

Shared Genetic Relationships Underlying Generalized Vitiligo and Autoimmune Thyroid Disease

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Background: Generalized vitiligo is an autoimmune disease of skin pigmentation that is associated with increased prevalence of other autoimmune diseases, particularly autoimmune thyroid disease (AITD; principally Hashimoto's disease and Graves' disease), both in vitiligo patients and their close relatives, suggesting a heritable predisposition involving, in part, shared susceptibility genes.

Summary: This review summarizes current knowledge of vitiligo epidemiology and genetics, highlighting recent findings from genome-wide approaches to disease gene identification, emphasizing susceptibility loci shared with other autoimmune diseases, particularly AITD, as well as some important differences.

Conclusions: Inherited susceptibility to generalized vitiligo involves a number of specific genes, many of which are shared with other autoimmune diseases that are epidemiologically associated with vitiligo, including AITD, confirming a longstanding hypothesis about the genetic basis of these disorders. These genes provide potential therapeutic targets for novel approaches to treatment as well as for approaches to presymptomatic diagnosis and disease prevention in individuals with inherited susceptibility to this group of autoimmune diseases.

Introduction

AUTOIMMUNE DISEASES ARE A DIVERSE GROUP of chronic disorders in which the immune system attacks one's own cells and tissues. More than 80 autoimmune diseases are known, at least one for almost every organ in the body (1). The most prevalent are the autoimmune thyroid diseases (AITD), principally Hashimoto's disease and Graves' disease (2–4), characterized by infiltration of the thyroid by thyroid-reactive T and B cells and by the production of thyroid autoantibodies (5,6). Perhaps the most recognizable autoimmune disease is generalized vitiligo, with descriptions of its visually striking clinical manifestations dating back several millennia (7).

Generalized vitiligo is characterized clinically by acquired patches of white skin and overlying hair, usually multifocal and often bilateral (7,8) (Fig. 1), resulting from progressive autoimmune loss of melanocytes from the involved areas. Development of generalized vitiligo results from a complex interaction of predisposing genetic factors and unknown environmental triggers that initiate the process of melanocyte destruction, resulting in the characteristic depigmented lesions (9,10).

It is well known that there is a tendency for multiple autoimmune diseases to occur concomitantly in some patients. Perhaps the first description was in 1855, when Addison reported a patient with idiopathic adrenal insufficiency,

vitiligo, and pernicious anemia (11). In 1926 Schmidt reported co-occurrence of multiple autoimmune diseases in what came to be called Schmidt syndrome (12). In 1980 Neufeld and Blizzard suggested classification of the so-called autoimmune polyglandular syndromes based on clinical grounds (13), of which Schmidt syndrome was denoted type II. Over the past few years it has become recognized that APS II is more complex, and in particular that generalized vitiligo is part of a genetically determined, autoimmune-autoinflammatory disease diathesis that also includes AITD, rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, pernicious anemia, Addison's disease, and systemic lupus erythematosus, all of which occur at elevated frequencies both among vitiligo patients themselves, and also among their first-degree relatives, even those who are not themselves affected with vitiligo (14–16). This has led to the hypothesis that general susceptibility to this constellation of diseases is a complex trait involving various shared susceptibility genes, while other genes and exposure to environmental triggers determine specific disease occurrence in individual patients (17).

Approaches to identification of genes involved in vitiligo pathogenesis have taken a number of forms, initially focusing on biological candidates and differential expression analyses. In recent years, technological advances enabled by the human genome project, and methodological advances applied to analyses of polygenic, multifactorial diseases, have permitted

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FIG. 1. A patient with generalized vitiligo. Note obvious patches of white skin in typical distribution involving the periorbital region and hands.

more global approaches, including a recent genome-wide association study. As the result, there has been considerable progress in identifying susceptibility genes for generalized vitiligo, some of which are shared with other autoimmune diseases and some of which are specific to vitiligo. These genes may thus provide novel therapeutic and even prophylactic targets for new interventional approaches to treat and prevent both generalized vitiligo and other autoimmune diseases in the APS type II constellation.

Here, we review the epidemiology of generalized vitiligo and associated autoimmune diseases, progress toward identifying vitiligo susceptibility genes and their occurrence in other, epidemiologically associated autoimmune diseases (especially AITD), and discuss biological pathways that appear to be specific to vitiligo but which may provide biological insight into other autoimmune diseases.

