Acta Med. Nagasaki 43 : 19−25

Mechanisms for the Occurrence of Three Uniparental Disomies Associated with Abnormal Phenotypes

Osamu MIYOSHI

Department of Human Genetics, Nagasaki University School of Medicine, Nagasaki

Results of a molecular-genetic study on the mechanism of uniparental disomy (UPD) in three individuals are reported. Case 1 was a physically normal adult whose Rh blood-type showed mosaicism of two phenotypes, D+ (or D/D genotype) and D- (or d/d genotype), while his father and mother were a D/d heterozygote and a D/D homozygote respectively. Allele-typing of his peripheral blood leukocytes and buccal membrane cells using polymorphic DNA markers on chromosome 1 revealed both paternal and maternal alleles, but demonstrated paternal uniparental transmissions of alleles in the monoclonal B-lymphocytes and in hair-root cells from various body regions. The results indicate that he had two cell lines each with paternal UPD1 and maternal UPD1. Only a plausible mechanism for the mosaicism includes abnormal segregation at first mitosis, where both chromatids of each homologs 1 migrated together to the same direction, resulting in two daughter cells having D/D and d/d genotypes. This sort of cell division has hitherto been undescribed in man. Case 2 was a Silver-Russell syndrome patient with a mosaic 46, XX / 47, XX, +r (7) karyotype. Allele-typing with chromosome 7 markers revealed that she inherited maternal uniparental alleles at telomeric regions of the chromosome but biparental alleles at the centromeric region, the result indicating that the two normal chromosomes 7 were of maternal UPD and the ring chromosome 7 was of paternal origin. A likely mechanism for her UPD7 is "monosomy duplication", followed by somatic loss of the ring chromosome. The finding also indicates that the putative SRS locus can be ruled out from the centromeric region, 7p13-q11. Case 3 had intrauterine growth retardation and a 45, XY, i (14) karyotype. Allele-typing revealed maternal uniparental transmissions of alleles at both centromeric and telomeric regions of chromosome 14, but showed biparental alleles at other regions. The results indicate that the isochromosome was of maternal UPD and may have arisen through "gametic complementation" mechanism.

Address Correspondence:
Osamu Miyoshi, M.D., Department of Human Genetics, Nagasaki University School of Medicine, Sakamoto 1-12-4, Nagasaki 852-8523, Japan

Key words: uniparental disomy (UPD); allele-typing; genotyping; Rh-phenotypic mosaicism; Silver-Russell syndrome; intrauterine growth retardation; mechanism

Introduction

In 1980, Engel[1] first introduced a concept of uniparental disomy (UPD). Normally, each member of homologous chromosomes originates from each parent, whereas UPD is a phenomenon where both homologous chromosomes come from a single parent. UPD is subdivided into two classes: contribution of both homologs of a parent to a child is heterodisomy; and double transmission of one parental homolog to a child is isodisomy[1-3]. Recent development of molecular-genetic analysis with polymorphic DNA markers has made it possible to ascertain the origin and mechanism of UPD. Dinucleotide (CA) repeat polymorphisms are useful multiallelic markers for this purpose[4]. UPD is not extremely rare in man and has been observed for chromosomes 1, 2, 4, 6-11, 13-16, 20-22, and X, and the majority of persons with UPD for a particular chromosome manifested abnormal phenotypes[2-3]. One of the explanations of the parent-of-origin specific phenotype is genomic imprinting that is defined as parent-of-origin dependent differential expression of a gene, i.e., only one parental allele is expressed (active) and the other allele is imprinted (silent)[5]. When children inherit UPD chromosomes in which no active alleles exist, they may have abnormal phenotypes, such as growth retardation and/or congenital malformations. UPD may arise through either of the following mechanisms (Fig. 1)[1,3] : (a) fusion of a nullisomic gamete with a gamete disomic for the same chromosome (gametic complementation); (b) loss of one

member of trisomic chromosomes in a zygote at an early mitotic division (trisomy rescue); or (c) duplication of a monosomic chromosome in a zygote (monosomy duplication). "Gametic complementation" may result in partial (or segmental) UPD, depending on meiotic cross-overs, and "trisomy rescue" may remake a normal zygote in 2/3 of cases and complete or segmental UPD in 1/3; and "monosomy duplication" leads to complete isodisomy. All of these events can save life from harmful effects of the abnormal karyotype. Postzygotic events are also possible for the latter two mechanisms, resulting in somatic mosaicism. This paper deals with a molecular-genetic study on the mechanisms of three different UPD chromosomes in three individuals with unusual phenotypes.

