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# Vitiligo susceptibility at workplace and in daily life: the contribution of oxidative stress gene polymorphisms

Pieranna Chiarella

## Abstract

**Objective:** Vitiligo is a frequently underestimated and little known dermal disease whose symptoms appear as white patches on several skin areas of the body. In this review, the impact of idiopathic and chemical-induced vitiligo at workplace and in daily life is discussed. Also, the influence of selected oxidative stress gene polymorphisms on melanocyte damage is described to understand their involvement in the disease.

**Methods:** A PubMed search was carried out to select the journal articles reporting an association between specific oxidative stress polymorphic genes and vitiligo.

**Results:** The double-null glutathione S-transferase T1 and M1 genotypes are associated with vitiligo while the relationship between nuclear factor erythroid 2-related factor 2, heme oxygenase, catalase and superoxide dismutase gene polymorphisms and the disease should be confirmed by further studies.

**Conclusions:** The polymorphic genes analysed here may have a role in the susceptibility of patients affected by vitiligo, while little is known about the affected workers, due to the lack of epidemiologic data on these subjects. However, the similarity of the skin lesions observed in both groups might have in common some genetic factors making all these individuals susceptible to the development of vitiligo, regardless of the disease-triggering factor.

**Keywords:** Exposure, Gene polymorphism, Occupational, Oxidative stress, Vitiligo

## Introduction

The idiopathic vitiligo, also known as leukoderma, and the occupational (i.e chemical-induced) vitiligo are apparently similar diseases in terms of symptomatology but different in the aetiology. Idiopathic vitiligo is a genetic and chronic autoimmune disease that progressively destroys the skin melanocytes, resulting in the appearance of patchy depigmentation (Rodrigues et al. 2017). It is not rare to note in affected individuals an association between vitiligo and other autoimmune and autoinflammatory conditions such as alopecia, asthma, Hashimoto's thyroiditis, Grave's disease, and type 1 insulin-dependent diabetes mellitus indicating the presence of multiple comorbidities (Dahir and Thomsen 2018).

Despite its severity, idiopathic vitiligo is sometimes recognized as "mere aesthetic discomfort" although the disease heavily affects individuals at the physical, social and psychological level. Symptoms are visible on the skin as white patches of different dimension on the face and many other body areas. These are particularly evident in the spring and summer time, creating embarrassment in the subjects and influencing their behaviour and quality of life. The negative feeling is much more devastating in individuals with dark complexion where depigmentation is more perceptible. Many people make use of camouflage and wear clothes covering the entire body to hide the depigmented areas as much as possible.

It has been estimated idiopathic vitiligo affects 0.5–2% of the global population, approximatively over 50 million individuals worldwide (Picardo et al. 2015). In Italy, 1 million people corresponding to 1.6% of the residents suffer from this disorder. In general, 95% of affected humans develop the symptoms before the age of 40, but

Correspondence: p.chiarella@inail.it
Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, INAIL Research, Via Fontana Candida 1, 00078 Monte Porzio Catone, RM, Italy

the onset may frequently occur between the age of 10 and 30, making the transition phase from adolescence to adultness critical and psycologically difficult. Although the disease depends on the inherited genetic background, it is not necessarily transmissible and may affect all individuals independently of race, ethnicity and gender.

Chemical induced or contact/occupational vitiligo is a depigmenting disorder of the skin caused by exposure to chemical and physical agents present at the workplace or in the environment (Alam and Ghosh 2017; Harris 2017). The disease is not genetically acquired, and the depigmentation occurs only when there is a persistent exposure or contact with the causative agent. Occupational vitiligo shows the same indistinguishable dermal symptoms observed in the idiopathic form. However, there is a huge difference in the therapeutic response to the two types of vitiligo. In the occupational vitiligo, the return to the normal condition is possible once the exposure to the agent is interrupted and in many cases, spontaneous repigmentation has been reported (Bonamonte et al. 2008). In the idiopathic vitiligo, despite the use of various therapies to reduce the number of skin lesions, such as phototherapy with PUVA light, excimer laser treatments and topical corticosteroids, the patient recovery does not necessarily occur.

In the occupational setting, the first chemical agents able to induce vitiligo have been characterized since 1939 when the workers of a leather manufacturing company developed patchy depigmentation on their hands and arms. Half of them wearing a particular brand of gloves developed depigmentation on the skin with similar lesions also on hidden body areas that did not get in contact with the gloves. In that case, the chemical inflammatory agent causing the occupational vitiligo was recognized as the monobenzyl ether of hydroquinone (Oliver et al. 1939).

Phenols, cathecols, quinones and their derivatives (Chivers 1972) are the commonest agents implicated in the induction of occupational vitiligo. Many other dangerous substances causing contact vitiligo have been identified, i.e. sealants/adhesives (4-tert-amylphenol,4-tert-butylphenol), lubricating oils, disinfectants and natural substances such as the blackwood dust used in making furniture (Knight 2008). However, some of these compounds may be found also as components in household commercial products, so environmental exposure may contribute to enhance the individual susceptibility to vitiligo. Many other substances commonly used in daily life may induce vitiligo symtomps; among these are rhododenol present in skin lightening cosmetics, paraphenylenediamine (PPD) found in hair dyes and several detergents containing chemical substances determining or aggravating vitiligo. Also, optical/physical radiations (ultraviolet, visible light, infrared) as well as systemic drugs (chloroquine, fluphenazine, physostigmine, imatinib) and topical drugs (imiquimod, long-term use of topical steroid) have been reported as vitiligo promoters (Harris 2017; Allam and Riad 2013).

