

# Familial Neuroendocrine Cell Hyperplasia of Infancy

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**Summary.** Background: Neuroendocrine cell hyperplasia of infancy (NEHI) is a recently described children's interstitial lung disease (chILD) disorder of unknown etiology. It manifests clinically with tachypnea, retractions, hypoxemia, and crackles. The characteristic radiographic appearance consists of pulmonary hyperexpansion and ground-glass densities on high-resolution computed tomography (HRCT). Lung histology shows hyperplasia of bombesin-immunopositive neuroendocrine cells within distal bronchioles and alveolar ducts without other identifiable lung pathology or developmental anomaly. Methods: We describe four families with multiple siblings diagnosed with NEHI. Cases were identified at three pediatric centers. Inclusion criteria included clinical findings consistent with NEHI, lung biopsy confirmation in the index case, and a diagnostic HRCT or biopsy in other siblings. Results: Each family had a proband diagnosed with NEHI based upon pathologic review, and at least one additional sibling diagnosed either by pathologic review or HRCT. All patients presented between 2 and 15 months of age. Both male and female children were affected. The majority of the patients underwent both HRCT and lung biopsy. There were no deaths among affected children. No environmental exposures or other potential etiologies were identified as a cause of presenting symptoms. Conclusions: The familial occurrence of NEHI suggests the possibility of a genetic etiology for this disorder and highlights the importance of taking a complete family medical history for infants presenting with a suggestive clinical picture. Identification of familial NEHI patients allows for the opportunity to further our understanding of this disorder, its natural history, the phenotypic spectrum, and potential genetic causes. **Pediatr Pulmonol.** 2010; 45:749–755. © 2010 Wiley-Liss, Inc.

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## INTRODUCTION

Neuroendocrine cell hyperplasia of infancy (NEHI) is a recently described respiratory disorder of unknown

etiology characterized clinically by tachypnea, retractions, crackles, and hypoxemia.<sup>1,2</sup> Considered to be a form of children's interstitial lung disease (chILD), NEHI has been included in the newly proposed classification scheme

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Cases were identified from three referral centers: Children's Hospital and University of Colorado (Aurora, CO), Johns Hopkins Children's Center (Baltimore, MD), and University of Western Australia (Perth, Australia).

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for children with diffuse lung disease as a “Specific disorder of unknown etiology” under the category of “Disorders more prevalent in infancy.”<sup>3</sup> The diagnostic gold standard is lung biopsy demonstrating increased numbers of bombesin-immunopositive pulmonary neuroendocrine cells (PNECs) within bronchioles and alveolar ducts without evidence of other abnormalities, and limited or absent inflammation. PNECs are normally distributed throughout the airway epithelium both as solitary cells and as innervated clusters, called neuroepithelial bodies (NEBs).<sup>4</sup> PNECs represent a significantly greater proportion of total airway epithelial area in NEHI, and NEBs within the lobular parenchyma are also enlarged and more numerous.<sup>2</sup>

On high-resolution computed tomography (HRCT), a characteristic pattern of ground-glass opacities (GGOs) has been consistently noted, with GGOs most commonly occurring in the right middle lobe and lingula; additionally, mosaic air trapping is also seen.<sup>5–7</sup> The term “NEHI syndrome” is used to indicate a diagnosis of NEHI without lung biopsy, based on a consistent clinical presentation and radiographic findings.

Treatment for NEHI is supportive, with oxygen supplementation and optimizing nutrition being mainstays of therapy. Failure to thrive (FTT) is often seen in infants with this disorder.<sup>2,3</sup> Consistent with the histological findings of limited inflammation, prolonged courses of oral corticosteroids have not been shown to eliminate symptoms. No deaths have been reported in the NEHI population. Long-term outcomes are unclear, although limited data suggest that in most patients, hypoxemia and symptoms will improve during childhood.<sup>2</sup>

The underlying etiology for NEHI is unknown and a genetic basis has not been reported. As we have observed multiple cases of NEHI within a number of kindreds, we hypothesize that the mechanism of disease may be related to an environmental cause or genetic etiology.

