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Brief Clinical Report

Two Cases of Mosaic RhD Blood-Group Phenotypes and Paternal Isodisomy for Chromosome 1

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We encountered a 22-year-old man (case 1) and a 23-year-old woman (case 2), both unrelated and healthy. They were mosaic for the Rh blood group phenotype: one erythrocyte population was D-positive and the other was D-negative. Flow cytometric analysis of density profile of RhD antigen in their erythrocytes, and cytogenetic analysis including in situ hybridization using an *RHD*/*RHCE*-containing PAC clone, excluded a deletion of the *RHD*/*RHCE* gene complex, but suggested the presence of cells with uniparental disomy for chromosome 1 (UPD1). Microsatellite marker analysis was performed in both probands and their family members. In case 1, the analysis with markers spanning the chromosome 1 revealed both maternal and paternal alleles in his peripheral blood leukocytes (PBL), Epstein-Barr virus-transformed lymphoblastoid cells (EBL), and buccal mucosal cells. However, only paternal alleles were detected in all of 50 individual pieces of his hair or hair-roots and all of five monoclonal cell lines cloned from his established EBL. There was no direct evidence of heterozygous, biparental alleles in these two tissues. The presence of maternal isodisomy 1 was not absolutely ruled out in other tissues examined in case 1. Similar results were obtained in case 2, showing biparental, disomic patterns in her PBL and in 15 of 20 pieces of her hair roots, and showing monoallelic patterns in the remaining five pieces of hair roots. Analysis with markers for other autosomes confirmed their biparental inheritance. These findings indicated that both cases had at least two cell populations, one population having paternal UPD1 (isodisomy 1), and another heterozygous, biparental disomy 1. We emphasize that isodisomy for chromosome 1 is not infrequent and may cause unusual RhD phenotype, as seen in cases we described.

KEY WORDS: isodisomy for chromosome 1; UPD; Rh blood group; microsatellite markers; hair root cells

INTRODUCTION

Uniparental disomy (UPD) is a genetic phenomenon in which a pair of homologous chromosomes in a disomic individual is derived from one parent [Engel, 1980; Ledbetter and Engel, 1995]. UPD originating in both members of homologous chromosomes of a parent is defined as uniparental heterodisomy, whereas

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UPD coming from one chromosome in duplicate of a parent is uniparental isodisomy. UPD arises either by (1) fertilization of a nullisomic gamete with a gamete disomic for the same chromosome (gametic complementation), (2) loss of one member of trisomic chromosomes in a zygote (trisomy rescue), or (3) by duplication of a monosomic chromosome in a zygote (monosomy duplication) [Spence et al., 1988; Ledbetter and Engel, 1995]. The first two mechanisms may lead to either heterodisomy or isodisomy, and the last generally results in isodisomy. Somatic occurrence of events results in mosaic UPD, especially in an event (3) that, when occurring in a somatic cell, leads to a cell line with complete isodisomy. UPD may lead to a recessive disorder through reduction to homozygosity, may be associated with lack of or over-expression of an active gene through genomic imprinting, or occur without apparent phenotypic consequences. UPD in humans has been observed in all but chromosomes 3, 5, 12, 18, and 19 [Ledbetter and Engel, 1995; Benlian et al., 1996; Gelb et al., 1998]. There have been seven individuals reported with UPD for chromosome 1 (UPD1): those with maternal heterodisomy [Pulkkinen et al., 1997; Field et al., 1998], paternal heterodisomy [Gelb et al., 1998], maternal isodisomy [Dufourcq-Lagelouse et al., 1999], complete paternal isodisomy [Miura et al., 2000; Takizawa et al., 2000], and with paternal isodisomy for 1p/1q [Chen et al., 1999].

Here we report on mosaic uniparental isodisomy for chromosome 1 in two individuals with unusual Rh blood-group phenotypes, showing both RhD-positive and RhD-negative erythrocyte cell populations.

