

## **Supplemental Items**

**(Supplemental Table S1 and Table S2; Supplemental Figure S1, Figure S2, and Figure S3)**

### **Relative frequency of underlying genetic causes for the development of UPD(14)pat-like phenotype**

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**Supplemental Table S1.** Summary of phenotypic findings of the 26 patients examined in this study.

Patient	Body phenotype				Placental phenotype			Reference
	Characteristic face <sup>a</sup>	Bell-shaped thorax with coat hanger appearance of the	Diastasis recti	Omphalocele	Polyhydramnios	Placental weight (%) <sup>b</sup>	Gestational age (wks)	
1	Yes	Yes	Yes	No	Yes	131%	34	1
2	Yes	Yes	No	Yes	Yes	198%	36	1
3	Yes	Yes	Yes	No	Yes	Unknown	37	This report
4	Yes	Yes	Yes	No	Yes	195%	37	1
5	Yes	Yes	No	Yes	Yes	Unknown	Unknown	This report
6	Yes	Yes	No	Yes	Yes	114%	34	1, 2
7	Yes	Yes	No	Yes	Yes	227%	34	1
8	Yes	Yes	Yes	No	Yes	117%	36	1
9	Yes	Yes	Yes	No	Yes	142%	37	1
10	Yes	Yes	No	Yes	Yes	Unknown	35	This report
11	Yes	Yes	Yes	No	Yes	190%	35	This report
12	Yes	Yes	Yes	No	Yes	262%	37	This report
13	Yes	Yes	No	Yes	Yes	Unknown	34	This report
14	Yes	Yes	No	Yes	Yes	227%	35	This report
15	Yes	Yes	Yes	No	Probable <sup>c</sup>	114%	24	1
16	Yes	Yes	Yes	No	Yes	161%	32	1, 2
17	Yes	Yes	Yes	No	Yes	227%	36	1, 2
18	Yes	Yes	Yes	No	Yes	143%	27	3
19	Yes	Yes	Yes	No	Yes	152%	35	3
20	Yes	Yes	Yes	No	Yes	147%	30	3
21	Yes	Yes	No	Yes	Yes	174%	33	4
22	Yes	Yes	No	Yes	No	No <sup>d</sup>	28	4
23	Yes	Yes	No	Yes	Yes	139%	35	3
24	Yes	Yes	No	Yes	Yes	156%	30	3
25	Yes	Yes	Yes	No	Yes	145%	35	3
26	Yes	Yes	No	Yes	Yes	Unknown	37	This report

(continued)

Detailed clinical features of the 18 previously reported patients are as described in the corresponding references, and The patient numbers correspond to those in Table 1 and Supplemental Table S2.

<sup>a</sup> All the patients have at least three of the following features: frontal bossing, hairy forehead, blepharophimosis, depressed nasal bridge, anteverted nares, small ears, protruding philtrum, puckered lips, and micrognathia.

<sup>b</sup> Assessed by the Japanese placental weight data reported by Kagami et al.<sup>1</sup>

<sup>c</sup> The precise assessment is difficult because of the young gestational age.

<sup>d</sup> The placenta has been described as normal in the hospital record.

#### References

1. Kagami M, Yamazawa K, Matsubara K, Matsuo N, Ogata T: Placentomegaly in paternal uniparental disomy for human chromosome 14. *Placenta* 2008; **29**: 760-761.
2. Kagami M, Nishimura G, Okuyama T *et al*: Segmental and full paternal isodisomy for chromosome 14 in three patients: narrowing the critical region and implication for the clinical features. *Am J Med Genet A* 2005; **138A**: 127-132.
3. Kagami M, Sekita Y, Nishimura G *et al*: Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. *Nat Genet* 2008; **40**: 237-242.
4. Kagami M, O'Sullivan MJ, Green AJ *et al*: The IG-DMR and the MEG3-DMR at human chromosome 14q32.2: hierarchical interaction and distinct functional properties as imprinting control centers. *PLoS Genet* 2010; **6**: e1000992.