Chemical-induced vitiligo has been included in the International Labour Organization (ILO) list of occupational diseases as "skin disease caused by other recognized agents arising from work activities not included in other items" (ILO List of Occupational Diseases 2010). Once the initial skin symptoms are evident, safety measures must be immediately adopted, including the worker removal from the exposure and/or the change of the job task. However, once a worker exposed to the recognized agent has been diagnosed with occupational vitiligo, this might be eligible for compensation. In Italy, the maximum duration of compensation for occupational vitiligo is 3 years (Dermal diseases and compulsory insurance against work accidents and professional diseases, INAIL 2010).

This review, though far from being comprehensive on the topic, aims to describe the safety measures adopted in the workplace for individuals affected by vitiligo and to focus on the disease impact on the subject at the workplace and in daily life. Furthermore, a critical look at the studies reporting the influence of some oxidative stress gene polymorphisms on vitiligo is provided.

## Safety precautions in occupational vitiligo

Chemical-induced vitiligo is acquired in the occupational context. The worker should pay attention to the first symptoms in order to avoid the worsening of the professional disease. In case of skin depigmentation, employers have to be sure that the employees' exposure to hazardous agents by skin contact or absorption is either prevented or adequately controlled. Besides the observation of initial depigmentation by the occupational physician, there are several strategies to minimize the exposure to the toxic agent inducing contact vitiligo. The first is to prevent exposure by eliminating the "toxic source" with the potential to cause adverse effects following skin contact; the second option is to substitute the substance with another which does not provoke the symptoms. If elimination or substitution is impractical, the most effective way of preventing skin depigmentation is the use of special personal protection equipment (PPE) or automatization of the work process to avoid direct contact. Typically the hands, face, neck and forearms are most likely to be exposed to hazardous substances, and suitable gloves and mask specifically for the job task should be provided to the subject. In such case, the vitiligo susceptibility of workers depends not only on the power of the chemical agent but also on the exposure time and on the severity of lesions caused by

the exposure. Also, the initial symptoms found on the body should be immediately perceived by the worker in order to allow immediate inspection of the depigmented area by a dermatologist. PPE are fundamental in skin protection and must be compatible with the worker and with other worn equipment such as apron, safety shoes, mask, glasses and helmet. If all these strategies do not improve the skin condition, the worker should be immediately addressed to a different job task where the known hazardous agent is absent.

## Vitiligo's impact on the worker's life

Independently on the origin of vitiligo (idiopathic or chemical-induced), the disease impacts enormously on the quality of the subject's life at different levels: physical, psychological, social and occupational. The majority of vitiligo subjects feel distressed and stigmatized by their condition because they feel excessive attention on themselves from other people. The white skin patches spoil the individual self-image leading to depression and, in the worst case, to a suicide attempt. These individuals often develop negative feelings reinforced by their negative experience accrued over the years. Vitiligo makes them very sensitive to the way others perceive their physical appearance. Consequently, they try to avoid social interactions having the feeling of being blamed (Parsad et al. 2003). Common sport and social activities like swimming, playing soccer, volleyball, tennis or simply having a SPA experience are generally avoided. Even dressing a bathing suit, a T-shirt and shorts in the summer might be embarrassing for people with vitiligo. The simplest work activities implying physical contact with the public, i.e. selling goods or working at helpdesk and front office, are rejected.

It is not rare that individuals with vitiligo ask to be moved to another job task where the social interactions are minimized. Most of these individuals report feelings of embarrassment which lead to a low self-esteem and isolation. Vitiligo lesions on the face may be particularly embarrassing in the work environment as well as in daily life. In particular, the white patches clearly visible on the face and particularly on the hands are often misperceived as transmissible fungal infections (Fig. 1). In youngsters, the presence of persistent lesions on the visible part of the body can lead to irritability and depression, making them feel ashamed of the disease (Parsad et al. 2003).

However, the worker's perception of the severity of chemical-induced vitiligo is different from the perception of the subject with idiopathic vitiligo. In the first case, the person knows the disease is temporary and after removal of the dangerous agent, the chance of recovery is very high; in the second case, the awareness of improbable recovery causes persistent sadness and loss of any hope.

## Distinction between exposed workers and patients with vitiligo

Workers occupationally exposed to chemical agents promoting vitiligo and having the disease are comparable to patients with idiopathic vitiligo since the biochemical mechanisms inducing the appearance of the white patches is a common feature to both subjects. The diagnosis of vitiligo in both individuals is actually the same. However, as stated above, in occupational vitiligo, the severity of the lesion may recover as soon as the worker is not exposed any longer to the causing agent and a chance to return to the normal condition is possible. In contrast, patients with

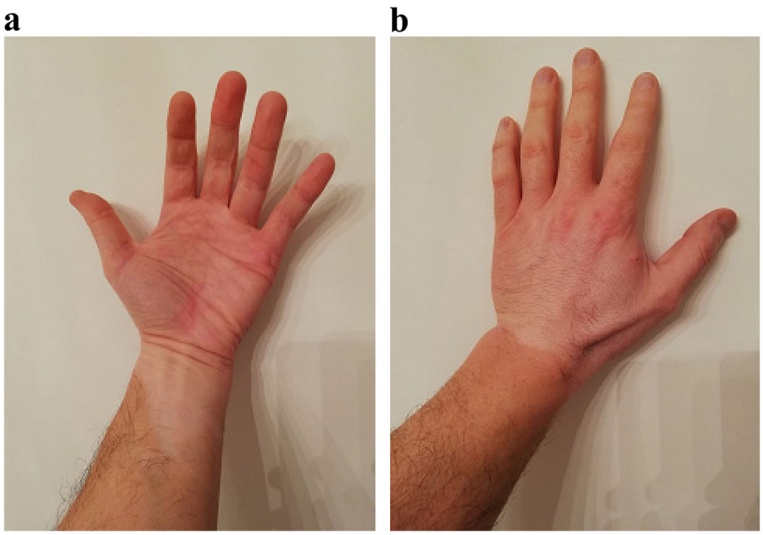


**Fig. 1** Depigmentation of the palm (**a**) and back (**b**) of the left hand in a male subject with vitiligo

idiopathic vitiligo, although in the absence of occupational exposure, have very little chance to repair or reduce the lesion, regardless of the severity and the extension. Therefore, all the vitiligo subjects occupationally or unoccupationally exposed are considered patients due to the genetic susceptibility to this disease. However, it should be remarked that not all exposed workers are necessarily susceptible, demonstrating the crucial role of the genetic background of each individual in the appearance of the disease.

