Research Use Statement for Application for Genomic Data from NIAGADS

Research Use Statement:

Psychosis, affective symptoms and agitation/aggression are a frequent and distressing features of Alzheimer's disease (AD) with a major impact on disease course for which there few effective licensed treatments. The development of safe and effective therapies is an urgent priority, which must start with a better understanding of disease mechanisms. We hypothesize that these symptoms have distinct disease mechanisms as reflected by a specific pattern of genetic risk when compared to individuals without these symptoms.

We will compile genetic (from three ADC datasets: NG00022, NG00023, and NG00024) and clinical data (from NACC) and over 5,000 cases available from an existing collaborative network in Europe to undertake the most comprehensive genomic analysis of these symptoms to date.

Objectives: **1)** conduct a GWAS of psychosis, affective symptoms and agitation/aggression in AD; and **2)** undertake in-depth bioinformatic analysis of the genetic data, with a focus on the identification of putative causal SNPs and genes and the functional mechanisms underlying the associations.

Phenotypes: Neuropsychiatric phenotypes will be derived from assessment by the Neuropsychiatric Inventory (NPI), a standardized, validated tool which is widely used in AD research. AD cases will be classified into two groups on the basis of established cut off scores on the NPI.

Analysis: Data will undergo phasing and imputation and stringent quality control using the same pipeline as our existing data. We will first conduct a GWAS for each symptom group using meta-analysis to account for variation between datasets. Our sample size will exceed 7,000 which will enable us to detect common variants, with modest effect sizes at >80% power. Because we expect these symptoms to be polygenic traits we will also polygenic risk scoring of other psychiatric phenotypes to assess shared genetic risk. We will finally conduct integrated genetic-epigenetic analysis using our existing collection of epigenetic data from AD and control brains held at the University of Exeter, which will provide essential functional annotation to the GWAS signal.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Symptoms like hallucinations, suspicious thoughts, depression, agitation and aggression are common features of Alzheimer's disease and extremely distressing to both the individual and those around them. While there is increasing recognition of the importance of the symptoms we still only partially understand why some people experience them and others do not. Moreover, we have so far only had a small number of successes in translating that understanding into effective treatments. Thus we need to find out more about the biology underlying these symptoms if we are to treat them effectively. Genetic studies provide a useful way of doing this. We can look for variation in people's genetic code and analyze whether this is associated with our symptoms of interest. If we detect any associations with particular genes we can then undertake further work to

understand what might be going wrong in those genes which causes them to increase risk for these symptoms.