VIT1 & Vitiligo – The Mysteries Unfold

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Abstract:

Recently discovered Vit1 gene in vitiligo has an N-recognin domain, which can explain most of the characteristics of vitiligo.

Keywords:

Vitiligo, N-recognin, ubiquitin

Vitiligo is characterized by well-circumscribed depigmented macules over the skin. The stigma associated with vitiligo especially on pigmented skin, makes this relatively innocuous disease, one of the most dreaded one in human history. It is often compared to leprosy, though both the conditions have very little in common.

Though extensively studied, the pathophysiology of vitiligo remains an enigma, Data available are like parts of a puzzle, and we have still not been able to fit everything together.

The striking features of vitiligo, which have to be explained by any hypothesis on vitiligo pathogenesis, are the following:

1- Its apparent heritability[1]
2- Absence of melanocytes from the area without any obvious signs of inflammation[2]
3- Its apparent association with ocular abnormalties[3] and other systemic disorders like thyroid disease[4].
4- Its apparent association with stress and trauma[5].
5- Its segmental distribution in few cases, along the distribution of a particular nerve.

The three traditionally used hypothesis to explain vitiligo, include the neural hypothesis, the self-destruct hypothesis and the immune hypothesis.

The neural hypothesis, motivated by the occurrence of the segmental form of the disease theorizes that Vitiligo may be due to melanocytotoxic neurotoxins liberated by nerve endings. However, conflicting reports of Vitiligo sparing neurologically compromised skin and Vitiligo involving only paralysed limbs are present. Segmental Vitiligo of often considered a special type due to its stable course, early age of onset and the absence of any systemic association or koebnerization[6].

According to self-destruct hypothesis, the melanocyte destruction may be due to toxic intermediates of melanin synthesis. However, it failed to explain its heritability, association with stress, trauma and other systemic disorders.

The third and the most widely accepted hypothesis is the autoimmune hypothesis[7]. However, consensus has not been reached as to whether it is a B-cell mediated[8] or T-cell mediated[9] disease. The histopathological evidence of infiltration in the form of cellular infiltrate is not prominent in Vitiligo, except in very early lesions[2].

Attempt to find a genetic marker for this heritable disease, especially in the HLA, system did not succeed. However, a new gene predominantly expressed in Vitiligo patients was discovered recently and was named V1T1[10]. It is located on chromosome 2p16.

The genomic study of VIT1 revealed the following interesting features. VIT1 has a ref/eq accession number of NM-018693 and the corresponding protein has an accession number of NP 061163. The genome has four exons. It has an overlapping region with the tumour marker MSH6.

The search for known domains on the protein yielded some very interesting results. It showed a single domain, a putative zinc finger in the N-recognin (ZnF-UBR1) with a Pfam accession number 02207 and smart00396.

N-recognin is an ubiquitin-protein ligase, the vital part of the N-end rule pathway[11]. N-end rule pathway is the main initiator of cellular apoptosis by destruction of specific proteins. It has various isoforms recognizing various N-terminal aminoacid sequences, hence the name N-end rule pathway.

The presence of this ubiquitin domain on Vitiligo-associated gene can explain many of the features described above. Ubiquitin expressed by VIT1 may be targeting any of the specific proteins expressed by melanocytes or those responsible for melanocyte activation, thereby leading to melanocyte apoptosis. This could explain the following features of Vitiligo.

1- Its genetic predisposition
2- Melanocyte destruction without significant inflammation

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3- Association with stress and trauma, both of which are known to increase ubiquitin production.
4- Responses to steroids, as steroids inhibit certain types of cellular apoptosis, especially TNF-a induced apoptosis.

Yet, another protein sharing the same domain is retinoblastoma-associated factor. This also may be a significant finding considering the fact that retinal pigmentary abnormalities are common in Vitiligo. The significance of the overlap of VIT1 gene with MSH6 is not known. MSH6 is involved in mismatch repair and mutation in this region leads to various colorectal tumours[12]. Pigmentary changes are common in various intestinal polyposis syndromes, and the role of MSH6 remains to be explored.

In conclusion, genomic evidence suggests an ubiquitin mediated melanocyte specific apoptosis as probable pathogenic mechanism in Vitiligo. Histopathological evidence of inflammation in the normal appearing skin adjacent to vitiliginous areas[13] may be secondary to the cell injury. However, further research is required to find the probable target protein of this "Vitiligo associated ubiquitin". It has got tremendous therapeutic application as synthetic proteins with same N-terminal sequence can act as a competitive inhibitor of the above enzyme.

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