Online-only Supplement

Association of Parkinson Disease Risk Loci with Mild Parkinsonian Signs in Older Persons

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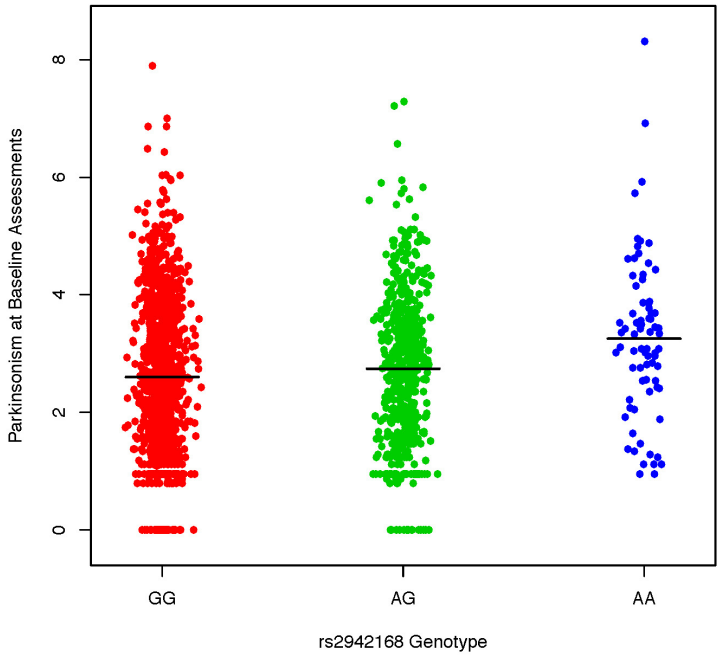
eTable 1 PD SNPs evaluated in this study.

LOCUS	SNP	A1	A2	FREQ	REFS
PARK16	rs11240572	C*	A	0.97	1,2
STK39	rs2102808	G	T*	0.87	1,3
ACMSD-TMEM163	rs6710823	G	A*	0.88	1,3
MCCC1	rs11711441	G*	A	0.85	1,3
NMD3	rs34016896	C	T*	0.69	4
SNCA	rs356220	C	T*	0.54	1,5
GAK	rs1564282	C	T*	0.89	1,6
BST1	rs4698412	A*	G	0.56	1,7
FAM47E-STBD1	rs6812193	C*	T	0.63	1,4
HLA-DRB5	rs3129882	A	G*	0.56	1,8
GPNMB	rs156429	T*	C	0.60	1,4
FGF20	rs591323	G*	A	0.73	1,4
CCDC62-HIP1R	rs12817488	G	A*	0.62	1,3
LRRK2	rs1491942	C	G*	0.81	1,3
SETD1A-STX1B	rs4889603	A	G*	0.60	1,4
MAPT	rs2942168	A	G*	0.20	1,3
SREBF1-RAI1	rs11868035	G*	A	0.71	5
RIT2-SYT4	rs12456492	G*	A	0.71	7

SNP, single nucleotide polymorphism; A1, reference allele used for analyses in this study; A2, alternative allele; FREQ, estimated allele frequency of A1 from dosage data. REFS, References. Under the A1/A2 columns, the asterisk denotes the published risk allele for PD.

1. Lill CM, Roehr JT, Mcqueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. PLoS Genet. 2012 Mar;8(3):e1002548.
2. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009 Dec;41(12):1308–12.
3. International Parkinson Disease Genomics Consortium, Nalls MA, Plagnol V, et al. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011 Feb 19;377(9766):641–9.
4. International Parkinson's Disease Genomics Consortium IPDGC, Wellcome Trust Case Control Consortium 2 WTCCC2. A two-stage meta-analysis identifies several new loci for Parkinson's disease. PLoS Genet. 2011 Jun;7(6):e1002142.
5. Do CB, Tung JY, Dorfman E, et al. Web-Based Genome-Wide Association Study Identifies Two Novel Loci and a Substantial Genetic Component for Parkinson's Disease. PLoS Genet. 2011 Jun 23;7(6):e1002141.
6. Pankratz N, Wilk JB, Latourelle JC, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet. 2009 Jan;124(6):593–605.
7. Pankratz N, Beecham GW, DeStefano AL, et al. Meta-analysis of Parkinson's Disease: Identification of a novel locus, RIT2. Ann Neurol. 2012 Mar;71(3):370–84.
8. Hamza TH, Zabetian CP, Tenesa A, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet. 2010 Aug 15.

eFigure 1: MAPT association with global parkinsonism.



rs2942168_A	N	mean global parkinsonism (SD)
0	1077	2.60 (1.30)
1	526	2.74 (1.27)
2	75	3.25 (1.36)

eTable 2: Associations with baseline global parkinsonism, removing PD cases.

