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Neocentric small supernumerary marker chromosomes (sSMC) – three more cases and review of the literature

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Abstract. Here we report on three new patients with neocentric small supernumerary marker chromosomes (sSMC) derived from chromosome 2, 13 and 15, respectively. The sSMC(13) and sSMC(15) had inverted duplicated shapes and the sSMC(2) a ring chromosome shape. All three cases were clinically severely abnormal. A review of the available sSMC literature revealed that up to the present 73 neocentric sSMC cases including these three new cases have been reported. Seven of these cases were not characterized morphologically; in the remainder, 80% had an inverted duplication, 17% a ring and 3% a minute shape. 81% of the reported neocentric sSMC carriers showed severe, 12% moderate and 8% no clinical abnormalities. In summary, we report three more neocentric sSMC cases, provide a review on all up to now published cases, highlight their special characteristics and compare them to centric sSMC.

Amongst reported patients with small supernumerary marker chromosomes (sSMC) neocentric ones constitute the second smallest group (see review of Liehr et al., 2004a). Nevertheless, in recent years increasing numbers of sSMC with centromeric constrictions but no detectable alpha-satellite DNA have been reported. Neocentric or also called analphoid markers 'carry newly derived centromeres (or 'neocentromeres') that are apparently formed within interstitial chromosomal sites that have not previously been known to express centromere function' (Choo, 1997).

As summarized in Liehr et al. (2004a) and Warburton (2004) the majority of neocentric sSMC are based on a U-type exchange and are small inverted duplicated chromosomes. Also ring and minute chromosome conformations are described and are mostly associated with a deletion of the corresponding region in one of the homologous chromosomes.

Here we report on three more neocentric sSMC cases, derived from chromosomes 2, 13 and 15, respectively. They are described in detail and are discussed together with the other reported 70 analphoid marker cases.

Materials and methods

Case reports

Neo #2-2. An 8-year-old female was referred to cytogenetic analysis due to severe psychomotor retardation, absent speech and developmental delay. Additionally she showed hypotonia, a short neck, small hands and feet, brachydactyly, short and broad hallux, pectus excavatum, mild pterygium colli, delayed teeth eruption and facial dysmor-

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phisms including frontal bossing, hypertelorism, low nasal bridge, small and short nose, anteverted nares, macrostomia, triangular mouth, thin upper lip, short philtrum and micrognathia. Unfortunately, neither for birth nor for the time of referring to cytogenetic analysis (8 years) auxological data is available. A karyotype 47,XX,+mar[14]/46,XX[36] was diagnosed from peripheral blood and fluorescence in situ hybridization (FISH) revealed a neocentric r(2)(::q35→q36::). Parental karyotypes were normal.

Neo #13-6. At the age of 3 months a boy was admitted to hospital because of developmental delay and poor sucking. He was born at term by cesarean section as a result of the second pregnancy of healthy non-consanguineous parents after an uneventful pregnancy (birth weight 3600 g, length 49 cm). At 3 months he presented with a weight of 5660 g (25–50th centile), length of 62 cm (25–50th centile) and head circumference (OFC) of 40.3 cm (25–50th centile). Physical examination revealed a hemangioma in the frontal region, syndactyly of the toes 2 and 3, broad thumbs and facial dysmorphisms (pit on right ear helix, hypertelorism, left epicanthal fold, broad and flat nasal bridge, bulbous nasal tip, anteverted nares, long philtrum, mild micrognathia, wide anterior fontanelle; see Fig. 2A). Abdominal ultrasonography and echocardiography were normal while cranial CT identified a Dandy-Walker variant, anarachnoid cyst at temporal lobe posteromedial region, a porencephaly at left caudate nucleus and frontal white matter. In cranial MRI a cerebellar vermis dysplasia, a broad fourth ventricle, a mega cisterna magna, a mild cortical cerebral atrophy and cerebral mild dysmyelinization were detected. In peripheral blood cytogenetic analysis revealed a male karyotype with a de novo sSMC in all studied cells. Molecular cytogenetics characterized an inv dup(13)(qter→q22.3∼31.1::q22.3∼31.1→qter).

