Association of common *KIBRA* variants with episodic memory and AD risk

Nilüfer Ertekin-Taner[1,2], Jeremy Burgess[1], Meron Hirpa[1], Thuy Nguyen[1], Ma Li[1], Zou Fanggeng[1], Steven G. Younkin[1], Julia Crook[3], V. Shane Pankratz[4], Ronald C. Petersen[5], Neill R. Graff-Radford[2], Otto Pedraza[6]

1) Dept. Neuroscience, Mayo Clinic, Jacksonville, FL; 2) Dept. Neurology, Mayo Clinic, Jacksonville, FL; 3) Biostatistics Unit, Mayo Clinic, Jacksonville, FL; 4) Dept. Biostatistics, Mayo Clinic, Rochester, MN; 5) Dept. Neurology, Mayo Clinic, Rochester, MN; 6) Dept. Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL.

ABSTRACT: *Background:* Recent studies suggest that the *KIBRA* SNP rs17017145 minor allele (T) is associated with better episodic memory and biologically-consistent fMRI activation patterns during episodic memory tasks. *KIBRA* mRNA expression is also higher in memory-related brain regions (Pappasotiroupoulos et al., 2006). Several studies also reported decreased risk of AD associated with the minor allele of rs1707145 (Rodriguez-Rodriguez et al., 2007; Li et al., 2008; Corneveaux et al., 2009). These findings need further replication in independent series, including non-Caucasian populations. *Methods:* We genotyped 8 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 measured and compared *KIBRA* mRNA levels in AD and non-AD subjects' temporal cortex and cerebella. *Results:* *KIBRA* SNP rs17070145 minor T allele shows a significantly protective effect in the older African-American (AA_Old) 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 T 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). 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

Series	AD Risk - Logistic Regression			
	OR	L95	U95	P
Mayo_AA_OLD	0.50	0.30	0.83	0.007
Mayo_JS_OLD	0.78	0.58	1.04	0.09
Mayo_RS_OLD	0.85	0.68	1.07	0.17
Mayo_AUT_OLD	1.08	0.74	1.56	NS
Mayo_NCRAD_OLD	0.90	0.58	1.40	NS
Mayo_AA_YOUNG	1.20	0.66	2.18	NS
Mayo_JS_YOUNG	1.02	0.79	1.32	NS
Mayo_RS_YOUNG	1.03	0.82	1.31	NS
Mayo_AUT_YOUNG	1.21	0.91	1.62	0.19
Mayo_NCRAD_YOUNG	0.87	0.60	1.26	NS
Mayo_Caucasian_OLD	0.88	0.77	1.02	0.08
Mayo_Caucasian_YOUNG	1.06	0.93	1.20	NS

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

Series	AD-N	AD-Freq (T)	CON-N	CON-Freq (T)	OR	L95	U95	Meta-Analysis P
Mayo+Published	4409	32%	4279	34%	0.94	0.87	1.01	0.08
Mayo+Published_Caucasian	4319	32%	4092	33%	0.94	0.88	1.01	0.07
Mayo_AA_OLD	48	59%	49	74%	0.50	0.26	0.96
Mayo_JS_OLD	229	30%	248	34%	0.84	0.63	1.12
Mayo_RS_OLD	271	33%	610	35%	0.92	0.74	1.15
Mayo_AUT_OLD	318	32%	103	29%	1.19	0.83	1.71
Mayo_NCRAD_OLD	154	33%	86	36%	0.88	0.58	1.33
Mayo_AA_YOUNG	42	64%	138	57%	1.36	0.80	2.35
Mayo_JS_YOUNG	357	32%	340	32%	1.01	0.80	1.28
Mayo_RS_YOUNG	269	31%	747	31%	0.99	0.79	1.23
Mayo_AUT_YOUNG	259	34%	254	31%	1.13	0.86	1.48
Mayo_NCRAD_YOUNG	546	31%	123	35%	0.83	0.61	1.12
TGen-PM US	457	30%	245	36%	0.78	0.61	0.99
TGen-AM Norway	143	33%	97	39%	0.75	0.50	1.11
TGen-AM German	219	33%	135	35%	0.90	0.64	1.29
TGen-AM Netherlands	16	28%	12	17%	1.96	0.45	9.95
Li et al (AlzGene)	690	31%	686	32%	0.93	0.79	1.10
Rodriguez et al.	391	31%	428	30%	1.01	0.81	1.25

Figure 1. *KIBRA* SNP rs17070145 T Allele Meta-Analysis in the Mayo + Published Series

