

Maternal uniparental disomy of chromosome 14 confined to an interstitial segment (14q23-14q24.2)

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Abstract

Maternal uniparental disomy for the complete long arm of chromosome 14 has been reported in 14 patients to date and is associated with a specific pattern of malformation. We report a child with clinical features of this syndrome who exhibits maternal uniparental disomy confined to a specific interstitial segment of chromosome 14.

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Table 1 Major clinical features of maternal UPD(14) syndrome

Findings	Previously reported cases (n=12)*	Present case	All cases (%)
Premature puberty	7/7†	Too young	100
Developmental delay	8/10‡	+	82
Hypotonia/joint laxity	9/12	+	77
Short stature	9/12	-	69
Small hands	9/12	-	69
Intrauterine growth retardation	7/12	-	54
Macrocephaly/hydrocephalus	4/12	+	38

*Refs 2-7, 10-15. The case reported by Papenhausen *et al*⁷ was not included because UPD(14)mat was not proven. The case reported by Sirchia *et al*⁶ was excluded because clinical evaluation was not possible.

†Five cases were too young to evaluate.

‡Two cases were too young to evaluate.

A specific pattern of malformation is associated with maternal uniparental disomy 14 (UPD(14)mat), which is distinct from that seen with paternal uniparental disomy 14 (UPD(14)pat). Intrauterine growth retardation (IUGR), developmental delay, premature puberty, hypotonia/joint laxity, macrocephaly, short stature, and small hands are all characteristic of UPD(14)mat (table 1). Polyhydramnios, small thorax, rib defects, small ears, protruding philtrum, small palpebral fissures, and camptodactyly are found in subjects with UPD(14)pat.¹ The differences in these phenotypes and the inheritance patterns suggest that this chromosome contains both maternally and paternally imprinted genes. All 14 UPD(14)mat patients reported to date appear to exhibit uniparental disomy for the complete long arm of this chromosome.²⁻¹⁵ In this paper we report a patient with UPD(14)mat confined to an interstitial segment of chromosome 14 (~14q23-14q24.2) and discuss the probable origin of this event.

Case report

The proband presented at the age of 3½ years for genetic evaluation secondary to developmental delay. She was born at term after an



Figure 1 Front view of patient (photograph reproduced with permission).

uncomplicated pregnancy with normal growth parameters. Her parents reported no problems at birth except for hypotonia. No records of her head size are available before 2 years of age, but at that time her OFC measured >98th centile. A subsequent head CT scan was normal. She sat at 8 months of age and walked at 15 months. By the age of 2½ years, concerns about her motor and speech delays led to formal developmental testing which indicated mild global developmental delay. Previous neurological and genetic evaluation showed global developmental delay, generalised hypotonia, macrocephaly, and joint laxity with a normal head MRI scan, normal karyotype, and normal DNA testing for the fragile X syndrome. On physical examination at 3½ years, her height was at the 25th centile, weight at the 10th centile, and head circumference above the 97th centile. No dysmorphic features were noted other than a slightly triangular face (fig 1). She continued to show generalised joint laxity. The possibility of UPD(14)mat was raised based on the triad of developmental delay, macrocephaly, and joint laxity, which are features characteristic of this syndrome.

Methods

Blood samples were collected from the patient and both of her parents. Genomic DNA was purified using a commercial kit (Gentra

Table 2 Genotypic analysis*

Genetic locus	Coordinate† (cM)	Father	Mother	Patient	Interpretation
D14S66	48	2.3	1.2	1.3	Biparental inheritance
D14S63	58	1.2	1.2	1.2	Heterozygous, parental origin undetermined
D14S277	67	2.2	1.1	1.1	UPD(14)mat
D14S268	68	1.2	1.2	1.2	Heterozygous, parental origin undetermined (presumed hetero-UPD(14)mat)
D14S77	69	2.2	1.3	1.3	Hetero-UPD(14)mat
D14S1028	69–70	1.3	2.2	1.2	Biparental inheritance
D14S61	75	1.2	3.3	2.3	Biparental inheritance
D14S59	76	2.3	1.2	1.3	Biparental inheritance
D14S74	76	1.2	1.2	1.2	Heterozygous, parental origin undetermined
D14S67	85	2.2	1.1	1.2	Biparental inheritance

Hetero-UPD(14)mat=maternal heterodisomy of chromosome 14.

