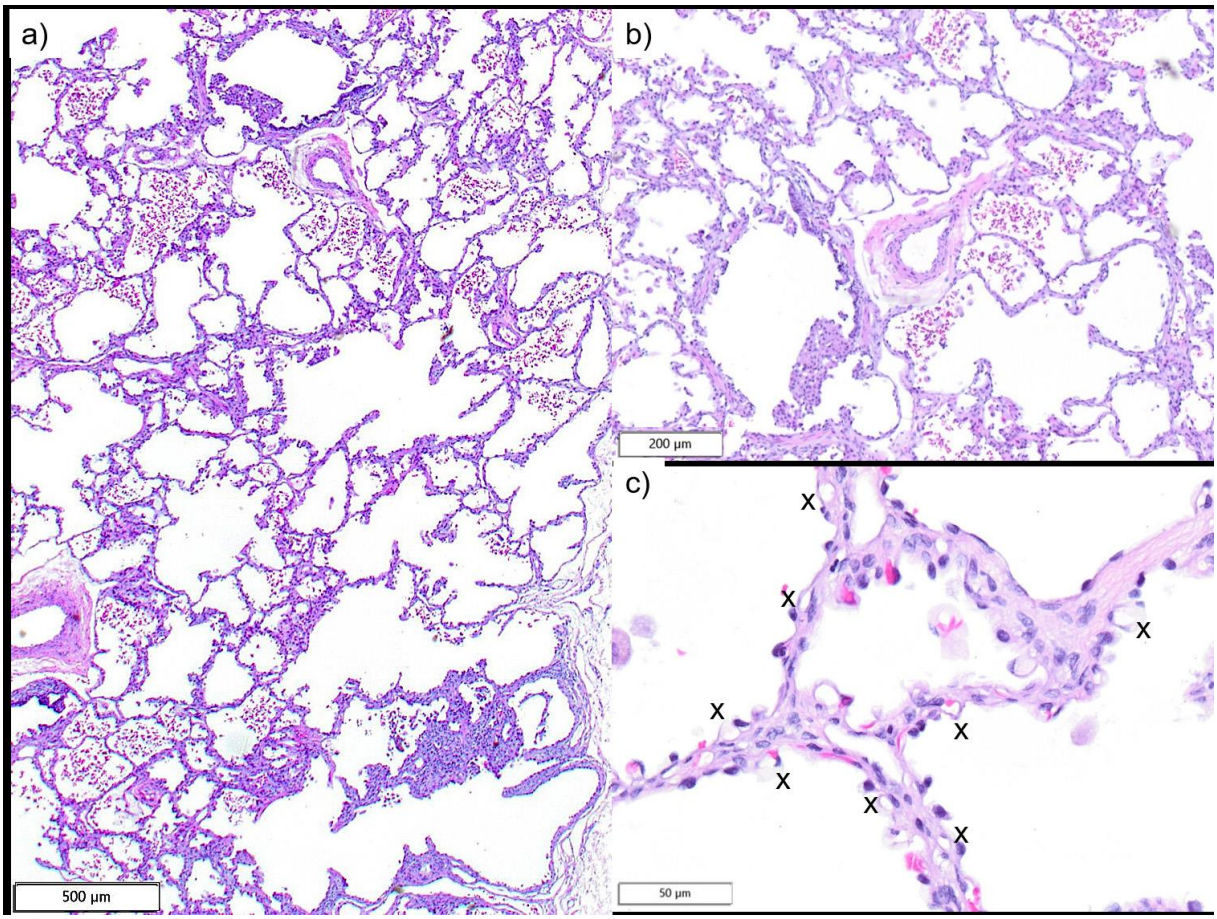
