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Review

Non-Coding Genetic Variation and Long Non-Coding RNA Dysregulation in Vitiligo: Genetic Associations and Functional Evidence

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Abstract

Vitiligo is an immune-mediated depigmenting disorder involving genetic susceptibility, melanocyte stress, and immune dysregulation. Although genome-wide association studies (GWAS) have identified numerous susceptibility loci, the functional consequences of non-coding genetic variants remain incompletely understood. Long non-coding RNAs (lncRNAs) regulate gene expression and may contribute to biological pathways implicated in vitiligo. This narrative review critically evaluates genetic associations, transcriptomic findings, and functional evidence concerning the potential involvement of lncRNAs in vitiligo pathogenesis. We examine susceptibility signals at chromosome 11q21 (rs4409785), the BCL2L11–MIR4435-2HG locus (rs4308124), and PVT1. Among these, only PVT1 has been independently confirmed in a subsequent study, whereas rs4409785 and rs4308124 were supported by replication cohorts within their original GWAS investigations. Notably, functional evidence at 11q21 implicates SESN3 regulation in $CD4^+$ T cells rather than an established lncRNA-mediated mechanism. We also discuss the roles of MALAT1, TUG1, and LOC100506314 in keratinocyte stress responses, melanocyte survival, and inflammatory signaling, alongside H19 expression in skin-derived exosomes. Although these studies support the biological relevance of specific lncRNAs, their findings vary across experimental models and biological compartments, and direct genotype–lncRNA–phenotype relationships remain unestablished. Furthermore, the clinical utility of circulating lncRNAs as biomarkers of disease activity, progression, or treatment response has not been validated. Integrating genetic fine-mapping, cell-specific transcriptomic analyses, expression quantitative trait loci, and functional perturbation studies will be essential to clarify the contribution of lncRNAs to vitiligo susceptibility and establish their potential clinical relevance.

Keywords: vitiligo; lncRNA; autoimmunity; genome-wide association study; expression quantitative trait loci

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1. Introduction

Vitiligo is an acquired depigmenting disorder characterized by well-defined white macules resulting from the loss of epidermal melanocytes [1,2]. A recent systematic review and meta-analysis estimated its global prevalence at 0.40%, although substantial geographical and methodological differences were observed across studies [3].

The current international consensus classifies vitiligo as non-segmental, segmental, mixed or unclassified vitiligo [4]. Although its pathogenesis involves genetic susceptibility [5], oxidative stress, and environmental factors, substantial evidence supports an autoimmune component, particularly in non-segmental vitiligo [6–9]. Melanocyte-reactive $CD8^+$ T cells contribute to melanocyte destruction, while interferon-γ (IFN-γ) signaling promotes the production of CXCL9 and CXCL10, facilitating the recruitment of cytotoxic T cells into affected skin [2,10,11].

Family studies and genome-wide association studies (GWAS) have identified susceptibility loci involved in antigen presentation, immune regulation, and melanocyte biology, supporting the interaction between inherited susceptibility and immune-mediated melanocyte injury [5–8,12]. These studies have also highlighted complex interactions between genetic and environmental factors in the development and progression of vitiligo [6–8,12].

Vitiligo GWAS have identified numerous susceptibility loci, many of which contain variants outside protein-coding exons [6,8,13]. These findings suggest that inherited susceptibility may involve changes in gene regulation, including effects on promoters, enhancers, and non-coding RNA-associated pathways [14].

Long non-coding RNAs (lncRNAs) are conventionally defined as RNA transcripts longer than 200 nucleotides without an established protein-coding function [15,16]. Based on their genomic position and orientation relative to protein-coding genes, lncRNAs are commonly classified as long intergenic non-coding RNAs (lincRNAs), antisense transcripts, sense-overlapping transcripts, or intronic transcripts [16,17]. In the nucleus, lncRNAs interact with protein complexes to modulate epigenetic regulation, phase separation, compartment formation, and nuclear organization [18]. Notably, lncRNAs have also been reported as modulators of immune cell function and of immune-related gene expression [19,20], and various lncRNAs have been implicated in the regulation of melanogenesis and in vitiligo-related expression changes [21,22].

LncRNAs can harbor disease-associated variants [14,23,24]. Single nucleotide polymorphisms (SNPs) within lncRNA sequences may alter lncRNA expression levels or functional properties, and these variants have been associated with increased risk of various complex diseases such as cancer and vitiligo [25]. GWAS analyses in vitiligo have identified several susceptibility variants within or near genomic regions containing annotated lncRNAs, although their effects on the corresponding transcripts remain incompletely understood [8,12,26].

This review aims to evaluate the evidence linking vitiligo-associated non-coding genetic variants to lncRNA loci, distinguishing genetic associations from experimentally demonstrated effects on lncRNA expression or function. We also examine the potential contributions of dysregulated lncRNAs to melanocyte survival, epidermal stress responses, and immune regulation, considering the strength and limitations of the available evidence. Finally, we consider, although limited based on current evidence, the applicability of lncRNAs as potential circulating biomarkers and identify the research strategies needed to establish genotype–lncRNA–phenotype relationships and determine their clinical relevance.

2. Methodology

The literature for this narrative review was identified through searches of PubMed, ScienceDirect, Scopus and Web of Science. The search terms were ("vitiligo") AND ("long non-coding RNA" OR "lncRNA" OR "non-coding RNA") and ("vitiligo") AND ("genome-wide association" OR "GWAS" OR "susceptibility locus"). Specific transcripts identified in the initial results (MALAT1, TUG1, H19, PVT1 and LOC100506314) were then searched individually. English-language articles from the past decade were prioritized; older studies were retained when they contributed essential evidence, such as the original GWAS reports.

Studies were selected when they addressed lncRNAs in the context of vitiligo through genetic association, expression, or functional data. The search was conducted between 10 May and 15 November 2026.

Genomic positions and transcript annotations were evaluated using the GRCh38.p14 human reference assembly and GENCODE release 50 (Ensembl release 116). Variants were included in this analysis when they had reached genome-wide significance for vitiligo in at least one published GWAS and a lncRNA had been reported at the lead signal in the vitiligo literature. The presence of annotated long non-coding RNA genes at or near the selected vitiligo susceptibility variants was examined using the corresponding genomic coordinates. Publicly available cis-expression quantitative trait locus (cis-eQTL) associations were retrieved from the Genotype-Tissue Expression (GTEx) Portal (https://gtexportal.org/, accessed on 7 September 2026), using analysis release V10 (INSERT CITATION [27]). All tissues were queried for both cis-eQTL and cis-sQTL associations, and, for each variant, the most significant association (lowest nominal *p*-value) among the variant–gene pairs reported as significant by GTEx was recorded, together with the target gene, QTL type, tissue, effect allele, normalized effect size (NES), and nominal *p*-value. These associations were interpreted as evidence of genetic regulation of transcript abundance rather than proof of a causal molecular mechanism, because eQTL associations may reflect linkage disequilibrium with other variants and no colocalization analysis was performed.

