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Report

Retinal Dystrophy Due to Paternal Isodisomy for Chromosome 1 or Chromosome 2, with Homoallelism for Mutations in *RPE65* or *MERTK*, Respectively

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Uniparental disomy (UPD) is a rare condition in which a diploid offspring carries a chromosomal pair from a single parent. We now report the first two cases of UPD resulting in retinal degeneration. We identified an apparently homozygous loss-of-function mutation of *RPE65* (1p31) in one retinal dystrophy patient and an apparently homozygous loss-of-function mutation of *MERTK* (2q14.1) in a second retinal dystrophy patient. In both families, the gene defect was present in the patient's heterozygous father but not in the patient's mother. Analysis of haplotypes in each nuclear kindred, by use of DNA polymorphisms distributed along both chromosomal arms, indicated the absence of the maternal allele for all informative markers tested on chromosome 1 in the first patient and on chromosome 2 in the second patient. Our results suggest that retinal degeneration in these individuals is due to apparently complete paternal isodisomy involving reduction to homoallelism for *RPE65* or *MERTK* loss-of-function alleles. Our findings provide evidence for the first time, in the case of chromosome 2, and confirm previous observations, in the case of chromosome 1, that there are no paternally imprinted genes on chromosomes 1 and 2 that have a major effect on phenotype.

Uniparental disomy (UPD) arises when a diploid individual carries both homologs of a chromosomal pair from a single parent (uniparental heterodisomy) or two copies of a single parental chromosome (uniparental isodisomy) (Engel 1980). Uniparental heterodisomy occurs most frequently in cases in which both homologs are maternally derived (maternal UPD), and uniparental isodisomy occurs most frequently in cases in which both homologs are paternally derived (paternal UPD), with the overall prevalence of maternal UPD being three times greater than that of paternal UPD (Kotzot 1999). Possible mechanisms of UPD include gamete complementation, trisomic zygote rescue (reduction to disomy), postzygotic monosomy duplication, and somatic crossing-over (Engel and DeLozier-Blanchet 1991; Robinson 2000). Disease phenotypes associated with UPD can be due to trisomy mosaicism, unmasking of autosomal recessive gene defects by reduction to homoallelism, or imprinting (Engel 1998; Kotzot 1999). Studies of UPD in humans and mice played an important part in establishment of the role that imprinting plays in parent-of-origin–specific gene expression and in identification of imprinted regions of the genome that have profound effects on fetal growth, development, and viability (Preece and Moore 2000). Studies of autosomal recessive disorders identified a number of cases of UPD resulting in reduction to homoallelism of disease-associated mutations (Engel 1998).

Inherited retinal dystrophies are a genetically heterogeneous group of diseases responsible for visual deficits that vary in severity and age at onset and include some

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forms of congenital blindness. Mutations in a number of genes expressed in the photoreceptor cells or the adjacent retinal pigment epithelium (RPE) have been shown to cause autosomal dominant and recessive forms of retinal degeneration (Phelan and Bok 2000). Our previous studies identified two disease genes, *RPE65* and *MERTK*, involved in essential aspects of RPE physiology necessary for photoreceptor-cell function and viability (Gu et al. 1997; Gal et al. 2000). *RPE65* (MIM 180069) encodes a unique protein localized in the RPE smooth endoplasmic reticulum and is required for the conversion of vitamin A to 11-*cis* retinal, the chromophore of the visual pigments (Hamel et al. 1993; Nicoletti et al. 1995; Redmond et al. 1998). Mutations in *RPE65* cause early-onset severe retinal degeneration that is often diagnosed as Leber congenital amaurosis (Gu et al. 1997; Marlhens et al. 1997). Over 50 different disease-associated mutations have been reported, with current estimates indicating that *RPE65* mutations are responsible for ~10% of cases of autosomal recessive retinal dystrophy with early onset and severe phenotype (Thompson et al. 2000). *MERTK* (MIM 604705) encodes a tyrosine kinase receptor that is the human ortholog of the Royal College of Surgeons (RCS) rat retinal-dystrophy gene (D'Cruz et al. 2000). In the RCS rat, mutations in *Mertk* cause retinal degeneration as a result of defective phagocytosis of shed photoreceptor outer segments by the RPE (Mullen and LaVail 1976; Edwards and Szamier 1977). Disease-associated mutations of *MERTK* have been reported in patients with autosomal recessive retinitis pigmentosa (Gal et al. 2000).

