

ORIGINAL ARTICLE

Interstitial Lung Disease in Children: Rare Genetic Variants Beyond Surfactant Dysfunction

Satı Özkan Tabakçı¹  | Şule Selin Akyan Soydaş¹  | Gökçen Dilşa Tuğcu¹  | Güzin Cinel^{1,2}  |
 Ayşe Ceren Sağdıç³  | Uğur Özçelik⁴  | Sinem Can Oksay⁵  | Çiğdem Korkmaz⁶  | Fazılcan Zirek⁷  |
 Handan Kekeç⁸  | Figen Gülen⁹  | Melih Hangül¹⁰  | Beste Özsezen¹¹  | Derya Ufuk Altıntaş¹²  |
 Hanife Tuğçe Çağlar¹³  | A. Erdem Başaran¹⁴  | Zeynep Seda Uyan¹⁵  | Ali Özdemir¹⁶  |
 Tuğba Ramaslı Gürsoy¹⁷  | Ebru Yalçın⁴  | Nagehan Emirlioğlu⁴  | Saniye Girit⁵  | Ayşe Ayzıt Kılınç⁶  |
 Nazan Çobanoğlu⁷  | Tuğba Şişmanlar Eyüboğlu⁸  | Sevgi Pekcan¹³  | Yasemin Gökdemir¹⁸  | Berna Oğuz¹⁹  |
 Diclehan Orhan²⁰  | Ahmet Cevdet Ceylan^{3,21}  | Nural Kiper⁴ 

¹Department of Pediatric Pulmonology, Ankara Bilkent City Hospital, Ankara, Türkiye | ²Faculty of Medicine, Department of Pediatric Pulmonology, Ankara Yıldırım Beyazıt University, Ankara, Türkiye | ³Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye | ⁴Faculty of Medicine, Department of Pediatric Pulmonology, Hacettepe University, Ankara, Türkiye | ⁵Faculty of Medicine, Department of Pediatric Pulmonology, Medeniyet University, İstanbul, Türkiye | ⁶Cerrahpaşa Faculty of Medicine, Department of Pediatric Pulmonology, İstanbul University—Cerrahpaşa, İstanbul, Türkiye | ⁷Faculty of Medicine, Department of Pediatric Pulmonology, Ankara University, Ankara, Türkiye | ⁸Faculty of Medicine, Department of Pediatric Pulmonology, Gazi University, Ankara, Türkiye | ⁹Faculty of Medicine, Department of Pediatric Pulmonology, Ege University, İzmir, Türkiye | ¹⁰Department of Pediatric Pulmonology, Adana Research and Training Hospital, Adana, Türkiye | ¹¹Faculty of Medicine, Department of Pediatric Pulmonology, Dokuz Eylül University, İzmir, Türkiye | ¹²Faculty of Medicine, Department of Pediatric Allergy and Immunology, Çukurova University, Adana, Türkiye | ¹³Faculty of Medicine, Department of Pediatric Pulmonology, Necmettin Erbakan University, Konya, Türkiye | ¹⁴Faculty of Medicine, Department of Pediatric Pulmonology, Akdeniz University, Antalya, Türkiye | ¹⁵Faculty of Medicine, Department of Pediatric Pulmonology, Koç University, İstanbul, Türkiye | ¹⁶Department of Pediatric Pulmonology, Mersin City Hospital, Mersin, Türkiye | ¹⁷Department of Pediatric Pulmonology, Van Research and Training Hospital, Van, Türkiye | ¹⁸Faculty of Medicine, Department of Pediatric Pulmonology, Marmara University, İstanbul, Türkiye | ¹⁹Faculty of Medicine, Department of Pediatric Radiology, Hacettepe University, Ankara, Türkiye | ²⁰Faculty of Medicine, Department of Pathology, Hacettepe University, Ankara, Türkiye | ²¹Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Correspondence: Satı Özkan Tabakçı (satiozkan.md@gmail.com)

Received: 27 October 2025 | **Revised:** 1 July 2026 | **Accepted:** 6 August 2026

Keywords: children | genetic variants | interstitial lung disease

ABSTRACT

Background: Advances in genetic analysis techniques and strategies have enabled the identification of rare novel genetic entities in children's interstitial lung disease (chILD).

Aims: To describe an extensive array of demographic, clinical, radiological, and laboratory data from a national registry of children with diffuse lung disease caused by rare and novel genetic variants.

Study Design: Retrospective cohort study.

Methods: This study used data from the chILD Türkiye (chILD-TR) registry to analyze rare genetic chILD subtypes, excluding surfactant protein gene variants, *ABCA3*, and *NKX2-1*, between November 2021 and January 2024. Of 671 patients in chILD-TR, 182 underwent genetic analysis excluding surfactant protein-related variants, resulting in 37 patients identified with rare genetic variants included in the study.

Results: Among the 37 patients with rare genetic variants, 19 (51.4%) were male, and the median age at diagnosis was 40.5 months (IQR 15.5–115.5). Genetic analysis conducted on 15 patients identified *COPA*, *STAT3*, *STING1*, *ADA*, *ZNFX1*, *PIK3CD*, *PLCG2*, *OAS1*, *CCR2*, *RNF168* and *ATM* gene variants, which are associated with immunodeficiency/dysregulation

and autoinflammation; 15 *NPC1*, *SMPD1*, *GBA1*, *SLC7A7*, *MARS1*, *FARSB*, and *PEPD* genes, variants linked to inherent metabolic errors. Seven patients were found with *TBX4*, *SLC34A2*, *PLG*, and *SMAD4* gene variants. All patients were born at term, and five (13.5%) of them were small for gestational age. Two patients (5.4%) had previously been on a mechanical ventilator in the neonatal intensive care unit, 25 (67.6%) had familial consanguinity, and 23 (62.1%) had comorbid systemic disease. Thirteen patients (35.1%) required oxygen support. All patients underwent chest computed tomography scans at initial assessment, showing ground-glass opacities in 29 (78.3%), infiltrations in 27 (72.9%), and interlobular septal thickening in 20 (54%). Eight patients (21.6%) received oral steroids, and six (16.2%) received pulse steroids in addition to their primary treatments for systemic diseases.

Conclusions: Interstitial lung disease rarely occurs in children, but increased awareness and genetic testing may enable earlier diagnosis. Recognizing that diffuse parenchymal lung disease can occur in rare systemic diseases may improve diagnoses and treatment.

1 | Introduction

Children's interstitial lung disease (chILD) refers to diffuse parenchymal lung disease in children involving the interstitium, alveoli, distal small airways, and/or terminal bronchioles [1]. Initially identified in pediatric patients with surfactant protein metabolism disorders, this rare disease has since been reportedly associated with systemic conditions such as immunodeficiency, immune dysregulation, autoinflammation, and inherent metabolic errors and is classified into various classifications [2, 3]. Advances in sequencing and genotyping have led to a rapid increase in genetic discoveries, which have significantly expanded the number of distinct chILDs [4].

Genetic advances, including next-generation sequencing and whole-exome sequencing (WES), have replaced single-gene approaches with panel-based analysis [5]. Numerous new monogenic syndromes have been identified, often with clinically diverse and extreme phenotypes resulting from single-gene mutations. Furthermore, seemingly unrelated clinical presentations have been interconnected through shared gene mutations or pathway-related variants, leading to the identification of new genetic entities in chILD, including rare genetic variants with low prevalence [4–6].

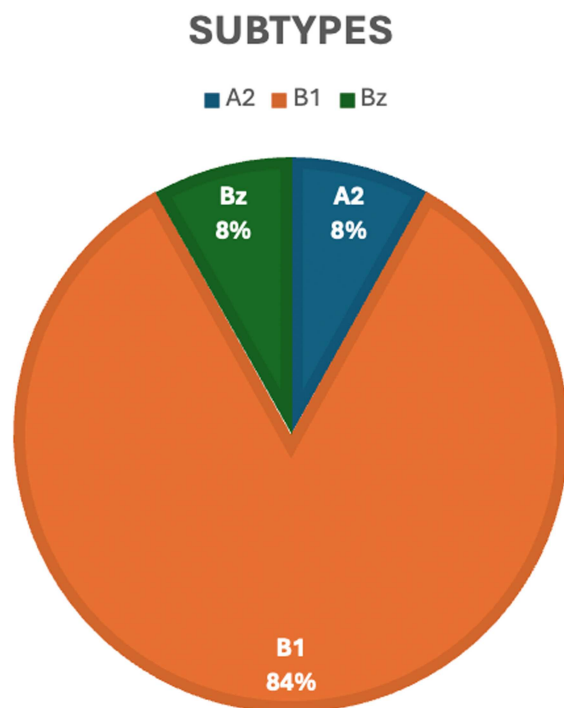
We analyzed data from patients with chILD with genetic variants, excluding surfactant protein gene variants, *ABCA3*, and *NKX2-1* as listed in the chILD Türkiye registry (chILD-TR) to highlight this subgroup. We aim to present clinical and demographic features of these rare diseases, as current literature is largely limited to case reports.

