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Recent progress in the genetics of generalized vitiligo

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Abstract

Vitiligo is an acquired disease characterized principally by patchy depigmentation of skin and overlying hair. Generalized vitiligo (GV), the predominant form of the disorder, results from autoimmune loss of melanocytes from affected regions. GV is a "complex trait", inherited in a non-Mendelian polygenic, multifactorial manner. GV is epidemiologically associated with other autoimmune diseases, both in GV patients and in their close relatives, suggesting that shared genes underlie susceptibility to this group of diseases. Early candidate gene association studies yielded a few successes, such as *PTPN22*, but most such reports now appear to be false-positives. Subsequent genomewide linkage studies identified *NLRP1* and *XBP1*, apparent true GV susceptibility genes involved in immune regulation, and recent genome-wide association studies (GWAS) of GV in Caucasian and Chinese populations have yielded a large number of additional validated GV susceptibility genes. Together, these genes highlight biological systems and pathways that reach from the immune cells to the melanocyte, and provide insights into both disease pathogenesis and potential new targets for both treatment and even prevention of GV and other autoimmune diseases in genetically susceptible individuals.

Keywords

Vitiligo; Autoimmune disease; Gene; Association; Linkage

1. Introduction

Vitiligo is an acquired, non-contagious disease in which progressive, patchy, multifocal loss of pigmentation of skin, overlying hair, and often mucous membranes results from loss of melanocytes from the involved areas (Taïeb and Picardo, 2009). In generalized vitiligo (GV), the predominant form of the disorder (includes acrofacial vitiligo, vitiligo universalis, vitiligo vulgaris, and non-segmental vitiligo), patches of depigmented skin result from autoimmune destruction of melanocytes (Birlea et al., 2010).

GV is perhaps the most common pigmentation disorder, occurring at a frequency of approximately 0.2–1.0 percent in different populations around the world (Spritz, 2008). Because of its visually striking phenotype, vitiligo has been recognized for thousands of years (Nordlund et al., 2006). Nevertheless, the pathobiological basis of GV has remained surprisingly controversial, with many different theories suggested (Picardo and Taïeb, 2010), most supported by little compelling evidence (Boissy and Spritz, 2009). Indeed, it is only the results of recent genome-wide association studies (GWAS), identifying GV

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susceptibility genes which almost universally involve immune regulation and immune targeting of melanocytes, that have led to the general consensus that GV is a primary autoimmune disease, though the biological triggers of the autoimmune process remain unknown.

In fact, there has long been considerable evidence in favor of an autoimmune basis of GV. Many, but not all GV patients have circulating antibodies to melanocytes and various melanocyte protein components, though most investigators believe these to be humoral responses to melanocyte destruction rather than a primary cause (Kemp et al., 2007). Perhaps of greater importance may be the occurrence of circulating skin-homing melanocyte-specific cytotoxic T lymphocytes (Ogg et al., 1998) and sparse infiltrates of activated and cytotoxic T cells at the margins of active lesions (Gross et al., 1987; Badri et al., 1993; Le Poole et al., 1996), though the fraction of GV patients with such infiltrates is uncertain (Harsoulis et al., 1978; Ongenae et al., 2003). Nevertheless, the strongest evidence for an auto-immune process underlying GV is its close epidemiological association with other autoimmune diseases, both in GV patients and in their close relatives (Alkhateeb et al., 2003a). In 1855 Addison reported a patient with idiopathic adrenal insufficiency, vitiligo, and pernicious anemia (Addison, 1855). Subsequently, Schmidt described concomitant occurrence of multiple auto-immune diseases, including GV, in what came to be called “Schmidt syndrome” (Schmidt, 1926). Much later, Neufeld and Blizzard categorized the so-called “autoimmune polyglandular syndromes” (APS), with Schmidt syndrome denoted type II (Neufeld and Blizzard, 1980). Over the past few years it has become clear that APS II is more complex than previously thought, and that GV is part of an autoimmune disease diathesis that also includes autoimmune thyroid disease (AITD, particularly Hashimoto’s thyroiditis and Graves’ disease), rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, pernicious anemia, Addison’s disease, and systemic lupus erythematosus (SLE), 10%–15% or more of patients with GV also manifesting one or more of these other autoimmune diseases (Alkhateeb et al., 2003a; Laberge et al., 2005; Sun et al., 2006). Moreover, these same autoimmune diseases also occur at increased frequency in GV patients’ first-degree relatives, regardless of whether or not those relatives have vitiligo themselves (Alkhateeb et al., 2003a; Laberge et al., 2005). Together, these findings indicate that GV patients and their close relatives have genetically determined susceptibility to this specific group of autoimmune diseases, most likely mediated by shared susceptibility genes that predispose to these diseases, other genes and exposure to environmental triggers determining the occurrence of GV and other specific autoimmune diseases in individual patients (Spritz, 2008).

