NIH genetic collaboration brings new meaning to the Silk Road

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Researchers with the National Institutes of Health have found susceptibility to Behcet's disease, a painful, inflammatory condition, to be associated with genes involved in the body's immune response.

Although the Greek physician Hippocrates described Behcet's disease (pronounced BET'-chet's), more than 2,000 years ago, the condition existed in relative obscurity until the early 20th century. Named for the Turkish physician who first classified it in 1937, Behcet's disease is found almost exclusively in populations with origins along the Silk Road, a trading route that stretched from Europe to the Far East. Marco Polo was among the most famous travelers along the Silk Road.

This distinctive distribution led researchers to suspect that the disease has a hereditary component, though they determined that a definitive genetic cause is unlikely due to the complexity of disease inheritance. Further investigation of the interleukin 10 (IL10) gene associated with immune response, showed that people with two copies of the Behcet's disease IL10 gene produced significantly lower levels of IL-10 protein than people with only one or no IL10 [disease gene](). The findings appear online in the current issue of the journal [Nature Genetics]().

Today, despite advances in genetics and genomics research, the diagnosis of Behcet's disease is still determined by the clinical picture, characterized by painful ulcers affecting the mouth and genitals and inflammation of the skin and eyes. Recurrent inflammatory attacks affecting the eyes may result in permanent loss of vision, and

inflammation of the brain and large blood vessels may be associated with increased mortality. In addition, treatments for the disease target individual symptoms rather than addressing an underlying mechanism.

In the current study, the NIH researchers from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), in collaboration with Professor Ahmet Gul's group at Istanbul University, have performed the first large genome-wide association study (GWAS) of Behcet's disease in a Turkish population. They looked at the genomes of more than 1,200 Behcet's patients and 1,200 people without the disease in an effort to identify places where the two groups differed. These places, called single nucleotide polymorphisms (SNPs), could point to genes that are associated with the disorder. Both groups of people were from Turkey, which has the highest prevalence rate for the disease, 4 cases per 1,000 individuals. Previous genetic studies have shown a strong association of Behcet's disease to the major histocompatibility complex (MHC), a section of the genome on chromosome 6 containing a large number of immune-related genes. The highest association is with the human leukocyte antigen (HLA)-B51 region of the MHC. However, since it accounts for less than 20 percent of the disease's genetic risk, other genetic factors must be involved.

"We knew that Behcet's disease had a strong genetic component, but until now, we haven't been able to search the entire genome to identify hidden candidate genes," said Elaine F. Remmers, Ph.D., an investigator in the NIAMS Laboratory of Clinical Investigation and lead author of the study. "With the GWAS, we were able to zero in on promising SNPs and then perform more extensive examinations of these regions."

In addition to conducting their own GWAS, the NIAMS group exchanged data with an independent group of investigators that concurrently performed a large GWAS for Behcet's disease in a Japanese population. This study's paper also appears online in *Nature*

Genetics. After identifying several possible targets, the NIAMS researchers performed a meta-analysis of genetic data from six independent cohorts, which included populations from Turkey, the Middle East, Europe, and Asia.

The researchers had several significant findings. They reconfirmed a strong association of Behcet's disease with the HLA-B51 region of the MHC and identified an independent association area within the MHC. The researchers also identified associations on chromosome 1 with a known variant of the IL10 gene and with a variant located between the genes for the IL-23 receptor (IL23R) and a component of the IL-12 receptor (IL12RB2). Interestingly, the genetic variants found to be associated with Behcet's disease in the Turkish population were identical to those independently identified in the Japanese population, lending credence to a genetic link between two disparate populations separated by thousands of miles, but tied together by the ancient trading route.

The most encouraging finding resulted from an analysis of the function of the IL10 gene variant. They found that cells from blood donors who had two copies of the IL10 gene variant produced significantly lower levels (approximately one-third) of IL-10 protein compared to people with one or two normal IL10 genes. Since the function of IL-10 is to decrease inflammation, the researchers suggest that low levels of IL-10 protein, in conjunction with external triggers, might be a risk factor for Behcet's disease. Additionally, IL10 has an extensive disease history, with different variants of IL10 having been associated with other autoimmune and autoinflammatory diseases, including ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, and severe juvenile rheumatoid arthritis. These findings suggest that there may be possible therapeutic targets that can be examined in future studies.

  More information: More information about Behcet's disease can be found at www.niams.nih.gov/Health_Info/ … Disease/default.asp