Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Evaluation value and mechanism of ADRB2 and FCER1B gene polymorphisms in preterm infants with congenital respiratory diseases

Jiangyue Liu, Qingwen Zhu, Hongru Jiang, Lingli Zhang, Xian Cao*

Department of Medical Genetics and Prenatal Diagnosis, Maternal and Child Health Hospital Affiliated to Nantong University, Nantong, Jiangsu, 226018, China

ARTICLE INFO

Original paper

Article history:
Received: March 19, 2023
Accepted: October 18, 2023
Published: December 10, 2023

Keywords:

Recombinant adrenergic receptor beta 2, Fc epsilon receptor Iβ, preterm infants, congenital respiratory diseases, genetic polymorphism

ABSTRACT

In this study, we observed the value of ADRB2 and FCER1B gene polymorphisms in evaluating congenital respiratory diseases in preterm infants (PTIs), analyzed their effects on airway smooth muscle cells (ASMCs), and preliminarily discussed the underlying mechanism. First, we placed 64 healthy PTIs (control group) and 45 PTIs with congenital respiratory diseases (research group) born at our hospital from April 2021 to June 2023 were selected as the research subjects. Through testing, we found that the carriers of AA genotype of the polymorphic marker rs1042713 of the ADRB2 gene and that of the rs569108 locus of the FCER1B gene were less in the research group compared with the control group (P<0.05). Preterm infants carrying the GG genotype had a 2.887-fold (P<0.05) increased risk of developing congenital respiratory disease under the recessive model at the rs1042713 locus of the ADRB2 gene. Under the dominant model, preterm infants who did not carry the AA genotype had a 3.070-fold (P<0.05) increased risk of developing congenital respiratory disease. Subsequently, the constructed abnormal expression vectors of ADRB2 and FCER1B were transfected into ASMCs to examine changes in cell activity and pyroptosis. We found that up-regulating ADRB2 and FCERIB expression promoted ASMC proliferation and inflammatory reactions, inhibited apoptosis, and accelerated pyroptosis (P<0.05); silencing their expression, however, led to the opposite effect. In conclusion, the ADRB2 and FCERIB gene polymorphisms are strongly correlated with congenital respiratory diseases, which can provide a reference for clinical evaluation of congenital respiratory diseases in PTIs.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.13.9

Introduction

Preterm infants (PTIs) refer to infants with a gestational age above 28 weeks but less than 37 weeks. The smaller the gestational age and lighter the weight, the more likely it is to develop other morbidities and the worse the prognosis, which is an important cause of neonatal death (1). According to statistics, the global premature birth rate is about 5-18%, with an average of 1 in 10 births (2). Congenital disorders are prevalent due to the prevalence of organ dysplasia in PTIs (3). Among them, congenital respiratory diseases, including congenital vascular malformation compressing the airway, laryngotracheobronchomalacia, asthma, and mediastinal tumors, are very common complications in PTIs (4). Despite markedly reduced mortality of PTIs with the development of medical level, how to avoid congenital respiratory diseases in PTIs is still a research hotspot and difficulty in clinical preventive medicine (5).

In recent years, a growing body of research has suggested a close relationship between the occurrence of congenital respiratory diseases in PTIs and heredity (6, 7). Therefore, the risk assessment of congenital diseases through genetic screening has gradually attracted clinical attention. Recently, a study has shown that the four-locus model consisting of IL-13 gene R110Q (IL-13 R110Q), IL-4 gene-590C>T, recombinant adrenergic receptor beta 2 R16G (ADRB2 R16G), and Fc epsilon receptor Iβ E237G (FCER1B E237G) is the best predictor of respiratory disease susceptibility genes in children (8). Among them, ADRB2 and FCER1B have been confirmed to have a close relationship with changes in respiratory function, and are considered as new clinical markers for future risk assessment of neonatal congenital diseases (9, 10). Hence, we speculate that ADRB2 and FCER1B gene polymorphisms may have the same potential early evaluation function for congenital respiratory diseases in PTIs, but no studies have been conducted to support our view.