## MATERIALS AND METHODS

We completed a retrospective case review of four families with two or more children diagnosed with NEHI

or NEHI syndrome. These patients were identified at two centers in the United States and one center in Australia. With the consent of all subjects, charts were reviewed for clinical presentation, clinical signs and symptoms, birth history, family history, environmental history, diagnostic evaluation performed, radiographic imaging, and lung biopsy results. We obtained family histories of lung disease or pulmonary symptoms, ages of death, supplemental oxygen use, altitude at both birth and childhood, occupations of parents, and travel and exposure history. A three-generation pedigree was completed for each family.

To be eligible for inclusion, each family had to have at least one child with a biopsy-confirmed diagnosis of NEHI, as determined by a pathologist experienced in reviewing pediatric pulmonary pathology. In addition, predefined histologic criteria including quantitative assessment of neuroendocrine cell proportion were applied.<sup>8</sup> In all cases, neuroendocrine cells were assessed using the same antibody for bombesin immunostaining (ImmunoStar, Inc., Hudson, WI; polyclonal antibody) and standard laboratory protocols. Most immunostaining was performed in a single laboratory. In order for additional siblings to be included, requirements included either lung biopsy with histological findings of NEHI, or consistent clinical NEHI symptoms and HRCT pattern (NEHI syndrome). All HRCTs were reviewed by a pediatric radiologist experienced in NEHI imaging.<sup>7</sup> The diagnostic evaluation to exclude other known causes of lung disease was determined by each center. However, most centers used similar diagnostic methods, including evaluation for infectious, immunologic, allergic, and rheumatologic causes. Sweat chloride testing was also performed on the majority of these patients. Several patients underwent genetic testing for inborn errors of surfactant metabolism. Most patients underwent bronchoscopy with bronchoalveolar lavage (BAL), and evaluations for recurrent aspiration.

## RESULTS

Table 1 provides the composite clinical data, and Figure 1 shows two-generation pedigrees for all four families described below.

### Family 1

The first affected child was born at full-term. She presented at 4 months of age with retractions, wheezing, crackles, hypoxemia, and FTT. She underwent lung biopsy at 15 months of age and again at 6 years of age. Both biopsies had increased bombesin-immunopositive PNECs consistent with NEHI. Chest CTs at both 16 months and 10 years of age showed GGOs concentrated in the right middle lobe, and some involvement of the right upper lobe and left upper lobe. She remained on supplemental oxygen from approximately 1½ to 6½ years of

#### ABBREVIATIONS

BAL	Bronchoalveolar lavage
chILD	Children’s interstitial lung disease
FTT	Failure to thrive
GGO	Ground-glass opacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
NEB	Neuroepithelial body;
NEHI	Neuroendocrine cell hyperplasia of infancy;
NICU	Neonatal intensive care unit;
PNEC	Pulmonary neuroendocrine cell;
SIDS	Sudden infant death syndrome

**TABLE 1—Characteristics of Patients With Familial NEHI**

Family	Birth order	Sex	Age at presentation	Clinical findings	HRCT consistent with NEHI per radiologist review (age at exam performed)	Biopsy consistent with NEHI per pathologist review
1	2/5	F	4 mo	Retractions Wheezing Crackles Hypoxemia FTT	Yes (16 mo)	Yes
	4/5	M	4 mo	Grunting Retractions Crackles Hypoxemia FTT	Yes (5 mo)	Yes
	5/5	M	15 mo	Grunting Retractions Pleural effusion Hypoxemia FTT	Yes (18 mo)	Not performed
2	1/2	M	4 mo	Grunting Retractions Tachypnea Cough Hypoxemia FTT	Yes (8 mo)	Yes
	2/2	M	2 mo	Tachypnea Hypoxemia FTT	Yes (3 mo)	Not performed
3	1/4	M	4 mo	Tachypnea Hypoxemia FTT	Yes (7 mo)	Yes
	4/4	F	2 mo	Chest deformity Tachypnea Wheezing FTT	Yes (8 mo)	Yes
4	1/3	F	10 weeks	Tachypnea Retractions FTT	Yes (11 years)	Yes
	3/3	F	5 mo	Tachypnea Retractions Chest deformity Hypoxemia FTT	Yes (5 mo)	Yes

FTT, failure to thrive; mo, months.

age. Pulmonary function testing showed persistent hyperinflation at 14 years of age.

