INTRODUCTION

Asthma is a common chronic pulmonary disease. The clinical features are recurrent wheezing, shortness of breath, chest tightness, cough, and variable expiratory airflow limitation. Symptoms are often aggravated at night and in the morning. In 2016, 339 million people worldwide were suffering from asthma (Collaborators, 2017). Asthma is caused by complex environmental and genetic interactions (Ober & Vercelli, 2011). Exposure to allergens, tobacco smoke, air pollution, occupational risk factors, viral and bacterial infections, obesity, hygiene, stress, and toxic exposures may be a trigger for asthma (Toskala & Kennedy, 2015). Studies on twins suggest that genetic factors involve asthma (Koppelman, Los, & Postma, 1999; Laitinen, Rasanen, Kaprio, Koskenvuo, & Laitinen, 1998). Genome-wide association studies of asthma have confirmed that the locus polymorphism of over 500 genes was involved in the pathogenesis of asthma (Macarthur et al., 2017). Various T cell subtypes (Th1, Th2, Th9, Th17, NK, ILC2, and T regulatory cells) involved in asthma...
pathogenesis (Holgate et al., 2015). Nucleotide-binding oligomerization domain-containing protein 2 is a protein that is encoded by the NOD2 (OMIM 605956) gene located on chromosome 16 in humans and spans a 39 kb genomic region comprised of 17 exons. NOD2-deficient mice increased Toll-like receptor 2–mediated T helper type 1 responses (Watanabe, Kitani, Murray, & Strober, 2004). Nucleotide binding and oligomerization domain 2 is an intracellular protein that recognizes bacterial muramyl dipeptide (Tigno-Aranjuez & Abbott, 2012). This bacterial sensor NOD2 can trigger a strong antigen specific immune response with a Th2-type polarization profile (Magalhaes et al., 2008). Moreover, NOD2 as a viral pattern recognition receptor that can sense viral to activate IFN-β production and antiviral defense (Sabbah et al., 2009). The expression of interferon-β in bronchial epithelial cells of asthma is impaired to infection with rhinovirus (Wark et al., 2005). NOD2 plays an important role in inflammatory and immune responses (Carneiro, Magalhaes, Tattoli, Philpott, & Travassos, 2008). NOD2 has been involved in the development of Crohn's disease, early onset sarcoidosis, Blau syndrome, autoimmune disease, allergy, and asthma (Ni, Chen, Wu, Zhu, & Song, 2017).

Previous studies have found that NOD2 polymorphism is associated with asthma in the German population (Kabesch et al., 2003; Weidinger et al., 2005). However, until now, the current studies failed to provide a basis for the genetic correlation of NOD2 variations and asthma in the Chinese populations. Therefore, the aim of this research was to identify the role of NOD2 polymorphisms in the genetic basis of asthma in the Chinese population and to evaluate the relationship between the NOD2 polymorphisms and the serum level of interferon-β.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This research was conducted in accordance with the ethical standards of the Declaration of Helsinki. The research has been approved by the Ethics Committee of the Yancheng Third People's Hospital. Informed written consent was obtained from all parents.

2.2 | Study subjects

The case-control study included 163 controls and 309 asthmatic children. The asthmatic children in this study were in the clinical remission stage. Children were diagnosed for asthma according to the following criteria: cough, wheezing, shortness of breath, chest tightness, and lung function test. Controls were children without a history of allergy and family history of asthma. The controls underwent a routine medical checkup in the Medical Examination Center, Yancheng Third People's Hospital, Yancheng, China, between January 2016 and December 2017. All study subjects were of the Chinese Han population and resided in Yancheng, China.

2.3 | DNA extraction and genotyping

Genomic DNA was extracted using the TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China) following the manufacturers' instructions and then stored at −80°C. SNP in the human NOD2 (GenBank: AF178930.1) genes with minor allele frequencies >10% were selected from the HapMap Chinese data set. Tag SNPs were then selected by a tagger, using Haploview 4.2 software. The designs of PCR primers were carried out by online primer 3.0 software (http://primer3.ut.ee/). The SNaPshot was used to analyze genotypes of SNPs.

2.4 | Serum IFN-β determination

The quantity determination of serum IFN-β levels was performed by IFN-β Human ELISA Kit (Invitrogen) following the manufacturer's instructions.

