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Genetic Variants of Vitiligo

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Abstract

Vitiligo is a progressive skin disorder characterized by white and depigmented formations. The etiology is still unknown but genetic hypothesis a positive family history for vitiligo has been reported. Most important hypothesis is autoimmune hypothesis and neural hypothesis. Numerous additional HLA association studies have been published in Vitiligo. Genetic studies associated with vitiligo are not only related to the identification of genes that are susceptible to disease, but can also lead to the identification of genes associated with clinical aspects of the disease, the dynamics of the disease process or the time of manifestation of the first skin lesion. Continuous research on susceptibility genes is important to better understand the underlying mechanisms of vitiligo pathogenesis.

Keywords: Vitiligo; Genetic variants; Etiology

Introduction

Vitiligo is a progressive skin disorder characterized by white and depigmented formations occur and continue to increase over time. It is caused by the disappearance of melanocytes in the epidermis and the absence of melanin [1]. The condition can be cosmetically disfiguring and sunburns. Regardless of gender and race, it affects 0.1-2% of the world population. Although there is no complete therapeutic method for vitiligo, many options are available. Treatment as well as medical and surgical repigmentation. Medical treatments include narrowband ultraviolet B (UVB), broadband UVB, psoralen plus UVA, corticosteroids and other new approaches. When medical treatment is insufficient position, surgical treatment consisting of autologous transplantation is generally recommended for stable / focal vitiligo [2].

The etiology is still unknown, but some hypotheses have been proposed to explain the loss of melanocytes in the epidermis. Genetic hypothesis a positive family history for vitiligo has been reported. In fact, family clustering of cases is not uncommon, because about 20% of patients have at least one affected first-degree relative, a multi-factor, non-Mendelian model suggesting polygenic inheritance [3]. Segregation analysis suggests that multiple interactive genes are involved in different populations [4]. Several candidate genes and chromosomal location have been proposed as effective for vitiligo [5]. In particular, various HLA abnormalities have been associated with vitiligo, including A30, B13, Dr4, BW35 [6]. A recent large epidemiological study supports the role of both genetic and non-genetic factors in the

pathogenesis of the disease. Some genetic factors may be associated with other autoimmune diseases [5].

Autoimmune Hypothesis

This hypothesis suggests that immune system damage causes the destruction of melanocytes. First, many autoimmune disorders (thyroid diseases, Sutton's, juvenile diabetes mellitus, pernicious anemia, and Addison's disease) are supported by frequent observation of vitiligo. In particular, the association of thyroid dysfunction and / or thyroid antibodies with a prominent vitiligo has been shown [7]. Regarding humoral immunity, surface antibodies and cytoplasmic antigens of melanocytes have been found in vitiligo patients mainly belonging to the IgG class. The most common autoantigens are HLA class I molecules, tyrosinase, tyrosinase associated protein (TRP) -1 and TRP-2 (the last three melanocyte-specific antigens) related antigens. The pathogenic role of antimelanocyte antibodies is still unclear. Serum levels of antibodies to melanocyte antigens, the activity and extent of the disease, and the presence of other immune disorders and seems to be related to the reduction in patients with vitiligo responding to treatment [8,9]. Both humoral and cellular immunity are likely to cooperate in the elimination of melanocytes. Regarding cellular immunity, the underlying infiltrate of pigmented lesion skin has an important role to play in detecting CD4 and CD8 positive T cells as well as expressing activation molecules [10]. A significant number of infiltrating T cells express the typical cutaneous lymphocyte antigen (CLA) of homing T cells in the skin, and in a recent study localized CLA positive cytotoxic T cells cause the disappearance of melanocytes lost in the percutaneous skin [11]. Melanin-A / Mart1 (melanosomal antigen) specific CD8 positive T cells were detected in peripheral blood in vitiligo patients. Melan-A / Mart1-specific CD8-positive T-cell clones in patients with melanoma infused Melan-A / Mart1-specific CD8-positive T lymphocytes in inflammatory lesions of melanocyte destruction following infusion [11,12].