**Supplemental Table S2.** Clinical features of the 15 patients with UPD(14)pat-like phenotype

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 26	UPD(14)pat (n=20) <sup>e</sup>
Genetic cause	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic UPD(14)pat	Sporadic Epimutation	Sporadic UPD(14)pat
Present age	6 months	2 3/12 years	7 years	6 months	Unknown	4 4/12 years	3 years	4 8/12 years	2 11/12 years	15 years	1 3/12 years	1 1/12 years	1 3/12 years	3 2/12 years	2 years	0–9 years
Sex	Male	Female	Female	Male	Female	Female	Male	Female	Female	Male	Male	Female	Female	Male	Male	M:F=9:11
Karyotype	46,XY	46,XX	46,XX	46,XY	46,XX	46,XX	46,XY	46,XX	46,XX	46,XY	46,XY	46,XX	46,XX	46,XY	46,XY	
Pregnancy and delivery																
Polyhydramnios	+	+	+	+	+	+	+	+	+	+	+	+	+	Probable <sup>d</sup>	+	20/20
Amnioreduction (wks)	4x (22–32)	3x (22–34)	5x (25–35)	7x (32–37)	Unknown	3x (Unknown)	2x (33,36)	3x (22–34)	1x (29)	3x (27–32)	4x (26–35)	1x (33)	6x (23–34)	None	None	6/6 (<30)
Placentomegaly	+	+	Unknown	+	+	+	±	+	+	+	+	+	+	Unknown	Unknown	10/10
Placental weight <sup>a</sup> g (%)	640 (131)	970 (198)	Unknown	1030 (195)	Unknown	1108 (227)	570 (117)	750 (142)	Unknown	930 (190)	1384 (262)	Unknown	1110 (227)	278 (114)	Unknown	114–227 %
Premature delivery	+	+	–	–	Unknown	+	+	–	+	+	–	+	+	+	–	18/20
Gestational age (wks)	34	36	37	37	Unknown	34	36	37	35	35	37	34	35	24	37	28–37
Delivery	Vaginal	Caesarean	Vaginal	Caesarean	Unknown	Caesarean	Vaginal	Caesarean	Caesarean	Caesarean	Caesarean	Caesarean	Caesarean	Caesarean	Caesarean	V:C=6:7
Growth pattern																
Prenatal growth failure	–	–	–	–	Unknown	–	–	–	–	–	–	–	–	–	–	1/13
Birth length <sup>b</sup> cm (SD)	47.0 (+0.9)	45 (–0.8)	48.5 (+0.6)	49.0 (+0.5)	Unknown	44.0 (–0.1)	46.2 (–1.0)	44.5 (–1.5)	51.0 (+2.8)	45.0 (–0.2)	48.0 (±0)	42.5 (–0.8)	48.0 (+1.5)	30.6 (WNR)	50.0 (+1.0)	
Birth weight <sup>b</sup> kg (SD)	2.5 (+1.0)	3.4 (+2.5)	3.5 (+2.4)	3.1 (+0.6)	Unknown	2.7 (+2.8)	2.8 (+0.8)	2.8 (+0.2)	2.6 (+1.2)	3.1 (+1.9)	2.7 (–0.4)	2.1 (–0.6)	2.9 (+2.1)	1.2 (WNR)	2.8 (–0.1)	
Postnatal growth failure	Unknown	–	–	+	Unknown	–	+	+	–	–	+	–	+	+	–	5/6
