Review paper

Current aspects of vitiligo genetics

Rafał Czajkowski, Kaja Męcińska-Jundziłł

Department of Dermatology, Sexually Transmitted Diseases and Immunodermatology, Nicolaus Copernicus University in Torun,
Ludwik Rydygier Medical College in Bydgoszcz, Poland
Head of Department: Rafał Czajkowski MD, PhD, DSc

Abstract

Vitiligo is a common acquired depigmentation disorder of the skin manifested by the presence of white macules. The disease occurs at a frequency of approximately 1–4% of the world population. Currently, the most popular theory of vitiligo development is a multifactorial hypothesis according to which genetic conditions predispose vitiligo macules to occur as a result of specific environmental factors. According to the genetic hypothesis, vitiligo inheritance is multigenic. Genetic studies conducted so far concern patients with non-segmental vitiligo. There are three basic techniques of genetic studies: candidate gene association studies, genomewide linkage studies and genome-wide association studies (GWAS). The GWAS are the "gold standard" for detecting susceptibility genes. Up to now, approximately 36 convincing non-segmental vitiligo susceptibility loci have been identified. Approximately 90% of them encode immunoregulatory proteins, while approximately 10% encode melanocyte proteins. The existence of various associations between vitiligo and other autoimmune diseases may provide new knowledge on the causes of many disorders. Examples include the inverse relationship between vitiligo and melanoma and association of vitiligo with other autoimmune diseases. The main goal of all researches is to find new, optimal therapeutic strategies for vitiligo and other autoimmune diseases.

Key words: vitiligo, genetics, pathogenesis.

Introduction

Vitiligo is a common acquired depigmentation disorder of the skin manifested by the presence of white macules [1]. The disease occurs at a frequency of approximately 1–4% of the world population without sex predilection [2, 3]. Clinical presentation includes segmental, non-segmental and mixed vitiligo. The differences between these subtypes concern not only clinical symptoms (occurrence of the first skin lesions, their localization and extent, coexistence of associated autoimmune diseases, natural progress of the dermatosis) but also etiology [3].

Vitiligo was first noted in the Old Testament, Koran and Buddhist literature in approximately 1400 B.C. Despite a long history of this dermatosis, its exact etiology remains unknown. The researchers are trying to explain the pathogenesis of vitiligo with different hypotheses, the most popular are genetic, autoimmune, autocyto-

toxic, neurogenic, microenvironmental, viral, apoptotic, cell adhesion disorders and multivariate theory [1, 4–7]. Currently, the most popular theory of the vitiligo development is a multifactorial hypothesis according to which genetic conditions predispose vitiligo macules to occur as a result of specific environmental factors [8].

Puberty, pregnancy, major infections, dietary imbalance, stress and skin trauma are factors which may reveal the first symptoms of the disease. So far the specific environmental factor causing vitiligo among genetically predisposed patients remains unknown [9].

Vitiligo occurrence among members of patients' families indicates that genetic factors play a role in pathogenesis of the disease. According to the genetic hypothesis, vitiligo inheritance is multigenic. The relative risk of vitiligo for first-degree relatives is increased 7 – to 10-fold [10, 11]. Very rarely, among multi-generation families inheritance occurs in an autosomal dominant pattern with

incomplete penetrance [12]. The concordance of vitiligo in monozygotic twins is not clear, what indicates an important influence of environmental factors. If one of the twins has vitiligo, the likelihood that the other twin will be afflicted by the disease is only 23%. These findings altogether led to many genetic analyses aimed to create a risk group pattern for vitiligo. The results of researches conducted so far are analyzed in this article.

Methods of genetic researches

One of the methods used to assess a genetic predisposition for a disease is a case-control association where differences in particular genes and their variants are studied among patients afflicted by vitiligo compared with healthy subjects. A specific variant of the gene is related with vitiligo if it is statistically significantly more frequent among afflicted patients than healthy subjects. Another method is family-based association where genetic differences are sought between patients and their first-degree relatives. These researches are useful to determine whether a specific variant of the gene is inherited from parents to offspring more frequently than with a random frequency.

There are three basic techniques of genetic studies: candidate gene association studies, genomewide linkage studies and genome-wide association studies.

Candidate gene association studies

The model of candidate gene studies is quite simple. The basic elements are identification of the gene conditioning the disease phenotype, finding a polymorphic marker within that gene and specifying a suitable set of subjects to the genotype for this marker. The most often analyzed genes are: functional and positional genes. Functional candidates are genes which encode proteins associated with regulation of melanocytes activity. Positional candidates are genes present within genomic regions, which have been shown to be genetically significant in genomewide linkage analyses, genome-wide association studies or by detection of chromosomal translocations disrupting the gene action [13, 14].

The described design of the study led to false-positive results because of the ethnic differences in case-control analyses (population stratification), inadequate statistical power and statistical fluctuation, and inadequate correction for multiple testing within and across studies [15, 16].

Genomewide linkage studies

In contrast to candidate association studies, linkage scans are used to detect a gene of a multiple feature through scanning a whole genome of related subjects. These researches help to determine the position of the genetic marker inherited together with a specific disease.

The analysis includes typing of families using polymorphic markers situated within the whole genome. In the next phase, the degree of the marker linkage to a disease trait is calculated. In contrast to candidate association studies, linkage scans do not rely on pre-existing knowledge of the genes associated with the studied trait [14].

