# Complete Maternal Isodisomy of Chromosome 3 in a Child with Recessive Dystrophic Epidermolysis Bullosa but No Other Phenotypic Abnormalities

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The mechanobullous disease Hallopeau–Siemens recessive dystrophic epidermolysis bullosa (HS-RDEB) results from mutations in the type VII collagen gene (*COL7A1*) on chromosome 3p21.31. Typically, there are frameshift, splice site, or nonsense mutations on both alleles. In this report, we describe a patient with HS-RDEB, who was homozygous for a new frameshift mutation, 345insG, in exon 3 of *COL7A1*. However, sequencing of parental DNA showed that although the patient's mother was a heterozygous carrier of this mutation, the father's DNA contained only wild-type sequence. Microsatellite marker analysis confirmed paternity and genotyping of 28 microsatellites spanning chromosome 3 revealed that the affected child was homozygous for every marker tested with all alleles originating from a single maternal chromosome 3. Thus, the HS-RDEB phenotype in this patient is due to complete maternal isodisomy of chromosome 3 and reduction to homozygosity of the mutant *COL7A1* gene locus. To our knowledge, there are no published reports of uniparental disomy (UPD) in HS-RDEB; moreover, this case represents only the third example of UPD of chromosome 3 to be reported. The severity of the HS-RDEB in this case was similar to other affected individuals and no additional phenotypic abnormalities were observed, suggesting an absence of maternally imprinted genes on chromosome 3.

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## INTRODUCTION

Recessive dystrophic epidermolysis bullosa (RDEB) is a mechanobullous disorder associated with defective anchoring fibrils at the dermal–epidermal junction and abnormalities in type VII collagen gene and protein expression (Christiano *et al.*, 1997a; Fine *et al.*, 2000). The molecular pathology of RDEB involves loss-of-function mutations in the *COL7A1* gene on chromosome 3p21.31 (Christiano *et al.*, 1994). Typically, the severe Hallopeau–Siemens (HS) subtype of RDEB (OMIM 226600) results from nonsense, frameshift, splice site or, less commonly, missense mutations on both *COL7A1* alleles (Jarvikallio *et al.*, 1997; Whittock *et al.*, 1999; Uitto and Richard, 2004). Clinically, HS-RDEB is associated with widespread mucocutaneous blisters and erosions, mutilating scarring and premature mortality, commonly from squamous cell carcinomas (Fine *et al.*, 2000; Mallipeddi, 2002).

Genetic counseling based on Mendelian principles usually advises that parents of affected offspring are asymptomatic heterozygous carriers with a 25% risk of recurrence in subsequent pregnancies, although a number of *de novo* *COL7A1* mutations have been reported (Uitto and Richard, 2004). Delineation of *de novo* mutations that are not present in parental germline may substantially reduce, but not completely abolish, the risk of recurrence. A further possibility, although not yet reported in RDEB, that has implications for the accuracy of genetic counseling and risk of recurrence is when molecular analysis discloses uniparental disomy (UPD), a term used to denote the inheritance of both copies of a chromosome pair from just one parent (paternal or maternal) (Engel, 1980). Uniparental heterodisomy refers to the presence of a pair of chromosome homologs, whereas uniparental isodisomy describes two identical copies of a single homolog, and meroisodisomy is a mixture of the two (Kotzot, 2001; Siegel and Slavotinek, 2005). In essence, uniparental isodisomy allows two copies of a recessive mutation to be transmitted from a heterozygous carrier parent.

We report the first case of HS-RDEB due to UPD, specifically complete maternal isodisomy, with reduction to homozygosity of the mutant *COL7A1* gene. Moreover, this is

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*Abbreviations: HS-RDEB, Hallopeau–Siemens recessive dystrophic epidermolysis bullosa; UPD, uniparental disomy*

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only the third reported example of UPD of chromosome 3 (Hoffman *et al*., 2004; Schollen *et al*., 2005).