## Methods

A pub-med search was carried out to select the journal articles reporting an association between specific oxidative stress polymorphic genes and vitiligo. Two anonymous volunteers affected by idiopathic vitiligo agreed to describe their physical symtomps and feelings perceived at the workplace and in the social context. One of the two volunteers agreed by informed consent to take a photo of the hand.

## Influence of gene polymorphisms on vitiligo patients

Several gene polymorphisms have been considered potential risk factors in the development of vitiligo, regardless of the type of disease (chemical-induced or idiopathic) in the search of an association between genotype and symptom.

In general, but not necessarily, the homozygous variant, often the minor allele, may confer to the affected individual a higher susceptibility in comparison with the homozygous wild-type and heterozygous condition, particularly in the occupational context wherein the exposure to chemical and physical agents may worsen the disorder. It is supposed the homozygous genotype with the variant allele is rarer and less favourable for the subject (apart from specific exceptions) with respect to the homozygous wild type, bearing the commonest allele, while the heterozygous genotype is represented as an intermediate condition.

One of the mechanisms proposed for melanocyte death is the oxidative stress hypothesis. Recent experimental and clinical evidence suggests oxidative stress with epidermis accumulation of free radicals, reactive oxygen species (ROS) and hydrogen peroxide ($H_2O_2$) leading to melanocyte apoptosis or degeneration (Taieb 2000; Gauthier et al. 2003; Shalbaf et al. 2008; Schallreuter et al.1999). $H_2O_2$ has been recognized to have a pivotal role in the onset and progression of vitiligo (Schallreuter et al. 2007). Oxidative stress with increased $H_2O_2$ epidermal levels and consequent inhibition of catalase activity is generally accepted as the leading cytotoxic mechanism of melanocyte loss in vitiligo (Kostyuk et al. 2010). An excess of oxidant agents may damage subcellular molecules including DNA, determining the activation of the repair mechanism. Another effect of oxidation could cause melanocyte failure and apoptosis, leading to the uptake by antigen-presenting cells, i.e. Langerhans and dendritic cells to initiate an autoimmune response.

Since idiopathic vitiligo is considered an acquired syndrome, the relevance of the genetic contribution should be taken into account even though the disease is not necessarily inherited by the offspring (Karelson et al. 2012).

In this section, a selection of polymorphic genes engaged in the oxidative stress mechanism of vitiligo and possibly associating with the disease has been shown exclusively in patients. Despite the cited literature on gene polymorphisms and vitiligo is reported exclusively on these individuals and no epidemiologic data have been produced on the affected workers, it is possible that patients and exposed workers might have in common some genetic factors making them both susceptible to the disease development. Therefore, it might be presumable but should be demonstratable that the genetic susceptibility found in patients is the same as the exposed workers.

The gene polymorphisms analysed here are described as follows, and they have been summarized in Table 1.

## Glutathione S-transferase

Glutathione S-transferases (GSTs) are intracellular detoxification enzymes involved in the second phase metabolism which, through conjugation reactions, produce water-soluble products excreted via efflux pumps or are modified into mercapturic acids (Boyland and Chasseaud 1969; Hayes et al. 2005). GST endogenous metabolites include xenobiotics, alkylating and free radical generating anti-cancer drugs. Some GSTs behave as glutathione peroxidases, and others possess non-enzymatic functions regulating a number of cellular processes that contribute to the intrinsic ability of cells to survive genotoxic, metabolic and oxidative stress.

The GST family harbours several single nucleotide polymorphisms (SNPs) whose enzymatic efficiency depends on the inherited genotype. Here, the focus is on the GST-M1 and GST-T1 enzymes; these are worthy of note since the homozygous null genotype results in unfunctional enzymes. For this reason, GST-M1 null and GST-T1 null are considered high-risk genes (Strange et al. 2000). In general, individuals bearing the null genotype, alone or in combination, should identify subjects who are detoxification-deficient and consequently more likely to suffer formation of carcinogen-DNA adducts and/or mutations (Ryberg et al. 1997). This means that the metabolism of the subject with null genotype is unfavourable in comparison with the subject with positive genotype.

The GST-M1- and T1-null allele frequencies of the global population have been estimated by the author of

**Table 1** Description of the investigational studies on oxidative stress gene polymorphisms in vitiligo workers and healthy controls

