J Med Genet 1990; 27: 582-587

Chromosome imbalance, normal phenotype, and imprinting

Livio Bortotto, Emanuela Piovan, Riccardo Furlan, Horacio Rivera, Orsetta Zuffardi

Abstract

A duplication of the sub-bands 1q42.11 and 1q42.12 was found in a boy and his mother. The proband has short stature (around the 10th centile) but a normal phenotype and psychomotor development. His mother is also asymptomatic. We found 30 published cases of normal subjects with an imbalance of autosomal euchromatic material. In these cases the imbalance involved either only one G positive band or a G positive and a G negative band. Thus the absence of a phenotypic effect cannot always be ascribed to the deficiency in the G positive bands of coding DNA. Moreover, in some cases, the method of transmission of the chromosome abnormality was such that an imprinting effect could be postulated.

Chromosome imbalances, especially if autosomal, are generally associated with phenotypic abnormalities and mental retardation, while changes in the amount of constitutive heterochromatin do not appear to have any clinical significance.[1 2] In recent years, improved banding techniques have helped to detect cases of duplication or deletion of euchromatic autosome regions in subjects with a normal phenotype. Because of the absence of obvious deleterious effects, such cases are sometimes called 'variants', but their biological significance is unclear and their detection may pose problems in genetic counselling.

We describe the finding of a familial direct duplication of bands q42.11 and q42.12 of chromosome 1 associated with a normal phenotype and review similar published cases.

Laboratorio di Citogenetica, Istituto Immunotrasfusionale, Ospedale Civile di Udine, Italy.
L Bortotto, E Piovan

Divisione di Neonatologia, Ospedale Civile di Udine, Italy.
R Furlan

Biologia Generale e Genetica Medica, Università di Pavia, Italy.
H Rivera*, O Zuffardi

Correspondence to Professor Zuffardi, CP 217, I-27100 Pavia, Italy.

*Present address: Division de Genetica, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.

Received for publication 19 February 1990.
Accepted for publication 20 March 1990.

Case report

The patient was born at term to a primiparous mother after an uneventful pregnancy and labour. The Apgar scores were 9 and 10. The infant's birth weight was 2380 g (<5th centile), his length was 47 cm (10th to 25th centile), and his head circumference (OFC) was 32 cm (10th centile). Neonatal screenings (Guthrie test, TSH, and T4) were normal. His parents were unrelated and phenotypically normal. The father's weight and height were 59 kg and 163 cm, respectively. The mother's weight and height were 49 kg and 155 cm. During the first year of life, the infant fed poorly and his growth curve stayed on the 10th centile.

At 12 months of age he appeared small but phenotypically and mentally normal and had just begun to speak. His weight, length, and OFC were 7850 g (<3rd centile), 71 cm (3rd centile), and 43 cm (3rd centile) respectively. The ocular fundi were normal.

All laboratory tests gave normal results and thyroid function was normal (T3 2·10 ng/ml, T4 69 ng/ml, and TSH 7·4 mU/ml). Apart from poor growth, the infant appeared to be healthy, with normal psychomotor development.

At present, aged 3 years 1 month, his height is 91 cm, his weight is 12 kg, and his OFC is 48 cm. All these values are around the 10th centile but his stature, correlated with that of his parents, is on the 25th centile.

CYTOGENETIC STUDIES

Chromosome preparations were obtained from phytohaemagglutinin (PHA) stimulated peripheral blood lymphocytes cultured in medium RPMI 1640 with 25% fetal calf serum. QFQ banding of the proband's chromosomes showed 46 chromosomes with a chromosome 1 with two additional bands, one Q negative and one Q positive, on the long arm. High