The second affected child was born at full-term. He presented at 4 months of age with grunting, retractions, hypoxemia, crackles, and FTT. He underwent a thoracic HRCT at 5 months of age which showed GGOs concentrated in the right middle lobe, with some involvement medially of the right upper lobe, left upper lobe, right lower lobe, left lower lobe, and lingula. Lung biopsy performed at 8 months of age showed characteristic findings of hyperplastic PNECs with bombesin immunostaining, and appeared similar to the first sibling’s biopsy. He remained on supplemental oxygen from 4 to 19 months.

Pulmonary function testing performed at 9 years of age showed persistent hyperinflation of lung volumes.

The third affected sibling was born at 31<sup>6</sup>/<sub>7</sub> weeks gestational age. He spent 1 month in a neonatal intensive care unit (NICU) and was discharged home without supplemental oxygen use or any respiratory issues. After discharge, he had persistent issues with weight gain, and was diagnosed with FTT. He presented at 15 months with symptoms of cough and increased work of breathing. Chest X-ray revealed a left-sided empyema, which required thoracentesis and chest tube placement. He received 14 days of intravenous antibiotics, and respiratory symptoms improved.

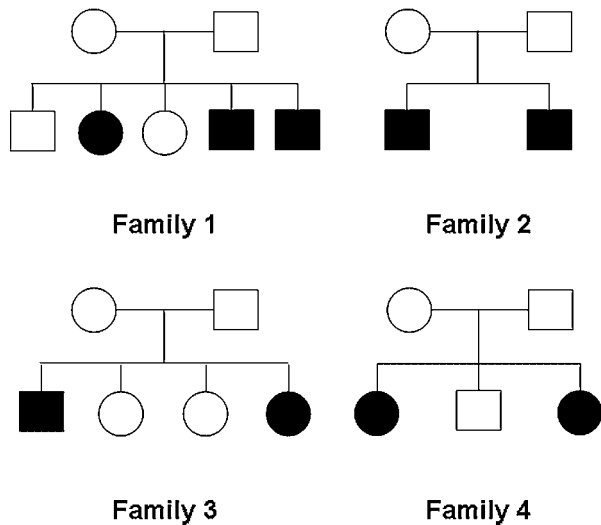


Fig. 1. Two-generation pedigrees for familial cases of NEHI.

A HRCT of the chest was obtained at 18 months of age, as cough and increased work of breathing had returned. The HRCT of the chest showed resolution of the empyema; however, GGOs were noted to be concentrated in the right upper and middle lobes, with some involvement of the lingula, right lower lobe, and left lower lobe. Patchy mosaic attenuation of the right lower lobe, right upper lobe, and left lower lobe was also noted. He did not have a lung biopsy performed as HRCT of his chest was consistent with NEHI and nearly identical to those of his siblings, fulfilling criteria for NEHI syndrome as previously defined. He required supplemental oxygen only sporadically, typically with upper respiratory infections.

The HRCT findings for the first two affected siblings in this family are shown in Figure 2 and demonstrate the classic radiographic findings for NEHI. A three-generational family history was obtained. A paternal aunt has a diagnosis of asthma, and her daughter (paternal first cousin) has been diagnosed with cystic fibrosis. The paternal grandfather was diagnosed with chronic obstructive pulmonary disease after many years of smoking. He was also diagnosed with unspecified interstitial lung disease (ILD) and spent 3 years on supplemental oxygen before his death at 69 years of age. No obvious environmental risk factors or exposures could be ascertained. The three affected siblings are now 14, 9, and 5 years of age, respectively. Currently the two older siblings have non-specific exercise complaints.

### Family 2

The first sibling was born at full-term. He presented at age 4 months with grunting, retractions, tachypnea, cough, and FTT. His chest CT showed GGOs in the right upper and middle lobes and lingula. He had minimal air-trapping

