

The Role of LMP7

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Our laboratory is investigating the possible roles of genes in vitiligo susceptibility, so that we can learn more about the cause of vitiligo. It is sometimes said that vitiligo "runs in the family," which means that some people may be born with genes that make them more susceptible to developing vitiligo, just as other people are born with genes that make them susceptible to developing diabetes or cancer. We believe that in the case of vitiligo, some of these genes may be important for the normal function of the pigment producing cells in the skin (melanocytes) and others may help educate cells of the immune system (Band T lymphocytes). Environmental factors, such as traumatic skin injury, sunburn, or stress, probably influence whether or not an individual with these "susceptibility genes" will ever actually develop vitiligo during their lifetime.

Depending on which genes are involved, what their normal functions are, and what genetic changes are found in vitiligo patients, it might be possible to design new treatments or to develop genetic testing to identify individuals who might be predisposed to developing vitiligo so that environmental risk factors can be avoided.

Our genetic studies have provided evidence for association of three different gene regions with vitiligo susceptibility. The first region is a tight cluster of four genes involved in a process called antigen processing, which determines how lymphocytes of the immune system detect microorganisms, such as viruses, that infect our cells, and genetic changes that lead to cancer. The LMP7 and LMP2 genes encode parts of a complex enzyme that breaks down proteins inside the cell into small fragments (peptides). The TAP1 and TAP2 genes encode parts of a channel that transports the peptides into a cell compartment where they are packaged for further transport to the cell surface.

There on the cell surface, the lymphocytes can examine the peptides that came from inside the cell. Most of these are usually from normal "self" proteins and are ignored by the lymphocytes. But if a cell is infected with a virus or becomes a cancer cell, the lymphocytes can recognize the virus or cancer-related peptides as being foreign, and the cell is then killed by the immune system. During an autoimmune response, as appears to occur in the skin of some vitiligo patients, lymphocytes mistakenly recognize normal self proteins as being foreign, contributing to the killing of normal melanocytes. Our studies of the LMP7 and LMP2 genes suggested that the LMP7 gene was associated with vitiligo susceptibility. Further analysis, including the neighboring TAP1 and TAP2 genes, revealed that the genetic association with vitiligo may actually be with the TAP1 gene.

Current experiments are focusing on a comparison of the expression of all four genes in "antigen-presenting cells", whose function is specialized to show protein fragments to the immune system, and in vitiligo versus control skin cells. We will then compare the LMP7 or TAP1 gene sequences between vitiligo patients and control subjects, in order to identify mutations that may be affecting LMP7 or TAP1 function in vitiligo patients.

The second gene region that appears to be associated with vitiligo encodes the genes CTLA4 and CD28, which regulate the activation of T lymphocytes in the immune system. CD28 is a cell surface receptor that helps "turn on" T cells, whereas CTLA-4 is a cell surface receptor that helps "turn off" T cells. A British group previously reported that CTLA-4 association occurs only in vitiligo patients with other autoimmune diseases. However, we have found weak evidence for association of this genetic region in vitiligo patients regardless of other autoimmune status.

The third genetic region we find associated with vitiligo encodes the catalase gene. The catalase gene was selected as a candidate gene due to the reduced catalase enzyme activity and accompanying build-up of excess hydrogen peroxide observed in the entire skin of vitiligo patients. This excess hydrogen peroxide is toxic to melanocytes, and is the biochemical basis for the use of pseudocatalase to treat vitiligo by breaking down the hydrogen peroxide. A genetic marker for the catalase gene was found to be significantly associated with vitiligo using two different association methods. Furthermore, our results suggest that variations in the catalase gene could possibly lead to lowered catalase activity in vitiligo patient skin and contribute to the accumulation of excess hydrogen peroxide. The catalase gene may therefore be a

susceptibility gene in some vitiligo patients. Continuing experiments are focused on comparisons of catalase gene function and DNA sequences between vitiligo patients and control subjects. We gratefully acknowledge the many vitiligo patients and family members who have made this research possible by providing blood samples and supporting the National Vitiligo Foundation.

For more information about our vitiligo research, please visit our website:
<http://www.med.ufl.edu/path/faculty/mccormac/vit-info.html>