Familial small supernumerary marker chromosomes are predominantly inherited via the maternal line**To the Editor:**

We read with interest the recently published paper of Dalprà et al.¹ in this journal. They report on 241 cases with small supernumerary marker chromosomes (sSMC) studied in 19 different Italian laboratories within the last 10 years. This paper is another important contribution to the still understudied field of sSMC-research. Among other interesting conclusions, the authors also report that 16% of their sSMC cases were maternally inherited and only 7% paternally inherited.¹ In their discussion, the authors¹ allude to a similar 2:1 ratio of maternally/paternally derived sSMC in a previous paper of Crolla et al.² However, no correlation was described or suggested in either a recent paper of Crolla et al. reporting on 137 sSMC-carriers³, nor in any previous paper.

This led us to analyze the recently summarized data on all reported sSMC cases to see if such a correlation really exists. By January, 2006, we collected 1,885 sSMC cases on the sSMC-homepage.⁴ One thousand, one hundred eighty-two of these cases were de novo, 102 inherited, and for the remainder, no information on the parental origin was available (Table 1). The following data are derived from the 1,284 cases in which information on the parental origin was available. As known by newborn studies,⁴⁻⁵ the incidence of familial sSMC cases is

Table 1
Parental and chromosomal origin of all reported sSMC cases

Chromosomal origin	Maternal	Paternal	de novo	N.A., unclear or neocentromere	In summary
Non-acrocentric chromosomes					
1	1	0	37	11	49
1/5/19	0	0	5	1	6
2	1	0	12	8	21
3	3	0	13	10	26
4	0	0	15	4	19
5	0	0	8	6	14
6	1	0	11	8	20
7	1	1	14	5	21
8	1	0	35	18	54
9	5	0	13	6	24
10	0	0	8	5	13
11	0	1	7	2	10
12	1	0	177	6	184
16	2	1	17	6	26
17	0	0	18	4	22
18	1	0	116	9	126
19	1	0	20	2	23
20	1	0	18	7	26
X	0	0	16	10	26
Y	0	2	6	1	9
Summary	19	5	566	129	719
Acrocentric chromosomes					
13	1	0	3	10	14
13/21	5	3	26	26	60
14	8	3	20	35	66
14/22	2	1	12	14	29
15	20	11	202	329	562
21	4	0	9	3	16
22	13	7	344	50	414
Any acrocentric chromosome	0	0	0	5	5
Summary	53	25	616	472	1166
Overall summary	72	30	1182	601	1885

40%. At present, only 8% of the cases were familial. Thus, this data shows that there is a bias in the available data.⁴ Interesting sSMC-cases are reported throughout the literature and sSMC which are not correlated with clinical problems are not that likely to be reported, i.e., sSMC in connection with clinical abnormalities.

However, when posing the question for the relation of maternal-to-paternal inheritance of familial sSMC there is no reason to suggest a similar bias for those 102 cases in which data are available for the parental origin of the sSMC. For those cases (Table 1), we find 72 sSMC inherited from the mother

versus 30 sSMC inherited from the father, which is similar to the 2.4:1 ratio suggested in the paper by Dalprà et al.¹ for the parental origin of sSMC. As detailed in Table 1, this ratio is more expressed in sSMC derived from non-acrocentric chromosomes. The data presented here is independent of that of Dalprà et al.,¹ as there were no details available on their individual patients.

