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Modern vitiligo genetics sheds new light on an ancient disease

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Abstract

Vitiligo is a complex disorder in which autoimmune destruction of melanocytes results in white patches of skin and overlying hair. Over the past several years, extensive genetic studies have outlined a biological framework of vitiligo pathobiology that underscores its relationship to other autoimmune diseases. This biological framework offers insight into both vitiligo pathogenesis and perhaps avenues towards more effective approaches to treatment and even disease prevention.

Keywords

autoimmune destruction; disease prevention; vitiligo; vitiligo genetics; vitiligo pathogenesis

INTRODUCTION

Vitiligo is a complex disorder in which white patches of skin and overlying hair result from autoimmune destruction of melanocytes within the lesions. Vitiligo appears to be of multifactorial causation, involving multiple underlying susceptibility genes and environmental triggers. Over the past several years there has been considerable progress in defining the genetic epidemiology and genetic pathogenesis of vitiligo, and its relationships to other autoimmune diseases. To date, almost all genetic studies have been of generalized or "non-segmental" vitiligo. Recently, advances by these genetic studies have outlined a biological framework that offers real insight into vitiligo pathogenesis and perhaps to more effective approaches to treatment and even disease prevention.

EARLY HISTORY

Human pigmentation diseases present the most visually striking of all disorders, and the phenotypes of oculocutaneous albinism, piebaldism and others have been known for thousands of years.[1] Vitiligo itself has had a remarkable history of discovery and re-discovery of key observations overlooked or forgotten over the passage of time. Certainly, patients with various forms of patchy leukoderma were recognized during ancient times; however, vitiligo per se was not described as a specific medical entity until the mid-18th century.[2]

The first clue to vitiligo pathogenesis came from the description and illustration of a patient with concomitant vitiligo, adrenal insufficiency and pernicious anemia,[3] highlighting a link between these three autoimmune diseases. Similar patients with multiple autoimmune diseases were later reported by Schmidt[4] and codified by Neufeld and Blizzard.[5] Further

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evidence of immune or inflammatory influences in vitiligo came from the recognition that new lesions often occur at sites of skin injury,[6] a phenomenon first described in 1872 by Köbner in the context of psoriasis and which came to bear his name.[7] Perhaps the most important observation regarding vitiligo pathogenesis also came from Kaposi, who illustrated histological lack of cells containing pigment granules within vitiligo skin lesions,[8] later re-described by Hu *et al.*[9] and yet again by Breathnach *et al.*[10]

Probably the landmark early study of vitiligo was that of Lerner,[11] who reported on clinical, epidemiological and genetic characteristics of 200 cases, thereby delineating many important clinical and epidemiological aspects of the disease, establishing the clinical terminology and classification scheme that is basically still in use today. This study provided an analytic framework that was adopted by many subsequent epidemiological surveys of vitiligo patients around the world,[12–21] providing key information in formulating the genetic underpinnings of the disorder.

GENETIC EPIDEMIOLOGY

The earliest formal considerations of the genetic basis of vitiligo appear to have been by Stuttgen,[22] Teindel[23] and later by Lerner,[11] all of whom noted familial aggregation of cases not clearly consistent with Mendelian single-gene inheritance. Stuttgen,[22] in particular, was remarkable in suggesting the simultaneous involvement of both recessive and dominant contributory influences, predating the modern genetic concept of "complex inheritance" by decades. Subsequently, Das *et al.*,[24,25] Bhatia *et al.*[26] and Majumder *et al.*[27] likewise all noted frequent familial clustering of vitiligo cases in a non-Mendelian pattern. Majumder *et al.*[28] and Nath *et al.*[29] suggested a multilocus recessive model, Arcos-Burgos *et al.*[30] postulated multiple forms of vitiligo with different genetic underlying models, whereas most other investigators favored polygenic, multifactorial inheritance,[12,26,31–33] which is now generally accepted.

Close relatives of vitiligo patients have elevated risk of vitiligo, as well as other autoimmune diseases, with relative risks for first-degree relatives estimated at approximately 6–18-fold elevated.[12,24,27,33–35] Estimates of vitiligo heritability range from 46% in India to 16% in China,[33] and Alkhateeb *et al.*[12] found that the concordance for vitiligo in monozygotic twins was 23%, supporting roles for both genetic and non-genetic factors in disease pathogenesis.