*Only informative markers are shown.

†Marker locations and order from the CEPH/Genethon Chromosome 14 Linkage Map. Positions of D14S1028 and D14S59 are inferred from the locations of common or linked loci on the Marshfield Sex Averaged Chromosome 14 Linkage Map.

Systems, Minneapolis, MN) and inheritance at polymorphic chromosome 14 genetic loci was analysed routinely by PCR.¹⁶ The genetic markers (Research Genetics, Huntsville, AL) studied included D14S66, D14S63, D14S1002, D14S277, D14S268, D14S1028, D14S77, D14S61, D14S59, D14S74, D14S67, and D14S68. PCR conditions and genetic, cytogenetic, and physical map locations were obtained from the CEPH/Genethon and Marshfield genetic maps at the Genome Database (<http://gdb.bioinfo.sickkids.on.ca/>). PCR products were separated on denaturing polyacrylamide gels and visualised by exposure on autoradiography film.

Results

UPD(14)mat was observed at D14S277 and D14S77 was informative for heterodisomy (hetero-UPD(14)mat) (table 2, fig 2). D14S268, which maps between D14S277 and D14S77,¹⁷ was heterozygous and presumed to show heterodisomy (table 2). D14S66, which is proximal to these loci, and D14S1028, D14S61, and D14S67, which are distal, were biparentally inherited (table 2). In addition, markers D14S63 and D14S74 were found to be heterozygous, but the origin could not be determined owing to the presence of an allele shared by both parents. D14S68 was uninformative.

Discussion

The maternal heterodisomic interval in this patient may be as small as 2 cM (the distance between D14S277 and D14S77) or as large as 21 cM (the distance between the flanking markers, D14S66 and D14S1028, displaying biparental inheritance). These genetic loci have been mapped to bands 14q23–14q24.2 (fig 3) and define the shortest genetic interval associated with the UPD(14)mat phenotype.

The ideogram in fig 3 compares the regions of UPD(14)mat in our patient with nine of the 14 previously reported cases, for which details of genetic markers were available. This patient with UPD(14)mat is unique because maternal disomy is confined to an interstitial segment of chromosome 14q (rather than the complete long arm, as reported in previous cases). Complete UPD(14)mat results from either gamete complementation or a meiotic non-disjunction event involving a derivative chromosome (iso-

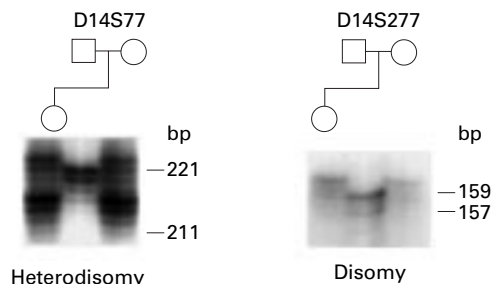


Figure 2 Autoradiographs of patient and parental genotypes at two loci that show UPD(14)mat.

chromosome 14 or a Robertsonian translocation) followed by trisomy rescue.¹⁸ Meiotic recombination may also ensue^{5,9,14} and generate both iso- and heterodisomic regions (fig 3). However, interstitial maternal heterodisomy confined between biparentally inherited loci also requires an early postzygotic recombination event to have occurred. In the present case, a mitotic double exchange first occurred between the paternal and one of two maternal chromosomes in a trisomy 14 zygote. This was followed by mitotic non-disjunction of the recombinant derivative chromosome containing the paternally derived interstitial segment.