Neo #15-5. After a normal pregnancy and vacuum-assisted delivery in week 40 a female baby was born with a birth weight of 2910 g (10–25th centile), a length of 52 cm (50–75th centile) and an OFC of 33.6 cm (∼25th centile). At 6 months of age developmental delay, muscular hypotonia, spastic legs and a hemangioma on right forearm were diagnosed. Developmental milestones were reached with delay: independent walking at 2 years and first words not before 2.5 years. At 3 years focal seizures appeared for the first time. Additionally mild craniofacial dysmorphism like long nose, relatively short philtrum and high-arched narrow palate are present. At 11 years the patient presented with mental retardation with a friendly personality and with restricted active speech ability (only single words) but good understanding. Moreover, severe progressive idiopathic thoracolumbal scoliosis, hip dysplasia, mitral valve prolapse, chronic constipation and reduced sensitivity to pain were diagnosed. Weight was 29 kg (3rd–10th centile), length was 155 cm (75–90th centile) and OFC was 54 cm (75–90th centile). Banding cytogenetics revealed a karyotype of 47,XX,+mar[4]/46,XX[46] in peripheral blood. The neocentric sSMC was characterized as an inv dup(15)(qter→q24.1::q24.1→qter).

Cytogenetics and molecular cytogenetics

Metaphase chromosome preparations were obtained from PHA stimulated lymphocyte cultures from each patient and their parents according to standard procedures.

FISH was done using standard protocols. Single- and two-color FISH, multicolor FISH using all 24 whole chromosome painting probes (M-FISH), multicolor banding (MCB) and chromosome microdissection with reverse chromosome painting were performed as previously described in Liehr et al. (2002, 2004b). The applied probes were either homemade and described in the aforementioned references or commercially available as: subtelomeric probe for 13qter (Abbott/Vysis) or all-human telomeric probe (DAKO). M-FISH and MCB were applied in all three cases; the all-human telomeric probe was hybridized in case Neo #15-5 and the subtelomeric probes in case Neo #13-6. In case Neo #2-2 microdissection and reverse painting of the sSMC were done.

Database analysis

All previously published neocentric sSMC cases were collected from the sSMC homepage (Liehr, 2007). According to the definition of sSMC (Liehr et al., 2004a) only those cases with neocentric chromosomes, which are equal in size or smaller than a chromosome 20 were included here.

The cases collected in Table 1 are classified in the following major clinical subgroups: Unclear, none, moderate, severe or severe and lethal. If no clinical data was available, the classification 'unclear' was applied. If no mental or physical handicaps or dysmorphism were reported, the clinical signs were classified as absent (= 'none'). If developmental delay was reported and/or only minor mental or physical handicaps were present, the clinical signs were classified as 'moderate'. Mental or severe mental retardation combined with physical handicaps was regarded as 'severe' clinic. If the patient was reported to die shortly after birth, the clinic was described as severe and lethal.

Results and discussion

Three new cases

Three new cases with neocentric sSMC are reported here. They were characterized by molecular cytogenetics as r(2)(::q35→q36::), inv dup(13)(qter→q22.3∼31.1::q22.3∼31.1→qter) and inv dup(15)(qter→q24.1::q24.1→qter), respectively (see Figs. 1–3). Case Neo #2-2 is the second now described case with a neocentric sSMC(2), while for Neo #13-6 and Neo #15-5 four and one cytogenetically similar cases, respectively, were previously reported. Case Neo #13-6 is the only one among the five similar cases now reported with the marker present in all peripheral blood cells. On the other hand, case Neo #15-5 shows the smallest amount of cells with a neocentric sSMC(15) ever described with only 8% (see Table 1).

Review of the literature – 73 neocentric sSMC cases

As summarized in Table 1, 73 neocentric sSMC cases have been reported up to now; there are examples for all chromosomes, apart from X, Y, 19, 21 and 22, even though neocentromere formation was also previously described on (larger) chromosomes X, Y and 22 (Warburton, 2004). The region of centromeric constriction was not determined exactly in most of the reported neocentric sSMC cases including the three presented here. The ∼20 cases in which this was done were summarized and discussed previously (Warburton, 2004).

Concluding from Table 1, there are three major clinical groups among the 73 neocentric sSMC cases: those with none (5 cases), those with moderate to severe (8 cases) and those with severe/severest (55 cases) clinical consequences. In five cases no information on the clinical outcome was available.

Neocentric sSMC and their (cyto-)genetic effects

An interesting issue of neocentric sSMC is that their presence can lead to no imbalance at all (e.g. case Neo #13-1), to gain of one (e.g. case Neo #11-1), two (e.g. case Neo #8-1) or four copies (e.g. case Neo #13-11) of the corresponding region present on the sSMC; even loss of one copy (e.g. case Neo #13-7) is possible (see also Warburton, 2004). The mechanisms of these imbalance formations are summarized in Fig. 4.

Table 1. Summary of all 73 cases with a small supernumerary marker chromosome (sSMC) available in the literature including the three new cases reported here. Cases with known clinical outcome and well defined size of the chromosomal imbalance are marked with an asterisk in the fourth column if they are included in Fig. 5.