Materials and Methods

Case 1

The proband was a 36-year-old Japanese man who visited West Tokyo Red-Cross Blood Center for a blood-donor volunteer in 1985. He was physically and mentally normal, and his healthy parents were not consanguineous. Two elder siblings were also healthy (Fig. 1). When the proband's blood types were determined, the Rh phenotype was found to be unusual. Flow cytometric analysis for RhD antigen density profile demonstrated that he had two cell lines each with the Rh phenotype D+ (or genotype D/D) and with D- (or genotype d/d), respectively (Fig. 1), suggesting a chimera for the Rh blood type. Family analysis revealed that his father was a D/d heterozygote, the mother a D/D homozygote, an elder sister a D/d heterozygote, and an elder brother a D/D homozygote. Cytogenetic studies on 100 metaphase cells from cultured lymphocytes of the proband revealed a mosaic 46, XY [71] / 46, XY, 1qh+, 1qh+ [29] karyotype, and

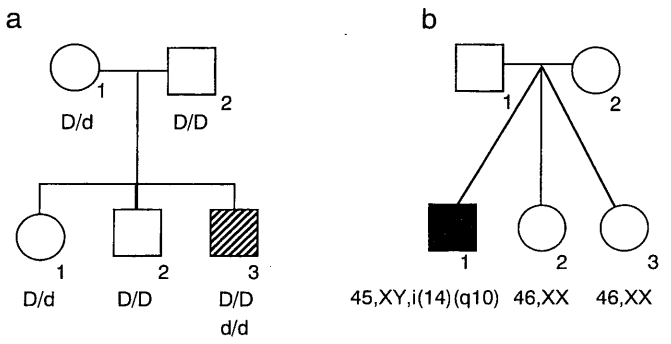

Fig 1. Family trees of Case 1 (a, II-3) and Case 2 (b, II-1). Letters below individual symbols implicate genotypes of the RhD gene (a) and karyotypes (b).

his parents had 46, XY, 1qh+ and 46, XX, 1qh+ karyotypes, respectively. The B-cell of the proband was transformed with Epstein-Barr virus (EBV) to lymphoblastoid cell lines and then they were cloned into monoclonal cell lines. Monoclonality of these cells was confirmed with the 1qh+ heteromorphism.

Case 2

The patient was a 20-month-old Japanese girl, who was born at 34 gestational weeks by caesarean section because of premature rupture of the membrane, intrauterine growth retardation (IUGR) and fetal distress, with a birthweight of 1,020 g (-3.0 SD) and length of 36 cm (-4.4 SD). Physical examination revealed the following abnormalities: triangular face, hypertelorism, micrognathia, clinodactyly of the fifth fingers, asymmetry of the trunk and limbs, patent ductus arteriosus (PDA), and right recurrent nerve paralysis. Re-examination at age 18 months revealed marked growth and developmental retardation with a length of 68.5 cm (-4.7 SD), weight of 5,900 g (-3.5 SD), OFC of 44.5 cm (-1.4 SD) and chest circumference of 39.0 cm (-3.7 SD). The muscle was hypotrophic and bone mineral density showed a low level for her age. These clinical manifestations led to the diagnosis of Silver-Russell syndrome. Chromosome analysis on 45 metaphase cells from her lymphocytes revealed a mosaic 46, XX [30]/47, XX,+r(?)[15] karyotype. Whole chromosome painting using a chromosome 7-specific probe pool (WCP probe, VYSIS, UK) demonstrated that 22 (73%) of 30 cells analyzed had two normal chromosomes 7, and 8 (27%) a ring chromosome 7 in addition to the normal homologs 7. Thus, the karyotype of the proband was finally identified as mos 46, XX/47, XX,+r (7).

Case 3

The patient, a 9-month-old Japanese boy, was one of triplets born to unrelated, healthy parents (Fig. 2). At 29 gestational weeks, the patient was delivered by caesarean section with a weight of 634 g (small for dates) and length of 31 cm. Two other members of the triplets, two girls, were healthy and both weighed 1,110 g, being appropriate for dates. Physical examination revealed the following abnormalities: dolichocephaly with frontal bossing, low-set ears, short neck, small hands and feet, overlapping fingers and PDA. A skeletal survey showed no abnormality. Re-examination at 259 days revealed growth and developmental retardation with a length of 59.3 cm, weight of 4,210 g and OFC of 41.0 cm. Chromosome analysis on his