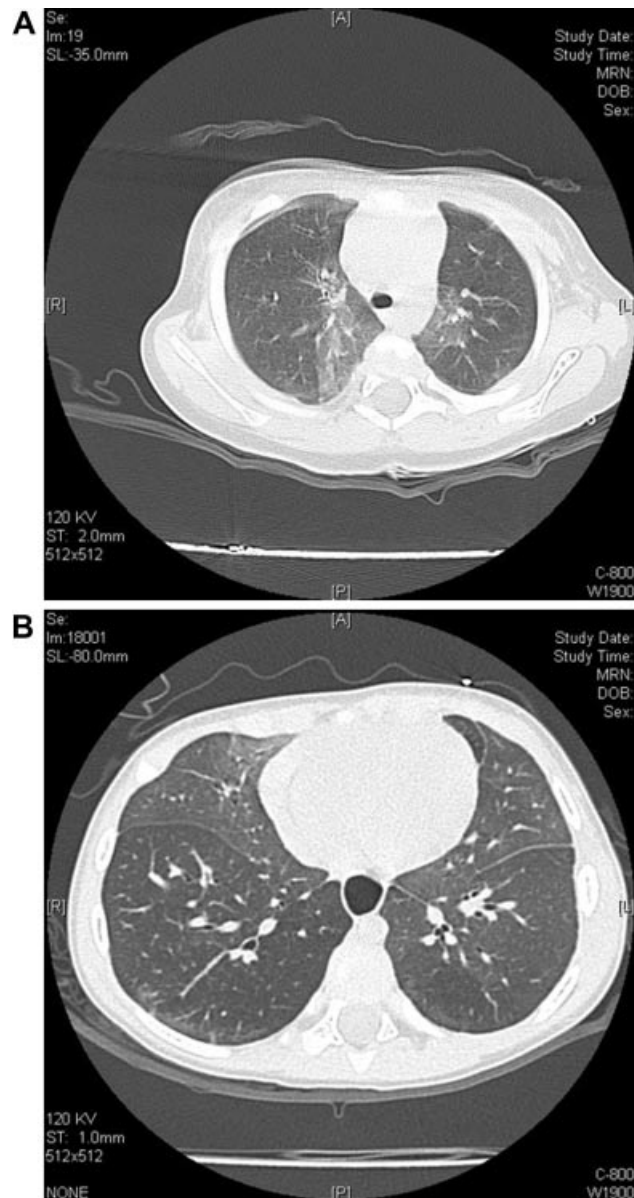


Fig. 2. Examples of characteristic chest HRCT findings in NEHI. **A:** This image is from affected Sibling 1 in Family 1. Findings include ground-glass opacities found most prominently in the medial parts of the RUL and LUL. **B:** This image is from affected Sibling 2 in Family 1. Findings include ground-glass opacities found most prominently in the RUL and lingula, and additionally in the RML and LLL.

in the lower lobes. Lung biopsy was performed at 5 months of age, which showed characteristic findings of hyperplastic bombesin-immunopositive PNECs. He required supplemental oxygen between 6 months and 3 years of age.

The second sibling was born at full term. He presented at 2 months of age with tachypnea, hypoxemia, and FTT. Chest HRCT was significant for GGOs concentrated in the lingula, with some involvement of the right middle and upper lobes, and left upper lobe. His parents refused lung

biopsy. He remained on supplemental oxygen between 2 months and 5 years of age.

No significant family history or history of environmental exposure history was obtained. The siblings are now 13 and 7 years of age, respectively.

**Family 3**

The first affected sibling was born at full-term. A heart murmur was noted and echocardiography revealed a small muscular ventricular septal defect. He presented with respiratory symptoms at 4 months of age when he was admitted for inpatient management of bronchiolitis. At that time, persistent tachypnea was noted. After discharge, his tachypnea persisted. Further evaluation included a lung biopsy at 7½ months of age and chest HRCT. The HRCT showed attenuation of the right middle lobe, left lower lobe, and lingula. Upon initial review, the biopsy showed no overt pathology. At that time, bombesin immunostaining was not performed as review of this specimen took place before the characteristic features of NEHI had been described.

A gastrostomy tube was placed because of persistent FTT. He had several presentations to the Emergency Department for tachypnea, hypoxemia, and suspected pneumonia. Another HRCT was performed at 4 years of age, which showed similar findings to the previous HRCTs. At 6½ years of age, the previously obtained lung biopsies were re-examined with bombesin immunohistochemistry. Increased PNECs and NEBs were noted, consistent with NEHI. The patient is currently 7 years old and has recently discontinued the use of supplemental oxygen.

