Lung Transplantation for FLNA-Associated Progressive Lung Disease

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Objective To describe a series of patients with pathogenic variants in FLNA and progressive lung disease necessitating lung transplantation.

Study Design We conducted a retrospective chart review of 6 female infants with heterozygous presumed loss-of-function pathogenic variants in FLNA whose initial presentation was early and progressive respiratory failure.

Results Each patient received lung transplantation at an average age of 11 months (range, 5-15 months). All patients had pulmonary arterial hypertension and chronic respiratory failure requiring tracheostomy and escalating levels of ventilator support before transplantation. All 6 patients survived initial lung transplantation; however, 1 patient died after a subsequent heart-lung transplant. The remaining 5 patients are living unrestricted lives on chronic immunosuppression at most recent follow-up (range, 19 months to 11.3 years post-transplantation). However, in all patients, severe ascending aortic dilation has been observed with aortic regurgitation.

Conclusions Respiratory failure secondary to progressive obstructive lung disease during infancy may be the presenting phenotype of FLNA-associated periventricular nodular heterotopia. We describe a cohort of patients with progressive respiratory failure related to a pathogenic variant in FLNA and present lung transplantation as a viable therapeutic option for this group of patients. (J Pediatr 2017; ■■: ■■: ■■).
was performed at Children’s Hospital Boston’s Genetic Diagnostic Laboratory (Boston, Massachusetts), and for case 6, Sanger sequencing of *FLNA* was performed at Ambry Genetics (Aliso Viejo, California). This study was approved by Baylor College of Medicine’s Institutional Review Board.

At age 4 months, a full-term female developed acute respiratory failure after a febrile illness. Her physical examination was significant for respiratory distress, ligamentous laxity, and strabismus. Echocardiography revealed a large patent ductus arteriosus (PDA), a patent foramen ovale (PFO), and pulmonary hypertension. The PDA was ligated. Because of increasing tachypnea and intermittent hypoxemia at age 7 months, lung ventilation-perfusion scintigraphy was ordered and revealed diffuse irregular matched defects of ventilation and perfusion, largest in the right upper lobe. Serial chest radiographs (Figure 1) showed multifocal atelectasis and pulmonary hyperinflation that worsened over time. Chest computed tomography (CT) (Figure 1) showed severe pulmonary hyperinflation and hyperlucency with peripheral pulmonary vascular attenuation and air-trapping, parahilar and dependent lower lobe atelectasis, central pulmonary artery enlargement, and tracheobronchomalacia. Chronic respiratory failure ensued, leading to the need for mechanical ventilation and tracheostomy at age 13 months. She was listed for lung transplantation at age 14 months, and bilateral lung transplantation was performed at age 15 months. Intraoperatively, the lungs were severely hyperinflated. Histopathology revealed a generalized lung growth abnormality with alveolar enlargement and simplification and pulmonary hypertensive arteriopathy (Figure 2; available at [www.jpeds.com](http://www.jpeds.com)). At age 21 months, head magnetic resonance imaging (MRI) showed PVNH, a thinned corpus callosum, and a posterior fossa arachnoid cyst (Figure 3; available at [www.jpeds.com](http://www.jpeds.com)). DNA testing identified a de novo heterozygous pathogenic variant in *FLNA* that results in a frameshift (c.4596het_dupG). She also developed progressive severe dilatation of the ascending aorta with mild dilation of the aortic root and mild aortic regurgitation. The patient, now 12 years old, has shown improved gross motor development with normal cognition, but has attention deficit hyperactivity disorder. Her cardiopulmonary status is stable despite airflow limitation with a forced expiratory volume in 1 second of 52% predicted and radiographic and physiological evidence of bronchiolitis obliterans syndrome.

### Results

#### Pulmonary Findings

Since the index case presented, we have cared for 5 additional females with heterozygous pathogenic variants in *FLNA* and progressive lung disease necessitating bilateral lung transplantation (Table 1). Five of the 6 patients had initial respiratory distress during the neonatal period, but all improved. Chronic respiratory failure developed at a median age of 9 months (range, 7 weeks to 11 months), and the duration of mechanical ventilation ranged from 2 weeks to 6 months before transplantation. Ventilatory requirements were high, with median peak inspiratory pressure of 31 cm H₂O and positive end-expiratory pressure of 10 cm H₂O. The fraction of inspired oxygen ranged from 0.35 to 0.90. All patients were heavily sedated owing to challenging ventilator management, and 4 patients required regular dosing of neuromuscular blockade. Each patient required elective tracheostomy between 3 and 13 months of age.
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