PRE-MOLECULAR GENETIC STUDIES

The earliest attempts to identify specific genes that may contribute to vitiligo were genetic association studies of vitiligo using a variety of protein polymorphic markers, including ABO and other blood groups,[15,25,36–42] blood group secretor status,[15,43] and a number of other serum proteins.[25,44,45] Essentially, all of these studies proved negative.

Subsequently, there were a number of case–control genetic association studies of histocompatibility antigen (human leukocyte antigen, HLA) types and vitiligo.[46–55] While several of these studies reported weak associations, the results were inconsistent, partly because of inadequate study designs and partly because of likely genetic heterogeneity among the many different populations analyzed. Nevertheless, meta-analysis of data from 11 of these studies[56] subsequently identified association of vitiligo with *HLA-A2* (odds ratio, 2.07).

MOLECULAR GENETIC ERA

Modern genetic studies of vitiligo have principally entailed five scientific approaches: genetic linkage analysis of families with multiple affected relatives (multiplex families),

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candidate gene association studies comparing relatively small numbers of vitiligo patients (cases) to unaffected controls, genome-wide association studies (GWAS) comparing far larger numbers of cases to controls, DNA sequencing studies and gene expression studies. Genetics researchers give highest credence to disease gene discoveries derived from genome-wide linkage and GWAS, as these approaches are relatively free of biases and are robust to several important sources of potential error. Candidate gene association studies, by contrast, are largely discounted by modern geneticists as an approach to gene discovery, as the vast majority report false-positives resulting from chance fluctuation due to insufficient statistical power, population stratification and the impossibility of adequate correction for multiple testing given publication bias of positive results.[57,58] DNA sequencing studies largely involve candidate genes previously identified by other means, and thus are subject to the caveats appropriate to the identification of these genes in the first place. Gene expression studies are generally considered invalid as a means of disease gene discovery as they cannot distinguish between primary causal differences versus secondary changes that are the result of pathway dysregulation or disease, but can be useful as a means of confirming the biological relevance of previous genetic findings.

Genetic linkage studies

The first vitiligo genetic linkage studies were of candidate genes. A linkage study of the *HLA* region in a large family with polyglandular autoimmune disease type II (Schmidt syndrome), including with vitiligo, was negative.[59] Tripathi *et al.*[60] tested linkage of vitiligo to *MITF*, again with negative results. The first positive results came from targeted linkage analysis of the major histocompatibility complex (MHC) on chromosome 6p, detecting linkage of vitiligo with microsatellite polymorphic markers in *HLA* gene regions in families from several different populations.[30,61,62]

The first detection of novel vitiligo loci by genome-wide study came from linkage analysis of families with systemic lupus erythematosus (SLE) that included at least one case of vitiligo, detecting the *SLEV1* locus on chromosome 17p13.[63] *SLEV1* was subsequently confirmed by direct genome-wide study of Caucasian multiplex vitiligo families,[64] and the corresponding causal gene was eventually identified as *NLRP1*,[65] encoding a key regulator of the innate immune response. Genome-wide analysis of a unique Caucasian family with auto-somal dominant vitiligo detected *AIS1* on chromosome 1p31.3-32.2,[66] and the corresponding gene was subsequently identified as *FOXD3*,[67] encoding a developmental regulator of melanoblast differentiation; thus far, additional families with dominant vitiligo and *FOXD3* mutations have not been described. Comprehensive genome-wide linkage analyses of other multiplex vitiligo families also detected a number of other vitiligo susceptibility loci, on chromosomes 1, 7, 8, 9, 11, 13, 19 and 21 in Caucasians,[64,68] and on chromosomes 4, 6 and 22 in Chinese,[61,69] some of which may correspond to genes detected in subsequent GWAS. Ren *et al.*[70] studied *XBP1* as a candidate gene within the 22q12 linkage region, though this assignment has not yet been confirmed. Xu *et al.*[71] studied *PDGFRA* as a candidate gene within the 4q12-q21 linkage region, finding more variation in familial vitiligo cases than controls. However, *PDGFRA* is not known to play a role in pigment cell biology, and the closely adjacent *KIT* gene would seem a better candidate for this linkage signal.