LOCUS	SNP	MODEL
PARK16	rs11240572	-0.094 (0.150, 0.529)
STK39	rs2102808	-0.013 (0.060, 0.832)
ACMSD	rs6710823	0.236 (0.208, 0.256)
MCCC1	rs11711441	0.003 (0.057, 0.959)
NMD3	rs34016896	0.028 (0.044, 0.528)
SNCA	rs356220	0.005 (0.046, 0.922)
GAK	rs1564282	-0.028 (0.062, 0.650)
BST1	rs4698412	0.010 (0.040, 0.809)
FAM47E	rs6812193	-0.069 (0.041, 0.091)
HLA-DRB5	rs3129882	0.033 (0.041, 0.416)
GPNMB	rs156429	0.031 (0.041, 0.457)
FGF20	rs591323	-0.002 (0.046, 0.970)
CCDC62	rs12817488	**0.300 (0.104, 0.004)**
LRRK2	rs1491942	-0.007 (0.050, 0.892)
SETD1A	rs4889603	0.000 (0.040, 0.997)
MAPT	rs2942168	**0.174 (0.049, 0.0004)**
SREBF1	rs11868035	-0.043 (0.048, 0.374)
RIT2	rs12456492	0.009 (0.043, 0.824)

Based on linear regression models examining the level of global parkinsonism to PD SNP genotypes. Estimates (SE, p-value) are based on the effect of increasing dosage of the SNP reference allele, after adjustment for age and gender. Subjects with diagnosis of PD (n=46), either at baseline or subsequent evaluations were excluded.

eTable 3: Associations with Parkinsonian Features.

LOCUS	SNP	Bradykinesia	Gait	Rigidity	Tremor
PARK16	rs11240572	-0.082 (0.256, 0.749)	-0.194 (0.235, 0.410)	-0.061 (0.296, 0.838)	0.391 (0.282, 0.166)
STK39	rs2102808	-0.003 (0.101, 0.974)	-0.044 (0.093, 0.634)	0.113 (0.122, 0.358)	0.004 (0.111, 0.968)
ACMSD	rs6710823	0.164 (0.352, 0.641)	0.219 (0.324, 0.499)	0.155 (0.415, 0.709)	0.716 (0.387, 0.064)
MCCC1	rs11711441	0.060 (0.096, 0.532)	-0.010 (0.088, 0.914)	0.082 (0.115, 0.476)	0.061 (0.105, 0.558)
NMD3	rs34016896	0.040 (0.074, 0.586)	0.064 (0.068, 0.350)	0.027 (0.088, 0.758)	0.098 (0.081, 0.227)
SNCA	rs356220	0.053 (0.078, 0.503)	0.025 (0.072, 0.728)	**-0.187 (0.092, 0.043)**	-0.126 (0.085, 0.141)
GAK	rs1564282	0.022 (0.106, 0.835)	-0.099 (0.097, 0.308)	-0.160 (0.122, 0.189)	**0.264 (0.119, 0.027)**
BST1	rs4698412	-0.030 (0.068, 0.662)	0.061 (0.063, 0.333)	-0.006 (0.080, 0.943)	0.030 (0.074, 0.688)
FAM47E	rs6812193	-0.121 (0.069, 0.080)	-0.083 (0.063, 0.189)	-0.120 (0.081, 0.139)	0.063 (0.075, 0.404)
HLA-DRB5	rs3129882	0.016 (0.069, 0.815)	0.015 (0.063, 0.817)	0.016 (0.081, 0.842)	0.107 (0.075, 0.153)
GPNMB	rs156429	0.013 (0.070, 0.848)	0.101 (0.064, 0.117)	0.019 (0.082, 0.819)	-0.079 (0.076, 0.299)
FGF20	rs591323	0.012 (0.077, 0.880)	-0.014 (0.071, 0.840)	0.000 (0.091, 0.999)	0.045 (0.084, 0.592)
CCDC62	rs12817488	**0.518 (0.176, 0.003)**	**0.332 (0.162, 0.040)**	-0.141 (0.208, 0.499)	0.254 (0.192, 0.186)
LRRK2	rs1491942	0.073 (0.085, 0.391)	-0.098 (0.078, 0.208)	0.067 (0.101, 0.508)	-0.138 (0.092, 0.133)
SETD1A	rs4889603	-0.018 (0.068, 0.793)	-0.015 (0.063, 0.808)	0.092 (0.081, 0.257)	0.018 (0.074, 0.811)
MAPT	rs2942168	**0.312 (0.082, 0.0002)**	**0.156 (0.076, 0.041)**	0.130 (0.096, 0.175)	0.136 (0.089, 0.127)
SREBF1	rs11868035	0.069 (0.081, 0.398)	**-0.210 (0.075, 0.005)**	-0.108 (0.095, 0.258)	-0.136 (0.088, 0.124)
RIT2	rs12456492	0.013 (0.072, 0.855)	-0.005 (0.066, 0.941)	-0.081 (0.086, 0.349)	0.023 (0.079, 0.770)

