

# Alopecia Areata: A Review of the Genetic Variants and Immunodeficiency Disorders Associated with Alopecia Areata

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## Keywords

General dermatology · Genodermatoses · Alopecia · Hair loss · Immunodeficiency · Immune mediated disease · Inborn errors of immunity

## Abstract

Alopecia areata (AA) is an autoimmune form of non-scarring hair loss that occurs on a spectrum from patchy loss of hair on the scalp, to complete hair loss. Histology features can vary, but increased abundance of telogen hair and miniaturized hair follicles are classic hallmarks [Clin Cosmet Investig Dermatol. 2015;8:397–403]. Additionally, lymphocytic infiltration of the hair bulb is a commonly observed histology feature of AA which underscores how the disease is an autoimmune-mediated one that results from immune-mediated attack of the hair follicle. In a healthy individual, the hair follicle is one of the body's immune-privileged sites, but the breakdown of this immune privilege is thought to be an important driver in AA disease development. Diagnosis of AA is usually based on phenotypic manifestations in conjunction with biopsies which can help conclude whether the hair loss is autoimmune based. However, varied manifestation of disease both clinically and histologically makes diagnosis criteria more ambiguous and early identification of disease harder to achieve. A better understanding of genes that are associated with increased AA risk may help elucidate potential gene targets for future therapeutics.

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## Introduction

Alopecia areata (AA) is an autoimmune disease with a lifetime risk of 1.7–2% globally [1]. AA phenotypically manifests as non-scarring hair loss that occurs on a spectrum of severity, with some patients experiencing limited patchy loss in hair-bearing areas and some losing all of the hair on their head and body. The hair follicle is an immune privileged site which limits local immune and inflammatory responses, but in AA, this privilege is lost. The pathogenesis is largely the result of an interferon gamma driven immune response excellent efficacy. We know other mechanisms may play roles in subsets of patients (especially those who do not respond to interferon gamma blockade). Here, we review available data on genetic risk variants identified through single gene studies and genome-wide association studies (GWASs). We also highlight the Mendelian diseases associated with specific gene variants in which AA can be seen. We aim to provide a background of genetic factors related to AA that may lead to improved understanding of disease subsets and perhaps lead to alternate therapeutics.

## Genetic Underpinnings of Disease Development

Inheritance of genetic diseases can be categorized as monogenic, chromosomal, or polygenic/multifactorial. There are 5,000–8,000 monogenic diseases that follow

**Table 1.** Genes identified through single-gene studies

Gene	Function	Method of evaluation	Implication in other autoimmune conditions
<i>FOXP3</i>	Transcription factor responsible for regulating T-reg cells	Human lesional AA skin analysis (Conteduca et al. [4], 2014; Ben Hmid et al. [5], 2015)	Thyroiditis, hypothyroidism, autoimmune hemolytic anemia, recurrent infections, and membranous nephropathy
<i>ICOSLG</i>	Modifies T-reg cell function	Human serum analysis (Conteduca et al. [4], 2014)	Vitiligo, inflammatory bowel disease, celiac disease, and autoimmune thyroid disease
<i>MICA</i>	NK and CD8+ cell activation	Human lesional AA skin and serum analysis (Ito et al. [6], 2008; Mingorance et al. [7], 2020)	Type 1 diabetes mellitus, ankylosing spondylitis, and Behçet's disease
<i>MIF</i>	Inhibits NK cells in immune-privileged areas	Human lesional AA skin and serum analysis (Salem et al. [8], 2016; Eldesouky et al. [9], 2020; Younan et al. [10], 2015)	Systemic juvenile rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, uveitis, psoriasis, Wegener's granulomatosis, and systemic sclerosis
<i>IL7RA</i>	Transduces signals from immune cells	Mouse lesional AA skin analysis (Dai et al. [11], 2021 )	Diabetes, Sjögren's syndrome, rheumatoid arthritis, and multiple sclerosis
<i>IL1RN</i>	Prevents IL-1 signaling	Human serum AA analysis (Tarlow et al. [12], 1994)	Systemic lupus erythematosus, ulcerative colitis, and Crohn's disease
<i>AIRE</i>	Eliminates self-reactive T cells	Human serum AA analysis (Tazi-Ahnini et al. [13], 2002)	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
<i>KRT82</i>	Hair-specific type II keratin exclusively expressed during anagen phase of hair follicle cycle	Human serum AA analysis (Erjavec et al. [14], 2022)	Only found in alopecia areata
<i>SOCS1</i>	Suppresses type I interferon function/signaling by inhibition of the JAK-STAT pathway	Clinical series	Thyroiditis, celiac disease, psoriasis, spondyloarthritis, hepatitis, systemic lupus erythematosus
<i>NFKB</i>	Transcription factor involved in inflammatory immune response, cell growth, and development	Clinical series	Inflammatory bowel disease, rheumatoid arthritis, psoriasis, and multiple sclerosis
<i>RAG</i>	Involved in V(D)J recombination to generate mature T and B cells	Clinical series	Autoimmune hemolytic anemia and neutropenia, vitiligo, vasculitis, autoimmune neuropathy, and myopathy

