The risk of atopic dermatitis may be affected by \textit{IL-1B} +3954 C/T and \textit{IL-18} -137G/C polymorphisms: evidence from a meta-analysis

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Adv Dermatol Allergol
DOI: https://doi.org/10.5114/ada.2020.95956

Abstract

Introduction: Whether Th1-related cytokine polymorphisms influence the risk of atopic dermatitis (AD) remain inconclusive.

Aim: The authors performed a meta-analysis to robustly explore relationships between Th1-related cytokine polymorphisms and the risk of AD by merging the results of eligible publications.

Material and methods: The authors strictly adhere to the PRISMA guidelines in study design and implementation. A thorough literature search in Medline, Embase, Wanfang, VIP and CNKI was performed by the authors to identify eligible publications. Relationships between \textit{TNF-\alpha/IL-1/IL-6/IL-18} polymorphisms and the risk of AD were estimated with odds ratio and its 95% confidence interval. The statistically significant \textit{p} value was set at 0.05. The quality of eligible publications was assessed by the Newcastle-Ottawa scale (NOS).

Results: In total twenty-one publications with a NOS score of 7-8 were selected for merged quantitative analyses. We have noticed that genotypic frequencies of \textit{IL-1B} +3954 C/T and \textit{IL-18} -137G/C polymorphisms among cases with AD and population-based controls differed significantly. Moreover, we have found that genotypic frequency of \textit{IL-1B} +3954 C/T polymorphism among cases with AD and population-based controls of Caucasian origin differed significantly, and genotypic frequency of \textit{IL-18} -137G/C polymorphism among cases with AD and population-based controls of both Caucasian and Asian origins also differed significantly. However, we did not observe such genotypic distribution differences for \textit{TNF-\alpha} -238 G/A, \textit{TNF-\alpha} -308 G/A, \textit{IL-1A} -889 C/T, \textit{IL-1B} -511 C/T and \textit{IL-6} -174 G/C polymorphisms.

Conclusions: The present meta-analysis shows that \textit{IL-1B} +3954 C/T and \textit{IL-18} -137G/C polymorphisms may affect the risk of AD.

Key words: atopic dermatitis, interleukin-1, interleukin-18.

Introduction

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease. Major clinical manifestations of AD include dry skin, intense itching and eczematous rash [1, 2]. The clinical course of AD generally starts from the childhood, and this disorder poses a serious impact on patients’ quality of life.

The etiological factors of AD are still not well understood, but accumulating evidence suggests that disturbance of the immune system serves as a critical contributing factor to onset and progression of this disorder, and an abnormal imbalance of Th1 and Th2 mediated immune responses has also been observed in patients with AD [3–5]. It is well established that cytokines play vital roles in regulating T cell mediated immune responses, and thus it is believed that gene polymorphisms of cytokines may somehow influence the risk of AD [6, 7].

Over the last decade, investigators all over the world have repeatedly attempted to estimate the relationships between cytokine polymorphisms and the risk of AD, yet the relationships between these gene polymorphisms and the risk of AD remain inconclusive. Considering that several previous meta-analyses have already covered Th2-related cytokines [8, 9], we decided to focus on polymorphisms of Th1-related cytokines, which include tumour necrosis factor-\alpha (\textit{TNF-\alpha}), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-18 (IL-18) in this meta-analysis.
Aim

We aimed to evaluate associations between Th1-related cytokine polymorphisms and the risk of AD through a meta-analysis.

Material and methods

The authors strictly adhere to the PRISMA guidelines in study design and implementation [10].

Literature search and inclusion criteria

A thorough literature search in Medline, Embase, Wanfang, VIP and CNKI was performed by the authors with the following key words: (Tumour necrosis factor-\(\alpha\) OR TNF-\(\alpha\) OR Interleukin-1 OR IL-1 OR Interleukin-6 OR IL-6 OR Interleukin-18 OR IL-18) AND (polymorphism OR polymorphic OR variation OR variant OR mutant OR genomic OR genetic OR genotype OR allele) AND (atopic dermatitis OR atopic eczema). Moreover, we also manually screened the reference lists of retrieved publications to make up for the potential incompleteness of electronic literature searching.

