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DETERMINATION OF THE EFFECT OF KIF3A GENE POLYMORPHISM IN CHILDREN WITH ATOPIC DERMATITIS

PHD THESIS

HÜLYA ERCAN SARIÇOBAN, MD

İSTANBUL

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ATOPİK DERMATİTLİ ÇOCUKLARDA KIF3A GEN POLİMORFİZMİNİN ETKİSİNİN BELİRLENMESİ

PHD THESIS

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THESIS APPROVAL FORM

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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..... and numbered .....

Prof. Dr. Bayram YILMAZ

Director of Institute of Health Sciences

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for an award of any other degree except where due acknowledgment has been made in the text.

Hülya ERCAN SARIÇOBAN

DEDICATION

I dedicate my thesis to my lovely daughters Ayda and Ada.

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LIST OF SYMBOLS AND ABBREVIATIONS

ACTL9	Actin-like protein 9
AD	Atopic Dermatitis
AR	Allergic Rhinitis
ARIA	The Allergic Rhinitis and its Impact on Asthma
ATOD6	Dermatitis, atopic, 6
β	Beta
C	Cytosine
℃	Celsius
CI	Confidence interval
CpG	Cytosine-phosphate- guanine
CRP	C reactive protein
DEG	Differentially expressed gene
DC	Dendritic cell
DNA	Deoxyribose nucleic acid
DNase	Deoxyribonuclease
EDTA	Ethylenediaminetetraacetic acid
Et al.	And others
FLG	Filaggrin
FISH	Fluorescent in situ hybridization
GINA	Global Initiative for Asthma

IDEC	Inflammatory dendritic epidermal cell
Ig	Immunoglobulin
IL	Interleukin
IU	International unit
kDa	Kilo Dalton
KIF3A	Kinesin family protein 3A
LC	Langerhans cells
LD	Linkage disequilibrium
MADAD	Meta-analysis derived atopic dermatitis
MAF	Minor allele frequency
µl	Microliter
ml	Milliliter
mm	micrometer
min	Minutes
NaCl	Sodium chloride
Nm	Nanometer
OD	Optical Density
OR	Odd ratio
OVOL1	Ovo like transcriptional repressor 1
PCR	Polimerase chain reaction
pH	Potential of hydrogen

RNase	Reoxyribonuclease
Rpm	Revolutions per Minute
RT-PCR	Real-time polymerase chain reaction
SCORAD	Atopic dermatitis score (score of atopic dermatitis)
SD	Standard deviation
sec	Seconds
SNP	Single nucleotide polymorphism
SPSS	Statistical package for social sciences
SPINK	Serine protease inhibitor Kazal type 5
T	Thymine
TEWL	Transepidermal water loss
Th	Helper T cell (Heper T cell)
Tp53 gene	Tumor protein p53
Tris-Cl	Trisaminomethane chloride
TSLP	Thymic stromal lymphopoietin
UV	Ultraviolet light
WHO	World health organization
χ^2	Chi square

ABSTRACT

Saricoban, H.E. (2023). Determination of the Effect of KIF3A Gene Polymorphism in Children with Atopic Dermatitis. Yeditepe University, Institute of Health Science, Department of Molecular Medicine. Doctorate thesis, Istanbul.

Atopic dermatitis (AD) is the most common chronic, pruritic, recurrent inflammatory skin disease in childhood. Disruption of the skin barrier and exaggeration of the immune response (especially the Th2 response) seem to be associated with the development, severity and persistence of atopic diseases. Skin barrier/epidermal regulation genes and genes involved in immune response/host defense play key roles. However, the mechanism of these relationships is not clear yet. In recent years, studies indicating that KIF3A may have an important role in skin barrier homeostasis and inflammation have been increasing. The literature has begun to reveal the relationship between the KIF3A gene (rs2897442) polymorphism and AD. To date, the relationship between atopic dermatitis and genetic mutation has not been demonstrated in Turkish population. it is aimed to investigate the KIF3A mutation and the inflammatory changes that occur in Turkish children with atopic dermatitis and their relationship with each other. The KIF3A gene (rs2897442) polymorphism was performed in 48 with atopic dermatitis and 46 healthy children aged 2 months to 16 years. Clinical data including age, gender, atopy status, SCORAD, presence of other concomitant allergic diseases, family history, and eosinophil count, percentage, total Ig E, skin prick test results were recorded. DNA isolation was performed using the DNA Isolation Robot. Real-Time PCR (RT-PCR) was then performed using the KIF3A detection kit. Allelic discrimination was then obtained from both the patient and control groups. Then, statistical analyzes were made using Fisher's Exact Tests and Chi-square tests in SPSS 26.0 program, and also student's t-test, Mann-Whitney U-test and Kruskal-Wallis test were used for numerical values. P values less than or equal to 0.05 are considered statistically significant. The KIF3A region of 48 patients with atopic dermatitis (M: 25, F: 23 with a mean age of 4.89 ± 3.67 years) and 46 healthy children in the control group (M: 27, F: 19 with a mean age of 3.76 ± 2.83) years was genotyped. Total IgE, absolute eosinophil count and eosinophil percentage are higher in individuals with atopic dermatitis than in healthy individuals. There was no significant difference between KIF3A genotype and atopic dermatitis and control groups (p=0.08). Carrying the CC genotype increased the risk of atopic dermatitis disease 4 fold

compared to the control group (p=0.043, $\chi 2$ =4.610, OR=4.053, 95%). CI=1.051-15.631). Carrying the T allele protects against atopic dermatitis (p=0.040, OR=0.235, 95%. CI=0.061-0.905). TT genotype had lower absolute eosinophil counts (p=0.023), and those with C allele had higher values (p=0.023). No statistically significant relationship was found between the KIF3A gene polymorphism and the severity of atopic dermatitis. In conclusion, It is the first pilot study showing the risk of KIF3A gene polymorphism in the development of atopic dermatitis for the Turkish population. Carrying a homozygous C (CCgenotype) increases the risk of developing AD, and carrying the T allele decreases the risk of AD. TT genotype had lower absolute eosinophil counts, and those with C allele had higher values In this regard, it is recommended to perform gene polymorphism in a larger study group and to conduct more analysis on the genotype-phenotype relationship and its effect on treatment.

Keywords: Atopic dermatitis, children, KIF3A, rs2897442

ÖZET

Saricoban, H.E. (2023). Atopik Dermatitli Çocuklarda KIF3A Gen Polimorfizminin Etkisinin Belirlenmesi. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Moleküler Tıp Anabilim Dalı. Doktora tezi, İstanbul.

Atopik dermatit (AD), çocukluk çağında en sık görülen kronik, kaşıntılı, tekrarlayan inflamatuar deri hastalığıdır. Deri bariyerinin bozulması ve immün yanıtın (özellikle Th2 yanıtının) abartılı olması, atopik hastalıkların gelişimi, şiddeti ve devamlılığı ile ilişkili görünmektedir. Deri bariyeri/epidermal düzenleme genleri ve bağışıklık yanıtı/konak savunmasında yer alan genler kilit roller oynar. Ancak bu ilişkilerin mekanizması henüz net değil. Son yıllarda KIF3A'nın cilt bariyeri homeostazı ve inflamasyonunda önemli rolü olabileceğini gösteren çalışmalar artmaktadır. Literatürde KIF3A geni (rs2897442) polimorfizmi ile AD arasındaki ilişkiyi ortaya koymaya başlamıştır. Bugüne kadar atopik dermatit ile genetik mutasyon arasındaki ilişki Türk popülasyonunda gösterilememiştir. Bu çalışmada, atopik dermatitli Türk çocuklarında meydana gelen inflamatuvar değişiklikler ve KIF3A mutasyonu ile bunların birbirleri ile ilişkisinin araştırılması amaçlanmaktadır. KIF3A geni (rs2897442) polimorfizmi 2 ay ile 16 yaş arası 48 atopik dermatitli, 46 sağlıklı çocukta araştırıldı. Yaş, cinsiyet, atopi durumu, SCORAD, eşlik eden başka alerjik hastalık varlığı, aile öyküsü gibi klinik veriler ile eozinofil sayısı, yüzdesi, total Ig E, deri prik testi sonuçları kaydedildi. DNA izolasyonu DNA İzolasyon Robotu kullanılarak yapıldı. Sonra sonra KIF3A tespit kiti kullanılarak Real-Time PCR (RT-PCR) yapıldı. Daha sonra hem hasta hem de kontrol gruplarından alelik ayrım elde edildi. Daha sonra SPSS 26.0 programında Fisher's Exact Testleri ve Ki-kare testleri kullanılarak istatistiksel analizler yapılmış ve ayrıca sayısal değerler için student's t-testi ve Mann-Whitney U-test ve Kruskal-Wallis testinden yararlanılmıştır. 0,05'ten küçük veya eşit olan p değerleri istatistiksel olarak anlamlı kabul edilir. Atopik dermatitli 48 hasta (E: 25, K: 23, ortalama yaş 4,89 ± 3,67 yıl) ve kontrol grubundaki 46 sağlıklı çocuğun (E: 27, K: 19, ortalama yaş 3,76 ±2.83 yıl) KIF3A bölgesi genotiplendi. Atopik dermatitli bireylerde total IgE, mutlak eozinofil sayısı ve eozinofil yüzdesi sağlıklı bireylere göre daha yüksekti. KIF3A genotipi ile atopik dermatit ve kontrol grupları arasında anlamlı fark yoktu (p=0,08). CC genotipini taşımak, atopik dermatit hastalık riskini kontrol grubuna göre 4 kat arttırmaktadır (p=0,043, $\chi 2$ =4,610, OR=4,053, %95). CI=1.051-15.631). T alelinin taşınması atopik dermatite karşı koruma sağlar (p=0.040,

OR=0.235, %95. CI=0.061-0.905). TT genotipinde mutlak eozinofil sayısı daha düşükken (p=0,023), C alleli olanlarda daha yüksek değerlere sahiptir (p=0,023). KIF3A gen polimorfizmi ile atopik dermatitin şiddeti arasında istatistiksel olarak anlamlı bir ilişki bulunmadı. Sonuç olarak, Bu çalışma,Türk popülasyonu için atopik dermatit gelişiminde KIF3A gen polimorfizmi riskini araştıran ilk pilot çalışmadır. Homozigot bir C (CCgenotip) taşımak AD geliştirme riskini artırır ve T aleli taşımak AD riskini azaltır. TT genotipinde mutlak eozinofil sayısı daha düşük, C aleli olanlarda ise daha yüksektir. Bu bağlamda gen polimorfizminin daha geniş bir çalışma grubunda yapılması, genotip-fenotip ilişkisi ve tedaviye etkisinin daha fazla analiz edilmesi önerilmektedir.

Anahtar Kelimeler: Atopik dermatit, çocuk, KIF3A, rs2897442

1. INTRODUCTION AND PURPOSE

Atopic Dermatitis (AD) is a chronic disease of the skin. It progresses with the repetition of dryness, redness and itching on the skin. Drying of the skin is caused by transepidermal water loss (1). Atopic dermatitis is diagnosed in 1 out of every 5 children (2). The incidence of atopic dermatitis increases in children with a family history of allergic disease. Infants with AD may later develop Allergic Rhinitis (AR) and/or asthma. This condition called atopic march (1). Hill and Sulzberger was first used the term atopic dermatitis in the literature in 1930 (3). Although many clinical, laboratory and experimental studies have been conducted on this subject, the pathophysiology of AD has not yet been fully elucidated. It is thought that genetic and environmental factors interact with each other and together. (4,5).

Atopic dermatitis is seen in two phenotypes as allergic (extrinsic, atopic) and non-allergic (intrinsic, non-atopic) (3). Atopic dermatitis is a complex condition that develops as fluid loss from the skin and an abnormal immune response as a result of encountering a genetic and/or environmental factors that causes disruption of the skin barrier. 4 out of 5 patients had eosinophilia, high levels of allergen-specific and total IgE, IL-13, IL-5, fitting the definition of 'extrinsic' atopic dermatitis, worsening with exposure to foods or aeroallergens. In the remaining patients, an 'intrinsic' type of atopic dermatitis was defined that does not show specific IgE-mediated allergic sensitization (4).

About 30% of infants and children with atopic dermatitis have food hypersensitivity. More than half of young children with atopic dermatitis progress to asthma over time, and 75% to allergic rhinitis. Especially in patients with atopic dermatitis who have a family history of allergic disease, the progression of their disease to asthma and then allergic rhinitis over time is called atopic march.' (6).

The genetics of atopic dermatitis is a focus of interest in research. Atopic dermatitis occurs in three quarters of monozygotic twins and 15% of dizygotic twins. Patients with atopic dermatitis have a family history of associated diseases such as allergic rhinitis and asthma. These results suggest that atopic dermatitis has a genetic predisposition (7). Disruption of the skin barrier and exaggeration of the immune response (especially the Th2 response) seem to be associated with the development, severity and persistence of atopic diseases. However, the mechanism of these relationships is not clear yet. Transcriptomic profiles of many common murine models

have been studied so far, but a single model that can explain atopic dermatitis has not been demonstrated (Ewald, D.A.),

Skin barrier/epidermal regulation genes and genes involved in immune response/host defense play key roles. Many studies have been designed to find candidate genes in the formation of atopic dermatitis. Candidate gene approaches have examined many genes in terms of susceptibility to atopic dermatitis (5).

As a result of mutations and polymorphisms in the genes, the deterioration of the skin barrier increases the loss of water from the skin and the passage of allergens, chemicals and antigens through the skin. As a result of these events, the inflammatory response of the skin occurs. Disruption of the skin barrier and changes in the immune response in the epidermis and dermis determine the occurrence and severity of atopic dermatitis. However, the cellular and molecular mechanisms are not fully understood (7). It was shown that the first and most risky gene for the formation of atopic dermatitis in the skin barrier is the FLG gene, which encodes the filagrin protein (6). But, we could not find the mutation in the FLG gene in our study in the Turkish population (7).

In populations without mutations in the FLG gene, genome wide association studies report a relationship between rs479844, rs 2897442, rs2164983, ACTL9, OVOL1 and KIF3A genes and atopic dermatitis (8).

KIF3A is in the 5q31 region. This region contains the silokine cluster of immune-related and cytokine genes, particularly IL13 and IL4 (9).

Lepre et al. When they found that the FLG mutation was not found in the Italian population, they investigated the relationship between rs2897442 in KIF3A and AD, since it is located in close proximity to atopic dermatitis genes. They determined that the KIF3A mutation was statistically higher in patients with atopic dermatitis compared to the control group (10).

Similarly, in a study conducted in Chinese children without FLG mutation, it was shown that the C allele in KIF3A rs2897442 had a statistically increased risk of developing atopic dermatitis in children with atopic dermatitis compared to the healthy control group. (11).

Stevens et al. It has been shown that with the decrease of KIF3A, the skin barrier is disrupted and plays an important role in the development of AD (12). This suggested that KIF3A has a major role in skin barrier homeostasis.

To date, the relationship between atopic dermatitis and genetic mutation has not

been demonstrated in Turkish population. Upon reading studies that held in the past few years and demonestrated the strong association between the KIF3A gene (rs2897442) polymorphism and the susceptibility for AD. As a result, The KIF3A gene may be a risk factor for the development of AD in the Turkish population.

In conclusion, in this study, it is aimed to investigate the KIF3A mutation and the inflammatory changes that occur in Turkish children with atopic dermatitis and their relationship with each other.

2. LITERATURE REVIEW

2.1 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, pruritic, recurrent inflammatory skin disease (1). The most common chronic disease of childhood is AD; 20% of children and 5% of adults are affected (13). Half of the patients develop AD during infancy, the remaining 30% develop AD between the first 1-5 years, while 70% of the patients recover spontaneously(14). The term atopic dermatitis was first mentioned by Hill and Sulzberger in 1930 (15). The frequency of atopic dermatitis was found to be 8.1% in 6963 school children in Turkey (16).

While one out of every three AD patients develops asthma by the age of four, patients develop asthma (approximately 50% of patients) and then allergic rhinitis (approximately 75% of patients) over time. This condition is called atopic march (14). Atopic dermatitis presents with different body distribution regions and lesion patterns in different age groups (Figure 1)(13). In all stages, itching occurs all day, increasing at night. Sleep loss and disturbances due to itching and consequently quality of life deteriorates. AD creates morbidity problems such as loss of school and work, and emotional stress (2).

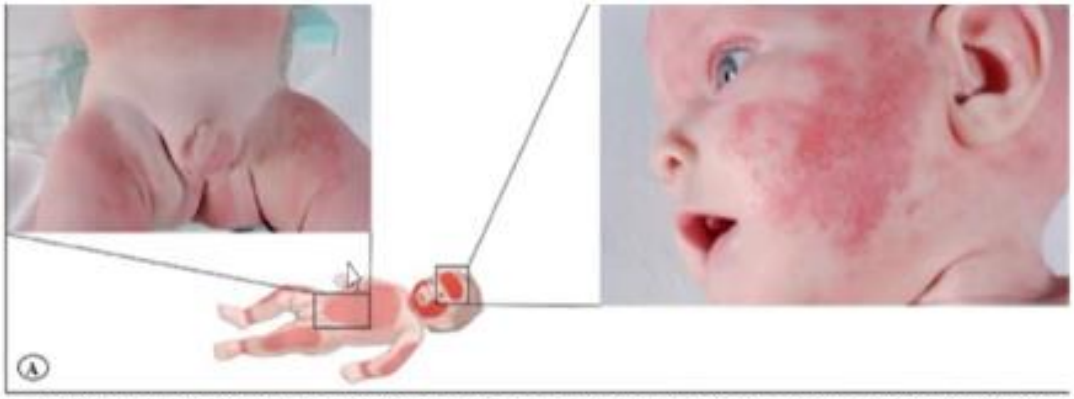

Figure1: Typical clinical locations and appearance of atopic dermatitis at different ages 1A: In infancy and young children (0 to 2 years of age), atopic dermatitis presents with itchy, red, scaly and crusty lesions on the cheeks, scalp, and extensor surfaces of the extremities. There are usually no lesions in the axilla and diaper area (13).