simple Mendelian inheritance where pathogenesis is linked to a single gene [2]. Even for monogenic diseases, gene expression can be influenced by the internal and external environment (epigenetics) [3]. Most diseases are polygenic, where pathogenesis is influenced by multiple genes. While AA is thought to be primarily polygenic like other autoimmune diseases, there are examples of single genes leading to the disease. Single gene studies highlight the monogenic variants and GWASs analyze hundreds of thousands of genetic variants (single nucleotide variants, SNPs) across many genomes to find those statistically associated with a specific trait or disease. Genome-wide analysis of copy number variants (CNVs) has shown additional contributions to AA.

### Single Gene Studies

Most single genes associated with AA are immune related and involved in CD4+ regulatory T cell (Treg) function, CD8+ T cell effector function and antigen presentation, and

natural killer (NK) cell defense. These genes include forkhead box P3 (*FOXP3*), inducible T cell co-stimulator ligand (*ICOSLG*), MHC class I polypeptide-related sequence A (*MICA*), macrophage migration inhibitory factor (*MIF*), human leukocyte antigens (*HLA*) subtypes, interleukin-7 receptor subunit alpha (*IL7RA*), interleukin 1 receptor antagonist (*IL1RN*), autoimmune regulator (*AIRE*), keratin 82 (*KRT82*), suppressor of cytokine signaling 1 (*SOCS1*), nuclear factor kappa B subunit 1 (*NFKB*), and recombinase activating genes (*RAG*). The majority of these genes have been studied in direct relationship to AA through either serum or lesional skin analysis (see Table 1). We highlight how immune dysregulation is intimately associated with autoimmune disease. Table 1 provides an overview of these genes, their function, and related comorbidities.

#### *Forkhead Box P3*

*FOXP3* encodes for a protein responsible for suppressing Tregs to ensure self-tolerance. AA has been associated with fewer subpopulations of CD39+ Treg

[2]. Specific variants of *FOXP3* (rs2294020-3675) which lead to lower expression and fewer FOXP3+ Tregs have been found in increased frequencies in AA patients compared to controls [4, 5]. Lower expression of *FOXP3* has also been found in other autoimmune disease [2]. [1] Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome is a rare disorder of the immune system caused by pathogenic variants in the *FOXP3* gene resulting in defective development of CD4+CD25+ Tregs (OMIM number 304790). In addition to autoimmune thyroid disease and hemolytic anemia, recurrent infections, and membranous nephropathy, some patients develop AA [15].

#### *Inducible T-Cell Costimulator Ligand*

*ICOSLG* and its ligand are critical for activation, proliferation, differentiation, and cytokine production of T cells and for antibody secretion from B cells during secondary immune responses. Polymorphisms in *ICOSLG* gene (rs378299) have been identified in higher frequency in AA especially in combination with HLA-DQB1\*03 [4, 15]. Immunodeficiency, common variable, 1 CVID1 (OMIM 607594) is an autosomal recessive disorder (AR) with pathogenic gene variants in *ICOS*. CVID is the most common form of primary immunodeficiency and primary antibody deficiency. Severe AA as well as vitiligo has been reported in patients with CVID1 [16].