Selection criteria of eligible publications include the following four points: 1. Studies of case-control or cohort design; 2. Explore relationships between polymorphisms in TNF-\(\alpha\), IL-1, IL-6 or IL-18 and the risk of AD; 3. Give genotypic frequencies of TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms in cases with AD and population-based controls; 4. The full manuscript with required genotypic frequencies of TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms is retrievable or buyable. Articles would be excluded if one of the following three criteria is met: 1. Studies without complete data about genotypic frequencies of TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms in cases with AD and population-based controls; 2. Narrative or systematic reviews, meta-analysis or comments; 3. Case series of subjects with AD. If duplicate publications are retrieved from literature search, we would only include the most complete one for quantitative analyses.

Data extraction and quality assessment

The authors extracted the following data items from eligible publications: 1. Last name of the leading author; 2. Publication year; 3. Country and ethnicity of study population; 4. The number of cases with AD and population-based controls; 5. Genotypic frequencies of TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms in cases with AD and population-based controls. Hardy-Weinberg equilibrium was then tested by using genotypic frequencies of TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms. The quality of eligible publications was assessed by the Newcastle-Ottawa scale (NOS) [11], and these with a score of 7–9 were considered to be publications of good quality. Two authors extracted data and assessed quality of eligible publications at the same time. A thorough discussion until a consensus is reached would be endorsed in case of any discrepancy between two authors.

Statistical analysis

All statistical analyses were performed with the Cochrane Review Manager software. Relationships between TNF-\(\alpha\), IL-1, IL-6 or IL-18 polymorphisms and the risk of AD were estimated by using odds ratio and its 95% confidence interval. The statistically significant \(p\) value was set at 0.05. The authors used \(I^2\) statistics to assess heterogeneities among eligible publications. The authors would use DerSimonian-Laird method, which is also known as the random effect model, to merge the results of eligible publications if \(I^2\) is larger than 50%. Otherwise, the authors would use Mantel-Haenszel method, which is also known as the fixed effect model, to merge the results of eligible publications. Meanwhile, subgroup analyses by ethnic groups were also performed by the authors. Stabilities of quantitative analysis results were tested by deleting one eligible publication each time, and then merging the results of the rest of eligible publications. Publication biases were evaluated by assessing symmetry of funnel plots.

Figure 1. Flowchart of the study selection for this meta-analysis
Results

Characteristics of included studies

One hundred and ninety-three publications were retrieved by the authors by using our searching strategy. Forty publications were then selected to be screened for eligibility after omitting unrelated and repeated publications. Ten reviews and five case series were further excluded, and another four publications without all necessary genotypic data were further excluded by the authors. In total twenty-one publications met the selection criteria, and were finally selected for quantitative analyses (Figure 1). Data extracted from eligible publications were summarized in Table 1.

