Understanding Chromosome & Gene Disorders

Small Supernumerary Marker Chromosomes (sSMC)

rarechromo.org

Small supernumerary marker chromosomes

This leaflet tells you what we know about the estimated 3.5 million people in the world who have a small supernumerary marker chromosome (sSMC).

sSMCs have been studied in detail and described in the medical literature in only a few people [~6,700 (2020)]. The first person with an sSMC was described in 1961 but overall we still do not know as much as we would like. Nonetheless, all the recently published literature on sSMC has been collected on a dedicated sSMC website. You can access it via the following links:

http://cs-tl.de
or
http://markerchromosomes.wg.am
or
http://markerchromosomes.ag.vu

The information is somewhat technical and we suggest that you discuss it with your doctor or geneticist or contact *Unique* to discuss it. This website, freely available to all, is the source of all the information in this leaflet.

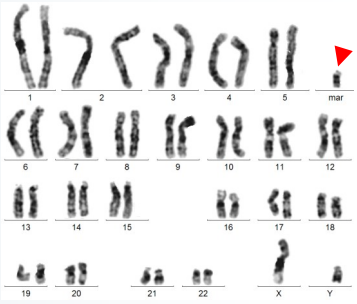
What are small supernumerary marker chromosomes (sSMC)?

Chromosomes are the structures in each of the body's cells that carry the genetic information telling the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. The sex chromosomes are the last pair, called X & Y in males and X & X in females. Each chromosome has a short (p) arm and a long (q) arm.

So we humans usually have 46 chromosomes. Geneticists write this in a code (karyotype) format: 46,XX (for a female) or 46,XY (for a male). The karyotype of a person with an sSMC shows that in addition to the 46 chromosomes, there is a 47th extra chromosome, known as a marker chromosome: 47,XX,+mar (for a female) or 47,XY,+mar (for a male). An sSMC can be derived from any of the 24 different chromosomes – that is, chromosomes 1 to 22, an X or a Y chromosome.

The chromosomes of a male with an sSMC derived from chromosome 15, marked ▼

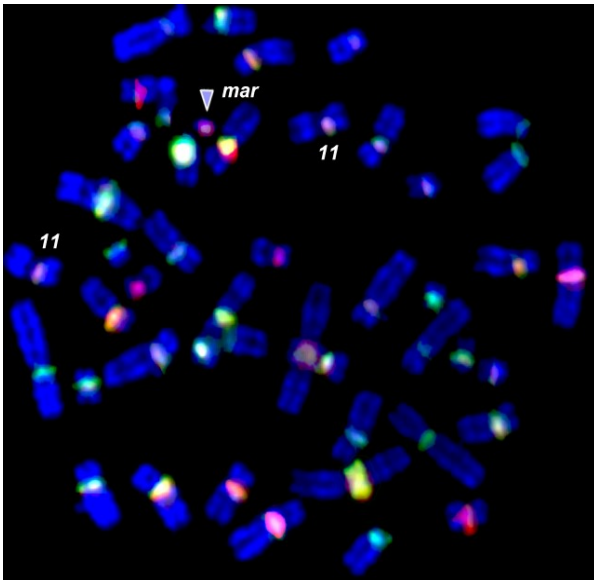
The karyotype would read: 47,XY,+mar(15)



A FISH result showing chromosomes with an sSMC derived from chromosome 11

The sSMC is marked with an arrowhead *mar*

The two unaffected chromosomes 11 are indicated by *11*

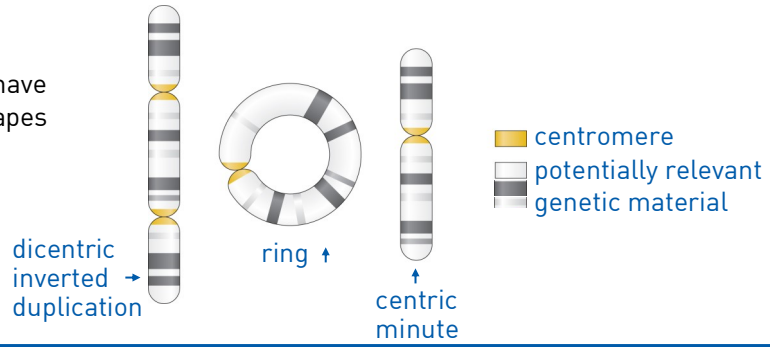


Names

A multitude of different names and abbreviations can be found in the medical literature for sSMC. Here are some examples: supernumerary marker chromosome (SMC), small accessory chromosome (SAC), extra structurally abnormal chromosome (ESAC), extra or additional marker chromosome, bisatellited marker chromosome or supernumerary ring chromosome (SRC). But do not be confused! All of these are sSMCs.

Shapes

sSMCs can have different shapes



There are different karyotypes for the different shapes. For example:

47,XX,+inv dup	- a female with an inverted duplication
47,XY,+r	- a male with a ring chromosome
47,XX,+min	- a female with a minute marker

What are the effects of an sSMC?