2 | Materials and Methods

2.1 | Study Design

This retrospective cohort study used a data entry software system to extract information from the chILD-TR registry, established in November 2021. Participating centers can access and update only their own patients' data, including demographics, initial clinical and laboratory findings, diagnostic and treatment details, and annual follow-up information. Each patient is assigned a unique code, and age-appropriate consent and written informed consent from caregivers are obtained before data entry [1]. The national registry and data input were approved by the Hacettepe

University Ethics Committee (reference numbers: GO 20/604), in accordance with the 1964 Declaration of Helsinki and its later amendments. The study focused on rare genetic chILD subtypes, excluding *NKX2-1*, *ABCA3*, and surfactant protein genes *SFTPB*, *SFTPA*, and *SFTPC* variants, using chILD-TR genetic examination data between November 2021 and January 2024. Patients with variants in *MARS*, *OAS1*, *COPA*, *STING1*, *TBX4*, *ZNFX1*, *PIK3CD*, *SLC7A7*, *SMPD1*, *NPC1*, *GBA*, *STAT3*, *TERT*, *MUC5B*, *SLC34A2*, *RNF168*, *CCR2*, *PLCG2*, *PEPD*, and *SMAD4* genes were identified [4, 5, 7–9]. Genetic analysis methods for rare variants included WES in 31 patients using various kits at different centers, Sanger sequencing for selected genes (*GBA1*, *NPC1*, *STING1*, *ADA*, *TERT*, and *PEPD*) in seven patients due to family history, and whole-genome sequencing (WGS) for *ATM*, *GBA1*, *SMAD4*, *MARS1*, and *SMPD1* in five patients. Although both *TERT* and *MUC5B* are implicated in ILD, the evidence supporting causality differs. Heterozygous *TERT* variants link to adult pulmonary fibrosis and telomere disorders, but in our cohort, *TERT* variants were VUS with no supporting evidence for short telomere syndromes, making diagnosis inconclusive [10]. *MUC5B*'s genetic link to ILD is genotype-dependent: rs35705950 is a known risk in adults, while biallelic loss-of-function variants cause childhood ILD [11, 12]. The *MUC5B* variants identified in our cohort were neither the established promoter risk variant rs35705950 nor biallelic loss-of-function variants previously associated with pediatric disease. Instead, they were classified as VUS, and no additional functional, segregation, or clinical evidence supporting pathogenicity was available. Therefore, these findings were considered insufficient to establish a molecular diagnosis in the context of our pediatric cohort, and these patients were excluded ($n = 6$). Genetic panel analysis did not detect chILD with rare genetic variants in all study patients. The final diagnoses for all patients were grouped based on Griesse et al.'s classification (Figure 1) [3]. We analyzed age, sex, geographical regions where patients were born and lived, birth weights, neonatal intensive care unit (NICU) history, parental consanguinity status, symptoms (hemoptysis, dyspnea, cough, wheeze), weight, height, and body mass index and Z-scores at the time of diagnosis and at the current visit, hypoxia, tachycardia, tachypnea status, types of respiratory support, chILD diagnoses, comorbidities, laboratory findings (anemia, acidosis, hypercarbia, antinuclear antibody [ANA]), antineutrophil cytoplasmic antibodies (ANCA), tissue transglutaminase IgA-IgG, anti-endomysium IgA, pigeon precipitating antibody, serum IgG, IgA, IgM, IgE values by age, anti-glomerular basement membrane antibody, thyroid-stimulating



A2: Diffuse parenchymal lung disease-growth abnormalities deficient alveolarization	Cases 3.13., 3.14., 5.1.
B1: Diffuse paranchimal lung disease-related to systemic disease processes	Cases 3.1.-12., 3.15., 4.1.-15., 5.5, 5.6., 5.7.
Bz: Diffuse paranchimal lung disease	Cases 5.2., 5.3., 5.4.

FIGURE 1 | Percentage distribution of subgroup diagnoses of ultra-rare genetic variants of chILD in our registry. [Color figure can be viewed at wileyonlinelibrary.com]

hormone, free-T4 (fT4), spirometry, diffusing capacity for carbon monoxide (DLCO), and 6-min walk (6 MW) test results, chest computed tomography (CT) findings (early-stage thickened interlobular septa and fine reticulation, subsequently accompanied by traction bronchiolectasis and a cluster of cysts within extensively scarred pulmonary tissue in advanced stages, are considered indicative of pulmonary fibrosis), treatments, and genetic analysis findings.

2.2 | Molecular Analysis

Variants were interpreted and classified according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines into five categories: pathogenic (P), likely pathogenic (LP), VUS, likely benign (LB), and benign (B). Variant nomenclature followed the Human Genome Variation Society's recommendations [13]. Population allele frequencies were evaluated using publicly available databases, such as the Genome Aggregation Database (gnomAD v4.1). In silico predictions were examined using multiple computational tools, such as CADD, DANN, REVEL, SIFT, PolyPhen-2, and SpliceAI.

Some patients had two heterozygous variants in the same gene, increasing the possibility of compound heterozygosity. However, parental segregation analysis was not possible due to the lack of parental DNA, preventing the determination of cis/trans configuration phase. Therefore, segregation-based ACMG evidence classification, such as PM3, could not be confidently applied in Cases 3.12., 4.11., 4.13., and 3.15., and variant interpretation relied on available genetic, computational, and clinical evidence.

2.3 | Statistical Analysis

Statistical analysis was performed using the IBM SPSS 23.0. Descriptive data were presented as number (*n*), percentage (%), interquartile range (IQR), median, minimum, and maximum.

3 | Results

3.1 | Demographic, Clinical, Laboratory, and Treatment Characteristics of Patients

Of the 671 patients in chILD-TR, 182 underwent genetic analysis. After excluding patients without variants (*n* = 49), those with surfactant protein gene variants (*SFTPB* (*n* = 1), *SFTPA* (*n* = 1), and *SFTPC* (*n* = 6), *ABCA3* (*n* = 8), *NKX2-1* (*n* = 3)), non chILD-associated variants (*n* = 27), incomplete analysis results (*n* = 28), insufficient data (*n* = 16), and heterozygous *TERT* and *MUC5B* VUS variants (*n* = 6) (Supporting Information S1: Table S3), 37 patients with rare child-related genetic variants were included in the final analysis (Figure 2).

Patients were registered from across Türkiye, and all were alive at the time of analysis. Birthplace and current residence showed representation from seven geographical regions (Figure 3).

All patients were born at term, and 5 (13.5%) of them were small for gestational age. Twenty-five (67.6%) of them had familial consanguinity. Cases 5.2 and 5.3 (*SLC34A2*) and cases 4.7 and 4.8 (*SMPD1*) are siblings. Table 1 shows the comprehensive demographic and clinical characteristics of patients.

Eight (21.6%) patients underwent a sweat test for the differential diagnosis of cystic fibrosis, and results were normal. All patients

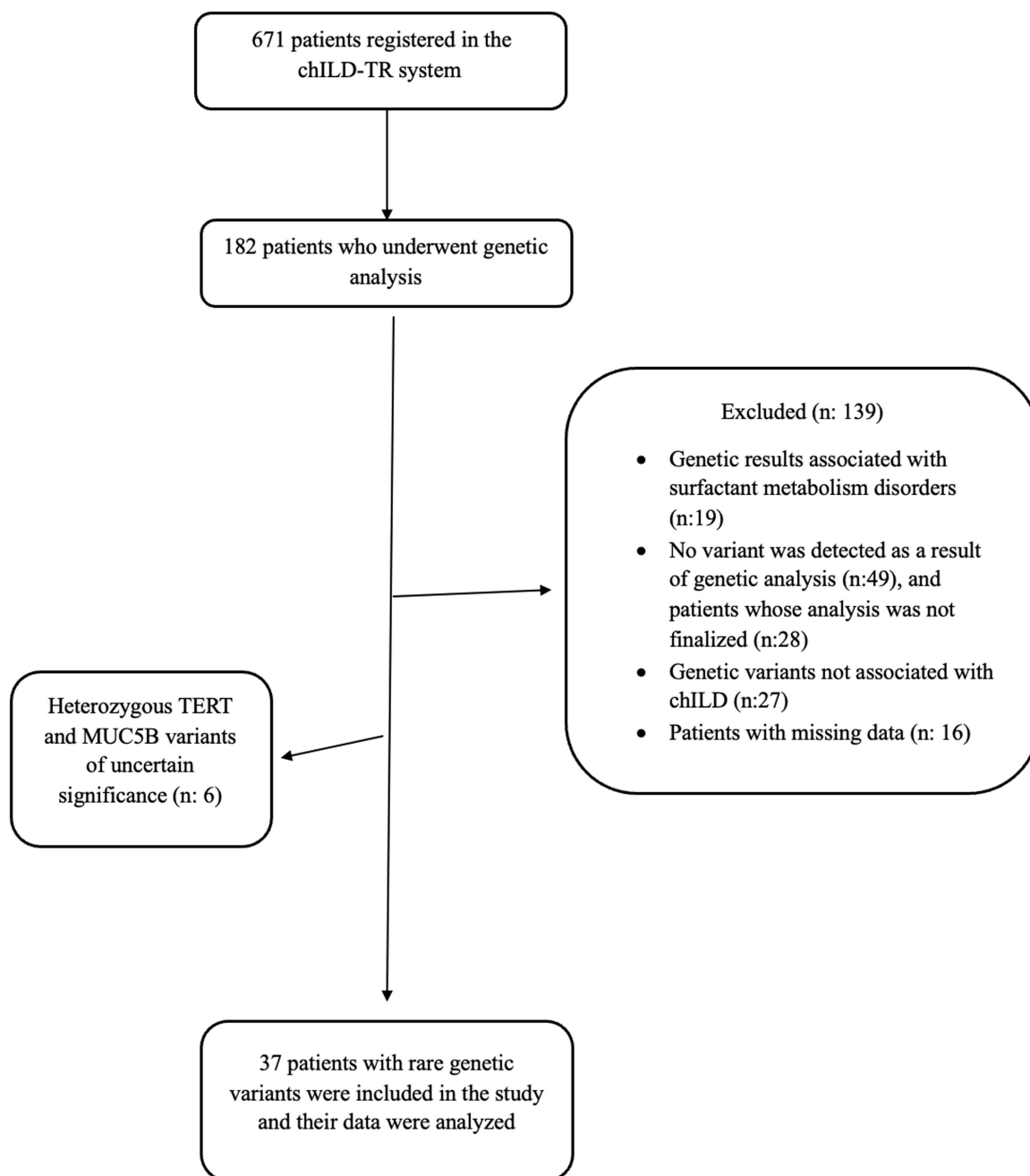


FIGURE 2 | Flowchart of the study.

