clinical phenotype for any human chromosome.

In summary, there is no simple genotype-phenotype correlation in sSMC. If an sSMC is exclusively heterochromatic it is most likely harmless; however, UPD of the sSMC's sister chromosomes may be present. If an sSMC is euchromatic it may be harmless, if it does not contain any dosage-sensitive genes and if it is not associated with iso- or hetero-UPD of its sister chromosomes. Euchromatic sSMC may be harmful, as they encompass gene-dosage sensitive genes, are associated with sister chromosomes' UPD and/or are present in the majority of the cells of a patient. However, like in Pallister—Killian-syndrome, the sSMC may not be always present in the tested tissue (Liehr et al., 2008). Overall, progress was already achieved for the genotype—phenotype correlation of sSMC, but there is still a way to go until every prenatal case can obtain a clear prognosis about its clinical outcome.

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МАЛЕНЬКИЕ СВЕРХЧИСЛЕННЫЕ МАРКЕРНЫЕ ХРОМОСОМЫ (sSMC): ЕСТЬ ЛИ КОРРЕЛЯЦИЯ МЕЖДУ ГЕНОТИПОМ И ФЕНОТИПОМ?

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Вплоть до последнего времени очень трудно было оценивать корреляцию между генотипом и фенотипом у пациентов с маленькими сверхчисленными маркерными хромосомами (sSMC). В настоящей работе дан обзор описанных случаев хромосомных нарушений и оценивается влияние размера, происхождения и мозаицизма sSMC в разных клетках организма, а также унипаретальной дисомии (UPD) хромосом, гомологичных sSMC, на клиническую картину.

Ключевые слова: генотип, фенотип, хромосомы, мозаицизм sSMC, унипаретальная дисомия.