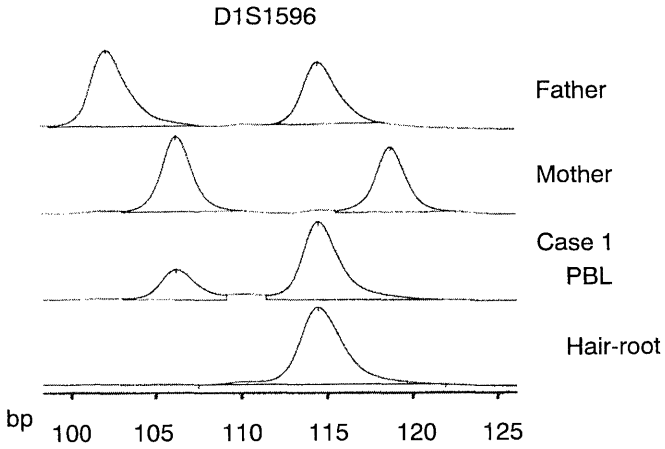

Fig 2. Electrophoretic patterns of CA-repeat polymorphic alleles at the D1S1596 locus in the family of Case 1.

lymphocytes revealed a 45, XY, i (14) (q10) karyotype. Karyotypes of the other two triplet-members and the parents were all normal. To know the zygosity of the triplets, quinacrine fluorescence Q (QFQ)-banded chromosomal heteromorphisms on chromosomes 3 and 4 and acrocentric chromosomes were analyzed as described previously[6]. The result demonstrated that the triplets were trizygotic, because the infants had different karyotypes or different QFQ polymorphic patterns (data not shown).

CA-repeat polymorphic marker analysis

Since UPD for chromosomes 1, 7, and 14 was suspected in Cases 1, 2, and 3, respectively, genotypes of the probands and their respective parents were analyzed as follows: Parent-child transmission modes of alleles were traced using dinucleotide (CA)- and/or tetranucleotide-repeat polymorphic markers which were located on respective chromosomes (Table 1), according to published genetic maps[4,7-8]. Markers on other chromosomes were also used as controls to confirm paternity as well as biparental transmission. Sets of oligonucleotides were synthesized for marker loci according to their base sequences[4]; one of each pair was labeled with fluorescence dye (Cy-5) and the other of the pair unlabeled, and used them as forward and reverse primers for polymerase chain reaction (PCR)-based DNA amplification. Genomic DNA was extracted with DNA-extraction kit (WAKO Chemical, Tokyo, Japan) from peripheral blood leukocytes (PBL) of Cases 1, 2 and 3, and of their parents. In addition, in Case 1, five monoclonal EBV-transformed cell lines, a total of 50 pieces of hairs and/or hair-root cells from the scalp, elbow, axillary and shin, and buccal membrane cells were used as the source of genomic DNA. PCR was cycled 30 times under the following conditions: denaturation at 95°C, annealing at 55°C and extension at 72°C, each for 30 sec in a mixture containing 50mM KCl, 20mM Tris-HCl (pH 8.5), 1.5mM $MgCl_2$, 200mM each of dNTP and 0.5U AmpliTaq (Perkin Elmer, USA). PCR products were electrophoresed on automated sequencer (ALFexpress™, Pharmacia Biotech, Sweden), electrophoretic patterns were analyzed with computer software, Fragment Manager™ (Pharmacia Biotech), and allele-types of the family members were finally determined, as described elsewhere[9-10]. Informative marker locus was defined when parental alleles are differentiated from those of their spouses.

Results

Genotype analysis in Case 1 revealed that 24 polymorphic marker loci on chromosome 1 were informative (Table 1). All these markers showed heterozygous patterns in PBL and buccal membrane cells, while only a paternally derived allele was detected at these loci in all of the 5 monoclonal B-cell lines and 50 pieces of hair-root cells from various body regions (Table 1). The results suggested biparental inheritance of the alleles in PBL and buccal membrane cells, but indicated paternal uniparental isodisomy (UPD) in the monoclonal B-lymphocytes and the hair-root cells. Transmission patterns of alleles from other chromosomes were consistent with biparental inheritance and confirmed the paternity.

Likewise, genotyping of PBL in Case 2 revealed only a maternal allele at 16 informative loci from telomeric regions of chromosome 7 (Table 1). On the other hand, she inherited biparental alleles at 4 centromeric loci (*D7S2552, D7S499, D7S494* and *D7S2503*), encompassing a 7p13-q11 region. The results suggested that two normal-looking homologues 7 were maternal isodisomy, and the ring chromosome 7 were of paternal origin. Biparental inheritance and paternity were confirmed at two loci on chromosomes 2 and 6.

