Vitiligo: Etiological Study

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Abstract:

Vitiligo, depigmented macules and patches are the hallmark of vitiligo, an acquired pigmentary skin condition. is thought to affect 0.5–2% of people globally. Hereditary susceptibility in vitiligo patients may tend to proteins expressed by melanin cell that are autoantigen that the immune system targets for destruction. The disease is often linked to autoimmune disorders. This article seeks to provide an overview of the biochemical, immunogenic, and genes that are either responsible for or may be candidate genes for the occurrences of vitiligo disease. It also highlights the current understanding of vitiligo.

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1.Introductin:

The decline of melanin cell from the cutaneous epidermis causes vitiligo, an idiopathic pigmentary condition marked by colored skin patches. Large-scale global surveys have revealed that the prevalence of this illness is between 1% and 2%. Mazzei-Weissmm (2020). Despite this, the incidence in India is 8.8%. This illness affects both sexes equally and is unaffected by age or race (Behl et al., 2003). Melanin cells are produced biologically through intricate processes that take place in unique organelles known as melanosomes. Approximately 1500 proteins have been found in melanosomes at every stage of development pigmented and non-pigmented melanin cells share about 100 proteins, which may constitute the main proteome structure in the melanin body (Chi et al., 2006). In order to ascertain their relationship to vitiligo, a number of genes involved in the formation of melanin cells were examined in this study. According to Bergqvist and Ezzedine (2020), sharing these genes may promote autoimmune and/or oxidative stress hypotheses of vitiligo epidemiology. A group of recessive mutations in the TYR and TYR1 genes were discovered to be linked to various forms of eye albinism, a genetic condition marked by melanin pigment loss in the eyes. This supports the primary role in pigmentation and is regarded as a candidate gene in vitiligo **(Jimbow *et al*., 2011).**Genes linked to variations in DCT may not be aware of the phenotype. However, a number of groups have noted that DCT in combination with TYR and TYR1 proteins are targets of autoantibodies seen in vitiligo patients' serum (Kemp et al. 2011; Delgadillo et al., 2019). Approximately 70–80% of patients develop vitiligo by the age of 30, and nearly half of all instances manifest before the age of 20 (Behl et al., 2003; Herane, 2003). According to Ongenae et al. (2006), vitiligo is typically regarded as a minor condition, although it

has psychological repercussions on sufferers and prevents them from interacting with others. The primary genetic and non-genetic reasons of vitiligo will be reviewed in this study, along with a thorough description of each gene that may be involved in the disease's processes.

2. Signs and symptoms:

White spots can be local or segmental, and they can vary in size and shape and spread throughout the body. In some people, the affected area's hair may turn white and lose its color. As a serious illness or disorder, vitiligo is a non-infectious disease whose physical manifestations can cause social isolation (Ezzedine et al., 2012; Chi et al., 2006).

3. Types of Vitiligo:

There are numerous forms of this illness (Rebat and Johnathan, 2009; Eleftheriadou, 2020), however the most significant ones are:

1- Focal Vitiligo: Usually affecting the neck and trunk, it is characterized by sporadic patches in a single area. Children are more likely to get this kind of vitiligo.
2- Mucosal Vitiligo: This kind of vitiligo solely affects the mucosa.
3- Universally Vitiligo: the spots appear over the body and may be linked to endocrine condition proliferation.
4- Segmented Vitiligo: This kind of vitiligo only affects one side of the body. This kind of vitiligo does not resemble other types and manifests early in childhood. It has nothing to do with autoimmune disorders or thyroid conditions. Polyposis affects half of segmental vitiligo sufferers.
5-Generalized vitiligo: This form alters the body's normal and basic skin tone and affects every part of the afflicted person.
6- Terminal Vitiligo: Characterized by the appearance of skin discoloration in the affected area, which is indicative of infection. Vitiligo affects the genitalia as well as the lips and limbs. Individuals with dark skin types differ significantly from those with normal skin in terms of skin color.

4. Mechanisms of Disease:

There are many mechanisms for the occurrence of Vitiligo, and the most important are:

4.1. The enzymatic Role:

Numerous investigations have confirmed the significance of phenylalanine hydroxylase (PHA) in the manufacture of melanin cells; PHA depletion is particularly prevalent in the recessive physical disorders of phenylketonuria (PKU) (Schallreuter et al., 2005). The 13 exons of the PHA gene, which is found on the 12q22 chromosome, encode the 453 amino acid phenylalanine. hydroxylase. Tyrosine(Tyr), the precursor of melanin cells that produced by this enzyme from the amino acid phenylalanine. PKU patients have significantly higher serum phenylalanine concentrations due to inactivation or total loss of phenylalanine activity in the liver. Because elevated levels of this amino acid have detrimental neurological effects, PUK patients follow a particular diet devoid of phenylalanine. In addition to the nervous system impairment, PKU patients' lack of therapy results in a shortage of dye and lends credence to the theory that the protein phenylalanine plays a important role in the development of melanin cell. Phenylalanine's activity in tyrosine synthesis is consistent with the notion that alterations in gene function may affect melanin cell growth by decreasing tyrosine abundance (Mohammed *et al*.,2015).

