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A Search for Uniparental Disomy in Carriers of Supernumerary Marker Chromosomes

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Abstract

As there is some evidence that individuals bearing supernumerary marker chromosomes (SMCs) might have an increased risk of being uniparentally disomic for the structurally normal homologues of the SMC, we made a systematic search for uniparental disomy of the autosomal homologues from which SMCs were derived. Of the 22 families studied, a biparental origin of the normal homologues was demonstrated in 21, and 1 case of paternal isodisomy of chromosome 6 was detected in the carrier of a supernumerary marker ring chromosome 6 which itself was of maternal origin. Our results confirm that uniparental disomy may be found in association with SMCs, but until more cases are studied we can only speculate on their frequency and the mechanism(s) which result in this phenomenon.

Introduction

Supernumerary marker chromosomes (SMCs) are detected in <0.1% of the general population, but in 0.327% of the mentally retarded [1]. Ramos et al. [2] and Buckton et al. [1] have suggested that the presence of a SMC at meiosis may interfere with normal chromosome disjunction resulting in aneuploidy, and it has been shown that an increased incidence of aneuploidy is associated with an increased risk of uniparental disomy (UPD) by mechanisms of aneuploidy correction [3, 4].

The first hypothesis suggesting a link between a SMC and UPD was that of Robinson

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et al. [5], who proposed that, in some individuals with a small inv dup(15) SMC and Prader-Willi syndrome (PWS), the disease phenotype may be the result of maternal uniparental disomy of the two normal homologues of chromosome 15. The first evidence that a SMC may be ascertained in combination with UPD was reported by Robinson et al. [6] who described 2 individuals with small inv dup(15) chromosomes; one had paternal isodisomy for chromosome 15 and Angelman syndrome. The other had maternal UPD and PWS.

The prediction of phenotypic risks associated with the ascertainment of an SMC is highly problematic and, with the exception of chromosome 15 markers [7, 8], correlations between the chromosomal origin of markers and their associated phenotypes have not convincingly emerged [9–11]. This karyotype/phenotype correlation would be further complicated if the presence of a SMC predisposes the patient to an increased risk of a concomitant UPD for the normal homologues, as it has been shown that developmental and growth defects may be associated with UPD.

As the frequency of UPD in association with SMCs is unknown,we have carried out a systematic study to determine the parental origin of the normal homologues of the chromosomes from which the SMCs are derived. The SMCs originating from chromosome 15 are reported elsewhere [8], and in this communication we present our results on 22 patients with a SMC which is not of chromosome 15 origin.

Materials and Methods

Study Population

Details of the study population are found in table 1. The chromosomal origin of the SMCs was defined by fluorescence in situ hybridisation in 39 families where the mother, father and proband were available, and of these, 22 have an autosomal origin other than chromosome 15. Peripheral blood was obtained from the proband and both parents in these 22 families and used for the extraction of DNA, the establishment of permanent lymphoblastoid cell lines at the European Collection of Animal Cell Cultures (ECACC), and for conventional cytogenetic and molecular cytogenetic studies. In cases where it was impossible to differentiate between markers of 13 or 21 origin, or between 5 or 19 origin, the parental origin of the normal homologues of both autosomes was determined. The seventeen probands with SMCs of chromosome 15 origin from part of a separate study [8].

Methods

The chromosomal origin of the SMCs was determined using non-isotopic in situ methods as described by Crolla et al. [10]. DNA was extracted from whole blood by a salt precipitation technique [12]. The parental origin of the normal homologues of the chromosomes from which the SMCs originated was determined by polymerase chain reaction (PCR) amplification of chromosome-specific microsatellite repeat sequences [13]. Primers were chosen that amplified sequences located distal to the regions represented by the SMCs, and PCR conditions were those described by Hudson et al. [14]. Details of the primers have been previously published and can be obtained from the Genome Data Base or on request from the authors. PCR products were visualised using a 6% denaturing polyacrylamide gel followed by autoradiography. Since the object of the study was to determine the frequency of UPD of whole chromosomes as opposed to chromosome regions, a single result indicating a biparental origin of the normal homologues was considered sufficient to exclude UPD.