Accordingly, in this study, we will analyze the evaluation value of ADRB2 and FCER1B gene polymorphisms for congenital respiratory diseases of PTIs, and preliminarily verify their mechanism of action through in vitro experiments, so as to provide reference and guidance for future clinical prevention and treatment of congenital respiratory diseases in PTIs.

Materials and Methods

Study subjects

The research subjects of this retrospective analysis were 64 healthy PTIs (control group) and 45 PTIs with congenital respiratory diseases (research group) born at our hospital between April 2021 and June 2023. This study was conducted strictly abiding by the *Declaration of Helsinki*, after obtaining the informed consent of all the

* Corresponding author. Email: cxlzc520@163.com

Table 1. Sequence of primers.

	F (3'-5')	R (3'-5')
ADRB2	TGATGAGGCTCAGGGT	GGAGTCATATCCACCAC
FCER1B	TCAGAGTTTTGACGATGATGATGATT	CAGAGGATGTTTATAGAGATTAA

babies' immediate family members.

Inclusion and exclusion criteria

Control group: Neonates with a gestational age of 28-37 weeks and no congenital diseases confirmed by examination after birth were included; those with organ dysfunction or disorders, or children whose parents had any genetic diseases were excluded. Research group: Infants with congenital respiratory diseases detected after birth were included; other criteria were the same as the control group.

Polymorphism detection

In both groups, maternal cubital venous blood was collected on an empty stomach before delivery and DNA was extracted by the column centrifugation method. After purity detection with an ultraviolet spectrophotometer, the DNA was amplified following the PCR amplification kit manuals. Reaction process: pre-denaturation at 95℃ for 5 minutes, denaturation at 94℃ for 20 seconds, annealing at 55℃ for 20 seconds, and extension at 72℃ for 40 seconds. Following amplification, the PCR products were measured by agarose gel electrophoresis, and the target bands were recovered by gel extraction, followed by purification and sequencing. The distribution of the ADRB2 gene rs1042713 locus and the FCER1B gene rs569108 locus was analyzed according to the sequencing results.

Cell data

Human airway smooth muscle cells (ASMCs) ordered from Shanghai Cell Bank of Chinese Academy of Sciences, China, were cultured in Dulbecco's Modified Eagle's medium (DMEM) that was added with 10% foetal bovine serum (FBS) in a 37℃ and 5% CO_2 incubator. Then, ASMCs grown to the logarithmic phase were transfected with ADRB2 and FCER1B overexpression vectors (ADRB2/FCER1B-ov), their silencing expression vectors (ADRB2/FCER1B-si), and negative expression vectors (ADRB2/FCER1B-nc), respectively, with the operation carried out in strict accordance with the Lipofectamine 2000 transfection kit recommendations. Polymerase chain reaction (PCR) was then carried out to determine ADRB2 and FCER1B mRNA expression to verify the transfection success rate (same method as above). The design and construction of primer sequences (Table 1) were commissioned by Jiangsu Genecefe Biotechnology Co., Ltd.

Cell cloning assay

A proper amount of cells were inoculated into 6-well plates, washed with PBS after 1 week of culture, and then fixed with methanol and stained with 0.4% crystal violet. Cell cloning was photographed and recorded, and the cloning rate was calculated.

Apoptosis assay

Cells in each group were cultured for 48 hours and collected to prepare a single-cell suspension, which was then fixed with 3mL of pre-cooled 70% ethanol, washed with buffer solution, and added with ribonuclease A (RNaseA) for a water bath (30 min, 37℃). Following the addition of propidium iodide (PI) for 30 min of room temperature culture at 4℃, the samples were loaded for apoptosis detection with a computer. Flow cytometry and DNA cell cycle analysis software were used to detect and analyze the cell cycle.

Detection of pyroptosis-associated proteins

The trypsin-digested cells were subjected to a BCA assay to extract total proteins, which were transferred to a PVDF membrane after gel electrophoresis. The PVDF membrane was then sealed with 5% skimmed milk powder for 1 h, and incubated overnight at 4℃ with NLRP3, GSDMD, IL-1β and Caspase-1 primary antibodies diluted at 1: 1000. Following 2 h of incubation with a secondary antibody (1: 5000), it was developed with ECL and analyzed by Image J software for the gray value of each band.