Candidate gene association studies

The earliest candidate gene association studies of vitiligo were of loci that previously had been shown to be genetically linked and/or associated with other autoimmune diseases. Though candidate gene association studies are not considered a valid approach to primary discovery of disease genes, this approach is considered acceptable for confirmation of established genes.

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The first such study reported genetic association of vitiligo with single nucleotide polymorphisms (SNP) within *CTLA4*,[72] a locus that had been previously associated with several other autoimmune diseases.[73] Even in that initial report, *CTLA4* was only associated with vitiligo in patients who also had concomitant autoimmune diseases, as confirmed in subsequent studies.[74–76] This has been interpreted as perhaps indicating that there are multiple genetically distinct subtypes of vitiligo[76] or that *CTLA4* is not actually causal for vitiligo, with apparent genetic association being secondary to epidemiological association of vitiligo with other autoimmune diseases for which *CTLA4* is causal.[74] Subsequently, Canton *et al.*[77] reported association of vitiligo with *PTPN22*, a gene that also had been previously associated with a number of other autoimmune diseases.[78] This association was subsequently confirmed by other investigators,[79,80] most importantly by the first GWAS of vitiligo.[81] A number of investigators reported association of vitiligo with loci in the MHC.[82–85] However, because of complex patterns of long-range linkage disequilibrium across the MHC, it has been difficult to assign genetic association to specific genes within the MHC.

Over the following years, a large number of candidate gene studies of vitiligo were published, many based on little or no compelling biological rationale. Birlea *et al.*[75] published a comprehensive review of 33 claimed vitiligo candidate genes (ACE, AIRE, CAT, CD4, CLEC11A, COMT, CTLA4, C12orf10, DDR1, EDN1, ESR1, FAS, FBXO11, FOXD3, FOXP3, GSTM1, GSTT1, IL1RN, IL10, KITLG, MBL2, NFE2L2, PDGFRA-KIT, PTGS2, STAT4, TAP1-PSMB8, TGFBR2, TNF, TSLP, TXNDC5, UVRAG, VDR, XBP1), finding support for only three (*TSLP, XBP1, FOXP3*) in analysis of a genome-wide vitiligo GWAS dataset.[81] Additional claimed candidate gene associations with vitiligo include *AHR*[86], *COX2*,[87] *GSTP1*,[88] *IL4*,[89] *IL19* and *IL20RB*,[90] *INOS*,[91] *PRO2268*,[92] *TLR2* and *TLR4*,[93] while candidate genes reported not to be associated include *CD28*,[94] *ICOS*,[94] *IL20*, *IL24e* and *IL20RA*,[90] *MTHFR*,[95] and *SMOC2*.[96] Some of these claimed novel candidate gene associations may be valid, though most are likely to represent false-positives.

GWAS

Genome-wide association studies are currently the "gold standard" of genetic studies of complex diseases. The first vitiligo GWAS was an analysis of patients from a population isolate in Romania with a high prevalence of vitiligo and other autoimmunity,[97] detecting association with *SMOC2* located at distal chromosome 6q27.[98] While association with *SMOC2* has not been detected in other GWAS, it is located very close to *CCR6* in chromosome 6q27, which was detected in GWAS of vitiligo in both Caucasians[81] and Chinese,[99] and it may be that all of three reports represent the same association signal.

Three large GWAS of vitiligo have been reported thus far; two in Caucasians [81,100,101] and one in Chinese,[99,102] while a small gene-centric GWAS of vitiligo has been reported in Indian–Pakistani patients.[103] These studies have detected 30 vitiligo susceptibility loci in Caucasians (Table 1): *PTPN22, RERE, IFIH1, CTLA4* (only in patients with other autoimmune diseases), *FOXP1, CD80, LPP, CLNK, TSLP, HLA-A*, MHC class II (*c6orf10-BTNL2-DRB1-DQA1*), *BACH2, CCR6, TG/SLA, IL2RA, CASP7, CD44, TYR*, a gene desert at 11q21, IKZF4, SH2B3, GZMB, OCA2, MC1R, TICAM1, UBASH3A, XBP1, C1QTNF6, TOB2, and *FOXP3*.[81,100,101,104] The parallel studies of Chinese have detected nine vitiligo susceptibility loci (Table 1): *LPP*, MHC class I (*HLA-B-HLA-C*), RNASET2-FGFR1OP-CCR6, IL2RA, ZMIZ1, IKZF4, IL2RB-C1QTNF6, an intergenic interval at 10q22.1 between *SLC29A3* and *CDH23*, and an intergenic interval at 11q23.3 between *DDX6* and *CXCR5*.[99,102] Thus, vitiligo association with at least *LPP*, the *HLA* class I gene region, *CCR6, IL2RA, IKZF4* and *C1QTNF6* appears to be shared between the Caucasian and Chinese populations, though other genes associated with vitiligo susceptibility or protection may be population-specific, particularly *TYR*, *OCA2* and *MC1R*. Similarly, the