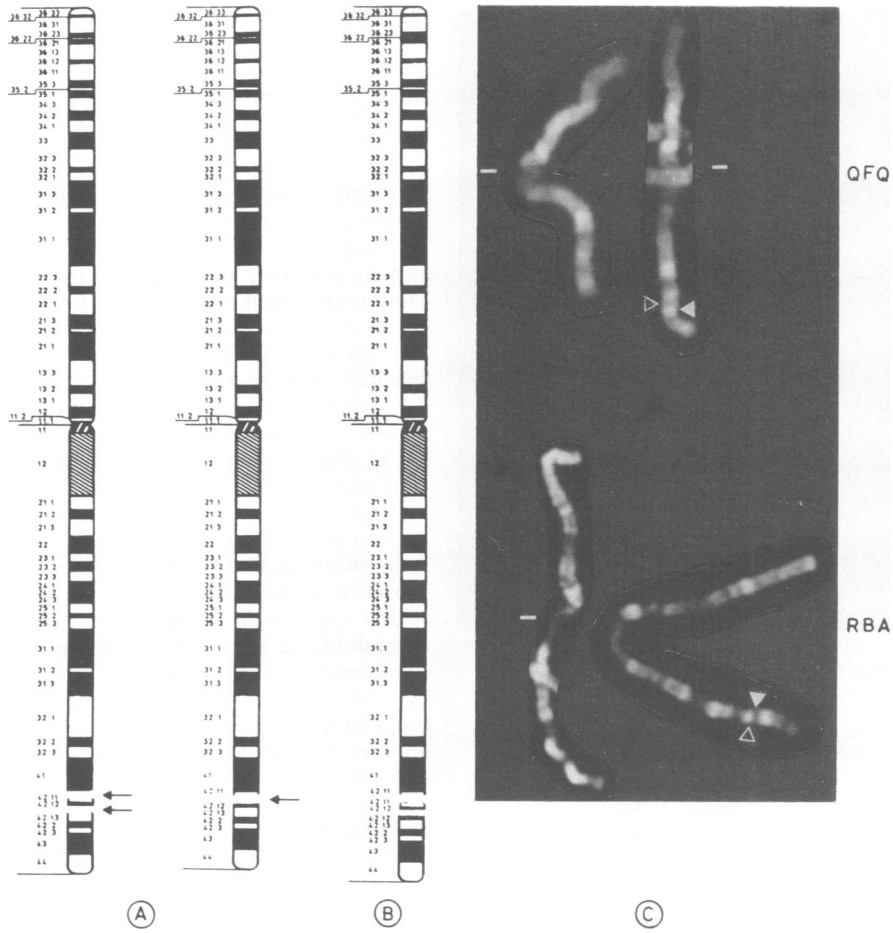

Figure 1 (A) Diagram of the duplication; arrows indicate the breakpoints. (B) Ideogram of the rearranged chromosome. (C) Chromosomes 1 after QFQ and RBA banding; the abnormal one is on the right. Open and solid arrowheads indicate bands 1q42.11 and 1q42.12 respectively.

resolution banding after methotrexate synchronisation followed by BrdU incorporation and acridine orange staining (RBA banding) confirmed the unbalanced karyotype with two additional, early and late replicating, bands on the long arm of a chromosome 1. This extra material stained negatively after DA–DAPI and CBG banding. We concluded that the additional material consisted of two euchromatic bands of the same width, located between 1q42.11 and 1q42.12, originating from a direct duplication of these two bands by an insertional translocation between homologous chromosomes (fig 1). The karyotype of the proband can thus be defined as: 46,XY,dir dup(1)(pter→q42.11::q42.11→q42.12→qter).

Chromosome studies of the parents showed that the mother had the same abnormal chromosome 1 as her son. A careful investigation of the whole karyotype showed no evidence for a balanced insertion in either the mother or the proband. The maternal grandmother and grandfather had a normal karyotype. Analysis of the 1qh polymorphisms after DA–DAPI staining indicated that the abnormal chromosome 1 originated from the grandmother (fig 2).

Discussion

The duplication of 1q42.11→1q42.12 present in the proband and his mother does not seem to be associated with any phenotypic effect. In fact, the proband's short stature, because of which chromosome analysis was requested, is correlated with that of his parents, both around the 10th centile. Moreover,