Two types of quantitative trait loci (QTL) are particularly useful for linking non-coding variants to their molecular targets. An expression QTL (eQTL) is a variant associated with the abundance of a transcript, whereas a splicing QTL (sQTL) is associated with the relative use of a specific intron, and therefore with transcript structure rather than overall quantity. For lncRNAs, the distinction is relevant because a variant may alter which isoforms are produced, and thus their interactions with proteins or miRNAs, without changing total expression. Both types of association are statistical: they indicate that a variant, or a variant in linkage disequilibrium with it, influences the transcript in a given tissue, but they do not identify the causal variant or demonstrate a functional effect.

For each locus, the genetic evidence was graded as follows: (A) genome-wide significant association confirmed in an independent study; (B) genome-wide significant association supported by a replication stage within the discovery study; (C) experimental evidence linking the risk variant to a target gene; and (D) experimental evidence that the risk variant alters the expression or function of the lncRNA itself.

3. Genetic Architecture of Vitiligo: Why Non-Coding Variants Matter

Vitiligo has long been recognizable by its irregular depigmentation phenotype, but it was not until 1950 that the condition began to be linked to autoimmune inheritance in multiplex families, as described by Stüttgen [28]. Since then, the field of genetics has evolved, and with it, our understanding of this disease, first by associating it with class I and class II HLA serotypes and eventually leading to whole-genome studies [29,30]. European GWAS have been the most informative, identifying more than 50 susceptibility loci spanning melanocyte function, cellular apoptosis, and immune regulatory gene expression [29,31].

In addition to protein-coding loci, non-coding regions have been identified that contribute to the pathogenesis of vitiligo through complex transcriptional and post-transcriptional mechanisms [32]. Among these, reduced serum levels of the lncRNA TUG1 have been reported together with lower tissue PPAR-γ and higher tissue IL-17, although a causal relationship has not been shown [33]. MiRNAs, including miR-23a, which is down-regulated in vitiligo and associated with apoptotic gene regulation, have been studied in plasma, serum, and blood cells [34,35]. Circular RNAs (circRNAs) also show enrichment

in pathways related to ubiquitin-mediated proteolysis, endocytosis, RNA degradation, and JAK-STAT signaling [36].

Genome-wide association studies have shown that many disease-associated variants occur outside protein-coding regions, suggesting an important contribution of regulatory genetic variation to complex disease susceptibility [37,38]. Findings from vitiligo studies support this interpretation. Jin et al. reported that approximately 58% of vitiligo susceptibility loci were located within or near transcriptional regulatory elements, whereas only 15% were in coding variants [7,8,12]. Functional evidence also supports the importance of regulatory variation in vitiligo. Hayashi et al. identified a susceptibility-associated regulatory haplotype near HLA-A that increased HLA-A transcription, providing an example of how non-coding genetic variation may influence antigen presentation and autoimmune recognition of melanocytes [30]. These findings illustrate how non-coding genetic variation can influence vitiligo susceptibility through altered gene regulation. However, a methodological constraint in GWAS is that variants must meet strict statistical significance thresholds, which may exclude biologically relevant variants with sub-threshold associations and regulatory annotation alone does not establish the causal variant or its molecular target [39].

Transcriptomic studies have further illustrated the complexity of lncRNA regulation in vitiligo. Pang et al. identified differentially expressed lncRNAs in vitiligo lesions and constructed co-expression networks involving genes associated with melanogenesis [21]. The study found that 50.8% of lncRNAs dysregulated in vitiligo had sense overlap with protein-coding genes and 36.2% were intronic lncRNAs [21]. These findings suggest potential regulatory relationships; however, co-expression alone does not establish direct molecular interactions. This structural complexity generates transcriptional interference that can mask GWAS signals and complicate the attribution of variants to specific regulatory targets [40].

4. Biological Basis: How Genetic Variants Can Affect lncRNA Function

Non-coding genetic variants may influence disease susceptibility through several regulatory mechanisms. Variants within promoters, enhancers, or other regulatory elements can alter transcription factor binding, chromatin accessibility, or interactions between regulatory regions and their target genes, thereby modifying gene expression [14,30]. Sequence changes within transcribed regions could potentially alter lncRNA structure or interactions with proteins, miRNAs, and other regulatory molecules [41–43].

LncRNAs regulate gene expression through transcriptional, post-transcriptional, translational, post-translational, and epigenetic mechanisms, influencing chromatin organization, cell-cycle regulation, and differentiation [10,16,17,36,44–48]. They can interact with chromatin-associated proteins, DNA methyltransferases, histone-modifying complexes, and transcription factors to modulate gene expression [16,17,49–51]. At the post-transcriptional level, lncRNAs influence mRNA processing, stability, and translation, and may act as competing endogenous RNAs by modulating miRNA availability [17,52–54]. In vitiligo, lncRNA dysregulation has been reported in skin and immune-cell compartments, while genome-wide association studies have identified non-coding susceptibility variants [10,36]. However, direct functional relationships between these findings remain largely unresolved.

LncRNAs may be associated with vitiligo because these molecules can participate in pathways involved in melanocyte survival, oxidative stress, immune activation, antigen presentation, $CD8^+$ T-cell migration, and inflammatory signaling [40,55,56]. For example, reported lncRNA–microRNA–mRNA axes such as TUG1–miR-375–GATA3 and MALAT1–miR-211-SIRT1 suggest that lncRNAs may influence immune regulation, melanocyte survival and keratinocyte stress responses [57,58]. Although these examples

do not yet establish direct genetic regulation by specific variants, they may suggest how lncRNA dysregulation may contribute to vitiligo.

An important feature of lncRNAs is their tissue- and cell-type-specific expression [59,60]. Therefore, the functional effect of a genetic variant on a lncRNA may only be detectable in disease-relevant compartments such as melanocytes, keratinocytes, lesional epidermis, $CD8^+$ T cells, regulatory T cells, peripheral blood mononuclear cells, or extracellular vesicles [24,61]. This context specificity may partly explain why many non-coding vitiligo-associated variants remain functionally unresolved (Figure 1).

