Review

Genetics and Epigenetics of Atopic Dermatitis: An Updated Systematic Review

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Abstract: Background: Atopic dermatitis is a common inflammatory skin disorder that affects up to 15–20% of the population and is characterized by recurrent eczematous lesions with intense itching. As a heterogeneous disease, multiple factors have been suggested to explain the nature of atopic dermatitis (AD), and its high prevalence makes it necessary to periodically compile and update the new information available. In this systematic review, the focus is set at the genetic and epigenetic studies carried out in the last years. Methods: A systematic literature review was conducted in three scientific publication databases (PubMed, Cochrane Library, and Scopus). The search was restricted to publications indexed from July 2016 to December 2019, and keywords related to atopic dermatitis genetics and epigenetics were used. Results: A total of 73 original papers met the inclusion criteria established, including 9 epigenetic studies. A total of 62 genes and 5 intergenic regions were described as associated with AD. Conclusion: Filaggrin (FLG) polymorphisms are confirmed as key genetic determinants for AD development, but also epigenetic regulation and other genes with functions mainly related to the immune system and extracellular matrix, reinforcing the notion of skin homeostasis breakage in AD.

Keywords: atopic dermatitis; genetics; epigenetics; skin barrier; genetic association studies; DNA methylation; omics

1. Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a common inflammatory skin disorder that affects up to 15–20% of children [1] and 7–10% of adults [2] in developed countries. AD typically develops during childhood and is characterized by recurrent eczematous lesions with intense itching [1]. It is considered the first step of the atopic march, associated with an increased risk of developing allergic rhinoconjunctivitis, asthma, or food allergy [3]. Worldwide, the prevalence of AD used to be higher in countries with higher incomes. However, due to the globalization process and a more westernized way of life, an increase of AD prevalence in low-income countries of Africa and East Asia has been reported, stressing the role of environment together with genetic and immunologic factors in the pathogenicity of AD [4].
AD is a heterogeneous disease. Thus, interactions between susceptibility genes, environmental factors, impaired barrier skin integrity, skin microbiota, and immune deregulation have been proposed to explain the nature of AD [5]. An urban way of life is one of the most clearly related environmental factors, as supported by a consistently higher incidence of eczema in urban versus rural areas [6]. Diet is also a risk factor, and a regular intake of fresh fruit and fish during pregnancy and childhood has shown some effectiveness in preventing AD [7–9]. Furthermore, it has been reported that a family history of asthma, hay fever, or eczema is associated with AD in the offspring, the risk being higher when both parents suffer from eczema [10].

AD is associated with atopic comorbidities such as asthma, allergic rhinoconjunctivitis, and food allergy, as well as with non-atopic entities such as inflammatory diseases and psychological disorders [11,12]. Genetic association studies have confirmed that atopic comorbidities share genetic susceptibility [13,14]. The heritability of AD in twin studies was estimated to be nearly 75%, and the association between asthma and AD was nearly 85% explained by genetic pleiotropy [15].

Two main reviews about the genetics of AD have been performed in the last decade. The first one was published in 2010 and compiled all the existent genetic studies related to AD [16], reporting variants in 81 genes, 46 of which had shown positive association with the disease. In 2016, Bin and Leung published an update on the topic, including genetic and epigenetic studies from 2009 to June 2016 [17]. The aim of this systematic review is to compile the most recent publications on the genetics of atopic dermatitis, also including epigenetic studies. Original articles about genetic variation and polymorphisms in patients with atopic dermatitis or atopic eczema were sought. Both adult and children studies were included. Comparison to healthy control was preferred, but not all studies performed it. Although literature reviews were excluded, we analyzed some meta-analyses due to the valuable information they contained.

2. Materials and Methods

This systematic review has been performed using the PRISMA guidelines for Systematic Reviews and Meta-Analysis 2009 checklist and GRADE recommendations [18].

Original articles and meta-analyses indexed from July 2016 to December 2019, describing genetic or epigenetic aspects of atopic dermatitis, were searched. We identified eligible studies using the following inclusion criteria: (1) primary study or meta-analysis, (2) written in English or Spanish, (3) human subjects, both children and adults, (4) patients suffering from atopic dermatitis or atopic eczema, and (5) studies describing mutations, single nucleotide polymorphisms (SNPs), or epigenetic modifications in association with disease onset, severity, or prevalence in the population. The exclusion criteria were: (1) animal, in vitro or in silico studies, (2) review articles, (3) proteomics or expression analysis without epigenetic/genotyping study, (4) articles focused in other diseases, such as psoriasis or ichthyosis vulgaris, in which AD was merely mentioned, and (5) articles whose full-text version was not available to us.

We performed the literature search between December 2019 and January 2020 in PubMed, Cochrane Library, and Scopus databases, using the following terms: “atopic dermatitis” OR “atopic eczema” AND “gene” OR “genetic” OR “mutation” OR “epigenetic” OR “DNA methylation” OR “sequencing” OR “microRNA” OR “polymorphism” OR “genome-wide association study” OR “microarray” OR “gene profiling”.

Three authors individually reviewed the database search results, assessing titles, evaluating abstracts, and considering or not the study for full review. Any disagreements in either the title/abstract or the full manuscript review phases were resolved by consensus. All eligible studies were formally evaluated and included in this systematic review.

The authors independently evaluated the quality appraisal and graded the risk of bias of the included studies. The risk of bias was assessed by Rob2, the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews [19], slightly adapted by the authors to fit the nature of the selected articles. Studies were classified as low, moderate, or high risk of bias.
Quality was assessed using the Newcastle–Ottawa scale [20]. Each study was awarded one point per positive item, according to the scale. Scores over 6 merited “high quality”; those below 4 were considered as “low quality”; the rest being classified as “moderate”.

Epigenetic methodology has some peculiarities that prevent the application of bias and quality scoring by the commonly used scales. Some notes regarding this will be mention when discussing the selected epigenetic studies.

Gene pathway analysis of the found genes was performed using FunRich [21], Reactome [22], and STRING [23].

3. Results

3.1. Selection, Bias and Quality of Articles

The database search yielded 914 articles (Figure 1). Atopic eczema was used for the search engine as a synonymous term. After title and abstract review, 810 articles were rejected since they did not fulfill eligibility criteria, i.e., those describing animal or in vitro studies, literature reviews, analysis of protein or gene expression, and articles written in languages other than English or Spanish. Therefore, 104 articles qualified for full text review. Of those, we eliminated 13 studies that mentioned AD in comparison to other conditions but were not fully dedicated to it and 18 studies that did not perform any genetic association with the disease. As a result, 73 articles were evaluated. Out of 73 studies, 11 were related to epigenetics [13,24–33], 39 were candidate gene studies [34–73], 5 were genome-wide association studies (GWAS) [5,13,74–76], whole-exome sequencing (WES) was performed in 7 articles [77–83], and phenome-wide association sequencing was done in 1 article [84]. Four studies described results from next-generation sequencing (NGS) [85–88], and 2 showed analyses of copy number variations (CNV) [89,90]. Besides, 6 meta-analyses were also included [91–96].

![Figure 1](image-url)  
**Figure 1.** The flow diagram depicts the flow of information through the different phases of the systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions.

A description of the 64 selected non-epigenetic studies is presented in Table 1. Epigenetic articles are summarized in Table 2.
### Table 1. Summary of findings from the selected genetic studies.

| Reference | Study Type                        | Population/Country | Objective                                                                 | Sample Size | Genes | SNP/Mutation | Results/Conclusion                                                                 |
|-----------|-----------------------------------|--------------------|----------------------------------------------------------------------------|-------------|-------|--------------|-----------------------------------------------------------------------------------|
| [77]     | Candidate gene, WES, (Whole-exome sequencing) | Iraq               | To determine DOCK8 deficiency                                                | 1 child     | DOCK8 | c.3332delT; Phe1113Leufs *2 (rs140392509) | Mutation present in hyperimmunoglobulin E syndrome (HIES) and non-Hodgkin lymphoma patient. |
| [65]     | Candidate gene                    | Denmark            | To determine association of atopic dermatitis (AD) with ichthyosis vulgaris (IV) and actinic keratosis (AK) | 481 AK patients, 9112 Healthy controls (HC) | FLG      | 1537C>T(R501X) (rs61816761) 2318.2321del (2282del4) 7375C>T (R2447X; rs13826443) | FLG homozygous loss of function and AK (in 0.8% of AK studied vs. 0.2% in control population) |
| [66]     | Candidate gene                    | Ethiopia           | To elucidate SNVs associated with AD                                          | 184 patients of AD and 186 HC | SPINK5 | rs2303063; rs2303067 | Significant association with AD.                                                   |
| [35]     | Candidate gene, WES               | Ethiopia           | To elucidate SNVs associated with AD To establish the role of CLDN1 variants in Ethiopian AD patients | 22 patients for WES; 159 AD patients and 192 HC for genotyping | CLDN1 | rs17501010 rs9290927 rs9290929 rs893051 | rs893051 is associated with development of AD in early life.                     |
| [46]     | Candidate gene                    | Jordan             | To study the association between resistin gene polymorphisms and AD          | 162 AD patients, 161 HC | RETN   | SNP +299 G>A (rs3745367) SNP +157 C>T (rs3219177) | rs3745367 associated with AD in a gender- and age-specific manner (male, less than 10 y) |
| [57]     | Candidate gene                    | Iran               | To identify association of SNPs in IL-10 and TGF-β1 and AD in Iranian patients | 89 children with AD, 138 HC | TGF-1 | cdn 10 cdn 25 | cdn10/C allele, CC genotype associated with AD cdn 25/C allele associated with AD |
| [68]     | Candidate gene                    | Chinese Han        | To identify variants in Chinese Han population associated to AD              | 4619 AD patients and 10789 HC | CD207/WAX2 | rs112111458 (allele G/A) | Association of rs112111458 and AD                                               |
| [69]     | Candidate gene                    | Turkish children   | To evaluate if some TLR2 gene polymorphisms are associated with AD          | 70 children with AD, 69 HC | TLR2   | rs5743708 (R753Q) rs4696480 (A-16934T) | None                                                                              |
| [70]     | Candidate gene                    | Isle of Wight      | To study the association of FLG loss of function with atopic march          | 1150 participants of the Isle of Wight birth cohort | FLG     | RS01X (rs61816761) 2282del S3247X (rs150997413) | FLG loss of function mutations are associated with early life eczema at age 1, 2 and 4 years and was consistently associated with rhinitis from 4 years onwards |
| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|--------------------|
| [71]      | Candidate genes | USA (mixed population of children) | To determine whether variations in FLG and TSLP genotype corresponded to differences in therapeutic treatment use over time | 842 children with AD | FLG | R501X (rs61816761) | Variations in FLG and TSLP genotype were associated with differences in self-reported skin clearance, TCI usage, and steroid usage |
| [78]      | WES | Canada | To identify the genetic aberration in 4 related patients with combined immunodeficiency, early-onset asthma, eczema, and food allergies, as well as autoimmunity | 4 related patients | CARD11 | hg19:chr7:2987341:G>A, NM_032415:exon3:c.C88T:p.R30W (rs145474800) | CARD11- R30W is associated with recurrent infections, autoimmunity, and severe atopy. The novel R30W mutations described abrogate the NF-κB pathway and lead to decreased IL-2 and IFN-γ secretion and lymphocyte proliferation |
| [72]      | Candidate gene | Poland | To investigate the importance of 4 common FLG null mutations in the susceptibility to eczema in Polish children population | 50 children with AD, 37 children with non-atopic eczema and 71 HC children | FLG | R501X (rs61816761) | FLG null mutations and AD are associated but explain only a part of AD cases (13.8%) |
| [73]      | Candidate gene | Different ethnic origins (Dutch, Cape Verdean, Dutch Antillean, Moroccan, Surinamese-Creole, Surinamese-Hindustani, Turkish children) | To study the association of known genetic factors and ethnic origin with the development of eczema | 3096 children | FLG | R501X (rs61816761) | Carrier frequencies of FLG mutations in children of non-Dutch origins were low. |
| [91]      | Meta-analysis | Canada (Caucasian) | Study the effect of FLG mutations on contact dermatitis (CD) | 165 patients with CD, 891 HC | FLG | R501X (rs61816761) | Association between FLG loss of function mutations and contact polysensitivity, especially in R501X polymorphism. |
| Reference | Study Type | Population/Country                  | Objective                                                                 | Sample Size | Genes        | SNP/Mutation            | Results/Conclusion                                                                 |
|-----------|------------|------------------------------------|---------------------------------------------------------------------------|-------------|--------------|-------------------------|-----------------------------------------------------------------------------------|
| [13]      | GWAS       | European ancestry                 | To identify shared risk variants of a broad allergic disease phenotype that considers the presence of asthma, hay fever and eczema | 180,129 cases with asthma and/or hay fever and/or eczema, and 180,709 HC | FLG          | R01X (rs61816761)       | This SNP is a stronger risk factor for eczema than for hay fever or asthma.       |
|           |            |                                    |                                                                           |             | RPTN-[-1]    | HRNR rs12123821         | This SNP is a stronger risk factor for eczema than for hay fever or asthma.       |
|           |            |                                    |                                                                           |             | IL1R2-[-1]   | IL18R1 rs12470864      | This SNP is a stronger risk factor for eczema than for hay fever or asthma.       |
|           |            |                                    |                                                                           |             | WDR36-[-1]   | CAMK4 rs6594499         | This SNP is a stronger risk factor for hay fever than for eczema or asthma.       |
|           |            |                                    |                                                                           |             | IL2RA        | rs61839660              | This SNP is a stronger risk factor for eczema than for hay fever or asthma.       |
|           |            |                                    |                                                                           |             | GSDMB        | rs6921650               | This SNP is a stronger risk factor for eczema than for hay fever or asthma.       |
| [36]      | Candidate gene | Russia                        | To explore the frequency FLG mutations and CNVs in AD patients and control subjects of Russian and Tatar ethnic origin living in Volga-Ural region of Russia | 177 Russian, 126 Tatar AD patients; and 152 Russian, 109 Tatar HC | FLG          | 2282del4 R01X rs61816761 | Significant differences in 2282del4 frequency were found between Tatar AD patients and HC. The allelic frequency of the R01X mutation in AD patients was 0.85% and in HC -0.47%. The allelic frequency of R2447X was 1.75% in patients, and 1.33% in HC. |
|           |            |                                    |                                                                           |             | S2889X       | rs792477344             | Mutations in S2889X constituted 96.4% of all FLG mutations.                      |
|           |            |                                    |                                                                           |             | 2282del4     |                                                                         | No carrier of R01X and Q2417X mutations was identified.                          |
| [37]      | Candidate gene | India                         | To investigate the personal consequences of having atopic dermatitis and/or hand eczema and FLG mutations | 163 patients and 86 HC | FLG          | R01X rs61816761         | FLG mutations are associated with irritant contact dermatitis with or without atopy, allergic contact dermatitis without atopy, and idiopathic subtypes. FLG mutations were associated with more severe hand eczema. |
|           |            |                                    |                                                                           |             | Q2417X rs528722713 |                                                                         |                                                                                 |
|           |            |                                    |                                                                           |             | 2282del4     |                                                                         |                                                                                 |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|-------------------|-----------|-------------|-------|--------------|-------------------|
| [83] WES | Korea      | To identify family-specific candidate genetic variants associated with early-onset AD in Koreans. | 3 families (2 affected AD and 2 unaffected individuals) for WES, 112 AD and 61 HC for validation studies. | COL6A6 | rs16830494 | rs9021909 | rs209963433 | COL6A6 variants may be risk factors for AD because the minor allele (AA) in rs16830494 and the rs9021909 (TT) allele and the rs209963433 heterozygous (CT) frequency were all higher in AD cases compared to controls, but no significant association was reached. |
| [38] Candidate gene | Chinese Han | To study in the Chinese Ham population the association AD with previously reported SNPs | 3013 AD patients, 5483 HC | TLR1-TLR6 | rs2101521 | WDR36-CAMK4 | rs1438673 | SNPs rs2158177 and rs1837253 are associated with AD in Chinese Han population |
| [39] Candidate gene | Sweden | To explore the longitudinal relation between preschool eczema, FLG mutation, or both and IgE sensitization in childhood. | 1890 children | FLG | rs2282664 | R501X (rs61816761) | R2447X (rs138726443) | Preschool eczema is associated with IgE sensitization to both food allergens and aeroallergens up to 16 years of age. FLG mutation is associated with IgE sensitization to peanut but not to other allergens. Sensitized children with preceding PSE are more often polysensitized. |
| [40] Candidate gene | USA | To elucidate the associations between KIF3A SNPs and asthma, eczema, and AR, alone and in combination. | 7000 children and 1020 HC. Results were replicated in 762 children with atopy. | KIF3A | rs9784600 | rs9784675 | rs11740584 | rs7737031 | rs17691077 | rs2299087 | rs3798130 | rs12186803 | rs1466164 | rs2023822 | rs2237059 | rs2023823 | KIF3A is associated with asthma + eczema. The presence of AR comorbidity did not increase the genetic association of KIF3A with asthma or even with asthma+ eczema. |
### Table 1. Cont.

