Somatic Mosaicism in Cases with Small Supernumerary Marker Chromosomes

Thomas Liehr*,1, Tatyana Karamysheva2, Martina Merkas1,3, Lukrecija Brecevic3, Ahmed B. Hamid1, Elisabeth Ewers1, Kristin Mrasek1, Nadezda Kosyakova1 and Anja Weise1

1Jena University Hospital, Institute of Human Genetics and Anthropology, Jena, Germany
2Institute for Cytology and Genetics, Nowosibirsk, Russian Federation
3School of Medicine Zagreb University, Croatian Institute for Brain Research, Zagreb, Croatia

Abstract: Somatic mosaicism is something that is observed in everyday lives of cytogeneticists. Chromosome instability is one of the leading causes of large-scale genome variation analyzable since the correct human chromosome number was established in 1956. Somatic mosaicism is also a well-known fact to be present in cases with small supernumerary marker chromosomes (sSMC), i.e. karyotypes of 47,+mar/46. In this study, the data available in the literature were collected concerning the frequency mosaicism in different subgroups of patients with sSMC. Of 3124 cases with sSMC 1626 (52%) present with somatic mosaicism. Some groups like patients with Emanuel-, cat-eye- or i(18p)- syndrome only tend rarely to develop mosaicism, while in Pallister-Killian syndrome every patient is mosaic. In general, acrocentric and non-acrocentric derived sSMCs are differently susceptible to mosaicism; non-acrocentric derived ones are hereby the less stable ones. Even though, in the overwhelming majority of the cases, somatic mosaicism does not have any detectable clinical effects, there are rare cases with altered clinical outcomes due to mosaicism. This is extremely important for prenatal genetic counseling. Overall, as mosaicism is something to be considered in at least every second sSMC case, array-CGH studies cannot be offered as a screening test to reliably detect this kind of chromosomal aberration, as low level mosaic cases and cryptic mosaics are missed by that.

Received on: April 20, 2010 - Revised on: May 30, 2010 - Accepted on: June 01, 2010

Keywords: Mosaic, small supernumerary marker chromosomes (sSMC), genotype-phenotype correlation.

SMALL SUPERNUMERARY MARKER CHROMOSOMES (sSMC)

In 1956, the exact chromosomal number in humans was established [1]. Since then it was possible to delineate numerical chromosomal aberrations in any body tissue where chromosomes could be prepared from, including clinical [2] and tumor cases [3]. After the introduction of molecular cytogenetics [4-7], it became even possible to analyze numerical chromosomal aberrations in non-dividing cells [8]. By that also low-level chromosomal aberrations could be detected in tumor [9-13], various clinical [14-18] and neuronal diseases [19-27], embryonic tissues [28-32] and different tissue types [9, 13, 15, 33-35]. Overall it can be stated that chromosome instability is one of the main causes of large-scale genome variation [36-39]. For review of cytogenetic and molecular cytogenetics see Refs. [4-5, 40].

Small supernumerary marker chromosomes (sSMC) are reported in 0.043% of newborn infants, 0.077% of prenatal cases, 0.433% of mentally retarded patients and 0.171% of subfertile people [41]. They are defined as structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone, and are generally equal in size or smaller than a chromosome 20 of the same metaphase spread; sSMC can either be present additionally in (1) an otherwise normal karyotype, (2) a numerically abnormal karyotype (like Turner- or Down-syndrome) or (3) a structurally abnormal but balanced karyotype with or without ring chromosome formation [42]. sSMCs are normally detected by banding cytogenetics in mentally retarded patients, in subfertile persons or during prenatal diagnosis and particularly prenatally ascertained ones, are not easy to correlate with a clinical outcome. It is known that ~30% of sSMCs are derived from chromosome 15; ~11% are i(12p) = Pallister-Killian, ~10% are der(22)-Emanuel-, ~7% are inv dup (22)-cat-eye- and ~6% are i(18p)-syndrome associated sSMC [42].

sSMC are for several reasons still a problem in clinical cytogenetics: (i) they are too small to be characterized for their chromosomal origin by traditional banding techniques and require molecular (cytogenetic) techniques for their identification [41]; (ii) apart from the correlation of about one-third of the sSMC cases with a specific clinical picture, as mentioned above, most of the sSMC have not been correlated with clinical syndromes, even though progress was achieved, recently [43, 44]; (iii) sSMC can be harmful due to different mechanisms like induction of genomic imbalance and/or uniparental disomy [42]; (iv) also sSMC can be found just by chance and cannot be correlated with the clinical problems of a patient [44]; finally (v) the percentage in
which an sSMC is present can, but must not have an influence on the clinical outcome [42-44].

Here we focus on the latter mentioned problem – the regularly appearing somatic mosaicism in cases with an sSMC.