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Indian–Pakistani GWAS reported association only with the MHC class II gene region, and formal trans-ethnic analysis indicated that association signals in Caucasians and Indian–Pakistani patients in this genomic region likely share the same ancestral origin.[103]

DNA sequencing studies

Gene-specific DNA sequencing analyses are, in effect, highly detailed candidate gene association studies, typically comparing the frequency of either specific variants or of all observed variation in specific candidate genes in cases versus in controls. Until recently, most such studies have lacked sufficient statistical power or rigor to prove that observed DNA sequence variations are truly causal for the disease versus being rare non-causal polymorphisms.

The first such study was of *GCH1*,[105] and the claimed association of vitiligo with *GCH1* mutations was quickly refuted.[106] DNA sequences of a number of additional vitiligo candidate genes have subsequently been compared in vitiligo cases versus controls, mostly in relatively small numbers. These include *ASIP*,[107,108] *MC1R*,[107–109] *MYG1*/*c12orf10*[110] and *POMC*.[109] None of these studies showed convincing significant differences in cases versus controls after appropriate correction for multiple testing.

More recently, several vitiligo susceptibility genes detected by GWAS have been subjected to NextGeneration DNA re-sequencing to identify sequence variation that is apparently causal for disease. Jin *et al.*[104] sequenced both *HLA-A* and *TYR* in Caucasian vitiligo patients, finding that the predominant *HLA-A* vitiligo-associated susceptibility allele is *HLA-A**02:01:01:01, while finding that two common non-synonymous substitutions of *TYR*, S192Y and R402Q, appear to exert both individual and synergistic protective effects. HLA-A2 presents tyrosinase peptide as an autoimmune antigen, whereas the *TYR* 192Y and 402Q substitutions likely reduce the amount of tyrosinase peptide available for presentation, suggesting that these loci and variants act via a common pathway. Ferrara *et al.*[111] sequenced *GZMB* and found that the causal allele involved a common multi-variant haplotype containing three non-synonymous substitutions in strong linkage disequilibrium, Q55R-P94A-Y247H, though the mechanism by which this multi-variant granzyme B affects vitiligo susceptibility is not yet known. Levandowski *et al.*[112] sequenced *NLRP1* and found that the common high-risk haplotype contains three non-synonymous substitutions in strong linkage disequilibrium, L155H-V1059M-M1184V, while a less common but even higher risk haplotype contains nine non-synonymous substitutions, L155H-T246S-T782S-T878M-T995I-M1119V-M1184V-V1241L-R1366C. These authors showed that the common multi-variant high-risk haplotype results in 1.8-fold elevation of processing of the inactive interleukin (IL)-1β precursor to biologically active IL-1β cytokine by the NLRP1 inflammasome, presenting a likely mechanism for disease pathogenesis associated with this haplotype.

Gene expression studies

A number of studies have compared expression of genes in normal versus vitiligo skin or melanocytes, either genome-wide or of selected candidate genes. A serious problem in such studies is the difficulty in distinguishing causal changes from those that result from the disease state or from melanocyte stress or senescence. The first such study identified *VIT1*, a gene downregulated in vitiligo melanocytes[113] and later renamed *FBXO11*, the role of which in vitiligo pathogenesis remains uncertain.[114] Analyses comparing genes differentially expressed in vitiligo lesions versus in uninvolved skin principally detect genes that encode melanocyte components,[115] which is not surprising given that a greatly reduced number of melanocytes within vitiligo lesions is the hallmark of the disease. Recently, Yu *et al.*[116] carried out transcriptome analyses of vitiligo patients and found evidence of

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upregulated innate immunity in non-lesional skin, perhaps consistent with implication of these pathways in vitiligo pathogenesis by previous genetic studies.

