Published in final edited form as:

J Pediatr. 2017 July ; 186: 118–123.e6. doi:10.1016/j.jpeds.2017.03.045.

Lung Transplantation for *FLNA*-Associated Progressive Lung Disease

Lindsay C. Burrage, M.D., Ph.D.^{1,2}, R. Paul Guillerman, M.D.³, Shailendra Das, D.O.⁴, Shipra Singh, M.D., M.P.H.⁵, Deborah A. Schady, M.D.⁶, Shaine A. Morris, M.D., M.P.H.⁷, Magdalena Walkiewicz, Ph.D.¹, Marc G. Schecter, M.D.⁸, Jeffrey S. Heinle, M.D.⁹, Timothy E. Lotze, M.D.¹⁰, Seema R. Lalani, M.D.^{1,2}, and George B. Mallory, M.D.⁴

¹Department of Molecular and Human Genetics, Baylor College of Medicine

²Texas Children's Hospital

³Department of Radiology, Baylor College of Medicine

⁴Section of Pediatric Pulmonology, Department of Pediatrics, Baylor College of Medicine

⁵Division of Pulmonology, Department of Pediatrics, State University of New York - Buffalo

⁶Department of Pathology and Immunology, Baylor College of Medicine

⁷Section of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine

⁸Division of Pulmonary Medicine, Department of Pediatrics, University of Cincinnati School of Medicine

⁹Division of Congenital Heart Surgery, Department of Surgery, Baylor College of Medicine

¹⁰Section of Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine

Abstract

OBJECTIVE—To review the outcome of patients with pathogenic variants in *FLNA* and progressive lung disease requiring lung transplantation.

STUDY DESIGN—We conducted a retrospective chart review of six 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 to 15 months). All patients had pulmonary arterial hypertension and chronic respiratory failure requiring tracheostomy and escalating levels of ventilator support prior to transplantation. All six patients survived initial lung transplantation; however, one patient died after a subsequent heart-lung transplant. The remaining five patients are living unrestricted lives on chronic

Address Correspondence to: George B. Mallory, M.D., Texas Children's Hospital, 6701 Fannin Street, Suite 1040, Houston, TX 77030, Phone: 832-822-3300, Fax: 832-825-3308, gbmallor@texaschildrens.org.

Financial Disclosure Statement: The authors have no financial relationship to this study.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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 the largest 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.

Keywords

periventricular nodular heterotopia; diffuse lung disease; lung growth disorder; pulmonary overinflation

Introduction

Heterozygous loss of function pathogenic variants in *FLNA*, the gene encoding filamin A, have been associated with X-linked periventricular nodular heterotopia (PVNH, MIM: 300049), which is characterized by masses of heterotopic gray matter adjacent to the walls of the lateral ventricles¹. In contrast, gain of function pathogenic variants in the same gene are associated with Melnick-Needles Syndrome (MIM:309350), Otopalatodigital Syndrome Type 1 (MIM:311300), Otopalatodigital Syndrome Type 2 (MIM:304120), and Frontometaphyseal Dysplasia (MIM:305620)². X-linked PVNH typically affects females and is associated with epilepsy and normal to near normal cognition, whereas hemizygous males often do not survive¹. Additional phenotypes that have been observed in a subset of patients with X-linked PVNH and *FLNA* pathogenic variants include Ehlers-Danlos syndrome-like features^{3–6}, cardiovascular anomalies^{4, 5, 7–9}, and intestinal pseudo-obstruction^{4, 10, 11}. Moreover, pulmonary complications of varying severity have been associated with this disorder^{3–5, 12–16}, and a few patients with progressive obstructive pulmonary disease in early childhood leading to respiratory failure have been described^{12, 13, 17–19}. In the present report, we describe the largest published cohort of patients with heterozygous pathogenic variants in *FLNA* and progressive lung disease leading to respiratory failure in infancy and delineate the first use of lung transplantation to promote survival in patients with severe pulmonary complications in this disorder. Some of the results of these studies have been previously reported in the form of abstracts and a case report^{14, 16, 20, 21}.