Results

The results are shown in table 1 from which it can be seen that the normal homologues are biparental in origin in all the probands except case 5 which showed paternal uniparental isodisomy for chromosome 6 in association with a SMC(6) of maternal origin. The proband is a female with intrauterine growth retardation who developed transient neonatal diabetes and details of this case have been reported elsewhere [15].

Table 1. The study population

Case No.	ID number at ECACC	Chromosome origin		Clinical features	Reference	Loci demonstrating biparental origin
1	DD0934	1	de novo	clinically normal		D1S199
2	DD0767	3	de novo	mild developmental delay, short stature		D3S1265
3	DD0068	4	de novo	TOP: apparently normal phenotype	case 2 [8]	D4S230
4	DD1329	6	de novo	severe mental retardation, seizures, dysmorphic		D6S311
5	DD1261	6	de novo	IUGR, transient neonatal diabetes	[15]	paternal isodisomy
6	DD0824	8	de novo	multiple congenital abnormalities	[17]	D8S167
7	N/A	9	de novo	mental retardation		D9S164
8	DD1362	9	maternal	clinically normal	case 1[a] [8]	D9S156
9	DD0085	12	de novo	clinically normal	case 3 [8]	D12S86
10	DD0227	14	de novo	mild developmental delay, mildly dysmorphic	case 7 [8]	D14S43
11	DD0357	14	de novo	TOP: phenotype unknown	case 8 [8]	D14S51
12	DD0618	14	de novo	clinically normal		D14S43
13	DD0922	14	de novo	mildly dysmorphic, learning difficulties		D14S68
14	DD1233	14	maternal	clinically normal		D14S43
15	DD1135	16	de novo	mild mental handicap, psychosis		D16S305
16	DD0817	16	de novo	clinically normal	case 9 [8]	D16S305
17	DD0375	19	maternal	clinically normal		APOC2
18	DD1315	22	de novo	mild developmental delay	case 12 [8]	D22S304
19	DD1145	5/19	de novo	clinically normal		D5S392 APOC2
20	DD0617	5/19	de novo	clinically normal	case 10 [8]	D5S392 APOC2
21	DD1364	13/21	de novo	clinically normal		D13S120 (paternal allele)[b] D13S64 (maternal allele)[b] D21S167
22	DD0876	13/21	de novo	mild mental retardation, mildly dysmorphic	case 5 [8]	D13S71 D21S167

ECACC = European Collection of Animal Cell Cultures; N/A = there is no cell line available at the ECACC; TOP = termination of pregnancy; IUGR = intrauterine growth retardation.

[a] This case was previously erroneously reported as a SMC of chromosome 4 origin.

[b] Biparental origin was determined by demonstrating a paternal allele and a maternal allele at 2 different loci.

Discussion

Uniparental disomy is recognised as a possible outcome of a number of mechanisms for aneuploidy correction including gamete complementation, monosomy duplication and trisomy correction [4]. In searching for examples of UPD in humans, efforts so far have been concentrated on those populations who, because of their abnormal chromosome constitutions, were thought to be at increased risk of non-disjunction involving specific chromosomes, and by definition at increased risk of producing UPD by aneuploidy correction [16]. In this context, it has been suggested that the presence of a SMC may interfere with normal disjunction during meiosis, resulting in aneuploidy [1]. Two cases of UPD in association with SMCs have been reported [6]: one was uniparental isodisomy and the other heterodisomy. In this study we have identified a case of paternal uniparental isodisomy in association with a SMC. There are a number of different mechanisms which could result in UPD in carriers of SMCs and some of the possibilities are shown in figure 1.

Postzygotic events resulting in marker formation or UPD might be associated with mosaicism for the SMC and/or UPD, in which case it is possible that the normal homologues may be biparental in a normal diploid line. In our case, the SMC was present in 80% of lymphocytes and although we have not formally ascertained the parental origin of the chromosomes 6 in those cells without the SMC, these techniques would be expected to detect biparental alleles present in 20% of cells.

Prior to this study, a systematic search for the frequency of UPD in association with SMCs had not been carried out. In 17 cases of SMCs of chromosome 15 origin, UPD for the normal homologues of chromosome 15 was excluded in all 10 cases where parental DNA was available [8]. We have shown that UPD of the normal homologues of the chromosome from which the SMC originated does occur, and there is therefore a case for determining the parental origin of the normal homologues in individuals where a SMC is detected prenatally.