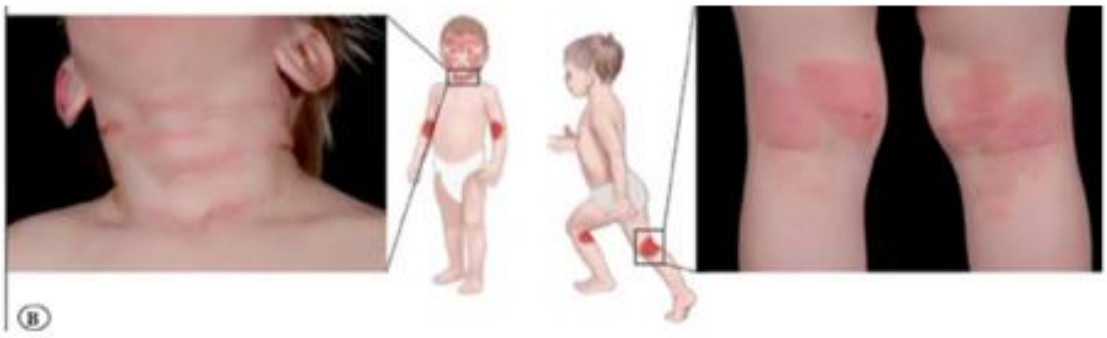

Figure 1B: Older children and adolescents (2 to 16 years of age) have less exuding, lichenified lesions on the flexor faces (especially the popliteal and antecubital fossa, ankles and neck flexor faces, wrist)(13).

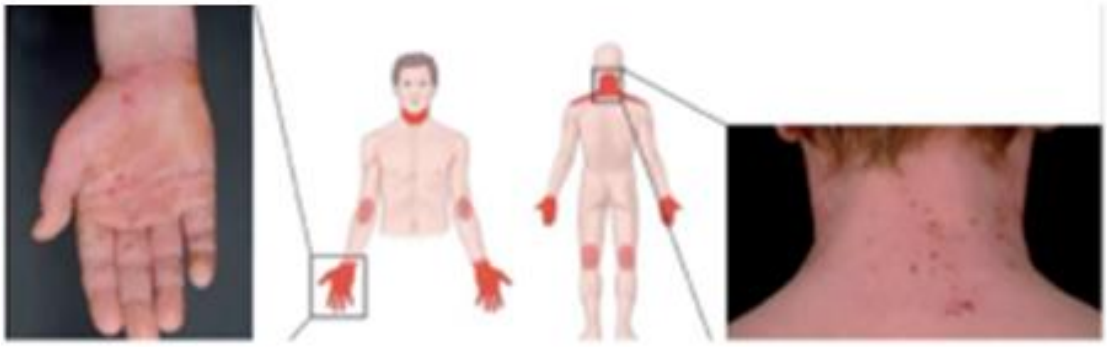

Figure 1C: In adults, atopic dermatitis is more localized and lichenified, usually where there are skin flexures. Sometimes it can affect the face, neck or hands(13).

2.2. Histology and Pathogenesis of Atopic Dermatitis

Atopic dermatitis is a recurrent chronic disease that develops with IgE-mediated sensitivity to allergens in the dry skin with the deterioration of epidermal barrier function.

The histological features of the acute phase of AD are as follows. monocytes, lymphocytes, dendritic cells, eosinophils and macrophages infiltrate the perivascular area of the dermiş. In adition, intercellular edema (spongiosis) occurs in the epidermis. In the subacute and chronic stages, lichenification and scraped plaques occur, causing thickening and hypertrophy of the epidermis (figure 2)(2).

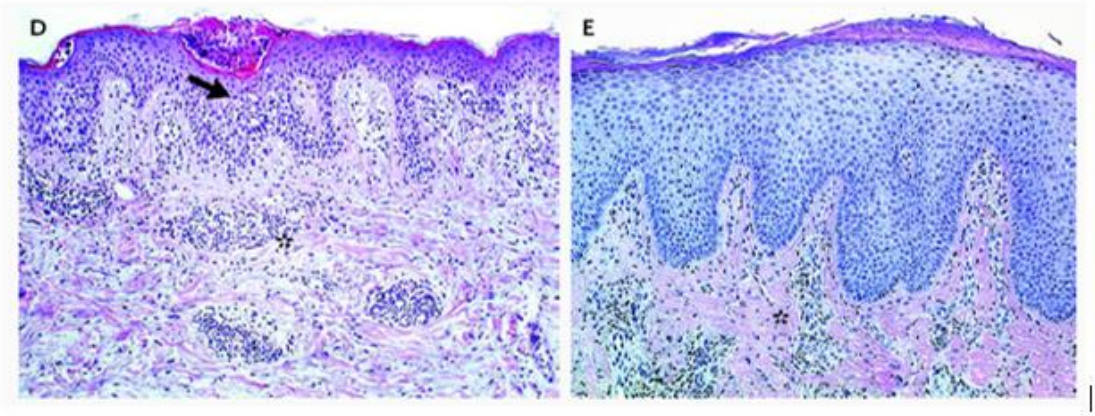

Figure 2 Histological and immunochemical appearance of atopic dermatitis. D. (hemothoxylin and eosin) Typical histological appearance of acute lesion showing spongotic area in epidermis. The marker indicates perivascular infiltrate E. (hemothoxylin and eosin) chronic lesion with thickening of the epidermis. The mark indicates perivascular infiltrate (2).

Atopic dermatitis is a multifactorial disease that occurs as a result of the interaction of environmental and immunological factors under appropriate conditions under genetic background. There is a complex pathogenesis of atopic dermatitis, which is affected by multiple factors such as genetics, changes in the skin microbiome, disruption of the epithelial barrier, immune dysregulation by Th2, exposure to allergens and irritants, resulting in the formation of different endotypes and phenotypes. (17).

Epidermal barrier dysfunction is caused by many factors, including reduced filagrin production, looseness of tight junctions, pruritus, epidermal composition-altered lipids and lamellar, microbial colonization and release of proinflammatory cytokines, imbalance between stratum corneum protease and antiprotease activity (13,18).

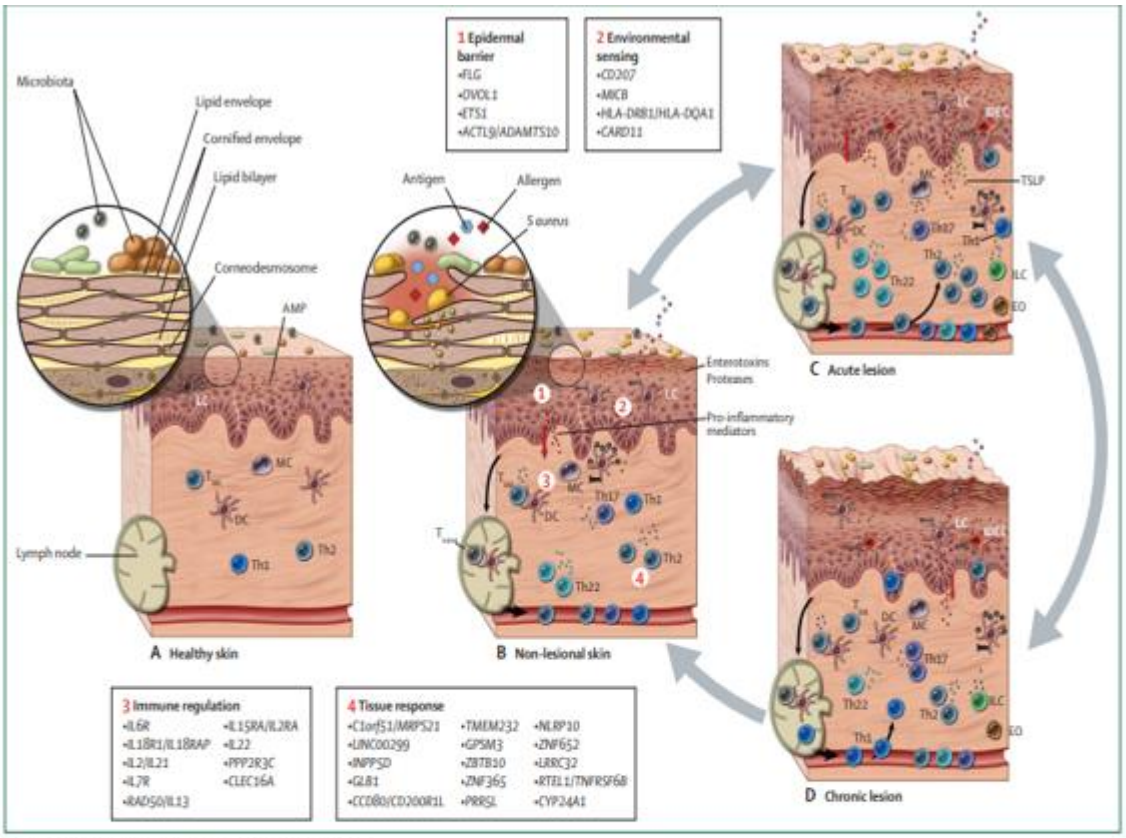

Figure 4: **Key pathophysiological changes in atopic dermatitis**

(A) The protective functions of the skin are mainly mediated by the stratum corneum, which consists of corneocytes filled with keratin fibrils and surrounded by a cornified cell envelope of a densely cross-linked layer of proteins. A monolayer of non-polar lipids is esterified to the cornified envelope and forms the matrix for the intercellular lipid bilayers. Corneodesmosomes form bridges between corneocytes and must be degraded for desquamation. (B) Clinically unaffected skin of patients with atopic dermatitis shows epidermal barrier dysfunction with reduced expression of several epidermal differentiation gene products such as filaggrin, altered lipid composition and organisation, release of innate immune cytokines from keratinocytes, and increased exposure to and uptake of antigens with subsequent B-cell and T-cell priming in the lymph nodes. Further, there are signs of low-level inflammation with some infiltration by Th2 and Th22 cells, and increased expression of Th2-promoting cytokines and chemokines. The microbial diversity is reduced in favour of S aureus. Text boxes show the most plausible candidate genes in susceptibility loci identified through genome-wide association studies. (C) The transition from non-lesional to acute lesional skin is associated with upregulation of a subset of terminal differentiation genes, in particular S100A7, S100A8, and S100A9, whereas the expression of other epidermal differentiation genes such as filaggrin remains low. Despite induction of AMPs, the abundance of S aureus further increases; S aureus-derived proteases and enterotoxins contribute to barrier disruption and inflammation. LCs and IDECs bearing specific IgE bound to the high-affinity receptor for IgE (FcεRI) and dermal DCs take up allergens and antigens encountered in the deficient epidermis. T_{em} cells are activated from local skin pools and in regional lymph nodes. Th2 and Th22 responses are amplified, and initial Th1 and Th17 responses are induced. Their pro-inflammatory mediators further impair epidermal differentiation and integrity, and activate keratinocytes to release pro-inflammatory and pruritogenic mediators. (D) Chronic lesions are characterised by further progression of epidermal hyperplasia, altered corneocyte composition and adhesion, and reduced amounts of intercellular lipids. Continued activation of Th2 and Th22 subsets and activation of Th1 and Th17 pathways further impair epidermal barrier function, accelerate local inflammation, and promote cutaneous remodelling and neuroinflammation. AMP=antimicrobial peptides. DC=dendritic cell. EO=eosinophil. IDEC=inflammatory dendritic epidermal cell. ILC=innate lymphoid cell. LC=Langerhans cell. MC=mast cell. S aureus=*Staphylococcus aureus*. T_{em}=effector memory T cell. Th=T-helper. TSLP=thymic stromal lymphopoietin.

Figure 3. Key pathophysiological changes in atopic dermatitis (13)

The histology of atopic and nonatopic dermatitis is similar. Perivascular T-cell infiltration in patients with clinically normal-appearing atopic dermatitis suggests minimal inflammation in these patients (19,20).

Studies have shown that the epithelial barrier is disrupted even in the nonlesional skin of patients. Decreased Filaggrin and lipid components, increased keratinocyte-derived cytokines, increased antigens from the external environment and S.aerius contact in the microbiota were determined. There is a low level of inflammation, especially in which Th2 and Th22 cells are increased and cytokines that cause Th2 increase (Figure 3B) (13). Disruption of the skin barrier causes allergens, irritants and bacterial toxins to easily pass through the keratinocytes. These antigens are captured by Langerhans cells

and presented to naive Th0 lymphocytes. Th0 cells transform into Th2 cells under the influence of TSLP, IL10 and IL4. While more eosinophils migrate to the environment under the influence of IL4, IL5, IL13, B cells synthesize specific IgE. When IgE on mast and basophil cells is stimulated again with allergen, it releases many histamine, cytokines and causes Type 1 hypersensitivity response. This causes skin reactions such as itching and redness. Acute papular skin lesions are characterized by intercellular edema of the epidermis (spongiosis). In the acute phase, eosinophils and degranulated mast cells predominate, while basophils and neutrophils are rare. In acute lesion, monocytes/macrophages are collected in the dermis with perivascular T cell infiltration. It is associated with upregulation of S100A7, S100A8 and S100A9 (terminal differentiation genes) in acutely lesioned skin. S aureus gradually increases; Proteases and enterotoxins secreted from S aureus cause further disruption of the barrier. High-affinity receptor (FcεRI)-bound specific IgE-bearing LCs and IDECs for IgE and dermal DCs take up allergens and antigens. As a result, while Th2 and Th22 responses increase, Th1 and Th17 responses begin to increase. Disruption of epidermal differentiation and integrity of the epidermis and activation of keratinocytes, leading to inflammation. Pruritogenic mediators are released (1,13).

In the chronic process of atopic dermatitis, the skin loses more water, dries out, and itching increases. Th1, Th17 response occurs via IL12, which causes proliferation in keratocytes and thickening of the skin. In the process, many factors that play a role in the chronic response, such as fibroblasts, lymphocytes, neutrophils, are added to the environment. In chronic lichenified lesions, there is mainly hyperkeratosis and minimal spongiosis in the hyperplastic epidermis. In conclusion, atopic dermatitis is a mixed-type allergic response in which the innate and adaptive immune systems act together, and Th1 and Th2 responses(1.4.13)

2.3 Classified of Atopic Dermatitis

If atopic dermatitis develops through IgE, it is called allergic, extrinsic atopic dermatitis, and if it is not IgE-mediated, it is called non-allergic, non-IgE-mediated or intrinsic atopic dermatitis. The initial phase is the nonatopic form. It starts in early infancy and there is no sensitization in this period. 60-80% of these patients are sensitized by IgE-mediated food (egg, cow-milk, wheat…), environmental allergens and atopic dermatitis due to the effect of genetic factors. In the third phase, autoantigens are released from skin

cells damaged by itching and IgE autoantibodies are formed against them. This condition is called autoallergic atopic dermatitis (13.21).

Atopic dermatitis is classified as mild, moderate and severe according to the extent of the disease, the intensity of the itching, and the sleep loss it causes. this classification, a scoring called SKORAD (score of atopic dermatitis) index is used (22). In this scoring, the extent and intensity of atopic dermatitis (papule, dryness, erythema, edema, liquefaction, peeling) and subjective symptoms (sleep loss, itching) are evaluated and scored together. Those with a SKORAD score of 0-15 are in the light group, those with a score of 15-40 are in the medium group, and those with a score of over 40 are in the severe group.

2.4. Genetics of Atopic Dermatitis

In twin studies, the rate of eczema concordance in monozygotic twins was 0.72-0.86, while it was 0.21-0.23 in dizygotic twins (23). Children whose parents have AD have an increased risk of developing AD compared to children whose parents have AR and asthma (24). All observations suggest that the risk genes are skin specific genes rather than systemic atopy or immunity genes.

In recent years, the focus has been on epithelial barrier dysfunction in atopic eczema. Genetic, physiological and biochemical studies have been related to this region (5).

In 2015, Paternostel et al performed a meta-analysis of more than 15 million genetic variants across 18 studies involving 21399 cases and 95464 controls, which included European, African, Japanese, and Latino races (25). As a result of the study, they identified 10 new risk loci. Thus, the number of risk loci in atopic dermatitis became 31 (table 1). The strongest risk factor for the development of AD is the Filagrin null mutation. FLG null mutation disrupts the skin barrier and has been associated with many skin and allergic diseases, especially AD, and an increase with severity of the diseases (6,26).

Table 1. A fixed effects meta-analysis of the 22 European studies identified 21 genome-wide significant ((25)

Table 1

Discovery Results. The index variant for loci with $p<5\times10^{-8}$ in the European analysis or log10BF>6.1 in the multi-ethnic MANTRA analysis. Previous atopy trait associations with these loci are listed.