2.5 | Statistical analysis

For comparison of values between cases and controls, Student's t tests and the χ²-test were used. The Hardy–Weinberg equilibrium was tested for using χ²-test goodness of fit. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for assessing the allele on the risk of asthma. The statistical significance was assumed at the p < 0.05 level. The statistical power to detect association of the polymorphisms with NOD2 was 0.80 and was estimated with PASS 11 software (https://www.ncss.com).

3 | RESULTS

3.1 | Clinical characteristics of the study participants

There were no significant differences in the age and gender between patients and controls (p > 0.05) (Table 1). Asthma patients showed a significantly high rate of household smoking and recurrent respiratory infection (p < 0.05). Total IgE concentration in serum of the children with asthma was significantly higher than the controls (p < 0.05). Compared with the control group, the serum IFN-β levels were significantly higher than the controls (50.2 ± 15.6 pg/ml, n = 309) vs. (70.2 ± 14.7 pg/ml, n = 163); t = 13.483, p = 0.000].
The genotype and allele frequencies of NOD2 gene polymorphisms

Thirty-four SNPs of NOD2, with minor allele frequencies >10%, were identified in the HapMap Chinese data set (Table 2), and all were captured by 4 tag SNPs of NOD2, using a tagger in Haplview software. For NOD2, pairwise tagging was performed at $r^2 > 0.8$, and the mean $r^2$ was 0.974. Next, genotyping was performed using the 4 tag SNPs. In the cases and the controls, the genotype distributions of rs1077861, rs3135499, rs1861759, and rs2111234 were consistent with the Hardy–Weinberg equilibrium (all $p > 0.05$).

The distribution of genotypes and alleles frequencies of the 4 tag SNPs in the group of cases and the group of controls are shown in Table 3. Under codominant and dominant models, the genotype frequencies of the NOD2 rs3135499 polymorphisms were statistically significant between the patients and the controls ($p < 0.05$). The rs3135499 C allele was associated with a significantly increased risk of asthma as compared with the rs3135499 A allele (OR = 1.762, 95% CI, 1.220–2.545, $p = 0.002$). However, the rs1077861, rs1861759, and rs2111234 SNPs were not significantly associated with asthma pathogenesis ($p > 0.05$).

Distribution of IFN-β between cases and controls

NOD2 gene polymorphisms and clinical parameters had been further investigated for the impact of serum IFN-β levels (Tables 4 and 5). We further found that severe asthma patients had lower levels of IFN-β than nonsevere asthma. But, we failed to find any association of the rs1077861, rs3135499, rs1861759, and rs2111234 with serum level of IFN-β.

DISCUSSION

Asthma is a common chronic respiratory disease in the world. Environmental and genetic factors affect the development of asthma. Environmental exposure to tobacco smoke is the most important risk factor for asthma, and causes airway inflammation (Sheikh, Pitts, Ryan-Wenger, Mccoy, & Hayes, 2016). As a potential innate immune mechanism, the nucleotide-binding oligomerization domain-like receptors (NLRs) based inflammasome can increase the response to pollutants (Bauer, Diaz-Sanchez, & Jaspers, 2012). As intracellular sensors, NLRs include 22 members in humans and 34 members in mice (Motta, Soares, Sun, & Philpott, 2015). NOD2 belongs to the NLR family and functions as a general sensor for both Gram-positive and Gram-negative bacteria by identifying muramyl dipeptide (Kufer, Banks, & Philpott, 2006). It was found that the physiological role of NOD2 in antiviral defense was the enhanced respiratory syncytial virus pathogenesis, lung disease, and greater viral susceptibility through the study of NOD2-deficient mice (Sabbah et al., 2009). NOD2 participates in host responses to infectious pathogens, including bacteria, viruses, and parasites (Al Nabhani, Dietrich, Hugot, & Barreau, 2017).