Present stature <sup>c</sup> cm (SD)	Unknown	78.6 (–1.9)	122.3 (+0.6)	61.5 (–2.6)	Unknown	99.3 (–0.6)	70 (–6.4)	96.0 (–2.0)	90.5 (–0.3)	159.0 (–1.1)	70.1 (–6.9)	76.0 (+0.8)	66.1 (–4.3)	61.8 (–8.7)	85.0 (–0.1)	
Present weight <sup>c</sup> kg (SD)	Unknown	10.1 (–1.0)	23.9 (+0.4)	7.1 (–0.9)	Unknown	14.2 (–1.0)	8.3 (–3.4)	15.8 (–0.4)	14.9 (+1.4)	38.0 (–1.8)	7.3 (–2.4)	9.5 (–0.5)	6.0 (–3.5)	4.2 (–6.0)	17.0 (+4.0)	
Characteristic face																
Frontal bossing	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	5/7
Hairy forehead	+	+	–	+	–	–	+	+	+	+	+	–	+	+	–	9/10
Blepharophimosis	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	14/15
Depressed nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Anteverted nares	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6/10
Small ears	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	11/12
Protruding philtrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15/15
Puckered lips	+	–	–	+	–	+	±	–	+	–	–	–	+	–	+	3/10
Micrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	11/12
Thoracic abnormality																
Bell-shaped thorax	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17/17
Mechanical ventilation	+ (6 months)	+ (5 days)	+ (9 days)	+ (on ventilator)	Unknown	+ (7 months)	+ (on ventilator)	+ (40 days)	+ (2 days)	+ (2 days)	+ (6 days)	+ (5 months)	+ (on ventilator)	+ (9 months)	+ (3 days)	17/17
Abdominal wall defect																
Diastasis recti	+	–	+	+	–	–	+	+	–	+	+	–	–	+	–	15/17
Omphalocele	–	+	–	–	+	+	–	–	+	–	–	+	+	–	+	2/17
Others																
Developmental delay	+	+	+	+	Unknown	+	+	+	+	+	+	+	+	+	+	12/12
Seizure	–	–	–	–	Unknown	–	–	+	–	–	–	–	–	–	–	2/9
Feeding difficulty	+	+	–	+	Unknown	+	+	+	+	+	+	+	+	+	–	2/6
Short webbed neck	+	+	+	+	Unknown	+	+	+	+	+	+	+	+	+	+	14/14
Laryngomalacia	–	–	–	±	Unknown	–	Unknown	–	–	–	+	–	–	+	–	3/5
Cardiac disease	–	–	–	–	Unknown	–	+ (Unknown)	–	+ (small ASD)	–	–	–	–	+ (PDA)	–	5/10
Inguinal hernia	–	–	–	–	Unknown	–	–	–	–	+	–	–	–	+	–	2/6
Coxa valga	–	–	–	–	Unknown	+	±	–	–	–	–	–	–	±	–	3/4
Joint contractures	+	–	+	–	Unknown	+	–	+	+	+	+	–	–	–	+	8/10
Kyphoscoliosis	+	–	+	–	Unknown	+	+	–	–	–	–	+	–	–	–	4/7
Thyroid dysfunction	–	–	–	–	Unknown	–	–	–	–	–	–	–	–	–	–	0/6
Extra features	NEC	–	–	–	Unknown	–	–	–	–	–	–	–	–	Hepatoblastoma	–	