| Single nucleotide polymorphism (SNP) | Genotype | Ethnicity | Number of subjects | Type of study | Findings | Reference |
|---|---|---|---|---|---|---|
| GST-M1 rs366631 GST-T1 rs17856199 | Positive/ null** | Egyptian | 122 cases 200 controls | Experimental | Subjects with GSTM1 null/heterozygous GSTT1 positive show a 2.97 OR protection from having generalized vitiligo compared with patients. | Aly et al. 2018 |
| | | Egyptian | 101 cases 101 controls | Experimental | GST-M1-null and GST-M1/GST-T1 double-null genotype represent a risk factor in women with vitiligo. | Bassiouny and Khorshied 2012 |
| | | Iraq | 100 cases 90 controls | Experimental | GST-M1- and GST-T1-null genotype show a significant association with vitiligo disorder. | Jalood et al. 2016 |
| | | Korean Chinese Mediterranean Egyptian | 1258 cases1573 controls | Meta-analysis | GST-M1- and GST-T1-null genotypes are significantly associated with vitiligo. | Park HK et al. 2016 |
| | | Han Chinese | 749 cases 763 controls | Experimental | Homozygous deletion of GST-T1 subjects have higher vitiligo risk than that of GST-M1 although both genotypes have a predisposition to vitiligo. | Liu et al. 2009 |
| | | Italian Egyptian Korean Chinese | 1358 cases 1673 controls | Meta-analysis | GST-M1-null polymorphism significantly associated with vitiligo risk in East Asian but not with Mediterranean subjects. GST-T1-null polymorphism correlated with vitiligo risk in Mediterranean but not with East Asian subjects. | Lu et al. 2014 |
| NRF2- 653 A/G rs35652124 | AA/AG/ GG | Han Chinese | 1136 cases 1200 controls | Experimental | Decreased risk of vitiligo associated with the NRF2 rs35652124 variant G allele (GG+GA genotype) while no evident risk is associated with NRF2 rs6721961 variant (AA). | Song P et al. 2016 |
| NRF2 -617 C/A rs6721961 formerly -650 C/A | CC/CA/ AA | Han Chinese | 300 cases 300 controls | Experimental | A -650 allele is higher in patients than in controls and may be a risk factor associated with the development of vitiligo. | Guan et al. 2008 |
| HO-1 rs2071746 -413 A/T | AA/AT/TT | Han Chinese | 1136 cases 1200 controls | Experimental | No evidence of correlation between allele and genotype frequencies of HO-1 rs2071746 A/T) and the disease. | Song P et al. 2016 |
| HO-1 (GT)n repeats S>L | GT lenght variability | Taiwanese | 367 cases 420 controls | Experimental | Reduced risk is associated to the presence of short (GT)n repeats in the HO-1 gene promoter when exposed to environmental toxicants (no data available on vitiligo). | Wu et al. 2010 |
| CAT (389 C/T) rs769217 $Asp^{389}$Asp Ex 9 | CC/CT/TT | US/Canadian | 235 cases 177 controls | Experimental | Excess of heterozygosis (CT) in vitiligo subjects. | Casp et al. 2002 |
| CAT (389 C/T) rs769217 $Asp^{389}$Asp Ex 9 | CC/CT/TT | Caucasian | 166 cases 169 controls | Experimental | CAT gene C/T SNP associated with vitiligo susceptibility with the C/T genotype being significantly more frequent among vitiligo patients than healthy controls. | Gavalas et al. 2006 |
| CAT (389 C/T) rs769217 $Asp^{389}$Asp Ex 9 | CC/CT/TT | US/Canadian/ UK Korean Gujarati Indian | 645 cases 689 controls | Meta-analysis | The authors suggest CT+TT genotype increases the susceptibility risk of vitiligo in the analysed populations. | Lv et al. 2011 |
| CAT (389 C/T) rs769217 $Asp^{389}$Asp Ex 9 | CC/CT/TT | Egyptian | 89 cases 90 controls | Experimental | Lack of association between CAT 389 C/T and vitiligo susceptibility in Egyptian patients. | Mehaney et al. 2014 |
| CAT -89A/T (rs7943316) | CC/CT/TT | Gujarati Indian | 126 cases 143 controls | Experimental | No association between CAT gene 389C/T polymorphism and vitiligo susceptibility. | Shajil et al. 2007 |
| CAT (C/T) rs769217 Asp389Asp Ex 9 | CC/CT/TT AA/ AT7TT | Korean | 118 cases 200 controls | Experimental | The catalase gene polymorphism (rs769217 and rs7943316) may contribute to the susceptibility of vitiligo in Korean population, although susceptibility difference | Park HH et al. 2006 |

**Table 1** Description of the investigational studies on oxidative stress gene polymorphisms in vitiligo workers and healthy controls *(Continued)*

| Single nucleotide polymorphism (SNP) | Genotype | Ethnicity | Number of subjects | Type of study | Findings | Reference |
|---|---|---|---|---|---|---|
| | | | | | among ethnic groups may be due to a change in the allele frequency. | |
| CAT (C/T) rs769217 Asp389Asp Ex 9 CAT (A/T) rs7943316 | CC/CT/TT AA/AT/TT | UK | 103 cases 107 ethnic controls | Experimental | Absence of association between CAT gene -89A>T and 389C>T polymorphism and vitiligo susceptibility. | Akbas et al. 2013 |
| SOD1 35A/C rs2234694 | AA/AC/ CC | Turkish | 101 cases 99 controls | Experimental | SOD1 35 A/C was similar in vitiligo patients and controls showing absence of significant difference between AA and AC genotypes. | Tuna et al. 2017 |
| SOD2 $A^{16}V$ (C/T) rs4880 | CC/CT/TT | | | | Significant difference between cases and controls in the SOD2 Ala16Val (C/T) polymorphism with increased risk in the TT genotype. | |
| SOD1 $Ile^{40}Thr$ (C/T) rs1804450 $Val^{82}Val$ (T/C) rs11556619 $Asn^{87}Ser$ (A/G) rs11556620 $Asn^{140}Asn$ (C/T) rs1804449 | CC/CT/TT TT/TC/CC AA/AG/ GG CC/CT/TT | Gujarati Indian | 950 cases 1650 controls | Experimental | No association between SOD1 SNPs and vitiligo. | Laddha et al. 2013a, b |
| SOD2 $Leu^{84}Phe$ (C/T) rs11575993) $Thr^{58}Ile$ (C/T) rs35289490) $Val^{16}Ala$ (T/C) rs4880) $Ile^{82}Thr$ (T/C ) rs1141718) | CC/CT/TT CC/CT/TT TT/TC/CC TT/TC/CC | | | | Association between SOD1 rs35289490 and rs11575993 with vitiligo. Absence of significant association of SOD2 rs4880 with vitiligo, although the C allele is prelavent in subjects with active vitiligo in comparison to patients with stable vitiligo. | |
| SOD3 $Arg^{213}Gly$ (C/G) rs8192291 $Ala^{40}Thr$ (G/A) rs2536512 | CC/CG/ GG GG/GA/ AA | | | | SOD3 rs8192291 SOD3 polymorphism was significantly associated with vitiligo susceptibility. The G allele was prevalent in patients compared to controls. | |