Table 1. The characteristics of included studies in the current meta-analysis

| First author, year | Country         | Ethnicity | Sample size | Genotypes (wt/wt/wtmt/mmtmt) | P-value for HWE | NOS score |
|--------------------|-----------------|-----------|-------------|------------------------------|-----------------|-----------|
|                    |                 |           |             | Cases Controls                |                 |           |
| **TNF-α -238 G/A rs361525:** |                 |           |             |                              |                 |           |
| Babić, 2016        | Croatia         | Caucasian | 36/127      | NA NA NA                     | NA              | 7         |
| Behniafard, 2012   | Iran            | Mixed     | 89/137      | 85/4/0 79/57/1               | 0.007           | 8         |
| Dai, 2004          | China           | Asian     | 111/152     | 106/5/0 148/4/0              | 0.869           | 8         |
| de Jongh, 2008     | The Netherlands | Caucasian | 197/217     | 182/15/0 195/21/1            | 0.597           | 7         |
| Reich, 2003        | Germany         | Caucasian | 94/214      | 86/7/1 195/18/1              | 0.414           | 7         |
| Stavric, 2012      | Republic of Macedonia | Caucasian | 66/303      | 62/3/1 27/62/3/4             | < 0.001         | 7         |
| Westphal, 2003     | Germany         | Caucasian | 119/367     | 115/4/0 339/26/2             | 0.065           | 8         |
| **TNF-α -308 G/A rs1800629:** |                 |           |             |                              |                 |           |
| Babić, 2016        | Croatia         | Caucasian | 37/133      | NA NA NA                     | NA              | 7         |
| Babić, 2019        | Croatia         | Caucasian | 56/144      | NA NA NA                     | NA              | 7         |
| Behniafard, 2012   | Iran            | Mixed     | 89/137      | 79/10/0 98/39/0              | 0.052           | 8         |
| Colagiovanni, 2016 | Italy           | Caucasian | 41/40       | 35/6/0 30/10/0               | 0.366           | 7         |
| Dai, 2004          | China           | Asian     | 111/152     | 104/7/0 130/22/0             | 0.336           | 8         |
| de Jongh, 2008     | The Netherlands | Caucasian | 197/217     | 134/54/9 160/52/5            | 0.751           | 7         |
| Ertam, 2009        | Turkey          | Caucasian | 50/100      | 34/14/2 54/31/15             | 0.007           | 7         |
| Huralt, 2018       | Saudi Arabia    | Mixed     | 104/211     | 51/53/0 116/80/15            | 0.813           | 8         |
| Khatri, 2015       | India           | Mixed     | 60/60       | 50/10/0 52/8/0               | 0.580           | 7         |
| Reich, 2003        | Germany         | Caucasian | 94/214      | 68/25/1 158/56/0             | 0.028           | 8         |
| Stavric, 2012      | Republic of Macedonia | Caucasian | 65/297      | 50/14/1 231/66/0             | 0.031           | 7         |
| Westphal, 2003     | Germany         | Caucasian | 124/367     | 83/39/3 269/98/0             | 0.003           | 8         |
| **IL-1A -889 C/T rs1800587:** |                 |           |             |                              |                 |           |
| Babić, 2016        | Croatia         | Caucasian | 37/131      | NA NA NA                     | NA              | 7         |
| Behniafard, 2014   | Iran            | Mixed     | 89/136      | 46/34/9 62/62/12             | 0.527           | 8         |
| de Jongh, 2008     | The Netherlands | Caucasian | 197/217     | 96/80/21 106/89/22           | 0.605           | 7         |
| Stavric, 2012      | Republic of Macedonia | Caucasian | 66/301      | 42/24/0 204/74/18            | 0.003           | 7         |
| **IL-1B +3954 C/T rs1143627:** |                 |           |             |                              |                 |           |
| Behniafard, 2014   | Iran            | Mixed     | 89/140      | 48/35/6 70/58/12             | 0.998           | 8         |
| de Jongh, 2008     | The Netherlands | Caucasian | 197/217     | 85/88/24 86/101/30           | 0.968           | 7         |
| Reich, 2003        | Germany         | Caucasian | 94/214      | 51/39/4 123/75/16            | 0.339           | 8         |
| Stavric, 2012      | Republic of Macedonia | Caucasian | 65/301      | 37/28/0 174/91/36            | < 0.001         | 7         |
| Westphal, 2003     | Germany         | Caucasian | 125/367     | 72/48/5 214/130/23           | 0.587           | 8         |
| **IL-1B -511 C/T rs16944:** |                 |           |             |                              |                 |           |
| Behniafard, 2014   | Iran            | Mixed     | 89/139      | 28/41/20 36/82/21            | 0.022           | 8         |
| Reich, 2003        | Germany         | Caucasian | 94/214      | 36/48/10 94/102/18           | 0.184           | 8         |
Seven publications explored the relationship between TNF-α -238 G/A polymorphism and the risk of AD, and twelve publications explored the relationship between TNF-α -308 G/A polymorphism and the risk of AD. The merged quantitative analyses did not reveal any positive results for TNF-α -238 G/A and -308 G/A polymorphisms (Table 2).

### Quantitative analyses of IL-1 polymorphisms and AD

Four publications explored the relationship between IL-1A -889 C/T polymorphism and the risk of AD, five publications explored the relationship between IL-1B +3954 C/T polymorphism and the risk of AD, and four publications explored the relationship between IL-1B -511 C/T polymorphism and the risk of AD. The merged quantitative analyses revealed that IL-1B +3954 C/T polymorphism was significantly associated with the risk of AD in overall population (dominant comparison: OR = 2.06, \( p = 0.007 \); recessive comparison: OR = 0.24, \( p < 0.001 \); over-dominant comparison: OR = 0.74, \( p = 0.05 \); allele comparison: OR = 2.04, \( p = 0.003 \)), Caucasians (allele comparison: OR = 1.45, \( p = 0.05 \)) and Asians (dominant comparison: OR = 3.75, \( p < 0.001 \); recessive comparison: OR = 0.18, \( p < 0.001 \); over-dominant comparison: OR = 0.64, \( p = 0.04 \); allele comparison: OR = 3.41, \( p < 0.001 \)) (Table 2).