Case number	Karyotype in peripheral blood (if not indicated differently)	sSMC	Clinical effects	Reference on sSMC homepage
Neo #1-1	47,XY,del(1)(p32p36.1),+mar1[87%]/ 47,XY,del(1)(p32p36.1),+mar2[10%]/ 46,XY,del(1)(p32p36.1)[3%]	mar1 = r(1)(::p32→p36.1::)/ mar2 = r(1)(::p32→p36.1::p23→p36.1::)	none* apart from infertility and oligospermia	01-N-p32/1-1
Neo #1-2	47,+mar[?]	r(1)(::q21→q22::)	unclear	01-N-q21/1-1
Neo #1-3	47,XY,del(1)(q23q32),+mar[100%]	r(1)(::q23→q32::) 'dynamic mosaic', i.e. variants of small supernumerary ring chromosome were detected but not characterized in detail	unclear	01-N-q23/1-1
Neo #1-4	47,XX,del(1q32),+mar [100%]	inv dup(1)(qter→q32::q32→qter)	severe*	01-N-q32/1-1
Neo #1-5	47,XY,+mar[50%]	r(1)(::q43→q44::)	none* at 6 months	01-N-q43/1-1
Neo #2-1	47,XY,del(2)(p11p21),+mar[100%]	r(2)(::p11→p21::)	severe	02-N-p21/1-1
Neo #2-2	47,XX,+mar[14]/46,XX[36]	r(2)(::q35→q36::)	severe*	02-N-q35/1-1
Neo #3-1	47,XY,+mar[57%]	inv dup(3)(qter→q26.2::q26.2→qter)	severe*	03-N-qt26.2/1-1
Neo #3-2	47,XY,+mar[2.5% in blood; 88% in skin fibroblasts]	inv dup(3)(qter→q26.2::q26.2→qter)	severe*	03-N-qt26.2/1-2
Neo #3-3	47,XY,+mar[?%; only in fibroblasts]	inv dup(3)(qter→q26.2::q26.2→qter)	severe*	03-N-qt26.2/1-3
Neo #3-4	47,XY,+mar[24% only in fibroblasts]	inv dup(3)(qter→q26.2::q26.2→qter)	severe*	03-N-qt26.2/1-4
Neo #3-5	47,XY,+mar[30% in blood; 6% in fibroblasts]	inv dup(3)(qter→q27.1::q27.1→qter)	severe*	03-N-qt27.1/1-1
Neo #3-6	47,XY,+mar[71%]	inv dup(3)(qter→q27.2::q27.2→qter)	severe*	03-N-qt27.2/1-1
Neo #3-7	47,XY,+mar[100%]	inv dup(3)(qter→q28::q28→qter)	severe*	03-N-qt28/1-1
Neo #4-1	47,XY,del(4)(q21.1q21.3),+mar[75%]/ 46,XY,del(4)(q21.1q21.3)[25%]	r(4)(::q21.1→q21.3::)	severe	04-N-q22.1/1-1
Neo #5-1	47,XX,+mar[100%]	inv dup(5)(pter→p14::p14→pter)	severe*	05-N-pt14/1-1
Neo #6-1	47,XY,t(4;15),del(6)(q16.2q22.2),+mar[100%]	r(6)(::q16.2→q22.2::)	severe	06-N-q16.2/1-1