Epidemiological studies have shown that GV is a complex trait, involving combinatorial pathogenic effects of multiple susceptibility genes and also environmental risk factors. Clustering of GV cases occurs in some families, almost always in non-Mendelian patterns indicative of polygenic, multifactorial causation (Alkhateeb et al., 2003a; Laberge et al., 2005). Indeed, the concordance of GV in monozygotic twins is only 23% (Alkhateeb et al., 2003a), highlighting the importance of environmental triggers, which as yet remain unknown.

2. Vitiligo gene identification

Approaches to identification of genes involved in vitiligo pathogenesis have taken four principal forms as human genetic technologies have evolved. Initial studies focused on differential expression analyses and biological candidate genes. These studies largely yielded false-positives, though there were some successes. In recent years, technological advances enabled by the human genome project, and methodological advances in statistical analyses of polygenic, multifactorial diseases, have permitted more global approaches,

including GWAS. As the result, there has been considerable progress in identifying true GV susceptibility genes, some of which are shared with other autoimmune diseases and some of which are specific to vitiligo. This has led to dramatic advances in understanding of disease pathogenesis; moreover, 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 II disease constellation.

2.1. Gene expression studies

Gene expression studies, either of individual candidate genes or global analyses using microarrays, can identify genes that are differentially expressed, in cells from GV patients *versus* controls, or in involved skin *versus* uninvolved skin. However, gene expression differences cannot distinguish between genes with primary effects on disease causation *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. As the result, such studies have not led to important insights into the pathogenesis of GV.

The first putative “vitiligo gene” identified by differential expression was *VIT1* (subsequently renamed *FBXO11*), originally so-named on the basis of its apparent aberrant expression in intralesional GV melanocytes (Le Poole et al., 2001). Similarly, *MYG1* is a widely expressed gene found by differential hybridization to have elevated expression in melanocytes from GV patients (Kingo et al., 2006). Variation in *MYG1* has been found to affect levels of gene expression and to be marginally associated with active GV (Philips et al., 2010), although this study did not apply appropriate correction for extensive multiple testing and therefore must be considered with caution. A global analysis of 16,000 transcripts in melanocytes cultured from GV patients *versus* controls identified a total of 859 differentially-expressed genes (Strömberg et al., 2008). However, neither *FBXO11* nor *MYG1*, nor any of the top-ranked genes from the global expression analysis have been identified as potential vitiligo susceptibility genes by either genomewide linkage studies or GWAS of GV, suggesting that none of these differentially-expressed genes may be causally involved in vitiligo pathogenesis.

2.2. Candidate gene association studies

Candidate gene association studies are best suited to detect genetic signals that represent relatively common causal variants with modest effect sizes. Moreover, candidate gene association studies are relatively easy to carry out, usually involving simple comparison of allele frequencies in cases *versus* controls. However, such studies are highly subject to false-positive results, due to inadequate ethnic matching of cases and controls, occult population stratification, inadequate statistical power and statistical fluctuation, and inadequate correction for multiple testing, both within and across studies (Hirschhorn et al., 2002; Freedman et al., 2004).