### Sensitivity analysis

The authors examined stabilities of quantitative analysis results by deleting one eligible publication each time, and then merging the results of the rest of publications. The trends of associations were not significantly altered in sensitivity analyses, which indicated that from a statistical perspective, our quantitative analysis results were reliable and stable.

### Publication biases

The authors examined potential publication biases in this meta-analysis by assessing the symmetry of funnel plots. Funnel plots were found to be generally symmetrical, which indicated that our merged quantitative analysis results were unlikely to be affected by publication biases.

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**Table 1. Cont.**

| First author, year | Country                   | Ethnicity   | Sample size | Genotypes (wt/wt/mt/mt) | P-value for HWE | NOS score |
|--------------------|---------------------------|-------------|-------------|-------------------------|----------------|-----------|
| Stavric, 2012      | Republic of Macedonia     | Caucasian   | 66/301      | 40/20/6                 | 0.052          | 7         |
| Westphal, 2003     | Germany                   | Caucasian   | 125/367     | 143/118/40              | 0.052          | 7         |
| Gharagozlou, 2013  | Iran                      | Mixed       | 89/139      | 63/22/4                 | 0.775          | 7         |
| Kayserova, 2012    | Czech Republic            | Caucasian   | 93/103      | 43/33/17                | 0.693          | 8         |
| Reich, 2003        | Germany                   | Caucasian   | 94/214      | 27/48/19                | 0.796          | 8         |
| Stavric, 2012      | Republic of Macedonia     | Caucasian   | 65/301      | 33/23/9                 | 0.492          | 7         |
| Westphal, 2003     | Germany                   | Caucasian   | 125/367     | 144/132/25              | 0.434          | 8         |

wt – wild type, mt – mutant type, HWE – Hardy-Weinberg equilibrium, NOS – Newcastle-Ottawa scale, NA – not available.

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**Quantitative analyses of IL-18 polymorphisms and AD**

Six publications explored the relationship between IL-18 -137G/C polymorphism and the risk of AD. The merged quantitative analyses revealed that IL-18 -137G/C polymorphism was significantly associated with the risk of AD in overall population (dominant comparison: OR = 2.06, \( p = 0.007 \); recessive comparison: OR = 0.24, \( p < 0.001 \); over-dominant comparison: OR = 0.74, \( p = 0.05 \); allele comparison: OR = 2.04, \( p = 0.003 \)), Caucasians (allele comparison: OR = 1.45, \( p = 0.05 \)) and Asians (dominant comparison: OR = 3.75, \( p < 0.001 \); recessive comparison: OR = 0.18, \( p < 0.001 \); over-dominant comparison: OR = 0.64, \( p = 0.04 \); allele comparison: OR = 3.41, \( p < 0.001 \)) (Table 2).
The risk of atopic dermatitis may be affected by IL-1B +3954 C/T and IL-18 -137G/C polymorphisms: evidence from a meta-analysis