Neo #6-2	47,+mar[60% in placenta only]	inv dup(6)(qter→q26::q26→qter)	moderate	06-N-q26/1-1
Neo #7-1	47,+mar[45%]	mar(7)	severe	07-N-mar/1
Neo #7-2	47,+mar[?%]	inv dup(7)(qter→q36.1::36.1→qter)	unclear	07-N-q36.1/1-1
Neo #8-1	47,XX,+mar[60%]	inv dup(8)(pter→p23.3::p23.3→pter)	severe* (history of drug abuse in mother during pregnancy)	08-N-pt23.3/1-1
Neo #8-2	47,XY,+mar[21%]	inv dup(8)(pter→p23.2∼23.1::p23.2∼23.1 →pter)	none*	08-N-pt23.2∼23.1/1-1
Neo #8-3	47,XY,+mar[90% in blood; 100% in skin fibroblasts]	inv dup(8)(pter→p23.1::23.1→pter)	moderate*	08-N-pt23.1/1-1
Neo #8-4	47,XX,+mar[100%]	inv dup(8)(pter→p23.1::23.1→pter)	moderate*	08-N-pt23.1/1-2
Neo #8-5	47,XY,+mar[100%]	inv dup(8)(pter→p23.1::23.1→pter)	moderate*	08-N-pt23.1/1-3
Neo #8-6	47,XY,+mar[25%]	inv dup(8)(pter→p23.1::23.1→pter)	moderate*	08-N-pt23.1/1-4
Neo #8-7	47,+mar [?%]	inv dup(8)(pter→p23.1::23.1→pter)	unclear	08-N-pt23.1/1-5
Neo #8-8	47,XY,+mar[40%]	inv dup(8)(pter→p23.1::23.1→pter)	moderate*	08-N-pt23.1/1-6
Neo #8-9	47,XX,+mar[50%]	inv dup(8)(pter→p22::p22→pter)	none* at 8 months	08-N-pt22/1-1
Neo #8-10	47,+mar[?%]	inv dup(8)(pter→p22::p22→pter)	unclear	08-N-pt22/1-2
Neo #9-1	47,XY,+mar[100%]	inv dup(9)(pter→p21.1::p21.1→pter)	severe*	09-N-pt21.1/1-1
Neo #9-2	47,XY,del(9)(p12),+mar[100%]	inv dup(9)(pter→p12::p12→pter)	severe*	09-N-pt12/1-1
Neo #10-1	47,XY,+mar[100%]	inv dup(10)(pter→p15∼14::p15∼14→pter)	severe*	10-N-pt15∼14/1-1
Neo #10-2	47,XX,del(10)(q11q23),+mar[62%]/ 46,XX,del(10)(q11q23)[38%]	?min(10)(q11q23)	severe	10-N-q11/1-1
Neo #11-1	47,XY,del(11)(q22),+mar[100%]	inv dup(11)(qter→q22::q22→qter)	severe*	11-N-qt22/1-1
Neo #12-1	47,+mar[?%]	mar(12)	severe	12-N-mar/1
Neo #12-2	47,XX,+mar[100%]	inv dup(12)(pter→p13::p13→pter)	severe*	12-N-pt13/1-1
Neo #12-3	47,XY,+mar[50%]	inv dup(12)(pter→p12.3::p12.3→pter)	severe*	12-N-pt12.3/1-1

