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Genetics of Vitiligo: An Insight

Shital Poojary*, Khushboo Minni

KJ Somaiya Medical College, Maharashtra, India

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: Generalized 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 melanocytorrhagy [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

***Corresponding author:** Shital Poojary, Professor and Head, Department of Dermatology, KJ Somaiya Medical College, Sion Chunnabhatti, Mumbai, Maharashtra 400067, India, Tel: +912224090253; E-mail: spoojary2004@gmail.com

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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 HLADRB1*03, DRB1*04, and HLA-DRB1*07 alleles in Turkish patients, while in Colombian patients association was found with alleles of microsatellites located in the MHC [8-10]. In Caucasian multiplex GV families, the MHC class II haplotype HLADRB1*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 most 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, mostly AITD. 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 NLRP1is 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, 4q13-q21, 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 XBP1 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 I diabetes mellitus and rheumatoid arthritis [18]. This region contains the gene SMOC2 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), 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). 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 autoimmunity 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: XBP1, FOXP3 (forkhead box P3), TSLP (thymic stromal lymphoprotein) [21]. Weak association was noted for CTLA4, as in previous studies.

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) *CD80* gene: SNPs at 3q13.33 region were detected within the area of *CD80* gene. *CD80* is a surface protein on activated B cells, monocytes and dendritic cells that co-stimulates T cells activation. 6) *CLNK* gene: SNPs within 4p16.1 gene inside the area of *CLNK* 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 thyroglobulin 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 *SLC1A2* 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 alopecia areata 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 (rs1126809) 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 HLAA2. One of the important epitopes presented by HLA-A2 is a specific modified tyrosinase nonapeptide, YMDGTMSQV, in which the genomically 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

Chromosome	Gene	Protein	Function	GV Susceptibility Variant	Other autoimmune disease associations
1p36.23	*RERE*	Atrophin-like protein 1	Atrophin-like protein 1		
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
1p31.3	*FoxD3*		Melanoblast lineage differentiation		
2q33.2	*CTLA4b*	Cytotoxic T-lymphocyte antigen 4	Inhibits T cells		Type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, inflammatory bowel disease, SLE
2q24.2	*IFIHI*	IFN induced RNA helicase	Anti-viral Innate Immune response		Type 1 diabetes, Graves' disease, multiple sclerosis, psoriasis, lupus
3p13	*FOXP1*	Forkhead box P1	Regulates lymphoid cell development		
3q28	*LPP*	LIM domain-containing preferred translocation partner in lipoma	Unknown		Celiac disease, rheumatoid arthritis
3q13.33	*CD80*		Co-stimulator of T- cell activation		
4p16.1	*CLNK*		Mast immunoreceptor		
5q22.1	*TSLP*	Thymic stromal lymphoprotein	Regulates T cell and dendritic cell maturation		
6p21.3	*MHC class I*	Human leukocyte antigen	Presents peptide antigens	HLA –A **02*	Several
	MHC class II	Human leukocyte antigen		HLA-DRB1*04	Several
	MHC class III	Human leukocyte antigen		HLA-A*3001 HLA-B*1302 HLA-C*0602 HLA DRB1*0701	Several
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
6q15	*BACH2*		Transcriptional repressor of B cells		
8q24.22	*TG/SLA*	Thyroglobulin Src like adaptor protein	Regulator of antigen receptor signalling		Autoimmune thyroid disease
10p15.1	*IL2RA*	Interleukin-2-receptor α chain	Regulates lymphocyte response to bacteria via IL-2		Type 1 diabetes, Graves' disease, multiple sclerosis, rheumatoid arthritis, SLE
10q25.3	*CASP7*	Caspase 7	Executioner protein of apoptosis		Rheumatoid arthritis, Type1 DM
11p13	*CD44* *SLC1A2*		Cell surface glycoprotein: T-cell development		Lupus
11q14.3	*TYR*	Tyrosinase	Key enzyme of melanin biosynthesis	R402Q	
12q13.2	*IKZF4*		Regulator of T-cell activation		Type 1DM, Alopecia Areata
12q24.12	*SH2B3*	LNK (Adaptor protein)	T-cell and B-cell development		
14q12	*GZMB*	Granzyme B	Mediates target cell apoptosis by cytotoxic T cells and natural killer cells activation- induced cell death of effector Th2 cells		Type 1 DM, Celiac disease. RA, Multiple sclerosis, Lupus
16q24.3	*MC1R*	MelanocortinR	Melanogenesis regulator		
17p13	*NLRP 1*	NACHT, LRR, PYD	Innate immune system Caspase 1 dependent		Addison's disease, Type1 DM, celiac disease, SLE, RA, Systemic sclerosis, Kawasaki disease
19p13.3	*TICAM1*	TLRI	Innate immune response		
21q22.3	*UBASH 3A*	Ubiquitin associated and SH3 domain containing A			
22q12.1-q12.3	*XBP1*	X-box binding protein 1	Activates MHC II alleles		Crohn's disease
22q 13.2	*TOB2*		T cell tolerance		