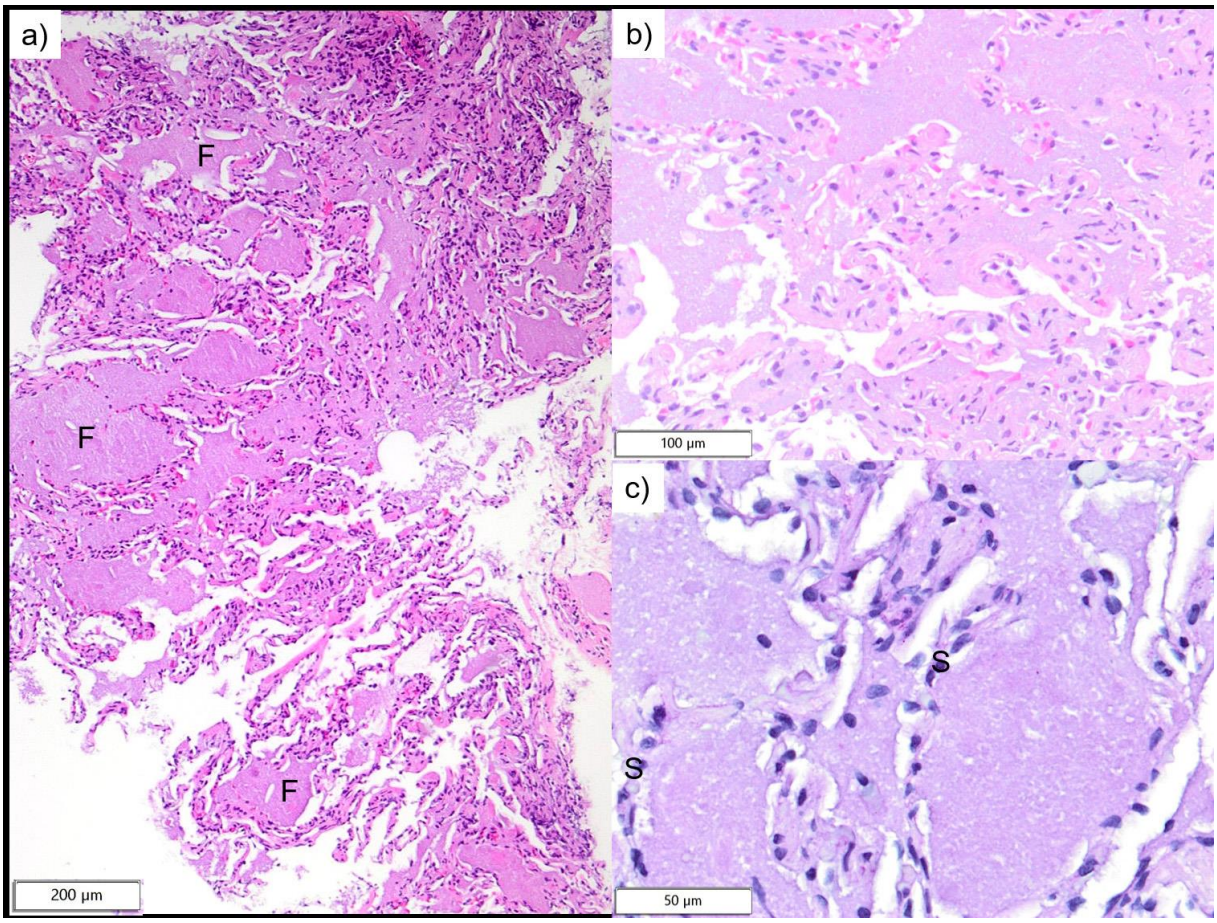