We identified two families in which a mutation of *RPE65* or *MERTK*, present in apparently homozygous form in the affected individual, was carried in heterozygous form by only one parent (Gal et al. 2000; Thompson et al. 2000). In the first case (patient 1723), a 51-year-old man diagnosed with Leber congenital amaurosis in childhood had an apparently homozygous mutation of *RPE65*, IVS1+5g→a, that is the most frequently occurring mutation in this gene (comprising ~19% of all reported *RPE65* disease alleles) (Thompson et al. 2000). The mutation identified in patient 1723 was present in heterozygous form in his unaffected father and brother but was not present in his mother. Evidence suggesting that no maternal *RPE65* allele was transmitted to the patient was obtained by analysis of two intragenic DNA polymorphisms; a microsatellite repeat (*D1S2803*) in the promoter region (Nicoletti et al. 1998) and an intronic single-nucleotide polymorphism (IVS6+22c→t). The patient appeared to be homozygous for both markers, and only the paternal allele was detected (fig. 1). Further analysis of 19 informative microsatellite markers, spread out along both arms of chromosome 1, suggested complete absence of the maternal homolog, since the patient appeared homozygous for the paternal allele in each case. Genotypes obtained for 12 other partially informative DNA polymorphisms on chromosome 1, including an intragenic 2-bp insertion/deletion–type polymorphism (2383ins/del) located in the 3′ UTR of *RPE65* (Nicoletti et al. 1995), were also consistent with the assumption of paternal isodisomy of chromosome 1. The assumed biological relationship of the patient to his parents was confirmed by analysis of a number of microsatellite markers on chromosomes 2, 3, 6, and X (data not shown). Routine cytogenetic analysis of metaphase spreads prepared from peripheral blood showed a normal male karyotype, 46,XY.

Patient 1723 has no obvious physical abnormalities and is currently engaged in a high-level professional career. He was born after a full-term pregnancy, when his mother and father were 22 and 25 years of age, respectively. The patient has hyperbetalipoproteinemia, which is also present in his father and in his father's siblings, as well as benign hyperbilirubinemia (Gilbert syndrome). Neither condition can be ascribed to the patient's UPD status. Onset of his retinal disease occurred at age <5 years, with severe visual loss and nystagmus. At age 8 years, his visual acuity was 20/200, with a refraction of +4.00. Signals on rod and cone electroretinograms were not detectable. At age 50 years, he had only small islands of vision remaining. The course and severity of the patient's visual disorder fit well within the range of clinical phenotypes exhibited by other reported patients with retinal dystrophy who had mutations of *RPE65* (Gu et al. 1997; Marlhens et al. 1997; Morimura et al. 1998; Perrault et al. 1999; Lorenz et al. 2000; Lotery et al. 2000; Thompson et al. 2000).

In the second case (that of patient arRP185), a woman diagnosed with retinitis pigmentosa had an apparently homozygous *MERTK* mutation, IVS10−2a→g, that was present in heterozygous form in her unaffected father but was not present in her mother (Gal et al. 2000). Analysis of a number of exonic and intronic, partially informative DNA polymorphisms was consistent with the assumption of a paternal isodisomy, since the patient appeared to be homozygous for one of the paternal alleles (data not shown). Further analysis of 17 informative microsatellite markers spread out along both arms of chromosome 2 suggested complete absence of the maternal homolog (fig. 2). Data obtained for eight other partially informative DNA polymorphisms on chromosome 2 were also consistent with the assumption of paternal isodisomy of chromosome 2. The assumed biological relationship of the patient to her parents was confirmed by analysis of a number of microsatellite markers on chromosomes 3–6, 9, 11, and 14–19 (data not shown). Routine cytogenetic analysis of metaphase

Locus	Cytogenetic Location	Mother 1725	Father 1724	Patient 1723
D1S2667	1p36.23-p36.31	2 , 4	1 , 2	1 , 1
D1S199	1p36	3 , 3	1 , 1	1 , 1
D1S2697	1p36	2 , 3	4 , 1	4 , 4
D1S234	1p34.2-p35.3	1 , 3	4 , 4	4 , 4
D1S2803	1p31	2 , 3	1 , 3	1 , 1
IVS1+5g→a	1p31	g , g	a , g	a , a
IVS6+22c→t	1p31	c , c	t , c	t , t
D1S1665	1p31.1-p31.3	1 , 1	2 , 1	2 , 2
D1S488	1p31.1-p31.2	1 , 2	4 , 3	4 , 4
D1S206	1p21.1-p21.3	1 , 3	4 , 4	4 , 4
D1S2726	1p13.1	2 , 2	1 , 3	1 , 1
D1S498	1q12-q21.2	1 , 3	4 , 2	4 , 4
D1S305	1q21.2	2 , 4	1 , 3	1 , 1
D1S2878	1q23.2	2 , 3	4 , 2	4 , 4
D1S218	1q24.3	2 , 3	1 , 2	1 , 1
D1S413	1q31.3	2 , 3	4 , 1	4 , 4
D1S306	1q31.3	1 , 2	4 , 3	4 , 4
D1S2785	1q42.3-q43	4 , 5	1 , 3	1 , 1
D1S2836	1q43-q44	3 , 4	4 , 1	4 , 4

