Original Article

ABCA3 gene mutations shape the clinical profiles of severe unexplained respiratory distress syndrome in late preterm and term infants

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Background: The majority of unexplained respiratory distress syndrome (URDS) cases in late preterm and term infants are caused by genetic abnormalities, with the most common of these being *ABCA3* gene mutation. At present, it is unclear to neonatologists whether URDS patients with *ABCA3* mutation have similar or more challenging clinical profiles to those without any defined genetic abnormalities. Our study aimed to answer this question by comparing the clinical characteristics of severe URDS patients with homozygous or compound heterozygous *ABCA3* mutations, a single *ABCA3* mutation, or no defined genetic abnormalities.

Methods: This retrospective cohort study involved 39 late preterm and term infants with URDS underwent a clinical exome sequencing at a tertiary neonatal intensive care unit between January 2013 and December 2019. Based on the sequencing result, the study subjects were classified into the homozygous or compound heterozygous mutations, single *ABCA3* mutation, or no defined genetic abnormalities groups. The major outcomes, including mortality, the age of symptom onset and development of severe RDS, and the radiological score, were compared between the groups.

Results: A novel splicing site (c.3862+1G>C) was identified in one twin with homozygous expression. Patients with homozygous or compound heterozygous *ABCA3* mutations exhibited symptom onset and development of severe respiratory distress syndrome (RDS) earlier than those with a single mutation or no genetic abnormalities (P<0.05). These patients also had higher mortality rates than those without genetic abnormalities (P=0.029). The total radiological scores were 51.14±4.91, 44.20±6.54, 35.91±4.42 for patients with homozygous or compound heterozygous mutations, a single mutation, and a wild-type gene, respectively, with significant differences between the groups observed by pairwise comparison (all P<0.05).

Conclusions: Late preterm or term infants with URDS due to homozygous or compound heterozygous *ABCA3* mutations exhibited more challenging clinical profiles than those without genetic abnormalities. However, whether this relationship exists between patients with a single *ABCA3* mutation and those without genetic abnormalities warrants further study.

Keywords: Late preterm infant; term infant; exome sequence; *ABCA3* gene mutation; respiratory distress syndrome (RDS)

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Introduction

Neonatal respiratory distress syndrome (RDS) is caused by the deficiency or inactivation of pulmonary surfactant, and is commonly seen in early preterm infants due to their immature lung development. However, some maternal and neonatal characteristics in late preterm and term infants such as maternal diabetes, meconium aspirated pneumonia, neonatal sepsis, and severe intrapartum asphyxia, could also contribute to RDS. Existing evidence has demonstrated that RDS in late preterm and term infants is a somewhat distinct disease entity, with risk factors and clinical profiles that differ from those in early preterm infants (1-3). In a neonatal unit, some late preterm or term infants experience RDS; however, the etiology has not been well defined after a routine workup. This unique RDS entity was referred to as unexplained respiratory distress syndrome (URDS) by numerous previous studies, as well as our study (4-7).

Given that a large body of literature has demonstrated the essential role genetic mechanism play in the pathogenesis of most URDS cases, numerous medical facilities have carried out clinical exome sequencing to identify the underlying genetic cause of URDS (8-10). Among all of the genetic factors that contribute to the RDS, the most common is *ABCA3* gene mutation, which involves the assembly of pulmonary surfactant in the lamellar body of pneumocyte II (11). Existing evidence indicated that patients with homozygous or compound heterozygous *ABCA3* gene mutations were commonly in critically ill conditions (12). A single *ABCA3* mutation was also likely to increase the risk and severity of RDS (4,13).

Unfortunately, in a considerable proportion of neonatal URDS patients, genetic testing fails to yield any abnormal findings, making these patients the "true URDS" patients. Currently, whether the *ABCA3*-mutated URDS patients have similar or more challenging clinical profiles to those without any genetic abnormalities continues to confound most neonatologists. An answer to this question would help to guide the management and predict the clinical outcomes of neonatal URDS patients. The present study aimed to address this by comparing the clinical characteristics of late preterm and term infants with severe URDS with homozygous or compound heterozygous *ABCA3* mutations, a single *ABCA3* mutation, or no defined genetic abnormalities.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-283).