At least 33 different candidate genes for GV have been reported on the basis of such studies (reviewed in Birlea et al., 2011, Table 1). Overall, only two biological candidate genes have been strongly supported by positive results in multiple studies, *HLA* and *PTPN22*, and findings for a third, cytotoxic T-lymphocyte antigen 4 (*CTLA4*), have been inconsistent and difficult to interpret. Many of these reported GV candidate gene studies found only marginally significant nominal associations, and had inadequate statistical correction for multiple testing, and most have not been replicated in independent studies.

The earliest genetic studies of vitiligo were case–control allelic association studies of candidate 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., Foley et al., 1983; Finco et al., 1991; Orecchia et al., 1992; Ando et al., 1993; Schallreuter et al., 1993; al-Fouzan et al., 1995). In general, these early studies found little consistent association between the occurrence of GV and specific HLA alleles, particularly among patients from different ethnic populations. However, re-analysis of these studies as a group shows that several found association between vitiligo and *HLA-DR4* alleles (Fain et al., 2006), and meta-analysis found association of vitiligo with *HLA-A2* (Liu et al., 2007). More recent studies employing modern analytical and statistical methods found association between GV and *HLA-DRB4*0101* and *HLA-DQB1*0303* in Dutch patients (Zamani et al., 2001), with *HLA-DRB1*03*, *DRB1*04*, and *HLA-DRB1*07* alleles in Turkish patients (Tastan et al., 2004), and with alleles of microsatellites located in the MHC in Colombian patients (Arcos-Burgos et al., 2002). In Caucasian multiplex GV families, the MHC class II haplotype *HLA-DRB1*04*-(*DQA1*0302*)-*DQB1*0301* is associated with both increased risk of GV and with relatively early disease onset (Fain et al., 2006), and in Han Chinese GV is associated with the MHC haplotype *HLA-A25-Cw*0602-DQA1*0302* (Xia et al., 2006). Association has also been reported between GV and genes of the *LMP/TAP* gene region of the MHC (Casp et al., 2003), although more recent studies indicate these likely merely reflect long-range linkage disequilibrium with the MHC class II gene region (Birlea et al., 2011).

Three independent candidate gene studies have shown association of the *PTPN22* R620W polymorphism with GV in Caucasians (Cantón et al., 2005; Laberge et al., 2008a,b), strongly supporting association of GV with what is believed to be the causal variant for *PTPN22*-related autoimmune susceptibility (Brand et al., 2005). An additional study, carried out in GV patients from the Gujarat region of India, found no association with the R620W variant (Laddha et al., 2008), though this result is not surprising given the rarity of the R620W variant in non-Caucasian populations and the small size (and thus very limited statistical power) of the study.

Interpretation of findings for *CTLA4* has been more problematic. Several studies have observed apparent association of *CTLA4* with GV (Blomhoff et al., 2005; Birlea et al., 2009; Pehlivan et al., 2009), but only in the subset of GV patients who have other concomitant autoimmune diseases, principally AITD, and even in this group association has been inconsistent (Laberge et al., 2008a,b; Pehlivan et al., 2009). A meta-analysis (Birlea et al., 2009) indicated that, overall, association of *CTLA4* with vitiligo is weak, and probably is secondary, the result of primary genetic association of *CTLA4* with other autoimmune diseases with which GV is epidemiologically associated, rather than actual primary genetic association between *CTLA4* and GV.

Birlea et al. (2011) systematically tested association of 33 previously reported GV candidate genes in a large GWAS dataset. Of these, only HLA class I, HLA class II, and *PTPN22* were strongly confirmed, with weaker support for *TSLP*, *XBP1*, and *FOXD3*. The other previously reported associations were not confirmed and likely represent false-positives.

2.3. Genomewide linkage studies

Whereas candidate gene studies of complex diseases have proven to be highly subject to false-positive artifacts (Hirschhorn et al., 2002; Freedman et al., 2004), genomewide *de novo* searches for disease susceptibility genes are not encumbered by *a priori* biological hypotheses that may bias results, and are relatively free of the methodological artifacts that plague candidate gene approaches. Accordingly, genomewide linkage and association studies are now considered the “gold standard” in human genetic research, while candidate gene studies have fallen into general disfavor.