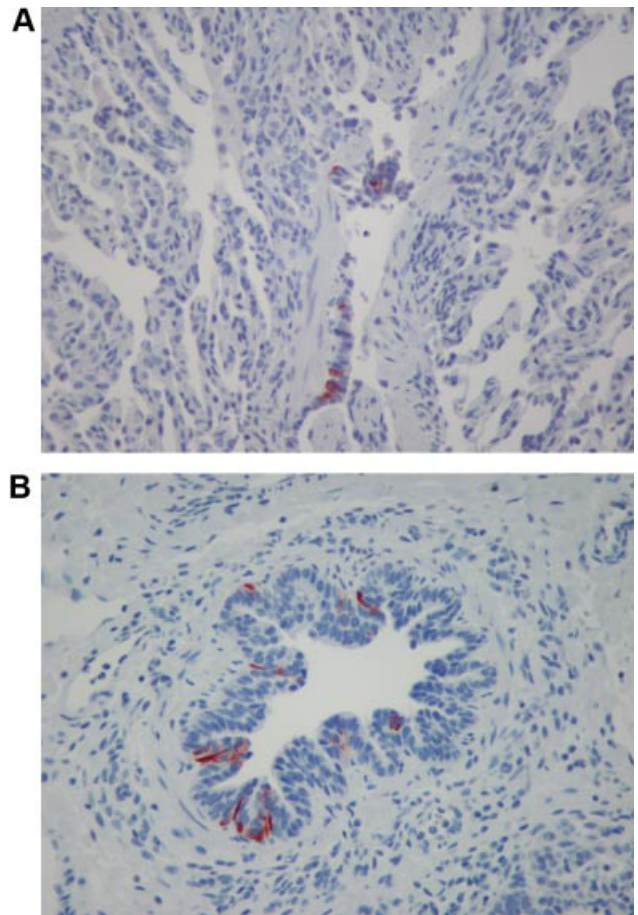
The second affected sibling was born at full-term. She first presented at 2 months of age with tachypnea. She was diagnosed with bronchiolitis at 4 months of age. Wheezing was noted at 7 months of age, and a chest X-ray showed bilateral hyperinflation. She also had FTT. A chest HRCT showed interstitial thickening and GGOs bilaterally. She was admitted at 8 months of age for wheezing and tachypnea. At that time, upper gastrointestinal imaging was normal, but a swallow evaluation revealed mild swallowing dysfunction. A gastrostomy tube was placed and supplemental oxygen was initiated. After several more admissions for hypoxemia and tachypnea, she underwent Nissen fundoplication and lung biopsy. The biopsy was noted to be consistent with NEHI, and similar in appearance to her brother’s biopsy. She remains gastrostomy tube dependent for adequate caloric intake at 2 years of age and requires 0.25 L/min of supplemental oxygen at all times.

Of note, a paternal uncle of the children in this family died at 4 months of age from presumed sudden infant death syndrome (SIDS) in the 1960s. There was no other family history of lung disease. No environmental exposures were identified.

**Family 4**

The first affected sibling presented with respiratory symptoms at 10 weeks of age. Symptoms included tachypnea, retractions, and FTT. A lung biopsy was performed and was initially reported as normal. There was gradual clinical improvement; however, home oxygen was required until 5 years of age. HRCT chest was performed at 11 years of age and showed mosaic attenuation. The diagnosis of NEHI was made retrospectively after sibling 2 was diagnosed. At most recent follow-up at 15 years of age, she had mild exercise-related symptoms, and a mild restrictive and moderate obstructive pattern on pulmonary function testing.

The second affected sibling presented with tachypnea and retractions at 5 months of age. Chest HRCT showed wide-spread GGOs and interstitial thickening. Bombesin immunostaining of her lung biopsy demonstrated



**Fig. 3. A: Lung biopsy of affected Sibling 1 in Family 4. Immunohistochemistry shows increased numbers of neuroendocrine cells (brown) as illustrated within this respiratory bronchiole (bombesin, 50×). B: Lung biopsy of affected Sibling 2 in Family 4. Bombesin immunostain of this terminal bronchiole similarly shows increased numbers of neuroendocrine cells distributed individually and in small groups (bombesin, 50×). A normal bronchiole of this size should contain only one or two isolated neuroendocrine cells.**

increased proportion of bronchioles containing bombesin-immunopositive cells, increased proportion of bombesin-immunopositive cells within airways, and frequent NEBs. The biopsy was compared to the previous biopsy performed on the patient's sister. Both were noted to be consistent with NEHI, and similar in appearance to each other. (Fig. 3 provides a comparison of the two sisters' biopsies.) She was discharged on home oxygen at 6 months of age and remains on nocturnal oxygen supplementation at 3 years of age.

