Review Article

Updates on the genetic characterization of vitiligo

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Summary:

Vitiligo is an autoimmune skin disorder in which autoimmune-mediated destruction of melanocytes caused depigmentation of skin patches. The complex genetics of vitiligo involves multiple susceptibility loci, genetic heterogeneity and incomplete penetrance with gene-gene and gene-environment interactions. In order to clarify the genetic factors, two different principal approaches have applied for the identification of genomic regions or candidate genes that mediate susceptibility to vitiligo. First approach is the genome-wide linkage analyses, which is conducted by scanning of entire human genome for genomic regions that are linked to the development of vitiligo. The other approach is functional candidate gene association (FCGA) analyses that detect specific candidate genes, which are expected to involve in disease on the basis of their priori biological functions. Genomic-wide scans have provided a strong support for vitiligo susceptibility genes on chromosomes 4q13-q21, 1p31, 7q22, 8p12 and 17p13, while loci of interest at 6p, 6q, 14q, 9q, 13q, 19p and 22q required further follow-up. Whereas, FCGA studies have identified some candidate genes which are associated with vitiligo, such as HLA, AIRE, VIT1, CAT, FOXD3, ESR1, COMT, PTPN22, NALP1, PDGFRA, MYG1, MITF, CD117, XBP1, FAS, COX2, EDN1 and ACE, but few of them reports now appear to be false-positive. This review will provides an update on genetics of vitiligo based on the identification of novel candidate genes that represent, in my opinion as optimal utility for future therapeutic targets in the pathogenesis of vitiligo.

Keywords: Vitiligo, genetics, novel candidate genes, melonocytes, genome.

Abbreviations:

HLA	Human leukocyte antigen
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
ACE	Angiotensin-converting enzyme
CAT	Catalase
PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
PTPN22	Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)
MYG1	Melanocyte proliferating gene 1
MITF	Microphthalmia- associated transcription factor
CD117	Cluster of differentiation 117
ESR 1	Estrogen receptor 1
FOXD3	Forkhead box D3
AIRE	The autoimmune regulator
COMT	Catechol O-methyl transferase
XBP1	X box binding protein 1
EDN1	Endothelin-1
COX2	Cyclooxygenase-2
VIT1	Vitiligo-associated protein 1

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Introduction

Vitiligo is a multifactorial autoimmune disorder characterized by the appearance of white maculae that may spread over the entire body skin. [1] In general, it is an acquired hypomelanotic skin disorder with 0.1-2% incidence worldwide. [1,2] Patterns of distribution of vitiligo are generalized, acrofacial, localized or segmental types. In fact, vitiligo is known for thousands years because of its visually evident phenotype. [3] Most vitiligo patients are in good health and have no symptoms other than depigmentation of skin lesions. [4] However, this disease is one of the most devastating psychologically disorder and its psychological effects are influenced by social perceptions of skin disfigurement and irregularities of skin color. [4,5] The etiology of vitiligo is still unknown, but genetic factors, autoimmunity, environmental factors, or lack of melanocytes growth factors might contribute for precipitating the disease in susceptible people [6-10]. In addition, many studies have shown a strong association of vitiligo patients with other autoimmune diseases, [11, 12] particularly autoimmune thyroid disease (AITD) [6], suggesting a heritable predisposition involving, in part, and shared susceptibility genes.

Genetic risk for vitiligo is well supported by multiple lines of evidence. [13-19] Vitiligo is frequently associated with familial clustering and approximately 20% of probands have at least one affected first-degree relatives. [11,13] The risk for first degree relatives of patients with vitiligo to develop the disease is increased by seven to ten fold compared with the risk for the general population. [14] But, now it is well accepted that the inheritance pattern of vitiligo does not follow the simple Mendelian pattern and its mode of heredity suggests that it is a polygenic and multifactorial disease. [11, 12, 15] This is supported by several genome-wide scans and functional gene association (FCGA) studies, which have been performed in the past years and multiple linkages to vitiligo have been identified from different populations [19-23] and different genetic models for vitiligo. [16,17] Despite formal proof that vitiligo is genetically dependent, and despite rapid progress in molecular genetics, the gene(s) directly implicated in this skin disorder remain to be identified. This comprehensive review is aimed to update the genetic knowledge of vitiligo, which provides some novel therapeutic targets for the new interventional approaches to treat and even prevent vitiligo in future.