In Case 3, 15 polymorphic loci on the chromosome 14 were informative. At all these loci, the patient lacked any of the paternal alleles but inherited one or two maternal alleles (Table 1). Based on the fact that he had an isochromosome 14, i.e., mirror-image of the chromosome, he must have two copies of one-maternal-allele at 4 centromeric and at 5 telomeric loci. On the other hand, he inherited both of the maternal alleles at the remaining 4 intermediate loci (*D14S1046, D14S277, D14S77* and *D14S999*). The results indicated that both centromeric and telomeric

Table 1. Polymorphic allele types at informative loci in Cases 1, 2 and 3 and their parents

Case 1						Case 2					Case 3				
		Allele type						Allele type					Allele type		
Marker	Location	P	M	C		Marker	Location				Marker	Location			
				PBL/B	H/MB			P	M	C			P	M	C
D1S468	1p36-pter	1,3	1,2	2,3	3	D7S2563	7pter-p22	1	2,3	2	D14S261	14q11	3	2,1	2
D1S228	1p36	1,2	1	1,2	2	D7S481	7p22-p21	2	1,2	1	D14S990	14q11.1-q12	2,4	1,3	1
D1S2734	1p35-36	1,3	1,2	1,3	3	D7S503	7p21-p15	3	1,2	1	D14S1032	14q11.1-q13	1,2	2,3	3
D1S513	1p35-36	2	1,3	2,3	2	D7S526	7p15-p14	1,3	2,3	2	D14S1040	14q12-q13	1,2	1,3	3
D1S441	1p34-35	2,3	1,3	1,2	2	D7S2497	7p13	2	1	1	D14S1048	14q12-q13	2,3	1,4	1
D1S1596*	1p32-34	2,4	1,3	2,3	2	D7S2422	7p13-q11	1,2	1,3	3	D14S1057	14q13-q21	2,3	1	1
D1S2770	1p32-34	1,3	2,3	1,2	1	D7S506	7p13-q11	2	1,2	1	D14S1046	14q23	1,2	3,4	3,4
D1S209	1p32-p33	3,4	1,2	2,4	4	D7S2552	7p13-q11	3	1,2	2,3	D14S277	14q23-q24.3	1,2	3,4	3,4
D1S219	1p32	1,2	1	1,2	2	D7S499	7p13-q11	2,3	1,4	1,2	D14S77	14q24	2,3	1,4	1,4
D1S216	1p31-p32	1,2	1	1,2	2	D7S494	7p13-q11	2,4	1,3	1,4	D14S999	14q24.3-q31	2,4	1,3	1,3
D1S430	1p31-p32	1,2	3	1,3	1	D7S2503	7p13-q11	1	2,3	1,2	D14S1058	14q24.3	2	1	1
D1S248	1p13-p21	1,3	2	1,2	1	D7S639	7q11	1	2	2	D14S995	14q24.3-q31	2,4	1,3	3
D1S502	1p13	1,3	2	2,3	3	D7S657	7q21-q22	2	1,3	1	D14S977	14q31	2,3	1	1
D1S534*	cen-1p13	1,3	1,2	1,3	3	D7S515	7q22-q31	1,3	2,3	2	D14S267	14q32	2,3	1,2	1
D1S2346	cen-1p13	2,4	1,3	3,4	4	D7S635	7q31-q32	1,2	3	3	D14S1010	14q32	2,4	1,3	1
D1S2635	cen	2	1,3	1,2	2	D7S530	7q31-q32	3	1,2	1					
D1S2844	cen-1q22	3	1,2	1,3	3	D7S512	7q32	1	2	2					
D1S2681	cen-1q22	1,2	1	1,2	2	D7S2513	7q33-q34	2,4	1,3	1					
D1S431	1q22-q23	1,3	2	2,3	3	D7S2426	7q35	1,3	2,4	4					
D1S2757	1q31	2,3	1,4	3,4	3	D7S550	7q36	1,2	1,3	3					
D1S2622	1q31	2,3	1,4	2,4	2										
D1S2872	1q31-q32	1	2	1,2	1										
D1S2880	1q32-q41	1,2	2	1,2	1										
D1S2800	1q42-q43	3,4	1,2	2,4	4										
D1S1609*	1q43-qter	1,2	1	1,2	2										
D1S2811	1q44	2,3	1,4	1,3	3										
D2S114	2p12	2,4	1,3	1,2	1,2	D2S156	2q23-q24	2,4	1,3	1,4	D10S196	10q11.2-q2	2, 4	1, 3	1, 4
D3S3556	3q12	1,3	2,3	1,2	1,2	D6S261	6q21-q23.3	1,3	2,4	3,4	D13S1253	13q13-q14	1, 4	2, 3	3, 4
D4S2974	cen-4p14	1,2	1,3	2,3	2,3						D18S57	18q12	2, 3	1	1, 3
D5S398	5q11-q12	2,3	1	1,3	1,3										
D6S1681	6q11	2	1	1,2	1,2										
D7S499	7p13-q11	1,4	2,3	1,2	1,2										
D8S507	cen-8p11	2	1,3	1,2	1,2										
D9S1799	cen-9q13	2,3	1	1,2	1,2										
D10S1661	10p12-p14	1,3	2	2,3	2,3										
D11S905	11p12-p13	1,3	2	1,2	1,2										
D12S1701	cen-12q13	2,3	1	1,2	1,2										
D13S1253	13q13-q14	2,3	1,4	1,2	1,2										
D14S990	14q12	1,4	2,3	1,2	1,2										
D15S1002	15q13-q14	3	1,2	2,3	2,3										
D16S3137	16q12-q13	1,3	2	2,3	2,3										
D17S1800	cen-17p11	3	1,2	2,3	2,3										
D18S1153	18p11	1	2,3	1,2	1,2										
D19S894	19p13.3	2,3	1,3	1,2	1,2										
D20S860	20p11	2,3	1,3	1,2	1,2										
D21S1895	21q22.1	2,4	1,3	3,4	3,4										
D22S281	22cen	1,3	2	2,3	2,3										