Linkage and linkage disequilibrium are two main concepts in genetic epidemiology. Two loci are linked if they are passed together from parents to offspring more frequently than expected under independent inheritance. Two loci are in linkage disequilibrium if they are found together on the same haplotype more frequently than it is expected across the whole population [17].

Genome-wide association studies

In genome-wide association studies (GWAS), a set of single nucleotide polymorphisms across the whole genome is examined in order to detect the most often genetic variants associated with a disease. Furthermore, it is used to identify hereditary quantitative traits responsible for analyzed disease development [18].

The GWAS are based on comparing the DNA of two large groups: a group consisting of patients (examined group) and a group consisting of healthy subjects (control group).

The GWAS are most useful to detect relatively common disease susceptibility alleles and are the "gold standard" for detecting complex trait susceptibility genes [19].

Genetic studies in vitiligo

Genetic studies conducted so far concern patients with non-segmental vitiligo.

Candidate gene association studies

Candidate gene association studies conducted up to now implicated at least 33 candidate genes: *ACE, AIRE, CAT, CD4, CLEC11A, COMT, CTLA4, C12orf10, DDR1, EDN1, ESR1, FAS, FBXO11, FOXD3, FOXP3, GSTM1, GSTT1, IL1RN, IL10, KITLG, MBL2, NFE2L2, PDGFRA-KIT, PTGS2, STAT4, TAP1-PSMB8, TGFBR2, TNF, TSLP, TXNDC5, UVRAG, VDR* and *XBP1* [20]. The participation of these genes in vitiligo pathogenesis is not clear. The study which was conducted to test the association of the above candidate genes detected and confirmed only the association of three of them: *XBP1, FOXP3, TSLP*. However, many studies have confirmed significant pathogenic participation of candidate gene *PTPN22* and HLA in vitiligo development [20].

Vitiligo frequently coexists with other autoimmune diseases. This fact leads to the search for the genetic conditions responsible for this relation. The loci HLA are highly linked to other loci localized in the major histocompatibility region of chromosome 6p. HLA alleles re-

lated to vitiligo may not cause the disease development but they may play a role of genetic markers which are usually co-inherited across the population (e.g. in the case of strong linkage disequilibrium) with the actual inducing disease alleles at another loci within the major histocompatibility region [14].

Many studies have been conducted to determine the localization of alleles and antigens predisposing to vitiligo within the HLA. The results of these studies varied between populations and ethnic groups, however some alleles and antigens occurred more often than the others (A2, DR4, DR7, DQB1*0303, Cw6, A30, A31 and DQ3) [14].

Using a family-based association study design, single nucleotide polymorphisms of *PTPN22* gene were examined among 126 Caucasian families with multiple cases of vitiligo and associated autoimmune diseases. The protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) gene encodes the protein which is a lymphoid-specific intracellular phosphatase (Lyp). Lyp inhibits T-cell activation through interaction with protein tyrosine kinase (Csk) and inhibition of signaling pathways mediated by T-cell receptor (TCR) [21]. The existence of a relation between *PTPN22* 1858T allele and risk of autoimmune diseases development such as diabetes mellitus type 1, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease and Hashimoto disease has been proven [22–25]. In summary, there is a significant relationship between the *PTPN22* 1858T allele of SNP rs2476601 and vitiligo with an expanded autoimmunity phenotype [26].

Genome-wide linkage studies

The first study showing highly probable linkage between vitiligo and the locus at chromosome 1p31.3-p32.2 called *AIS1* was conducted among a single family compound of 24 members including 14 affected with autoimmune diseases [12]. The next study included a group of 71 families from North America and the United Kingdom with multiple vitiligo cases. In this study, *AIS1* located at chromosome 1p31 met criteria for highly significant linkage confirming its role of an important vitiligo susceptibility locus [27].

Another study analyzing DNA sequences of chromosome 1p among family members with damaged *AIS1* gene showed an overexpression of *FOXD3* gene which encodes a forkhead transcriptional factor that is a primary regulator of melanoblast differentiation in the embryonic neural crest [28, 29].

Many linkage studies in the Caucasian population among people with vitiligo enabled identification of other loci at chromosomes 7, 8, 9, 11, 13, 17, 19 and 22 [27, 30]. The strongest signal came from chromosome 17p13 and corresponded with the *SLEV1* (*NALP1, NRLP1, CARD7, DEFCAP, NAC*) gene locus. The analysis involved members of families with multiple cases of systemic lupus erythematosus (SLE) coexisting with vitiligo and initiated

a series of studies showing the association of this gene not only with SLE and vitiligo but with diabetes mellitus type 1, Addison disease, celiac disease, scleroderma and chronic inflammatory bowel diseases as well [31–39].

The *NALP1* gene mediates activation of the innate immune system in response to molecular patterns such as bacterial pathogens [40–42]. *NALP1* is widely expressed at low levels but is highly expressed in immune cells, especially in T-cells and Langerhans' cells [43, 44]. This fact implies a relationship between the gene and skin autoimmune disorders. The *NALP1* protein together with the adapter protein ASC, caspase 1 and caspase 5 form a complex termed *NALP1* inflammasome activating the proinflammatory cytokine IL-1β [41–45]. Serum levels of IL-1β are elevated among patients with vitiligo [46]. It proves the contribution of mentioned proteins in disease pathogenesis.

