



The role of epidermal differentiation gene complex studies in atopic dermatitis

Atopik dermatitte epidermal farklılaşma gen kompleksi çalışmalarının rolü

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Abstract

Atopic dermatitis (AD) is a chronic skin disease affecting mainly children with an increasing prevalence worldwide. AD is a complex trait resulting from genetic predisposition, skin barrier dysfunction, immune dysregulation, and environmental factors. The major risk factors for AD are a family history of atopy (eczema, asthma, or allergic rhinitis) and the loss-of-function mutations in the *filaggrin* (*FLG*) gene. This review highlights the role of the genetic abnormalities identified in AD, from the susceptibility loci in genome-wide associations to epigenetic studies.

Keywords: Atopic dermatitis, genetics, epidermal differentiation gene complex, filaggrin

Öz

Atopik dermatit (AD), dünya çapında yaygınlığı artmış çocukları etkileyen kronik bir deri hastalığıdır. AD, genetik yatkınlık, deri bariyeri işlev bozukluğu, immün disregülasyon ve çevresel faktörlerin etkileşiminden kaynaklanan karmaşık bir özelliktir. AD için başlıca risk faktörleri, ailede atopi öyküsü (egzama, astım veya alerjik rinit) ve *filaggrin* (*FLG*) genindeki fonksiyon kaybı mutasyonlarıdır. Bu derleme, genom çapında ilişkilendirme çalışmalarındaki duyarlılık lokuslarından epigenetik çalışmalara kadar tanımlanan genetik anormalliklerin AD'deki rolünü vurgulamaktadır.

Anahtar Kelimeler: Atopik dermatit, genetik, epidermal farklılaşma gen kompleksi, filaggrin

Introduction

Atopic dermatitis [AD, (MIM 603165)] is the most common chronic inflammatory skin disease affecting between (0.2-30%) of children worldwide. Data in developing countries is lacking, but its increasing prevalence is noted. This presents a major public health problem worldwide¹. AD usually manifests during infancy with a varied clinical presentation and is dependent on the patients' age. It has a chronic relapsing course over months to years. In addition, lesions

compatible with acute, sub-acute, and chronic eczema may be evident in the same patient at the same time².

AD is a complex trait resulting from genetic predisposition, skin barrier dysfunction, immune dysregulation, and environmental factors. The epidermal skin barrier is a gatekeeper that prevents excessive water loss, assists with temperature regulation, and restricts immunological "invasion" by microbes. The pathogenesis of AD involves abnormalities in the pathophysiology of this barrier.

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Inflammation with an increased T helper 2 (Th2) response to allergens presented following the above abnormalities leads to the manifestations of AD³. The major risk factors for AD are a family history of atopy (eczema, asthma, or allergic rhinitis) and the loss-of-function mutations in the *FLG* [*FLG*, (*MIM* 135940)] gene that is essential for maintaining skin barrier function⁴.

This review summarizes the genetic abnormalities identified in AD, from susceptibility loci in genome-wide associations (GWAS) to epigenetic studies. We aim to highlight the role of *epidermal differentiation complex* (*EDC*) genes in the pathogenesis of AD.

Epidermal skin barrier proteins in atopic dermatitis

Profilaggrin, a large repetitive polyprotein, is the main component of keratohyaline granules in the stratum granulosum layer of the epidermis. During terminal differentiation of granular cells to flattened squames of the stratum corneum, profilaggrin is processed into multiple free 37 kDa filaggrin monomers that condense the cytoskeleton of the skin. *FLG* is broken down by chemical modification and proteolytic processing within the squames and forms a natural moisturizing factor, a natural humectant within the residual cytoplasmic space of the squames⁵. The *FLG* gene is located on chromosome 1q21 within the *EDC* genes that encode the structural epidermal proteins, named S100-fused type proteins, and include profilaggrin, filaggrin-2, hornerin, repetin, trichohyalin, cornulin, and trichohyalin-like 1⁶. The *FLG* gene has three exons, and the profilaggrin protein is encoded by the third exon. It comprises almost identical tandem repeats of about 972 base pairs and has allelic variants of 10, 11, and 12 repeats (Figure 1)⁷.