Mosaicism in association with sSMC is a well-known fact. Crolla (1998) [45] summarized 144 sSMC cases excluding those derived from chromosomes 15 and 22, 78 of which (54%) showed mosaic karyotypes. To get a more detailed view on mosaicism in sSMC the following subgroups are focused separately below: cases with sSMC duplication and multiple sSMC, cases with four known “sSMC-syndromes” Pallister-Killian-, i(18p)-, Emanuel-, and cat-eye-syndrome, cases with sSMC and Prader-Willi- and Angelman-syndrome, cases with an sSMC present in a structurally abnormal but balanced karyotype, neocentric sSMC cases and patients with numerically abnormal basic karyotypes. The remaining sSMC with a normal basic karyotype of 46 chromosomes plus an sSMC are the group of patients this review starts with.

**SOMATIC MOSAICISM IN sSMC PRESENT IN A NORMAL BASIC KARYOTYPE**

According to Liehr (2010) [44] 731/1512 sSMC cases (52%) studied by cytogenetics are mosaic (see Table 1).

**Table 1. Cases with Mosaics 47,+mar, Excluding Cases with Known Syndromes, with Neocentric sSMC and such with Unclear Mosaicism Status**

| sSMC derived from chromosome | Number of cases with 47,+mar[100%] | Total number of sSMC cases | Cases with mos 47,+mar/46 |
|-----------------------------|-----------------------------------|---------------------------|--------------------------|
| 1                           | 6                                 | 67                        | 91%                      |
| 1/5/19                      | 0                                 | 8                         | 100%                     |
| 2                           | 6                                 | 36                        | 83%                      |
| 3                           | 7                                 | 21                        | 67%                      |
| 4                           | 7                                 | 21                        | 67%                      |
| 5                           | 10                                | 34                        | 71%                      |
| 6                           | 2                                 | 14                        | 86%                      |
| 7                           | 5                                 | 23                        | 78%                      |
| 8                           | 11                                | 92                        | 88%                      |
| 9                           | 4                                 | 59                        | 93%                      |
| 10                          | 5                                 | 18                        | 72%                      |
| 11                          | 3                                 | 16                        | 81%                      |
| 12                          | 6                                 | 29                        | 79%                      |
| 13                          | 7                                 | 9                         | 22%                      |
| 13/21                       | 54                                | 84                        | 36%                      |
| 14                          | 62                                | 99                        | 37%                      |
| 14/22                       | 31                                | 49                        | 37%                      |
| 15                          | 361                               | 459                       | 21%                      |
| 16                          | 4                                 | 46                        | 91%                      |
| 17                          | 6                                 | 26                        | 77%                      |
| 18                          | 14                                | 43                        | 67%                      |
| 19                          | 7                                 | 40                        | 83%                      |
| 20                          | 7                                 | 33                        | 79%                      |
| 21                          | 12                                | 25                        | 83%                      |
| 22                          | 78                                | 115                       | 32%                      |
| acro                        | 3                                 | 6                         | 50%                      |
| X                            | 7                                 | 27                        | 74%                      |
| Y                            | 6                                 | 13                        | 54%                      |
| **overall**                 | **731**                           | **1512**                  | **52%**                  |
| acrocentric                 | 608                               | 846                       | 28%                      |
| non-acrocentric             | 123                               | 666                       | 82%                      |
However, there is a strong difference between acrocentric and nonacrocentric derived sSMC: while 72% of acrocentric derived sSMC present no mosaic, 82% of nonacrocentric derived sSMCs are mosaic.

The real grade and complexity of mosaicism seems to be even slightly higher as recently repeatedly cryptic mosaicism was detected in sSMC cases by molecular cytogenetics. There were either cases showing an sSMC in all studied metaphase spreads, however, interphase-FISH in uncultured cells showed a mosaic situation like in case 16-CW-2 [44]. More often it is found that more than one variant of an sSMC is present in different studied cells of a patient. As summarized in Table 2, at least 5% of sSMC cases have, after a detailed molecular cytogenetic analysis, a more complex mosaicism than suggested after simple cytogenetic diagnostics. In 20% of these cases, unexpected complex somatic mosaicism was detectable where cytogenetics did not suggest any mosaicism, i.e. in cases 04-U-7, 08-W-p11.2/1-2, 11-O-p11.1/2-1, 11-U-9, 13-U-13, 15-W-q11.1+q11.2/1-1, 21-O-q11.21/1-1, 21-U-5, 22-O-q11.1/5-1, 22-O-q11.1/5-2, 0X-W-p11.?3/1-1, 0X-W-p11.21/1-1 [44]. Interestingly, acrocentric derived sSMC are by far more stable than nonacrocentric derived ones (2% versus 9%, Table 2).

