ABSTRACT:

Background: SNP rs17070145 minor allele (T) is associated with better episodic memory and AD risk, consistent fMRI activation patterns during episodic memory tasks. mRNA expression is also higher in memory-related brain regions (Pappasotiroupoulos et al., 2006). These findings need replication in independent series, including non-Caucasian populations. Methods: We genotyped 14 Caucasian and 2 African-American AD case-control series for rs17070145 SNP (Internal ID=1212) previously identified in a cognition GWAS. We also genotyped 14 additional SNPs within and flanking KIBRA. We analyzed these 15 SNPs for association with LOAD risk in these 10 series using logistic regression with age, gender, and APOE as covariates. We also assessed rs17070145 (1212) in a Meta-analysis including all Mayo series and the published series. Four Caucasian and both African-American series had cognitive data. We tested these 15 SNPs for association with delayed episodic memory (AVLT Delayed, AVD, WMS-R Logical Memory, MRMLD) in elderly, cognitively normal subjects from these series. We also compared KIBRA mRNA levels in AD and non-AD subjects' temporal cortex and cerebellum. Results: KIBRA SNP rs17070145 minor T allele shows a significantly protective effect in the older African-American (AA) series, and marginally protective trends in the older Mayo Clinic Jacksonville (JS_Old) and Rochester (RS_Old) series (Tables 1A, 1B, Figure 1). This allele is marginally protective when all the older Mayo Clinic series are analyzed jointly. Meta-analysis of all Mayo series, together with all published series also reveals a marginally protective effect for KIBRA SNP rs17070145 minor allele. Analysis of 14 additional SNPs in the 10 Mayo series, identified SNPs with significant or marginal AD risk associations with consistent effects in two or more series (Table 2). Table 1B. We identified nominally significant associations with cognitive scores AVD and MRMLD in the JS_old series (Table 3). KIBRA mRNA expression levels were significantly higher in the temporal cortex of ADs vs. non-ADs (Figure 2A), and showed the same trend in the cerebella (Figure 2B).

Conclusions: Although modest, rs17070145 demonstrates association with AD risk with stronger effects among older subjects and significantly associates with AD risk in African-Americans. There appears to be additional SNPs within and flanking KIBRA that demonstrate nominally significant associations with AD risk and cognition that are stronger in the older series. Furthermore, we demonstrate differential expression of KIBRA mRNA between ADs and non-ADs particularly in the temporal cortex. Overall, these results provide additional evidence suggesting a role for KIBRA as a gene that influences both memory and risk of AD.

Table 1A. KIBRA SNP rs17070145 T Allele Association with LOAD in the Mayo Series

Table 1B. KIBRA SNP rs17070145 T Allele Association with LOAD in the Mayo + Published Series

Table 2. LOAD Association of 15 SNPs within and flanking KIBRA

Table 3. Delayed Episodic Memory Score Association of 15 SNPs within and flanking KIBRA