Genetics of Vitiligo: An Insight
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Abstract
Vitiligo is the most common depigmenting disorder having a major impact on the quality of life of patients. Despite continued progress toward an elucidation of the biochemical, genetic and immunopathological pathways in vitiligo, a definitive cure remains elusive. During the past few decades, advances in the field of molecular genetics have enriched us in understanding the etiopathogenesis of vitiligo.

Several candidate genes have been associated with susceptibility to vitiligo. They include genes important for melanin biosynthesis, response to oxidative stress and/or regulation of autoimmunity. A recent genome-wide scan performed on families with numerous members presenting with vitiligo has clearly revealed linkage of susceptibility loci especially autoimmune susceptibility loci.

Genetic studies have helped us identify not only the natural course and clinical aspects of vitiligo but also the shed profound light on the inverse relationship between genetic susceptibility to GV and malignant melanoma. In the future, dissection of the complex genetic architecture of vitiligo will provide new approaches for treatment and prevention. In this article, we review the genes involved in vitiligo and also focus on the pathogenic mechanisms of the same.

Keywords: Vitiligo; Genetic; Depigmenting disorder

Introduction
Vitiligo is an acquired, non-contagious disease characterised by progressive, patchy, multifocal depigmentation of skin, with or without depigmentation of overlying hair, and mucous membranes results from loss of melanocytes from the involved areas. Vitiligo is classified into two main types: Generalised Vitiligo (GV) and segmental vitiligo. GV is possibly the most common pigmentation disorder, occurring at a frequency of approximately 0.2–1.0% in different populations around the world.

Etiological hypotheses suggested for etiopathogenesis of vitiligo include genetic, immunological, neurohormonal, cytotoxic, oxidative stress and melanocytorrhexis [1]. Genes possibly play a role in all aspects of pathogenesis of generalised vitiligo. Most genes associated with susceptibility to GV are involved in immune regulation and immune targeting of melanocytes. However the triggers which set off this autoimmune process are not completely clear.

The autoimmune and genetic hypothesis was initially supported by 1. Clustering of vitiligo cases in certain families (Multiplex vitiligo families) and 2. Increased frequency of autoimmune diseases in patients of vitiligo as in their first degree relatives (with or without vitiligo) more so in multiplex vitiligo families [2]. This indicated a genetic predisposition to a specific group of autoimmune disorders including vitiligo with exposure to environmental triggers possibly determining the occurrence of GV and other specific autoimmune diseases in individual patients.

Historical Aspects
Probably the earliest evidence relating to the genetic basis of vitiligo was the description by Addison, of a patient with idiopathic adrenal insufficiency (now known as Addison’s disease), GV, and pernicious anaemia in 1855. In 1908 Claude suggested the possibility of a common cause of clustering of autoimmune diseases. This was followed by several reports of generalised vitiligo with autoimmune diseases. In 1980, Neufeld and Blizzard re-classified the so-called “autoimmune polyglandular syndromes” (APS) into 4 types all of which can have vitiligo as one of its components. Evidence for genetic basis of vitiligo has travelled a long way from the epidemiological studies to the most recent sophisticated genome wide association analysis resulting in identification of several specific susceptibility genes [3-5].

Epidemiological Studies
Epidemiological studies have shown that GV far from following a single gene locus associated Mendelian pattern of inheritance is more of a complex trait, involving multiple susceptibility genes and also environmental risk factors. Clustering of GV cases occurs in multiplex families, almost always in non-Mendelian patterns indicative of polygenic, multifactorial causation. So, it is indeed not surprising that the concordance of GV in monozygotic twins is only 23%, highlighting the possible effect of environmental triggers, which as yet remain unknown.

Methods of Identification of Susceptibility Genes in Vitiligo
Initial studies focused on differential expression analyses and biological candidate genes. However in recent years, biomedical and technological advances including the human genome project, sophisticated data and statistical analyses of polygenic, multifactorial diseases, have permitted more global approaches such as Genome wide association studies, which have largely overcome the shortfalls of the earlier techniques and has enabled identification of several GV susceptibility genes, some of which are shared with other autoimmune diseases and some of which are specific to vitiligo.

Gene expression studies
Gene expression studies can identify genes on the basis of differential expression, in cells from GV patients versus controls, or in involved skin versus uninvolved skin. However, the disadvantage of gene expression studies is that it cannot distinguish between genes with primary effects on disease causation versus the genes whose expression

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may be dysregulated secondarily or a mere variation in expression, unrelated to vitiligo. Therefore, genes identified by such studies have not been strongly proven to be vitiligo susceptibility genes.

