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Interleukins Gene Polymorphism in Alopecia Areata Patients: A Systematic Review

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Abstract:

Introduction: Alopecia areata is an autoimmune disorder that causes hair loss without scarring on the scalp or any part of the body with hair. There are various genetic variations in the interleukin genes, although the findings are inconsistent. This systematic study aimed to determine the correlation among specific genes (12B, 15, 16, 13, 12, 17A, 23, 17RA, and 18) of the interleukin family and alopecia areata.

Aim of the study: To assess the potential connection between gene variation in interleukins and the Probability of getting alopecia areata, as well as to examine its correlation with illness severity.

Methods: This systematic review included all relevant case-control association trials that included cases with alopecia areata and healthy controls.

Results and Conclusion: Alopecia areata is associated with IL-17A, IL-18, IL17RA, and IL16 gene polymorphisms. More genetic studies should be conducted to ensure that interleukins play a role in the progression of alopecia areata.

Keywords: Interleukins; Alopecia Areata; Polymorphism.

1. Introduction

Alopecia areata is a prevalent, persistent, and inflammatory condition. It is classified as a tissue-specific autoimmune disease. Alopecia areata cases exhibit an immune response where they produce antibodies against their hair follicles, resulting in the inhibition of hair development [1].

Alopecia areata is a condition that causes hair loss without scalp or body scarring [2]. Alopecia areata commonly presents as round or oval patches on the head or other areas of the body in ninety percent of cases. Another form, known as alopecia totalis, involves complete or near-complete hair loss on the scalp. The most severe form, alopecia universalis, is distinguished from the other two types by the fact that it affects hair loss not only on the scalp and face but also on the whole body [3].

Alopecia areata is an intricate condition caused by multiple factors, and its underlying cause is not well known. The phenotypic and genotypic differences correlated with Alopecia areata are influenced by a range of environmental, epigenetic, immunological, and genetic variables, making them unpredictable [4].

The immune response, along with genetic and environmental variables, significantly influences the development and advancement of alopecia areata. Genetic polymorphism is a significant factor in the development of Alopecia areata [5].

There is evidence of a T cell-mediated autoimmune mechanism targeting an unknown autoantigen located in the hair follicle. The presence of activated CD4+ cells outside the hair follicles, coupled with CD8+ cells inside the hair follicles, occurs simultaneously with hair loss throughout the active stage of the illness [6].

The primary factors are likely to be genetics and immunity. Multiple investigations have clearly shown that Alopecia areata is caused by autoimmune inflammatory processes, in which cytokines play a crucial role [7].

Cytokines and interleukins (ILs) are the focus of multiple investigations studying their correlation with autoimmune illnesses. These investigations utilize candidate gene correlation investigations, transcriptional profiling, and large-scale genome-wide association approaches to understand the crucial role of cytokines and interleukins in the development of these illnesses [8]. The presence of genetic polymorphisms in cytokines has been observed to influence the transcriptional activity of genes, leading to variances between cases and subsequently impacting the outcome of illnesses [9]. This investigation has chosen numerous IL genes, namely 15, 12B, 13, 16, 17A, 12, 23, 17RA, and 18, for specific reasons. These genes are known to be related to several autoimmune illnesses and have major clinical variables

for cases with alopecia. The objective of this investigation was to assess the potential correlation among gene polymorphism in interleukins and the risk of developing Alopecia areata, as well as to examine its correlation with the severity of the condition.

2. Methods

2.1. Criteria for considering investigations for this review

Types of studies: case-control association investigations

Types of participants: people diagnosed with alopecia areata and control subjects with no known skin conditions.

Search strategy: A comprehensive investigation has been performed on PubMed, Google Scholar, EMBASE, Scopus, MEDLINE, Cochrane Library, and Web of Science databases to locate relevant articles and text keywords related to "alopecia areata, interleukin, polymorphism." We reached out to authors to obtain more information or clarification as needed. Additionally, we contacted authors of registered, unpublished trials to discover current investigations. Additionally, we conducted a manual evaluation of the reference lists of the clinical trials and previous reviews that have been involved to identify any supplementary investigations.