Based on linear (bradykinesia, gait) or logistic (rigidity, tremor) regression models examining the level of parkinsonian features to PD SNP genotypes. Estimates (SE, p-value) are based on the effect of increasing dosage of the SNP reference allele, after adjustment for age and gender.

eTable 4: Associations with other motor traits.

LOCUS	Purdue Pegboard	Finger Taps	Gait (Speed)	Gait (Steps)	Turn (Speed)	Turn (Steps)
PARK16	0.013 (0.026, 0.617)	-0.006 (0.022, 0.788)	0.094 (0.040, 0.018)	0.074 (0.026, 0.005)	0.079 (0.063, 0.211)	0.045 (0.042, 0.286)
STK39	-0.014 (0.010, 0.173)	-0.007 (0.009, 0.450)	-0.007 (0.016, 0.651)	-0.003 (0.010, 0.766)	-0.004 (0.024, 0.875)	-0.006 (0.016, 0.703)
ACMSD	-0.065 (0.035, 0.060)	-0.058 (0.030, 0.050)	-0.019 (0.053, 0.719)	-0.039 (0.035, 0.268)	-0.064 (0.082, 0.440)	-0.015 (0.055, 0.778)
MCCC1	0.023 (0.010, 0.018)	-0.010 (0.008, 0.217)	-0.012 (0.015, 0.425)	0.001 (0.010, 0.921)	-0.057 (0.022, 0.011)	-0.032 (0.015, 0.032)
NMD3	0.0005 (0.007, 0.945)	0.002 (0.006, 0.742)	-0.009 (0.011, 0.412)	-0.004 (0.007, 0.630)	0.008 (0.017, 0.645)	0.017 (0.011, 0.145)
SNCA	-0.002 (0.008, 0.832)	0.003 (0.007, 0.631)	0.013 (0.012, 0.283)	-0.0003 (0.008, 0.973)	0.007 (0.018, 0.698)	-0.008 (0.012, 0.501)
GAK	-0.009 (0.011, 0.388)	0.006 (0.009, 0.543)	0.006 (0.016, 0.719)	0.014 (0.011, 0.197)	0.015 (0.026, 0.562)	0.013 (0.017, 0.441)
BST1	-0.013 (0.007, 0.057)	0.003 (0.006, 0.621)	-0.012 (0.010, 0.252)	-0.0005 (0.007, 0.943)	-0.019 (0.016, 0.220)	-0.005 (0.010, 0.645)
FAM47E	-0.007 (0.007, 0.293)	-0.003 (0.006, 0.561)	0.018 (0.010, 0.079)	0.017 (0.007, 0.016)	0.002 (0.016, 0.920)	-0.004 (0.011, 0.671)
HLA-DRB5	-0.011 (0.007, 0.108)	-0.003 (0.006, 0.669)	-0.005 (0.010, 0.653)	0.0001 (0.007, 0.988)	-0.010 (0.016, 0.527)	-0.002 (0.011, 0.832)
GPNMB	-0.003 (0.007, 0.640)	0.006 (0.006, 0.283)	-0.018 (0.011, 0.080)	-0.018 (0.007, 0.008)	-0.039 (0.016, 0.016)	-0.015 (0.011, 0.175)
FGF20	-0.0003 (0.008, 0.972)	-0.003 (0.007, 0.664)	0.007 (0.012, 0.530)	0.001 (0.008, 0.926)	0.013 (0.019, 0.469)	0.004 (0.012, 0.750)
CCDC62	-0.018 (0.017, 0.309)	-0.032 (0.015, 0.036)	-0.041 (0.027, 0.120)	-0.027 (0.018, 0.130)	-0.038 (0.041, 0.354)	-0.032 (0.027, 0.248)
LRRK2	0.006 (0.008, 0.438)	-0.007 (0.007, 0.360)	0.008 (0.013, 0.513)	0.009 (0.008, 0.266)	0.027 (0.020, 0.178)	0.009 (0.013, 0.485)
SETD1A	0.0004 (0.007, 0.955)	-0.007 (0.006, 0.242)	0.002 (0.010, 0.837)	0.013 (0.007, 0.048)	0.013 (0.016, 0.419)	0.015 (0.011, 0.167)
MAPT	-0.003 (0.008, 0.755)	-0.005 (0.007, 0.452)	-0.004 (0.013, 0.762)	-0.001 (0.008, 0.877)	-0.001 (0.020, 0.953)	-0.017 (0.013, 0.178)
SREBF1	0.005 (0.008, 0.507)	-0.011 (0.007, 0.105)	0.008 (0.012, 0.516)	0.002 (0.008, 0.768)	0.015 (0.019, 0.442)	0.007 (0.013, 0.565)
RIT2	-0.007 (0.007, 0.348)	-0.006 (0.006, 0.341)	0.005 (0.011, 0.628)	0.011 (0.007, 0.130)	-0.003 (0.017, 0.857)	-0.003 (0.011, 0.760)