4.2. The Biochemicals Role:

There are a number of theories regarding the illness, such as the biochemical theory that the buildup of harmful metabolites from melanin causes melanocyte death and that the breakdown of free radical defenses results in an excess of hydrogen peroxide (Schallreuter et al., 2005; Dell'Anna and Picardo, 2006).Furthermore, a number of studies have suggested that vitiligo is caused by both humeral immunity and cellular immunity (Palermo et al., 2001). Finally, the idea of confluence (Bergqvist and Ezzedine 2020) suggests that these different stimuli may operate separately or in concert to produce the same results, namely the removal of melanin cells from the skin. For instance, autoimmunity may develop as a secondary phenomena that is followed by pigment cell self-destruction, which could exacerbate melanin cell damage. Additionally, the various disease-causing pathways may be in charge of the neurological mechanisms typically associated with segmental vitiligo as well as the clinical forms of vitiligo, while autoimmune that is often associated with the non-segmental form of vitiligo (Taieb, 2013).

4.3. Immunological Role:

One theory that explains how vitiligo is inherited is that immunity-regulating genes may help vitiligo sufferers develop self-immunity. The AIRE gene, which is found on chromosome 21q22.2 and has 14 exons that coding for (2445) pb of mRNA, is one gene implicated in immune function. During translation, it yields 546 amino acids with a molecular mass of roughly 57.5 KDa (Jin et al., 2007). The AIRE gene is present in the cell nucleus as a pattern called Nuclear Dots (Bjorses et al., 1999).

5. Genetics Role:

According to (Nordlund et al., 2000; Passeron and Ortonne, 2005; Fain et al., 2006; Hu et al., 2006), vitiligo is largely caused by genetic causes. According to Nicolaidou et al. (2012), the relative risk of vitiligo grows from first to seven to tenfold among relatives, and about 20% of vitiligo patients experience at least one approximately first-degree damage. In human genes, this is linked to MHC (Spritz, 2012; Shen et al., 2016; Casp et al., 2003). Encourage the idea that genes related to the HLA antigen region may have immunological implications. Research has indicated that early exposure to the white blood cell antigen (HLA) contributes to the development of vitiligo. Different causes and genetic variables may be involved in the development of late cases of vitiligo, as well as in segmental vitiligo versus non-segmental vitiligo (Burgos et al., 2002), as well as additional genes that may contribute to vitiligo, such as ACE, ESR1, and NALP1 (Jin et al., 2004; Akhtar et al., 2005). Vitiligo was thought to be a polymorphic disease with distinct sounds in multiple possibly mismatched sites based on all the observations. It either directly causes vitiligo or increases susceptibility to it. Although evident, vitiligo susceptibility rarely follows Mendelian heredity (Alkhateeb et al, 2005). There is number of genes have been recorded that contribute to the increase in Vitiligo incidence.

5.1. Autoimmune Regular I gene (AIRE I):

The mutation in AIRE gene referred to as polyglandular syndrome (APS) or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome (APECED). Addison's disease, parathyroidism, and thyroid sensitivity to Candiasis are the most prevalent signs of APECED syndrome. Alopecia areata, vitiligo, ovarian failure, testicular shrinkage, stomach wall cell atrophy, intestinal malabsorption, and insulin-dependent diabetes are other autoimmune conditions linked to APECED syndrome. Vitiligo susceptibility may result from slight alterations in this gene (Jin et al., 2004). AIRE gene plays a crucial role in immunological modulation and molecular binding (Kumar et al., 2001). The thymus gland's skin cells are the primary source of AIRE protein, but it is also present in monocytes, which are derived from thymus gland cells, lymph node subcells, the spleen, and the fetus's liver. White blood cells have low levels of the messenger RNA AIRE, while the thymus gland expresses it far more than other tissues (Su and Anderson, 2004 ; Mathis and Benoist, 2009). Although the AIRE protein can contribute to the maintenance of the thymus gland, where it controls the genetic expression of unique organ antigens to enable negative selection for the auto-interaction of T cells, thereby improving immunotolerance and decreasing autoimmunity, many studies have assumed such an expressionistic pattern (Anderson et al., 2002). The inadequate Passive selection of autoantigens, which eventually resulted in the development of some autoimmune diseases, may be caused by AIRE mutations (Liston et al., 2004; Liston and Goodnow, 2005). Nevertheless, numerous investigations into AIRE gene mutations causing non-APECED autoimmune disorders failed to produce meaningful findings (Turunen *et al*., 2006; Wolff *et al*., 2008).