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

1. Boissy RE, Spritz RA (2009) Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff. Exp Dermatol 18: 583-585.
2. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA (2003) Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 16: 208-214.
3. Neufeld M, Blizzard RM (1980) Polyglandular autoimmune diseases. Symposium on Autoimmune Aspects of Endocrine Disorders. Academic Press; New York. p. 357-365.
4. Spritz RA (2011) Recent progress in the genetics of generalized vitiligo. J Genet Genomics 38: 271-278.
5. Spritz RA (2012) Six decades of vitiligo genetics: Genomewide studies provide insights into autoimmune pathogenesis. J Invest Dermatol 132: 268–273.
6. Le Poole IC, Sarangarajan R, Zhao Y, Stennett LS, Brown TL, et al. (2001) 'VIT1', a novel gene associated with vitiligo. Pigment Cell Res 14: 475-484.
7. Kingo K, Philips MA, Aunin E, Luuk H, Karelson M, et al. (2006) MYG, novel melanocyte related gene, has elevated expression in vitiligo. J Dermatol Sci 44: 119-122.
8. Zamani M, Spaepen M, Sghar SS, Huang C, Westerhof W, et al. (2001) Linkage and association of HLA class II genes with vitiligo in a Dutch population. Br J Dermatol 145: 90-94.
9. Taştan HB, Akar A, Orkunoğlu FE, Arca E, Inal A (2004) Association of HLA class I antigens and HLA class II alleles with vitiligo in a Turkish population. Pigment Cell Res 17: 181-184.
10. Arcos-Burgos M, Parodi E, Salgar M, Bedoya E, Builes J, et al. (2002) Vitiligo: complex segregation and linkage disequilibrium analyses with respect to microsatellite loci spanning the HLA. Hum Genet 110: 334-342.
11. Fain PR, Babu SR, Bennett DC, Spritz RA (2006) HLA class II haplotype DRB1*04-DQB1*0301 contributes to risk of familial generalized vitiligo and early disease onset. Pigment Cell Res 19: 51-57.
12. Xia Q, Zhou WM, Liang YH, Ge HS, Liu HS, et al. (2006) MHC haplotypic association in Chinese Han patients with vitiligo. J Eur Acad Dermatol Venereol 20: 941-946.
13. Laddha NC, Dwivedi M, Shajil EM, Prajapati H, Marfatia YS, et al. (2008) Association of PTPN22 1858C/T polymorphism with vitiligo susceptibility in Gujarat population. J Dermatol Sci 49: 260-262.
14. Alkhateeb A, Stetler GL, Old W, Talbert J, Uhlhorn C, et al. (2002) Mapping of an autoimmunity susceptibility locus (AIS1) to chromosome 1p31.3-p32.2. Hum Mol Genet 11: 661-667.
15. Alkhateeb A, Stetler GL, Old W, Talbert J, Uhlhorn C, et al. (2002) Mapping of an autoimmunity susceptibility locus (AIS1) to chromosome 1p31.3-p32.2. Hum Mol Genet 11: 661-667.
16. Alkhateeb A, Fain P, Spritz RA (2005) Candidate functional promoter variant in the FOXD3 melanoblast developmental regulator gene in autosomal dominant vitiligo. J Invest Dermatol 125: 388–391.
17. Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, et al. (2007) NALP1 in vitiligo-associated multiple autoimmune disease. N Engl J Med 356: 1216-1225.
18. Chen JJ, Huang W, Gui JP, Yang S, Zhou FS, et al. (2005) A novel linkage to generalized vitiligo on 4q13-q21 identified in a genomewide linkage analysis of Chinese families. Am J Hum Genet 76: 1057-1065.
19. Birlea SA, Gowan K, Fain PR, Spritz RA (2010) Genome-wide association study of generalized vitiligo in an isolated European founder population identifies SMOC, in close proximity to IDDM8. J Invest Dermatol 130: 798-803.
20. Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, et al. (2010) Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. N Engl J Med 362: 1686-1697.
21. Quan C, Ren YQ, Xiang LH, Sun LD, Xu AE, et al. (2010) Genome-wide association study for vitiligo identifies susceptibility loci at 6q27 and the MHC. Nat Genet 42: 614-618.
22. Birlea SA, Jin Y, Bennett DC, Herbstman DM, Wallace MR, et al. (2011) Comprehensive association analysis of candidate genes for generalized vitiligo supports XBP, FOXP3, and TSLP. J Invest Dermatol 131: 371-381.
23. Jin Y, Birlea SA, Fain PR, Ferrara TM, Ben S, et al. (2012) Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. Nat Genet 44: 676-680.