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Association of late-onset Alzheimer's disease with genetic variation in multiple members of the GAPD gene family

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Association of Late-onset Alzheimer's Disease with Genetic Variation in Multiple Members of the GAPD Gene Family

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Abstract

Background: While several genes have been implicated in the development of the early-onset autosomal dominant form of Alzheimer's disease (AD), the genetics of the late onset form of the disease is complex. Multiple loci on various chromosomes are known to be associated with the disease, but so far only APOE has been consistently shown to be a risk factor accounting for <50% of the Alzheimer's cases.

Objective: To identify risk factors for late onset Alzheimer's disease (LOAD).

Methods: We performed a comprehensive, large-scale single nucleotide polymorphism (SNP) based association study on chromosome 12p, a region that had shown linkage with LOAD. Three case-control sample collections totaling 1,089 LOAD patients and 1,196 control subjects were used.

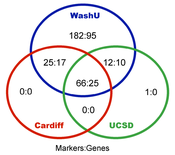
Results: The study led us to identify one SNP in GAPD that was significantly associated with LOAD in one sample set (p<0.005) and was replicated in another case-control sample set (p<0.03). We next tested markers in 5 genes that are homologous to GAPD and located within other reported linkage regions. This led to the identification of one other gene with significant association to LOAD (p<0.002, Cochran-Mantel-Haenszel test of all 3 samples combined) on chromosome 19. This marker appeared to be strongly correlated with age of disease onset before 75 years (p<0.00005, all 3 samples combined). When we determined if other markers showed strong association with age of disease onset we identified another marker on chromosome 12q that was correlated to later age of onset (≥ 75 years, p<0.05, all 3 samples combined). A significant trend between risk of LOAD and a multi-locus genotype among the three genes was observed in all individual sample sets at p<0.05 and the combined sample set at p<0.001 (Cochran-Armitage test of trend).

Conclusions: These observations appear to suggest that variants in functionally similar genes may account for a potential series-to-series heterogeneity of disease risk and raise the possibility that the genes in this family are AD risk factors, which is consistent with the known role for GAPD in neuronal apoptosis and neurodegenerative disease.

Case-control Series Characteristics

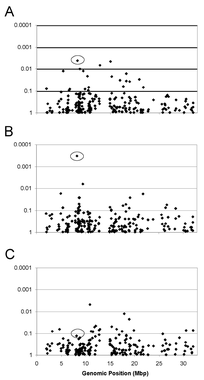
		WashU		Cardiff		UCSD		Linkage
		case	control	case	control	case	control	cases
Total Subjects	N = 2285	419	377	392	407	278	412	461
Gender	female	265	237	301	303	126	262	336
	male	154	140	91	104	152	150	125
Age (years)	Mean	81.6	77.5	81.7	76.5	79.4	78.4	81.7
	Std.Dev	6.6	7.5	6.6	6.3	6.4	7.7	7.1
	Min - Max	66-101	65-104	63-97	61-95	64-102	61-104	63-103
	Range	35	39	34	34	38	43	40
Age of Onset (years)	Mean	76.2	na	75.7	na	72.2	na	73.3
	Std.Dev	6.8	na	7.0	na	6.2	na	6.3
	Min-Max	65-98	na	60-92	na	60-89	na	60-93
	Range	33.0	na	32.0	na	29.0	na	33.0
MMSE	Mean	18.8	28.7	10.9	29.0	12.5	29.3	12.4
	Std.Dev	7.5	1.4	8.5	0.8	9.6	1.3	8.4
	Min-Max	0-30	21-30	0-29	28-30	0-30	24-30	0-30
	Range	30.0	9.0	29.0	2.0	30.0	6.0	30.0
# Yrs Education	Mean	12.8	14.2	10.2	11.2	na	na	11.4
	Std.Dev	3.6	3.4	2.5	2.9	na	na	3.3
	Min-Max	3-21	6-25	0-23	6-28	na	na	3-21
	Range	18.0	19.0	23.0	22.0	na	na	18.0
ApoE Allele Frequency	e2	0.03	0.08	0.05	0.09	0.03	0.08	0.02
	e3	0.62	0.79	0.57	0.76	0.57	0.78	0.54
	e4	0.33	0.12	0.36	0.13	0.38	0.13	0.44
	Missing	0.01	0.02	0.02	0.02	0.01	0.01	0.00