Identifying the link between AD and loss-of-function (LOF) mutations of *FLG* gene has led to studies on the pathogenetic role of *FLG* in AD⁸. *FLG*-null mutations lead to *FLG* deficiency and cause increased skin permeability, increased penetration of environmental allergens, irritants, and microorganisms, causing an inflammatory response. The LOF mutations in *FLG* are major risk factors for the early onset of AD, more severe disease, and the greater incidence of other allergic diseases, including food allergies and asthma. In two meta-analyses, AD risk was higher in individuals carrying either one or both R501X and 2282del4 mutations compared with non-carriers^{9,10}. Around 10% of European ancestry individuals carry a single null mutation in *FLG*. The most common LOF mutations in white Europeans are R501X, 2282del4, S3247X, and R2447X⁴. In European populations, carriage of one or more *FLG* LOF mutations results in three times increased risk for AD⁴, indicating a substantial effect for a single gene in a disease of a complex trait.

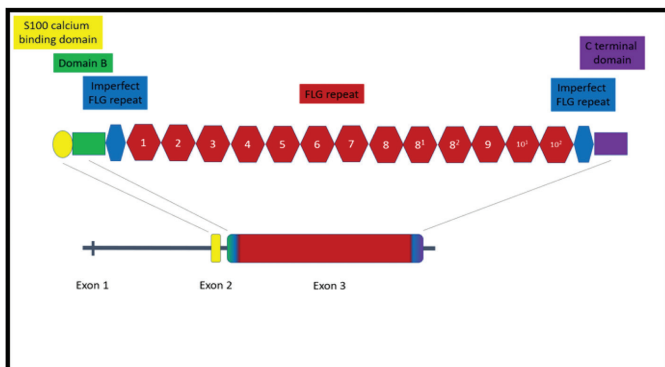


Figure 1. The structure of the *filaggrin* (*FLG*) gene

In contrast, in populations from Asia, Africa, or African ancestry, the *FLG* mutations that are highly prevalent in European patients are uncommon, and unique *FLG* mutations in these ethnic groups were found¹. The R501X mutation in the *FLG* gene is not seen in any of the children in the AD (n=49) and control (n=50) groups in a sample population of Turkish children¹¹. In addition, the mutations in the *FLG* gene and the copy number variations or epigenetic regulation of *FLG* were shown to modulate *FLG* expression. The low intragenic copy number variation of *FLG* in different ethnic groups of patients with AD correlates with disease severity^{12,13}.

FLG-2 and hornerin (*HRNR*) are other proteins critical for the stratum corneum and its barrier function. The expression of *FLG*-2 and *HRNR* are significantly reduced in both lesional and non-lesional skin of patients with AD compared with healthy subjects¹⁴. Recently, novel mutations in *FLG* and other *EDC* genes, such as *FLG*-2 and *claudin 1* (*CLDN1*), were associated with AD patients, with either disease severity or the early onset of AD in children younger than five years old, respectively^{15,16}. Immune-mediated skin inflammation does not differ in AD patients with or without *FLG* mutations. However, the upregulation of Th2 cytokines interleukin-4 (IL-4) and IL-13 leads to the downregulation of *FLG* expression, causing a *FLG* deficiency and consequently impairs epidermal barrier function¹⁷. Treating human keratinocytes with proinflammatory cytokines reduces the expression of pro*FLG*, *FLG*-2, and *HRNR*, which negatively affects the cytokines on the epidermal barrier¹⁴.