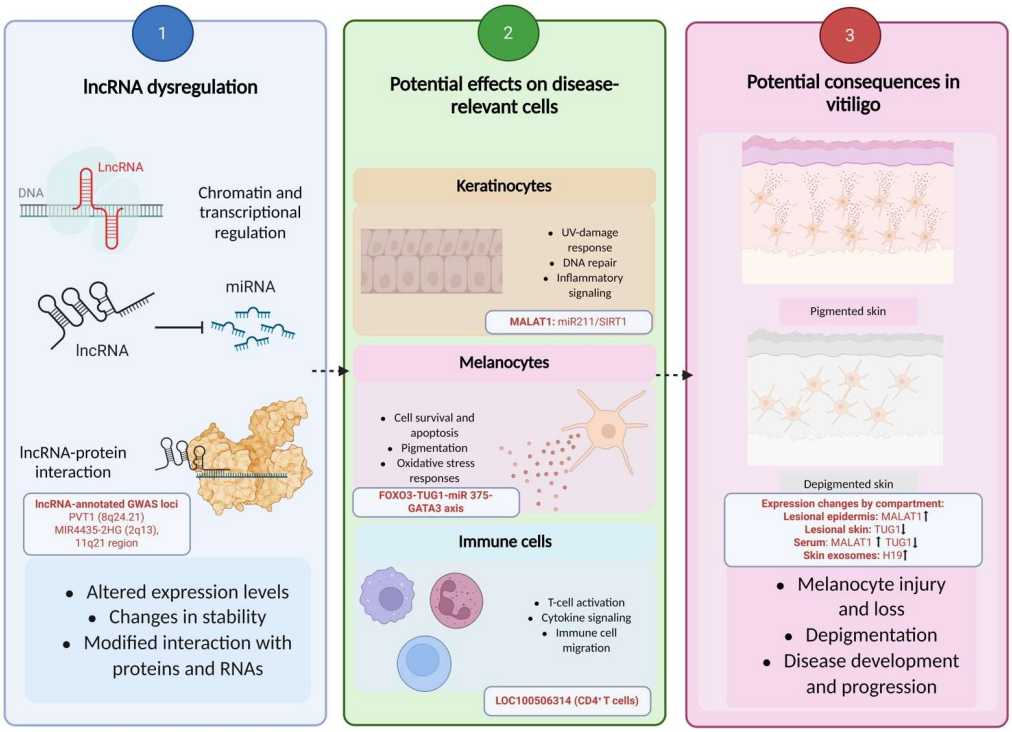

Figure 1. Genetic associations and potential regulatory roles of long non-coding RNAs in vitiligo pathogenesis. The figure summarizes three complementary aspects of current evidence: genetic associations at loci with reported long non-coding RNA (lncRNA) annotations, experimentally investigated lncRNA functions in disease-relevant cells, and their potential implications for vitiligo pathogenesis. Genetic associations involving PVT1, MIR4435-2HG, and the 11q21 region overlapping two annotated lncRNA genes (ENSG00000306211 and ENSG00000285842), previously associated with LNCRNA-IUR through genomic annotation, have been reported [62]. However, the effects of these susceptibility variants on the corresponding lncRNA transcripts remain unconfirmed [8,12,26,62,63]. Functional studies have investigated MALAT1-mediated protection against ultraviolet B-induced DNA damage in keratinocytes through the miR-211/SIRT1 axis [57]; TUG1-mediated melanocyte survival through the FOXO3–TUG1–miR-375–GATA3 axis [58]; and LOC100506314-associated regulation of inflammatory signaling in $CD4^+$ T cells through interactions with STAT3 and MIF [64]. Altered expression of MALAT1 and TUG1 has been reported in serum, whereas H19 has been investigated in skin-derived exosomes [33,65,66]. MALAT1 has also been reported to be increased in lesional epidermis [36,57,67], and TUG1 decreased in lesional skin [68]. These findings may be relevant to cellular stress responses, immune regulation, and melanocyte survival; however, the proposed relationships with disease development and progression remain incompletely established. Dashed arrows represent hypothetical connections rather than demonstrated causal pathways, and no direct genotype–lncRNA–phenotype relationship has been established for the susceptibility loci presented. Created in BioRender. Cadena-Ullauri, S. (2026) https://BioRender.com/vrtpw5o.

Thus, these findings suggest that lncRNAs may contribute to the regulatory networks involved in vitiligo, although their relationship with inherited susceptibility variants re-

mains incompletely understood. Variants within lncRNA loci or associated regulatory elements may influence transcription, RNA processing, transcript stability, or molecular interactions. However, their functional consequences must be distinguished from regulatory effects mediated by the underlying DNA sequence or nearby protein-coding genes. Establishing a lncRNA-mediated mechanism therefore requires evidence linking the genetic variant to altered transcript expression or function and, subsequently, to a disease-relevant cellular phenotype.

5. Evidence Linking LncRNA-Associated Variants and LncRNAs Dysregulation to Vitiligo

The evidence linking genetic variants, lncRNAs, and vitiligo is still emerging [5,7,8,32,40]. Multiple GWAS indicate that the strongest vitiligo-associated SNPs are located primarily within the Major Histocompatibility Complex (MHC) on chromosome 6p21, followed by non-MHC immunoregulatory and melanocyte-specific loci [7,32,69]. In addition, several vitiligo-associated SNPs and susceptibility loci are located within, or closely linked to, annotated lncRNA regions, including lncRNA-IUR, MIR4435-2HG/LINC00978, PVT1, and other poorly characterized non-coding loci [8,62]. In parallel, transcriptomic studies have reported dysregulated lncRNAs in serum, epidermal lesions, peripheral blood mononuclear cells (PBMCs), and immune-cell subsets from patients with vitiligo [7,36]. However, studies connecting specific genetic variants to vitiligo-associated lncRNAs remain lacking [7,8,70]. Therefore, most variant–lncRNA relationships in vitiligo should currently be interpreted as candidate regulatory mechanisms rather than established causal pathways.

The MHC region contains the most statistically significant genetic associations with vitiligo and remains central to disease biology because of its role in antigen presentation and immune-mediated melanocyte destruction [7,8,69]. Among the strongest reported MHC signals, rs9271597 in the HLA-DRB1–DQA1 region has shown a highly significant association in European-ancestry populations, with a reported p-value of 3.15×10^{-89} [8]. Another major signal, rs60131261 in HLA-A, represents a strong MHC class I association, with a reported p-value of 1.56×10^{-66} [8]. In East Asian populations, rs11966200 and rs9468925 in the HLA-C/HLA-B region have been identified as independent association signals, with reported p-values of 1.48×10^{-48} and 2.21×10^{-33}, respectively [5,7]. However, differences in allele frequencies and linkage disequilibrium patterns should be considered when interpreting their relevance across populations.

rs11966200 has been replicated across Asian and European cohorts, whereas rs9468925 has also been associated with psoriasis, suggesting partially shared immune-genetic mechanisms between inflammatory skin diseases [5,7]. Although these variants are usually interpreted through HLA-mediated antigen presentation, the MHC region is also enriched in regulatory elements and non-coding transcription, making it a relevant region for lncRNA-focused reannotation [5,7,71].

Outside the MHC, highly replicated non-HLA loci define additional pathways in which lncRNAs may act as downstream regulators or context-dependent modulators. TYR variants, including rs1126809 and rs1393350, are major melanocyte-related susceptibility alleles [7,8,62,69]. The rs1126809 variant, which encodes the Arg402Gln substitution, has been consistently associated with vitiligo in European populations, with a reported p-value of 1.16×10^{-43} [7]. Moreover, *MC1R* rs4268748, associated with normal pigmentary variation, has also shown strong association with vitiligo, with a reported p-value of 2.88×10^{-33} [8]. Other replicated non-MHC signals include rs13076312 in *LPP*, rs229527 in *C1QTNF6*, rs2017445 in *IKZF4*, rs12482904 in *UBASH3A*, and rs706779 in *IL2RA*, with reported p-values ranging from 10^{-27} to 10^{-31} [5,7,8,72]. Additional replicated variants, including rs2111485 near IFIH1, rs2476601 in PTPN22, rs2247314 in CCR6, and rs8192917

in GZMB, further support the involvement of innate immunity, T-cell receptor signaling, immune-cell trafficking, cytotoxicity, and melanocyte apoptosis [5,7,8,72]. Although most of these variants are not currently annotated as lncRNA variants, they define biological pathways in which lncRNAs may mediate, amplify, or reflect genetic risk [59–61].