## DISCUSSION

NEHI has become an acknowledged disorder within the chILD literature.<sup>1-4,6,7</sup> To our knowledge, this is the first case series describing familial NEHI. As we were not able to define an environmental exposure or alternative etiology, we propose that NEHI has a genetic etiology. Although it cannot be completely excluded, a purely environmental cause is less likely given that both affected and unaffected siblings were identified who shared a common environment. The pattern of inheritance most closely resembles an autosomal recessive mechanism. An autosomal dominant mechanism with incomplete penetrance or multigenic involvement is also possible. Alternatively, a two-hit model of genetic predisposition followed by an as-yet unidentified environmental trigger may best account for the pathogenesis of NEHI.

The significance of the finding that some of the NEHI patients lived at altitude is unclear. The lower atmospheric oxygen tension at altitude may make subtle lung disease more clinically apparent. Whether altitude plays a role in the development of NEHI or simply makes the clinical findings more pronounced remains to be determined. Of the families described in this article, two resided at altitude and two at sea level. As additional cases of NEHI are identified, the role of altitude, either prenatally or postnatally, will need further examination.

PNECs express both neural and endocrine cell phenotypes, including the synthesis and release of amines (serotonin), and a variety of neuropeptides.<sup>4</sup> They appear to play a role in oxygen sensing,<sup>9-11</sup> in lung development as modulators of fetal pulmonary growth and differentiation,<sup>12</sup> and also in lung carcinogenesis.<sup>13,14</sup> It is plausible that PNECs contribute primarily to the pathology of NEHI, as hyperplasia of these cells is the most consistent pathologic finding in NEHI patients. Alternatively, PNEC hyperplasia could represent a response to chronic hypoxemia, cytokine effects, or dysregulation of neurogenic genes.<sup>4</sup>

Increased numbers of PNECs have been described in patients with SIDS, bronchopulmonary dysplasia, and cystic fibrosis, as well as a form of ILD seen in adults.<sup>15-22</sup> The roles played by PNECs in these diseases remain to be clearly defined. Interestingly, a paternal uncle in one of our families

died of SIDS, and relatives in another family carried diagnoses of asthma, cystic fibrosis, and adult-onset ILD.

Our study has some limitations. There are only a small number of patients. HRCTs were not obtained on asymptomatic family members, so we cannot be sure that they did not have radiographic abnormalities, and potentially a milder form of the disease. It may be hard to identify older individuals in a family where there are other NEHI patients, as the clinical findings tend to become less pronounced with age. A reliable biomarker would be useful in order to follow disease progression, and to evaluate individuals with quiescent NEHI. Biopsies were not obtained on all symptomatic members of all families. Finally, potential exists for recall bias, especially as it pertains to parental report of environmental exposures and family history of lung disease.

Goals of future research within the NEHI population should include elucidation of the exact role of PNECs in the pathophysiology of NEHI. A more exhaustive and descriptive case series including more patients with longer follow-up would help to better define long-term prognosis and response to therapy, as some of our patients continue to have pulmonary abnormalities. Finally, family-based genetic linkage analysis could be used to search for potential candidate genes. Identification of a genetic cause for NEHI would provide a non-invasive means for diagnosis. Such a discovery would also be expected to offer insight into the pathogenesis of this idiopathic disorder, as well as suggesting potential avenues for therapeutic development.

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Dr. Popler primarily wrote the manuscript and coordinated the collection of data from all families. Dr. Gower assisted in the writing and editing of the manuscript and collected data on one of the families. Dr. Mogayzel provided data on one family and participated in the editing of the manuscript. Dr. Wilson provided data on one of the families. Dr. Noguee provided data on one of the families as the principal investigator of the protocol in which they are enrolled, and provided expertise in the formulation of genetic hypotheses. He also participated in the editing of the manuscript. Dr. Langston reviewed pathological specimens and contributed expertise to the sections of the manuscript describing histological findings. Dr. Hay reviewed radiographic images and contributed expertise to the sections of the manuscript describing radiologic findings. Dr. Deterding provided oversight and expertise in all phases of the study including initial data collection through manuscript preparation. She is the principal investigator on the protocol under which two of the families are enrolled. Additionally, the authors wish to thank Dr. Frederic Askin, Dr. Gail Deutsch, Dr. Megan Dishop, and Dr. Frank Accurso for their assistance and expertise. This

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