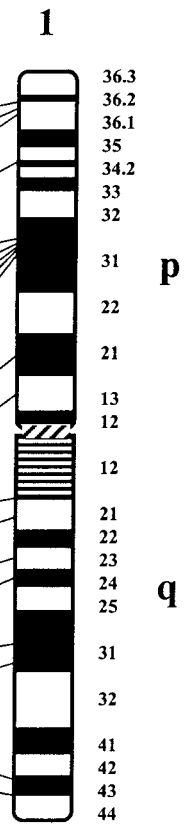

Figure 1 Genotype analysis of chromosome 1 in the family of patient 1723, who carries an *RPE65* mutation. The disease-relevant *RPE65* mutation is shown in boldface italics; marker order is as in the NCBI draft of the human genome (build 25), with cytogenetic locations derived from NCBI Locus Link and Genome Database Map View. Data from a total of 12 additional chromosome 1 polymorphisms were only partially informative, because the parents shared at least one allele. All data were consistent with paternal uniparental isodisomy of chromosome 1.

chromosome spreads prepared from peripheral blood showed a normal female karyotype (46,XX).

Patient arRP185 (currently 34 years of age), the mother of two healthy children, appears phenotypically normal in all aspects except for her retinal disease and a general connective-tissue weakness. She was born after a full-term pregnancy, when her mother and father were 36 and 33 years of age, respectively, and was of normal birth weight. She was noted to be night blind in preschool, and, in primary school, she had poor vision that was uncorrectable by refractive lenses. At 12 years of age, she was diagnosed with retinitis pigmentosa. At 18 years of age, her peripheral vision was largely reduced (10° visual fields). At her current age, she has 5-degree visual fields and has difficulty reading. Her visual handicap is similar to that of the two other retinal dystrophy patients reported to have mutations of *MERTK* (Gal et al. 2000).

Our studies have identified the first known cases of UPD resulting in retinal degeneration. In both cases, the patient's ocular phenotype appears to result from reduction to homoallelism of a disease-causing mutation of paternal origin, since marker analysis suggests that each patient carries two complete and identical homologs of a single paternal chromosome. Such cases of uniparental isodisomy can be thought of as resulting from compensatory UPD—that is, from replacement of a missing chromosome by early somatic duplication in cases of postzygotic monosomy (Robinson 2000). The mutations involved, IVS1+5g→a in *RPE65* and IVS10−2a→g in *MERTK*, are predicted to interfere with correct splicing and to generate loss-of-function alleles of known disease genes that are expressed in the RPE and are necessary for photoreceptor-cell function. The associated ocular phenotypes appear to be very similar to those of other patients who carried mutations in the same genes in homozygous or compound heterozygous form, without additional severe abnormalities in our patients that would indicate multiple autosomal recessive defects, major effects of imprinting, or both.

Previous studies have identified UPD involving various chromosomes in patients affected with different auto-

Locus	Cytogenetic Location	Mother	Father	Patient arRP185
D2S1780	2p24.1-p24.3	1 , 2	3 , 2	3 , 3
D2S423	2p24.1-p24.2	1 , 3	2 , 3	2 , 2
D2S1360	2p23.3	3 , 3	2 , 1	2 , 2
D2S1788	2p21-p22.3	3 , 4	1 , 2	1 , 1
D2S1356	2p21.1	1 , 3	2 , 3	2 , 2
D2S1352	2p21	1 , 3	2 , 2	2 , 2
D2S1394	2p13.1	1 , 3	2 , 1	2 , 2
D2S1790	2p11.2-p12	1 , 2	3 , 3	3 , 3
IVS10–2a→g	2q14.1	a , a	g , a	g , g
D2S1328	2q14.3-q21.1	1 , 2	3 , 2	3 , 3
D2S442	2q22.1-q22.3	1 , 3	2 , 3	2 , 2
D2S1326	2q22.3	2 , 4	1 , 3	1 , 1
D2S1399	2q23.1	1 , 2	3 , 2	3 , 3
D2S1776	2q24.3-q32.1	1 , 1	2 , 2	2 , 2
D2S1384	2q33.1	1 , 1	2 , 1	2 , 2
D2S434	2q35	1 , 2	3 , 2	3 , 3
D2S125	2q35-q37	1 , 1	2 , 3	2 , 2
D2S427	2q37.3	1 , 1	2 , 1	2 , 2