Methods

Patient selection

This single-center retrospective cohort study involved infants ≥34 weeks' gestation with severe URDS who were admitted to Children's Hospital of Chongqing Medical University between January 2013 and December 2019. In this study, severe RDS was mainly defined according to the consensus of the Pediatric Acute Lung Injury Consensus Conference (14), and Montreux definition (15): (I) manifestations and chest radiograph compatible with RDS; (II) on invasive mechanical ventilation with oxygenation index ≥16, which was calculated based on the daily blood gas, or as an alternative measurement, on the subcutaneous oxygen tension (16,17).

Almost all infants with severe RDS had undergone a comprehensive workup, including serial infection markers, chest radiograph, echocardiography, and blood and sputum pathogen testing. For all patients with severe RDS who responded inadequately to interventions and had unremarkable workup findings, trio exome sequencing on samples from patients and their parents were usually recommended. All URDS patients who underwent genetic testing were enrolled in this study. Those whose parents rejected genetic testing, or who had cardiopulmonary malformations, pulmonary hypoplasia, culture-positive sepsis, or known respiratory disease-associated gene mutations (such as *SFTPA1*, *SFTPA2*, *SFTPB*, *SFTPC*, *CHPT1*, *LPCAT1*, *PCYT1B*, *NKX2*, *CFTR*, and *FOXF1*) were excluded. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Children's Hospital of the Chongqing Medical University (No. 2018-158) and was registered on clinicaltrials.gov (NCT04137783).

Exome sequencing and gene mutation detection

All infants in this study underwent trio exome sequencing after written consent had been obtained from their parents. A gene company (Chigene, Beijing) offered the sequencing as a clinical laboratory service. Sequence analysis of coding exons and flanking introns were performed as previously described (18,19). All samples were analyzed to detect frame-shift mutations, nonsense mutations, missense mutations, splicing site mutations, and in-frame indel mutations. Assessment of copy number variation

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was also performed from exome sequencing data using computational tools. A variant was strictly defined as a mutation if it had been previously described to cause disease with a presentation consistent with these patients, or resulted in an amino acid change or protein structure alteration to disrupt protein function that was predicted by both SIFT and PolyPhen for missense mutations (20,21), and MaxEntScan and dbscSNV for splicing site mutations (22). In the case of a novel mutation, phastCons and phyloP were used to determine the evolutionary conservation of the region where the mutation was located (23). The American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG-AMP) criteria were applied to interpret the mutations (24). The subjects in this study were categorized into three groups: homozygous or compound heterozygous *ABCA3* mutations, a single *ABCA3* mutation, and no defined genetic abnormalities.

Clinical profiles data

All relevant clinical data were extracted from a hospital information system. All antepartum and postpartum data were collected and included: maternal age, parity, and pregnancy-related complications; mode of birth, amniotic fluid condition, and history of asphyxia and resuscitation; postnatal age of respiratory symptom onset, modalities of respiratory support, and the daily record of blood gas and subcutaneous oxygen tension; laboratory data including complete blood count, C-reactive protein, procalcitonin, blood and sputum culture, respiratory viral detection test, and genetic testing; radiographic examination including chest X-ray and echocardiogram; medications taken during the hospital stay.

Radiological scoring

All chest X-rays were reviewed on a hospital information system by one radiologist. The most severe images were scored according to the Fleischner Society criteria (25). The chest X-ray was rated in three sections on both sides of the lung: apex to the carina, carina to the lower pulmonary vein, and lower pulmonary vein to the diaphragm. The incidence of radiological features, including ground-glass opacity, reticular pattern, air bronchogram, atelectasis, and air leak, were evaluated for each lung section. Each finding was scored as 0 = none, 1 = discrete, 2=diffuse, or 3 = strong at each section. An overall cumulative score was calculated by adding the individual section scores together, with a maximum score of 18 for each patient.

Statistical analysis

Analysis of variance (ANOVA) and the Chi-square or Fisher's exact tests were used to compare clinical characteristics and radiographic scores between different groups of patients. Tests for the differences in the age of symptom onset and the age of development of severe RDS between the groups were carried out using the log-rank test. A two-tailed P value of <0.05 was considered statistically significant.

Results

A total of 59 infants (≥34 weeks gestation) satisfied the criteria for URDS. Of these infants, 43 underwent clinical exome sequencing between 8 to 25 days after birth. Two patients with *SFTPB* mutations, one with *SFTPC* mutations, and one with cardiopulmonary malformation were excluded from the study. Finally, 39 infants were included for analysis (*Figure 1*). No significant difference in the gestational age, birth weight, sex, multiplets, or maternal complications were noted between the groups (*Table 1*).