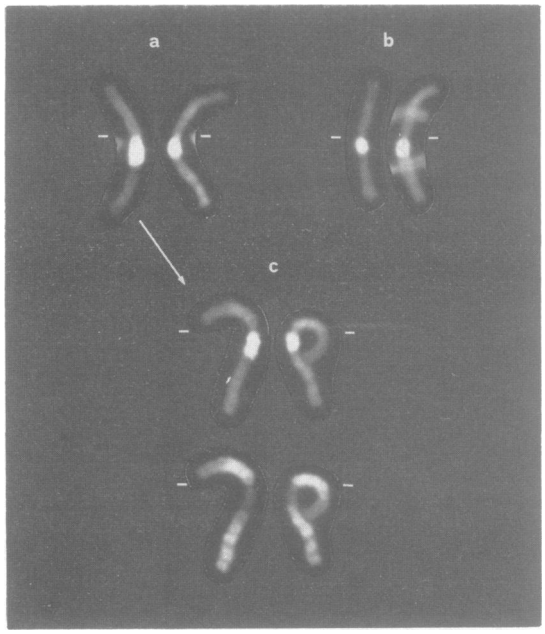

Figure 2 Partial karyotype of the grandmother (a), grandfather (b), and the mother (c) of the proband. The Q banded chromosomes of the mother indicate that the chromosome with the bigger constriction is in fact the abnormal one. Arrow indicates the parental derivation of the abnormal chromosome.

although IQ testing was not performed, both mother and proband appear mentally normal, and the latter is considered by the nursery school teachers to be a normal intelligent child.

We were unable to find published reports of either duplication or deletion of only this portion of band 1q42. We reviewed all the published cases with 46 or 47 chromosomes and deletion, duplication, or trisomy of identified or unidentified material, provided that either the proband or at least one carrier relative was reported to have a 'normal phenotype' (table). We excluded the carriers of supernumerary, small, unidentified, marker chromosomes because the subject has been thoroughly reviewed by several authors.[14 21–23]

We found only two instances of deficiencies in normal subjects. The first one (case 2 in the table) was a deletion of nearly the whole of band 5p14, found at amniocentesis for advanced maternal age and present in five relatives, all completely asymptomatic. The hemizygous state of the carriers was confirmed at the molecular level. The second case was a deletion (case 10 in the table) of band 13q21 and was found in a male whose wife had had two abortions and in his mother. In 12 of the cases in the table, extra material was present in the proximal short arm of a chromosome 9 (cases 3 to 9) and of a chromosome 16 (cases 24 to 28). In all these cases it consisted of an unidentified G positive band and was considered to be a variant in the absence of any associated symptomatology. In cases 8 and 9 we interpreted the extra material as consisting of a proximal, narrow, G negative band and a distal larger G positive band, but it is likely that the difference between these and the other cases was only because we used high resolution banding. It is puzzling that while both chromosomes 9 and 16 contain polymorphic regions of constitutive heterochromatin in their proximal long arm, chromosome 1, which also contains the same polymorphic qh region, has never been reported to have extra G positive material on its short arm.

In all the other cases listed in the table, a specific identified region was present in excess. Two cases (11, 12) of duplication of parts of 13q13 and 13q14 have been reported. While their relatives carrying the same deletion had retinoblastoma, psychomotor retardation, and, in case 12, failure to thrive, no evident phenotypic effect was found in the trisomic subjects. This is especially striking since at least part of the duplicated region contains structural genes that are expressed in adult life, as shown by the finding in both families of a gene dosage effect for esterase D activity. It must be noted that even the triplication of the longer (approximately 45% of 13q) portion 13q12.5→q22.1 appears to have a small effect. Riccardi *et al*[26] described this in a girl ascertained through her brother with multiple congenital anomalies and retinoblastoma.

Among the other cases listed in the table, 11 (cases 13 to 23), ascertained for different reasons, had a duplication of the proximal long arm of chromosome 15. In four of them, one of the chromosomes 15 had a duplication of the region q11–q13, while in the remaining seven, there was tetrasomy of roughly the same region owing to the presence of an extra inv dup(15). The proximal 15q region is liable to various types of rearrangements essentially resulting in (1) supernumerary inv dup(15) whose carriers, recently reviewed by Maraschio *et al*,[15] are either dysmorphic and mentally retarded, or have Prader-Willi syndrome, or have a normal phenotype (cases 17 to 23 in the table); (2) deletions associated either with Prader-Willi syndrome,[25] or with Angelman's syndrome,[26–29] or with dysmorphism and mental retardation similar to that found in some carriers of inv dup(15)[30]; (3) duplications associated either with Prader-Willi syndrome[27] or with subjects with a normal phenotype (cases 13 to 16 in the table).

How either deletions or duplications of 15q11–q13 result in the same phenotype, as in Prader-Willi syndrome, is at present obscure. Another point which is not at all clear is how apparently identical deletions and duplications give rise to such a wide spectrum of phenotypic manifestations, such as the association

Non-mosaic autosomal imbalances in phenotypically normal subjects.

