THE CONTRIBUTION OF RARE VARIANT AND COPY-NUMBER VARIATION TO RISK OF SPORADIC CREUTZFELDT-JAKOB DISEASE AND PLEIOTROPY WITH OTHER NEURODEGERATIVE DISEASES

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The objective of the study is to identify genetic factors that contribute to the risk of developing sporadic Creutzfeldt-Jakob disease (sCJD). To accomplish this, we performed DNA sequencing of the protein-coding portion of the genome for 403 sCJD patients and 23000 unrelated controls and 1000 patients with late-onset Alzheimer disease (LOAD). We identified several genes and genetic variants associated with sCJD alone or that are associated when we combine sCJD and LOAD data, suggesting a shared genetic liability for these two neurodegenerative diseases. We are working to replicate these findings in collaboration with Dr. Simon Mead at the UK National Prion Clinic who has performed similar sequencing on a separate cohort of 350 sCJD patients. Our goal is to publish our findings from this collaboration as soon as possible. These findings will have implications for early diagnosis of some forms of sCJD, lead to a better understanding of the biological mechanisms underlying sCJD and potentially lead to new therapies by targeting these novel mechanisms. The next steps in our work will be to obtain DNA for a larger number of patients and perform further sequencing and genotyping to improve statistical power to detect genetic associations and follow up our findings by modeling these genetic findings in cell culture and mouse models of prion disease.