| Reference | Study Type            | Population/Country | Objective                                           | Sample Size | Genes          | SNP/Mutation | Results/Conclusion                                                                                                                                 |
|-----------|-----------------------|--------------------|-----------------------------------------------------|-------------|----------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| [84]      | Phenome-WAS (Phenome-wide association study) | Turkey            | To dissect the role of immunogenetics in allergy and asthma. | 974 children | ADAM33         | rs2787094    | rs2280090 was associated with reduced MEF240s (i.e., the ratio of mean expiratory flow after 240 s of hypertonic saline inhalation with respect to the age- and ancestry-matched reference value) and with an increased risk of allergic bronchitis; rs3918396 was associated with wheezing and eczema comorbidity. |
| [42]      | Candidate gene        | Korean             | To study MIF promoter polymorphisms and total plasma IgE in AD Korean patients | 178 AD patients, 80 HC | MIF            | rs755622 (~173 G to C) | MIF promoter polymorphisms in the −173 C allele and the MIF C/5-CATT and MIF C/7-CATT haplotypes were significantly associated with an increased risk for AD. |
| Reference | Study Type  | Population/Country                  | Objective                                                                 | Sample Size | Genes | SNP/Mutation Results/Conclusion                                                                 |
|-----------|-------------|-------------------------------------|----------------------------------------------------------------------------|-------------|-------|------------------------------------------------------------------------------------------------|
| [41]      | Candidate gene | Korea                              | To identify FLG SNP variations and evaluated its association with clinical phenotypes, including AD and other parameters. | 81 patients | FLG   | rs71626704 and rs76413899 were significantly associated with a history of asthma and cheilitis. rs62623409 and rs71625199 were associated with sensitization to environmental allergens. |
| [43]      | Candidate gene | Korea                              | To investigate the association between four possible TSLP polymorphisms and atopic disease in a Korean population. | -           | TSLP  | rs2289276 rs2289278 rs3806932, rs62623409, and rs2289278 are associated with susceptibility of AD. rs3806932, rs3806933, and rs2289278 form one linkage disequilibrium block. The GTT haplotype strongly contributes to atopic march. |
| [44]      | Candidate gene | UK                                 |                                                                           | 224 patients and 40 HC | FLG   | R501X (rs61816761) S3247X (rs150597413) R2447X (rs138726443) Subjects with FLG-null mutations have more mature Langerhans cells in non-lesional skin irrespective of whether they have AD. |
| [45]      | Candidate gene | Chinese Han/ Singapore, Chinese Han/ Shanghai, Chinese Han/Shanxi, Korean, Japanese/Kyushu and Japanese/ mainland | To assess the significance of FLG mutations as clinical biomarkers in East Asian populations. | 1384 patients and 1031 HC | FLG   | K4022X (rs146466242) 6950del8 Q2417X (rs528722713) E2422X (rs374588791) S2554X (rs121909626) S2889X (rs782477344) S3296 (rs760426769) Q1701X (rs4547271) c.3321delA was found in all populations. Some mutations showed south-to-north (or north-to-south) distribution gradient: p.K4022X, the most prevalent FLG mutation in northern China and Korea, declined in frequency moving southward; in contrast, c.6950del8 (e.g., p.Q2417X, p.E2422X) showed the reverse. p.S2554X/p.S2889X/p.S3296X/Q1701X mutations were Japanese-specific. |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|---------------------|-----------|-------------|-------|--------------|-------------------|
| [92]      | Meta-analysis | China, Taiwan, Japan and Saudi Arabia (Asian population) and Poland, Czech R., Macedonia, Egypt (Caucasian) | To study the association between IL-4-590C/T polymorphism and AD susceptibility. | 923 patients and 1215 HC | IL-4 | -590C/T | The IL-4 -590C/T polymorphism may contribute to AD susceptibility in the overall population and children, especially for Asian children. |
| [89]      | CNV analysis | UK | To assess the contribution of LILR and LILRA3 genes CNV to AD | 1482 patients from 378 families | LILR, LILRA3 | R501X | (rs61816761) 2822del4 was significantly associated with early-onset AD and asthma. R501X was associated with early-onset and suggestively with keratosis pilaris. | |
| [47]      | Candidate gene | Finland | To test the association of the 4 most prevalent European FLG null mutations, the 2 Finnish enriched FLG null mutations, the FLG 12-repeat allele, and 50 additional epidermal barrier gene variants, with risk of AD, disease severity, clinical features, risk of other atopic diseases, age of onset, and treatment response. | 501 patients with AD and 1710 HC | FLG R501X | (rs138726443) S3247X | (rs150597413) S1020X | (rs200360684) V603M | (rs2300942) rs12730241 | No significant association with AD |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|-------------------|
| [79]      | WES        | USA                | To study CARD11 mutations in four families with recalcitrant, severe atopic disease. | 8 patients | CARD11 | L194P, R975W (rs1064795307), E57D dup183_196 | The study describes rare hypomorphic dominant negative mutations in CARD11 in 4 unrelated families, which lead to dominantly inherited, severe atopy, with variable infection beyond the skin. |
| [5]       | GWAS       | UK                 | To test whether genetically lowered vitamin D levels were associated with risk of asthma, atopic dermatitis, or elevated serum IgE levels. | 33996 children | DHCR7 | rs12785878 | No association |
| [48]      | Candidate gene | Italy          | To evaluate the role of FLG polymorphisms expression and risk of developing a concomitant Molluscum contagiosum sustained skin infection in the pediatric population with AD. | 100 children with AD and 97 healthy children | FLG | rs9808464, rs116222149, rs11584340, rs113136594, rs145828067, rs374910442, rs747005144 | FLG mutations are associated with early onset of AD, more severe clinical course of disease, and a significantly increased risk of M. contagiosum sustained skin infection. |
Table 1. Cont.

| Reference   | Study Type           | Population/Country             | Objective                                                                 | Sample Size | Genes   | SNP/Mutation        | Results/Conclusion                                                                 |
|-------------|----------------------|--------------------------------|----------------------------------------------------------------------------|-------------|---------|---------------------|----------------------------------------------------------------------------------|
| [86]        | NGS (Next-generation sequencing) | German                         | To identify disease association in the locus 11q13.5 using combination of sequencing and functional annotation. | 31 AD patients | LRRC32  | A407T                | R518W (rs142940871)                                                                 |
|             |                      |                                |                                                                            |             |         | R312                | Association of low-frequency and rare missense mutations within the LRRC32 gene with AD. |
|             |                      |                                |                                                                            |             |         | S411R (rs201424816) |                                                                                  |
|             |                      |                                |                                                                            |             |         | R414W (rs201431152) |                                                                                  |
|             |                      |                                |                                                                            |             |         | R652C                |                                                                                  |
| [95]        | Meta-analysis         | French, French-Canadian and UK | To detect new interacting genes involved in eczema                         | 388 French families | COL5A3  | rs2287807            | Identified significant interaction between two new genes, COL5A3 and MMP9, which may be accounted for by a degradation of COL5A3 by MMP9 influencing eczema susceptibility. |
|             |                      |                                | Replication in 253 French-Canadian and 207 UK family datasets.              |             |         | MMP9                |                                                                                  |
|             |                      |                                |                                                                            |             |         | rs17576              |                                                                                  |
| [85]        | NGS                  | USA                            | To evaluate FLG LoF variation in children of African ancestry and the association with AD and AD persistence. | 262 African American children and 133 Caucasians | FLG      | R501X (rs61816761)   | Rare FLG LoF variants in African American children are associated with AD and more persistent AD. In contrast to Europeans, no FLG LoF variants predominate in African American children. The most common variants were R501X, S3316X, and R826X. |
|             |                      |                                |                                                                            |             |         | S3316X (rs149484917) |                                                                                  |
|             |                      |                                |                                                                            |             |         | R826X (rs115746363) |                                                                                  |
|             |                      |                                |                                                                            |             |         | R2447X (rs138726443) |                                                                                  |
|             |                      |                                |                                                                            |             |         | Q590X (rs192402912) |                                                                                  |
|             |                      |                                |                                                                            |             |         | R3409X (rs201356558) |                                                                                  |
|             |                      |                                |                                                                            |             |         | S3247X (rs15097413) |                                                                                  |
|             |                      |                                |                                                                            |             |         | Q3818X (rs148606936) |                                                                                  |
|             |                      |                                |                                                                            |             |         | H440fs                |                                                                                  |
| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|-------------------|-----------|-------------|-------|--------------|--------------------|
| [90]      | CNV (Copy number variations) analysis | African American (USA) | To study FLG LoF and CNV in African American population | 39 children with AD | FLG | R501X (rs61816761) | rs149484917 is a population-specific FLG LoF unique to several populations of African Ancestry. Two new FLG LoF were identified (488delG and S3101X) |
|           |            |                   |           |             |       | R826X (rs115746363) |                     |
|           |            |                   |           |             |       | S3316X (rs149484917) |                     |
|           |            |                   |           |             |       | 488delG |                     |
|           |            |                   |           |             |       | S3101X |                     |
| [49]      | Candidate gene | Japan | To study polymorphisms of SPINK5 gene in Japanese AD patients | 37 patients, 50 HC | SPINK5 | Q26/R (rs6892205) | Only S368N frequency differed between Japanese patients and data from Human Genetic Variation Database. Algorithms predicting functional effects of amino acids substitution showed significant scores for R654H |
|           |            |                   |           |             |       | A335V (rs34482796) |                     |
|           |            |                   |           |             |       | S368N (rs230306) |                     |
|           |            |                   |           |             |       | D386N (rs2303064) |                     |
|           |            |                   |           |             |       | R711Q (rs3777134) |                     |
|           |            |                   |           |             |       | E82SD (rs2303070) |                     |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|-------------------|-----------|-------------|-------|--------------|-------------------|
| [50]      | Candidate gene | Korea | To examine the spectrum of null-mutations and compare with other Asian countries | 70 patients | FLG | RS301X (rs61816761) | Only 11 AD patients had FLG mutations. This frequency was lower than that described for other Asian populations (Chinese, Japanese, Singaporean) |
|           |            |                   |           |             |       | 3321delA     |                   |
|           |            |                   |           |             |       | Y1767X (rs1222103354) |                   |
|           |            |                   |           |             |       | S1695X (rs772851618) |                   |
|           |            |                   |           |             |       | Q1701X (rs145738429) |                   |
|           |            |                   |           |             |       | Q1745X (rs1209640261) |                   |
|           |            |                   |           |             |       | Q1790X (rs200622741) |                   |
|           |            |                   |           |             |       | S2554X (rs121090626) |                   |
|           |            |                   |           |             |       | S2899X |                   |
|           |            |                   |           |             |       | S3296X (rs761212672) |                   |
|           |            |                   |           |             |       | K4022X (rs146466242) |                   |
|           |            |                   |           |             |       | 3222del4 |                   |
|           |            |                   |           |             |       | S1515X (rs180768115) |                   |
|           |            |                   |           |             |       | Q2417X (rs528722713) |                   |
| [51]      | Candidate gene | Korea | To investigate the genetic polymorphisms of FLG in Korean AD patients | 9 ichthyosis vulgaris patients, 50 AD patients, 55 HC | FLG | K4022X (rs146466242) | This loss-of-function mutation was only found in AD patients. 62 new SNPs were identified |
|           |            |                   |           |             |       | 3322del4 |                   |
|           |            |                   |           |             |       | S1515X (rs180768115) |                   |
|           |            |                   |           |             |       | Q2417X (rs528722713) |                   |
| [87]      | NGS         | Korea | To investigate clinical characteristics of AD patients with FLG mutations. To determine differences between patients with and without FLG mutations | 1110 patients, 68 with mutations in FLG gene | FLG | K4022X (rs146466242) | Null alleles were associated with early onset of AD and higher risk of developing the disease by age 2 years. |
|           |            |                   |           |             |       | 3321delA | EASI score was also higher in these patients |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|---------------------|-----------|-------------|-------|--------------|--------------------|
| [76]      | GWAS       | UK, Netherlands     | To investigate longitudinal phenotypes of AD in two independent cohorts | UK: 9894 individuals (ALSPAC) NL: 3652 individuals (PIAMA) | INPP5D | rs1057258-c | Six classes based on temporal trajectories of rash were identified: persistent, early-onset/late resolving, early-onset/early-resolving, medium-onset/early-resolving, late-onset/resolved. FLG null mutations were strongly associated with early-onset and late-onset of AD ($p < 0.00001$: ALSPAC) and early-onset/late-resolving ($p = 0.0006$: PIAMA) |
| [80]      | WES        | USA (Hispanic, Caucasian, African-American) | To identify rare DNA variants conferring significant risk for AD | 3 patients | CARD14 | c.1778T>C, I593T | Downregulation of CARD14 led to severe AD and reduced skin protection against infection and dysregulated cutaneous inflammation pathways |
| [81]      | WES, rare enrichment analysis | Bangladeshi | To analyze the genetic architecture of patients with AD from a Bangladeshi community in London, UK | 53 cases and 42 HC from 70 families | SCAND3-TCHHL1-ADCY10-MTF1-MCM10-ORM2-CUX2-MAST2-PHLDB1-FLG | | Some rare sequence variations of candidate genes have been identified. FLG loss-of-function variations were carried by almost 50% of AD-affected individuals. |
| [52]      | Candidate gene | Poland | To explore the role of different SNPs at 11q13.5 in predisposing to allergic phenotypes | 270 AD patients, 540 HC | rs7927894 | The haplotype TATG in these SNPs fully explained the association with AD ($p = 0.00021$) The TG haplotype in the last two SNPs was also related to allergic rhinitis |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|--------------------|
| [94]      | Meta-analysis | Asian, Caucasian | To assess the genetic relationship between IL-10 polymorphisms and susceptibility to AD. | 16 case-control studies | IL-10 | IL-10 -1082a/G | These polymorphisms showed a weak association with AD susceptibility |
|           |            |                    |           |             |       | IL-10 -819T/C |                    |
|           |            |                    |           |             |       | IL-10 -592a/C |                    |
| [53]      | Candidate gene | Netherlands (Caucasians, Asians, Afro-Caribbean) | To investigate whether FLG mutations influence the outcome of immunosuppressive therapy | 42 patients with severe AD: 3 Asians, 1 Afro-Caribbean, 38 Caucasians | FLG | R501X (rs61816761) | FLG mutation group showed a trend towards less improvement in the course of 24 weeks of treatment with methotrexate and azothiopine |
|           |            |                    |           |             |       | 2282del4 |                    |
|           |            |                    |           |             |       | R2447X (rs138726443) |                    |
|           |            |                    |           |             |       | S3247X (rs150597413) |                    |
|           |            |                    |           |             |       | 5321delA |                    |
| [54]      | Candidate gene | Japan | To elucidate the effect of bi-allelic FLG mutation on AD incidence and severity | 6 individuals from 3 families | FLG | Q1790X+S3296X | The most severe AD was associated with c.3321delA+S2889X bi-allelic combination. |
|           |            |                    |           |             |       | Q1790X+S2889X | By contrast, individuals with S2889X+S3296X did not develop AD |
|           |            |                    |           |             |       | S2889X+S3296X |                    |
|           |            |                    |           |             |       | Q1701X+S2889X |                    |
|           |            |                    |           |             |       | 3321delA+S2889X |                    |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|--------------------|
| [67]      | Candidate gene | Inuit | To study the effect of environment on genotype-phenotype association in a genetically homogeneous population, living in two separate areas | 615 Greenlandic Inuit individuals, 643 Danish Inuit individuals | ADAM | rs12709 | LTα rs2844484 was associated with AD in Greenland patients \( (p = 0.035) \) The risk of AD was related to the genotype distribution of this SNP, with a significant interaction with the place of residence |
|           |            |                   |           |             | ALOX5 | rs4986832 | rs892690 rs2113819 |
|           |            |                   |           |             |       | rs2844484 | rs909253 rs1041981 |
|           |            |                   |           |             | LT-α  | rs730012 | rs528537 rs44707 rs2787094 |
|           |            |                   |           |             |       | rs2844484 | rs909253 rs1041981 |
|           |            |                   |           |             |       | rs977109 | rs2113819 |
| [82]      | WES        | Japan             | To investigate rare genetic variants associated with AD | 469 AD patients, 935 HC | APOB | rs145862664 | Gene polymorphism in CYP27A1, a gene involved in vitamin D3 metabolism, was related to AD |
|           |            |                   |           |             |       | rs199691576 | rs3193146105 |
|           |            |                   |           |             |       | rs199691576 | rs142107211 |
|           |            |                   |           |             |       | rs200230703 | rs200193128 |
|           |            |                   |           |             | VNN2  | rs76428401 | rs76428401 |
|           |            |                   |           |             | USP35 | rs200230703 | rs76428401 |
|           |            |                   |           |             | ZNF749| rs76428401 | rs76428401 |
| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|-------------------|-----------|-------------|-------|--------------|--------------------|
| [55]      | Candidate gene | China | To investigate the potential role of *SHARPIN* in the pathogenesis of AD | 65 AD patients, 100 HC | SHARPIN | g.480G>A | SNPs g.4320, g.4334, g.4343, g.4344, g.5363 were present both in patients and controls. The mutations in *SHARPIN* were only present in AD patients, decreasing the expression in AD lesions. |
| [56]      | Candidate gene | Japanese, Korean | To determine prevalence of *FLG* mutation in AD and IV patients in Japan and South Korea | Japan: 26 IV patients, 91 AD patients, South Korea: 76 AD patients | FLG | R501X (rs61816761), S255X (rs121909626), S2889X, S1695X (rs772851618), Q1701X (rs145738429), R826X (rs15746363) | Mutation S3296X only appeared in Japanese AD patients. R501X and R826X only appeared in IV patients. The rest of the mutations were found in both Korean and Japanese patients. |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|--------------------|
| [58]      | Candidate gene | Denmark       | To examine the association between loss-of-function mutations in FLG and AD and asthma in adult twins | 575 adults twins with asthma | FLG   | R501X (rs61816761) | Within the dizygotic twin population, 11 pairs were discordant for FLG mutation. The risk of AD increased in the twin with FLG mutation. No significant association was found with FLG mutations and asthma. |
| [59]      | Candidate gene | Denmark       | To explore heritable, environmental, and clinical factors related to persistent AD | 417 children: 186 patients (40 with persistent AD), 231 HC. Follow-up study from birth to age 13 y | FLG   | R501X (rs61816761) | 29% of patients with persistent AD had FLG mutations. The higher AD genetic risk score, the higher risk of persistent AD. |
| [60]      | Candidate gene | Poland        | To identify new potential markers of AD | 159 AD patients, 108 HC | RPTN, CRNN, FLG | rs284544, rs28441202, rs3001978, rs12117644, rs941934, R2447X (rs138726643) | In FLG WT patients, RPTN rs3001978CC was significantly associated with AD early age onset ($p = 0.033$), pruritus ($p = 0.021$), severity of AD ($p = 0.045$) and concomitant asthma ($p = 0.041$). Rs 941934 allele A was more frequent in AD patients ($p = 0.007$), the homozygous AA only appeared in AD patients ($p = 0.019$). The association depended on FLG mutations. |
Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|---------------------|-----------|-------------|-------|--------------|-------------------|
| [61]      | Candidate gene | Russia              | To determine the relationship of TLRs polymorphisms with AD | 25 AD patients, 25 AD and rhinitis/asthma patients, 100 HC | TLR2  | rs55743708 (G>A) | Increased levels of IL-4 and IL-10. Dysfunction of cell activation. |
|           |            |                     |           |             |       |              |                   |
|           |            |                     |           |             | TLR4  | rs4986790(A>G) | Increased levels of IL-4 and IL-1. Weaker cell response to microbial antigens. |
| [62]      | Candidate gene | USA                 | To examine the effect of FLG mutations and TSLP (thymic stromal lymphopoietin) polymorphisms on the age of AD onset | 822 children (age 2–17 y) | FLG   | R501X (rs61816761) | FLG null mutations were associated with early onset of AD. Number of mutations was associated with timing of onset. |
|           |            |                     |           |             |       | R2447X (rs138726443) | No association was found between TSLP polymorphism and timing of onset. |
|           |            |                     |           |             |       | S3247X (rs150397413) |                     |
|           |            |                     |           |             |       | TSLP         | rs1898671          |
| [63]      | Candidate gene | Taiwan              | To investigate the association between gene–environmental interaction and childhood AD | 839 mother–child pairs | GST   | GST-T1/M1 mutants | GST null genotypes in association with high levels of perfluoroalkyl substances in blood increased the risk of developing AD |
| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|---------------------|-----------|-------------|-------|--------------|--------------------|
| [88]      | NGS        | Singapore population: Chinese, Indian, Malay | To sequence the entire FLG coding region in Singaporeans from different ethnicities | 334 patients with AD and/or IV | FLG   | S1515X (rs180768115) | A new technology that improved accuracy and cost-effectiveness is described. New mutations have been identified |
|           |            |                     |           |             |       | E2422X (rs374588791) |                     |
|           |            |                     |           |             |       | S406X (rs189114758) |                     |
|           |            |                     |           |             |       | c.6950-6957del8 |                     |
|           |            |                     |           |             |       | c.1640delG |                     |
|           |            |                     |           |             |       | Q368X (rs746899204) |                     |
|           |            |                     |           |             |       | 3321delA |                     |
|           |            |                     |           |             |       | 7945delA |                     |
|           |            |                     |           |             |       | Q2417X (rs528722713) |                     |
|           |            |                     |           |             |       | 2952delC |                     |
|           |            |                     |           |             |       | 9040-9058dup19 |                     |
|           |            |                     |           |             |       | Q1790X (rs200622741) |                     |
|           |            |                     |           |             |       | S1302X (rs754812742) |                     |
|           |            |                     |           |             |       | S1515X (rs180768115) |                     |
|           |            |                     |           |             |       | 4004del2 |                     |
|           |            |                     |           |             |       | 2282del4 |                     |
|           |            |                     |           |             |       | R2447X (rs138726443) |                     |
|           |            |                     |           |             |       | 477insA |                     |
|           |            |                     |           |             |       | 679delA |                     |
|           |            |                     |           |             |       | S378X (rs755134998) |                     |
|           |            |                     |           |             |       | 3036delT |                     |
|           |            |                     |           |             |       | 10866delA |                   |
|           |            |                     |           |             |       | rs10067777 |                  |
### Table 1. Cont.

| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|---------------------|-----------|-------------|-------|--------------|--------------------|
| [74]      | GWAS       | China               | To identify AD susceptibility genes in 5q22.1 and observe expression in AD tissues | 3031 cases, 5075 HC | TMEM232 | rs7701890, rs13369927, rs13361382, rs5870488, rs1400764268, rs35639206, rs137936676, rs10617471 | rs11357450 had the strongest association with risk of AD (OR = 1.20; p = 0.04) |
| [64]      | Candidate gene | Korea | To identify mutations and SNPs in barrier- or immune-related genes | 279 AD patients, 224 HC | KLK7, FLG, SPINK5, DEFB1, KDR, IL5RA, IL9, IL12RB1, IL13 | More frequent in AD patients (p = 0.04). No differences between AD groups |
| Reference | Study Type | Population/Country | Objective | Sample Size | Genes | SNP/Mutation | Results/Conclusion |
|-----------|------------|--------------------|-----------|-------------|-------|--------------|-------------------|
| [95]      | Meta-analysis | Germany, Turkey, Italy, Finland, Ukraine, Russia | To assess whether TLRs polymorphisms are associate with risk of AD | TLR2: 9 studies; 733 cases, 807 HC | TLR2 | rs5743708 | Increased risk of AD for GA heterozygous |
|           |            |                    |           | TLR4: 6 studies; 646 cases, 601 HC | TLR4 | rs4986790 | AG showed some correlation with risk of AD, but was non-conclusive. |
| [96]      | Meta-analysis | Saudi Arabia, Iran, India, Netherlands, Italy, Poland, Macedonia, Czech Republic, China, Korea, Taiwan, Germany, UK | To summarize the current evidence on association between IL-10 polymorphisms and susceptibility to AD | 15 case-control studies, 1647 patients, 2031 HC | IL-10 | IL-10-1092 G/A | Increased risk of AD associated with IL-10-819 G/A mutation in Caucasian subjects and with IL-10-1092 G/A in Asian patients |
| [75]      | GWAS       | UK | To assess whether FLG expression in umbilical cord blood associates with and predicts AD | 94 infants | FLG | S3247X (rs150597413) | FLG expression in cord blood correlated with AD risk. 2.94-increased risk for mutated FLG variants |

**Table 1. Cont.**
Table 2. Summary of findings from the selected epigenetic studies.

| Cell/Tissue Types       | Epigenetic Assay                          | Significant Findings                                                                 | Reference |
|-------------------------|-------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| Primary adult human keratocytes | miFinder miRNA PCR Array                  | Broad dysregulation of miRNAs upon IL-4 treatment                                    | [27]      |
| Whole blood samples     | DNA methylation profiling                 | Identifying CpG methylation sites in IL4 and IL13 associated with AD phenotype        | [28]      |
| Serum                   | Real-time PCR for miR-146a                | miR-146a levels are unaltered in AD patients                                         | [29]      |
| Serum                   | RNA sequencing                            | miR-151a and miR-409 overexpressed in Chinese AD patients                             | [30]      |
| AD lesioned skin        | Microarray expression data from GSE32924  | Regulatory network comprising 182 miRNAs                                            | [24]      |
| Umbilical cord serum    | Exiqon Serum/Plasma Focus micro-RNA PCR Panel (179 miRNAs) | miR-144 levels are higher in the umbilical cord of AD children                      | [26]      |
| Whole blood samples     | DNA methylation profiling                 | Association between smoking and the methylation state of PITPNM2                    | [13]      |
| Monocytes and neutrophils | VSTM1 methylation                      | Polymorphism dependent VSTM1 methylation                                            | [31]      |
| AD lesioned skin        | Microarray miRNA expression (GSE31408)   | Hsa-let-7a-5p, has-miR-26a-5p and has-miR-143-3p differentially expressed in lesioned tissues | [32]      |
| Whole blood samples     | NLRP2 methylation                        | NLRP2 methylation is associated both to the environment and SNP                     | [33]      |
| AD lesioned skin        | Real-time PCR assay                       | miR-124 downregulated in AD lesional tissue                                         | [25]      |

As mentioned above, we followed the Cochrane guidelines to assess the risk of bias of the selected non-epigenetic studies, using the current version of the Rob2 tool [19]. As this tool has been developed for randomized trials, the authors decided to make some assumptions in order to adapt it to the specific nature of the genetic analysis. Taking into account that our main concern with respect to bias referred to the lack of appropriate controls or non-adequate genetic or epigenetic techniques for achieving the intended aim, we responded to questions about intervention or randomization consequently. Therefore, a study was classified as high risk when healthy controls were missing or the methodology to analyze the samples was not clearly explained in the text.

Under these conditions, 20.3\% of the non-epigenetic studies were considered at a high risk of bias. Healthy controls were not included in 14 studies, some of them referring to very few patients. One of the studies had no reference to the sample size, and another one did not describe the used methodology. We found some concerns in 4 studies, mainly referring to the selection of subjects. The rest of the selected studies (71.9\%) accomplished our criteria for low risk of bias (Figure 2, Table S1).

Correspondingly, 71.2\% of the articles merited high quality after running the NOS questionnaire (Table S2). Overall, the representativeness of the cases was the better-scored category. Thirteen articles were considered low-quality studies, mainly due to failed selection and definition of relevant controls.

3.2. Genetic Studies

A total of 62 genes and 5 intergenic regions were described as associated with AD in the selected studies; 32 of them were related to the disease for the first time during this period. Among them, filaggrin was the most widely reported gene, being over 90\% of the other genes cited in only one article.

The interaction analysis performed by STRING showed some connectivity enrichment of the listed proteins \( p\)-value < 1e-16. The network was clustered using the k-means method. Clustering results are shown in Figure 3 (non-linked proteins were removed from the graph). Three main clusters were found. The most populated included cytokines related to STAT3, with connections with ORM2 and RETN, and TNF.
Figure 2. Risk of bias (upper panel) and quality assessment (bottom panel) of the selected genetic studies, as a percentage of the total.

Figure 3. Functional association protein networks in STRING software (STRING consortium: Swiss Institute of Bioinformatics, Lausanne, Switzerland; Novo Nordisk Foundation CPR, Copenhagen, Denmark; EMBL Heidelberg, Germany) established from the genes reported in the selected studies. The diverse clusters are colored differently. Protein–protein interactions are drawn in blue, when obtained from curated databases, or purple if experimentally determined. Inter-cluster edges are represented by dashed-lines.
With respect to the pathway analysis, a genome-wide overview from Reactome is shown as a Reacfoam in Figure 4 (for a higher resolution, a zoomable pdf version is available as Figure S1). Reacfoam shows a high-level pathway overview visualization based on Voronoi tessellation. Darker functions correspond to those that are over-represented in the list of genes identified in the selected studies, i.e., immune system, developmental biology, signal transduction, and extracellular matrix (ECM). Immune system functions stood up among the high hierarchy pathways (False Discovery Rate (FDR) 2.21e-6; \( p \)-value 2.22e-8).

![Reacfoam visualization](image)

**Figure 4.** Reacfoam shows a high-level pathway overview of the genes reported in the selected studies. Significantly enriched pathways are shown in dark shade. The three main pathways have been zoomed in as (A) cytokine signaling in immune system, (B) extracellular matrix organization, and (C) signaling by receptor tyrosine kinases.

The most significant pathways were related to signaling by interleukins (FDR 1.7e-11; \( p \)-value 4.17e-11) or different variants, i.e., IL-4/IL-13 (FDR 7.02e-10; \( p \)-value 5.2e-10), IL-2 (FDR 3.89e-5; \( p \)-value 4.8e-7) or IL-12 signaling (FDR 1.42e-4; \( p \)-value 2.11e-6). Identifiers found in the former pathway were IL6R, IL10, TGFB1, TNF, STAT3, ADAM33, IL4, IL13, and MMP9. IL5RA, STAT3, IL2RA, INPP5D, IL9, and IL21 were associated with the IL-2 signaling pathway, while MIF, STAT3, IL10, and IL12RB1 were the IL-12 pathway entities found in the analysis. IL22 and INNP5D had not been related to AD before 2016. Moreover, enrichment was also found in transcriptional regulation of granulopoiesis (FDR 0.074; \( p \)-value 0.009), the process leading to the production of neutrophils, eosinophils, and basophils. Signaling cascades by MAPK1 (FDR 0.04; \( p \)-value 0.002) and FGFR (FDR 0.04; \( p \)-value 0.003) were also significantly enriched. The related entities found in the analysis were STAT3, FLG, IL2RA, IL5RA, IL6R, and MCM10.
Seven out of the 62 genes described in the period covered by this review have been curated with functions in pathways related to extracellular matrix organization (FDR 4.58e-2; \( p \)-value 3.81e-3). Interestingly, 6 of these genes (COL5A3, COL6A6, KDR, MCM10, MMP9, and STS) had not been associated with AD yet, and only TGF-\( \beta \)1, involved in a broad spectrum of pathways, had been previously associated [97].

We also performed an analysis of disease-related genes using the FunRich software. The results are shown in Figure 5. The appearance of DOCK8 in all these biological processes stands out, taking into account that it has been described as related to AD only in one study reporting a single case [77]. COSMIC analysis located 75.4\% of genes in the skin (ACTL9, ADAM33, ADCY10, C11orf30, CARD11, CARD14, CLDN1, COL5A3, CRNN, CUX2, CYP27A1, DEFB1, DOCK8, FLG, GSDMB, IL12RB1, IL22, IL2RA, IL4, IL5RA, IL6R, IL9, KDR, LILRA6, LRRC32, MAST2, MCM10, MMP9, MTF1, NLRP2, ORM2, PANX3, PHLDDB1, PR5L, RPTN, RTEL1, SPINK5, STS, TCHHL1, TGF\( \beta \)1, TLR2, TLR4, and TNF).

![Biological process](image-url)

**Figure 5.** Most relevant biological processes involving the reported genes. Percentages indicate the number of genes with respect to total that is included in each process.

Additionally, 17 of the new AD identified genes could not be ascribed to significant biological functions, i.e., CARD14, CRNN, TCHHL1, RPTN, PANX3, PHLDDB1, LILRA6, NLRP2, MTF1, LTA, MAST2, DOCK8, CUX2, ADCY10, VSTM1, and RTEL1.

### 3.3. Filaggrin

During the period of this revision, we have identified 33 studies on the *filaggrin* (FLG) gene association with AD. It is remarkable that 16 novel mutations have been reported [56,81,85,88].

#### 3.3.1. Filaggrin Mutations and Other Allergic Diseases

Eleven studies analyzed the association between *FLG* mutations and allergic sensitization, showing that *FLG* alleles conferred an increased risk, mainly in children with eczema [13,39,41,44,47,50,51,58,70,72,76]. In Polish children, Debinska et al. showed that several *FLG* mutations predisposed patients to eczema plus asthma, increasing more than 6-fold the risk of this complex phenotype (\( p \)-value 0.043) [72]. By contrast, such increased risk of asthma in *FLG* mutation was not confirmed in adult twins, although the risk of having AD was increased in those individuals with asthma, compared to individuals without asthma (27.6\% vs. 18.5\%; OR 1.68, 95\% CI 1.12–2.52; \( p \)-value 0.012) [58]. Chan et al. showed a significant effect of *FLG* loss-of-function (LoF) mutations on both asthma and rhinitis at ages 1, 2, 4, 10, and 18 years, particularly at the age of 10 years (RR 1.96; 95\% CI 1.70–2.26; \( p \)-value 0.003), early eczema being a requisite to suffer asthma at all ages [70].
Ferreira et al. carried out GWAS on individuals suffering from asthma, hay fever, and eczema to identify shared risk variants. The rs6181676[A] FLG variant was 1.32-fold more common in individuals suffering only from eczema when compared to individuals suffering only from hay fever (p-value 7.2e-8), and 1.26-fold comparing with asthma-only cases [13]. Two FLG single nucleotide polymorphisms (SNP), rs71626704 and rs76413899, were significantly associated with a history of asthma and cheilitis (p-value 0.002 and p-value 0.003, respectively) and rs62623409 and rs71625199 SNPs were associated with sensitization to environmental allergens (p-value 0.038 and p-value 0.008, respectively). Rs11584340 was associated with an increase of eosinophil-derived neurotoxin serum levels in allergic rhinitis patients and eosinophilic cationic protein serum levels in asthmatic patients [41].

Park et al. reported an association between FLG LoF mutation and early onset of asthma and AD [87]. The association between an FLG mutation and IgE sensitization to peanut at age 4 years (OD, 1.88; 95% CI 1.03–3.44), but not to other allergens was reported by Johansson et al. [39]. Equally FLG mutations were significantly associated with elevated IgE in a population of Korean patients with AD (>200KIU/L and/or MAST-CLA>+, p-value 0.005), palmar hyperlinearity (p < 0.001), and a family history of allergic disease (p-value 0.021) [50]. However, there was no significant difference in IgE levels between AD patients with non-mutated FLG and those carrying FLG LoF mutations (p-value 0.062) [44].