Genetic polymorphisms may be related to the development of diseases (Huang, 2015). There are some SNPs of NOD2 that have been identified as susceptibility loci of Crohn's disease, including 1007 fs, G908R, P268S, and R702W (Cao et al., 2018). A research reported that the NOD2 gene rs2066842 and rs2066843 polymorphisms showed a significant association with ulcerative colitis, but not with Crohn's in Indian patients (Pugazhendhi, Santhanam, Venkataraman, Creveaux, & Ramakrishna, 2013). Ahangari, Salehi, Salehi, & Khanahmad (2014) showed that the rs3135500 AA
genotype had a significant association with risk of Colorectal cancer in the Iran population. The research data of Cao et al. suggest that the rs3135500 variant might increase the risk for multiple system atrophy. A previous study found that the rs751271 polymorphism was associated with inflammatory reactions in leprosy (Sales-Marques et al., 2017). Weidinger et al., (2005) study found that the rs1077861 T allele decreased the risk of asthma, whereas the rs3135500 A allele was significantly associated with an increased risk of asthma.

| SNPs      | Model     | Asthma | Control | OR (95%CI) | p       |
|-----------|-----------|--------|---------|------------|---------|
| rs1077861 | Codominant| TT     | 198     | 115        | 1.378 (0.902–2.105) | 0.297   |
|           |           | AT     | 102     | 43         | 1.045 (0.342–3.195)  | 0.157   |
|           |           | AA     | 9       | 5          | 1.343 (0.892–2.022)  | 0.225   |
| rs3135499 | Codominant| AA     | 183     | 122        | 1.667 (0.511–5.435)  | 0.001   |
|           |           | AC     | 116     | 37         | 2.090 (1.353–3.230)  | 0.003   |
|           |           | CC     | 10      | 4          | 1.667 (0.511–5.435)  | 0.001   |
| rs1861759 | Codominant| AA     | 209     | 112        | 1.012 (0.660–1.553)  | 0.840   |
|           |           | AC     | 85      | 45         | 1.340 (0.506–3.549)  | 0.812   |
|           |           | CC     | 15      | 6          | 1.012 (0.660–1.553)  | 0.840   |
| rs2111234 | Codominant| CC     | 129     | 77         | 1.162 (0.782–1.727)  | 0.247   |
|           |           | CT     | 146     | 75         | 1.845 (0.884–3.852)  | 0.253   |
|           |           | TT     | 34      | 11         | 1.249 (0.853–1.830)  | 0.135   |

Nod1 (Nucleotide-binding oligomerization domain-containing protein 1, encoded by the NOD1 gene) and NOD2 are important recognition receptors involved in inflammation and immune response (Elia, Tolentino, Bernardazzi, & de Souza, 2015). NOD1 and NOD2 conferred a upregulation of NF-κB transactivation in transfected cells (Rosenstiel et al., 2006). NOD1 insertion/deletion polymorphism was correlated with and inflammatory bowel disease in Caucasian populations (Lu, 2010). Previous research reported that
**NOD1** +32656 polymorphism is associated with elevated serum IgE levels (Hysi et al., 2005). The **NOD1** +32656 locus insertion allele exhibit a significantly elevated production of IL-1β and IL-6 (Plantinga et al., 2013). Three locus polymorphisms within the coding region of **NOD2**, G908R, R702W, and L1007fsinsC display a deficit in NF-kB activation.

**Table 4** Distribution of IFN-β between cases and controls

| Model        | Asthma          | Control         |
|--------------|-----------------|-----------------|
|              | IFN-β levels (pg/ml) | p    | IFN-β levels (pg/ml) | p    |
| Codominant   |                 |                 |
| AA           | 50.7 ± 16.6     | 0.734           | 71.1 ± 14.2         | 0.334 |
| AC           | 49.6 ± 12.8     | 0.463           | 68.0 ± 16.4         | 0.182 |
| CC           | 47.8 ± 25.5     | 0.772           | 63.0 ± 10.8         | 0.327 |
| Dominant     |                 |                 |
| AA           | 50.7 ± 16.6     | 0.463           | 71.1 ± 14.2         | 0.182 |
| AC+CC        | 49.4 ± 14.1     |               | 67.5 ± 15.9         |       |
| Recessive    |                 |                 |
| CC           | 47.8 ± 25.5     | 0.772           | 63.0 ± 10.8         | 0.327 |
| AA+AC        | 50.3 ± 15.2     |               | 70.4 ± 14.8         |       |