Vitiligo Genetics

Genetics of vitiligo is characterized by incomplete penetrance, multiple susceptibility loci and genetic heterogeneity. [11,14] Approaches for the identification of genes involved in vitiligo pathogenesis have taken a number of forms, initially focusing on biological candidates and differential expression analyses. In the last decade, technological advances enabled by human genome project, and methodological advances applied to the analyses of polygenic, multifactorial diseases, have permitted more global approaches, including a genome-wide scans and FCGA studies. As the result, there has been considerable progress in identifying susceptibility genes for vitiligo. Approaches for the identification of genes involved in vitiligo pathogenesis are summarized in Figure 1.

1- Identification of vitiligo susceptibility loci by genome-wide linkage analysis

Genome-wide linkage studies are the best suited to detecting genetics signals that represent relatively rare causal variants with modest-large effect sizes. This approach involves the typing of families using polymorphic markers that are positioned across the whole genome, followed by measuring the degree of linkage of the marker to a disease trait, and then the positional candidate genes can be identified by examining the regions around the peaks of linkage. [24] However, it must be borne in mind that most vitiligo patients are singleton cases, with few or no affected relatives, and thus susceptibility genes and variants detected by linkage in multiple families may not be typical of the majority of cases. Moreover, in many instances it has proved difficult to identify positional genes that underlie candidate genetic linkage signals. But this approach has sufficient powered to minimize statistical variations and allows adequate control for multiple testing within the study, and provide full-genome datasets that enable both detection of and adjustment for population stratification.

Several genome-wide linkage analyses/scans of vitiligo have been performed and multiple linkages associated to vitiligo are identified. [1, 19-22] These studies identified 15 potential vitiligo susceptible loci on 12 different chromosomes. First positive linkage of vitiligo was identified on chromosome17p13 in European-American Caucasian pedigrees with co-segregation of SLE. [19] This approach was also proved successful as identified a significant linkage on chromosome 1p32.2-p31.3 (named as "AIS1") among Caucasian families with co-segregation of vitiligo and Hashimoto thyroiditis [20]. Another genome-wide linkage scan identified an additional seven suggestive linkages on chromosomes 1, 7, 8, 11, 19 and 22. [19,20] Another linkage scan from 102 multiplex family cohorts provides a strong for AIS1 locus at 73.7 cM on chromosome 1p. [21] This study has also provided supporting evidence for a disease locus on chromosome 17, which may correspond to SLEV1 locus and the linkage evidence at AIS1, AIS2 on chromosomes 7q and 8p, respectively. [19,21] Genome wide linkage scan of Chinese population also identified linkages to generalized vitiligo on 1p36, 4q13-q21, 6p21-p22, 6q24-q25, 14q12-q13, 22q12 and a novel linkage on 4q13-q21, [22], this suggests that 4q13-q21 may be a major susceptibility locus for vitiligo in this population.

2-Functional candidate genes associated with vitiligo susceptibility

The first critical step in conducting candidate gene studies is the choice of a suitable candidate gene that may plausibly play a relevant role in the process or disease under investigation. A few genes that are reported to contribute to vitiligo susceptibility are presented in Figure 1 and are described below.