MATERIALS AND METHODS

Rh Blood Group Typing and Cytogenetic Analysis of Case 1 and His Family Members

Case 1 is a 22-year-old Japanese man (proband II-5 in family 1, Fig. 1), who visited Japanese Red Cross Blood Center in 1985 to donate his blood. Blood group typing was performed with serological methods (data not shown). Routine Rh blood typing using anti-D antiserum showed a mixture of agglutinated and non-agglutinated red cells. Since the result suggested the presence of at least two erythrocyte populations, i.e., one population with D-positive and another population with D-negative, we performed flow cytometric analysis of density profile of RhD antigen. Erythrocytes from the proband, his parents and siblings were incubated at 37°C for one hour with FITC-conjugated human monoclonal anti-D antiserum (HIRO-8, provided by Central Blood Center, Tokyo), and fluorescence intensity was measured by flow cytometry, as described previously [Van Bockstaele et al., 1986; Smythe et al., 1996]. As a result, the proband's erythrocytes were separated into two cell populations: one population (79%) was D-positive, and the other (21%) D-negative (Fig. 2). The D-negative cells had c and e antigens but lacked C and E antigens (haplotype, dce), while D-positive cells had both c and E antigens and lacked e antigen (haplotype, DcE). These findings indicated that he had a "dce/dce" genotype-bearing cell population. The data also suggested that a second cell population would have had a "DcE/DcE" genotype, and the presence of a third population with a "dce/DcE" genotype would have been less likely, because his Rh e-antigen-positive erythrocyte was Rh D-antigen-negative.

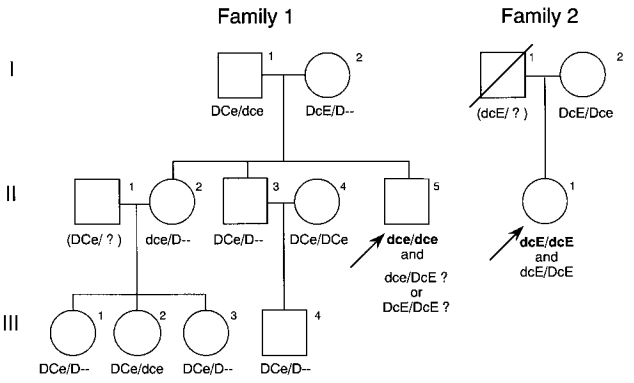

Fig. 1. Pedigrees of family 1 and family 2, with genotypes of the RhD and Rh CE gene complex. Cases 1 and 2 are indicated by arrow. Genotypes in bold letter and in parenthesis are those proved and those deduced from children's genotypes.

Genotype of his father (I-1, Fig. 1) was DCe/dce and that of the mother (I-2) was DcE/D−. The strength of D antigen in the mother's cells was increased, compared with that in erythrocytes in a normal control individual (DcE/DcE) with an apparent double dose of the antigen (data not shown). A deletion (D−) in the Rh gene complex of the mother was therefore supported, because normal individuals with the intact gene complex show increased strength of D antigen [Nance, 1994].

Chromosome analysis of the proband's cultured peripheral blood lymphocytes showed a mos 46,XY[71] /46, XY,1qh +,1qh +[29] karyotype. His father's karyotype was 46,XY,1qh + and the mother's was 46,XX, 1qh +. Chromosome fluorescence in situ hybridization (FISH) using a P1-derived artificial chromosome (PAC) clone that contains the sequence of the Rh blood group gene complex as a probe gave twin FISH signals on both of the proband's chromosomes 1 in 100 cells screened, an indication that there were no cells with deletion the Rh gene complex (data not shown). The Rh gene complex (*RHD* and *RHCE*) was assigned to 1p34.3-p36.2 [Chérif-Zahar et al., 1991]. In view of these findings, we assumed that the mosaic RhD phenotype of the proband resulted from UPD1, and studied other members of his family in more detail.

Rh Blood Group Typing of Case 2 and Her Mother

Case 2, a 23-year-old woman in family 2 (II-1, Fig. 1), was admitted to a maternity hospital at 34 weeks of her first pregnancy due to threatened premature delivery associated with preeclampsia. Her erythrocytes strongly reacted to monoclonal and polyclonal anti-D antibodies, but revealed a pattern of mix-field