Methods and Materials

A retrospective review was conducted of medical charts of all patients in the pulmonary clinic at Texas Children's Hospital with both pathogenic variants in *FLNA* and lung disorders diagnosed from 2005–2015. Data on clinical presentation, physical examinations, genetic testing, imaging study findings, bronchoscopy findings, intra-operative observations, pathology findings, management and outcome were compiled and compared. All genetic testing was performed during the course of routine clinical care through commercial genetic testing laboratories. For cases 1–5, Sanger sequencing and deletion/duplication analysis of

FLNA was performed at Children's Hospital Boston Genetic Diagnostic Laboratory (Boston, MA), and for case 6, Sanger sequencing of *FLNA* was performed at Ambry Genetics (Aliso Viejo, CA). This study was approved by the Institutional Review Board of Baylor College of Medicine.

Index Case Review

At four months of age, a full-term female developed acute respiratory failure after a febrile illness. Physical exam was significant for respiratory distress, ligamentous laxity and strabismus. Echocardiography revealed a large patent ductus arteriosus (PDA), patent foramen ovale (PFO), and pulmonary hypertension. The PDA was ligated. Because of increasing tachypnea and intermittent hypoxemia at 7 months of age, 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 (CXR) (Figure 1) showed multi-focal 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 mechanical ventilation (MV) and tracheostomy at 13 months of age. She was listed for lung transplantation at age 14 months, and bilateral lung transplantation was performed at 15 months of age. Intra-operatively, the lungs were severely hyperinflated. Histopathology revealed a generalized lung growth abnormality with alveolar enlargement and simplification and pulmonary hypertensive arteriopathy (Figure 2). At 21 months of age, head magnetic resonance imaging (MRI) showed PVNH, a thinned corpus callosum and a posterior fossa arachnoid cyst (Figure 3, Online). 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 is now 12 years old and 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 one second (FEV1) of 52% predicted and radiographic and physiologic evidence of bronchiolitis obliterans syndrome.

Results

Pulmonary Findings

Since the index case presented, we have cared for five additional females with heterozygous pathogenic variants in *FLNA* and progressive lung disease requiring bilateral lung transplantation (Table 1). Five of six 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 MV ranged from 2 weeks to 6 months prior to transplantation. Ventilatory requirements were high with median peak inspiratory pressures of 31 cm H₂O and positive end expiratory pressure of 10 cm H₂O. FiO₂ ranged from 0.35 to 0.90. All patients were heavily sedated due to challenging

ventilator management and four required regular dosing of neuromuscular blockade. Each patient required elective tracheostomy between 3 and 13 months of age.

All patients demonstrated progressive pulmonary hyperinflation accompanied by scattered atelectasis on serial CXRs (Figure 1). On chest CT, all exhibited severe pulmonary hyperinflation and hyperlucency with peripheral pulmonary vascular attenuation with parahilar and dependent lower lobe atelectasis and central pulmonary artery enlargement (Figure 1). Air trapping and airway malacia were noted in both patients in whom the chest CT scans included inspiratory/expiratory series. Airway malacia was observed at bronchoscopy in five patients (Figure 2).

Pulmonary Artery Hypertension

All patients were diagnosed with pulmonary arterial hypertension via echocardiography in infancy; sildenafil was prescribed in each infant and prostacyclin therapy was added in one patient just days before transplantation. While all patients had pre-operative right ventricular dilation, none developed right ventricular dysfunction.

Cardiovascular Findings

Each patient had a PDA and a PFO (Table 2, Online). All patients had mild to severe dilation of the ascending aorta early in life, with universal progression to severe dilation (Figure 4; Figure 5, Online). Given that the main area of dilation was >1.5 cm distal to the sinotubular junction, which is an area not routinely imaged on echocardiography, and not well-visualized on non-contrast chest CT, the dilation was first noted on contrast-enhanced chest CT or magnetic resonance angiography. One patient had supraventricular tachycardia and frequent premature ventricular contractions.