The first genomewide studies of GV were genetic linkage analyses of "multiplex" families with multiple relatives affected by GV. Genetic linkage studies are best suited to detect relatively uncommon disease susceptibility alleles that exert relatively large effects, as in such multiplex families, though such alleles may be less relevant to more typical singleton cases. The first genomewide genetic linkage study reported for GV analyzed a single, large European-derived white Caucasian family in which GV was inherited as a virtual Mendelian trait, an apparent autosomal dominant with incomplete penetrance (Alkhateeb et al., 2002). Significant linkage was detected in chromosome 1p31.3–p32.2, and DNA sequence analysis of genes within the linkage interval identified a promoter variant of *FOXD3* (encoding Forkhead box D3), a key regulator of melanoblast lineage differentiation and development. This variant significantly up-regulated *FOXD3* transcription *in vivo* (Alkhateeb et al., 2005), which would be predicted to negatively affect development of the melanocyte lineage. However, linkage of GV to the *FOXD3* region of chromosome 1p has thus far only been observed in this unique family, and remains to be confirmed.

More extensive genomewide studies of additional Caucasian multiplex GV families identified additional linkage signals on chromosomes 7p13-q21, 8p12, and 17p, and suggestive signals on chromosomes 9q22, 11p15, 13q33, 19p13, and 22q11. The chromosome 7p and 17p linkages derived principally from families with other autoimmune diseases, mostly AITD (Fain et al., 2003; Spritz et al., 2004). The 17p13 linkage coincided with a linkage signal previously detected in SLE families that included at least one case of GV and other autoimmune diseases (Nath et al., 2001; Johansson et al., 2004). Targeted family-based genetic association analysis of SNPs spanning the 6.19 Mb chromosome 17p linkage interval identified the corresponding gene as *NALP1* (subsequently renamed *NLRP1*), which encodes NACHT, LRR, and PYD domains-containing protein 1 (Jin et al., 2007a), a key regulator of the innate immune system that may monitor bacterial infection of the skin (Lamkanfi and Dixit, 2009). In addition to confirming genetic association of *NLRP1* with GV (Jin et al., 2007b; Alkhateeb and Qarqaz, 2010), subsequent studies have also shown genetic association of *NLRP1* with genetic risk of type 1 diabetes (Magitta et al., 2009), Addison's disease (Magitta et al., 2009; 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).

At about the same time, genetic linkage studies of GV in Chinese Han detected linkage signals on chromosomes 1p36, 4q13-q21, 6p21-p22, 6q24-q25, 14q12-q12, and 22q12 (Chen et al., 2005; Liang et al., 2007). Except perhaps for the signal on proximal chromosome 22q, these generally did not correspond to the linkage signals detected in Caucasians, suggesting that different genes may be involved in GV susceptibility in these two different populations. Candidate gene association analysis of several genes within the 9.7 Mb chromosome 22q12.1-q12.3 linkage peak subsequently indicated that this linkage signal likely results from *XBP1* (Ren et al., 2009), which encodes a transcription factor (X-box binding protein 1) that activates expression of MHC class II genes, regulates differentiation of plasma cells, mediates inflammatory response to endoplasmic reticulum stress, and has been independently associated with genetic risk of Crohn's disease (Kaser et al., 2008).

The remaining GV linkage signals have not yet been specifically identified, and it remains uncertain which of these represent true GV susceptibility loci *versus* which may have been false-positives.

2.4. Genome-wide association studies

Genome-wide association studies (GWAS), in contrast to linkage studies, are best suited to detect relatively common disease susceptibility alleles that exert modest effects, as may be

most relevant to typical singleton cases. Unlike candidate gene association studies, GWAS can be corrected for population stratification and appropriate multiple testing, and are not subject to *a priori* bias by choice of candidate genes. Accordingly, GWAS have yielded reproducible association signals that appear to represent true susceptibility genes for many complex diseases, though the proportion of total risk accounted for by the loci detected by GWAS remains unclear.