3.3.2. Filaggrin Mutations and Early Onset of AD

Patients who carried FLG mutation alleles are associated with early-onset AD [62,72]. Wan et al. found a dose-dependent association between the number of common FLG mutations and early onset [62]. In a Finish population, the combination of FLG mutations was shown to be significantly associated with early-onset of AD (<2 years) (OR 4.15, p-value 1.82e-10) and asthma (OR 2.76, p-value 1.57e-6) [47]. In two independent cohorts, FLG LoF mutations were associated with subphenotypes of AD. Thus, in a cohort study of 14,701 children from Avon (UK), the strongest association was detected with early-onset-persistent AD (OR 4.31; 95% CI 3.29–5.63; p-value 2e-26) and in a Dutch cohort of 3963 children, only the group of children with early-onset-late-resolving AD was associated with FLG LoF mutations (OR 5.63; 95% CI 2.65–11.95; p-value 7e-6) [76].

Additionally, it has been demonstrated that FLG expression in umbilical cord blood was associated with eczema development in infancy, being significantly lower in children with FLG variants when compared to children with wild-type FLG genotype (p-value 0.007) [75].

3.3.3. Filaggrin Mutations and other Skin Diseases

Andersen et al. studied the prevalence of FLG null mutations in adult patients with actinic keratosis (AK), premalignant intra-epidermal skin lesions that can progress into squamous cell carcinomas (SCCs). In their study, 7.5% AK patients had an FLG LoF mutation, of whom only the homozygous mutation carriers (0.8%), but not heterozygous, showed an increased risk of AK compared with wild-types (p-value 0.0017) [65]. Elhaji et al. found a significant association between the R501X mutation with polysensitivity in contact dermatitis when three or more positive patch test reaction occurred (8.5% patients vs. 4% controls; p-value 0.008) [91].

FLG mutations were significantly associated with palm hyperlinearity in a population of Korean patients with AD (p < 0.001) [50], and also in a Finish population (OR 4.67, p-value 1.46e-5) [47]. The specific variant rs558269137 was exclusively detected in Italian children with AD and Molluscum contagiosum virus (MCV) infection, while rs374910442, rs138055273, rs113136594, and rs11584340 variants were found both in AD children and AD plus MCV-infected children [48].

3.3.4. Filaggrin Mutations and Eczema Severity

Seven studies analyzed the association between FLG mutations and eczema severity [48,50,53,71,87,88,90]. Chang et al. found that FLG LoF homozygotes and heterozygotes were less likely to report periods of skin clearance (OR 0.20; 95% CI 0.07–0.55) and more likely to report frequent steroid use (OR 3.18; 95% CI 1.22–8.30) [71].
Specific gene variants of FLG have been associated with moderate to severe SCORAD (Scoring Atopic Dermatitis) indexes. Rs145627745, rs79808464, rs150957860, and rs145828067 variants were entirely associated with moderate disease severity (SCORAD 25-50), whereas rs374910442, rs138055273, rs183942200, rs1584340, and rs11313694 variants were associated with both moderate and severe disease [48].

In a population of African American (AA) children with AD and FLG LoF, 77% exhibited severe AD (SCORAD >50) [90]. A negative effect on the success of the immunosuppressive treatment was reported in FLG mutated patients when compared with those without FLG mutations [53]. When exploring the correlation between Eczema Area and Severity Index (EASI) and FLG-related AD in Korea, contradictory results were reported [50,87]. In addition, Wong et al. did not find any significant association between FLG LoF and the severity of AD [88].

3.3.5. Filaggrin Mutations and Ethnicity Risk Factors

Fifteen studies were carried out on European ancestor populations [12,13,36,39,44,47,48,53,58,70,72,75,76,91,98], 11 studies in Asia populations [37,45,50,51,54,56,64,67,81,87,88], 2 studies in African ancestor populations [85,90], and 3 studies in mixed populations [62,71,73]. The most prevalent LoF in patients with European ancestors were R501X, 2282del4, S3247X and R2447X, analyzed in 27 studies [12,13,36,37,39,44,47,48,50,53,54,56,58,60,62,64,70–73,75,76,81,85,88,90,91]. Other ethnic ancestors and rare variants were analyzed in 15 studies [37,41,45,47,50,51,53,54,56,64,81,85,87,88,90].

Elbert et al. carried out a study to analyze the association of ethnic origin with FLG mutations and environmental risk factors in children from multiethnic origins but living in the Netherlands, showing that minority ethnicity children had a higher risk of eczema than Dutch children [73]. Gimalova et al. studied LoF variants in Russians and Tartars AD patients, reporting that c.2282del4 was the most prevalent mutation in both populations, whereas R501X and R2447X mutations were rare [36]. In India, a study of the association between FLG mutations and hand eczema showed that mutations in S2889X constituted 96.4% of all FLG mutations, while European mutations were not found [37].

An overview of the genetic map and geographic distribution of FLG mutations across East Asia found that 3321delA is a pan-Asian mutation [45]. K4022X, the most prevalent FLG mutation in Korea and northern China, showed a south-to-north distribution gradient. In contrast, c.6950del8 showed the reverse effect. On the other hand, S2554X, S2889x, S3296X, and Q1701X mutations were Japanese-specific. These FLG mutations were associated with an increased risk of AD but did not confer a risk of asthma [45].

On et al. carried on a study of FLG mutations previously detected in Korean, Japanese, and Chinese patients on seventy Korean patients with AD. Four LoF mutations (3321delA, K4022X, S3296X, and S2889X) were identified in 15.7% patients [50]. The most commonly detected variants in Korean patients with AD were 3321delA (9.1%) and Y1767X (1.6%), K4022X (4.3–4.5%) [50,51,87]. Interestingly, Y1767X was only found in AD patients, whereas K4022X was found in both patients and controls [51].

Pigors et al. analyzed the genetic scheme of AD patients from the South Asian Bangladeshi community using WES combined with rare variant enrichment analysis [81], showing that FLG carried the highest number of enriched dominant (OR 12.1; p-value <0.0001) and recessive (OR 43.4; p-value <0.0001) LoF mutations. Three of the LoF mutations were previously unreported (S923Ffs*2, T1545Qfs*163, and S2352X). Furthermore, these genetic data revealed intrafamilial heterogeneity with multiple FLG variants often segregating within the Bangladeshi families with AD [81].

The common European FLG LoF R501X and 2282del4 were significantly associated with the risk of developing AD (OR 11.29, p-value 0.00022 and OR 2.66, p-value 0.00016, respectively) in Finnish patients [47]. In addition, having two 12-repeat alleles (rs12730241) was found to be significantly associated with a higher risk of AD (OR 1.96, 95% CI 1.36–2.81, p-value 0.00056) [47].

Using massively parallel sequencing, Margolis et al. identified nine FLG LoF variants in AA children, including 6 newly reported and 3 previously described, suggesting multiple and rare FLG LoF variants. Those children with FLG LoF variants had more persistent AD than wild-type children for
Genes 2020, 11, 442 30 of 46

FLG LoF [85]. These findings were supported by Mathyer et al., who identified five FLG LoF variants in 9 heterozygous AA AD patients (488delG, R501X, R826X, S3101X, and S3316X) [90].

New mutations were also found in Japanese (R826X) and Korean (S2889X) ichthyosis vulgaris (IV) patients [56]. Although the R826X mutation has not been detected in Japanese and Korean AD patients to date, it had been previously reported in Chinese and AA populations [95,99], suggesting that it is not a population-specific FLG mutation. Japanese and Korean patients shared 4 FLG mutations, Gly1109Glufs*13, Ser2889X, Ser3296X, and Lys4022X, being the latter more frequent in Korean than in Japanese AD or IV patients [56].

A robust and cost-effective high-throughput PCR-based method using microfluidics technology and NGS was applied to study the FLG coding region in cohorts of Chinese, Malaysian, and Indian AD patients living in Singapore. Thirty-three FLG LoF variants were identified in Chinese subjects, being 5 of them novel mutations. Unreported FLG LoF variants in Indian and Malaysian patients confirmed the diversity depending on the ethnic group [88].

3.4. Other Genes

Significant associations with AD have been reported for most of the analyzed genes and variants. Thus, ACTL9, C11orf30, IL6R, IL21, IL22, INPP5D, KIF3A, OVOL1, PRR5L, PPP2R3D, and STAT3 were investigated in two cohorts, ALSPAC and PIAMA [76]. ADCY10, CUX2, MAST2, MCM10, MTF1, ORM2, PHLD1B, and TCHHL1 were analyzed in Bangladeshi patients [81]. A CLDN1 polymorphism was positively associated with early onset of AD in Ethiopian patients [35], but no association was found in the Finnish variants [47]. CARD11-R30W has been associated with recurrent infections, autoimmunity, and severe atopy [78], and other dominant, negative mutations in CARD11, leading to dominantly inherited, severe atopy have been described in 4 unrelated USA families [79]. Within the same protein family, downregulation of CARD14 was reported to lead to severe AD and reduced skin protection against infection as well as dysregulated cutaneous inflammation pathways [80].

Mutations in barrier and immune-related genes, i.e., KLK7, SPINK5, DEFB1, KDR, ILSRA, IL9, IL12RB1, and IL13, were found more frequently in Korean AD patients than in healthy controls [64]. SPINK5 (serine peptidase inhibitor kazal type 5), a protein involved in epidermal cell differentiation, was also associated with AD in Ethiopian [66] and Japanese patients [49].

Other genes involved in immune functions, such as IL2RA [13,76], IL4 and ADAM33 [84], TGFBI [57], and MIF promoter [42] have also been significantly associated to increased risk of AD. The relationship of TLRs polymorphisms with AD, i.e., TLR2 rs55743708(G>A) and TLR4 rs4986790(A>G) were reported to increase levels of IL-4 and IL-10 in Russian AD patients [61], while other authors found no association of TLR2 polymorphisms, i.e., rs5743708 and rs4696480, in Turkish children with AD [69]. Also, significant SNPs in TSLP, a lymphopoietin, have been reported in Chinese Han [38], Korean [43], and American [62,71] patients. Lymphotoxin α, a protein involved in IL-2 and IL-4 signaling events, more specifically, LTA rs2844484, was associated with AD in Greenland patients [67].

In a study performed in Jordan investigating the relationship between RETN gene polymorphisms and AD, rs3745367 was found significantly associated with AD in a gender- and age-specific manner [46].

Variants in extracellular matrix genes such as COL5A3 rs2287807 and MMP9 rs17575 were found as significantly related to AD in a meta-analysis performed in French, Canadian, and UK families [93]. COL6A6 minor allele (AA) in rs16830494 and the rs59021909 (TT) allele and the rs200963433 heterozygous (CT) showed higher frequency in patients than in controls, although no statistical significance was reached [83]. TMEM232 rs11357450 had the strongest association with the risk of AD among all the variants analyzed by Wu et al. [74]. Mutations in SHARPIN, a protein involved in epidermis development, that were exclusively present in patients, decreased its expression in AD lesions [55]. GSDMB rs921650 was characterized as a strong risk factor for eczema [13].
3.5. Epigenetic Studies

Over the period included in this revision, the studies of epigenetic modifications on atopic dermatitis were focused on DNA methylation and microRNAs. These epigenetic mechanisms have been shown to be crucial regulators in different allergic conditions [100,101], although histone modifications have also been studied in the context of allergic diseases and have been shown to play a role in their development [102].

With respect to DNA methylation, two articles studied such modification at a whole-genome level in blood samples. In the first one, Ferreira et al. analyzed the association of DNA methylation with different allergic risk factors. In this manner, they detected 36 genes with DNA methylation sites nearby that were associated with differences in gene expression between allergic patients and healthy controls. Additionally, they found an association between smoking and the methylation state of PITPNM2 [13], potentially involved in neutrophil function [103,104]. The second study found 490 CpGs differentially methylated between AD patients with eczema herpeticum and healthy controls and 6 CpGs differentially methylated when comparing AD patients without eczema herpeticum and healthy controls. Among these sites, they identified CpG methylation sites in IL4 and IL13, which suggested that there was a significant association between these methylations and the phenotype observed in the patients [28]. Another two studies were centered on the methylation state and its effect on gene expression of NLRP2 [33] and SIRL-1 [31]. These studies showed the influence of single nucleotide polymorphisms, a correlation of the gene expression level, and the presence or absence of AD condition.

Regarding the miRNA research, the different analyzed studies can be grouped by two main approaches to the function of miRNAs in the development of AD. On the one hand, the studies that assessed for the upregulation or downregulation of miRNAs in lesional tissue of AD patients. In this way, several differentially expressed miRNAs were described in AD lesions. When comparing the lesional tissue of AD patients with normal skin samples of healthy controls, Yang et al. described miR-124 downregulation in AD lesional tissue [25] and in an in silico interaction analysis of differentially expressed miRNAs, Li et al. [32] postulated that downregulation of hsa-let-7a-5p would potentially upregulate CCR7, a chemokine receptor involved in the activation of T cells [105]. They also found a differential expression of miR-143, whose potential target is DENND1B, which is involved in the proliferation of T-cells [34]. In addition, the authors suggest that the downregulation of miR-26 would regulate hyaluronan synthase 3 (HAS3), which is upregulated in AD skin [32,106]. After comparing lesional skins samples with non-lesional skin samples in AD patients, Ding et al. proposed a regulatory network of differentially expressed genes that included 182 miRNAs, and among them, hsa-miR-148b, hsa-miR-152, and hsa-miR-324 [24]. Finally, using primary adult human keratocytes, several out of the 372 most common miRNAs were dysregulated when exposed to IL-4, which plays a key role in the development of AD [27].

On the other hand, there are some studies that look for miRNAs differentially expressed in sera from AD patients compared with healthy controls. Thus, the levels of miR-144 detected in umbilical cord serum were higher in those Japanese children that would develop AD at one year of age [26], levels of miR-151a and miR-409 were found to be higher in sera from Chinese AD patients compared with healthy controls [30], and finally, miR-146a showed no difference in serum levels between patients with AD and healthy individuals [29], despite previously demonstrating a role in the regulation of the immune system and inflammatory responses pathways [107,108]. This second method of retrieving candidate miRNAs may serve as a feasible and less invasive way of obtaining new AD biomarkers, whereas the former procedure in lesioned tissue focused more on the mechanistic action of such RNAs.

4. Discussion

Herein, we have systematically reviewed the literature related to genetics and epigenetics of AD published between June 2016 and December 2019. We have found 58 original articles and
6 meta-analyses and also 9 epigenetic studies. A total of 62 genes have been analyzed in the selected publications, 31 of which had not been reported as potentially associated with AD before June 2016.

One remarkable feature about allergic diseases is the diversity in the potential phenotypes sharing the same genotype, indicating that there appear to be additional components that increase the complexity of the regulation and development of such conditions, or at least shape its evolution over time [109,110]. Epigenetic regulation has emerged as a key factor that was missing to completely understand the molecular basis of allergic disease [111].

4.1. Filaggrin

Up to the revision date of this review, FLG LoF mutations were the most significantly associated genetic variants for AD. Filaggrin is a key protein in the differentiation of the epidermis and the formation of the skin barrier, which is necessary to prevent water loss through the epidermis and to avoid the entry of allergens, toxins, and pathogens [112]. Its precursor profilaggrin is encoded by the FLG gene, which is located on chromosome 1q21.3 [113] within a region known as the epidermal differentiation complex (EDC) comprising over 50 genes encoding proteins involved in terminal differentiation and cornification of keratinocytes [114]. LoF mutations in the exon 3 completely hinder FLG protein expression, increasing the risk of AD [113,115–119]. A meta-analysis of 24 studies on FLG mutations determined a 3-fold increased risk of AD in those individuals carrying one or more FLG LoF, singling out the influence of one gene in such a heterogeneous disease [120]. More than 300 FLG LoF variants have been identified in the gnomAD browser, an international database of exome and genome sequencing data (https://gnomad.broadinstitute.org), more than 20 of them associated with susceptibility to AD [85].

The results showing that FLG null mutations conferred risk for allergic sensitization and susceptibility to eczema-associated asthma are well aligned with previous studies [121–127]. All these findings support the idea that FLG mutations lead to functional epidermal barrier defects, increasing skin permeability and subsequent allergic sensitization, promoting the Th2 inflammatory response, and eventually leading to asthma [122]. The “outside–inside” theory of AD pathogenesis proposes that epidermal APCs in AD patients are overexposed to danger signals because of their impaired skin barrier, leading to APC maturation and T-cell-mediated inflammatory skin disease [128].

AD has been divided into early-onset and late-onset forms. Early-onset AD would be especially driven by genetic factors, whereas late-onset AD might depend on environmental exposures [129]. Common FLG null mutations associated with early-onset AD are described in different populations [126, 130–133]. FLG LoF mutations have also associated with moderate-or-severe AD cases [117,122,134–138].

The most frequent FLG LoF mutations (R501X, 2282del4, S3247X, and R2447X) are present in 7–10% of Europeans [115,120] while these mutations are rare in Asian patients, who carry specific mutations [45,50,139,140]. Thus, K4022X has been reported as the most prevalent variant in Korean AD patients [50,51,87]. Interestingly, FLG mutations in Korean AD patients seem to be less frequent than in other East Asian countries, most likely due to genetic and environmental factors or mutations in other barrier genes [50,87]. Also, the analysis of FLG mutations in East Asia showed a geographic distribution in agreement with the history of human migrations [45].