Case No	Karyotype	Properties of unbalanced bands	Ascertainment	Age at examination	Relatives with the same imbalance*	Inheritance of the imbalance in the family	Reference
1	46,XY,dup(1)(q42.11→q42.12)	G+, G−	Small stature	3 y	+	Mat	Present case
2	46,XX,del(5)(p14)	G+	Amniocentesis (at birth, normal)	Newborn	+	Mat	3
3	46,XY,9p+	G+	Newborn survey	Newborn	+	Mat	4
4	46,XX,9p+	G+	Neurological impairment	15 y	+	Mat	5
5	46,XY,9p+	G+	Amniocentesis (at birth, normal)	Newborn	+	Pat	6
6	46,XX,9p+	G+	Amniocentesis (at birth, normal)	Newborn	+	Mat	6
7	46,XX,9p+	G+	Protruding tongue	Newborn	+	Mat and Pat	7
8	46,XY,9p+	G+, G−	X linked disease	10 y	+	Mat	Personal observation
9	46,XY,9p+	G+, G−	Dysmorphic facies	3 y	+	Pat	Personal observation
10	46,XY,del(13)(q21)	G+	Repeated abortions	25 y	+	Mat	8
11	46,XY,dup(13)(q13→q14·3)	G+, G−	Retinoblastoma in one sib with del(13)	Child	−	Mat	9
12	46,XX or XY,dup(13)(q13.1→q14.3)	G+, G−	Retinoblastoma in relatives with del(13)	Variable	+	Mat and Pat	10
13	46,XX,invdup(15)(q11.2→q13.3)	G+, G−	Amniocentesis	Fetus	+	Pat	11
14	46,XX,dirdup(15)(q11.2→q13)	G+, G−	Malformed stillborn	Stillborn	+	Mat	11
15	46,XY,dirdup(15)(q11→q13)	G+, G−	Congenital anomalies	Newborn	+	Pat	12
16	46,XY,dirdup(15)(q11→q13)	G+, G−	Repeated abortions	34 y	?	?	12
17	47,XY,+invdup(15)(q1)	G+, G−	Amniocentesis	Fetus	+	Mat	13
18	47,XX,+invdup(15)(?)	G+, G−	Thyrotoxicosis	50 y	+	Mat	14
19	47,XY,+invdup(15)(?)	G+, G−	Squamous cell cancer	61 y	+	Mat	14
20	47,XY,+invdup(15)(?)	G+, G−	Newborn survey	Newborn	?	?	14
21	47,XY,+invdup(15)(?)	G+, G−	Prison survey	58 y	?	?	14
22	47,XX,+invdup(15)(q11.2)	G+, G−	Repeated abortions	23 y	+	Mat	15 case 5
23	47,XY,+invdup(15)(q11)	G+, G−	Amniocentesis	Fetus	+	Pat	15 case 6
24	46,XY,16p+	G+	Amniocentesis (at birth, normal)	Newborn	+	Pat	16
25	46,XY,16p+	G+	Amniocentesis (at birth, normal)	Newborn	+	Pat	16
26	46,XY,16p+	G+	Congenital anomalies	3 y	+	Mat and Pat	16
27	46,XY,16p+	G+	Daughter with trisomy 18	Adult	?	?	17
28	46,XX,16p+	G+	Congenital anomalies	Adult	?	?	17
29	47,XX,del(18)(cen),+i(18p)	G+, G−	Sibs with monosomy and tetrasomy 18p	Adult	?	?	18
30	47,XX,del(18)(cen),+i(18p)	G+, G−	Sibs with monosomy 18p	Adult	?	?	19
31	47,XX,del(18)(cen),+i(18p)	G+, G−	Sibs with tetrasomy 18p	Adult	?	?	20

*All the carrier relatives are phenotypically normal.

between deletion 15q11–q13 and Prader-Willi or Angelman's syndromes or dysmorphism and mental retardation, and the association between duplication 15q11–q13 and Prader-Willi syndrome or a normal phenotype. An obvious hypothesis is that deletions or duplications of different but cytogenetically indistinguishable gene sequences are responsible for the different phenotypes, but an imprinting effect (see below) has also been suggested, at least for the manifestation of Prader-Willi syndrome rather than Angelman's syndrome.[31]

Three cases (29 to 31) of trisomy 18p owing to a deletion of a chromosome 18 short arm and a supernumerary i(18p) have been described in normal women who give birth to children tetrasomic or monosomic for 18p. It is known that duplication 18p has a mild phenotypic effect but a careful examination in at least two (29, 30) of the three cases in the table showed a completely normal phenotype.