A. Human leukocyte antigen (HLA) genes

The inherited origin of vitiligo and its frequent association with autoimmune diseases suggest an association between HLA systems to vitiligo predisposition. The HLA loci are strongly linked to other loci in the major histocompatibility complex (MHC) region of chromosome 6p. [1,25] Therefore, vitiligo associated HLA alleles may not be disease specific, but are the genetic markers that usually co-inherit in the population with the actual disease allele at another locus within the MHC region. [6] Allelic linkage or association studies in different populations have consistently showed a significant association between HLA system and vitiligo. [24-36] Recent advancement in gene technology with accurate statistical methods found association between generalized vitiligo and HLA-DRB4*0101 and HLA-DQB1*0303 in Dutch patients [32], with HLA-DRB1*03, DRB1*04 and HLA-DRB1*07 alleles in Turkish patients, [34] and with alleles of microsatellites located in the MHC in Columbian patients. [33] Furthermore, in Caucasian multiplex generalized vitiligo families, the MHC class II haplotype HLA DRB1A*04-(DQA1*0302)-DQB1*0301 showed consistent association with both increased risk of vitiligo and with relatively early disease onset. [35] In short, studies in different populations provide consistent association between vitiligo predisposition and HLA-A2, A30, A31, B13, B27, B46, B56, B60, Cw4, Cw6, DR4, DR5, DR7, DR53 and DQ3 [1-4]. Genetic models of vitiligo also show a positive association to DQB1*0303, DQB1*0503 and DRB1*0901 alleles with vitiligo susceptibility. [16] Association has also been reported between generalized vitiligo and genes with low molecular weight polypeptide-2 and -7 (LMP2 and LMP7) and with transporter associated with antigen processing protein-1 (TAP-1) gene region of the MHC. [36] All these data discuss under this subheading clearly suggest that HLA genes represent attractive therapeutic targets for vitiligo pathogenesis.

B. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene

CTLA-4 is involved in the negative regulation of T-cell activation and in controlling T-cell apoptosis. [37] Several CTLA-4 ploymorphic alleles are associated with susceptibility to autoimmune disease and some of these have now been associated with vitiligo. [38-40] Interpretation of finding for CTLA-4 has been more problematic. A meta-analysis [38] indicated that, overall association of CTLA-4 with vitiligo is weak, and probably is secondary driven by primary genetic association of CTLA-4 with other autoimmune diseases that are epidemiologically associated with vitiligo. In short, studies suggest that

vitiligo when not associated with an autoimmune disorder is not influenced by CTLA-4 polymorphism [reviewed in 24].

C. Angiotensin-converting enzyme (ACE) gene

Neural system plays an important role in the pathogenesis of vitiligo (especially segmental vitiligo). [15] It is known that substance P is neuropeptides which is released from sensory nerves in the skin under noxious stimuli like chemical and mechanical injury, which then induced augmented inflammatory responses, including plasma extravasations, proinflammatory cytokine production, leukocytes and mast cell activation. [41] ACE gene is located on chromosome 17q23.3 encode angiotensin- converting enzyme. This is capable of inactivating bradykinin, modulating cutaneous neurogenic inflammation and degrading substance P and other neuropeptides. [41] Many studies have shown an association of ACE gene insertion/deletion (I/D) polymorphism in intron 16 and autoimmune diseases. [42-44] Furthermore, the ACE genotype distribution and allelic frequencies are significantly different between vitiligo patients and controls, indicating a strong association of ACE gene polymorphisms with vitiligo. [42, 43] However, few studies reported that an I/D polymorphism in ACE gene is not associated with generalized vitiligo in different populations. [44, 45] Therefore, the interpretation of findings for ACE gene has been confusing and should be investigated further.