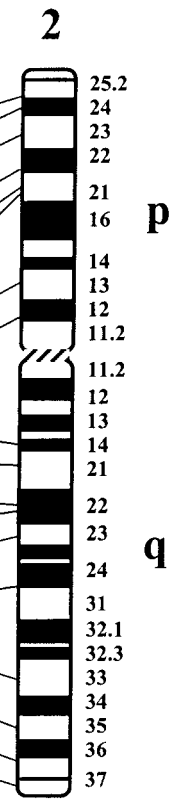

Figure 2 Genotype analysis of chromosome 2 in the family of patient arRP185, who carries a *MERTK* mutation. The disease-relevant *MERTK* mutation is shown in boldface italics; marker order is as in the NCBI draft of the human genome (build 25), with cytogenetic locations derived from Genome Database Map View. Data from a total of eight additional chromosome 2 polymorphisms were only partially informative, because the parents shared at least one allele. All data were consistent with paternal uniparental isodisomy of chromosome 2.

somal recessive disorders (Engel 1998). Reported cases of UPD of chromosome 1 (UPD 1) involving full or partial isodisomy include a number of cases of maternal UPD 1 (Pulkkinen et al. 1997; Field et al. 1998; Dufourcq-Lagelouse et al. 1999), as well as cases of paternal UPD 1 (Gelb et al. 1998; Chen et al. 1999; Miura et al. 2000; Takizawa et al. 2000). Of the latter, two are cases of likely complete paternal isodisomy associated with either (*a*) congenital insensitivity to pain, with anhidrosis due to mutation in *TRKA* (MIM 191315) (Miura et al. 2000), or (*b*) Herlitz junctional epidermolysis bullosa due to mutation in *LAMC2* (MIM 150292) (Takizawa et al. 2000), with both patients having phenotypes characteristic of autosomal recessive disease but being too young (ages 8 mo and 2 years) to exclude with certainty any additional abnormalities suggestive of an effect of imprinting. Cases of UPD of chromosome 2 (UPD 2) reported elsewhere include a case of paternal i(2p) with maternal i(2q) in a phenotypically normal female with two isochromosomes (Albrecht et al. 2001). All other cases were of maternal UPD 2, with four reported cases apparently due to trisomy rescue resulting in uniparental heterodisomy (Harrison et al. 1995; Webb et al. 1996; Hansen et al. 1997; Heide 2000) and with two reported cases of maternally derived isochromosomes i(2p),i(2q) (Bernasconi et al. 1996; Shaffer et al. 1997).

The case of UPD 2 described in the present study represents the first example of complete paternal isodisomy of chromosome 2, providing evidence, for the first time, that there are no paternally imprinted genes on chromosome 2 that have a major effect on growth or development. The case of UPD 1 described in the present study represents the first example of complete paternal isodisomy of chromosome 1 in an adult individual, establishing that there are no paternally imprinted genes on chromosome 1 that have a major effect on phenotype. In addition, our findings suggest that, in general, the total number of recessive mutations per chromosome in any one individual may be low. It is tempting to speculate that future genetic studies may find that UPD of chromosomes or chromosomal regions unaffected by imprinting may be a more common cause of autosomal recessive disease than has been appreciated previously.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Genome Database, The, http://www.gdb.org
National Center for Biotechnology Information (NCBI) draft of the human genome, http://www.ncbi.nlm.nih.gov/ (for Map Viewer and Locus Link)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *RPE65* [MIM 180069], *MERTK* [MIM 604705], *TRKA* [MIM 191315], and *LAMC2* [MIM 150292])

References

Albrecht B, Mergenthaler S, Eggermann K, Zerres K, Passarge E, Eggermann T (2001) Uniparental isodisomy for paternal 2p and maternal 2q in a phenotypically normal female with two isochromosomes, i(2p) and i(2q). J Med Genet 38:214

