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# Six decades of vitiligo genetics: Genomewide studies provide insights into autoimmune pathogenesis

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## Abstract

Generalized vitiligo (GV) is a complex disease in which patchy depigmentation results from autoimmune loss of melanocytes from affected regions. Genetic analyses of GV span six decades, with the goal of understanding biological mechanisms and elucidating pathways that underlie the disease. The earliest studies attempted to describe the mode of inheritance and genetic epidemiology. Early genetic association studies of biological candidate genes resulted in some successes, principally *HLA* and *PTPN22*, but in hindsight many such reports now seem to be false-positives. Later genomewide linkage studies of multiplex GV families identified *NLRP1* and *XBP1*, which appear to be valid GV susceptibility genes that control key aspects of immune regulation. Recently, the application of genomewide association studies to analysis of GV has produced a rich yield of validated GV susceptibility genes that encode components of biological pathways reaching from immune cells to the melanocyte. These genes and pathways provide insights into underlying pathogenetic mechanisms and potential triggers of GV, establish relationships to other autoimmune diseases, and may provide clues to potential new approaches to GV treatment and perhaps even prevention. These results thus validate the hopes and efforts of the early investigators who first attempted to comprehend the genetic basis of vitiligo.

### Keywords

vitiligo; autoimmune disease; gene; association; linkage

## INTRODUCTION

Generalized vitiligo (GV) is a complex disorder in which acquired, progressive, multifocal loss of pigmentation of skin and hair results from loss of melanocytes from the affected areas (Taïeb and Picardo, 2009; Birlea et al., 2011b). While the striking phenotype of GV has been recognized for thousands of years (Nordlund et al., 2006), its underlying pathobiology has remained largely unknown, despite the suggestion of numerous theories



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**CONFLICT OF INTEREST**

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(Boissy and Spritz, 2009; Picardo and Taïeb, 2010). Some of the earliest attempts to understand the biology of GV considered its possible genetic basis, in the hope that understanding the genetics would lead to insights into basic pathogenetic mechanisms of disease (Stüttgen, 1950; Teindel, 1950; Lerner, 1959). Over the next four decades, various types of genetic studies aimed to discover genes involved in mediating GV susceptibility, with limited success. However, recently genomewide genetic association studies have succeeded in identifying a veritable cornucopia of GV susceptibility genes, encoding components of biological networks that largely regulate elements of the immune system and their targeting and destruction of melanocytes.

## EPIDEMIOLOGICAL STUDIES

Probably the earliest evidence relating to the genetic basis of vitiligo was the 1855 description by Addison, of a patient with idiopathic adrenal insufficiency (now known as Addison's disease), GV, and pernicious anemia (Addison, 1855). Over the next century numerous case reports described co-occurrence of GV and various other autoimmune diseases, and in 1908 Claude suggested the likelihood of a causal connection among autoimmune diseases that tended to occur concomitantly (Claude, 1908).

In 1926 Schmidt codified the concomitant occurrence of Addison's disease and autoimmune thyroid disease, in what came to be called "Schmidt syndrome" (Schmidt, 1926), and in1980 Neufeld and Blizzard re-classified the so-called "autoimmune polyglandular syndromes" (APS), denoting a rare autosomal recessive form (sometimes including GV) as APS-1, denoting Schmidt syndrome (sometimes including GV) as APS-2, denoting concomitant occurrence of autoimmune thyroid disease with at least one other autoimmune disease (again, often including GV) as APS-3, and denoting all other combinations of autoimmune diseases as APS-4 (Neufeld and Blizzard, 1980). While there have been a number of subsequent attempts to refine the APS classification, except for APS-1 (now renamed APECED; autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy, resulting from mutations in the *AIRE* gene), this system is no longer widely used. Instead, it has become clear that "multiple autoimmune disease" is more complex, and that GV is part of a more general autoimmune disease diathesis. Indeed, the frequencies of many other autoimmune diseases, particularly including autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease), adult-onset type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, pernicious anemia, Addison's disease, and systemic lupus erythematosus (SLE), are elevated among GV patients (Alkhateeb et al., 2003; LaBerge et al., 2005; Sun et al., 2006). Furthermore, the frequencies of these same autoimmune diseases are elevated among the first-degree relatives of GV patients, even those who do not have GV (Alkhateeb et al., 2003; LaBerge et al., 2005). This has led to the belief that general susceptibility to autoimmunity is a complex trait involving various shared susceptibility genes, while other genes and exposure to unknown environmental triggers determine the occurrence of GV and other specific autoimmune diseases in individual patients (Spritz, 2008).