D. Catalase (CAT) gene

Catalase is well known antioxidant enzyme, which prevents cell damage from highly reactive oxygen species (ROS). The CAT gene was selected as a candidate gene because of the reduction of catalase enzyme activity during vitiligo condition [46] and concomitant accumulation of excess hydrogen peroxide in the entire epidermis of vitiligo patients. [46] Many allelic variants of catalase have been reported, [47] and the first form was known as catalasemia, which occurred due to splicing mutation in Japanese population. [47] The CAT gene composed of 13 exons spanning 33 kb of genomic DNA located on chromosome 11p13 with the complete cDNA sequence revealing a coding region 1584 base pairs in length. [43] It is known that SNP in exon 9 of the CAT gene is associated with vitiligo, [48] as T/C heterozygocity is more frequent in vitiligo patients than in controls. C allele is transmitted more frequently to patients than to controls, suggesting that linked mutations in or near CAT gene may contribute to a quantitative deficiency of catalase activity in patients with vitiligo. All these data indicate that CAT gene is an attractive therapeutic target for vitiligo.

E. Platelet-derived growth factor receptor alpha (PDGFRA) gene

PDGFRA gene is a proto-oncogene, located on chromosome 4q12. It belongs to the human type III family of transmembrane receptors, with an intrinsic tyrosine kinase component. The PDGFRA protein is involved in several cellular and tissue processes, such as proliferation, apoptosis, chemotaxis, melanogenesis, hematopoiesis and gametogenesis [reviewed in 49]. Studies have shown a mutation in PDGERA gene in patients with familial vitiligo [49], suggesting a strong association of this gene with vitiligo. Furthermore, genetic linkage analysis of a large Chinese family of cohort vitiligo, identified a vitiligo linkage locus AIS4 within chromosome 4q12-q21, a region containing PDGFRA gene, [49] further supports the candidature for vitiligo pathogenesis and should be targeted and offer a suitable therapeutic options for vitiligo.

F. Protein tyrosine phosphatase non receptor 22 (PTPN22) gene

PTPN22 gene is located on chrososome 1p13 which encodes lymphoid protein tyrosine phosphatase (LYP), which is important in negative control of T lymphocyte activation and is believed to be a general autoimmunity susceptibility locus. [50-53] Three independent case-control studies have shown strong association of the PTPN22 1858T variant with vitiligo, in a Caucasians cohort from UK, [54] Gujarat, India, [55] and from Romania. [56] These results strongly indicating true association with what is believed to be the causal variant for PTPN22-related autoimmune susceptibility. Genetic linkage and association studies on PTPN22 gene further support its candidature for generalized vitiligo. [57-58]

G. Melanocyte proliferating gene 1(MYG1)

MYG1 (also known as C12 or f10) is considered to be a novel candidate gene for vitiligo genetics. It is composed of seven exons that span 7.5 kb of genomic DNA located in chromosomal region 12q13. [59] MYG1 has differential pattern and level of expression during embryonic development of experimental animals; [59] however, MYG1 expression in normal adult tissues is stable and seems to be changed under pathological conditions. [60-62] Moreover, MYG1 expression has demonstrated with subcellular localization in the mitochondria and nucleus. Elevation of MYG1 mRNA has shown in both uninvolved and involved skin of vitiligo patients [60] and atopic eczema [63]. MYG1 gene contains 10 polymorphisms that are defined as SNPs but two polymorphisms are potentially functional. SNP is located at 119 bp upstream of MYG1 translation start site (ATG) and MYG1 promoter polymorphism (-119C/G). [64]. Promoter polymorphism 119C/C in MYG1 gene is associated to vitiligo susceptibility, [64] suggesting a strong role of MYG1 gene polymorphism with vitiligo.

H. Microphthalmia-associated transcription factor (MITF) gene

MITF gene is also considered to be a candidate gene for vitiligo, which is located on chromosome 3p14, encodes a specialized transcription factor that binds to & activates target genes required for development of pigment cells. [65] Otherwise, the antioxidant catalase selectively and significantly reduced death of vitiligo associated melanocytes. [45] In healthy melanocytes, MITF expression inhibits the onset of elevated oxidative stress. [65, 66] Melanocyte stimulating hormone induced expression of MITF protein, which caused an increase in the sensitivity of 4-tyrosinase-related proteins (4-TBP). [65, 66] MITF stimulates melanin synthesis by up-regulating expression of melanogenic enzymes such as TRP-1. It is reported that melanocytes in vitiligo reduced their abilities to handle oxidative stress, which partly caused disruption in MITF regulation of TRP-1[65]. Furthermore, it is also reported that MITF locus lacks linkage to human vitiligo. [66] This foregoing discussion suggesting a strong association of MITF gene with vitiligo but clearly warrants further studies.