An sSMC can have different effects. Most people - 70 per cent - grow and develop normally and have no health problems (apart from some possible impact on fertility). This leaflet tells you about those people (about 30 per cent) who's growth, development, learning or health is affected by their sSMC.

Some sSMCs lead to specific syndromes. For example, Pallister-Killian syndrome is caused by a chromosome made up of material from the short arm of chromosome 12 (see *Unique*'s leaflet on Pallister-Killian syndrome). An sSMC made from material from the short arm of chromosome 18, causes a syndrome known as isochromosome 18p (i18p). An sSMC containing extra material from the short arm of chromosome 22 and the long arm as far as 22q11 causes Cat-eye syndrome. Emanuel or derivative chromosome 22 syndrome is caused by an extra chromosome made up of specific material from chromosomes 22 and 11. Recently, the impact of mocaicism in these syndromes has been highlighted; i.e. if the sSMC (e.g. i18p) is present in a low percentage of the bodies cells, the sSMC carrier may only have minor, or none of the possible symptoms. For other sSMCs, it is still not possible to predict outcomes, although as more people are diagnosed, their symptoms can be compared with those of others with the same diagnoses.

When is an sSMC diagnosed?

There are three different situations in which an sSMC may be diagnosed:

- in pregnancy, during prenatal screening and diagnosis (see below)
- in a newborn baby due to clinical problems and/or unusual facial features (known as dysmorphic)
- in an otherwise healthy adult who has experienced problems with fertility. We know that more people with infertility have an sSMC than the general population.

How is an sSMC diagnosed in pregnancy?

An sSMC is usually detected by chance in pregnancy, either when screening in older mothers or after screening tests such as ultrasound scans and blood tests for certain chemicals (maternal serum screening) have suggested that there may be a problem. When a test for the most common chromosome abnormalities is then performed either on the developing placenta (with chorionic villus sampling, CVS) or on amniotic fluid (by amniocentesis), an sSMC may be found. What this might mean depends on whether the sSMC was detected by amniocentesis or CVS.

When an sSMC is found in cells in the amniotic fluid the unborn baby will have the sSMC as well.

For CVS things are a little bit more complicated: two types of early pregnancy CVS test can be done on the cells from the developing placenta. A rapid test (called direct sampling) gives a result within a day or two. The placenta cells are also cultured (grown), with the results in a week or two.

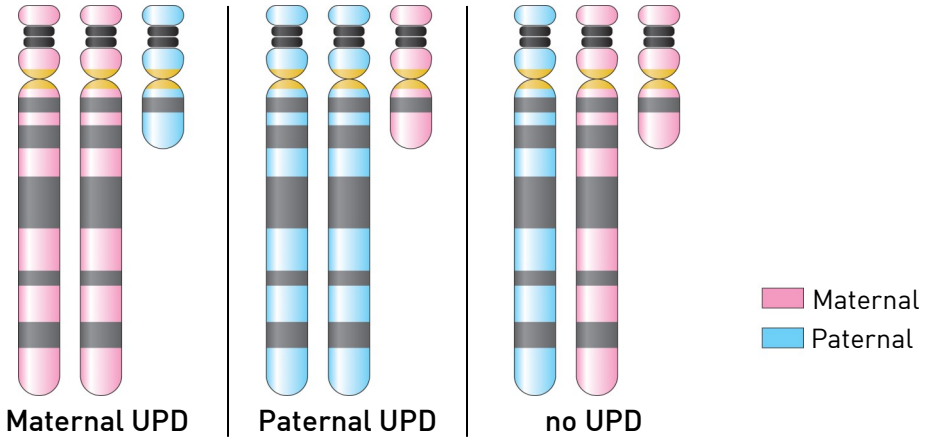
It is important to wait for both results. If both tests show an sSMC is present (usually in a mosaic distribution whereby there are also cells without the sSMC) it is very likely that the baby will also have an sSMC. If the sSMC is present in only one of the two samples, further testing is needed. An amniocentesis or cordocentesis (blood is taken directly from the umbilical cord) will clarify if the baby has the sSMC or if this was a false positive result. sSMCs may also be detected by a non-invasive prenatal test (NIPT) - it is important that this test is also based on placental and not fetal cells; i.e. the placenta may have the sSMC and the fetus may not, or vice versa.

An sSMC has been detected: what might this mean?

We cannot always be certain, but it is helpful to know:

- If one of the parents has the same sSMC. If the sSMC has been inherited from one of the parents and they are healthy, it is very likely that the baby will be all right as well (although there are rare exceptions).
- This is the rule, but exceptions have been reported, so it is important to discover whether the sSMC only contains genetically irrelevant material or if it contains material that is likely to affect development. It is important that up-to-date molecular (cytogenetic) techniques are used to assess what material the sSMC contains. Only when this information is available can the actual case be compared with others and conclusions drawn on what the sSMC may mean.
- One further consideration is a phenomenon called uniparental disomy (UPD - see diagram below). Usually one chromosome in each pair comes from the mother and one from the father. UPD means that both the complete chromosomes that correspond to the sSMC have come from the same parent and the sSMC has come from the other parent. UPD is found in approximately 5 % of people with an sSMC. It is especially important for chromosomes 6, 7, 11, 14, 15, 16 and 20. Occasionally UPD of other chromosomes can also cause problems so it is suggested that UPD is always tested for when an sSMC is detected.