Inclusion criteria and exclusion criteria: We chose papers based on the following parameters:

- The correlation among variations in interleukin genes and the probability of developing alopecia areata.
- The investigation design must be a case-control investigation that examines genotypic frequencies.
- Control persons, who were not blood relatives of the cases in the study, were selected. Furthermore, they did not have any inflammatory disorders.

The exclusion criteria included the following:

- Review papers and animal model investigations.
- Investigations with inadequate genotype data.
- Research involving other genes and polymorphisms associated with alopecia areata.

Data extraction: The following information includes the author's name, year of

publication, research location, kind of investigation, number of cases and controls, and genotyping data for both the case and control groups in each unique investigation.

3. Results

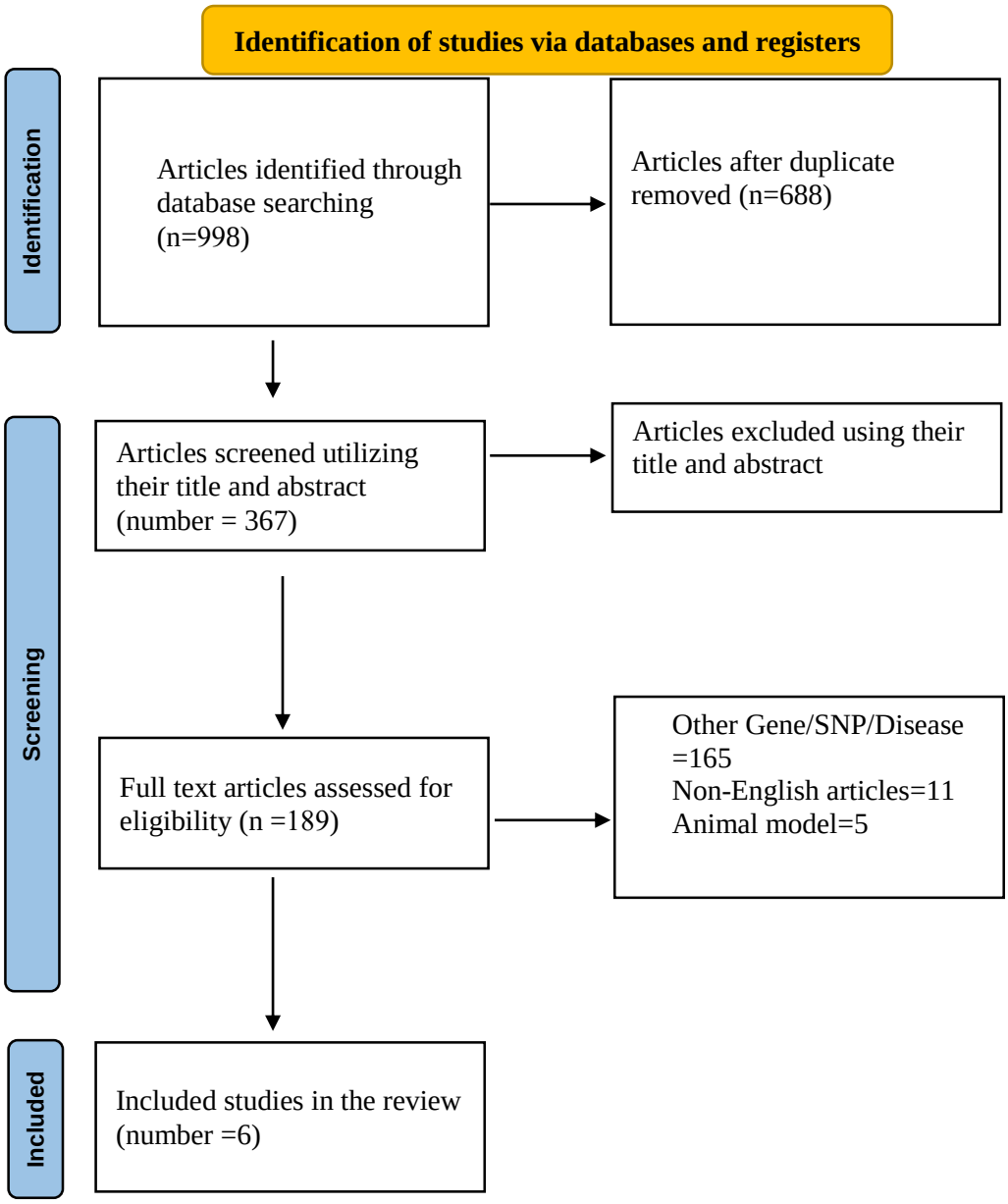

Figure 1: Flow diagram of the investigation involved in the systematic review.

Figure 2: Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

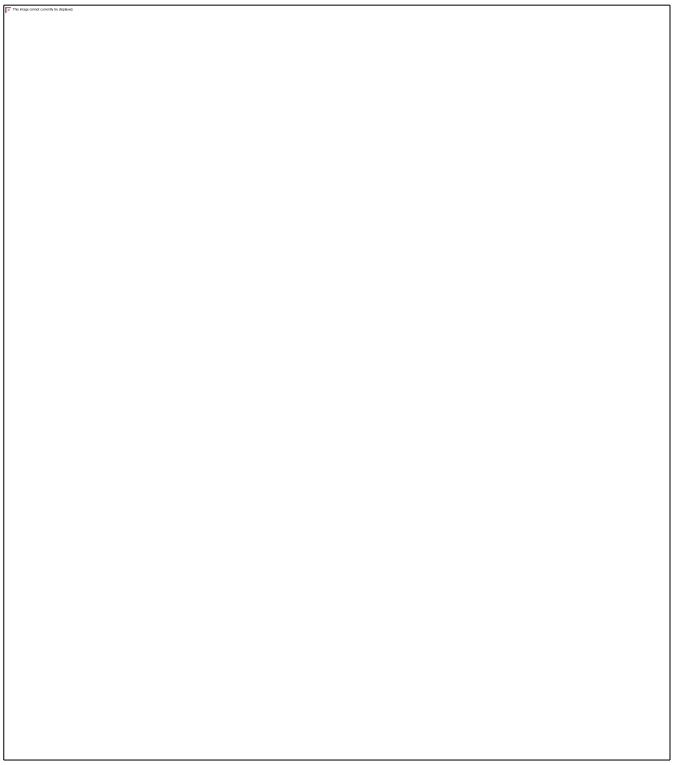

Figure 3: Risk of bias summary. Review authors' judgements about each risk of bias item for each included study.

Table 1: Characteristics of the involved investigation.

Authors (Ref)	Publication year	Country	Sample size (control/case)	Type of study	Age (y) (control/case)
Seleit et al. [10]	2021	Egypt	40/60	case–control study	30.22 ±9.9, 29.7 ± 9.45 years