P, M, C, PBL, B, H, MB implicate father, mother, child, peripheral blood leukocytes, buccal membrane cells, hair-root cells, and monoclonal B-lymphocytes, respectively.
Markers with asterisks are tetra-nucleotide repeats.

regions of chromosome 14 were of isodisomy, whereas the other region is heterodisomic (segmental UPD). Biparental inheritance and paternity were confirmed with markers from chromosomes 10, 13 and 18.

Discussion

Case 1 was coincidentally found by flow cytometric analysis for RhD antigen to have unusual Rh

phenotypes composed of D+ and D- bearing cells, i.e., a mosaic for the Rh phenotype with the D/D genotype and the d/d genotype (Fig. 1). Since his father was a D/d heterozygote and mother a D/D homozygote, and the RhD gene is located at 1p36-p34, it was assumed that the d/d cells in Case 1 reflect UPD for chromosome 1 (UPD1) that was derived from his father. Chromosomal heteromorphism, 1qh+, that was observed in one cell line supported the presumption. Allele-typing of the proband's PBL with polymorphic loci on the chromosome 1 revealed biparental transmissions of alleles. This transmission mode may be due to the mosaicism of this tissue. Integral analysis of allele-curves (electrophoretic patterns, Fig. 2) revealed that the ratio of the paternal allele to the maternal allele was 4:1, probably reflecting their proportions in PBL (data not shown). On the other hand, analysis of the same alleles in the monoclonal B-cells and the hair-root cells from various skin areas demonstrated the paternal uniparental inheritance. Since each hair and /or its root-cells is derived from a single cell, this tissue may have represented monoclonality with paternal UPD1. In addition, the finding that all the 50 hair cells examined showed the same transmission pattern may indicate that the skin tissue originates from one or a few ancestral cells. In contrast, another ectodermal tissue, the buccal membrane cell, was composed of two different cells, as was PBL, suggesting that these tissues were derived from at least two ancestral cells. The phenomenon that one individual has two cell lines each with maternal or paternal UPD1 seems very unusual and has not been known in the literature. Only a following mechanism is plausible to explain the finding: the zygote may have resulted from the normal fertilization of a "D" allele-bearing ovum by a "d" allele-bearing sperm, followed by abnormal segregation at the first cleavage division, where both chromatids of a homologous chromosome 1 may have migrated together to the same direction with opposite-directed migration of chromatids of the counterpart chromosome, resulting in two daughter cells having D/D and d/d genotypes (Fig. 3). The hair-root cells belong to the same "d/d" cell lineage, while PBL and buccal membrane cells are the mixture of "D/D" and "d/d" cells. The abnormal cell division at first mitosis, a similar manner to the first meiotic division, has hitherto been undescribed in man. Two previously reported individuals with UPD1 had only one cell line with either maternal or paternal UPD[11-12]. However, the author was recently informed about another individual who is a mosaic for the Rh phenotype as was Case 1, indicating that such segregation may not be very rare. Further analysis is needed in this second case.

Allele-typing of Case 2 detected only one maternal allele at 16 telomeric loci on the chromosome 7, but revealed biparental alleles at 4 centromeric loci (Table 1). Since each of her cell lines, 46, XX and 47,XX,+r(7), contains two normal chromosomes 7, these transmission patterns indicated that she inherited