The patient numbers correspond to those in Table 1.

<sup>a</sup> Evaluated by the gestational age–matched Japanese placental weight<sup>†</sup>.

<sup>b</sup> Assessed by the gestational age- and sex-matched Japanese reference data.

<sup>c</sup> Assessed by the age- and sex-matched Japanese reference data.

<sup>d</sup> The precise assessment is difficult because of the young gestational age.

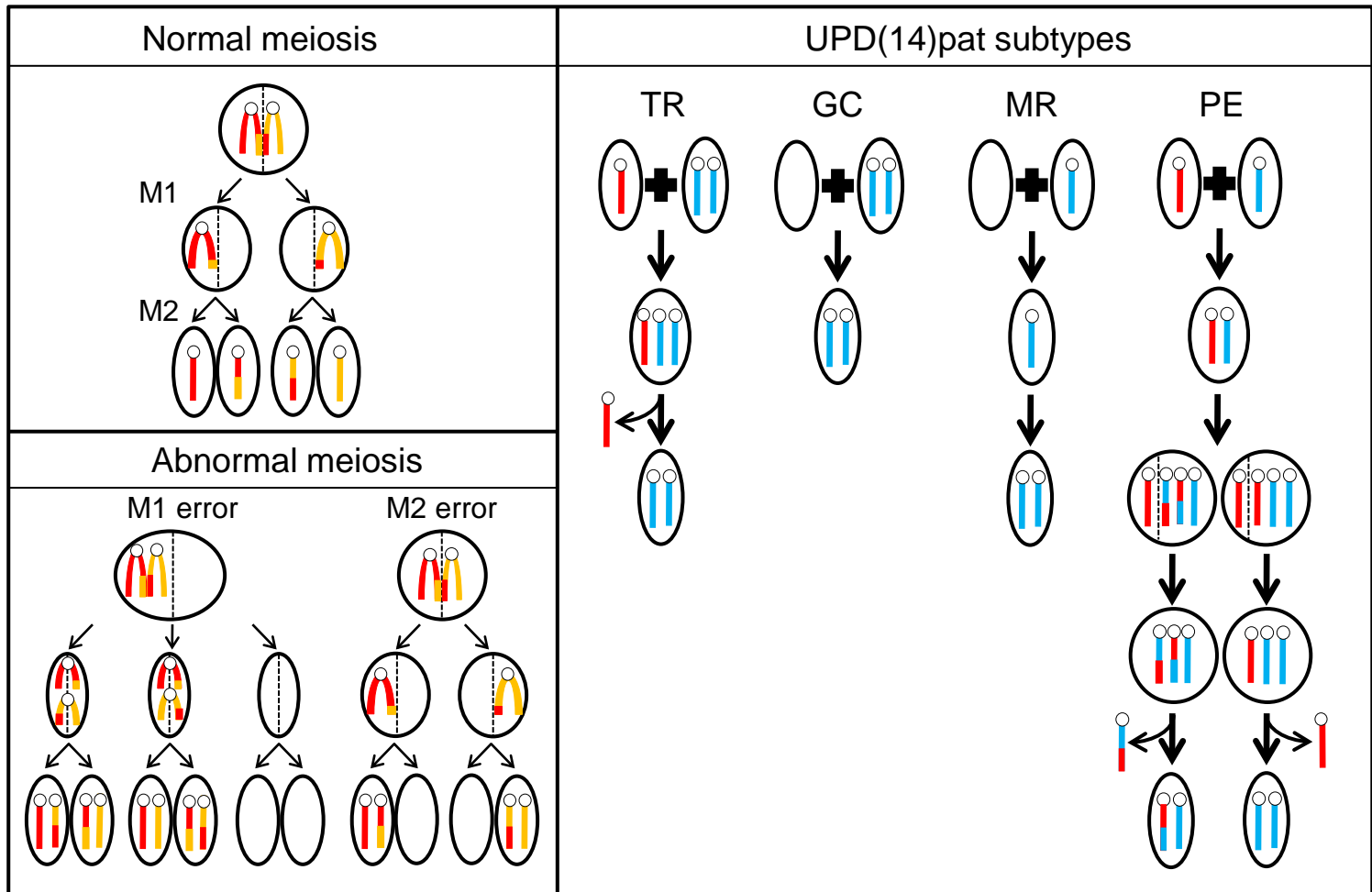
<sup>e</sup> Adopted from ref. 1 and 2.

Abbreviations. SD: standard deviation; WNR: within the normal range; ASD: atrial septal defect; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis.

In the column summarizing the clinical features of 20 patients with UPD(14)pat, the denominators indicate the number of patients examined for the presence or absence of each feature, and the numerators represent the number of patients assessed to be positive for that feature; thus, the differences between the denominators and the numerators denote the number of patients evaluated to be negative for that feature.

References

- Kagami M, Yamazawa K, Matsubara K, Matsuo N, Ogata T: Placentomegaly in paternal uniparental disomy for human chromosome 14. *Placenta* 2008; **29**: 760-761.
- Kagami M, Sekita Y, Nishimura G et al: Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. *Nat Genet* 2008; **40**: 237-242.