Overview of Genotyped Markers and Corresponding Number of Genes



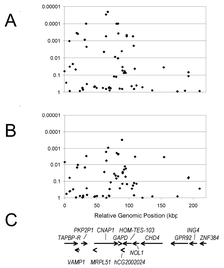
SNP CLASS	COUNT
Missense Mutation	121
Nonsense Mutation	6
Acceptor splice site	1
Donor splice site	1
Human-Mouse Syntenic region	25
Transcription Factor Binding Site	31
UTR3	13
UTR5	3
Silent Mutation	5
Intron	77
Intergenic/Unknown	7
Total	290

Chromosome 12p Mapping Markers



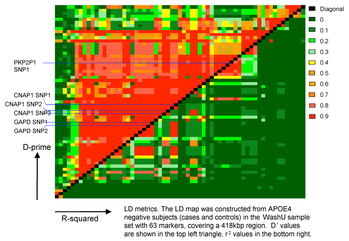
Allelic p-values are plotted for a 30-Mbp region of chromosome 12p. p-values were for genotyping results of all exploratory markers tested in the WashU case-control set. (A) ALL stratum: analysis of all case and control samples in the set. (B) The APOE4 absent stratum includes samples without an APOE4 allele. (C) The APOE4 present stratum includes samples that have one or two APOE4 alleles. SNP1 in GAPD is highlighted with a circle.

Fine Mapping Markers Near GAPD



Allelic p-values are presented for the All stratum (A) and the APOE4 absent stratum (B) of the WashU sample set, along with a gene map of the region based on Celera's R27 human genome assembly (C).

LD Metrics



LD metrics. The LD map was constructed from APOE4 negative subjects (cases and controls) in the WashU sample set with 63 markers, covering a 418kbp region. D' values are shown in the top left triangle, r^2 values in the bottom right.

Replicated Marker Statistics

Strata Gene SNP ID Type/Pos	Sample	Cs allele freq	Co allele freq	P-value	OR (95%CI)	Power
All	WashU	29.4	23.1	0.0041	1.38 (1.11:1.74)	n/c
GAPD	UCSD	27.5	22.9	0.027	1.27 (1.00:1.64)	0.74
SNP1	UK	28.1	30.9	0.89	0.87 (0.70:1.09)	0.81
	W/UC/UK	28.5	25.6	0.047	1.14 (1.00:1.30)	1.00
	Linkage	28.0	23.0	0.006	1.31 (1.06:1.61)	n/c
SNP2	WashU	20.6	16.3	0.033	1.33 (1.02:1.74)	n/c
	UCSD	21.6	17.6	0.036	1.28 (0.98:1.69)	0.51
	UK	19.5	19.7	0.53	0.99 (0.77:1.27)	0.59
	W/UC/UK	20.5	17.9	0.030	1.18 (1.02:1.37)	0.96
	Linkage	19.0	16.6	0.027	1.24 (1.00:1.55)	n/c
ApoE4-	WashU	27.7	37.5	0.0030	0.63 (0.47:0.86)	n/c
PKP2P1	UCSD	33.5	33.5	0.51	1.00 (0.70:1.43)	0.69
SNP1	UK	27.0	33.5	0.024	0.73 (0.54:1.00)	0.84
	W/UC/UK	28.8	34.8	0.0025	0.75 (0.63:0.91)	1.00
	Linkage	31.0	35.4	0.092	1.22 (0.91:1.65)	n/c
CNAP1	WashU	19.6	14.2	0.036	1.47 (1.02:2.12)	n/c
SNP1	UCSD	21.5	15.7	0.029	1.47 (0.99:2.20)	0.43
	UK	18.1	18.9	0.61	0.95 (0.66:1.36)	0.53
	W/UC/UK	19.5	16.3	0.040	1.25 (1.01:1.55)	0.93
SNP2	WashU	24.5	34.6	0.002	0.61 (0.45:0.84)	n/c
	UCSD	29.0	31.7	0.24	0.87 (0.62:1.25)	0.77
	UK	23.3	29.0	0.034	0.74 (0.54:1.02)	0.88
	W/UC/UK	25.2	31.7	0.0008	0.72 (0.60:0.88)	1.00
	Linkage	28.4	33.1	0.074	1.24 (0.92:1.69)	n/c
SNP3	WashU	24.7	34.6	0.0023	0.62 (0.46:0.84)	n/c
	UCSD	28.8	31.8	0.21	0.86 (0.61:1.23)	0.75
	UK	23.5	29.0	0.039	0.75 (0.54:1.03)	0.86
	W/UC/UK	25.2	31.7	0.0009	0.72 (0.60:0.88)	1.00
GAPD	WashU	31.9	21.4	0.0003	1.72 (1.28:2.33)	n/c
SNP1	UCSD	28.4	22.0	0.030	1.41 (0.98:2.02)	0.84
	UK	28.0	30.6	0.79	0.88 (0.65:1.20)	0.92
	W/UC/UK	29.7	24.7	0.0084	1.27 (1.06:1.53)	1.00
	Linkage	27.7	21.7	0.042	1.38 (0.96:1.99)	n/c
SNP2	WashU	20.6	14.8	0.028	1.49 (1.04:2.14)	n/c
	UCSD	22.5	16.8	0.036	1.43 (0.97:2.13)	0.46
	UK	17.3	19.1	0.75	0.88 (0.62:1.27)	0.58
	W/UC/UK	19.9	17.0	0.065	1.22 (0.99:1.51)	0.95
	Linkage	15.9	15.6	0.19	1.18 (0.81:1.72)	n/c