On the other hand, FLG LoF mutations could be less common in patients with African descent than in those with European or Asian descent [139,140], although other studies have shown that AA children had an increased risk of AD compared with European children [140]. The prevalence of AD in the US was reported as the highest among AA patients, but this population remains largely understudied [141,142]. Recently, two studies using current sequencing methods were able to identify rare FLG LoF variants in AA children associated with more persistent AD [85,90]. The prevalence of common FLG variants in children of African ancestry is less frequent than those of European or Asian ancestry [85]. Moreover, hygiene habits, vitamin D level, sun exposure, microbiota, genetics, and skin barrier characteristics could also influence the association of ethnicity with AD [1,143].
The implementation of new technologies like NGS to analyze cohorts of understudied populations, as well as newer bioinformatic tools, will allow the identification of new FLG LoF mutations and confirm the variation among the different ethnicities.

4.2. Other Genes

Regarding research contributions in the period of this review, new components of the extracellular matrix have been described to be associated with AD [64, 81, 83, 93, 144]. These new associations highlight the importance of such structure in the development of AD and in the integrity of the skin barrier. Thus, COL5A3, COL6A6, and MMP9 are important for the collagen formation [145–147]; KDR, one of the two receptors of the VEGF, has been associated with integrin cell surface interactions with extracellular matrix [148]; mutations in STS (steroid sulfatase) have been associated to X-linked ichthyosis [148]; rare variants of MCM10, a key component of the pre-replication complex, have been described for the first time associated to AD [81]. Regarding TGF-β [57], besides its roles in other pathways, different works have shown its role in extracellular matrix assembly and disassembly [149, 150].

Some genes associated to AD have been related to innate immune system pathways, providing solid evidences of the relationship of the innate immune system with the disease and its progression. On its behalf, most of the genes of the review associated to innate immune pathways (ADAM33, MIF, MMP9, ORM2, RETN, and TLR2) are related to neutrophil degranulation that contributes to the inflammation of the tissue in the AD [151, 152]. In addition, a substantial number of publications [61, 69, 95, 153] emphasize the importance of Toll-like receptor cascades on the development of AD and its link with other allergic diseases [154, 155]. The TLR-2 rs4696480 polymorphism has also been associated with AD severity in adult patients in two different populations, and supported with functional studies [156, 157]. However, one of the studies included in this review reported a lack of association of this polymorphism in Turkish children with AD [69], which could be due to the fact that differences in genetics and environmental factors appear to be relevant in the development of allergy. New pieces of evidence have been added to the previously reported association of genes such as ADAM33, CARD11, and DEFB1 with AD [64, 67, 78, 79, 84]. In this line, ADAM33 has also been associated to other allergic diseases like asthma [158] and allergic rhinitis [159]. CARD11 is required for B- and T-cell receptor signal transduction and activation of NF-κB transcription factor [160]. DEFB1 is an antimicrobial peptide implicated in the resistance of epithelial surfaces to microbial colonization. It is a member of the family of defensins, peptides made by neutrophils, and it has been proposed as a link between the innate and the adaptive immune systems [161, 162].

It is noteworthy that several of the new genes listed in this revision do not fall into any of these functional groups. This may be due to different causes, as because of little knowledge about some genes or because they are not properly curated yet. This might be the cases of CARD14, with similar functions to CARD11 [163]; VSTM1, which behaves as a cytokine [164]; LILRA6, a member of the leukocyte immunoglobulin-like receptor family [165]; mutations in DOCK8 are responsible for an immunodeficiency syndrome [166]; NLRP2 is involved in inflammatory processes [167, 168]; RTELI, a helicase involved in telomere maintenance, has also been found associated to severe dyskeratosis congenita [169]; LT-α (also known as TNF-β), which is a cytokine produced by lymphocytes [170]. Additionally, ADCY10, CUX2, MAST2, MTF1, PANX3, PHLDB1, and SCAND3 have been associated to AD in a single study of exome sequencing [81]. The S100 fused type protein (SFTP) family includes genes which are mainly expressed in stratified epithelia and play a role in epithelial homeostasis [114]. SFTPs contain two calcium-binding domain EF-hand motifs and are associated with cytoplasmic intermediate filaments as well as minor components of the cornified envelope [114]. This family of proteins include 7 members, FLG being its most studied member and certainly showing an association with AD. Besides FLG, only FLG2 and HRNR were previously associated with AD [171–173]. Interestingly, over the last 5 years, other 3 members of the family have been associated with AD. The three members now associated with AD, CRNN, RPTN, and TCHHL1 were known to be involved in different epithelial
disorders [174–176]. Taken together, SFTP family proteins pose as pivotal players in the proper skin cornification and in the development of AD.

4.3. AD Epigenetics

In recent years, the search for risk factors that help to understand how allergic diseases develop has become one of the main objectives of the research. The plasticity observed in the different phenotypes associated to an underlying genotype suggests that additional components may provide complexity to the processes that lead to the development of the disease, or, at least, influence its evolution [109,177]. In the last years, the focus has been set on epigenetic modifications, which can lead to the development of allergic diseases. Epigenetic regulation has emerged as a pivotal key in the comprehension of the molecular basis of allergic conditions [111,178].

Most of the research on AD epigenetic regulation has focused on the posttranscriptional regulation mediated by miRNAs. miRNAs constitute a class of small non-coding RNAs, with a size ranging from 17 to 25 nucleotides, and a sequence that allows them to bind to specific mRNAs. This key feature permits the posttranscriptional modulation of targeted genes by triggering mRNA degradation and/or inhibition of translation [179]. According to several functional studies, miRNAs are involved in virtually every cellular process [180]. miRNAs have also been related to immune system regulation, miR-21, miR-146a, and miR-155 being the most extensively studied. A role in the regulation of the immune response and tissue inflammation in allergic diseases has been shown [101].

The analysis of lesional tissues has provided new miRNA molecules that could regulate different mechanisms and signalling pathways that are altered in AD lesions. As a general feature, a decrease of miRNAs involved in the regulation of the immune response and an increase of miRNAs involved in epidermis development is observed in these studies. Thus, downregulation of miR-124 in AD lesions has been shown to control NF-κB-dependent inflammatory responses in keratinocytes and chronic skin inflammation in atopic eczema [25]. Bioinformatics analyses from two studies suggest that miRNAs can influence the transcriptional regulation of signalling pathways related to the synthesis of extracellular matrix components, such as arachidonic acid and hyaluronic acid, as well as participate in processes such angiogenesis, lymphangiogenesis and apoptosis, all of which are involved in AD progression [24,27].

In addition, the use of miRNAs as biomarkers in allergic diseases is increasingly described [181,182]. In this sense, miR-151a and hsa-mir-144-3p have been proposed as potential biomarkers in AD, as they have been shown to be differentially expressed in serum and umbilical cord serum, respectively [26,30]. miR-151a would reduce IL12RB2 levels in T-cells, favouring the increase of Th2 cells, which are central in the pathogenesis of AD [30,183]. Also, an increased expression of miR-144 would reduce ABCA1 mRNA and protein levels and induce a proinflammatory response via NF-κB [26]. Nevertheless, the differences in the expression of these small non-coding RNAs observed in the lesional skin does not necessarily translate to changes in serum levels, which impairs their use as biomarkers. This is the case of miR-146a, which has been shown to be upregulated in AD lesional skin when compared to healthy controls [184] but showed no differences in serum levels [29].

Another extensively studied epigenetic mechanisms is DNA cytosine methylation [185]. This modification occurs in CpG dinucleotides which are grouped in the so called CpG islands, frequently located in intergenic regions, as well as in promoter region of genes [186]. CpG islands methylation of gene promoters is related to the repression of the transcription, i.e., CpG islands of genes that are being actively transcribed do not usually present methylation, while non-transcribed genes present CpG islands with high degrees of methylation [187]. Cytosine methylation suppresses gene transcription, as it causes chromatin condensation and prevents transcription factors from binding to their target sequences in promoters [185]. Different EWAS have shown differential methylation patterns associated with some pathologies [188,189] or even with the exposure to different agents [190–192]. Two studies showed gene expression modulation due to exposure to tobacco smoke in AD [13,33]. Thürmann et al. showed that NLRP2 was differentially methylated, due to both the effect of polymorphisms and tobacco
smoke [33], and Ferreira et al. found differences in the methylation of PITPNM2, which were partly associated with environmental tobacco smoke [13]. Interestingly, both genes are involved in innate immune responses, with NLRP2 involved in inflammatory processes related to macrophages [193,194] and PITPNM2 related to neutrophils [103,104]. Other two studies found differences in DNA methylation patterns in AD patients. The first one found differences in methylation of the promotor region of the VSTM1 gene locus [31], which encodes the protein SIRL-1 that has been proposed to inhibit crucial pro-inflammatory functions in human myeloid cells [195,196]. The second one was a genome wide methylation study that found different patterns of methylation in over 490 sites in AD patients with eczema herpeticum, and where Boorgula et al. identified a significant association between IL4 and IL13 methylation and the AD phenotype, as well as with serum IgE levels [28]. However, this methylation patterns where shown to be highly influenced by the eosinophilic count [28].

5. Final Remarks

In the present article, we have evaluated the last 5 years of AD-related literature using systematic review methodology. We have focused on genetics and epigenetics aspects of the disease, monitoring the different polymorphisms and gene variations associated to the onset or severity of AD, comparing studies performed in different locations and including several ethnicities, therefore showing an up-to-date picture of current knowledge. Some of the retrieved articles used state-of-the-art technology when assessing their findings, including genome-wide sequencing of representative samples of patients. An exhaustive analysis of risk of bias and quality of the 64 selected articles have allowed us to ponder the validity of the reported associations. Another strong point is the inclusion of epigenetic studies.

Regarding limitations to the present review, it has to be point out that we have restricted our analysis to those genes included in the articles published in the last 5 years. Although the main genes related to disease onset and development, i.e. filaggrin, have been included, we are aware that other important genes, already reported elsewhere, may be missing here. Since our goal is to update the topic with new results, we highly recommend the interested reader to consult the previous reviews for more information [16,17].

In addition, we should remark that most genes have been described only once and for a limited number of patients. For instance, DOCK8 has been identified in a single case report. Larger clinical trials would be required to unambiguously link these genes to AD. The universalization of the whole genome techniques will allow the discovery of new mutations or confirm the already known ones in different populations.

New developments in genetics and epigenetics technology offer opportunities to improve the diagnosis of AD patients, ascribing them to specific genetic groups and allowing the tailoring of therapy with the best response to ensure the most convenient patient care.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4425/11/4/442/s1, Figure S1: Reactfoam of pathways overview of the genes reported in the selected studies; Table S1: Analysis of the risk of bias for the selected genetic studies; Table S2: Quality assessment of the selected genetic studies.

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References

1. Weidinger, S.; Beck, L.A.; Bieber, T.; Kabashima, K.; Irvine, A.D. Atopic dermatitis. Nat. Rev. Dis. Prim. 2018, 4, 1. [CrossRef] [PubMed]
2. Silverberg, J.I. Atopic Dermatitis in Adults. Med. Clin. N. Am. 2020, 104, 157–176. [CrossRef] [PubMed]
3. Dharmage, S.C.; Lowe, A.J.; Matheson, M.C.; Burgess, J.A.; Allen, K.J.; Abramson, M.J. Atopic dermatitis and the atopic march revisited. Allergy 2014, 69, 17–27. [CrossRef] [PubMed]
4. Bonamonte, D.; Filoni, A.; Vestita, M.; Romita, P.; Foti, C.; Angelini, G. The Role of the Environmental Risk Factors in the Pathogenesis and Clinical Outcome of Atopic Dermatitis. Biomed. Res. Int. 2019, 2019, 2450605. [CrossRef]
5. Manousaki, D.; Paternoster, L.; Standl, M.; Moffatt, M.F.; Farrall, M.; Bouzigon, E.; Strachan, D.P.; Demenais, F.; Lathrop, M.; Cookson, W.O.C.M.; et al. Vitamin D levels and susceptibility to asthma, elevated immunoglobulin E levels, and atopic dermatitis: A Mendelian randomization study. PLoS Med. 2017, 14, e1002294. [CrossRef] [PubMed]
6. Schram, M.E.; Tedja, A.M.; Spijker, R.; Bos, J.D.; Williams, H.C.; Spuls, P.I. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. Br. J. Dermatol. 2010, 162, 964–973. [CrossRef]
7. Romieu, I.; Torrent, M.; García-Esteban, R.; Ferrer, C.; Ribas-Fitó, N.; Antó, J.M.; Sunyer, J. Maternal fish intake during pregnancy and atopy and asthma in infancy. Clin. Exp. Allergy 2007, 37, 518–525. [CrossRef]
8. Leermakers, E.T.M.; Sonnenstein-van der Voort, A.M.M.; Heppe, D.H.M.; de Jongste, J.C.; Moll, H.A.; Franco, O.H.; Hofman, A.; Jaddoe, V.W.V.; Duijts, L. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: The Generation R Study. Eur. J. Clin. Nutr. 2013, 67, 353–359. [CrossRef]
9. Willers, S.M.; Devereux, G.; Craig, L.C.A.; McNeill, G.; Wijga, A.H.; Abou El-Magd, W.; Turner, S.W.; Helms, P.J.; Seaton, A. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Thorax 2007, 62, 773–779. [CrossRef]
10. Apfelbacher, C.J.; Diepgen, T.L.; Schmitt, J. Determinants of eczema: Population-based cross-sectional study in Germany. Allergy 2011, 66, 206–213. [CrossRef]
11. Dalgard, F.J.; Gieler, U.; Tomas-Aragones, L.; Lien, L.; Poot, F.; Jemec, G.B.E.; Misery, L.; Szabo, C.; Linder, D.; Sampogna, F.; et al. The Psychological Burden of Skin Diseases: A Cross-Sectional Multicenter Study among Dermatological Out-Patients in 13 European Countries. J. Investig. Dermatol. 2015, 135, 984–991. [CrossRef] [PubMed]
12. Andersen, Y.M.F.; Egeberg, A.; Skov, L.; Thyssen, J.P. Comorbidities of Atopic Dermatitis: Beyond Rhinitis and Asthma. Curr. Dermatol. Rep. 2017, 6, 35–41. [CrossRef] [PubMed]
13. Ferreira, M.A.; Vonk, J.M.; Baurecht, H.; Marenholz, I.; Tian, C.; Hoffman, J.D.; Helmer, Q.; Tillander, A.; Ullemaar, V.; van Dongen, J.; et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat. Genet. 2017, 49, 1752–1757. [CrossRef] [PubMed]
14. Ferreira, M.A.R.R.; Vonk, J.M.; Baurecht, H.; Marenholz, I.; Tian, C.; Hoffman, J.D.; Helmer, Q.; Tillander, A.; Ullemaar, V.; Lu, Y.; et al. Eleven loci with new reproducible genetic associations with allergic disease risk. J. Allergy Clin. Immunol. 2019, 143, 691–699. [CrossRef]
15. Elmose, C.; Thomsen, S.F. Twin Studies of Atopic Dermatitis: Interpretations and Applications in the Filaggrin Era. J. Allergy Clin. Immunol. 2015, 125, 16–29. [CrossRef]
16. Bin, L.; Leung, D.Y.M. Genetic and epigenetic studies of atopic dermatitis. Allergy Asthma Clin. Immunol. 2016, 12, 52. [CrossRef]
17. Guyatt, G.; Oxman, A.D.; Akl, E.A.; Kunz, R.; Vist, G.; Brozek, J.; Norris, S.; Falck-Ytter, Y.; Glasziou, P.; Debeer, H.; et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J. Clin. Epidemiol. 2011, 64, 383–394. [CrossRef]
18. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.-Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. BMJ 2019, 366, l48981.
21. Pathan, M.; Keerthikumar, S.; Ang, C.; Gangoda, L.; Quek, C.Y.J.; Williamson, N.A.; Mouradov, D.; Sieber, O.M.; Simpson, R.J.; Salim, A. FunRich: An open access standalone functional enrichment and interaction network analysis tool. *Proteomics* 2015, 15, 2597–2601. [CrossRef] [PubMed]

22. Jassal, B.; Matthews, L.; Viteri, G.; Gong, C.; Lorente, P.; Fabregat, A.; Sidiroopoulos, K.; Cook, J.; Gillespie, M.; Haw, R.; et al. The reactome pathway knowledgebase. *Nucleic Acids Res.* 2020, 48, D498–D503. [CrossRef] [PubMed]

23. Szklarczyk, D.; Gable, A.L.; Lyon, D.; Junge, A.; Wyder, S.; Huerta-Cepas, J.; Simonovic, M.; Doncheva, N.T.; Morris, J.H.; Bork, P.; et al. STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res.* 2019, 47, D607–D613. [CrossRef] [PubMed]

24. Ding, Y.; Shao, X.; Li, X.; Zhai, Y.; Zhang, Y.; Wang, S.; Fang, H. Identification of candidate genes in atopic dermatitis based on bioinformatic methods. *Int. J. Dermatol.* 2016, 55, 791–800. [CrossRef]

25. Yang, Z.; Zeng, B.; Wang, C.; Wang, H.; Huang, P.; Pan, Y. MicroRNA-124 alleviates chronic skin inflammation in atopic eczema via suppressing innate immune responses in keratinocytes. *Cell. Immunol.* 2017, 319, 53–60. [CrossRef]

26. Dissanayake, E.; Inoue, Y.; Ochiai, S.; Eguchi, A.; Nakano, T.; Yamaide, F.; Hasegawa, S.; Kojima, H.; Suzuki, H.; Mori, C.; et al. Hsa-mir-144-3p expression is increased in umbilical cord serum of infants with atopic dermatitis. *J. Allergy Clin. Immunol.* 2019, 143, 447–450. [CrossRef]