Among vitiligo-associated variants, rs4409785 is one example of a GWAS signal with direct lncRNA annotation [5,7,62,63]. The rs4409785 variant maps to chromosome 11q21 and has previously been annotated as intronic to LNCRNA-IUR [62]. However, examination of GENCODE release 50 (GRCh38.p14) Basic transcript annotations indicates that rs4409785 does not overlap the annotated LNCRNA-IUR transcripts. Instead, the variant overlaps transcripts belonging to two other annotated lncRNA genes, ENSG00000306211 and ENSG00000285842 [73]. Furthermore, the experimentally characterized regulatory mechanism at this locus implicates SESN3 expression in $CD4^+$ T cells rather than a demonstrated lncRNA-mediated effect [63]. In European populations, rs4409785-C reached genome-wide significance in a meta-analysis of two GWAS combined with a replication cohort of 1377 cases and 1284 controls (replication $p = 1.58 \times 10^{-4}$; combined $p = 1.57 \times 10^{-13}$; odds ratio, 1.34) [7,8,12]. rs4409785 appears to be a pleiotropic risk variant, having also been associated with rheumatoid arthritis, multiple sclerosis, and autoimmune thyroid disease, which supports its potential relevance to shared autoimmune regulatory mechanisms [63,74–77].

Recent functional studies have provided further insight into this locus. Hamley et al. demonstrated that the rs4409785 risk allele creates a CTCF-binding site that restricts interactions between a T-cell-specific super-enhancer and the SESN3 promoter, resulting in reduced SESN3 expression in $CD4^+$ T cells [63]. SESN3 restrains mTORC1 signaling, which provides a potential protein-coding mechanism for the shared autoimmune risk at this locus [63]. Thus, the only experimentally characterized mechanism at 11q21 implicates SESN3 in T cells, not a lncRNA. Direct evidence showing that rs4409785 alters lncRNA-IUR expression, processing, stability, or molecular interactions in vitiligo has not been reported. Therefore, rs4409785 should be considered a potential candidate for functional validation rather than a confirmed causal lncRNA-regulatory variant. In GTEx V10, the most significant association of rs4409785 was with ENSG00000306211: the risk allele C was associated with higher ENSG00000306211 expression in whole blood (NES = 0.44; $p = 8.7 \times 10^{-18}$).

The rs4308124 variant represents another vitiligo-associated signal within a genomic region containing both protein-coding and non-coding genes [8,12]. Jin et al. (2016) identified this variant at the BCL2L11–MIR4435-2HG locus on chromosome 2q13, reporting genome-wide significance in the combined analysis of three GWAS and a replication cohort ($p = 3.96 \times 10^{-9}$; OR = 1.15, 95% CI: 1.10–1.21) [8]. MIR4435-2HG, also known as LINC00978, is an annotated lncRNA, whereas BCL2L11 encodes a protein involved in the regulation of apoptosis. Although the association provides genetic evidence implicating this region in vitiligo susceptibility, the genetic association does not establish whether the relevant regulatory effects involve BCL2L11, MIR4435-2HG, or another target within the region [8]. BCL2L11 encodes BIM, a pro-apoptotic BH3-only protein required for the deletion of autoreactive lymphocytes, and Bim-deficient mice develop lymphoid hyperplasia and autoimmune disease [78]. Altered BIM-dependent apoptosis of autoreactive T cells, or of stressed melanocytes, therefore offers a protein-coding rationale for this signal. For a lncRNA-mediated effect to be inferred, MIR4435-2HG would need to be shown to regulate BCL2L11 in *cis*, or to have an independent function in disease-relevant cells. To our knowledge, no study has linked rs4308124 genotype to the expression of either transcript in melanocytes or T cells. In GTEx V10, the risk allele C was most significantly associated with the expression of the pseudogene ENSG00000227992 in cultured fibroblasts (NES = −0.32; $p = 2.9 \times 10^{-16}$).

The PVT1 locus on chromosome 8q24.21 provides further evidence of an association between genetic variation in a lncRNA-containing region and vitiligo susceptibility [8,62]. In a GWAS meta-analysis involving individuals of European ancestry, Jin et al. identified two variants within PVT1 that reached genome-wide significance: rs10087240 ($p = 7.74 \times 10^{-9}$; OR = 1.18) and rs4733823 ($p = 3.04 \times 10^{-8}$; OR = 1.17) [8]; however, these variants could not be genotyped in the replication stage, limiting the available evidence of its role in vitiligo risk. Ben et al. subsequently confirmed the association in an independent European-ancestry cohort, providing stronger evidence that PVT1 could be a vitiligo susceptibility locus [26]. PVT1 has been strongly correlated with MYC, which lies immediately upstream of PVT1. In cancer cells, PVT1 transcripts stabilize MYC protein [79], whereas the PVT1 promoter competes with the MYC promoter for shared enhancers, so that DNA elements within the locus can regulate MYC independently of the PVT1 RNA [80]. Therefore, a vitiligo risk variant in PVT1 could act through either the PVT1 transcript, MYC, or via independent enhancer elements; however, none of these hypotheses has been tested in melanocytes, keratinocytes, or immune cells, making the underlying molecular mechanism unclear. GTEx V10 identified cis-sQTL associations between rs10087240 and rs4733823 and PVT1 in cultured fibroblasts, suggesting genotype-associated variation in PVT1 splicing. However, these associations do not establish that the variants are causal or that altered PVT1 splicing mediates vitiligo susceptibility. The most significant association was in cultured fibroblast (sQTL; NES = 0.40; $p = 3.4 \times 10^{-13}$ for rs10087240 and NES = 0.39; $p = 1.2 \times 10^{-12}$ for rs4733823).

Other non-coding susceptibility signals illustrate the challenges of assigning functional targets to GWAS variants. At chromosome 22q13.2, rs4822024 is located between ZC3H7B and TEF and has been associated with vitiligo susceptibility in European and Chinese Han populations [12,81]. An association between rs4822024 and TEF expression in blood has also been reported, suggesting a potential regulatory mechanism that remains to be functionally validated [81]. Separately, the lncRNA locus LOC101060498 at chromosome 4p14 reached genome-wide significance in the discovery analysis of Jin et al. but failed independent replication [8]. Therefore, neither locus currently provides evidence of an established lncRNA-mediated mechanism in vitiligo.