## RESULTS

### The clinicopathological features of the blistering neonate support a diagnosis of HS-RDEB

The proband was the first-born son of healthy unrelated parents from Hong Kong. The mother was 34 years old and the father was aged 35. There was no family history of blistering skin diseases. The pregnancy, labor, and delivery were uncomplicated and the proband was born at 39 weeks gestation weighing 2,570 g (5th centile). At birth, there were extensive erosions at acral sites and on his legs (Figure 1a and b). He was otherwise clinically normal with no dysmorphic features and cytogenetic analysis showed a normal 46XY karyotype. Immunofluorescence microscopy demonstrated type IV collagen immunostaining to the roof of a skin blister (Figure 1c) and a complete absence of immunoreactivity for type VII collagen (Figure 1d), but normal labeling intensities for all other basement membrane components. These investigations are consistent with a diagnosis of HS-RDEB. Now aged 1 year, he continues to have fragile skin with widespread trauma-induced blistering and erosions, more prominent on his hands and face; however, with supportive medical care he is thriving and is on the 50th centile for both weight and height. Complete assessment of his psychomotor development shows that he has achieved his appropriate developmental milestones and no physical abnormalities, other than the HS-RDEB, have been noted.

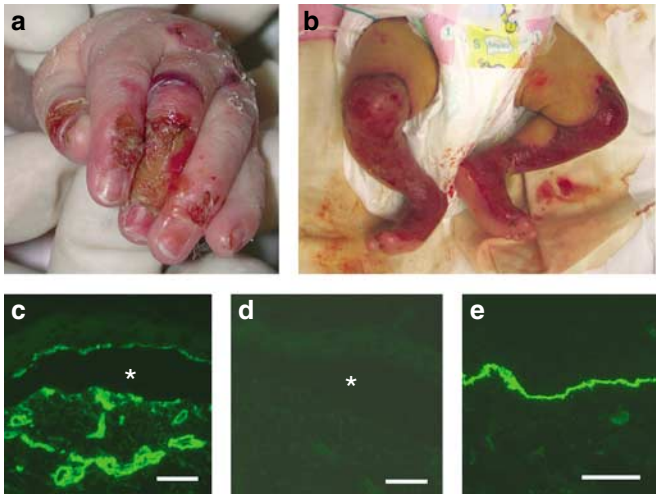


**Figure 1. Clinical examination and skin immunohistochemistry indicate that this child has Hallopeau–Siemens recessive dystrophic epidermolysis bullosa.** (**a**) Skin erosions and wound exudate/crust on the dorsum of the left hand and fingers; (**b**) extensive skin loss and erosions on the lower legs and feet; (**c**) type IV collagen immunostaining maps to the roof of a blister in the child's skin (blister cavity indicated by asterisk; bar = 50 $\mu$m); (**d**) there is a complete absence of type VII collagen labeling in the child's skin (blister cavity indicated by asterisk; bar = 50 $\mu$m); and (**e**) in contrast, type VII collagen immunolabeling in normal control skin shows bright linear fluorescence at the dermal–epidermal junction (bar = 50 $\mu$m).

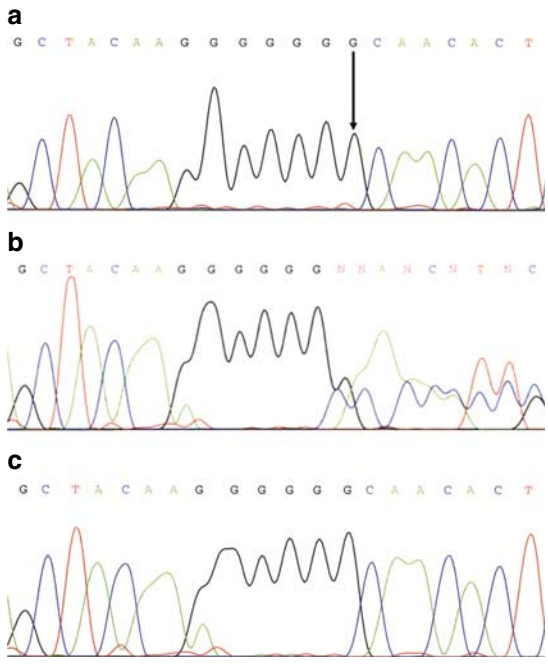


**Figure 2. Nucleotide sequencing reveals a homozygous frameshift in *COL7A1* in the affected child.** Mother is a heterozygous carrier but father is not. (**a**) Within exon 3 in the affected child's DNA, there is a homozygous single nucleotide insertion, 345insG (arrow): this frameshift results in a premature termination codon 36-bp downstream; (**b**) sequencing of the mother's DNA reveals that she is a heterozygous carrier of 345insG; and (**c**) by contrast, the father's DNA shows wild-type exon 3 sequence only.

