Supplementary Methods:

1. study protocol

Patients who were undiagnosed following routine clinical procedure and were suspected to have genetic disorders between January 1, 2015, and December 31, 2019 in the Children's Hospital of Fudan University—one of the major referral centres with more than 20,000 referrals from lower-level hospitals per year—were enrolled if they had one of the following respiratory phenotypes: (1) respiratory distress after birth; (2) dyspnoea, progressive respiratory failure and/or oxygen dependence; and (3) recurrent/persistent lower respiratory infections [RLRI/PLRI]). Each patient was evaluated by a pulmonologist and a clinical geneticist. Exome sequencing was performed in all of the patients and available parents within 5 days after enrolment. The detailed medical histories were collected by an experienced physician until discharge from the hospital or death; the data were no longer collected after receiving the result of genetic testing of patients that without a positive molecular diagnosis. Informed consent was obtained from the parents of patients who were recruited in the present study. This prospective, observational cohort study was approved by the Ethics Committee of the Children's Hospital of Fudan University (approval number: 2014-121).

2. Follow-up

Data pertaining to the genetic counselling, general condition, and survival of each patient at one month after discharge were documented through outpatient visits and/or telephone conversations.

3. Exome sequencing and data analysis

Genomic DNA fragments of patients and their parents were extracted from 2 ml of venous whole blood and were ligated with adaptors to form two paired-end DNA libraries. Exome capturing via a 2742-gene panel and whole-exome sequencing (WES) were performed using the Agilent ClearSeq Inherited Disease panel kit (Agilent, Santa Clara, CA, USA) and Agilent SureSelectXT Human All Exon 50-Mb kit (Agilent, CA, USA), respectively. Exome sequencing was performed using the HiSeq2000/2500 sequencer (Illumina, San Diego, CA, USA), resulting in an average of more than 90× coverage for each sample. Additionally, more than 95% of targeted regions were sequenced with a coverage of more than 20×, and low-quality reads were discarded. Useable reads were aligned to the reference human genome (UCSC hg19) via the Burrows–Wheeler Aligner (BWA v.0.7.9a). Then, SAMtools and Picard (http://picard.sourceforge.net/index.shtml) were used to sort, merge, and remove duplicate paired-end reads of BAM files. Subsequent types of variation that differed from those of the reference sequence were determined by GATK (version v3.2).

The pathogenic/likely-pathogenic variants obtained after the bioinformatic analysis that described in the main text were confirmed by Sanger sequencing.

Supplementary Results:

1. Demographic and clinical characteristics of the patients

In the entire cohort of 971 patients, a total of 140 (14.4%) patients received a positive molecular diagnosis and were included for further analysis (Figure S1). Neonates mostly received 2742-gene-panel sequencing (results usually within one month), while children primarily received WES (results usually within 2–3 months) depending on the clinical urgency and complexity of symptoms. All 140 diagnosed patients were unrelated, with the exception of one pair of siblings. There were 98 (70%) males and 42 (30%) females, with a mean age at enrolment of 3.6 years (range, 0 days to 17.8 years). The main respiratory manifestations at inclusion were respiratory distress (n=18,

12.9%), respiratory failure (n=18, 12.9%), and RLRI/PLRI (n=93, 66.4%), with the mean onset age shown in Table 1. Based on enrolment age, the 140 diagnosed patients were categorised into a neonatal group (age range, 0–1 months; n=31, 22.1%), infant group (age range, 1–12 months; n=38, 27.1%), and children group (age range, 12 months–18 years; n=71, 50.7%). The most prevalent phenotype in each group is shown in Table 1.

2. Table S1 Inheritance pattern of disorders in 140 patients provided by exome sequencing.

Inheritance Pattern	Number of probands (% of total)
Autosomal dominant	56 (40%)
De novo	33
Inherited	3
Inheritance unknown	20
Autosomal recessive	45 (32.1%)
Homozygous	14
Compound heterozygous	31
X-linked	38 (27.1%)
De novo	2
Carrier mother	31
Inheritance unknown	5
Two diagnoses	1(0.7%)
Autosomal dominant + X-linked	1

3. Table S2 The detailed information of genetic findings in 140 molecular positive patients and specific medical procedures taken and possible taken.

