

## ORIGINAL ARTICLE

# NALP1 in Vitiligo-Associated Multiple Autoimmune Disease

Ying Jin, M.D., Ph.D., Christina M. Mailloux, B.S., Katherine Gowan, B.S., Sheri L. Riccardi, B.S., Gregory LaBerge, M.S., Dorothy C. Bennett, Ph.D., Pamela R. Fain, Ph.D., and Richard A. Spritz, M.D.

## ABSTRACT

**BACKGROUND**

From the Human Medical Genetics Program (Y.J., C.M.M., K.G., S.L.R., G.L., P.R.F., R.A.S.) and the Barbara Davis Center for Childhood Diabetes (P.R.F.), University of Colorado at Denver and Health Sciences Center, Aurora; and the Division of Basic Medical Sciences, St. George's, University of London, London (D.C.B.). Address reprint requests to Dr. Spritz at the Human Medical Genetics Program, University of Colorado at Denver and Health Sciences Center, P.O. Box 6511, Mailstop 8300, Aurora, CO 80045, or at richard.spritz@uchsc.edu.

Autoimmune and autoinflammatory diseases involve interactions between genetic risk factors and environmental triggers. We searched for a gene on chromosome 17p13 that contributes to a group of epidemiologically associated autoimmune and autoinflammatory diseases. The group includes various combinations of generalized vitiligo, autoimmune thyroid disease, latent autoimmune diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison's disease.

**METHODS**

We tested 177 single-nucleotide polymorphisms (SNPs) spanning the 17p13 linkage peak for association with disease and identified a strong candidate gene. We then sequenced DNA in and around the gene to identify additional SNPs. We carried out a second round of tests of association using some of these additional SNPs, thus elucidating the association with disease in the gene and its extended promoter region in fine detail.

**RESULTS**

Association analyses resulted in our identifying as a candidate gene *NALP1*, which encodes NACHT leucine-rich-repeat protein 1, a regulator of the innate immune system. Fine-scale association mapping with the use of DNA from affected families and additional SNPs in and around *NALP1* showed an association of specific variants with vitiligo alone, with an extended autoimmune and autoinflammatory disease phenotype, or with both. Conditional logistic-regression analysis of *NALP1* SNPs indicated that at least two variants contribute independently to the risk of disease.

**CONCLUSIONS**

DNA sequence variants in the *NALP1* region are associated with the risk of several epidemiologically associated autoimmune and autoinflammatory diseases, implicating the innate immune system in the pathogenesis of these disorders.

N Engl J Med 2007;356:1216-25.

Copyright © 2007 Massachusetts Medical Society.