

Association of Candidate Gene Susceptibility Alleles on Chromosome 10 with AD Risk and Endophenotypes



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Background: Alpha-T catenin (VR22) is an excellent functional and positional candidate LOAD gene. We previously found two VR22 SNPs which showed significant association with plasma A β levels and accounted for our chromosome 10 linkage signal in LOAD families. Leucine-rich repeat transmembrane protein 3 (LRRTM3) resides within intron 7 of VR22. **Methods:** To identify AD susceptibility alleles within LRRTM3 and VR22, we genotyped SNPs within these genes in 3 independent case-control series collected at Mayo Clinic Rochester (RS), Jacksonville (JS) and an autopsy series (AUT). We tested for association with LOAD and Braak neurofibrillary tangle (NFT) staging. We assessed 26 SNPs in VR22 and 71 SNPs in LRRTM3 using single SNP, haplotype and multilocus genotype (MLG) approaches. **Results:** We identified 6 MLG groups within VR22 and 7 within LRRTM3 with significant and replicable AD risk association. Analysis of combined risky VR22 and LRRTM3 MLGs yielded AD association with greater odds ratios (ORs) and stronger p values across all series, compared to only risky LRRTM3 MLGs or only risky VR22 MLGs alone. Combined risky VR22 and LRRTM3 MLGs also associate significantly with Braak neurofibrillary tangle (NFT) staging in AD brains.

A. NO SIGNIFICANT SINGLE SNP-AD ASSOCIATIONS FOR LRRTM3 OR VR22

71 LRRTM3 and 26 VR22 SNPs were analyzed. Conserved and/or HapMap tagging SNPs were chosen. All SNPs were in HWE and had minor allele frequencies (MAF)>0.01.

B. HAPLOTYPIC AND GLOBAL MLG-AD ASSOCIATIONS FOR LRRTM3 AND VR22

LRRTM3 SNPs

- 71 SNPs:
 - 3 SNPs with allelic association $p < 0.05$
 - 16 SNPs with allelic association $p < 0.25$
- Haplotypic association:
 - 5 haplotype blocks identified
 - Not significant for any of the blocks.
- MLG association:
 - Significant for LRRTM3 Block 1 MLGs only
 - Global $p = 0.015$ (all series)

VR22 SNPs

- 26 SNPs:
 - 1 SNP $p < 0.05$
 - Block 1 with 4 SNPs $p < 0.25$
- Haplotypic association:
 - 3 haplotype blocks identified
 - Not significant for VR22 Blocks 1-3
 - Block 1 global $p = 0.13$ (4-SNP haplotype)
- MLG association:
 - Significant for VR22 4-SNP Block 1 MLGs only
 - Global $p = 0.034$ (all series)

LRRTM3 MLG MODEL
BASED ON RS BLOCK 1 MLGs

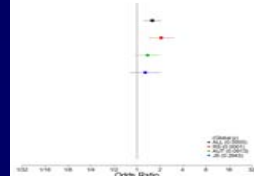
VR22 MLG MODEL
BASED ON RS BLOCK 1 4-SNP MLGs

D. BOTH LRRTM3 AND VR22 MLGS ASSOCIATE WITH AD

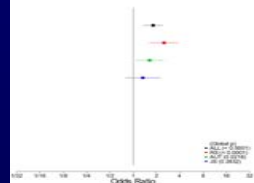
LRRTM3 Block 1 MLGs Show Replicable Association with LOAD

		Risky vs. All Others				Risky vs. Protective			
		P	OR	Low	Up	P	OR	Low	Up
ALL	0.0005	1.58	1.22	2.04	< 0.0001	1.80	1.35	2.40	
RS	0.0001	2.06	1.43	2.98	< 0.0001	2.48	1.62	3.79	
AUT	0.09	1.37	0.95	1.98	0.02	1.62	1.07	2.43	
JS	0.29	1.28	0.81	2.02	0.28	1.33	0.79	2.22	

LRRTM3 Block 1 Risky vs All MLGs



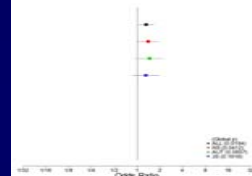
LRRTM3 Block 1 Risky vs Protective MLGs



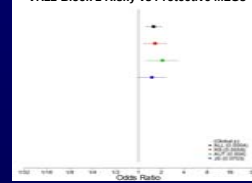
VR22 Block 1 MLGs Show Replicable Association with LOAD

		Risky vs. All Others				Risky vs. Protective			
		P	OR	Low	Up	P	OR	Low	Up
ALL	0.019	1.31	1.05	1.65	0.0004	1.58	1.23	2.03	
RS	0.04	1.40	1.01	1.93	0.0058	1.65	1.16	2.35	
AUT	0.09	1.46	0.95	2.25	0.004	2.05	1.26	3.35	
JS	0.19	1.30	0.88	1.93	0.07	1.49	0.97	2.29	

VR22 Block 1 Risky vs All Other MLGs



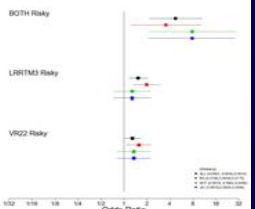
VR22 Block 1 Risky vs Protective MLGs



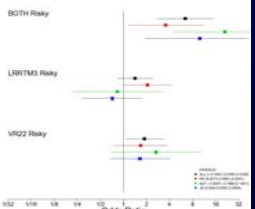
E. COMBINED LRRTM3-VR22 MLGS ASSOCIATE REPLICABLY WITH AD