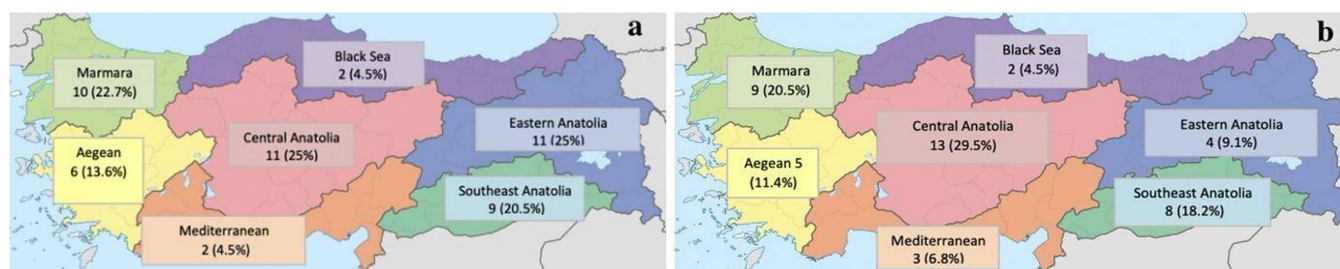


FIGURE 3 | Türkiye regions where patients with chILD are born (a) and live (b). [Color figure can be viewed at wileyonlinelibrary.com]

were examined for immunodeficiency, and 12 (32.4%) of them were diagnosed: three were identified with hypogammaglobulinemia (*CCR2*—case 3.13., *PEPD*—case 4.15. and *OAS1*—case 3.12.), 2 with hyper IgE syndrome (*STAT3*—case 3.3. and 3.4.), 2

with sting-associated vasculopathy (infantile-onset) (*STING1*—case 3.5. and 3.6.), one with severe combined immunodeficiency (T-cell-negative, B-cell-negative, NK-cell-negative) resulting from adenosine deaminase deficiency (*ADA*—case 3.7.), one with

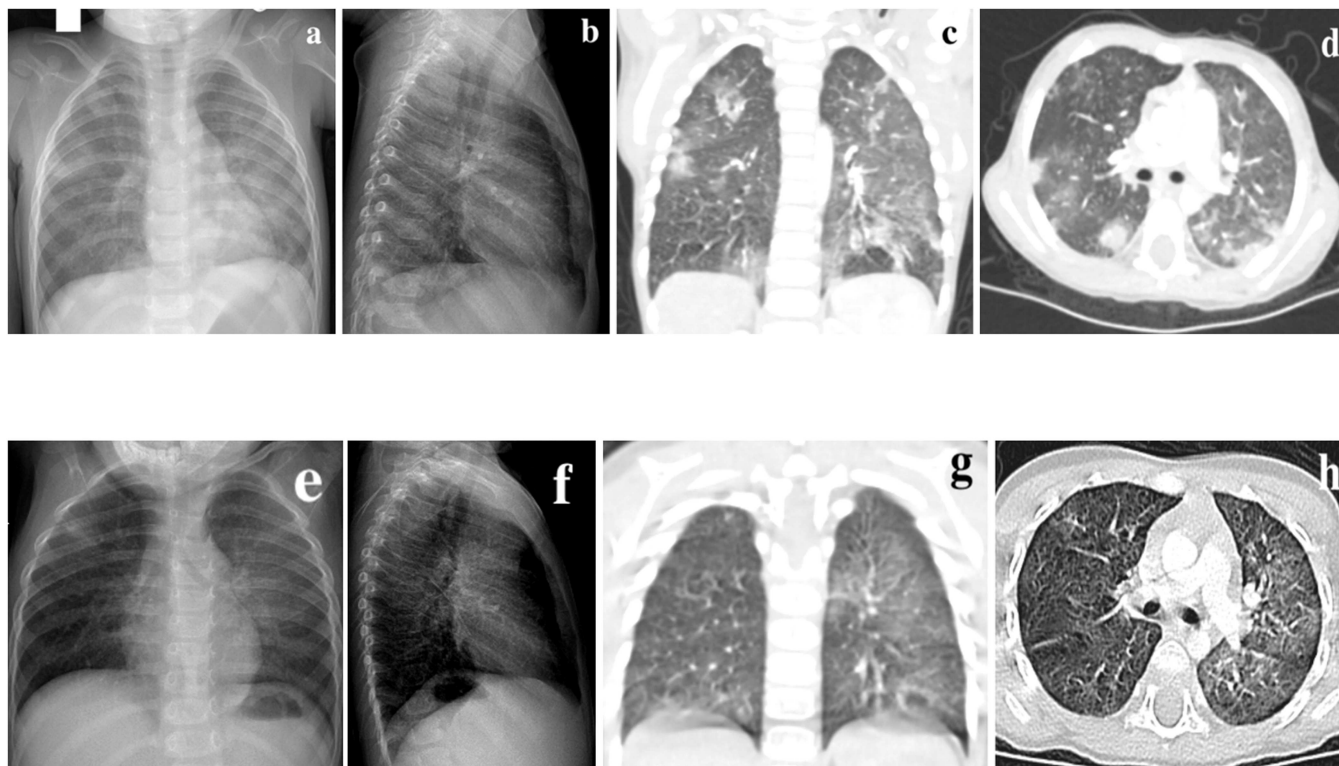


FIGURE 4 | CXR and chest CT scans of a 21-month-old girl (Case 3.1.) who had pulmonary hemorrhage and was diagnosed with COPA syndrome, both at diagnosis and after six doses of pulse steroid treatment. (a, b) Diffuse reticular appearance and GGO on CXR; (c, d) GGO, septal thickening, and nodules on chest CT; (e, f) regression in diffuse reticular appearance on CXR; and (g, h) regression in GGO, septal thickening, and nodules on chest CT posttreatment.

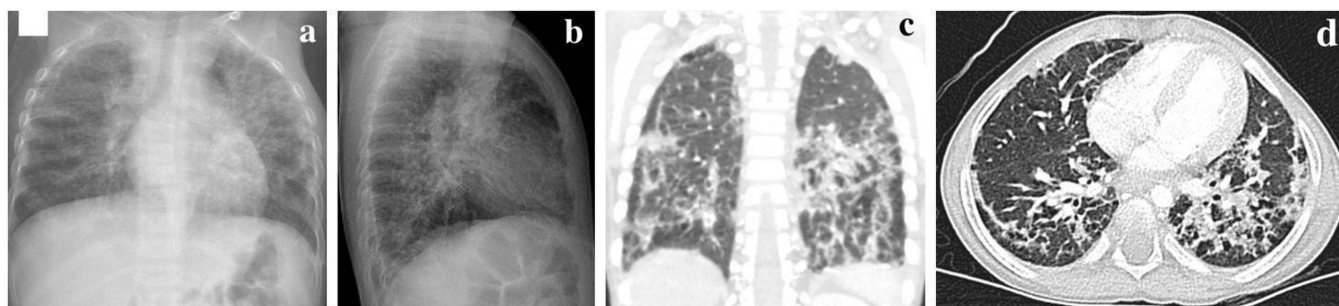


FIGURE 5 | CXR (a, b) and chest CT (c, d) scans of a 1.5-year-old boy with *CCR2* variant (Case 3.13.). (a, b) Reticular appearance and suspicious parenchymal cysts in both lungs on CXR, and (c, d) multiple parenchymal cysts and interlobular septal thickening in both lungs compatible with interstitial fibrosis on chest CT.

immunodeficiency 91 and hyperinflammation (*ZNFX1*—case 3.8.), one with immunodeficiency 14a featuring lymphoproliferation (*PIK3CD*—case 3.9.), one with autoinflammation, antibody deficiency, and immune dysregulation syndrome (*PLCG2*—case 3.10.), and one with ataxia-telangiectasia syndrome (*ATM*—case 3.11.).

Spirometry could be performed in seven (18.9%) patients to analyze pulmonary function: five patients exhibited normal spirometry results, while one patient with plasminogen deficiency, type 1 (*PLG*—case 5.5.) and another with sting-associated vasculopathy, infantile-onset (*STING1*—case 3.6.) showed a restrictive pattern in their spirometry tests. The median DLCO was 97% (IQR 52.5–109.7) among three patients (8.1%), and one patient had low DLCO (*COPA*—case 3.2.). A total of 12 (32.4%) patients underwent measurements of pulmonary artery pressure, five of

them (*COPA*—case 3.2., *STING1*—case 3.6., *ZNFX1*—case 3.8., *MARS1*—case 4.13., and *FARSB*—case 4.14.) had abnormal pulmonary artery pressure (> 20 mmHg). A 6 MW test was conducted in nine (24.3%) patients, yielding a median walking distance of 465 (range: 330–566) m. One patient with Gaucher disease (case 4.10.) and another patient with lysinuric protein intolerance (case 4.11.) exhibited SPO₂ levels of < 90% during the test.

In the venous blood gas analysis of 33 (89.1%) children, only six (16.2%) exhibited hypercarbia (pCO₂ above 50 mmHg) (*SMPD1*—case 4.6., *ZNFX1*—case 3.8., *GBA1*—case 4.9., *STING1*—case 3.6., *STAT3*—case 3.3., and *FARSB*—case 4.14.). A patient with a *COPA* variant (case 3.2.) tested positive for ANA, anti-dsDNA, and ANCA. The positive tissue transglutaminase IgG was deemed not clinically

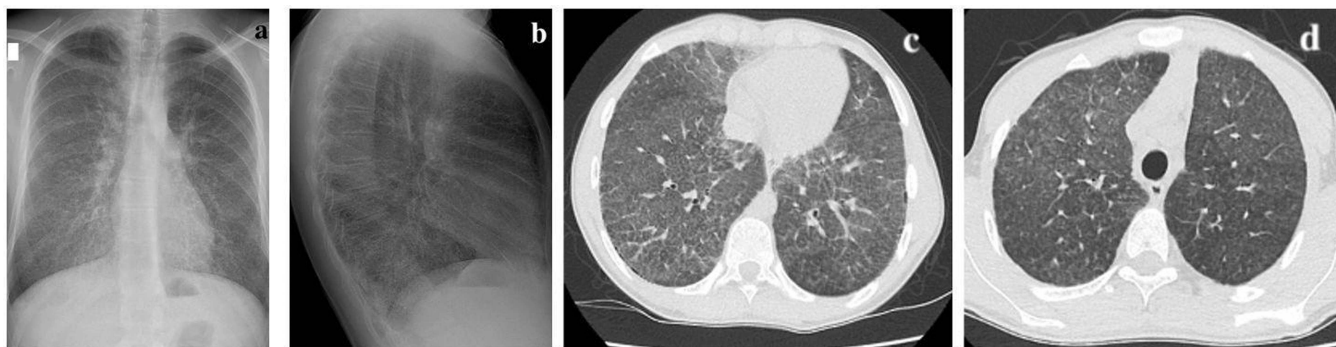


FIGURE 6 | CXR (a, b) and chest CT (c, d) scans of a 12.5-year-old boy diagnosed with PAM (Case 5.3). (a, b) Sand-like scattered fine high-density nodules over both lungs, suggestive of microlithiasis. (c, d) Many tiny dense nodules throughout both lung parenchyma with interlobular septal thickening compatible with pulmonary alveolar microlithiasis.

significant. A patient with a *STING1* variant tested positive for ANA, ANCA, and anti-dsDNA. In the patient with the *SLC34A2* variant, the pigeon precipitant antibody tested positive; however, this finding was deemed clinically insignificant. Comprehensive laboratory evaluations were performed to determine the differential diagnosis of patients.