Epidemiology of Generalized Vitiligo and Associated Autoimmune Diseases

Generalized vitiligo is the most common depigmenting disorder, occurring with a frequency of $\sim 0.5\%$ in various populations around the world (18–20) and an average age of onset of ~ 24 years (14). Women have been overrepresented in virtually all large patient surveys, whereas men and women

are affected equally among probands' affected first-degree relatives (14,15). Large-scale epidemiological surveys have shown that most cases of generalized vitiligo occur sporadically, though about 15%–20% of patients report one or more affected first-degree relatives (14). Very rarely, large multi-generation families segregate vitiligo in an autosomal dominant pattern with incomplete penetrance (21). More typically, however, family clustering of generalized vitiligo cases exhibits a non-Mendelian pattern (14–16,22–29), with overall vitiligo prevalence among probands' first-degree relatives $\sim 7.0\%$ in Caucasians, 6.1% in Indian-Pakistanis, 4.8% in U.S. Hispanic-Latinos (14), and 2.6% in Han Chinese (16). Concordance of generalized vitiligo in monozygotic twin-pairs is $\sim 23\%$ (14), >60 times the general population risk. Together, these findings indicate that susceptibility to generalized vitiligo is a complex, polygenic multifactorial trait.

Melanocyte loss in generalized vitiligo occurs primarily on an autoimmune basis (7,30–32), although the triggers of the autoimmune response remain unknown. Many patients have circulating antibodies to various melanocyte components, most frequently tyrosinase (33), the key enzyme of melanin biosynthesis (34), as well as circulating skin-homing melanocyte-specific cytotoxic T-lymphocytes (35). Sparse infiltrates of activated and cytotoxic T cells are seen at the margins of active lesions (36–38). Moreover, generalized vitiligo is a component of the APECED (APS type I) and Schmidt (APS type II) multiple autoimmune disease syndromes, and in small studies has been associated with AITD (39,40), pernicious anemia (41,42), Addison's disease (43), and perhaps alopecia areata (44,45). Much larger surveys of vitiligo patients (14,15,46–48) have generally found elevated frequencies of AITD, pernicious anemia, rheumatoid arthritis, psoriasis, type 1 diabetes, Addison's disease, and systemic lupus erythematosus; about 15%–25% of patients with generalized vitiligo have at least one additional concomitant autoimmune disorder. Moreover, these same autoimmune diseases also occur with increased prevalence in vitiligo patients' first-degree relatives, regardless of whether or not those relatives have vitiligo themselves (14,15). Together, these findings indicate that vitiligo patients and their close relatives have a genetically determined susceptibility to this specific group of autoimmune diseases, most likely mediated by shared susceptibility genes that predispose to these diseases, with other genes and environmental triggers determining disease specificity.

Vitiligo Susceptibility Genes

Four very different approaches have been used to identify genes that mediate susceptibility to vitiligo: gene expression analyses, candidate gene association studies, genome-wide linkage studies, and genome-wide association studies.

Gene expression studies

Gene expression studies, either of candidate genes or via global analysis using microarrays, can identify genes that are differentially expressed, in cells from vitiligo patients versus controls, or in involved skin versus uninvolved skin. However, gene expression differences cannot distinguish between genes with primary effects versus the many more genes whose expression may be dysregulated on a secondary basis or whose expression merely varies on the outbred genetic background of humans, unrelated to vitiligo.

VIT1 (subsequently renamed *FBXO11*) was originally named on the basis of its apparent aberrant expression in intralesional vitiligo melanocytes (49). Similarly, *MYG1* is a widely expressed gene shown on the basis of differential hybridization to have elevated expression in melanocytes from vitiligo patients (50). Variation in *MYG1* has been found to affect levels of gene expression and to be marginally associated with active vitiligo (51), although this study did not apply appropriate correction for extensive multiple testing. A recent more global analysis of 16,000 transcripts in melanocytes cultured from vitiligo patients versus controls identified a list of 859 differentially expressed genes (52). However, neither *FBOX11* nor *MYG1*, nor any of the top-ranked genes from the more global expression analysis have been identified as potential vitiligo susceptibility genes by either genome-wide linkage studies or a recent genome-wide association study of generalized vitiligo (53), suggesting that none of these genes may be causally involved in vitiligo pathogenesis.