The vitiligo genetic study conducted at the same time among Chinese families detected signals at 1p36, 4q13-q21, 6p21-p22, 6q24-q25, 14q12-q13 and 22q12 localizations [47]. Other analysis revealed two significant linkages which determined main susceptibility loci: 6p21-p22 and 22q12 [48]. These localizations do not coincide with the Caucasian families loci suggesting that vitiligo susceptibility genes differ among individual populations.

Genome-wide association studies

The first GWAS study was conducted among the community of an isolated village in Romania. Within this population an elevated prevalence of generalized vitiligo and other autoimmune diseases (autoimmune thyroid diseases, rheumatoid arthritis, diabetes mellitus type 1) was observed [49]. The results of researches obtained among this group confirmed the association of vitiligo with single nucleotide polymorphism (SNP) within chromosome 6q27, in the close vicinity to IDDM8, a linkage and association signal for type 1 diabetes mellitus and rheumatoid arthritis [50].

Another study conducted on Caucasians revealed a significant association between generalized vitiligo and SNP within loci related to other autoimmune diseases confirmed in past studies [50]. Within the MHC region at chromosome 6p21.3 there were two main signals detected. The first signal was in the class I gene region, between HLA-A and HCG9. The second signal was detected in the class II gene region between HLA-DRB1 and HLA-DQA1 [51]. It is consistent with the past studies supporting vitiligo association with HLA-A*02 and HLA-DRB1*04 [52, 53]. Outside the MHC region, the study revealed 7 different regions of significant association with generalized vitiligo:

– Region of *PTPN22* gene mentioned above,
– Region of *LPP* gene encoding *LPP* protein, associated with celiac disease and rheumatoid arthritis which function is unknown [54],

– Region of *IL2RA* gene (encoding the interleukin-2-receptor α chain) localized at chromosome 10p15.1 of which variants showed an association with diabetes mellitus type 1, Graves' disease, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus [55–59],
– Region of *UBASH3A* gene localized at chromosome 21q22.3 encoding a regulator of T-cell-receptor signaling, associated with diabetes mellitus type 1 and SLE [60, 61],
– Region of *RERE* gene encoding protein (atrophin-like protein 1), which is a transcriptional corepressor highly expressed in lymphoid cells, and it probably regulates apoptosis [62, 63],
– Region of *TYR* gene localized at chromosome 11q14.3 encoding tyrosinase, which is a melanosomal enzyme catalyzing melanin biosynthesis and which is a major autoantigen in generalized vitiligo [64],
– Region of *GZMB* gene (the granzyme *B* gene) localized at chromosome 14q12 of which product is a serine protease that mediates targeted cell apoptosis induced by the immune system with contribution of cytotoxic T cells and NT cells and activation-induced cell death of effector type 2 helper T cells [65, 66].

Five of these regions contain genes with a previously confirmed association with other autoimmune diseases.

So far, the biggest conducted association study included 33 candidate genes of generalized vitiligo. Only three genes showed an association with the disease: *FOXP3*, *XBP1* and *TSLP* [20]. *FOXP3* gene localized at Xp11.23 region encodes protein – scurfine (SFN). The gene is expressed in CD25+CD4+ regulatory T cells and has an important role in their development and function [67]. *FOXP3* gene mutations lead to IPEX syndrome (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome), characterized by development of multiple autoimmune diseases, such as diabetes mellitus type 1, thyroid autoimmune diseases, inflammatory bowel diseases, allergic diseases (e.g. atopic dermatitis, food allergies) and vitiligo [68–70]. The next gene, associated with generalized vitiligo *XBP1* (X-box binding protein 1) gene is localized at chromosome 22. *XBP1* protein plays a role of a transcription factor through recognition of the X2 promoter element of both HLA DR-α and HLA DP-β. In view of the autoimmune vitiligo aspect supported by the significant relation with HLA-DR region, *XBP1* gene has been approved as a convincing candidate gene due to its reliable role in disease development through the interaction with this region [71]. Studies concerning the region where *XBP1* gene is localized, conducted among completely different ethnic groups confirmed its relation with vitiligo development within each of them [30, 48, 71]. The next gene, *TSLP* gene localized at chromosome 5q22.1 encodes thymic stromal lymphopoietin. This protein induces naive CD4+ T cells to produce cytokines related with Th2 response (IL-4, IL-5, IL-13, TNF-α) and inhibits production of cytokines related with Th1

response (IL-10, IFN-γ) [72]. As a result, when deficiency of *TSLP* gene expression occurs, the dominance of Th1 response, which is involved in vitiligo development, is expected.