#### *MHC Class I Polypeptide-Related Sequence A*

*MICA* is an antigen that is induced by oxidative stress, typically on cells from epithelial origin. When expressed, *MICA* stimulates the NKG2D receptor on NK and CD8+ T cells, activating them against the stressed cell [6, 17]. In one small study, there was strongly increased *MICA* expression found in lesioned AA skin [2]. Specific alleles including *MICA*\*009 suggest a protective role [7]. A significant positive correlation between *MICA*\*005.1 and patchy AA and *MICA*\*006 and AA has been reported [18]. GWASs have evaluated the single nucleotide polymorphisms of *MICA* association with AA (discussed below). Autoimmune Polyendocrine Syndrome Type 2 (OMIM 269200) is an autosomal dominant disorder [19]. This syndrome often presents with AA, as well as autoimmune Addison's disease, thyroid disease, and diabetes mellitus. Autoimmune polyendocrine syndrome type 2 related Addison's disease has been associated with the *MICA* 5.1 and *MICB*-CA-25 alleles and combination of the *MICA* 5.1 allele and *DRB1*\*03-*DQA1*\*0501-*DQB1*\*0201 haplotypes may increase risk for Addison disease [20]. *MICA* variants are also reported in type 1 diabetes, ankylosing spondylitis, and Behçet's disease [21–24].

#### *Macrophage Migration Inhibitory Factor*

*MIF* is an immunoregulatory cytokine which inhibits NK cells in immune-privileged areas. There have been conflicting studies about whether it is elevated or decreased in serum and tissue of patients with AA [6]. Several studies have found upregulated *MIF* levels (correlating with severity of disease) in AA serum and lesional skin [8–10]. A lower frequency of the C allele or rs755622 SNP has been found among AA patients in one study but another larger study disputes this [25]. Certain *MIF*173\*C alleles may be a risk factor for early onset AA [26]. *MIF* has also been implicated in systemic juvenile rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and uveitis [27, 28].

#### *HLA Subtypes*

HLAs are protein markers responsible for presenting antigens to T cells and are classified as either subclass I or subclass II. Subclass I molecules are located on all nucleated cells and are encoded by HLA-A, HLA-B, and HLA-C alleles. Subclass II molecules are located on antigen-presenting cells and are encoded by HLA-DP, HLA-DQ, or HLA-DR alleles. HLA subclass II types, *HLA-DQB1*\*0502 allele, *HLA-DQB1*\*0301 allele, and in combination with *HLA-DQB1*\*0301-*HLA-DQB1*\*0303 have been associated with AA [29]. Combined *HLA-DQB1*\*03 alleles are associated with increased disease severity as were *DRB1*\*16 alleles. *HLA-DQB1*\*0603, *DRB1*\*03, *DRB1*\*13, and *DRB1*\*15 were decreased amongst AA patients [30]. GWASs HLA alleles with AA will also be discussed below. HLA haplotypes have been associated with celiac disease, ankylosing spondylitis, psoriatic arthritis, multiple sclerosis, type 1 diabetes mellitus, system lupus erythematosus [30].

#### *Interleukin-7-Receptor Subunit Alpha*

*IL7RA* encodes a receptor on the cell surface of lymphocytes responsible for transducing signals from immune cells. It signals through JAK-STAT signaling and is key for VDJ recombination seen in T and B cells [31–33]. *IL-7* has been shown to play a direct role in mouse models of AA by upregulating cytotoxic T cells. Blocking *IL7RA* in this model led to reduced cytotoxic T cells (not Tregs) in lesional skin [11]. *IL7RA* has also been linked type 1 diabetes, Sjögren's syndrome, rheumatoid arthritis, and multiple sclerosis [11].

#### *Interleukin-1 Receptor Antagonist*

*IL1RN* encodes the interleukin-1 receptor antagonist (*IL-1RA*; *IL-1RA* dampens excessive inflammatory

response) [34]. A polymorphism in *IL1RN*, known as allele 2, has been associated with increased severity of AA [12]. Allele 2 for *IL1RN* is associated with other inflammatory autoimmune diseases including systemic lupus erythematosus, ulcerative colitis, and Crohn's [35].

#### *Autoimmune Regulator*

*AIRE* encodes the autoimmune regulator protein which typically functions to eliminate self-reactive T cells as they mature in the thymus. It is associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. The three main features associated with this disease include recurrent fungal infection by *candida*, adrenal gland insufficiency, and hypoparathyroidism. AA is a common comorbidity condition in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy with 30% of patients developing it [13]. However, not all variants in *AIRE* resulted in the same risk or severity of AA. One study identified 20 variants in a cohort of 202 AA patients and 175 matched controls and found variants at position G961C were associated with a >3 risk factor for alopecia universalis and early disease onset [13].