Candidate gene association studies

Candidate gene association studies are best suited to detecting genetic signals that represent relatively common causal variants with modest effect sizes, and hence the typical occurrence of these diseases in singleton patients who have limited or no family history of the disease. However, candidate gene association studies are highly subject to false-positive results, due to population stratification, inadequate statistical power and fluctuation, and inadequate correction for multiple testing, both within and across studies.

Apparent association of vitiligo with many different biological candidate genes has been reported in a large number of studies (Table 1). However, many of these studies reported only marginally significant nominal associations, with inadequate correction for multiple testing, and most have not been replicated in independent studies. Most of these associations thus most likely represent false-positives due to population stratification, low statistical power and fluctuation, and failure to adequately correct for multiple testing. As the result, only two biological candidate genes have been supported by positive results in multiple studies, *HLA* and *PTPN22*, and findings for a third, *CTLA4*, have been difficult to interpret.

The earliest genetic studies of vitiligo were case-control allelic association studies of genes in the major histocompatibility complex (MHC), carried out by genotyping various MHC markers in patients with various different vitiligo phenotypes versus in controls, from many different populations (e.g., 54–59). In general, these early studies found no consistent association between the occurrence of vitiligo and specific *HLA* alleles. However, re-analysis of these studies as a group shows that several found association between vitiligo and *HLA-DR4* alleles (60), and meta-analysis found association of vitiligo with *HLA-A2* (61). More recent studies that used modern analytical and statistical methods found association between generalized vitiligo and *HLA-DRB4*0101* and *HLA-DQB1*0303* in Dutch patients (62), with *HLA-DRB1*03*, *DRB1*04*, and *HLA-DRB1*07* alleles in Turkish patients (63), and with alleles of microsatellites located in the MHC in Colombian patients (64). In Caucasian multiplex generalized vitiligo families, the MHC class II haplotype *HLA DRB1A *04-(DQA1*0302)-DQB1*0301* is associated with both increased

risk of vitiligo and with relatively early disease onset (60), and in Han Chinese generalized vitiligo is associated with the MHC haplotype *HLA-A25-Cw*0602-DQA1*0302* (65). Association has also been reported between generalized vitiligo and genes of the *LMP/TAP* gene region of the MHC (66), although this may merely reflect long-range linkage disequilibrium with the MHC class II gene region.

Three independent candidate gene studies have shown association of the *PTPN22* R620W polymorphism with generalized vitiligo in Caucasians (67–69), thus strongly supporting true association with what is believed to be the causal variant for *PTPN22*-related autoimmune susceptibility (70). An additional study, carried out in Indians from the Gujarat region, failed to observe association of vitiligo with the R620W variant (71), an unsurprising result given the rarity of the R620W variant in non-Caucasian populations and the small size (and thus very limited statistical power) of that study.

Interpretation of findings for *CTLA4* has been more problematic. Several studies have observed apparent association of *CTLA4* and generalized vitiligo (72–74), but principally limited to the subset of patients who have other concomitant autoimmune diseases, although even in this group association has been inconsistent (74,75). A meta-analysis (74) indicated that, overall, association of *CTLA4* with vitiligo is weak, and probably is secondary, driven by primary genetic association of *CTLA4* with other autoimmune diseases that are epidemiologically associated with vitiligo, particularly AITD.

Genome-wide linkage studies

Genetic linkage studies are best suited to detecting genetic signals that represent relatively rare causal variants with large effect sizes; hence, segregation of the corresponding phenotype in the multiplex families needed for linkage analysis. However, it must be borne in mind that most vitiligo patients are singleton cases, with few or no affected relatives, and thus the susceptibility genes and variants detected by linkage in multiplex families may not be typical of the majority of cases. Moreover, in many instances it has proved difficult to identify causal genes that underlie candidate genetic linkage signals.

The first genome-wide linkage study of vitiligo was of a single large family with generalized vitiligo and other autoimmune diseases, inherited as an apparent autosomal dominant trait with incomplete penetrance. Vitiligo in this family was mapped to a 7.4 Mb interval in chromosome segment 1p31.3–p32.2 (76), and detailed studies of genes in this region of chromosome subsequently identified a promoter variant in *FOXD3*, which encodes an embryonic transcription factor that regulates melanoblast differentiation and development (77). However, this family with autosomal dominant vitiligo appears to be unique, and other generalized vitiligo patients do not have mutations of *FOXD3* or show linkage to this region of chromosome 1p.