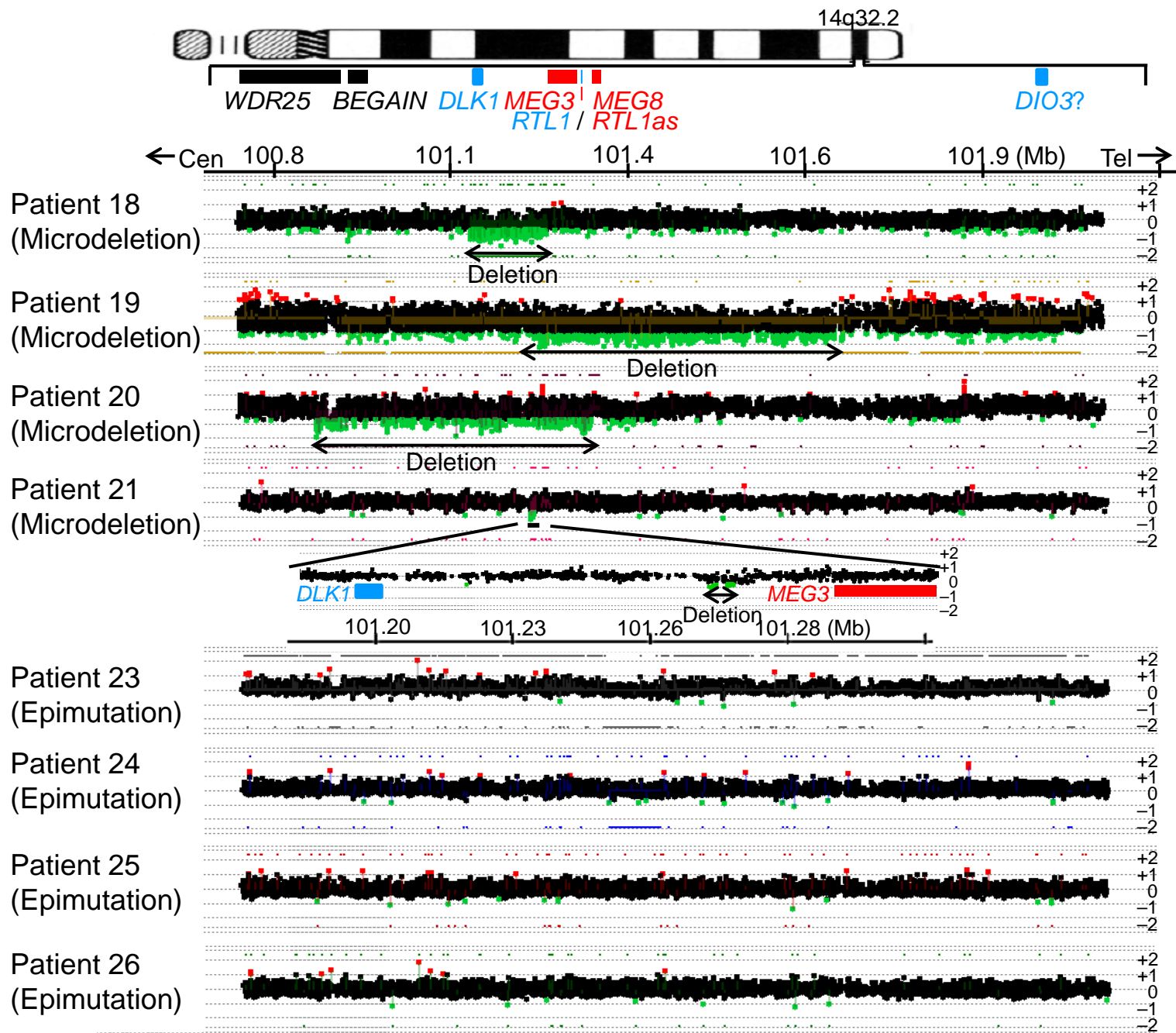


**Supplemental Figure S1.** Schematic representation of the normal and abnormal meiosis and the four subtypes for the generation of UPD(14)pat.