patient number	gene	variant information	variants classification	zygo	inheritance pattern	origin	molecular diagnosis age (day)	specific medical procedures taken	possible medically actionable procedures could be taken
P001	ABCA3	NG_011790.1(NM_001089.3):c.3862+1G>C	LP	Hom	AR	NA	28	Redirection of care/diagnosis explained death	Glucocorticoid/hydroxychloroquine/azitromycin
P002	ABCA3	NG_011790.1(NM_001089.3):c.3862+1G>C	LP	Hom	AR	NA	28	Redirection of care/diagnosis explained death	Glucocorticoid/hydroxychloroquine/azitromycin
P087	ACVRL1	NM_000020.3:exon3:c.199C>T(p.R67W)	LP	Het	AD	NA	3604	/	Tyrosine kinase inhibitors (Nintdanib, Pazopanib, etc.)
P063	AGL	NM_000642.3:exon20:c.2590C>T(p.R864X)	P	Het	AR	NA	283	/	High protein intake (~ 25% of energy)
P063	AGL	NM_000642.3:exon3:c.118C>T(p.Q40X)	P	Het	AR	NA	283	/	High protein intake (~ 25% of energy)
P088	ATM	NM_000051.4:exon62:c.8929_8930insT(p.E2977Vfs*3)	P	Het	AD/AR	Maternal	2184	/	/
P088	ATM	NM_000051.4:exon62:c.8918_8927del(p.R2973Mfs*9)	P	Het	AD/AR	Maternal	2184	/	/
P088	ATM	NM_000051.4:exon19:c.2872G>T(p.E958X)	P	Het	AD/AR	Paternal	2184	/	/
P061	BTK	NM_000061.3:exon18:c.1764G>C(p.W588C)	LP	Hemi	XLR	Maternal	440	/	/

P089	BTK	NM_000061.3:exon12:c.1039del(p.A347Lfs*56)	P	Hemi	XLR	Maternal	705	/	/
P090	BTK	NM_000061.3:exon2:c.118T>G(p.Y40D)	P	Hemi	XLR	Maternal	879	/	/
P091	BTK	NM_000061.3:exon11:c.919dup(p.R307Kfs*16)	P	Hemi	XLR	Maternal/Sister(Normal)	1489	/	/
P092	BTK	NM_000061.3:exon12:c.1039G>C(p.A347P)	P	Hemi	XLR	NA	1884	/	/
P093	BTK	NM_000061.3:exon2:c.37C>T(p.R13X)	P	Hemi	XLR	Maternal	2118	/	/
P094	BTK	NM_000061.3:exon14:c.1181C>A(p.S394X)	P	Hemi	XLR	Maternal	2193	/	/
P095	BTK	NM_000061.3:exon2:c.119A>G(p.Y40C)	P	Hemi	XLR	Maternal	2485	/	/
P096	BTK	NM_000061.3:exon15:c.1558C>T(p.R520X)	P	Hemi	XLR	Maternal	4786	/	/
P097	BTK	NM_000061.3:exon2:c.82C>T(p.R28C)	P	Hemi	XLR	Maternal	5238	/	/
P098	BTK	NG_009616.1(NM_000061.3):c.1751-1G>C	P	Hemi	XLR	Maternal	5244	/	/
P099	BTK	NM_000061.3:exon15:c.1506C>A(p.C502X)	P	Hemi	XLR	Maternal	5518	/	/

P074	CCDC103	NM_213607.3:exon3:c.170_175delinsGG(p.K57Rfs*121)	LP	Hom	AR	Maternal/Paternal	803	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P075	CCDC114	NM_144577.4:exon7:c.702_705dup(p.P236Afs*11)	LP	Het	AR	Maternal	1005	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P075	CCDC114	NG_033251.1(NM_144577.4):c.-41-2A>C	VUS	Het	AR	Paternal	1005	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P076	CCDC40	NM_017950.4:exon6:c.901C>T(p.R301X)	LP	Het	AR	Maternal	6535	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P076	CCDC40	NM_017950.4:exon20:c.3224T>C(p.L1075P)	VUS	Het	AR	Paternal	6535	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P077	CFTR	NM_000492.4:exon14:c.2052dup(p.Q685Tfs*4)	P	Het	AD/AR	De novo	3761	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P077	CFTR	NM_000492.4:exon8:c.935_937del(p.F312del)	P	Het	AD/AR	Maternal	3761	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P078	CFTR	NM_000492.4:exon3:c.263T>G(p.L88X)	P	Hom	AD/AR	Maternal/Paternal/Sister (het)	4445	Airway clearance therapy and administration of acute and prophylactic antibiotics	/

P079	CFTR	NG_016465.4(NM_000492.4):c.2988+1G>A	P	Hom	AD/AR	NA	6461	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P023	CHD7	NG_007009.1(NM_017780.4):c.2957+5G>A	P	Het	AD	De novo	31	Redirection of care	Monitoring other malformations and specialized nursing
P024	CHD7	NM_017780.4:exon12:c.3106C>T (p.R1036X)	P	Het	AD	NA	34	/	Monitoring other malformations and specialized nursing
P025	CHD7	NM_017780.4:exon31:c.6416dup(p.N2139Kfs*27)	LP	Het	AD	NA	44	Redirection of care	Monitoring other malformations and specialized nursing
P026	CHD7	NM_017780.4:exon31:c.6165_6166del(p.Y2056Pfs*3)	P	Het	AD	NA	47	Redirection of care	Monitoring other malformations and specialized nursing
P027	CHD7	NM_017780.4:exon31:c.6135_6153dup(p.S2052Dfs*14)	LP	Het	AD	NA	48	Redirection of care	Monitoring other malformations and specialized nursing
P028	CHD7	NM_017780.4:exon34:c.7192C>G(p.R2398G)	P	Het	AD	De novo	48	Diagnosis explained death	Monitoring other malformations and specialized nursing
P029	CHD7	NM_017780.4:exon15:c.3634_3637del(p.N1212Ffs*30)	LP	Het	AD	NA	56	/	Monitoring other malformations and specialized nursing
P070	CHD7	NM_017780.4:exon8:c.2504_2508del(p.Y835Sfs*14)	P	Het	AD	NA	87	Diagnosis explained death	Monitoring other malformations and specialized nursing
P073	CHD7	NM_017780.4:exon32:c.6850C>T(p.R2284X)	P	Het	AD	NA	223	/	Monitoring other malformations and specialized nursing