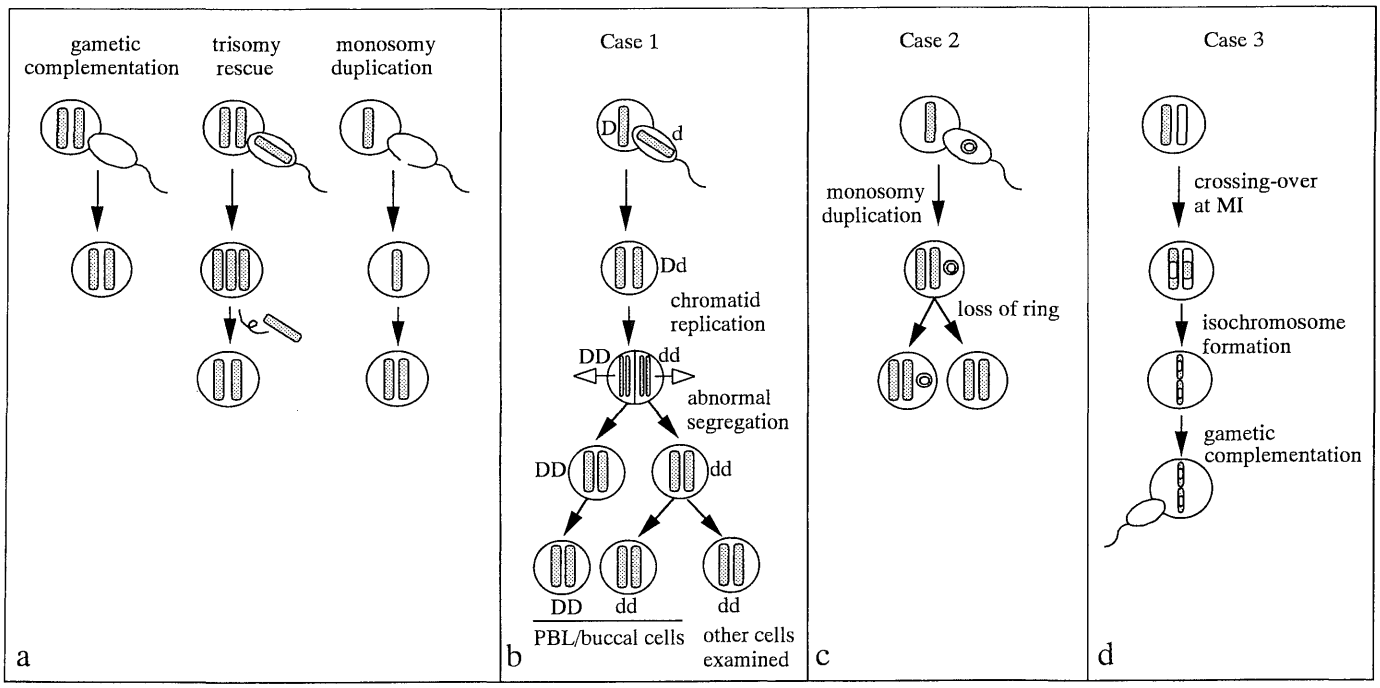

Fig 3. Possible mechanisms for UPD in man (a) and those for UPD in Case 1 (b), Case 2 (c) and Case 3 (d).

one maternal-allele in duplicate at the telomeric loci, and one copy of paternal-allele in addition to two copies of maternal-allele at the centromeric loci. This indicates that the two normal chromosomes 7 were of maternal isodisomy (UPD), and the ring chromosome 7 was of paternal origin. There was no evidence of recombinations on chromosome 7 in the maternal meiosis. From these findings, "monosomy duplication" is the most likely mechanism for her UPD7 (Fig. 3), although monosomy was restricted to distal regions of chromosome 7. The patient may have arisen as a 46,XX,r(7) zygote (partial monosomy for most part of chromosome 7), where the normal chromosome 7 and the r(7) were of maternal and paternal origin, respectively. Then, duplication of the maternally-derived chromosome 7 may have occurred at an early postzygotic cell division, followed by death of the partially monosomic cells and survival of the UPD cells because of resistibility against cell selection[13-15], resulting in a 47, XX, upd (7),+r (7) karyotype. Finally, the ring chromosome 7 may have been lost in a subset of cells during somatic cell divisions due to ring chromosome fragility[16]. Maternal UPD7 has been identified in 17 individuals including our patient[17-24]. Of the 17 individuals, 13 had a common phenotype reminiscent of Silver-Russell syndrome (SRS). It has been suggested that there is at least one maternally imprinted gene on chromosome 7 that controls intrauterine and postnatal growth[17, 20, 24]. If the putative SRS gene is maternally imprinted (paternally expressed), it can be ruled out from the centromeric region, 7p13-q11, that corresponds to the retaining extent of the paternally-derived ring chromosome in Case 2.

UPD with an isochromosome without its normal chromosome member, as in Case 3, can arise through either of the 3 different mechanisms described above[25]. Allele-typing of Case 2 demonstrated maternal isodisomy for the centromeric and telomeric regions and heterodisomy for the middle region of chromosome 14 (Table 1). This indicates that meiotic recombinations had occurred between the maternal homologs 14, and thus prefers "gametic complementation" as the mechanism (Fig. 3). Non-mosaicism in Case 3 denied any postzygotic events. Maternal UPD for chromosome 14 has been identified in 12 individuals including Case 3[26-36]. All but two such individuals had a common phenotype, such as growth and developmental retardation, neonatal hypotonia, small hands and feet, and precocious puberty. On the other hand, paternal UPD for chromosome 14 is associated with different manifestations[37-38]. Thus, the phenotype characteristic for the maternal UPD is most likely due to lack of paternally-derived allele(s) through genomic imprinting mechanism.