Aytekin et al. [11]	2015	Turkey	71 / 100	case–control study	25.3 ±3.8, 24.2 ±4.3 years
Celik et al. [12]	2018	Turkey	200/200	case–control study	37.38 ±11.31, 36.62 ±9.6 years
Lew et al. [13]	2012	Korean	270/238	case–control study	35.7 ±11.8, 28.6 ±13.2 years
Montaser et al. [14]	2022	Egypt	50/50	case control study	26 years (3-45years)
Eitan et al. [15]	2022	Jordan	150/152	case–control study	33.9 ±9.8, 31.1 ±12.4 years

Table 2: The main findings of the included studies.

Study ID	Type of interleukin gene polymorphism	Outcomes
Seleit et al. [10]	IL-17A gene polymorphism	By assessing the distribution of the rs2275913 single-nucleotide polymorphism in cases and controls, they found significant variations in both genotypic and allelic frequencies. The alopecia areata and GA genotypes and the A allele were significantly more frequent among the cases with alopecia areata than control subjects. These results recommend that ALOPECIA AREATA and GA genotypes and the A allele of IL-17 (G197A) may be involved in the etiopathogenesis of ALOPECIA AREATA and may be correlated with an enhanced predisposition to the illness. The IL-17 (G197A) ALOPECIA AREATA genotype and A allele were significantly correlated with type of Alopecia areata (patchy ALOPECIA AREATA), severity, progressive course of the disease, nail changes, and the response to treatment (p =0.00 for all). So that IL-17 (G197A) polymorphism was associated with increases in the risk of Alopecia areata.