Table 1 (continued)

Case number	Karyotype in peripheral blood (if not indicated differently)	sSMC	Clinical effects	Reference on sSMC homepage
Neo #13-1	47,XX,del(13)(q21.32q22.2),+mar[100%]	r(13)(::q21.31→q22.2::)	none	13-N-p21.31/1-1
Neo #13-2	47,XX,+mar[54%]	inv dup(13)(qter→q31::q31→qter)	severe*	13-N-qt31/1-1
Neo #13-3	47,XY,+mar[60%]	inv dup(13)(qter→q31::q31→qter)	severe*	13-N-qt31/1-2
Neo #13-4	47,XX,+mar[13%]	inv dup(13)(qter→q31::q31→qter)	severe*	13-N-qt31/1-3
Neo #13-5	47,+mar[?%]	inv dup(13)(qter→q31::q31→qter)	severe*	13-N-qt31/1-4
Neo #13-6	47,XY,+mar[100%]	inv dup(13)(qter→q31::q31→qter)	severe*	13-N-qt31/1-5
Neo #13-7	47,XY,del(13)(q31.1q32.3),+mar[50%]/ 46,XY,del(13)(q31.1q32.3)[50%]	r(13)(::q31.1q32.3::)	moderate	13-N-q31.1/1-1
Neo #13-8	47,XX,+mar[98% in blood; 8% in skin fibroblasts]	inv dup(13)(qter→q32::q32→qter)	severe*	13-N-qt32/1-1
Neo #13-9	48,XX,+marx2[15%]/ 47,XX,+mar[75%] 46,XX[5%] at birth – at 7years 5%/75%/20%	inv dup(13)(qter→q32::q32→qter)	severe*	13-N-qt32/1-2
Neo #13-10	47,XY,+mar[100%]	inv dup(13)(qter→q32::q32→qter)	severe*	13-N-qt32/1-3
Neo #13-11	48,XY,+mar × 2[12%]/ 46,XY[88%] at 6 months; at 7 years 26%/74%	inv dup(13)(qter→q32::q32→qter)	severe*	13-N-qt32/1-3
Neo #14-1	47,XX,del(14)(q32.1),+mar[100%]	inv dup(14)(qter→q32.1:q32.1→qter)	severe*	14-N-qt32.1/1-1
Neo #15-1	47,+mar[?]	mar(15)	severe	15-N-mar/1
Neo #15-2	47,XX,+mar[100%]	mar(15)	severe	15-N-mar/2
Neo #15-3	47,+mar[?]	r(15)(::q22.1→q22.3::)	moderate*	15-N-q22.1/1-1
Neo #15-4	47,XY,+mar[70% in blood; 11% in fibroblasts]	inv dup(15)(qter→q23::q23→qter)	severe*	15-N-qt23/1-1
Neo #15-5	47,XX,+mar[8%]	inv dup(15)(qter→q23::q23→qter)	severe*	15-N-qt23/1-1
Neo #15-6	47,XX,+mar[66%]	inv dup(15)(qter→q24::q24→qter)	severe*	15-N-qt24/1-1
Neo #15-7	47,XX,+mar[80%]/	inv dup(15)(qter→q24.1::q25.1→qter)	severe*	15-N-qt24.1-25.1/1-1
Neo #15-8	47,XX,+mar[100%]	inv dup(15)(qter→q25::q25→qter)	severe, lethal*	15-N-qt25/1-1
Neo #15-9	47,XY,+mar[79%]	inv dup(15)(qter→q25::q25→qter)	severe, lethal*	15-N-qt25/1-2
Neo #15-10	47,XX,+mar[100% at 2 years] at 10 years only in 50%; in fibroblasts in 18%	inv dup(15)(qter→q25::q25→qter)	severe*	15-N-qt25/1-3
Neo #15-11	47,XY,+mar[80%]	inv dup(15)(qter→q25::q25→qter)	severe*	15-N-qt25/1-4
Neo #15-12	47,+mar[?%]	inv dup(15)(qter→q25.3::q25.2→qter)	severe*	15-N-qt25.2-25.3/1-1
Neo #15-13	47,XX,+mar[82%]	inv dup(15)(qter→q25.3::q25.3→qter)	severe*	15-N-qt25.3/1-1
Neo #15-14	47,XY,+mar[74%]	inv dup(15)(qter→q25.3::q25.3→qter)	severe*	15-N-qt25.3/1-2
Neo #15-15	47,XX,+mar[95%]	inv dup(15)(qter→q25.3::q25.3→qter)	severe*	15-N-qt25.3/1-3
Neo #15-16	47,XY,+mar[95% in amniocytes]	inv dup(15)(qter→q25.3::q25.3→qter)	severe*	15-N-qt25.3/1-4
Neo #15-17	47,XY,+mar[86%]	inv dup(15)(qter→q26.1::q26.1→qter)	severe*	15-N-qt26.1/1-1
Neo #15-18	47,XY,+mar[66%]	inv dup(15)(qter→q26.1::q26.1→qter)	severe, lethal*	15-N-qt26.1/1-2
Neo #16-1	47,+mar[?%]	mar(16)	severe	16-N-mar/1
Neo #16-2	47,XY,i(16)(q10),+mar[15]	min(16)(pter→p11.2:)	severe	16-N-pt11.2/1-1
Neo #17-1	47,XY,del(17)(q22q23),+mar[100%]	inv dup(17)(:q22→q23::q23→q22:)	severe*	17-N-q22/1-1
Neo #18-1	47,XY,+mar[64%]	mar(18)	severe	18-N-mar/1
Neo #20-1	47,XX,del(20)(qter→p11.2:),+mar[100%]	inv dup(20)(pter→p11.2::p11.2→pter)	severe*	20-N-pt11.2/1-1

