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, autotoxic, 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, genomewide 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, CIITA, DDI1, EDN1, ESR1, FAS, FBXO11, FOXD3, FOXP3, GNP1, GTP1, IL10, KITLG, MBL2, NFE2L2, PTGFRK, PTG52, STAT4, TAP1-PSMB8, TGFBR2, TNF, TSLP, TXNDC5, UVAG, 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, DQ81*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 SLEVI (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 HLA-B. 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 UBAH3A 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 coressor 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 targeter cell apoptosis induced by the immune system with contribution of cytotoxic T cells and NK cells and activation-induced cell death of effector type 2 helper T cells [65, 66].

Four 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, XBPI 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 XBPI (X-box binding protein 1) gene is localized at chromosome 22. XBPI 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, XBPI 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 XBPI gene is localized, conducted among completely different ethnic groups confirmed its association 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 ocucutaneous 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].
– MCIR gene. At chromosome 16, the region of association 16q24.3 containing 20 genes was detected, especially MCIR 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 role in apoptotic process and is associated with autoimmune diseases [96].

So far, the most promising candidate gene is IFIH1, which is involved in the regulation of the response to the virus in lymphoid tissues and regulates cell differentiation and development. Its deficiency might lead to an increased risk of autoimmune vitiligo.
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 allopacia 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 include 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.

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