The latest conducted GWAS study leads to identification of 13 so far unknown susceptibility genes [73]:
– *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 [74]. 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 [75–79]. Among the group of vitiligo patients, the researchers confirmed an elevated prevalence of tan/brown and green/hazel eye color indicating the occurrence of additional genes of eye color beside the *OCA2* gene related to the elevated risk of vitiligo. This gene is *TYR* associated both with vitiligo and green/hazel pigmentation of eyes' irises [51, 80].
– *MC1R* gene. At chromosome 16, the region of association 16q24.3 containing 20 genes was detected, especially *MC1R* gene encoding the melanocortin receptor which is a melanogenesis regulator and secondary vitiligo autoantigen. It is associated with melanoma and with eye and skin pigmentation [81].
– The study detected SNPs at 11q21 region containing no known genes. The researchers speculate that this region might store a regulatory element affecting *TYR* gene transcription in cis.
– *IFIH1* gene. The study indicated 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 [82]. It is associated with diabetes mellitus type 1, Graves' disease, multiple sclerosis, psoriasis and probably with lupus [83–87].
– *CD80* gene. There were SNPs at 3q13.33 region 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 [88].
– *CLNK* gene. SNPs within 4p16.1 gene inside the area of *CLNK* gene associated with the mast cells immunoreceptor [89].
– *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 [90–93].
– *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 [94]. *SLA* gene encodes Src-like adaptor protein [95].
– *CASP7* gene. SNPs at 10q25.3 region with *CASP7* gene encoding caspase 7 which has an important executive

function in apoptosis and inflammation [96]. The gene is associated with rheumatoid arthritis and diabetes mellitus type 1 [97, 98].

– *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 what is important it plays a role in T cell development. It is associated with lupus erythematosus [99, 100].

– *IKZF4* gene. SNPs at 12q13.2 region containing *IKZF4* gene associated with diabetes mellitus type 1 and alopecia areata encoding the transcriptional factor for T cell activation [101–103].

– *SH2B3* gene. SNPs at 12q24.12 region localized inside and close to *SH2B3* gene and SNP within *ATXN2* gene encoding Ataxin-2. More important in vitiligo development seems to be *SH2B3* gene encoding adaptor protein LNK regulating development of both B and T cells [104]. The gene is associated with diabetes mellitus type 1 and celiac disease, rheumatoid arthritis, multiple sclerosis and probably with lupus erythematosus [54, 87, 105, 106].

– *TOB2* gene. SNPs at 22q13.2 region close to *TOB2* gene and SNPs between ZC3H7B and TEF. *TOB2* gene encodes a regulator of cell cycle progression involved in T cell tolerance [107].

Most of these genes encode immunoregulatory proteins or melanocyte proteins. Many of these loci are shared with other autoimmune diseases.

Other aspects of genetic studies

Genetics and clinical signs

Genetic studies of generalized vitiligo do not only concern identification of disease predisposing genes but might lead to identification of genes linked to clinical aspects of disease, e.g. dynamics of the disease process or the time of first skin lesion manifestation.

In the study conducted among the Chinese Han population, clinical features of vitiligo patients HLA-DRB1*07 positive and negative were compared [108]. Among patients HLA-DRB1*07 positive the study showed an earlier disease onset, higher frequency of family history and coexistence of autoimmune diseases compared with DRB1*07 negative patients.

The GWAS study conducted identified locus linked to the time of first skin lesion manifestation localized at MHC class II region [109].

Vitiligo and skin melanoma

Among some patients, during the treatment of melanoma vitiligo macules occur. In the opinion of many authors, this symptom is a favorable prognostic factor. The inverse relationship between genetics of vitiligo and melanoma was proven. The *TYR* gene encodes tyrosinase which is a key melanosomal enzyme responsible for melanin biosynthesis. The tyrosinase not only plays an important role in skin pigmentation but also, as it was already mentioned, is a major autoantigen in generalized vitiligo. In the case of *TYR* gene, the vitiligo susceptibility variant seems to be the major (Arg) allele of rs1126809. This polymorphism is rare among populations other than European-derived white individuals [110]. On the other hand, the minor (Gln) allele, which is protective with respect to generalized vitiligo, is associated with susceptibility to melanoma in this population [111, 112]. From a genetic susceptibility point of view, the *TYR* Arg402Gln polymorphism shows an inverse relationship between vitiligo and melanoma. Most of the biological processes responsible for this relation are already known. Tyrosinase is presented to the immune system on the surface of both melanocytes and melanoma cells making it an important signal by which the immune system recognizes these cells. The presentation is mediated by HLA class I molecules, principally by HLA-A*0201 which itself is a major risk allele of generalized vitiligo. HLA-A*0201 and *TYR* 402Arg genes show an important genetic interaction conducive to the occurrence of vitiligo susceptibility which is reflected by biological interaction [51]. *TYR* 402Gln variant encodes unstable polypeptide stored and degraded within the endoplasmic reticulum. The degradation results in reduced amount of polypeptide available to presentation on the cell surface. Furthermore, the presentation of this peptide with the HLA-A*0201 participation requires posttranslational modification via a mechanism which is likely to be inefficient in the case of *TYR* 402Gln polypeptide. In consequence, tyrosinase-402Arg presented with a greater efficiency on the cell surface seems to have a bigger contribution to immune surveillance (as a consequence in protection) against melanoma and to vitiligo susceptibility than tyrosinase-402Gln. While conversely tyrosinase-402Gln is associated with a lower vitiligo susceptibility but a greater risk of melanoma [110].

Summary

Up to now, approximately 36 convincing non-segmental vitiligo susceptibility loci have been identified. Most of them are localized directly within or in close proximity to reliable biological candidate genes. Approximately 90% of them encode immunoregulatory proteins, while approximately 10% encode melanocyte proteins. The proteins of melanocytes are probably autoantigens which stimulate specific immune response, they are identified by the immune system and eliminated. These proteins altogether create a dense network regulating the immune system that highlights systems and pathways which have an influence on vitiligo susceptibility development [113].