Given the prior description of tortuosity in a patient with a pathogenic variant in *FLNA*, vertebral artery tortuosity as a measure of arterial tortuosity was assessed in 3/6 patients who were undergoing CT angiography^{7, 22–24}. The vertebral artery tortuosity index (VTI) has been shown to be a reproducible measure that is derived from 3D magnetic resonance or CT angiography, and higher VTI has been associated with adverse cardiovascular outcomes in connective tissue disorders²². Two patients showed mildly increased tortuosity with a VTI of 14 (normal VTI = 4.0 ± 2.5 , Table 2, Online; Figure 6, Online).

Neurologic Findings

Brain imaging demonstrated PVNH in all patients, thinning or dysgenesis of the corpus callosum in four patients, and an enlarged cisterna magna or retrocerebellar arachnoid cyst in five patients (Table 2, Online). At the time of this report, no patient in our cohort has developed seizures. One patient has persistent developmental delays in the setting of additional head MRI findings of cortical atrophy and gliosis presumed secondary to chronic hypoxia prior to transplantation.

Lung Transplantation

Patients were listed for lung transplantation at 5 to 14 months of age. Bilateral lung transplantation was performed at 5 to 15 months of age with a median wait time of 35 days

(range: 18 to 104 days). At transplantation, the explanted lungs were severely hyperinflated and emphysematous. Tracheostomies of five patients were decannulated within four months of transplantation. All survivors were on ambient air at 19 months, 3 years, 4 years, 5.1 years, and 11.3 years of post-transplant follow-up. One patient has a complex tracheal stenosis and malacia with chronic compensated symptoms leading to delayed decannulation. One patient developed progressive respiratory insufficiency preventing tracheostomy decannulation after an early adenovirus pneumonia. Because of the ensuing development of bronchiolitis obliterans and development of moderate aortic valve regurgitation and severe dilation of the ascending aorta, she underwent heart-lung transplantation at 3 years of age but died of viral pneumonia 8 weeks after surgery. Otherwise, the post transplant course of the other five patients was similar to patients without pathogenic variants in *FLNA* except for the cardiac manifestations outlined above which required close monitoring. Notably, although mild tracheomalacia was noted in all patients after transplantation, in only one was there clinical significance, specifically, a delay in decannulation.

Pulmonary Histopathology

Histopathology of lung biopsies and explants showed severe alveolar enlargement and simplification, scattered pulmonary hemorrhage and widespread hemosiderin-laden macrophages (Table 3, Online). A variable degree of hypertensive pulmonary arteriopathy was seen in all patients with muscularization of lymphatics and veins observed in most patients. Airway cartilage was judged deficient in four patients. Elastic fibers in the lungs were abnormal with loss of elastin peripherally and nodular aggregates noted in others. The terminal bronchioles were abnormally placed adjacent to the pleura in three patients.

Molecular Findings

In the first two patients, a presumed diagnosis of *FLNA*-associated PVNH was based on findings from head MRI, and commercially available *FLNA* testing was not available until years later. In the remaining patients, presumptive diagnosis followed by confirmatory genetic testing was made at an increasingly early stage of the pulmonary disease. Four patients had frameshift pathogenic variants and one patient had a missense variant that was previously reported (Table 4, Online)²⁵. The sixth patient has a missense variant of unknown significance at a lysine residue that is conserved in most vertebrate organisms except zebrafish, chicken and lamprey. Although prediction software (Polyphen-2, Sift) predicts that this amino acid change may be benign or tolerated, this variant is novel and not present in the ExAC database (<http://exac.broadinstitute.org/>) which supports pathogenicity^{26, 27}. Pathogenic variants were *de novo* in all four patients (Cases 1, 2, 3, 5) in which parental testing could be performed.

Discussion

Our series of six patients demonstrates that heterozygous presumed loss of function pathogenic variants in *FLNA* can be associated with a lung disorder characterized by simplified enlarged alveolar air spaces and hyperinflation simulating emphysema, implying an important role of filamin A in alveolar modeling during lung growth. Our patients had a similar clinical course with respiratory disease as their presenting feature and similar

associated clinical findings. In our patients, this unique lung growth disorder led to unrelenting respiratory failure during infancy. Although the pathogenic variant in *FLNA* was diagnosed at an earlier stage in recent cases, the lung disease was nonetheless progressive and relentless. Early clinical recognition on the basis of findings on imaging and/or histopathology is important to guide genetic testing and counseling, and referral for consideration for lung transplant evaluation.