Neocentric sSMC cases without clinical effects

In the one case with a mild clinical outcome the sSMC was detected only in placenta; two of the cases with no clinical signs had a balanced karyotype in the majority of their cells even though a neocentric sSMC was present (cases Neo #1-1, Neo #13-1). It is noteworthy that the other clinically normal cases with gain of euchromatic material due to sSMC-presence were mosaic cases (see Fig. 5). I.e. the cases Neo #1-1, Neo #1-5, Neo #8-2 and Neo #8-9 carry an sSMC causing an imbalance only in 10–50% of the peripheral blood cells. However, for the two of these cases having the sSMC in 50% of their blood the observation 'no clinical signs' was made at very young age; thus, no final conclusion on eventual mental effects possibly expressed in later lifetime can be drawn here from literature. On the other hand the newly reported case Neo #15-5 with sSMC in only 8% of the blood cells and severe clinical outcome shows that a low mosaic level is not necessarily a good prognostic factor.

Neocentric sSMC cases with clinical effects

The diagnosis 'case with a neocentric sSMC plus clinical signs' can be in connection with the following cytogenetic conditions:

Cases exhibiting the most frequent principle are summarized in Fig. 5 and could be observed in 51 cases; here the

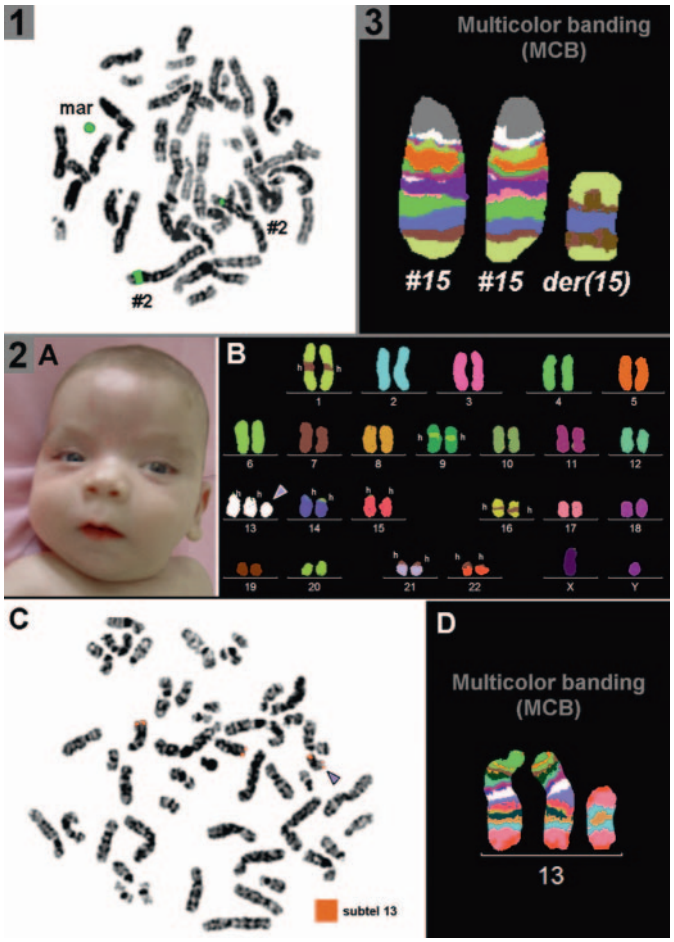

Fig. 1. Metaphase spread of case Neo #2-2 after reverse FISH applying a microdissection derived probe of the sSMC labeled in green. Thus, the origin of the sSMC could be narrowed down to 2q35 to 2q36.

Fig. 2. (**A**) Frontal view of the patient Neo #13-6 at 3 months of age. (**B**) M-FISH characterized that the sSMC (arrowhead) was derived from chromosome 13. The heterochromatic regions (h) in the short arms of the acrocentric chromosomes and in the pericentric region of chromosomes 1, 9 and 16 are differently labeled. (**C**) Metaphase spread of patient Neo #13-6 after FISH with a subtelomere probe for 13qter. (**D**) The neocentric sSMC(13) was characterized as inv dup(13)(qter→q22.3∼31.1::q22.3∼31.1→qter) by multicolor banding (MCB).

Fig. 3. Multicolor banding (MCB) with a probe-set for chromosome 15 revealed that the neocentric sSMC in case Neo #15-5 was an inv dup(15)(qter→q24.1::q24.1→qter).

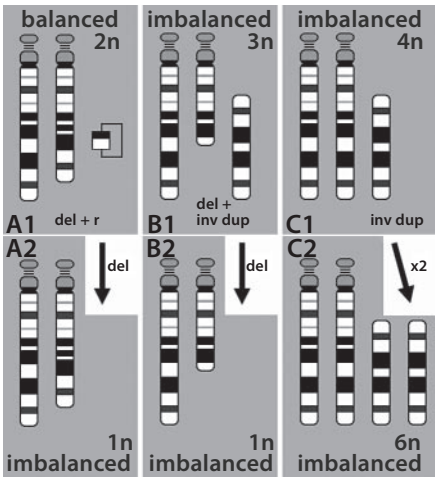

Fig. 4. Chromosomal rearrangements associated with neocentric sSMC. When an intrachromosomal deletion is associated with formation of a neocentric ring chromosome a cytogenetically balanced situation evolves (**A1**). This can lead to an unbalanced one in a subset of the cells if the neocentric chromosome is lost (**A2**). Deletion of a terminal part of a chromosome can be accompanied by formation of a neocentric inverted duplicated chromosome and lead to three copies of the corresponding segment (**B1**); if in a subset of cells this inv dup chromosome is lost a partial monosomy evolves (**B2**) similar as shown in **A2**. If a neocentric inv dup chromosome appears additionally to two normal sister chromosomes this leads to a partial tetrasomy (**C1**), which can evolve to a partial hexasomy (**C2**) by duplication of the neocentric sSMC. Abbreviations: 1n to 6n = one to six copies of the region covered by the sSMC are present; del = deletion; inv dup = inverted duplication; r = ring, ×2 = duplication of sSMC.

clinical signs and symptoms are caused most likely by the genetic imbalance due to the presence of the neocentric sSMC.

In two of the remaining 11 cases (Neo #4-1 and Neo #13-7) a deletion due to loss of the sSMC in a cellular subpopulation of a previously balanced karyotype is suspected to be the reason for clinical abnormalities.

In one case a partial trisomy of a whole long arm arose in connection with sSMC formation of the short chromosome arm (case Neo #16-2).