1. Genome-wide association studies

Genome-wide association studies are the methods for identifying genes in complex disorders and have helped identify novel genes for AD (i.e., *FLG* on chromosome 1p21)¹⁸. In 2009, the first AD GWAS was conducted in a European population. It detected the locus on chromosome 1q21.3 (the *EDC*, including *FLG*) with a novel susceptibility locus on chromosome 11q13.5¹⁹. The largest meta-analyses of GWAS data on AD in different ethnic groups (European, African, Japanese, Latino, and mixed non-European ancestry) included 21,399 cases and 95,464 controls, with 15 million genetic variants and 31 AD risk loci detected²⁰. However, out of 31 risk loci, only three loci (IL-13, *FLG*, and IL-6R) were coding variants. The function of most GWAS loci remains unclear, but they correlate with skin barrier development and immunological dysfunctions, i.e., innate immune signaling, T-cell activation, and differentiation in acquired immunity^{20,21}. Despite recent advances, the loci identified by GWAS explain approximately 15% of the variance^{20,21}. This unaccountable 85% is called “missing heritability” of complex diseases and may be explained by the marked heterogeneity of AD, the cumulative effects of these structural variations and genome copy number variants, and heritable epigenetic mechanisms²¹.

2. Exome sequencing studies

With recent advances in next-generation sequencing technologies, the protein-coding region of genes in a genome (called an exome) of an individual can be sequenced (whole-exome sequencing, WES). This allows the study to discover the rare variations in polygenic diseases²². On the other hand, the limitation of the exome sequencing studies is that they have shown limited success for complex traits²³.

To date, few studies of WES analyses of AD focusing on *EDC* genes have been published. A WES study of 22 Ethiopian patients with ichthyosis vulgaris and AD identified several rare variants consistent

with a heterogenous disease pathogenesis²⁴. Also, the same research group showed an association between the *CLDN1* gene and early onset AD (younger than five years old) in their Ethiopian cohort¹⁶. Another WES that entailed a targeted analyses of the EDC region in 60 African-American children with AD found a *FLG-2* variant associated with a more persistent phenotype²⁵. In a WES study of a cohort of three families, Heo et al.²⁶ identified both rare and common variants of the *COL6A6* gene as possible novel candidates for early onset AD in Koreans. In the same study, missense mutations of *FLG* [A3262T, Q3520P (rs80088153)] and *FLG-2* [C298S (rs2282302)] were found in three families on chromosome one. In another WES study, 13 LOF *FLG* variants (five were novel) were identified in 21 of the 43 probands of 42 Bangladeshi families residing in the United Kingdom²⁷.

These findings show that WES is effective for identifying rare population-specific variants. However, it must be considered that these studies were done in a limited number of patient cohorts with specific ethnicities. It thus might be difficult to replicate these results in other populations²⁸.

3. Transcriptome analyses

The accessibility of skin tissue has enabled the comparison of gene expression patterns between lesional, non-lesional, and normal skin. Gene expression profiling assays, namely RNA-sequencing technology, have improved the analyses and quantification of mRNA over those of the past with previous microarray studies²⁹. High-throughput gene expression profiling showed that the expression of keratinocyte differentiation genes was dysregulated (i.e., downregulation of *FLG* and *involucrin*; up regulation of *loricrin*) in AD skin biopsy specimens compared with healthy controls¹. In a transcriptome profiling study using RNA-sequencing, differences in genes expressed between AD and normal skin were reported in pathways involving lipid metabolism, the extracellular space, and the stress response. When the transcriptome data were stratified according to *FLG* genotype, *FLG* deficient skin expressed a type-1 interferon-mediated stress response³⁰. A meta-analysis of four microarray studies (meta-analysis derived AD transcriptome) shed light on novel key AD pathways; atherosclerosis signaling (IL-37, selectin-E, S100A8), lipid abnormalities (FA2H, ELOVL3), and negative correlations between the expression of Th2 cytokines and epidermal lipids³¹. In another study using transcriptome data from public databases, Ghosh et al.³² presented an 89 gene panel that could be utilized as a signature for AD. The differentially regulated genes were categorized into the following functional classes: (a) barrier function-related genes, e.g., *LOR*, *LCE2B*; (b) dysregulated lipid genes, e.g., *FABP7*, *FADS1*; (c) chemokine/cytokine genes, e.g., *CCL17*, *CCL18*; (d) protease and protease-inhibitor genes, e.g., *SERPINB3*, *KLK5*; (e) anti-microbial function, e.g., *LTF*, *MSMB*; and (f) genes with diverse metabolic functions, e.g., *ARGAP18*³². In a study of rare-protein variants employing exome chip and replication genotype data of 15,574 AD patients and 377,839 controls, Mucha et al.³³ identified CD200 receptor 1 (*CD200R1*) and (*DOK2*) as two novel susceptibility genes.