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 duplica-

| sSMC derived from chromosome | Number of cases with cryptic mosaicism | Number of cases with cryptic mosaicism |
|-----------------------------|----------------------------------------|----------------------------------------|
| 1                           | 0/67                                   | 0%                                     |
| 1/5/19                      | 0/8                                    | 0%                                     |
| 2                           | 2/36                                   | 5%                                     |
| 3                           | 5/21                                   | 24%                                    |
| 4                           | 1/21                                   | 5%                                     |
| 5                           | 5/34                                   | 15%                                    |
| 6                           | 4/14                                   | 29%                                    |
| 7                           | 4/23                                   | 17%                                    |
| 8                           | 8/92                                   | 9%                                     |
| 9                           | 6/59                                   | 10%                                    |
| 10                          | 0/18                                   | 0%                                     |
| 11                          | 4/16                                   | 25%                                    |
| 12                          | 2/29                                   | 7%                                     |
| 13                          | 2/9                                    | 15%                                    |
| 13/21                      | 0/84                                   | 0%                                     |
| 14                          | 2/99                                   | 2%                                     |
| 14/22                      | 0/49                                   | 0%                                     |
| 15                          | 4/459                                  | 1%                                     |
| 16                          | 3/46                                   | 19%                                    |
| 17                          | 0/26                                   | 0%                                     |
| 18                          | 2/43                                   | 5%                                     |
| 19                          | 6/40                                   | 15%                                    |
| 20                          | 4/33                                   | 12%                                    |
| 21                          | 2/25                                   | 8%                                     |
| 22                          | 5/115                                  | 4%                                     |
| acro                       | 0/6                                   | 0%                                     |
| X                          | 2/27                                   | 7%                                     |
| Y                          | 0/13                                   | 0%                                     |
| overall                     | 73/1512                                | 5%                                     |
| acrocentric                 | 15/846                                | 2%                                     |
| nonacrocentric              | 58/666                                | 9%                                     |
tion starting from a centric minute-shaped chromosome and in the end to the 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 [46].

In summary, somatic mosaics are to be expected in at least 50% of sSMC cases with normal basic karyotype. More complex mosaics can be met in up to 10% of the cases; however, the overall rate of mosaic cases is not significantly altered by cryptic mosaicism, while the genetic complexity of individual cases may be severely influenced.

SOMATIC MOSAICISM IN CASES WITH sSMC DUPLICATION AND MULTIPLE sSMC

sSMC in a small subset of cases tend to duplicate, leading to a karyotype 48,+marx2 [42]. Up to now 64 such cases are reported [44] and 45% of those are derived from non-acrocentric chromosomes (Table 3). While, cases with acrocentric derived sSMC tend to be by mosaic only in 54% of the cases, non-acrocentric derived ones are always mosaic with an exception of 1/29 reported patients (Table 3). Thus, in sSMC duplication cases we find a similar situation as in

| sSMC derived from chromosome | Number of cases with 48,+marx2 [100%] | Total number of sSMC cases | Cases with mosaic |
|-----------------------------|---------------------------------------|----------------------------|------------------|
| 1                           | n.a.                                  | 2 (diff. sizes)            | 100%             |
| 1/5/19                      | n.a.                                  | n.a.                       | n.a.             |
| 2                           | n.a.                                  | 2                          | 100%             |
| 3                           | n.a.                                  | 2 (diff. sizes)            | 100%             |
| 4                           | n.a.                                  | 1/1 (diff. sizes)          | 100%             |
| 5                           | n.a.                                  | 1/1 (diff. sizes)          | 100%             |
| 6                           | n.a.                                  | 1/1 (diff. sizes)          | 100%             |
| 7                           | n.a.                                  | n.a.                       | n.a.             |
| 8                           | n.a.                                  | 2/1 (diff. sizes)          | 100%             |
| 9                           | n.a.                                  | 2/1 (diff. sizes)          | 100%             |
| 10                          | n.a.                                  | n.a.                       | n.a.             |
| 11                          | n.a.                                  | n.a.                       | n.a.             |
| 12                          | n.a.                                  | n.a.                       | n.a.             |
| 13                          | 1                                     | 1                          | 0%               |
| 13/21                       | 1                                     | 1/1 (diff. sizes)          | 50%              |
| 14                          | 2                                     | 3/1 (diff. sizes)          | 50%              |
| 14/22                       | 1                                     | 3                          | 67%              |
| 15                          | 11                                    | 22                         | 50%              |
| 16                          | n.a.                                  | 1/1 (diff. sizes)          | 100%             |
| 17                          | n.a.                                  | 1/1 (diff. sizes)          | 100%             |
| 18                          | n.a.                                  | n.a.                       | n.a.             |
| 19                          | 1                                     | 1                          | 0%               |
| 20                          | n.a.                                  | 3/1 (diff. sizes)          | 100%             |
| 21                          | n.a.                                  | 1                          | 100%             |
| 22                          | n.a.                                  | 2                          | 100%             |
| acro                       | n.a.                                  | n.a.                       | n.a.             |
| X                           | n.a.                                  | 1                          | 100%             |
| Y                           | n.a.                                  | 1                          | 100%             |
| overall                     | 17                                    | 64                         | 73%              |
| acrocentric                 | 16                                    | 35                         | 54%              |
| non-acrocentric             | 1                                     | 29                         | 97%              |
cases with one single sSMC and a karyotype 47, +mar concerning mosaicism.