All patients underwent chest CT at their initial evaluation, and 12 (32.4%) underwent follow-up scans showing persistent findings consistent with chILD. Analysis of chest CT findings generally revealed regression of reticulonodular infiltration, ground-glass opacities (GGOs), and interlobular/intralobular septal thickening, whereas honeycombing and cystic lesions increased posttreatment. Despite ongoing treatment during follow-up, the patient with *ZNF1* genetic variant developed increased reticular infiltration and honeycombing. The patient with *STAT3* genetic variant developed cystic lesions, fibrosis, and nodules emerged during follow-up despite treatment; one patient with a *COPA* variant developed fibrosis developed despite treatment, whereas another developed cystic lesions and honeycombing (Supporting Information S1: Table S1).

A total of 23 (62.1%) patients underwent bronchoscopy. The predominant macroscopic pathologies identified included airway malacia (10.8%) (three cases of bronchomalacia (*SLC34A2*, *SLC34A2*, *NPC*), one tracheomalacia (*CCR2*), and increased secretions (13.1%). In bronchoalveolar lavage fluid (BALF) microbiological analysis, cultures from 20 patients were negative for pathogens. Among others, one patient tested positive for *Pseudomonas aeruginosa* (*STAT3*—case 3.4), one for *Haemophilus influenzae*, and one for *Streptococcus pneumoniae*. One patient (*CCR2*—case 3.13.) had 214,000 copies of CMV identified in the BALF sample. Seven (18.9%) patients underwent lung biopsy, and cytopathologic findings are summarized in Supporting Information S1: Table S2.

Thirteen patients (35.1%) had received only primary treatment for their systemic diseases, without any targeted therapy for chILD. Eight (21.6%) patients were on daily oral steroids, whereas six (16.2%) patients received pulse steroid treatment as lung disease targeted therapy. Alongside systemic steroid treatment, three children were administered hydroxychloroquine (*ZNF1*, *FARSB*, *DNAJB4*), two azithromycin (*COPA*, *CCR2*), one azathioprine (*FARSB*), four inhaled corticosteroids (*STING1*, *GBA1*, *CCR2*,

CCR2), one (*CCR2*) montelukast, one (*COPA*) cyclophosphamide, one (*COPA*) tofacitinib, one (*COPA*) etanercept, and two (*ZNF1*, *CCR2*) mycophenolate mofetil. Four patients (*STAT3*, *PLCG2*, *NPC1*, and *SMPD1*) received only inhaled corticosteroids, whereas one (*SLC34A2*) was treated with etidronate for pulmonary alveolar microlithiasis. Additionally, one patient (*SLC7A7*) underwent whole lung lavage therapy for pulmonary alveolar proteinosis (PAP); another patient (*PLG*) was administered endobronchial fresh frozen plasma due to type 1 plasminogen deficiency. Patients with chILD-TR presenting rare genetic variants were categorized based on current literature analysis [4, 6, 14], and detailed information about diseases and cases is presented in Tables 2–4.

4 | Discussion

Diagnosing and treating chILD present significant challenges due to their rarity within the pediatric population. With advances in genetic diagnostic techniques and their increasing adoption, even less common conditions that may be associated with systemic diseases are now being recognized. In this study, we aimed to highlight rare diseases with uncommon genetic variants using data from a national registry.

National and international registries play an important role in improving the diagnosis and treatment of rare diseases. Numerous national and international registries have provided valuable data to improve understanding of interstitial lung diseases in pediatric populations [3, 15, 16]. Despite being a recent initiative, ChILD-TR includes a wide and varied patient population. In this study, rare variants and their associated attributes were identified within this comprehensive database, which has been thoroughly described previously [1]. We anticipate that it will significantly enhance the diagnosis and treatment of these conditions.

ILDs can develop in specific conditions that result in immunodeficiency, immune dysregulation, autoinflammatory diseases, and inherent metabolic errors [17, 18]. This study identified lung involvement with interstitial changes in patients with either immunodeficiency or autoinflammatory disease genetic variants, excluding those with infectious pulmonary complications. In patients with immunodeficiency, autoinflammatory disease, such as those caused by *STAT3*, *STING1* variants, and *ADA* deficiency,

TABLE 1 | Demographical and clinical characteristics of patients.

Gender	
Male, <i>n</i> (%)	19 (51.4)
Age at the onset of complaints, month, median (IQR)	15 (6–36.5)
Group 1: Birth onset (STING1, MARS1, PLCG2)	3 (8.1)
Group 2: Onset 1 month to 24 months (CCR2, TBX4, COPA, OAS1, NPC1, FARSF, SLC7A7, ADA, SMPD1, RNF168, ZNFX1, STAT3, MARS1, ATM, PEPD)	21 (56.7)
Group 3: Onset after 24 months (STAT3, SLC34A2, GBA1, SMPD1, PLG, SMAD4, STING1, PICK3CD, DNAJB4)	13 (35.1)
Age at diagnosis, month, median (IQR)	40.5 (15.5–115.5)
Current age, year, median (IQR)	8.7 (3.6–14)
Birth weight, <i>n</i> (%)	
AGA	32 (86.4)
SGA	5 (13.5)
MV in NICU, <i>n</i> (%)	2 (5.4)
TBX4	1 (2.7)
PLCG2	1 (2.7)
Days median (IQR)	3 (1–5)
Accompanying systemic disease, <i>n</i> (%)	23 (62.1)
Cardiac disease	6 (16.2)
Neurologic disease	4 (10.8)
Gastrointestinal system disease	5 (13.5)
Immunodeficiency	3 (8.1)
Hematologic disease	1 (2.7)
Skeletal problems	3 (8.1)
Myopathy	1 (2.7)
Family consanguinity, <i>n</i> (%)	25 (67.6)
1st degree	18 (48.6)
2nd degree	2 (5.4)
3rd degree	1 (2.7)
Distant relationship	4 (10.8)
Chronic lung disease family history, <i>n</i> (%)	6 (16.2)
PAM in elder brother	1 (2.7)
FMF-ILD on father	1 (2.7)
Grandfather ILD	2 (5.4)
IPF in a cousin	1 (2.7)
Ataxia telangiectasia-ILD in sister	1 (2.7)
Oxygen requirement at first/last clinic visit, <i>n</i> (%)	13 (30.2)/13 (30.2)
Duration, month, median (IQR)	15.4 (1.5–30.0)
NIMV in first/last clinic visit (<i>n</i> :37), <i>n</i> (%)	1 (2.7)/2 (5.4)
BPAP-ST (DNAJB4/STAT3)	1 (2.7)/1 (2.7)
IMV (/DNAJB4)	0/1 (2.7)

Abbreviations: AGA, appropriate for gestational age; BPAP-ST, bilevel positive airway pressure spontaneous/timed; CPAP, continuous positive airway pressure; FMF, familial Mediterranean fever; ILD, interstitial lung disease; IMV, intermittent mandatory ventilation; IPF, idiopathic pulmonary fibrosis; MV, mechanical ventilation; NICU, newborn intensive care unit; NIMV, noninvasive mechanical ventilation; PAM, pulmonary alveolar microlithiasis; SGA, small for gestational age.

pulmonary symptoms may occur not only from recurrent lower respiratory infections but also from interstitial lung disease. For patients with genetic variants like *COPA*, *ZNFX1*, *PIK3CD*, *PLCG2*, and *ATM*, where manifestations are more pronounced in

other systems, a pediatric pulmonologist should be involved for monitoring pulmonary health whenever possible. While polycystic lung disease has mainly been associated with patients with biallelic *CCR2* gene variants in the existing literature, chILD

TABLE 2 | The genetic variants recorded in the chILD-TR that could be linked to immunodeficiency/dysregulation, autoinflammation.

Genetic test result/method	ACMG classification**	Phenotype/associated systemic disease*	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of cHILD-TR patients	Other clinical findings	Treatment for pulmonary features
3.1. COPA (NM_004371.4): c.680 G > A p. (Arg227His), homozygous/WES	LP (PM1, PM2, PM5) Note: PM5 was applied because a different missense variant affecting the same amino acid residue has previously been reported as likely pathogenic (PMID: 37877458).	Autoimmune interstitial lung, joint, and kidney disease (COPA syndrome) (#616414)	F/21	AD/N/A	Chest CT findings compatible with diffuse alveolar hemorrhage (Figure 4)	Juvenile idiopathic arthritis, epilepsy, malnutrition	Pulse and daily oral steroid, cyclophosphamide
3.2. COPA(NM_004371.4): c.690 G>Tp. (Lys230Asn), heterozygous/WES	LP (PM1, PM2, PP3, PS4_supporting) Note: PS4_supporting was applied because this variant has been reported in multiple unrelated individuals with COPA syndrome (PMIDs: 25894502, 41395910).	Autoimmune interstitial lung, joint, and kidney disease (COPA syndrome) (#616414)	F/170	AD/f = 0.000000686	Follicular bronchiolitis, lymphoid aggregate formation in the parenchyma on lung biopsy		Azithromycin, daily oral steroid, tofacitinib, etanercept
3.3. STAT3(NM_139276.3): c.1938C>A p. (Asn646Lys), heterozygous/WES	P (PS1, PM1, PM2, PP2, PP3) Note: Same amino acid change reported in ClinVar (Variation ID: 144031).	Autoimmune disease, multisystem, infantile-onset, I (#615952)	M/147	AD/N/A	Chest CT findings compatible with diffuse alveolar hemorrhage	Atopic dermatitis	ICS
3.4. STAT3(NM_139276.3): c.1145 G > A p. (Arg382Gln)), Heterozygous/WES	P (PS4, PM1, PM2, PP2, PP3) Reported in multiple affected individuals in ClinVar.	Hyper Ig E syndrome (#147060)	F/40	AD/N/A	Pneumatocele, interlobular septal thickening, bronchiectasis on chest CT	Recurrent LRTIs	ICS
3.5. STING1(NM_198282.4): c.841 C > T p. (Arg281Trp)), heterozygous/Sanger sequencing	LP (PM1, PM2, PS4_supporting) The variant has been previously reported in an affected individual in ClinVar (Variation ID: 839824).	Sting-associated vasculopathy, infantile-onset (#615934)	F/34	AD/f = 0.0000006815	Interlobular septal thickening on chest CT	Recurrent LRTIs, malnutrition	No specific treatment for pulmonary features
3.6. STING1(NM_198282.4): c.841 C > T p. (Arg281Trp), homozygous/WES	P (PM1, PM2, PS3, PS4_supporting) Note: PS3 was assigned based on published in vitro and ex vivo functional evidence, and PS4_supporting was assigned based on reports of this variant in multiple affected individuals from four	Sting-associated vasculopathy, infantile-onset (#615934)	F/148	AD/f = 0.0000006815	Multiple air cysts, interlobular septal thickening on chest CT	Arthritis, thrombophlebitis	Pulse and daily oral steroid, ICS