27. Bao, L.; Chau, C.; Bao, J.; Tsoukas, M.M.; Chan, L.S. IL-4 dysregulates microRNAs involved in inflammation, angiogenesis and apoptosis in epidermal keratinocytes. *Microbiol. Immunol.* 2018, 62, 732–736. [CrossRef]

28. Boorgula, M.P.; Taub, M.A.; Rafaeis, N.; Daya, M.; Campbell, M.; Chavan, S.; Shetty, A.; Cheadle, C.; Barkataki, S.; Fan, J.; et al. Replicated methylation changes associated with eczema herpeticum and allergic response. *Clin. Epigenetics* 2019, 11, 122. [CrossRef]

29. Carreras-Badosa, G.; Runnel, T; Plaa, M.; Karner, J.; Ruckert, B.; Lattekivi, F.; Koks, S.; Akdis, C.A.; Kingo, K.; Rebane, A. microRNA-146a is linked to the production of IgE in mice but not in atopic dermatitis patients. *Allergy* 2018, 73, 2400–2403. [CrossRef]

30. Chen, X.-F.; Zhang, L.-J.; Zhang, J.; Dou, X.; Shao, Y.; Jia, X.-J.; Zhang, W.; Yu, B. MiR-151a is involved in the pathogenesis of atopic dermatitis by regulating interleukin-12 receptor beta2. *Exp. Dermatol.* 2018, 27, 427–432. [CrossRef]

31. Kumar, D.; Puan, K.J.; Andiappan, A.K.; Lee, B.; Westerlaken, G.H.A.; Haase, D.; Melchiotti, R.; Li, Z.; Yusof, N.; Lum, J.; et al. A functional SNP associated with atopic dermatitis controls cell type-specific methylation of the VSTM1 gene locus. *Genome Med.* 2017, 9, 18. [CrossRef]

32. Li, H.M.; Xiao, Y.J.; Min, Z.S.; Tan, C. Identification and interaction analysis of key genes and microRNAs in atopic dermatitis by bioinformatics analysis. *Clin. Exp. Dermatol.* 2019, 44, 257–264. [CrossRef]

33. Thürmann, L.; Grützmann, K.; Klös, M.; Bieg, M.; Winter, M.; Polte, T.; Bauer, T.; Schick, M.; Bewerunge-Hudler, M.; Röder, S.; et al. Early-onset childhood atopic dermatitis is related to NLRP2 repression. *J. Allergy Clin. Immunol.* 2018, 141, 1482–1485. [CrossRef] [PubMed]

34. Yang, C.-W.; Hojer, C.D.; Zhou, M.; Wu, X.; Wuster, A.; Lee, W.P.; Yaspan, B.L.; Chan, A.C. Regulation of T Cell Receptor Signaling by DENND1B in TH 2 Cells and Allergic Disease. *Cell* 2016, 164, 141–155. [CrossRef]

35. Asad, S.; Wingc, M.C.G.; Wahlgren, C.-F.; Bilcha, K.D.; Nordenskjöld, M.; Taylan, F.; Porter, H. The tight junction gene Claudin-1 is associated with atopic dermatitis among Ethiopians. *J. Eur. Acad. Dermatol. Venereol.* 2016, 30, 1939–1941. [CrossRef] [PubMed]

36. Gimalova, G.F.; Karunas, A.S.; Fedorova, Y.Y.; Khusnutdinova, E.K. The study of filaggrin gene mutations and copy number variation in atopic dermatitis patients from Volga-Ural region of Russia. *Gene* 2016, 592, 85–89. [CrossRef] [PubMed]

37. Handa, S.; Khullar, G.; Pal, A.; Kamboj, P.; De, D. Filaggrin gene mutations in hand eczema patients in the Indian subcontinent: A prospective case-control study. *Contact Dermat.* 2019, 80, 359–364. [CrossRef]

38. Jiang, X.-Y.; Zhao, J.-H.; Yu, C.-X.; Fang, L.; Zheng, X.-D.; Yin, X.-Y.; Wu, Y.-Y.; Tang, X.-F.; Zhou, F.-S.; Zhang, X.-J.; et al. Association analyses identify two susceptibility loci 5q31 and 5q22.1 for atopic dermatitis in Chinese Han population. *Asian Pac. J. Allergy Immunol.* 2018, 35, 196–202.

39. Johansson, E.K.; Bergström, A.; Kull, I.; Lind, T.; Söderhäll, C.; van Hage, M.; Wickman, M.; Ballardini, N.; Wahlgren, C.-F. IgE sensitization in relation to preschool eczema and filaggrin mutation. *J. Allergy Clin. Immunol.* 2017, 140, 1572–1579. [CrossRef]
40. Johansson, E.; Biagini Myers, J.M.; Martin, L.J.; He, H.; Pilipenko, V.; Mersha, T.; Weirauch, M.; Salomonis, N.; Ryan, P.; LeMasters, G.K.; et al. KIF3A genetic variation is associated with pediatric asthma in the presence of eczema independent of allergic rhinitis. *J. Allergy Clin. Immunol.* 2017, 140, 595–598. [CrossRef]

41. Kim, M.; Yoo, J.; Kim, J.; Park, J.; Han, E.; Jang, W.; Chae, H.; Lee, J.H.; Park, Y.M.; Kim, Y. Association of FLG single nucleotide variations with clinical phenotypes of atopic dermatitis. *PLoS ONE* 2017, 12, e0190077. [CrossRef]

42. Kim, J.S.; Choi, J.; Hahn, H.-J.; Lee, Y.-B.; Yu, D.-S.; Kim, J.-W. Association of Macrophage Migration Inhibitory Factor Polymorphisms with Total Plasma IgE Levels in Patients with Atopic Dermatitis in Korea. *PLoS ONE* 2016, 11, e0162477. [CrossRef]

43. Ko, E.J.; Heo, W.I.; Park, K.Y.; Lee, M.-K.; Seo, S.J. Genetic polymorphism of thymic stromal lymphopoietin in Korean patients with atopic dermatitis and allergic march. *J. Eur. Acad. Dermatol. Venereol.* 2018, 32, e468–e470. [CrossRef] [PubMed]

44. Leitch, C.S.; Natafji, E.; Vu, C.; Abdul-Gha, C.; Galván, B.; Al-Hasan, M.; et al. Filaggrin-null mutations are associated with increased maturation markers on Langerhans cells. *J. Allergy Clin. Immunol.* 2016, 138, 482–490. [CrossRef] [PubMed]

45. Li, K.; Oh, W.J.; Park, K.Y.; Kim, K.-H.; Seo, S.J. FLG mutations in the East Asian atopic dermatitis patients: Genetic and clinical implication. *Exp. Dermatol.* 2016, 25, 816–818. [CrossRef] [PubMed]

46. Banihani, S.A.; Abu-Alia, K.F.; Khabour, O.F.; Alzoubi, K.H. Association between Resistin Gene Polymorphisms and Atopic Dermatitis. *Biomolecules* 2018, 8, 17. [CrossRef]

47. Luukkonen, T.M.; Kiiski, V.; Ahola, M.; Mandelin, J.; Virtanen, H.; Poyhonen, M.; Kivirikko, S.; Surakka, I.; Reitamo, S.; Palotie, A.; et al. The Value of FLG Null Mutations in Predicting Treatment Response in Atopic Dermatitis: An Observational Study in Finnish Patients. *Acta Derm. Venereol.* 2017, 97, 456–463. [CrossRef]

48. Manti, S.; Amorini, M.; Cuppari, C.; Salpietro, A.; Porcino, F.; Leonardi, S.; Del Giudice, M.M.; Marseglia, G.; Caimmi, D.P.; Salpietro, C. Filaggrin mutations and Molluscum contagiosum skin infection in patients with atopic dermatitis. *Ann. Allergy. Asthma Immunol.* 2017, 119, 446–451. [CrossRef]

49. Morizane, S.; Ouchida, M.; Sunagawa, K.; Sugimoto, S.; Kobashi, M.; Sugihara, S.; Nomura, H.; Tsuji, K.; Sato, A.; Miura, Y.; et al. Analysis of All 34 Exons of the SPINK5 Gene in Japanese Atopic Dermatitis Patients. *Acta Med. Okayama* 2018, 72, 275–282.

50. On, H.R.; Lee, S.E.; Kim, S.C.S.E.; Hong, W.J.; Kim, H.J.; Nomura, T.; Suzuki, S.; Shimizu, H.; Kim, S.C.S.E. Filaggrin Mutation in Korean Patients with Atopic Dermatitis. *Yonsei Med. J.* 2017, 58, 395–400. [CrossRef]

51. Park, K.Y.; Li, K.; Seok, J.; Seo, S.J. An Analysis of the Filaggrin Gene Polymorphism in Korean Atopic Dermatitis Patients. *J. Korean Med. Sci.* 2016, 31, 1136–1142. [CrossRef]

52. Ponińska, J.K.; Samoliński, B.; Tomaszewska, A.; Raciborski, F.; Samel-Kowalik, P.; Walkiewicz, A.; Lipiec, A.; Piekarska, B.; Krzych-Fałta, E.; Namysłowski, A.; et al. Haplotype dependent association of rs7927894 (11q13.5) with atopic dermatitis and chronic allergic rhinitis: A study in ECAP cohort. *PLoS ONE* 2017, 12, e0162477. [CrossRef] [PubMed]

53. Roekevisch, E.; Leeflang, M.M.G.; Schram, M.E.; Campbell, L.E.; Irwin McLean, W.H.; Kezic, S.; Bos, J.D.; Spuls, P.I.; Middelkamp-Hup, M.A. Patients with atopic dermatitis with filaggrin loss-of-function mutations show good but lower responses to immunosuppressive treatment. *Br. J. Dermatol.* 2017, 177, 1745–1746. [CrossRef]

54. Sekiya, A.; Kono, M.; Tsujiuchi, H.; Kobayashi, T.; Nomura, T.; Kitakawa, M.; Suzuki, N.; Yamanaka, K.; Sueki, H.; McLean, W.H.I.; et al. Compound heterozygotes for filaggrin gene mutations do not always show severe atopic dermatitis. *J. Eur. Acad. Dermatol. Venereol.* 2017, 31, 158–162. [CrossRef]

55. Tang, L.; Wang, J.; Zhu, J.; Liang, Y. Down-regulated SHARPIN may accelerate the development of atopic dermatitis through activating interleukin-33/ST2 signalling. *Exp. Dermatol.* 2018, 27, 1328–1335. [CrossRef] [PubMed]

56. Teye, K.; Numata, S.; Krol, R.P.; Ishii, N.; Matsuda, M.; Lee, J.-B.; Hamada, T.; Hashimoto, T. Prevalence of filaggrin gene mutations in patients with atopic dermatitis and ichthyosis vulgaris in Kyushu area of Japan and South Korea. *J. Dermatol. Sci.* 2017, 86, 174–177. [CrossRef]

57. Behniafard, N.; Amirzargar, A.A.; Gharghazolou, M.; Delavari, F.; Hosseinverdi, S.; Sotoudeh, S.; Farhadi, E.; Mahmoudi, M.; Khaliedi, M.; Moghaddam, Z.G.; et al. Single nucleotide polymorphisms of the genes encoding IL-10 and TGF-β1 in Iranian children with atopic dermatitis. *Allergol. Immunopathol.* 2018, 46, 155–159. [CrossRef] [PubMed]
58. Thomsen, S.F.; Elmose, C.; Szecsi, P.B.; Stender, S.; Kvit, K.O.; Backer, V.; Thyssen, J.P. Filaggrin gene loss-of-function mutations explain discordance of atopic dermatitis within dizygotic twin pairs. *Int. J. Dermatol.* 2016, 55, 1341–1344. [CrossRef]

59. Thorsteinsdottir, S.; Stokholm, J.; Thyssen, J.P.; Norgaard, S.; Thorsen, J.; Chawes, B.L.; Bonnelykke, K.; Waage, J.; Bisgaard, H. Genetic, Clinical, and Environmental Factors Associated with Persistent Atopic Dermatitis in Childhood. *JAMA Dermatol.* 2019, 155, 50–57. [CrossRef] [PubMed]

60. Trzeckiat, M.; Sakowicz-Burkiewicz, M.; Wesserling, M.; Glen, J.; Dobaczewska, D.; Bandurski, T.; Nowicki, R.; Pawelczyk, T. Altered Expression of Genes Encoding Cornulin and Repetin in Atopic Dermatitis. *Int. Arch. Allergy Immunol.* 2017, 172, 11–19. [CrossRef] [PubMed]

61. Tyurin, Y.A.; Shamsutdinov, A.E.; Kalinin, N.N.; Sharifullina, A.A.; Reshetnikova, I.D. Association of Toll-Like Cell Receptors TLR2 (p.Arg753GLN) and TLR4 (p.Asp299GLY) Polymorphisms with Indicators of General and Local Immunity in Patients with Atopic Dermatitis. *J. Immunol. Res.* 2017, 2017, 8493545. [CrossRef] [PubMed]

62. Wan, J.; Mitra, N.; Ho, E.; Andersen, Y.M.F.; Egeberg, A.; Balslev, E.; Jørgensen, C.L.T.; Szecsi, P.B.; Stender, S.; Kaae, J.; Linneberg, A.; Wen, H.-J.; Wang, S.-L.; Chen, P.-C.; Guo, Y.L. Prenatal perfluorooctanoic acid exposure and glutathione s-transferase T1/M1 genotypes and their association with atopic dermatitis at 2 years of age. *PloS ONE* 2019, 14, e0210708. [CrossRef] [PubMed]

63. Yoon, N.Y.; Wang, H.Y.; Jun, M.; Jung, M.; Kim, D.H.; Lee, N.R.; Hong, K.-W.; Seo, S.J.; Choi, E.H.; Lee, J.; et al. Simultaneous detection of barrier- and immune-related gene variations in patients with atopic dermatitis by reverse blot hybridization assay. *Clin. Exp. Dermatol.* 2018, 43, 430–436. [CrossRef] [PubMed]

64. Andersen, Y.M.F.; Egeberg, A.; Balslev, E.; Jørgensen, C.L.T.; Szecsi, P.B.; Stender, S.; Kaae, J.; Linneberg, A.; Gislason, G.; Skov, L.; et al. Filaggrin loss-of-function mutations, atopic dermatitis and risk of actinic keratosis: Results from two cross-sectional studies. *J. Eur. Acad. Dermatol. Venereol.* 2017, 31, 1038–1043. [CrossRef]

65. Asad, S.; Tapia-Páez, I.; Montano Montes, A.; Wahlgren, C.-F.; Bilcha, K.D.; Nordenskjöld, M.; Bradley, M. Evaluation of Single Nucleotide Variants in Ethiopian Patients with Atopic Dermatitis. *Acta Derm. Venereol.* 2019, 99, 101–102. [CrossRef]

66. Song, Y.; Schwager, M.J.; Backer, V.; Guo, J.; Porsbjerg, C.; Khoo, S.-K.; Laing, I.A.; Moses, E.K.; LeSouëf, P.; Zhang, G. Environment Changes Genetic Effects on Respiratory Conditions and Allergic Phenotypes. *Sci. Rep.* 2017, 7, 6342. [CrossRef]

67. Cai, X.-Y.; Zheng, X.-D.; Fang, L.; Zhou, F.-S.; Sheng, Y.-J.; Wu, Y.-Y.; Yu, C.-X.; Zhu, J.; Xiao, F.-L. A variant on chromosome 2p13.3 is associated with atopic dermatitis in Chinese Han population. *Gene* 2017, 628, 281–285. [CrossRef]

68. Can, C.; Yazicioglu, M.; Gurkan, H.; Tozkir, H.; Gorgulu, A.; Sut, N.H. Lack of Association between Toll-like Receptor 2 Polymorphisms (R753Q and A-16934T) and Atopic Dermatitis in Children from Thrace Region of Turkey. *Balk. Med. J.* 2017, 34, 232–238. [CrossRef]

69. Chan, A.; Terry, W.; Zhang, H.; Karmaus, W.; Ewart, S.; Holloway, J.W.; Roberts, G.; Kurukulaaratchy, R.; Arshad, S.H. Filaggrin mutations increase allergic airway disease in childhood and adolescence through interactions with eczema and aeroallergen sensitization. *Clin. Exp. Allergy* 2018, 48, 147–155. [CrossRef]

70. Chang, J.; Mitra, N.; Hofstad, O.; Margolis, D.J. Association of Filaggrin Loss of Function and Thymic Stromal Lymphopoietin Variation with Treatment Use in Pediatric Atopic Dermatitis. *JAMA Dermatol.* 2017, 153, 275–281. [CrossRef] [PubMed]

71. Debinska, A.; Danielewicz, H.; Drabik-Chamerska, A.; Kalita, D.; Boznanski, A. Filaggrin loss-of-function mutations as a predictor for atopic eczema, allergic sensitization and eczema-associated asthma in Polish children population. *Adv. Clin. Exp. Med.* 2017, 26, 991–998. [CrossRef] [PubMed]

72. Elbert, N.J.; Duijts, L.; den Dekker, H.T.; Jaddoe, V.W.V.; Sonnenschein-van der Voort, A.M.M.; de Jongste, J.C.; Pasmans, S.G.M.A. Role of environmental exposures and filaggrin mutations on associations of ethnic origin with risk of childhood eczema. The Generation R Study. *Pediatr. Allergy Immunol.* 2016, 27, 627–635. [CrossRef] [PubMed]