In the majority of the cases listed in the table, the karyotypic abnormality involved a G positive band. The finding that most genes are associated with CpG islands,[32] that in turn occur rarely in G positive bands, led to the hypothesis that G positive bands may contain non-coding DNA.[33] If this were true, it would not be surprising that excess or deficient G positive DNA has no phenotypic consequences. In fact this explanation fits only a few of the cases listed in the table: the finding either of G negative imbalances (cases 1, 8, 9, 11 to 23, 29 to 31) or of a gene dosage compensation for some duplications (cases 11 and 12) indicates that, whatever the reason, a few megabases of DNA can be duplicated or deficient without phenotypic effect. Another appealing hypothesis to explain the absence of a phenotypic effect in subjects with a chromosome imbalance would be to assume the existence of an imprinting effect, that is, the presence of genes active only when contributed by one parent but not by the other. The evidence is striking in the mouse where maternal duplication/paternal deficiency for the same genomic region can be lethal while the other way around is without effect.[34 35] In humans the effect of parental origin on genomic and chromosome defects has recently been reviewed by Reik[31] and the evidence for imprinting of chromosomes is remarkable.

The absence of phenotypic abnormalities in some carriers of unbalanced karyotypes could also be related to an imprinting effect. If this were the case, we would expect that in these subjects the chromosome imbalance would always be transmitted either only from the fathers or only from the mothers and moreover that, whenever transmitted from the other parent, there would be a phenotypic effect associated with the chromosome imbalance. Cases 1, 2, and 10 might satisfy the first requirement but in none of the cases could we find instances of the opposite transmission associated with a phenotypic effect.

We wish to stress that all these cases raise problems in genetic counselling, since the occurrence of meiotic recombination leading to gametes with new imbalances cannot be excluded in any of them.

We thank Professor M Fraccaro for his help in the preparation of this paper.