Constant researches of susceptibility genes give an opportunity to get a better understanding of the mechanisms underlying the vitiligo pathogenesis, perhaps will

allow to select patients with an increased genetic risk of the disease development and will lead to discovery of interactions between genes and environmental factors to eliminate negative conditions.

The existence of various associations between vitiligo and other autoimmune diseases may provide new knowledge on the causes of many disorders thanks to genetic researches. Examples inlude the inverse relationship between vitiligo and melanoma genetics which in the future may lead to new opportunities for this extremely dangerous skin neoplasm therapy.

The main goal of all researches is to find new, optimal therapeutic strategies for vitiligo and other autoimmune diseases. It is possible that in the future these researches will even find new methods of prevention in this specific group of diseases.

Conflict of interest

There is no conflict of interest.

References

1. Taïeb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med 2009; 360: 160-9.
2. Ortonne JP, Bose SK. Vitiligo: where do we stand? Pigment Cell Res 1993; 6: 61-72.
3. Passeron T, Ortonne JP. Physiopathology and genetics of vitiligo. J Autoimm 2005; 25 Suppl: 63-8.
4. Gavalas NG, Gottumukkala RV, Gawkrodger DJ, et al. Mapping of melanin-concentrating hormone receptor 1 B cell epitopes predicts two major binding sites for vitiligo patient autoantibodies. Exp Dermatol 2009; 18: 454-63.
5. Westerhof W, D'Ischia M. Vitiligo puzzle: the pieces fall in place. Pigment Cell Res 2007; 20: 345-59.
6. Nath SK, Majumder PP, Nordlund JJ. Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. Am J Hum Gen 1994; 55: 981-90.
7. Picardo M, Taïeb A, editors. Vitiligo. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010.
8. Spritz RA. Recent progress in the genetics of generalized vitiligo. J Genet Genom 2011; 38: 271-8.
9. Boissy RE, Spritz RA. Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff. Exp Dermatol 2009; 18: 583-5.
10. Bhatia PS, Mohan L, Pandey ON, et al. Genetic nature of vitiligo. J Dermatol Sci 1992; 4: 180-4.
11. Nath SK, Majumder PP, Nordlund JJ. Genetic epidemiology of vitiligo: multilocus recessivity cross – validated. Am J Hum Genet 1994; 55: 981-90.
12. Alkhateeb A, Stetler GL, Old W, et al. Mapping of an autoimmunity susceptibility locus (AIS1) to chromosome 1p31.3-p32.2. Hum Mol Gen 2002; 11: 661-7.
13. Alkhateeb A, Fain PR, Thody A, et al. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 2003; 16: 208-14.
14. Zhang XJ, Chen JJ, Liu JB. The genetic concept of vitiligo. J Dermatol Sci 2005; 39: 137-46.
15. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. Genet Med 2002; 4: 45-61.
16. Freedman ML, Reich D, Penney KL, et al. Assessing the impact of population stratification on genetic association studies. Nat Genet 2004; 36: 388-93.
17. Dawn Teare M, Barrett JH. Genetic linkage studies. Lancet 2005; 366: 1036-44.
18. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nature reviews. Genetics 2005; 6: 95-108.
19. Spritz RA. Six decades of vitiligo genetics: genome-wide studies provide insights into autoimmune pathogenesis. J Investig Dermatol 2012; 132: 268-73.
20. Birlea SA, Jin Y, Bennett DC, et al. Comprehensive association analysis of candidate genes for generalized vitiligo supports XBP1, FOXP3, and TSLP. J Investig Dermatol 2011; 131: 371-81.
21. Zhang Q, Hou S, Jiang Z, et al. No association of PTPN22 polymorphisms with susceptibility to ocular Behcet's disease in two Chinese Han populations. PloS one 2012; 7: e31230.
22. Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nat Genet 2004; 36: 337-8.
23. Kyogoku C, Langefeld CD, Ortmann WA, et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. Am J Hum Genet 2004; 75: 504-7.
24. Velaga MR, Wilson V, Jennings CE, et al. The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. J Clin Endocrinol Metabol 2004; 89: 5862-5.
25. Criswell LA, Pfeiffer KA, Lum RF, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet 2005; 76: 561-71.
26. LaBerge GS, Bennett DC, Fain PR, Spritz RA. PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. J Investig Dermatol 2008; 128: 1757-62.
27. Fain PR, Gowan K, LaBerge GS, et al. A genomewide screen for generalized vitiligo: confirmation of AIS1 on chromosome 1p31 and evidence for additional susceptibility loci. Am J Hum Genet 2003; 72: 1560-4.
28. Alkhateeb A, Fain PR, Spritz RA. Candidate functional promoter variant in the FOXD3 melanoblast developmental regulator gene in autosomal dominant vitiligo. J Investig Dermatol 2005; 125: 388-91.
29. Kos R, Reedy MV, Johnson RL, Erickson CA. The winged-helix transcription factor FoxD3 is important for establishing the neural crest lineage and repressing melanogenesis in avian embryos. Development (Cambridge, England) 2001; 128: 1467-79.
30. Spritz RA, Gowan K, Bennett DC, Fain PR. Novel vitiligo susceptibility loci on chromosomes 7 (AIS2) and 8 (AIS3), confirmation of SLEV1 on chromosome 17, and their roles in an autoimmune diathesis. Am J Hum Genet 2004; 74: 188-91.
31. Nath SK, Kelly JA, Namjou B, et al. Evidence for a susceptibility gene, SLEV1, on chromosome 17p13 in families with vitiligo-related systemic lupus erythematosus. Am J Hum Genet 2001; 69: 1401-6.
32. Jin Y, Birlea SA, Fain PR, Spritz RA. Genetic variations in NALP1 are associated with generalized vitiligo in a Romanian population. J Investig Dermatol 2007; 127: 2558-62.
33. Alkhateeb A, Qarqaz F. Genetic association of NALP1 with generalized vitiligo in Jordanian Arabs. Arch Dermatol Res 2010; 302: 631-4.