P030	COL2A1	NG_008072.1(NM_001844.5):c.2050-1G>C	P	Het	AD/AR	De novo	31	Prevention and evaluation of joint damage and ocular lesions	/
P031	COL2A1	NM_001844.5:exon23:c.1420_1430del(p.G474Pfs*10)	P	Het	AD	NA	52	Prevention and evaluation of joint damage and ocular lesions	/
P016	CPS1	NM_001875.5:exon18:c.2161C>T(p.R721X)	P	Het	AR	NA	28	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P016	CPS1	NM_001875.5:exon30:c.3572C>A(p.A1191D)	LP	Het	AR	NA	28	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P017	CPS1	NM_001875.5:exon28:c.3443T>A(p.M1148K)	P	Hom	AR	Maternal	35	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P018	CPS1	NM_001875.5:exon32:c.3875A>G(p.H1292R)	LP	Het	AR	Paternal	36	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P018	CPS1	NM_001875.5:exon37:c.4325_4327dup(p.N1442dup)	P	Het	AR	NA	36	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P018	CPS1	NM_001875.5:exon20:c.2440C>T(p.R814W)	LP	Het	AR	NA	36	Diagnosis explained death	Hemodialysis and medicine therapy (N-carbamyl-L-glutamate)
P015	CPT2	NM_000098.3:exon4:c.1033G>A(p.G345R)	LP	Het	AR	NA	28	Diagnosis explained death	Medicine therapy (Bezafibrate)

P015	CPT2	NM_000098.3:exon4:c.764A>G(p.D255G)	LP	Het	AR	NA	28	Diagnosis explained death	Medicine therapy (Bezafibrate)
P072	CREBBP	NG_009873.2(NM_004380.3):c.1941+1G>T	P	Het	AD	De novo	217	Prevention of renal and eye phenotypes, recurrent respiratory infections, sleep apnea, and cancer risk	/
P043	CYBB	NG_009065.1(NM_000397.4):c.253-2A>C	P	Hemi	XLR	Maternal/Sister(Normal)	70	Medicine therapy (IFN-gamma)	Avoiding BCG vaccination
P045	CYBB	NM_000397.4:exon7:c.779C>T(p.P260L)	P	Mosaic	XLR	De novo	257	/	Avoiding BCG vaccination
P049	CYBB	NG_009065.1(NM_000397.4):c.484-1G>C	P	Hemi	XLR	Maternal	392	Umbilical cord blood stem cell transplantation	Avoiding BCG vaccination
P050	CYBB	NM_000397.4:exon7:c.771C>A(p.C257X)	P	Hemi	XLR	Maternal	126	Umbilical cord blood stem cell transplantation	Avoiding BCG vaccination
P056	CYBB	NM_000397.4:exon5:c.388C>T(p.R130X)	P	Hemi	XLR	Maternal	384	/	Avoiding BCG vaccination
P059	CYBB	NM_000397.4:exon9:c.1038del(p.E347Rfs*39)	P	Hemi	XLR	Maternal	258	Ongoing transplantation	Avoiding BCG vaccination
P100	CYBB	NM_000397.4:exon11:c.1414G>A(p.G472S)	LP	Hemi	XLR		503	Peripheral blood stem cell transplantation	Avoiding BCG vaccination
P100	CYBB	NG_009065.1(NM_000397.4):c.1315-1G>T	P	Hemi	XLR	Maternal/Brother(Normal)	503	Peripheral blood stem cell transplantation	Avoiding BCG vaccination
P101	CYBB	NM_000397.4:exon7:c.676C>T(p.R226X)	P	Hemi	XLR	Maternal	1063	/	Avoiding BCG vaccination

P102	CYBB	NG_009065.1(NM_000397.4):c.674+5G>A	P	Hemi	XLR	Maternal/Brother(Normal)	1110	Ongoing transplantation	Avoiding BCG vaccination
P103	CYBB	NM_000397.4:exon6:c.560_567dup(p.I190Yfs*2)	P	Hemi	XLR	Maternal	1642	/	Avoiding BCG vaccination
P104	CYBB	NG_009065.1(NM_000397.4):c.252+1G>C	P	Hemi	XLR	Maternal	2129	Umbilical cord blood stem cell transplantation	Avoiding BCG vaccination
P035	DNAAF3	NM_001256714.1:exon5:c.680del(p.L227Pfs*28)	P	Hom	AR	Maternal/Paternal	345	Airway clearance therapy	/
P080	DNAAF3	NM_001256714.1:exon2:c.200C>A(p.S67Y)	LP	Het	AR	Maternal	565	Airway clearance therapy	/
P080	DNAAF3	NM_001256714.1:exon6:c.811_815dup(p.R273Tfs*13)	P	Het	AR	Paternal	565	Airway clearance therapy	/
P081	DNAAF3	NM_001256714.1:exon6:c.811_815dup(p.R273Tfs*13)	P	Het	AR	Maternal	6105	Airway clearance therapy	/
P081	DNAAF3	NG_032759.1(NM_001256714.1):c.325_369+59del	P	Het	AR	Paternal	6105	Airway clearance therapy	/
P082	DNAH11	NM_001277115.2:exon55:c.9017C>T(p.T3006M)	VUS	Het	AR	Paternal	971	Airway clearance therapy	/