				European – fixed effects				All cohorts – MANTRA		Known atopy loci?	
Variant	Locus	Nearest Gene[δ]	EA/OA	N (studies)	EAF	OR (95% CI)	P-value	N (studies)	log10 BF	trait	references
KNOWN LOCI											
rs61813875	1q21.3	CRCT1/**LCE3E** (FLG)[δ]	G/C	93,326 (18)	0.02	1.61 (1.48–1.75)	5.6×10^{-29}	96,419 (20)	**25.53**	AD	3,4,5
rs10791824	11q13.1	**OVOL1**	G/A	102,761 (21)	0.57	1.12 (1.09–1.15)	2.1×10^{-19}	116,556 (25)	**21.56**	AD	9
rs12188917	5q31.1	RAD50/**IL13**	C/T	102,761 (21)	0.21	1.14 (1.10–1.17)	4.0×10^{-17}	116,554 (25)	**17.24**	AD,A,IgE	9,18,58
rs6419573	2q12.1	IL18R1/**IL18RAP**	T/C	102,760 (21)	0.26	1.11 (1.08–1.14)	1.5×10^{-13}	116,557 (25)	**18.10**	AD,A,AS,SRA	8,14,18,21
rs2212434	11q13.5	**C11orf30**/LRRC32	T/C	102,761 (21)	0.45	1.09 (1.07–1.12)	4.6×10^{-13}	116,557 (25)	**13.02**	AD,AS,SRA,AR,A	11,14,15,21,59
rs4809219	20q13.33	**RTEL1–TNFRSF6B**	C/A	102,760 (21)	0.27	0.90 (0.87–0.93)	7.0×10^{-13}	116,555 (25)	**11.98**	AD	7,10
rs2918307	19p13.2	ADAMTS10/**ACT1.9**	G/A	100,707 (20)	0.16	1.12 (1.08–1.16)	4.6×10^{-12}	114,504 (24)	**12.98**	AD	9
rs2041733	16p13.13	**CLEC16A**	C/T	103,066 (22)	0.55	0.92 (0.90–0.94)	2.5×10^{-11}	116,862 (26)	**10.11**	AD,A+HF	7,53
rs12730935[#]	1q21.3	**IL6R**	A/G	102,760 (21)	0.39	1.08 (1.05–1.11)	6.1×10^{-11}	116,556 (25)	**7.15**	AD,A	12,15
4:123243592[δ]	4q27	**KIAA1109** (IL2)[δ]	R/I	102,761 (21)	0.37	1.08 (1.05–1.10)	4.2×10^{-9}	107,119 (24)	**7.32**	AD,AS,SRA	7,14,21
rs4713555	6p21.32	**HLA-DRB1**/HLA-DQA1	T/G	91,217 (15)	0.27	0.91 (0.89–0.94)	5.4×10^{-9}	105,014 (19)	**10.76**	AD,AS,SRA,A	6,8,14,18,21
rs2944542	10q21.2	**ZNF365**	C/G	102,762 (21)	0.41	0.94 (0.92–0.96)	1.2×10^{-6}	116,559 (25)	**7.56**	AD	8,10
rs145809981	6p21.33	**MICB**	T/C	97,697 (19)	0.14	0.91 (0.88–0.95)	1.5×10^{-6}	110,228 (22)	**7.33**	AD,AS,SRA	8,14,21
rs4312054	11p15.4	OR10A3/**NLRP10**	G/T	102,760 (21)	0.41	1.00 (0.97–1.02)	0.744	116,556 (25)	**7.00**	AD	8
rs1249910	3q13.2	**CCDC80**/CD200R1L	A/G	99,164 (20)	0.34	0.98 (0.96–1.01)	0.137	112,960 (24)	**6.86**	AD	8
rs2592555	11p13	**PRR5L**	C/T	102,760 (21)	0.27	0.93 (0.90–0.96)	8.7×10^{-7}	116,551 (25)	**6.78**	AD	7
NOVEL LOCI											
rs2038255	14q13.2	**PPP2R3C**	T/C	102,760 (21)	0.18	1.11 (1.07–1.14)	1.8×10^{-10}	116,557 (25)	**8.40**		
rs7127307	11q24.3	–/**ETS1**	C/T	103,066 (22)	0.47	0.93 (0.90–0.95)	3.9×10^{-10}	116,855 (26)	**9.08**	SRA	14
rs7512552	1q21.2	C1orf51/**MRPS21**	T/C	102,762 (21)	0.49	0.93 (0.91–0.95)	9.1×10^{-10}	116,544 (25)	**6.91**		
rs6473227	8q21.13	MIR5708/**ZBTB10**	A/C	102,761 (21)	0.61	0.93 (0.91–0.95)	1.4×10^{-9}	116,557 (25)	**7.54**	(AD),SRA,A+HF	9,14,53
rs6602364	10p15.1	IL15RA/**IL2RA**	G/C	103,065 (22)	0.45	1.08 (1.05–1.10)	1.5×10^{-9}	116,855 (26)	**7.86**	(SRA)	14

				European – fixed effects				All cohorts – MANTRA		Known atopy loci?	
Variant	**Locus**	**Nearest Gene**[‡]	**EA/OA**	**N (studies)**	**EAF**	**OR (95% CI)**	**P-value**	**N (studies)**	**log10 BF**	**trait**	**references**
rs10214237	5p13.2	**IL7R**/CAPSL	C/T	102,761 (21)	0.27	0.93 (0.90–0.95)	**2.9×10^{-8}**	116,554 (25)	4.79		
rs10199605	2p25.1	**LINC00299**/–	A/G	102,760 (21)	0.30	0.93 (0.90–0.95)	**3.4×10^{-8}**	116,557 (25)	4.67	(SRA)	14
rs4643526	2p16.1	**PUS10**	A/G	103,066 (22)	0.19	1.09 (1.06–1.12)	**3.5×10^{-8}**	107,425 (25)	**6.31**		
rs12951971	17q21.2	**STAT3**	G/T	102,761 (21)	0.09	1.13 (1.08–1.17)	**4.1×10^{-8}**	107,120 (24)	5.33		
rs7625909	3p21.1	**SFMBT1**/RFT1	T/C	102,761 (21)	0.32	1.07 (1.05–1.10)	**4.9×10^{-8}**	116,558 (25)	5.83		
rs112111458	2p13.3	CD207/**VAX2**	G/A	102,760 (21)	0.13	0.91 (0.87–0.94)	1.4×10^{-7}	116,553 (25)	**6.57**		

[*] in LD with known functional mutation rs2228145 (r^2=0.86)

[†] nearby SNP (rs6827756, bp position: 123184411) in LD (r^2=0.97 in 1000genomes) showed similar association, log10BF=7.21, European fixed effects p-value 3×10^{-9}

[‡] Nearest genes are the two flanking genes if intergenic (with the closer gene in **bold**, - indicates no gene within 250kb), single genes denote the variant is intronic.

[§] at 1q21.2: variant is closest to LCE3A, but previously associated FLG is within 250kb, at 4q27: variant is within an intron of KIAA109, but previously associated IL2 is within 150kb, AD= atopic dermatitis, A=asthma, AS=allergic sensitization, SRA=self-reported allergy, AR=allergic rhinitis, A+HF=asthma and hayfever combined,

P-values and −log 10 Bayes Factors (BF) in **bold** indicate genome-wide significant results

EA/OA = effect allele/other allele, EAF = effect allele frequency, OR=odds ratio, CI=confidence interval, N= sample size, BF= bayes factor

Table 2

Replication results for the novel genome-wide significant loci and loci identified in the MAGENTA gene-set enrichment analysis. Discovery, replication and combined results are shown.

					Discovery European			Replication European			Overall European - fixed effects			het	random effects p-values	
Variant	Locus	Nearest Gene	EA/OA	EAF	N (studies)	OR (95% CI)	P-value	N (studies)	OR (95% CI)	P-value[‡]	N	OR (95% CI)	P-value	p-value	European	all studies
NOVEL GENOMEWIDE SIGNIFICANT LOCI																
rs7512552	1q21.2	C1orf51/MRPS21	T/C	0.49	102762 (21)	0.93(0.91–0.95)	9.1×10^{-10}	257019 (15)	0.98(0.96–0.99)	0.0048	359781	0.96(0.94–0.97)	**5.41×10^{-9}**	**0.002**	1.5×10^{-7}	1.3×10^{-7}
rs10199605	2p25.1	LINC00299/–	A/G	0.30	102760 (21)	0.93(0.90–0.95)	3.4×10^{-8}	256958 (15)	0.97(0.95–0.99)	0.0045	359718	0.96(0.94–0.97)	**3.97×10^{-8}**	**0.024**	4.1×10^{-6}	1.5×10^{-5}
rs4643526	2p16.1	PUS10	A/G	0.19	103066 (22)	1.09(1.06–1.12)	3.5×10^{-8}	257050 (14)	1.03(1.01–1.05)	0.0058	360116	1.05(1.03–1.07)	5.94×10^{-8}	0.249	3.8×10^{-6}	1.1×10^{-5}
rs112111458	2p13.3	CD207/VAX2	G/A	0.13	102760 (21)	0.91(0.87–0.94)	1.4×10^{-7}	257019 (15)	0.95(0.93–0.98)	**7.95×10^{-4}**	359779	0.94(0.92–0.96)	**9.38×10^{-9}**	0.076	4.4×10^{-6}	1.6×10^{-7}
rs11923593[#]	3p21.1	SFMBT1/RFT1	G/A	0.32	102761 (21)	1.07(1.04–1.10)	9.7×10^{-8}	257002 (15)	1.01(0.99–1.03)	0.2600	359763	1.03(1.01–1.05)	1.30×10^{-4}	0.081	8.7×10^{-5}	1.7×10^{-5}
rs10214237	5p13.2	IL7R/CAPSL	C/T	0.27	102761 (21)	0.93(0.90–0.95)	2.9×10^{-8}	257010 (15)	0.94(0.93–0.96)	**6.71×10^{-8}**	359771	0.94(0.92–0.95)	**2.86×10^{-14}**	0.773	**2.9×10^{-14}**	**1.5×10^{-10}**
rs6473227	8q21.13	MIR5708/ZBTB10	A/C	0.61	102761 (21)	0.93(0.91–0.95)	1.4×10^{-9}	257006 (15)	0.95(0.93–0.97)	**4.53×10^{-9}**	359767	0.94(0.93–0.95)	**2.22×10^{-16}**	0.622	**2.2×10^{-16}**	**5.3×10^{-18}**
rs6602364	10p15.1	IL15RA/IL2RA	G/C	0.45	103065 (22)	1.08(1.05–1.10)	1.5×10^{-9}	256993 (15)	1.03(1.01–1.05)	**3.91×10^{-4}**	360058	1.05(1.03–1.06)	**1.33×10^{-10}**	**0.041**	3.6×10^{-6}	1.6×10^{-6}
rs7127307	11q24.3	–/ETS1	C/T	0.47	103066 (22)	0.93(0.90–0.95)	3.9×10^{-9}	257034 (15)	0.94(0.93–0.96)	**2.51×10^{-10}**	360100	0.94(0.92–0.95)	**1.48×10^{-18}**	0.935	**1.5×10^{-18}**	**1.0×10^{-20}**
rs2143950[#]	14q13.2	PPP2R3C	T/C	0.17	102762 (21)	1.10(1.07–1.14)	6.8×10^{-10}	249940 (12)	1.07(1.04–1.09)	**9.92×10^{-8}**	352702	1.08(1.06–1.10)	**1.78×10^{-15}**	0.092	4.8×10^{-7}	**8.6×10^{-10}**
rs17881320[#]	17q21.2	STAT3	T/G	0.08	96796 (19)	1.12(1.07–1.17)	2.0×10^{-6}	249949 (12)	1.05(1.02–1.09)	**1.47×10^{-3}**	346745	1.08(1.05–1.11)	1.41×10^{-7}	0.405	6.2×10^{-7}	2.6×10^{-6}
MAGENTA GENE-SET ENRICHMENT ANALYSIS LOCI																
rs1057258	2q37.1	INPP5D	T/C	0.18	101012 (21)	0.94(0.91–0.97)	6.57×10^{-5}	257030 (15)	0.94(0.92–0.96)	**3.79×10^{-7}**	358042	0.94(0.92–0.96)	**1.72×10^{-10}**	0.811	**1.7×10^{-10}**	**4.1×10^{-13}**
rs6872156	5q35.1	DUSP1	A/G	0.24	103066 (22)	0.93(0.91–0.96)	2.35×10^{-6}	257047 (15)	0.97(0.95–0.99)	0.0055	360113	0.96(0.94–0.97)	8.08×10^{-7}	0.340	1.8×10^{-6}	2.7×10^{-7}
rs7016497	8q24.3	PTK2	T/C	0.21	103066 (22)	0.94(0.91–0.97)	1.09×10^{-4}	257040 (15)	0.98(0.95–1.00)	0.0290	360106	0.96(0.95–0.98)	9.37×10^{-5}	0.757	9.4×10^{-5}	1.4×10^{-6}
rs2905493	11q12.2	CD6/CD5	T/C	0.01	89617 (15)	0.78(0.68–0.89)	2.63×10^{-4}	254992 (13)	1.01(0.94–1.08)	0.6040	344609	0.95(0.90–1.02)	0.1432	0.150	0.419	0.098
rs1799986	12q13.3	LRP1(STAT6)[†]	T/C	0.15	99165 (20)	0.91(0.88–0.94)	1.14×10^{-7}	257022 (15)	0.98(0.96–1.01)	0.1140	356187	0.96(0.94–0.98)	2.90×10^{-5}	0.182	1.1×10^{-4}	1.6×10^{-3}
rs2227483	12q15	IL22(& IFNG)[†]	A/T	0.44	102762 (21)	0.94(0.92–0.97)	2.27×10^{-6}	253446 (14)	0.94(0.92–0.96)	**3.55×10^{-11}**	356208	0.94(0.93–0.96)	**6.66×10^{-16}**	0.664	**6.7×10^{-16}**	**1.2×10^{-17}**
rs7146581	14q32.32	TRAF3	T/C	0.24	102760 (21)	0.95(0.92–0.97)	1.44×10^{-4}	256971 (15)	0.96(0.94–0.98)	**5.67×10^{-5}**	359731	0.95(0.94–0.97)	6.17×10^{-8}	0.219	1.2×10^{-4}	4.1×10^{-6}
rs11657987	17q25.3	PGS1(SOCS3)[†]	T/G	0.49	100695 (21)	1.06(1.04–1.09)	1.07×10^{-6}	257019 (15)	1.03(1.01–1.05)	**1.04×10^{-3}**	357714	1.04(1.03–1.06)	5.09×10^{-8}	0.235	9.7×10^{-5}	6.0×10^{-5}
rs77714197	19q13.11	CEBPA	T/C	0.02	87690 (14)	1.35(1.19–1.54)	3.31×10^{-6}	256447 (14)	0.98(0.89–1.08)	0.6540	344137	1.10(1.02–1.18)	0.0139	**0.048**	0.102	0.116

[#] rs11923593 replaces rs7625909 (r^2=0.98), rs2143950 replaces rs2038255 (r^2=0.94), rs17881320 replaces rs12951971 (r^2=0.75) in the replication analysis

[†] rs1799986 is within LRP1, but was selected in the MAGENTA analysis due to its proximity to STAT6. rs2227483 is with IL22, but was selected due to its proximity to both IL22 and IFNG. rs11657987 is within PGS1, but was selected due to its proximity to SOCS3

[‡] Replication p-values for a 1-sided test

Replication p-values in **bold** were considered significant (p<0.0025), overall p-values in **bold** are genome-wide significant, heterogeneity p-values<0.05 are in bold

EA/OA= effect allele/other allele, EAF = effect allele frequency, OR=odds ratio, CI=confidence interval, N= sample size, het=heterogeneity

Table 2. Replication results for the novel genome-wide significant loci (25).

Their results underline the importance of both epidermal barrier function and immune dysregulation (innate host defenses and T-cell function) in atopic dermatitis pathogenesis. 3q21, 1q21, 16q, 17q25, 20p,3p26 recurred in two or more studies. Three genes located at locus 5q31-33 were associated with the cytokines IL-4, IL-13 and a protease inhibitor SPINK5 (serine protease inhibitor Kazal type 5). Among all gene mutations, skin barrier dysfunction genes are prominent(8,25).

Three SNPs reached genome-wide significance in the discovery and replication cohorts combined, including rs479844 upstream of OVOL1 and rs2164983 near ACTL9, both of which are near genes that have been implicated in epidermal proliferation and differentiation, as well as rs2897442 in KIF3A within the cytokine cluster at 5q31. (8). They observed an association signal in the cytokine cluster at 5q31.1 that appeared to consist of two distinct signals, one centered on IL13-RAD50 and the other IL4-KIF3A, which was moderately associated with IL13 expression (8,25) (figüre 3, Table 1, Table 2).

2.5 Kinesin Family Protein 3A Gene (KIF 3A)

KIF3A encodes the subunit of the cilia component kinesin-2, which is required for immotile and motile cilia formation (27,28). KIF3A is in the 5q31 region. This region contains the silokine cluster of immune-related and cytokine genes, particularly IL13 and IL4 (9).

The null mutation of KIF3A is fatal in the embryonic period. (29). Deletion of KIF3A causes lung-specific barrier dysfunction and develops a Th2 allergen response, leading to the development of the asthma phenotype. A similar effect was also detected in atopic dermatitis with KIF3A (30,31).