(Continues)

TABLE 2 | (Continued)

Genetic test result/method	ACMG classification**	Phenotype/associated systemic disease*	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of CHILD-TR patients	Other clinical findings	Treatment for pulmonary features
3.7. ADA(NM_000022.4): c.736 C > T p. (Gln246Ter), homozygous/Sanger sequencing	unrelated families with autosomal recessive SAVI (PMID: 32673614). P (PVS1, PM2, PM3)	Severe combined immunodeficiency, T cell-negative, B cell-negative, NK cell-negative, due to adenosine deaminase deficiency (#102700)	F/3	AR/N/A	Chest CT findings compatible with PAP	Immunodeficiency	Whole lung lavage for PAP
3.8. ZNF1X1(NM_021035.3): c.1414_1415del p. (Arg472GlyfsTer16), homozygous/WES	P (PVS1, PM2, PM3)	Immunodeficiency 91 and hyperinflammation (#619644)	F/2.5	AR/f = 0.0000004336	Mosaic attenuation, interlobular septal thickening on chest CT	Congenital CMV infection, immunodeficiency	HQ, MMF, pulse, and daily oral steroid
3.9. PIK3CD(NM_005026.5): c.3061 G > A p. (Glu1021Lys), heterozygous/WES	P (PS4, PM1, PM2, PP2) Reported in multiple affected individuals in ClinVar.	Immunodeficiency 14a with lymphoproliferation (#615513)	F/173	AD/f = 0.0000006196	Bronchiectasis on chest CT		No specific treatment for pulmonary features
3.10. PLCG2(NM_002661.5): c.1930A > C p. (Lys644Gln), heterozygous/WES	VUS (PM2)	APLAID syndrome, autoinflammation, antibody deficiency, and immune dysregulation (#614878)	M/27	AD/f = 0.0000006220	Peribronchial thickening, mosaic perfusion on chest CT	Total pulmonary venous return anomaly, ASD, immunodeficiency	ICS
3.11. ATM(NM_000051.4): c.3576 G > A p. (Lys1192 =), homozygous/WGS	P(PS4, PM1, PM2) Reported in multiple affected individuals in ClinVar.	Ataxia-telangiectasia syndrome (#208900)	M/210	AR/AD/ f = 0.000002480	Interlobular septal thickening, bronchiectasis on chest CT	Ataxia, scleral telangiectasias, immunodeficiency	No specific treatment for pulmonary features
3.12. OAS1 (NM_016816.4) c.1042 G > T p.(Glu348*), heterozygous; OAS1 (NM_016816.4) c.187 T > C p.(Ser63Pro), heterozygous/WES	VUS (PM2, BP4), VUS (PM2)	Immunodeficiency 100 with pulmonary alveolar proteinosis and hypogammaglobulinemia (#618042)	M/9	AD/f = 0.00001055, f = 0.000007472	Diffuse reticulonodular infiltration and GGO on chest CT		No specific treatment for pulmonary features
3.13. CCR2 (NM_001123396.4) c.878 T > C p. (Leu293Pro), homozygous/WES	VUS (PM2, PM3, PP3)	Polycystic lung disease (#219600)	M/18	AR/f = 0.0000006195	Chest CT findings compatible with interstitial fibrosis (Figure 5)	Congenital CMV, immunodeficiency, epilepsy	Pulse and daily oral steroid, ICS, MMF, pirfenidone

(Continues)

TABLE 2 | (Continued)

Genetic test result/method	ACMG classification**	Phenotype/associated systemic disease*	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features		Treatment for pulmonary features
					of CHILD-TR patients	Other clinical findings	
3.14. CCR2 (NM_001123396.4) c.569 G > A (p. Cys190Tyr), homozygous/WES	LP (PM2, PM3, PP3, BP4)	Polycystic lung disease (#219600)	M/56	AR/N/A	Multiple cysts on chest CT and fibrosis, giant cell reaction, and granulomas in lung biopsy		Azithromycin, ICS, montelukast
3.15. RNF168(NM_152617.4): c.644 G > A p. (Ser215Asn), homozygous	VUS (PM2, PM3, BP4) VUS (PM2, BP4) VUS (PM2, BP4)	Riddle syndrome (#611943) Interstitial lung disease 2 (#178500)	F/14	AR/f = 0.000001863 AD/f = 0.00002055 AD/f = 0.0004400	Emphysema, interlobular septal thickening on chest CT	Growth and developmental delay	Pulse and daily oral steroid, HQ
MUC5B(NM_002458.3): c.2333 G > A p. (Gly778Asp)), heterozygous		Interstitial lung disease 2 (#178500)					
MUC5B(NM_002458.3): c.7517 C > T p. (Thr2506Ile)), heterozygous/WES							

Abbreviations: AD, autosomal dominant; ASD, atrial septal defect; AR, autosomal recessive; BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CT, computed tomography; F, female; HQ, hydroxychloroquine; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; M, male; MMF, mycophenolate mofetil; PAP, pulmonary alveolar proteinosis; WES, whole exome sequencing; WGS, whole genome sequencing.

*Prepared with reference to <https://omim.org>

**Variants were interpreted according to ACMG/AMP guidelines. Evidence codes were applied as follows:

PVS1: Predicted loss-of-function variant in a gene where loss-of-function is a known disease mechanism.

PS4: Increased prevalence of the variant in affected individuals compared with controls.

PS4 supporting: Limited evidence of increased prevalence of the variant in affected individuals, such as a small number of reported cases or ClinVar submissions.

PM1: Variant located in a mutational hotspot or critical functional domain without benign variation.

PM2: Variant absent or extremely rare in population databases (e.g., gnomAD).

PM3: Detected in trans with another pathogenic variant in recessive disorders or identified in the homozygous state.

PM4: Protein length change due to in-frame deletion/insertion.

PP2: Missense variant in a gene where pathogenic variants are predominantly missense.

PP3: Multiple computational tools predict a deleterious effect on the gene or gene product.

BP4: Computational evidence suggests no impact on gene or gene product.

BP7: Synonymous or intronic variant with no predicted effect on splicing.

LB: Likely benign LP: Likely pathogenic

P: Pathogenic B: Benign

VUS: Variant of uncertain significance N/A: Not available in the gnomAD dataset.

***Allele frequencies are based on the gnomAD v4.1.0 total dataset.

TABLE 3 | The genetic variants registered in chILD-TR that may be associated with inborn errors of metabolism.

Genetic test result	ACMG classification**	Phenotype/ associated systemic disease*/	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of chILD-TR patients	Other clinical findings	Treatment for pulmonary features
4.1. NPC1(NM_000271.5): c.1073del p. (Leu358ArgfsTer91), homozygous/ targeted sequencing	P (PV51, PM2, PM3)	Niemann-pick disease, type C1 (#257220)	M/12	AR/N/A	Interlobular septal thickening on chest CT	Growth and mental retardation	No specific treatment for pulmonary features
4.2. NPC1(NM_000271.5): c.852del p. (Phe284LeufsTer26), homozygous/ targeted sequencing	P (PS4, PV51, PM2, PM3) Reported in multiple affected individuals in ClinVar.	Niemann-pick disease, type C1 (#257220)	F/17	AR/N/A	Interlobular septal thickening on chest CT	Retardation in motor skills	ICS
4.3. SMPD1(NM_000543.5): c.416 T > C p. (Leu139Pro), homozygous/WGS	P (PS4, PM2, PM3, PP3, PP2) Reported in multiple affected individuals in ClinVar.	Niemann-pick disease, type A (#257200)	M/72	AR/N/A	Interlobular septal thickening, millimetric nodules, crazy paving pattern on chest CT		No specific treatment for pulmonary features
4.4. SMPD1(NM_000543.5): c.1652 T > C p. (Leu551Pro), homozygous/WES	LP (PM2, PM3, PP2, PP3)	Niemann-pick disease, type A (#257200)	M/71	AR/N/A	Centrilobular micronodules, interlobular septal thickening on chest CT		No specific treatment for pulmonary features
4.5. SMPD1(NM_000543.5): c.416 T > C p. (Leu139Pro), homozygous/WES	P (PS4, PM2, PM3, PP3, PP2) Reported in multiple affected individuals in ClinVar.	Niemann-pick disease, type A (#257200)	M/99	AR/N/A	Interlobular septal thickening, millimetric nodules on chest CT		No specific treatment for pulmonary features
4.6. SMPD1(NM_000543.5): c.272 G > A p. (Cys91Tyr), homozygous/WES	LP (PM2, PM3, PP2, PP3, PS4_supporting) The variant has been previously reported in an affected individual in ClinVar (Variation ID: 3754295).	Niemann-pick disease, type A (#257200)	F/12	AR/N/A	Interlobular septal thickening on chest CT	Hepatomegaly, hypertransaminasemia	ICS
4.7. SMPD1(NM_000543.5): c.1468 T > A, p. (Tyr490Asn), homozygous/WES	LP (PM2, PM3, PP2, PP3)	Niemann-pick disease, type B (#257200)	F/24	AR/N/A	Interlobular septal thickening on chest CT	HSM	No specific treatment for pulmonary features
4.8. SMPD1(NM_000543.5): c.1468 T > A, p. (Tyr490Asn), homozygous/WES	LP (PM2, PM3, PP2, PP3)	Niemann-pick disease, type B (#257200)	F/24	AR/N/A	Interlobular septal thickening on chest CT	HSM	No specific treatment for pulmonary features
4.9. GBA1(NM_001005742.3): c.1193 G > T p. (Arg398Leu), homozygous/WGS	LP (PM2, PM3, PP2, PP3, PS4_supporting) The variant has been previously reported in an affected individual in ClinVar (Variation ID: 3257292).	Gaucher disease type 1 (#230800)	M/42	AR/N/A	Interlobular septal thickening on chest CT	Mental-motor retardation	Pulse steroid, ICS
4.10. GBA1(NM_001005742.3): c.1448 T > C p. (Leu483Pro), homozygous/targeted sequencing	P (PS4, PM2, PM3, PP3, PP2) Reported in multiple affected individuals in ClinVar.	Gaucher disease type 1 (#230800)	M/114	AR/f = 0.00009858	Interlobular and intraalobular septal thickening, millimetric air cysts on chest CT	Splenomegaly	No specific treatment for pulmonary features
4.11. SLC7A7(NM_001126105.3): c.1100 T > C p. (Ile367Thr)), heterozygous	VUS(PM2) VUS (PM2, PP3)	Lysinuric protein intolerance (#222700)	F/169	AR/N/A	Crazy paving pattern on chest CT and milky	Epilepsy, HSM	Whole lung lavage for PAP