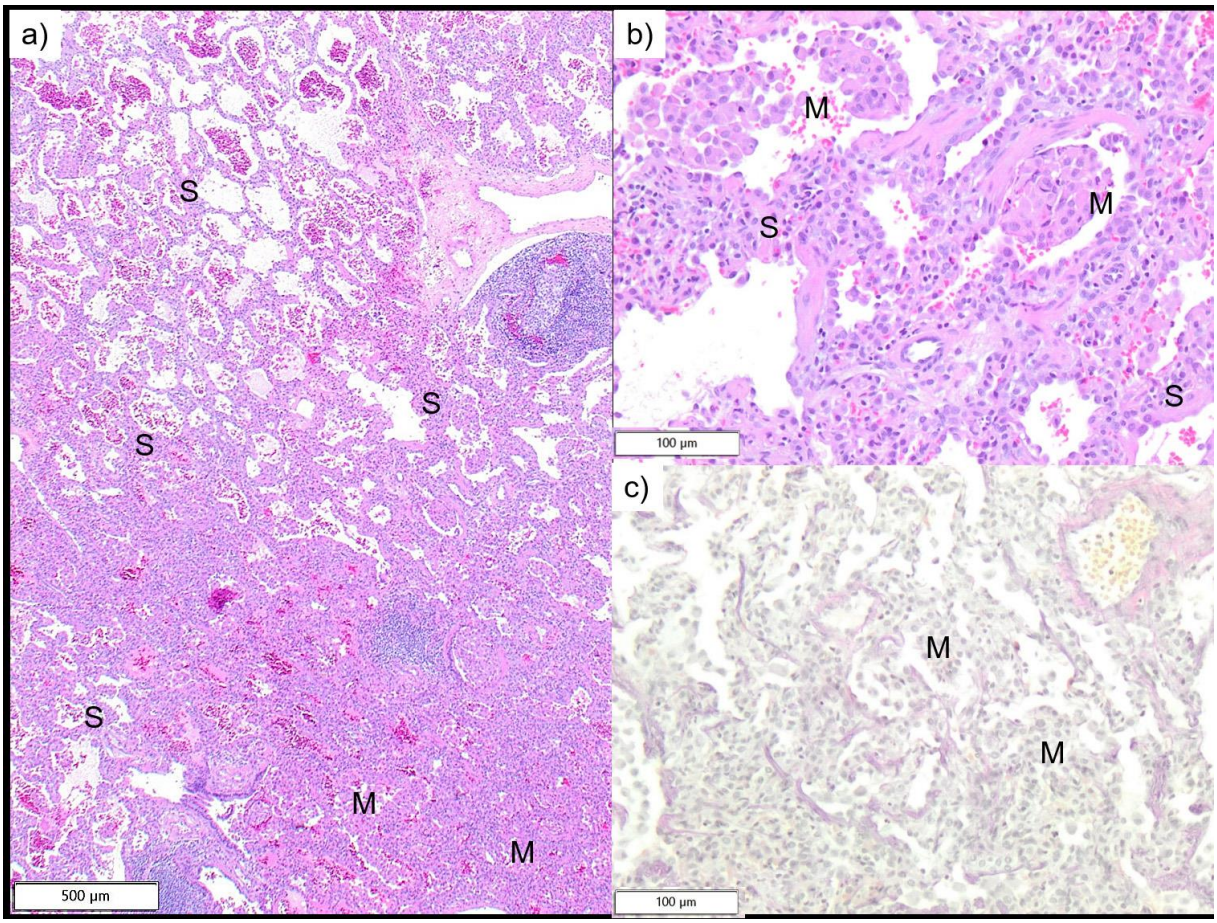
Supp. fig. S1 Lung biopsy of 2 years old girl with alveolar simplification caused by trisomy 21.