Aytekin et al. [11]	IL-17, IL-12, and IL-23 receptor gene polymorphisms	Alopecia areata genotype was found in most cases, with Alopecia areata and control cases, about the IL-17 (A7488G) gene polymorphism. IL-17 (A7488G) gene polymorphism's GG genotype is significantly higher in cases with alopecia areata (OR =7.788; p =0.021), whereas the GA genotype was significantly less prevalent (OR =0.055; p =0.014) in these cases than in control persons. IL-17 (A7488G) gene polymorphism potentially plays a role in the development and severity of alopecia areata. This polymorphism could also be related to a susceptibility to other autoimmune illnesses. There was insignificant variation in the genotypes of the IL-12 (1188A/C) gene polymorphism among the cases with Alopecia areata and the control group. Furthermore, there was insignificant variance in the IL-23R (þ2199A/C) gene polymorphism genotypes among those diagnosed with Alopecia areata and those in the control group.
Celik et al. [12]	IL-18 gene polymorphisms	The study investigated the distribution of genotypes and incidences of alleles for the rs187238 and rs1946518 single-nucleotide polymorphisms found in the promoter region of the IL-18 gene. This analysis was conducted in both cases with Alopecia areata and a control group. The distribution of genotypes for the rs187238 SNP showed a significant variance between cases with ALOPECIA AREATA and controls (p =0.0014). The distribution of genotypes and the frequency of alleles for the rs1946518 polymorphism have been observed to be significantly distinct between the case and control groups (p =0.0008 and 0.001, respectively). Ultimately, their research showed that IL-18 single-nucleotide polymorphisms, specifically the −137/G and −607/C allelic variations, which are associated with higher levels of IL-18 production, could be an important genetic component for alopecia areata. The status elucidates the elevated concentration of serum IL-18 in cases with alopecia areata. Additionally, understanding the pathogenesis of alopecia areata will require a greater understanding of IL-18, its receptors, and inhibitors.
Lew et al. [13]	IL-17A/IL-17RA Gene Polymorphisms	A specific genetic variation (rs879577) in the IL-17RA gene exhibited a significant variance among the group of cases with Alopecia areata and the control group (p =0.0288). A specific genetic variation (rs4819554) in the IL-17RA gene exhibited significant variations among cases who had Alopecia areata at an early age and those who developed it later in life (p =0.0421). The presence of IL-17RA gene polymorphism may potentially lead to a higher vulnerability to ALOPECIA AREATA, and this genetic variation could be related to the age at which the condition first appears. The IL-17A gene's two SNPs, rs3819024 and rs2275913, exhibited statistically insignificant variance among the Alopecia areata case group and the control group.

Montaser et al. [14]	IL-15 gene polymorphism	The gene under investigation, identified as rs17015014, exhibits two alleles: G and C. The G allele is considered the reference allele, while the C allele is regarded as the alternative allele. Statistically insignificant correlation has been found between genotypes, alleles, and alopecia areata cases. The study did not discover any significant correlations between IL-15 genotypes and family history, illness course, recurrence, body involvement, or dermoscopic findings in the alopecia areata group. Insignificant correlation was seen between IL-15 genotypes and grades of the alopecia areata group (p more than 0.05 for each grade). The study did not find any meaningful connections between the IL-15 single-nucleotide polymorphism (rs17015014) and the chance of developing alopecia areata or the severity of the condition.
Eitan et al. [15]	IL-12B, IL-13, IL-16, IL-17A, and IL-18 genes polymorphism	The rs11073001 single-nucleotide polymorphism in the exon region of the IL-16 gene showed a higher frequency of the A allele in alopecia areata cases (p =0.01). A significant variation has been observed among the cases and the controls regarding the rs17875491 single-nucleotide polymorphism in the promoter region of the IL-16 gene (p-value equal 0.04). In Jordanian cases, the presence of the A allele of rs11073001 and the homozygous CC genotype of rs17875491 may elevate the probability of developing alopecia areata. In summary, these results indicate that the IL-16 gene likely has a significant influence on the development of Alopecia areata. There was no evidence of a correlation among the genotypes of the IL-13, IL-17A, IL-12B, and IL-18 genes polymorphism and Vulnerability to alopecia areata in cases compared to control subjects.