Multiple sSMC cases [42] differ from sSMC duplication ones by the fact that the observed sSMC are not derived from the identical chromosome. Only 48 such cases are known by now [44], having between 2 and 7 sSMC of different origin, each; and all reported cases with multiple sSMC are mosaic. Formation of this rare cytogenetic condition is unclear, even though polysonic rescue or triploid rescue maybe suggested. As in most cases markedly chromosomal imbalances are induced by multiple sSMC presence, ~90-95% of them are correlated with clinical symptoms, irrespective of mosaicism status detectable in peripheral blood.

**SOMATIC MOSAICISM PRESENT IN THE FOUR KNOWN 'sSMC-SYNDROMES': PALLISTER-KILLIAN-, I(18P)-, EMANUEL-, AND CAT-EYE-SYNDROME**

Somatic mosaicism is reported to different extents in four sSMC-related syndromes.

Patients suffering from Pallister-Killian-syndrome (PKS) due to the presence of an additional isochromosome 12p are known to have somatic mosaicism in practically every case. In peripheral blood the +(12p) tends to be lost either already during pregnancy or shortly after birth in practically all cells.

In the alternatively studied skin fibroblasts, the sSMC derived from chromosome 12 is normally easily to detect in >70% to 100% of the cells [47]. However, besides a mosaic of cells with 46 and 47 chromosomes exceptional cases also exist with two different shapes of sSMC (12-Wpks-4, 12-Wpks-159, [44]) or two isochromosomes 12p (12-Wpks-174 [44]) and under-represented ones by the fact that the observed sSMC are not derived from the identical chromosome. Only 48 such cases are known by now [44], having between 2 and 7 sSMC of different origin, each; and all reported cases with multiple sSMC are mosaic. Formation of this rare cytogenetic condition is unclear, even though polysonic rescue or triploid rescue maybe suggested. As in most cases markedly chromosomal imbalances are induced by multiple sSMC presence, ~90-95% of them are correlated with clinical symptoms, irrespective of mosaicism status detectable in peripheral blood.

**SOMATIC MOSAICISM IN THE FOUR KNOWN 'sSMC-SYNDROMES': PALLISTER-KILLIAN-, I(18P)-, EMANUEL-, AND CAT-EYE-SYNDROME**

Somatic mosaicism is reported to different extents in four sSMC-related syndromes.

Patients suffering from Pallister-Killian-syndrome (PKS) due to the presence of an additional isochromosome 12p are known to have somatic mosaicism in practically every case. In peripheral blood the +(12p) tends to be lost either already during pregnancy or shortly after birth in practically all cells.

In the alternatively studied skin fibroblasts, the sSMC derived from chromosome 12 is normally easily to detect in >70% to 100% of the cells [47]. However, besides a mosaic of cells with 46 and 47 chromosomes exceptional cases also exist with two different shapes of sSMC (12-Wpks-4, 12-Wpks-159, [44]) or two isochromosomes 12p (12-Wpks-174 [44]) and under-represented ones by the fact that the observed sSMC are not derived from the identical chromosome. Only 48 such cases are known by now [44], having between 2 and 7 sSMC of different origin, each; and all reported cases with multiple sSMC are mosaic. Formation of this rare cytogenetic condition is unclear, even though polysonic rescue or triploid rescue maybe suggested. As in most cases markedly chromosomal imbalances are induced by multiple sSMC presence, ~90-95% of them are correlated with clinical symptoms, irrespective of mosaicism status detectable in peripheral blood.

**SOMATIC MOSAICISM IN NEOCENTRIC sSMC**

For mosaicism in neocentric sSMC formed by McClintock mechanism, [48] the same holds true, like for the aforementioned centric sSMC present in structurally abnormal but balanced karyotype. If balanced and no or only minimal mosaicism is present, the carriers of such a chromosomal condition are clinically normal. If the neocentric sSMC is lost in a higher percentage of the body cells this has an adverse prognosis.

In general, in at least around 50% of the cases with a neocentric sSMC somatic mosaicism is observable (Table 4). Strikingly, as in centric sSMC, mosaicism is more frequent in non-acrocentric derived compared to acrocentric derived ones (58% vs. 24%).

**SOMATIC MOSAICISM IN sSMC PRESENT IN NUMERICALLY ABNORMAL BASIC KARYOTYPES**

As above mentioned, sSMC can appear in a numerically normal basic karyotype of 46 chromosomes, but also in numerically abnormal basic karyotypes [42]. Up to now, sSMC are reported additionally to a basic karyotype 45, X (= Turner syndrome), 47, XXX (= Klinefelter syndrome), 47, XXX (triple-X syndrome) and 47, +21 (Down syndrome) [44, 49-51].

542 cases are available in the literature with a basic karyotype typical for Turner syndrome and an additional sSMC, i.e. 46,X,+mar [44, 49]. Only 73 of these are reported without mosaicism; thus, 76% of these Turner syndrome cases are mosaic [44].

Only three cases, each of them are known by now with Klinefelter- or triple-X syndrome and an additional sSMC. Concerning the Klinefelter-syndrome two cases of those are mosaic (07-U-6, 0X-U3) and one not (09-U5) [44]. For tri-
ple-X syndrome the same holds true: cases 09-U16 and 14-O-q11.1/1-5 are mosaic, case 14-U-5 is not [44].