Several intergenic vitiligo-associated variants may also represent candidate lncRNA-regulatory loci. These include rs2111485 near *IFIH1*, rs59374417 near *CD80*, rs16872571 near *CLNK*, rs7758128 in the C6orf10/BTNL2 region, and rs638893 near CXCR5/DDX6 [7,8,70]. These variants have not yet been definitively linked to specific lncRNAs in vitiligo, but their genomic context supports regulatory reannotation, particularly because several vitiligo GWAS loci are intergenic or located near immune-regulatory regions [7,8]. Intergenic variants may overlap annotated or unannotated lncRNAs, enhancer-associated transcripts, chromatin accessibility peaks, expression quantitative trait loci, or methylation quantitative trait loci; therefore, assigning them exclusively to the nearest protein-coding gene may be insufficient [82]. In immune loci, this is highly relevant because regulatory effects may be cell-type-specific and detectable only in disease-relevant compartments such as activated T cells, PBMCs, melanocytes, keratinocytes, or lesional skin [7,8,62,70].

From a potential pathogenic perspective, these loci fall into two groups. In melanocytes, TYR variants (rs1126809 and rs1393350) and MC1R rs4268748 may converge with lncRNA-mediated pathways involved in pigmentation, antigenicity, DNA damage adaptation, stress responses, and cell survival [5,7,8,83,84]. In immune cells, variants in the MHC region, PTPN22, IL2RA, IFIH1, CCR6, UBASH3A, GZMB, IKZF4, and related loci may intersect with lncRNAs involved in antigen presentation, interferon signaling, T-cell activation, cytotoxicity, immune-cell trafficking, and inflammatory regulation [7,8,70,85]. However, a

direct regulatory relationship between these genetic variants and lncRNA expression or function has not yet been demonstrated.

Additional lncRNA-linked loci, including MIR4435-2HG/LINC00978, PVT1, and LOC101060498, broaden this framework by suggesting that non-coding RNA regulation may extend beyond pigmentation genes and involve immune and apoptotic pathways [7,8,77,82,86].

The level of replication differs among the lncRNA-containing loci. rs4409785 and rs4308124 reached genome-wide significance in analyses that combined discovery GWAS with replication cohorts recruited within the same studies [8,12], whereas the PVT1 signal, which could not be tested in the original replication stage, was later confirmed in a separate study [8,26]. Nevertheless, these studies were performed on European cohorts, and their results cannot be directly extrapolated to other populations, while susceptibility loci involving MHC, LPP, CCR6, IL2RA, IKZF4, and C1QTNF6 have also been reported in East Asian populations [5,7,70]. However, differences in associated variants and effect sizes, together with the identification of additional susceptibility variants in Chinese Han populations [6], highlight the influence of genetic ancestry and the need for cross-population validation, particularly for loci associated with lncRNAs. Table 1 summarizes selected vitiligo susceptibility loci, including their genetic association statistics, reported lncRNA annotations, candidate protein-coding targets, and levels of supporting evidence. Table 2 summarizes the most significant cis-QTL associations for each lead variant in GTEx (V10), including the effect allele, target gene, QTL type, associated tissue, normalized effect size (NES), and nominal *p*-value.

Table 1. Vitiligo susceptibility loci with an annotated lncRNA at or near the lead signal.

Locus	Lead SNP (GRCh38 Position)	lncRNA Gene Overlapping the SNP	Candidate Protein-Coding Gene	Risk Allele	Ancestry; Study Design	OR	*p*-Value	Evidence Level *	Reference
11q21	rs4409785 (chr11:95,578,258)	ENSG00000306211 and ENSG00000285842	SESN3	C	European; GWAS-MA (GWAS 1 + GWAS 2)	1.36	2.26×10^{-10}	B (association); C (SESN3 in CD4$^+$ T cells); D not met	[12,63]
					European; Replication Study	1.30	1.58×10^{-4}		
					Overall meta-analysis (GWAS1 + GWAS2 + replication)	1.34	1.57×10^{-13}		
2q13	rs4308124 (chr2:111,252,809)	MIR4435-2HG (intronic)	BCL2L11 (BIM)	C	European; GWAS123 meta-analysis	1.17	4.99×10^{-8}	B; C and D not met	[8]
					European; GWAS3 replication study	1.12	1.67×10^{-2}		[8]
					European; GWAS123 and GWAS3 replication study meta-analysis	1.15	3.96×10^{-9}		[8]
8q24.21	rs10087240 (chr8:128,000,328)	PVT1 (intronic)	MYC	T	European; GWAS1	1.17	9.12×10^{-5}	A; C and D not met	[26]
					European; GWAS2	1.12	1.36×10^{-1}		[26]
					European; GWAS3	1.21	4.62×10^{-5}		[8]
					European; Replication Study	1.16	1.62×10^{-3}		[26]
					CMH-Meta analysis	1.17	5.11×10^{-11}		[26]
8q24.21	rs4733823 (chr8:128,002,451)	PVT1 (intronic)	MYC	T	European; GWAS1	1.13	3.00×10^{-4}	A at locus level (proxy of rs10087240); not tested directly in replication	[26]
					European; GWAS2	1.12	1.40×10^{-1}		[26]
					European; GWAS3	1.21	5.34×10^{-5}		[8]

* A, genome-wide significant association confirmed in an independent study; B, genome-wide significant association supported by a replication stage within the discovery study; C, experimental evidence linking the risk variant to a target gene; D, experimental evidence that the risk variant alters the expression or function of the lncRNA itself. Positions refer to GRCh38; overlapping genes are given according to GENCODE 50 (Ensembl release 116). OR, odds ratio (95% confidence interval where reported).

Table 2. Most significant cis-QTL association of each lead variant in GTEx (V10).

Variant (Effect Allele)	Target Gene	QTL Type	Tissue	NES	*p*-Value	Significant *
rs4409785 (C, risk)	ENSG00000306211	eQTL	Whole Blood	0.44	8.7×10^{-18}	Yes
rs4308124 (C, risk)	ENSG00000227992	eQTL	Cultured fibroblasts	−0.32	2.9×10^{-16}	Yes
rs10087240 (T)	PVT1	sQTL	Cultured fibroblasts	0.40	3.4×10^{-13}	Yes
rs4733823 (T)	PVT1	sQTL	Cultured fibroblasts	0.39	1.2×10^{-12}	Yes

* Significant associations were retrieved from the GTEx Portal (analysis release V10) in September 2026. All available tissues were screened for cis-eQTL and cis-sQTL associations. For each variant, the most significant GTEx-reported association, based on the lowest nominal *p*-value, was selected, and the target gene, QTL type, tissue, effect allele, normalized effect size (NES), and nominal *p*-value were recorded.

6. Expression and Functional Evidence Across Pathogenic Compartments

Expression studies provide complementary evidence for the involvement of lncRNAs in vitiligo, although their findings vary according to the biological samples and experimental approaches used.