Normal meiosis: The homologous chromosomes shown in red and orange recombine at the prophase and undergo meiosis 1 (M1) and meiosis 2 (M2), to produce gametes with a haploid set of chromosomes.

Abnormal meiosis: When non-disjunction occurs at M1, this can produce nullisomic gametes and four types of disomic gametes. When non-disjunction occurs at M2, this can produce nullisomic gametes and two types of disomic gametes. Of note, disomic gametes generated by M1 and M2 non-disjunctions can be distinguished by the microsatellite data. Indeed, when the pericentromeric region is present in a heterodisomic and an isodisomic conditions, this indicates the generation of disomic gametes through M1 and M2 non-disjunctions, respectively. Here, when two recombinations take place, this can influence the status (isodisomy or heterodisomy) of the middle to distal region, but not that of the pericentromeric region. Thus, the status of the pericentromeric region is informative for the assessment of the timing of a non-disjunction. By contrast, it is impossible to discriminate between nullisomic gametes generated by M1 and M2 non-disjunctions,

UPD(14)pat subtypes: Paternally derived chromosomes are depicted in blue and maternally derived chromosomes in red. In trisomy rescue (TR), a maternally derived normal oocyte is fertilized with a disomic sperm and, subsequently, the maternally inherited chromosome is lost from a trisomic zygote. In gamete complementation (GC), a maternally derived nullisomic oocyte is fertilized with a disomic sperm. Note that the disomic sperms in TR and GC harbor a heterodisomic region(s), as shown in the schema of abnormal meiosis. In monosomy rescue (MR), a maternally derived nullisomic oocyte is fertilized with a normal sperm and, subsequently, the paternally inherited chromosome is replicated in a monosomic zygote. Thus, MR results in the formation of a full paternal isodisomy. In post-fertilization mitotic error (PE), a post-zygotic non-disjunction takes place with and without a recombination between non-sister chromatids, which is followed by loss of an excessive chromosome containing a maternally derived region. Thus, PE leads to the generation of a segmental and full isodisomy, respectively.