P082	DNAH11	NM_001277115.2:exon45:c.7292G>T(p.S2431I)	VUS	Het	AR	Paternal	971	Airway clearance therapy	/
P082	DNAH11	NM_001277115.2:exon82:c.13373C>T(p.P4458L)	LP	Het	AR	Maternal	971	Airway clearance therapy	/
P082	DNAH11	NM_001277115.2:exon45:c.7364A>C(p.D2455A)	VUS	Het	AR	Paternal	971	Airway clearance therapy	/
P083	DNAH5	NM_001369.2:exon14:c.1852C>T(p.R618X)	P	Het	AR	Maternal	2371	Airway clearance therapy	/
P083	DNAH5	NM_001369.2:exon37:c.6139C>T(p.Q2047X)	P	Het	AR	Paternal	2371	Airway clearance therapy	/
P084	DNAH5	NM_001369.2:exon38:c.6304C>T(p.R2102C)	LP	Het	AR	Paternal	3142	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P084	DNAH5	NG_013081.2(NM_001369.2):c.278-1_295delinsACAACAACAA	LP	Het	AR	Maternal	3142	Airway clearance therapy and administration of acute and prophylactic antibiotics	/
P032	EFTUD2	NG_032674.1(NM_004247.4):c.869+1G>A	P	Het	AD	NA	35	/	Monitoring other abnormalities and specialized nursing
P105	ELANE	NM_001972.4:exon3:c.242G>C(p.R81P)	P	Het	AD	De novo	875	/	Hemopoietic stem cell transplantation; Monitoring the risk of developing

									myelodysplasia or acute myelogenous leukemia
P106	ELANE	NM_001972.4:exon2:c.158A>G(p.H53R)	P	Het	AD	De novo	1836	/	Hemopoietic stem cell transplantation; Monitoring the risk of developing myelodysplasia or acute myelogenous leukemia
P147	EVC	NM_153717.3:exon19:c.2731C>T(p.R911X)	P	Hom	AD/AR	NA	30	/	/
P142	FBN1	NG_008805.2(NM_000138.5):c.6038-1G>A	P	Het	AD	NA	1325	/	/
P143	FBN1	NM_000138.5:exon2:c.2T>G(p.?)	P	Het	AD	NA	3601	/	/
P144	FBN1	NM_000138.5:exon66:c.8557dup(p.Y2853Lfs*5)	LP	Het	AD	NA	6528	/	/
P005	FOXF1	NM_001451.3:exon1:c.147del(p.Y51Ifs*19)	P	Het	AD	NA	28	Diagnosis explained death	/
P064	GAA	NM_000152.5:exon19:c.2662G>T(p.E888X)	P	Het	AR	Maternal	260	High-protein and raw corn starch diet	RhGAA (Myozyme)
P064	GAA	NM_000152.5:exon4:c.796C>T(p.P266S)	P	Het	AR	Paternal	260	High-protein and raw corn starch diet	RhGAA (Myozyme)
P065	GAA	NM_000152.5:exon7:c.1082C>T(p.P361L)	P	Het	AR	NA	362	Prenatal diagnosis of amniocentesis	High-protein diet and RhGAA (Myozyme)

P065	GAA	NM_000152.5:exon14:c.2015G>A(p.R672Q)	P	Het	AR	NA	362	Prenatal diagnosis of amniocentesis	High-protein diet and RhGAA (Myozyme)
P067	GAA	NM_000152.5:exon2:c.258del(p.N87Tfs*55)	P	Het	AR	Maternal	269	/	High-protein diet and RhGAA (Myozyme)
P067	GAA	NM_000152.5:exon10:c.1548G>A(p.W516X)	P	Het	AR	Paternal	269	/	High-protein diet and RhGAA (Myozyme)
P138	GAA	NM_000152.5:exon12:c.1669A>T(p.I557F)	LP	Het	AR	Maternal	420	High-protein and raw corn starch diet	RhGAA (Myozyme)
P138	GAA	NM_000152.5:exon6:c.1013A>T(p.D338V)	LP	Het	AR	Paternal	420	High-protein and raw corn starch diet	RhGAA (Myozyme)
P107	GATA2	NM_032638.5:exon6:c.1187G>A(p.R396Q)	P	Het	AD	Paternal	5897	/	/
P108	HAX1	NM_006118.4:exon3:c.430dup(p.V144Gfs*5)	P	Het	AR	Maternal	482	Early G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/
P108	HAX1	NG_007369.1(NM_006118.4):c.557-1G>C	P	Het	AR	Paternal	482	Early G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/
P109	HAX1	NM_006118.4:exon3:c.430dup(p.V144Gfs*5)	P	Het	AR	Paternal	1470	Early G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/
P109	HAX1	NM_006118.4:exon2:c.216_217insC(p.I73Hfs*6)	LP	Het	AR	Maternal	1470	Early G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/

