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Respiratory Failure in a Term Infant with *Cis* and *Trans* Mutations in *ABCA3*

Tara Jackson, MD[1], **Daniel J. Wegner, MS**[1], **Frances V. White, MD**[2], **Aaron Hamvas, MD**[3], **F. Sessions Cole, MD**[1], and **Jennifer A. Wambach, MD, MS**[1]

[1]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

[2]Department of Pathology, Washington University School of Medicine, St. Louis, MO, USA

[3]Department of Pediatrics, Northwestern University School of Medicine, Chicago, IL, USA

Abstract

A full-term female neonate presented with persistent respiratory failure and radiologic studies consistent with surfactant deficiency. Sequencing of the ATP-binding cassette transporter A3 gene (*ABCA3*) revealed 3 mutations: R280C, V1399M, and Q1589X. The infant underwent bilateral lung transplantation at 9 months of age and is alive at 3 years of age. Parental sequencing demonstrated that 2 of the mutations (R280C and Q1589X) were oriented on the same allele (*cis*) while V1399M was oriented on the opposite allele (*trans*). As more than one mutation in *ABCA3* can be present on the same allele, parental studies are needed to determine allelic orientation to inform clinical decision making and future reproductive counseling.

INTRODUCTION

ATP Binding Cassette member A3 (ABCA3), a member of a family of transporter proteins that hydrolyze ATP to move substrates across biological membranes, is expressed in alveolar type II cells and localized to the membrane of lamellar bodies, the intracellular organelles where pulmonary surfactant is assembled and processed.[1, 2] ABCA3 transports phospholipids into the lamellar bodies which then assemble with surfactant proteins B and C to form mature surfactant.[3] Recessive, loss of function mutations in *ABCA3* have been associated with lethal neonatal respiratory failure and childhood interstitial lung disease (chILD).[4, 5] Here, we describe a full term female infant with persistent respiratory failure for whom genetic sequencing revealed 3 mutations in *ABCA3* and parental studies demonstrated that 2 mutations were present on the same allele (*cis*). Parental studies are needed to determine whether 2 or more *ABCA3* mutations in a symptomatic infant or child disrupt expression of both alleles and, therefore, result in ABCA3 deficiency.

Corresponding Author: Jennifer A. Wambach, MD, MS, Campus Box 8116, 660 S. Euclid Ave, St. Louis, MO 63110, USA, Phone: (314)747-9363, Fax: (314)454-4633, wambach_j@kids.wustl.edu.

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CASE

Term female infant (birth weight 2870 grams) was born to a 30 year old G2, P1 mother via spontaneous vaginal delivery. Mother had one previous child who was healthy and both mother and father were healthy. Immediately after birth, the infant developed respiratory distress and was placed on continuous positive airway pressure (CPAP). Her physical examination was notable for bilateral coarse breath sounds, subcostal and intercostal retractions. Apgar scores were 3, 3, and 9 at 1, 5, and 10 minutes, respectively. Chest radiograph demonstrated diffuse bilateral granular opacities consistent with surfactant deficiency. Her respiratory distress persisted and prompted intubation and surfactant administration on day of life (DOL) 2. Over the next 2-3 days, she developed progressive hypoxic respiratory failure that necessitated high frequency oscillatory ventilation, FiO2 1.0, and nitric oxide administration. She developed a left-sided pneumothorax that required thoracostomy tube drainage. Repeat chest radiograph demonstrated persistent diffuse bilateral granular opacities, and she received a second dose of surfactant. At a week of life, she was transitioned to conventional ventilation and tolerated discontinuation of nitric oxide. On DOL 11, she was extubated to CPAP with FiO2 0.4-0.5, but had persistent tachypnea. An echocardiogram demonstrated no evidence of anatomic heart disease or pulmonary hypertension. Chest computed tomography at 7 weeks of life showed coarse bilateral granular opacities.