Neural Hypothesis

This hypothesis suggests that some neurochemical mediators, possibly secreted from adjacent nerve endings, are cytotoxic to pigment cells. This theory is supported by the presence of a segmental variant of vitiligo affecting the onset of disease and the onset of disease in patients with vitiligo and neurological disorders or peripheral nerve damage after a serious emotional stress period [13,14]. Abnormalities of neuropeptides have been observed in the blood of peril skin and vitiligo patients [15]. In addition, increased catecholamine discharge or synthesis has been associated with disease activity and suggests the role of catecholamines in the depigmentation process [16]. Significant support for this theory has been demonstrated by demonstrating morphological and functional communication between epidermal melanocytes and the nervous system [17]. Autocytotoxic / metabolic hypothesis It has been suggested that oxidative stress is the initial pathogenic event in melanocyte degeneration [18,19] with H_2O_2 accumulation in the epidermis of patients with active disease. Defective recycling of tetrahydrobiopterin, vitiligo associated with intracellular production of H2O2 has been reported in the epidermis [18]. In addition, a change in the antioxidant pattern with a significant reduction in catalase activity has been demonstrated in both the lesion and the non-lesion epidermis and melanocytes [19]. However, the antioxidant imbalance was also confirmed in peripheral blood mononuclear cells of active vitiligo patients; It was associated with increased intracellular production of reactive oxygen species and appeared to be due to mitochondrial disorder [20]. These findings support a possible systemic oxidative stress concept in vitiligo. Hypothesis related to the new microenvironment The cytokine imbalance in epidermal microenvironment in the skin with active vitiligo is shown. This can disrupt the normal life and activity of melanocytes. A decrease in cytokines inducing melanocytes and an increase in cytokines inhibiting melanocytes (especially tumor necrosis factorα) were detected in depressed lesions [21]. According to this hypothesis, a central role is given to the cutaneous microenvironment. Convergence theory. The identification of many reliable ingredients against the pathogenesis of vitiligo has led to this theory that different causal elements may act synergistically or independently to provoke the loss of melanocytes. Genetic factors, oxidative stress, autoimmunity, mutations, altered cellular environment may contribute to the disease [22].

Genome-Wide Association Studies

Numerous additional HLA association studies have been published in Vitiligo. However, the relationship between vitiligo and genetic variation of the class I and class II gene regions of the Major Histocompatibility Complex (MHC) was investigated. Detailed molecular genetics and genome wide association studies (GWAS) were performed. Kemp, et al. reported the first vitiligo non-MHC candidate gene association. CTLA4 encoding a T cell co-receptor associated with other autoimmune diseases, which are involved in the regulation of T-cell activation and which are associated epidemiologically with vitiligo. In fact, CTLA4 incorporation was the highest in vitiligo patients with other comorbid autoimmune

diseases [23], a finding that was later amplified by another study and meta-analysis [24]. A second significant non-MHC candidate gene association, also reported by Kemp [25], was also with PTPN22 encoding LYP protein tyrosine phosphatase, which was genetically related to many different autoimmune diseases. Again, this review was replicated in most of the other European-based whites [26,27] and other studies by GWAS, but not in many other populations. Thus, in conjunction with HLA class II, CTLA4 and PTPN22 are two of the genes underlying the epidemiological relationship of vitiligo, possibly with at least other European autoimmune diseases, in whites of European origin. Genomewide studies Candidate gene analysis is based on a bias based on the selection of genes for study. In contrast, genomic analysis of polygenic, multifactorial diseases is, in principle, neutral, beyond the assumption that genetic factors play a role. There are three approaches to genetic analysis of genome analysis. Genome-bond linkage analysis for collecting polymorphic markers between families with multiple affected relatives and among these families. Such families are rare, the genetic resolution of the link is low, and genetic assays require a few important assumptions that may not be accurate. For reasons that are not clear, the connection and GWAS often do not detect the same genetic signals. Genome wide or exome DNA sequencing studies can be constructed similarly to linkage or GWAS, but are much more expensive and have not yet been applied to vitiligo.

Candidate Gene Association Studies

Recently, candidate gene association studies involving many candidate genes: ACE, AIRE, CAT, CD4, CLEC11A, COMT, CTLA4, C12orf10, DDR1, EDN1, ESR1, FAS, FBXO11, FOXD3, FOXP3, GSTM1, GSTT1, IL1RN, IL10, KITLG, MBL2, NFE2L2, PDGFRA-KIT, PTGS2, STAT4, TAP1-PSMB8, TGFBR2, TNF, TSLP, TXNDC5, UVRAG, VDR, XBP1 TNFA TNFB, IL4, NLRP1, MYG1, ICAM1, HLA SOD, CAT, GPX1, FOXO3a, SIRT1,IFNG, IL1B, PSMB8, VDR, DR4. Also some studies have shown genetic variants of DEFB1, SOD2, GSTM1/T1 genes are related with vitiligo [29-35]. The effect of these genes on the pathogenesis of vitiligo is not yet clear. Significant pathogenic effects of candidate gene PTPN22 and HLA have been proposed in the development of vitiligo [29]. Generally cytokines, antigen processing and presentation, redox homeostasis related genes were studied. These studies shown that these genes are associated with vitiligo disease.