Genetic characteristics

By looking at the variants on the three patients with homozygous *ABCA3* mutations, one novel intronic mutation (c.3862+1G>C) was identified in twins, which was predicted to affect the splicing site at exon 42. Both phastCons and phyloP computation indicated that the located region was highly evolutionarily conserved, with 0.954 and 0.852, respectively. Hazard predictions of the novel splicing site by MaxEntScan and dbscSNV were deleterious, with 6.97–>–1.31 and 0.9999 | 0.9020, respectively. Sequencing of asymptomatic parents revealed the same variant in each of them with heterozygous expression. This was classified as pathologic according to the ACMG-AMP criteria (24). One nonsense mutation (R1561X), previously reported by Kröner *et al.*, was identified in the third patient. Their study revealed the pathogenic characteristics of this mutation based on clinical and histological investigations (26).

For patients with compound heterozygous mutations and a single mutation, 12 missense mutations, 1 intronic mutation (c.1897-1G>C), and 1 synonymous mutation (S1372=) were identified. Interestingly, patient no. 4 and

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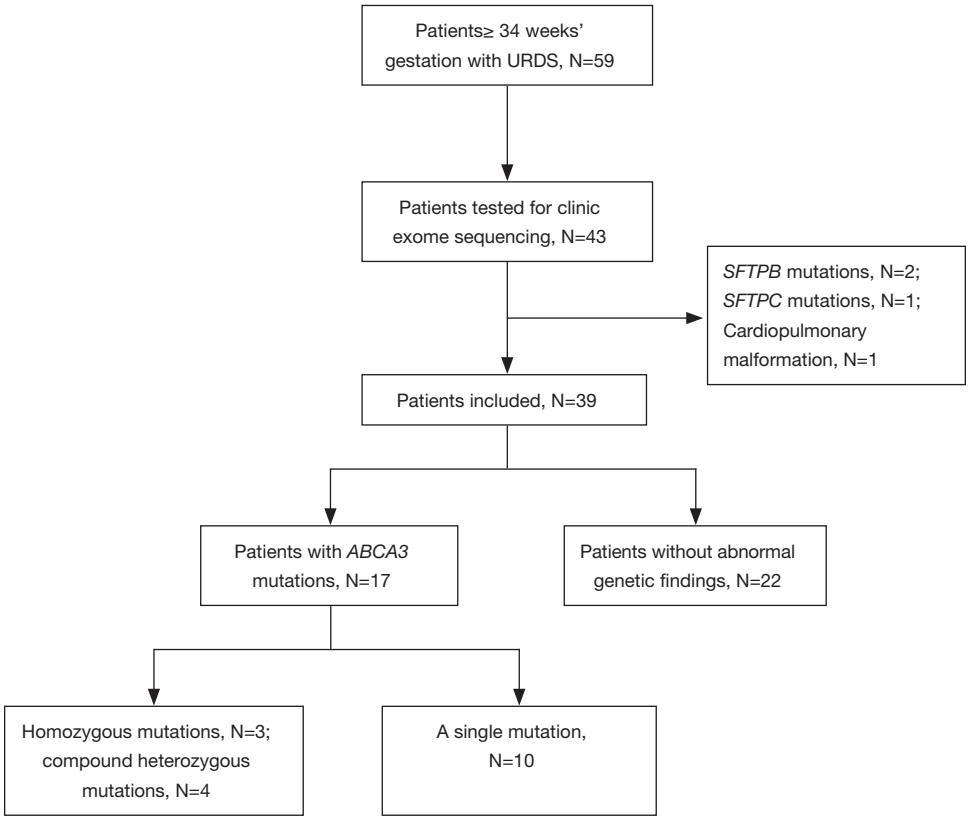

Figure 1 Flow chart of patient inclusion in the study.

Table 1 Patient characteristics

Characteristics	Homozygous or compound heterozygous mutations (N=7)	Single mutation (N=10)	No mutation (N=22)	P
Gestational age (weeks)	36.85±2.12	36.80±1.81	37.27±2.27	0.809
Birthweight (grams)	2,996.57±351.92	2,934.10±517.68	3,043.59±358.03	0.775
Female/male	3/4	5/5	10/12	0.954
Cesarean section, n (%)	5 (71.43)	5 (50.00)	14 (63.64)	0.640
Resuscitation, n (%)	4 (57.14)	4 (40.00)	6 (27.27)	0.340
Fetal distress, n (%)	2 (28.57)	3 (30.00)	4 (18.18)	0.710
MSAF, n (%)	2 (28.57)	3 (30.00)	3 (13.64)	0.480
Maternal history, n (%)				
PROM	2 (28.57)	3 (30.00)	5 (22.73)	0.892
GDM	2 (28.57)	2 (20.00)	7 (31.82)	0.789
Preeclampsia	1 (14.29)	1 (10.00)	3 (13.64)	0.952

MSAF, meconium-stained amniotic fluid; PROM, premature rupture of membrane; GDM, gestational diabetes mellitus.