73. Wu, Y.-Y.; Tang, J.-P.; Liu, Q.; Zheng, X.-D.; Fang, L.; Yin, X.-Y.; Jiang, X.-Y.; Zhou, F.-S.; Zhu, F.; Liang, B.; et al. Scanning indels in the 5q22.1 region and identification of the TMEM232 susceptibility gene that is associated with atopic dermatitis in the Chinese Han population. *Gene* 2017, 617, 17–23. [CrossRef] [PubMed]
75. Ziyab, A.H.; Ewart, S.; Lockett, G.A.; Zhang, H.; Arshad, H.; Holloway, J.W.; Karmaus, W. Expression of the filaggrin gene in umbilical cord blood predicts eczema risk in infancy: A birth cohort study. *Clin. Exp. Allergy* 2017, 47, 1185–1192. [CrossRef] [PubMed]

76. Paternoster, L.; Savenije, O.E.M.; Heron, J.; Evans, D.M.; Vonk, J.M.; Brunekreef, B.; Wiiga, A.H.; Henderson, A.J.; Koppelman, G.H.; Brown, S.J. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J. Allergy Clin. Immunol.* 2018, 141, 964–971. [CrossRef]

77. Al-Kzayer, L.F.Y.; Al-Aradi, H.M.H.; Shigemura, T.; Sano, K.; Tanaka, M.; Hamada, M.; Ali, K.H.; Aldaghir, O.M.; Nakazawa, Y.; Okuno, Y. DOCK8 mutation diagnosed using whole-exome sequencing of the dried blood spot-derived DNA: A case report of an Iraqi girl diagnosed in Japan. *BMC Med. Genet.* 2019, 20, 114. [CrossRef]

78. Dadi, H.; Jones, T.A.; Merico, D.; Sharfe, N.; Ovadia, A.; Schejter, Y.; Reid, B.; Sun, M.; Yong, L.; Atkinson, A.; et al. Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11). *J. Allergy Clin. Immunol.* 2018, 141, 1818–1830. [CrossRef]

79. Peled, A.; Sarig, O.; Sun, G.; Samuelov, L.; Ma, C.A.; Zhang, Y.; Dimaggio, T.; Nelson, C.G.; Stone, K.D.; Friedman, A.F.; et al. Loss-of-function mutations in caspase recruitment domain-containing protein 14 (CARD14) are associated with a severe variant of atopic dermatitis. *J. Allergy Clin. Immunol.* 2019, 143, 173–181. [CrossRef]

80. Pigors, M.; Common, J.E.A.; Wong, X.F.C.C.; Malik, S.; Scott, C.A.; Tabarra, N.; Liany, H.; Liu, J.; Limphivuhavdh, V.; Maurer-Stroh, S.; et al. Exome Sequencing and Rare Variant Analysis Reveals Multiple Filaggrin Mutations in Bangladeshi Families with Atopic Eczema and Additional Risk Genes. *J. Investig. Dermatol.* 2018, 138, 2674–2677. [CrossRef] [PubMed]

81. Suzuki, H.; Makino, Y.; Nagata, M.; Furuta, J.; Hirota, T.; Tamari, M.; Noguchi, E. A rare variant in CYP27A1 and its association with atopic dermatitis with high serum total IgE. *Allergy* 2016, 71, 1486–1489. [CrossRef]

82. Manz, J.; Rodriguez, E.; ElSharawy, A.; Oesau, E.-M.; Petersen, B.-S.; Baurecht, H.; Mayr, G.; Weber, S.; Harder, J.; Reischl, E.; et al. Targeted Resequencing and Functional Testing Identifies Low-Frequency Missense Variants in the Gene Encoding GARP as Significant Contributors to Atopic Dermatitis Risk. *J. Investig. Dermatol.* 2018, 138, 1501–1506. [CrossRef]

83. Park, K.Y.; Park, K.M.; Seok, J.; Li, K.; Seo, S.J. Clinical characteristics of Korean patients with filaggrin-related atopic dermatitis. *Clin. Exp. Dermatol.* 2016, 41, 595–600. [CrossRef]

84. Wong, X.F.C.C.; Denil, S.L.I.J.; Foo, J.N.; Chen, H.; Tay, A.S.L.; Haines, R.L.; Tang, M.B.Y.Y.; McLean, W.H.I.I.; Sandilands, A.; Smith, F.J.D.D.; et al. Array-based sequencing of filaggrin gene for comprehensive detection of disease-associated variants. *J. Allergy Clin. Immunol.* 2018, 141, 814–816. [CrossRef]

85. Lopez-Alvarez, M.R.; Jiang, W.; Jones, D.C.; Jayaraman, J.; Johnson, C.; Cookson, W.O.; Mo; Wong, X.F.C.C.C.; Denil, S.L.I.J.I.; Foo, J.N.; Chen, H.; Tay, A.S.L.; Haines, R.L.; Tang, M.B.Y.Y.; McLean, W.H.I.I.; Brown, S.J.; Common, J.E.; de Guzman Strong, C. Tiled array-based sequencing identifies enrichment of loss-of-function variants in the highly homologous filaggrin gene in African-American children with severe atopic dermatitis. *Exp. Dermatol.* 2018, 27, 989–992. [CrossRef]
91. Elhaji, Y.; Sasseville, D.; Pratt, M.; Asai, Y.; Matheson, K.; McLean, W.H.I.; Hull, P.R. Filaggrin gene loss-of-function mutations constitute a factor in patients with multiple contact allergies. Contact Dermat. 2019, 80, 354–358. [CrossRef] [PubMed]

92. Liang, J.; Liu, Y.; Xue, R.; Chen, L.; Chen, H.; Shao, L.; Wang, J.; Zhang, X. Interleukin 4-590C/T (rs2243250) Polymorphism Is Associated with Increased Risk of Atopic Dermatitis: Meta-Analysis of Case-Control Studies. Dermat. Contact Atopic Occup. Drug 2017, 28, 144–151. [CrossRef] [PubMed]

93. Margaritte-Jeannin, P.; Babron, M.-C.; Laprise, C.; Lavielle, N.; Sarnowski, C.; Brossard, M.; Moffatt, M.; Gagne-Ouellet, V.; Etcheto, A.; Lathrop, M.; et al. The COL5A3 and MMP9 genes interact in eczema susceptibility. Clin. Exp. Allergy 2018, 48, 297–305. [CrossRef] [PubMed]

94. Qi, Y.; Kong, J.; He, J. Genetic relationship between IL-10 gene polymorphisms and the risk of clinical atopic dermatitis. BMC Med. Genet. 2019, 20, 83. [CrossRef] [PubMed]

95. Zhao, J.; Chen, Z.-Y.; Li, L.-F. Association between the IL-10-1082G/A, IL-10-592A/C, and IL-10-819G/A Polymorphisms and Atopic Dermatitis Susceptibility: A Meta-Analysis. Genet. Test. Mol. Biomark. 2019, 23, 332–341. [CrossRef]

96. Arkwright, P.D.; Chase, J.M.; Babbage, S.; Pravica, V.; David, T.J.; Hutchinson, I.V. Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. J. Allergy Clin. Immunol. 2001, 108, 281–284. [CrossRef]

97. Polcari, I.; Becker, L.; Stein, S.L.; Smith, M.S.; Paller, A.S. Filaggrin gene mutations in African Americans with both ichthyosis vulgaris and atopic dermatitis. Pediatr. Dermatol. 2014, 31, 489–492. [CrossRef] [PubMed]

98. Yan, S.R.; Novak, M.J. Beta2 integrin-dependent phosphorylation of protein-tyrosine kinase Pyk2 stimulated by tumor necrosis factor alpha and fMLP in human neutrophils adherent to fibrinogen. FEBS Lett. 1999, 451, 33–38. [CrossRef]

99. Calabresi, P.A.; Allie, R.; Mullen, K.M.; Yun, S.H.; Georgantas, R.W.; Whartenby, K.A. Kinetics of CCR7 expression differ between primary activation and effector memory states of T(H)1 and T(H)2 cells. J. Neuroimmunol. 2003, 139, 58–65. [CrossRef]

100. Malaise, J.; Bourguignon, V.; De Vuyst, E.; Lambert de Rouvroit, C.; Niggelaars, A.F.; Flamion, B.; Pousmay, Y. Hyaluronan metabolism in human keratinocytes and atopic dermatitis skin is driven by a balance of hyaluronan synthases 1 and 3. J. Investig. Dermatol. 2014, 134, 2174–2182. [CrossRef] [PubMed]

101. Quinn, S.R.; O’Neill, L.A. A trio of microRNAs that control Toll-like receptor signalling. Int. Immunol. 2011, 23, 421–425. [CrossRef]

102. Sonkoly, E.; Stähle, M.; Pivarcsi, A. MicroRNAs and immunity: Novel players in the regulation of normal immune function and inflammation. Semin. Cancer Biol. 2008, 18, 131–140. [CrossRef]

103. Renz, H.; Autenrieth, I.B.; Brandtzæg, P.; Cookson, W.O.; Coler, R.; Haller, D. Gene-environment interaction in chronic disease: A European Science Foundation Forward Look. J. Allergy Clin. Immunol. 2011, 128, S27–S49. [CrossRef]

104. von Mutius, E. Gene-environment interactions in asthma. J. Allergy Clin. Immunol. 2009, 123, 3–11. [CrossRef]

105. Potaczek, D.P.; Harb, H.; Michel, S.; Alhamwe, B.A.; Renz, H.; Tost, J. Epigenetics and allergy: From basic mechanisms to clinical applications. Epigenomics 2017, 9, 539–571. [CrossRef]
112. Candi, E.; Schmidt, R.; Melino, G. The cornified envelope: A model of cell death in the skin. *Nat. Rev. Mol. Cell Biol.* 2005, 6, 328–340. [CrossRef] [PubMed]

113. Irvine, A.D.; McLean, W.H.I.; Leung, D.Y.M.M. Filaggrin mutations associated with skin and allergic diseases. *N. Engl. J. Med.* 2011, 365, 1315–1327. [CrossRef] [PubMed]

114. Kypriotou, M.; Huber, M.; Hohl, D. The human epidermal differentiation complex: Cornified envelope precursors, S100 proteins and the “fused genes” family. *Exp. Dermatol.* 2012, 21, 643–649. [CrossRef] [PubMed]

115. Brown, S.J.; McLean, W.H.I. One remarkable molecule: Filaggrin. *J. Investig. Dermatol.* 2012, 132, 751–762. [CrossRef]

116. Margolis, D.J.; Apted, A.J.; Gupta, J.; Hoffstad, O.; Papadopoulos, M.; Campbell, L.E.; Sandilands, A.; McLean, W.H.I.; Rebbeck, T.R.; Mitra, N. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. *J. Allergy Clin. Immunol.* 2012, 130, 912–917. [CrossRef]

117. Palmer, C.N.A.; Irvine, A.D.; Terron-Kwiatkowski, A.; Zhao, Y.; Liao, H.; Lee, S.P.; Goudie, D.R.; Sandilands, A.; Campbell, L.E.; Smith, F.J.D.; et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat. Genet.* 2006, 38, 441–446. [CrossRef]

118. Rogers, A.J.; Celedón, J.C.; Lasky-Su, J.A.; Weiss, S.T.; Raby, B.A. Filaggrin mutations confer susceptibility to atopic dermatitis but not to asthma. *J. Allergy Clin. Immunol.* 2007, 120, 1332–1337. [CrossRef]

119. Smith, F.J.D.; Irvine, A.D.; Terron-Kwiatkowski, A.; Zhao, Y.; Liao, H.; Evans, A.T.; Goudie, D.R.; Lewis-Jones, S.; et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat. Genet.* 2006, 38, 337–342. [CrossRef]

120. Rodríguez, E.; Baurecht, H.; Herberich, E.; Wagenpfel, S.; Brown, S.J.; Cordell, H.J.; Irvine, A.D.; Weidinger, S. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust risk factors in atopic disease. *J. Allergy Clin. Immunol.* 2009, 123, 1361–1370. [CrossRef]

121. Van Den Oord, R.A.H.M.; Sheikh, A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: Systematic review and meta-analysis. *BMJ* 2009, 339, 86–88. [CrossRef]

122. Marenholz, I.; Nickel, R.; Rüscheidorf, F.; Schulz, F.; Esparza-Gordillo, J.; Kerscher, T.; Grüber, C.; Lau, S.; Worm, M.; Keil, T.; et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J. Allergy Clin. Immunol.* 2006, 118, 866–871. [CrossRef] [PubMed]

123. Bonnelykke, K.; Pipper, C.B.; Tavendale, R.; Palmer, C.N.A.; Bisgaard, H. Filaggrin gene variants and atopic diseases in early childhood assessed longitudinally from birth. *Pediatr. Allergy Immunol.* 2010, 21, 954–961. [CrossRef]

124. Weidinger, S.; O'Sullivan, M.; Illig, T.; Baurecht, H.; Depner, M.; Rodriguez, E.; Ruether, A.; Klopp, N.; Vogelberg, C.; Weiland, S.K.; et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J. Allergy Clin. Immunol.* 2008, 121, 1203–1210. [CrossRef] [PubMed]

125. Weidinger, S.; Rodriguez, E.; Stahl, C.; Wagenpfel, S.; Klopp, N.; Illig, T.; Novak, N. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. *J. Investig. Dermatol.* 2007, 127, 724–726. [CrossRef] [PubMed]

126. Henderson, J.; Northstone, K.; Lee, S.P.; Liao, H.; Zhao, Y.; Pembrey, M.; Mukhopadhyay, S.; Smith, G.D.; Palmer, C.N.A.; McLean, W.H.I.; et al. The burden of disease associated with filaggrin mutations: A population-based, longitudinal birth cohort study. *J. Allergy Clin. Immunol.* 2008, 121, 872–877. [CrossRef] [PubMed]

127. Marenholz, I.; Kerscher, T.; Bauerfeind, A.; Esparza-Gordillo, J.; Nickel, R.; Keil, T.; Lau, S.; Rohde, K.; Wahn, U.; Lee, Y.A. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J. Allergy Clin. Immunol.* 2009, 123, 911–916. [CrossRef]

128. Elias, P.M. Therapeutic Implications of a Barrier-based Pathogenesis of Atopic Dermatitis. *Ann. Dermatol.* 2010, 22, 245–254. [CrossRef]

129. Loo, E.X.L.; Shek, L.P.; Goh, A.; Teoh, O.H.; Chan, Y.H.; Soh, S.E.; Saw, S.M.; Kwek, K.; Gluckman, P.D.; Godfrey, K.M.; et al. Atopic Dermatitis in Early Life: Evidence for at Least Three Phenotypes? Results from the GUSTO Study. *Int. Arch. Allergy Immunol.* 2015, 166, 273–279. [CrossRef]

130. Greisenegger, E.; Novak, N.; Maintz, L.; Bieber, T.; Zimprich, F.; Haubenberger, D.; Gleiss, A.; Stingl, G.; Kopp, T.; Zimprich, A. Analysis of four prevalent filaggrin mutations (R501X, 2282del4, R2447X and S3247X) in Austrian and German patients with atopic dermatitis. *J. Eur. Acad. Dermatol. Venereol.* 2010, 24, 607–610. [CrossRef]
131. Rupnik, H.; Rijavec, M.; Korošec, P. Filaggrin loss-of-function mutations are not associated with atopic dermatitis that develops in late childhood or adulthood. *Br. J. Dermatol.* **2015**, *172*, 455–461. [CrossRef] [PubMed]

132. Flohr, C.; Johansson, S.G.O.; Wahlgren, C.-F.; Williams, H. How atopic is atopic dermatitis? *J. Allergy Clin. Immunol.* **2004**, *114*, 150–158. [CrossRef] [PubMed]

133. Brown, S.J.; Sandilands, A.; Zhao, Y.; Liao, H.; Relton, C.L.; Meggitt, S.J.; Trembath, R.C.; Barker, J.N.W.N.; Reynolds, N.J.; Cordell, H.J.; et al. Prevalent and Low-Frequency Null Mutations in the Filaggrin Gene Are Associated with Early-Onset and Persistent Atopic Eczema. *J. Investig. Dermatol.* **2008**, *128*, 1591–1594. [CrossRef] [PubMed]

134. Sandilands, A.; Terron-Kwiatkowski, A.; Hull, P.R.; O’Regan, G.M.; Clayton, T.H.; Watson, R.M.; Carrick, T.; Evans, A.T.; Liao, H.; Zhao, Y.; et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat. Genet.* **2007**, *39*, 650–654. [CrossRef] [PubMed]

135. Barker, J.N.W.N.; Palmer, C.N.A.; Zhao, Y.; Liao, H.; Hull, P.R.; Lee, S.P.; Allen, M.H.; Meggitt, S.J.; Reynolds, N.J.; Trembath, R.C.; et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J. Investig. Dermatol.* **2007**, *127*, 564–567. [CrossRef] [PubMed]

136. Stemmler, S.; Parwez, Q.; Petrasch-Parwez, E.; Epplen, J.T.; Hoffjan, S. Two common loss-of-function mutations within the filaggrin gene predispose for early onset of atopic dermatitis. *J. Investig. Dermatol.* **2007**, *127*, 722–724. [CrossRef] [PubMed]

137. Ercan, H.; Ispir, T.; Kirac, D.; Baris, S.; Ozen, A.; Oztezcan, S.; Cengizlier, M.R. Predictors of atopic dermatitis phenotypes and severity: Roles of serum immunoglobulins and filaggrin gene mutation R501X. *Allergol. Immunopathol. (Madr)* **2013**, *41*, 86–93. [CrossRef]

