Need for funding: World Wide Genome Wide Association Study in Narcolepsy

Narcolepsy affects ~1 in 3000 individuals, causing uncontrollable sleepiness and muscle weakness, resulting from loss of cells producing hypocretin (hcrt)- a critical wake promoting substance. Previous Stanford genetic studies have demonstrated an association of narcolepsy with specific variants in the human leukocyte antigen (HLA), T-cell Receptor (TCR) and other immune related genes, suggesting that hypocretin cell loss occurs through autoimmune destruction.

The Stanford center for narcolepsy has now identified circulating immune T cells that react to hypocretin, together with a specific protein target of the autoimmune attack, conclusively demonstrating the autoimmune basis for the disease in a process called molecular mimicry.

This dramatic discovery follows from insights gained after the recent H1N1 swine flu pandemic. In 2010, a study in collaboration with China showed an increase in narcolepsy in children living in areas where the then-novel pandemic 2009 H1N1 influenza virus had spread the previous year. Clusters of narcolepsy cases in Scandinavian children who had been vaccinated with Pandemrix, an anti-H1N1 vaccine were noted at the same time. The team noted a similarity between portions of the hcrt and H1N1 influenza hemagglutinin proteins. Cross reactive T cells were present in narcolepsy patients both before and after the H1N1 pandemic, suggesting other pathogens may also trigger disease development.

The decision to focus on cross reactive T cells followed directly from genetic studies demonstrating a critical role of Class II HLA DQ0602 heterodimer that presents antigens to T cells. A relatively small Stanford genome wide analysis study (GWA) implicated specific T cell receptor alpha variants in susceptibility, a finding that was extended in a larger GWA study of Europeans that also identified additional proteins in the antigen processing and presentation pathway for disease susceptibility (CTSH, TNFS4). Our recent GWA study of narcolepsy in China confirmed the previous results in Europeans, and also identified HLA variants associated with earlier disease onset, and possible differences in genetic susceptibility factors with respect to the H1N1 pandemic. With each larger sample, additional genetic factors have been identified. Study of different ethnic backgrounds has identified genetic factors that act across ethnicity, but are not readily detectible in all backgrounds, due to different baseline gene frequencies.

Together, recent immune and genetic results create a unique opportunity to extend narcolepsy research from the realm of exploration into the development of preventative measures and new diagnostics, potentially extending to other autoimmune diseases of the brain including schizophrenia and Parkinson disease.

Many questions remain, and we believe a global GWA of narcolepsy will help us to: identify and purify the culprit T cells, by more thorough mapping of the TCR alpha and beta locus variants; understand how risk genes interact with Class II and class I HLA risk alleles to trigger the disease in different individuals; newly identified susceptibility genes will allow us to construct a more detailed molecular model of the pathogenic antigen presentation/response interaction that will improve our new ability to predict and prevent the disease.

We are nearing the final stage of our world wide GWA study of narcolepsy, planned to include 5000 cases gathered from the US (Caucasian and African American), Europe, Korea, China and Japan. We require $148,000 for genotyping of the final 1,152 narcolepsy samples to be performed at UCSF on Affymetrix Axiom World Array chips ($128.43 each).

Contact: Mali einen, einen@stanford.edu
Or follow instructions at http://med.stanford.edu/psychiatry/narcolepsy/funding.html