The causative mechanism has been investigated in recent years. Among asthma and AD-associated KIF3A SNPs, one-third of them were found to form new cytosine-phosphate-guanine (CpG) sites (32). CpG regions are amenable to modification of cytosine by the addition of a methyl group at the 5' position. There are known to regulate gene transcription. Genetic variations are highly associated with DNA methylation and CpG regions, and SNPs are epigenetic and gene-related (33,34,35,36).

Stevens et al. found that the KIF3A SNP rs11740584 and rs2299007 risk alleles form CpG that are highly methylated and result in lower KIF3A expression. They demostrated that this methylation was associated with an increased risk of transepidermal water loss (TEWL). Kif3a$^{14\Delta/\Delta}$ mice have increased TEWL, disrupted junction proteins, and increased susceptibility to develop AD. Therefore, KIF3A is required for skin barrier

homeostasis. Decreased skin expression of KIF3A causes disruption of skin barrier function and promotes AD development (figüre 4) (12)

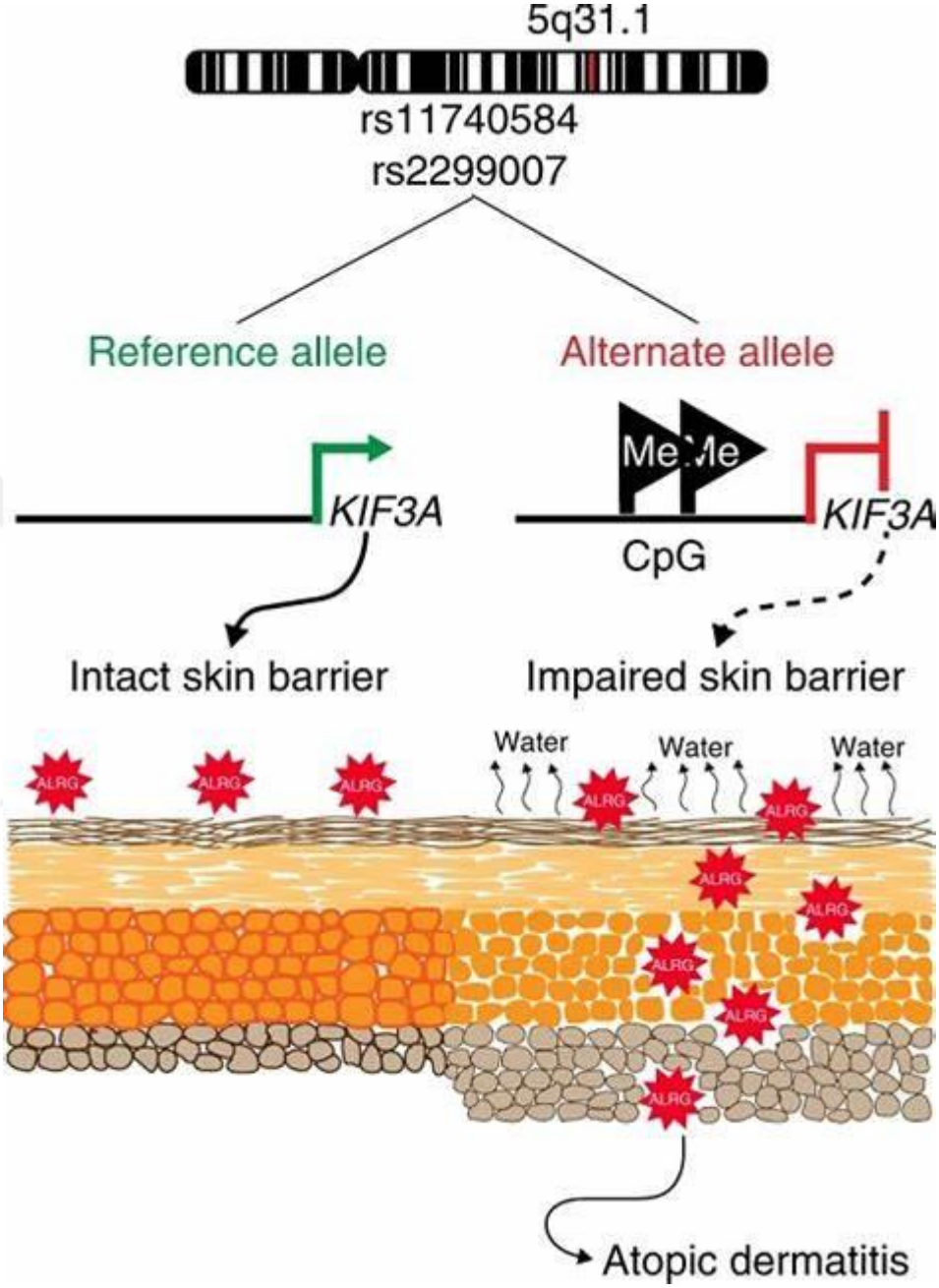

Figure 4. Mechanistic underpinnings of the contribution of KIF3A SNPs to skin barrier dysfunction (12)

Stevens et al. investigated how close the Kif3a$^{14\Delta/\Delta}$ mice were to the human AD transcriptome. To determine skin transcriptomics, they examined the profile of Kif3a$^{14\Delta/\Delta}$ mice and compared them to other murine AD models and human AD. 3-week-old mouse models were used to represent the pediatric group and 8-week-old mouse models were used for the adult group. To study both the epidermis and dermis level, whole-layer skin

samples were examined. Kif3aK14Δ/Δ mice have 3.5 and 4.5 times more DEGs overlapping with the MADAD and pediatric DEGs, respectively, than flaky tail or Flgft/ft mice. In the absence of Kif3a, epidermal changes occur even in areas of the epidermis without lesions. Mice in the absence of Kif3a, at 8 weeks of age, it spontaneously develops an AD-like transcriptomic signature. These mice have increased TEWL without any manipulation. Kif3a deficiency causes increased cell proliferation and thickening of the skin (figüre 5). Disruption of skin barrier function causes an excessive immune response. When the relationship between Kif3a deletion and drugs that can be used in the prevention and treatment of atopic dermatitis was examined, it was determined that many anticancer drugs and antihistamines could be used. (37)

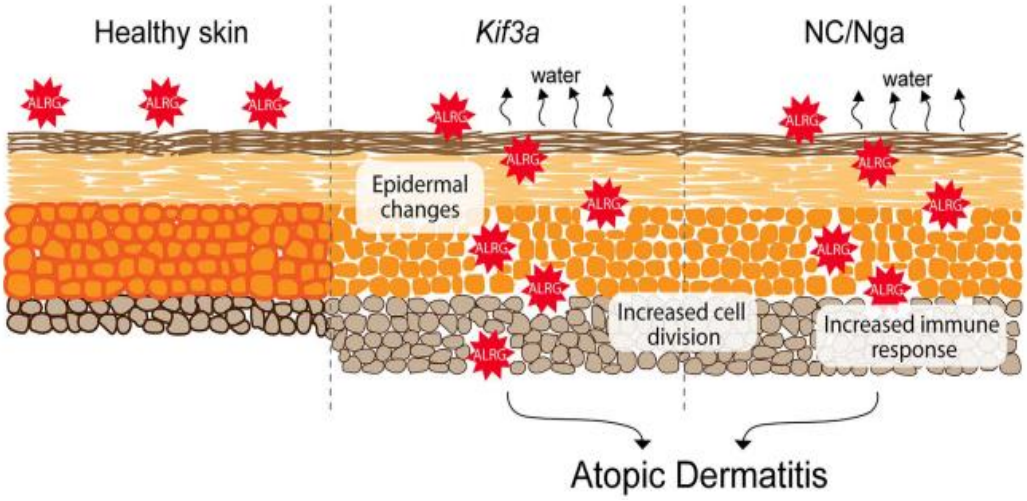

Figure 5. Skin schematic of the proposed model of the contribution of Kif3a to skin barrier homeostasis (37).

When children with a high risk of developing asthma were examined, it was observed that eczema and food sensitivity in infancy were observed in a group of them. Polyaerosensitization was observed in children with asthma without a history of eczema. Interestingly, children in both groups had the KIF3A rs12186803 risk allele. These results suggest that KIF3A deletion disrupts the barrier in the skin and respiratory epithelium and is associated with food allergy in early childhood, aeroallergen sensitivity in late childhood, and severe eczema and asthma (figure 6)(38).

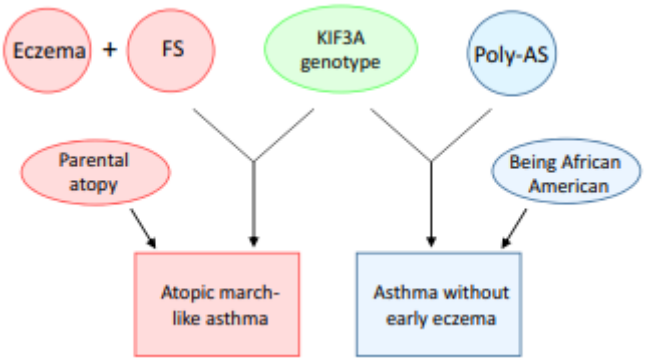

Figure 6. Schematic summary of the predictors of the two groups at high risk for asthma

Gridhar et al. showed that the KIF3A polymorphism disrupts the respiratory epithelial barrier and cilia structure, resulting in impaired mucociliary clearance and epithelial repair mechanisms. KIF3A prevents Th2 infiltration and airway hypersensitivity after exposure to aeoallergens. So KIF3A has a protective function. (30) (30). it is thought that KIF3A may be involved in airway pathologies in many places, from immune response to allergens to cilia movement.

rs2897442 is located in intron 8 of KIF3A(27), encoding a motor subunit of kinesin-2. In cilia formation, It is an important component. This gene is important for apoptosis and cell proliferation. This gene is also implicated in Hedgehog signaling and βcatenin-dependent Wnt signaling in the regulation of the expression of various genes (11).

In two case-control studies conducted in Italian and Chinese children without FLG mutation, it was shown that the C allele in KIF3A rs2897442 had a statistically increased risk of developing atopic dermatitis in children with atopic dermatitis compared to the healthy control group (10,11).

3. MATERIAL AND METHOD

3.1 Sample Selection and Definition

This project contains both patients diagnosed with Atopic dermatit (n=48) and healthy children as a control group (n=46). The patient group composed of patients who get diagnosed by pediatric immunology and allergy department and also a control group consist of healthy persons. Also, ethical approval was obtained from the Yeditepe University Ethics Committee for project (decision no:1600).

3.1.1 Patient group

Forty-eight children between the ages of 2 months and 16 years with atopic dermatitis who applied to Yeditepe University Hospital Pediatric Allergy-Immunology Unit, Istanbul between May 2022 and November 2022 were inclueded. Serum samples was obtain from 2 months-18 years-old children with newly diagnosed atopic dermatitis.

Atopic dermatitis (eczema) was diagnosed in patients with three of the four major criteria (skin pruritus, typical morphological distribution on the extensor face in infants and on the flexor face in older children, chronic and recurrent features, family history of atopic person) or three of 21 minor criteria of Hanifin and Rajka (Table3) (39).

Table 3. Diagnostic criteria of Hanifin and Rajka for atopic dermatitis (39)

Major criteria(3 or more required)	Minor criteria(3 or more required)
Pruritus Typical morphology and distribution • Flexural lichenification or linearity in adults • Facial and extensor involvement in infants and children Chronic or chronically-relapsing dermatitis Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)	Xerosis Ichthyosis, palmar hyperlinearity, or keratosis pilaris Immediate (type 1) skin-test reactivity Raised serum IgE Early age of onset Tendency toward cutaneous infections (especially *S. aureus* and herpes simplex) or impaired cell-mediated immunity Tendency toward non-specific hand or foot dermatitis Nipple eczema Cheilitis Recurrent conjunctivitis Dennie-Morgan infraorbital fold Keratoconus Anterior subcapsular cataracts Orbital darkening Facial pallor or facial erythema Pityriasis alba Anterior neck folds Itch when sweating Intolerance towool and lipid solvents Perifollicular accentuation Food intolerance Course influenced by environmental oremotional factors White dermographism or delayed blanch

The severity of eczema was determined according to the SCORAD index. Those with an index score less than 15 were classified as mild, those with 15-40 as moderate, and those with a higher than 40 as severe. In this scoring, the extent of atopic dermatitis was calculated so that the width of the palm of the patient's palm was 1% and recorded as "A". The intensity of atopic dermatitis, erythema, papule/edema, liquefaction, dryness, peeling, each of the criteria was evaluated as 0=absent, 1=mild, 2=moderate, 3=intensive, and recorded as "B". Finally, they were asked to score itching and sleep loss as subjective symptoms from 1 to 10, and the scores given for the two complaints were added and recorded as "C". SCORAD was calculated using the formula SCORAD=A/5+(7B/2)+C (22).

Family history of allergic disease, school loss and duration in the last 6 months, need for and duration of oral steroids were recorded.

Patients diagnosed with physician-diagnosed asthma according to GINA (Global Initiative for Asthma) criteria and allergic rhinitis according to “The Allergic Rhinitis and its Impact on Asthma (ARIA)” criteria were determined (40,41).

3.1.2 Control group

The control group consisted of 46 healthy children in the same age group as the patient group, who applied to the pediatrics department for general medical examination, did not have any active disease complaints at the time of admission, and did not have a history of chronic diseases such as atopic dermatitis, asthma, allergic rhinitis, kidney, liver disease, diabetes mellitus.

3.1.3 Detection of Atopy, Eosinophil and Measurement of Total Immunoglobulin E

Total Ig E levels were determined by Cobas C 411 Device by Electrochemiluminescence / Sandwich Method, and eosinophil count was determined by Counter counter (Pharmacia, Kalamazoo, MI). In the patient group, Epidermal skin test was performed with 20 allergens, consisting of 10 aero-allergens and 10 food allergens, in children who could undergo epidermal skin testing. Histamine was used as a positive control and physiological saline was used as a negative control. Indurations larger than 3 mm compared to the negative control were considered positive. Children with at least one positive skin test were considered atopic.

3.2.Materials and Devices Used in Experiment

3.2.1. Material used in DNA isolation

In the antecubital region of the children, 2 ml of peripheric venous blood samples in EDTA medium was collected for isolation of DNA and blood samples were stored at +4oC until used. EDTA is used for prevent of coagulation.

To make the DNA isolation, DNA Isolation Robot (iPrep pure link, Invitrogen and the Thermo Fischer Scientific Inc) system was used. In addition, 8 M Guanidine hydrochloride, 1.12mg/ml Proteinase K, 10.5 nM NaCl, 10.5 nM EDTA, and 10.5 nM Tris-Cl pH 8.8 were used in the DNA isolation mixture.

3.2.2. Devices and materials used in the experiment

In this study, DNA Isolation Robot (iPrep Purelink, Invitrogen, Thermo Fisher Scientific Inc), Real Time PCR (Fast Real Time 7500, Applied Biosystems), Nanodrop 2000 (Thermo Fischer Scientific Inc), 7500 Fast Real-Time PCR Instrument, Plate

Centrifuge (Hettich), Centrifuge (Centrifuge 22R-Beckman Coulter), -20°C Refrigerator (Haier), +4°C Refrigerator (Haier), Vortex (V.I Plus Biosan), Pipette Kit (Thermo Fischer Scientific Inc) and Ultra Pure Water (Pure Lab Option Q,EICT) was used.

3.3. Methods

3.3.1. Genomic DNA isolation from blood

All blood samples of the control and patient groups were taken into tubes containing EDTA with a volume of 2 mL and stored in the refrigerator at +4°C. The iPrep genomic DNA isolation Kit and an iPrep DNA extraction (Invitrogen) robot were used for DNA isolation. Thus, DNA isolation can be made from 350 µL of peripheral blood, allowing 13 blood samples to be taken at once. Cartridges that were shaken for a period of time were used for each sample to effectively bind the magnetic beads with DNA before placing the samples in their cartridges.

The iPrep robot works according to ChargeSwitch® (CST®) technology, which acts as a calibrated extraction procedure. Thus, high amounts of pure genomic DNA are obtained from samples using paramagnetic particles. A DNA binding surface surrounds these particles, and the pH of the buffer surrounding the particles changes the charge of the beads. Under low pH conditions, the negatively charged DNA backbone binds to the positively charged beads. By using a higher pH low salt buffer for DNA elution, these charged rays are neutralized. After the nucleic acid molecules pass into the washing buffer, the DNA samples are ready and the aqueous DNA samples are taken and stored in the refrigerator at +4°C.

3.3.2. DNA purity measurement

NanoDrop is used for UV (ultraviolet) light absorbance of nucleic acids at 260 nm. OD260/OD280 ratio and OD260/OD230 ratio are measured to obtain DNA purity. NanaDrop is a type of UV spectrophotometer. NanoDrop measures concentration of DNA as well. More realistic results are obtained with NanoDrop than with other UV spectrometers because the Nanodrop does not contain any cuvettes or capillaries, so the samples are directly measured away from external influences.

NanoDrop 2000 (Thermo Fisher Scientific Inc.) was used for DNA purity measurement. 0.5-1 µl DNA sample from each child known as both atopic dermatitis

patient and control group was used. In addition, distilled water was used as a blank sample. Distilled water was used both to clean the sample insertion step after every 15-20 measurements and to clean the NanoDrop 2000 at the end of the measurement.