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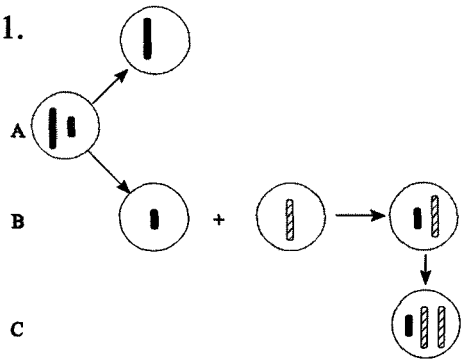
Fig. 1. Possible mechanisms for UPD in association with a SMC. (1) A = Premeiotic marker formation followed by meiosis; B = fusion of gamete bearing SMC with normal gamete; C = duplication of normal homologue rescues partial monosomy. (2) A = Fusion of normal gametes results in disomic zygote; B = postzygotic homologue breakage and marker formation; C = partial monosomy corrected by duplication of remaining normal homologue. (3) A = Fusion of normal gametes results in disomic zygote; B = postzygotic duplication of one homologue results in trisomic zygote; C = trisomy corrected by loss of extra homologue with concomitant SMC formation results in (a) uniparental isodisomy + SMC or (b) biparental normal homologues + SMC. (4) A = Nondisjunction at meiosis; B = fusion of disomic gamete with normal gamete; C = trisomy corrected with breakage of homologue resulting in (a) uniparental heterodisomy of normal homologues + SMC or (b) biparental normal homologues + SMC. (5) A = Premeiotic/familial marker formation and nondisjunction at meiosis; B = fusion of disomic gamete (+ SMC) with normal gamete; C = random loss of one of the normal homologues results in (a) uniparental heterodisomy of normal homologues + SMC of same parental origin or (b) biparental normal homologues + SMC.

1.



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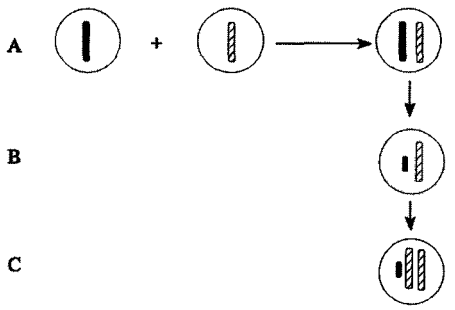

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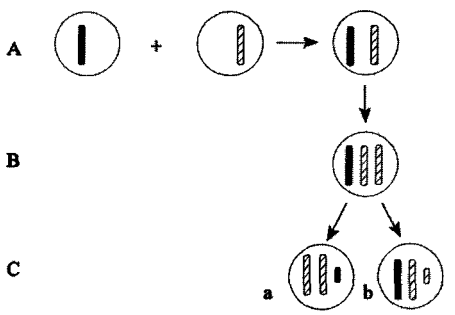

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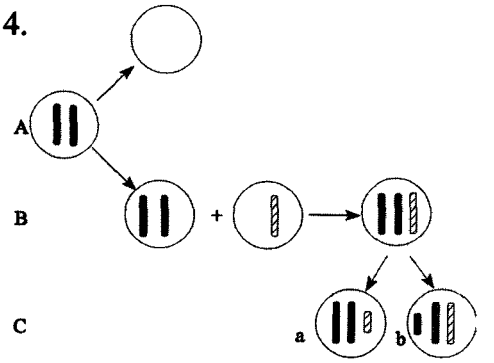

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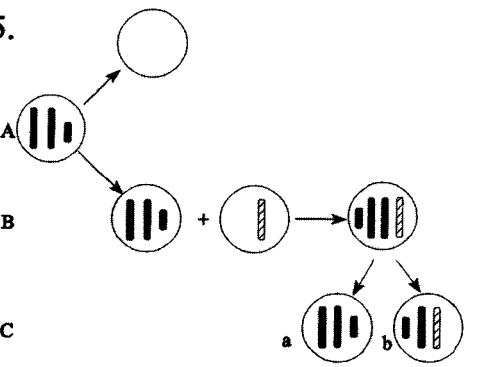

KEY

= CHROMOSOME FROM PARENT 1

= CHROMOSOME FROM PARENT 2

= SMC FROM PARENT 1

= SMC FROM PARENT 2

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