We first described this novel association of pathogenic variants in *FLNA* and PVNH with a characteristic lung growth disorder resembling severe emphysema on imaging and pathology in our initial two cases^{14, 16}. Additional cases of lung disease associated with pathogenic variants in *FLNA* have been subsequently reported (Table 5, Online)^{3, 4, 7, 12, 13, 17–19, 28, 29}. The association of pulmonary pathology with pathogenic variants in *FLNA* is further supported by a mouse model³⁰. Approximately 20% of female mice heterozygous for the *FLNA* null allele died within the first 3–4 months of life with evidence of lung edema and emphysema on necropsy³⁰. Since the lungs are subjected to markedly varying spatiotemporal mechanical forces during respiration, and filamin A is necessary for the mechano-sensing and mechano-transducing behavior of cells³¹, abnormal filamin A interactions could alter lung viscoelasticity and disturb alveolar modeling, although the exact mechanisms are unclear.

We propose that the lung disease in our case series and in previously published reports has features of “lung growth disorders”³². The lung growth disorders are characterized by defective alveolarization with lobular simplification, deficient alveolar septation, and airspace enlargement that may be misinterpreted as “emphysematous” changes. Chest CT findings of a lung growth disorder exhibited by all six patients include distortion of the lung architecture with hyperlucency related to alveolar enlargement and reduced distal vascularization¹⁴. However, our patients had several imaging findings not previously associated with lung growth disorders, including progressively severe pulmonary hyperinflation and ascending aorta dilation in all six patients, and airway malacia in five of six patients, findings that likely represent manifestations of altered viscoelastic properties of the affected tissues. The histopathologic evidence of abnormal elastin suggests that loss of elastic recoil plays a role in the development of chronic respiratory failure. The pulmonary hyperinflation in our patients worsened after sustained positive pressure ventilation, while at least one other reported case of lung disease associated with a pathogenic variant in *FLNA* and no ventilator requirement improved over time suggesting exacerbation of the abnormalities in lung viscoelasticity and alveolar modeling by barotrauma^{12, 33}. These abnormalities likely contribute to the chronic irreversible airflow limitation, due to loss of elastic recoil and an increase in airflow resistance through the complex conducting system of the lungs.

In our cases, chest CT showed central pulmonary artery enlargement and echocardiography demonstrated right ventricular hypertrophy with an elevated tricuspid regurgitant jet and flattened interventricular septum. All six patients were treated empirically for pulmonary arterial hypertension with enteral sildenafil. Pulmonary hypertension did not regress in the three patients who underwent surgical PDA ligation prior to lung transplantation and histopathology demonstrated arteriopathy in each case (Figure 2). Factors contributing to the

pulmonary arterial hypertension likely include alveolar hypoxia, diminished alveolar septal vasculature and blood flow, and progressive disruption of lung tissue integrity via pulmonary barotrauma. Right heart changes resolved after lung transplantation in each case. However, the ascending aorta dilation progressed after transplantation.

All of our patients had cardiovascular manifestations including PDA, PFO, and ascending aortic dilation. Two patients had mild arterial tortuosity, and one patient had arrhythmia. Pathogenic variants in *FLNA* have been described in association with a broad spectrum of cardiovascular disease often in conjunction with joint laxity and other signs of connective tissue disorders. This includes presence of PDAs, atrial septal defects, ventricular septal defects, mitral valve prolapse, diffuse valve dysplasia, aortic regurgitation, dilation of the aortic root (sinus of Valsalva), ascending aortic, abdominal aorta, and other arteries, coarctation of the aorta, arterial stenosis, and arterial tortuosity^{4, 7, 9, 23, 34, 35}. A single case report described complex congenital heart disease (mitral atresia, double outlet right ventricle, coarctation of the aorta) in an infant with a *FLNA* pathogenic variant³⁵. *FLNA* pathogenic variants have also been noted in patients with rhythm disorders and sudden death³⁶.

