

Vitiligo: Etiological Study

Mahdi Saber Al-Deresawi ¹ and Aseel Razaq Al-Rekabi ²

^{1,2} College of Science / University of Wasit

Author for correspondence: E-mail maladeresawi@uowasit.edu.iq

Abstract:

Vitiligo is an acquired pigmentary disorder of the skin that is characterized by circumscribed, depigmented macules and patches. Has an estimated prevalence of 0.5–2% of the population worldwide. The condition is frequently associated with disorders of autoimmune origin and hereditary susceptibility in vitiligo patients may refer to proteins that are shown by melanin cells that are autoantigens that target melanin cells to destroy by the immune system.

This review summarizes the current knowledge on vitiligo and attempts to give an overview of biochemical, immunogenic and genes that responsible or that may be candidates for the events of the Vitiligo disease.

1. Introduction:

Vitiligo is an idiopathic pigmentary disorder characterized by the presence of pigmented skin spots due to the loss of melanin cells from the cutaneous epidermis. Surveys of large groups around the world have shown this disease to be 1-2% (**Mazzei-Weissmm, 2020**)

Although the prevalence of 8.8% in India. This disease occurs independently of age and race and occurs equally in both genders (**Behl et al., 2003**). The biological synthesis of melanin cells is complex processes that occur in special organelles called melanosome. About 1500 proteins have been identified in the melanosome during all stages of their maturity. Approximately 100 proteins shared by the melanin body are pigmented and non-pigmented melanin cells, and this potential number represents the primary proteome structure in the body of melanin (**Chi et al., 2006**). Several genes involved in the biosynthesis of melanin cells were studied in this study to determine their association with Vitiligo. Sharing these genes can support autoimmunity and / or support theories of oxidative stress epidemiology of Vitiligo (**Bergqvist and Ezzedine, 2020**).

It was found that there are a group of recessive mutations in TYR and TYR1 genes that are associated with different types of eye skin and eye albinism (a genetic disorder characterized by eye loss to melanin pigment); This supports the primary role in pigmentation and is considered candidate genes in Vitiligo (**Jimbow et al., 2011**).

The phenotype may not be known to genes related with changes in DCT. However, DCT that is combined with TYR and TYR1 proteins has been observed by several groups to be targets of

autoantibodies that are found in serum for vitiligo patients (**Kemp *et al.* 2011; Delgadillo *et al.* ,2019**).

In almost half of all cases, vitiligo appears before the age of 20, about 70-80% of patients develops the disease at the age of 30 (**Behl *et al.*, 2003; Herane, 2003**). Usually, Vitiligo is seen as a minor illness but it has psychological effects on patients and lack of social contact (**Ongenae *et al.*, 2006**). This study aims to review the most important genetic and non-genetic causes of vitiligo, in addition to a detailed explanation of all the genes responsible or that may be candidates for the events of the disease.

2. Signs and symptoms of Vitiligo:

White spots vary in size, shape, and may extend throughout the body; it may be local or segmental. In some individuals, the hair that in the affected area may lose its color and become white. Vitiligo is a non-infectious disease and the physical symptoms of Vitiligo patients may lead to social isolation and its consequences as a major disease or disorder (**Ezzedine *et al.*, 2012; Chi *et al.*, 2006**)

3. Types of Vitiligo:

This disease has many types (**Rebat and Johnathan, 2009; Eleftheriadou, 2020**) the most important of which are: -

- Focal Vitiligo: It is scattered spots in one area, more common in the neck and trunk. This type of vitiligo occurs more commonly in children.
- Mucosal Vitiligo: This type of Vitiligo affects only the mucosa
- Universal Vitiligo: the spots spread throughout the body and can also be associated with a multiplication of endocrine syndrome
- Segmented Vitiligo: This type of Vitiligo is located on one side of the body. This type of Vitiligo appears early in life and does not similar other of Vitiligo. It is not associated with thyroid disease or autoimmune diseases. Half of the patients with segmental vitiligo have polyposis
- Generalize vitiligo: This type affects all parts of the affected person and changes the natural and basic skin color of the body.
- Terminal Vitiligo: is a form of vitiligo and signs of infection are caused by the appearance of signs of discoloration of the skin of the affected area. Vitiligo affects the lips and extremities and affects the genitals. People who have a dark skin type, there is a big difference between the skin color change and normal skin.