a) At low magnification diffusely distended alveolar spaces with rather unremarkable alveolar septa and bronchoalveolar bundles can be appreciated (HE). b) The alveolar lining and interstitium retain their regular architecture and cellular composition (HE). c) Only high magnification reveals the (still) double layered capillary net (x) within the septa, a frequent but not pathognomonic parenchymal feature of patients harboring trisomy 21 (HE).



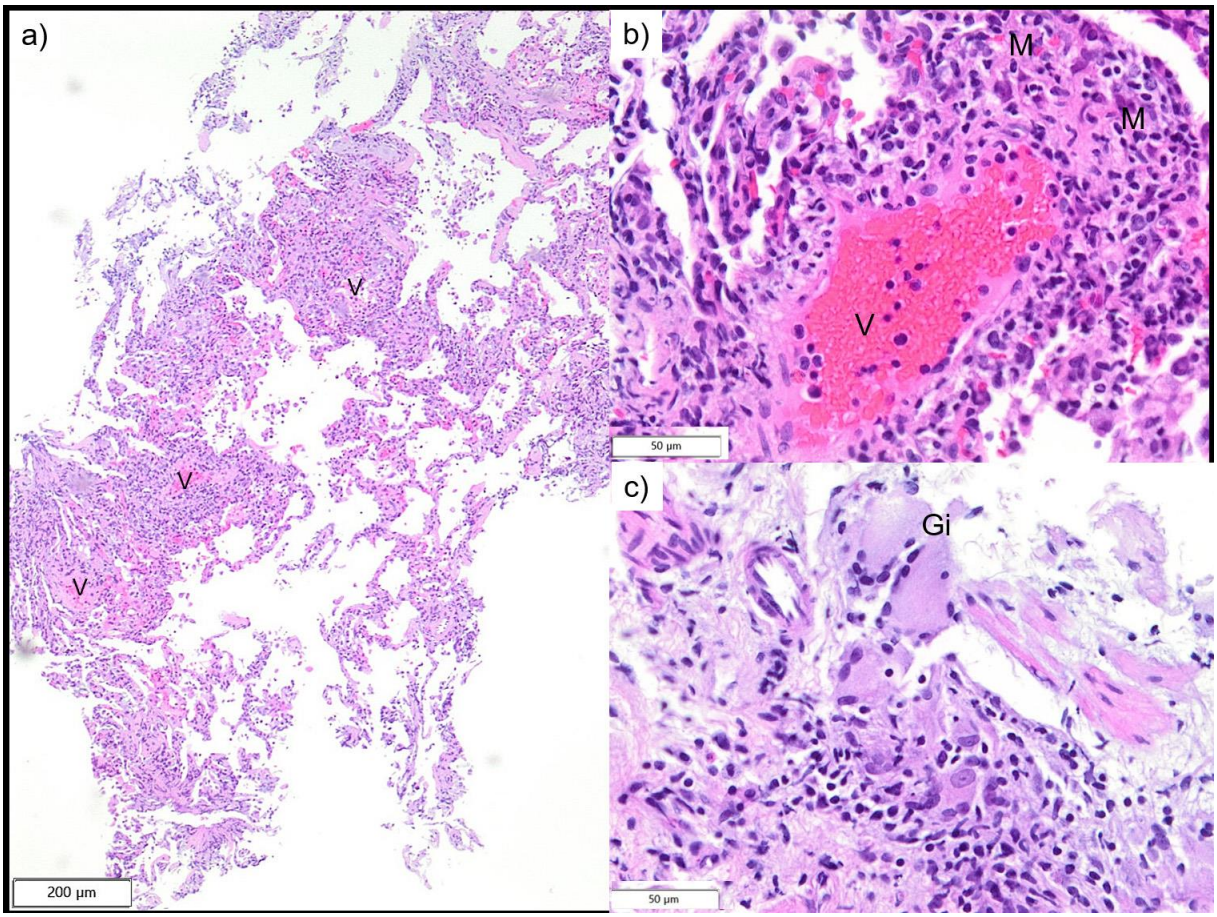
Suppl. fig. S2 Lung biopsy of a newborn at term with pulmonary alveolar proteinosis (PAP) caused by CSF2RA mutation.

a) The main pathological finding consists of the protein-rich intraalveolar exudate (F). The septal structures do not show relevant inflammatory infiltrates or hypercellularity (HE). b) The intraalveolar exudate is finely granular and mostly cell free (HE). c) The alveolar septa (S) as well as the alveoli are mostly free from inflammatory infiltrates (PAS).



