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Inherited surfactant deficiency due to uniparental disomy of rare mutations in the surfactant protein-B and ATP binding cassette, subfamily A, member 3 genes

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Abstract

Objective—To characterize inheritance of homozygous, rare, recessive loss-of-function mutations in the surfactant protein-B (*SFTPB*) or ATP binding cassette, subfamily A, member 3 (*ABCA3*) genes in newborns with lethal respiratory failure.

Study design—We resequenced parents whose infants were homozygous for mutations in *SFTPB* or *ABCA3*. For infants with only one heterozygous parent, we performed microsatellite analysis for chromosomes 2 (*SFTPB*) and 16 (*ABCA3*).

Results—We identified one infant homozygous for the c.1549C>GAA mutation (121ins2) in *SFTPB* for whom only the mother was heterozygous and 3 infants homozygous for mutations in *ABCA3* (p.K914R, p.P147L, and c.806_7insGCT) for whom only the fathers were heterozygous. For

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the SP-B deficient infant, microsatellite markers confirmed maternal heterodisomy with segmental isodisomy. Microsatellite analysis confirmed paternal isodisomy for the three ABCA3 deficient infants. Two ABCA3 deficient infants underwent lung transplantation at 3 and 5 months of age, respectively, and two infants died. None exhibited any non-pulmonary phenotype.

Conclusions—Uniparental disomy should be suspected in infants with rare homozygous mutations in *SFTPB* or *ABCA3*. Confirmation of parental carrier status is important to provide recurrence risk and to monitor expression of other phenotypes that may emerge through reduction to homozygosity of recessive alleles.

Keywords

respiratory distress syndrome; pulmonary surfactant; genetic disorders; newborn

Introduction

Inherited disorders of pulmonary surfactant metabolism due to recessive loss-of-function mutations in the genes encoding surfactant protein-B (SP-B, MIM #178640) and the ATP binding cassette family member A3 (ABCA3, MIM #601615) present as lethal surfactant deficiency in the newborn period (1,2). Approximately 35 loss of function mutations have been identified in the SP-B gene (*SFTPB*, NCBI gene ID: 6439) which is localized to chromosome 2p12-11.2, and over 150 loss of function mutations have been identified in the *ABCA3* gene (*ABCA3*, (NCBI gene ID: 21), which is localized to chromosome 16p13.3 [(3–6) and unpublished data]. All previously reported cases have resulted from homozygous or compound heterozygous expression of the mutated alleles, and either confirmed or assumed to be inherited from each parent, in which case a 25% risk of recurrence would be predicted. Alternative mechanisms of inheritance have not been previously reported.

Uniparental disomy (UPD) occurs when a chromosome pair is inherited from only one parent. It is termed isodisomy when a single parental chromosome is duplicated and is termed heterodisomy when both copies of a single chromosome pair are present. Segmental uniparental iso- or hetero- disomy results from crossing over between a single chromosome pair. The frequency with which UPD occurs is probably rare, and any estimates are likely to be biased by ascertainment (7,8). Cases of maternally derived UPD most commonly involve chromosomes 7, 14, 15, and 16 and are identified more frequently than cases of paternally derived UPD, which most often involve chromosomes 6 and 15 (extensive reviews of UPD can be found in References 7 and 8). No specific phenotype has been directly attributed to uniparental disomy for chromosomes 2 or 16, however, single gene defects that become manifest through reduction of a recessive allele to homozygosity have been reported (9–16). In this report, we describe the first cases of inherited surfactant deficiency resulting from uniparental disomy.

Case reports

Patient with SP-B deficiency—This 3.0 kg term male infant was the first child of non-consanguineous parents born via Cesarean for fetal distress after an uneventful pregnancy. Apgar scores were 6 and 9 at 1 and 5 minutes, respectively. The child developed respiratory distress with diffuse haziness on chest radiograph. He required intubation within 24 hours of age and received surfactant with a transient improvement in oxygenation. He received additional surfactant at 5 and 6 days with limited response, and thus proceeded to lung biopsy at 8 days of age. A persistent pneumothorax following the biopsy prompted three attempts at pleurodesis with tetracycline. Due to progressive respiratory dysfunction, he subsequently required high frequency ventilation and neuromuscular blockade. There was no response to administration of granulocyte-macrophage colony stimulating factor or hydroxychloroquine.

