faster and more precise than the dosage studies or polymorphic marker methods previously used.[6 7] The phenotypic map of DS constructed by Korenberg *et al*[7] assigned 25 features to regions spanning 2 to 20 Mb and they concluded that DS is a contiguous gene syndrome with duplications distinct from distal 21q22 contributing to the main features of DS. Given that the partial trisomy of chromosome 21 in the patient does not involve any other chromosome, it further supports the hypothesis that the genes contained in the region from 21q22 to the telomere are responsible for the majority of the features of DS, as previously reported by Korenberg *et al*.[7] Three other cases have been reported with a similar duplicated region.[6 7 14] As shown in table 1, the case reported here further confirms that the majority of the phenotypic features of DS are contained in the region triplicated in the four cases. However, the penetrance of the majority of the clinical features of DS is not complete, so to establish the correlation only the presence (not the absence) of a given trait should be taken into account. When the three published cases of DS with a similar partial trisomy and the present case are compared, we can see that almost all the physical traits typical of DS are present, perhaps with the exception of the furrowed tongue which has an overall frequency of 55% in the DS population.[16] One of the difficulties in the construction of a phenotypic map of DS, based on cases of partial trisomy, is that a large proportion of these cases have in addition other chromosomal abnormalities which may contribute to the clinical findings. Our patient presents no other chromosomal abnormality, so all his clinical traits can be assumed to be associated with the duplication of chromosome 21. However, we have established comparisons with other cases with a very small partial monosomy of another chromosome, which may have a very small contribution to the final phenotype of the patients.

With the continued development of molecular cytogenetic tools and the availability of methods and probes for the accurate determination of the chromosomal rearrangements in each case, phenotype/genotype correlations can be obtained with a high degree of accuracy and diagnosis can be performed at the molecular level with a high degree of certainty.

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Stable non-Robertsonian dicentric chromosomes: four new cases and a review

EDITOR—Dicentric autosomes are rarely encountered as stable constitutional chromosomes in humans, with the exception of Robertsonian translocations. The presence of two alpha satellite sequences on the same chromosome leads to a high risk of attachment of the same chromatid to the mitotic spindle from opposite poles and to the formation of anaphase bridge during cell division. Therefore, breakage of the dicentric can occur with subsequent cell death.[1] Stability can be achieved when the centromeres are very close together and form only one heterochromatin block, or when one of them is inactivated. One report by Vianna-Morgante and Rosenberg[2] shows a rarer mechanism of stabilisation, the deletion of one centromere. Several mechanisms can lead to dicentric chromosomes: meiotic recombination within a paracentric inversion loop, isochromatid break with U shaped rejoining, mitotic crossing over, Robertsonian translocation, and non-homologous non-Robertsonian translocation. Non-homologous dicentric autosomes are expected to be formed by the latter. We

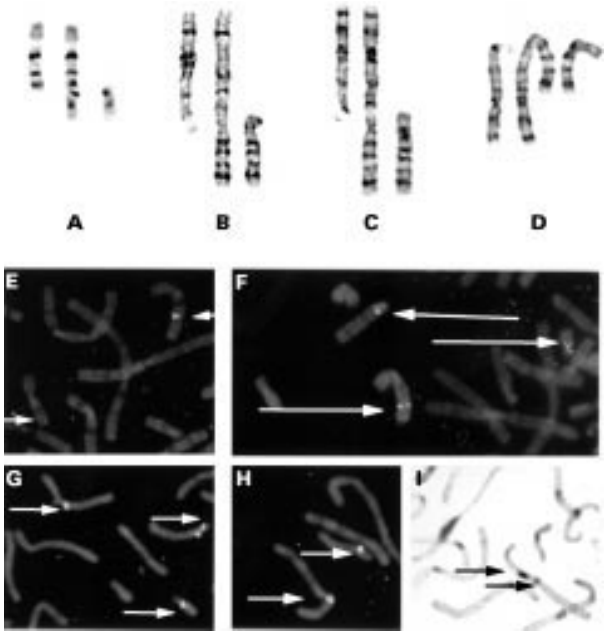

Figure 1 Dicentric chromosomes of our cases. Panels A-D: chromosomes G banded at the 450-500 band level of resolution from cases 1-4, respectively. In all four panels, the dicentric chromosome is placed in between its normal monocentric homologues. Panels E and F: subtelomeric sequence specific to the long arm of 16q and 14/22 alpha satellite hybridised, respectively, to chromosomes of case 1 (hybridisation signals indicated by arrows). Panels G and H: 13/21 alpha satellite sequence and 18 alpha satellite sequence hybridised, respectively, to chromosomes of case 3 (hybridisation signals indicated by arrows). C banded dicentric of case 2 (centromeric heterochromatin indicated by arrows).

have found 22 reported cases of cytogenetically recognisable, non-homologous, non-Robertsonian dicentric autosomes.[1–19] We present four new cases of non-homologous, non-Robertsonian dicentric autosomes with centromeres distinguishable by standard cytogenetic techniques; two were inherited from asymptomatic carriers and two occurred de novo in children with deletion 18p syndrome phenotype.