### The molecular basis of the HS-RDEB is a new homozygous frameshift mutation, 345insG, in exon 3 of *COL7A1*

Direct automated sequencing revealed that the affected child was homozygous for a single-nucleotide insertion mutation, 345insG, in exon 3 of *COL7A1* (Figure 2a), resulting in a premature termination codon 36-bp downstream. This mutation provides an explanation for the complete absence of type VII collagen immunolabeling on the skin biopsy (Figure 1d) and, although specific to this family, this mutation is fully consistent with HS-RDEB. Examination of the maternal DNA revealed that the mother was a heterozygous carrier of this mutation (Figure 2b). The father's DNA, however, showed only wild-type sequence (Figure 2c). Thus, the affected child was homozygous for the frameshift mutation, 345insG, and at least one allele was inherited from the mother.

### Microsatellite analysis identifies complete maternal isodisomy of chromosome 3 and excludes non-paternity

To establish the origin of the affected child's second mutant allele, haplotype analysis of the *COL7A1* locus was initially performed based on inheritance of seven highly heterozygous microsatellite markers within 2 cM of the gene. These microsatellites comprised: D3S3678, D3S1581, D3S3629, D3S1568, D3S3026, D3S1578, and D3S1289 (see Table 1). The results showed that the affected child was homozygous for all seven markers, three of which (D3S3678, D3S1581, and D3S1578) showed an absence of a paternally derived

**Table 1. Haplotype analysis using microsatellite markers spanning chromosome 3 is consistent with complete maternal isodisomy**

| Locus | Cytogenetic location | Mother | | Affected child | | Father | |
|---|---|---|---|---|---|---|---|
| D3S1297 | 3p26.3 | 358 | **358** | **358** | **358** | 352 | 362 |
| D3S1304 | 3p26.1 | 258 | **268** | **268** | **268** | 258 | 268 |
| D3S1263* | 3p25.3 | 200 | **196** | **196** | **196** | 204 | 208 |
| D3S2338* | 3p24.3 | 90 | **102** | **102** | **102** | 104 | 104 |
| D3S1277 | 3p23 | 297 | **295** | **295** | **295** | 293 | 295 |
| D3S3678* | 3p22.1 | 311 | **313** | **313** | **313** | 307 | 309 |
| D3S1581 | 3p21.31 | 161 | **161** | **161** | **161** | 157 | 157 |
| *COL7A1* 345insG | 3p21.31 | −/+ | | +/+ | | −/− | |
| D3S3629 | 3p21.31 | 339 | **337** | **337** | **337** | 337 | 337 |
| D3S1568 | 3p21.31 | 337 | **335** | **335** | **335** | 335 | 343 |
| D3S3026 | 3p21.2 | 224 | **224** | **224** | **224** | 224 | 224 |
| D3S1578 | 3p21.1 | 200 | **200** | **200** | **200** | 188 | 196 |
| D3S1289 | 3p21.1–p14.3 | 245 | **241** | **241** | **241** | 241 | 247 |
| D3S1300* | 3p14.2 | 254 | **250** | **250** | **250** | 235 | 235 |
| D3S1285 | 3p14.1 | 245 | **241** | **241** | **241** | 241 | 243 |
| D3S1566* | 3p13 | 167 | **173** | **173** | **173** | 167 | 175 |
| D3S3681* | 3p12.3–p12.2 | 138 | **154** | **154** | **154** | 146 | 150 |
| D3S1271 | 3q12.2 | 92 | **88** | **88** | **88** | 88 | 88 |
| D3S1278 | 3q13.31 | 231 | **231** | **231** | **231** | 231 | 231 |
| D3S1267* | 3q21.1 | 120 | **116** | **116** | **116** | 96 | 96 |
| D3S1292* | 3q22.1 | 128 | **131** | **131** | **131** | 120 | 143 |
| D3S1569* | 3q24 | 170 | **162** | **162** | **162** | 164 | 178 |
| D3S1279* | 3q25.1 | 270 | **266** | **266** | **266** | 272 | 272 |
| D3S1614 | 3q26.2 | 108 | **108** | **108** | **108** | 108 | 118 |
| D3S1565 | 3q26.31 | 180 | **180** | **180** | **180** | 186 | 186 |
| D3S1262* | 3q27.3 | 130 | **122** | **122** | **122** | 112 | 124 |
| D3S1580 | 3q28 | 231 | **231** | **231** | **231** | 226 | 234 |
| D3S1601 | 3q28 | 306 | **306** | **306** | **306** | 306 | 320 |
| D3S1311 | 3q29 | 135 | **135** | **135** | **135** | 145 | 151 |

