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Original Article

The relationship between single nucleotide polymorphisms of pulmonary surfactant protein B gene and respiratory distress syndrome in premature infants

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Abstract: Objective: To investigate the relationship between single nucleotide polymorphisms of pulmonary surfactant protein B gene and respiratory distress syndrome in premature infants. Methods: Ninety-two preterm infants with neonatal respiratory distress syndrome (NRDS) were selected as the NRDS group. Another 92 cases without respiratory distress syndrome were selected as the non-NRDS group. The single nucleotide polymorphisms of SPB-18 A/C locus and SPB-1580 C/T locus were detected in the groups, and the genotype distributions of the SPB-18 A/C locus and the SPB-1580 C/T locus were compared between the two groups. The relative risk of both sites and the onset of respiratory distress syndrome were analyzed using an χ^2 test. Results: In the SPB-18 A/C locus genotype test, AA, CC, and AC in the NRDS group were 20.65%, 35.87%, and 43.47%, respectively, which were not significantly different from 19.57%, 32.61%, and 47.83% in the non-NRDS group (P = 0.854, P = 0.641 and P = 0.554). In the SPB-1580 C/T locus genotype test, CC in the NRDS group accounted for 66.30%, which was higher than the corresponding value in the non-NRDS group (40.22%, P = 0.000). T in the NRDS group accounted for 5.43%, and CT accounted for 28.26%, which were lower than the corresponding values in the non-NRDS group (14.13%, P = 0.047; 45.65%, P = 0.015). SPB-18 A/C was not associated with NRDS in preterm infants (P = 0.833), whereas the SPB-1580 C/T site was associated with respiratory distress syndrome in preterm infants (P = 0.000). Respiratory distress syndrome in preterm delivery of C allele with SPB-1580 locus was 2.410 times higher than it was in preterm infants with a confidence interval of (1.504, 3.862). Conclusion: The SPB-1580 A/C polymorphism is associated with respiratory distress syndrome in preterm infants. Carrying the C allele of SPB-1580 may be a risk factor for respiratory distress syndrome in preterm infants.

Keywords: Premature infants, neonatal respiratory distress syndrome, SPB, single nucleotide polymorphisms, relationship

Introduction

Respiratory distress syndrome is a common, clinical critical illness, and includes acute respiratory distress syndrome and neonatal respiratory distress syndrome (NRDS). NRDS, is also known as neonatal hyaline membrane disease, and is also a common newborn pediatric disease that has a higher incidence in preterm infants. According to a previous study, the younger the gestational age of premature infants, the higher the incidence of NRDS, which is about 52% if the gestational age is higher than 30 weeks, and the prevalence of the disease in preterm infants below 26 weeks is as high as 90%. NRDS can affect the growth and prognosis of premature infants [1]. Studies have found that the incidence of NRDS is closely related to the lack of alveolar surfactant [2].

Premature infants have a shorter gestational age, congenital hypoplasia, immature lung development, and lack pulmonary surfactant (PS), which in turn causes alveolar damage and dyspnea. PS is a phospholipid-protein mixture, which has plays a great role in maintaining the function and metabolism of pulmonary surfactant, reducing the surface tension of the alveoli

and maintaining the lung function of the newborn. It is mainly composed of phospholipid and pulmonary surfactant protein (SP). Although SP is low in content, it is a carrier for PS to exert physiological functions [3, 4]. SP-B is an important class of pulmonary surfactant proteins that promote the formation, distribution and adsorption of phospholipid films.

Reports suggest that heredity is one of the factors that causes NRDS [5-7]. Neonatal SP-B gene polymorphisms are associated with NRDS. The SP-B gene is about 9,500 bp in length and contains 11 exons. The SPB-18 gene is located upstream of the transcriptional promoter and is a transport initiation signal. Its polymorphism is related to the level of SPB secretion in lung tissue, while the SPB1580 C/T polymorphism can affect the processing of SPB by changing the N-terminal glycosylation site. The process leads to a change in the function of the SPB protein [8, 9]. A study showed that the distribution frequencies of the SP-B T131 gene in the NRDS group and non-NRDS group was different [10]. The polymorphism of the C-allele in the SP-B T131 locus is related to NRDS.

Based on those studies, this research selected NRDS preterm infants and non-NRDS preterm infants to conduct a controlled study to further explore the relationship between SPB and NRDS in preterm infants.