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

OLD AGE GROUP

SNP	BP	rs	Afr-Amer OR	L95	U95	P	NCRAD OR	L95	U95	P	JS OR	L95	U95	P	RS OR	L95	U95	P	AUT OR	L95	U95	P	ALL-Caucasian OR	L95	U95	P
1212	167778369	rs17070145	0.50	0.30	0.83	0.007	0.78	0.58	1.04	NS	0.85	0.68	1.07	0.17	1.08	0.74	1.56	NS	0.88	0.77	1.02	0.08
1499	167727354	rs1030182	1.61	1.02	2.55	0.04	1.24	0.81	1.90	NS	1.10	0.83	1.46	NS	1.15	0.92	1.44	0.21	1.29	0.97	1.71	0.08	0.98	0.85	1.13	0.04
1501	167666718	rs11750709	0.56	0.34	0.92	0.02	0.90	0.58	1.38	NS	1.02	0.76	1.36	NS	1.05	0.83	1.32	NS	1.47	0.98	2.21	0.06	0.98	0.85	1.13	NS
1502	167665378	rs1422422	0.53	0.32	0.88	0.01	0.89	0.58	1.37	NS	0.98	0.74	1.32	NS	1.04	0.82	1.31	NS	1.52	1.01	2.28	0.04	0.97	0.84	1.12	NS
1504	167777769	rs1477306	0.48	0.29	0.81	0.006	0.89	0.57	1.38	NS	0.78	0.58	1.04	0.09	0.86	0.68	1.08	0.20	1.05	0.72	1.51	NS	0.88	0.77	1.02	0.09
1505	167696276	rs1477307	0.97	0.52	1.84	NS	1.17	0.76	1.80	NS	0.98	0.74	1.30	NS	0.99	0.80	1.25	NS	0.97	0.70	1.35	NS	1.05	0.92	1.20	NS
1508	167673397	rs17775705	1.56	0.93	2.60	0.09	1.14	0.72	1.80	NS	0.87	0.65	1.18	NS	0.89	0.71	1.11	NS	0.78	0.56	1.10	0.16	0.96	0.84	1.11	NS
1513	167609314	rs2337158	0.82	0.48	1.39	NS	0.75	0.48	1.15	0.19	1.07	0.81	1.41	NS	1.11	0.88	1.40	NS	1.36	0.96	1.93	0.08	1.07	0.94	1.23	NS
1514	167622795	rs3733989	1.60	0.85	3.02	0.14	0.76	0.49	1.19	0.23	1.06	0.78	1.44	NS	1.17	0.93	1.46	0.19	1.16	0.81	1.66	NS	1.08	0.94	1.24	NS
1515	167676785	rs4976592	1.03	0.63	1.69	NS	1.11	0.69	1.78	NS	1.02	0.75	1.40	NS	1.01	0.79	1.29	NS	1.19	0.78	1.80	NS	0.96	0.83	1.12	NS
1518	167653043	rs6555791	1.34	0.81	2.23	0.25	0.98	0.63	1.53	NS	1.26	0.94	1.70	0.12	0.89	0.70	1.13	NS	0.96	0.67	1.38	NS	1.09	0.94	1.25	NS
1519	167758744	rs6555807	0.88	0.55	1.40	NS	0.91	0.61	1.37	NS	1.19	0.90	1.58	0.23	0.89	0.72	1.11	NS	1.01	0.72	1.43	NS	1.00	0.88	1.14	NS
1520	167675987	rs749235	1.14	0.63	2.05	NS	1.13	0.66	1.95	NS	0.91	0.64	1.30	NS	1.06	0.81	1.38	NS	1.22	0.79	1.88	NS	1.06	0.90	1.25	NS
1521	167661613	rs7700355	2.66	1.28	5.56	0.009	1.45	0.78	2.72	0.24	0.68	0.43	1.07	0.10	0.97	0.70	1.36	NS	0.93	0.56	1.55	NS	0.98	0.80	1.21	NS
1522	167721923	rs7700508	1.32	0.78	2.24	NS	1.02	0.69	1.50	NS	0.73	0.55	0.97	0.03	1.00	0.80	1.24	NS	1.01	0.72	1.41	NS	0.95	0.84	1.09	NS