Allelic mitotic recombination occurs more often than has been previously recognized.^{19–21} For example, between 20 and 28% of patients with sporadic Beckwith-Wiedemann syndrome show paternal isodisomy for the distal segment of chromosome 11p, felt to be the result of a single, rather than a double, postzygotic crossover event.^{22–24} Double mitotic recombination is also associated with loss of heterozygosity (LOH)^{19,25} and has recently been suggested as a possible mechanism for leukaemia in patients with mutations in the NF1 gene²⁵ and revertant mosaicism in epidermolysis bullosa.²⁶ By contrast, the present case involves double reciprocal recombination without concomitant LOH.

Autosomal recessive inheritance has been suggested as an explanation for the UPD(14)mat phenotype based on previous observations of maternal isodisomy.⁴ However, autosomal recessive inheritance is unlikely because no consistent isodisomic interval exists between all of the cases reported to date (fig 3). Imprinting has also been suggested as the mechanism to explain the UPD(14)mat phenotype.^{1,27} Although no human genes in

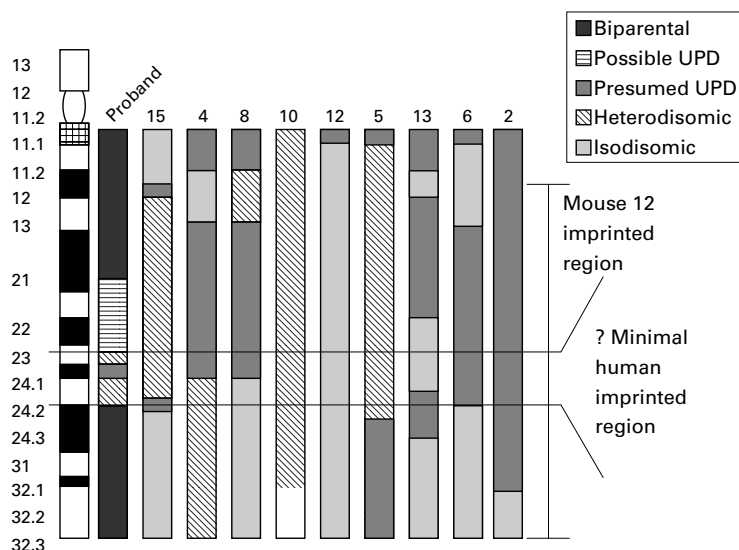


Figure 3 Ideogram of chromosome 14 comparing locations of informative markers in previous reports of UPD(14)mat to those defining the maternal heterodisomy interval in this study. (Numbers across the top are reference numbers.) Cytogenetic assignments of markers have been interpolated from the physical assignments of adjacent anchor loci on genetic, physical, and chromosome maps.

this region are yet proven to be imprinted,²⁷ an imprinting effect is supported by studies in the mouse indicating that the distal portion of chromosome 12, recognised as a probable imprinted region,²⁸ is syntenic with human chromosome 14q. Maternal origin effects based on studies of partial trisomy of chromosome 14q also suggest that 14q24.3-qter contains imprinted genes.²⁷ Paternally imprinted gene(s) have been localised to 14q22, based on transmission of an interstitial chromosome 14 duplication from a normal father to abnormal offspring.²⁹ We propose that reciprocally imprinted genes are present within 14q22-q24.2, as has been found previously in 11p15.5 and in 15q11.2-q13.^{30 31}

The extent of the disomic interval presented in this case should assist in refining the locations of imprinted genes associated with certain features found in UPD(14)mat syndrome. IUGR, short stature, and small hands have been seen in the majority of UPD(14)mat cases, but were not observed in our patient, suggesting that gene loci associated with their occurrence may be located outside the 14q23-14q24.2 region. Patients with partial trisomy 14q owing to maternal non-disjunction exhibit intrauterine growth retardation and small hands more frequently than those with trisomy resulting from paternal segregation errors.²⁷ This common trisomy 14 interval is distal to the UPD(14)mat segment delineated in the current study. Finally, the occurrence of premature puberty (or lack thereof) in our patient, a consistent finding in other cases of UPD(14)mat, may facilitate localisation of imprinted gene(s) responsible for pathogenesis of this phenotype.

Note added in proof

Four additional patients with UPD(14)mat have recently been documented by Kotzot.³²

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