Transcriptomic profiling studies of AD found that using full-thickness skin biopsies leads to an over representation in the expression of epidermis-specific genes due to epidermal hyperplasia. In contrast, dermis-specific genes are found to be underrepresented³⁴. This bias also results in the up regulation of false positives or down regulation of false negatives.

This could be overcome by using laser capture microdissection to achieve compartment-specific transcriptional profiling³⁵. Different AD pathways were detected in different patient groups, i.e., Th1 profiles were observed in adult AD patients, whereas enriched Th17/Th22-associated gene profiles (e.g., *CCL20*, *IL36*, *IL36RN*, and *IL23*) were found in pediatric patients³⁴. A similar bias was detected when comparing the manifestation of AD among different ethnic groups. While European-Americans exhibited a Th-1 type AD profile, in African-American and Asian AD patients, the TH17 axis was enhanced³⁶.

4. Epigenetic studies

Epigenetics focuses on heritable changes in DNA expression through DNA methylation, histone modification, and non-coding RNA (microRNA) expression. Abnormal epigenetic gene regulation via methylation involved in innate immune responses and skin barrier functions contributes to the pathogenesis of AD²⁸. Hypomethylation of the promoters of *FCERG* that encode *FcεRγ*, a high-affinity immunoglobulin E receptor chain, and *TSLP*, results in the overexpression of these genes in AD²². Global DNA hypomethylation and demethylation of regulatory elements of *FCER1G* contribute to *FcεRI* overexpression on the monocytes of AD patients³⁷. Rodríguez et al.³⁸ described significant differences in the methylation pattern for various CpG islands between lesional AD skin samples versus healthy control skin. However, no significant difference was observed in genome-wide DNA methylation levels of whole blood, B-cell, and T-cell samples obtained from AD cases and controls³⁸. Ziyab et al.³⁹ reported that methylation levels of the CpG site had an increased risk of eczema in *FLG* haploinsufficient individuals compared with those with the wild *FLG* genotype. However, another study for this apparent role of *FLG* methylation yielded contradicting results⁴⁰. These conflicting results in DNA methylation findings indicate that blood does not function as an ideal surrogate for skin and demonstrates the roles of tissue-specific epigenomic changes^{38,41}.

MicroRNAs (miRNAs) are short, single-stranded RNA molecules that, together with partner proteins, result in the degradation of target mRNAs³⁷. The increased expression of miRNA-155 on Th1 and Th2 cells is detected in skin lesions and blood samples of AD patients and is regulated by allergens and superantigens. MiRNA-155 increases Th cell responses by decreasing the expression of cytotoxic T-lymphocyte-associated antigen 4, which is the key molecule that inhibits the T-cell response⁴². MiRNA-146a may also play an important role in AD. It was unregulated in both affected and intact skin⁴³. On the other hand, miRNA-143, which was downregulated in skin samples of AD patients, suppressed IL-13-induced inflammation and downregulation of *FLG*, the epidermal barrier proteins, by targeting its receptor⁴⁴.

Conclusion

AD is a complex disease trait. Identifying genetic mutations in the *FLG* gene causing skin barrier dysfunction in 2006 was a pioneering step in understanding its pathogenesis. However, these mutations cannot be shown in every individual with AD. This provides the need for research into explaining the latter. It has also been shown that there are *FLG*-null mutations specific to different populations.