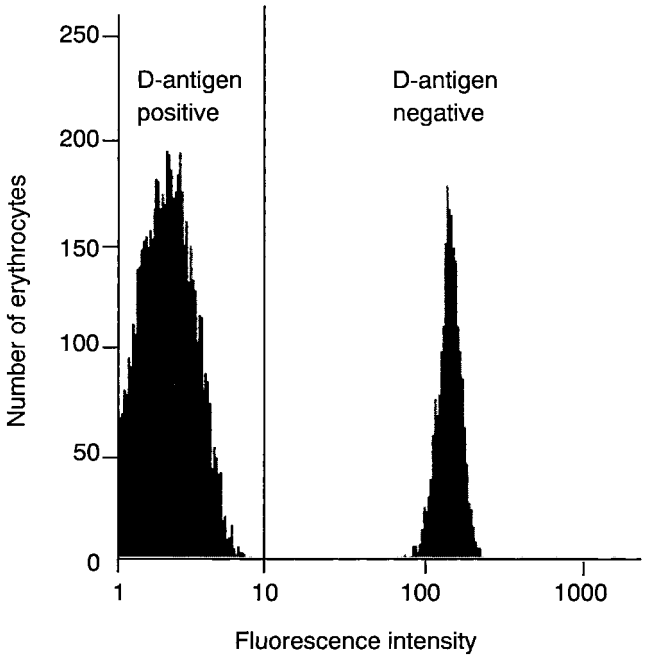

Fig. 2. Flow cytometry of intensity profile of the erythrocyte D antigen of the Rh blood group system in case 1. The presence of two cell populations with the D-antigen (79%) and without it (21%) is evident among a total of 9,863 red cells sorted.

agglutination. However, she had no history of blood transfusion. A level of HbF in her erythrocytes denied a possibility of feto-maternal transfusion. Flow cytometric analysis of density profile of RhD antigen separated her erythrocytes into two cell populations: one population (31%) was RhD-positive and the other population (69%) RhD-negative. Both of her D-positive and D-negative cells had c and E antigens but lacked C and e antigens, and therefore, her genotype was DcE/dcE. Her mother's genotype was either DCE/Dce or dCe/DcE. As the father had died in her childhood, his genotype was unknown. G-banding chromosomal analysis of peripheral blood lymphocytes of the proband showed a 46,XX karyotype without any visible deletions.

DNA Samples Obtained and Microsatellite Marker Analysis

With informed consent, blood samples were obtained from case 1, his parents, and from an elder sister and brother (Fig. 1). From case 1, oligoclonal Epstein-Barr virus-transformed lymphoblastoid cell lines (EBL) were established. Five monoclonal cell lines were subsequently established from the EBL with the soft-agar method [Mizuno et al., 1976; Sugden and Mark, 1977]. In short, cells (5,000 cells/dish) in a seed-layer medium (0.3% soft-agar/MEM) were seeded onto a basal layer medium (0.4% agar/MEM) and incubated at 37°C. When colonies appeared, cells at the central part of individual colonies were transferred into a 96-well plate, and cultured in liquid RPMI1640 medium supplemented with 20% FBS until cell confluence. Monoclonality was confirmed by the presence or absence of the 1q + heteromorphism on both chromosomes 1. We also collected his buccal mucosal cells and 50 pieces of hair and/or hair roots from the scalp, eyebrow, axillary, and shin skin. Likewise, we collected blood samples and 20 pieces of hair roots of the scalp and eyebrow from case 2, and blood samples from her mother.

Genomic DNA was extracted from each sample with the standard method. Hair and/or hair roots were individually placed in microtubes, and DNA was extracted from each piece of the hair roots by the use of Isohair™ kit (Nippon Gene, Tokyo, Japan). DNA samples were subjected to microsatellite marker analysis to know parent-child transmissions of alleles on chromosome 1 as well as on other autosomes. Highly polymorphic microsatellite markers at 102 loci were selected, including 47 dinucleotide and three tetranucleotide repeat markers spanning chromosome 1, and 52 dinucleotide repeats on chromosomes 2-22, according to the maps reported by Bruns et al. [1995] and by Dib et al. [1996] and those obtained through internet database (Cooperative Human Linkage Center Integrated Maps, CHLC Integrated Maps, http://www.chlc.org; Human Transcript Map, http://www.ncbi.nlm.nih.gov/SCIENCE96; A New Gene Map of the Human Genome, http://www.ncbi.nlm.nih.gov/genemap99). Oligonucleotide primer sets, i.e., forward primers labeled with fluorescence dye Cy-5 (Pharmacia Biotech, Uppsala, Sweden) (kindly provided by Dr. Yusuke Nakamura) and unlabeled reverse primers, were synthesized to amplify the marker DNA sequences. Polymerase chain reaction (PCR) was carried out for 30 cycles 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 50 mM KCl, 20 mM Tris-HCl (pH 8.5), 1.5 mM $MgCl_2$, 200 mM each of dNTP and 0.5 U AmpliTaq (Perkin Elmer, Foster City, CA). Electrophoretic patterns of PCR products were analyzed with an automated sequencer (ALFexpress™, Pharmacia Biotech) and a software (Fragment Manager™, Pharmacia Biotech). Genotypes of the markers were determined, as described elsewhere [Miyoshi et al., 1999; Ghadami et al., 2000]. Integral analysis on the allele-curve size (electrophoretic patterns for alleles) was carried out with an image analyzer.