		Risky vs. All Others				Risky vs Protective			
		P	OR	Low	Up	P	OR	Low	Up
BOTH									
ALL	0.0001	4.71	2.13	10.42	0.0001	6.36	2.74	14.78	
RS	0.02	3.52	1.23	10.08	0.03	3.53	1.15	10.85	
AUT	0.002	7.76	2.13	28.18	0.0001	20.87	4.50	96.73	
JS	0.01	6.91	1.47	32.45	0.006	9.83	1.92	50.25	
Only LRRTM3									
ALL	0.004	1.52	1.14	2.03	0.21	1.41	0.83	2.40	
RS	0.001	1.98	1.32	2.95	0.06	2.04	0.98	4.26	
AUT	0.39	1.28	0.73	2.23	0.79	0.83	0.21	3.24	
JS	0.85	1.05	0.64	1.73	0.46	0.71	0.29	1.75	
Only VR22									
ALL	0.06	1.28	0.99	1.66	0.03	1.86	1.07	3.26	
RS	0.02	1.56	1.08	2.25	0.22	1.66	0.74	3.75	
AUT	0.24	1.34	0.82	2.18	0.16	2.64	0.68	10.21	
JS	0.76	1.07	0.69	1.65	0.28	1.63	0.67	3.97	

LRRTM3-VR22 Risky vs All MLGs



LRRTM3-VR22 Risky vs Protective MLGs



C. MULTILOCUS GENOTYPE - AD ASSOCIATIONS FOR LRRTM3 AND VR22

LRRTM3 Block 1 Putative-Risky and Protective MLGs in the Model-Building RS Series

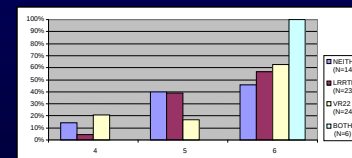
MLG	OR	Lower	Upper	AD	CON	p-value
MLG11002011120	5.65E-07	0	0	13	0.97	
MLG11101111001	0.549	0.056	5.427	1	5	0.608
MLG00010100001	0.658	0.132	3.295	2	8	0.611
MLG10102001220	0.765	0.306	1.913	7	21	0.567
MLG1110011001	0.787	0.5	1.239	29	92	0.301
MLG0000200220	0.791	0.566	1.107	58	172	0.171
MLG0002000002	0.811	0.172	3.818	2	10	0.791
MLG11101011110	0.879	0.674	1.145	110	288	0.34
MLG22201022000	0.908	0.509	1.62	19	47	0.744
MLG00010100011	1.024	0.3	3.49	4	10	0.97
MLG00010100011	1.06	0.658	1.707	29	66	0.811
MLG22200202000	1.118	0.814	1.537	71	162	0.491
MLG11100110000	1.14	0.509	2.557	10	20	0.75
MLG11102011110	1.15	0.59	2.242	15	30	0.682
MLG0000100110	1.251	0.562	2.785	11	19	0.583
MLG0000100111	1.286	0.651	2.543	14	29	0.469
MLG1110011001	1.414	0.809	2.471	23	42	0.224
MLG22200011110	1.584	0.265	9.465	2	4	0.614
MLG00101000110	1.722	0.441	6.726	4	6	0.435
MLG21201012110	2.119	0.832	5.397	10	10	0.116
MLG11100110000	2.201	0.944	5.132	11	14	0.068
MLG22101022010	2.702	0.863	8.462	6	7	0.088
MLG00010100002	6.014	1.695	21.347	8	4	0.006

VR22 Block 1 Putative-Risky and Protective MLGs in the Model-Building RS Series

MLG	OR	Lower	Upper	AD	CON	p-value
MLG2001	0.342	0.072	1.616	2	15	0.176
MLG1002	0.684	0.144	3.245	2	9	0.633
MLG1000	0.782	0.599	1.021	103	289	0.071
MLG0111	0.793	0.561	1.122	56	151	0.19
MLG0222	0.85	0.293	2.466	5	15	0.765
MLG1001	0.966	0.674	1.385	52	127	0.85
MLG2000	1.012	0.667	1.535	37	95	0.954
MLG0110	1.047	0.604	1.817	21	51	0.87
MLG0001	1.065	0.783	1.449	76	171	0.689
MLG1111	1.154	0.761	1.75	40	81	0.5
MLG0000	1.161	0.872	1.546	96	190	0.306
MLG0002	1.208	0.653	2.236	18	35	0.547
MLG1110	1.283	0.686	2.397	17	34	0.435
MLG0112	1.297	0.771	2.184	25	51	0.327
MLG.rare	1.395	0.206	9.434	2	3	0.733
MLG0221	1.792	0.741	4.332	10	13	0.195
MLG1112	4.815	0.737	31.456	3	2	0.101

F. COMBINED LRRTM3-VR22 MLGS ASSOCIATE WITH BRAAK NFT STAGE

Variable	Regression Coefficient	P-value
Sex	-0.17	0.091
ApoE4	0.01	0.923
DxAge	-0.02	0.045
BOTH-RISKY	0.71	0.015
ONLY-LRRTM3-RISKY	0.19	0.215
ONLY-VR22-RISKY	0.07	0.656



G. CONCLUSIONS

Both LRRTM3 and VR22 genes have variants that associate replicably with AD. Combined risky LRRTM3 and VR22 variants associate with AD and Braak NFT stage. These results strongly suggest that LRRTM3 and VR22 may have multiple AD susceptibility variants that influence disease pathology. Additional replication of these findings will be necessary for further confirmation. (*Equal contribution)