YOUNG AGE GROUP

SNP	BP	rs	Afr-Amer OR	L95	U95	P	NCRAD OR	L95	U95	P	JS OR	L95	U95	P	RS OR	L95	U95	P	AUT OR	L95	U95	P	ALL-Caucasian OR	L95	U95	P
1212	167778369	rs17070145	1.20	0.66	2.18	NS	0.87	0.60	1.26	NS	1.02	0.79	1.32	NS	1.03	0.82	1.31	NS	1.21	0.91	1.62	0.19	1.06	0.93	1.20	NS
1499	167727354	rs1030182	0.94	0.53	1.66	NS	1.15	0.79	1.66	NS	1.08	0.84	1.39	NS	1.00	0.81	1.24	NS	0.96	0.72	1.28	NS	1.09	0.96	1.23	0.17
1501	167666718	rs11750709	0.94	0.52	1.71	NS	0.95	0.65	1.39	NS	1.05	0.81	1.35	NS	1.05	0.84	1.32	NS	1.05	0.78	1.42	NS	1.01	0.89	1.15	NS
1502	167665378	rs1422422	0.95	0.53	1.72	NS	0.94	0.65	1.38	NS	1.04	0.84	1.39	NS	1.04	0.83	1.30	NS	1.07	0.79	1.43	NS	1.02	0.90	1.16	NS
1504	167777769	rs1477306	1.20	0.66	2.17	NS	0.87	0.60	1.27	NS	1.08	0.84	1.39	NS	1.07	0.85	1.35	NS	1.22	0.91	1.63	0.18	1.09	0.96	1.24	0.20
1505	167696276	rs1477307	0.73	0.32	1.69	NS	0.80	0.56	1.16	0.24	1.02	0.80	1.29	NS	0.90	0.73	1.12	NS	0.99	0.75	1.30	NS	0.98	0.86	1.10	NS
1508	167673397	rs17775705	1.60	0.82	3.11	0.17	1.14	0.78	1.66	NS	1.15	0.89	1.48	NS	0.98	0.74	1.30	NS	1.07	0.95	1.22	0.25
1513	167609314	rs2337158	0.64	0.34	1.22	0.17	0.81	0.57	1.15	0.24	1.13	0.88	1.43	NS	0.98	0.78	1.25	NS	0.93	0.69	1.25	NS	0.94	0.83	1.07	NS
1514	167622795	rs3733989	0.77	0.32	1.89	NS	1.31	0.89	1.93	0.17	1.09	0.84	1.40	NS	0.98	0.78	1.25	NS	0.97	0.71	1.31	NS	1.00	0.88	1.14	NS
1515	167676785	rs4976592	0.87	0.44	1.72	NS	0.95	0.62	1.45	NS	0.93	0.71	1.21	NS	1.07	0.84	1.36	NS	0.98	0.72	1.35	NS	0.96	0.84	1.10	NS
1518	167653043	rs6555791	1.05	0.57	1.93	NS	1.01	0.70	1.45	NS	0.88	0.63	1.03	0.08	0.82	0.65	1.04	0.11	1.05	0.78	1.40	NS	0.95	0.84	1.08	NS
1519	167758744	rs6555807	0.78	0.43	1.41	NS	0.87	0.60	1.25	NS	0.85	0.67	1.09	0.21	0.98	0.79	1.22	NS	1.00	0.75	1.33	NS	0.96	0.85	1.08	NS
1520	167675987	rs749235	0.83	0.38	1.77	NS	0.89	0.60	1.33	NS	1.30	0.97	1.73	0.08	1.03	0.79	1.34	NS	1.10	0.78	1.56	NS	1.12	0.97	1.29	0.13
1521	167661613	rs7700355	0.95	0.45	2.04	NS	1.09	0.62	1.90	NS	1.29	0.91	1.83	0.15	1.07	0.79	1.47	NS	0.98	0.65	1.50	NS	1.12	0.94	1.34	0.20
1522	167721923	rs7700508	1.20	0.61	2.36	NS	0.76	0.54	1.06	0.10	1.09	0.85	1.39	NS	1.09	0.88	1.36	NS	0.91	0.70	1.19	NS	1.03	0.91	1.16	NS