In addition, genetic epidemiological studies have addressed the likely mode of inheritance of GV. While there had been a number of previous case reports describing the occurrence of GV in occasional relatives, perhaps the first to address the inheritance of GV specifically

were Stüttgen (1950) and Teindel (1950), who described multigenerational families with multiple cases of GV ("multiplex families") and other autoimmune diseases, concluding that autosomal dominant inheritance seemed likely. Based on a survey of 128 vitiligo patients, Lerner (1959) noted that 38% reported affected relatives, and concluded the "disease is often transmitted as a dominant trait." However, while many subsequent patient surveys around the world confirmed frequent clustering of vitiligo cases within families (*e.g*. Mehta et al., 1973; Howitz et al., 1977; Obe, 1984; Das et al., 1985; Bhatia et al., 1992; Majumder et al., 1993; Kim et al., 1998; Alkhateeb et al., 2003; Sun et al., 2006), a single-locus Mendelian pattern of inheritance was not supported, and most favored a polygenic, multifactorial model involving multiple genes and also environmental risk factors, what is now termed a "complex trait". An major environmental component in GV is also indicated by its limited concordance in monozygotic twins; among 22 such twin-pairs, Alkhateeb et al. (2003) reported a concordance of only 23%, underscoring the importance of environmental triggers in disease pathogenesis.

## CANDIDATE GENE ASSOCIATION STUDIES

The earliest analyses testing the involvement of specific genes in the pathogenesis of GV were candidate gene association studies, of HLA (Retornaz et al., 1976), ABO (Kareemullah et al., 1977), and other blood groups (Wasfi et al., 1980), and were generally negative. A large number of 'positive' candidate gene associations with GV have been reported subsequently (reviewed in Birlea et al., 2011a). However, candidate gene association studies of complex diseases have generally proven to be highly subject to false-positive artifacts, principally due to occult ethnic differences between cases and controls (population stratification) and inadequate correction for multiple-testing (Hirschhorn et al., 2002; Freedman et al., 2004), and thus have fallen into general disfavor. Except for *HLA* and *PTPN22*, most candidate gene associations reported for GV have not been confirmed by subsequent studies (reviewed in Birlea et al., 2011a).

## GENOMEWIDE LINKAGE STUDIES

Genomewide linkage and association studies are not biased by *a priori* biological hypotheses and are less subject to methodological pitfalls than are candidate gene approaches. Genetic linkage studies are best suited to detecting relatively rare disease susceptibility alleles with large effects, as in multiplex families. While genetic linkage studies are typically carried out genomewide, in fact the first linkage analysis reported for GV was a negative study, testing linkage of a candidate gene, *MITF* (Tripathi et al., 1999). The first direct genomewide linkage study of GV, in a unique large Caucasian kindred with apparent autosomal dominant inheritance with incomplete penetrance, detected linkage in chromosome 1p31.3–p32.2 ("*AIS1*"; Alkhateeb et al., 2001). Subsequent DNA sequence analysis of genes in the chromosome 1p linkage interval identified a transcriptional regulatory variant of *FOXD3*, which encodes Forkhead box D3), a key regulator of melanoblast lineage differentiation and development (Alkhateeb et al., 2005).

Genomewide linkage studies of many other Caucasian multiplex GV families identified additional linkage signals on chromosomes 7, 8, 9, 11, 13, 17, 19, and 22 (Fain et al., 2003;