For each polymorphism, the alternating nucleotides reported in brackets are coincident with those found on the DNA forward strand
The name of each gene polymorphism is listed by using its common abbreviation, e.g., GST, NRF2, SOD
The rs code is an accession number used in databases to refer to specific and unique SNPs
**GST-M1 and GST-T1 null means the absence of both polymorphic genes

this review as 0.462 for GST-M1 and 0.244 for GST-T1, calculated as the average frequencies of different ethnic groups in the African, Asian and Caucasian races reported by Kasthurinaidu et al. 2015.

The association of GST-M1/T1-null polymorphisms with vitiligo has been investigated in many papers. In a study conducted on 122 vitiligo Egyptian patients and 200 healthy controls, age- and gender-matched, the authors found a significant trend towards the combination of the GST-M1/GST-T1 double-null polymorphism and generalized vitiligo. Individuals with GST-M1-null and GST-T1-positive heterozygosis showed a 2.97 odd ratio (OR) protection from having generalized vitiligo compared with vitiligo patients (Aly et al. 2018). In another study, genotyping by multiplex PCR of GST-M1 and GST-T1 in 101 Egyptian women with nonsegmental vitiligo vulgaris and 101 age female healthy matched controls show that the absence of GST-M1 gene and the presence of the GST-M1/GST-T1 double-null genotype represent a risk factor for vitiligo in these women ($p$ = 0.01; OR = 2.694) (Bassiouny and Khorshied 2012).

Another study included 100 patients with vitiligo (80 males and 20 females) and 90 controls who have been genotyped for GST-M1 and GST-T1 alleles. Here, the authors found that the GST-M1- and GST-T1-null genotypes showed a significant association with vitiligo disorder (GST-M1-null, GST-T1-null and GST-M1 and T1 double-null patients) versus controls (OR 1.56; 1.66; 2.70). It has been postulated the increase in vitiligo risk with a null genotype of both GST polymorphisms is associated with the deficiency of the antioxidant system caused by the lack of both functional enzymes (Jalood et al. 2016).

Park and Kim (2016) reported a meta-analysis on 1258 patients and 1573 controls confirming a significant association of GST-M1- and GST-T1-null genotypes with vitiligo (GST-M1 OR = 1.494, $p$ = 0.005;

GSTT1 OR = 1.318, $p < 0.001$). They also concluded the combination of GST-M1- and GST-T1-null genotype represents a risk factor for vitiligo. The association of vitiligo with GST-M1, T1 and P1 was investigated by Liu et al. (2009) who included in the genotyping analysis of 749 Han Chinese patients with vitiligo and 763 age- and gender-matched controls. The results confirmed individuals with homozygous deletion of GST-T1 had a vitiligo risk higher than that of GST-M1 subjects. However, they conclude both genotypes had a greater predisposition to vitiligo. Differently, the GST-P1 gene variants ($Ile^{104}Val$, $Ala^{113}Val$, $Gly^{169}Asp$) assayed in the study did not show a major function in the in susceptibility to the disease.

Another research group performed a meta-analysis to assess a possible correlation of GST-M1/T1 polymorphisms with the risk of vitiligo in Mediterranean and East Asian patients. Six studies were chosen to collect the data. The overall analysis showed that GST-M1-null polymorphism was significantly associated with vitiligo risk (OR = 1.59, $p = 0.001$). In the subgroup analysis made by ethnicity, the authors found the GST-M1-null polymorphism was related with vitiligo risk in East Asian (OR = 1.71, $p = 0.014$), but not in Mediterranean (OR = 1.40, $p = 0.094$). The GST-T1-null polymorphism correlated with the risk of vitiligo in the overall analysis (OR = 1.30, $p = 0.001$) or in the subgroup analysis of Mediterranean subjects (OR = 1.76, $p = 0.010$). However, there was no association with the risk of vitiligo in East Asian (OR = 1.21, $p = 0.122$) (Lu et al. 2014). Based on the evidence reported here, it might be interesting to quantify the presence of double-null genotype in vitiligo cases of different ethnic groups with respect to controls.

## Nuclear factor erythroid 2-related factor 2

The nuclear factor E2-related factor 2-antioxidant response element (NRF2-ARE) is a key regulator of the antioxidant response by activating the detoxifying phase II gene, i.e. heme oxygenase (HO-1), catalase (CAT), superoxide dismutase (SOD), GSTs and glutathione peroxidase (GPx) (Zhu et al. 2005). NRF2 has been recently discovered as polymorphic gene with a role in the susceptibility to vitiligo. Aberrant NRF2 translocation and transcriptional activity may lead to a decreased defence from the cellular oxidative stress determining a strong susceptibility in individuals with a genetic predisposition to vitiligo (Jian et al. 2014). In particular, the HO-1 enzyme has a crucial role in protecting melanocytes from $H_2O_2$-induced oxidative stress. A significant decrease in HO-1 serum level in 113 vitiligo Chinese patients when compared with the same number of healthy controls has been found. The result demonstrates that impaired activation of NRF2 under oxidative stress could lead to reduced expression of downstream antioxidant enzymes and increased death of vitiligo melanocytes (Jian et al. 2014).