Other investigators have carried out differential expression studies of a very large number of candidate genes, but it is difficult to have confidence that any of the reported differences are in fact causal for vitiligo, or would even remain statistically significant could appropriate multiple-testing corrections be applied across the numerous such reports. Two such studies[89,92] have correlated altered gene expression with genetic association of specific SNPs in the corresponding genes, and thus provide at least some external validation that the candidate gene in question may be relevant to vitiligo pathogenesis.

CURRENT UNDERSTANDING

To date, approximately 36 loci with convincing or strongly suggestive evidence for a role in vitiligo susceptibility have been identified (Table 1). Most of these loci contain or are in close proximity to plausible biological candidate genes. Approximately 90% of these genes encode immunoregulatory proteins, whereas approximately 10% encode melanocyte proteins that likely serve as autoantigens that both stimulate the melanocyte-specific immune response and act as targets for immune recognition and cell killing (or in the case of HLA class I and perhaps class II molecules, present those autoantigens to the immune system). Together, these proteins constitute a dense immunoregulatory network that highlights systems and pathways that mediate vitiligo susceptibility.[101] Moreover, DNA sequencing and functional analyses have identified apparent causal variation for *TYR*,[104] *HLA-A*,[104] *NLRP1*[112] and *GZMB*,[111] yielding deeper insights into the roles played by these proteins in disease pathogenesis.

Several of the genes identified as conferring vitiligo susceptibility, particularly those expressed in melanocytes, have also emerged as genes involved in susceptibility to malignant melanoma, the same SNP having genetically opposite roles in vitiligo versus melanoma susceptibility.[81,101] This apparent genetically inverse relationship of melanocyte-specific genes to vitiligo versus melanoma led to the suggestion that vitiligo may represent a dysregulated normal process of immune surveil-lance against malignant melanoma.[117]

These genetic and functional studies have begun to provide a hypothetical framework for understanding the initial triggering, immune propagation and ultimate cytotoxicity of the anti-melanocyte immune response (Fig. 1). A likely common pathway for initial vitiligo triggering may be Köbnerization, with various types of skin damage resulting in localized cell killing and perhaps localized microinfection. Melanocyte peptide antigens are presented to skin-resident dendritic cells (principally Langerhans cells) by HLA class I molecules on the melanocyte surface. At the same time, Langerhans cells take up infection-derived molecules that display "pathogen-associated molecular patterns" (PAMP) and damage-derived molecules that display "damage-associated molecular patterns" (DAMP), which bind to NLRP1 and thereby induce assembly of the NLRP1 inflammasome; other pathways of inflammasome activation and innate immune induction are also possible. NLRP1 inflamma-some assembly activates caspases that cleave the IL-1β precursor to biologically active secreted IL-1β. IL-1β is a potent pro-inflammatory cytokine, perhaps facilitating presentation of autoantigens that trigger or provide specificity to the immune response. Within the dendritic cells, melanocyte autoantigens are transferred from HLA class I molecules to HLA class II mol ecules, which then present these antigens to immature T cells. Immature T cells then express and secrete IL-2, which binds to IL-2 receptor expressed on the cell surface, inducing their maturation to cytotoxic T-cells (cytotoxic T lymphocytes, CTL) that express T-cell receptor molecules specific to the cognate melanocyte autoantigen, as well as cytolytic molecules such as granzyme B. Melanocyte-

specific CTL then recognize the cog-nate melanocyte autoantigens presented on the melanocyte surface by HLA class I molecules, and the target cells are ultimately lysed by granzyme B. This “circuit” of melanocyte triggering, immune propagation, autoantigen programming and target cell killing by immune effector cells thus incorporates many of the genes and proteins that modulate vitiligo susceptibility. While certainly not complete in all details, and perhaps not even substantially correct, this model nevertheless provides for the first time a conceptualization of vitiligo pathogenesis that encompasses advanced biological knowledge of the disease and that may highlight potential new avenues for therapy and even disease prevention in individuals with high genetic susceptibility.