5.2. Cytotoxic T lymphocyte antigen 4 (CTLA4):

The surface T cell molecule controls the efficacy of T-cell cells and is involved in the programmer's death of T cells (Birlea et al., 2011). Mutations generated in polymorphous alleles have a significant impact on the expression or function of the candidate gene that aids in the formation of T cells that cause immunological disorders. Research has indicated that the CTLA 4 polymorphism has no effect on vitiligo when it is not linked to autoimmune disorders (Blomhoff et al., 2005).

5.3. Catalase Gene:

It is a contributing factor to vitiligo. A single nucleotide polymorphism(SNP) found in exon 9 of the gene-blockase is probably altered in form by C\T. Patients' damaged and uninfected skin decide how effective the reductase catalase enzyme is with vitiligo. Nearly all oxygen-prone creatures contain the enzyme catalase, which causes hydrogen peroxide to breakdown into oxygen molecule and a H2O. Due to the buildup of hydrogen peroxide in vitiligo patients' skin, it is referred to as a potential gene that decreases catalase's efficacy (Marie et al. 2014). The single polymorphism nucleotide (SNP) in exon 9 of the Catalase gene that has been linked to vitiligo Patients with vitiligo are more likely than normal persons to have T-C in their viable eggs. Patients with vitiligo are especially susceptible to the C allele from healthy individuals. The amount or efficacy of the catalase gene may be diminished in vitiligo patients due to mutations linked to or close to the catalase gene (Kumar et al., 2001).

5.4. Catechol-O- Methyl Transferase Gene:

This gene, which contains six exons and encodes 272 amino acids, is found on the 22q11.21 chromosome. By keeping harmful o-quinones from developing during the production of melanin cells, COMT protein contributes to the regulation of oxidative stress in melanin cells (Al-Shobaili, 2011). The autocytotoxic model, which is one of the pathogens, is supported by this rise in COMT protein, which may imply higher levels of oxidative stress in vitiligo patients. According to a number of theories, COMPT directly controls the biological synthesis of melanin cells (Manga et al., 2006).The methylation status of the melanin precursor dihydroxy indole-2-carboxylic acid (DHI-2C) by COMT, which prevents it from being incorporated into melanin cells, is the suggested mechanism for this control (Das et al., 2001).

5.5. Light Molecular Weight Protein (LMP) and Transporter Associated Protein:

Numerous autoimmune disorders are linked to genes that belong to the second class of the main complicated histological compatibility area. In addition to the presence of the carrier linked to antigen and TAP-1 protein synthesis, the region with a high number of polymorphisms includes some genes that help prepare and display antigens and make them accessible to the immune

system. These genes include several low molecular weight protein peptides. Ubiquitin-tagged cytoplasmic proteins are destroyed by a number of low molecular weight protein peptides (Casp et al., 2003).

5.6. Melanocortin 1 Receptor (MCIR) and Agouti Signaling Protein (ASIP):

Numerous genetic variants have been identified in the MCIR gene, which stimulates melanin cells and hormonal receptors (Jimenez et al., 2001). Sunlight sensors are mostly determined by this gene (Strum et al., 2002). Alpha-melanin chain stimulates hormones, and the ASIP gene are connected to melanin cells and hormonal receptors to control melanin induction. A lack of regulation of melanin induction results from the ASIP gene's interaction with melanin cells and hormonal receptors, which stops alpha-melanin cells from beginning to signal and closes the cyclic monoadnosine phosphate (cMAP) products (Kingo et al., 2007).

5.7. Angiotensin Converting Enzyme gene (ACE):

Research has demonstrated that this gene is linked to autoimmune disorders (Papadopoulos et al., 2000). This gene produces an enzyme that can block bradykinin, change it at the skin's nerve endings, and degrade substance P and other neuropeptides (Scholzen et al., 2003). Patients with vitiligo and healthy individuals differ significantly in the distribution of genotypes and alleles within this gene. The ACE gene is thought to be strongly linked to all forms of vitiligo disease (Jin et al., 2004).