Immunohistochemical analysis of the lung biopsy revealed absence of SP-B and intra-alveolar accumulation of pro surfactant protein-C (SP-C), and genetic analysis revealed that he was homozygous for the g.1549C>GAA (121ins2) mutation in *SFTPB* (17). The infant progressively deteriorated and expired at 30 days of age. The parents are of Western European descent and the family history is negative for respiratory disease.

Patient 1 with ABCA3 deficiency—This 3.7 kg term male infant was born to a 27 year old Gravida 3 with an uneventful pregnancy and delivery. Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. The child developed respiratory distress with diffuse haziness on chest radiograph and required intubation at approximately 36 hours of age, coincident with development of a pneumothorax requiring thoracostomy tube placement. Due to progressive respiratory dysfunction, he subsequently was managed with inhaled nitric oxide and high frequency ventilation. Open lung biopsy performed at 13 days of age revealed pneumocyte hyperplasia and finely granular intra-alveolar eosinophilic material, consistent with a disorder of surfactant metabolism. With electron microscopy, dense inclusions within the lamellar bodies were identified, as reported previously with ABCA3 deficiency (4,18). Sequence analysis of *ABCA3* revealed a novel homozygous A>G transition in the second nucleotide of codon 914 (c.2741A>G) that changes lysine to arginine (p.K914R) and is predicted to be “not tolerated” by SIFT (<http://blocks.flhrc.org/sift/SIFT.html>) and “potentially damaging” by Polyphen (<http://genetics.bwh.harvard.edu/pph/>). This variant has not been identified in over 600 non-ethnically matched chromosomes that have been evaluated through ongoing analyses in our laboratories. Continuing deterioration and the likelihood that the respiratory process was irreversible prompted listing for lung transplantation at 3 months of age; lung transplantation was performed at 5 months of age.

Two older siblings from a previous marriage are healthy. There was no history of consanguinity: the mother is of Mexican ancestry, the father is of Mexican and Irish ancestry. The family history is negative for respiratory disease.

Patient 2 with ABCA3 deficiency—This 3.3 kg term female infant was born to a 29 year old prima gravida via elective Cesarean. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively and she was discharged after an uneventful hospital course. Over the first 2 weeks, she exhibited poor weight gain and developed pallor and hypoxemia, which prompted hospitalization. Chest radiography and computed tomography demonstrated interstitial infiltrates; the hypoxemia improved with nasal cannula oxygen. Lipid laden macrophages in bronchoalveolar lavage fluid prompted evaluation for aspiration as well as disorders of surfactant metabolism. Deteriorating gas exchange and increasing infiltrates on chest imaging prompted fundoplication and gastrostomy tube placement at 5 weeks of age, following which she was unable to be extubated. Progressive respiratory dysfunction necessitated high frequency ventilation; corticosteroids and hydroxychloroquine failed to provide any improvement in gas exchange. Sequence analysis of *ABCA3* revealed a homozygous C>T transition in codon 147 that changes a proline to leucine (c.440C>T; p.P147L) and is predicted to be deleterious by SIFT and Polyphen. This variant was previously identified in two unrelated subjects with respiratory dysfunction and another deleterious mutation in *ABCA3* [(19) and unpublished data]. Continuing deterioration and the likelihood that the respiratory process was irreversible prompted listing for lung transplantation at 2 months of age; lung transplantation was performed at 3 months of age.

There is no history of consanguinity: the mother is of German descent and the father is of German and Native American descent. The family history is negative for respiratory disease.

Patient 3 with ABCA3 deficiency—This 3.8 kg term male infant was born to a 25 year old Gravida 2 via elective Cesarean for pregnancy-induced hypertension and footling breech.

Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. He rapidly developed respiratory failure and required intubation and surfactant administration. Chest radiograph demonstrated bilateral streaky infiltrates. He was briefly extubated at 24 hours of life, but developed a pneumothorax that required thoracostomy tube placement, re-intubation, and high frequency ventilation. He had transient responses to repeated surfactant and corticosteroid administration, but each subsequent course was less effective. Sequence analysis of *ABCA3* revealed a homozygous 3 nucleotide insertion in exon 8 (c.806_807insGCT). This finding prompted discussions regarding lung transplantation, which ultimately the parents declined and the infant expired at 6 weeks of age.

An older sibling is healthy. There is no history of consanguinity: the parents are of Western European descent. The family history is negative for respiratory disease.

Methods

SFTPB sequencing

SFTPB amplification and allele-specific PCR were performed as previously described on DNA obtained from the SP-B deficient infant and his parents (17).