3.3.3. Genotyping with real-time PCR

Genotyping analysis was performed with a 7500 Fast-Real-Time Polymerase Chain Reaction (Applied Biosystems) device known as Real-Time PCR device.

Single nucleotide polymorphisms (SNPs) were detected using fluorescent dyes of the probes. Detection of fluorescent signals is clearly visible. In the Real-Time PCR method, fluorescent dye probes with two different wavelengths specific to the alleles called mutant and wild type are used. Used to detect two different TaqMan probes. One of them was VIC and the other was FAM. VIC can detect the mutant variant of the allele. FAM can detect the wild-type variant of the allele. Fluorescent dye-linked probes of each allele are attached to the amplified region. The Taq polymerase enzyme is performed to hydrolyze the probes.

The primer was designed depending on the sequence of KIF3A gene in human. Determination of KIF3A gene (rs2897442) polymorphism was performed in Applied Biosystems 7500 Fast Real- Time PCR instrument (Applied Biosystems, Foster City, CA, USA) by using TaqMan Genotyping Assay and TaqMan Genotyping Master Mix (TaqMan Reagents, Applied Biosystems, Foster City, CA, USA). Based on this procedure, the polymorphism-contained region was amplified by 5'TTAATAAGACTATATCAATGTAAAT**[C/T]**TCCTGGTTTCAATAACTGTTGTATG 3'. Due to the Minor allele frequency (MAF) analysis, allele frequencies considered as G wild type and T mutant form.

3.3.3.1. Real-time PCR protocol

5 µl of Master Mix, 0.25 µl of Taqman genotyping assay, 3.75 µl of DNAse, RNAse free water, and 1 µl of template DNA were used. The total volume of reagents used in Real-Time PCR and reaction mixtures are also shown in Table 4.

First, mixture was prepared with Master Mix, DNAse, RNAse free water and TaqMan genotyping assay and then mixture separates to each well of 96-well.

After that, each template DNA samples were added onto the mixture one by one. Later, 96-well plate were covered carefully.

Centrifuge was performed 2 min at 3000 rpm to make the solution more homogeneous and to precipitate all liquids to the bottom. Then the plate is carefully placed in the PCR device and Real-Time PCR is started.

Table 4: The mixtures of Real-Time PCR reaction

The Agent	Quantity of Agent
Master Mix	5 µL
DNAse, RNAse Free Water	3,75 µL
TaqMan Genotyping Assay	0,25 µL
Template DNA	1 µL

Real-Time PCR stages were designed. First there were 10 minutes waiting time at 95 °C, then the denaturation process was continued for 15 seconds per cycle at 92 °C and last stage were elongation to 1 minute for each cycle at 60 °C. As it is shown in Table 5, denaturation and annealing/extension processes were applied as 40 cycles.

Table 5: Real-time PCR protocol.

	Stages	Temperature °C	Duration / Period of Time
40 cycles	Hold	95 °C	10 minutes
	Denaturation	92 °C	15 seconds
	Annealing/ Extension	60 °C	1 minute

3.4. Statistical analysis

In this study, a comparison was made between children with atopic dermatitis and healthy control group.SPSS 26.0 program was used for statistical analysis. Clinical parameters are shown in Table 3 and 4. Percentage and number of eosinophils, and total IgE levels were not normally distributed. Therefore, the median and interquartile ranges were used in the results, and all statistics were performed using the nonparametric Mann-Whitney U-test and Kruskal-Wallis test. Chi-square and Fisher's Exact Tests were applied to statistically analyze the genotype distribution and alleles in the groups. The chi-squared test was used for cross tables. P values less than 0.05 were considered significant.

4. RESULTS

4.1.Demographic Characteristics

The KIF3A region of 48 patients with atopic dermatitis and 46 healthy children in the control group was successfully genotyped. Analyzes were performed in this genotyping population. Demographic and biochemical characteristics of children are shown in Table 6.

Table 6. Demographic and biochemical characteristics of children

	Atopic Dermatitis N=48 (%)	**Control N=46 (%)**	***P=value***
Age (years) mean ±SD	4.86 (±3.67)	3.76(±2.83)	0.11
Gender			
Male	25 (52.1)	27 (58.7)	0.54
Female	23 (47.9)	19 (41.3)	
Total Ig E			
Median	**105.0 (33.1-1201.7)**	**28.3 (10.4-64.9)**	**<0.001**
(25-75 percentile)			
Absolute eosinophil count			
Median (25---75 percentile)	**400.0 (200.0-700.0)**	**170.0 (117.5-252.5)**	**<0.001**
% eosinophil count			
Median (25---75 percentile)	**3.8 (2.3-8.8)**	**1.9 (1.0-2.6)**	**<0.001**
CRP			
Median (25-75 percentile)	0.6 (0.3-1.7)	0.6 (0.3-2.3)	0.89
consanguinity between parents +	3.0 (3.2)		

Family history of allergic disease	24.0 (50.0)		
Family history of atopic dermatitis	12.0 (25.0)		
Severity of Atopic Dermatitis **Mild** **Moderate** **Severe**	 19.0 (39.6) 15.0 (31.3) 14.0 (29.2)		
Having an additional allergic disease+	21.0 (43.8)		
Asthma+	18.0 (37.5)		
Severity of Ashma **İntermittent** **Persistent**	 7.0 (38.9) 11.0(61.1)		
Allergic Rhinitis+	9.0 (1.75)		
Severity of Allergic Rhinitis **İntermittent** **Persistent**	 1.0 (11.1) 8.0 (88.9)		
Atopy+	21.0 (43.8)		
Hause dust mite+	17.0 (35.4)		
Food+	5.0 (10.6)		

n=number of individuals, SD=standart deviation, p-values less than 0.05 denoted statistical significance.

As shown in Table 6, demographic data in the patient and healthy control groups were statistically analyzed. Study group consisted of 48 patients (M: 25, F: 23) with a mean age of 4.89 ± 3.67 years and control group consisted of 46 children (M: 27, F: 19) with a mean age of 3.76 ± 2.83 years. As a result of the analysis, There was no statistically significant difference in the mean age, gender, presence of consanguinity between parents, CRP in the atopic dermatitis patient group compared to the control group. However, a statistically significant difference was observed in the total Ig E, absolute eosinophil count, and eosinophil percentage in the atopic dermatitis patient group compared to the control group.

Half of the patients had a family history of at least one allergic patient, and one-fourth had a history of an individual with eczema. In addition to atopic dermatitis, 44% of the patients had an additional allergic disease. They were most often associated with asthma. Atopy was present in 44% of the patients, the most common being house dust mite sensitivity. According to the severity of atopic dermatitis, 19 patients were classified as mild, 15 as moderate, and 14 as severe atopic dermatitis (Table6).

4.2.Statistical Assessment of Real-Time PCR Results

There was no significant difference between the groups regarding genotype analysis (Table 7).

Table 7. The distribution of KIF3A(rs2897442) genotype in patient and control groups

KIF 3A rs2897442	**AD n=48**	**Control n=46**	***p* value**
CC Genotype	11 22.9 %	3 6.5 %	0.08
CT Genotype	19 39.6 %	21 45.7%	
TTGenotype	18 37.5 %	22 47.8%	

n=number of individuals, p-values less than 0.05 denoted statistical significance.

The distribution of each genotype in the atopic dermatitis patient and healthy control group was analyzed separately. The distribution of the CC genotype was found to be statistically significantly higher in the atopic dermatitis patient group than in the control group, and in the risk analysis, it was determined that carrying the CC genotype increased the risk of atopic dermatitis disease 4 fold compared to the control group (p=0.043, $\chi 2$ =4.610, OR=4.053, 95%. CI=1.051-15.631). There was no significant difference between the groups in the distribution of CC and CT in patient and control genotypes (Table 8).

Table 8. The distribution of KIF3A(rs2897442) genotype with risk analysis in patient and control groups.

KIF 3A rs2897442	AD n=48	Control n=45	*p* value	OR	95%CI
CC Genotype	**11 22.9 %**	**3 6.5 %**	**0.040**	**4.26**	**1.105-16.440**
CT Genotype	19 39.6 %	21 45.7%	0.677	0.780	0.344-1.770
TTGenotype	18 37.5 %	22 47.8%	0.440	0.404	0.288-1.490

n=number of individuals, OR= odd ratio, CI=confidence interval, Chi square χ^2 =Chi square used for comparison of patients with AD and control group, p<0.05 denoted statistically significant differences.

4.3.Genotype and Allele Analysis Among Patient and Control Group

Carrying the T allele reduces the development of atopic dermatitis 4.04 times compared to the healthy group. Carrying the T allele protects against atopic dermatitis (p=0.040, OR=0.235, 95%. CI=0.061-0.905)(Table 9).

Table 9. The distribution of KIF3A(rs2897442) allele frequencies in patient and control groups

KIF 3A rs2897442 Allele frequencies	AD	Control	*p* value	OR	95%CI
C Allele	41 0.43	27 0.29	0.404	1.528	0.671-3.477
T Allele	**55** **0.57**	**65** **0.71**	**0.040**	**0.235**	**0.061-0.905**

n=number of individuals, OR= odd ratio, CI=confidence interval, Chi square χ^2 =Chi square used for comparison of patients with AD and control group, p<0.05 denoted statistically significant differences.

The allele type of each individual in both the patient and control groups was examined using 7500 Fast-Real Time PCR. Allelic discrimination graph obtained automatically from this device is shown below. (figure). Acording to figure, CC which is seen as red dots is homozygote wild type, CT which is seen as green dots is heterozygote and TT which is seen as blue dots is heterozygote mutant type.

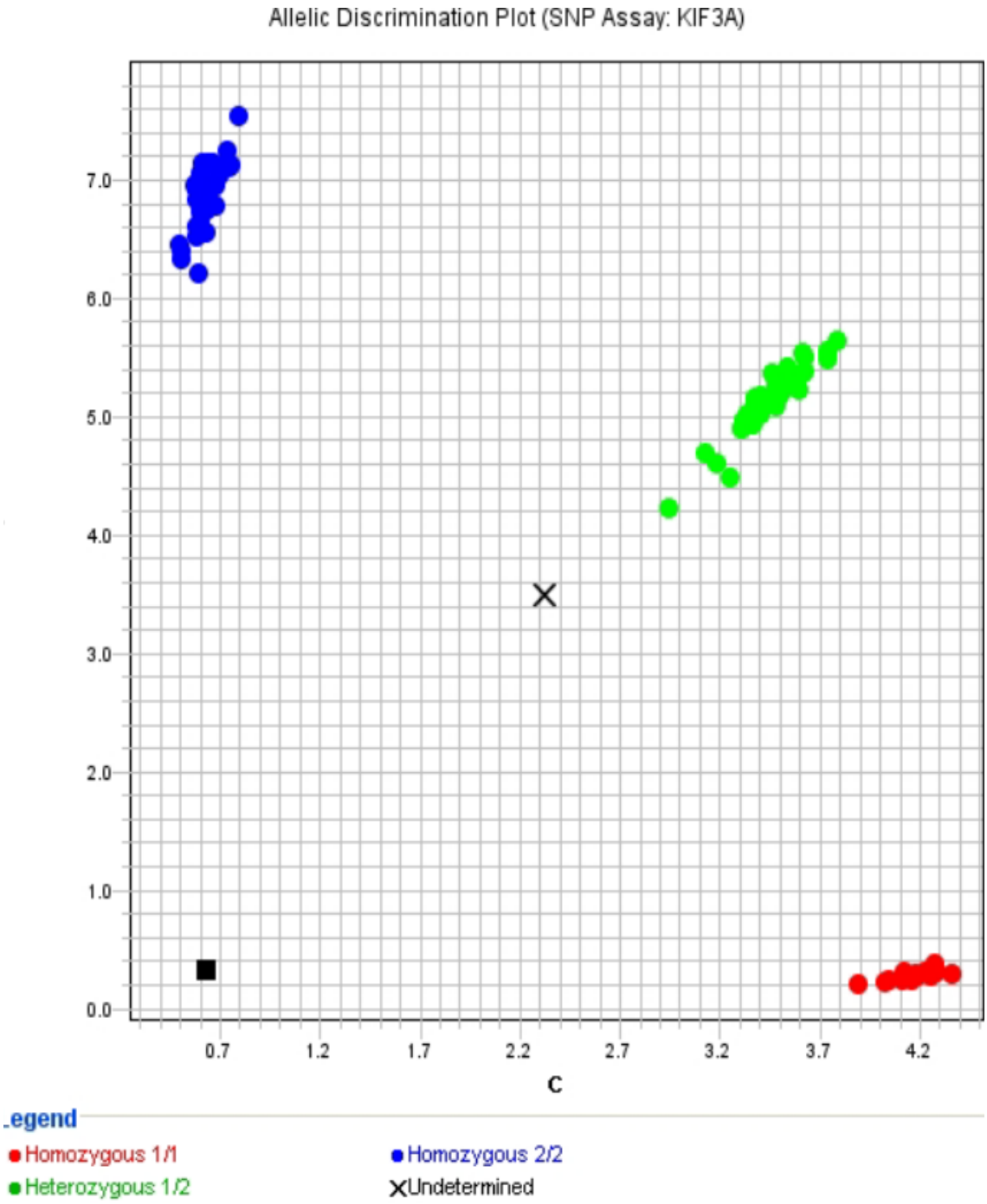

Figure 7. Allelic discrimination KIF3A(rs2897442). CC means homozygote wild type, CT means heterozygote, and TT means homozygote mutant type

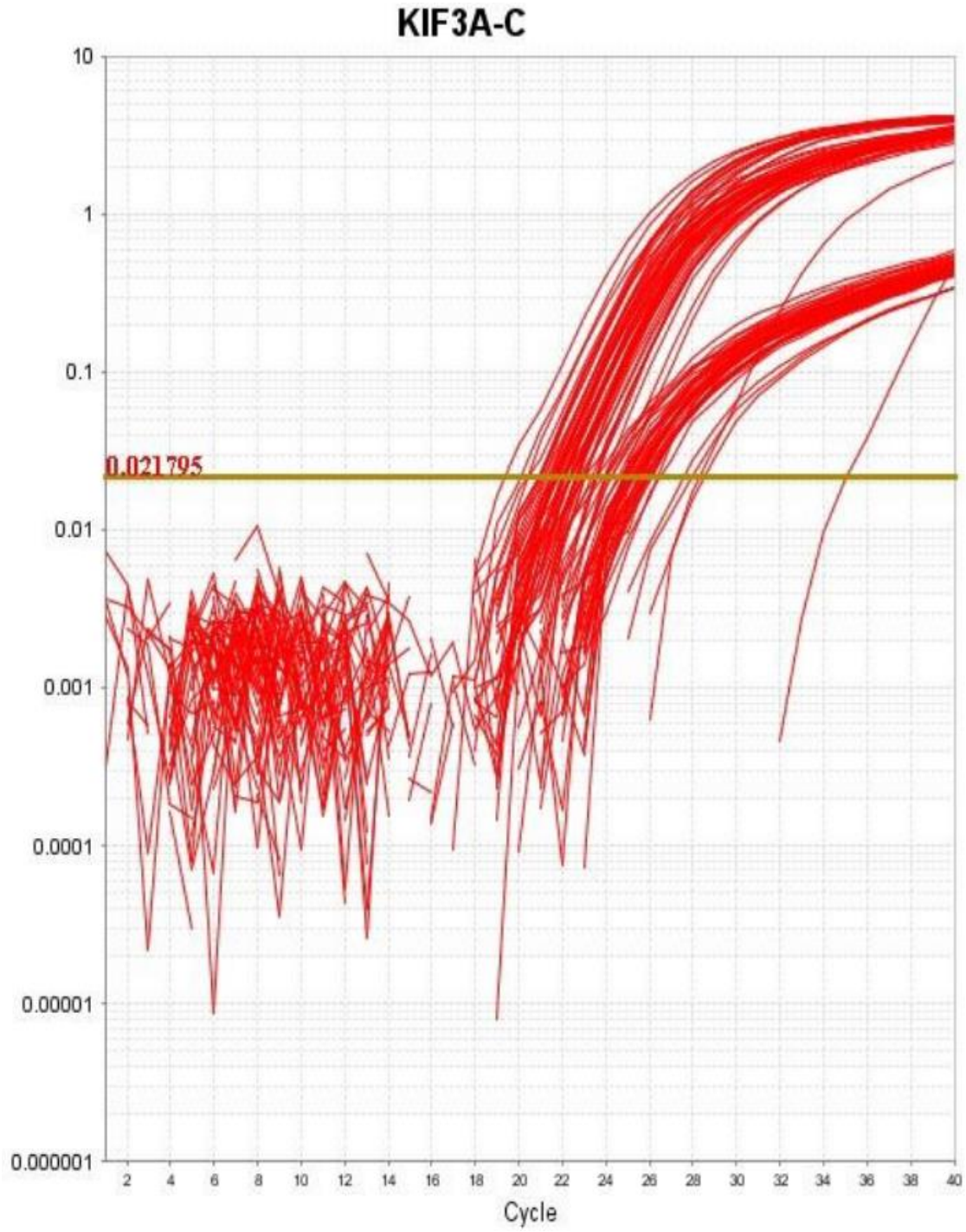

Figure 8. Allele C amplification plot

The plot (Figure 8) represents that amplification plots of Allele C. Yellow line also shows to threshold value (0.021795).