Bernasconi F, Karagüzel A, Celep F, Keser I, Luleci G, Dutly F, Schinzel AA (1996) Normal phenotype with maternal isodisomy in a female with two isochromosomes: i(2p) and i(2q). Am J Hum Genet 59:1114–1118

Chen H, Young R, Mu X, Nandi K, Miao S, Prouty L, Ursin S, Gonzalez J, Yanamandra K (1999) Uniparental isodisomy resulting from 46,XX,i(1p),i(1q) in a woman with short stature, ptosis, micro/retrognathia, myopathy, deafness, and sterility. Am J Med Genet 82:215–218

D'Cruz PM, Yasumura D, Weir J, Matthes MT, Abderrahim H, LaVail MM, Vollrath D (2000) Mutation of the receptor tyrosine kinase *Mertk* in the retinal dystrophic RCS rat. Hum Mol Genet 9:645–652

Dufourcq-Lagelouse R, Lamber N, Duval M, Viot G, Vilmer E, Fischer A, Prieur M, de Saint Basile G (1999) Chediak-Higashi syndrome associated with maternal uniparental isodisomy of chromosome 1. Eur J Hum Genet 7:633–637

Edwards RB, Szamier RB (1977) Defective phagocytosis of isolated rod outer segments by RCS rat retinal pigment epithelium in culture. Science 197:1001–1003

Engel E (1980) A new genetic concept: uniparental disomy and its potential effect, isodisomy. Am J Med Genet 6:137–143

Engel E (1998) Uniparental disomies in unselected populations. Am J Hum Genet 63:962–966

Engel E, DeLozier-Blanchet CD (1991) Uniparental disomy, isodisomy, and imprinting: probable effects in man and strategies for their detection. Am J Med Genet 40:432–439

Field LL, Tobias R, Robinson, WP, Paisey R, Bain S (1998) Maternal uniparental disomy of chromosome 1 with no apparent phenotypic effects. Am J Hum Genet 63:1216–1220

Gal A, Li Y, Thompson DA, Weir J, Orth U, Jacobson SG, Apfelstedt-Sylla E, Vollrath D (2000) Mutations in *MERTK*, the human ortholog of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. Nat Genet 26:270–271

Gelb BD, Willner JP, Dunn TM, Kardon NB, Verloes A, Poncin J, Desnick RJ (1998) Paternal uniparental disomy for chromosome 1 revealed by molecular analysis of a patient with pycnodysostosis. Am J Hum Genet 62:848–854

Gu S-M, Thompson DA, Srikumari CRS, Lorenz B, Finckh U, Nicoletti A, Murthy KR, Rathmann M, Kumaramanickavel G, Denton MJ, Gal A (1997) Mutations in RPE65 cause autosomal recessive childhood-onset severe retinal dystrophy. Nat Genet 17:194–197

Hamel CP, Tsilou E, Pfeffer BA, Hooks JJ, Detrick B, Redmond TM (1993) Molecular cloning and expression of RPE65, a novel retinal pigment epithelium-specific microsomal protein that is post-transcriptionally regulated in vitro. J Biol Chem 268:15751–15757

Hansen WF, Bernard LE, Langlois S, Rao KW, Chescheir NC, Aylsworth AS, Smith DI, Robinson WP, Barrett IJ, Kalousek DK (1997) Maternal uniparental disomy of chromosome 2 and confined placental mosaicism for trisomy 2 in a fetus with intrauterine growth restriction, hypospadias, and oligohydramnios. Prenat Diagn 17:443–450

Harrison K, Eisenger K, Anyane-Yeboa K, Brown S (1995) Maternal uniparental disomy of chromosme 2 in a baby with trisomy 2 mosaicism in amniotic fluid culture. Am J Med Genet 58:147–151

Heide E, Heide K-G, Rodewald A (2000) Maternal uniparental disomy for chromosome 2 discovered by exclusion of paternity. Am J Med Genet 92:260–263

Kotzot D (1999) Abnormal phenotypes in uniparental disomy uniparental disomy: Fundamental aspects and a critical review with bibliography of uniparental disomy other than 15. Am J Med Genet 82:265–274

Lorenz B, Gyurus P, Preising M, Bremser D, Gu S, Andrassi M, Gerth C, Gal A (2000) Early-onset, severe, rod-cone dystrophy in young children with *RPE65* mutations. Invest Ophthalmol Vis Sci 41:2735–2742