Materials and methods

General information

Ninety-two NRDS preterm infants admitted to the Affiliated Hospital of Hebei University from March 2017 to March 2018 were selected as the NRDS group. The inclusion criteria consisted of (A) premature infants who met the *European diagnostic criteria for NRDS (2010 Edition)* [11]; (B) premature infants who showed progressive and increasing dyspnea symptoms within 12 hours after birth, accompanied by hypoxemia; (C) premature infants with chest X-rays that showed a drusen-like change in the lungs, air bronchogram, and a “white lung” manifestation. The exclusion criteria consisted of (A) premature infants whose mother received PS replacement therapy or had diabetes in pregnancy; (B) premature infants with fetal distress or severe asphyxia during production; (C) premature infants who received an intrauterine infection during childbirth, or with a clear history of infection during pregnancy; (D) premature infants with congenital malformations and inherited metabolic diseases; (E) premature infants who have recently received fresh whole blood, blood products or blood components.

A total of 92 cases of preterm infants without NRDS were selected as the non-NRDS group. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Hebei University, and all the families of the premature infants agreed to participate in the study.

Sample collection

The DNA kit used in the study was provided by Northeast Pharmaceutical Co., Ltd., and 2 mL of venous blood was collected from the subjects, which was anticoagulated with an EDTA anticoagulation tube and stored in a refrigerator at -80°C for later use.

DNA extraction

DNA extraction was performed using the Tanami Blood DNA Kit, and the procedure was carried out strictly in accordance with the instructions. The concentration of DNA was measured using a Thermo instrument. DNA concentration > 25 ng/μL suggested a high purity of the prepared DNA, which was applicable in subsequent experiments.

Polymerase chain reaction (PCR) amplification

The primer sequences were designed and synthesized by Beijing Anmeisheng Medical Technology Co., Ltd., as shown in **Table 1**. Next, 0.5 μL of genomic DNA (content 25 ng), 1.0 μL of 10× PCR buffer (pH 8.3), 0.2 μL of replication material dNTPs, and 0.2 μL Taq DNA polymerase (content 1U), 0.3 μL of upstream and downstream primers were collected, and double distilled water was added to form a solution of 10.0 μL. A PCR reaction system was created, and a PCR experiment was performed. The steps were completed in strict accordance with the instructions of TaKaRa PCR Amplification Kit.

The specific reaction parameters were as follows: for SPB-18 A/C detection: (A) pre-denaturation at 95°C for 5 minutes, then denaturation at 95°C for 45 seconds, annealing at 64.5°C for 45 seconds (down 0.5°C per time), 72°C for

Table 1. Primer sequence for detection site

Detection object	Primer sequence	Product length
SPB-18 A/C locus	Forward: F5'-GTCCAGCTATAAGGGGCCGTG-3'	168 bp
	Reverse: R5'-GTGAGTGGTGGAGCTGCCTA-3'	
SPB-1580 C/T locus	Forward: F5'-CTCGAATTCCGTGAACTCCAGCACCAGGACCC-3'	270 bp
	Reverse: R5'-GTGAGCTTGCAGCCCTCTCA-3'	

primers extension for 60 s (5 cycles); (B) denaturation at a temperature of 95°C for 45 seconds, annealing at 58.5°C for 45 seconds (down 0.5°C per time), then primer extension at a temperature of 72°C for 60 seconds. The B step was carried out for 30 cycles, and then the primer was extended for 60 s at 72°C, and the reaction was completed.

For SPB-1580 C/T detection: (A) pre-denaturation at 95°C for 5 minutes, then denaturation at 95°C for 45 seconds, annealing at 65.5°C for 45 seconds (down 0.5°C each time), primer extension at 72°C for 60 s (5 cycles). (B) denaturation at a temperature of 95°C for 45 seconds, annealing at 59.5°C for 45 seconds (down 0.5°C each time), then primer extension at 72°C for 60 seconds. The B step was carried out for 30 cycles, and then the primer was extended for 60 s at 72°C, and the reaction was completed.

Restriction enzyme digestion of each product

The 2 μL of 10× Buffer, 1.0 μL endonuclease (ApaII for -18 A/C, ApaI for 1580 C/T), 4.0 μL of PCR product were placed in a 0.5 mL EP tube, and 0.5 mL of double distilled water was added to create an enzyme reaction system. After shaking the solution well, it was digested at 37°C for 60 minutes and then subjected to a water bath at 65°C for 30 minutes to obtain a digested product, and the above product 15.0 μL with 3.0 μL of the loading buffer was separately added for polyacrylamide condensation. For the gel electrophoresis, 120 V, 1.5-2.5 h, silver nitrate staining was employed after electrophoresis. The relative molecular mass of the reference DNA was determined according to the electrophoresis band, and the gene product obtained by SPB-18 A/C site was 168 bp in length. The cut product fragment included 168 bp, 149 bp, and 19 bp. Among them, the CC genotype consisted of 168 bp, the AA genotype consisted of 149 bp and 19 bp, and the AC genotype consisted of 168 bp, 149 bp and 19 bp. The gene product obtained by the SPB-1580 C/T site was 270 bp in length, and the digested products included fragments: 184 bp, 164 bp, 80 bp and 20 bp. Among them, the CC genotype consisted of 20 bp, 80 bp and 164 bp, the TT genotype consisted of 80 bp and 184 bp, and the CT genotype consisted of 184 bp, 164 bp, 80 bp and 20 bp [12].