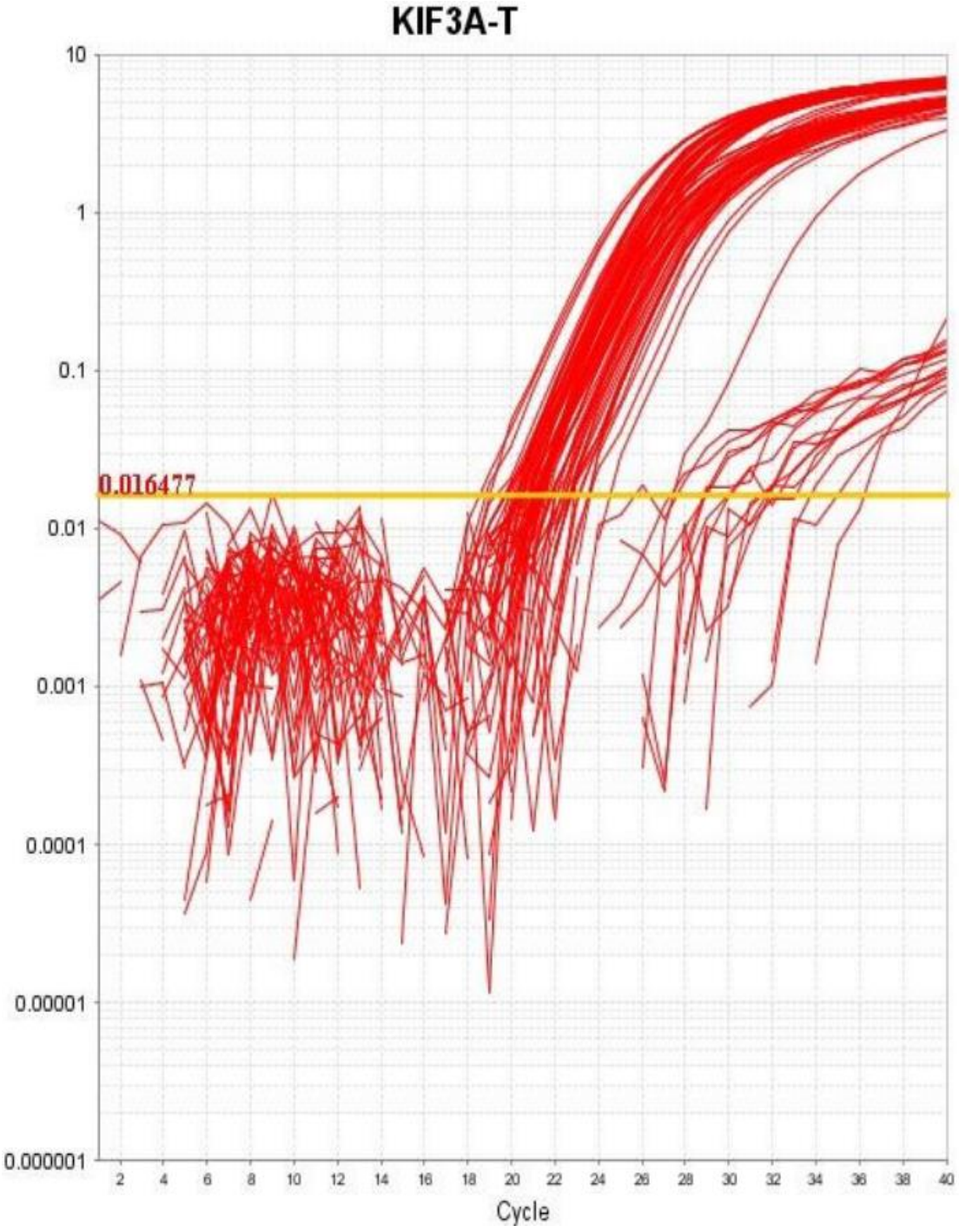

Figure 9. Allele T amplification plot.

It is indicated amplification plot of Allele T in Figure 9 and also the yellow line represents the threshold value (0.016477).

4.4.Evaluation of Atopic Dermatitis Patients According to KIF 3A Genotype

Of the 48 patients, 11 had the CC genotype, 19 had the CT genotype, and 18 had the TT genotype. Distribution of patients according to KIF3A Genotype is shown in Table 10.

Table 10. Distribution of patients according to KIF3A Genotype

	CC Genotype n=11 (%)	CT Genotype n=19 (%)	TT Genotype n=18 (%)	*P*=value
Age	**5.0 ±3.53**	5.26 ±4.26	4.34±3.21	
Mild AD **Moderate AD** **Severe AD**	**2.0 (18.2)** 6.0 (54.5) 3.0 (12.5)	8.0 (42.1) 4.0 (21.1) 7.0 (36.8)	9.0 (50.0) 5.0 (27.8) 4.0 (22.2)	0.27
Mild AD +	2.0 (18.2)	8.0 (42.1)	9.0 (50.0)	
Moderate+Severe AD +	9.0 (81.8)	11.0 (57.9)	9.0 (50.0)	
Atopy+	2.0 (18.2)	9.0 (47.4)	10.0 (55.6)	0.11
Eoz abs	520 (200-700)	470 (260-1527)	335 (162-422)	0.09
Eoz %	4.80 (2.10-8.00)	8.65 (2.95-11.72)	3.22 (0.25-1.17)	0.31
Total Ig E	114.0 (30.5-948.0)	356.3(23.7-2056.0)	89,9(38.9-827.4)	0.94

n=number of individuals, p-values less than 0.05 denoted statistical significance.

It was observed that 81.8% of the patients with the CC genotype had moderate and severe atopic dermatitis. However, this was not statistically significant. Although absolute eosinophil count of patients with CC genotype was higher than other genotypes, it was not statistically significant. (Table 10, figure 10).

When the relationship between absolute eosinophil count and KIF3A genotypes and carrying C or T alleles was investigated, it was observed that those with TT genotype had lower absolute eosinophil counts, and those with C allele had higher values (figure11, figure 12).

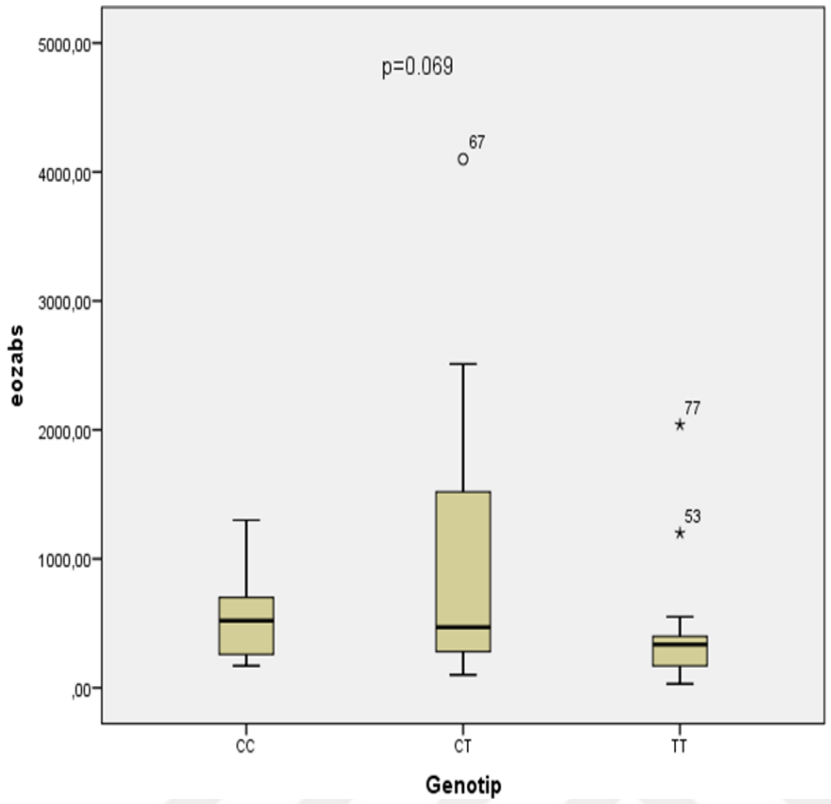

Figure 10. Relationship between the KIF3A genotype and absolute eosinophil count

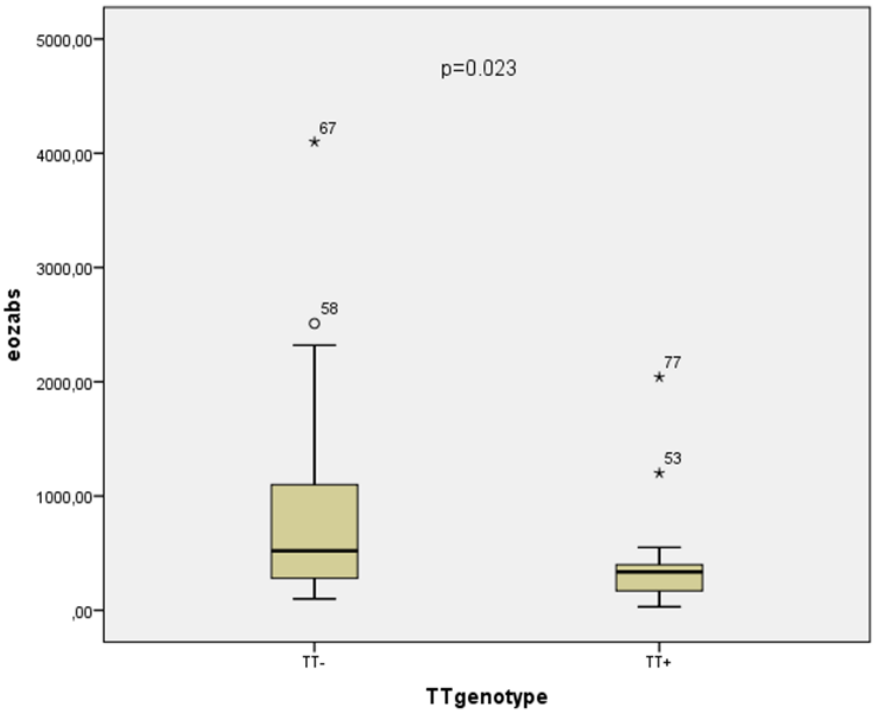

Figure 11. Relationship between the TT genotype and absolute eosinophil count

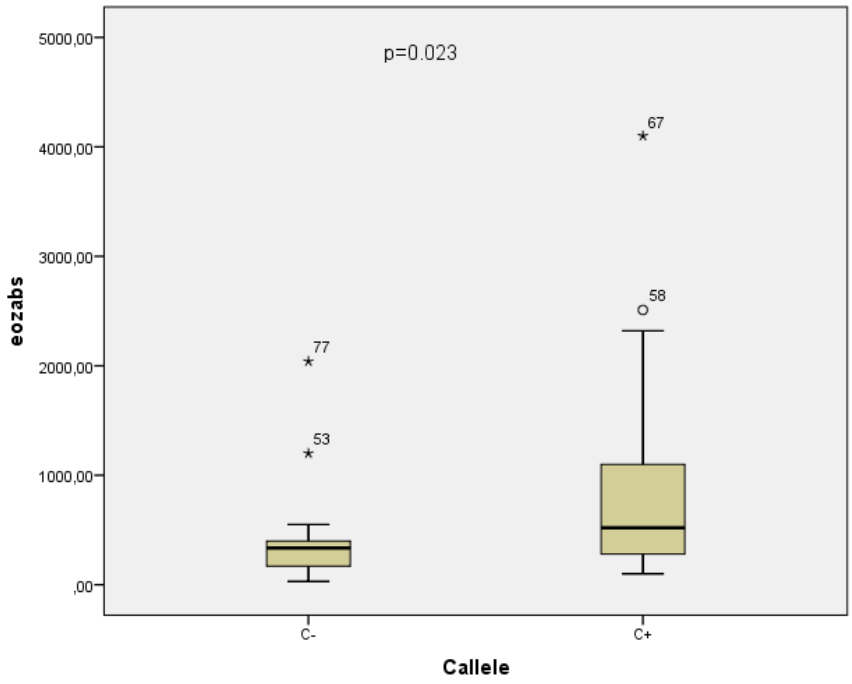

Figure 12. Relationship between the C allele and absolute eosinophil count

Of 48 patients, 19 had mild, 15 moderate and 14 severe atopic dermatitis. The analyzes made according to the severity of the disease are shown in Table 11.

Table 11. Distribution of patients according to severity of the dissease

	Mild AD n=19 (%)	**Moderate AD n=15 (%)**	**Severe AD n=14 (%)**	***P*=value**
CC genotype	**2.0 (10.5)**	6.0 (40.0)	3.0 (21.4)	
CT Genotype	8.0 (42.1)	4.0 (26.7)	7.0 (50.0)	0.27
TT Genotype	9.0 (47.4)	5.0 (33.3)	4.0 (28.6)	
	Mild AD	**Moderate+Severe AD**	P=value	
CC+ Genotype	2.0 (10.5)	9.0 (31.1)	0.16	
CT Genotype	8.0 (42.1)	11.0 (37.9)	1.00	
TT Genotype	9.0 (47.4)	9.0 (31.0)	0.36	

n=number of individuals, p-values less than 0.05 denoted statistical significance.

Table 12. The distribution of KIF3A(rs2897442) allele frequencies in severity of the dissease

KIF 3A rs2897442 Allele frequencies	Mild AD	Moderate+Severe AD	***p* value**	**OR**	**95%CI**
C Allele	12 0.32)	29 (0.50)	0.362	2.00	0.605-6.612
T Allele	26 (0.68)	29 (0.50)	0.161	0.261	0.050-1.379

n=number of individuals, OR= odd ratio, CI=confidence interval, Chi square used for comparison of patients with AD and control group, $p<0.05$ denoted statistically significant differences.

The relationship between the severity of atopic dermatitis and carrying the CC, CT and TT genotypes was examined separately. no significant relationship was found (Table11). When the relationship between the severity of atopic dermatitis and carrying the C or T allele was investigated, there was no statistical significance, but results suggesting that the C allele increases the risk for moderate-severe AD, while the T allele may be protective (table 12). As can be seen in the figure, the SCORAD of those carrying the TT genotype is lower (figüre 13).

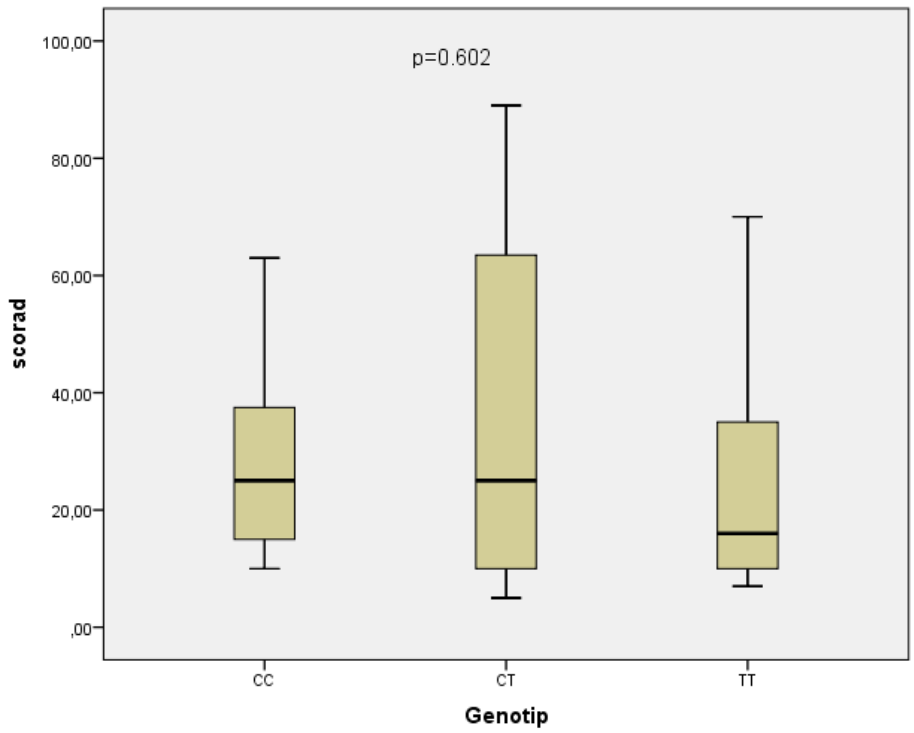

Figure 13. Relationship between the KIF3A genotype and SCORAD

5. DISCUSSION AND CONCLUSION

The KIF3A region of 48 patients with atopic dermatitis (M: 25, F: 23 with a mean age of 4.89 ± 3.67 years) and 46 healthy children in the control group (M: 27, F: 19 with a mean age of 3.76 ± 2.83) years was genotyped. A statistically significant difference was observed in the total Ig E, absolute eosinophil count, and eosinophil percentage in the atopic dermatitis patient group compared to the control group. Total IgE, absolute eosinophil count and eosinophil percentage are higher in individuals with atopic dermatitis than in healthy individuals (1,13). In our study, our findings were found to be compatible with the literature.

Atopic dermatitis is a multifactorial chronic disease in which genetic and environmental factors act together. It is known that the patients have a family history of patients with allergic diseases. Atopic dermatitis may be accompanied by other allergic diseases such as asthma and allergic rhinitis. Patients with atopic dermatitis may be sensitive to foods such as eggs and milk during infancy, and to aeroallergens such as house dust, acrid and mold in childhood (1,2,3,13,). Consistent with the literature in our study, half of the patients had a family history of at least one allergic patient, and one-fourth had a history of an individual with eczema. In addition to atopic dermatitis, 44% of the patients had an additional allergic disease. They were most often associated with asthma. Atopy was present in 44% of the patients, the most common being house dust mite sensitivity. According to the severity of atopic dermatitis, 19 patients were classified as mild, 15 as moderate, and 14 as severe atopic dermatitis.