#### *Keratin 82*

Keratin 82 is a keratin that is specific to the hair shaft. Keratins are proteins that make up the fibrous structure of hair, nails, and outer layer of skin. These proteins can be divided into two classes: type I and type II, of which *KRT82* is classified as. Type II keratins are larger and have been previously associated with other hair-related genetic disorders including ectodermal dysplasia, pseudofolliculitis barbae, and Monilethrix, unlike Type I keratins [14]. *KRT82* is exclusively expressed during the anagen (active growth) phase of the hair follicle life cycle, which is extremely relevant in the context of AA since the autoimmune attack that is evident in active disease flares is also exclusive to the anagen phase [14]. Eight hundred and forty-nine patients with AA and 15,640 controls were analyzed with whole-exome sequencing. In 6% of patients with AA, *KRT82* was identified as an AA risk gene due to damaging variants with notable significance ( $p = 2.18E-7$ ) [14]. A negative correlation between *KRT82* expression and CD8+ infiltrates was also identified.

#### *Suppressor of Cytokine Signaling 1*

*SOCS1* encodes the suppressor of cytokine signaling 1 protein and is a member of the STAT-induced JAK inhibitors. *SOCS1* works to prevent constitutive activation of the JAK-STAT pathway [36]. Clinical phenotype analysis of newly described early onset autoimmunity

with *SOCS1* deficiency shows AA is one autoimmune manifestation and unpublished data (L.C.S.) has identified multiple family members with a *SOCS1* pathogenic variant and AA/universalis as the primary phenotypic manifestation.

#### *Nuclear Factor Kappa B*

*NFKB* is a family of transcription factors that are implicated in inflammatory signaling cascade, immune regulation, and cell proliferation and differentiation [37, 38]. As such, *NFKB* is responsible for the expression of various pro-inflammatory cytokines, chemokines, and adhesion molecules. B-cell deficiency due to *NFKB* is associated with AA. Additionally, *NFKB* signaling has further been implicated in asthma, inflammatory bowel disease, rheumatoid arthritis, psoriasis [39].

#### *Recombinase Activating Genes*

Recombinase activating genes (RAG), such as *RAG1* and *RAG2*, are responsible for V(D)J recombination, which determines T- and B-cell antigen receptor diversity [40]. Mutations or deficiencies in *RAG1* or *RAG2* have serious immune effects, including leading to the development of severe combined immunodeficiency disorders (SCID) and Omenn syndrome (OMIM:603554). SCID can often present with lymphocytopenia or absent immunoglobulins, T-cell proliferation and function defects, and thymic dysfunction. Clinically AA can be part of both SCID and Omenn syndromes.

### **Alopecia Genome Wide-Association Studies**

Two GWASs have identified risk variants in genetic loci in AA. The first (2010) included 1,054 North American patients and 3,278 controls [41]. Results yielded 139 SNPs spread across eight loci which included cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*), interleukin-2 receptor alpha (*IL2RA*), zinc finger protein Eos (*IKZF4*), UL16 binding protein 3/6 (*ULBP3/ULBP6*), interleukin-2/21 (*IL-2/IL-21*), *HLA* subtypesyntaxin 17 (*STX17*), and peroxiredoxin 5 (*PRDX5*) [41]. A follow-up study (2012) included 1,702 Central European patients and 1,723 controls confirmed 5 and tested 12 additional ones [42]. [3] The identified susceptibility loci were subdivided into those pertaining to the immune system, those pertaining to the hair follicle, and "other." The eight genes to be discussed next are the ones found to have the strongest association with AA.

Analyses of copy number variants (CNVs), the number of copies of a given gene an individual possesses, have also been included in GWAS [43]. A study including 16,984 AA patients and controls showed that fourteen genes had varied expression due to CNVs [43].

#### *Immune System Related Genes*

It is not a surprise that most of the susceptible loci identified in the first AA GWAS are genes that play a role in leukocyte activity.

#### *Cytotoxic T-Lymphocyte-Associated Protein 4*

*CTLA-4* encodes cytotoxic T-lymphocyte-associated protein 4 which is highly expressed in Tregs, a subpopulation of T cells that suppress the immune response and reduce inflammation and allow tissue to remain self-tolerant [44]. In the GWAS, *CTLA4* was observed with the highest correlation with AA [41]. This is not surprising to those who care for with monogenic disease from *CTLA4* deficiency which is marked by autoimmune disease (type-1 diabetes, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus and AA), respiratory infections, and intestinal diseases [45].