**Table 5** The distribution of NOD2 genotype and IFN-β protein in different clinical characteristics

| Group      | Variable           | Genotype | IFN-β levels (pg/ml) | p     |
|------------|--------------------|----------|----------------------|-------|
| Asthma     | Household smoking | AA       | 57                   | 0.715 | 50.7 ± 16.0 | 0.687 |
|           |                    | AC       | 31                   |       | 50.0 ± 15.5 |       |
|           |                    | CC       | 3                    |       | 50.0 ± 15.5 |       |
|           | Recurrent respiratory infection | Positive | 65 | 0.755 | 50.6 ± 15.3 | 0.736 |
|           |                    | Negative | 118                  |       | 50.0 ± 15.8 |       |
|           | Atopy              | Positive | 122                  | 0.304 | 50.8 ± 15.8 | 0.31  |
|           |                    | Negative | 61                   |       | 48.8 ± 15.3 |       |
|           | Severity           | Positive | 25                   | 0.802 | 39.5 ± 16.1 | 0.000 |
|           |                    | Negative | 158                  |       | 52.0 ± 14.8 |       |
|           | Rhinitis           | Positive | 90                   | 0.747 | 50.2 ± 15.3 | 0.979 |
|           |                    | Negative | 93                   |       | 50.2 ± 16.0 |       |
|           | Medication         | Positive | 152                  | 0.659 | 50.0 ± 16.1 | 0.698 |
|           |                    | Negative | 31                   |       | 50.9 ± 13.4 |       |
| Control   | Household smoking | Positive | 21                   | 0.784 | 70.3 ± 16.9 | 0.964 |
|           |                    | Negative | 101                  |       | 70.1 ± 14.2 |       |
|           | Recurrent respiratory infection | Positive | 16 | 0.646 | 70.1 ± 16.7 | 0.986 |
|           |                    | Negative | 106                  |       | 70.2 ± 14.4 |       |
in response to bacterial components (Bonen et al., 2003; Rosenstiel et al., 2006). R702W, G908R, and Leu1007fsinsC polymorphisms in the NOD2 gene were reported to be associated with sepsis susceptibility (Tekin et al., 2012). A study found that the NOD2 rs3135499 polymorphism is associated with enhanced production of IL-17A in human toxoplasmosis (Dutra et al., 2012). Therefore, it might be possible that mutations in NOD1 or NOD2 gene influence directly or indirectly to change in levels of inflammatory factors that may lead to an abnormal immune response.

In this study, we have analyzed the potential associations of polymorphisms in the NOD2 gene with asthma in Chinese population. Among 4 tag SNPs of NOD2 that were identified using tagger in Haploview software. The rs3135499 polymorphisms in the NOD2 gene was significantly associated with asthma in the Chinese Han population. Furthermore, the rs3135499 C allele increased the risk of asthma as compared with the rs3135499 A allele. In addition, previous studies had found that rs3135499 polymorphisms involved in retinochoiditis and leprosy (Dutra et al., 2012; Xiong et al., 2016). And the serum level of IFN-β was significantly reduced in the cases as compared with the controls in this study. However, the distribution of the serum IFN-β levels of individuals with cases as compared with the controls in this study. However, the distribution of the serum IFN-β levels of individuals with AA, AC, and CC genotypes were no differences in the asthma group or the controls. These results suggested that rs3135499 polymorphisms may not affect the expression of serum IFN-β. Previous studies had found IFN-β expression was deficient in asthmatic patients (Sykes et al., 2012; Uller et al., 2010). A statistical significance was observed in the distribution of IFN-β levels between severe asthma and nonsevere asthma patients. The result indicated that low levels of IFN-β may be contribute to the susceptibility to severe asthma.

In summary, this study provided evidence that the NOD2 gene rs3135499 polymorphism genotypes differed between children with asthma and healthy children in the Chinese Han population. The rs3135499 C allele as a risk factor may influence the development of asthma. Nonetheless, due to the limited sample size and the specific genetic characteristics of the Chinese population, the pathogenesis of NOD2 in asthma needs further study to verify our results.

ACKNOWLEDGMENTS

We acknowledge the children with asthma, volunteers, and their families for their collaboration.

CONFLICT OF INTEREST

All authors report no conflict of interest relevant to this article.

ORCID

Qiaolan Xu https://orcid.org/0000-0002-5848-0292

REFERENCES

Ahangari, F., Salehi, R., Salehi, M., & Khanahmad, H. (2014). A miRNA-binding site single nucleotide polymorphism in the 3'-UTR region of the NOD2 gene is associated with colorectal cancer. Medical Oncology, 31, 173.

Al Nabhani, Z., Dietrich, G., Hugot, J., & Barreau, F. (2017). Nod2: The intestinal gate keeper. PLoS Pathogens, 13, e1006177.