NRF2 is a gene harbouring several SNPs. Single nucleotide polymorphism -617 C/A could affect the positive feedback loop of transcriptional activation of the NRF2 gene, regulating the protein levels. It is proposed that the homozygote -617 C/A significantly attenuates the positive feedback loop of transcriptional activation of the NRF2 gene. Seventeen polymorphisms have been identified and associated with disease risk (Cho et al. 2015); two of these SNPs located in the gene promoter, i.e. NRF2 -653A/G rs35652124 and NRF2 -617 C/A rs6721961 (formerly -650 C/A), have been studied to assess their possible association with the disease (Song et al. 2016). In East Asians, the authors observed a decreased risk of vitiligo associated with the NRF2 rs35652124 variant G allele (AG+GG genotype) as it seems the G allele is associated with increased level of proteins conferring higher protection from oxidative stress, while no evident risk was observed with NRF2 rs6721961 variant (AA homozygous genotype) probably due to the protective role of the major allele (CC). However, Guan et al. (2008), referring to the same polymorphism rs6721961 (formerly indicated as -650 C/A), considered the A allele a risk factor for vitiligo.

## Heme oxygenase

Since oxidative stress has a critical role in the pathogenesis of vitiligo, it is presumed that enhanced NRF2 transcription leading to increased HO-1 levels may represent an advantage to limit melanocyte damage in vitiligo lesions. Although HO-1 is the main target gene of the NRF2-ARE pathway in protecting human melanocytes against oxidative stress (Jian et al. 2014), very little is known on the role of HO-1 polymorphisms in the susceptibility of vitiligo.

The only paper investigating a potential association between vitiligo and HO-1 rs2071746 -413 A/T polymorphisms in the Han Chinese population showed no evidence of the correlation between allele and genotype frequencies of HO-1 rs2071746 A/T ($p = 0.124$) and the disease. However, a higher, although not significant, OD ratio (1.19) was found in vitiligo TT subjects versus the control genotypes (AA, AT) suggesting a possible balanced role of the two homozygous (AA) wild-type and (TT) homozygous variant genotype. HO-1 protein was detected in the serum of vitiligo patients with NRF2 rs35652124 AG+GG rather than in the AA genotypes. The authors attributed such HO-1 levels to the increased transcriptional activity of the NRF2 rs35652124 genotype (Song et al. 2016).

Another HO-1 polymorphism containing $(GT)_n$ repeats in the 5′-flanking region of the HO-1 gene was identified and grouped into short (S) allele (< 27 repeats) and long (L) allele (≥ 27 repeats), modulating the level of gene transcription. It seems a reduced risk is associated with the presence of short $(GT)_n$ repeats in the HO-1 gene promoter when exposed to environmental toxicants (Wu et al. 2010). However, there are no indications on the effect of this polymorphism on vitiligo.

## Catalase

The antioxidant catalase enzyme (CAT) converts $H_2O_2$ into water and oxygen. Low levels of CAT has been detected both in the epidermis or in the serum of vitiligo patients suggesting a systemic redox defect in this disease (Schallreuter et al. 1991). SNPs interfering with the CAT enzyme's subunit assembly and function have been found more frequently in patients with vitiligo. CAT (C/T) rs769217 ($Asp^{389}Asp$) synonymous variant is the most widely studied polymorphism in relationship to vitiligo although the results go into different directions.

An excess of heterozygosis (C/T) in vitiligo US/Canadian subjects (235 cases and 177 controls) having CAT (C/T) rs769217 polymorphism was detected with respect to controls leading to the conclusion that the CT allele might be more frequently associated with the disease (Casp et al. 2002). This result was confirmed by Gavalas et al. (2006) who found a higher and significant frequency of the C/T genotype among 166 Caucasian vitiligo subjects than in 169 healthy controls. A meta-analysis of 4 studies published in the scientific literature performed on US, Canadian, UK, Korean and Gujarati Indian populations on CAT (C/T) rs769217 SNP suggests CT+TT genotype is associated with a significantly increased risk of vitiligo in comparison with subjects with CC genotype (Lv et al. 2011).

The same SNP was investigated in Egyptian patients (89 cases versus 90 controls), but a lack of association between CAT (C/T) rs769217 and vitiligo susceptibility was observed (Mehaney et al. 2014). Shajil et al. (2007) analysed the CAT (C/T) rs769217 polymorphism in 126 cases and 143 controls among Gujarati Indians (South Asia). Here, neither the allele frequencies of C/T SNP ($p < 0.434$) nor the genotype frequencies ($p < 0.259$) differed significantly between the control and patient population concluding that CAT activity did not show any significant change in vitiligo patients compared with healthy subjects.

Park et al. (2006) are cautious in suggesting a direct association of CAT (C/T) rs769217 polymorphism with vitiligo in the Korean population since they did not find significant differences between allele and genotype frequencies among patients and controls. However, when the haplotype frequencies of two CAT SNPs (C/T) rs769217 and -89A/T (rs7943316) were compared between patients and controls, a significant association with vitiligo ($p < 0.01$) was obtained. Another research group studied the CAT SNPs -89A>T (rs7943316) and 389C>T (rs769217) in 103 Turkish patients with vitiligo and 107 ethnic-matched controls concluding that there was no association between CAT gene -89A>T and 389C>T polymorphism and vitiligo susceptibility (Akbas et al. 2013).