#### *Interleukin-2 Receptor Subunit Alpha*

*IL2RA* is a protein receptor present on T cells and B cells. Tregs constitutively express *IL2RA*, and therefore *IL2RA* plays a key role in T cell regulation and preventing autoimmunity by immune tolerance. The 10p15.1 region of this gene was found to have the strongest association with AA [41]. Similar to *CTLA-4*, this gene is also implicated in autoimmune disease, including type-1 diabetes, multiple sclerosis, and Guillain-Barré syndrome [41].

#### *Zinc Finger Protein Eos*

*IKZF4* is the gene that encodes the zinc finger protein Eos, which is a transcription factor expressed in Tregs. Eos Knock out mice exhibited decreased Treg function and develops autoimmune disease [46]. The 12q13 region on the *IKZF4* gene has been the most strongly associated with AA [41]. The follow-up GWAS also confirmed this association [42].

#### *UL16 Binding Protein 3/6*

The family of *ULBP* genes encodes six distinct proteins and is the ligands which bind to NKG2D receptors of NK cells. Ligand binding to NKG2D triggers cytotoxic mediated effects including cytokine secretion and targeted cell death through cytotoxic granule release. It had been previously found that

the two classes of NKG2D ligands (*MICA/B* and *ULBP1-6*) both have varying degree of polymorphisms which is associated with a higher risk of autoimmunity and *ULBP6* was found to be the most polymorphic [47]. In both GWASs, *ULBP6* gene was found to have an extremely strong association with AA [41, 42]. *ULBP3* was also found to have a strong association with AA [41, 42]. Among all the loci studied in the European GWAS, the strongest association was in the *ULBP* genes [42].

#### *Interleukin-2/21*

*IL2/21* encodes protein interleukin-2/21, which binds to IL-2 receptors on lymphocytes. *IL-2* is involved in the body's ability to recognize self from non-self. Therefore, it is not a surprise that both GWASs found this gene to be another SNP target that has an association with AA [41, 42]. It is also found in GWASs of type 1 diabetes, rheumatoid arthritis, Crohn disease [41].

#### *HLA Subtypes*

*HLA* encodes HLA proteins present on leukocytes and recognized by T-cells to help distinguish between self from non-self. The North American GWAS identified correlation between *HLA-DRA*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB2*, and AA [41]. The European GWAS did not further confirm the HLA findings due to initial GWAS producing convincing and definitive results.