(Continues)

TABLE 3 | (Continued)

Genetic test result	ACMG classification**	Phenotype/ associated systemic disease*/	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of chILD-TR patients	Other clinical findings	Treatment for pulmonary features
SLC7A7(NM_001126105.3): c.1208 T > C p.(Leu403Pro)), heterozygous/WES					appearance in BALF; compatible with PAP		
4.12. MARS1(NM_004990.4): c.854 T > C p. (Ile285Thr), homozygous/WES	VUS (PM2, PM3) Note: The same homozygous variant has previously been reported in an unrelated patient with pulmonary alveolar proteinosis (PMID: 30723866).	Interstitial lung and liver disease (#615486)	M/117	AR/f = 0.00002974	Subpleural cysts and mosaic attenuation on chest CT	Generalized hypotonicity, HSM, chronic malnutrition	No specific treatment for pulmonary features
4.13. MARS1(NM_004990.4): c.854 T > C p. (Ile285Thr)), heterozygous MARS1(NM_004990.4): c.793 A > G p.(Asn265Asp)), heterozygous/WGS	VUS(PM2) VUS(PM2)	Interstitial lung and liver disease (#615486)	F/8	AR/f = 0.00002974, N/A	Interlobular septal thickening, subpleural cysts, bronchiectasis on chest CT	Growth retardation	No specific treatment for pulmonary features
4.14. FARS1(NM_005687.5): c.853 G > A p. (Glu285Lys), homozygous/WES	VUS (PM2, PM3, PS4_supporting) The variant has been previously reported in an affected individual in ClinVar (Variation ID: 559418)	Rajab interstitial lung disease with brain calcifications 1 (#613658)	F/105	AR/N/A	Thickening of the bronchial wall, cystic lesions on chest CT	Growth retardation	Daily oral steroid, HQ, azathioprine
4.15. PEPD(NM_000285.3): c.1153_1344del (p. Gly385_Gly448del), homozygous/targeted sequencing	LP (PM2, PM3, PM4)	Prolidase deficiency (#170100)	M/27	AR/N/A	Mosaic attenuation on chest CT		No specific treatment for pulmonary features

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ASD, atrial septal defect; BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CT, computed tomography; F, female; HQ, hydroxychloroquine; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; M, male; MMF, mycophenolate mofetil; PAP, pulmonary alveolar proteinosis; WES, whole exome sequencing; WGS, whole genome sequencing.

*Prepared with reference to <https://omim.org>

**Variants were interpreted according to ACMG/AMP guidelines. Evidence codes were applied as follows:

PVS1: Predicted loss-of-function variant in a gene where loss-of-function is a known disease mechanism.

PS4: Increased prevalence of the variant in affected individuals compared with controls.

PS4_supporting: Limited evidence of increased prevalence of the variant in affected individuals, such as a small number of reported cases or ClinVar submissions.

PM1: Variant located in a mutational hotspot or critical functional domain without benign variation.

PM2: Variant absent or extremely rare in population databases (e.g., gnomAD).

PM3: Detected in trans with another pathogenic variant in recessive disorders or identified in the homozygous state.

PM4: Protein length changes due to in-frame deletion/insertion.

PP2: Missense variant in a gene where pathogenic variants are predominantly missense.

PP3: Multiple computational tools predict a deleterious effect on the gene or gene product.

BP4: Computational evidence suggests no impact on gene or gene product.

BP7: Synonymous or intronic variant with no predicted effect on splicing.

LB: Likely benign LP: Likely pathogenic

P: Pathogenic B: Benign

VUS: Variant of uncertain significance N/A: Not available in the gnomAD dataset.

***Allele frequencies are based on the gnomAD v4.1.0 total dataset.

TABLE 4 | The other rare genetic variants documented in the chILD-TR.

Genetic test result	ACMG classification**	Phenotype/ associated systemic disease*	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of our chILD-TR patients	Other clinical findings	Treatment for pulmonary features
5.1. TBX4 (NM_001321120.2) c.781 C > T (p. Arg261Ter), heterozygous/WES	P (PM2, PVS1, PS4_supporting) /The variant has been previously reported in an affected individual in ClinVar (Variation ID: 1341404)	Ischiocoxopodopa- tellar syndrome with or without pulmonary arterial hypertension (#147891)	M/7	AD/ $f = 0.00000006196$	Interlobular septal thickening, millimetric parenchymal cysts		No specific treatment for pulmonary features
5.2. SLC34A2(NM_006424.3): c.1456 C > T p. (Gln486Ter), homozygous/WES	LP (PM2, PVS1)	Pulmonary alveolar microlithiasis (#265100)	M/65	AR/N/A	Calcified structures on chest CT, compatible with pulmonary alveolar microlithiasis		No specific treatment for pulmonary features
5.3. SLC34A2(NM_006424.3): c.1456 C > T p. (Gln486Ter), homozygous/WES	LP (PM2, PVS1)	Pulmonary alveolar microlithiasis (#265100)	M/152	AR/N/A	Calcified structures scattered in most of the alveolar spaces and interstitium in lung biopsy and chest CT compatible with pulmonary alveolar microlithiasis (Figure 6)		Etidronate
5.4. SLC34A2(NM_006424.3): c.1456 C > T p. (Gln486Ter), homozygous/WES	LP (PM2, PVS1)	Pulmonary alveolar microlithiasis (#265100)	F/37	AR/N/A			No specific treatment for pulmonary features
5.5. PLG (NM_000301.5): c.974 G > A p. (Arg325His), homozygous/WES	VUS (PM2, PP3)	Plasminogen deficiency, type 1 (#217090)	M/146	AR/ $f = 0.000002479$	Bronchiectasis, peribronchial thickening on chest CT	Growth retardation, ligneous conjunctivitis	EBFPF, EBTPA, ICS
5.6. DNAJB4(NM_007034.5): c.775 C > T p. (Arg259Ter), homozygous/WES	LP (PVS1, PM2, PM3)	Congenital myopathy 21 with early respiratory failure (#620326)	F/84	AR/ $f = 0.000003177$	Interlobular septal thickening on chest CT	Myopathy	Oral steroid, HQ

(Continues)

TABLE 4 | (Continued)

Genetic test result	ACMG classification**	Phenotype/ associated systemic disease*	Sex/age (month)	Inheritance/allele frequency***	Pulmonary features of our cHILD-TR patients	Other clinical findings	Treatment for pulmonary features
5.7. SMAD4 (NM_005359.6); c.1081 C > A p. (Arg361Ser)), heterozygous/WGS	P (PM2, PM5, PP2, PP3, PS4_supporting) The variant has been previously reported in an affected individual in ClinVar (Variation ID: 24822)	Juvenile polyposis/ hereditary hemorrhagic telangiectasia syndrome (#175050)	M/102	AD/N/A	Nodular lesions in parenchyma on chest CT	Familial adenomatous polyposis	No specific treatment for pulmonary features

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ASD, atrial septal defect; BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CT, computed tomography; EBFP, endobronchial fresh frozen plasma; EBTPA, endobronchial tissue plasminogen activator; F, female; GERD, gastroesophageal reflux disease; GGO, ground glass opacities; HQ, hydroxychloroquine; ICS, inhaled corticosteroids; LRTI, lower respiratory tract infection; M, male; MMF, mycophenolate mofetil; PAP, pulmonary alveolar proteinosis; WES, whole exome sequencing; WGS, whole genome sequencing.

*Prepared with reference to <https://omim.org>

**Variants were interpreted according to ACMG/AMP guidelines. Evidence codes were applied as follows:

PVS1: Predicted loss-of-function variant in a gene where loss-of-function is a known disease mechanism.

PS4: Increased prevalence of the variant in affected individuals compared with controls.

PS4_supporting: Limited evidence of increased prevalence of the variant in affected individuals, such as a small number of reported cases or ClinVar submissions.

PM1: Variant located in a mutational hotspot or critical functional domain without benign variation.

PM2: Variant absent or extremely rare in population databases (e.g., gnomAD).

PM3: Detected in trans with another pathogenic variant in recessive disorders or identified in the homozygous state.

PM4: Protein length changes due to in-frame deletion/insertion.

PP2: Missense variant in a gene where pathogenic variants are predominantly missense.

PP3: Multiple computational tools predict a deleterious effect on the gene or gene product.

BP4: Computational evidence suggests no impact on gene or gene product.

BP7: Synonymous or intronic variant with no predicted effect on splicing.

LB: Likely benign LP: Likely pathogenic

P: Pathogenic B: Benign

VUS: Variant of uncertain significance N/A: Not available in the gnomAD dataset.

***Allele frequencies are based on the gnomAD v4.1.0 total dataset.

symptoms and immunodeficiency can manifest even without pulmonary cysts.

Variants in *STING1* are associated with STING-associated vasculopathy with onset in infancy, a type I interferonopathy characterized by systemic inflammation and ILD. Previous studies have reported that patients with *STING1* variants may present with a wide spectrum of pulmonary manifestations, including GGOs, interlobular septal thickening, cystic lung changes, and progressive fibrosis [19]. In our cohort, clinical characteristics of patients with *STING1* variants are summarized in Table 2. Consistent with previous reports, the heterozygous patient presented mainly with recurrent lower respiratory tract infections, whereas the homozygous patient exhibited a more complex phenotype, such as arthritis, thrombophlebitis, and cystic and interstitial changes on chest CT. These observations support the expanding phenotypic spectrum of *STING1*-associated disease and indicate that clinical severity may vary with the underlying genotype and allelic configuration.