34. Magitta NF, Bøe Wolff AS, Johansson S, et al. A coding poly-morphism in NALP1 confers risk for autoimmune Addison's disease and type 1 diabetes. Genes Imm 2009; 10: 120-4.

35. F Magitta N, Pura M, S Bøe Wolff A, et al. Autoimmune poly-endocrine syndrome type I in Slovakia: relevance of screen-ing patients with autoimmune Addison's disease. Eur J En-docrinol 2008; 158: 705-9.

36. Zurawek M, Fichna M, Januszkiewicz-Lewandowska D, et al. A coding variant in NLRP1 is associated with autoimmune Addison's disease. Hum Immunol 2010; 71: 530-4.

37. Pontillo A, Vendramin A, Catamo E, et al. The missense vari-ation Q705K in CIAS1/NALP3/NLRP3 gene and an NLRP1 hap-lotype are associated with celiac disease. Am J Gastroenterol 2011; 106: 539-44.

38. Dieudé P, Guedj M, Wipff J, et al. NLRP1 influences the sys-temic sclerosis phenotype: a new clue for the contribution of innate immunity in systemic sclerosis-related fibrosing alveolitis pathogenesis. Ann Rheumat Dis 2011; 70: 668-74.

39. De Iudicibus S, Stocco G, Martelossi S, et al. Genetic pre-dictors of glucocorticoid response in pediatric patients with inflammatory bowel diseases. J Clin Gastroenterol 2011; 45: e1-7.

40. Hlaing T, Guo RF, Dilley KA, et al. Molecular cloning and char-acterization of DEFCAP-L and -S, two isoforms of a novel member of the mammalian Ced-4 family of apoptosis pro-teins. J Biol Chem 2001; 276: 9230-8.

41. Kufer TA, Fritz JH, Philpott DJ. NACHT-LRR proteins (NLRs) in bacterial infection and immunity. Trends in Microbiology 2005; 13: 381-8.

42. Petrilli V, Papin S, Tschopp J. The inflammasome. Current Biology 2005; 15: R581.

43. Su AI, Wiltshire T, Batalov S, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci U S A 2004; 101: 6062-7.

44. Kummer JA, Broekhuizen R, Everett H, et al. Inflammasome components NALP 1 and 3 show distinct but separate ex-pression profiles in human tissues suggesting a site-specific role in the inflammatory response. J Histochem Cytochem 2007; 55: 443-52.

45. Jin Y, Mailloux CM, Gowan K, et al. NALP1 in vitiligo-asso-ciated multiple autoimmune disease. N Engl J Med 2007; 356: 1216-25.

46. Tu CX, Gu JS, Lin XR. Increased interleukin-6 and granulo-cyte-macrophage colony stimulating factor levels in the sera of patients with non-segmental vitiligo. J Dermatol Sci 2003; 31: 73-8.

47. Chen JJ, Huang W, Gui JP, et al. A novel linkage to general-ized vitiligo on 4q13-q21 identified in a genomewide link-age analysis of Chinese families. Am J Hum Genet 2005; 76: 1057-65.

48. Liang Y, Yang S, Zhou Y, et al. Evidence for two susceptibility loci on chromosomes 22q12 and 6p21-p22 in Chinese gen-eralized vitiligo families. J Investig Derm 2007; 127: 2552-7.

49. Birlea SA, Gowan K, Fain PR, Spritz RA. Genome-wide asso-ciation study of generalized vitiligo in an isolated European founder population identifies SMOC2, in close proximity to IDDM8. J Investig Dermatol 2010; 130: 798-803.

50. Birlea SA, Fain PR, Spritz RA. A Romanian population isolate with high frequency of vitiligo and associated autoimmune diseases. Arch Dermatol 2008; 144: 310-6.

51. Jin Y, Birlea SA, Fain PR, et al. Variant of TYR and autoimmu-nity susceptibility loci in generalized vitiligo. N Engl J Med 2010; 362: 1686-97.

52. Liu JB, Li M, Chen H, et al. Association of vitiligo with HLA-A2: a meta-analysis. J Eur Acad Dermatol Venereol 2007; 21: 205-13.

53. Fain PR, Babu SR, Bennett DC, Spritz RA. HLA class II hap-lotype DRB1*04-DQB1*0301 contributes to risk of familial generalized vitiligo and early disease onset. Pigment Cell Research 2006; 19: 51-7.

