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With contributions by Unique

Small Supernumerary Marker Chromosomes (sSMC)

A Guide for Human Geneticists and Clinicians

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(The Rare Chromosome Disorder Support Group)

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Dr. Thomas Liehr
Universitätsklinikum Jena
Institut für Humangenetik
Kollegiengasse 10
07743 Jena, Germany
i8lith@mti.uni-jena.de

UNIQUE
(The Rare Chromosome Disorder Support Group)
P.O. Box 2189
Caterham, Surrey
CR3 5GN, UK
info@rarechromo.org
www.rarechromo.org

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Author's Disclaimer: The clinical details given for specific chromosomal imbalances, including such regions causing, according to present knowledge, no harm, represent the presently available data. They can be used for interpretation of cytogenetic findings – however, there are always exceptions from the findings to be expected. Some are described in this book. Thus, please use this information carefully! The author does not take any responsibility for (mis)interpretation of the data provided in this book.

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Foreword

When Unique started up in 1984 as the Trisomy 9p Support Group, there was virtually no information or support for families about any rare chromosome disorder. Today it is different for people diagnosed with a known syndrome, but for the majority, including most people with a small supernumerary marker chromosome, little has changed. With its ever-increasing membership – currently standing at more than 10,000 individuals in 80 different countries – Unique fills that gap.

Small Supernumerary Marker Chromosomes is a welcome collaboration between a leading scientist and a family support group to create an up-to-date picture of one type of rare chromosome disorder. Scientific and clinical reports are brought to life by families' descriptions of the consequences of having a child with a small extra chromosome. Eighteen Unique families tell you in words and photographs what having this rare chromosome disorder means. Most of the children's names have been changed in accordance with their parents' wishes.

Unique
The Rare Chromosome Disorder Support Group
PO Box 2189
Caterham, Surrey
CR3 5GN, UK
http://www.rarechromo.org

Preface

Since 1992 I have been working in the field of clinical cytogenetics. My diploma, i.e., a master's thesis, was about a special subgroup of patients with small supernumerary marker chromosomes (sSMC), the cat eye syndrome (Liehr et al. 1992). Since that time much progress has been achieved in the field of sSMC. Especially the sSMC homepage (Liehr 2011) with presently more than 4,000 single sSMC case reports together with the advance of technical possibilities for a comprehensive characterization of this special group of rearranged chromosomes enables today much better genotype–phenotype correlations than when I started to study sSMC.

Nonetheless, I recently met a family with the following story, providing evidence that lots of knowledge on sSMC that is nowadays available did not reach the public health system as it should. An sSMC was detected after amniocentesis in the fetus of a pregnant woman who was referred for cytogenetic analysis because of advanced maternal age; sonographic findings were normal. The gynecologist told the couple that the cytogenetic finding was connected with an adverse prognosis and that the developing child would be "100% disabled and mentally retarded." The parents thus terminated the pregnancy. Later, it turned out that the sSMC was not only parentally derived but also that the first healthy child of the couple also had the same sSMC. This book is intended to help avoid similar situations and to be informative to clinicians, cytogeneticists, and families.

Besides the present knowledge on sSMC, including the biological background, also clinically relevant information is included together with personal reports of families having a child affected with an sSMC. The latter was realized in close collaboration with Unique, the Rare Chromosome Disorder Support Group (http://www.rarechromo.org/), and by contributions provided by families in contact with the author.

Jena, October 2011 Thomas Liehr

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Contents

Abbreviations

AC	Accessory chromosome
aCGH	Array-based comparative genomic hybridization
ACH	Accessory chromosome
AS	Angelman syndrome
BWS	Beckwith–Wiedemann syndrome
caNC	Cancer-associated neochromosome
CBG	C bands by barium oxide using Giemsa stain
CES	Cat eye syndrome
CGH	Comparative genomic hybridization
CVS	Chorionic villus sampling
der	Derivative chromosome
ES	Emanuel syndrome
ESAC	Extra structurally abnormal chromosome
FISH	Fluorescence in situ hybridization
GTG	G bands by trypsin using Giemsa stain
hUPD	Heterodisomy
i18pS	Isochromosome 18p syndrome
inv dup	Inverted-duplication-shaped small supernumerary marker chromosome
ISCN	International System for Human Cytogenetic Nomenclature
iUPD	Isodisomy
LCR	Low copy repeat
Mb	Megabase
min	Centric minute-shaped small supernumerary marker chromosome
NMC	Neocentric marker chromosome
NOR	Nucleolus organizing region
OMIM	Online Mendelian Inheritance in Man
p	Short chromosome arm
PCR	Polymerase chain reaction
PKS	Pallister–Killian syndrome
PWS	Prader–Willi syndrome