OAS1 gene variants are associated with immunodeficiency 100, which presents with pulmonary alveolar proteinosis and hypogammaglobulinemia, and are inherited following an autosomal dominant pattern. Although *OAS1* variants in Case 3.12 are classified as VUS, they could not be definitively interpreted for compound heterozygosity due to the lack of segregation analysis results. Nevertheless, the c.187T>C p. (Ser63Pro) variant was considered a potential pathogenic variant, owing to its rarity in population databases and the presence of thoracic CT findings consistent with the condition.

Inborn metabolic errors are typically rare, and although the lungs are not usually the primary site of involvement, some cases can cause severe respiratory complications and or even isolated pulmonary manifestations [20–23]. In this study, patients with genetic variants causing inborn errors of metabolism, we observed that some developed PAP (*MARS1*) whereas others exhibited milder respiratory symptoms such as chronic cough, including interlobular septal thickening on chest CT. Given these findings, interstitial lung disease can be a part of rare systemic diseases (Gaucher disease, lysinuric protein intolerance, Niemann–Pick type A, C) and may sometimes occur as the only manifestation (Niemann–Pick type B) [24–26].

Symptoms in patients with genetic variants causing ILDs may manifest at any stage, ranging from the neonatal period onward to adulthood. Although surfactant protein metabolism disorders associated with ILDs are the first thing that comes to mind in newborns with respiratory distress, respiratory distress may also occur in the neonatal period in patients with variants in *MARS1*, *STING1*, and *PLCG2* genes, which can cause multi-systemic diseases with a severe clinical course, as in our cohort.

A primary goal of our study was to underscore the genetic causes and clinical features of these rare diseases. chILD refers to a group of diseases that remain difficult to diagnose and treat, with new and unique traits being identified daily. Genetic analyses of six patients with ILD included in the registry who benefited from nonspecific drugs used across the general chILD spectrum (such as systemic and inhaled corticosteroids, pirfenidone in fibrotic lung disease, and immunosuppressive drugs)

revealed heterozygous variants and variants classified as VUS in the *MUC5B* and *TERT* genes (Supporting Information S1: Table S3). These variants do not fully account for the clinical and radiological features of chILD in patients according to the current literature; however, further genetic and functional studies are ongoing at the centers caring for them [27–29]. Although studies reported that *MUC5B* gene variants are associated with ILD in adults, their relationship with chILD remains an unresolved area of ongoing studies in the current literature [28]. Studies examining the relationship between *MUC5B* genetic variants and postinfectious bronchiolitis obliterans, another ILD observed in children, are also available [30]. Although *TERT* gene variants are linked to various diseases associated with telomere shortening, recent studies report that they may also be associated with interstitial fibrosis. Therefore, these genes should be considered in patients with chILD [29, 31].

Classifications and diagnostic algorithms rely on lung biopsies for diagnosing chILD. However, due to the invasive nature of biopsies and the considerable risk of complications in children, researchers have sought less invasive diagnostic methods [32]. Nowadays, chest CT is widely recognized as an important diagnostic procedure after routine laboratory tests in the diagnostic process of patients with suspected chILD in clinical aspects, family history, and chest x-ray (CXR) [5, 33]. Certain chILD entities may show characteristic imaging findings on CT, which can lead to a diagnosis or help refine the differential diagnosis [34]. For patients showing chILD findings on chest CT, the next-step genetic tests help clinicians, thereby reducing the need for unnecessary biopsy procedures [5, 34, 35]. In our study group, chest CT findings, such as interlobular septal thickening, GGOs, parenchymal cysts, and mosaic attenuation, were consistent with all chILD subtypes, leading to the decision not to perform a biopsy in numerous patients. We found rare variants in genes, including *CCR2*, *MARS*, and *OAS1*, during genetic tests conducted with a prediagnosis of chILD based on symptoms and radiologic results, and presented the characteristics of these patients. However, when genetic testing is difficult to access and radiological findings are inconclusive, biopsy remains crucial for confirming the diagnosis [36].

In this chILD group with rare genetic variants, as found in other subtypes, primary treatments included systemic corticosteroids, antifibrotics, and immunomodulators alongside systemic disease treatment. We aimed to highlight that in chILD subtypes with systemic diseases, medications controlling the primary disease are also an essential part of chILD treatment. Additionally, whole lung lavage serves as an effective palliative approach for managing patients with chILD types that lead to PAP.

Posttreatment chest CT scans showed that chILD-related findings generally improved, while honeycomb patterns and cystic lesions significantly increased. This observation might be explained by the late diagnosis, progression of fibrosis, and ineffectiveness of commonly used anti-inflammatory drugs after fibrosis develops, which could be linked to this finding. In our study cohort, genetic variants like *CCR2* and *OAS1*, which impair lung tissue development and contribute to diffuse

parenchymal lung disease, may also play a role in the lack of treatment response observed. Furthermore, the limited number of control chest CTs and the relatively higher incidence of cellular nonspecific interstitial pneumonia in early-onset cases of chILD may be other reasons for this result [37].

Analysis of ChILD-TR data from all seven geographical regions of the country, although contributing centers and patient numbers were inconsistent. Fewer patients with ultra-rare genetic variants were observed in Southeastern and Eastern Anatolia, whereas higher numbers were reported in Central Anatolia, Marmara, and the Aegean, likely reflecting the location of major referral centers. Additionally, our study patients had approximately 2 years between symptom onset and diagnosis, highlighting the need for improved pediatric pulmonologists' availability for early diagnosis and treatment. Establishing more centers capable of advanced genetic analyses and recognizing ultra-rare genetic variants linked to systemic diseases, beyond surfactant metabolism disorders usually seen in infancy, will facilitate earlier diagnosis. Furthermore, the prevalence of consanguinity was notably high in our study population. The sustained high rate of consanguineous marriages in our country, especially in Southeastern and Eastern Anatolia, contributes significantly to the high incidence of autosomal recessive disorders. Consequently, delivering genetic counseling to families is critically important, particularly in societies with prevalent consanguineous marriages.

In this context, rare genetic variants identified in this study will positively impact the diagnoses and treatments for comparable patients by increasing awareness through their incorporation into the academic literature.

Our study has several limitations. Although most patients with chILD can be diagnosed through genetic analysis in the literature, only 24% of patients in our study underwent genetic analysis, which limits interpretation [3]. Another limitation was missing data. In addition, the high rate of consanguineous marriages in our society may increase the frequency of autosomal recessive variants among patients, thereby limiting data generalizability. Along with these limitations, the study analyzed and presented data from many specialized centers, comprising a large number of patients nationwide.

5 | Conclusion

In conclusion, beyond surfactant protein disorders, ChILD has a broad genetic spectrum, including conditions involving immunodeficiency, immune dysregulation, autoinflammation, and inherent metabolic errors, as well as rarer gene variants such as CCR2. These diseases may lack typical radiological features, and consanguineous marriages may contribute to their increased prevalence. Some variants were classified as VUS under ACMG criteria, but compatible clinical and radiological findings suggest that some of these variants may represent potential disease-associated variants. Further functional studies and additional case reports are needed to clarify their roles. Ongoing updates in definitions and treatment approaches remain essential in this evolving field.

Author Contributions

Satı Özkan Tabakçı: conceptualization, investigation, funding acquisition, writing – original draft, methodology, writing – review and editing, formal analysis, data curation. **Şule Selin Akyan Soydaş:** investigation, data curation. **Gökçen Dilşa Tuğcu:** investigation, data curation, supervision, writing – review and editing. **Güzin Cinel:** writing – review and editing, methodology, validation, visualization, supervision, conceptualization. **Ayşe Ceren Sağdıç:** investigation, data curation, methodology, writing – review and editing. **Uğur Özçelik:** investigation, data curation. **Sinem Can Oksay:** investigation, data curation. **Çiğdem Korkmaz:** investigation, data curation. **Fazılcan Zirek:** investigation, data curation. **Handan Kekeç:** investigation, data curation. **Figen Gülen:** investigation, data curation. **Melih Hangül:** investigation, data curation. **Beste Özsezen:** investigation, data curation. **Derya Ufuk Altıntaş:** investigation, data curation. **Hanife Tuğçe Çağlar:** investigation, data curation. **A. Erdem Başaran:** investigation, data curation. **Zeynep Seda Uyan:** data curation, investigation. **Ali Özdemir:** investigation, data curation. **Tuğba Ramazlı Gürsoy:** investigation, data curation. **Ebru Yalçın:** investigation, data curation. **Nagehan Emiralioğlu:** investigation, data curation. **Saniye Girit:** investigation, data curation. **Ayşe Ayzıt Kılınç:** investigation, data curation. **Nazan Çobanoğlu:** investigation, data curation. **Tuğba Şişmanlar Eyüboğlu:** investigation, data curation. **Sevgi Pekcan:** investigation, data curation. **Yasemin Gökdemir:** investigation, data curation. **Berna Oğuz:** data curation, investigation. **Diclehan Orhan:** investigation, data curation. **Ahmet Cevdet Ceylan:** investigation, data curation, writing – review and editing. **Nural Kiper:** investigation, data curation, supervision, conceptualization.

Acknowledgments

The authors would like to thank all participants and centers involved in establishing the registry and collecting the data. The study received the Oral Presentation Award at the 11th Pediatric Respiratory Diseases and Cystic Fibrosis Congress held in Türkiye and presented at the European Respiratory Society Congress '2025.

Funding

The authors have nothing to report.

Consent

Before being registered in the registry system, the patients and their families provided informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supporting information files. Further enquiries can be directed to the corresponding author.