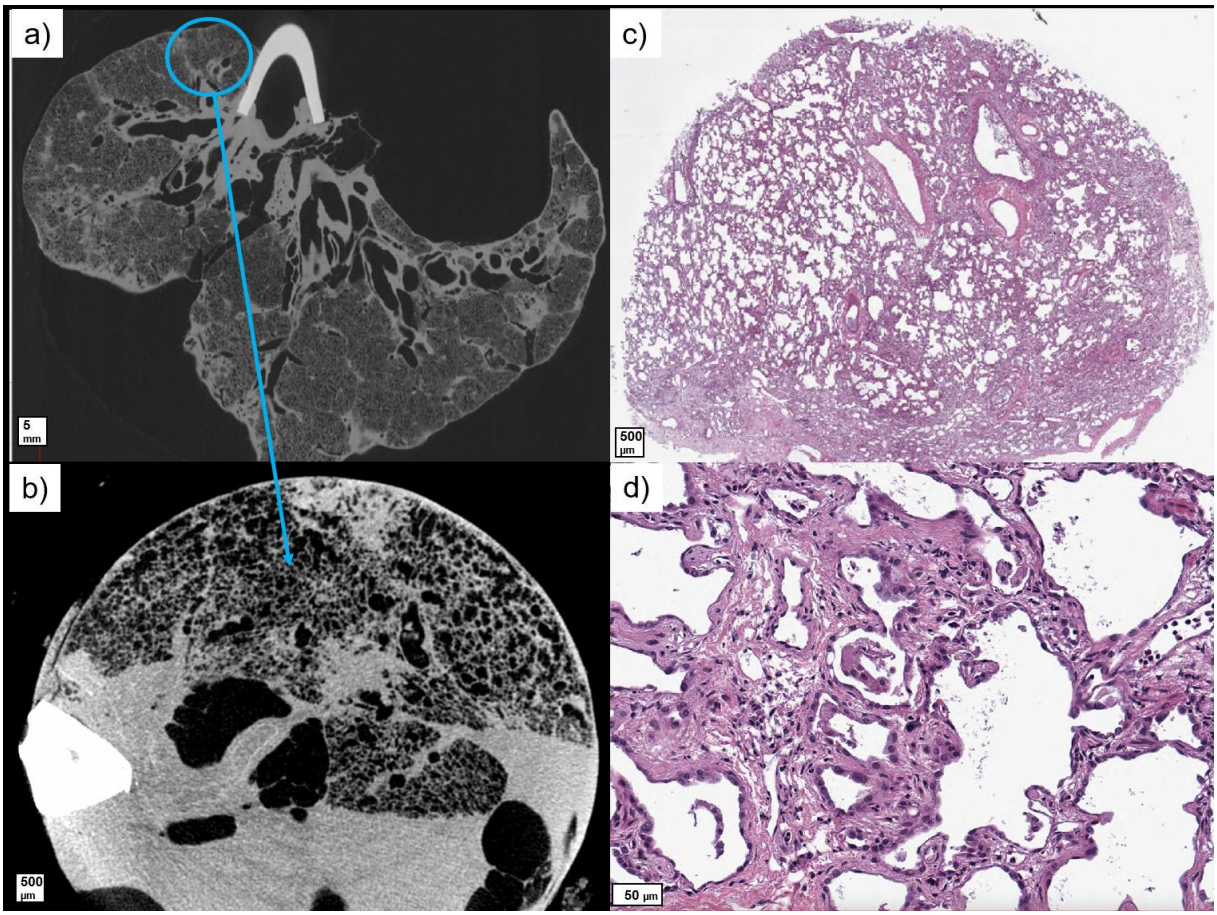
Suppl. fig. S3 Lung biopsy of a neonate with chronic pneumonitis of infancy (CPI) and desquamative interstitial pneumonia (DIP) caused by ABCA3 mutation.

a) At low power a mixture of morphological patterns can be appreciated: widened and hypercellular septa (S) are next to alveoli with a DIP-like intraalveolar accumulation of macrophages (M) (HE). b) The alveoli show dense aggregates of macrophages (M) and a type-2 cell lining. Within the septal interstitium (S) immature stromal cells predominate (PAS-negative, not depicted) with only sparse accompanying inflammatory cells (HE). c) Trichrome staining highlights the accumulation of intraalveolar macrophages (M).