For sSMC, at present additionally to a trisomy 21 (Down-syndrome), information on mosaic status is available in 16 cases; 7 of those (44%) have somatic mosaicism with a cell line 47, +21 without sSMC [44].

Overall, mosaicism is a frequent finding when an sSMC is present additionally to a numerically abnormal basic karyotype.

SOMATIC MOSAICISM IN sSMC AND THE RESULTING PITFALLS

Summarizing all above mentioned groups, 1626 of 3124 cases with sSMC (52%) present with somatic mosaicism. Even though, expressed to a different extent in various subgroups, mosaicism is something to be considered in at least every second such case. However, if a specific genetic imbalance caused by an sSMC is known to be harmful, in the overwhelming majority of the cases there is no influence of the grade of somatic mosaicism detectable in peripheral blood or amnion cells and the observed clinical effects. This seems to be due to the fact that the mosaicism rate in different human tissues is practically not predictable and very variable [52]. Only in exceptional cases the presence of specific sSMC with known adverse prognosis was reported which did not lead to clinical problems due to low somatic mosaicism; examples are 07-W-p10/1-1, 15-O-q13/1-1, 15-O-q13/1-2, 15-O-q13/2-1, 15-O-q13/3-1, 15-O-q13.1/1-1, 22-O-q11.21/4-2, 22-O-q11.21/4-3, 22-O-q11.21/5-1 [44]. Even though rare, this knowledge is extremely important for prenatal counseling.

Knowing that somatic mosaicism happens in ~50% of the cases with sSMC, array-CGH studies cannot be offered as a screening test to reliably detect this kind of chromosomal aberration. On the one hand, low level mosaic cases and on

| sSMC derived from chromosome | Number of cases with mosaicism | Percentage of cases with mosaicism |
|-----------------------------|-------------------------------|----------------------------------|
| 1                           | 3/5                           | 60%                              |
| 2                           | 3/4                           | 75%                              |
| 3                           | 10/11                         | 91%                              |
| 4                           | 1/1                           | 100%                             |
| 5                           | 0/1                           | 0%                               |
| 6                           | 1/2                           | 50%                              |
| 7                           | 1/1                           | 100%                             |
| 8                           | 7/9                           | 77%                              |
| 9                           | 1/3                           | 33%                              |
| 10                          | 1/2                           | 50%                              |
| 11                          | 0/2                           | 0%                               |
| 12                          | 2/3                           | 75%                              |
| 13                          | 5/14                          | 56%                              |
| 14                          | 1/1                           | 100%                             |
| 15                          | 2/19                          | 11%                              |
| 16                          | 1/1                           | 100%                             |
| 17                          | 0/1                           | 0%                               |
| 18                          | 1/1                           | 100%                             |
| 19                          | n.a.                          | n.a.                             |
| 20                          | 0/1                           | 0%                               |
| 21                          | n.a.                          | n.a.                             |
| 22                          | n.a.                          | n.a.                             |
| X                           | 0/1                           | 0%                               |
| Y                           | 0/1                           | 0%                               |
| overall                     | 40/86                         | 47%                              |
| acrocentric                 | 8/34                          | 24%                              |
| nonacrocentric              | 32/55                         | 58%                              |
the other hand, cryptic mosaics are missed. Thus, cytogenetics is still the gold-standard to detect any kind of chromosomal aberration, which then, in further steps can be characterized by molecular (cyto-) genetic approaches.

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 is therefore at present not available.

CONCLUSION

Somatic mosaicism is a feature of the human body, which has to be considered much more than up to now in future. It is known as a fact, but not understood why man with age (in peripheral blood) develops something like a ‘Turner-syndrome- mosaic’ 46,XY/45,X. Similarly, in cases with sSMC it is known since years, that PKS patients lose the i(12p) in peripheral blood or that some inv dup(15) sSMC are stable and cytogenetically identical ones in another carrier are not. For all these facts to the best of our knowledge, no studies were undertaken to come closer to an understanding of these phenomena. Here we present, some details ‘mosaicism map’ for the different subtypes of sSMC.

ACKNOWLEDGEMENTS

This work was supported in parts by DAAD (DF07/00070), BMBF/DLR (BLR 08/004 and ARM 08/001), Prochance 2008 and 2009, and DFG (LI 820/22-1).