1 Verma RS, Dosik H. Human chromosomal heteromorphisms: nature and clinical significance. *Int Rev Cytol* 1980;**62**: 361–85.
2 Erdtmann B. Aspects of evaluation, significance and evolution of human C-band heteromorphism. *Hum Genet* 1982;**61**:281–94.
3 Overhauser J, Golbus MS, Schonberg SA, Wasmutt JJ. Molecular analysis of an unbalanced deletion of the short arm of chromosomes that produces no phenotypes. *Am J Hum Genet* 1986;**39**:1–10.
4 Buckton KE, O'Riordan ML, Ratcliffe S, *et al.* A G-band study of chromosomes in liveborn infants. *Ann Hum Genet* 1980;**43**: 227–39.
5 Sutherland GR, Eyre H. Two unusual G-bands variants of the short arm of chromosome 9. *Clin Genet* 1981;**19**:331–4.
6 Archidiacono N, Pecile V, Rocchi M, Dalpra L, Nocera G, Simoni G. A rare non-heterochromatic 9p+ variant in two amniotic fluid cell cultures. *Prenat Diagn* 1984;**4**:231–3.
7 Spedicato FS, Di Comite A, Tohidast-Akrad M. An unusual variant chromosome 9 with an extra C-negative, G-dark segment in the short arm. *Clin Genet* 1985;**28**:162–5.
8 Couturier J, Morichon-Delvallez N, Dutrillaux B. Deletion of band 13q21 is compatible with a normal phenotype. *Hum Genet* 1985;**70**:87–91.
9 Rivera H, Turleau C, de Grouchy J, Junien C, Despoisse S, Zucker JM. Retinoblastoma del(13q14). Report of two patients, one with a trisomic sib due to a maternal insertion. Gene dosage effect for esterase D. *Hum Genet* 1981;**59**:211–4.
10 Strong LC, Riccardi VM, Ferrel FE, Sparkes RS. Familial retinoblastoma and chromosome 13 deletion transmitted via insertional translocation. *Science* 1981;**213**:1501–3.
11 Stallard R, Van Dyke D. Familial duplications of proximal 15q in normal individuals. *Am J Hum Genet* 1986;**39**:133A.
12 Brookwell R, Velaba A. Proximal 15q variant with normal phenotype in three unrelated individuals. *Clin Genet* 1987;**31**: 311–4.
13 Stetten G, Sroka-Zallzek B, Corson VL. Prenatal detection of an accessory chromosome identified as an inversion duplication (15). *Hum Genet* 1981;**57**:357–9.
14 Buckton KE, Spowart G, Newton MS, Evans HJ. Forty four probands with an additional "marker" chromosome. *Hum Genet* 1985;**69**:353–70.
15 Maraschio P, Cuoco C, Gimelli G, Zuffardi O, Tiepolo L. Origin and clinical significance of invdup(15). In: Sandberg A, ed. *The cytogenetics of mammalian autosomal rearrangements*. New York: Alan R Liss, 1988:615–34.
16 Thompson PW, Roberts SH. A new variant of chromosome 16. *Hum Genet* 1987;**76**:100–1.
17 Pinel I, Diaz de Bustamante A, Urioste M, Felix V, Ureta A, Martinez-Frias ML. An unusual variant of chromosome 16. Two new cases. *Hum Genet* 1988;**80**:194.
18 Taylor KM, Wolfinger HL, Brown MG, Chadwick DL. Origin of a small metacentric chromosome: familial and cytogenetic evidence. *Clin Genet* 1975;**8**:364–9.
19 Rosano M, de Salazar E, Bringhi V, Dallapiccola B. Due casi 18p– ed un caso di trisomia 18p in una stessa fratria. *Neuropsychol Infant* 1977;**197**:1221–37.
20 Takeda K, Toshihiro O, Hagesawa T. Sibs with tetrasomy 18p born to a mother with trisomy 18p. *J Med Genet* 1989;**26**:195–7.
21 Steinbach P, Djalali M, Hansmann I, *et al.* The genetic significance of accessory bisatellited marker chromosomes. *Hum Genet* 1983;**65**:155–64.
22 Benn BA, Hsu LYF. Incidence and significance of supernumerary marker chromosomes in prenatal diagnosis. *Am J Hum Genet* 1984;**36**:1092–102.
23 Mattei JF, Philip N, Mattei MG, Giraud F. Les petits chromosomes supernumeraires. *J Genet Hum* 1985;**33**:396–8.
24 Riccardi VM, Mintz Hittner H, Francke U, *et al.* Partial triplication and deletion of 13q: study of a family presenting with bilateral retinoblastomas. *Clin Genet* 1979;**15**:332–45.

25 Ledbetter DH, Greenberg R, Holm VA, Cassidy SB. Conference report: second annual Prader-Willi syndrome scientific conference. *Am J Med Genet* 1987;**28**:779–90.

26 Kaplan LC, Wharton R, Elias E, Mandell F, Donlon T, Latt S. Clinical heterogeneity associated with deletions in the long arm of chromosome 15: report of 3 new cases and their possible genetic significance. *Am J Med Genet* 1987;**28**:45–53.

27 Magenis RE, Brown MG, Lacy DA, Budden S, LaFranchi S. Is Angelman syndrome an alternate result of del(15)(q11–q13)? *Am J Med Genet* 1987;**28**:829–38.

28 Pembrey M, Fennell SJ, Van den Berghe J, *et al.* The association of Angelman's syndrome with deletions within 15q11–13. *J Med Genet* 1989;**26**:73–7.

29 Williams CA, Gray BA, Hendrickson JE, Stone JW, Cantù ES. Incidence of 15q deletions in the Angelman syndrome: a survey of twelve affected persons. *Am J Med Genet* 1989;**32**:339–45.

30 Greenberg F, Ledbetter DH. Deletions of proximal 15q without Prader-Willi syndrome. *Am J Med Genet* 1987;**28**:813–20.

31 Reik W. Genomic imprinting and genetic disorders in man. *Trends Genet* 1989;**5**:331–6.

32 Bird AP. CpG islands as gene markers in the vertebrate nucleus. *Trends Genet* 1987;**3**:342–7.

33 Bickmore WA, Sumner AT. Mammalian chromosome banding. An expression of genome organization. *Trends Genet* 1989;**5**: 144–8.

34 Cattanach BM. Parental origin effects in mice. *J Embryol Exp Morphol* 1986;**97**(suppl):137–50.

35 Searle AG, Peters J, Lyon MF, *et al.* Chromosome maps of man and mouse. IV. *Ann Hum Genet* 1989;**53**:89–140.