P137	IDS	NM_000202.8:exon3:c.253G>A(p.A85T)	P	Hemi	XLR	Maternal/Normal	1195	Hemopoietic stem cell transplantation	/
P110	IFNGR1	NG_007394.1(NM_000416.3):c.861+2T>A	P	Hom	AD/AR	NA	1192	/	avoiding BCG vaccination
P039	IL10RA	NM_001558.4:exon3:c.301C>T(p.R101W)	P	Het	AR	NA	72	Umbilical cord blood stem cell transplantation	/
P039	IL10RA	NM_001558.4:exon4:c.537G>A(p.T179T)	P	Het	AR	NA	72	Umbilical cord blood stem cell transplantation	/
P041	IL10RA	NM_001558.4:exon3:c.301C>T(p.R101W)	P	Hom	AR	Paternal/Maternal	75	/	Umbilical cord blood stem cell transplantation
P044	IL2RG	NM_000206.3:exon7:c.865C>T(p.R289X)	P	Hemi	XLR	Maternal	284	/	Umbilical cord blood stem cell transplantation
P046	IL2RG	NM_000206.3:exon3:c.371T>G(p.L124R)	P	Hemi	XLR	Maternal	143	Diagnosis explained death	Umbilical cord blood stem cell transplantation
P053	IL2RG	NM_000206.3:exon5:c.664C>T(p.R222C)	P	Hemi	XLR	Maternal	224	Diagnosis explained death	Umbilical cord blood stem cell transplantation
P054	IL2RG	NM_000206.3:exon6:c.816_819del(p.I273Sfs*20)	P	Hemi	XLR	Maternal	137	Diagnosis explained death	Umbilical cord blood stem cell transplantation
P058	IL2RG	NM_000206.3:exon4:c.548T>A(p.L183X)	P	Het	XLR	NA	129	/	Umbilical cord blood stem cell transplantation
P062	IL2RG	NM_000206.3:exon5:c.719G>A(p.W240X)	LP	Hemi	XLR	Maternal	197	Umbilical cord blood stem cell transplantation	/
P111	IL2RG	NM_000206.3:exon5:c.670C>T(p.R224W)	P	Het	XLR	Maternal	551	Umbilical cord blood stem cell transplantation	/

P112	IL2RG	NM_000206.3:exon8:c.982C>T(p.R328X)	P	Hemi	XLR	Maternal	703	Umbilical cord blood stem cell transplantation	/
P051	IL7R	NG_009567.1(NM_002185.5):c.537+1G>A	P	Hom	AR	Maternal/Paternal	181	/	Avoiding BCG vaccination
P141	MMP21	NM_147191.1:exon2:c.557_558delinsTT(p.S186I)	LP	Het	AR	Paternal	5575	/	/
P141	MMP21	NM_147191.1:exon2:c.414dup(p.R139Qfs*119)	LP	Het	AR	Maternal	5575	/	/
P006	MTM1	NM_000252.3:exon12:c.1262G>A(p.R421Q)	P	Hemi	XL/XLR	NA	28	Redirection of care	Prevention of choke after eating and specialized nursing
P007	MTM1	NG_008199.1(NM_000252.3):c.231+1G>T	P	Hemi	XLR	NA	28	Redirection of care	Prevention of choke after eating and specialized nursing
P008	MTM1	NM_000252.3:exon9:c.832G>A(p.D278N)	LP	Hemi	XLR	Maternal	28	Redirection of care	Prevention of choke after eating and specialized nursing
P009	MTM1	NG_008199.1(NM_000252.3):c.528+1G>A	P	Het	XLR	NA	33	Redirection of care	Prevention of choke after eating and specialized nursing
P010	MTM1	NM_000252.3:exon9:c.721C>T(p.R241C)	P	Hemi	XLR	Maternal	48	Redirection of care	Prevention of choke after eating and specialized nursing
P060	NCF2	NM_000433.4:exon13:c.1180T>G(p.Y394D)	LP	Hom	AR	Maternal/Paternal	214	/	/
P071	NIPBL	NM_015384.5:exon10:c.1660C>T(p.Q554X)	P	Het	AD	De novo	118	/	/