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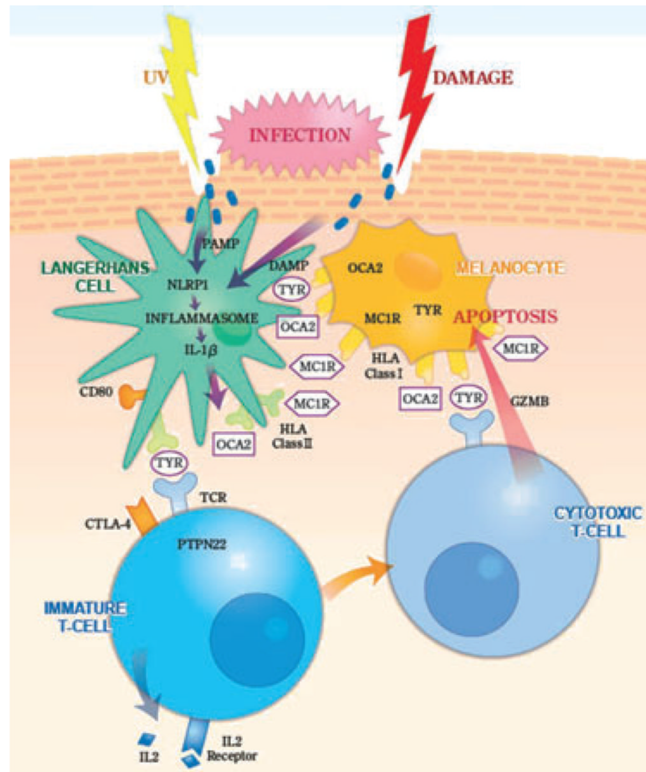

Figure 1.

"Circuit" of melanocyte damage, melanocyte autoantigen presentation, immune triggering and propagation, T-cell programming and melanocyte target cell killing in vitiligo. Skin is damaged by ultraviolet (UV) or other trauma, perhaps facilitating microinfection. Molecules displaying pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP) interact with NLRP1 in the cytoplasm of Langerhans cells, stimulating nucleation of an NLRP1 inflammasome, thereby activating caspases that cleave the interleukin (IL)-1b precursor to biologically active secreted IL-1β. Langerhans cells take up peptide autoantigens presented by human leukocyte antigen (HLA) class I molecules expressed on the surface of nearby melanocytes, including peptides derived from tyrosinase (TYR), OCA2 and the melanocortin-1 receptor (MC1R), and these peptide autoantigens are then transferred to HLA class II molecules expressed on the Langerhans cell surface. Perhaps stimulated by IL-1β and facilitated by interaction of CD80 with CTLA4 and by the action of PTPN22, these melanocyte-derived peptide autoantigens are then presented to immature T cells that express cognate T-cell receptors (TCR), the response of which is regulated by PTPN22. The activated T cells express IL-2, which binds to the IL-2 receptor expressed on their surface, stimulating maturation to cytotoxic T cells that express granzyme B (GZMB). The TCR expressed by these autoreactive cytotoxic T cells binds its cognate autoantigen presented on the surface of target melanocytes by HLA class I molecules, and GZMB is introduced into the target melanocyte, inducing apoptosis.

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Table 1

Confirmed and suggestive vitiligo susceptibility loci identified by genome-wide association or linkage studies