138. Weidinger, S.; Illig, T.; Baurecht, H.; Irvine, A.D.; Rodriguez, E.; Diaz-Lacava, A.; Klopp, N.; Wagenpfeil, S.; Zhao, Y.; Liao, H.; et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J. Allergy Clin. Immunol.* **2006**, *118*, 214–219. [CrossRef]

139. Brunner, P.M.; Guttman-Yassky, E. Racial differences in atopic dermatitis. *Ann. Allergy Asthma Immunol.* **2019**, *122*, 449–455. [CrossRef]

140. Kaufman, B.P.; Guttman-Yassky, E.; Alexis, A.F. Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation and treatment. *Exp. Dermatol.* **2018**, *27*, 340–357. [CrossRef]

141. Margolis, D.J.; Gupta, J.; Apter, A.J.; Hoffstad, O.; Papadopoulos, M.; Rebbeck, T.R.; Wubbenhorst, B.; Mitra, N. Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. *J. Investig. Dermatol.* **2014**, *134*, 2272–2274. [CrossRef]

142. Shaw, T.E.; Currie, G.P.; Koudelka, C.W.; Simpson, E.L. Eczema Prevalence in the United States: Data from the 2003 National Survey of Children’s Health. *J. Investig. Dermatol.* **2011**, *131*, 67–73. [CrossRef] [PubMed]

143. Stefanovic, N.; Flohr, C.; Irvine, A.D. The exposome in atopic dermatitis. *Allergy* **2020**, *75*, 63–74. [CrossRef] [PubMed]

144. Zhang, Q.; Si, N.; Liu, Y.; Zhang, D.; Wang, R.; Zhang, Y.; Wang, S.; Liu, X.; Deng, X.; Ma, Y.; et al. Steroid sulfatase and filaggrin mutations in a boy with severe ichthyosis, elevated serum IgE level and moyamoya syndrome. *Gene* **2017**, *628*, 103–108. [CrossRef] [PubMed]

145. Imamura, Y.; Scott, I.C.; Greenspan, D.S. The pro-alpha3(V) collagen chain. Complete primary structure, expression domains in adult and developing tissues, and comparison to the structures and expression domains of the other types V and XI procollagen chains. *J. Biol. Chem.* **2000**, *275*, 8749–8759. [CrossRef]

146. Fitzgerald, J.; Holden, P.; Hansen, U. The expanded collagen VI family: New chains and new questions. *Connect. Tissue Res.* **2013**, *54*, 345–350. [CrossRef] [PubMed]

147. LeBert, D.C.; Squirrell, J.M.; Rindy, J.; Broadbridge, E.; Lui, Y.; Zakrzewska, A.; Eliceiri, K.W.; Meijer, A.H.; Huttenlocher, A. Matrix metalloproteinase 9 modulates collagen matrices and wound repair. *Development* **2015**, *142*, 2136–2146. [CrossRef]

148. Soldi, R.; Mitola, S.; Strasly, M.; Defilippi, P.; Tarone, G.; Bussolino, F. Role of alphavbeta3 integrin in the activation of vascular endothelial growth factor receptor-2. *EMBO J.* **1999**, *18*, 882–892. [CrossRef]
149. Maegdefessel, L.; Azuma, J.; Toh, R.; Merk, D.R.; Deng, A.; Chin, J.T.; Raaz, U.; Schoelmerich, A.M.; Raiesdana, A.; Leeper, N.J.; et al. Inhibition of microRNA-29b reduces murine abdominal aortic aneurysm development. J. Clin. Investig. 2012, 122, 497–506. [CrossRef]

150. Salazar, K.D.; Lankford, S.M.; Brody, A.R. Mesenchymal stem cells produce Wnt isoforms and TGF-beta1 that mediate proliferation and procollagen expression by lung fibroblasts. Am. J. Physiol. Lung Cell. Mol. Physiol. 2009, 297, L1002–L1011. [CrossRef]

151. Rørvig, S.; Østergaard, O.; Heegaard, N.H.H.; Borregaard, N. Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: Correlation with transcriptome profiling of neutrophil precursors. J. Leukoc. Biol. 2013, 94, 711–721. [CrossRef]

152. Foley, S.C.; Megas, A.K.; Olivenstein, R.; Fiset, P.O.; Chakir, J.; Bourjeau, J.; Ernst, P.; Lemiere, C.; Martin, J.G.; Hamid, Q. Increased expression of ADAM33 and ADAM8 with disease progression in asthma. J. Allergy Clin. Immunol. 2007, 119, 863–871. [CrossRef] [PubMed]

153. Huls, A.; Klumper, C.; MacIntyre, E.A.; Brauer, M.; Melen, E.; Berdel, D.; Bergstrom, A.; Bruneckreef, B.; Chan-Yeung, M.; et al. Atopic dermatitis: Interaction between genetic variants of GSTP1, TNF, TLR2, and TLR4 and air pollution in early life. Pelastr. Allergy Immunol. 2018, 29, 596–605. [CrossRef] [PubMed]

154. Nakashima, K.; Hirota, T.; Obara, K.; Shimizu, M.; Jodo, A.; Kameda, M.; Doi, S.; Fujita, K.; Shirakawa, T.; Enomoto, T.; et al. An association study of asthma and related phenotypes with polymorphisms in negative regulator molecules of the TLR signaling pathway. J. Hum. Genet. 2006, 51, 284–291. [CrossRef] [PubMed]

155. Kormann, M.S.D.; Depner, M.; Hartl, D.; Klopp, N.; Illig, T.; Adamski, J.; Vogelberg, C.; Weiland, S.K.; von Mutius, E.; Kabesch, M. Toll-like receptor heterodimer variants protect from childhood asthma. J. Allergy Clin. Immunol. 2008, 122, 86–92. [CrossRef] [PubMed]

156. Oh, D.-Y.; Schumann, R.R.; Hamann, L.; Neumann, K.; Worm, M.; Heine, G. Association of the toll-like receptor 2 A-16934T promoter polymorphism with severe atopic dermatitis. Allergy 2009, 64, 1608–1615. [CrossRef]

157. Potaczek, D.; Nastalek, M.; Okumura, K.; Wojis-Pelc, A.; Undas, A.; Nishiyama, C. An association of TLR2-16934A > T polymorphism and severity/phenotype of atopic dermatitis. J. Eur. Acad. Dermatol. Venereol. 2011, 25, 715–721. [CrossRef]

158. Li, H.-F.; Yan, L.-P.; Wang, K.; Li, X.-T.; Liu, H.-X.; Tan, W. Association between ADAM33 polymorphisms and asthma risk: A systematic review and meta-analysis. Respir. Res. 2019, 20, 38. [CrossRef]

159. Li, Z.; Yan, F.; Yang, Z.; Zhou, J.; Chen, Y.; Ding, Z. Association between ADAM33 S2 and V4 polymorphisms and susceptibility to allergic rhinitis: A meta-analysis. Allergol. Immunopathol. 2016, 44, 170–176. [CrossRef]

160. Bedsaul, J.R.; Carter, N.M.; Deibel, K.E.; Hutcherson, S.M.; Jones, T.A.; Wang, Z.; Yang, Y.-K.; Yang, D.; Chertov, O.; Bykovskiaia, S.N.; Chen, Q.; Shogan, J.; Anderson, M.; Schröder, J.M.; Wang, J.M.; Howard, O.M.; et al. Beta-defensins: Linking innate and adaptive immunity through dendritic and T cell CCR6. Science 1999, 287, 525–528. [CrossRef]

161. Jurevic, R.J.; Bai, M.; Chadwick, R.B.; White, T.C.; Dale, B.A. Single-nucleotide polymorphisms (SNPs) in human beta-defensin 1: High-throughput SNP assays and association with Candida carriage in type I diabetics and nondiabetic controls. J. Clin. Microbiol. 2003, 41, 90–96. [CrossRef] [PubMed]

162. Bertin, J.; Wang, L.; Guo, Y.; Jacobson, M.D.; Poyet, J.L.; Srnivasula, S.M.; Merriam, S.; DiStefano, P.S.; Alnemri, E.S. CARD11 and CARD14 are novel caspase recruitment domain (CARD)/membrane-associated guanylate kinase (MAGUK) family members that interact with BCL10 and activate NF-kappa B. J. Biol. Chem. 2001, 276, 11877–11882. [CrossRef]

163. Guo, X.; Zhang, Y.; Wang, P.; Li, T.; Fu, W.; Mo, X.; Shi, T.; Zhang, Z.; Chen, Y.; Ma, D.; et al. VSTM1-v2, a novel soluble glycoprotein, promotes the differentiation and activation of TH17 cells. Cell. Immunol. 2012, 278, 136–142. [CrossRef] [PubMed]

164. Hirayasu, K.; Arase, H. Leukocyte Immunoglobulin-Like Receptor (LILR). In Encyclopedia of Signaling Molecules; Springer International Publishing: Cham, Switzerland, 2018; pp. 2854–2861.

165. Su, H.C.; Jing, H.; Angelus, P.; Freeman, A.F. Insights into immunity from clinical and basic science studies of DOCK8 immunodeficiency syndrome. Immunol. Rev. 2019, 287, 9–19. [CrossRef] [PubMed]
167. Minkiewicz, J.; de Rivera Vaccari, J.P.; Keane, R.W. Human astrocytes express a novel NLRP2 inflammasome. *Glia* 2013, 61, 1113–1121. [CrossRef]

168. Tschopp, J.; Martinon, F.; Burns, K. NALPs: A novel protein family involved in inflammation. *Nat. Rev. Mol. Cell Biol.* 2003, 4, 95–104. [CrossRef]

169. Walne, A.J.; Vulliamy, T.; Kirwan, M.; Plagnol, V.; Dokal, I. Constitutional mutations in RTE1 cause severe dyskeratosis congenita. *Am. J. Hum. Genet.* 2013, 92, 448–453. [CrossRef]

170. Gray, P.W.; Aggarwal, B.B.; Benton, C.V.; Bringman, T.S.; Henzel, W.J.; Jarrett, J.A.; Leung, D.W.; Moffat, B.; Ng, P.; Svedersky, L.P. Cloning and expression of cDNA for human lymphotoxin, a lymphokine with tumour necrosis activity. *Nature* 1984, 312, 721–724. [CrossRef]

171. Trzeciak, M.; Wesserling, M.; Bandurski, T.; Glen, J.; Nowicki, R.; Pawelczyk, T. Association of a Single Nucleotide Polymorphism in a Late Cornified Envelope-like Proline-1 Gene (LELP1) with Atopic Dermatitis. *Acta Derm. Venereol.* 2016, 96, 459–463. [CrossRef]

172. Knüppel, S.; Esparza-Gordillo, J.; Marenholz, I.; Holzhütter, H.-G.; Bauerfeind, A.; Ruether, A.; Weidinger, S.; Lee, Y.-A.; Rohde, K. Multi-locus stepwise regression: A haplotype-based approach for detecting genetic associations applied to atopic dermatitis. *BMC Med. Genet.* 2012, 13, 8. [CrossRef]

173. Margolis, D.J.; Gupta, J.; Apter, A.J.; Ganguly, T.; Ho

174. Li, C.; Xiao, L.; Jia, J.; Li, F.; Wang, X.; Duan, Q.; Jing, H.; Yang, P.; Chen, C.; Wang, Q.; et al. Cornulin Is a Protein, a Member of Fused S100 Proteins, Is Expressed in Normal and Pathologic Human Skin. *Development* 2002, 129, 1775–1784. [PubMed]

175. Yamakoshi, T.; Makino, T.; Ur Rehman, M.; Yoshihisa, Y.; Sugimori, M.; Shimizu, T. Trichohyalin-like 1 protein, a member of fused S100 proteins, is expressed in normal and pathologic human skin. *Cell Biol.* 2003, 94, 95–104. [PubMed]

176. Kantor, R.; Silverberg, J.I. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev. Clin. Immunol.* 2017, 13, 15–26. [CrossRef] [PubMed]

177. Isidoro-García, M.; Dávila-González, I.; Pascual de Pedro, M.; Sanz-Lozano, C.; Lorente-Toledano, F. Interactions between genes and the environment. Epigenetics in allergy. *Allergol. Immunopathol.* 2013, 41, 71–80. [CrossRef] [PubMed]

178. Makeyev, E.V.; Maniatis, T. Multilevel Regulation of Gene Expression by MicroRNAs. *Science* 2008, 319, 1789–1790. [CrossRef] [PubMed]

179. Krol, J.; Loedige, I.; Filipowicz, W. The widespread regulation of microRNA biogenesis, function and decay. *Nat. Rev. Genet.* 2010, 11, 597–610. [CrossRef] [PubMed]

180. Maes, T.; Cobos, F.A.; Schleich, F.; Sorbello, V.; Henket, M.; De Preter, K.; Bracke, K.R.; Conixx, G.; Mesnil, C.; Vandesompele, J.; et al. Asthma inflammatory phenotypes show differential microRNA expression in sputum. *J. Allergy Clin. Immunol.* 2016, 137, 1433–1446. [CrossRef]

181. Sinha, A.; Yadav, A.K.; Chakraborty, S.; Kabra, S.K.; Lodha, R.; Kumar, M.; Kulshreshtha, A.; Sethi, T.; Pandey, R.; Malik, G.; et al. Exosome-enclosed microRNAs in exhaled breath hold potential for biomarker discovery in patients with pulmonary diseases. *J. Allergy Clin. Immunol.* 2013, 132, 219–222. [CrossRef]

182. Bauer, S.M. Atopic Eczema: Genetic Associations and Potential Links to Developmental Exposures. *Int. J. Toxicol.* 2017, 36, 187–198. [PubMed]

183. Rebane, A.; Runnel, T.; Aab, A.; Maslovskaja, J.; Rückert, B.; Zimmermann, M.; Plaa, M.; Kärner, J.; Treis, A.; Pihlap, M.; et al. MicroRNA-146α alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. *J. Allergy Clin. Immunol.* 2014, 134, 836–847. [CrossRef] [PubMed]

184. Deaton, A.M.; Bird, A. CpG islands and the regulation of transcription. *Genes Dev.* 2011, 25, 1010–1022. [CrossRef]

185. Takai, D.; Jones, P.A. Comprehensive analysis of CpG islands in human chromosomes 21 and 22. *Proc. Natl. Acad. Sci. USA* 2002, 99, 3740–3745. [CrossRef] [PubMed]

186. Schübeler, D. Function and information content of DNA methylation. *Nature* 2015, 517, 321–326. [CrossRef]
188. Nestor, C.E.; Barrenäs, F.; Wang, H.; Lentini, A.; Zhang, H.; Bruhn, S.; Jörnsten, R.; Langston, M.A.; Rogers, G.; Gustafsson, M.; et al. DNA Methylation Changes Separate Allergic Patients from Healthy Controls and May Reflect Altered CD4+ T-Cell Population Structure. *PLoS Genet.* 2014, 10, e1004059. [CrossRef]

189. Pascual, M.; Suzuki, M.; Isidoro-Garcia, M.; Padrón, J.; Turner, T.; Lorente, F.; Dávila, I.; Greally, J.M. Epigenetic changes in B lymphocytes associated with house dust mite allergic asthma. *Epigenetics* 2011, 6, 1131–1137. [CrossRef]

190. Joubert, B.R.; Felix, J.F.; Yousefi, P.; Bakulski, K.M.; Just, A.C.; Breton, C.; Reese, S.E.; Markunas, C.A.; Richmond, R.C.; Xu, C.-J.J.; et al. DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. *Am. J. Hum. Genet.* 2016, 98, 680–696. [CrossRef]

191. Joehanes, R.; Just, A.C.; Marioni, R.E.; Pilling, L.C.; Reynold, L.M.; Mandaviya, P.R.; Guan, W.; Xu, T.; Elks, C.E.; Aslibekyan, S.; et al. Epigenetic Signatures of Cigarette Smoking. *Circ. Cardiovasc. Genet.* 2016, 9, 436–447. [CrossRef]

192. Liang, Y.; Chang, C.; Lu, Q. The Genetics and Epigenetics of Atopic Dermatitis-Filaggrin and Other Polymorphisms. *Clin. Rev. Allergy Immunol.* 2016, 51, 315–328. [CrossRef]

193. Fontalba, A.; Gutierrez, O.; Fernandez-Luna, J.L. NLRP2, an inhibitor of the NF-kappaB pathway, is transcriptionally activated by NF-kappaB and exhibits a nonfunctional allelic variant. *J. Immunol.* 2007, 179, 8519–8524. [CrossRef] [PubMed]

194. Bruyé, J.M.; Bruyé-Sedano, N.; Newman, R.; Chandler, S.; Stehlik, C.; Reed, J.C. PAN1/NALP2/PYPAF2, an inducible inflammatory mediator that regulates NF-kappaB and caspase-1 activation in macrophages. *J. Biol. Chem.* 2004, 279, 51897–51907. [CrossRef] [PubMed]

195. Steevels, T.A.M.; van Avondt, K.; Westerlaken, G.H.A.; Stalpers, F.; Walk, J.; Bont, L.; Coffer, P.J.; Meynard, L. Signal inhibitory receptor on leukocytes-1 (SIRL-1) negatively regulates the oxidative burst in human phagocytes. *Eur. J. Immunol.* 2013, 43, 1297–1308. [CrossRef] [PubMed]

196. Steevels, T.A.M.; Lebbink, R.J.; Westerlaken, G.H.A.; Coffer, P.J.; Meynard, L. Signal inhibitory receptor on leukocytes-1 is a novel functional inhibitory immune receptor expressed on human phagocytes. *J. Immunol.* 2010, 184, 4741–4748. [CrossRef]

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