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

OLD AGE GROUP

SNP	BP	rs	MRMLD AA_OLD BETA	L95	U95	P	JS_OLD BETA	L95	U95	P	RS_OLD BETA	L95	U95	P	AVLT AA_OLD BETA	L95	U95	P	JS_OLD BETA	L95	U95	P	RS_OLD BETA	L95	U95	P
1212	167778369	rs17070145	-1.10	-1.11	3.31	NS	-0.50	-2.60	1.60	NS	-0.39	-1.26	0.48	NS	0.02	-0.96	0.93	NS	0.12	-0.72	0.95	NS	-0.22	-0.57	0.12	0.20
1499	167727354	rs1030182	1.81	-2.27	2.13	NS	1.53	-3.86	0.81	0.20	-0.04	-0.88	0.79	NS	0.35	-0.53	1.24	NS	-0.32	-1.25	0.61	NS	-0.01	-0.34	0.32	NS
1501	167666718	rs11750709	0.75	-1.29	2.78	NS	-2.68	-4.85	-0.50	0.02	0.61	-0.25	1.48	0.16	0.03	-0.83	0.89	NS	-1.42	-2.27	-0.57	0.001	-0.04	-0.32	0.36	NS
1502	167665378	rs1422422	0.75	-1.28	2.77	NS	-2.73	-4.94	-0.53	0.02	0.77	-0.10	1.65	0.08	0.03	-0.83	0.90	NS	-1.46	-2.33	-0.60	0.001	0.08	-0.26	0.43	NS
1504	167777769	rs1477306	-1.40	-0.85	3.66	0.23	-0.52	-2.62	1.59	NS	-0.37	-1.25	0.52	NS	-0.14	-1.10	0.82	NS	-0.17	-0.52	0.18	NS
1505	167696276	rs1477307	-0.87	-2.15	3.89	NS	1.88	-0.29	4.05	0.09	-0.07	-0.83	0.83	NS	0.38	-1.66	0.91	NS	1.18	0.33	2.04	0.01	0.04	-0.27	0.29	NS
1508	167673397	rs17775705	-0.99	-3.42	1.45	NS	-0.07	-2.19	4.33	0.07	0.88	0.07	1.71	NS	0.11	-0.92	1.15	NS	1.09	0.20	1.98	0.02	-0.11	0.96	0.35	NS
1513	167609314	rs2337158	2.51	-5.04	0.03	0.06	1.85	-0.23	3.92	0.08	0.25	-0.60	1.11	NS	0.48	-1.57	0.62	NS	0.14	-0.69	0.97	NS	-0.16	-0.50	0.18	NS
1514	167622795	rs3733989	2.39	-0.64	5.43	0.13	0.89	-1.42	3.21	NS	0.13	-0.60	1.00	NS	0.68	-0.60	1.97	NS	-0.02	-0.94	0.90	NS	-0.04	-0.41	0.32	NS
1515	167676785	rs4976592	-1.52	-3.70	0.65	0.17	-1.48	-3.39	-0.01	NS	0.01	-0.89	0.92	NS	-1.44	0.40	NS	-1.48	-2.39	-0.56	0.0019	0.04	-0.32	0.39	NS
1518	167653043	rs6555791	0.88	-3.03	1.67	NS	1.48	-0.70	3.66	0.19	-0.13	-1.02	0.77	NS	0.05	-1.04	0.40	NS	0.06	-1.78	0.04	NS	-0.36	-0.63	0.35	NS
1519	167758744	rs6555807	-0.78	-1.28	2.84	NS	-2.87	-4.37	-0.20	0.03	0.46	-0.38	1.29	NS	-0.16	-0.73	1.04	NS	-0.38	-1.22	0.46	NS	-0.16	-0.18	0.49	NS
1520	167675987	rs749235	1.72	-1.33	4.76	0.27	1.89	-0.71	4.49	0.16	0.48	-0.58	1.53	NS	0.15	-1.16	1.45	NS	0.54	-0.49	1.58	NS	-0.30	-0.71	0.11	0.15
1521	167661613	rs7700355	-3.15	-6.79	0.48	0.09	1.00	-2.19	4.19	NS	-0.12	-1.43	1.20	NS	0.11	-1.45	1.68	NS	1.19	-0.06	2.44	0.06	-0.28	-0.79	0.24	NS
1522	167721923	rs7700508	0.64	-2.87	1.59	NS	-2.07	-4.11	-0.02	0.06	-0.25	-1.11	0.61	NS	-0.36	-0.60	1.33	NS	-0.62	-1.43	0.20	0.14	-0.04	-0.38	0.31	NS

