This proposal is intended to investigate the association between the single nucleotide polymorphisms (SNPs) of human Kv1.3 (KCNA3) gene and Alzheimer disease-associated dementia. KCNA3 encodes alpha subunits of the *Shaker*-related voltage-gated potassium channels Kv1.3 that are important for normal functioning of several cell types in the CNS including neurons, astrocytes and microglia, where they are implicated in regulation of excitability, cell survival, neurogenesis and production of reactive oxygen species. Given the Kv1.3 channel's pattern of expression in the cells and structures implicated in Alzheimer's disease (AD), it is compelling to hypothesize that naturally occurred mutations in the gene that encodes Kv1.3 are likely to differentially affect the properties of the channels which, in turn, may have functional relevance, presenting higher (or lower) risk for the development of AD. We had demonstrated that properties of heterologously expressed Kv1.3 channels are modulated by soluble amyloid beta oligomers (Lioudyno et al., 2012), suggesting the role of Kv1.3 in mediating the effects of amyloid beta peptide. Furthermore, our preliminary analysis (unpublished), that utilized UCI MIND ADRC data set, suggests possible association between two KCNA3 SNPs, rs2821557 and rs1058184, and dementia. We would like to perform similar analysis using larger data set in order to confirm our preliminary findings and extend the analysis by including additional variables.

The specific aims of the proposal are:

1. To summarize the demographic characteristics and available neuropathology data of the sample by SNP for the following variables: age, sex, ethnicity, clinical dementia, age of dementia onset, rate of cognitive decline, APOE variants, A score (Thal phase for amyloid plaques), B score (BRAAK stage for neurofibrillary degeneration), and C score (density of neuritic plaques).

2. To estimate the association between clinical dementia and the presence of minor allele in SNPs (rs2821557, rs1058184). This analysis will consider a modification of the association between SNPs and dementia by age, sex, ethnicity, age of dementia onset, APOE variants, A score, B score and the C score.

3. To estimate the correlation between the rate of cognitive decline in subjects with dementia and the presence of minor allele in SNPs (rs2821557, rs1058184).

We request two data sets, NG00024 (ADC3- Alzheimer Disease Center Dataset 3) and NG00026 (GWA Analysis of Age at Onset in AD) that include genotyping results for SNPs rs2821557 and rs1058184 as well as standard demographic characteristics of the eligible participants. The eligible participants are those diagnosed with dementia, Alzheimer's disease, or MCI, as well as healthy control subjects. The analysis will be performed separately for each SNP.

Revealing the association between AD-associated dementia and KCNA3 variant(s) will provide crucial information that will guide us in our current studies of the Kv1.3 role in the mechanisms of AD, and in particular – in the neurotoxicity associated with the exposure to general inhalational anesthetics. The proposed studies should also provide knowledge for achieving our long-term objectives that ultimately aim at the therapeutic targeting of Kv1.3 for prevention and/or treatment the AD-associated neurodegeneration.