4. Mechanisms of disease occurrence:

There are several mechanisms for the occurrence of Vitiligo, the most important of which are:

4.1. The enzymatic role:

The loss of phenylalanine hydroxylase (PHA) is most common in the recessive physical disorders of phenylketonuria (PKU), that the role of this enzyme in the biosynthesis of melanin cells has been supported by a number of studies (**Schallreuter *et al.*, 2005**). PHA gene is located on the 12q22 chromosome and has 13 exon, which encodes 453 amino acid phenylalanine

hydroxylase. This enzyme converts the amino acid phenylalanine into tyrosine, the precursor of the melanin cells. Inactivation or complete loss in the activity of phenylalanine in the liver results in a significant increase in serum concentration of phenylalanine in PKU patients. PUK patients have a special diet that lacks phenylalanine, because increased accumulations of this amino acid have harmful neurological effects. In addition to the disability of the nervous system, the lack of treatment of patients (PKU) leads to a lack of dye, and support to the hypothesis that says that the function of the protein phenylalanine is a vital function that works to develop melanin cells. The role of phenylalanine in the production of tyrosine fit with the idea of changes in the function of the gene can have an impact on the development of melanin cells by reducing the abundance of tyrosine (Mohammed *et al.*,2015)

4.2. The biochemical role:

There are several hypotheses of the disease, including the biochemical hypothesis that the destruction of melanocytes is due to the accumulation of toxic metabolites from melanin, the collapse in free radical defenses lead to presence of excess hydrogen peroxide (Schallreuter *et al.*, 2005; Dell'Anna and Picardo, 2006).

In addition, several studies have indicated a role for both cellular immunity (Palermo *et al.*, 2001) and humeral immunity that cause vitiligo. finly, these various factors may work independently or together to lead to the same effects, namely the disappearance of melanin cells from the skin and this is suggested in the theory of confluence (Bergqvist and Ezzedine 2020). For example, autoimmunity may arise as a secondary phenomenon followed by the self-destruction of pigment cells and this may amplify the damage to melanin cells. In addition, the different mechanisms that cause the disease may be responsible for the clinical types of vitiligo and the neurological mechanisms that are usually related to segmental vitiligo, while autoimmune that is often associated with the non-segmental form of vitiligo (Taieb, 2013).

4.3. Immunological role:

One hypothesis explaining the inheritance of Vitiligo is that the genes that regulate immunity may contribute to stimulating self-immunity in Vitiligo patients. One gene involved in the immune function is AIRE gene that located on chromosome 21q22.2 and consists of 14 exon coding to 2445 base pairs in mRNA; In the translation process, it produces 546 amino acids with a molecular mass equivalent to approximately 57.5 KDa (Jin *et al.*, 2007). AIRE gene can be found in the cell nucleus in the form of a pattern known as Nuclear Dots (Bjorses *et al.*, 1999).

5. Genetics role:

Genetic factors are important in causing vitiligo, and this is suggested by (Nordlund *et al.*,2000; Passeron and Ortonne, 2005; Fain *et al.*, 2006; Hu *et al.*, 2006). About 20% of vitiligo patients have at least one relatively first degree harm, and the relative risk of vitiligo increases among relatives from first to seven to tenfold (Nicolaidou *et al.* 2012). This is associated with MHC in human genes (Spritz,2012; Shen *et al.* 2016 ; Casp *et al.*, 2003). Support the possibility of immuno-implication of genes that are relevant to the HLA antigen region. Studies have shown that the association of white blood cells antigen (HLA) at an early start helps in the occurrence of vitiligo. It is possible that there are different causes and genetic factors early in exchange for the occurrence of late cases of vitiligo, as well as in segmental