Genome-wide linkage analyses of more typical small multiplex generalized vitiligo families have yielded a number of other linkage signals (Table 1), for only a few of which have corresponding genes been identified. In Caucasians, besides chromosome 1p, significant vitiligo linkage signals were detected on chromosomes 7p13–q21, 8p12, and 17p, and suggestive signals on chromosomes 9q22, 11p15, 13q33, 19p13, and 22q11, the chromosome 7 and 17p linkages deriving principally from families with other autoimmune diseases, mainly AITD (78,79). In Chinese, a major vitiligo linkage

TABLE 1. GENES SUGGESTED FOR INVOLVEMENT IN GENERALIZED VITILIGO

Chromosome	Gene or Locus	Method	Comments
1p36.23	<i>RERE</i>	Genome-wide association	Confirmed
1p31.3	<i>FOXD3</i>	Genome-wide linkage	Rare autosomal dominant
1p13.3	<i>GSTM1</i>	Candidate gene association	Unconfirmed
1p13.2	<i>PTPN22</i>	Candidate gene association, genome-wide association	Confirmed; associated with many autoimmune diseases
1q25	<i>PTGS2 (COX2)</i>	Candidate gene association	Unconfirmed
2p16.3	<i>FBXO11 (VIT1)</i>	Expression analysis	No evidence causally involved in vitiligo
2q31.2	<i>NRF2</i>	Candidate gene association	Unconfirmed
2q33.2	<i>CTLA4</i>	Candidate gene association	Associated with many autoimmune diseases; inconsistent association with vitiligo
3p13	<i>MITF</i>	Candidate gene linkage	No linkage
3q28	<i>LPP</i>	Genome-wide association	Confirmed; associated with celiac disease and rheumatoid arthritis
5q22.1	<i>TSLP</i>	Candidate gene association	Unconfirmed
6p21.3	<i>HLA-A, MHC class I, class II</i>	Candidate gene association, genome-wide linkage, genome-wide association	Confirmed; associated with many autoimmune disorders
6p21.3	<i>TAP1, LMP2, DDR1</i>	Candidate gene association	Unconfirmed; within MHC; may reflect linkage disequilibrium
6q25.1	<i>ESR1</i>	Candidate gene association	Unconfirmed
6q27	<i>SMOC2</i>	Genome-wide association	Unconfirmed
7	<i>AIS2</i>	Genome-wide linkage, association	Confirmed; autoimmunity-associated
8	<i>AIS3</i>	Genome-wide linkage	Unconfirmed
10p15.1	<i>IL2RA</i>	Genome-wide association	Associated with many autoimmune diseases
10q21.1	<i>MBL2</i>	Candidate gene association	Data conflicting
10q23.31	<i>TNFRSF6 (FAS, APO1)</i>	Candidate gene association	Unconfirmed
11p13	<i>CAT</i>	Candidate gene association	Data conflicting
11p11.2	<i>LXRA</i>	Candidate gene association	Unconfirmed
11q14.3	<i>TYR</i>	Genome-wide association	Confirmed
12q12-q14	<i>VDR</i>	Candidate gene association	Unconfirmed
12q13	<i>MYG1</i>	Gene expression analysis, candidate gene association	Unconfirmed
12q22	<i>KITLG (SCF)</i>	Candidate gene association	Unconfirmed
14q12	<i>GZMB</i>	Genome-wide association	Confirmed
14q22.2	<i>GCH1</i>	Candidate gene association	Now considered invalid
17p13	<i>NLRP1</i>	Genome-wide linkage, candidate gene association	Confirmed; principally in multiplex families
17q23	<i>ACE</i>	Candidate gene association	Data conflicting
19q13.33	<i>SCGF</i>	Candidate gene association	Unconfirmed
21q22.3	<i>UBASH3A</i>	Genome-wide association	Confirmed; associated with type 1 diabetes
21q22.3	<i>AIRE</i>	Candidate gene association	Data conflicting
22q11.21	<i>COMT</i>	Candidate gene association	Unconfirmed
22q11.23	<i>GSTT1</i>	Candidate gene association	Data conflicting
22q12.1	<i>XBPI</i>	Genome-wide linkage, candidate gene association	Unconfirmed
22q13.1	<i>C1QTNF6</i>	Genome-wide association	Confirmed; associated with type 1 diabetes and rheumatoid arthritis

