Supernumerary marker chromosomes (SMC) and uniparental disomy (UPD): coincidence or consequence?

D Kotzot

METHODS AND RESULTS

An extensive search in the Medline database showed only 19 cases of a SMC associated with UPD. Maternal UPD was found in 15 cases and paternal UPD in four cases (table 1). One case each was found for chromosomes 1, 6, 7, 9, 10, 12, 20, and 22,1–3 and 11 cases for chromosome 15, eight of them with Prader-Willi syndrome and three of them with Angelman syndrome, were found.1–13 FISH investigations of one of the maternal UPD(15) cases indicated X chromosomal origin of the SMC.14 In another case, maternal UPD(22) was segmental and associated with a de novo 11;22 translocation.12 Analysis of the molecular results showed only two isodisomic cases in 10/15 of the maternal UPD group15 and also only one heterodisomic case in 3/4 of the paternal UPD group.16 No molecular results delineating heterodisomy versus isodisomy were reported in the remaining cases.

A survey on systematic searches for UPD associated with a SMC other than inv dup(15) in postnatally ascertained cases showed only retrospective and therefore biased studies with two out of 49 cases testing positively,17–20 one case with paternal UPD(6),21 and one case with maternal UPD(9) (table 2).22 In eight postnatal searches for UPD(15) in a total of 122 cases with an additional inv dup(15) and various phenotypes,16–22 only two positive cases were found (table 3).23 One prenatal study, only two cases with UPD(15) out of 26 cases with an additional inv dup(15) were found (table 3).23

Prenatal incidence of SMC is approximately 1:2500 and approximately 30-50% originate from chromosome 15.23–30 The incidence of specific markers other than inv dup(15) is not known. Most studies were performed before FISH with centromeric probes was established, and therefore the number of SMCs of unknown chromosomal origin is extremely high.23

DISCUSSION

Coexistence of UPD with a SMC has mainly been explained by the following four mechanisms (fig 1).

1. The zygote may have originated as a trisomy with parts of the single parental homologue having been lost through one or two breakage events in an early embryonic cell division (“functional trisomy rescue”), either at random or even by an active mechanism (fig 1A). Here, two subclasses can be delineated. The first is characterised by two breakage events in a normal homozygous or vice versa; and fertilisation of a disomic gamete by a gamete already carrying a marker chromosome. Apart from the first, all these mechanisms increase the likelihood for UPD being present in cases with a SMC.

2. Mechanisms of formation assumed are functional rescue by mitotic reduction of the monosomic homologue to a SMC in a trisomic zygote; somatic reduplication of the normal homologue in a 46,XXN,mar zygote; completely mitotic formation by non-disjunction and subsequent reduction of the monosomic homologue or vice versa; and fertilisation of a disomic gamete by a gamete already carrying a marker chromosome. Apart from the first, all these mechanisms increase the likelihood for UPD being present in cases with a SMC.

3. Mechanisms of formation seem to be different in additional inv dup(15), other additional isochromosomes, and SMCs characterised by one or two deletions. The low incidence of SMC associated with UPD, the formation of additional inv dup(15), and other isochromosomes, as well as the results of molecular investigations of trisomy 21 mosaicism are all evidence against an active mechanism creating a SMC in a trisomic zygote.

4. Supernumerary marker chromosomes (SMCs) are predominantly in only a proportion of cells leading to a specific kind of trisomy mosaicism. The presence of a cell line with two normal chromosomes and a second hyperploid cell line promoted speculation that people with a SMC might have an increased risk for UPD of the structurally normal homologues from which the SMC was derived.

In the present article, published reports of UPD associated with a SMC as well as fundamental aspects of chromosome segregation and UPD are reviewed. Additionally, two questions will be discussed. Is the association of UPD with a SMC only coincidence or the consequence of an active mechanism? Which mechanisms are most likely for the formation of a SMC?
Survival should correlate inversely with the size and the chromosomal origin of the marker.

(2) Duplication of the normal homologue in a zygote which has inherited a SMC in place of the normal corresponding chromosome (karyotype 46,XN,mar) “rescuing” an aneuploidy (fig 1B). In this case, UPD arises by “postzygotic reduction” and therefore complete isodisomy should always be observed. This mechanism seems not to be frequent. Only four cases with isodisomy out of 19 cases investigated were reported.

This low number argues against an active mechanism.

(3) A completely postzygotic formation by either non-disjunction in an early mitosis and subsequent reduction of the monosomic homologue or by an inverse sequence (“post-fertilisation error”) (fig 1C). This subclass is the most complex and hard to demonstrate, and no cases have been reported so far.

(4) Fertilisation of a disomic gamete by a gamete with a SMC formed before or during meiosis (“complementation”) (fig 1D). Combined incidence of SMC and UPD is very low, but both figures are strongly biased by selection owing to survival and by the method of ascertainment. However, illustrated by the presence of large polymorphic satellites on the short arm of one chromosome 15 of the father and on the inv dup(15) of the affected daughter, this mechanism is most likely in a case with maternal UPD(15) and an additional inv dup(15). The same mechanism can be assumed in a case of maternal UPD(15) and an additional marker of X chromosomal origin. Otherwise, a double aneuploidy simultaneous with subsequent reduction of one X chromosome and loss or lack of the paternal chromosome 15 must be postulated.

In nine out of the 12 cases investigated by molecular methods, only the mechanisms of “functional trisomy rescue” and “complementation” could explain the outcome. In neither mechanism can it be differentiated whether the SMC was formed before or during meiosis or in an early somatic cell division. If it was formed before or during meiosis, the coexistence of a SMC with UPD would be only coincidental. Two independent events, non-disjunction in the meiosis of one parent and aberrant segregation or even formation of the SMC in the meiosis of the other parent, must have occurred. The question of which mechanism is more likely cannot be answered definitely. However, the mechanism of “functional trisomy rescue” is the more complex one and there are some arguments against it, particularly against an active mechanism. (1) Mosaicism in the placenta or even in the fetus with a cell line trisomic for a whole chromosome and not detected by routine investigations but relevant to the clinical outcome.

### Table 1

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H=heterodisomy, I=isosomdy, UPD=uniparental disomy.

### Table 2

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### Table 3

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<td>Webb et al</td>
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<tr>
<td>Prenatal</td>
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<td>Christian et al</td>
<td>26</td>
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<td>Total</td>
<td>148</td>
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The monosomic homologue or by an inverse sequence (“post-fertilisation error”) (fig 1C). This subclass is the most complex and hard to demonstrate, and no cases have been reported so far.

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In conclusion, the data on UPD associated with a SMC are scarce. At this time, there are no hints towards an active mechanism creating a SMC in a trisomic zygote, but the incidence of UPD in cases with a SMC is increased by coincidence, ascertainment bias, and because for most chromosomes only then is the fetus viable. Further reports of cases with a SMC both associated and not associated with UPD and particularly more systematic studies would provide more information on a topic extremely relevant for prenatal genetic counselling.

Therefore, after careful genetic counselling, molecular investigations for UPD should be performed more often in cases with a SMC, particularly in chromosomes for which genomic imprinting is known or at least assumed.

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**Authors’ affiliations**

D Kotzot, Institute of Human Genetics, Klinikum Rechts der Isar, Technical University München, München, Germany

Correspondence to: Dr D Kotzot, Institut für Humangenetik, Technische Universität München Trogerstrasse 32, 81675 München, Germany; DieterKotzot@gmx.de

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