Chromosome	Candidate gene	Populations	Protein	Function
1p13.2	*PTPN22*	C	LYP protein tyrosine phosphatase	Regulates T-cell signaling
1p31.3	*FOXD3* [†]	C	Forkhead box D3	Transcriptional regulator of neural crest; melanoblast differentiation
1p36.23	*RERE*	C	Atrophin-1-like protein isoform b	Lymphoid transcriptional co-repressor; apoptotic regulator
2q24.2	*IFIH1*	C	Interferon-induced RNA helicase	Regulates innate antiviral immune responses
2q33.2	*CTLA4* [‡]	C	Cytotoxic T-lymphocyte-associated-4	Inhibits T cells via interaction with CD80 and CD86
3p13	*FOXP1*	C	Forkhead box P1	Transcriptional regulator of B-cell, T-cell, monocyte development
3q13.33	*CD80*	C	B-cell activation antigen B7-1	T-cell priming by B cells, T cells, dendritic cells; interacts with CTLA-4
3q28	*LPP*	A,C	LIM domain containing preferred translocation	Transcriptional co-activator?
4p16.1	*CLNK*	C	Mast cell immunoreceptor signal transducer	Positive regulator of immunoreceptor signaling
5q22.1	*TSLP* [§]	C	Thymic stromal lymphopoietin protein	Cytokine regulator of skin dendritic (Langerhans) cell maturation
6p22.1	*HLA-A*	C	Leucocyte antigen A α-chain	Presents peptide antigens
6p22.1	*HLA-B-C*	A	Leukocyte antigen B or C α-chain	Presents peptide antigens
6p21.32	*HLA-DRB1-DQA1*	C,I	Major histocompatibility complex class II region	Presents peptide antigens
6q15	*BACH2*	C	BTB and CNC homology 1, basic leucine zipper	B-cell transcriptional repressor
6q27	*CCR6*	A,C	Chemokine (C-C motif) receptor 6	Regulates differentiation and function of B cells, T cells, dendritic cells
6q27	*SMOC2* [¶]	C	SPARC-related modular calcium-binding protein	Regulate cellextracellular matrix i nteractions
8q24.22	*TG/SLA*	C	Thyroglobulin, Src-like adaptor isoform c	Regulates antigen receptor signaling in T cells, B cells, dendritic cells
10p15.1	*IL2RA*	A,C	Interleukin 2 receptor α-chain	Regulates interleukin 2-mediated activation of T-cells, regulatory T-cells
10q22.1	Gene desert	A		
10q25.3	*CASP7*	A	Caspase 7	Apoptotic executioner protein
11p13	*CD44*	C	CD44 antigen	T-cell regulator
11q14.3	*TYR*	C	Tyrosinase	Melanin biosynthetic enzyme
11q21	Gene desert	C	None	*TYR* regulation?
11q23.3	Gene desert	A		
12q13.2	*IKZF4*	A,C	Ikaros zinc finger protein, subfamily 1A, 4	T-cell transcriptional regulator
12q24.12	*SH2B3*	C	LNK adaptor	B-cell, T-cell developmental regulator
14q12	*GZMB*	C	Granzyme B	Mediates CTL-induced target cell apoptosis, helper T-cell apoptosis
15q12-13.1	*OCA2*	C	Oculocutaneous albinism II	Melanosomal membrane transporter/pump
16q24.3	*MC1R*	C	Melanocortin-1 receptor	Regulates melanogenesis
17p13.2	*NLRP1*	C	NLR family, pyrin domain containing 1	Regulates IL-1 β innate immune response via NLRP1 inflammasome

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Chromosome	Candidate gene	Populations	Protein	Function
19p13.3	*TICAM1* ††	C	Toll-like receptor adaptor molecule 1	Mediates innate antiviral immune responses
21q22.3	*UBASH3A*	C	Ubiquitin associated and SH3 domain containing	Regulates T-cell signaling, apoptosis
22q12.1	*XBP1* §	A,C	X-box binding protein 1	Transcriptional regulator of MHC class II expression, plasma cells
22q12.3	*C1QTNF6*	A,C	C1q and tumor necrosis factor related protein 6	Innate immune response to light-induced apoptosis?
22q13.2	*TOB2*	C	Transducer of ERBB2, 2	Inhibitor of cell cycle progression; involved in T-cell tolerance
Xp11.23	*FOXP3* §	C	Forkhead box P3	Transcriptional regulator of regulatory T-cell function and development

† Found only in a single family with autosomal dominant vitiligo.[66,67]

‡ *CTLA4* is only associated with vitiligo in patients with other concomitant autoimmune diseases.[74–76] Association of *CTLA4* with vitiligo may thus be secondary, driven by primary association with these other diseases.

§ *XBP1, FOXP3* and *TSLP* are the only vitiligo candidate genes that achieve suggestive association in analysis of genome-wide association study data in Caucasians.[75] *XBP1* was identified as a positional candidate based on linkage in Chinese.[70]

¶ *SMOC2* is located very close to *CCR6* and may represent the same association signal.

†† *T/CAM1* achieves highly suggestive association in analysis of GWAS data in Caucasians.[101]