54. Coenen MJH, Trynka G, Heskamp S, et al. Common and dif-ferent genetic background for rheumatoid arthritis and co-eliac disease. Hum Mol Genet 2009; 18: 4195-203.

55. Vella A, Cooper JD, Lowe CE, et al. Localization of a type 1 diabetes locus in the IL2RA/CD25 region by use of tag sin-gle-nucleotide polymorphisms. Am J Hum Genet 2005; 76: 773-9.

56. Brand OJ, Lowe CE, Heward JM, et al. Association of the in-terleukin-2 receptor alpha (IL-2Ralpha)/CD25 gene region with Graves' disease using a multilocus test and tag SNPs. Clin Endocrinol 2007; 66: 508-12.

57. Hafler DA, Compston A, Sawcer S, et al. Risk alleles for mul-tiple sclerosis identified by a genomewide study. N Engl J Med 2007; 357: 851-62.

58. Hinks A, Ke X, Barton A, et al. Association of the IL2RA/CD25 gene with juvenile idiopathic arthritis. Arthr Rheumat 2009; 60: 251-7.

59. Carr EJ, Clatworthy MR, Lowe CE, et al. Contrasting genetic association of IL2RA with SLE and ANCA-associated vasculi-tis. BMC Med Genet 2009; 10: 22.

60. Concannon P, Onengut-Gumuscu S, Todd JA, et al. A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. Diabetes 2008; 57: 2858-61.

61. Diaz-Gallo LM, Sánchez E, Ortego-Centeno N, et al. Evidence of new risk genetic factor to systemic lupus erythematosus: the UBASH3A gene. PloS One 2013; 8: e60646.

62. Wang L, Tsai CC. Atrophin proteins: an overview of a new class of nuclear receptor corepressors. Nucl Recept Signal 2008; 6: e009.

63. Waerner T, Gardellin P, Pfizenmaier K, et al. Human RERE is localized to nuclear promyelocytic leukemia oncogenic do-mains and enhances apoptosis. Cell Growth Different 2001; 12: 201-10.

64. Rezaei N, Gavalas NG, Weetman AP, Kemp EH. Autoimmu-nity as an aetiological factor in vitiligo. J Eur Acad Dermatol Venereol 2007; 21: 865-76.

65. Trapani JA, Sutton VR. Granzyme B: pro-apoptotic, antiviral and antitumor functions. Curr Opin Immunol 2003; 15: 533-43.

66. Devadas S, Das J, Liu C, et al. Granzyme B is critical for T cell receptor-induced cell death of type 2 helper T cells. Immuni-ty 2006; 25: 237-47.

67. Yagi H, Nomura T, Nakamura K, et al. Crucial role of FOXP3 in the development and function of human CD25+CD4+ regu-latory T cells. Inter Immunol 2004; 16: 1643-56.

68. Chatila TA, Blaeser F, Ho N, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmuni-ty-allergic disregulation syndrome. J Clin Investig 2000; 106: R75-81.

69. Wildin RS, Ramsdell F, Peake J, et al. X-linked neonatal dia-betes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 2001; 27: 18-20.

70. Bennett CL, Christie J, Ramsdell F, et al. The immune dys-regulation, polyendocrinopathy, enteropathy, X-linked syn-drome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001; 27: 20-1.

71. Ren Y, Yang S, Xu S, et al. Genetic variation of promoter sequence modulates XBP1 expression and genetic risk for vitiligo. PLoS Genet 2009; 5: e1000523.

72. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol 2002; 3: 673-80.

73. Jin Y, Birlea SA, Fain PR, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. Nat Genet 2012; 44: 676-80.

74. Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. Nature 1993; 361: 72-6.

75. Jannot AS, Meziani R, Bertrand G, et al. Allele variations in the OCA2 gene (pink-eyed-dilution locus) are associated with genetic susceptibility to melanoma. Eur J Hum Genet 2005; 13: 913-20.

76. Amos CI, Wang LE, Lee JE, et al. Genome-wide association study identifies novel loci predisposing to cutaneous melanoma. Hum Mol Genet 2011; 20: 5012-23.

77. Kayser M, Liu F, Janssens ACJW, et al. Three genome-wide association studies and a linkage analysis identify HERC2 as a human iris color gene. Am J Hum Genet 2008; 82: 411-23.

78. Sturm RA, Duffy DL, Zhao ZZ, et al. A single SNP in an evolutionary conserved region within intron 86 of the HERC2 gene determines human blue-brown eye color. Am J Hum Genet 2008; 82: 424-31.

79. Eiberg H, Troelsen J, Nielsen M, et al. Blue eye color in humans may be caused by a perfectly associated founder mutation in a regulatory element located within the HERC2 gene inhibiting OCA2 expression. Hum Genet 2008; 123: 177-87.

80. Sulem P, Gudbjartsson DF, Stacey SN, et al. Genetic determinants of hair, eye and skin pigmentation in Europeans. Nat Genet 2007; 39: 1443-52.

81. Dessinioti C, Antoniou C, Katsambas A, Stratigos AJ. Melanocortin 1 receptor variants: functional role and pigmentary associations. Photochem Photobiol 2011; 87: 978-87.