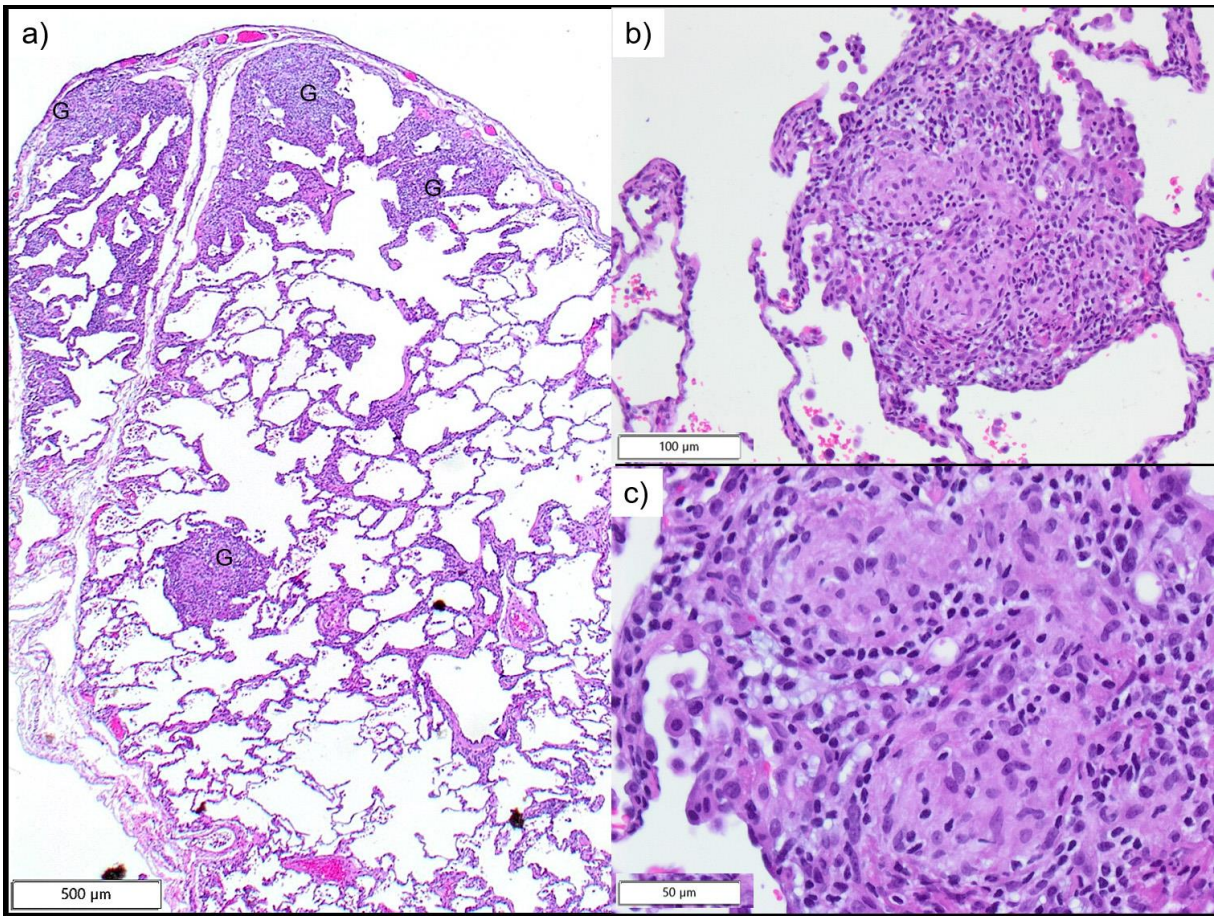
Suppl. fig. S4 Transbronchial biopsy of 9 years old male with hypersensitivity pneumonitis triggered by avian antigens.

a) Low power shows perivascular (V), circumferential inflammatory infiltrates. The alveolar septa appear only slightly broadened and hypercellular (HE). b) The infiltrates show a mixture of lymphocytes, plasma cells, occasional eosinophils and loose aggregates of macrophages (M). In this biopsy a pattern of organizing pneumonia often found in HP cases cannot be demonstrated, although this may be due to sampling issues (HE). c) The peribronchial stroma shows loose aggregates of giant cells (Gi)(HE).