Bauer, R. N., Diaz-Sanchez, D., & Jaspers, I. (2012). Effects of air pollutants on innate immunity: The role of Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. Journal of Allergy and Clinical Immunology, 129, 14–24.

Bonen, D. K., Ogura, Y., Nicolae, D. L., Inohara, N., Saab, L., Tanabe, T., … Nuñez, G. (2003). Crohn's disease-associated NOD2 variants share a signaling defect in response to lipopolysaccharide and peptidoglycan. Gastroenterology, 124, 140–146.

Cao, B., Chen, Y., Zhou, Q., Zhang, L., Ou, R., Wei, Q., … Shang, H. F. (2018). Functional variant rs3135500 in NOD2 increases the risk of multiple system atrophy in a Chinese population. Frontiers in Aging Neuroscience, 10, 150.

Carneiro, L., Magalhaes, J. G., Tattoli, I., Philpott, D. J., & Travassos, L. H. (2008). Nod-like proteins in inflammation and disease. The Journal of Pathology, 214, 136–148.

Collaborators G. D. A. I. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet, 390, 1211–1259.

Dutra, M. S., Bela, S. R., Peixoto-Rangel, A. L., Fakiola, M., Cruz, A. G., Gazzinelli, A., … Gazzinelli, R. T. (2012). Association of a NOD2 gene polymorphism and T-helper 17 cells with presumed ocular toxoplasmosis. Journal of Infectious Diseases, 207, 152–163.

Elia, P. P., Tolentino, Y. F. M., Bernardazzi, C., & de Souza, H. S. P. (2015). The role of innate immunity receptors in the pathogenesis of inflammatory bowel disease. Mediators of Inflammation, 2015, 936193.

Holgate, S. T., Wenzel, S., Postma, D. S., Weiss, S. T., Renz, H., & Sly, P. D. (2015). Asthma. Nature Reviews Disease Primers, 1, 15025.

Huang, Q. (2015). Genetic study of complex diseases in the post-GWAS era. The Journal of Genetics and Genomics, 42, 87–98.

Hysi, P., Kabesch, M., Moffatt, M. F., Schedel, M., Carr, D., Zhang, Y., … Cookson, W. O. C. (2005). NOD1 variation, immunoglobulin E and asthma. Human Molecular Genetics, 14, 935–941.

Kabesch, M., Peters, W., Carr, D., Leupold, W., Weiland, S. K., & von Mutius, E. (2003). Association between polymorphisms in caspase recruitment domain containing protein 15 and allergy in two German populations. The Journal of Allergy and Clinical Immunology, 111, 813–817.

Koppelman, G. H., Los, H., & Postma, D. S. (1999). Genetic and environmental in asthma: The answer of twin studies. European Respiratory Journal, 13, 2–4.

Kufer, T. A., Banks, D. J., & Philpott, D. J. (2006). Innate immune sensing of microbes by nod proteins. Annals of the New York Academy of Sciences, 1072, 19–27.

Laitinen, T., Rasanen, M., Kaprio, J., Koskenvuo, M., & Laitinen, L. A. (1998). Importance of genetic factors in adolescent asthma: A population-based twin-family study. American Journal of Respiratory and Critical Care Medicine, 157, 1073–1078.
Lu, W. (2010). Association of NOD1 (CARD4) insertion/deletion polymorphism with susceptibility to IBD: A meta-analysis. *World Journal of Gastroenterology*, 16, 4348–4356.

Macarthur, J., Bowler, E., Cerezo, M., Gil, L., Hall, P., Hastings, E., … Parkinson, H. (2017). The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Research*, 45, D896–D901.

Magalhaes, J. G., Fritz, J. H., Le Bourhis, L., Sellge, G., Travassos, L. H., Selvanantham, T., … Philpott, D. J. (2008). Nod2-dependent Th2 polarization of antigen-specific immunity. *The Journal of Immunology*, 181, 7925–7935.

Motta, V., Soares, F., Sun, T., & Philpott, D. J. (2015). NOD-like receptors: Versatile cytosolic sentinels. *Physiological Reviews*, 95, 149–178.

Ni, G., Chen, Y., Wu, F., Zhu, P., & Song, L. (2017). NOD2 promotes cell proliferation and inflammatory response by mediating expression of TSLP in human airway smooth muscle cells. *Cellular Immunology*, 312, 35–41.