5.8. Estrogen Receptor Gene-I (ESR-I):

According to reports, vitiligo has been successfully treated with estrogen since high levels of the hormone in this blood serum are linked to increasing pigmentation (Nagai et al., 2000). According to Jin et al. (2004), vitiligo in women or both sexes is linked to the ESR I gene in intron 1 identified in polymorphisms C \ T.

5.9. Lmphoid Protein Tyrosine Phosphatase (PTPN 22) gene:

Tyrosine phosphatase, which is encoded by this gene, is crucial for controlling T-cell efficacy (Hill et al., 2002). Tyrosine phosphatase in lymphoid proteins This exhibits presentation T-lymphocytes (T-cells) and forms a complex with C-terminal sertinase (CSK) to block the FNY signal and T-cell receptor (Palacios and Weiss, 2004). Autoimmune disorders are linked to polymorphisms of the R620W type in the PTPN22 gene at position 1858 (1858 C>T) in the 620 code 620 Arg>Trp (Bottini et al., 2004). The illness linked to lymphoid protein tyrosine phosphatase is different in Trp620 and stops lymphoid protein tyrosine phosphatase from interacting with C-terminal srckinase. As a result, the T-cell receptor is linked to kinase, which may exhibit an irregular T-

cell induction feature. This might boost the immune system's overall response and prime people for autoimmune disorders. Research on the PTPN22 gene revealed that the 1858T alleles are more common in vitiligo patients than in healthy individuals. This suggests that multiple forms of lymphoid protein tyrosine phosphatase inhibit R620W and may have an impact on the overall development of vitiligo disease, which increases the evidence of self-immunization as a causative agent (Canton et al., 2005).

6- Role of micoRNAs Vitiligo Susceptibility.

MicroRNAs are small, endogenous noncoding RNA molecules that cause mRNA halt and degradation, encourage translational repression, and control posttranscriptional gene expression. Vitiligo patients' serum miRNA expression profiles have been noted (Shi et al. 2013). The pathophysiology of vitiligo has been linked to dysregulated miRNA metabolism, which is a sign of inflammatory skin conditions (Mansuri et al. 2016). Melanocyte loss results from the combined action of miRNAs in oxidative stress and autoimmune could accelerate the course of the illness. Oxidative stress was discovered to raise the expression levels of miR-1, miR-135a, and miR-9, which target Sirtuin 1 (SIRT1), which controls inflammation and stress responses (Saunders et al. 2010). MiR-183 targets the stress-responsive antioxidant and anti-inflammatory factor heme oxygenase 1 (HO1) mRNA (Chang et al. 2011).Vitiligo-affected skin has also been demonstrated to have increased expression levels of miR-99b, miR-125b, miR-155, and miR-199a-3p, which is linked to suppression of melanogenesis-related gene expression. Patients with vitiligo have dysregulated skin, which may contribute to the pathophysiology of the condition (Sahmatova et al. 2016).

7. Vitiligo and Apoptosis:

Although the precise mechanism by which melanin cells in vitiligo sufferers are destroyed is yet unknown, one possibility for melanin cell death is apoptosis. Tumor necrosis factor (TNF), IFN, and IL I are examples of cytokines that are released by lymphocytes and external cells. Both melanin cells and the skin can undergo apoptosis. According to recent research, wounds and skin ulcers may have an impact on cytokine production, which weakens melanin cells and their functions (Lee and Bae 2015).It has been observed that elevated TNF production, a paracrine enzyme, inhibits cells' ability to produce melanin, which results in a The mechanism of programmed cell death by perforin/granzyme is impacted by the enhanced efficacy of lymphocytes. Melanin cells from vitiligo patients include chemicals that control apoptosis, and these compounds accelerate melanocytes' programmed cell death in comparison to human melanin cells. To produce melanin, a number of genes are required. Tyrosinase (TYR), tyrosinase-related

protein1 (TYR1), dopachrome tautamerase (DCT), and tyrosinase-related protein2 (TYR2) are all members of the tyrosine gene pool that is expressed in melanin cells (Delgadillo et al., 2019; Oetting, 2000).

Conclusions:

This study suggests that vitiligo is a prevalent multifactorial skin condition with a complicated etiology. To find new therapeutic targets and medications that could prevent, halt the progression of the disease, or even cure vitiligo, it is crucial to understand the biological mediators and molecular mechanisms that cause metabolic abnormalities and, consequently, melanocyte degeneration and autoimmune. The most significant of the disease's several hereditary causes is a malfunction in a few genes, and psychology plays a significant part in the disease's development.

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