ABCA3 sequencing

We designed M13-tailed primers to amplify all exons and at least 50 nucleotides of surrounding intron sequence of *ABCA3* and performed automated sequencing as described previously (20). To eliminate the possibility that a deletion of greater than 50 nucleotides was present that would appear as a homozygous variant on sequencing, we performed ethidium bromide agarose gel electrophoresis to ensure uniform and anticipated fragment sizes (21).

Chromosome 2 and 16 microsatellite markers

Chromosome 2 (n=35) and 16 (n=9) STR markers were selected from an ABI PRISM Linkage Mapping Set (Applied Biosystems, Foster City, CA). PCR was carried out in standard fashion and amplification performed in a Veriti Thermal Cycler (Applied Biosystems) for chromosome 16 markers and a Thermo Hybaid MBS 0.2S (Needham Heights, MA) for chromosome 2 markers. Amplification of PCR products was confirmed prior to fragment sizing on a 3730xl DNA Sequencer (Applied Biosystems) using polymer POP7. When possible, PCR products were pooled by multiplexing markers of different size ranges and dyes. Data were collected and analyzed with GeneMapper v3.7 (Applied Biosystems) that calculates fragment length in reference to an internal lane standard (Genescan 500). Allele calls were manually checked for accuracy.

Selected markers on chromosomes 18, 19, 21, and 22 were similarly analyzed to confirm paternity for the SP-B deficient infant (22).

Survey of cases of SP-B or *ABCA3* deficiency

To determine the proportion of homozygous loss of function mutations in *SFTPB* or *ABCA3* that these cases represented, we surveyed databases at Ambry Genetics, Johns Hopkins University, and Washington University for cases of homozygous SP-B or *ABCA3* deficiency and for whom parental confirmation was available.

The study was approved by Washington University Human Research Protection Office and the Johns Hopkins University Institutional Review Board; informed consent was obtained from the parents.

Results

SP-B mutation

Allele specific PCR for 121ins2 confirmed that the SP-B deficient infant was homozygous for c.1549C>GAA (121ins2) and the mother was heterozygous; however the mutation could not be identified in the father. Analysis of microsatellite markers on chromosome 2 showed unequivocal reduction to homozygosity of the maternal allele at 9 loci with absence of paternal contribution at 9 other loci where the infant was heterozygous (Table 1). Heterozygosity at loci separated by markers that were reduced to homozygosity suggests maternal heterodisomy with segmental isodisomy resulting from 5 meiotic recombination events. Paternal markers from Chromosomes 18, 19, 21, and 22 were present, confirming paternity (data not shown). Two structurally normal copies of chromosome 2 were present on karyotype analysis.

ABCA3 mutations

ABCA3 deficient infant 1—This infant was homozygous for G at c.2741; the father was heterozygous A/G and the mother was homozygous A. Similar results were found for 4 other informative variants spanning approximately 7 kb around the site of the mutation: the infant was homozygous for the rare variant, the mother was homozygous for the common variant, and the father was heterozygous (Table 2). All fragments were of the predicted size by electrophoresis, suggesting that a deletion more than 50 nucleotides in length in this region was unlikely. The infant was homozygous for the paternal allele at 7 informative markers that were located along the length of chromosome 16, suggesting paternal isodisomy (Table 3). Two copies of chromosome 16 were present on karyotype analysis and no other deleterious variants in *ABCA3*, *SFTPB*, or the SP-C gene (*SFTPC*) were identified; the patient was heterozygous for the common, benign nonsynonymous *SFTPC* variants, p.T138N and p.S186N.

ABCA3 deficient infant 2—This infant was homozygous for T at position c.440; the father was heterozygous C/T and the mother was homozygous C. The infant was homozygous for the rare variant, the mother was homozygous for the common variant, and the father was heterozygous for the only other informative variant in *ABCA3* (Table 2). All fragments were of the predicted size by electrophoresis. The infant was also homozygous at all markers along chromosome 16, three of which were unequivocal for the paternal allele (Table 3). No other deleterious variants in *ABCA3*, *SFTPB*, or *SFTPC* were identified; the patient was heterozygous for the common, benign nonsynonymous *SFTPB* variant, p.I131T. Chromosome analysis demonstrated two copies of chromosome 16 with no apparent structural abnormalities.