Ober, C., & Vercelli, D. (2011). Gene-environment interactions in human disease: Nuisance or opportunity? *Trends in Genetics*, 27, 107–115.

Plantinga, T. S., Fransen, J., Knevel, R., Netea, M. G., Zwerina, J., Helsen, M. M. A., … Joosten, L. A. B. (2013). Role of NOD1 polymorphism in susceptibility and clinical progression of rheumatoid arthritis. *Rheumatology*, 52, 806–814.

Pugazhendhi, S., Santhanam, S., Venkataaraman, J., Creveaux, I., & Ramakrishna, B. S. (2013). NOD2 gene mutations associate weakly with ulcerative colitis but not with Crohn’s disease in Indian patients with inflammatory bowel disease. *Gene*, 512, 309–313.

Rosenstiel, P., Hellmig, S., Hampe, J., Ott, S., Till, A., Fischbach, W., … Schreiber, S. (2006). Influence of polymorphisms in the NOD1/CARD4 and NOD2/CARD15 genes on the clinical outcome of Helicobacter pylori infection. *Cellular Microbiology*, 8, 1188–1198.

Sababgh, A., Chang, T. H., Harnack, R., Frohlich, V., Tominaga, K., Dube, P. H., … Bose, S. (2009). Activation of innate immune antiviral responses by Nod2. *Nature Immunology*, 10, 1073–1080.

Sales-Marques, C., Cardoso, C. C., Alvarado-Arnez, L. E., Illaramendi, X., Sales, A. M., Hacker, M. D. A., … Moraes, M. O. (2017). Genetic polymorphisms of the IL6 and NOD2 genes are risk factors for inflammatory reactions in leprosy. *PLOS Neglected Tropical Diseases*, 11, e0005754.

Sheikh, S. I., Pitts, J., Ryan-Wenger, N. A., Mccoy, K. S., & Hayes, D. J. (2016). Environmental exposures and family history of asthma. *Journal of Asthma*, 53, 465–470.

Sykes, A., Edwards, M. R., Macintyre, J., Del Rosario, A., Bakhsolian, E., Trujillo-Torralbo, M., … Johnston, S. L. (2012). Rhinovirus 16-induced IFN-α and IFN-β are deficient in bronchoalveolar lavage cells in asthmatic patients. *Journal of Allergy and Clinical Immunology*, 129, 1506–1514.e6.

Tekin, D., Dalgic, N., Kayaalti, Z., Soylemezoglu, T., Diler, B., & Isin Kutlubay, B. (2012). Importance of NOD2/CARD15 gene variants for susceptibility to and outcome of sepsis in Turkish children*. *Pediatric Critical Care Medicine*, 13, e73–e77.

Tigno-Aranjuez, J. T., & Abbott, D. W. (2012). Ubiquitination and phosphorylation in the regulation of NOD2 signaling and NOD2-mediated disease. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1823, 2022–2028.

Toskala, E., & Kennedy, D. W. (2015). Asthma risk factors. *International Forum of Allergy & Rhinology*, 5, S11–S16.

Uller, L., Leino, M., Bedke, N., Sammut, D., Green, B., Lau, L., … Davies, D. E. (2010). Double-stranded RNA induces disproportionate expression of thymic stromal lymphopoietin versus interferon-γ in bronchial epithelial cells from donors with asthma. *Thorax*, 65, 626–632.

Wark, P. A., Johnston, S. L., Bucchieri, F., Powell, R., Puddicombe, S., Laza-Stanca, V., … Davies, D. E. (2005). Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *Journal of Experimental Medicine*, 201, 937–947.

Watanabe, T., Kitani, A., Murray, P. J., & Strober, W. (2004). NOD2 is a negative regulator of Toll-like receptor 2–mediated T helper type 1 responses. *Nature Immunology*, 5, 800–808.

Weidinger, S., Klop, N., Rummel, L., Wagenpfeil, S., Baurecht, H. J., Gauger, A., … Illig, T. (2005). Association of CARD15 polymorphisms with atopy-related traits in a population-based cohort of Caucasian adults. *Clinical & Experimental Allergy*, 35, 866–872.

Xiong, J. H., Mao, C., Sha, X. W., Jin, Z., Wang, H., Liu, Y. Y., & Ning, Y. (2016). Association between genetic variants in NOD2, C13orf31, and CCDC122 genes and leprosy among the Chinese Yi population. *International Journal of Dermatology*, 55, 65–69.