REFERENCES

[1] Tjio, J.-H.; Levan, A. The chromosome number of man. Hereditas, 1956, 42, 1-6.
[2] Yunis, J.J.; Chandler, M.E. High-resolution chromosome analysis in clinical medicine. Prog. Clin. Pathol., 1978, 7, 267-288.
[3] Miettinen, F. Cytogenetics of experimental neoplasms and non-random chromosome correlations in man. Clin. Haematol., 1980, 9, 195-219.
[4] Liehr, T.; Claussen, U. Current developments in human molecular cytogenetic techniques. Curr. Mol. Med., 2002, 2, 283-297.
[5] Liehr, T.; Claussen, U. Multicolor-FISH approaches for the characterization of human chromosomes in clinical genetics and tumor cytogenetics. Curr. Genomics, 2002, 3, 213-235.
[6] Liehr, T.; Starke, H.; Weise, A.; Lehrer, H.; Claussen, U. Multicolor FISH probe sets and their applications. Histol. Histopathol., 2004, 19, 229-237.
[7] Liehr, T.; Starke, H.; Heller, A.; Kosyakova, N.; Mrasek, K.; Gross, M.; Karst, C.; Steinhaeuser, U.; Hunstig, F.; Fickelscher, I.; Kuechler, A.; Tjio, J.-H.; Levan, A. The chromosome number of man. Hereditas, 1956, 42, 1-6.
[8] Yunis, J.J.; Chandler, M.E. High-resolution chromosome analysis in clinical medicine. Prog. Clin. Pathol., 1978, 7, 267-288.
[9] Miettinen, F. Cytogenetics of experimental neoplasms and non-random chromosome correlations in man. Clin. Haematol., 1980, 9, 195-219.
[10] Liehr, T.; Claussen, U. Current developments in human molecular cytogenetic techniques. Curr. Mol. Med., 2002, 2, 283-297.
[11] Liehr, T.; Claussen, U. Multicolor-FISH approaches for the characterization of human chromosomes in clinical genetics and tumor cytogenetics. Curr. Genomics, 2002, 3, 213-235.
[12] Gross, M.; Mtkrtychyan, H.; Glaser, M.; Fricke, H.J.; Hoffken, K.; Heller, A.; Weise, A.; Liehr, T. Delineation of yet unknown cryptic subtelomere aberrations in 50% of acute myeloid leukemia with abnormal GTG-banding karyotype. Int. J. Oncol., 2009, 34, 417-423.
[13] Dimmler, A.; Kiesewetter, F.; Liehr, T.; Neubauer, S.; Schell, H.; Gebhart, E. Interphase-FISH examinations in paraffin sections from benign, precancerous, and cancerous lesions of the skin and oral mucosa. Int. J. Oncol., 1997, 10, 83-88.
[14] Iourov, I.Y.; Vorsanova, S.G.; Liehr, T.; Monakhov, V.V.; Soloviev, I.V.; Yurov, Y.B. Dynamic mosaicism manifesting as loss; gain and rearrangement of an isodicentric Y chromosome in a male child with growth retardation and abnormal external genitalia. Cytogenet. Genome Res., 2008, 121, 302-306.
[15] Liehr, T.; Ziegler, M. Rapid prenatal diagnostics in the interphase nucleus – procedure and cut-off rates. J. Histochem. Cytochem., 2005, 53, 289-291.
[16] Liess, J.; Rautenstrauss, B.; Grehl, H.; Bathke, K.D.; Ekiic, A.; Rauch, A.; Rott, H.D. Mosaicism for the Charcot-Marie-Tooth disease type I duplication suggests somatic reversion. Hum. Genet., 1996, 98, 22-28.
[17] Koç, A.; Kan, D.; Karaer, K.; Ergün, M.A.; Karaoğuz, M.Y.; Güçütyener, K.; Hineiner, S.; Liehr, T.; Perçin, E.F. An unexpected finding in a child with neurological symptoms: mosaic ring chromosome 18. Eur. J. Pediatr., 2008, 167, 655-659.
[18] Soysal, Y.; Balci, S.; Hekimler, K.; Liehr, T.; Ewers, E.; Schoumans, J.; Bui, T.H.; Içduygu, F.M.; Kosyakova, N.; Imizalijoglu, N. Characterization of double ring chromosome 4 mosaicism associated with bilateral hip dislocation, cortical dysgenesis, and epilepsy. Am. J. Med. Genet. A, 2009, 149A, 2782-2787.
[19] Yurov, Y.B.; Vostrikov, V.M.; Vorsanova, S.G.; Monakhov, V.V.; Iourov, I.Y. Multicolor fluorescent in situ hybridization on post mortem brain in schizophrenia as an approach for identification of low-level chromosomal aneuploidy in neuropsychiatric diseases. Brain Dev., 2001, 23(Suppl 1), 186-190.
[20] Yurov, Y.B.; Iourov, I.Y.; Monakhov, V.V.; Soloviev, I.V.; Vostrikov, V.M.; Vorsanova, S.G. The variation of aneuploidy frequency in the developing and adult human brain revealed by an interphase FISH study. J. Histochem. Cytochem., 2005, 53, 385-390.
[21] Iourov, I.Y.; Liehr, T.; Vorsanova, S.G.; Kolotii, A.D.; Yurov, Y.B. Visualization of interphase chromosomes in postmitotic cells of the human brain by multicolour banding (MCB). Chromosome Res., 2006, 14, 223-229.
[22] Yurov, Y.B.; Iourov, I.Y.; Vorsanova, S.G.; Liehr, T.; Kolotii, A.D.; Kutsev, S.I.; Pellestor, F.; Beresheva, A.K.; Demidova, I.A.; Kravets, V.S.; Monakhov, V.V.; Soloviev, I.V. Aneuploidy and confined chromosomal mosaicism in the developing human brain. PLoS ONE, 2007, 2, e558.
[23] Yurov, Y.B.; Vorsanova, S.G.; Iourov, I.Y.; Demidova, A.L.; Beresheva, A.K.; Kravets, V.S.; Monakhov, V.V.; Kolotii, A.D.; Voinova-Ulas, V.Y.; Gorbachevskaya, N.L. Unexplained autism is frequently associated with low-level mosaic aneuploidy. J. Med. Genet., 2007, 44, 521-535.
[24] Yurov, Y.B.; Iourov, I.Y.; Vorsanova, S.G.; Demidova, I.A.; Kravets, V.S.; Beresheva, A.K.; Kolotii, A.D.; Monakhov, V.V.; Uranova, N.A.; Vostrikov, V.M.; Soloviev, I.V.; Liehr, T. The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. Schizophr. Res., 2008, 98, 137-147.
[25] Iourov, I.Y.; Vorsanova, S.G.; Yurov, Y.B. Molecular cytogenetics and cytogenomics of brain diseases. Curr. Genomics, 2008, 9, 452-465.
[26] Iourov, I.Y.; Vorsanova, S.G.; Liehr, T.; Yurov, Y.B. Aneuploidy in the normal, Alzheimer’s disease and ataxia-telangiectasia brain: differential expression and pathological meaning. Neurobiol. Dis., 2009, 34, 212-220.
[27] Iourov, I.Y.; Vorsanova, S.G.; Liehr, T.; Kolotii, A.D.; Yurov, Y.B. Increased chromosome instability dramatically disrupts neural genome integrity and mediates cerebellar degeneration in the ataxia-telangiectasia brain. Hum. Mol. Genet., 2009, 18, 2656-2669.
[28] Vanneste, E.; Voet, T.; Le Caïnnec, C.; Ampe, M.; Königs, P.; Mellote, C.; Debrock, S.; Amyere, M.; Vikkula, M.; Schuit, F.; Pyns, J.P.; Verbeke, G.; D’Hooghe, T.; Moreau, Y.; Vermeesch, J.R. Chromosome instability is common in human cleavage-stage embryos. Nat. Med., 2009, 15, 571-583.
Somatic Mosaicism in Cases with Small Supernumerary Marker