I. Cluster of differentiation 117 (CD117) gene

CD117 is also called KIT gene, which is located on chromosome 4 at map locus 4q12. [67] It encodes tyrosine kinase receptor c-kit, which is expressed on the surface of melanocytes, mast cells, germ cells and hematopoietic stem cells. [67] The c-kit ligand, stem cell factor (SCF) is known to be involved in proliferation and survival of melanoblasts. [68] Mutations in the human CD117 gene caused Piebaldism, a rare autosomal dominant disorder of melanogenesis which is characterized by depigmentation of skin patches. [69] Therefore, CD117 is considered to be a candidate gene for vitiligo but more studies are needed to find its exact association to vitiligo onset.

J. Estrogen receptor (ESR) 1 gene

ESR 1 gene is larger than 140 kb, contains 8 exons, and is located on chromosome 6q25.1 in humans. The ESR1 is a ligand-activated transcription factor composed of several domains, which are important for hormone binding, DNA binding, and activation of transcription. [70] It is reported that high estrogen levels in serum is associated with increase in skin pigmentation and successful treatment of vitiligo is possible with estrogen. [70] Therefore ESR1 is considered to be a candidate gene for vitiligo. Case-control association study on Korean population shows that ESR1 intron 1 C/T polymorphism is associated with female or generalized vitiligo, [70] further supports its candidature for vitiligo. These data clearly indicating that ESR1 gene offers potential as a therapeutic target for vitiligo.

K. Forkhead box D3 (FOXD3) gene

FOXD3 gene is found in AIS1 region of chromosome 1p32-p31. It encodes a forkhead transcription factor that is a primary regulator of melanoblast differentiation in the embryonic neural crest. [71] Now, it is known that families are affected with vitiligo and that had a -639G>T promoter mutation in FOXD3, which significantly increased transcriptional activity of the gene. [72] A microarray study examining melanocytes from the family members with vitiligo and this FOXD3 variant versus normal control melanocytes showed dysregulation of many genes involved in controlling cell cycle,

cell division, and growth and proliferation. This suggests that the FOXD3 variant in this family may results in primary cell-autonomous dysregulation of melanocytes growth, leading to vitiligo. Taken all together, these data clearly indicating that FOXD3 gene has potential as a candidate gene for vitiligo.

L. The autoimmune regulator (AIRE) gene

AIRE is transcription factor composed of 552 amino acids and its gene (AIRE) is located on chromosome 21q22.3. [73-75] Vitiligo is commonly associated with autoimmune polyglandular syndrome type 1 (APS1). APS1 associated vitiligo is proposed to be a consequence of immune dysregulation resulting from mutations in AIRE 1 gene. [73-75] This indicates that AIRE gene offers potential as a candidate gene for vitiligo and should also be investigated further.

M. Catechol O-methyl transferase (COMT) gene

COMT gene is located on chromosome 22q11.21-q11.23. [76, 77] It encodes catechol O-methyl transferase protein, which is one of several enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine. It is reported that COMT-158 polymorphism reduced COMT enzyme activity, this may caused overproduction of toxic radicals in the melanocyte microenvironment. [76, 77] This suggests that COMT gene polymorphism may be contributed in the etiology of vitiligo. Large population-based studies should be required to verify these findings.