6.1. Keratinocytes and Epidermal Stress Responses

MALAT1 has been implicated in the protection of epidermal keratinocytes against ultraviolet-induced DNA damage. Brahmbhatt et al. profiled paired lesional and non-lesional epidermis from five patients with stable non-segmental vitiligo and identified a MALAT1–miR-211–SIRT1 regulatory axis, in which miR-211 was the most strongly down-regulated miRNA in lesional epidermis, and MALAT1, reported to be elevated in lesional epidermis [36,57,67], acted as an upstream negative regulator of miR-211. In primary keratinocytes, MALAT1 overexpression increased SIRT1 expression and reduced UVB-induced cyclobutane pyrimidine dimer formation [57]. In this model, MALAT1 elevation could represent an adaptive response of melanin-deprived keratinocytes rather than a driver of melanocyte loss; however, the study did not examine melanocytes.

In other compartments, a separate study reported elevated MALAT1 levels in serum from 20 patients compared with 20 controls, together with higher miR-9 levels and a positive correlation between the two molecules in serum and skin [65]. However, RNA sequencing of PBMCs did not identify significant differences in MALAT1 or TUG1 expression between patients and controls [67]. Functional studies have demonstrated a regulatory role for MALAT1 in keratinocytes, whereas expression analyses have reported increased levels in serum but no significant changes in PBMCs. These differences may reflect tissue-specific expression and distinct cellular sources of circulating RNA. Consequently, serum MALAT1 levels cannot be assumed to reflect its regulatory activity in keratinocytes, and the available evidence does not support its use as a consistent systemic biomarker of vitiligo.

6.2. Melanocyte Survival, Oxidative Stress, and Melanogenesis

TUG1 has been investigated through both patient-based expression analyses and functional experiments. Alhelf et al. reported reduced serum TUG1 expression in thirty patients with vitiligo, compared with 30 controls (quantitative RT-PCR), alongside lower tissue PPAR-γ, higher serum miR-377, and higher tissue IL-17 levels, although these associations did not establish a direct regulatory relationship [33]. Lower TUG1 expression has also been reported in lesional skin of 30 patients compared with normal skin of 30 controls, with a partial increase after 12 weeks of narrowband UVB phototherapy [68]. In experimental models, Nie et al. demonstrated that FOXO3 promotes TUG1 transcription and

that the TUG1–miR-375–GATA3 axis enhances melanocyte survival [58]. These findings suggest that reduced TUG1 expression in serum and lesional skin may be associated with impaired melanocyte survival, consistent with its protective role observed in experimental models. However, TUG1 expression was unchanged in PBMCs [67], and the cellular origin of circulating TUG1 remains unclear. Further validation in independent cohorts and disease-relevant experimental models is needed to establish whether TUG1 downregulation contributes to melanocyte loss in vivo.

Evidence linking lncRNAs to melanogenesis and melanin transfer in vitiligo is indirect. Pang et al. described lncRNAs that were differentially expressed in vitiligo lesions and co-expressed with melanogenesis genes, but these relationships were not tested experimentally [21]. The lncRNA Mir17hg promoted melanogenesis by inhibiting TGF-β receptor 2 in a psychological stress model [22]; nevertheless, this finding has not yet been examined in human vitiligo. To our knowledge, no lncRNA has been studied in relation to melanosome transfer from melanocytes to keratinocytes in vitiligo.

6.3. Immune Dysregulation and Autoimmunity

LOC100506314 provides further evidence linking lncRNA dysregulation to immune-cell function in vitiligo. Lai et al. identified LOC100506314 by microarray analysis of T cells from three patients and three controls and validated the finding by quantitative PCR in 41 patients with non-segmental vitiligo and 41 controls. Expression was increased in CD4+ T cells (1.94-fold) but not in CD8+ T cells and was positively associated with disease extent, but not with disease activity [64].

Functional experiments identified interactions with STAT3 and macrophage migration inhibitory factor (MIF), while LOC100506314 overexpression, in Jurkat and patient T cells, reduced STAT3, AKT, and ERK phosphorylation, nuclear NF-κB-associated signaling, and IL-6 and IL-17 expression [64]. The increased expression of LOC100506314 in patients with more extensive vitiligo, despite its anti-inflammatory effects in experimental models, may reflect a compensatory response to T-cell activation. However, this hypothesis requires validation through longitudinal studies and analyses of treatment-associated expression changes. Therefore, current evidence does not establish LOC100506314 as a contributor to disease progression or a biomarker of immune activation. Furthermore, this lncRNA has not been linked to any established vitiligo susceptibility locus.

Several immune compartments central to vitiligo pathogenesis remain unexplored. No lncRNA has been characterized in melanocyte-specific CD8+ cytotoxic T cells, resident memory T cells, or regulatory T cells from patients with vitiligo, and LOC100506314 itself was unchanged in CD8+ T cells [64]. Similarly, although IFN-γ-induced CXCL9 and CXCL10 are central to T-cell recruitment [11], to our knowledge, no study has examined lncRNAs that regulate this axis in vitiligo keratinocytes or melanocytes. In PBMCs, RNA sequencing identified 292 differentially expressed lncRNAs enriched in apoptosis, JAK–STAT, and PI3K–AKT pathways, but only two of six candidates (ENST00000460164.1 and NR_046211.1) were confirmed by quantitative PCR in 30 patients and 30 controls, and their functions are unknown [67].

6.4. Circulating and Extracellular Vesicle-Associated lncRNAs

H19 has also been investigated in exosomal RNA from skin biopsies of fifty patients with vitiligo and 50 controls. Doss et al. reported increased H19 expression and a positive correlation with disease activity [66]; however, the study did not include functional experiments. This is the only study of vesicle-associated lncRNAs in vitiligo. Serum measurements of MALAT1 and TUG1 [33,65] provide the only other data on circulating lncRNAs, but they were not obtained from isolated extracellular vesicles and should not be regarded

as vesicle-associated. These lncRNAs do not yet have clearly established associations in vitiligo, but they represent potential downstream targets for genotype–expression, eQTL, allele-specific expression, and functional studies [56–58].

6.5. lncRNA-miRNA Interactions

The MALAT1–miR-211 and TUG1–miR-375 axes have been proposed as ceRNA interactions on the basis of functional experiments [57,58]. In contrast, the TUG1–miR-377 relationship rests only on an inverse association of their serum levels [33] and should not be regarded as a ceRNA axis without experimental confirmation. Bioinformatic studies have proposed larger lncRNA–miRNA–mRNA networks in vitiligo [56,87]. Such networks are useful for generating hypotheses, but they are inferred from co-expression and sequence complementarity, requiring experimental confirmation, including evidence that the lncRNA is expressed at levels sufficient to sequester the miRNA [52]. They also represent potential downstream targets for genotype–expression, eQTL, allele-specific expression, and functional studies [56,57]. Table 3 summarizes expression and functional studies of lncRNAs in vitiligo, including the study populations, biological compartments, analytical methods, direction of expression changes, and available functional evidence.

These studies suggest that lncRNAs may participate in epidermal stress responses, immune regulation, and melanocyte survival, but the strength of the evidence differs considerably among transcripts. Functional experiments support specific regulatory roles for MALAT1 in keratinocytes, TUG1 in melanocytes, and LOC100506314 in $CD4^+$ T cells, whereas findings involving H19 remain primarily associative. Each of these findings derives from a single cohort or experimental study. Importantly, none of these studies establish a direct relationship between a replicated vitiligo susceptibility variant and the corresponding lncRNA transcript, and none of these lncRNAs is located at an established vitiligo susceptibility locus. Moreover, the reported mechanisms are not necessarily specific to vitiligo, emphasizing the need for independent validation in disease-relevant cell populations.