Acknowledgements

I express my gratitude to Professor Norio Niikawa for his helpful comments and suggestions.

References

1) Engel E: A new genetic concept: Uniparental disomy and its potential effect, isodisomy. Am J Med Genet 6: 137-143, 1980
2) Ledbetter DH, Engel E: Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. Hum Mol Genet 4: 1757-1764, 1995
3) Spence JE, Perciaccanate RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, O'Brien WE, Beaudet AL: Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 42: 217-226, 1988
4) Dib C, Faur S, Fizames C, Samson D, Drouot N, Vignal N, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J: A comprehensive genetic map of the human genome based on 5,264 microsatellites. "The Généthon Human Genetic Linkage Map". Nature 380: 152-154, 1996
5) Niikawa N: Genomic imprinting and its relevance to genetic diseases. Jpn J Hum Genet 41: 351-362, 1996
6) Abe K, Harada N, Itoh T, Hirakawa O, Niikawa N: Trisomy 13/trisomy 18 mosaicism in an infant. Clin Genet 50: 300-303, 1996
7) The Cooperative Human Linkage Center, CHLC: Integrated Maps: http://www.chlc.org
8) Bruns GA, Matise TC, Weith A: Report of the committee on the genetic constitution of chromosome 1. In: Cuticchia AJ, Chipperfield MA, Foster PA, eds. Human Gene Mapping 1995. Baltimore: Johns Hopkins Univ Press, 165-233, 1995
9) Miyoshi O, Hayashi S, Fujimoto M, Tomita H, Sohda M, Niikawa N: Maternal uniparental disomy for chromosome 14 in a boy with intrauterine growth retardation. J Hum Genet 43, 138-142, 1998
10) Miyoshi O, Kondoh T, Taneda H, Otsuka K, Matsumoto T, Niikawa N: 47,XX,upd(7)mat,+r(7)pat/46,XX,upd(7)mat mosaicism in a girl with Silver-Russell syndrome (SRS): Possible exclusion of the putative SRS gene from a 7p13-q11 region. J Med Genet (in press)
11) Pulkkinen L, Bullrich F, Czarnecki P, Weiss L, Uitto J: Maternal uniparental disomy of chromosome 1 with reduction to homozygosity of the LAMB3 locus in a patient with Herlitz junctional epidermolysis bullosa. Am J Hum Genet 61: 611-619, 1997
12) Gelb BD, Willner JP, Dunn TM, Kardon NB, Verloes A, Poncin J, Desnick RJ: Paternal uniparental disomy for chromosome 1 revealed by molecular analysis of a patient with pycnodysostosis. Am J Hum Genet 62: 848-854, 1998
13) Petersen MB, Bartsch O, Adelsberger PA, Mikkelsen M, Schwinger E, Antonarakis SE: Uniparental isodisomy due to duplication of chromosome 21 occurring in somatic cells monosomic for chromosome 21. Genomics 13: 269-274, 1992
14) Bartsch O, Petersen MB, Stuhlmann I, Mau G, Frantzen M, Schwinger E, Antonarakis SE, Mikkelsen: "Compensatory" uniparental disomy of chromosome 21 in two cases. J Med Genet 31: 534-540, 1994
15) Niikawa N, Kajii T : The origin of mosaic Down syndrome: Four cases with chromosomal markers. Am J Hum Genet 36: 123-130, 1984
16) Kosztolnyi G : Does "ring syndrome" exist? Analysis of 207 case reports on patients with a ring autosome. Hum Genet 75: 174-179, 1987
17) Voss R, Ben-Simon E, Avital A, Godfrey S, Zlotogora J, Dagan J, Tikochinski Y, Hillel J: Isodisomy of chromosome 7 in a patient with cystic fibrosis. Could uniparental disomy be common in