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Table 2 Phenotypic groups of patients with *ABCA3* mutations

ID	Mutation type	Mutation	Type of mutation	Female/ male	GA (weeks)	Birthweight (grams)	Treatment	Outcome
1†	Homozygous	c.3862+1G>C/ c.3862+1G>C	Splicing site/ splicing site	Male	37	3,000	iNO, PS, ster	Died, 45 d
2†	Homozygous	c.3862+1G>C/ c.3862+1G>C	Splicing site/ splicing site	Male	37	2,860	iNO, PS, ster	Died, 45 d
3	Homozygous	R1561X/R1561X	Nonsense/ nonsense	Female	35	2,930	iNO, PS, azt	Died, 18 d
4	Compound heterozygous	P193S/G1412R	Missense/ missense	Male	36	2,870	iNO, PS	Died, 24 d
5	Compound heterozygous	P193S/G1412R	Missense/ missense	Male	34	2,455	iNO, PS, ster, azt	Discharged, 30 d
6	Compound heterozygous	E1266Q/A1223T	Missense/ missense	Female	39	3,300	iNO, PS, ster, azt	Discharged, 42 d
7	Compound heterozygous	c.1897-1G>C/ R280H	Splicing site/ missense	Female	40	3,561	iNO, PS	Died, 20 d
8	Single mutation	P248S/–	Missense/–	Male	38	3,315	iNO, PS	Discharged, 29 d
9	Single mutation	R395W/–	Missense/–	Male	38	3,261	iNO, PS, azt	Discharged, 34 d
10	Single mutation	P32S/–	Missense/–	Female	35	2,405	iNO, PS, ster	Died, 28 d
11	Single mutation	S1372=/–	Synonymous/–	Male	39	3,580	iNO, PS, ster	Discharged,24 d
12	Single mutation	L39V/–	Missense/–	Female	36	2,510	iNO, PS	Discharged,28 d
13	Single mutation	V93I/–	Missense/–	Female	38	3,275	iNO, PS, ster, azt	Died, 42 d
14	Single mutation	R605Q/–	Missense/–	Female	34	2,235	iNO, PS	Discharged, 20 d
15	Single mutation	G1221S/–	Missense/–	Male	36	2,540	iNO, PS	Discharged, 29 d
16	Single mutation	E292V/–	Missense/–	Female	35	2,630	iNO, PS	Died, 115 d
17	Single mutation	E292V/–	Missense/–	Male	39	3,590	iNO, PS, ster	Discharged, 25 d

†, twin. GA, gestation age (complete week); iNO, inhaled nitric oxide; PS, pulmonary surfactant; ster, systemic steroids; azt, azithromycin.

no. 5 shared a genotype (P193S/G1412R) but experienced a different clinical course; patient no. 4 died on his 24th day, whereas patient no. 5 recovered and was discharged 20 days after birth. Patient no. 16 and no. 17 also had the same genotype (E292V/–); however, they exhibited different phenotypes (*Table 2*).

Clinical course

Of the seven patients with homozygous or compound heterozygous *ABCA3* mutations, three presented with respiratory symptoms immediately after birth, while the remaining four patients presented with respiratory symptoms between 1 and 5 hours after birth, which was much earlier than those with a single *ABCA3* mutation and those without genetic abnormalities (χ^2=13.500, P<0.001; χ^2=30.400, P<0.001). Meanwhile, all patients with homozygous or compound heterozygous mutations developed severe RDS (with an oxygenation index of 16 as an indicator) on the first day of life, which was also earlier than those with a single mutation, or a wild-type gene (χ^2=6.067, P=0.014; χ^2=25.150, P<0.001). However, no differences were noted between patients with a single *ABCA3* mutation and those without genetic abnormalities in terms of the time of symptom onset or progression to severe RDS (χ^2=1.407, P=0.236; χ^2=0.304, P=0.581). All patients with URDS were given surfactant administration and nitric oxide inhalation, and some were also administered intravenous steroids