Table 3. Expression and functional studies of lncRNAs in vitiligo.

lncRNA	Study	Sample/Compartment	Patients/Controls (*n*)	Method	Direction in Vitiligo	Functional Data
MALAT1	Brahmbhatt et al. [57]	Paired lesional vs. non-lesional epidermis (stable NSV)	5 (paired)	Next-generation sequencing (miRNA profiling); functional assays	Increased in lesional epidermis	Suppresses miR-211, increases SIRT1, and reduces UVB-induced CPDs in primary keratinocytes
MALAT1	Raia et al. [65]	Serum; lesional and peri-lesional skin	20/20	Quantitative expression analysis	Increased (serum)	None
MALAT1, TUG1	Zhang et al. [67]	PBMCs (NSV)	5/5 (RNA-seq); 30/30 (qPCR for six other lncRNAs)	RNA-seq; qPCR	No significant change	None
TUG1	Alhelf et al. [33]	Serum (TUG1, miR-377); skin (PPAR-γ, IL-17)	30/30	qRT-PCR	Decreased	None
TUG1	Doss et al., 2024 [68]	Lesional skin vs. normal skin; before/after NB-UVB	30/30	qRT-PCR	Decreased; increased after 12 weeks of NB-UVB without normalization	None
TUG1	Nie et al. [58]	Melanocyte experimental models	—	Gain- and loss-of-function assays	—	FOXO3 induces TUG1; TUG1–miR-375–GATA3 promotes melanocyte survival
LOC100506314	Lai et al. [64]	$CD4^+$ and $CD8^+$ T cells (NSV)	3/3 (microarray); 41/41 (qPCR)	Microarray; qPCR	Increased in $CD4^+$ (1.94-fold), unchanged in $CD8^+$ T cells	Binds STAT3 and MIF; overexpression reduces pSTAT3, pAKT, pERK, nuclear p65, IL-6, and IL-17
H19	Doss et al., 2020 [66]	Exosomal RNA from skin biopsies	50/50	RT-PCR	Increased	None

CPD, cyclobutane pyrimidine dimer; NB-UVB, narrowband ultraviolet B; NSV, non-segmental vitiligo; PBMCs, peripheral blood mononuclear cells; qPCR, quantitative polymerase chain reaction; —, not applicable. None of the studies reported sensitivity, specificity, or area under the curve.

7. Clinical and Biomarker Implications

Genetic variants located within or near lncRNA loci may contribute to vitiligo susceptibility, although their potential clinical applications remain largely unexplored. Vitiligo has a substantial polygenic component, and higher polygenic risk has been associated with earlier disease onset [88]. However, these findings do not establish that lncRNA-associated variants can independently predict disease development. Their potential contribution to risk assessment will depend on identifying functional relationships between susceptibility variants, regulatory transcripts, and disease-relevant biological pathways [36,88,89].

At present, inherited risk is better understood as polygenic rather than attributable to a single variant. Individuals with a higher polygenic risk burden may develop vitiligo at an earlier age, suggesting that genetic risk models could be informative in selected contexts, such as familial or high-risk populations [32]. Nevertheless, clinical implementation would require standardized risk thresholds, ancestry-specific validation, and evidence that genetic information improves prediction beyond clinical assessment alone.

Given that vitiligo is primarily diagnosed clinically, the potential utility of lncRNAs as biomarkers may be more relevant to assessing disease activity, stability, progression, and treatment response than to establishing a diagnosis. Their clinical value should therefore be evaluated against previously investigated biomarkers, including serum CXCL10 and CXCL9 in suction-blister fluid from lesional skin, both of which have been associated with disease activity [90,91]. However, the lncRNA studies reviewed have not yet reported diagnostic or prognostic performance metrics, making their clinical utility unestablished.

In vitiligo, expression quantitative trait locus (eQTL)-based approaches could help determine whether disease-associated SNPs regulate lncRNA expression in relevant compartments, including melanocytes, keratinocytes, PBMCs, $CD4^+$ T cells, lesional skin, or circulating extracellular vesicles [32,92]. The integration of genetic and transcriptomic data may also support the development of tools for patient stratification, but this remains a prospective goal rather than a current clinical application.

LncRNAs such as MALAT1 have been proposed as potential biomarkers in vitiligo, although altered expression in serum or skin should not be interpreted as direct evidence of inherited predisposition without genotype–expression validation [93]. The variability in MALAT1 expression across serum, PBMCs, and epidermal tissue highlights the need to clarify the cellular sources of circulating MALAT1 and validate its expression patterns before assessing its potential as a biomarker of vitiligo. Combining genotype data with lncRNA expression profiles in PBMCs or circulation may provide a more dynamic representation of disease biology, particularly if correlated with disease activity, progression, or therapeutic response [32,89]. Integrated models combining risk-associated SNPs with circulating RNA markers, such as MALAT1 or miR-9, may eventually help differentiate individuals with genetic susceptibility from those with active inflammatory disease; however, this application remains exploratory and requires longitudinal validation [93].

LncRNAs and circRNAs may also contribute to risk stratification for progression or relapse. Longitudinal monitoring of lncRNA–miRNA–mRNA networks could, in principle, provide information on evolving immune activity, melanocyte stress, or treatment response. However, evidence supporting this approach in vitiligo remains limited, and extrapolation from other autoimmune contexts should be interpreted cautiously. Dysregulated lncRNAs involved in antigen presentation or inflammatory signaling may indicate a molecular environment permissive to persistent melanocyte injury, but their value as prognostic biomarkers has not yet been established [36,92–94].

Integrating genetic, epigenetic, and lncRNA expression profiles may eventually support the molecular stratification of patients with vitiligo according to pathways involving immune dysregulation and melanocyte or keratinocyte stress. However, no lncRNA-based molecular

subtypes have been established, and their potential clinical relevance requires validation in well-characterized longitudinal cohorts.

8. Challenges and Current Gaps

Studies on the relationship between lncRNAs and SNPs in vitiligo are scarce [32]. Although many GWAS variants may have functional relevance by modulating lncRNA or gene regulation, their target transcripts remain largely unknown. Because these variants fall outside protein-coding regions, determining their influence on gene expression in specific cell types is challenging [21,32]. Thus, assignment based solely on the nearest coding gene may overlook the regulatory role of lncRNAs, particularly in genomic regions distant from annotated coding sequences where positional proximity does not necessarily reflect functional relationships [21,32,36,57]. Conversely, the 11q21 and 8q24.21 examples show that positional overlap with a lncRNA does not exclude a protein-coding effector [63,80].

