

ABSTRACT

RESULTS

Paternal Uniparental Disomy as a Mechanism for Inherited Surfactant Deficiency

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Introduction: Uniparental disomy (UPD) has not been recognized as a mechanism of genetic disruption of neonatal pulmonary surfactant metabolism. The gene that encodes the ATP binding cassette family member A3 (*ABCA3*) has been mapped to chromosome 16 (16p13.3), the chromosome most commonly duplicated in cases of placental aneuploidy. Recessively inherited, loss-of-function *ABCA3* mutations disrupt surfactant metabolism and function and cause lethal, neonatal respiratory disease.

Objective: To determine the frequency of UPD in infants homozygous for recessive loss of function mutations in *ABCA3*

Methods: We searched datasets from 3 laboratories that perform sequence analysis for *ABCA3* for infants with respiratory dysfunction (n=600) to identify those who were homozygous for loss of function mutations and for whom parental DNA was available. For infants with only one heterozygous parent, we used 9 microsatellite markers that span the length of chromosome 16 to characterize allele inheritance.

Results: We found 18 infants homozygous for loss of function mutations in *ABCA3* and for whom parental DNA was available. We identified 2 cases in which the infant was homozygous for a rare loss of function mutation (K914R and P147L, respectively) and for whom only the father was heterozygous for the respective mutation. One infant (K914R) was homozygous for all 9 markers, 7 of which confirmed paternal isodisomy, while the other infant (P147L) was homozygous for 7 markers, 3 of which were informative for the paternal allele, and heterozygous for 2 markers, a pattern that suggests partial isodisomy (heterodisomy). We identified no extrapulmonary phenotypic abnormalities in either infant. Both underwent lung transplantation at 5 and 3 months of age, respectively, for progressive pulmonary failure.

Conclusions: Uniparental disomy is not a rare mechanism of *ABCA3* deficiency. Confirmation of parental carrier status is important to provide informed and specific reproductive counseling to families of affected infants.

- *ABCA3* sequenced in 610 infants
- 57 infants identified with surfactant deficiency due to homozygous loss of function mutation in the *ABCA3* gene.
 - 31 infants from unique families
 - 18 with parental DNA available
 - 2 cases in which the infant was homozygous for a rare loss of function mutation (K914R, P147L), and for whom only the father was a carrier for the respective mutation.

Chromosome 16 microsatellite marker analysis

Marker	Position	Patient 1	Mother 1	Father 1	Patient 2	Mother 2	Father 2
D16S423	16p13.3	5	2	3,5	4	1,2	4
K914R	16p13.3	K914R	wild type (wt)	K914R/wt	wt	wt	wt
P147L	16p13.3	wt	wt	wt	P147L	wt	P147L/wt
D16S407	16p13.2	2	1,3	2,6	4,5	4,5	4,5
D16S405	16p13.1	3	2	3,4	1,4	1,4	1,4
D16S420	16p12.3	3	2,4	3	5	5	1,5
D16S401	16p12.3	1	1,4	1,4	3	2,3	3,4
D16S411	16q12.1	3	2,3	1,3	2	3,4	2
D16S503	16q21	3	2,4	3	3	1,2	1,3
D16S516	16q23	3	2	3,4	1	1,4	1
D16S511	16q23	2	1,6	2,3	5	3,5	4,5

•Red numbers indicate informative markers.

•Gray background indicates heterodisomy.

BACKGROUND

- *ABCA3* – ATP binding cassette, subfamily A member 3, chromosome 16p13.3.
- Recessive loss-of-function mutations in *ABCA3* cause acute and chronic respiratory dysfunction
- Over 150 mutations identified; fewer than 10 identified in more than 1 family
- Uniparental disomy (UPD) – both copies of a chromosome pair are inherited from a single parent.
- UPD can result from trisomy or monosomy rescue, gametic complementation, and somatic recombination.
- UPD has not been recognized as a mechanism of genetic disruption of neonatal pulmonary surfactant metabolism.

OBJECTIVE

To determine the frequency of UPD in infants homozygous for recessive loss of function mutations in *ABCA3*.

METHODS

- Database search from 3 laboratories for infants homozygous for a single mutation in *ABCA3*
 - Cole / Hamvas lab at Washington University, St. Louis, MO.
 - Noguee lab at Johns Hopkins University, Baltimore, MD.
 - Ambry Genetics, Inc., Aliso Viejo, CA.
- Identify infants for whom parental DNA was available.
- Sequence confirm mutations in patient and parental DNA to characterize mode of inheritance.
- Chromosome 16 microsatellite marker analysis in cases where UPD is suspected.

Outcomes

- Both infants with clinical course suggestive of *ABCA3* deficiency
 - refractory respiratory failure requiring mechanical ventilation
 - abnormal lamellar bodies on electron microscopy of the lung
- Both infants underwent lung transplantation at 3 months of age
- No unique, unanticipated issues post-transplantation (at 6 and 18 months)

CONCLUSIONS

- Paternal uniparental disomy may be a common mechanism for transmission of *ABCA3* mutations causing surfactant deficiency.
- Confirmation of parental carrier status is important to provide informed and specific reproductive counseling to families of affected individuals.
- Surveillance for abnormalities that could result from reduction to homozygosity of recessive alleles in other genes on chromosome 16 will be necessary

SUPPORT

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