ABCA3 deficient infant 3—This infant was homozygous for the three nucleotide c.806_7insGCT insertion; the father was heterozygous and the mother was homozygous for the consensus sequence. Although the infant was homozygous for the rare variant at four additional sites in *ABCA3*, these loci were not informative because each parent also carried at least one rare allele at each site. The infant was homozygous at all markers along chromosome 16, four of which were unequivocal for the paternal allele, suggesting paternal isodisomy. Two copies of chromosome 16 were present on karyotype analysis and no other deleterious variants in *ABCA3*, *SFTPB*, or *SFTPC* were identified; the patient was heterozygous for the same *SFTPB* variant, p.I131T.

Rate of uniparental disomy in surfactant dysfunction syndromes

In the Ambry Genetics, Johns Hopkins, and Washington University databases there were 38 unique families with homozygous loss of function mutations in *SFTPB* for whom parental genotypes were available; the case of SP-B deficiency in this report was the only identified case of UPD for chromosome 2 among them. In these databases, there were 33 unique families

with homozygous loss of function mutations in *ABCA3*, 20 for whom the parental genotypes were available. The three cases in this report were the only identified cases of UPD for chromosome 16.

Discussion

We have identified the first four known cases of inherited surfactant dysfunction mutations due to uniparental disomy: one child with SP-B deficiency due to maternal heterodisomy of chromosome 2 with segmental isodisomy and three cases of *ABCA3* deficiency due to paternal uniparental disomy of chromosome 16. The low, but perceptible prevalence in our combined experience highlights the importance of confirming that the parents are truly carriers of the specific mutation.

Mechanisms of UPD

Maternal UPD is estimated to be approximately 3 times as prevalent as paternal UPD (8,23) and is thought to result from nondisjunction during maternal meiosis I leading to trisomy and a post-zygotic mitotic correction that eliminates the paternal chromosome (23–25). Most of these cases result in heterodisomy, in which the child carries both homologs of one of the mother's chromosome pairs. Although there is likely to be ascertainment bias in identifying disorders associated with chromosomes known to be imprinted, among the reports of maternal UPD, cases involving chromosomes 7, 14, 15, and 16 are most common, and those involving chromosomes 1 and 2 are more infrequent (25). In the case of the SP-B deficient infant, the reduction to homozygosity at loci along chromosome 2 where the mother was heterozygous, including the mutated allele in *SFTPB*, the presence of both maternal alleles at other loci, and the absence of paternal contribution suggest heterodisomy for maternal chromosome 2 but with several recombination events that resulted in segmental isodisomy, as well (Table 1).

Paternal UPD is much rarer, with cases involving chromosomes 6 and 15 occurring more frequently than those involving chromosomes 1, 2, and 7, and with only isolated reports involving chromosome 16 (25). Paternal UPD is thought to arise from one of three mechanisms: from nondisjunction at paternal meiosis II and trisomy rescue eliminating the maternal chromosome; from maternal meiotic nullisomy and mitotic duplication of the lone paternal chromosome (monosomy rescue); or from a postzygotic mitotic error (23,25). The latter two mechanisms would be more likely to result in isodisomy, such as that seen with the *ABCA3* deficient infants. In the absence of placental pathology to determine mosaicism for trisomy 16 or high density SNP array analysis, we can only speculate about which mechanisms resulted in the paternal UPD for these infants (26).

The frequency with which *ABCA3* mutations are being identified in newborns and children with lethal and chronic respiratory disease coupled with the frequency of aneuploidy 16 in pregnancy suggests that disease due to homozygous recessive alleles would occur with some regularity (27–29). However, the limited number of reports suggests that a high rate of fetal loss rate or a lack of phenotype otherwise prevents identification of these occurrences. Furthermore, the fact that all these cases are paternally derived also seems unusual, but could have occurred by chance.

Phenotypes associated with UPD2 and UPD16

In trying to determine if phenotypes can be ascribed to UPD 2 or 16, it is difficult to know if reported cases simply reflect ascertainment, or if there are true phenotypes that could result from reduction to homozygosity of variants in one or more genes. For example, normal phenotypes have been reported with known maternal isodisomy and heterodisomy for chromosome 2, but intrauterine growth restriction has also been commonly reported among

the cases of UPD2 and in the absence of an identifiable gene defect (30–33). The first report of maternal UPD for chromosome 2 was a baby with intrauterine growth restriction, hypothyroidism and hyaline membrane disease that evolved into bronchopulmonary dysplasia (34). It would be of interest to determine whether this infant had a mutation in *SFTPB* that contributed to the respiratory dysfunction.