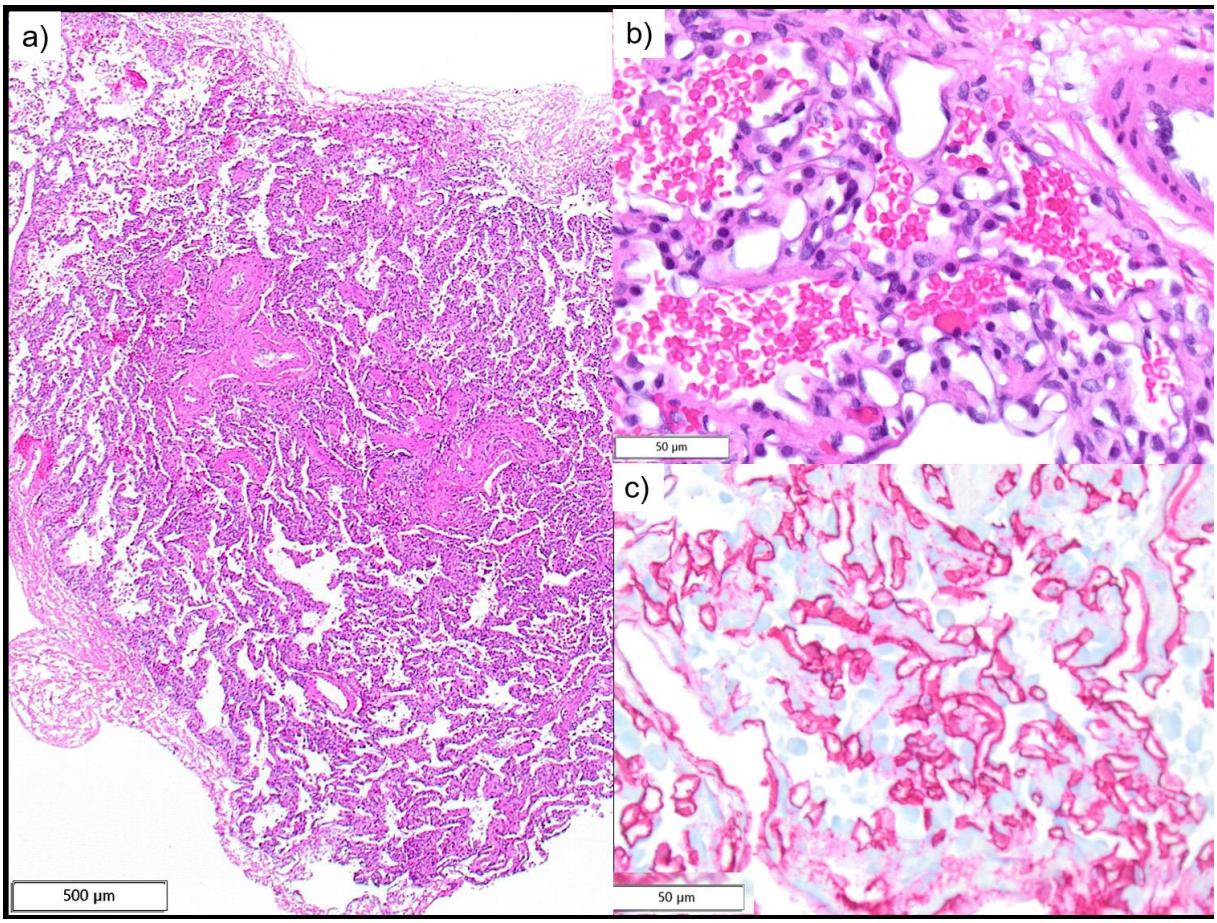
Suppl. Fig. S5 Lung explant from 4 years old boy with PLGC2 mutation that received a double lung transplant.