Spritz et al., 2004). The strongest of these signals, on chromosome 17p13, coincided with *SLEV1*, a linkage signal for SLE detected in families that also included at least one relative with GV (Nath et al., 2001) or other autoimmune diseases (Johansson et al., 2004). Targeted family-based genetic association analysis of SNPs spanning the chromosome 17p linkage interval identified the corresponding gene as *NALP1* (now renamed *NLRP1*), encoding NACHT, LRR, and PYD domains-containing protein 1 (Jin et al., 2007a), a key regulator of the innate immune system that apparently acts as a sentinel for bacterial infection in the skin (Lamkanfi and Dixit, 2009). Several studies have subsequently confirmed association of *NLRP1* with GV, (Jin et al., 2007b; Alkhateeb and Qarqaz, 2010), and also with type 1 diabetes (Magitta et al., 2008), Addison's disease (Magitta et al., 2008; Zurawek et al., 2010), celiac disease (Pontillo et al., 2011), systemic sclerosis (Dieudé et al., 2010), and perhaps inflammatory bowel disease (De Iudicibus et al., 2011).

Parallel genetic linkage studies of GV in Han Chinese detected linkage signals on chromosomes 1, 4, 6, 14, and 22 (Chen et al., 2005; Liang et al., 2007). These linkage signals generally did not correspond to those detected in Caucasian families, suggesting that different genes might underlie GV susceptibility in these different populations. By candidate gene association analysis of several genes located within the chromosome 22q12.1–12.3 linkage peak, Ren et al. (2009) subsequently identified *XBP1*, encoding transcription factor X-box binding protein 1, which activates MHC class II gene expression, regulates plasma cell differentiation, and mediates inflammatory response to endoplasmic reticulum stress. Additional support for involvement of *XBP1* in the pathogenesis of GV came from a subsequent genomewide association study of Caucasians (Birlea et al., 2011a), and *XBP1* has been independently associated with genetic risk of Crohn's disease (Kaser et al., 2008).

## GENOMEWIDE ASSOCIATION STUDIES

Genomewide association studies (GWAS) are best suited to detecting relatively common disease susceptibility alleles with modest effects, as may be most relevant to typical singleton cases of a complex disease such as GV. Of particular importance, GWAS can adequately correct for both population stratification and multiple-testing (Hirschhorn et al., 2002; Freedman et al., 2004), and so are currently considered the "gold standard" for identifying complex trait susceptibility genes.

The first GV GWAS (Birlea et al., 2010) involved a "special population", an isolated village with a very high prevalence of GV located in the mountains of northwestern Romania (Birlea et al., 2008). This analysis detected GV association with SNPs in distal chromosome 6q27, in the vicinity of *IDDM8*, a linkage and association signal for type I diabetes mellitus and rheumatoid arthritis.

A subsequent, much larger GWAS in Caucasians detected at least 13 different GV susceptibility loci (Jin et al., 2010a,b; Table 1), and confirmed three others that had been reported in previous candidate gene studies (Birlea et al., 2011a). A parallel GV GWAS in Chinese (Quan et al., 2010) detected two association signals, one or both of which were among those detected in Caucasians (Table 1). In both the Caucasian and Chinese studies, strong GV association signals were detected in the major histocompatibility complex (MHC)

on chromosome 6p21.3. In Caucasians, independent associations were detected in both the MHC class I and class II gene regions. In the class I region, the major association signal was in the vicinity of *HLA-A*, in strong linkage disequilibrium with *HLA-A*02*. In the class II region, the major association signal was located between *HLA-DRB1* and *HLA-DQA1*, in moderate linkage disequilibrium with *HLA-DRB1**04 (Jin et al., 2010a). These results are thus consistent with previous reports of association of GV with both *HLA-A**02 (Liu et al., 2007) and *HLA-DRB1**04 (Fain et al., 2006) alleles. However, in Chinese, the major MHC association signal was in the class III gene region, with some evidence for additional association in the class II gene region (Quan et al., 2010).