Given the clinical suspicion for a genetic disorder of surfactant dysfunction, sequencing was performed for surfactant protein B (*SFTPB*) and *ABCA3*. No mutations were identified in *SFTPB*, and three rare, missense and nonsense mutations were identified in *ABCA3:* p.R280C (c.838C>T), p.V1399M (c.4195G>A), and p.Q1589X (C.4765C>T). Parental sequencing for *ABCA3* demonstrated that these mutations were present on both maternal (V1399M) and paternal (R280C and Q1589X on same allele in *cis*) alleles. Sequencing was performed in our research laboratory, informed consent was obtained from parents, and this study was approved by the Washington University School of Medicine Human Research Protection Office.

The infant was transferred to a lung transplant center at 2.5 months of age and underwent bilateral lung transplantation at 9 months of age. Pathologic examination of her native lungs showed diffuse interstitial fibrosis with alveolar remodeling and prominent type II pneumocyte hyperplasia. Electron microscopy demonstrated some small, dense lamellar bodies and occasional fused lamellar bodies (Figure). After postoperative tracheostomy, she was decannulated 2 months later. She was weaned to room air at approximately 1 year of age. A gastrostomy tube was placed at 18 months for nutritional supplementation. She is currently alive at 3 years of age with mildly delayed speech and motor developmental milestones.

DISCUSSION

ABCA3 consists of 1704 amino acids and is encoded by an 80kb gene on human chromosome 16. Recessive, loss of function mutations in *ABCA3* were first identified in term neonates dying of respiratory distress syndrome,[4] and later in children with interstitial

lung disease.[5] Mice genetically engineered to be deficient for ABCA3 (abca3-/-) die from respiratory failure within the first hour of life and demonstrate absent surfactant in the alveolar space, loss of mature lamellar bodies, and reduced phospholipid content of their lung tissue.[3, 6] Lamellar bodies from patients with ABCA3 deficiency usually are small with densely packed phospholipid membranes and eccentrically-placed, dense inclusion bodies.[4, 7]

Over 180 *ABCA3* mutations have been identified among ethnically and geographically diverse symptomatic infants and children.[8] Most *ABCA3* mutations are rare and private.[8] Frameshift, nonsense, missense, splice site mutations, and insertions/deletions have been identified.[8, 9, 10] However, phenotype and prognosis are difficult to predict based on mutation type or location, especially for individuals with missense and splice site mutations and in-frame insertion/deletions.[8, 11] Approximately 1.5-3.6% of European and African-descent individuals carry single mutations in *ABCA3*.[12] While no specific therapies exist for ABCA3 deficiency, some patients have responded to medical therapies including steroids, hydroxychloroquine, and azithromycin,[13] while others have progressed to requiring lung transplantation.[14]

This infant was found to have 3 rare *ABCA3* mutations and parental sequencing determined that 2 of the mutations were paternally inherited in *cis:* p.R280C and p.Q1589X. Three out of 6498 individuals of African- and European-descent in the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP) (http://evs.gs.washington.edu/EVS/, accessed 12/2014) are heterozygous for p.R280C, and this mutation has been identified both in isolation and in *cis* with p.Q1589X in an unrelated patient,[8] likely attributable to different haplotype backgrounds. P.V1399M is rare and has been previously reported in symptomatic infants.[8, 15] Neither p.V1399M nor p.Q1589X is identified among individuals in the ESP database. P.Q1589X is predicted to result in a truncated protein. Both p.R280C and p.V1399M are predicted to be damaging to ABCA3 protein function by the majority of *in silico* prediction programs in ANNOVAR.[16] P.R280C has been studied *in vitro* and impairs intracellular trafficking.[17]

In a recent study of 185 subjects with ABCA3 deficiency, approximately 10 percent of subjects had *ABCA3* mutations in *cis*,[8] emphasizing the importance of parental DNA samples to determine mutation orientation. Symptomatic infants and children with more than 2 *ABCA3* mutations have also been reported.[18, 19, 20, 21] As single (monoallelic) mutations in *ABCA3* have been associated with reversible respiratory distress syndrome among term and late preterm infants,[12] confirming that a symptomatic infant or child has mutations on both alleles is necessary to inform clinical decision making and future reproductive counseling.