RESULTS AND DISCUSSION

The microsatellite marker study on peripheral blood leukocytes (PBL), buccal mucosal cells, and the established primary (oligoclonal) EBV-transformed lymphoblastoid cell line of case 1 confirmed that alleles at all loci examined were inherited in a Mendelian fashion, i.e., biallelic, biparental inheritance. However, in all of the five monoclonal cell lines secondarily established from EBL, alleles at every informative locus on chromosome 1 showed seemingly monoallelic inheritance lacking the maternal alleles (Table I). Such a monoallelic pattern was also observed in all of the 50 pieces of her hair roots, irrespective of different skin

TABLE I. Allelotypes at Microsatellite Marker Loci in Case I and His Parents

				Case 1			
					EBL		
Marker	Location	Father PBL	Mother PBL	PBL and BUC	Primary	MCL	Hair root
D1S468	1p36-pter	1,3	1,2	2,3	2,3	3	3
D1S228	1p36	1,2	1	1,2	1,2	2	2
D1S2734	1p35-p36	1,3	1,2	1,3	1,3	3	3
D1S513	1p35-p36	2	1,3	2,3	2,3	2	2
D1S441	1p34-p35	2,3	1,3	1,2	1,2	2	2
D1S1596[a]	1p32p-34	2,4	1,3	2,3	2,3	2	2
D1S2770	1p32-p34	1,3	2,3	1,2	1,2	1	1
D1S209	1p32-p33	3,4	1,2	2,4	2,4	4	4
D1S219	Ip32	1,2	1	1,2	1,2	2	2
D1S216	1p31-p32	1,2	1	1,2	1,2	2	2
D1S430	1p31-p32	1,2	3	1,3	1,3	1	1
D1S248	1p13-p21	1,3	2	1,2	1,2	1	1
D1S502	1p13	1,3	2	2,3	2,3	3	3
D1S534[a]	1p13-cen	1,3	1,2	1,3	1,3	3	3
D1S2346	1p13-cen	2,4	1,3	3,4	3,4	4	4
D1S2635	Cen	2	1,3	1,2	1,2	2	2
D1S2844	1cen-q22	3	1,2	1,3	1,3	3	3
D1S2681	1cen-q22	1,2	1	1,2	1,2	2	2
D1S431	1q22-q23	1,3	2	2,3	2,3	3	3
D1S2757	1q31	2,3	1,4	3,4	3,4	3	3
D1S2622	1q31	2,3	1,4	2,4	2,4	2	2
D1S2872	1q31-q32	1	2	1,2	1,2	1	1
D1S2880	1q32-q41	1,2	2	1,2	1,2	1	1
D1S2800	1q42-q43	3,4	1,2	2,4	2,4	4	4
D1S1609[a]	1q43-qter	1,2	1	1,2	1,2	2	2
D1S2811	1q44	2,3	1,4	1,3	1,3	3	3
D2S114	2p12	2,4	1,3	1,2			1,2
D3S3556	3q12	1,3	2,3	1,2			1,2
D4S2974	4p14-cen	1,2	1,3	2,3			2,3
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	8p11-cen	2	1,3	1,2			1,2
D9S1799	9cen-q13	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	12cen-q13	2,3	1	1,2			1,2
D13S1253	13q13-q14.2	2,3	1,4	1,2			1,2
D14S990	14q11.1-q12	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	17p11-cen	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

[a]Tetranucleotide repeat markers; PBL, peripheral blood leukocytes; BUC, buccal mucosal cells; EBL, EBV-transformed lymphoblastoid cells; primary, established primary cell line; MCL, monoclonal cell lines isolated from EBL.

areas from which hair was collected, whereas both parental alleles at all other autosomal loci appeared in this tissue. Similar results were obtained in case 2, showing biallelic patterns in PBL and monoallelic patterns for loci on chromosome 1 in her hair roots (Table II).