The data show that the affected child has inherited two copies of a single maternal chromosome 3 (highlighted in bold). Marker order and cytogenetic location are derived from USCS Genome Bioinformatics (http://genome.ucsc.edu/); fully informative markers are indicated by asterisks (*).

chromosome 3, and one marker (D3S3678) was fully informative for the child inheriting two copies of the mutated maternal allele. To examine the inheritance of the mutated alleles in the affected child further and to explore the possibility of UPD in this family, extensive genotype analysis of the entire chromosome 3 was performed using 21 additional microsatellite markers along the entire chromosome 3 (Table 1). The affected child was homozygous for all 21 of these markers, 10 of which were fully informative for inheritance of two copies of a single maternal chromosome 3 in the affected child. For the non-chromosome 3 markers, there were no discrepancies in the segregation of maternal and paternal alleles to the affected child, thus excluding non-paternity (data not shown). Normal karyotyping ruled out monosomy of chromosome 3. The results in this family are consistent with the inheritance of two identical copies of a single chromosome 3 homolog from the mother, thus indicating complete maternal isodisomy as the molecular basis of the HS-RDEB in this family.

## DISCUSSION

UPD (isodisomy or meroisodisomy) with homozygosity of recessive alleles is being increasingly recognized as the molecular basis for several autosomal recessive disorders (Zlotogora, 2004). In fact, there have been over 35 reported cases of recessive diseases resulting from UPD (Kotzot and Utermann, 2005), although only two have involved chromosome 3. The first was a case of Fanconi Bickel syndrome

(OMIM 227810) caused by maternal isodisomy of chromosome 3 and reduction to homozygosity of a mutation in the glucose transporter gene *GLUT2* (Hoffman *et al.*, 2004). The second was a patient with a congenital disorder of glycosylation type Id (OMIM 601110) caused by a homozygous mutation in a mannosyl transferase gene, *ALG3*, resulting from a *de novo* mutation in combination with segmental maternal isodisomy (Schollen *et al.*, 2005). Our case of HS-RDEB represents the third case of UPD of chromosome 3 and the second case of complete maternal isodisomy for this chromosome. However, this is not the first case of epidermolysis bullosa to result from UPD. Indeed, there have been four reported cases, all involving chromosome 1 in patients with Herlitz junctional epidermolysis bullosa (OMIM 226700). Three of these cases resulted from reduction to homozygosity of a mutation in the *LAMB3* gene (locus 1q32.2) (Pulkkinen *et al.*, 1997; Takizawa *et al.*, 1998; Fassihi *et al.*, 2005) and one involved a mutation in *LAMC2* (1q25.3) (Takizawa *et al.*, 2000).

For certain chromosomes, UPD can also result in distinct phenotypes depending on the parental origin of the chromosomes, a phenomenon known as genomic imprinting. This parent-of-origin specific gene expression is determined by epigenetic modification of a specific gene or, more often, a group of genes, such that gene transcription is altered and only one inherited copy of the relevant imprinted gene(s) is expressed in the embryo. (Swales and Spears, 2005). This means that during development, the parental genomes function unequally in the offspring, the most common examples of genomic imprinting being Prader–Willi (OMIM 176270) and Angelman (OMIM 105830) syndromes, which can result from maternal or paternal UPD for chromosome 15, respectively (Nicholls and Knepper, 2001). Three phenotype abnormalities commonly associated with UPD for chromosomes with imprinting are intrauterine growth retardation, developmental delay, and reduced stature (Miozzo and Simoni, 2002; Coan *et al.*, 2005). For the chromosome 3 UPD in our case of HS-RDEB, the child did have a low birth weight; however, it is plausible that any intrauterine growth restriction could simply have been due to the blistering skin disease (Fox *et al.*, 2003). Moreover, physical examination over the first year of this child's life has not shown any significant growth or developmental abnormalities, observations that suggest an absence of clinically significant maternally imprinted genes on chromosome 3, although clearly further clinical follow-up will be necessary to confirm this initial impression. Indeed, thus far there have been no reports of imprinted genes on human chromosome 3 (Morison *et al.*, 2005).