q	Long chromosome arm
r	Ring chromosome
SAC	Small accessory chromosome
SBAC	Small bisatellited additional chromosome
SMRC	Supernumerary minute ring chromosome
SMC	Supernumerary marker chromosome(s)
SRC	Supernumerary ring chromosome
SRS	Silver–Russell syndrome
sSMC	Small supernumerary marker chromosome(s)
TND	Transient neonatal diabetes
TS	Turner syndrome
UBCA	Unbalanced chromosomal abnormality
UPD	Uniparental disomy

Chapter 1
Introduction

The topic of this book is small supernumerary marker chromosomes (sSMC). Below, sSMC will be introduced, defined, and information will be given about their nomenclature, shapes, the frequencies with which they appear, and their effects. But first we have to understand the field we are entering by focusing on sSMC. So, in general we are talking here about a group of patients identifiable by human genetic diagnostics, especially by cytogenetics. The latter is a branch of genetics concerned with the study of the structure and function of chromosomes.

The cytogenetic era started when the first chromosomes were visualized through microscopes, which was around 1880 (Arnold 1879). However, the first really evaluable human metaphase chromosome spread for diagnostics was published almost six decades ago (Tjio and Levan 1956). Interestingly, the determination of the correct modal human chromosome number (Tjio and Levan 1956), the detection of the first chromosomal abnormalities such as Down syndrome (Lejeune 1959), and the detection of the presence of sSMC (Ilberry et al. 1961) occurred before the invention of the Q-banding method by Dr. Lore Zech from Uppsala, Sweden (Caspersson et al. 1968). The ability to generate a black-and-white banding along the chromosomes enabled the detection of more abnormalities, such as translocations, inversions, deletions, and insertions. Nowadays, the G bands by trypsin using Giemsa stain (GTG) banding approach (Seabright 1971) is still the starting point and gold standard of all cytogenetic techniques (see Sect. 4.1). It is relatively cheap, easy to perform, and gives an overview of the whole human genome; the resolution is limited to some ten million base pairs (Mb).

The pure chromosome banding era ended in 1986 with the first so-called "molecular cytogenetic" experiment on human chromosomes, which was at the same time the starting point of the youngest discipline in human genetic diagnostics (for a review see Liehr and Claussen 2002; see Sect. 4.1). The major technique in molecular cytogenetics is fluorescence in situ hybridization (FISH; for reviews see Liehr and Claussen 2002; Liehr 2009a). FISH is an approach that allows nucleic acid sequences to be examined inside cells or on chromosomes, and was described first in 1986 for humans (Pinkel et al. 1986). Between 1986 and 1996 one-color to three-color FISH experiments were performed, but since 1996 multicolor FISH

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probe sets have become more and more important in routine cytogenetics (for reviews see Liehr et al. 2006b; Liehr 2011b). Recently, the so-called array techniques (Forster et al. 2003) were introduced in cytogenetic diagnostics, providing high resolution for the determination of chromosomal breakpoints. Particularly, array-based comparative genomic hybridization (aCGH; for reviews see Tabor and Cho 2007; Liehr 2009a), which is a refined molecular cytogenetic technique (chromosome-based comparative genomic hybridization, CGH; Kallioniemi et al. 1992), is widely used nowadays for sSMC characterization (Backx et al. 2007; Pietrzak et al. 2007; Tsuchiya et al. 2008).