Lotery AJ, Namperumalsamy P, Jacobson SG, Weleber RG, Fishman GA, Musarella MA, Hoyt CS, Héon E, Levin A, Jan J, Lam B, Carr RE, Franklin A, Radha S, Andorf JL, Sheffield VC, Stone EM (2000) Mutation analysis of 3 genes in patients with Leber congenital amaurosis. Arch Ophthalmol 118:538–543

Marlhens F, Bareil C, Griffoin JM, Zrenner E, Amalric P, Eliaou C, Liu SY, Harris E, Redmond TM, Arnaud B, Claustres M, Hamel CP (1997) Mutations in *RPE65* cause Leber's congenital amaurosis. Nat Genet 17:139–141

Miura Y, Hiura M, Torigoe K, Numata O, Kuwahara A, Matsunaga M, Hasegawa S, Boku N, Ino H, Mardy S, Endo F, Matsuda I, Indo Y (2000) Complete paternal uniparental isodisomy for chromosome 1 revealed by mutation analyses of the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with congenital insensitivity to pain with anhidrosis. Hum Genet 107: 205–209

Morimura H, Fishman, GA, Grover SA, Fulton AB, Berson EL, Dryja TP (1998) Mutations in the *RPE65* gene in patients with autosomal recessive retinitis pigmentosa or Leber congenital amaurosis. Proc Natl Acad Sci USA 95:3088–3093

Mullen RJ, LaVail MM (1976) Inherited retinal dystrophy: primary defect in pigment epithelium determined with experimental rat chimeras. Science 192:799–801

Nicoletti A, Kawase K, Thompson DA (1998) Promoter analysis of *RPE65,* the gene encoding a 61-kDa retinal pigment epithelium-specific protein. Invest Ophthalmol Vis Sci 39: 637–644

Nicoletti A, Wong DJ, Kawase K, Gibson LH, Yang-Feng TL, Richards JE, Thompson DA (1995) Molecular characterization of the human gene encoding an abundant 61 kDa protein specific to the retinal pigment epithelium. Hum Mol Genet 4:641–649

Perrault I, Rozet J-M, Ghazi I, Leowski C, Bonnemaison M, Geber S, Ducroq D, Cabot A, Souied E, Dufier J-L, Munnich A, Kaplan J (1999) Different functional outcome of RetGC1 and RPE65 gene mutations in Leber congenital amaurosis. Am J Hum Genet 64:1225–1228

Phelan JK, Bok D (2000) A brief review of retinitis pigmentosa and the identified retinitis pigmentosa genes. Mol Vis 6: 116–124

Preece MA, Moore GE (2000) Genomic imprinting, uniparental disomy and foetal growth. Trends Endocrinol Metab 11:270–275

Pulkkinen L, Bullrich F, Czarnecki P, Weiss L, Uitto J (1997) 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

Redmond TM, Yu S, Lee E, Bok D, Hamasaki D, Chen N, Goletz P, Ma JX, Crouch RK, Pfeifer K (1998) *Rpe65* is necessary for production of 11-*cis*-vitamin A in the retinal visual cycle. Nat Genet 20:344–351

Robinson WP (2000) Mechanisms leading to uniparental disomy and their clinical consequences. Bioessays 22:452–459

Shaffer LG, McCaskill C, Egli CA, Baker JC, Johnston KM (1997) Is there an abnormal phenotype associated with maternal isodisomy for chromosome 2 in the presence of two isochromosomes? Am J Hum Genet 61:461–462

Takizawa Y, Pulkkinen L, Chao SC, Nakajima H, Nakano Y, Shimizu H, Uitto J (2000) Complete paternal uniparental isodisomy of chromosome 1: a novel mechanism for Herlitz junctional epidermolysis bullosa. J Invest Dermatol 115: 307–311

Thompson, DA, Gyürüs P, Fleischer L, Bingham EL, McHenry CL, Apfelstedt-Sylla E, Zrenner E, Lorenz B, Richards JE, Jacobson SG, Sieving PA, Gal A (2000) Genetics and phenotypes of RPE65 mutations in inherited retinal degeneration. Invest Ophthalmol Vis Sci 41:4293–4299

Webb AL, Sturgiss S, Warwicker P, Robson SC, Goodship JA, Wolstenholme J (1996) Maternal uniparental disomy for chromosome 2 in association with confined placental mosaicism for trisomy 2 and severe intrauterine growth retardation. Prenat Diagn 16:958–962