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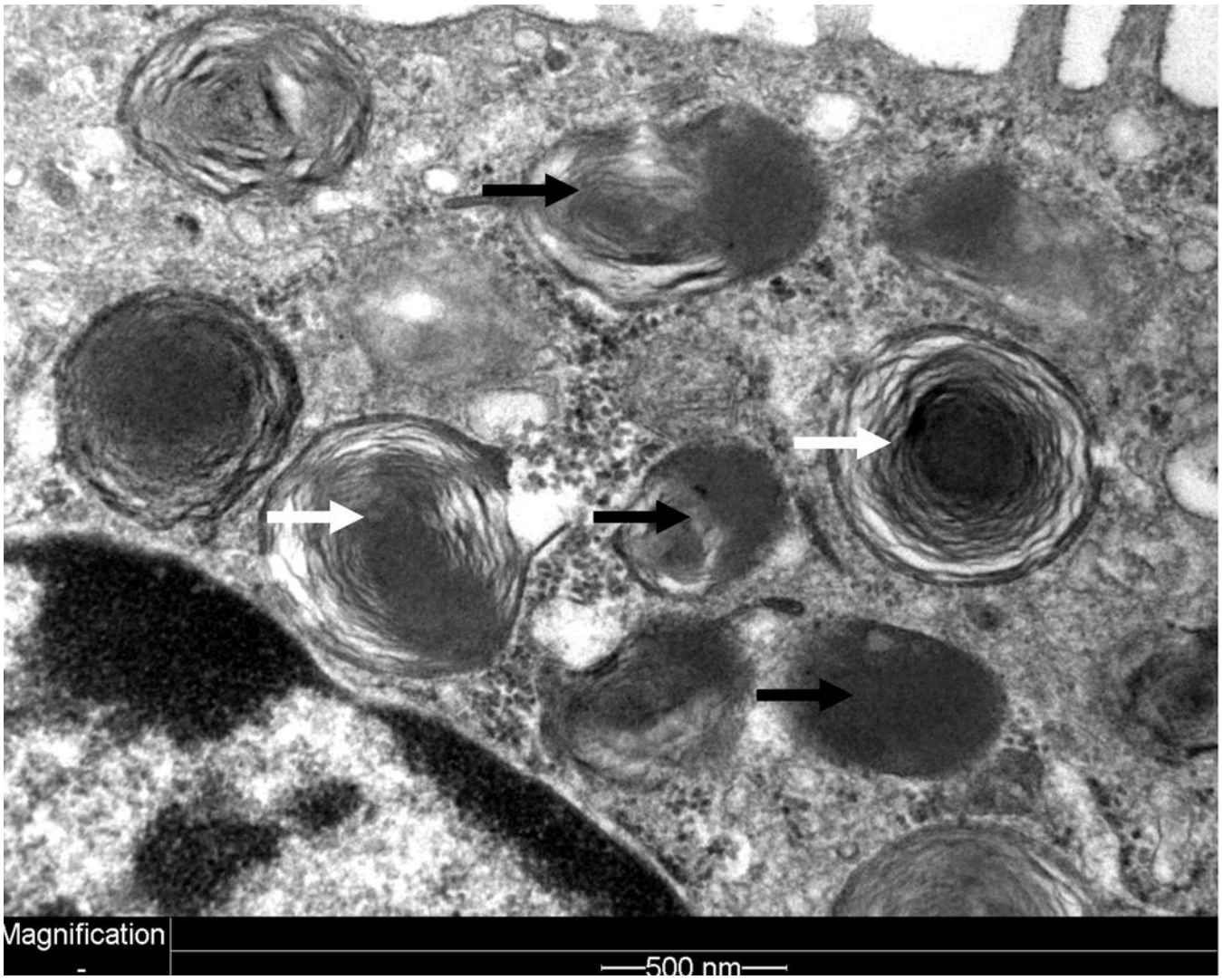

Figure.

Electron microscopy image of alveolar type II cell demonstrating small, densely wound lamellar bodies and dense body (black arrows). Some relatively normal-appearing small lamellar bodies are also observed (white arrows).