In this study, We aimed to determine the relationship between AD and rs2897442 (KIF3A) SNPs in 48 pediatric AD patients and 46 healthy controls. Our findings provide preliminary evidence suggesting that 2897442 rs is involved in the pathogenesis of AD in the Turkish pediatric population. There was no significant difference between KIF3A genotype and atopic dermatitis and control groups (p=0.08). When the distribution of each genotype in the study group was compared individually, it was determined that carrying the CC genotype increased the risk of atopic dermatitis disease 4 fold compared

to the control group (p=0.043, $\chi 2$ =4.610, OR=4.053, 95%). CI=1.051-15.631). When the distribution of KIF3A (rs2897442) allele frequencies in the patient and control groups was examined, it was observed that carrying the T allele reduces the development of atopic dermatitis 4.04 times compared to the healthy group. Carrying the T allele protects against atopic dermatitis (p=0.040, OR=0.235, 95%. CI=0.061-0.905). In our study, we determined that carrying a homozygous C (CCgenotype) increases the risk of developing AD, and carrying the T allele decreases the risk of AD. We could not show that the C allele poses a risk at the allele frequency, but not carrying C seems to be the main risk-reducing factor. Lepre et al. determined that the CC genotype and the C allele were more frequent in atopic dermatitis, that carrying the CC genotype created a 2.77-fold risk for the development of atopic dermatitis, that the TT genotype was more common in the control group and had a protective effect (10). Similarly, Kang et al. showed that the C allele poses a 1.74-fold risk of developing atopic dermatitis in the Chinese population (11). As seen in the literature, while CC genotype poses a risk in the development of atopic dermatitis, a protective effect of TT genotype has been shown. It is thought that there was a similar effect in our study,

Unlike other studies, we could not statistically demonstrate that the C allele poses a risk. We think that this is due to the low number of children included in our study group (235 patients and 200 control in the Chinese study; 359 patients and 778 controls in the Italian study).

In Kang's study, the C allele was reported with a frequency of 0.91 in cases and 0.86 in controls, achieving an OR risk of 1.74 [95% CI: 1.14–2.66] (11). Similarly, the C allele was defined as a risk allele in the European study (OR 1.11 [95% CI: 1.07–1.15]) (42). In our study, C allele of rs2897442 was identified with a frequency of 0.43 in cases and 0.29 in controls

Paternoster et al (8) performed a genome-wide association meta-analysis showing three distinct single nucleotide polymorphisms (SNPs) associated with AD: ACTL9 (19p13.2), rs479844, rs2164983 and near OVOL1 (11q13) and rs2897442 (5q31) in KIF3A.) genes respectively. The strongest genetic risk factor shown to date is the FLG null mutation (5,6,13). This mutation seems to be effective for many diseases such as atopic dermatitis, ichthyosis and asthma in many groups. In addition, the disease progresses more severely in atopic dermatitis patients with this mutation (26). Previously, we did not find any FLG mutations in children with atopic dermatitis (7). Similarly, atopic

dermatitis FLG null mutation could not be demonstrated in the Italian population (43). Vardar et al (44) investigated R501X, 2282del4, R2447X, and S3247X mutations in Turkish children, but they could not detect these mutations. In conclusion, we aimed to investigate other risky genes indicated by Paternoster et al. (8,25) for Turkish population with atopic dermatitis.

rs2897442 is an intronic SNP found in the KIF3A gene (kinesin family protein 3A) and encodes a subunit involved in the assembly of the kinesin II complex and primary cilia. It is located in the same region as ATOD6, one of the susceptibility loci for atopic eczema. The region is characterized by a complex. It is a cluster of immune and cytokine genes, especially IL-13, which has been recently associated with atopic dermatitis. Linkage disequilibrium (LD) pattern of 5q31. It does not allow AE to determine development by itself. Its presence in the same region makes KIF3A rs2897442 a potential makes a gene/variant (9,27).

Of the 48 patients, 11 had the CC genotype, 19 had the CT genotype and 18 had the TT genotype. Of 48 patients, 19 had mild, 15 moderate and 14 severe atopic dermatitis. In our study, although not statistically significant, 81.8% of patients with CC genotype had moderate to severe atopic dermatitis. When the relationship between the severity of atopic dermatitis and carrying the C or T allele was investigated, there was no statistical significance, but results suggesting that the C allele increases the risk for moderate-severe AD, while the T allele may be protective. When the relationship between absolute eosinophil count and KIF3A genotypes and carrying C or T alleles was investigated, it was observed that those with TT genotype had lower absolute eosinophil counts, and those with C allele had higher values. Polyaerosensitization was observed in children with asthma without a history of eczema. Interestingly, children in both groups had the KIF3A rs12186803 risk allele. These results suggest that KIF3A deletion disrupts the barrier in the skin and respiratory epithelium and is associated with food allergy in early childhood, aeroallergen sensitivity in late childhood, and severe eczema and asthma. Jahansson at al (38) investigated risk factors for developing asthma. It was observed that children with eczema carrying the KIF3A rs12186803 risk allele had food allergy and developed asthma in the future. Aeroallergen sensitivity was observed in children without eczema and carrying the KIF3A risk allele. KIF3A, like FLG (45), affects the epithelial barrier and food sensitivity in patients with eczema; in others, they concluded that it was associated with aeroallergen sensitization. These results suggest that KIF3A is associated

with atopic march. The resulting change affects the barrier and inflammation, suggesting that it may be related to other allergic diseases and/or the severity of the disease.
The increase in the number and percentage of eosinophils is associated with the development of atopic dermatitis and the severity of atopic dermatitis (1,2,7). In our study, the number of eosinophils was higher in those with C allele and lower in those with T allele. Carrying these alleles or having the genotype CC or TT may be associated with disease severity. It may be appropriate to repeat this study in a larger population.

The strengths of our study are that it was conducted in a pediatric patient population, there were patient and control groups, and the KIF3A gene polymorphism had not been investigated in the Turkish population before. A genetic mutation or polymorphism that may carry a risk of developing atopic dermatitis has not been identified in the Turkish population to date.

There are some factors that limit our study. First of all, the number of patients and controls was a little less. If it was more, risk factors and p values could be more significant. The relationship of the KIF3A gene with allergic diseases has been recognized relatively recently and the mechanism in the pathophysiology is not fully clear. This may have limited the demographic data parameters and statistical tests selected for the study.

In conclusion, It is the first pilot study showing the risk of KIF3A gene polymorphism in the development of atopic dermatitis for the Turkish population. we determined that carrying a homozygous C (CCgenotype) increases the risk of developing AD, and carrying the T allele decreases the risk of AD. Absolute eosinophil count and KIF3A genotypes and carrying C or T alleles was investigated, it was observed that those with TT genotype had lower absolute eosinophil counts, and those with C allele had higher values In this regard, it is recommended to perform gene polymorphism in a larger study group and to conduct more analysis on the genotype-phenotype relationship and its effect on treatment.

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7. APPENDICES

Statistics

hastakontrol			yasyil	totalgE	eozabs	eozyuzde	CRP	scorad
control	N	Valid	460	397	460	460	388	0
		Missing	0	7	0	0	8	46
	Mean		3,7680	59,7562	195,6522	1,9570	3,1011	
	Median		3,0000	29,4100	170,0000	1,9000	,6000	
	Std. Deviation		2,83324	97,59119	162,68104	1,32342	6,14294	
	Minimum		1,00	1,11	,00	,00	,10	
	Maximum		14,00	566,30	1030,00	5,50	28,50	
	Percentiles	25	2,0000	10,4500	117,5000	1,0000	,3000	
		50	3,0000	29,4100	170,0000	1,9000	,6000	
		75	5,1250	65,1100	252,5000	2,6250	2,8250	
AD	N	Valid	480	480	471	471	360	480
		Missing	0	0	1	1	12	0
	Mean		4,8663	1244,4719	678,9362	6,4383	3,2136	30,0417
	Median		3,4200	104,9950	400,0000	3,8000	,5500	25,0000
	Std. Deviation		3,67435	3378,37214	783,34077	6,40708	6,29807	23,53174
	Minimum		,17	1,69	30,00	,20	,10	5,00
	Maximum		14,67	22425,00	4100,00	32,00	27,50	89,00
	Percentiles	25	1,6900	33,1550	200,0000	2,3000	,3000	10,0000
		50	3,4200	104,9950	400,0000	3,8000	,5500	25,0000
		75	8,0225	1201,7250	700,0000	8,8000	1,7250	44,0000

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of yasyil is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	,277	Retain the null hypothesis.
2	The distribution of totalgE is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	,000	Reject the null hypothesis.
3	The distribution of eozabs is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	,000	Reject the null hypothesis.
4	The distribution of eozyuzde is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	,000	Reject the null hypothesis.
5	The distribution of CRP is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	,952	Retain the null hypothesis.
6	The distribution of scorad is the same across categories of hastakontrol.	Independent-Samples Mann-Whitney U Test	.	Unable to compute.

Asymptotic significances are displayed. The significance level is ,05.

Crosstabs

Genotip * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
Genotip	CC	Count	3	11	14
		% within Genotip	21,4%	78,6%	100,0%
		% within hastakontrol	6,5%	22,9%	14,9%
		% of Total	3,2%	11,7%	14,9%
	CT	Count	21	19	40
		% within Genotip	52,5%	47,5%	100,0%
		% within hastakontrol	45,7%	39,6%	42,6%
		% of Total	22,3%	20,2%	42,6%
	TT	Count	22	18	40
		% within Genotip	55,0%	45,0%	100,0%
		% within hastakontrol	47,8%	37,5%	42,6%
		% of Total	23,4%	19,1%	42,6%

Total	Count	46	48	94
	% within Genotip	48,9%	51,1%	100,0%
	% within hastakontrol	100,0%	100,0%	100,0%
	% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,031[a]	2	,081
Likelihood Ratio	5,318	2	,070
Linear-by-Linear Association	3,332	1	,068
N of Valid Cases	94		

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 6,85.

CCgenotype * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
CCgenotype	CC-	Count	43	37	80
		% within CCgenotype	53,8%	46,3%	100,0%
		% within hastakontrol	93,5%	77,1%	85,1%
		% of Total	45,7%	39,4%	85,1%
	CC+	Count	3	11	14
		% within CCgenotype	21,4%	78,6%	100,0%
		% within hastakontrol	6,5%	22,9%	14,9%
		% of Total	3,2%	11,7%	14,9%
Total		Count	46	48	94
		% within CCgenotype	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4,981[a]	1	,026		
Continuity Correction[b]	3,772	1	,052		
Likelihood Ratio	5,268	1	,022		
Fisher's Exact Test				,040	,024
Linear-by-Linear Association	4,928	1	,026		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 6,85.

b. Computed only for a 2x2 table

8.

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for CCgenotype (CC- / CC+)	4,261	1,105	16,440
For cohort hastakontrol = control	2,508	,901	6,980
For cohort hastakontrol = AD	,589	,410	,845
N of Valid Cases	94		

CTgenotype * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
CTgenotype	CT-	Count	25	29	54
		% within CTgenotype	46,3%	53,7%	100,0%
		% within hastakontrol	54,3%	60,4%	57,4%
		% of Total	26,6%	30,9%	57,4%
	CT+	Count	21	19	40
		% within CTgenotype	52,5%	47,5%	100,0%
		% within hastakontrol	45,7%	39,6%	42,6%
		% of Total	22,3%	20,2%	42,6%
Total		Count	46	48	94
		% within CTgenotype	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,354[a]	1	,552		
Continuity Correction[b]	,149	1	,699		
Likelihood Ratio	,354	1	,552		
Fisher's Exact Test				,677	,350
Linear-by-Linear Association	,350	1	,554		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 19,57.

b. Computed only for a 2x2 table

TTgenotype * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
TTgenotype	TT-	Count	24	30	54
		% within TTgenotype	44,4%	55,6%	100,0%
		% within hastakontrol	52,2%	62,5%	57,4%
		% of Total	25,5%	31,9%	57,4%
	TT+	Count	22	18	40
		% within TTgenotype	55,0%	45,0%	100,0%
		% within hastakontrol	47,8%	37,5%	42,6%
		% of Total	23,4%	19,1%	42,6%
Total		Count	46	48	94
		% within TTgenotype	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1,025[a]	1	,311		
Continuity Correction[b]	,646	1	,422		
Likelihood Ratio	1,026	1	,311		
Fisher's Exact Test				,404	,211
Linear-by-Linear Association	1,014	1	,314		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 19,57.

b. Computed only for a 2x2 table

Callele * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
Callele	C-	Count	22	18	40
		% within Callele	55,0%	45,0%	100,0%
		% within hastakontrol	47,8%	37,5%	42,6%
		% of Total	23,4%	19,1%	42,6%

	C+	Count	24	30	54
		% within Callele	44,4%	55,6%	100,0%
		% within hastakontrol	52,2%	62,5%	57,4%
		% of Total	25,5%	31,9%	57,4%
Total		Count	46	48	94
		% within Callele	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1,025[a]	1	,311		
Continuity Correction[b]	,646	1	,422		
Likelihood Ratio	1,026	1	,311		
Fisher's Exact Test				,404	,211
Linear-by-Linear Association	1,014	1	,314		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 19,57.

b. Computed only for a 2x2 table

Tallele * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
Tallele	T-	Count	3	11	14
		% within Tallele	21,4%	78,6%	100,0%
		% within hastakontrol	6,5%	22,9%	14,9%
		% of Total	3,2%	11,7%	14,9%
	T+	Count	43	37	80
		% within Tallele	53,8%	46,3%	100,0%
		% within hastakontrol	93,5%	77,1%	85,1%
		% of Total	45,7%	39,4%	85,1%
Total		Count	46	48	94
		% within Tallele	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4,981[a]	1	,026		
Continuity Correction[b]	3,772	1	,052		
Likelihood Ratio	5,268	1	,022		
Fisher's Exact Test				,040	,024
Linear-by-Linear Association	4,928	1	,026		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 6,85.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Tallele (T- / T+)	,235	,061	,905
For cohort hastakontrol = control	,399	,143	1,109
For cohort hastakontrol = AD	1,699	1,184	2,439
N of Valid Cases	94		

akrabalik * hastakontrol

Crosstab

			hastakontrol		Total
			control	AD	
akrabalik	yok	Count	46	45	91
		% within akrabalik	50,5%	49,5%	100,0%
		% within hastakontrol	100,0%	93,8%	96,8%
		% of Total	48,9%	47,9%	96,8%
	var	Count	0	3	3
		% within akrabalik	0,0%	100,0%	100,0%
		% within hastakontrol	0,0%	6,3%	3,2%
		% of Total	0,0%	3,2%	3,2%
Total		Count	46	48	94
		% within akrabalik	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

aideADoyku * hastakontrol

Crosstab

	hastakontrol	Total

			AD	
aideADoyku	yok	Count	36	36
		% within aideADoyku	100,0%	100,0%
		% within hastakontrol	75,0%	75,0%
		% of Total	75,0%	75,0%
	var	Count	12	12
		% within aideADoyku	100,0%	100,0%
		% within hastakontrol	25,0%	25,0%
		% of Total	25,0%	25,0%
Total		Count	48	48
		% within aideADoyku	100,0%	100,0%
		% within hastakontrol	100,0%	100,0%
		% of Total	100,0%	100,0%

aileoyku * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
aileoyku	yok	Count	46	24	70
		% within aileoyku	65,7%	34,3%	100,0%
		% within hastakontrol	100,0%	50,0%	74,5%
		% of Total	48,9%	25,5%	74,5%
	egzema	Count	0	24	24
		% within aileoyku	0,0%	100,0%	100,0%
		% within hastakontrol	0,0%	50,0%	25,5%
		% of Total	0,0%	25,5%	25,5%
Total		Count	46	48	94
		% within aileoyku	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

atopi * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
atopi	yok	Count	46	27	73
		% within atopi	63,0%	37,0%	100,0%
		% within hastakontrol	100,0%	56,3%	77,7%
		% of Total	48,9%	28,7%	77,7%
	var	Count	0	21	21
		% within atopi	0,0%	100,0%	100,0%

	% within hastakontrol	0,0%	43,8%	22,3%
	% of Total	0,0%	22,3%	22,3%
Total	Count	46	48	94
	% within atopi	48,9%	51,1%	100,0%
	% within hastakontrol	100,0%	100,0%	100,0%
	% of Total	48,9%	51,1%	100,0%

cins * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
cins	kız	Count	19	23	42
		% within cins	45,2%	54,8%	100,0%
		% within hastakontrol	41,3%	47,9%	44,7%
		% of Total	20,2%	24,5%	44,7%
	erkek	Count	27	25	52
		% within cins	51,9%	48,1%	100,0%
		% within hastakontrol	58,7%	52,1%	55,3%
		% of Total	28,7%	26,6%	55,3%
Total		Count	46	48	94
		% within cins	48,9%	51,1%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	48,9%	51,1%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,416[a]	1	,519		
Continuity Correction[b]	,191	1	,662		
Likelihood Ratio	,416	1	,519		
Fisher's Exact Test				,541	,331
Linear-by-Linear Association	,411	1	,521		
N of Valid Cases	94				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 20,55.

