Genetic approaches to corticobasal degeneration, progressive supranuclear palsy, and other tauopathies.

Gerard D Schellenberg, PhD

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are both neurodegenerative diseases that have tau aggregates as a prominent neuropatholgic feature. These and other disorders are called tauopathies. The tau aggregates can be present in neurons as neurofibrillary tangles, or in oligodendrocytes or as tufted astrocytes. The most common tauopathy is Alzheimer's disease (AD), where, unlike PSP or CBD, the aggregated tau is accompanied beta-amyloid deposits and sometime synuclein or TDP-43 deposits. For different tauopathies, the distribution of tau aggregates and neurodegeneration differs.

There are several reasons for using genetics to study human diseases including tauopathies. **1)** The disease is being studied in the organism that is to be treated – man. If a gene is identified where genetic variation increases expressions and results in elevated risk, pharmacologic inhibition of the gene product or reduction in expression should reduce risk. This conclusion comes directly from human studies and not non-human model studies or *in vitro* experiments. **2)** Genetic findings can be used to predict who will develop a disease. This is important for determining who should be treated and will be particularly important for disease prevention. **3)** Gene discovery can provide valuable clues to determining the molecular mechanism of a disease, and are a starting point for further targeted experimentation. **4)** Causative and risk-factor genes can directly encode proteins that are drug targets. An example of gene discovery leading to an approved therapeutic is PCSK9. In 2006, cardiovascular disease researchers identified PCSK9 loss-of-function variants that protected against heart disease. Monoclonal antibody trials began in 2013, leading to an approved drug in 2016. Numerous other examples show that proteins encoded by disease risk genes are proven therapeutic targets.

Genetic studies of PSP identified 4 genetic signals that alter risk for PSP. In a genome-wide search, signals at MOBP, STX6, EIF2AK3, and MAPT altered risk for PSP. The strongest signal was at MAPT, the gene that encodes for tau, the same protein found aggregated in PSP, CBD, and other tauopathies. The high-risk allele at MAPT increases risk ~5.5 fold. This is on the same order of magnitude as the risk associated with APOE for AD which is ~3-4 fold. The signal at MAPT is particularly complex with 4 separate sites influencing risk. One of these signals is in an adjacent gene, KANSL1. Studies of CBD also show that MAPT is a CBD risk factor as well as MOBP. Since CBD is rarer, genome-wide studies do not have the same power as those on PSP. MAPT is also a genetic risk factor for AD and for Parkinson's disease (PD). Since MAPT is a risk factor for multiple tauopathies, a common mechanism is assumed. Also since synuclein deposits are seen both PD and some cases of AD, aggregation of these proteins may involve a common mechanism. CRISPR/CAS9 experiments in mouse are now underway to identify how MAPT variants influence risk across multiple tauopathies. Hopefully these studies will lead to therapeutic strategies that work for PSP and CBD, and possibly AD.