ROS content detection

Cells were seeded at 1×10/mL in 24-well plates (1 mL per well). After 24 hours, dichlorofluorescin diacetate (DCFH-DA) was diluted into a 10 μmol/L working solution with serum-free medium (1: 1000) and added into the wells (100 μL/well) for 30 min of light-tight incubation. After three rinses with a serum-free medium, the sample was photographed under a fluorescence microscope.

Inflammatory reaction detection

Finally, the supernatant of the cell culture medium of each group was collected via centrifugation to detect the concentrations of tumor necrosis factor-α (TNF-α) and interleukin-6/8 (IL-6/8), with the procedure conducted strictly following the enzyme-linked immunosorbent assay (ELISA) kit manuals.

Statistical methods

The data were statistically analyzed by SPSS24.0. To identify statistical significance indicated by a *P*-value <0.05, we employed chi-square tests to compare counting data expressed by [n(%)], and independent sample t-tests (between group comparisons) as well as analysis of variance and Bonferroni post-hoc tests (multi-group comparisons) to analyze measurement data described as by ($\bar{x}$±s).

Results

Comparison of maternal and infant clinical baseline data between two groups

No statistically significant differences were found between the two groups in terms of birth weight, gestational age, maternal age, and delivery mode (P>0.05, Table 2).

Comparison of genotypes and allele frequencies at rs1042713 locus of the ADRB2 gene

The rs1042713 locus of the ADRB2 gene included three genotypes: AA, AG, and GG. The two groups showed no statistical difference in the number of AG genotype carriers (P>0.05), but the research group had fewer AA geno-

type carriers and more GG genotype carriers (P<0.05). In addition, lower A allele frequencies and higher G allele frequencies were determined in the research group compared with the control group (P>0.05, Table 3).

Comparison of genotypes and allele frequencies at rs569108 locus of the FCER1B gene

The rs569108 locus of the FCER1B gene was also classified into AA, AG and GG genotypes. No notable intergroup differences were identified in the number of AG and GG genotype carriers (P>0.05), but fewer AA genotype carriers were found in the research group (P<0.05). In terms of alleles, the A allele frequency was lower and the G allele frequency was higher in the research group compared with the other (P<0.05, Table 4).

Efficacy of ADRB2 and FCER1B in assessing congenital respiratory disease in preterm infants

Through analysis, we found that the FCER1B gene rs569108 locus did not show a significant effect on congenital disorders in preterm infants (P>0.05), whereas, under the recessive model of the ADRB2 gene rs1042713 locus, preterm infants carrying the GG genotype showed an increased risk of congenital respiratory disorders by 2.887-fold (P<0.05). Under the dominant model, preterm infants not carrying the AA genotype had a 3.070-fold increased risk of developing congenital respiratory disease (P<0.05, Table 5).

Influences of ADRB2 and FCER1B on ASMC activity

First, we detected the expression of ADRB2 and FCER1B in cells transfected with abnormal expres-

Table 2. Clinical baseline information table.

Group	Birth weight (g)	Gestational age (weeks)	Maternal age (years)	Sex Male/female	Male/Female
Control group (n=64)	2346.56±129.39	34.66±1.26	27.56±2.14	26 (40.63)/38 (59.38)	30 (46.88)/34 (53.13)
Research group (n=45)	2381.02±144.47	34.16±1.54	26.78±3.04	20 (44.44)/25 (55.56)	24 (53.33)/21 (46.67)
t (χ^2)	1.304	1.862	1.582	0.158	0.441
P	0.195	0.065	0.117	0.691	0.507

Table 3. rs1042713 locus of the ADRB2 gene.