#### *Hair Related Genes*

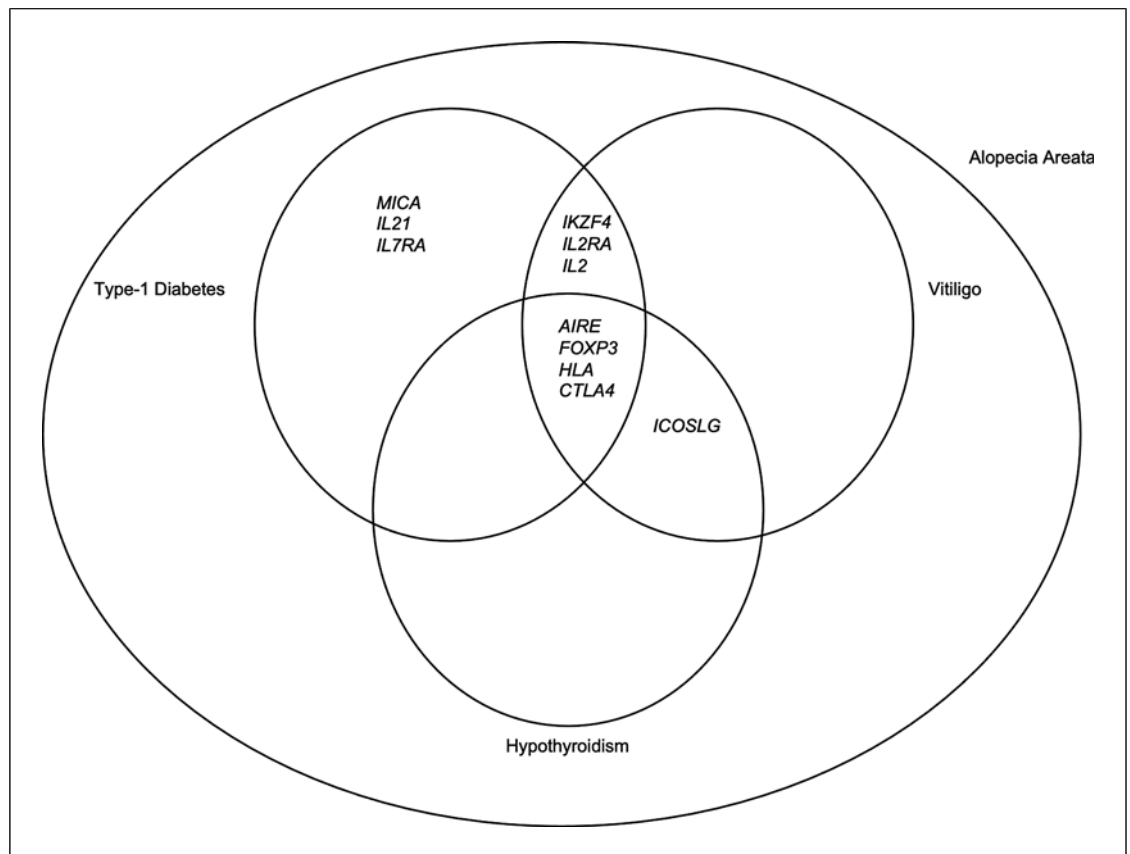
##### *Syntaxin 17*

*STX17* has high correlation with AA in the GWASs. It is expressed within the hair follicle itself, and it had been previously found to cause graying of hair/mane in horses [48]. AA appears to preferentially attack pigmented hair, and one study found that it preferentially attacks dark hair [49]. Whole genome sequencing in 849 AA patients and 15,640 controls identified *KRT82* as an associated gene, with 51 of the AA patients who were heterozygous exhibiting damaging variants for this gene [14]. *KRT82* encodes a keratin protein that is exclusively expressed in the hair shaft during anagen. In AA, hair follicles experience attack in this phase of hair growth, and patients are found to have decreased *KRT82* expression [14].

##### *Other*

##### *Peroxiredoxin 5*

*PRDX5* encodes an antioxidant enzyme which was found to have a high correlation with AA in GWASs. Overexpression of *PRDX5* reduces cell death from toxic



**Fig. 1.** This diagram depicts an overview of the overlap of genes implicated in the pathogenesis of alopecia areata, type-1 diabetes, vitiligo, and hypothyroidism.

**Table 2.** Genes in which polymorphisms have been most strongly associated with AA from GWAS [41, 42]

Gene	Function	Implication in other autoimmune conditions
<i>CTLA4</i>	T-reg activation	Type-1 diabetes, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus
<i>IL-2RA</i>	Immune tolerance/T-cell proliferation/differentiation	Type-1 diabetes, multiple sclerosis, Guillain-Barré syndrome
<i>Eos (IKZF4)</i>	T-reg regulation	Type-1 diabetes, systemic lupus erythematosus
<i>ULBP6/ULBP3</i>	NK cell activation	Only found in alopecia areata
<i>IL2/IL21</i>	Self-tolerance	Type-1 diabetes, rheumatoid arthritis, Crohn's disease, psoriasis
<i>HLA</i>	Antigen presentation	Type-1 diabetes, rheumatoid arthritis, celiac disease, multiple sclerosis
<i>STX17</i>	Hair pigmentation	Only found in alopecia areata
<i>PRDX5</i>	Antioxidant defense	Multiple sclerosis

peroxide and under expression renders cells susceptible to oxidative damage [50]. Lipid peroxidation occurs when toxic oxidants degrade lipids such as those present in cell membranes. Lipid peroxides release a

break-down product known as malondialdehyde (MDA), and patients with AA have been shown to have higher serum levels of MDA than controls and levels increase with disease length and severity [51].

## Conclusion

Single gene and GWASs show that largely immune genes have been correlated with AA like what has been observed in other autoimmune diseases (Fig. 1). Many of these genes have also been implicated in innate errors of immunity where AA is often part of the phenotype. This suggests we may learn more about pathogenesis of AA and potential new targets for therapeutics from these monogenic diseases (Tables 1, 2). Additional genes identified in hair specific genes and oxidative stress-related genes may provide alternative targets for patients who do not respond to immune mediated therapies. These types of targets may also be considered in the future for combination therapy or maintenance therapy.

## Conflict of Interest Statement

B.P. and H.E. have no conflicts of interest to declare. L.C.S. has in the past received Honorarium and grant from

Pfizer (relationship has ended); Medical Advisory Board for the National Alopecia Areata Foundation (volunteer position).

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## Author Contributions

B.P., H.E., and L.C.S. made substantial contributions to concept of the work, all provided final approval of version to be published, and drafted the work. L.C.S. revised it critically for important intellectual content and agreed to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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