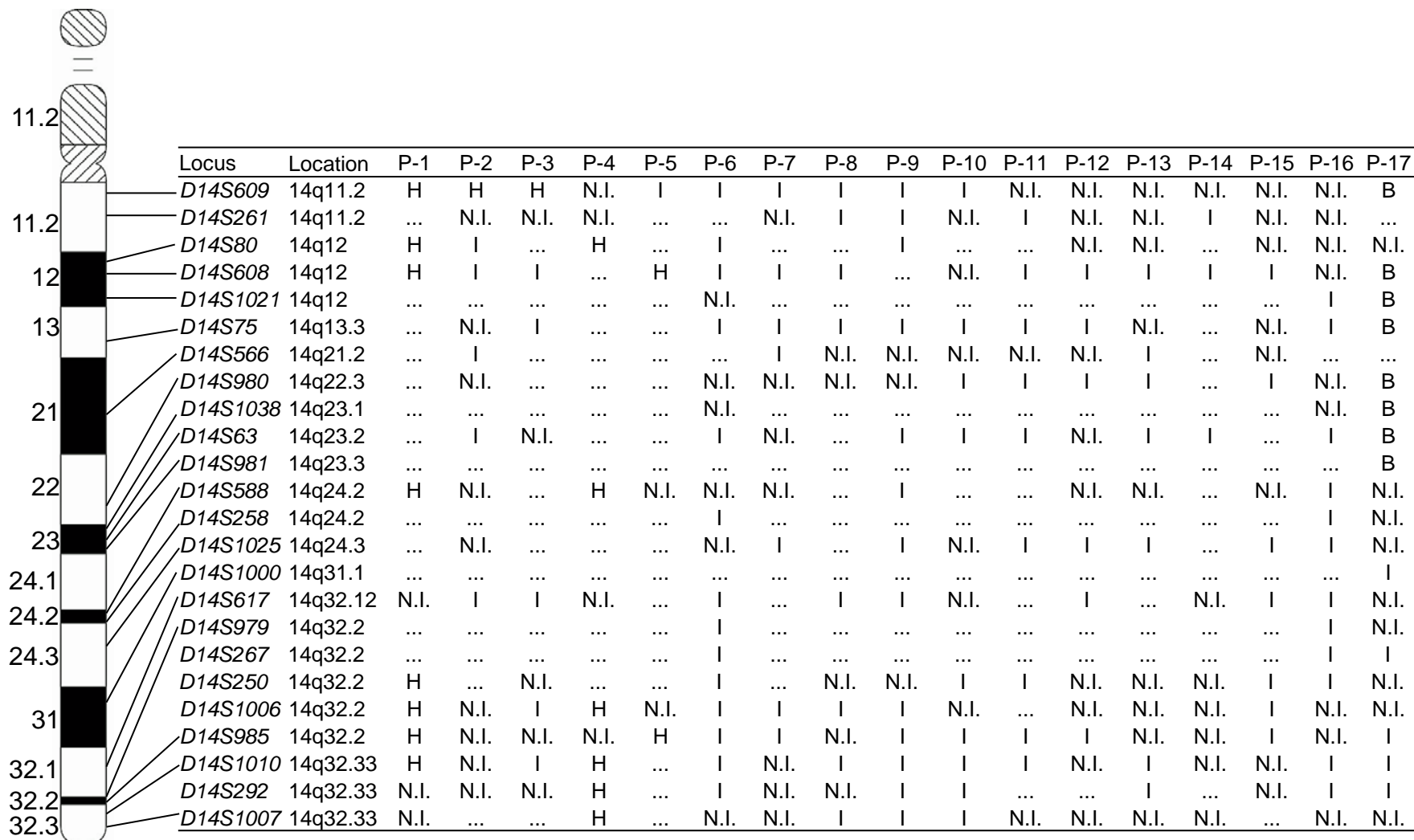


**Figure S2.** Oligonucleotide array-based comparative genomic hybridization (CGH) analysis in non-UPD(14)pat patients except for patient 22 without available DNA sample. This analysis was carried out using a custom-build oligo-microarray containing 12,600 probes for 14q32.2–q32.3 encompassing the imprinted region and ~10,000 reference probes for other chromosomal region (4x180K format, Design ID 032112) (Agilent Technologies, Palo Alto, CA). The procedure was as described in the manufacturer’s instructions. Physical map of the 14q32.2 imprinted region is shown on the top, together with the physical distance from the 14p telomere based on UCSC Genome Browser (<http://genome.ucsc.edu/cgi-bin/hgGateway>). *PEGs* are shown in blue, *MEGs* in red, and biparentally expressed genes in black. It remains to be clarified whether human *DIO3* is a *PEG*.<sup>1</sup> In CGH analysis, the black, the red, and the green dots denote signals indicative of the normal, the increased (>+0.5), and the decreased (<-1.0) copy numbers, respectively. Patients 18–21 have microdeletions of various sizes, whereas patients 23–26 have no discernible microdeletions.

#### References

1. Tsai CE, Lin SP, Ito M, Takagi N, Takada S, Ferguson-Smith AC: Genomic imprinting contributes to thyroid hormone metabolism in the mouse embryo. *Curr Biol* 2002; **12**: 1221-1226.





**Supplemental Figure S3.** Summary of microsatellite analysis of patients with UPD(14)pat. The numbers of patients correspond to those in Table 1. The ideogram of chromosome 14 is shown with the chromosomal locations of microsatellite loci examined (Ensembl Genome Browser; <http://www.ensembl.org>). I: Isodisomy; H: Heterodisomy; B: Biparental; and N.I.: not informative.