P069	OFD1	NM_003611.3:exon11:c.1089del(p.R364Efs*5)	P	Het	XLD	De novo	336	/	/
P136	PHKA2	NM_000292.3:exon33:c.3614C>T(p.P1205L)	LP	Hemi	XLR	Maternal	1449	High-protein and raw corn starch diet	/
P011	PHOX2B	NM_003924.4:exon3:c.756_776dup(p.A254_A260dup)	P	Het	AD	De novo	88	Redirection of care	/
P012	PHOX2B	NM_003924.4:exon3:c.741_761dup(p.A254_A260dup)	P	Het	AD	De novo	44	Redirection of care	/
P013	PHOX2B	NM_003924.4:exon3:c.744_761dup(p.A255_A260dup)	LP	Het	AD	NA	52	Redirection of care	/
P014	PHOX2B	NM_003924.4:exon3:c.726_743dup(p.A255_A260dup)	P	Het	AD	De novo	54	Redirection of care	/
P113	PIK3CD	NM_005026.5:exon24:c.3061G>A(p.E1021K)	P	Het	AD	De novo	2705	/	Monitoring occurrence of thrombocytopenia, Transplantation
P114	PIK3CD	NM_005026.5:exon24:c.3074A>G(p.E1025G)	P	Het	AD	De novo	3163	/	Monitoring occurrence of thrombocytopenia, Transplantation
P115	PIK3CD	NM_005026.5:exon24:c.3061G>A(p.E1021K)	P	Het	AD	De novo	3274	Medicine therapy (Rapamycin)	Monitoring occurrence of thrombocytopenia, Transplantation

P116	PIK3CD	NM_005026.5:exon24:c.3061G>A(p.E1021K)	P	Het	AD	NA	3297	Medicine therapy (Rapamycin)	Monitoring occurrence of thrombocytopenia, Transplantation
P117	PIK3CD	NM_005026.5:exon24:c.3061G>A(p.E1021K)	P	Het	AD	De novo	3891	/	Monitoring occurrence of thrombocytopenia, Transplantation
P118	PIK3R1	NG_012849.2(NM_181523.3):c.1425+2T>G	P	Het	AD/AR	NA	4136	/	/
P033	PTPN11	NM_002834.3:exon4:c.417G>C(p.E139D)	P	Het	AD	De novo	41	/	/
P034	PTPN11	NM_002834.3:exon7:c.853T>C(p.F285L)	P	Het	AD	NA	56	/	/
P052	RAG1	NM_000448.3:exon2:c.2095C>T(p.R699W)	LP	Het	AD/AR	Paternal	345	Diagnosis explained death, Prenatal diagnosis of amniocentesis	Avoiding BCG vaccination
P052	RAG1	NM_000448.3:exon2:c.1971_1978del(p.L658Yfs*5)	P	Het	AD/AR	Maternal	345	Diagnosis explained death, Prenatal diagnosis of amniocentesis	Avoiding BCG vaccination
P055	RAG1	NM_000448.3:exon2:c.100C>T(p.R34W)	LP	Het	AD/AR	Maternal	408	Diagnosis explained death	Avoiding BCG vaccination
P055	RAG1	NM_000448.3:exon2:c.1088G>A(p.C363Y)	P	Het	AD/AR	Maternal	408	Diagnosis explained death	Avoiding BCG vaccination
P055	RAG1	NM_000448.3:exon2:c.2095C>T(p.R699W)	P	Het	AD/AR	Paternal	408	Diagnosis explained death	Avoiding BCG vaccination
P119	RAG1	NM_000448.3:exon2:c.424C>T(p.R142X)	P	Het	AD/AR	Paternal	640	Redirection of care	Avoiding BCG vaccination

P119	RAG1	NM_000448.3:exon2:c.333C>A(p.C111X)	LP	Het	AD/AR	Maternal	640	Redirection of care	Avoiding BCG vaccination
P120	RAG1	NM_000448.3:exon2:c.1186C>T(p.R396C)	P	Het	AD/AR	Maternal	773	/	Avoiding BCG vaccination
P120	RAG1	NM_000448.3:exon2:c.2240A>C(p.H747P)	LP	Het	AD/AR	Paternal	773	/	Avoiding BCG vaccination
P121	RAG1	NM_000448.3:exon2:c.2333G>A(p.R778Q)	LP	Het	AD/AR	Paternal	5111	/	Avoiding BCG vaccination
P121	RAG1	NM_000448.3:exon2:c.2104_2105insGAAA(p.K702Rfs*11)	P	Het	AD/AR	Maternal	5111	/	Avoiding BCG vaccination
P145	SAMD9	NM_017654.4:exon3:c.2944C>T(p.R982C)	P	Het	AD/AR	De novo	550	/	/
P146	SBDS	NM_016038.4:exon2:c.184A>T(p.K62X)	P	Het	AR	Maternal	1947	Pancreatin replacement therapy, G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/
P146	SBDS	NG_007277.1(NM_016038.4):c.258+2T>C	P	Het	AR	Paternal	1947	Pancreatin replacement therapy, G-CSF treatment, Monitoring occurrence of myelodysplastic syndrome or acute myeloid leukemia	/
P003	SFTPC	NM_003018.4:exon3:c.218T>C(p.I73T)	P	Het	AD/AR	De novo	210	Hydroxychloroquine	/
P004	SFTPC	NM_003018.4:exon5:c.563T>C(p.L188P)	P	Het	AD/AR	NA	22	Redirection of care	Glucocorticoid/hydroxychloroquine/azitromycin