Another limitation is the difficulty of identifying causal variants and their regulatory targets within regions of strong linkage disequilibrium [95,96]. Although eQTL analyses can associate genetic variation with transcript abundance, these associations may reflect correlated variants rather than direct regulatory effects [97]. Furthermore, expression patterns identified in blood or other accessible tissues may not reflect those of melanocytes or immune cells within vitiligo lesions.

Another important limitation is that few studies integrate genotype data with lncRNA expression profiles. Most focus independently on genetic susceptibility or on transcriptomic changes using RNA-seq, maintaining a single-omics approach that does not allow for a complete understanding of the interaction between genetic variants and molecular expression [32,57].

Furthermore, there is wide variability in the types of samples used, including skin, serum, PBMCs, T lymphocytes, and epidermal lesions. Although this diversity allows for the study of different components of the immune and cutaneous disorders, it also increases the heterogeneity of the results, as lncRNA expression can vary depending on the tissue analyzed. Consequently, the lack of standardization across samples limits the comparability and generalizability of the findings [21,57,87].

Similarly, relevant clinical variables such as disease activity, treatment status, disease duration, and lesion distribution are not always adequately controlled. These characteristics can alter the expression of lncRNAs and other non-coding RNAs, leading to discrepancies between studies and complicating the interpretation of results [21,32,36,89]. Furthermore, studies on circulating lncRNAs and those associated with extracellular vesicles remain limited. Most research in this field has focused primarily on microRNAs (miRNAs), while the analysis of circulating and exosomal lncRNAs remains in its early stages, with insufficient evidence to date [21,32,36].

Finally, functional validation of the identified lncRNAs remains limited. Furthermore, population-specific differences in allele frequencies and linkage disequilibrium patterns have not yet been adequately assessed, which limits our understanding of the genetic impact of these variants in different population groups [21,32,36].

9. Future Directions

Future studies should focus on determining whether vitiligo-associated genetic variants influence disease susceptibility through lncRNA-mediated regulatory mechanisms. Although GWAS have identified numerous susceptibility loci, the functional targets of many non-coding variants remain unresolved. Integrating genetic fine-mapping with current genomic annotations, transcriptomic profiles, and chromatin accessibility data may

help prioritize regulatory elements and candidate lncRNAs in disease-relevant cell populations [85,86].

Although GWAS have identified more than 50 vitiligo susceptibility loci, the majority map to intergenic or intronic regions [8,31,98]. Systematic reannotation of these variants with current resources, such as GENCODE, Ensembl, and epigenomic maps of immune cells and skin, would clarify how many lie within or near lncRNA genes or their regulatory elements [82,85,99]. To our knowledge, such an analysis has not been published for vitiligo, and its results should be interpreted cautiously, because overlap with a lncRNA does not identify the effector transcript. This reannotation effort should prioritize loci implicated in autoimmunity, melanocyte biology, and the oxidative stress response.

Integrating GWAS with RNA-seq can help prioritize candidate causal variants by correlating genotype with lncRNA expression across different compartments [14,97]. Analysis of PBMCs, serum, and plasma allows the identification of circulating lncRNA biomarkers associated with systemic adaptive and innate immune activation [21,67,94]. Comparative transcriptomic studies of lesional and non-lesional skin can map the local inflammatory microenvironment and gene expression gradients associated with active depigmentation [21,57]. Cell-type-specific sequencing of melanocytes and T cells can reveal lncRNAs involved in cellular stress responses, homeostasis, and regulation of T-cell infiltration and differentiation in the skin [100].

Analysis of extracellular vesicles is an increasingly important research avenue, given that miRNAs encapsulated in exosomes mediate paracrine intercellular communication and are emerging as functional contributors to the vitiligo microenvironment [101]. Further research is required to determine if this also applies to lncRNAs [66]. Complementing these approaches, eQTL mapping using resources such as GTEx, eQTLGen and CRISPR-based functional validation of lncRNAs overlapping risk loci represent essential steps toward mechanistic understanding [86,100,102,103].

eQTL and allele-specific expression (ASE) analyses are critical tools for determining whether non-coding variants identified by GWAS regulate lncRNA abundance relevant to vitiligo pathogenesis [14,97]. eQTL mapping can establish whether a risk-associated SNP acts as a cis-regulator or a trans-regulator by correlating genotype with transcript levels in skin- and blood-specific expression profiles, using reference datasets such as GTEx and eQTLGen [86,103]. In vitiligo, this approach has so far been applied mainly to protein-coding genes, through monocyte eQTL colocalization and transcriptome-wide association analyses [8]. ASE analysis complements this approach by quantifying the relative expression of both alleles within heterozygous individuals in the same cellular context, providing direct evidence of cis-regulation and genetic control over non-coding RNA expression [104]. Integrating these strategies may allow studies to determine the role of loci already implicated in vitiligo susceptibility, particularly those involved in autoimmunity, oxidative stress response, and melanocyte adhesion [8,32].

To prioritize lncRNAs for future investigation in vitiligo, we propose four complementary criteria: (i) association with replicated vitiligo susceptibility loci; (ii) evidence of genetic regulation through eQTL, allele-specific expression, or GWAS colocalization; (iii) reproducible differential expression in disease-relevant tissues across independent cohorts; and (iv) functional evidence linking lncRNA activity to vitiligo-associated processes, ideally supported by perturbation experiments that distinguish RNA-mediated effects from those of the underlying DNA sequence. Based on these criteria, no candidate currently has sufficient evidence to establish a genotype–lncRNA–phenotype relationship. PVT1 has replicated genetic associations but lacks vitiligo-specific functional validation, whereas MIR4435-2HG remains a positional candidate. At the 11q21 locus, rs4409785 overlaps annotated lncRNA genes, but functional evidence currently supports SESN3 regulation

rather than an established lncRNA-mediated mechanism [8,12,26,63]. Conversely, MALAT1, TUG1, and LOC100506314 have expression and functional evidence in vitiligo-related models but lack established links to susceptibility variants [57,58,64]. Accordingly, genetically associated loci require genotype–expression analyses and functional validation, whereas expression-based candidates require independent replication and longitudinal assessment of their clinical relevance.

10. Conclusions

Genetic association studies have identified several vitiligo susceptibility loci within or near non-coding genomic regions, highlighting the potential contribution of regulatory mechanisms to disease risk. Among the loci that harbor annotated lncRNAs, only PVT1 has been confirmed in a separate study, and the only mechanism characterized experimentally at these loci involves a protein-coding gene (SESN3 at 11q21). In parallel, transcriptomic and functional studies have implicated lncRNAs in immune regulation, epidermal stress responses, and melanocyte survival. However, direct relationships between specific susceptibility variants, lncRNA activity, and vitiligo phenotypes remain unresolved. Although several lncRNAs have been proposed as candidate biomarkers, none has reported performance data, and their most plausible future role is in monitoring disease activity or treatment response rather than diagnosis. Integrating genetic fine-mapping, cell-specific transcriptomic analyses, and functional experiments will be essential to clarify whether lncRNAs mediate inherited susceptibility or primarily reflect disease-associated molecular changes. These approaches may improve our understanding of vitiligo pathogenesis and help establish the biological and clinical relevance of lncRNAs.

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