Phenotypes associated with maternal UPD for chromosome 16 have included body stalk anomaly, intrauterine growth restriction, imperforate anus, and congenital heart disease (29, 35–39). There has only been one previously published and confirmed report of a phenotype associated with paternal UPD for chromosome 16 in the absence of an identified single gene defect: a growth restricted female with bilateral pes calcaneus and rudimentary mandibular dental arch that were described to be of minimal consequence (29).

Identified single gene defects arising from paternal and maternal uniparental disomy 2 are summarized in Table 4. The SP-B deficient infant in this report adds to the expanding list of disorders resulting from reduction to homozygosity of deleterious mutations in chromosome 2. Fewer single gene defects have been reported for UPD 16 (Table 4). Aside from these cases of ABCA3 deficiency, the only other known single gene defect resulting from paternal UPD for chromosome 16 is a child with Type 1a congenital disorder of glycosylation (CDG) due to a mutation in the phosphomannomutase 2 gene (*PMM2*) (G.E. Tiller, personal communication).

Lung transplantation for the two ABCA3 deficient infants permits longer-term surveillance for other potential phenotypes associated with paternal UPD 16. Although no specific consequences have emerged in the first 6 and 12 months following transplantation, it will be important to determine if any future adverse consequences are a result of the underlying ABCA3 deficiency, the pre- and post-transplant illness and treatment, or the unmasking of other functional variants that have been reduced to homozygosity. These cases also demonstrate the necessity for confirming heterozygosity in the parents, not only to confirm the mutation and to exclude the presence of a large deletion, especially with novel mutations, but to accurately relay the recurrence risk for families, which, in the case of UPD, decreases to significantly less than the 25% expected from Mendelian inheritance patterns.

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Abbreviations

ABCA3	ATP binding cassette subfamily A, member 3
<i>ABCA3</i>	ABCA3 gene
CDG	congenital disorder of glycosylation
PCR	polymerase chain reaction
SP-B	surfactant protein-B, <i>SFTPB</i> , SP-B gene
SP-C	surfactant protein-C
<i>SFTPC</i>	SP-C gene
UPD	uniparental disomy

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Table 1

Analysis of Chromosome 2 microsatellite markers

Marker	Position	Child Allele	Mother Allele	Father Allele	
D2S319 *	2p25	1 ⁺	1, 3	2, 3	Likely UPID **
D2S162	2p24	2	2	1, 3	
D2S1360		2	1, 2	2, 3	
D2S131		1	1	1, 2	
D2S305 *		1	1, 2	2, 3	
D2S168 *	2p23	1	1, 3	2, 4	Likely UPID **
D2S1788	2p21	1, 2	1, 2	3, 4	
D2S165		3, 4	3, 4	1, 2	
D2S367		1, 3	1, 3	2, 4	
D2S177	2p16	2, 3	2, 3	1, 4	
D2S391		2	2	1, 2	Likely UPID
D2S337	2p15	1, 2	1, 2	3, 4	
D2S285 *		3	3, 4	1, 2	
D2S286		1	1	2, 3	
D2S139	2p12	2	1, 2	2, 3	
D2S1331 *		1	1, 2	3, 4	
D2S2161		2	2	1, 2	
<i>SFTPB</i> *	2p12	c.1549 C>GAA	c.1549 C>GAA, WT	WT, WT	
D2S2232	2p11	(1) ⁰	1, 2	1, 3	
D2S388		1	1	1, 2	
D2S113 *		3	1, 3	1, 2	Likely UPID
D2S347	2q21	1	1	1, 2	
D2S151		2	2	1, 2	
D2S142		2	2	1, 2	
D2S1326 *	2q22	1	1, 3	2, 4	
D2S326 *		4	2, 4	1, 3	
D2S364		1, 2	1, 2	2, 3	
D2S117		2, 3	2, 3	1, 4	Likely UPID

Marker	Position	Child Allele	Mother Allele	Father Allele	
D2S325		1,2	1,2	2,3	
D2S164		1	1	2,3	
D2S126		1,2	1,2	3,4	
D2S396		(2) ^o	2,3	1,2	Likely UPID
D2S172	2q37	(1) ^o	1,3	1,2	
D2S206		1,2	1,2	1,2	
D2S338		1,2	1,2	2	Likely UPHD
D2S125		2,4	2,4	1,2	

⁺ relative amplicon length

^{*} unequivocal reduction of maternal allele to homozygosity (isodisomy)

^{**} UPID uniparental isodisomy; UPHD uniparental heterodisomy

- italics indicate absence of paternal contribution

- Lighter shaded area indicates region of heterozygosity for both maternal alleles (heterodisomy)