Current Genomics, 2010, Vol. 11, No. 6 439

[29] Vorsanova, S.G.; Koloti, A.D.; Iourov, I.Y.; Monakhov, V.V.; Kirillova, E.A.; Soloviev, I.V.; Yurov, Y.B. Evidence for high frequency of chromosomal mosaicism in spontaneous abortions revealed by interphase FISH analysis. J. Histochem. Cytochem., 2005, 53, 375-380.

[30] Vorsanova, S.G.; Iourov, I.Y.; Demidova, I.A.; Kirillova, E.A.; Soloviev, I.V.; Yurov, Y.B. Chimerism and multiple numerical chromosome imbalances in a spontaneously aborted fetus. Tsitot. Genet., 2006, 40, 28-30.

[31] Vorsanova, S.G.; Yurov, Y.B.; Deryagin, G.V.; Soloviev, I.V.; Bytenskaya, G.A. Diagnosis of aneuploidy by in situ hybridization: analysis of interphase nuclei. Ball. Exp. Biol. Med., 1991, 112, 413-415.

[32] Mkrtchyan, H.; Gross, M.; Hinreiner, S.; Polytiko, A.; Manvelyan, M.; Mrasek, K.; Kosyakova, N.; Ewers, E.; Nelle, H.; Liehr, T.; Vollet, M.; Weise, A. Early embryonic chromosome instability results in stable mosaic pattern in human tissues. PLoS One, 2010, 3, e9591.

[33] Felka, T.; Lemke, J.; Lemke, C.; Michel, S.; Liehr, T.; Claussen, U. DNA degradation during maturation of erythrocytes-molecular cytogenetic characterization of Howell–Jolly bodies. Cytogenet. Genome Res., 2007, 119, 2-8.

[34] Kinne, R.W.; Liehr, T.; Beensen, V.; Kunisch, E.; Zimmermann, T.; Holland, H.; Pfeiffer, R.; Stahl, H.-D.; Langer, H.-W.; Hein, G.; Roth, A.; Emmrich, F.; Claussen, U.; Froster, U.G. Mosaic chromosomal aberrations in synovial fibroblasts of patients with rheumatoid arthritis, osteoarthritis, and other inflammatory joint diseases. Arthritis. Res., 2001, 3, 319-330.

[35] Kinne, R.W.; Kunisch, W.; Beensen, V.; Zimmermann, T.; Emmrich, F.; Petrov, P.; Lungershausen, W.; Hein, G.; Braun, R.K.; Foerster, M.; Kroegel, C.; Winter, R.; Liesaus, E.; Fuhrmann, R.A.; Roth, A.; Claussen, U.; Liehr, T. Synovial fibroblasts and synovial macrophages from patients with rheumatoid arthritis and other inflammatory joint diseases show chromosomal aberrations. Genes Chromosomes Cancer, 2003, 38, 53-67.