82. Kato H, Takeuchi O, Sato S, et al. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 2006; 441: 101-5.

83. Smyth DJ, Cooper JD, Bailey R, et al. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet 2006; 38: 617-9.

84. Sutherland A, Davies J, Owen CJ, et al. Genomic polymorphism at the interferon-induced helicase (IFIH1) locus contributes to Graves' disease susceptibility. J Clin Endocrinol Metabolism 2007; 92: 3338-41.

85. Martínez A, Santiago JL, Cénit MC, et al. IFIH1-GCA-KCNH7 locus: influence on multiple sclerosis risk. Eur J Hum Genet 2008; 16: 861-4.

86. Li Y, Liao W, Cargill M, et al. Carriers of rare missense variants in IFIH1 are protected from psoriasis. J Investig Dermatol 2010; 130: 2768-72.

87. Gateva V, Sandling JK, Hom G, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet 2009; 41: 1228-33.

88. Peach RJ, Bajorath J, Naemura J, et al. Both extracellular immunoglobin-like domains of CD80 contain residues critical for binding T cell surface receptors CTLA-4 and CD28. J Biol Chem 1995; 270: 21181-7.

89. Wu JN, Koretzky GA. The SLP-76 family of adapter proteins. Sem Immunol 2004; 16: 379-93.

90. Sasaki S, Ito E, Toki T, et al. Cloning and expression of human B cell-specific transcription factor BACH2 mapped to chromosome 6q15. Oncogene 2000; 19: 3739-49.

91. Cooper JD, Smyth DJ, Smiles AM, et al. Meta-analysis of genome-wide association study data identifies additional type 1 diabetes risk loci. Nat Genet 2008; 40: 1399-401.

92. Dubois PCA, Trynka G, Franke L, et al. Multiple common variants for celiac disease influencing immune gene expression. Nat Genet 2010; 42: 295-302.

93. Franke A, McGovern DPB, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet 2010; 42: 1118-25.

94. Tomer Y, Greenberg D. The thyroglobulin gene as the first thyroid-specific susceptibility gene for autoimmune thyroid disease. Trends Molecul Med 2004; 10: 306-8.

95. Dragone LL, Shaw LA, Myers MD, Weiss A. SLAP, a regulator of immunoreceptor ubiquitination, signaling, and trafficking. Immunol Rev 2009; 232: 218-28.

96. Lamkanfi M, Kanneganti T-D. Caspase-7: a protease involved in apoptosis and inflammation. Int J Biochem Cell Biol 2010; 42: 21-4.

97. García-Lozano JR, Torres B, Fernández O, et al. Caspase 7 influences susceptibility to rheumatoid arthritis. Rheumatology (Oxford, England) 2007; 46: 1243-7.

98. Babu SR, Bao F, Roberts CM, et al. Caspase 7 is a positional candidate gene for IDDM 17 in a Bedouin Arab family. Ann New York Acad Sci 2003; 1005: 340-3.

99. Baaten BJ, Li CR, Bradley LM. Multifaceted regulation of T cells by CD44. Com Integrat Biol 2010; 3: 508-12.

100. Ramos PS, Williams AH, Ziegler JT, et al. Genetic analyses of interferon pathway-related genes reveal multiple new loci associated with systemic lupus erythematosus. Arthr Rheumat 2011; 63: 2049-57.

101. Hakonarson H, Qu HQ, Bradfield JP, et al. A novel susceptibility locus for type 1 diabetes on Chr12q13 identified by a genome-wide association study. Diabetes 2008; 57: 1143-6.

102. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature 2010; 466: 113-7.

103. Pan F, Yu H, Dang EV, et al. Eos mediates Foxp3-dependent gene silencing in CD4+ regulatory T cells. Science (New York, N.Y.) 2009; 325: 1142-6.

104. Devallière J, Charreau B. The adaptor Lnk (SH2B3): an emerging regulator in vascular cells and a link between immune and inflammatory signaling. Biochem Pharmacol 2011; 82: 1391-402.

105. Smyth DJ, Plagnol V, Walker NM, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008; 359: 2767-77.

106. Alcina A, Vandenbroeck K, Otaegui D, et al. The autoimmune disease-associated KIF5A, CD226 and SH2B3 gene variants confer susceptibility for multiple sclerosis. Genes Imm 2010; 11: 439-45.

107. Jia S, Meng A. Tob genes in development and homeostasis. Develop Dynam 2007; 236: 913-21.

108. Hu DY, Ren YQ, Zhu KJ, et al. Comparisons of clinical features of HLA-DRB1*07 positive and negative vitiligo patients in Chinese Han population. J Eur Acad Dermatol Venereol 2011; 25: 1299-303.

109. Jin Y, Birlea SA, Fain PR, et al. Genome-wide analysis identifies a quantitative trait locus in the MHC class II region

associated with generalized vitiligo age of onset. J Investig Dermatol 2011; 131: 1308-12.

110. Spritz RA. The genetics of generalized vitiligo: autoimmune pathways and an inverse relationship with malignant melanoma. Gen Med 2010; 2: 78.

111. Gudbjartsson DF, Sulem P, Stacey SN, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet 2008; 40: 886-91.

112. Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet 2009; 41: 920-5.

113. Spritz RA. Modern vitiligo genetics sheds new light on an ancient disease. J Dermatol 2013; 40: 310-8.