MHC, major histocompatibility complex.

signal was detected on chromosome 4q13–q21, and weaker signals at 1p36, 6p21–p22, 6q24–q25, 14q12–q13, and 22q12 (80,81). Except perhaps for the signals on proximal chromosome 22q, none of linkages observed in Caucasians align with those observed in Chinese, suggesting that, if these linkages are valid, different genes may be involved in the pathogenesis of vitiligo in different populations around the world.

The 17p vitiligo linkage signal, detected principally in multiplex vitiligo families with other associated autoimmune diseases, principally AITD (79), coincided with the location of

SLEVI1, a linkage signal originally detected in multiplex lupus families that included at least one case of vitiligo (82) and subsequently confirmed in multiplex lupus families with various other autoimmune diseases (83). Together, these findings suggested that this locus mediates susceptibility to multiple autoimmune diseases, including at least generalized vitiligo and lupus. Association analysis across the 17p linkage region, first in the same multiplex vitiligo families used for linkage and subsequently in a second set of multiplex vitiligo families, identified *NLRP1* (previously, *NALP1*) as the

vitiligo-autoimmunity gene in this region (84). *NLRP1* encodes a key regulator of the innate immune system that, on interaction with unknown bacterial or viral triggers, stimulates formation of an inflammasome complex that activates the interleukin-1 β inflammatory pathway and perhaps also modulates apoptosis. Subsequent studies have confirmed association of variation in *NLRP1* with generalized vitiligo (85), as well as with Addison's disease (86,87) and type 1 diabetes (86).

A similar approach led to identification of the 22q12 locus detected in Chinese as *Xbp1* (88), encoding a DNA-binding protein, the downstream targets of which are X boxes in many genes, including several *HLA* loci. Association of *Xbp1* with vitiligo has not yet been confirmed in other populations, although variation in *Xbp1* has also been associated with inflammatory bowel disease (89).

Two of the other generalized vitiligo linkage signals, on chromosomes 7p13–q21 and 9q22, have also been subjected to detailed analysis (90). However, specific vitiligo susceptibility genes in these regions have not yet been identified.

Genome-wide association studies

Genome-wide association studies, like candidate gene association studies, are best suited to detecting genetic signals that represent relatively common causal variants with modest effect sizes. However, unlike candidate gene association studies, genome-wide association studies are sufficiently powered to minimize statistical fluctuation and permit adequate control for multiple testing within the study, and provide full-genome datasets that enable both detection of and adjustment for population stratification. As the result, genome-wide association studies have provided robust, highly replicable genetic findings for many different complex human diseases.

Two different genome-wide association studies have been reported for generalized vitiligo, both in Caucasians. The first, of a founder population in an isolated Romanian village with a high prevalence of generalized vitiligo, AITD, and other autoimmune diseases (91), detected association at chromosome 6qter near *IDDM8*, a type 1 diabetes–rheumatoid arthritis locus. This study tentatively identified the causal gene as *SMOC1* (92). The second genome-wide association study of generalized vitiligo studied over 1500 unrelated Caucasian cases in the initial genome-wide screening phase (53). This analysis detected and replicated association with at least 12 different loci (53,93). Most of these appear to represent genes with known functions in the immune response, including *HLA* class I (specifically, *HLA-A*02*), *HLA* class II, *PTPN22*, *RERE*, *FOXP1*, *LPP*, *IL2RA*, *GZMB*, *UBASH3A*, *C1QTNF6*, and probably *CCR6*. Many of these genes have been associated with susceptibility to various other autoimmune diseases. Like the Romanian study, this larger genome-wide association study also detected association at a locus at 6qter near *IDDM8*, though apparently at *CCR6*, located 1.44 Mb proximal to *SMOC2*; the relationship between these two association signals remains to be clarified. Interestingly, although association with *NLRP1* was not detected in the initial genome-wide screen, which included mostly sporadic cases, association with *NLRP1* was confirmed in a subset analysis consisting of multiplex vitiligo families, consistent with a large odds ratio for variation in *NLRP1* that enabled its original mapping by genetic linkage analysis.