In two further patients cytogenetically balanced karyotypes and neocentric sSMC were observed – however, micro-rearrangements in the breakpoint region, uniparental disomy of the chromosomes involved in the rearrangements or other reasons for the clinical picture were not excluded (cases Neo #2-1 and Neo #6-1).

In the remaining six cases the sSMC were not characterized in detail, however, the presence of the neocentric sSMC and the resulting genetic imbalance is most likely the reason for clinical problems here (Neo #7-1, Neo #12-1, Neo #15-1, Neo #15-2, Neo #16-1, Neo #18-1).

Within the human genome only two regions are currently known which are prone to form neocentric sSMC leading eventually to less severe or moderate clinical outcome when present in three to four copies: a region in 13q21 (case Neo #13-7) and the terminal part of chromosome 8p (cases Neo #8-3 to Neo #8-6 and Neo #8-8). However, in this connection the problem of mosaicism is faced (see below). Aforementioned case Neo #13-7 and cases Neo #8-6 and Neo #8-8 have the sSMC in only 25–50% of their peripheral blood cells and this could explain their moderate phenotype. Nevertheless, in cytogenetically similar cases Neo #8-3 to Neo #8-5 all cells have the same genetic imbalance and similar clinical outcomes as the mosaic sSMC(8) cases.

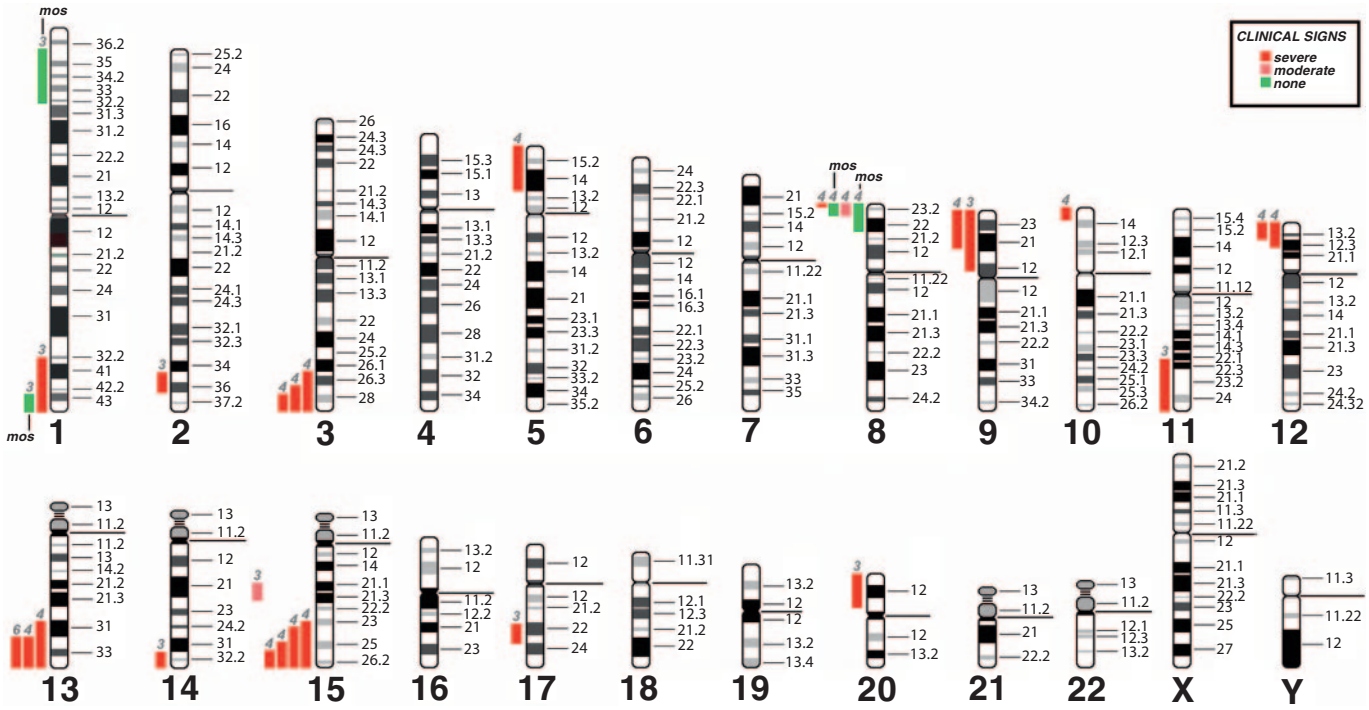

Fig. 5. Summary of chromosomal imbalances observed in 54 neocentric sSMC cases with known clinical outcome. Cases with no clinical signs are depicted in green, cases with moderate or severe clinical outcome in light or dark red, respectively. All cases without clinical abnormalities were mosaic cases (mos). The figures above the red or green bars indicate the grade of imbalance present; 3, 4 or even 6 copies of the chromosomal region were present in the corresponding cases.