vitiligo versus non-segmental vitiligo (**Burgos *et al.*, 2002**), other genes involved in its ability to cause vitiligo, including ACE, ESR1 and NALP1 (**Jin *et al.*, 2004; Akhtar *et al.*, 2005**) Based on all the observations, Vitiligo was assumed to be a polymorphic disease, with different noises in several potentially unmatched locations It contributes to increasing susceptibility and / or direct cause of vitiligo. The susceptibility to vitiligo rarely follows Mendelian heredity, though noticeable (**Alkhateeb *et al.*, 2005**). A number of genes have been recorded that contribute to the increase in Vitiligo disease:

5.1. Autoimmune regular I gene (AIRE I):

Mutations that occur in the AIRE gene are known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), or polyglandular syndrome (APS). The most common symptoms of APECED syndrome are Parathyroid, thyroid susceptibility to Candidiasis, Addison's disease. Other autoimmune diseases that are associated with APECED syndrome include alopecia areata, vitiligo, ovarian failure, testicular atrophy, stomach wall cells atrophy, intestinal malabsorption, insulin dependent diabetes. Minor changes in this gene can give susceptibility to Vitiligo (**Jin *et al.*, 2004**).

AIRE gene is important for binding to molecules and involved in immune regulation (**Kumar *et al.*, 2001**). AIRE protein is mostly found in the skin cells of the thymus gland, but it is also found in Monocytes that originate from the thymus gland cells, and in the sub cells of the lymph nodes, as well as in the spleen, as well as in the fetus liver. AIRE, the messenger RNA, is poorly detected in white blood cells, but the thymus gland expresses AIRE in folds higher than other tissues (**Su and Anderson, 2004 ; Mathis and Benoist, 2009**). Many studies have assumed such an expressionistic pattern, although the AIRE protein can participate in the maintenance of the thymus gland, where AIRE regulates the genetic expression of special organ antigens to facilitate negative selection for the auto-interaction of T cells, thus enhancing immunotolerance and reducing autoimmunity (**Anderson *et al.*, 2002**). It is possible that AIRE mutations may be responsible for the incomplete passivity selection of autoantigens, which ultimately led to the development of multiple autoimmune disorders (**Liston *et al.*, 2004; Liston and Goodnow, 2005**). However, many studies in the search for AIRE gene mutations leading to non_APECED autoimmune diseases did not yield significant results (**Turunen *et al.*, 2006; Wolff *et al.*, 2008**).

5.2. Cytotoxic T lymphocyte antigen 4 (CTLA4):

The surface T cell molecule is included in the programmer's death of T cells and also regulates the effectiveness of T-Cell cells (**Birlea *et al.*, 2011**). Although the candidate gene that contributes to the development of T cells that mediate within immune diseases, they either display or function are highly influenced by mutations produced in polymorphous alleles. Studies have suggested that vitiligo when not associated with autoimmune diseases is not affected by CTLA 4 Polymorphism (**Blomhoff *et al.*, 2005**).

5.3. Catalase (CAT) gene:

It is one of the causes of Vitiligo. It is likely that C \ T is responsible for a change in the shape of a single nucleotide present in exon 9 in the gene-blockase. The effectiveness of reductase catalase enzyme is determined by the affected skin and the uninfected skin in patients

with vitiligo. Catalase is an enzyme found in almost all oxygen-prone organisms that stimulates hydrogen peroxide to dissolve into an oxygen molecule and a water molecule. It is known as a candidate gene which reduces the effectiveness of catalase due to the accumulation of hydrogen peroxide in the skin of vitiligo patients (Marie *et al.* 2014). The proven association between vitiligo and single polymorphic nucleotide (SNP) found in exon 9 in the Catalase gene. The presence of T \ C found in the fertile, fertile egg is more common in patients with vitiligo than in normal subjects. C allele is highly transmitted to patients with vitiligo from normal subjects. It has been suggested that mutations associated with or near the catalase gene may contribute to reducing the amount or effectiveness of the catalase gene in patients with vitiligo (Kumar *et al.*, 2001).