Thus, the observation that familial small supernumerary marker chromosomes (sSMC) are predominantly inherited via the maternal line is substantiated by this analysis. However, an explanation still lacks. One has to suggest that a yet unknown

Table 2

Gender of the offspring of sSMC-cases as summarized in Table 1

Offspring	Male	Female	No info on gender
sSMC derived from non-acrocentric chromosomes			
Paternal/maternal	3/12 (in sum. 68%)	0/7 (in sum. 32%)	0/1
De novo	136 (45%)	163 (55%)	267
sSMC derived from acrocentric chromosomes			
Paternal/maternal	11/19 (in sum. 42%)	12/30 (in sum. 58%)	3/4
De novo	130 (55%)	106 (45%)	380
sSMC derived from acrocentric and nonacrocentric chromosomes			
Familial	45 (48%)	49 (52%)	8
De novo	266 (50%)	269 (50%)	647
sSMC derived from chromosome 14			
Paternal/maternal	1/1 (in sum. 18%)	2/7 (in sum. 82%)	0/0
De novo	14 (70%)	6 (30%)	0/0

Table 3

Clinical outcome of sSMC-cases as summarized in Table 1

Origin of sSMC	No clinical signs	Clinical signs	No clinical information or known syndrome like CES, PKS, i(18p)-, der(22)- syndrome
sSMC derived from non-acrocentric chromosomes			
Paternal/maternal	2/12 (in sum. 82%)	3/4 (in sum. 18%)	-/3
De novo	68 (25%)	205 (75%)	293
sSMC derived from non-acrocentric chromosomes			
Paternal/maternal	23/39 (in sum. 80%)	1/14 (in sum. 20%)	1/-
De novo	59 (25%)	178 (75%)	379
sSMC derived from acrocentric and non-acrocentric chromosomes			
Familial	76 (76%)	22 (22%)	4
De novo	127 (25%)	383 (75%)	672

effect is driving selection via fertilization-success of sperm without an sSMC. Problems in connection with sSMC-replication arising predominantly in the more rapidly progressing sperm meiosis or a 'weight-effect' making sperm without more rapid than those with an sSMC, similar to the effect known from Y- versus X-chromosome carrying sperm⁶ could be envisaged as possible mechanisms involved here.

The next question that we had based on the available data⁴ was if there is a difference in sex ratio in the offspring coming from the parentally inherited compared to de novo sSMC cases. As summarized in Table 2, 94 familial and 535 de novo cases were available for this problem. There was not enough data to distinguish between maternally and paternally inherited ones for that question. When looking at the overall summary of Table 2 there is a 1:1 sex ratio in the offspring of de novo (266:269) and familial cases (45:49). However, splitting into acrocentric and non-acrocentric derived sSMC there is a

difference in the latter familial cases (male-to-female ratio of 2:1). Though, this could easily be a bias due to low case numbers (22 cases). Moreover, it could be that single chromosomes form exceptions here, as shown for chromosome 14 in Table 2: among 11 parentally inherited sSMC (14) cases, only 20% were male offspring, while in the 20 available de novo sSMC (14) cases 70% were male. Further studies are required to clarify this point.

As summarized in Table 3, there is a difference in the clinical outcome of familial versus de novo cases. While 76% of the familial cases are without clinical signs, 75% of the reported de novo cases show clinical abnormalities. However, for this question one, has to admit that the bias is valid, that predominantly 'interesting' cases are reported in the literature. As summarized on the sSMC-homepage⁴ it is known by studies performed in newborn cohorts,⁷⁻⁹ that de novo sSMC are associated with clinical signs only in 11-30%. Thus, the only

conclusions to be drawn from this data are that a small but considerable part of familial sSMC can lead to clinical problems in the offspring. This has to be considered in genetic counseling of familial cases as well. Moreover, there was a first genotype-phenotype correlation for sSMC published recently,¹⁰ which can be considered in clinical cases, too.

In summary, the analysis of all in detail reported sSMC cases⁴ concerning the differentiation of maternal and paternal origin, sex ratio, and clinical signs of the offspring gave the following results. As suggested by Dalprà et al.¹ in this journal, there is a yet unexplained doubled transmittance rate of sSMC via the maternal compared to the paternal line. Apart from chromosome 14 it seems quite clear, that there is a 1:1 sex ratio in the offspring of familial and de novo sSMC cases. Finally, clinical signs in connection with an sSMC are to be expected in a subset of parentally inherited as well as de novo cases.

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