N. X box binding protein 1 (XBP1) gene

XBP1gene is located on chromosome 22q12. It acts as a transcription factor that is recognized by X2 promoter element on human DR-A and DP-B. [78] XBP1 gene is considered to be a candidate gene for vitiligo due to its plausible role in the onset of the disease through its interaction with HLA-DR, [79] however, clearly warrants further study.

O. NALP1 gene

NALP1 (also known as CARD7, DEFCAP, or NAC gene) is located in the susceptibility locus 17p, encodes NACHT leucine-rich repeat protein 1, which is a regulator of the innate immune system. [80] Frequency of NALP1 genotype showed an association with vitiligo alone, or with an extended autoimmune disease phenotype, or with both. [81] Caucasian population-based case control study shows a strong association of generalized vitiligo with NALP1 variants. [82] This indicates that NALP1 gene may offers as a candidate gene for vitiligo pathogenesis and should also be investigated further.

P. FAS gene

Human FAS gene (also known as TNFSF6/CD95L) is a member of the tumor necrosis factor (TNF) superfamily, which is mapped to chromosome 10q24.1, consists of nine exons and eight introns. [33] FAS is participated in apoptotic signaling in many types of cells, [83] and triggered cell death signal cascade through FASLG. [84] Therefore, this FAS/FASLG system plays a crucial role in apoptosis. It is reported that two polymorphisms in their promoter regions at position 1377 and at 670 with G-A substitution and with A-G substitution increased the risk of vitiligo onset in Han Chinese populations. [85] This indicates that FAS gene may has a role in the onset of vitiligo but further investigations should be needed to investigate its exact role in this skin disease.

Q. Endothelin-1 (EDN1) gene

EDN1 gene is located on chromosome 6p23-p24 and it encodes a potent vasoconstrictor peptide expressed in vascular endothelial cells and in keratinocytes. [86, 87] Several polymorphisms in this gene were identified [86] and the role of genotyping and allele frequencies of EDN1 in the onset of vitiligo was reported. [87, 88] These data show a strong association between EDN1 gene polymorphisms and susceptibility to vitiligo in different populations. [86, 87] Therefore, it may also offers a therapeutic target for vitiligo, but further studies must be needed to prove its candidature.

R. Cyclooxygenase-2 (COX2) gene

COX2 gene (also known as prostaglandin endoperoxide synthase 2 or PTGS2 gene) is mapped to chromosome 1q25.2–q25.3. It plays an important role in the production of

prostaglandin E2 (PGE2), which is made by epidermal keratinocytes in response to ultraviolet radiation (UVR). [88-90] PGE2 is important for the proliferation and melanogenesis of epidermal melanocytes, the loss of which leads to vitiligo. [91-93] This suggests a strong association of COX-2 gene polymorphism with vitiligo onset, therefore it should also be targeted and offer a suitable therapeutic options for vitiligo.

S. Vitiligo-associated protein 1 (VIT1) gene

VIT1 gene (also known as FBXO11gene) is located on chromosome 2p16 [6,94] and was found to be associated with vitiligo. [94,95] A detailed study of the structure of this gene using computational methods revealed features that could explain many of the distinctive features of vitiligo. [95] The 3`-end of the VIT1 cDNA sequence is complementary to the 3`-end of hMSH6, a G/T mismatch repair gene. Some studies indicate that decreased levels of VIT1 are associated with increased levels of hMSH6. [96] However, the expression of the VIT1 gene in melanocytes of vitiligo patients and potential function in pathogenesis of vitiligo remains unknown.