## Superoxide dismutase

SOD enzyme has the role to convert the pro-oxidant superoxide radical ($O^{2-}$) into molecular oxygen ($O_2$) and hydrogen peroxide ($H_2O_2$). This protein protects cells from the toxic effects of superoxide radicals, and its role is relevant in the pathogenesis of vitiligo. There are three SODs in human tissues: (i) copper-zinc SOD defined as SOD1 cytosolic enzyme; (ii) Mn SOD, i.e. SOD2, a mitochondrial enzyme; and (iii) SOD3, an extracellular enzyme circulating in plasma, lymphoid tissues and cerebrospinal liquids (Marklund et al. 1982). Published data suggest the oxidant/antioxidant system may be affected in various types or stages of vitiligo although the results are inconsistent (Laddha et al. 2013a). As far as the SOD gene polymorphisms are concerned, only few recently published articles have been identified by PubMed search.

The impact of SOD1 and SOD2 polymorphisms was investigated in Turkish vitiligo patients. In particular, the polymorphisms SOD1 35A/C (rs2234694) and SOD2 $Ala^{16}Val$ (C/T; rs4880) (Harris, 2017) were analysed by PCR-RFLP in 101 Turkish vitiligo patients and in 99 controls. The distribution of the SOD1 35A/C was similar in vitiligo patients and controls showing the absence of significant difference between AA and AC genotypes. In contrast, a significant difference was found between cases and controls in the SOD2 Ala $^{16}$Val (C/T) (Harris, 2017) polymorphism (CC versus TT: OR = 2.158, $p = 0.038$). The relative risk for the development of vitiligo was found as a twofold increase in the TT genotype, reducing the efficacy of the antioxidant enzyme (Tuna et al. 2017). A second study after detecting a significantly higher activity of SOD1, SOD2 and SOD3 enzymes in vitiligo patients proceeded with the investigation on many SOD polymorphisms to verify the contribution of the genetic variation on the disease. SOD1 $Ile^{40}Thr$ (C/T; rs1804450) (Rodrigues et al. 2017) $Val^{82}Val$ (T/C; rs11556619), $Asn^{87}Ser$ (A/G; rs11556620) and $Asn^{140}Asn$ (C/T; rs1804449); SOD2 $Leu^{84}Phe$ (C/T; rs11575993), $Thr^{58}Ile$ (C/T; rs35289490), $Ala^{16}Val$ (C/T; rs4880) (Harris, 2017) and $Ile^{82}Thr$ (T/C; rs1141718); and SOD3 $Arg^{213}Gly$ (C/G; rs8192291) and $Ala^{40}Thr$ (G/A; rs2536512) (Rodrigues et al. 2017) polymorphisms were analysed in 950 vitiligo patients and 1650 ethnically, age- and gender-matched controls (Laddha et al. 2013b). All the SOD polymorphisms investigated by

the authors have been reported in Table 1, but only the most significant have been discussed here. In particular, lipoperoxidation as well as the activity of the three SOD enzymes was evaluated by quantitative PCR and western blot, resulting significantly higher in patients than in controls. However, on determining the association between SOD1, SOD2 and SOD3 polymorphisms and vitiligo susceptibility, the authors did not find a strong association between SOD1 SNPs and vitiligo. In contrast, SOD2 SNPs $Thr^{58}Ile$ (rs35289490) and $Leu^{84}Phe$ (rs11575993) polymorphisms significantly associated with vitiligo patients, while the $Ala^{16}Val$ (C/T; rs4880) (Harris, 2017) polymorphism did not show significant correlation with the disease. However, when patients with active and stable vitiligo were compared, a prevalence of the C allele in the "active" patient group was detected with respect to the "stable" patient group. Lastly, SOD3 $Arg^{213}Gly$ polymorphism was significantly associated with vitiligo susceptibility. In particular, the $Arg^{213}Gly$ (C/G; rs8192291) G allele was prevalent in the patient group compared to controls. The authors conclude that the indicated SOD2 and SOD3 polymorphisms may be genetic risk factors for the susceptibility and progression of vitiligo suggesting the increased activity of SOD isoforms caused by the variant gene polymorphisms may lead to the accumulation of $H_2O_2$ in cytoplasmic, mitochondrial and extracellular compartments resulting in melanocyte oxidative damage.

## Discussion

Skin diseases represent more than 7% of all occupational illnesses in Europe related to working with dangerous substances (European Agency for Safety and Health at Work 2008). The chemical-induced, i.e. occupational, vitiligo is one of the listed dermal diseases occurring in the workplace following exposure to specific pro-inflammatory substances. Although it is still unclear if individuals who do not develop spontaneous vitiligo might have a genetic predisposition, the disease occurs in case of specific and continuous exposure.

In the occupational context, the difference between idiopathic and chemical-induced vitiligo is not negligible, particularly when the individual suffering from the idiopathic form is exposed to chemical or physical agents also in the workplace. In such case, the precautionary principle should be immediately adopted so as to address the susceptible worker to a "safe" job task in the absence of vitiligo-promoting agents. However, the idiopathic vitiligo worker assignment to activity involving social interactions and contact with the public is not easy to deal with. In theory, the unexposed subject should feel safe and relaxed, but the feelings of embarrassment in the presence of other people may be a problem in accomplishing the job task.

Taking into account the considerations mentioned above on vitiligo, it is evident that besides the "genetic or constitutional susceptibility", there might be also a secondary issue associated with vitiligo which is the "psychological and emotional susceptibility" strongly felt by individuals permanently affected by the disease. The physical and psychological health condition of these subjects should be taken into consideration on recruitment.

In this review, the influence of oxidative stress gene polymorphisms on vitiligo onset and susceptibility was also explored by bibliographic search in PubMed to identify the critical genotypes that may confer high susceptibility to the affected individuals. Despite the search was limited to a selection of common oxidative stress polymorphisms, the data collected here are not homogeneous enough to go into a univocal direction.