Group	Genotypes			Allele frequencies	
	AA	AG	GG	A	G
Control group (n=64)	24 (37.50)	34 (53.13)	6 (9.38)	82 (64.06)	46 (51.11)
Research group (n=45)	5 (11.11)	26 (57.78)	14 (31.11)	36 (35.94)	54 (48.89)
χ^2	9.423	0.231	8.332	12.320	
P	0.002	0.631	0.004	<0.001	

Table 4. rs569108 locus of the FCER1B gene.

Group	Genotypes			Allele frequencies	
	AA	AG	GG	A	G
Control group (n=64)	19 (29.69)	38 (59.38)	7 (10.94)	76 (59.38)	52 (57.78)
Research group (n=45)	6 (13.33)	28 (62.22)	11 (24.44)	40 (31.25)	50 (55.56)
χ^2	3.998	0.090	3.496	4.732	
P	0.046	0.765	0.062	0.030	

Table 5. Diagnostic efficacy of ADRB2 and FCER1B.

		Control group (n=64)	Research group (n=45)	χ^2	P	OR (95%CI)
rs1042713 locus of the ADRB2 gene	Implicit model			8.332	0.004	2.887 (2.040-4.663)
	AA/AG	58 (90.63)	31 (68.89)			
	GG	6 (9.38)	14 (31.11)			
	Explicit model			9.423	0.002	3.070 (2.064-3.847)
	GG/AG	40 (62.50)	40 (88.89)			
	AA	24 (37.50)	5 (11.11)			
rs569108 locus of the FCER1B gene	Implicit model			3.496	0.062	1.870 (1.142-3.016)
	AA/AG	57 (89.06)	34 (75.56)			
	GG	7 (10.94)	11 (24.44)			
	Explicit model			2.011	0.156	1.418 (0.887-1.943)
	GG/AG	45 (70.31)	37 (82.22)			
	AA	19 (29.69)	8 (17.78)			

sion vectors of ADRB2 and FCER1B. The ADRB2 and FCER1B mRNA levels were found to be higher in ADRB2/FCER1B-ov groups than in ADRB2/FCER1B-si and ADRB2/FCER1B-nc groups, and those in ADRB2/FCER1B-si groups were lower compared with ADRB2/FCER1B-nc groups (P<0.05, Figure 1A), confirming successful transfection. Subsequently, we found that compared with ADRB2/FCER1B-nc groups, the cell cloning rate of ADRB2/FCER1B-ov groups increased significantly, and the apoptosis rate decreased; while the cloning rate reduced and the apoptosis rate elevated in ADRB2/FCER1B-si groups (P<0.05, Figure 1B, C). Moreover, the G0-G1 phase was shortened in ADRB2/FCER1B-ov groups but lengthened in ADRB2/FCER1B-si groups (P<0.05, Figure 1D).

Effects of ADRB2 and FCER1B on pyroptosis of ASMCs

According to the detection results of pyroptosis-associated proteins, NLRP3, GSDMD, IL-1β, and Caspase-1 protein levels were the highest in ADRB2/FCER1B-ov groups among the groups, while those in ADRB2/FCER1B-si groups were lower compared with ADRB2/FCER1B-nc groups (P<0.05, Figure 2A). Similarly, the fluorescence intensity of ROS in ADRB2/FCER1B-ov groups was the highest, and that in ADRB2/FCER1B-si groups was lower versus ADRB2/FCER1B-nc groups (P<0.05, Figure 2B).

Effects of ADRB2 and FCER1B on inflammatory responses of ASMCs

Compared with ADRB2/FCER1B-nc groups, the concentrations of TNF-α and IL-6/8 in ADRB2/FCER1B-ov groups increased, while those in ADRB2/FCER1B-si groups decreased (P<0.05, Figure 3).

Discussion

For PTIs, rapid and accurate assessment of congenital diseases and timely formulation of effective intervention measures are of great significance to ensure their prognostic health (11). Although the role of ADRB2 and FCER1B gene polymorphisms in asthma has been widely discussed (12, 13), there is no research on their evaluation value for congenital respiratory diseases in PTIs. This study confirms for the first time the correlation of ADRB2 and FCER1B gene polymorphisms with congenital respiratory diseases in PTIs, which can provide a reliable reference for clinical practice.