| Variables | Sample size | Dominant comparison | Recessive comparison | Over-dominant comparison | Allele comparison |
|-----------|-------------|---------------------|----------------------|--------------------------|-------------------|
|           |             | P-value OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) |
| TNF-α -238 G/A rs361525: | Overall 712/1517 | 0.12 1.88 (0.85–4.19) | 0.90 0.92 (0.24–3.45) | 0.13 0.52 (0.22–1.22) | 0.14 1.80 (0.83–3.90) |
|           | Caucasian 512/1228 | 0.09 1.46 (0.95–2.24) | 0.90 0.92 (0.24–3.45) | 0.10 0.68 (0.43–1.07) | 0.09 1.43 (0.95–2.16) |
| TNF-α -308 G/A rs1800629: | Overall 1028/2072 | 0.13 1.29 (0.93–1.79) | 0.58 1.61 (0.30–8.56) | 0.62 0.92 (0.67–1.26) | 0.37 1.14 (0.85–1.53) |
|           | Caucasian 664/1512 | 0.31 1.21 (0.84–1.75) | 0.24 2.66 (0.52–13.55) | 0.57 0.93 (0.74–1.17) | 0.87 1.03 (0.75–1.41) |
| IL-1A -889 C/T rs1800587: | Overall 389/785 | 0.71 1.05 (0.81–1.36) | 0.67 0.90 (0.55–1.47) | 0.77 1.07 (0.68–1.67) | 0.81 1.03 (0.83–1.27) |
|           | Caucasian 300/649 | 0.95 0.99 (0.74–1.33) | 0.55 0.52 (0.06–4.43) | 0.41 1.26 (0.72–2.22) | 0.96 0.99 (0.77–1.28) |
| IL-1B +3954 C/T rs1143627: | Overall 570/1239 | 0.79 1.03 (0.84–1.26) | 0.02 0.61 (0.41–0.91) | 0.25 1.13 (0.92–1.39) | 0.19 1.11 (0.95–1.33) |
|           | Caucasian 481/1099 | 0.96 1.01 (0.80–1.26) | 0.02 0.59 (0.38–0.91) | 0.17 1.17 (0.94–1.47) | 0.26 1.11 (0.93–1.32) |
| IL-1B -511 C/T rs16944: | Overall 374/1021 | 0.21 1.17 (0.92–1.50) | 0.78 1.05 (0.73–1.52) | 0.16 0.84 (0.66–1.07) | 0.43 1.07 (0.90–1.29) |
|           | Caucasian 285/882 | 0.33 1.14 (0.87–1.50) | 0.57 0.88 (0.56–1.37) | 0.53 0.92 (0.70–1.20) | 0.32 1.11 (0.90–1.36) |
| IL-6 -174 G/C rs1800795: | Overall 466/1124 | 0.11 1.21 (0.96–1.52) | 0.62 1.08 (0.80–1.47) | 0.06 0.80 (0.64–1.01) | 0.38 1.08 (0.91–1.27) |
|           | Caucasian 377/985 | 0.14 1.21 (0.94–1.56) | 0.71 1.06 (0.77–1.46) | 0.09 0.81 (0.63–1.03) | 0.42 1.08 (0.90–1.28) |
| IL-18 -137G/C rs187238: | Overall 507/498 | 0.007 2.06 (1.22–3.47) | < 0.001 0.24 (0.15–0.41) | 0.05 0.74 (0.56–0.99) | 0.003 2.04 (1.28–3.25) |
|           | Caucasian 263/304 | 0.11 1.39 (0.92–2.09) | 0.11 0.32 (0.08–1.27) | 0.34 0.82 (0.54–1.24) | 0.05 1.45 (1.01–2.09) |
| Asian 219/169 | 0.001 3.75 (2.45–5.73) | < 0.001 0.18 (0.10–0.34) | 0.04 0.64 (0.42–0.97) | < 0.001 3.41 (2.50–4.66) |

OR – odds ratio, CI – confidence interval, NA – not available, UC – ulcerative colitis, CD – Crohn’s disease. The values in bold represent statistically significant differences between cases and controls.
Discussion

This meta-analysis robustly estimated associations between \( \text{TNF-} \alpha \), IL-1, IL-6 or IL-18 polymorphisms and the risk of AD. The quantitative analysis results showed that IL-1B +3954 C/T and IL-1B -137G/C polymorphisms were significantly associated with the risk of AD. Nevertheless, we did not observe any positive associations for TNF- \( \alpha \) -238 G/A, TNF- \( \alpha \) -308 G/A, IL-1A -889 C/T, IL-1B -511 C/T and IL6 -174 G/C polymorphisms.

A few points should be considered when interpreting our findings. First, based on findings of previous observational studies, it is believed that investigated TNF- \( \alpha \), IL-1, IL-6 and IL-18 polymorphisms may alter mRNA expression level or protein function of TNF- \( \alpha \), IL-1, IL-6 and IL-18, generate an imbalance status between Th1 and Th2-related immune responses, and then influence the risk of AD [12, 13]. Nevertheless, the functionalities of investigated polymorphisms are still not well understood, and thus further studies are still needed to explore the exact underlying molecular mechanisms of the observed positive results for IL-1B +3954 C/T and IL-1B -137G/C polymorphisms. Second, we wish to study all polymorphic loci of TNF- \( \alpha \), IL-1, IL-6 and IL-18. Nevertheless, our literature search did not reveal sufficient eligible publications to support quantitative analyses for other polymorphic loci of these cytokines, so we only explored associations with the risk of AD for several most common common TNF- \( \alpha \), IL-1, IL-6 and IL-18 polymorphisms. Additionally, it is also worth noting that polymorphisms in other Th1-related cytokines such as IL-8 and IL-12 could not be investigated in a meta-analysis because only a few previous publications tried to elucidate the roles of these polymorphisms in AD, and therefore, we could not find sufficient relevant publications to warrant quantitative analyses. Third, considering that only a few studies were found to be eligible for quantitative analyses, it is also possible that the sample sizes of our quantitative analyses were still inadequate to reveal the real associations of TNF- \( \alpha \), IL-1, IL-6 and IL-18 polymorphisms with the risk of AD. So future studies with larger sample sizes still need to confirm our findings.