5.4. Catechol- o - methyl transferase (COMT):

This gene is located on the 22q11.21 chromosome and has 6 exon, which encodes 272 amino acids. COMT protein participates in regulating the oxidative stress in melanin cells by preventing toxic o-quinones from forming during the process of making melanin cells (Al-Shobaili , 2011). This increase in the level of COMT protein may indicate higher levels of oxidative stress in vitiligo patients, which supports the autocytoxic model, which is one of the pathogens. There are several hypotheses that suggest that COMPT plays a direct role in regulating the biological synthesis of melanin cells (Manga *et al.*, 2006). The proposed mechanism for this regulation is the methylation of the melanin precursor molecule dihydroxy indole-2-carboxylic acid (DHI-2C) by COMT, which makes it unavailable for incorporation into melanin cells (Das *et al.*, 2001).

5.5. Light molecular weight protein (LMP) and transporter associated protein (TAP):

Genes that fall into the second class of the major complex histological compatibility region are associated with many autoimmune diseases. In the region that contains a large number of polymorphism, including some genes that participate in the process of preparing and display antigens and making them available to the immune system, including multiple protein peptides that have low molecular weights, in addition to the presence of the carrier associated with Antigen and TAP 1 protein synthesis. Multiple protein peptides with low molecular weights that participate in the destruction of ubiquitin tagged cytoplasmic proteins (Casp *et al.*, 2003).

5.6. Melanocortin 1 receptor (MCIR) and agouti signaling protein (ASIP):

The MCIR gene, which stimulates melanin cells and hormonal receptors, has recorded a number of genetic mutations (Jimenez *et al.*, 2001). This gene is the main determinant of sunlight sensors (Strum *et al.*, 2002). Melanin induction is regulated by the interconnection of alpha-melanin that stimulates hormones and the ASIP gene to melanin cells and hormonal receptors. The association between the ASIP gene and the melanin cells and hormonal receptors prevents alpha-melanin cells from starting to signal and the cyclic monoadenosine phosphate (cMAP) products are closed, which leads to a lack of regulation of melanin induction (Kingo *et al.*, 2007).

5.7. Angiotensin converting enzyme gene (ACE):

Studies have shown the association of this gene with autoimmune diseases (**Papadopoulos *et al.*, 2000**). This gene converts an enzyme that has the ability to inhibit bradykinin, alter it at the nerve endings of the skin and break down substance P, as well as other neuropeptides (**Scholzen *et al.*, 2003**). The distribution of genotypes within this gene as well as alleles varies markedly between patients with vitiligo and normal subjects. There is a belief that there is a very strong association between the ACE gene and all types of vitiligo (**Jin *et al.*, 2004**).

5.8. Estrogen receptor gene (ESR-I):

Reports have shown that the presence of high levels of estrogen in this blood serum is associated with increased pigmentation and thus treatment of vitiligo with estrogen has been successful (**Nagai *et al.*, 2000**). The association of the ESR I gene and Vitiligo disease showed that the ESR I gene in intron 1 found in polymorphisms C \ T is associated with Vitiligo in women or in both sexes (**Jin *et al.*, 2004**).