First of all, it was found in the detection of polymorphisms that the AG genotype was the dominant polymorphism at the rs1042713 locus of the ADRB2 gene and the rs569108 locus of the FCER1B gene in both the research and control groups, with no difference between the two groups. However, in the research group, the number of AA genotype carriers of the ADRB2 gene decreased and the GG genotype increased, while the number of AA genotype carriers of the FCER1B gene decreased. In addition, the A allele frequencies of ADRB2 and FCER1B gene polymorphisms were lower in the research group, which demonstrates an important potential link between ADRB2 and FCER1B with the occurrence of congenital respiratory diseases in PTIs. However, the dominant/recessive model of FCER1B did not show a significant assessment of the occurrence of congenital respiratory disease in preterm infants. In contrast, under the recessive model of the

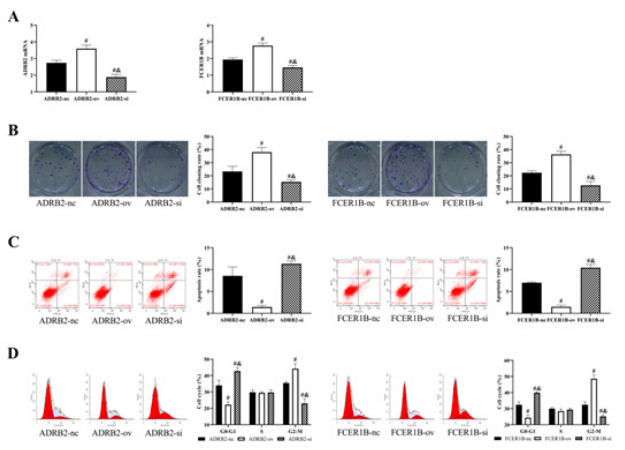

Figure 1. Influences of ADRB2 and FCER1B on ASMC activity. A: Detection of ADRB2 and FCER1B expression to verify the transfection success rate.B: Effect of ADRB2 and FCER1B on ASMC clonogenic ability. C: Effect of ADRB2 and FCER1B on the apoptotic rate of ASMC.D: Effect of ADRB2 and FCER1B on the cycle change of ASMC. *vs.* ADRB2/FCER1B-nc groups, #P<0.05, *vs.* ADRB2/FCER1B-ov groups, &P<0.05.

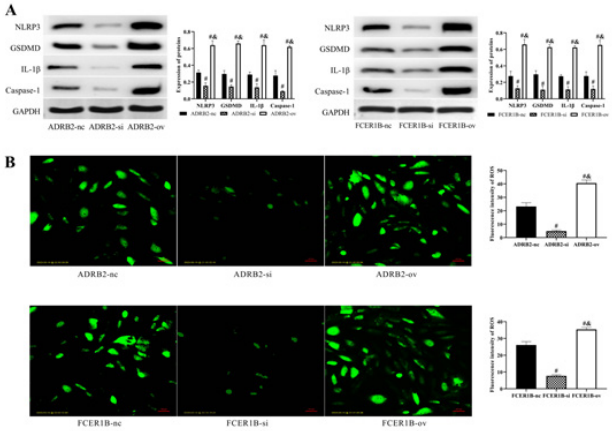

Figure 2. Effects of ADRB2 and FCER1B on pyroptosis of ASMCs. A: Effect of ADRB2 and FCER1B on ASMC focal death proteins. B: Effect of ADRB2 and FCER1B on ROC intensity in ASMC. *vs.* ADRB2/FCER1B-nc groups, #P<0.05, *vs.* ADRB2/FCER1B-si groups, &P<0.05.