The major limitations of this meta-analysis were summarized as below. Firstly, our quantitative analysis results were only based on unadjusted integrating of previous publications. Without access to raw data of eligible publications, we can only estimate associations based on re-calculation of raw genotypic frequencies, but we have to admit that lack of further adjustment for baseline characteristics may certainly influence authenticity of our findings [14]. Secondly, environmental factors may also affect relationships between TNF- \( \alpha \), IL-1, IL-6 or IL-18 polymorphisms and the risk of AD. However, the majority of authors only focused on genetic associations in their publications, so it is impossible for us to explore genetic-environmental interactions in a meta-analysis of these previous publications [15]. Thirdly, we did not include grey literatures for quantitative analyses because these literatures are always incomplete and it is impossible for us to extract all required data from these literatures or assess their quality. Nevertheless, since we did not consider grey literatures for quantitative analyses, despite the fact that funnel plots were found to be overall symmetrical, we acknowledged that publication biases still may impact reliability of our merged results [16].

Conclusions

This meta-analysis demonstrates that IL-1B +3954 C/T and IL-1B -137G/C polymorphisms may affect the risk of AD. However, further studies with larger sample sizes are still needed to confirm our findings. Besides, scholars should also try to explore underlying molecular mechanisms of associations between above-mentioned polymorphisms and the risk of AD in the future.

Conflict of interest

The authors declare no conflict of interest.

References

1. Waldman AR, Ahluwalia J, Udoff J, et al. Atopic dermatitis. Pediatr Rev 2018; 39: 180-93.
2. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care 2017; 23 (8 Suppl): S115-23.
3. Boothe WD, Tarbox JA, Tarbox MB. Atopic dermatitis: pathophysiology, Adv Exp Med Biol 2017; 1027: 21-37.
4. Gavrilova T. Immune dysregulation in the pathogenesis of atopic dermatitis. Dermatitis 2018; 29: 57-62.
5. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunol Rev 2011; 242: 233-46.
6. Trier AM, Kim BS. Cytokine modulation of atopic itch. Curr Opin Immunol 2018; 54: 7-12.
7. Gürkan A, Yücel AA, Sönmez C, et al. Serum cytokine profiles in infants with atopic dermatitis. Acta Dermatovenerol Croat 2016; 24: 268-73.
8. Qi Y, Kong J, He J. Genetic relationship between IL-10 gene polymorphisms and the risk of clinical atopic dermatitis. BMC Med Genet 2019; 20: 83.
9. Liang J, Liu Y, Xue R, et al. Interleukin 4-590C/T (rs2243250) polymorphism is associated with increased risk of atopic dermatitis: meta-analysis of case-control studies. Derma titis 2017; 28: 144-51.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.
The risk of atopic dermatitis may be affected by IL-1B +3954 C/T and IL-18 -137G/C polymorphisms: evidence from a meta-analysis

12. Smith AJ, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev 2009; 20: 43-59.
13. Thompson SR, Humphries SE. Interleukin-18 genetics and inflammatory disease susceptibility. Genes Immun 2007; 8: 91-9.
14. Banihani SA, Abu-Alia KF, Khabour OF, et al. Association between resistin gene polymorphisms and atopic dermatitis. Biomolecules 2018; 8: 17.
15. Lee JU, Kim JD, Park CS. Gene-environment interactions in asthma: genetic and epigenetic effects. Yonsei Med J 2015; 56: 877-86.
16. Kiç S, Silan F, Hız MM, et al. Vitamin D receptor gene BSMI, FOKI, APAI, and TAQI polymorphisms and the risk of atopic dermatitis. J Investig Allergol Clin Immunol 2016; 26: 106-10.