P036	SFTPC	NM_003018.4:exon4:c.337T>C(p.Y113H)	P	Het	AD/AR	De novo	120	Hydroxychloroquine	/
P037	SFTPC	NM_003018.4:exon3:c.314A>G(p.D105G)	P	Het	AD/AR	Paternal	320	Hydroxychloroquine	/
P038	SFTPC	NM_003018.4:exon3:c.218T>C(p.I73T)	P	Het	AD/AR	De novo	210	Hydroxychloroquine	/
P085	SFTPC	NM_003018.4:exon3:c.218T>C(p.I73T)	P	Het	AD/AR	Maternal/Brother(ILD)	451	/	Glucocorticoid/hydroxychloroquine/azitromycin
P086	SFTPC	NM_003018.4:exon3:c.218T>C(p.I73T)	P	Het	AD/AR	De novo	994	Hydroxychloroquine	/
P135	SLC7A7	NM_001126106.4:exon3:c.235G>A(p.G79R)	LP	Het	AR	Maternal	2352	Low-protein diet and citrulline supplement	/
P135	SLC7A7	NG_012851.2(NM_001126106.4):c.625+1G>A	P	Het	AR	Paternal/Brother	2352	Low-protein diet and citrulline supplement	/
P022	SPINK5	NM_006846.4:exon24:c.2260A>T(p.K754X)	P	Hom	AD/AR	NA	40	/	/
P122	STAT1	NM_007315.4:exon14:c.1132A>G(p.R378G)	LP	Het	AD/AR	De novo	771	Antibiotic prophylaxis	Avoiding BCG vaccination, Monitoring multiple organ diseases and autoimmune diseases
P123	STAT1	NM_007315.4:exon12:c.1078G>T(p.V360F)	P	Het	AD/AR	De novo	1370	Antibiotic prophylaxis	Avoiding BCG vaccination, Monitoring multiple organ diseases and autoimmune diseases

P124	STAT1	NM_007315.4:exon10:c.882C>G(p.I294M)	LP	Het	AD/AR	De novo	3935	Antibiotic prophylaxis	Avoiding BCG vaccination, Monitoring multiple organ diseases and autoimmune diseases
P125	STAT1	NM_007315.4:exon10:c.854A>G(p.Q285R)	P	Het	AD/AR	De novo/Sister(Normal)	4955	Antibiotic prophylaxis	Avoiding BCG vaccination, Monitoring multiple organ diseases and autoimmune diseases
P040	STAT3	NM_139276.3:exon13:c.1144C>T(p.R382W)	P	Het	AD	De novo	274	IFN-gamma treatment	Monitoring phenotypes not appeared at present
P042	STAT3	NM_139276.3:exon13:c.1144C>T(p.R382W)	P	Het	AD	NA	293	IFN-gamma treatment	monitoring phenotypes not appeared at present
P048	STAT3	NM_139276.3:exon13:c.1144C>T(p.R382W)	P	Het	AD	De novo	450	IVIG, Antibiotic prophylaxis	Monitoring multiple organ diseases
P112	STAT3	NM_139276.3:exon5:c.454C>T(p.R152W)	P	Mosaic	AD	De novo	703	Umbilical cord blood stem cell transplantation	/
P126	STAT3	NM_139276.3:exon20:c.1826G>C(p.R609T)	LP	Het	AD	De novo/S(Normal)	559	IVIG, Antibiotic prophylaxis	Monitoring multiple organ diseases
P127	STAT3	NM_139276.3:exon15:c.1311C>A(p.H437Q)	LP	Het	AD	De novo	2400	IVIG, Antibiotic prophylaxis	Monitoring multiple organ diseases
P128	STAT3	NM_139276.3:exon20:c.1863C>G(p.F621L)	LP	Het	AD	De novo	3853	IVIG, Antibiotic prophylaxis	Monitoring multiple organ diseases
P129	STAT3	NM_139276.3:exon15:c.1311C>G(p.H437Q)	LP	Het	AD	De novo	4567	IVIG, Antibiotic prophylaxis	Monitoring multiple organ diseases

P130	STAT3	NM_139276.3:exon14:c.1261G>A(p.G421R)	P	Het	AD	De novo	5363	IFN-gamma treatment	Monitoring multiple organ diseases
P068	TMEM173	NM_198282.4:exon5:c.461A>G(p.N154S)	P	Het	AD	De novo	282	Ruxolitinib	/
P140	TMEM173	NM_198282.4:exon7:c.842G>A(p.R281Q)	P	Het	AD	De novo	2261	Tofacitinib and hydroxychloroquine	/
P131	TNFRSF13B	NM_012452.3:exon3:c.365G>A(p.R122Q)	LP	Het	AD/AR	Maternal	1299	/	/
P132	TYK2	NM_003331.5:exon4:c.209_212del(p.C70Sfs*21)	P	Hom	AR	Paternal/Maternal	1253	Umbilical cord blood stem cell transplantation	/
P057	ZAP70	NG_007727.1(NM_001079.4):c.703-1G>A	P	Het	AR	Paternal	259	Monitoring renal disease and severe autoimmune syndrome	/
P057	ZAP70	NM_001079.4:exon12:c.1523C>A(p.P508H)	LP	Het	AR	Maternal	259	Monitoring renal disease and severe autoimmune syndrome	/
P134	ZBTB24	NM_014797.3:exon2:c.649_652del(p.E217Nfs*92)	LP	Het	AR	Paternal	3678	/	/
P134	ZBTB24	NM_014797.3:exon2:c.705del(p.D236Mfs*74)	LP	Het	AR	Maternal	3678	/	/