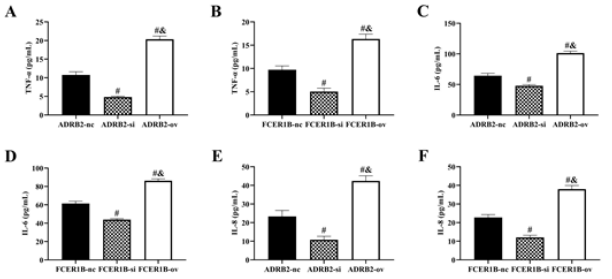

Figure 3. Effects of ADRB2 and FCER1B on inflammatory responses of ASMCs. A: Effect of ADRB2 on TNF-α. B: Effect of FCER1B on TNF-α. C: Effect of ADRB2 on IL-6. D: Effect of FCER1B on IL-6. E: Effect of ADRB2 on IL-8. F: Effect of FCER1B on IL-8. *vs.* ADRB2/FCER1B-nc groups, #P<0.05, *vs.* ADRB2/FCER1B-si groups, &P<0.05.

ADRB2 gene rs1042713 locus, preterm infants carrying the GG genotype had a 2.887-fold increased risk of developing congenital respiratory disease. Under the dominant model, preterm infants not carrying the AA genotype had a 3.070-fold increased risk of developing congenital respiratory disease. This suggests that by monitoring ADRB2 gene polymorphisms in the future, we can effectively determine the risk of congenital respiratory disease in preterm infants, and can also use this to provide early targeted interventions. These results are also consistent with previous research results (14, 15), which can support our view. The changes of single nucleotide polymorphism of the ADRB2 gene mainly include the mutation of arginine to glycine at position 16 (Arg16Gly), glutamine to glutamic acid at position 27 (GIn27Glu), and valine to methionine at position (Val34Met) (16). However, the results of various reports are not completely consistent. For example, Karimi L et al. found that the polymorphism of Arg16Cly and GI27Glu loci of the ADRB2 gene is related to asthma susceptibility (17). Zhang YQ et al. also believed that the polymorphism of the Arg16Cly locus of the ADRB2 gene may be a determinant of asthma severity and response to salbutamol (18). However, a study on the Saudi Arabian asthma population suggests that the ADRB2 gene single nucleotide polymorphism was not associated with asthma (19). FCERIB is a high-affinity IgE receptor and participates in IgE-mediated type I hypersensitivity. The mutation of this gene can lead to an elevation in serum total IgE levels, which in turn increases the release of inflammatory mediators by mast cells, triggering inflammatory changes in organs and tissues (20). Yet, the research of Amo G et al. also showed that the polymorphism of the rs569108 locus of the FCERIB gene was not related to changes in lung function (21). We can thus see that ADRB2 and FCERIB gene polymorphisms may have different manifestations in different populations, regions, and loci, warranting validation with a large sample size to realize their practical clinical applications.

Subsequently, in order to preliminarily understand the role of ADRB2 and FCERIB in respiratory diseases, we conducted in vitro experiments on ASMCs. This is because ASMCs are one of the important components of the respiratory tract, which have the functions of controlling airway patency and gas exchange and adjusting airway inner diameter, with great significance in respiratory diseases such as asthma and tracheal stenosis (22). After transfecting ADRB2 and FCERIB abnormal expression vectors into ASMCs, we found that increasing ADRB2 and FCERIB expression could promote the proliferation and inflammatory reaction of ASMCs, inhibit apoptosis, and accelerate cell pyroptosis; Conversely, silencing their expression contributed to decreased activity and inflammatory response of ASMCs, enhanced apoptosis, and suppression of cell pyroptosis processes. This suggests that ADRB2 and FCERIB play a vital role in modulating the biological behavior of ASMCs. Combined with the above experimental results, we speculated that the transformation from AA genotype to GG genotype of ADRB2 and FCERIB may cause the abnormal proliferation of ASMCs and promote the release of ROS in large quantities in cells, thus activating the process of cell pyroptosis, promoting airway inflammation, and eventually leading to respiratory diseases. For example, abnormally proliferated ASMCs and aggravated inflammation can lead to airway obstruction, asthma, obstructive lung, etc. (23). Similarly, highly expressed ADRB2 has also been shown to be involved in the occurrence and development of allergic rhinitis (24), which can also preliminarily support the potential influence of ADRB2 and FCERIB on cellular inflammatory response. While Xu Y et al. reported that the up-regulating ADRB2 expression was beneficial to the chemotherapy of lung cancer (25), contrary to our results, which may be due to the polymorphism of ADRB2 at different loci and the different manifestations in different diseases.