^o indicates region of likely isodisomy, though a paternal contribution cannot be excluded

Table 2Informative variants in *ABCA3*

Variant ID		Child	Mother	Father
ABCA3 infant 1				
rs323017	c.2514-93 A>G (Intron 19)	G/G	A/A	A/G
rs313908	c.2701-33 C>G (Intron 20)	G/G	C/C	C/G
Mutation	c.2741A>G (p.K914R)	G/G	A/A	A/G
rs313909	c.3004+34 C>T (Intron 21)	C/C	T/T	C/T
rs1183064	c.3704-116 A>T (Intron 24)	T/T	A/A	A/T
ABCA3 infant 2				
N/A	(c.-27 + 126 G>A (Intron 3)	A/A	G/G	A/G
Mutation	c.440C>T (p.P147L)	T/T	C/C	C/T
rs170447	c.1741+33 G>A (Intron 14)	A/A	A/G	A/G
rs2240523	c.1742-116 C>T (Intron 14)	C/C	C/T	C/T
ABCA3 infant 3				
Mutation	c.806_807insGCT	ins/ins	normal/normal	ins/normal

Table 3

Analysis of chromosome 16 microsatellite markers

Marker	Position	ABCA3 Pt 1 marker	Mother 1 marker	Father 1 marker	ABCA3 Pt 2 marker	Mother 2 marker	Father 2 marker	ABCA3 Pt 3 marker	Mother 3 marker	Father 3 marker
D16S423	16p13	7*	4	5,7	6	2,4	6	3	3	1,3
DS16S407	16p13	3	2,5	3,10	9	8,9	8,9	1	6,7	1,4
D16S405	16p13	3	2	3,5	5	1,5	5	4	4,5	4,5
D16S420	16p12	4	2,5	4	6	6	1,6	3	6	3,6
D16S401	16p12	2	2,6	2,6	5	3,5	5,6	5	3,4	1,5
D16S411	16q12	3	2,3	1,3	2	3,4	2	1	1,2	1,1
D16S503	16q21	6	5,7	6	6	2,5	2,6	1	1,4	1,3
D16S516	16q21-22	6	4	6,8	3	3,8	3	5	2,7	1,5
D16S511	16q23-24	3	1,8	3,5	7	5,7	6,7	4	2,4	4,9

Shaded cells indicate informative marker

* Relative amplicon lengths

*** regions of likely uniparental isodisomy (UPID) and heterodisomy (UPHD) for ABCA3 Patient 2 only. Patients 1 and 3 are likely to have isodisomy for the entire chromosome 16.

Table 4

Single gene defects identified with UPD 2 and 16.

Gene	Location	Phenotype	Parental origin	Reference number
Chromosome 2				
thyroid peroxidase (<i>TPO</i>)	2p25	hypothyroidism	Maternal	(10)
5 α -reductase (<i>SRD5A2</i>)	2p23	pseudohermaphroditism	Paternal	(9)
α -subunit of mitochondrial trifunctional protein (<i>HADHA</i>)	2p23	cardiomyopathy due to fatty acid β -oxidation defect	Maternal	(12)
surfactant protein-B (<i>SFTPB</i>)	2p12-11.2	Lethal SP-B deficiency	Maternal	Current case
c-mer proto-oncogene tyrosine kinase (<i>MERTK</i>)	2q14.1	retinal dystrophy	Paternal	(11)
low density lipoprotein-related protein 2 (<i>LRP2</i>)	2q24-31	Donnai-Barrow Syndrome	Paternal	(15)
alanine:glyoxylate aminotransferase (<i>AGXT</i>)	2q36-37	primary hyperoxaluria type 1	Maternal	(13)
bilirubin uridine diphosphate glucuronyltransferase (<i>UGT1A1</i>)	2q37	Crigler-Najjar syndrome type 1	Paternal	(14)
Chromosome 16				
hemoglobin, alpha 1 (<i>HBA1</i>)	16p13.3	α -thalassemia	Maternal	(40)
ATP binding cassette, A3 (<i>ABCA3</i>)	16p13.3	Lethal ABCA3 deficiency	Paternal	Current cases
phosphomannomutase 2 <i>PMM2</i>	16p13.3-13.2	CDG type 1a	Paternal	G.E. Tiller, personal communication
malonyl-CoA decarboxylase (<i>MLYCD</i>)	16q24	Malonyl CoA decarboxylase deficiency	Maternal	(16)