A combination of serological Rh genotyping and flow cytometric analysis of density profile of RhD antigen strongly suggested the presence of two erythrocyte populations with different RhD blood types in each of the cases studied. Since no deletion or duplication of chromosome 1 or its Rh gene complex region was detected by conventional cytogenetic analysis and/or in situ hybridization, it was assumed that a cell line with UPD1 must be present in these individuals. The presence of paternal UPD1 was unequivocally proven in case 1 by the paternal haploid origin of microsatellite polymorphisms spanning chromosome 1 in the five monoclonal cell lines from the primary EBL. In addition, the 50 hair roots from case 1, each of which is assumed to be of monoclonal origin, all showed paternal monoallelic patterns (Table I). The result

TABLE II. Allelotypes at Marker Loci in Case 2 and Her Mother

Marker	Location	Mother PBL	Case 2		
			PBL	Hair 1	Hair 2
D1S468	1p36	2	1,2	1,2	1
D1S214	1p36	2,3	1,3	1,3	1
D1S436	1p36	2,3	1,3	1,3	1
D1S2722	1p34	1,2	1,3	1,3	3
D1S219	1p31	1,3	1,2	1,2	2
D1S216	1p31	1,2	2,3	2,3	3
D1S430	1p31	2,3	1,2	1,2	1
D1S3471[a]	1p22	2,3	1,2	1,2	1
D1S248	1p13-p21	1,2	2,3	2,3	3
D1S502	1p13	2	1,2	1,2	1
D1S2696	1p13	1,2	2,3	2,3	3
D1S2707	1q21-q23	1,2	2,3	2,3	3
D1S2681	1q21-q23	1,2	1,3	1,3	3
D1S2762	1q21-q23	1,3	2,3	2,3	2
D1S2880	1q32-q42	2,3	1,2	1,2	1
D1S459	1q42	2	1,2	1,2	1
D1S2682	1q42-q44	2,3	1,3	1,3	1
D2S113	2p11-q11	1	1,2	1,2	1,2
D3S1284	3p12-q12	1,3	1,2	1,2	1,2
D4S2974	4p14-q12	2,3	1,3	1,3	1,3
D5S2101	5p13-q11	1,2	1,3	1,3	1,3
D6S1681	6q13	1,2	2,3	2,3	2,3
D7S506	7p11.1-p11.2	2	1,2	1,2	1,2
D8S530	8q13-q21	1,2	1,3	1,3	1,3
D9S1678	9p21-q13	2,3	1,3	1,3	1,3
D10S1791	10p12-q11	2	1,2	1,2	1,2
D11S905	11p12-q13	1,2	1,3	1,3	1,3
D12S1586	12q13	1,3	2,3	2,3	2,3
D13S1253	13q13-q14	2,3	1,2	1,2	1,2
D14S990	14q11	2	1,2	1,2	1,2
D15S1035	15q11	1,2	1,3	1,3	1,3
D16S3045	16p12	1,2	2,3	2,3	2,3
D17S1800	17p11-q21	1,2	2,3	2,3	2,3
D18S57	18p12	2,3	1,2	1,2	1,2
D19S414	19q12	1,2	1,3	1,3	1,3
D20S96	20p11-q12	1,2	1,3	1,3	1,3
D21S1895	21q22.1	2	1,2	1,2	1,2
D22S281	22cen	2,3	1,2	1,2	1,2

[a]Tetranucleotide repeat marker; PBL, peripheral blood leukocytes.

indicated that he had at least a cell line with complete paternal isodisomy for chromosome 1, most likely resulting from duplication of a paternally derived chromosome 1. Although the presence of another cell line with maternal isodisomy 1 had also been suggested by histogram patterns of the flow cytometry of his erythrocytes and by his karyotype (46,XY,1qh+,1qh+), no such cells were detected by microsatellite analysis on any tissues examined. Repeated attempts at establishing monoclonal cell lines from the primary EBL have been unsuccessful. Thus, its remains to be investigated whether a cell line with maternal isodisomy 1 is present in case 1. Instead, the data obtained were not inconsistent with normal, biparental, and biallelic cells as his second somatic cell line. Judging from the microsatellite patterns, the paternal alleles were identical at any loci between the two cell lines. These findings ruled out chimerism, and indicated that the two cell lines were derived from the same conceptus.