Two genes including VIT1 (FBXO11) and MYG1 were identified initially by gene expression studies, but have not been identified as potential vitiligo susceptibility genes by either genome wide linkage studies or GWAS of GV [6,7].

**Candidate gene association studies:** Candidate gene association studies, of HLA and ABO and other blood groups were the earliest studies performed for detecting specific causative genes of vitiligo.

Candidate gene association studies detect genetic signals representing 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 have high false positive results, due to inherent differences between cases and controls, inadequate statistical power and statistical fluctuation, and inadequate correction for multiple testing, both within and across studies.

Not surprisingly, although initial gene association studies reported at least 33 different candidate genes for GV, only two genes have been subsequently supported by positive results in multiple studies, HLA and PTPN22. A third gene, cytotoxic T-lymphocyte antigen 4 (CTLA4), has been reported with inconsistent results.

Recent studies using sophisticated analytical and statistical methods found association between GV and HLADRB4*0101 and HLA-DQB1*0303 in Dutch patients with HLADRBI*03, DRB1*04, and HLA-DRBI*07 alleles in Turkish patients, while in Caucasian patients association was found with alleles of microsatellites located in the MHC [8-10]. In Caucasian multiplex GV families, the MHC class II haplotype HLADRBI*04-DQA1*0302-DQB1*0301 is associated with both increased risk of GV and with relatively early age of onset [11]. In Han Chinese GV is associated with the MHC haplotype HLA-A25-Cw*0602-DQA1*0302 [12]. Association has also been reported between GV and genes of the LMP/TAP gene region of the MHC, although more recent studies indicate these may probably reflect long range linkage disequilibrium with the MHC class II gene region.

The PTPN22 R620W polymorphism is associated with GV in Caucasians on a background of PTPN22-related autoimmune susceptibility. However a study, carried out in GV patients from Gujarat in India, found no association with the R620W variant [13]. Possible explanation of this variation include rarity of the R620W variant in non-Caucasian populations and the small size (and thus limited statistical power) of the study.

The association of CTLA4 with vitiligo is weak, and probably is 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.

**Genome wide linkage studies:** Genome wide linkage studies are useful in detecting those disease susceptibility genes which while being rare result in significantly large effects. e.g in multiplex vitiligo families.

The first direct genome wide linkage study of GV was carried out in a unique large Caucasian kindred with an unusual vitiligo phenotype which had an apparent autosomal dominant inheritance with incomplete penetrance and detected linkage in chromosome 1p31.3–p32.2 [14]. Subsequently a promoter variant of FOXD3 (encoding Forkhead box D3) was identified within the linkage interval. FOXD3 is a key regulator of melanoblast lineage differentiation and development. This variant significantly up-regulated FOXD3 transcription in vivo, indicating that this would result in potentially altering the differentiation profile of the melanoblast lineage [15]. 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.

Other genome wide linkage studies of 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 were derived principally from families with other autoimmune diseases, mostlyAITD. 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 and other autoimmune diseases. The corresponding gene was identified as NALP1 (subsequently renamed NLRP1), which encodes NACHT, LRR, and PYD domains-containing protein 1, a key regulator of the innate immune system [16]. NLRP1 haplotypes have been found to be associated with vitiligo and autoimmunity by promoting caspase-1–dependent processing of bioactive interleukin-1β (IL-1β) via the NLRP1 inflammasome, resulting in IL-1β secretion and subsequent inflammatory responses. In addition to the association of NLRP1 with GV NLRP1s also associated with genetic risk of type 1 diabetes, Addison’s disease, celiac disease, systemic sclerosis, and inflammatory bowel disease.

Similarly, genetic linkage studies of GV in Chinese Han detected linkage signals on chromosomes 1p36, 4q31-q32, 6p21-p22, 6q24-q25, 14q12-q12, and 22q12 [17]. This shows that different genes may be involved in GV susceptibility in these two different populations.

Candidate gene association analysis of several genes within the chromosome 22q12.1-q12.3 linkage peak subsequently indicated that this linkage signal likely results from XBPI which encodes a transcription factor (Xbox 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 Cohn’s disease.

The other GV linkage signals mentioned above remain to be identified, and it is an open question as to which of these represent true susceptibility loci for GV.

**Genome-Wide Association Studies**

Genome-wide association studies (GWAS), in contrast to linkage studies, are useful to detect relatively common disease susceptibility alleles that exert modest effects, as may be most relevant to typical single cases. Unlike candidate gene association studies, GWAS can be corrected for population stratification and appropriate multiple testing, and have yielded reproducible association signals that appear to represent true susceptibility genes for many complex diseases. They are currently considered the “gold standard” for identifying complex trait susceptibility genes.