Conclusion

Genetic studies associated with vitiligo are not only related to the identification of genes that are susceptible to disease, but can also lead to the identification of genes associated with clinical aspects of the disease, the dynamics of the disease process or the time of manifestation of the first skin lesion. Most of the studies conducted so far have been evaluated as reliable biological candidate genes. Approximately 90% of them encode immunoregulatory proteins, while approximately 10% encode melanocyte proteins. The proteins of the melanocytes are probably autoantigens identified by the immune system and identified and eliminated by the immune system. These proteins form a dense network that fully regulates the immune system, emphasizing the system and pathways that have an effect on the development of sensitivity to vitiligo [36]. Continuous research on susceptibility genes is important to better understand the underlying mechanisms of vitiligo pathogenesis. The presence of various relationships between vitiligo and other autoimmune diseases can provide new information about the causes of many disorders through genetic research. Samples inhaled the inverse relationship between vitiligo and melanoma genetics, which in the future could lead to new opportunities for the treatment of this extremely dangerous skin neoplasm. The main objective of all research is to find new and optimal therapeutic strategies for vitiligo and other autoimmune diseases. In the future, these investigations are likely to find new prevention methods in this particular disease group.

References

1. Taïeb A, Picardo M (2009) Clinical practice. Vitiligo. N Engl J Med 360(2): 160-169.

2. Ortonne JP, Bose SK (1993) Vitiligo: where do we stand? Pigment Cell Res 6(2): 61-72.

3. Passeron T, Ortonne JP (2005) Physiopathology and genetics of vitiligo. J Autoimm 25: 63-68.

4. Bateia PS, Mohan L, Pandey ON, Singh KK, Arora SK, et al. (1992) Genetic nature of vitiligo. J Dermatol Sci 4(3): 180-184.

5. Nath SK, Majumder PP, Nordlund JJ (1994) Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. Am J Hum Genet 55(5): 981-990.

6. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA (2003) Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 16(3): 208-214.

7. Bystryn JC (1997) Immune mechanisms in vitiligo. Clin Dermatol 15(6): 853-861.

8. Hegedus L, Heindenheim M, Hjalgrim H, Høier-Madsen M (1994) High frequency of thyroid dysfunction in patients with vitiligo. Acta Derm Venereol 74(2): 120-123.

9. Ongenae K, Van Geel N, Naeyaert JM (2003) Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 16(2): 90-100.

10. Badri AM, Todd PM, Garioch JJ, Gudgeon JE, Stewart DG (1993) An immunohistochemical study of cutaneous lymphocytes in vitiligo. J Pathol 170(2): 149-155.

11. Van den Wijngaard R, Wankowicz-Kalinska A, Le Poole C, Tigges B, Westerhof W, et al. (2000) Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes is associated with the prominent presence of CLA+ T cells at the perilesional site. Lab Invest 80(8): 1299-1309.

12. Yee C, Thompson JA, Roche P, Byrd DR, Lee PP, et al. (2001) Melanocyte destruction after antigenic-specific immunotherapy of melanoma: direct evidence of T cell mediated vitiligo. J Exp Med 192(11): 1637-1644.

13. Westerhof W, Bolhaar B, Menke HE (1996) Resultaten van een enquet onder vitiligo patienten. Ned Tijdschr Dermatol Venereol 6: 100-105.

14. Arnozan L (1992) Vitiligo avec troubles nerveux sensitifs et sympathiques : l'origine sympathique du vitiligo. Bull Soc Fr Dermatol Syphiligr 29: 338-342.

15. Al'Abadie MS, Senior HJ, Bleeh SS, Gawkrodger DJ (1994) Neuropeptide and neuronal marker studies in vitiligo. Brit J Dermatol 131(2): 160-165.

16. Cucchi ML, Frattini P, Santagostino G, Orecchia G (2000) Higher plasma catecholamine and metabolite levels in the early phase of nonsegmental vitiligo. Pigment Cell Res 13(1): 28-32.

17. Hara M, Toyoda M, Yaar M (1996) Innervation of melanocytes in human skin. J Exp Med 184(4): 1385-1395.

18. Schallreuter KU, Wood JM, Pittelkow MR, Gütlich M, Lemke KR, et al. (1994) Regulation of melanin biosyntheis in the human epidermis by tetrahydrobiopterin. Science 263(5152): 1444-1446.

19. Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, et al. (1997) Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol 109(3): 310-313.

20. Dell'Anna ML, Mare sca V, Briganti S, Camera E, Falchi M, et al. (2001) Mithocondrial impairment in peripheral mononuclear cells durino the active phase of vitiligo. J Invest Dermatol 117(4): 908-813.

21. Moretti S, Spallanzani A, Amato L, Hautmann G, Gallerani I, et al. (2002) New insights into the pathogenesis of vitiligo: imbalance of epidermal cytokines at sites of lesions. Pigment Cell Res 15(2): 87-92.

22. Le Poole IC, Das PK, van den Wijngaard RM, Bos JD, Westerhof W (1993) Review of ethiopathomechanism of vitiligo: a convergence theory. Exp Dermatol 2: 145-153.

23. Blomhoff A, Kemp EH, Gawkrodger DJ, Weetman AP, Husebye ES, et al. (2004) CTLA4 polymorphisms are associated with vitiligo, in patients with concomitant autoimmune diseases. Pigment Cell Res 18(1): 55-58.

24. Birlea SA, La Berge GS, Procopciuc LM, Fain PR, Spritz RA (2009) CTLA4 and generalized vitiligo: two genetic association studies and a meta-analysis of published data. Pigment Cell Melanoma Res 22(2): 230-234.

25. Kemp EH, Ajjan RA, Waterman EA, Gawkrodger DJ, Cork MJ, et al. (1999) Analysis of a microsatellite polymorphism of the cytotoxic T-lymphocyte antigen-4 gene in patients with vitiligo. Br J Dermatol 140(1): 73-78.

26. Cantón I, Akhtar S, Gavalas NG, Gawkrodger DJ, Blomhoff A, et al. (2005) A single-nucleotide polymorphism in the gene encoding lymphoid protein tyrosine phosphatase (PTPN22) confers susceptibility to generalised vitiligo. Genes Immun 6(7): 584-587.

27. LaBerge GS, Bennett DC, Fain PR, Spritz RA (2008) PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. J Investig Dermatol 128(7): 1757-1762.

28. LaBerge GS, Birlea SA, Fain PR, Spritz RA (2008) The PTPN22 -1858C>T (R620W) functional polymorphism is associated with generalized vitiligo in the Romanian population. Pigment Cell Melanoma Res 21(2): 206-208.

29. Birlea SA, Jin Y, Bennett DC, Herbstman DM, Wallace MR, et al. (2011) Comprehensive association analysis of candidate genes for generalized vitiligo supports XBP1, FOXP3, and TSLP. J Investig Dermatol 131(2): 371-381.

30. Ochoa-Ramírez LA, Becerra-Loaiza DS, Díaz-Camacho SP, Muñoz-Estrada VF, Ríos-Burgueño ER, et al. (2018) Association of human beta-defensin 1 gene polymorphisms with nonsegmental vitiligo. Clin Exp Dermatol.

31. A T, G O, Tb G, E K, Associacte Professor, et al. (2017) Superoxide Dismutase 1 and 2 Gene Polymorphism in Turkish Vitiligo Patients. Balkan J Med Genet 20(2): 67-74.

32. Singh M, Mansuri MS, Jadeja SD, Marfatia YS, Begum R (2018) Association of interleukin 1 receptor antagonist intron 2 variable number of tandem repeats polymorphism with vitiligo susceptibility in Gujarat population. Indian J Dermatol Venereol Leprol 84(3): 285-291.

33. Jadeja SD, Mansuri MS, Singh M, Patel H, Marfatia YS, et al. (2018) Association of elevated homocysteine levels and Methylenetetrahydrofolate reductase (MTHFR) 1298 A > C polymorphism with Vitiligo susceptibility in Gujarat. J Dermatol Sci 90(2): 112-122.

34. Ozel Turkcu U, Solak Tekin N, Gokdogan Edgunlu T, Karakas Celik S, Oner S (2014) The association of FOXO3A gene polymorphisms with serum FOXO3A levels and oxidative stress markers in vitiligo patients. Gene 536(1): 129-134.

35. Edgunlu T, Solak Tekin N, Ozel Turkcu Ü, Karakaş-Çelik S, Urhan-Kucuk M, Tekin L (2016) Evaluation of serum trail level and DR4 gene variants as biomarkers for vitiligo patients. J Eur Acad Dermatol Venereol 30(10): e97-e98.

36. Spritz RA (2013) Modern vitiligo genetics sheds new light on an ancient disease. J Dermatol 40(5): 310-318.