5.9. Lymphoid protein tyrosine phosphatase (PTPN 22) gene:

This gene encodes tyrosine phosphatase, which is very important in regulating the effectiveness of T-lymphocytes (**Hill *et al.*, 2002**) (T-Cell). Lymphoid protein tyrosine phosphatase This displays presentation T-lymphocytes (T-Cell) and is associated with C-terminal src kinase (CSK) to form a complex that inhibits the T-Cell Receptor and FcγR signal (**Palacios and Weiss, 2004**). Polymorphisms of the R620W type found in the PTPN22 gene at the nucleotide sequence 1858 (1858 C> T) in the 620 code (620 Arg>Trp) that are associated with autoimmune diseases (**Bottini *et al.*, 2004**). The disease associated with Lymphoid protein tyrosine phosphatase differs in Trp620 and prevents the interaction of Lymphoid protein tyrosine phosphatase with C-terminal src kinase. Accordingly, the T-Cell receptor is associated with kinase, which may show an irregular induction feature of T-Cells, and this can increase the general reaction in the immune system and prepare individuals for autoimmune diseases. Studies conducted on the PTPN22 gene showed that the 1858T alleles are found in large numbers in vitiligo patients in comparison with normal people, indicating that Lymphoid protein tyrosine phosphatase that has multiple forms inhibits R620W and may have the ability to affect the general development of vitiligo disease, which increases Evidence of self-immunization as a causative agent (**Canton *et al.*, 2005**).

6- Role of miRNAs on vitiligo susceptibility.

microRNAs are small, conserved endogenous noncoding RNA molecules that regulate posttranscriptional gene expression, promote translational repression, and cause mRNA cleavage and degradation. Serum miRNA expression profiles have been observed in vitiligo patients (**Shi *et al.* 2013**). Deregulated miRNA metabolism is an indicator of inflammatory skin diseases and has been reported to be associated with the pathogenesis of vitiligo (**Mansuri *et al.* 2016**). The collective role of miRNAs in oxidative stress and autoimmunity leads to melanocyte destruction

and further disease progression. Expression levels of miR-1, miR-135a, and miR-9, which target Sirtuin 1 (SIRT1), which regulates stress responses and inflammation, were found to increase in response to oxidative stress (Saunders et al. 2010). Heme oxygenase 1 (HO1) mRNA, targeted by miR-183, is a stress-responsive antioxidant and anti-inflammatory factor (**Chang et al. 2011**). Increased expression of miR-99b, miR-125b, miR-155, and miR-199a-3p has also been reported in vitiligo-affected skin, which is associated with inhibition of expression of melanogenesis-related genes, Expression of these miRNAs is shown. It is dysregulated in the skin of vitiligo patients, suggesting a contribution to vitiligo pathogenesis (**Sahmatova et al. 2016**)

7. Vitiligo and apoptosis:

The specific pathway for the destruction of melanin cells in vitiligo patients is not yet known, apoptosis (apoptosis) is one of the probabilities of melanin cell death. Cytokines such as IL I, IFN γ or tumor necrosis factor (TNF) are these enzymes secreted from lymphocytes and exogenous cells present In the skin, as well as melanin cells, you can perform apoptosis. Recently, it was discovered that wounds and skin ulcers may affect the production of Cytokines and this leads to weakening of melanin cells and their functions (**Lee and Bae 2015**). It is noted that increased production of TNF γ , a paracrine enzymes inhibit the function of cells Melanin and thus leads a The increased effectiveness of lymphocytes affects the process of programmed cell death by perforin/granzyme. The molecules that regulate apoptosis are found in melanin cells for vitiligo patients, and these molecules increase the process of programmatic cell death of melanocytes compared to melanin cells in people. There are several genes that are necessary to induce melanin. These genes fall within the tyrosine gene pool that is expressed in the melanin cells: Tyrosinase (TYR), tyrosinase-related protein1 (TYR1), dopachrome tautomerase (DCT), (known as tyrosinase-related protein2 (TYR2) (**Delgadillo et al .,2019 ; Oetting, 2000**).

8. Conclusions:

It is possible to conclude from this study: Vitiligo is a common multifactorial skin disorder with a very complex pathogenesis. The uncovering the biological mediators and the molecular mechanisms that lead to metabolic defects and therefore melanocyte degeneration and autoimmunity is important in order to identify new therapeutic targets and drugs that could prevent, stop disease progression or even cure vitiligo. The disease has many genetic causes and the most important one is due to the malfunction in some genes and the psychology has a major role in the creation of the disease.

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