a) Whole lung microCT of the lung explant after air-inflation and fixation with liquid nitrogen fumes, scanned at 70µm resolution showing central bronchiectasis and diffuse patches of fibrosis. b) MicroCT image from an extracted lung core (from area within blue circle of a), scanned with a microCT with a resolution of 10µm showing evidence of patchy fibrosis and acinar distension (HE). c) Low scanning micrograph of histology of tissue core of fig. 2b) showing patchy areas of fibrosis and distended acini, corresponding to alveolar simplification. d) A mixed pattern of alveolar simplification with discrete interstitial fibrosis and inflammatory infiltration can be appreciated, which is characteristic but not pathognomonic for the auto-inflammatory reactions associated with PLGC2 mutations (HE).



Suppl. fig. S6 Lung biopsy of 4 years old female with a granulomatous-lymphocytic interstitial lung disease injury pattern caused by innate hypogammaglobulinemia.

a) Multifocal aggregates of predominantly histiocytic aggregates without relevant septal extension or distorsion are the predominant finding (HE). b) The nodular inflammatory aggregates show non-necrotizing granulomas with a peripheral rim of lymphocytes (HE). c) The granulomas lack giant cells, in special stains (not shown) no infectious agents can be demonstrated (HE).



Suppl. fig. S7 Lung biopsy of a respirator dependent 12 months old female infant with preterm delivery showing capillary hemangiomatosis.

a) Alveolar septa appear broadened and hypercellular at low power (HE). b) Multifocally the septa reveal irregular aggregates of dilated capillaries, the postcapillary venules are unremarkable (not shown) (HE). c) By immunohistochemistry consistent expression of CD31 can be demonstrated (IHC for CD31).

Suppl. Table S1 Causes of alveolar simplification (modified after [1])

Pulmonary hypoplasia caused by mechanical hindrance of lung expansion	oligohydramnios
	intrathoracic mass lesions
	neuromuscular disturbances of respiratory movements
	diaphragmatic hernia
Chronic neonatal lung disease (CNLD)	care dependent lung disease of the pre-term infant
Early-onset lung disease of term infants	intrauterine lung damage
	early post-partal lung damage
Chromosomal anomalies	trisomy 21
	other genetic anomalies
Congenital heart disease without chromosomally anomalies	

Suppl. Table S2 Pulmonary manifestations of rheumatological disease in children [70,74-76]

Disease group	Disease Entities	Pulmonary injury patterns
CTD	juvenile idiopathic arthritis	pleuritis, necrotizing granulomas, obliterative bronchiolitis, organizing pneumonia, lipoid pneumonia, lymphocytic interstitial pneumonia
	juvenile onset systemic sclerosis	non-specific interstitial pneumonia, usual interstitial pneumonia, pulmonary hypertension
	systemic lupus erythematosus	pleuritis, acute pneumonitis, diffuse alveolar damage, diffuse alveolar hemorrhage, obliterative bronchiolitis, pulmonary hypertension
	Sjögren syndrome	follicular bronchiolitis, lymphocytic interstitial pneumonia, pulmonary hypertension
	juvenile dermatomyositis/polymyositis	acute pneumonitis, pulmonary hypertension, acute fibrinous and organizing pneumonia, aspiration pneumonia
	mixed CTD	pleuritis, interstitial pulmonary fibrosis, pulmonary hypertension
Vasculitis	anti-neutrophil cytoplasmic antibody-associated vasculitis	ulcerative bronchitis, necrotizing granulomas, small vessel vasculitis
	anti-glomerular basement membrane diseases (granulomatosis with polyangiitis, Churg-Strauss syndrome, microscopic polyangiitis)	diffuse alveolar hemorrhage, alveolar capillaritis, tissue eosinophilia
	Henoch-Schönlein purpura	

	cryoglobulinemia vasculitis	
Sarcoidosis		non-necrotizing granulomas, interstitial fibrosis