This challenges earlier studies on the pathogenesis of AD based on European mutations. A study on AD in Turkey analyzed only one

European *FLG* LOF mutation. This highlights the need for further genetic studies that include the cosmopolitan population groups in Turkey. Genes controlling the innate and adaptive immune system are crucial to maintaining the immunological stability of the skin. Polymorphisms of the Th2 signaling pathway genes have been implicated in the pathogenesis and clinical manifestations of AD. Polymorphisms of IL-4, IL-13, and IL-31 and their receptors (IL4R α and IL13R α 1) are associated with an increased risk of AD due to the alternations in signal transduction pathways. The insights gained from these and further genetic studies will enable the development of novel targeted therapies and ultimately lead to individualized treatments for the heterogeneous phenotypes of AD.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.G., Design: Ö.G., D.M., R.D., Literature Search: Ö.G., Writing: Ö.G., D.M., R.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation and treatment. *Exp Dermatol* 2018;27:340-57.
2. McAleer MA, O'Regan GM, Irvine AD. Atopic dermatitis. *Dermatology*. Ed. Bologna JL, Schaffer JV, Cerroni L. 4th Edition. Elsevier, 2018;208-27.
3. Weidinger S, Novak N: Atopic Dermatitis. *Lancet* 2016;387:1109-22.
4. Irvine AD, McLean WH, Leung DY: Filaggrin mutations associated with skin and allergic diseases. *N Eng J Med* 2011;365:1315-27.
5. McLean WH: Filaggrin failure-from ichthyosis vulgaris to atopic eczema and beyond. *Br J Dermatol* 2016;175(Suppl 2):4-7.
6. Cabanillas B, Novak N: Atopic dermatitis and filaggrin. *Curr Opin Immunol* 2016;42:1-8.
7. Mathyer ME, Quiggle AM, Wong XFCC, et al: Tiled array-based sequencing identifies enrichment of loss-of-function variants in the highly homologous filaggrin gene in African-American children with severe atopic dermatitis. *Exp Dermatol* 2018;27:989-92.
8. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
9. Rodríguez E, Baurecht H, Herberich E, et al: Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009;123:1361-70.e7.
10. van den Oord RA, Sheikh A: Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009;339:b2433.
11. Ercan H, Ispir T, Kirac D, et al: Predictors of atopic dermatitis phenotypes and severity: roles of serum immunoglobulins and filaggrin gene mutation R501X. *Allergol Immunopathol (Madr)* 2013;41:86-93.
12. Brown SJ, Kroboth K, Sandilands A, et al: Intragenic copy number variation within filaggrin contributes to the risk of atopic dermatitis with a dose-dependent effect. *J Invest Dermatol* 2012;132:98-104.
13. Quiggle AM, Goodwin ZA, Marfatia TR, et al: Low filaggrin monomer repeats in African American pediatric patients with moderate to severe atopic dermatitis. *JAMA Dermatol* 2015;151:557-9.
14. Pellerin L, Henry J, Hsu CY, et al: Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol* 2013;131:1094-102.
15. Margolis DJ, Gupta J, Apter AJ, et al: Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. *J Invest Dermatol* 2014;134:2272-4.
16. Asad S, Winge MC, Wahlgren CF, et al: The tight junction gene Claudin-1 is associated with atopic dermatitis among Ethiopians. *J Eur Acad Dermatol Venereol* 2016;30:1939-41.
17. Howell MD, Kim BE, Gao P, et al: Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120: 150-5.
18. Portelli MA, Hodge E, Sayers I: Genetic risk factors for the development of allergic disease identified by genome-wide association. *Clin Exp Allergy* 2014;45:21-31.
19. Esparza-Gordillo J, Weidinger S, Fölster-Holst R, et al: A common variant on chromosome 11q13 is associated with atopic dermatitis. *Nat Genet* 2009;41:596-601.
20. Paternoster L, Standl M, Waage J, et al: Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015;47:1449-56.
21. Løset M, Brown SJ, Saunes M, Hveem K: Genetics of atopic dermatitis: From DNA sequence to clinical relevance. *Dermatology* 2019;235:355-64.
22. Bin L, Leung DY: Genetic and epigenetic studies of atopic dermatitis. *Allergy Asthma Clin Immunol* 2016;12:52.
23. Stemmler S, Hoffjan S: Trying to understand the genetics of atopic dermatitis. *Mol Cell Probes* 2016;30:374-85.
24. Taylan F, Nilsson D, Asad S, et al: Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 2015;136:507-9.
25. Margolis DJ, Gupta J, Apter AJ, et al: Filaggrin-2 variation is associated with more persistent atopic dermatitis in African American subjects. *J Allergy Clin Immunol* 2014;133:784-9.
26. Heo WI, Park KY, Jin T, et al: Identification of novel candidate variants including COL6A6 polymorphisms in early-onset atopic dermatitis using whole-exome sequencing. *BMC Med Genet* 2017;18:8.
27. Pigors M, Common JEA, Wong XFCC, et al: Exome sequencing and rare variant analysis reveals multiple filaggrin mutations in bangladeshi families with atopic eczema and additional risk genes. *J Invest Dermatol* 2018;138:2674-7.
28. Stemmler S, Hoffjan S: Trying to understand the genetics of atopic dermatitis. *Mol Cell Probes* 2016;30:374-85.
29. Brown SJ: Molecular mechanisms in atopic eczema: Insights gained from genetic studies. *J Pathol* 2017;241:140-5.
30. Cole C, Kroboth K, Schurch NJ, et al: Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis. *J Allergy Clin Immunol* 2014;134:82-91.
31. Ewald DA, Malajian D, Krueger JG, et al: Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. *BMC Medical Genomics* 2015;8:60.
32. Ghosh D, Ding L, Sivaprasad U, et al: Multiple transcriptome data analysis reveals biologically relevant atopic dermatitis signature genes and pathways. *PLoS One* 2015;10:e0144316.
33. Mucha S, Baurecht H, Novak N, et al: Protein-coding variants contribute to the risk of atopic dermatitis and skin-specific gene expression. *J Allergy Clin Immunol* 2020;145:1208-18.
34. Schwigen J, Kaplan M, Kurschus FC: Review-current concepts in inflammatory skin diseases evolved by transcriptome analysis: in-depth analysis of atopic dermatitis and psoriasis. *Int J Mol Sci* 2020;21:699.
35. Esaki H, Ewald DA, Ungar B, et al: Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. *J Allergy Clin Immunol* 2015;135:153-63.
36. Sanyal RD, Pavel AB, Glickman J, et al: atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation. *Ann Allergy Asthma Immunol* 2019;122:99-110.
37. Liang Y, Chang C, Lu Q. the genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. *Clin Rev Allergy Immunol* 2016;51:315-28.