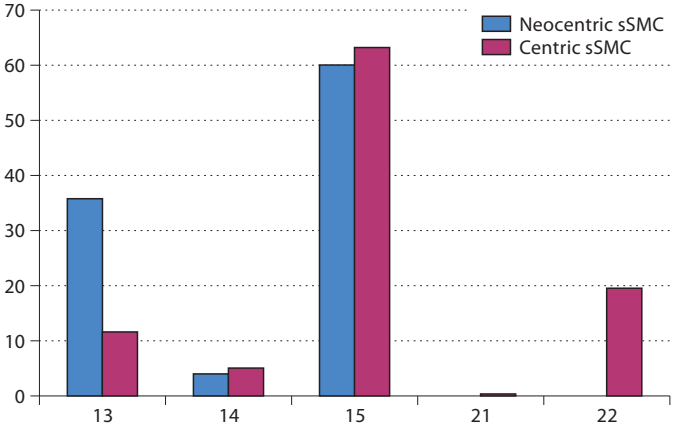

Fig. 6. Comparison of the frequency of acrocentric chromosome derived centric and neocentric sSMC cases based on the case numbers collected by Liehr (2007).

Mosaicism in neocentric sSMC

In general, mosaicism observed in neocentric sSMC and clinical outcome of the cases cannot be correlated at present; this is similar to all other sSMC cases as previously reviewed (Liehr et al., 2004a). Overall, neocentric sSMC were detected in varying degrees, i.e. in 2.5–100% of the cells studied (Table 1). In cases of similar neocentric sSMC and different degrees of mosaicism, e.g. like in all examples of neocentric sSMC(3) or sSMC(15), the same unfortunate clinical outcome could be observed in all patients.

Also no general conclusion can be drawn from the data summarized in Table 1 for the question where is it more likely to find a higher proportion of sSMC, in peripheral blood or in fibroblasts. In the literature there are examples for both, a higher percentage of abnormal cells in fibroblasts (cases Neo #3-2, Neo #8-3) or in peripheral blood (cases Neo #3-5, Neo #13-8, Neo #15-4). The same holds true for the marker chromosome frequency in the same tissue over the life-time: in case Neo #13-11 with age the cells carrying the sSMC became more and in cases Neo #13-9 and Neo #15-10 less frequent in peripheral blood.

Chromosome-specific comparison of neocentric and centric sSMC

When comparing neocentric and centric sSMC frequencies (Liehr, 2007) no overall correlation is obvious (data not shown). This is to be expected, as sSMC can form by various mechanisms. Only in case of inverted duplicated chromosomes an interrelationship exists between neocentric and centric sSMC: both can evolve due to a U-type-exchange during meiosis (Liehr et al., 2004a). Comparing the percentage of published neocentric to centric acrocentric sSMC for all five chromosomes (apart from chromosome 22; for #13 see below) no major difference exists between both groups (Fig. 6). The great majority of centric and neocentric sSMC are derived from chromosome 15, followed (among the acro-

centrics) by chromosomes 13, 14 and 21; the latter with practically no cases at all for both groups. However, here it has also been taken into account that centric sSMC(13 or 21) cannot be distinguished by centromeric probes. The only exception from this rule of frequency-correlation of neocentric and centric sSMC is chromosome 22. Here the inv dup(22q11.1) and Cat-Eye-syndrome cases constitute around 20% of the reported centric sSMC, while no neocentric sSMC(22) has yet been reported. This can be due to the fact that a corresponding neocentric sSMC(22) leads to an almost complete tetrasomy 22q which is not viable plus the fact, that up to now no neocentromere has been observed in chromosome 22 (Warburton, 2004). At present, the striking similarity of distribution in neocentric and centric acrocentric sSMC can only be stated. Whether it is really a result of U-type-exchange during meiosis and whether there are two endpoints of this meiotic error has to be evaluated in future studies.

Conclusion

Neocentric sSMC carriers are a rare and heterogeneous, but due to characteristic cytogenetic features of the sSMC itself, a special clinical group of patients. The diagnosis of a neocentric sSMC is correlated with an adverse clinical outcome in ~90% of the cases. This is mainly caused by the sheer size of the imbalance, and largely independent of the chromosomal region the sSMC derived from. Nonetheless in ~10% of the cases none or mild symptoms can be present in a carrier of a neocentric sSMC. If valid this is in most cases caused either by a mosaic or a balanced cytogenetic situation. These facts have to be considered by clinicians involved in genetic counseling of prenatal de novo cases with neocentric sSMC.

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