Overall, cytogenetics means chromosomal analysis at the single-cell level. In contrast, molecular analysis of DNA, including aCGH, and other new whole-genome-directed approaches such as "next- or second-generation sequencing" (ten Bosch and Grody 2008) are investigations of millions of cells. Thus, cytogenetics and molecular genetics can complement and assist each other to achieve the goal of characterizing aberrant karyotypes as comprehensively as possible. For sSMC detection and characterization, cytogenetic analysis is in almost all cases the initial step.

1.1 The Problem

Marker chromosomes, in general, are according to the International System for Human Cytogenetic Nomenclature (ISCN) "structurally abnormal chromosomes of unknown origin, frequently found in karyotypes of cancer patients and patients with constitutional genetic disorders" (ISCN 2009). This definition of markers includes a conglomerate of differently shaped and sized chromosomes, including those this book is about. However, sSMC are something special, as outlined below.

In older literature, the report most often cited as the first description of an sSMC is that of Froland et al. (1963), describing an isochromosome 18p (Rivera et al. 1984). However, this was in fact the third sSMC report, preceded by the report of Ellis et al. (1962), who reported "an aberrant small acrocentric chromosome," and that of Ilberry et al. (1961), who reported the first sSMC ever.

1.1.1 Definition of sSMC

Up to 2003 a clear definition of sSMC was lacking throughout the literature. A "minimal definition" for sSMC was that they are "small structurally abnormal chromosomes that occur in addition to the normal 46 chromosomes" (Crolla et al. 1997). Part of the problem with definition is that the phenotypes associated with sSMC are hugely variable, from normal to severely abnormal (Paoloni-Giacobino et al. 1998). Additionally, sSMC are a morphologically heterogeneous group of structurally abnormal chromosomes (see Sect. 1.1.3). Thus, the denomination of

sSMC as "markers" makes sense and should be maintained even after their identification by molecular cytogenetics, even though ISCN (2009) recommends the use of "derivative" if the chromosomal origin is known.

Nowadays, sSMC can be defined cytogenetically as *structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone, and are (in general) equal in size to or smaller than a chromosome 20 of the same metaphase spread*. sSMC can be present additionally (1) in a karyotype of 46 normal chromosomes, (2) in a numerically abnormal karyotype (e.g., Turner syndrome or Down syndrome), or (3) in a structurally abnormal but balanced karyotype (e.g., Robertsonian translocation; Wolff and Schwartz 1992) or ring chromosome formation (Baldwin et al. 2008).

In contrast, an sSMC larger than chromosome 20 can usually be identified on the basis of chromosome banding. Thus, the definition of sSMC vs. large(r) supernumerary marker chromosomes (SMC) is a cytogenetic not a "functional" one, i.e., sSMC and larger SMC can have the same modes of formation and karyotypic evolution (Liehr et al. 2004; see Chap. 3).

1.1.2 Nomenclature

sSMC have been given various names over the last few decades. The three best known are "SMC," which does not distinguish between larger and smaller SMCs, extra structurally abnormal chromosome (ESAC), and supernumerary ring chromosome (sSRC). In addition, the following names can be found: accessory chromosome (AC or ACH), small accessory chromosome (SAC), marker chromosome (MC), extra or additional marker chromosome, supernumerary or extra microchromosome, additional or metacentric chromosome fragment, (centric) fragment, small bisatellited additional chromosome (SBAC), neocentric marker chromosome (NMC), supernumerary minute ring chromosome (SMRC), and cancer-associated neochromosome (caNC) in exceptional cases where an sSMC is acquired in neoplasia (reviewed in Liehr et al. 2004; Liehr 2011a).

This flood of names is presently tending to be replaced by the use of sSMC, facilitating tremendously a literature search.

1.1.3 Shapes of sSMC

sSMC can have three different shapes (Fig. 1.1). There are (1) inverted duplicated (shaped) sSMC, abbreviated in the karyotype formula as "inv dup" (2) ring-shaped sSMC, written as "r" in the karyotype, and (3) centric minute-shaped sSMC. The latter are most often referred to as "min" or also as "del" (for deleted in parts) or as "der" (for derivative). As outlined in Liehr (2009b) there is ongoing discussion about the correct karyotypic nomenclature for sSMC.