The mechanism of cardiovascular disease has not been elucidated. It is postulated that pathogenic variants in *FLNA* lead to impaired binding abilities of filamin A, which may impair cellular actin cytoskeleton remodeling in response to mechanical stress and cytokine stimulation³⁷. Another hypothesis is that aberrations in filamin A alter TGF- β signaling through its interactions with Smad proteins³⁸.

The most concerning of the cardiovascular features is the progressive aortic dilation. In other genetically-mediated disorders with similar features like Marfan syndrome, Loeys-Dietz syndrome, and familial thoracic aneurysm and dissection disorders, aortic dilation is a precursor of aortic dissection and rupture, which is associated with high mortality. As far as the authors are aware, aortic dissection has not been reported to date in a patient with a confirmed pathogenic variant in *FLNA*, although carotid artery aneurysm rupture has been reported³⁵. The same study reported an aortic rupture at age 57 years in the mother of an affected girl; the mother's DNA could not be tested³⁵. One other study reported a history of aortic dissection in the 54 year-old mother of an affected patient, but testing for the pathogenic variant had not been performed⁵. Given this history, there are reports of pre-emptive aortic replacement surgery in patients with pathogenic variants in *FLNA* and aortic aneurysms⁵. It is unclear if medical therapy is effective for reducing the rate of dilation. The ascending aorta dilation did not resolve after transplantation, and periodic monitoring with echocardiography and/or chest magnetic resonance angiography may be warranted.

Our case series provides evidence that loss of function pathogenic variants in *FLNA* can result in a unique form of abnormal lung development and should be considered in the differential diagnosis of congenital lung disease with marked hyperinflation. However, the phenotype is not completely penetrant in the mouse model or in the human patients. Thus, although all pathogenic variants for which parental testing was available were *de novo*, a review of the literature indicates that severe pulmonary complications may be observed in females who inherit the pathogenic variant in *FLNA* from their healthy or only mildly

affected mothers, a factor that complicates genetic counseling for this disorder^{12, 19}. Moreover, pulmonary complications have not been described in many previously reported patients with pathogenic variants in *FLNA*. Perhaps, skewed X-inactivation in pulmonary tissues contributes to the incomplete penetrance for the phenotype.

Our study is a retrospective chart review performed at a tertiary care referral center for pediatric lung transplantation. Given the retrospective nature of this study, we are unable to estimate the prevalence of pulmonary complications in patients with pathogenic variants in *FLNA*. In addition, since our center is a referral center for pediatric lung transplantation, the lung complications that we describe likely represent the most severe pulmonary phenotypes associated with this disorder. Interestingly, there are several reports of patients with pathogenic variants in *FLNA* who recovered from severe pulmonary complications^{12, 17}. We speculate that limiting the exposure to positive pressure ventilation, if possible, may modify the pulmonary course of these patients. Alternatively, recovery may be more likely to occur in patients with a milder or a more localized or patchy pulmonary phenotype.

In conclusion, in a subset of patients, pathogenic variants in *FLNA* are associated with a severe lung growth disorder characterized by enlarged simplified alveolar air spaces and hyperinflation simulating emphysema, implying an important role of the filamin A in alveolar modeling during lung growth. This lung growth disorder may lead to respiratory failure during infancy, and these pulmonary complications may be the presenting feature of this disorder. Recognition on chest imaging is important to guide genetic testing, brain imaging, and potential referral for lung transplant evaluation in patients with severe, progressive lung disease. Lung transplantation for children with end-stage lung disease secondary to a pathogenic variant in *FLNA* should be considered as therapy for the pulmonary complications of this disorder. Moreover, even after lung transplantation, close cardiology follow-up is necessary in these patients given the risk for severe ascending aortic dilation with aortic regurgitation which was observed in all of our patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Source: This work was supported by NIH K08DK106453 (L.C.B) and NIH K23HL127266 (S.A.M.). No specific funding, grant or honorarium was provided to produce this manuscript.