Metaphase chromosomes were obtained from peripheral blood or amniocytes harvested according to standard protocols. GTG banding was performed on all cases. C banding using $Ba(OH)_2$ was used. Fluorescence in situ hybridisation (FISH) of alpha satellite sequences was performed on metaphase chromosomes according to the protocols provided by ONCOR. FISH with a 16q subtelomeric sequence was performed according to the protocol provided by AL Technology.

Case 1 was ascertained through amniocentesis at 14 weeks' gestation for advanced maternal age. The mother was a 41 year old gravida 3, para 2, aborta 0. The couple's family history was unremarkable. The GTG banded karyotype at a resolution of approximately 350 bands showed the presence of an apparently balanced translocation between the telomeric regions of 16q and 22p, creating a dicentric 45,XY,dic(16;22)(q24;p11.2). The phenotypically normal father was proven to carry the same translocation which, in his case, had arisen de novo (fig 1A). The dicentric showed only one primary constriction on G banding in all cells analysed in the fetus and his father, corresponding to chromosome 16 centromere. It hybridised with probes for the alpha satellite sequences of chromosomes 14 and 22 (fig 1F) and for the subtelomeric sequence of the long arm of chromosome 16 (fig 1E). After genetic counselling, the couple decided to continue the pregnancy. However, in the 20th week of gestation, intrauterine fetal death (IUFD) was diagnosed. The fetus showed severe autolytic changes and had measurements compatible with intrauterine death at 15 weeks. External and internal pathological examination showed no malformation. Therefore, post-amniocentesis intrauterine fetal death was not excluded.

Case 2 was ascertained through fetal tissues received for IUFD at 32 weeks of gestation. The mother was a 29 year old gravida 3, para 1, aborta 1. The second trimester screening ultrasound at 18 weeks' gestation showed an isolated choroid plexus cyst. At 32 weeks, IUFD was diagnosed. Necropsy showed a growth retarded male fetus with a weight of 650 g and with crown-heel length of 32 cm. The phenotype was consistent with trisomy 18, including mild hirsutism, small mouth, overlapping fingers, rocker bottom feet, short hallux, nail hypoplasia, interventricular septal defect, and Meckel's diverticulum. The tissue cultures showed two abnormal and discordant G banded cell lines: 46,XY,+18,dic(14;18)(p11.2;p11.3)[12]/45,XX,dic(14;18)(p11.2;p11.3)[12]. One cell line was an unbalanced male karyotype composed of a dicentric chromosome formed by an apparently balanced translocation between the short arms of chromosomes 14 and 18, as well as two normal chromosomes 18, resulting in trisomy 18. The other cell line was female, carrying the same dicentric with a chromosome count of 45 as a result of the formation of the dicentric. This finding could be explained by the presence of a female resorbed twin or by maternal contamination. The latter was more likely since the phenotypically normal mother did indeed carry the dicentric (fig 1B). The grandmother's karyotype was normal. The maternal grandfather could not be reached. The dicentric showed only one primary constriction at the site of chromosome 18 centromere in all cells analysed from the fetus and the mother. C banding confirmed the presence of two blocks of centromeric heterochromatin (fig 1I).

Case 3 was born at 40 weeks of gestation after an uneventful pregnancy. The birth weight was 3960 g (75th centile), birth length was 54 cm (90th centile), and OFC was 36.5 cm (75th centile). Apgar scores were 8, 9, and 10 at one, five, and 10 minutes respectively. Karyotyping was requested at the age of 4½ years because of psychomotor retardation. He was globally delayed with severe difficulties in language. At the age of 4½ years, he could walk, hop, and ride a tricycle but had difficulty with his balance, could only speak 20 words with no sentences, and would not play with other children. Physical examination showed mild dysmorphic features, including a long face, bilateral epicanthic folds, bulbous nose, large and slightly anteverted ears, high arched and narrow palate, microretrognathia, pectus excavatum, and bilateral fifth finger clinodactyly. Thyroid evaluation was normal. The karyotype, 45,XY,dic(13;18)(p12;p11.2), showed an unbalanced translocation between the short arms of chromosomes 13 and 18 creating a dicentric chromosome with a deletion of the distal band of chromosome 18p, 18p11.3 (fig 1C). There was only one primary constriction corresponding to chromosome 18 centromere in all cells analysed. FISH with probes against the alpha satellites 13/21 (fig 1G) and 18 (fig 1H) confirmed the presence of two centromeres.