38. Rodríguez E, Baurecht H, Wahn AF, et al: An integrated epigenetic and transcriptomic analysis reveals distinct tissue-specific patterns of DNA methylation associated with atopic dermatitis. *J Invest Dermatol* 2014;134:1873-83.
39. Ziyab AH, Karmaus W, Holloway JW, Zhang H, Ewart S, Arshad SH: DNA methylation of the filaggrin gene adds to the risk of eczema associated with loss-of-function variants. *J Eur Acad Dermatol Venereol* 2013;27:e420-3.
40. Tan HT, Ellis JA, Koplin JJ, et al: Methylation of the filaggrin gene promoter does not affect gene expression and allergy. *Pediatr Allergy Immunol* 2014;25:608-10.
41. Ghosh D, Bernstein JA, Khurana Hershey GK, Rothenberg ME, Mersha TB. Leveraging multilayered "omics" data for atopic dermatitis: a road map to precision medicine. *Front Immunol* 2018;9:2727.
42. Ma L, Xue HB, Wang F, Shu CM, Zhang JH: MicroRNA-155 may be involved in the pathogenesis of atopic dermatitis by modulating the differentiation and function of T helper type 17 (Th17) cells. *Clin Exp Immunol* 2015;181:142-9.
43. Rożalski M, Rudnicka L, Samochocki Z: MiRNA in atopic dermatitis. *Postepy Dermatol Alergol* 2016;33:157-62.
44. Zeng YP, Nguyen GH, Jin HZ: MicroRNA-143 inhibits IL-13-induced dysregulation of the epidermal barrier-related proteins in skin keratinocytes via targeting to IL-13R α 1. *Mol Cell Biochem* 2016;416:63-70.