The mechanisms underlying UPD are diverse and include gamete complementation (non-disjunction in meiosis leading to a diploid gamete with two copies of a chromosome fertilized by a nullosomic gamete lacking the same chromosome), trisomy rescue (chromosome loss in trisomy), monosomy rescue (chromosome duplication in monosomy), and postfertilization error (Robinson, 2000). In monosomy rescue, non-disjunction in meiotic division II in one parent results in disomic and nullisomic gametes. Subsequent to fertilization of the nullisomic gamete with a haploid gamete, the entire chromosome is duplicated, yielding two identical copies of this chromosome. Monosomy rescue must occur early after fertilization as most monosomies are lethal, resulting in miscarriage early in pregnancy. In our patient, fertilization of a nullisomic sperm by a normal egg with subsequent salvage of a monosomy by postfertilization duplication of the maternal chromosome 3 is the most likely cause of UPD and homozygosity for the *COL7A1* locus containing the mutation 345insG (Kotzot and Utermann, 2005). However, loss of paternally derived chromosome 3 from a trisomic zygote (trisomy rescue) or fertilization between a disomic egg (non-disjunction at meiosis II) and a nullisomic sperm (gamete complementation) with no preceding recombination at meiosis I might also be possible.

UPD is a rare but important cause of autosomal recessive disorders, with significant implications for both mutation screening and genetic counseling. In screening for mutations in HS-RDEB, or indeed any autosomal recessive condition, DNA samples should be obtained from both parents as well as the proband so that transmission of the mutated allele(s) can be fully determined. Parents, in whom UPD has occurred, can be counseled that the possibility of recurrence of HS-RDEB is much lower than the usual 25% risk in parents who are both heterozygous carriers of this autosomal recessive disorder. Indeed, thus far there have been no reports of recurrence of any genetic disease in such couples.

In summary, this is the first case of UPD to be described in HS-RDEB and is only the third example of UPD of chromosome 3 to be reported. The lack of an observable phenotype during the first year of life other than the HS-RDEB in this case of maternal isodisomy suggests that maternally derived genes on human chromosome 3 are not imprinted.

## MATERIALS AND METHODS

### Immunofluorescence microscopy

Following ethical approval, informed consent and in compliance with the Declaration of Helsinki Principles, a skin biopsy was taken under local anesthesia from clinically uninvolved skin on the buttock. Indirect immunofluorescence staining was performed on 5 $\mu$m cryosections of skin with the monoclonal antibodies LH7:2 (NC-1 domain of type VII collagen, a gift from Dr I.M. Leigh) (Leigh *et al.*, 1988), GB3 (conformational epitope on $\gamma$2 chain of laminin 5, Oxford Biotechnology Ltd (Kidlington, UK) (Verrando *et al.*, 1991) and COL94 (type IV collagen, Sigma, Poole, UK). The antibodies were diluted 1:1,000, 1:300, and 1:500, respectively, in phosphate-buffered saline/bovine serum albumin. Labeling procedures were as described previously (Kennedy *et al.*, 1985). Fluorescein isothiocyanate-labeled anti-mouse and anti-rabbit secondary antibodies (Dako, Glostrup, Denmark) were used diluted 1:200 in phosphate-buffered saline/bovine serum albumin.

### Mutation analysis

DNA was extracted from peripheral blood samples taken from the proband and his parents using standard protocols. Mutation detection strategy consisted of heteroduplex scanning by conformation-sensitive gel electrophoresis of all 118 exons of *COL7A1*. Laboratory protocols and details of the specific primers have been

described elsewhere (Christiano *et al.*, 1997b). The corresponding PCR products showing heteroduplexes were subjected to bi-directional automated nucleotide sequencing using an ABI Prism 310 Genetic Analyzer.

### Genotype analysis

For haplotype analysis of the *COL7A1* locus, seven highly heterozygous microsatellite markers within 2 cM of the gene were initially tested (D1S3678, D3S1581, D3S3629, D3S1568, D3S3026, D3S1578, and D1S1289). In addition, 21 further microsatellite markers spanning the entire chromosome 3, approximately 10 cM apart, were analysed from the proband and his parents. Non-paternity was investigated using six non-chromosome 3 markers (D1S425, D1S2703, D1S205, D1S491, D6S291, and D6S276). All microsatellite markers were from the ABI Prism Linkage Mapping Set Version 2.5 (Applied Biosystems, Warrington, UK), were amplified with fluorescently labeled oligonucleotides, and used under conditions recommended by the manufacturer. Electrophoretic analysis was performed on an ABI Prism 310 Genetic Analyzer with Performance Optimized Polymer 4 (POP4) using Genescan software (Applied Biosystems). The allele sizes were analysed using Genotyper software (Applied Biosystems).

## CONFLICT OF INTEREST

The authors state no conflict of interest.

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