humans? Am J Hum Genet 45: 373-380, 1989
18) Shuman C, Weksberg R, Nedelcu R, Northey A, Scherer S: Chromosome 7 uniparental disomy in Silver-Russell syndrome. Am J Hum Genet 59: A648, 1996
19) Spotila LD, Sereda L, Prockop DJ : Partial isodisomy for maternal chromosome 7 and short stature in an individual with a mutation at the COLIA2 locus. Am J Hum Genet 51: 396-1405, 1992
20) Kotzot D, Schmitt S, Bernasconi F, Robinson WP, Lurie IW, Ilyina H, Méhes K, Hamel BCJ, Otten BJ, Hergersberg M, Werder E, Schoenle E and Schinzel A: Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet 4: 583-587, 1995
21) Langlois S, Yong SL, Wilson RD, Kwong LC, Kalousek DK: Prenatal and postnatal growth failure associated with maternal heterodisomy for chromosome 7. J Med Genet 32: 871-875, 1995
22) Eggermann T, Wollmann HA, Kuner R, Eggermann K, Enders H, Kaiser P, Ranke MB: Molecular studies in 37 Silver-Russell syndrome patients: Frequency and etiology of uniparental disomy. Hum Genet 100: 415-419, 1997
23) Preece MA, Price SM, Davies V, Clough L, Stanier P, Trembath RC, Moore GE: Maternal uniparental disomy 7 in Silver-Russell syndrome. J Med Genet 34: 6-9, 1997
24) Cuisset L, LeStunff C, Dupont JM, Vasseur C, Cartigny M, Despert F, Delpech M, Bougnere P, Jeanpierre M: PEG1 expression in maternal uniparental disomy 7. Ann Génét 40: 211-215, 1997
25) Robinson WP, Bernasconi F, Basaran S, Yuksel-Apak M, Neri G, Serville F, Balicek P, Haluza R, Farah LMS, Schinzel AA: A somatic origin of homologous Robertsonian translocations and isochromosomes. Am J Hum Genet 54: 290-302, 1994
26) Temple IK, Cockwell A, Hassold T, Pettay D, Jacobs P: Maternal uniparental disomy for chromosome 14. J Med Genet 28: 511-514, 1991
27) Pentao L, Lewis RA, Ledbetter DH, Patel PI, Lupski JR: Maternal uniparental isodisomy of chromosome 14: Association with autosomal recessive rod monochromasy. Am J Hum Genet 50: 690-699, 1992
28) Antonarakis SE, Blouin JL, Maher Joseph, Avramopoulos D, Thomas G, Talbot CCJr: Maternal uniparental disomy for human chromosome 14, due to loss of a chromosome 14 from somatic cells with t(13;14) trisomy 14. Am J Hum Genet 52: 1145-1152, 1993
29) Healey S, Powell F, Battersby M, Chenevix-Trench G, McGill J: Distinct phenotype in maternal uniparental disomy of chromosome 14. Am J Med Genet 51: 147-149, 1994
30) Morichon-Delvallez N, Segues B, Pinson MP, Brub D, Dommergues M, Aubry MC, Cessot F, Lyonnet S, Munnich A, Vekemans M: Maternal uniparental disomy for chromosome 14 by secondary nondisjunction of an initial trisomy. Am J Hum Genet 55: A2224, 1994
31) Sirchia SM, DeAdnreis C, Pariani S, Grimoldi MG, Molinari A, Buscaglia M, Simoni G: Chromosome 14 maternal uniparental disomy in the euploid cell line of a fetus with mosaic 46,XX/47,XX,+14 karyotype. Hum Genet 94: 355-358, 1994
32) Papenhausen PR, Mueller OT, Johnson VP, Sutcliffe M, Diamond TM, Kousseff BG: Uniparental disomy of chromosome 14 in two cases: An abnormal child and a normal adult. Am J Med Genet 59: 271-275, 1995
33) Tomkins DJ, Roux AF, Waye J, Freeman VCP, Cox DW, Whelan DT: Maternal uniparental isodisomy of human chromosome 14 associated with a paternal t(13q14q) and precocious puberty. Eur J Hum Genet 4: 153-159, 1994
34) Coviello DA, Panucci E, Mantero MM, Perfumo C, Guelfi M, Borronco C, Dagna-Bricarelli F: Maternal uniparental disomy for chromosome 14. Am J Hum Genet 57: 111A, 1995
35) Splitt MP, Goodship JA: Another case of maternal uniparental disomy chromosome 14 syndrome. Am J Med Genet 72: 239-240, 1997
36) Wang JC, Passage MB, Yen PH, Shapiro LJ, Mohandas TK: Uniparental heterodisomy for chromosome 14 in a phenotypically abnormal familial balanced 13/14 Robertsonian translocation carrier. Am J Hum Genet 48: 1069-1074, 1991
37) Walter CA, Shaffer LG, Kaye CI, Huff RW, Ghidoni PD, McCaskill C, McFarland MB, Moore CM: Short limb dwarfism and hypertrophic cardiomyopathy in a patient with paternal isodisomy 14: 45,XY,idic(14)(p11). Am J Med Genet 65: 259-265, 1996
38) Cotter PD, Kaffe S, McCurdy LD, Jhaveri M, Willner JP, Hirschhorn K: Paternal uniparental disomy for chromosome 14 A case report and review. Am J Med Genet 70 74-79, 1997