Outcome measures

Main outcome measures: (A) The genotype and length of SPB-18 A/C PCR amplification products; (B) A comparison of the distribution of alleles in premature infants between the two groups. Secondary outcome measures: analysis of the relative risk of SPB genotypes and preterm infants with respiratory distress syndrome.

Statistical analysis

All statistical data were processed using SPSS software, version 19.0. Measurement data with a normal distribution were described as the mean ± standard deviation ($\bar{x}$ ± sd) and processed by an independent samples t test. The count data was expressed by percentage and compared by χ^2 test. The allele frequencies were compared using a four-fold table or R×C list and χ^2 test. The relative risk was expressed as an odds ratio (OR) and 95% confidence interval (CI). $P < 0.05$ indicated statistically significant difference.

Results

General information

There were no significant differences in gender, maternal age, gestational age, birth weight, or maternal glucocorticoid ratio in the preterm infants between the two groups (all $P > 0.05$, **Table 2**).

Comparison of SPB genotypes

The results of SPB-18 A/C locus genotype detection in the NRDS group showed that AA

Table 2. Comparison of general data ($\bar{x}$ ± sd)

Group	Case	Gender		Mother age (years)	Gestational age (week)	Birth weight (g)	Mother's prenatal use of glucocorticoids (Case)
		Male	Female				
NRDS	92	52	40	28.12 ± 4.91	32.24 ± 3.15	1,217.52 ± 257.85	43
Non-NRDS	92	47	45	28.23 ± 5.32	32.09 ± 3.32	1,183.76 ± 262.26	35
t/χ^2		0.547		0.106	0.314	0.880	0.551
P		0.460		0.915	0.754	0.380	0.458

Note: NRDS: neonatal respiratory distress syndrome.

Table 3. Comparison of SPB genotypes (n, %)

Group	Case	SPB-18 A/C site			SPB-1580 C/T site		
		AA	CC	AC	CC	TT	CT
NRDS	92	19 (20.65)	33 (35.87)	40 (43.48)	61 (66.30)	5 (5.43)	26 (28.26)
Non-NRDS	92	18 (19.57)	30 (32.61)	44 (47.83)	37 (40.22)	13 (14.13)	42 (45.65)
χ^2		0.034	0.217	0.351	12.575	3.941	5.971
P		0.854	0.641	0.554	0.000	0.047	0.015

Note: NRDS: neonatal respiratory distress syndrome.

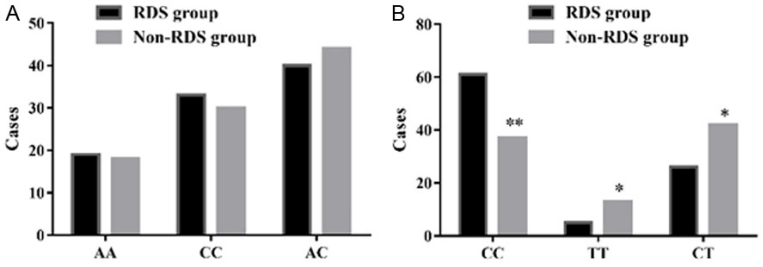

Figure 1. Comparison of results of SPB genotype detection. A: Indicated SPB-18 A/C spot; B: Indicated SPB-1580 C/T spot; compared with the NRDS group, $^{*}P < 0.05$, $^{**}P < 0.01$.

accounted for 20.65%, CC accounted for 35.87%, AC accounted for 43.48%, and in the non-NRDS group, they accounted for 19.57%, and 32.61%, and 47.83%, respectively (**Table 3** and **Figure 1**). There was no statistically significant difference between the two groups (all P > 0.05). In the NRDS group, SPB-1580 C/T locus genotype detection, CC accounted for 66.30%, higher than the level in the non-NRDS group (40.22%); TT accounted for 5.43%, CT accounted for 28.26%, lower than those in the non-NRDS group (14.13%, 45.65%); the differences were statistically significant (all P < 0.05).

Comparison of alleles

There was no significant difference in the distribution of A and C alleles between the SPB-18 A/C sites in the preterm infants between the two groups (P = 0.833, **Table 4**). The distributions of the T and C alleles in the SPB-1580 C/T loci were significantly different between the two groups. The frequency of the C allele in the NRDS group was higher than the frequency in the non-NRDS group (P = 0.000).