In addition to immune-related genes, the vitiligo genome-wide association study detected association to only a single non-immune-related gene, *TYR*, which encodes tyrosinase, the key enzyme of melanin biosynthesis and an important autoantigen in generalized vitiligo. Generalized vitiligo is thus analogous to type 1 diabetes and AITD, in which inherited variation in *INS* and *TG*, respectively, each encoding an important intracellular component of the target cell type, and each constituting a major autoantigen in the corresponding disease, each predisposes to disease susceptibility. For generalized vitiligo, the causal *TYR* vitiligo susceptibility variant appears to be the major allele of the common R402Q polymorphism. The minor *TYR*402R allele encodes a thermosensitive tyrosinase polypeptide that is present in greatly reduced amounts and is incorrectly glycosylated, and which thus is less available for presentation to the immune system. In fact, tyrosinase peptide is presented on the melanocyte surface by *HLA-A*0201*, which corresponds to the high-risk allele of *HLA-A*, and there was significant genetic interaction between the most associated single-nucleotide polymorphisms in *TYR* and *HLA-A* (53). Importantly, the *TYR*402Q allele, while conferring apparent susceptibility to generalized vitiligo, is also associated with genetic protection from malignant melanoma (94,95). A unifying hypothesis is that the *TYR* R402Q variant may mediate alternative susceptibility to vitiligo versus melanoma via modulating immune surveillance of malignant melanomas.

Genetic Relationships Between Generalized Vitiligo and AITD

There is strong epidemiological association between generalized vitiligo and AITD, which occurs (88% hypothyroidism and 12% hyperthyroidism) in 17%–25% of vitiligo probands and 6%–15% of their first-degree relatives (14,15), while the prevalence of vitiligo among patients with AITD is ~7% (96,97). This epidemiological association strongly suggests that generalized vitiligo and AITD share common genetic susceptibility factors.

Genome-wide linkage and candidate gene association studies have identified a number of loci potentially involved in AITD (98–100). The strongest association is to *HLA-DR3* (101), in which a 74R variant allele appears to be causal for disease predisposition (102–104). In contrast, generalized vitiligo is associated with *HLA-DR4* on an MHC class II *DRB1*04–DQB1*0301* haplotype (60).

A number of non-MHC candidate genes have been associated with AITD, although only six have been confirmed in multiple studies (105). These include four immunomodulatory genes, *CTLA4* (106), *PTPN22* (107), *CD40* (108), and *FCRL3* (109), and two thyroid-specific genes, thyroglobulin (*TG*) (110), and *TSHR* (111), though undoubtedly additional unidentified genes contribute to AITD susceptibility. Of these, genetic association of *PTPN22* with generalized vitiligo is well established, whereas association of *CTLA4* with generalized vitiligo appears to be indirect, reflecting primary association with other concomitant autoimmune diseases that occur in some vitiligo patients, principally AITD. At present, there is no evidence for association of either *CD40* or *FCRL3* with generalized vitiligo, and association signals were not observed in the vicinity of these genes in the recent vitiligo genome-wide association studies (53,91). Likewise, there was

association with *TSHR* or *TG*, even in the subset of vitiligo patients with concomitant AITD, suggesting that these loci may be relevant principally to patients with isolated AITD, and that broader autoimmunity susceptibility genes may be of greater importance in patients with concomitant generalized vitiligo and AITD.

Conclusions

Recent studies have identified a number of confirmed genes that underlie susceptibility to generalized vitiligo. Whereas one of these, *TYR*, encodes a melanocyte-specific protein that likely plays a key role in target cell specificity of the autoimmune response, most vitiligo susceptibility genes encode proteins involved in immune functions. Indeed, many of these have also been identified as susceptibility genes for other autoimmune diseases with which generalized vitiligo is epidemiologically associated. The overall situation in AITD appears to be similar, with both general autoimmunity genes and thyroid-specific genes identified as conferring disease susceptibility. Generalized vitiligo and AITD are closely associated epidemiologically, and it is likely that, as additional susceptibility genes are identified for both of these autoimmune diseases, many will be shared in common, leading to a convergence of shared autoimmune susceptibility genes as well as sets of specific genes and ultimately environmental triggers that determine disease specificity and onset.

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Disclosure Statement

The author declares that no competing financial interests exist.

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