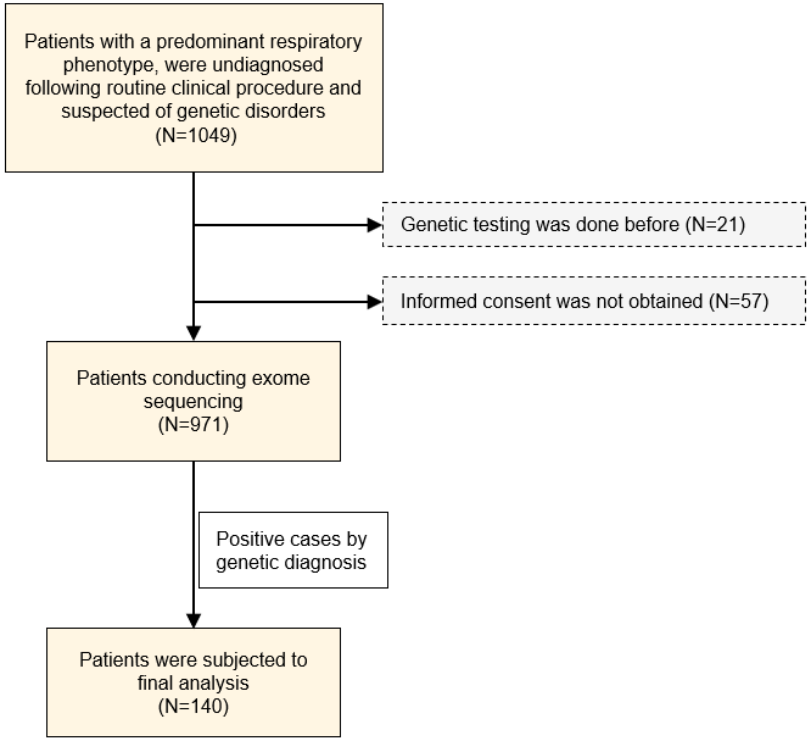

Figure S1. Collection of patients.

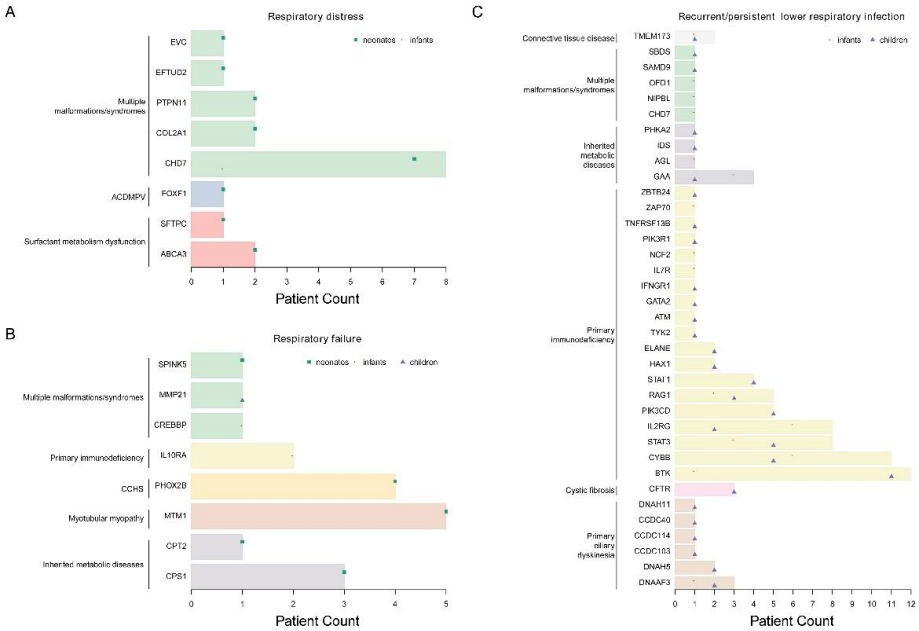

Figure S2. Causative gene distribution among respiratory distress, respiratory failure and recurrent/persistent lower respiratory infection.

(A) Causative gene distribution of patients with onset manifestation of respiratory distress; (B) Causative gene distribution of patients with onset manifestation of respiratory failure; (C) Causative gene distribution of patients with onset manifestation of recurrent/persistent respiratory infection; ACDMPV, alveolar capillary dysplasia with misalignment of pulmonary veins; CCHS, congenital central hypoventilation syndrome.