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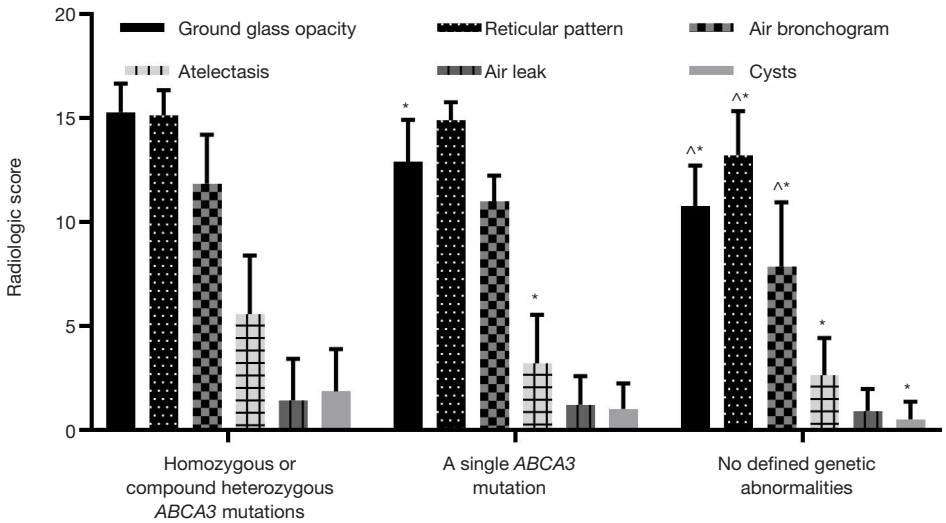

Figure 2 Comparison of chest X-ray radiological scores. A chest X-ray was rated in three sections on both sides of the lung. Features including ground-glass opacity, reticular pattern, air bronchogram, atelectasis, and air leak were evaluated for each lung section. Each finding was scored as 0 = none, 1 = discrete, 2 = diffuse, or 3 = strong at each section, with a maximum score of 18 for each patient. *, significant difference when compared to patients with homozygous or compound heterozygous *ABCA3* mutations (all P<0.05); ^, significant difference between patients with a single *ABCA3* mutation and those without genetic abnormalities (all P<0.05).

and azithromycin. The subjects responded differently to these interventions (*Table 2*). All but two patients with homozygous or compound heterozygous mutations died at an early stage of life, and the mortality rate was marginally higher than that of infants with a single mutation, although the difference was not statistically significant (χ^2=2.837, P=0.092). However, this mortality rate was markedly higher than that of infants without genetic abnormalities, five of whom died (χ^2=5.575, P=0.018).

Radiological score

Patients with homozygous or compound heterozygous *ABCA3* mutations had a higher radiological score than those with a single mutation (51.14±4.91 *vs.* 44.20±6.54, P=0.025). Meanwhile, patients with a single mutation had a higher radiological score than those without genetic abnormalities (44.20±6.54 *vs.* 35.95±4.31, P<0.001). The primary abnormalities observed in the chest X-rays in each group were ground-glass opacity, reticular pattern, and air bronchogram. Furthermore, except for air leaks, patients with homozygous or compound heterozygous mutations had significantly higher individual subset scores than those without genetic abnormalities, and their scores for ground-glass opacity and atelectasis were also higher than that of patients with a single mutation. Patients with a single mutation had higher scores for ground-glass opacity, reticular pattern, and air bronchogram than those with wild-type *ABCA3* gene (*Figure 2*).

Discussion

Numerous studies have suggested that the *ABCA3* mutation is the most common etiology of genetic RDS. A study by Brasch *et al.* involving 14 term infants with severe URDS (from six consanguineous families and two nonconsanguineous families) reported that 10 (71.43%) of them exhibited homozygous or compound heterozygous *ABCA3* mutations (5). Similarly, Shulenin *et al.* reported that 16 of 21 (76.19%) infants with severe URDS from 14 families had homozygous *ABCA3* gene mutations (27). Our study detected homozygous or compound heterozygous *ABCA3* mutations in 4 out of 43 (9.30%) patients with severe URDS; a lower detection rate than the aforementioned studies. This discrepancy may be explained by the fact that a higher proportion of the subjects in these previous studies were twins, some with consanguineous histories.