Case 4 was first evaluated at 20 months of age because of developmental delay and dysmorphic features. She was born at 37 weeks of gestation after an uneventful pregnancy. Her birth weight was 2565 g (5th-10th centile), birth length was 47 cm (10th centile), and OFC was 30.8 cm (<5th centile). At birth she was diagnosed with transposition of the great arteries and operated on as a neonate. At 3 months of age she suffered from a urinary tract infection and renal ultrasound showed mild bilateral hydronephrosis. Her psychomotor development was de-

layed.She started to crawl at 14 months and was not walking at 20 months; she was not speaking any words at the time of the first evaluation. At that age, she weighed 9.0 kg (<5th centile), her length was 79 cm (10th-25th centile), and her OFC was 45.5 cm (2nd centile). Physical examination showed dysmorphic features, including bilateral ptosis of the eyelids (right>left), mild bilateral epicanthic folds, bulbous nose, large and anteverted simple ears, central dimple on the chin, slightly short neck, mild pectus excavatum, bilateral 5th finger clinodactyly, partial 2-3 syndactyly of the toes, and a blind sacral dimple. Ophthalmological evaluation showed myopia. Growth hormone and IgA levels were normal. The karyotype, 45,XX,dic(13;18)(p11.2;p11.2), showed an unbalanced translocation between the short arms of chromosomes 13 and 18 creating a dicentric chromosome with a deletion of the distal band of chromosome 18p, 18p11.3 (fig 1D). All cells analysed showed one primary constriction at the level of chromosome 18 centromere. The derivative chromosome hybridised with alpha satellite sequences of chromosomes 13/21 and 18.

The four cases reported here bring to 26 the total number of non-Robertsonian heterodicentric autosomes reported since the seventies (table 1). Many of these are associated with a deletion of the chromosomes involved (13/26) and, consequently, with phenotypic abnormality. This significant number of unbalanced cases could be the result of a bias of ascertainment. In those cases parental karyotypes were normal, as expected. Phenotypically normal people have also been observed to carry a balanced heterodicentric autosome (12 cases). However, among those, infertility was present in three cases[2 14 19] caused either by gonadal dysgenesis or severe oligospermia associated with abnormal sperm morphology. One other case was ascertained through recurrent spontaneous abortions. Four cases were found in skin cultures established from phenotypically normal induced abortuses.[15] Including two cases presented here, only four cases of non-Robertsonian heterodicentric autosomes were transmitted over two or more generations. Their heritability indicates their unique stability. In these cases there is a possibility of transmitting unbalanced gametes by non-disjunction as seen in case 2.

In the vast majority of cases (22/26), the short arm of an acrocentric chromosome is involved in the translocation. A number of hypotheses can be advanced to explain the non-random participation of acrocentrics in the formation of non-Robertsonian heterodicentric chromosomes. There may be an increased rate of dicentric formation with acrocentrics based on non-random nuclear positioning of chromosomes. However, the latter explanation does not account for the randomness of the non-acrocentric chromosomes involved in the formation of the dicentrics. The predominance of acrocentics is probably more a reflection of the higher likelihood of stability of the dicentric formed. Deletion of the short arm of an acrocentric is often present, so the distance between the centromere of the acrocentric and the translocation breakpoint is always relatively small, which is in favour of dicentric stability. Moreover, absence of a phenotype related to a deletion of the p arm of an acrocentric is in favour of embryonic viability. It has been suggested by Roberts *et al*[12] that there may be a tendency for the centromeres of acrocentrics to become inactivated, making those dicentrics most likely to be stable and therefore visible in patients.