Abbreviations

PVNH	Periventricular nodular heterotopia
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
CXR	Chest radiograph
CT	Chest computed tomography

MV	Mechanical ventilation
MRI	Magnetic resonance imaging
VTI	vertebral artery tortuosity index

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Figure 1.

Serial anteroposterior chest radiographs of the index patient at age 4 months (A), 7 months (B), and 12 months (C) show parahilar atelectasis and progressively severe pulmonary hyperinflation. Axial chest computed tomography (CT) images (D,E) of the index patient at 10 months of age demonstrate severe pulmonary hyperinflation and hyperlucency with peripheral pulmonary vascular attenuation, most marked of the upper and middle lobes, and atelectasis of the dependent posterior lung regions.

Table 1

Pulmonary Complications and Transplant Course for Each Patient

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gestational age (weeks)	39	40	38	34	39	38
Birth weight (kg)	3.57	Unknown	3.15	2.48	3.91	3.52
Onset respiratory symptoms	2–4 mos	Neonatal	Neonatal	Neonatal	Neonatal	Neonatal
Age chronic respiratory failure	10 mos	2 mos	10 mos	1.7 mos	8 mos	11 mos
Duration PPV before transplant	3 mos	3 mos	5 mos	6 mos	3 mos	2 weeks
Vent settings at transplant [RR, Pressures, FIO ₂]	24, 32/6, 0.60	22, 35/10, 0.65	18, 37/15, 0.40	34, 26/9, 0.60	26, 30/10, 0.35	22, 28/10, 0.90
Age of diagnosis of pulmonary hypertension	4 mos	2 mos	1 mo	2 mos	7 mos	5 mos
Age at tracheostomy	13 mos	5 mos	9 mos	3 mos	7 mos	12 mos
Age at transplant	15 mos	5 mos	15 mos	8 mos	11 mos	13 mos
Duration transplant hospitalization	60 days	96 days	70 days	50 days	30 days	26 days
Diagnosis of tracheobronchomalacia	Yes/8 mos	Yes/2 mos	Yes/6 mos	Yes/9 mos	No	Yes/6 mos

Abbreviations: PPV: positive pressure ventilation, RR: respiratory rate, mos: months

Table 2

Cardiovascular and Neurologic Features

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Congenital heart disease	PFO, PDA, mild pulmonary valve tethering without stenosis	PFO, PDA, small perimembranous VSD	PFO, PDA,	PFO, PDA, left coronary artery dilation	PFO, PDA	PFO, PDA, mild pulmonary valve tethering without stenosis
Cardiac surgery	PDA Ligation	PDA ligation Heart transplant (with 2 nd lung transplant)	PDA ligation PFO closure (with lung transplant)	PDA ligation and PFO closure (with lung transplant)	PDA ligation and PFO closure (with lung transplant)	PFO closure (with lung transplant)
Aortic root dilation	Mild	None	None	Moderate	None	None
Asc. aortic dilation	Severe	Severe	Severe	Severe	Severe	Severe
Max asc. aortic z-score*/dimension	6.9/2.9 cm	8.0/2.8 cm	9.3/2.9 cm	5.6/2.3 cm	5.4/2.4 cm	6.6/2.5 cm
Age at imaging	9.2 yr	3.5 yr	4.3 yr	3.8 yr	3.6 yr	2.6 yr
Weight, height at imaging	19.1 kg, 114.6 cm	15.6 kg, 89 cm	13.2 kg, 88.5 kg	13.0 kg, 88.2 cm	14.1 kg, 94.3 kg	14.0 kg, 88.0 cm
Aortic regurgitation	Mild	Moderate	Mild	Mild	Mild	Mild
Vertebral artery tortuosity(VTI)**	Mild (14)	Not assessed	None (2)	Mild (14)	Not assessed	Not assessed
Rhythm disorders	No	No	SVT, frequent PVCs	No	No	No
Strabismus	Yes	Yes	Yes	Yes	Yes?	No
Periventricular Nodular Heterotopia	Yes	Yes	Yes	Yes	Yes	Yes
Seizures	No	No	Single hypoglycemic seizure	No	No	No
Developmental Delay	ADHD	No	Global dev delay	No	No	No