The first GWAS of GV (Birlea et al., 2010) was of a Caucasian "special population", an isolated mountain village with an extraordinarily high prevalence of GV, 2.9% (Birlea et al., 2008). This study detected significant association on distal chromosome 6q27, close to *IDDM8*, a linkage and association signal for type I diabetes mellitus and rheumatoid arthritis, near *SMOC2* (encoding SPARC-related modular calcium-binding protein 2). A subsequent, much larger GWAS of the general European-derived Caucasian population studied over 2300 unrelated patients, detected at least 12 different significant GV susceptibility loci across the genome (Jin et al., 2010a,b; Table 1), and supported three others that, though not themselves significant, had been reported in previous candidate gene studies (Birlea et al., 2011). A simultaneous GV GWAS, carried out in the Chinese population (Quan et al., 2010), detected two significant association signals, one or perhaps both of which were among those detected in the Caucasian study.

The proteins encoded by the genes detected by these GV GWAS comprise components of immunoregulatory pathways that span the melanocyte, dendritic cells of the skin, regulatory lymphocytes, T lymphocytes, B lymphocytes, and back to the melanocyte (Table 1). Both the Caucasian and Chinese GV GWAS detected major association signals in the MHC on chromosome 6p21.3, though the specific associations differed between the two populations. In Caucasians, independent major associations were detected in the class I gene region, represented by *HLA-A*02*, and in the class II region, principally between *HLA-DRB1* and *HLA-DQA1*, in 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). In contrast, in the Chinese study, the major MHC association signal was in the class III gene region, though there was also some evidence for independent association in the class II region (Quan et al., 2010).

Additionally, these large-scale GV GWAS detected a number of non-MHC associations, almost all of involving loci that encode proteins implicated in immunoregulation. The Caucasian GWAS (Jin et al., 2010a,b) detected ten principal non-MHC associations: *TYR* (tyrosinase; R402Q variant), *PTPN22* (lymphoid-specific protein tyrosine phosphatase nonreceptor type 22; R620W variant), *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 is quite close to the 6q27 association signal detected in the Romanian village (Birlea et al., 2010), and furthermore was the only confirmed non-MHC association detected in the Chinese GWAS (Quan et al., 2010). Deeper analysis of the Caucasian GWAS dataset (Birlea et al., 2011) also provided support for association of GV with three candidate genes previously suggested for GV: *XBP1* (see above), *FOXP3* (forkhead box P3), *TSLP* (thymic stromal lymphoprotein). Weak association was noted for *CTLA4*, but as in previous studies, association with *CTLA* was limited to patients with other, concomitant autoimmune diseases, suggesting that "association" with GV is secondary, reflecting primary genetic association of *CTLA4* with other autoimmune diseases that are epidemiologically associated with GV. Indeed, many of these genes for which genetic association was detected by the GV GWAS have also been genetically associated

with other autoimmune diseases that are epidemiologically associated with GV (Table 1), consistent with the hypothesis that these epidemiological associations reflect underlying shared genetic associations (Spritz, 2008). Nevertheless, the GV loci identified thus far together account for 10% of the total genetic liability for GV, suggesting that many additional GV susceptibility genes remain to be discovered, as with other autoimmune diseases that have been subjected to much more extensive genomewide analyses using much larger sample sizes.