Almost similar findings were obtained in case 2. Her PBL had biallelic patterns at any loci examined. There were two groups of hair roots: Of the 20 pieces analyzed, 15 showed biallelic patterns at all loci on chromosome 1, while the remaining five pieces gave monoallelic patterns at the same loci, lacking maternal alleles (Table II). Although the genotype of her father was not available, it is most likely that the proband had mosaic UPD1: one cell population with complete paternal isodisomy for chromosome 1 and the other population with normal biparental disomy 1. With this finding, we constructed her Rh genotype as DcE/dcE, and dcE/dcE.

If the presence of a cell population with isodisomy 1 under the normal cell background with biparental alleles is the case for case 1, as is for case 2, the most likely mechanism is an early somatic occurrence of either trisomy rescue or monosomy duplication [Spence et al., 1988; Ledbetter and Engel, 1995]. If we assume that case 1 had mosaic double UPD1 (maternal and paternal isodisomies for chromosome 1 without any

biparental-disomic cells) as suggested by flow cytometric analysis, much more complex events would have occurred, e.g., a normal fertilization followed by migration of chromosome homologs 1 to the opposite poles at the first mitotic division, together with non-segregation of the sister chromatids, resulting in two cell populations - one with maternal complete isodisomy 1 and the other with paternal isodisomy 1.

To our knowledge, three individuals have been reported with mosaicism (often called "chimeric" in previous papers) for the RhD and Duffy blood types [Jenkins and Marsh, 1964; Northoff et al., 1984; Salaru and Lay, 1985]. Since the genetic loci for the Rh and the Duffy (Fy) systems are at 1p36.2-p34 and at 1q21-q22, respectively, the occurrence of mosaicism involving both blood groups is not surprising. A person reported by Jenkins and Marsh [1964] was a child of a DCe/dCe and Fy(a+) father and a DCe/dce and Fy(a−) mother. The child had two red cell populations: DCe/dce and Fy(a+), and cde/cde and Fy(a−). Another individual [Northoff et al., 1984] had one population of D/d and Fy(a+b+), and the other population of d/d and Fy(a+b−). The third individual [Salaru and Lay, 1985] showed a mixed cell population of DCe/Dce and Fy(a−b+) haplotype and cde/cde and Fy(a−b+) haplotype. In all these three persons, one cell population was consistent with UPD1. Thus, mosaicism composing UPD1 cells and biparental cells can occur more frequently than previously thought.

UPD1 has been identified in seven individuals [Pulkkinen et al., 1997; Field et al., 1998; Gelb et al., 1998; Dufourcq-Lagelouse et al., 1999; Chen et al., 1999; Miura et al., 2000; Takizawa et al., 2000]. They were found accidentally either through studies on rare autosomal recessive disorders, i.e., Herlitz junctional epidermolysis bullosa [Pulkkinen et al., 1997; Takizawa et al., 2000], pycnodysostosis [Gelb et al., 1998], Chediak-Higashi syndrome [Dufourcq-Lagelouse et al., 1999], congenital insensitivity to pain with anhidrosis [Miura et al., 2000], multiple congenital anomalies [Chen et al., 1999], or during a genome screening of families with insulin-dependent diabetes mellitus using polymorphic DNA markers [Field et al., 1998]. We would like to emphasize here that isodisomy 1 is not infrequent and also causes unusual Rh phenotypes. Of the total of nine individuals including Cases 1 and 2 we described, eight had no apparent abnormal phenotypes other than the recessive disorders or unusual Rh phenotypes. Furthermore, UPD1 in these individuals was either maternal or paternal. Neither maternal nor paternal UPD1 showed an apparent imprinting effect.

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