4. Discussion

Alopecia areata is an autoimmune condition characterized by inflammation of the hair follicles, resulting in hair loss from the scalp and/or body. The condition does not cause permanent scarring. AA is a type of autoimmune illness that specifically affects organs. It is defined by the presence of T-cells and the production of cytokines surrounding hair follicles in the anagen stage. Scientific data indicate the loss of immunological privilege, together with the attack of hair follicle autoantigens by T cells [16]. The presence of cytokines and T-cells in alopecia areata is supported by the positive impact of systemic steroids and calcineurin inhibitors. Autoimmune illnesses arise from a combination of inherited variables in the immune system and environmental influences [17].

The association between alopecia areata and genetic variables is supported by the observation that four percent to twenty-

eight percent of cases have a familial history. Alopecia areata and other autoimmune illnesses are likely to be polygenic, meaning they are influenced by several genes and have various possible genetic susceptibilities [18].

A polymorphism is a genetic variation that occurs in a minimum one percent of the population. These genetic alterations may appear in the noncoding regions of the gene, thereby remaining undetectable in the resulting protein [2]. Tojo et al. found a direct correlation between the quantity of interferon-producing cells (IL-17) and the intensity and advancement of alopecia [19].

Kang et al. found that there were significant variations in rs187238 in IL-18 among alopecia areata and control subjects [20]. Furthermore, rs549908 demonstrated a noteworthy correlation among and control participants. The study of allele distribution revealed that the allele of rs187238 exhibited a significant connection with alopecia areata, whereas the allele of rs549908 also had a significant association with alopecia areata. In a similar vein, Alghamdi et al. discovered that the incidence of the IL-17RA rs879575 allele is significantly greater in cases, although insignificant changes have been observed for the IL-2RA, IL-23R, and IL-31RA SNPs [21]. Furthermore, the recessive model of IL-31RA rs161704 demonstrates a significant correlation between the alopecia areata genotype and the progression of alopecia areata.

Also, case-control evidence conducted by Al-Azzawi et al. revealed that the serum concentration of IL-16 was non-significantly increased in the alopecia areata patient group compared to the controls [22]. In addition, IL-16 SNPs rs11325 genotypes and allele frequencies showed that the GG genotype and G allele percentages were non-significantly enhanced in the patients' group (64.6% vs. 55.8% and 81.0% vs. 77%, respectively). Also, the results of rs1131445 recorded that the TC and CC genotypes and C allele frequency percentages were significantly increased in the patients' group. The TT genotype and T allele of the IL-16 SNPs rs11325 and TC, CC genotypes, and C allele of the IL-16 SNPs rs1131445 have a role as relative risks for alopecia areata.

5. Conclusion

In summary, genetic research is crucial for understanding the development and cause of alopecia areata. The IL-17 (G197A) and (A7488G) polymorphisms

were shown to be related to a greater probability of developing alopecia areata and may play a role in the development and severity of the condition. The presence of genetic variations in the IL-17RA gene may have a role in the greater susceptibility to alopecia areata, and these genetic variations may also be linked to the age at which the condition first appears. The IL-18 single nucleotide polymorphisms, specifically the −137/G and −607/C allelic variations, are associated with elevated IL-18 production and may play a significant role as a genetic component in alopecia areata. The IL-16 gene is likely to have a significant impact on the development of alopecia areata. Further investigation is required in larger cohorts of patients to ascertain the precise impact of genetic variations in cytokine genes on the development of alopecia areata.

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