Association of GAPD Paralogs

Strata Gene SNP ID Type	Sample	Cs allele freq	Co allele freq	P-value	OR (95%CI)	Power to Replicate
ALL	UK	34.8	42.1	0.0031	0.73 (0.60:0.90)	n/c
Homolog 1	WashU	37.3	42.3	0.027	0.81 (0.66:1.00)	0.82
SNP1	UCSD	39.4	40.6	0.34	0.95 (0.75:1.20)	0.73
	W/UC/UK	36.9	41.7	0.0016	0.81 (0.72:0.93)	1.00
SNP2	UK	34.8	41.9	0.0039	0.74 (0.60:0.91)	n/c
	WashU	36.9	42.4	0.016	0.79 (0.64:0.98)	0.80
	UCSD	39.0	40.3	0.33	0.95 (0.75:1.20)	0.70
	W/UC/UK	36.6	41.5	0.0011	0.81 (0.72:0.92)	1.00
LT75	UK	28.3	44.4	0.00002	0.49 (0.35:0.69)	n/c
Homolog 1	WashU	34.3	40.7	0.048	0.76 (0.55:1.05)	0.99
SNP1	UCSD	36.7	39.5	0.25	0.88 (0.63:1.26)	0.98
	W/UC/UK	33.1	41.7	0.00012	0.68 (0.57:0.83)	1.00
SNP2	UK	27.8	44.4	0.00001	0.48 (0.35:0.67)	n/c
	WashU	33.9	41.3	0.027	0.72 (0.53:1.01)	0.99
	UCSD	36.1	39.8	0.19	0.85 (0.60:1.21)	0.98
	W/UC/UK	32.6	42.0	0.00003	0.66 (0.55:0.80)	1.00
GE75	WashU	31.4	38.2	0.039	0.74 (0.56:0.99)	n/c
Homolog 2	UCSD	34.9	33.1	0.66	1.08 (0.74:1.59)	0.33
SNP1	UK	28.8	34.9	0.024	0.75 (0.57:1.00)	0.59
	W/UC/UK	30.8	35.2	0.018	0.80 (0.68:0.97)	0.93

LT75: Age of onset < 75 years
GE75: Age of onset ≥ 75 years

Multilocus Genotype Analysis

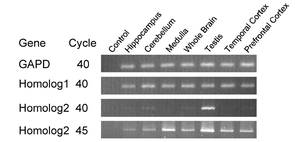
Sample	Multi-locus Genotype*	Case	Control	OR	95% CI	Test of Proportions P-value
W/UC/UK	CG-CC-GG	78	54	1.40	1.11: 1.76	0.047**
	CG-CG-GG	93	90	1	n/c	
	CG-GG-GG	17	38	0.43	0.31: 0.6	
UCSD	CG-CC-GG	17	16	1.24	0.77: 1.99	0.047
	CG-CG-GG	18	21	1	n/c	
	CG-GG-GG	2	10	0.23	0.1: 0.54	
UK	CG-CC-GG	33	25	1.41	1.01: 1.98	0.025
	CG-CG-GG	44	47	1	n/c	
	CG-GG-GG	7	16	0.47	0.28: 0.77	
WashU	CG-CC-GG	28	13	1.53	0.99: 2.36	0.045
	CG-CG-GG	31	22	1	n/c	
	CG-GG-GG	8	12	0.47	0.28: 0.81	

Each individual sample set p-value was calculated with a two-tailed test of proportions.

** W/UC/UK sample p-value was derived with Fisher's combined p-value from a two-tailed test for the UCSD sample and one-tailed tests for the other two samples. Dunn-Sidak correction for 27 tests was applied (uncorrected: p=0.0018).

* The multi locus genotype represents GAPD-homolog1-homolog2. The odds ratio was calculated relative to the most common genotype.

Expression Analysis of GAPD Genes



RT-PCR results. Cycle indicates the number of amplification cycles in the PCR reaction.

Acknowledgments

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