More information about UPD is available at http://cs-tl.de/DB/CA/UPD/0-Start.html



How important is the amount of additional material?

An sSMC can consist of genetically relevant or irrelevant material. The most important issue for the clinical outcome is the amount of genetically relevant material introduced by the sSMC into the cells. UPD for certain chromosomes is another consideration (*see page 5*).

What we know about the possible effects of an sSMC containing genetically relevant material comes from reports in the medical literature. Recent reports have been collected on the sSMC website and you can find there provisional predicted outcomes for the different parts of each chromosome. These are known as genotype-phenotype correlations.

Another source of information is Unique, which has reports from many families with a child or adult member with an sSMC.

Does the ratio of sSMC in the cells matter?

In many cases, the sSMC will be present in some but not all of the cells. You will probably be given a karyotype which will read something like this:

47,XX,+mar(21)[30]/46,XX[20]

The number in round brackets (21) is the number of the chromosome, so chromosome 21 here. The numbers in square brackets [30 and 20] show the ratio of affected cells. So this child, a girl, has a small extra part of chromosome 21 in 30 out of the total of 50 cells tested and the normal number of 46 chromosomes in the remaining 20 cells.

In most cases this ratio of sSMC does not make any difference to the clinical outcome. This is because only one body tissue (such as blood, amniotic fluid or cells from the developing placenta) is usually studied even though the ratio of sSMC differs in different tissues. This unfortunately means that no conclusions can be drawn from this information. [See also https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC6859531/ for further information (Liehr and Al-Rikabi 2019)].

Will a child with an sSMC be healthy?

We cannot unfortunately give a clear answer yet. Children with an sSMC are individually very different from each other, even when the sSMC causes a known syndrome. The clinical outcome (prognosis) can range from extremely positive through moderate to severe. The most important thing in terms of predicting the outcome is to have an accurate, detailed diagnosis with a comprehensive characterisation of the sSMC. Some conclusions can be drawn afterwards by comparing other cases from the medical literature and from Unique. If a baby or child has problems with growth or development, it is more likely that the sSMC has affected them. But it's important not to jump to conclusions. The cause of a child's development and health problems could be something different, not the sSMC.

What are the effects of an sSMC on fertility?

There are many different reasons for fertility problems and it is difficult to say just how much the genetic contribution is in each individual. But having an sSMC is associated with difficulties in conceiving and with repeated pregnancy loss. So fertility problems are more likely in people with an sSMC but they are not inevitable. Surprisingly, more than 50 per cent of people with fertility problems and an sSMC inherited their marker chromosome from one of their parents. This shows that despite the raised rate of fertility problems it is perfectly possible for people with an sSMC to have children. Some of their children will inherit the marker chromosome, others will have normal chromosomes.

sSMCs are found almost three times as often in people with fertility problems as in the general population. They are found in 0.044 per cent of the general population but in 0.125 per cent of people with fertility problems.

As for differences between men and women, studies show that men with fertility problems are 7.5 times more likely to have an sSMC than women with fertility problems. Selection against transmitting the sSMC occurs during sperm development but not oocyte development. This means that a mother with an sSMC is twice as likely to pass it on to her children as a father with an sSMC.

In men, reports show a clear link between an sSMC and a low sperm count (oligospermia) as well as a condition known as OAT (oligoasthenoteratospermia) syndrome, in which the sperm count is low and there is an unusually high proportion of abnormally formed and moving sperm. Seven per cent of men with OAT syndrome have an sSMC.

Although we know that an sSMC derived from any of the chromosomes can lead to fertility problems, we don't yet understand how. Only about 30 per cent of the men with fertility problems who have an sSMC have one that contains genetically relevant material.

Why did it happen and can it happen again?

Most people (70 per cent) with an sSMC have parents with normal chromosomes. Some people inherit their sSMC from one of their parents.

If one of the parents has the same sSMC as the child, it has been passed down in the same way as the other chromosomes. This type of sSMC is called familial. In this case the sSMC can be passed on to further children as well. In most cases - but not all - a familial sSMC does not cause problems with health or development.

If both parents have normal chromosomes, the sSMC has arisen as a one-off event and it is unlikely to happen again in a subsequent pregnancy. Geneticists call this type of event de novo.

Inform Network Support

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Please help us to help you!

This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The information is believed to be the best available at the time of publication and was compiled and written for Unique by Privatdozent Dr Thomas Liehr, Institut für Humangenetik, University of Jena, Germany.

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