Due to limited conditions, the actual clinical expression of ADRB2 and FCERIB was not explored in this study, and the role of polymorphisms at different loci of ADRB2 and FCERIB in congenital respiratory diseases of PTIs needs further exploration. Later, we will increase relevant experiments and further analyze the role of ADRB2 and FCERIB in different respiratory diseases, so as to provide a more comprehensive clinical reference.

ADRB2 and FCERIB are closely related to congenital respiratory diseases in PTIs, both of which can participate in the occurrence and development of respiratory diseases by modulating the activity of ASMCs and the pyroptosis process. In the future, we can rapidly assess congenital respiratory diseases in PTIs by monitoring ADRB2 and FCERIB gene polymorphisms and formulating intervention measures in a timely manner.

Conflicts of interest

The authors report no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

Not applicable.

References

1. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Pract Res Clin Obstet Gynaecol. 2018;52: 3-12.
2. Price JC, Lei S, Diacovo TG. General Anesthesia and the Premature Baby: Identifying Risks for Poor Neurodevelopmental Outcomes. J Neurosurg Anesthesiol. 2023;35(1): 130-2. doi: 10.1097/ANA.0000000000000877.
3. Machado JS, Ferreira TS, Lima RCG, Vieira VC, Medeiros DS. Premature birth: topics in physiology and pharmacological characteristics. Rev Assoc Med Bras (1992). 2021;67(1): 150-5. doi: 10.1590/1806-9282.67.01.20200501.
4. Hallman M, Haapalainen A, Huusko JM, Karjalainen MK, Zhang G, Muglia LJ, et al. Spontaneous premature birth as a target of genomic research. Pediatr Res. 2019;85(4): 422-31. doi: 10.1038/s41390-018-0180-z.
5. Xiang X, Wang F, Zhao N, Zhou Z. Treatment of pregnancy-induced hypertension compared with labetalol, low dose aspirin and placebo. Cell Mol Biol (Noisy-le-grand). 2020;66(8): 9-13.
6. Uberos J. The significance of genetics in pathophysiologic models of premature birth. Minerva Pediatr. 2018;70(4): 383-90. doi: 10.23736/S0026-4946.17.04994-5.
7. Gil AM, Duarte D. Biofluid Metabolomics in Preterm Birth Research. Reprod Sci. 2018;25(7): 967-77. doi: 10.1177/1933719118756748.
8. Hua L, Zuo XB, Bao YX, Liu QH, Li JY, Lv J, et al. Four-locus

gene interaction between IL13, IL4, FCER1B, and ADRB2 for asthma in Chinese Han children. Pediatr Pulmonol. 2016;51(4): 364-71. doi: 10.1002/ppul.23322.