Comparison of SPB gene single nucleotide polymorphism frequency and risk relationship with NRDS

SPB-18 A/C was not associated with respiratory distress syndrome in preterm infants (P = 0.833, **Table 5**). The SPB-1580 C/T locus was associated with respiratory distress syndrome in preterm infants (P = 0.000), and the relative risk (OR) of respiratory distress syndrome in preterm infants carrying the C-allele of the SPB-1580 C/T locus was 2.410 times as high as it was in the non-carrying premature infants, with a CI (1.504, 3.862).

Discussion

The previous studies have manifested that mutations in the SP-B gene can lead to a decrease in the synthesis and secretion of PS [13, 14]. The SP-B gene single nucleotide polymorphism is closely related to SP-B content [15]. Therefore, the SP-B gene single nucleotide polymorphism may have a relationship with NRDS in preterm infants.

Table 4. Comparison of alleles in preterm infants (n, %)

Group	Case	SPB-18 A/C site		SPB-1580 C/T site	
		A	C	C	T
NRDS	184	78 (42.39)	106 (57.61)	148 (80.43)	36 (19.57)
Non-NRDS	184	80 (43.48)	104 (56.52)	116 (63.04)	68 (36.96)
χ^2		0.044		13.725	
P		0.833		0.000	

Note: NRDS: neonatal respiratory distress syndrome.

Table 5. The relationship between a single nucleotide polymorphism of the SPB gene and respiratory distress syndrome in premature infants

		NRDS group	Non-NRDS group	OR	95% CI	P
SPB-18 A/C	A	0.424	0.435	0.957	(0.633, 1.446)	0.833
	C	0.576	0.565			
SPB-1580 C/T	T	0.196	0.370	2.410	(1.504, 3.862)	0.000
	C	0.804	0.630			

Note: NRDS: neonatal respiratory distress syndrome; OR: odds ratio; CI: confidence interval.

The SPB-18 A/C site is adjacent to the transcription initiation site of the SP-B promoter, and the SP-B promoter DNA sequence is an important factor affecting the expression of the SP-B gene [16, 17]. The SPB-1580 C/T site is located on the exon of the SP-B gene, which has the functions of encoding threonine at 131 and promoting aspartate glycosylation, which may affect the synthesis and secretion of SP-B [18, 19]. Therefore, SPB-18 A/C and SPB-1580 C/T may affect the expression level of SP-B, which in turn impacts PS substances.

In this study, there was no significant difference in the AA genotype, the CC genotype and the AC genotype between the SPD-18 A/C locus in preterm infants with NRDS and non-NRDS preterm infants. The proportion of CC genotypes in SPB-1580 C/T loci in NRDS preterm infants was higher than it was in non-NRDS preterm infants, indicating that there were more CC genotypes in the SPB-1580 C/T locus in NRDS preterm infants. Previous studies have demonstrated that the SP-B gene polymorphism is associated with the incidence of NRDS, lung dysplasia, and lung injury in children. The study also showed that there was no significant difference in the frequency of AA, AC, and CC genotypes in the NRDS group SPB-18 A/C gene, which is consistent with the results of this study [20].

However, a study on neonatal NRDS syndrome in Inner Mongolia found that the SPB-1580 C/T locus was not significant associated with Mongolian NRDS in Inner Mongolia, but among Han, German Caucasians, and American Caucasians, the SPB-1580 C/T locus gene distribution was statistical significant between NRDS and non-NRDS [21]. A study on idiopathic interstitial lung disease in children in southern China found that there is no correlation between the gene polymorphism at the SP-B exon 4th position of the neurite and the susceptibility to idiopathic interstitial lung disease in children [22]. The results of this study showed that the gene distribution of the SPB-1580 C/T locus is similar to the results documented in the above study.

Further analysis revealed that the SPB-1580 C/T locus was associated with respiratory distress syndrome in preterm infants. The C-allele in the NRDS preterm infants was 2.410 times as high as in the non-NRDS preterm infants, with a CI (1.504, 3.862). This indicates that the SPB-1580 C/T polymorphism is an important factor affecting respiratory distress syndrome in premature infants. Premature infants carrying the SPB-1580 C/T locus C allele are more likely to develop respiratory distress syndrome. It suggests that SPB-1580 C/T is a susceptibility gene for NRDS. However, some studies have suggested that SPB-1580 C/T has no association with Mongolian neonatal NRDS, which is inconsistent with the conclusion of this study. The reason for the variant findings in the literature may be related to the racial differences and regional distribution of RDS disease [20].

In conclusion, the SPB-1580 C/T polymorphism is associated with respiratory distress syndrome in preterm infants, and preterm infants carrying the SPB-158 C/T locus C allele are more likely to develop respiratory distress syndrome. However, due to our small sample size, there are weaknesses in this study, so the its conclusions may be biased. It is necessary to

expand the sample size for further confirmation.

Disclosure of conflict of interest

None.

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