YOUNG AGE GROUP

SNP	BP	rs	MRMLD AA_YOUNG BETA	L95	U95	P	JS_YOUNG BETA	L95	U95	P	RS_YOUNG BETA	L95	U95	P	AVLT AA_YOUNG BETA	L95	U95	P	JS_YOUNG BETA	L95	U95	P	RS_YOUNG BETA	L95	U95	P
1212	167778369	rs17070145	0.36	-2.16	1.45	NS	-0.34	-2.66	1.98	NS	0.54	-0.72	1.81	NS	-0.43	-0.36	1.22	NS	-0.70	-1.65	0.24	0.14	-0.08	-0.37	0.53	NS
1499	167727354	rs1030182	0.48	-1.17	2.13	NS	-0.85	-3.17	1.48	NS	0.57	-0.61	1.75	NS	0.04	-0.70	0.79	NS	-0.22	-1.17	0.73	NS	0.06	-0.33	0.46	NS
1501	167666718	rs11750709	0.75	-1.37	2.87	NS	0.19	-2.27	2.64	NS	0.98	-0.30	2.27	NS	0.24	-0.79	0.79	NS	-0.32	-1.31	0.68	NS	0.02	-0.43	0.46	NS
1502	167665378	rs1422422	0.10	-1.67	1.86	NS	0.09	-2.37	2.51	NS	0.95	-0.31	2.21	0.14	-0.03	-0.80	0.75	NS	-0.33	-1.32	0.66	NS	0.02	-0.43	0.47	NS
1504	167777769	rs1477306	-1.02	-1.92	1.69	NS	-0.26	-2.60	2.08	NS	0.48	-0.77	1.73	NS	-0.50	-0.30	1.29	0.22	-0.71	-1.66	0.24	0.15	-0.16	-0.55	0.23	NS
1505	167696276	rs1477307	-1.07	-1.39	3.42	NS	0.25	-2.13	2.63	NS	0.46	-0.72	1.63	NS	-0.00	-0.80	0.80	NS	-0.24	-1.20	0.72	NS	-0.09	-0.51	0.33	NS
1508	167673397	rs17775705	-0.42	-2.34	1.51	NS	-0.40	-3.01	2.21	NS	-0.64	-1.94	0.59	NS	-0.37	-0.33	1.08	NS	0.25	-0.68	1.18	NS	-0.11	-0.53	0.30	NS
1513	167609314	rs2337158	-0.55	-1.38	2.49	NS	-0.30	-2.21	1.61	NS	-0.18	-1.94	0.58	NS	0.53	-0.42	0.85	NS	0.25	-0.68	1.18	NS	0.17	-0.24	0.59	NS
1514	167622795	rs3733989	-0.55	-3.25	2.15	NS	-0.29	-2.66	2.09	NS	-0.68	-1.94	0.58	NS	0.03	-0.72	0.79	NS	0.25	-0.68	1.18	NS	0.09	-0.53	0.36	NS
1515	167676785	rs4976592	0.84	-1.64	3.40	NS	0.88	-1.64	3.40	NS	0.88	-0.40	2.16	0.18	0.01	-0.79	0.77	NS	0.08	-0.99	1.15	NS	-0.13	-0.51	0.45	NS
1518	167653043	rs6555791	0.22	-1.99	1.54	NS	0.22	-2.11	2.14	NS	0.88	-0.40	2.16	0.18	0.01	-0.79	0.77	NS	0.10	-1.36	0.37	NS	-0.11	-0.57	0.47	NS
1519	167758744	rs6555807	-1.51	-0.26	3.28	0.10	-2.17	-0.30	4.53	0.09	-0.72	-2.33	0.89	NS	-0.28	-0.51	1.08	NS	0.17	-0.71	1.06	NS	0.03	-0.35	0.42	NS
1520	167675987	rs749235	0.23	-2.04	2.50	NS	-1.48	-4.37	-0.20	NS	-0.72	-2.33	0.89	NS	-0.04	-1.16	1.08	NS	-0.01	-0.64	0.88	NS	-0.02	-0.51	0.39	NS
1521	167661613	rs7700355	0.04	-3.92	1.35	NS	-1.65	-4.70	1.40	NS	-0.44	-2.53	1.64	NS	0.07	-1.03	1.18	NS	0.03	-0.58	0.57	NS	-0.09	-0.59	0.35	NS
1522	167721923	rs7700508	-1.92	-0.20	4.05	0.08	-0.49	-2.92	1.93	NS	-1.05	-1.34	NS	-0.53	-1.36	0.59	NS	-0.38	-1.35	0.59	NS	-0.04	-0.45	0.37	NS

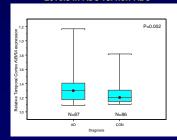### Figure 2A. Temporal Cortex *KIBRA* mRNA Levels in ADs vs. non-ADs
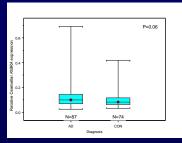

Figure 2B. Cerebellar *KIBRA* mRNA Levels in ADs vs. non-ADs

Figure 3. 15 *KIBRA* and flanking SNPs