The first GWAS for vitiligo was carried out in specific Caucasian population with a very high prevalence of vitiligo and other autoimmune disorders. Significant association was detected on distal chromosome 6q27, close to IDDM8, a linkage and association signal for type 1 diabetes mellitus and rheumatoid arthritis [18]. This region contains the gene SMCOC2 encoding SPARC-related modular calcium-binding protein 2 whose function is unknown.

Subsequently, two large GWAS were carried out in both Caucasian and Chinese population. The proteins encoded by the genes detected...
by these GWAS are mostly components of immune regulatory pathways that span the melanocyte, dendritic cells of the skin, regulatory lymphocytes, T lymphocytes, B lymphocytes, and back to the melanocyte. 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 [19]. On the other hand, in the Chinese study, the major MHC association signal was in the class III gene region (HLA-A*3001, HLA-B*1302, HLA-C*0602 and HLA- DRB1*0701 alleles) [20].

The Caucasian GWAS detected ten principal non-MHC associations: TYR (tyrosinase; R402Q variant), PTEN2 (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 prefer 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). CCR6 was also the only confirmed non-MHC association detected in the Chinese GWAS. Also, CCR6 is quite close to the 6q27 association signal mentioned above.

GZMB has not been genetically associated with other autoimmune diseases thus suggesting the possibility that GZMB may be relatively specific for melanocyte-directed autoimmune susceptibility. GZMB cleaves target proteins at aspartic acid residues including both caspases associated with induction of apoptosis and most target cell autoantigens, potentially enhancing presentation of cryptic epitopes and leading to activation of self-reactive T-cells High probability GZMB cleavage site in TYR, TYRP1, TYRP2, SOX10 suggest that in vivo GZMB cleavage of melanocyte proteins that constitute GV autoantigens may contribute to initiation and propagation of autoimmune directed against melanocytes.

Additional evidence in the Caucasian GWAS dataset also provided support for association of GV with three candidate genes previously suggested for GV: XBPI, FOXP3 (forkhead box P3), TSLP (thymic stromal lymphoprotein) [21]. Weak association was noted for CTLA4, supporting for association of GV with three candidate genes previously associated with induction of apoptosis and most target cell autoantigens.

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A recent GWAS study has identified 13 so far unknown susceptibility genes [22]. 1) OCA2-HERC2 gene within the region of chromosome 15q12-q13.1. OCA2 gene is related to oculocutaneous albinism type 2, encodes a protein that is a melanosomal membrane transporter determining the skin, hair and eye color. The study confirmed an association of two SNPs. The SNP alleles of OCA2 that are low-risk for vitiligo are associated with an elevated risk of melanoma and with gray/blue pigmentation of eyes’ irises. 2) MC1R gene: chromosome 16q24.3 MC1R gene encoding the melanocortin receptor which is a melanogenesis regulator and secondary vitiligo autoantigen. 3) SNPs at 11q21 region containing no known genes. This region possibly stores a regulatory element affecting TYR gene transcription. 4) IFIH1 gene: SNPs association at 2q24.2 region localized between IFIH1 gene and FAP gene. IFIH1 gene encodes interferon-induced RNA helicase involved in antiviral innate immune responses. It is associated with diabetes mellitus type 1, Graves’ disease, multiple sclerosis, psoriasis and probably with lupus. 5) CDAO gene: SNPs at 3q13.33 region were detected within the area of CDAO gene. CDAO is a surface protein on activated B cells, monocytes and dendritic cells that co-stimulates T cells activation. 6) CLN5 gene: SNPs within 4p16.1 gene inside the area of CLN5 gene associated with the mast cells immunoreceptor. 7) BACH2 gene: SNPs at 6q15 region where BACH2 gene is localized. The gene encodes a transcriptional repressor of B cells, and it is associated with diabetes mellitus type 1, celiac disease and Crohn’s disease. 7) TG/SLA gene. SNPs at 8q24.22 region where two genes TG/SLA are interdigitated and encoded on the opposite strands. TG gene encodes thryoglobulin and is associated with autoimmune thyroid disease. SLA gene encodes Src-like adaptor protein. 8) CASP7 gene. SNPs at 10q25.3 region with CASP7 gene encoding caspase 7 which has an important function in apoptosis and inflammation. The gene is associated with rheumatoid arthritis and type 1 diabetes mellitus. 9) CD44 gene. SNPs at 11p13 region containing portions of CD44 gene and SLCA12A gene. CD44 gene encodes cell surface glycoprotein playing a role in cell-cell interaction, cell adhesion and migration and plays a role in T cell development. It is associated with lupus erythematosus. 10) IKZF4 gene: SNPs at 12q13.2 region containing Change to and encodes IKZF4 gene associated with diabetes mellitus type 1 alopeca area encoding the transcriptional factor for T cell activation 11) SH2B3 gene: SNPs at 12q24.12 region localized inside and close to SH2B3 gene and SNP within ATXN2 gene encoding Ataxin-2. SH2B3 gene encodes adaptor protein LNK regulating development of both B and T cells. The gene is associated with diabetes mellitus type 1 and celiac disease, rheumatoid arthritis, multiple sclerosis and probably with lupus erythematosus. 12) TOB2 gene. SNPs at 22q13.2 region close to TOB2 gene and SNPs between ZC3H7B and TEF [23]. TOB2 gene encodes a regulator of cell cycle progression involved in T cell tolerance (Table 1).