9. Pino-Yanes M, Corrales A, Cumplido J, Poza P, Sanchez-Machin I, Sanchez-Palacios A, et al. Assessing the validity of asthma associations for eight candidate genes and age at diagnosis effects. PLoS One. 2013;8(9): e73157. doi: 10.1371/journal.pone.0073157.
10. Hua L, Liu Q, Li J, Zuo X, Chen Q, Li J, et al. Gene-gene and gene-environment interactions on cord blood total IgE in Chinese Han children. Allergy Asthma Clin Immunol. 2021;17(1): 69. doi: 10.1186/s13223-021-00571-0.
11. Mericq V, Martinez-Aguayo A, Uauy R, Iniguez G, Van der Steen M, Hokken-Koelega A. Long-term metabolic risk among children born premature or small for gestational age. Nat Rev Endocrinol. 2017;13(1): 50-62. doi: 10.1038/nrendo.2016.127.
12. Zhang X, Zhang Y, He Z, Yin K, Li B, Zhang L, et al. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death Dis. 2019;10(11): 788. doi: 10.1038/s41419-019-2030-2.
13. Sandford AJ, Chagani T, Zhu S, Weir TD, Bai TR, Spinelli JJ, et al. Polymorphisms in the IL4, IL4RA, and FCERIB genes and asthma severity. J Allergy Clin Immunol. 2000;106(1 Pt 1): 135-40. doi: 10.1067/mai.2000.107926.
14. Wei X, Chen L, Yang A, Lv Z, Xiong M, Shan C. ADRB2 is a potential protective gene in breast cancer by regulating tumor immune microenvironment. Transl Cancer Res. 2021;10(12): 5280-94. doi: 10.21037/tcr-21-1257.
15. Sallis BF, Acar U, Hawthorne K, Babcock SJ, Kanagaratham C, Goldsmith JD, et al. A Distinct Esophageal mRNA Pattern Identifies Eosinophilic Esophagitis Patients With Food Impactions. Front Immunol. 2018;9: 2059. doi: 10.3389/fimmu.2018.02059.
16. Hikino K, Kobayashi S, Ota E, Mushiroda T, Urayama KY, Kobayashi T. A meta-analysis of the influence of ADRB2 genetic polymorphisms on albuterol (salbutamol) therapy in patients with asthma. Br J Clin Pharmacol. 2021;87(4): 1708-16. doi: 10.1111/bcp.14570.
17. Karimi L, Vijverberg SJ, Engelkes M, Hernandez-Pacheco N, Farzan N, Soares P, et al. ADRB2 haplotypes and asthma exacerbations in children and young adults: An individual participant data meta-analysis. Clin Exp Allergy. 2021;51(9): 1157-71. doi: 10.1111/cea.13965.
18. Zhang YQ, Zhu KR. The C79G Polymorphism of the beta2-Adrenergic Receptor Gene, ADRB2, and Susceptibility to Pediatric Asthma: Meta-Analysis from Review of the Literature. Med Sci Monit. 2019;25: 4005-13. doi: 10.12659/MSM.913780.
19. Stolk RF, Bruse N, Ter Horst R, Jansen A, Ricano Ponce I, Gerretsen J, et al. The impact of ADRB2 polymorphisms on immune responses and norepinephrine-induced immunosuppression. J Leukoc Biol. 2023;113(1): 84-92. doi: 10.1093/jleuko/qiac005.
20. Chan IH, Tang NL, Leung TF, Huang W, Lam YY, Li CY, et al. Study of gene-gene interactions for endophenotypic quantitative traits in Chinese asthmatic children. Allergy. 2008;63(8): 1031-9. doi: 10.1111/j.1398-9995.2008.01639.x.
21. Amo G, Garcia-Menaya J, Campo P, Cordobes C, Plaza Seron MC, Ayuso P, et al. A Nonsynonymous FCER1B SNP is Associated with Risk of Developing Allergic Rhinitis and with IgE Levels. Sci Rep. 2016;6: 19724. doi: 10.1038/srep19724.
22. Gu W, Lei J, Zhu H, Xiao Y, Zhang Z, Zhao L. Effect of the BMPR-II-SMAD3/MRTF pathway on proliferation and migration of ASMCs and the mechanism in asthma. Mol Biol Rep. 2022;49(10): 9283-96. doi: 10.1007/s11033-022-07764-9.
23. Liu H, Ma X, Wang X, Ma X, Mao Z, Zhu J, et al. Hsa_circ_0000345 regulates the cellular development of ASMCs in response to oxygenized low-density lipoprotein. J Cell Mol Med. 2020;24(20): 11849-57. doi: 10.1111/jcmm.15801.
24. Wang L, Lv Q, Song X, Jiang K, Zhang J. ADRB2 suppresses IL-13-induced allergic rhinitis inflammatory cytokine regulated by miR-15a-5p. Hum Cell. 2019;32(3): 306-15. doi: 10.1007/s13577-019-00259-z.
25. Xu Y, Wang J, Wang X, Zhou X, Tang J, Jie X, et al. Targeting ADRB2 enhances sensitivity of non-small cell lung cancer to VEGFR2 tyrosine kinase inhibitors. Cell Death Discov. 2022;8(1): 36. doi: 10.1038/s41420-022-00818-8.