In the majority of cytogenetically recognisable heterodicentric autosomes, only one primary constriction is seen (14/18) in all cells of a given subject. The primary constriction corresponds to the activity of the centromere.[20] Even if this is a crude estimate, this suggests that only one centromere is active. Immunostaining against active centromere kinetochore specific protein (CENPs) is more reliable in assessing centromeric activity. Unfortunately, it was not possible to perform these studies in our cases. Earnshaw *et al*[21] have shown the presence of only one immunostaining signal against CENP-C on a dicentric chromosome consistent with the presence of one active centromere. The mechanism by which centromere inactivation occurs is still unknown. The primary constriction is found at the site of the non-acrocentric centromere in most instances (12/14). Only two cases showed one primary constriction at the site of the acrocentric centromere.[8 18] Among non-Robertsonian heterodicentric autosomes, there were four cases of mosaicism for centromeric activity.[1 2 4] Intercentromeric distance seems to be one important factor in determining if a dicentric will be functionally dicentric or monocentric.[22] To be stable and lead to a viable embryo, dicentrics with distanced centromeres have to inactivate one centromere very soon after

Table 1 Summary of cases reported to carry non-homologous non-Robertsonian heterodicentric autosomes

Reference	*Dicentrics*	*Acrocentric*	*Primary constriction*	*Phenotype*	*Inheritance*
10	(5;13)(p12;p12)	+	Chrom 5 &13 (34%), chrom 5 (54%), chrom 13 (10%)	Abnormal	De novo
19	(12;14)(p13;p13)	+	Chrom 12	Primary amenorrhoea	De novo
13	(19;20)(p?;p?)	−	NA	Abnormal	NA
9	(7;15)(p21;p11)	+	Chrom 7	Abnormal	De novo
16	(13;18)(p1;p11)	+	NA	NA	De novo
12	(8;22)(p23;p13)	+	Chrom 8	Abnormal	De novo
14	(15;18)(p12;p11)	+	NA	Oligospermia	De novo
3	(13;18)(p12;p11.2)	+	Chrom 18	Normal	Familial
3	(9;22)(p22;p11)	+	Chrom 9	Abnormal	NA
1	(5;15)(p31;p11)	+	Chrom 5 & 15 (85%),chrom 15 (8%), chrom 5 (7%)	Abnormal	De novo
8	(14;18)(p1?;q22)	+	Chrom 14	Abnormal	De novo
15	(2;22)(p25;p12)	+	NA	Normal	NA
	(1;19)(p36;q13)	−	NA	Normal	NA
	(12;17)(p13;q23)	−	NA	Normal	NA
	(13;18)(q36;q23)	+	NA	Normal	NA
6	(6;19)(pter;qter)	−	Chrom 19	Abnormal	De novo
4	(9;13)(p22;p13)	+	Chrom 9 & 13	Abnormal	De novo
7	(13;18)(p13;p11.32)	+	Chrom 8	Normal	Familial
17	(13;18)(p11;p11)+r13	+	NA	Abnormal	NA
2	(13;20)(p12;q13)	+	Chrom 20 80%	Primary amenorrhoea	De novo
11	(15;20)(ter;ter)	+	Chrom 20 in lymphocytes	Abnormal	De novo
18	(4;21)(p16;q22)	+	Chrom 21	Normal (miscarriage)	De novo
Case 1	(16;22)(q24;p11.2)	+	Chrom 6	Normal	Familial
Case 2	(14;18)(p11.2;p11.3)	+	Chrom 18	Normal	Familial
Case 3	(13;18)(p12;p11.2)	+	Chrom18	Abnormal	De novo
Case 4	(13;18)(p11.2;p11.2)	+	Chrom 18	Abnormal	De novo

NA: not available.

formation. However, when the centromeres are close to each other, the inactivation process can occur later, leading to mosaicism for centromere inactivation. Vig and Zinkowski[23] observed centromere separation in dicentric chromosomes at the metaphase-anaphase point. In prometaphase, most dicentrics showed two primary constrictions. However, 18% already showed premature centromere separation of one centromere, suggesting the activity of only one centromere. There was consistency from cell to cell with respect to which centromere separated early. By metaphase, 95% of the dicentrics showed premature separation of one centromere.

After the acrocentrics, chromosome 18 is most frequently involved in non-Roberstonian heterodicentrics (10 cases). The high frequency of involvement of this chromosome may reside in the fact that both 18p− and 18q− are viable syndromes. Other chromosomes are involved more or less randomly (table 1).

In conclusion, our cases indicate further the predominance of acrocentric chromosomes in stable dicentric autosomes. Most of them will reach stability by inactivating one centromere and will be functionally monocentric. If an acrocentric is involved, its centromere is most often the inactivated one.

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Correction

In the February 2000 issue of the journal, on page 88, in the paper "Haim-Munk syndrome and Papillon-Lefèvre syndrome are allelic mutations in cathepsin C", we regret that Dr Zlotogorski's name was misspelt.