To date, about 200 *ABCA3* mutations have been identified, with the majority of them resulting in varying

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degrees of surfactant function impairment (28). To our knowledge, the novel splicing site (c.3862+1G>C) in our study has not been reported in any previous literature and is not documented on dbSNP or the China National Genebank Database (http://db.cngb.org). Based on the ACMG-AMP interpretation, evolutionary conservation of the affected region, and patients' clinical phenotype, this novel splicing site was considered the etiology of RDS in twins. Most *ABCA3* mutations in this study cohort were missense mutations, which could be classified into three groups based on the pathway through which they affect surfactant homeostasis. Essentially, type 1 and type 2 refer to the abnormal intracellular location and decreased adenosine triphosphate hydrolysis, respectively, while type 3 combines both type 1 and type 2 (9,28). Therefore, the diversity of clinical profiles might be attributable to the variable mutation group. Interestingly, both patients no. 4 and no. 5 had an identical mutation (P193S/G1412R) but showed different clinical characteristics. Hallik *et al.* reported a similar case in which two siblings expressed an identical compound heterozygous mutation but developed extremely different clinical courses of respiratory disease (29). It is thought that epigenetics, some accompanying neonatal disorders, and environmental factors play a part in the pathogenesis and prognosis of RDS to some extent.

Homozygous or compound heterozygous mutations in the *ABCA3* gene have been confirmed to disrupt surfactant metabolism and have been associated with severe RDS (5,27,30). Our study found that five of the seven patients with homozygous or compound heterozygous *ABCA3* mutations died at an early stage of life, which further confirmed the lethality of such mutations (5,27). Concerning clinical profiles, these patients had symptom onset and developed severe RDS much earlier than those with a single mutation or those without defined genetic abnormalities. Their radiographs were also markedly more severe. Ultrastructural analysis of neonatal lung specimens with *ABCA3* homozygous or compound heterozygous mutations revealed a small lamellar body with densely packed phospholipid membranes and eccentrically placed, dense inclusion bodies (27), which is strongly indicative of immature lamellar bodies, and is predictive of surfactant impairment. Thus, the homozygous or compound heterozygous *ABCA3* mutation could be strongly predictive of a challenging clinical course.

Pathological *ABCA3* mutations are inherited in an autosomal recessive manner. However, numerous studies have noted that a single *ABCA3* mutation could also worsen the severity of lung disease (4,13,31). Our study did not sufficiently distinguish patients with a single *ABCA3* mutation from those without genetic abnormalities based on the clinical course. However, in this study, radiographic findings seemed adequate to discriminate between them. Some previous studies reported that although the *ABCA3* protein could be detected in patients with a single *ABCA3* mutation, the presence of type II pneumocytes hyperplasia, inflammatory cell infiltration, and lamellar bodies with smaller vesicles still suggested a deleterious effect of a single mutation on surfactant metabolism (31,32). However, the underlying mechanism of this has not been well defined. Some gene mutations might be overlooked in general clinical sequencing (33); a single *ABCA3* mutation might couple with other gene mutations on the opposite allele to affect surfactant homeostasis (34).

The limitations of our study are primarily attributable to the characteristics of a retrospective study. We did not enroll all patients with URDS in our clinical setting. It is uncertain to what extent the genetic and clinical data of the missed 16 patients would have altered the current results. Also, we did not perform a long-term follow-up study. Some literature has revealed that a single *ABCA3* mutation is correlated with a higher risk of interstitial lung disease at a late stage (31,33). Thus, a long-term follow-up study might identify more unique characteristics of patients with a single *ABCA3* mutation compared to those without genetic abnormalities. Meanwhile, our study only focused on the *ABCA3* gene, and did not address all respiratory disease-associated genetic abnormalities. However, most respiratory-associated genes have not been associated with severe RDS, and in a clinical setting, the *ABCA3* gene mutation contributes to the majority of severe genetic RDS cases.

In conclusion, our study suggests that in a neonatal clinical setting of caring for severe URDS patients, identification of homozygous or compound heterozygous *ABCA3* gene mutations commonly predicted more challenging clinical profiles and poor outcomes compared to patients without genetic abnormalities. Early aggressive treatment or innovative interventions should be applied to treat these patients. However, whether the same relationship exists between patients with a single *ABCA3* mutation and those with no defined genetic abnormalities warrants further study.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-20-283

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-283). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (No. 2018-158) and individual consent for this retrospective analysis was waived. All infants in this study underwent trio exome sequencing after written consent had been obtained from their parents.

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