[36] Iourov, I.Y.; Vorsanova, S.G.; Soloviev, I.V.; Yurov, Y.B. Interphase FISH: detection of intercellular genomic variations and somatic chromosomal mosaicism. In Fluorescence in situ hybridization (FISH) - Application guide. Liehr T. Ed. Berlin; Heidelberg: Springer Verlag; 2009, pp. 301-311.

[37] Iourov, I.Y.; Vorsanova, S.G.; Yurov, Y.B. Chromosomal variations in mammalian neuronal cells: known facts and attractive hypotheses. Int. Rev. Cytol., 2006, 249, 143-191.

[38] Iourov, I.Y.; Vorsanova, S.G.; Yurov, Y.B. Intercellular genomic (chromosomal) variations resulting in somatic mosaicism: mechanisms and consequences. Curr. Genomics, 2006, 7, 435-446.

[39] Iourov, I.Y.; Vorsanova, S.G.; Yurov, Y.B. Chromosomal mosaicism goes global. Mol. Cytogenet., 2008, 1, 26.

[40] Pathak, S. Cytogenetic research techniques in humans and laboratory animals that can be applied most profitably to livestock. J. Dairy Sci., 1979, 62, 836-843.

[41] Liehr, T.; Weise, A. Frequency of small supernumerary marker chromosomes in prenatal, newborn, developmentally retarded and infertility diagnostics. Int. J. Mol. Med., 2007, 19, 719-731.

[42] Liehr, T.; Claussen, U.; Starke, H. Small supernumerary marker chromosomes (sSMC) in humans. Cytogenet. Genome Res., 2004, 107, 55-67.

[43] Liehr, T.; Mrasek, K.; Weise, A.; Dufke, A.; Rodríguez, L.; Martínez Guardia, N.; Sanchis, A.; Vermeesch, J.R.; Ramel, C.; Polityko, A.; Haas, O.A.; Anderson, J.; Claussen, U.; von Eggeling, F.; Starke, H. Small supernumerary marker chromosomes—progress towards a genotype-phenotype correlation. Cytogenet. Genome Res., 2006, 112, 23-34.

[44] Liehr, T. Homepage on small supernumerary marker chromosomes (sSMC). http://www.med.uni-jena.de/fish/sSMC/00START.htm (Accessed January 11, 2010).

[45] Crolla, J.A. FISH and molecular studies of autosomal supernumerary marker chromosomes excluding those derived from chromosome 15: I. Review of the literature. Am. J. Med. Genet., 1998, 75, 367-381.

[46] Liehr, T. Small supernumerary marker chromosomes (sSMCs): a spotlight on some nomenclature problems. J. Histochem. Cytochem., 2009, 57, 991-993.

[47] Liehr, T.; Wegner, R.-D.; Stumm, M.; Joksi, G.; Polityko, A.; Kosyakova, N.; Ewers, E.; Reich, D.; Wagner, R.; Weise, A. Pallister-Killian syndrome. Rare phenotypic features and variable karyotypes. Balkan J. Med. Genet., 2008, 12, 65-67.

[48] Baldwin, E.L.; May, L.F.; Justice, A.N.; Martin, C.L.; Ledbetter, D.H. Mechanisms and consequences of small supernumerary marker chromosomes: from Barbara McClintock to modern genetic-counseling issues. Am. J. Hum. Genet., 2008, 82, 398-410.

[49] Liehr, T.; Mrasek, K.; Hinreiner, S.; Reich, D.; Ewers, E.; Bartels, I.; Seidel, J.; Manolakis, E.; Petersen, M.; Polityko, A.; Dufke, A.; Iourov, I.; Trifonov, V.; Vermeesch, J.; Weise, A. Small supernumerary marker chromosomes (sSMC) in patients with a karyotype 45,XY/46.X;+mar – 17 new cases and a review of the literature. Sex. Dev., 2007, 1, 353-362.

[50] Starke, H.; Mitulla, B.; Nietzel, A.; Heller, A.; Beensen, V.; Grosswendt, G.; Claussen, U.; von Eggeling, F.; Liehr, T. First patient with trisomy 21 accompanied by an additional der(4)(p11 → q11) plus partial uniparental disomy 4p15-16. Am. J. Med. Genet., 2003, 116A, 26-30.

[51] Liehr, T.; Mrasek, K.; Starke, H.; Claussen, U.; Schreiber, G. Unusual small supernumerary marker chromosome (sSMC) 9 in a Klinefelter patient. Cytogenet. Genome Res., 2005, 111, 179-181.

[52] Fickelscher, I.; Starke, H.; Schulze, E.; Ernst, G.; Kosyakova, N.; Mkrtchyan, H.; Macdermont, K.; Sebire, N.; Liehr, T. A further case with a small supernumerary marker chromosome (sSMC) derived from chromosome 1-evidence for high variability in mosaicism in different tissues of SMC carriers. Prenat. Diagn., 2007, 27, 783-785.