Of all of these genetic relationships, perhaps the most interesting are those observed in the Caucasian study of MHC class I and *TYR*, which indicate an inverse relationship between genetic susceptibility to GV *versus* to malignant melanoma (Jin et al., 2010a; Spritz, 2010). The MHC class I association with GV is specifically with *HLA-A*02* (predominantly the **0201*) allele, and the *TYR* association with GV is specifically with the major (R; Arg) allele of the R402Q polymorphism (rs1126809) that is relatively common among Caucasians (minor allele frequency 0.22–0.40) 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). Moreover, the *HLA-A*02* and *TYR* 402R GV risk alleles exhibited genetic interaction, indicative of an underlying functional interaction (Jin et al., 2010a). Tyrosinase is a major GV autoantigen, and tyrosinase epitopes are presented to the immune system on the surface of melanocytes and melanoma cells by HLA class I molecules, principally HLA-A2. One of the important epitopes presented by HLA-A2 is a specific modified tyrosinase nonapeptide, YMDGTMSQV (modification underscored), in which the genomically encoded 371N is altered to 371D concomitant with degradative removal of an *N*-linked oligosaccharide from this site (Skipper et al., 1996). Indeed, the 371D modification is required for presentation of this non-apeptide by HLA-A2; the unmodified 371N form cannot be presented. However, the variant 402Q form of tyrosinase is a thermosensitive polypeptide that at 37°C tends to be mis-folded, retained in the endoplasmic reticulum. The misfolded, non-glycosylated tyrosinase polypeptide is then trafficked directly for proteasomal degradation, rather than to the Golgi for glycosylation (Toyofuku et al., 2001), resulting in steady-state tyrosinase activity that is only 25% that of the major 402R form of the polypeptide. Thus, tyrosinase-402Q is effectively protective for GV, making a quantitatively smaller contribution than tyrosinase-402R to tyrosinase antigen presentation by HLA-A*02; accordingly, *TYR* 402Q likewise makes a smaller contribution to immune surveillance (and thus recognition of melanocytes) and both protection against malignant melanoma and susceptibility to GV, *versus TYR* 402R, and thus *TYR* 402Q is associated with lower susceptibility to GV but greater risk of melanoma (Spritz, 2010).

Finally, in addition to primary searches for genes that influence disease susceptibility as a discrete dichotomous trait, genomewide approaches can also be used to identify genes that influence disease natural history. Recently, Jin et al. (2011) took this approach to identify loci that contribute to GV age of onset. The previous Caucasian GWAS dataset was reanalyzed, assessing GV age of onset as a quantitative trait. This analysis identified a major GV age of onset locus within the MHC class II gene region, possibly reflecting the same locus that was previously associated with GV susceptibility (Jin et al., 2010a). In contrast, none of the other loci that had been associated with GV susceptibility were associated with age of onset. One possible explanation is that some loci mediate GV susceptibility *per se*, whereas variation in the MHC class II region might mediate response to environmental triggers that are encountered over the course of life by genetically susceptible individuals, and which thus influence age of disease onset.

3. Concluding remarks

For GV and many other complex diseases, application of genomewide approaches, especially GWAS, have yielded rapid progress in identifying true disease susceptibility genes, whereas most previously suggested candidate genes have remained unconfirmed. Thus, we have entered a new era of understanding the true genetic basis and underlying pathobiology of GV, which appears to be predominantly autoimmune. These studies have identified new biological pathways that may constitute new targets for disease treatment and perhaps disease prevention. Nevertheless, these studies have only accounted for a limited fraction of the total risk of GV, and larger genomewide studies can be expected to identify even more GV susceptibility genes, shed even more light on the nature of the disease, and perhaps even provide clues to environmental triggers. Furthermore, 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, detailed bioinformatics analysis, and targeted functional studies to assess specific variants, both individually and in combination. Nevertheless, the way forward is now clear, with doors opening to new understanding and new opportunities for treating patients with GV.

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Table 1

GV susceptibility loci confirmed on the basis of genomewide studies.

Chromosome	Gene	Protein	Function	GV susceptibility variant[a]	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*[b]	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	Many
	MHC class II[c]	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 and 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

Chromosome	Gene	Protein	Function	GV susceptibility variant[a]	Other autoimmune disease associations
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		IPEX

[a]GV susceptibility variant is underlined;

[b]Numerous studies have indicated that *CTLA4* is only associated with GV in patients who also have other auto-immune diseases, suggesting that apparent association of *CLTA4* with GV is secondary to epidemiological association with these other diseases;

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