Perhaps more important, these two large-scale GV GWASs also detected association with a number of non-MHC loci, almost all of which encode immunoregulatory proteins. The Caucasian GWAS (Jin et al., 2010a,b) detected associations with at least ten non-MHC loci: *TYR* (tyrosinase), *PTPN22* (lymphoid-specific protein tyrosine phosphatase nonreceptor type 22), *RERE* (arginine-glutamic acid dipeptide [RE] repeats protein; atrophin-like protein 1), *FOXP1* (forkhead box P1), *LPP* (LIM domain-containing preferred translocation partner in lipoma), *IL2RA* (interleukin-2-receptor alpha chain), *GZMB* (granzyme B), *UBASH3A* (ubiquitin-associated and SH3 domain-containing A), *C1QTNF6* (C1q and tumor necrosis factor-related protein 6), and *CCR6* (C-C chemokine receptor type 6). This last gene is located very close to the 6q27 association signal detected in the Romanian village (Birlea et al., 2010), and was the only non-MHC locus detected in the Chinese GWAS (Quan et al., 2010). The Caucasian GWAS also provided evidence of association of GV with additional loci previously suggested as candidate genes for GV: *XBP1* (see above), *FOXP3* (forkhead box P3), *TSLP* (thymic stromal lymphoprotein), and *CTLA4* (cytotoxic T-lymphocyte antigen 4), though as in previous studies association of GV with *CTLA4* appeared to reflect primary association with other concomitant autoimmune diseases in the GV cases, rather than with GV itself (Birlea et al., 2011a).

Among the most illuminating associations with GV are those of MHC class I and *TYR*, which together highlight one of the pathways by which the immune system “sees” and thus targets melanocytes. The MHC class I association in Caucasians with GV is with SNP rs12206499, which tags *HLA-A*02* (predominantly *HLA-A*02:01*), while the *TYR* association with GV is with the major (R; Arg) allele of the R402Q polymorphism (SNP rs1126809) that is relatively common among Caucasians (minor allele frequency 0.22 to 0.40) but is rare in other populations (Tripathi et al., 1991). In contrast, the minor (Q; Gln) allele of the *TYR* R402Q polymorphism is associated with susceptibility to malignant melanoma (Gudbjartsson et al., 2008; Bishop et al., 2009), while *HLA-A*02* is associated with relatively favorable response to melanoma immunotherapy (Mitchell et al., 1992). Tyrosinase is a major GV autoantigen presented to the immune system on the surface of melanocytes and melanoma cells by HLA class I molecules, principally HLA-A*02. One of the important epitopes presented by HLA-A*02 is a modified tyrosinase nonapeptide, YMDGTMSQV (Skipper et al., 1996). However, the variant 402Q form of tyrosinase is hypoglycosylated (Toyofuku et al., 2001), which in turn would prevent the modification that is essential for its antigenic presentation by HLA-A*02. As the result, tyrosinase-402R likely makes a quantitatively greater contribution than tyrosinase-402Q to presentation of

antigenic tyrosinase by HLA-A*02. Together, these findings indicate an apparent inverse relationship between genetic susceptibility to GV and genetic susceptibility to malignant melanoma as mediated by *TYR* and *HLA-A*02* (Jin et al., 2010a), suggesting that GV may represent a dysregulated mechanism of immune surveillance against malignant melanoma, with *TYR* R402Q modulating immune recognition of melanocytes by modulating availability of tyrosinase peptide for presentation by HLA-A*02 (Spritz, 2010).

In addition to primary searches for genes that influence disease susceptibility *per se*, genomewide approaches can also be used to identify genes that influence the natural history of disease. Such an approach has recently been taken to identify a locus that contributes to GV age of onset (Jin et al., 2011). These authors' reanalyzed their previous GV GWAS dataset, considering only the affected individuals, in whom GV age of onset was assessed as a quantitative trait. This analysis identified a major GV age of onset locus in the MHC class II region, apparently reflecting the same locus that was associated with GV susceptibility (Jin et al., 2010a), while none of the other loci that had been associated with GV susceptibility *per se* were associated with age of onset. These results suggest that some loci likely mediate GV susceptibility *per se*, whereas other loci, particularly variation in the MHC class II region, might mediate response to environmental triggers encountered over the course of life, thereby influencing age of disease onset.

## PERSPECTIVE

For GV as for many other complex diseases, application of genomewide approaches, particularly GWAS, has resulted in rapid progress in identifying true disease susceptibility genes, while most genes suggested as *a priori* biologically-based candidates have remained unconfirmed. Accordingly, for GV as for many other diseases, we have entered a new era of understanding the true underlying pathobiology, which in the case of GV appears to be predominantly autoimmune. Furthermore, many of the genes that are genetically associated with GV are also genetically associated with some of the other autoimmune diseases with which GV is epidemiologically associated, confirming the longstanding hypothesis that these epidemiological associations reflect underlying shared causal elements (Claude, 1908).