However, the investigational studies reported here allow to extrapolate some useful observations. For instance, the simultaneous absence of both GST-T1 and GST-M1 enzymes has been shown by many authors as having a negative effect on vitiligo populations (Aly et al. 2018). The high frequency of the double-null genotypes found in different ethnicities further corroborates the association between enzyme deficiency and vitiligo risk (Park et al. 2016). Since GSTs are indirectly involved in many metabolic reactions, the lack of such enzymes in susceptible subjects affects not only vitiligo but also other metabolic pathways where the enzyme function is necessary. Therefore, vitiligo patients with double-null GST genotypes might host multiple susceptibilities (e.g. exposure to tobacco smoke, benzene, carcinogens) independently on the vitiligo type. The broad substrate specificity of GSTs allows them to protect cells against a range of toxic chemicals, and a lack of these enzymes is a disadvantage for the susceptible individual (Salinas and Wong 1999) whose risk may increase in many biochemical pathways. Several studies correlated high GST levels with increased resistance to oxidative stress, and the safe elimination of toxicants via functional GST pathways has been shown to protect cellular DNA against reactive oxygen species-induced damage (Ryberg et al. 1997).

As far as the other polymorphic genes are concerned (NRF2, HO-1, CAT, SOD), the examined studies do not allow to confirm for each a conclusive and causative role in vitiligo onset and progression. NRF2 has been recently investigated only on two polymorphisms of the gene promoter restricted to the Asian population so that the number of published results is still preliminary to define a strong association between the NRF2 SNPs and the disease (Song et al. 2016). In particular, the analysis should be conducted on other ethnicities to identify the differences in the allele frequency which might be favourable for a group but unfavourable for another.

There is also insufficient evidence on the effect of HO-1 SNPs on vitiligo susceptibility despite this gene is the main actor involved in protecting human melanocytes against oxidative stress through the NRF2-ARE pathway (Jian et al. 2014). As far as the HO-1 polymorphisms are concerned, the number of investigated SNPs as well as the relative studies available is not sufficient to draw a conclusion (Song et al. 2016; Wu et al. 2010).

With regard to CAT polymorphisms, i.e. the (C/T) rs769217, the data found in the scientific literature are controversial, although it might depend on the ethnicity analysed. Considering the two research studies on SOD (C/T) Ala$^{16}$Val (rs 4880) (Harris, 2017) polymorphic gene, there is divergent evidence on the correlation of this enzyme with vitiligo. In the first study, the SOD2 Ala$^{16}$Val (C/T) (rs 4880) polymorphism, (Harris, 2017) was found to associate with the TT genotype, a genetic variation considered disadvantageous for the individual because of the reduced efficacy of the antioxidant enzyme. Therefore, the T allele has been considered to associate with the development of vitiligo (Tuna et al. 2017). In the second study, the same polymorphism did not show significant association with vitiligo subjects, although the authors found a prevalence of the C allele in patients with active vitiligo compared to patients with stable vitiligo (Laddha et al. 2013b). Based on the results of different groups of subjects, patients versus controls and patients with active versus patients with stable vitiligo, it is difficult to assess what allele (C or T) is definitively associated with the vitiligo risk. In the SOD2 C/T (Thr$^{58}$Ile) polymorphism, the $^{58}$Ile amino acid has been indicated as favourable in comparison with the $^{58}$Thr form, reducing the vitiligo risk (Laddha et al. 2013b).

## Conclusions

Idiopathic and occupational vitiligo are similar dermal diseases sharing the same symptoms but differing in the aetiology. While the genetic background of the individual with idiopathic vitiligo strongly influences the disease development preventing a successful recovery, the occupational vitiligo is generally induced by exposure and the return to the skin repigmentation is feasible, once the agent to which the subject is exposed to is removed from the work environment. As temporary disease, occupational vitiligo is a condition compatible with normal life. Unfortunately, little chance of recovery is offered to idiopathic vitiligo individuals, despite novel therapies are being explored and used in the medical field (Rahman and Hasija 2018). Being the disorder chronic and persistent, the best achievable result is the stabilization of the disease.

The oxidative stress gene polymorphisms analysed here may influence both types of vitiligo in the same manner. However, despite the limitations of the gene number reported here, excluding GSTs, their role in vitiligo is still not conclusive. Furthermore, since the occurrence of vitiligo at the workplace is a field still unexplored, it could be helpful to compare the gene polymorphisms in workers versus patients to find genetic similarity or difference in the two groups. Nonetheless, other genes recently discovered are being studied to determine the contribution to the disease onset and development (Shen et al. 2016).

The risk of vitiligo worsening is much higher in individuals with permanent vitiligo, as the disease may be aggravated by exposure to depigmenting agents. The increase of white patches on the skin is a stressful and devastating condition with the consequence to amplify the symptoms. The aesthetic and social embarrassment felt by these subjects represents an important issue to address, affecting the people's quality of life.

To conclude, there is a double vulnerability in subjects with acquired and permanent vitiligo compared to those affected by occupational vitiligo. The first mainly depends on the genetic inheritance, and the other depends on the exposure intensity and frequency. The oxidative stress gene polymorphisms may affect the disease, independently of the type, although there is a high data variability due to the difference in genotype frequency among ethnicities and the possibility of functional compensation by other genes.

The vulnerability of idiopathic vitiligo workers is extremely high, being perceived not only at the physical but also at the emotional and social level. Particular attention should be dedicated to these subjects, who may be intrinsically and also occupationally susceptible, in order to adopt all the necessary measures to promote a safe, protective and healthy work environment.

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#### Author's contribution

The author conceived this review, analysed the scientific literature and critically discussed the results and the perspectives concerning the subject of the review.

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#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

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**Competing interests**
The author declares that there are no competing interests.

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## Publisher's Note