Key points

Vitiligo is a common depigmentary disorder of the skin and hair, which results from a selective destruction of melanocytes. It affects approximately 0.5-2% of the world population without preferences for specific skin tone or gender. In recent years, technological advances enabled by the human genome project, and methodological advances applied to analyses of polygenic, multifactorial diseases, have permitted more global approaches, including a recent genome-wide linkage scans and functional candidate gene association studies. As the result, there has been considerable progress in identifying susceptibility genes for vitiligo, some of which are shared with other autoimmune diseases and some of which are specific to vitiligo. The linkage and association studies also provide a strong evidence for the presence of multiple vitiligo susceptibility genes on different chromosomes. These genes may thus provide novel therapeutic and even prophylactic targets for new interventional approaches to treat and prevent vitiligo and other autoimmune diseases. In the coming years developments in this area are going to be exciting and will influence the therapeutic approaches for the suppression of vitiligo.
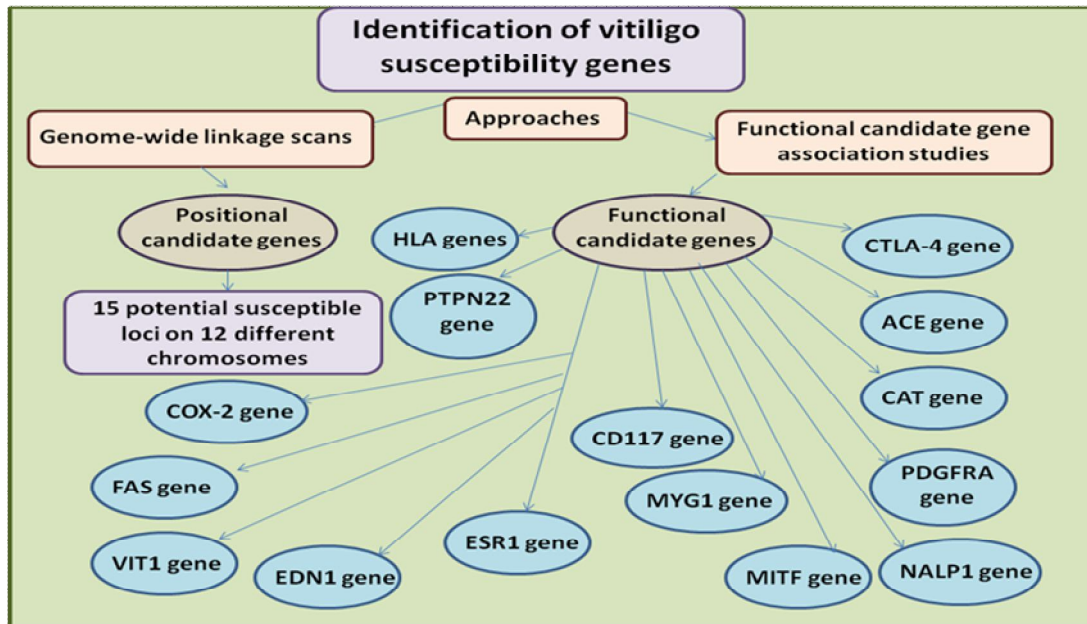
Figure 1. Identification of vitiligo susceptibility genes. Two different approaches have been used to identify genes that mediate susceptibility to vitiligo: genome-wide linkage scans and functional candidate gene association (FCGA) studies. Genome-wide linkage analysis is conducted by scanning of entire human genome for positional candidates genes (genomic regions) that are linked to the onset of vitiligo, whereas FCGA studies detect specific candidate genes which are believed to involve in disease on the basis of their priori biological functions. These approaches provide number of candidate genes that are reported to contribute to vitiligo susceptibility. Abbreviations: HLA, human leukocyte antigen; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ACE, angiotensin-converting enzyme; CAT, catalase; PDGFRA, platelet-derived growth factor receptor alpha; PTPN22, protein tyrosine phosphatase non-receptor 22; MYG1, melanocyte proliferating gene 1; MITF, microphthalmia- associated transcription factor; CD117, cluster of differentiation 117; ESR 1, estrogen receptor 1; FOXD3, forkhead box D3; AIRE, the autoimmune regulator; COMT, catechol O-methyl transferase; XBP1, X box binding protein 1; EDN1, endothelin-1; COX2, cyclooxygenase-2; VIT1, vitiligo-associated protein 1.

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