Other Aspects of Genetic Studies

Impact of genes on natural history and clinical aspects of vitiligo

Jin et al. identified a locus within the MHC class II gene region that contributes to GV age of onset. Similarly in a study conducted in Chinese Han population, HLA-DRB1*07 positivity was associated with an earlier disease onset, higher frequency of family history and coexistence of autoimmune diseases.

TYR gene, vitiligo risk and melanoma: TYR encodes tyrosinase, an enzyme of the melanocyte that catalyzes the rate-limiting steps of melanin biosynthesis. It is also a major autoantigen in generalized vitiligo. There is an inverse relationship between genetic susceptibility to GV versus to malignant melanoma. In the Caucasian study of MHC class I and TYR, the MHC class I association with GV was found to be 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 (rs1162809) that is relatively common among Caucasians but is rare in other populations. In contrast, the minor (Q; Gln) allele of the TYR R402Q polymorphism is associated with susceptibility to malignant melanoma. Moreover, the HLA-A*02 and TYR 402R GV risk alleles exhibited genetic interaction, indicative of an underlying functional interaction. 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, YMDGTM5QV, in which the genetically encoded 371N is altered to 371D concomitant with degradative removal of an N-linked oligosaccharide from this site. The 371D modification is required for presentation of this non-peptide by HLA-A2.