References

1. H. Nayır-Büyüksahin, N. Emiralioğlu, A. A. Kılınç, et al., “Childhood Interstitial Lung Disease in Turkey: First Data From the National Registry,” *European Journal of Pediatrics* 183 (2024): 295–304, <https://doi.org/10.1007/s00431-023-05290-9>.
2. G. Kurland, R. R. Deterding, J. S. Hagood, et al., “An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy,” *American Journal of Respiratory and Critical Care Medicine*

- 188, no. 3 (August 2013): 376–394, <https://doi.org/10.1164/rccm.201305-0923ST>.
3. M. Griese, E. Seidl, M. Hengst, et al., “International Management Platform for Children’s Interstitial Lung Disease (chILD-EU),” *Thorax* 73, no. 3 (March 2018): 231–239, <https://doi.org/10.1136/thoraxjnl-2017-210519>.
4. C. K. Garcia, “Genetic Interstitial Lung Disease,” in *Interstitial Lung Disease* (Elsevier Inc., 2018), 1–24, <https://doi.org/10.1016/B978-0-323-48024-6.00001-X>.
5. N. Nathan, M. Griese, K. Michel, et al., “Diagnostic Workup of Childhood Interstitial Lung Disease,” *European Respiratory Review* 32, no. 167 (March 2023): 220188, <https://doi.org/10.1183/16000617.0188-2022>.
6. J. Popler, T. J. Vece, D. R. Liptzin, and W. A. Gower, “Pediatric Pulmonology 2021 Year in Review: Rare and Diffuse Lung Disease,” *Pediatric Pulmonology* 58 (2023): 374–381, <https://doi.org/10.1002/ppul.26227>.
7. A. L. Neehus, B. Carey, M. Landekic, et al., “Human Inherited CCR2 Deficiency Underlies Progressive Polycystic Lung Disease,” *Cell* 187, no. 2 (January 2024): 390–408.e23, <https://doi.org/10.1016/j.cell.2023.11.036>.
8. V. Nir, A. Ilivitzky, F. Hakim, et al., “Pulmonary Manifestations of Prolidase Deficiency,” *Pediatric Pulmonology* 51, no. 11 (November 2016): 1229–1233, <https://doi.org/10.1002/ppul.23435>.
9. K. Baysac, C. Fisher, H. Nakano, J. Milner, and M. Ombrello, “Functional Characterization of PLCG2 Mutations Found in Subjects With Autoinflammation and PLCG2-Associated Antibody Deficiency and Immune Dysregulation (APLAID) Reveals Both Hypermorphic and Hypomorphic Mutants,” [abstract], *Arthritis Rheumatology* 72, no. S10 (2020).
10. K. D. Tsakiri, J. T. Cronkhite, P. J. Kuan, et al., “Adult-Onset Pulmonary Fibrosis Caused by Mutations in Telomerase,” *Proceedings of the National Academy of Sciences* 104, no. 18 (2007): 7552–7557, <https://doi.org/10.1073/pnas.0701009104>.
11. G. Costain, Z. Liu, V. Mennella, et al., “Hereditary Mucin Deficiency Caused by Biallelic Loss of Function of MUC5B,” *American Journal of Respiratory and Critical Care Medicine* 205, no. 7 (2022): 761–768, <https://doi.org/10.1164/rccm.202106-1456OC>.
12. M. A. Seibold, A. L. Wise, M. C. Speer, et al., “A Common MUC5B Promoter Polymorphism and Pulmonary Fibrosis,” *New England Journal of Medicine* 364, no. 16 (2011): 1503–1512, <https://doi.org/10.1056/NEJMoA1013660>.
13. S. Richards, N. Aziz, S. Bale, et al., “Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology,” *Genetics in Medicine* 17, no. 5 (May 2015): 405–424, <https://doi.org/10.1038/gim.2015.30>.
14. C. Fletcher, A. Hadchouel, C. Thumerelle, et al., “Epidemiology of Childhood Interstitial Lung Disease in France: The Respirare Cohort,” *Thorax* 79 (August 2024): 842–852, <https://doi.org/10.1136/thorax-2023-221325>.
15. A. M. Casey, R. R. Deterding, L. R. Young, M. P. Fishman, E. K. Fiorino, and D. R. Liptzin, “Overview of the chILD Research Network: A Roadmap for Progress and Success in Defining Rare Diseases,” *Pediatric Pulmonology* 55 (2020): 1819–1827.
16. L. McKnight, A. Schultz, N. Vidic, E. E. Palmer, and A. Jaffe, “Learning to Make a Difference for chILD: Value Creation Through Network Collaboration and Team Science,” *Pediatric Pulmonology* 59, no. 9 (September 2024): 2257–2266, <https://doi.org/10.1002/ppul.26377>.
17. H. Wobma, R. Perkins, L. Bartnikas, et al., “Genetic Diagnosis of Immune Dysregulation Can Lead to Targeted Therapy for Interstitial Lung Disease: A Case Series and Single Center Approach,” *Pediatric Pulmonology* 57, no. 7 (July 2022): 1577–1587, <https://doi.org/10.1002/ppul.25924>.
18. M. Pac, T. Bielecka, K. Grzela, et al., “Interstitial Lung Disease in Children With Selected Primary Immunodeficiency Disorders—A Multicenter Observational Study,” *Frontiers in Immunology* 11, (August 2020): 557792, <https://doi.org/10.3389/fimmu.2020.01950>.
19. R. Wan, J. Fänder, I. Zakaraia, et al., “Phenotypic Spectrum in Recessive STING-Associated Vasculopathy With Onset in Infancy: Four Novel Cases and Analysis of Previously Reported Cases,” *Frontiers in Immunology* 13, (October 2022): 1029423, <https://doi.org/10.3389/fimmu.2022.1029423>.
20. C. Tran, F. Barbey, R. Lazor, and L. Bonafé, “Pulmonary Involvement in Adult Patients With Inborn Errors of Metabolism,” *Respiration* 94 (2017): 2–13, <https://doi.org/10.1159/000475762>.
21. B. Gülhan, U. Özçelik, F. Gürakan, et al., “Different Features of Lung Involvement in Niemann-Pick Disease and Gaucher Disease,” *Respiratory Medicine* 106, no. 9 (September 2012): 1278–1285, <https://doi.org/10.1016/j.rmed.2012.06.014>.
22. A. Miller, L. Brown, G. Pastores, and R. Desnick, “Pulmonary Involvement in Type 1 Gaucher Disease: Functional and Exercise Findings in Patients With and Without Clinical Interstitial Lung Disease,” *Clinical Genetics* 63, no. 5 (2003): 368–376, <https://doi.org/10.1034/j.1399-0004.2003.00060.x>.
23. R. Borie, B. Crestani, A. Guyard, and O. Lidove, “Interstitial Lung Disease in Lysosomal Storage Disorders,” *European Respiratory Review* 30, no. 160 (2021): 200363, <https://doi.org/10.1183/16000617.0363-2020>.
24. M. S. Devine and C. K. Garcia, “Genetic Interstitial Lung Disease,” *Clinics in Chest Medicine* 33: 95–110, <https://doi.org/10.1016/j.ccm.2011.11.001>.
25. R. Sousa Martins, S. Rocha, A. Guimas, and R. Ribeiro, “Niemann-Pick Type B: A Rare Cause of Interstitial Lung Disease,” *Cureus* 14 (2022): e21230, <https://doi.org/10.7759/cureus.21230>.
26. J. Cassibba, R. Epaul, L. Berteloot, et al., “The Significance of Multidisciplinary Team Meetings in Diagnosing and Managing Childhood Interstitial Lung Disease Within the Respirare Network,” *Pediatric Pulmonology* 59, no. 2 (February 2024): 417–425, <https://doi.org/10.1002/ppul.26765>.
27. H. Marczak, K. Krenke, M. Griese, et al., “An Update on Diagnosis and Treatments of Childhood Interstitial Lung Diseases,” *Breathe* 21 (2025): 250004, <https://doi.org/10.1183/20734735.0004-2025>.
28. A. Dressen, A. R. Abbas, C. Cabanski, et al., “Analysis of Protein-Altering Variants in Telomerase Genes and Their Association With MUC5B Common Variant Status in Patients With Idiopathic Pulmonary Fibrosis: A Candidate Gene Sequencing Study,” *Lancet Respiratory Medicine* 6, no. 8 (August 2018): 603–614, [https://doi.org/10.1016/S2213-2600\(18\)30135-8](https://doi.org/10.1016/S2213-2600(18)30135-8).
29. R. Borie, L. Tabèze, G. Thabut, et al., “Prevalence and Characteristics of TERT and TERC Mutations in Suspected Genetic Pulmonary Fibrosis,” *European Respiratory Journal* 48, no. 6 (December 2016): 1721–1731, <https://doi.org/10.1183/13993003.02115-2015>.
30. S. N. Tongal, G. Kayhan, Ö. Yılmaz, M. Öçalan, and H. Yüksel, “The Role of Pulmonary Genetic Variations in the Pathogenesis of Pediatric Postinfectious Bronchiolitis Obliterans,” *Thoracic Research and Practice* 26 (2025): 191–196, <https://doi.org/10.4274/thoracrespract.2025.2024-11-1>.
31. H. Nayır Büyüksahin, N. Emiralioglu, E. Yalçın, et al., “Two Cases With Undefined Childhood Interstitial Lung Disease: Can It Be Related to Telomere Variants?,” *Journal of Paediatrics and Child Health* 60 (2024): 754–756.
32. G. Cinel, N. Kiper, D. Orhan, et al., “Childhood Diffuse Parenchymal Lung Diseases: We Need a New Classification,” *Clinical Respiratory Journal* 14, no. 2 (February 2020): 102–108, <https://doi.org/10.1111/crj.13106>.
33. P. Miraftehi, T. Kirjavainen, J. S. Suominen, J. Lohi, and L. Martelius, “Children’s Interstitial Lung Disease: Multidetector Computed Tomography Patterns and Correlations Between Imaging and Histopathology,”

European Journal of Radiology 165 (August 2023): 110886, <https://doi.org/10.1016/j.ejrad.2023.110886>.

34. K. I. Ramirez-Suarez, S. Martinez-Correa, L. O. Tierradentro-Garcia, et al., "Pediatric Diffuse Lung Disease in Infants: Imaging Findings and Histopathologic Correlation," *Radiographics* 44, no. 11 (2024): e240022, <https://doi.org/10.1148/rg.240022>.

35. K. Buschulte, V. Cottin, M. Wijsenbeek, M. Kreuter, and R. Diesler, "The World of Rare Interstitial Lung Diseases," *European Respiratory Review* 32, no. 167 (March 2023): 220161, <https://doi.org/10.1183/16000617.0161-2022>.

36. G. H. Deutsch and L. R. Young, "Lung Biopsy in the Diagnosis and Management of chILD," *Pediatric Pulmonology* 59, no. 9 (2024): 2298–2312, <https://doi.org/10.1002/ppul.26454>.

37. B. Sunman and N. Kiper, *Fibrotic Lung Diseases in Children*, (John Wiley and Sons Inc., 2024), <https://doi.org/10.1002/ppul.26905>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: ppul71791-sup-0001-cleanREV2_Supplementary_Tables.docx.