b. Computed only for a 2x2 table

assid2 * hastakontrol

Crosstab

			hastakontrol	
			AD	Total
assid2	intermitant	Count	7	7

		% within assid2	100,0%	100,0%
		% within hastakontrol	38,9%	38,9%
		% of Total	38,9%	38,9%
	orta-agır	Count	11	11
		% within assid2	100,0%	100,0%
		% within hastakontrol	61,1%	61,1%
		% of Total	61,1%	61,1%
Total		Count	18	18
		% within assid2	100,0%	100,0%
		% within hastakontrol	100,0%	100,0%
		% of Total	100,0%	100,0%

rinsidet2 * hastakontrol

Crosstab

			hastakontrol	
			AD	Total
rinsidet2	hafif-intermitant	Count	1	1
		% within rinsidet2	100,0%	100,0%
		% within hastakontrol	11,1%	11,1%
		% of Total	11,1%	11,1%
	persistenorta ve agir	Count	8	8
		% within rinsidet2	100,0%	100,0%
		% within hastakontrol	88,9%	88,9%
		% of Total	88,9%	88,9%
Total		Count	9	9
		% within rinsidet2	100,0%	100,0%
		% within hastakontrol	100,0%	100,0%
		% of Total	100,0%	100,0%

akar * hastakontrol

Crosstab

			hastakontrol	
			AD	Total
akar	,00	Count	31	31
		% within akar	100,0%	100,0%
		% within hastakontrol	64,6%	64,6%
		% of Total	64,6%	64,6%
	1,00	Count	17	17
		% within akar	100,0%	100,0%
		% within hastakontrol	35,4%	35,4%
		% of Total	35,4%	35,4%

Total	Count	48	48
	% within akar	100,0%	100,0%
	% within hastakontrol	100,0%	100,0%
	% of Total	100,0%	100,0%

besinmiks * hastakontrol

Crosstab

			hastakontrol		
			control	AD	Total
besinmiks	yok	Count	1	42	43
		% within besinmiks	2,3%	97,7%	100,0%
		% within hastakontrol	100,0%	89,4%	89,6%
		% of Total	2,1%	87,5%	89,6%
	var	Count	0	5	5
		% within besinmiks	0,0%	100,0%	100,0%
		% within hastakontrol	0,0%	10,6%	10,4%
		% of Total	0,0%	10,4%	10,4%
Total		Count	1	47	48
		% within besinmiks	2,1%	97,9%	100,0%
		% within hastakontrol	100,0%	100,0%	100,0%
		% of Total	2,1%	97,9%	100,0%

allhast2 * hastakontrol

Crosstab

			hastakontrol	
			AD	Total
allhast2	egzema	Count	27	27
		% within allhast2	100,0%	100,0%
		% within hastakontrol	56,3%	56,3%
		% of Total	56,3%	56,3%
	egzema+diiğer	Count	21	21
		% within allhast2	100,0%	100,0%
		% within hastakontrol	43,8%	43,8%
		% of Total	43,8%	43,8%
Total		Count	48	48
		% within allhast2	100,0%	100,0%
		% within hastakontrol	100,0%	100,0%
		% of Total	100,0%	100,0%

cins * Genotip

Crosstab

	Genotip	Total

			CC	CT	TT	
cins	kız	Count	6	8	9	23
		% within cins	26,1%	34,8%	39,1%	100,0%
		% within Genotip	54,5%	42,1%	50,0%	47,9%
		% of Total	12,5%	16,7%	18,8%	47,9%
	erkek	Count	5	11	9	25
		% within cins	20,0%	44,0%	36,0%	100,0%
		% within Genotip	45,5%	57,9%	50,0%	52,1%
		% of Total	10,4%	22,9%	18,8%	52,1%
Total		Count	11	19	18	48
		% within cins	22,9%	39,6%	37,5%	100,0%
		% within Genotip	100,0%	100,0%	100,0%	100,0%
		% of Total	22,9%	39,6%	37,5%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	,482[a]	2	,786
Likelihood Ratio	,483	2	,785
Linear-by-Linear Association	,018	1	,894
N of Valid Cases	48		

ADsiddeti * Genotip

Crosstab

			Genotip			
			CC	CT	TT	Total
ADsiddeti	hafif(0-14	Count	2	8	9	19
		% within ADsiddeti	10,5%	42,1%	47,4%	100,0%
		% within Genotip	18,2%	42,1%	50,0%	39,6%
		% of Total	4,2%	16,7%	18,8%	39,6%
	orta 15-40	Count	6	4	5	15
		% within ADsiddeti	40,0%	26,7%	33,3%	100,0%
		% within Genotip	54,5%	21,1%	27,8%	31,3%
		% of Total	12,5%	8,3%	10,4%	31,3%
	ağır(41-	Count	3	7	4	14
		% within ADsiddeti	21,4%	50,0%	28,6%	100,0%
		% within Genotip	27,3%	36,8%	22,2%	29,2%
		% of Total	6,3%	14,6%	8,3%	29,2%
Total		Count	11	19	18	48
		% within ADsiddeti	22,9%	39,6%	37,5%	100,0%

	% within Genotip	100,0%	100,0%	100,0%	100,0%
	% of Total	22,9%	39,6%	37,5%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,104[a]	4	,277
Likelihood Ratio	5,120	4	,275
Linear-by-Linear Association	1,437	1	,231
N of Valid Cases	48		

a. 3 cells (33,3%) have expected count less than 5. The minimum expected count is 3,21.

egzsid2 * Genotip

Crosstab

			Genotip			
			CC	CT	TT	Total
egzsid2	1,00	Count	2	8	9	19
		% within egzsid2	10,5%	42,1%	47,4%	100,0%
		% within Genotip	18,2%	42,1%	50,0%	39,6%
		% of Total	4,2%	16,7%	18,8%	39,6%
	2,00	Count	9	11	9	29
		% within egzsid2	31,0%	37,9%	31,0%	100,0%
		% within Genotip	81,8%	57,9%	50,0%	60,4%
		% of Total	18,8%	22,9%	18,8%	60,4%
Total		Count	11	19	18	48
		% within egzsid2	22,9%	39,6%	37,5%	100,0%
		% within Genotip	100,0%	100,0%	100,0%	100,0%
		% of Total	22,9%	39,6%	37,5%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2,974[a]	2	,226
Likelihood Ratio	3,195	2	,202
Linear-by-Linear Association	2,617	1	,106
N of Valid Cases	48		

a. 1 cells (16,7%) have expected count less than 5. The minimum expected count is 4,35.

atopi * Genotip

Crosstab

			Genotip			Total
			CC	CT	TT	
atopi	yok	Count	9	10	8	27
		% within atopi	33,3%	37,0%	29,6%	100,0%
		% within Genotip	81,8%	52,6%	44,4%	56,3%
		% of Total	18,8%	20,8%	16,7%	56,3%
	var	Count	2	9	10	21
		% within atopi	9,5%	42,9%	47,6%	100,0%
		% within Genotip	18,2%	47,4%	55,6%	43,8%
		% of Total	4,2%	18,8%	20,8%	43,8%
Total		Count	11	19	18	48
		% within atopi	22,9%	39,6%	37,5%	100,0%
		% within Genotip	100,0%	100,0%	100,0%	100,0%
		% of Total	22,9%	39,6%	37,5%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4,043[a]	2	,132
Likelihood Ratio	4,342	2	,114
Linear-by-Linear Association	3,467	1	,063
N of Valid Cases	48		

a. 1 cells (16,7%) have expected count less than 5. The minimum expected count is 4,81.

Frequencies

Statistics

Genotip			yasyil	totaIgE	eozabs	eozyuzde	CRP
CC	N	Valid	11	11	11	11	6
		Missing	0	0	0	0	5
	Mean		5,0218	832,6418	569,0909	5,3091	2,2417
	Median		3,7500	114,9000	520,0000	4,8000	1,0000
	Std. Deviation		3,53110	1489,58484	371,65722	3,09013	2,52476
	Minimum		1,08	7,98	170,00	1,40	,40
	Maximum		10,25	4753,00	1300,00	10,00	6,65
	Percentiles	25	1,7500	30,4900	200,0000	2,1000	,4750
		50	3,7500	114,9000	520,0000	4,8000	1,0000

		75	8,5000	948,0000	700,0000	8,0000	4,5875
CT	N	Valid	19	19	18	18	17
		Missing	0	0	1	1	2
	Mean		5,2679	1923,8411	1003,8889	8,6500	3,5471
	Median		3,4200	356,3000	470,0000	4,9000	,6000
	Std. Deviation		4,25255	5058,22584	1075,17516	8,21815	6,33819
	Minimum		,25	8,43	100,00	1,30	,10
	Maximum		14,67	22425,00	4100,00	32,00	22,00
	Percentiles	25	1,5800	23,7000	260,0000	2,9500	,2500
		50	3,4200	356,3000	470,0000	4,9000	,6000
		75	8,1700	2056,0000	1527,5000	11,7250	2,4000
TT	N	Valid	18	18	18	18	13
		Missing	0	0	0	0	5
	Mean		4,3472	779,0339	421,1111	4,9167	3,2262
	Median		3,2100	89,0300	335,0000	3,2000	,4000
	Std. Deviation		3,21903	1517,83667	482,84560	5,42838	7,67085
	Minimum		,17	1,69	30,00	,20	,10
	Maximum		10,83	5765,00	2040,00	20,90	27,50
	Percentiles	25	1,8550	38,3925	162,5000	1,9750	,2500
		50	3,2100	89,0300	335,0000	3,2000	,4000
		75	5,6850	827,4750	422,5000	5,6750	1,1700

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of yasyil is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,901	Retain the null hypothesis.
2	The distribution of totalgE is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,793	Retain the null hypothesis.
3	The distribution of eozabs is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,069	Retain the null hypothesis.
4	The distribution of eozyuzde is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,207	Retain the null hypothesis.
5	The distribution of CRP is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,403	Retain the null hypothesis.
6	The distribution of scorad is the same across categories of Genotip.	Independent-Samples Kruskal-Wallis Test	,602	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is ,05.

Plate Layout

7.1. Ethical Approval

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15- 2340 **14/04/2022**
Konu: Klinik Araştırmalar
Etik Kurul Başvurusu hk.

İlgili Makama (Hülya Ercan Sarıçoban)

Yeditepe Üniversitesi Moleküler Tıp AD. Prof. Dr. Turgay İsbir'in proje koordinatörü olduğu Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları, Çocuk İmmünoloji ve Alerji AD. Prof. Dr. Hülya Ercan Sarıçoban'ın sorumlu araştırmacı olduğu, **"Atopik Dermatitli Çocuklarda KIF3A Gen Polimorfizminin Etkisinin Belirlenmesi"** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası **(2402)** kayıtlı Numaralı KAEK Başvuru Dosyası, Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **13.04.2022** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isim belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir. **(KAEK Karar No: 1600)**

Prof. Dr. Turgay ÇELİK

Yeditepe Üniversitesi
Klinik Araştırmalar Etik Kurul Başkanı

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7.2. Curriculum Vitae

Name and Surname: Hülya ERCAN SARICOBAN

H-Index: 12 (WEB of Science), 13 (Scopus
Total Citation: 831

1. Education:

1993-2000	Hacettepe University Faculty of Medicine	Medical School
2000-2005	Hacettepe University Faculty of Medicine, Medical School	Pediatrics
2007-2011	Yeditepe University, Medical School	Pediatric Allergy
2012	Turkish Ministry of Health, Medical Specialist Board	Pediatric Allergy and Immunology
2017-	Yeditepe University, Medical School	Molecular Medicine ,Phd
2019	European Academy of Allergology and Clinical Immunology Board	European Pediatric Allergist

2. Position:

20.10.2000-9.06.2005	Residency	Hacettepe University, Medical School	Department of Pediatrics
2005-2007	Pediatrician	Yeditepe University, Medical School	Department of Pediatrics
2007-2011	Fellowship	Yeditepe University, Medical School	Pediatric Allergy and Immunology
14.4.2007-1.3.2011	Asistant Profesor	Yeditepe University, Medical School	Department of Pediatrics
01.04.2011-31.08.2014	Pediatric allergy and immunolog	Sureyyapaşa Chest Hospital	Pediatric Allergy and Immunology
1.9.2014-01.05.2018	Associate Professor	Yeditepe University, Medical School	Pediatric Allergy and Immunology
02.05.2018-	Professor	Yeditepe University, Medical School	Pediatric Allergy and Immunology
01.09.2014-	Chief	Yeditepe University, Medical School	Pediatric Allergy and Immunology
2015-2022	Co-coordinator	Yeditepe University, Medical School	Yeditepe University Faculty of Medicine Phase IV
2016-	Member	Yeditepe University, Medical School	Yeditepe University Faculty of Medicine curriculum board
2022-	Chief	Yeditepe University, Medical School	Department of Pediatrics
2022-	Co-coordinator	Yeditepe University, Medical School	Yeditepe University Faculty of Medicine Phase VI

3. **Thesis:**

1. Ercan H, Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma.J Allergy Clin Immunol. 2005 (Prof. Dr. C. Ömer KALAYCI)

2. Ercan H,. Predictors of AD phenotypes and severity: roles of serum immunoglobulins and Filaggrin gene mutation R501X. 2011 (Prof. Dr. Reha Cengizlier)

4.Awards:

1. XVII. Ulusal Alerji ve Klinik İmmünoloji Kongresi 2009: Sackesen C, **Ercan H**, Dizdar E, Soyer O, Gumus P, Tosun BN, Büyüktuncer Z, Karabulut E, Besler T, Kalayci O. A comprehensive evaluation of the enzymatic and nonenzymatic antioxidant systems in childhood asthma. J Allergy Clin Immunol. 2008 Jul;122(1):78-85. Epub 2008 May 16.Makalesi ile 2008 yılında SCI kapsamında yayınlanmış makale ödülü
2. XV. Ulusal Alerji ve Klinik İmmünoloji Kongresi 2007: **Ercan H**, Birben E, Dizdar EA, Keskin O, Karaaslan C, Soyer OU, Dut R, Sackesen C, Besler T, Kalayci O. Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma.J Allergy Clin Immunol. 2006 Nov;118(5):1097-104.Makalesi 2006 yılında SCI kapsamında yayınlanmış makale ödülü
3. 10 XXV European Academy of Allergology and Clinical Immunology, Vienna, Austria, 10-14 June 2006 Kongresi en iyi poster ödülü **: Ercan H**, Birben E, Keskin O, Karaaslan C, soyer O, dizdar E, Sackesen C, Besler T, Kalayci O. Oxidative stres and genetic and epidemiologic determinants of oxidant injury in childhood. XXV European Academy of Allergology and Clinical Immunology, Vienna, Austria, 10-14 June 2006
4. 27.09-01.10-2005 XIII. Ulusal Alerji ve Klinik İmmünoloji Kongresi poster ödülü : Özlem Keskin, Esra Birben, Cansın Saçkesen, Özge U soyer, Evrim Alyamaç, Çağatay Karaaslan, **Hülya Ercan**, Ömer Kalaycı. CD14 polimorfizminin IgE sentezinde rol alan sitokinler üzerine protein ve transkripsiyon düzeyinde etkisi. XIII. Ulusal alerji ve klinik immünoloji kongresi. 27 Eylül-01 Ekim 2005
5. 27.09-01.10-2005 XIII. Ulusal Alerji ve Klinik İmmünoloji Kongresi poster ödülü: **Hülya Ercan**, Esra Birben, Özlem Keskin, Çağatay Karaaslan, Özge U Soyer, Evrim A Dizdar, Cansın Saçkesen, Tanju Besler, Ömer Kalaycı. Astımda oksidatif stres ve antioksidan enzimlerin genetik varyantları.

5. Publications:

1. **Saricoban HE**, Ozen A, Harmanci K, Razi C, Zahmacioglu O, Cengizlier R. Common behavioral problems among children with asthma: Is there a role of asthma treatment?

Annals of Allergy, Asthma, & Immunology. 2011 Mar;106(3):200-4 doi:10.1016/j.anai.2010.11.016

2. Ozen A, Furman A, Berber M, Karatepe HO, Mutlu N, **Sarıçoban HE**, Büyükgebiz B. The effect of Helicobacter pylori and economic status on growth parameters and leptin, ghrelin, and insulin-like growth factor (IGF)-I concentrations in children. Helicobacter. 2011 Feb;16(1):55-65. doi:10.1111/j.1523-5378.2010.00814.x.

3. Baris S, Ozen A, **Ercan H**, Karakoc-Aydiner E, Cagan H, Ozdemir C, Barlan M,Bahceciler NN, Barlan IB. Osteoporosis: An ignored complication of CVID. Pediatr Allergy Immunol. 2011 Nov;22(7):676-83. doi: 10.1111/j.1399-3038.2011.01187.x.Epub 2011 Jun 6.

4. Bakar FT, Ozen A, Karatepe HO, Berber M, **Ercan H**. Impact of early weight loss on growth of Caesarean delivered babies: how long does it last? Child Care Health Dev. 2011 Aug 9. doi: 10.1111/j.1365-2214.2011.01291.x.

5. Baris S, **Saricoban HE**, Ak K, Ozdemir C. Papaverine chloride as a topical vasodilator in accidental injection of adrenaline into a digital finger. Allergy.2011 Nov;66(11):1495-6. doi: 10.1111/j.1398-9995.2011.02664.x. Epub 2011 Jul 4.

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