The studies carried out so far have identified a plethora of new biological pathways that constitute potential targets for therapeutic intervention and perhaps even disease prevention. However, these findings only scratch the surface, accounting for a relatively small portion of total disease risk. Larger genomewide studies can be expected to identify even more GV susceptibility genes and thus shed even more light on the nature of the disease, and perhaps even provide clues to environmental triggers. Moreover, for only a few of the GV susceptibility genes found thus far have the corresponding underlying causal variants been identified; this will require extensive DNA sequencing of large numbers of GV patients, careful bioinformatics analysis, and targeted functional studies to assess the effects of specific variants, both individually and in combination. Nevertheless, the way forward is now clear, with many doors opening to new understanding and new opportunities for treating patients with GV.

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**Table 1**

Loci with confirmed involvement in GV susceptibility on the basis of genomewide studies[1]

| Chromosome | Gene | Protein | Function | Causal Variant | Other Autoimmune Disease Associations |
|---|---|---|---|---|---|
| 1p36.23 | *RERE* | Atrophin-like protein 1 | Regulates apoptosis | | |
| 1p13.2 | *PTPN22* | Lymphoid-specific protein tyrosine phosphatase nonreceptor type 22 | Regulates T cell receptor signaling | R620W | Type 1 diabetes, SLE, Graves' disease, rheumatoid arthritis, Addison's disease, psoriasis, inflammatory bowel disease |
| 2q33.2 | *CTLA4*[2] | Cytotoxic T-lymphocyte antigen 4 | Inhibits T cells | | Type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, inflammatory bowel disease, SLE |
| 3p13 | *FOXP1* | Forkhead box P1 | Regulates lymphoid cell development | | |
| 3q28 | *LPP* | LIM domain-containing preferred translocation partner in lipoma | Unknown | | Celiac disease, rheumatoid arthritis |
| 5q22.1 | *TSLP* | Thymic stromal lymphoprotein | Regulates T cell and dendritic cell maturation | | |
| 6p21.3 | MHC class I (*HLA-A*) | Human leukocyte antigen α chain | Presents peptide antigens | *02:01 | Many |
| | MHC class II[3] | Unknown | | | Many |
| | MHC class III | Unknown | | | Many |
| 6q27 | *CCR6* | C-C chemokine receptor type 6 | Regulates B cell differentiation, function of dendritic and Th17 cells | | Inflammatory bowel disease, rheumatoid arthritis, Graves' disease |
| 10p15.1 | *IL2RA* | Interleukin-2 receptor α chain | Regulates lymphocyte response to bacteria via IL2 | | Type 1 diabetes, Graves' disease, multiple sclerosis, rheumatoid arthritis, SLE |
| 11q14.3 | *TYR* | Tyrosinase | Key enzyme of melanin biosynthesis | R402Q | |
| 14q12 | *GZMB* | Granzyme B | Mediates target cell apoptosis by cytotoxic T cells and natural killer cells, activation-induced cell death of effector Th2 cells | | |
| 17p13.2 | *NLRP1* | NACHT, LRR, and PYD domains-containing protein 1 | | | Type 1 diabetes, Addison's disease, celiac disease, systemic sclerosis |
| 21q22.3 | *UBASH3A* | Ubiquitin-associated and SH3 domain containing A | Regulates T cell receptor signaling | | Type 1 diabetes |
| 22q12.1 | *XBP1* | X-box binding protein 1 | Regulates expression of MHC class II genes, IL6, B cell and plasma cell differentiation | | Crohn's disease |
| 22q13.1 | *C1QTNF6* | C1q and tumor necrosis factor-related protein 6 | Unknown | | Type 1 diabetes, rheumatoid arthritis |
| Xp11.23 | *FOXP3* | Forkhead box P3 | Regulates regulatory T cells | | Defective gene in Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) |

[1] Adapted from Spritz (2011).

[2] Numerous studies have indicated that *CTLA4* is only associated with GV in patients who also have other autoimmune diseases, suggesting that apparent association of *CLTA4* with GV is secondary to epidemiological association with these other diseases.

[3] The MHC class II region is associated with both GV susceptibility and age of onset.