Tyrosinase-402Q is effectively protective for GV, making a quantitatively smaller contribution than tyrosinase-402R to tyrosinase
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>GV Susceptibility Variant</th>
<th>Other autoimmune disease associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36.23</td>
<td>RERE</td>
<td>Atrophin-like protein 1</td>
<td>Atrophin-like protein 1</td>
<td>R620W</td>
<td>Type 1 diabetes, SLE, Graves’ disease, rheumatoid arthritis, Addison’s disease, psoriasis, inflammatory bowel disease</td>
</tr>
<tr>
<td>1p13.2</td>
<td>PTPN22</td>
<td>Lympoths-specific protein tyrosine phosphatase nonreceptor type 22</td>
<td>Regulates T cell receptor signaling</td>
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<td>1p31.3</td>
<td>FoxD3</td>
<td></td>
<td></td>
<td>Melanoblast lineage differentiation</td>
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<td>2q32.2</td>
<td>CTLA4b</td>
<td>Cytotoxic T-lymphocyte antigen 4</td>
<td>Inhibits T cells</td>
<td>Type 1 diabetes, Graves’ disease, Hashimoto’s thyroiditis, inflammatory bowel disease, SLE</td>
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<tr>
<td>2q24.2</td>
<td>IFI16</td>
<td>IFN induced RNA helicase</td>
<td>Anti-viral Innate Immune response</td>
<td>Type 1 diabetes, Graves’ disease, multiple sclerosis, psoriasis, lupus</td>
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<td>3p13</td>
<td>FOXP1</td>
<td>Forkhead box P1</td>
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<td></td>
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<td>3q28</td>
<td>LPP</td>
<td>LIM domain-containing preferred translocation partner in lipoma</td>
<td>Unknown</td>
<td>Celiac disease, rheumatoid arthritis</td>
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<td>3q13.33</td>
<td>CD80</td>
<td></td>
<td></td>
<td>Mast immunoreceptor</td>
<td></td>
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<tr>
<td>4p16.1</td>
<td>CLN6</td>
<td></td>
<td></td>
<td>Mast immunoreceptor</td>
<td></td>
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<tr>
<td>5q22.1</td>
<td>TSLP</td>
<td>Thymic stromal lymphoprotein</td>
<td>Regulates T cell and dendritic cell maturation</td>
<td></td>
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<tr>
<td>6p21.3</td>
<td>MHC class I</td>
<td>Human leukocyte antigen</td>
<td>Presents peptide antigens</td>
<td>HLA – A ’02</td>
<td>Several</td>
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<tr>
<td></td>
<td>MHC class II</td>
<td>Human leukocyte antigen</td>
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<td>HLA-DRB1*04</td>
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<td></td>
<td>MHC class III</td>
<td>Human leukocyte antigen</td>
<td></td>
<td>HLA-A<em>3001, HLA-B</em>1302, HLA-C<em>0602, HLA-DRB1</em>0701</td>
<td>Several</td>
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<td>6q27</td>
<td>CCR6</td>
<td>C–C chemokine receptor type 6</td>
<td>Regulates B cell differentiation, function of dendritic and Th17 cells</td>
<td>Inflammatory bowel disease, rheumatoid arthritis, Graves’ disease</td>
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<tr>
<td>6q15</td>
<td>BACH2</td>
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<td>Transcriptional repressor of B cells</td>
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<td>8q24.22</td>
<td>TG/SLA</td>
<td>Thyroglobulin</td>
<td>Regulator of antigen receptor signalling</td>
<td>Autoimmune thyroid disease</td>
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<tr>
<td>8q24.22</td>
<td>Src like adaptor protein</td>
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<tr>
<td>10p15.1</td>
<td>IL2RA</td>
<td>Interleukin-2 receptor α chain</td>
<td>Regulates lymphocyte response to bacteria via IL-2</td>
<td>Type 1 diabetes, Graves’ disease, multiple sclerosis, rheumatoid arthritis, SLE</td>
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<tr>
<td>10q25.3</td>
<td>CASP7</td>
<td>Caspase 7</td>
<td>Executioner protein of apoptosis</td>
<td>Rheumatoid arthritis, Type1 DM</td>
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<tr>
<td>11p13</td>
<td>CD44</td>
<td></td>
<td></td>
<td>Lupus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLC1A2</td>
<td></td>
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<tr>
<td>11q14.3</td>
<td>TYR</td>
<td>Tyrosinase</td>
<td>Key enzyme of melanin biosynthesis</td>
<td>R402Q</td>
<td></td>
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<tr>
<td>12q13.2</td>
<td>IKZF4</td>
<td></td>
<td>Regulator of T-cell activation</td>
<td>Type 1 DM, Alpoeica Areata</td>
<td></td>
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<tr>
<td>12q24.12</td>
<td>SH2B3</td>
<td>LNK (Adaptor protein)</td>
<td>T-cell and B-cell development</td>
<td></td>
<td></td>
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<tr>
<td>14q12</td>
<td>GZMB</td>
<td>Granzyme B</td>
<td>Mediates target cell apoptosis by cytotoxic T cells and natural killer cells activation-induced cell death of effector Th2 cells</td>
<td>Type 1 DM, Celiac disease, RA, Multiple sclerosis, Lupus</td>
<td></td>
</tr>
<tr>
<td>16q24.3</td>
<td>MC1R</td>
<td>MelanocortinR</td>
<td>Melanogenesis regulator</td>
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<td>17p13</td>
<td>NLRP1</td>
<td>NACHT, LRR, PYD</td>
<td>Innate immune system Caspase 1 dependent</td>
<td>Addison’s disease, Type1 DM, celiac disease, SLE, RA, Systemic sclerosis, Kawasaki disease</td>
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<tr>
<td>19p13.3</td>
<td>TICAM1</td>
<td>TLRI</td>
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<tr>
<td>21q22.3</td>
<td>UBA59</td>
<td>Ubiquitin associated and SH3 domain containing A</td>
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<tr>
<td>22q12.1-q12.3</td>
<td>XBP1</td>
<td>X-box binding protein 1</td>
<td>Activates MHC II alleles</td>
<td></td>
<td></td>
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<tr>
<td>22q 13.2</td>
<td>T0B2</td>
<td></td>
<td>T cell tolerance</td>
<td></td>
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</table>

**Table 1:** A comprehensive list of Vitiligo associated susceptibility genes.
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.

Concluding Remarks

Essentially most of the confirmed GV susceptibility genes regulate function of the immune system, and many have also been associated with other autoimmune diseases, highlighting shared pathways of autoimmune susceptibility among these diseases. These genes however constitute only 10% of the total genetic risk of GV in that group, indicating that additional loci probably remain to be discovered. Genome wide association studies are now the gold standard for identification of susceptibility genes and may possibly identify new genes and new biological pathways, throwing up new potential targets for therapeutic intervention and possibly even prevention.

References