Based on linear regression models examining the level of motor performance tasks to PD SNP genotypes. Estimates (SE, p-value) are based on the effect of increasing dosage of the SNP reference allele, after adjustment for age and gender.

eTable 5: Associations with Nigral Pathology

LOCUS	SNP	Lewy Bodies	Nigral loss
PARK16	rs11240572	0.225 (0.510, 0.660)	0.043 (0.396, 0.913)
STK39	rs2102808	0.103 (0.195, 0.598)	0.135 (0.155, 0.383)
ACMSD	rs6710823	-0.490 (0.631, 0.438)	-0.149 (0.511, 0.771)
MCCC1	rs11711441	-0.016 (0.173, 0.926)	0.010 (0.139, 0.941)
NMD3	rs34016896	0.084 (0.140, 0.552)	0.245 (0.113, 0.031)
SNCA	rs356220	0.004 (0.148, 0.978)	-0.105 (0.118, 0.374)
GAK	rs1564282	-0.128 (0.184, 0.488)	-0.132 (0.149, 0.378)
BST1	rs4698412	0.060 (0.128, 0.641)	-0.137 (0.102, 0.179)
FAM47E	rs6812193	0.069 (0.129, 0.593)	0.191 (0.104, 0.065)
HLA-DRB5	rs3129882	0.004 (0.129, 0.978)	-0.020 (0.103, 0.848)
GPNMB	rs156429	0.086 (0.131, 0.510)	-0.057 (0.103, 0.582)
FGF20	rs591323	-0.136 (0.136, 0.320)	-0.092 (0.110, 0.401)
CCDC62	rs12817488	-0.415 (0.326, 0.204)	-0.390 (0.260, 0.134)
LRRK2	rs1491942	-0.172 (0.154, 0.266)	-0.214 (0.124, 0.085)
SETD1A	rs4889603	0.088 (0.126, 0.484)	-0.176 (0.099, 0.076)
MAPT	rs2942168	0.069 (0.148, 0.640)	-0.202 (0.123, 0.100)
SREBF1	rs11868035	-0.171 (0.149, 0.251)	-0.062 (0.120, 0.606)
RIT2	rs12456492	0.113 (0.131, 0.387)	0.047 (0.105, 0.654)

Based on logistic regression models examining the presence of Lewy bodies or severity of nigral neuronal loss to PD SNP genotypes. Estimates (SE, p-value) are based on the effect of increasing dosage of the SNP reference allele, after adjustment for age and gender.

eTable 6: Associations with Alzheimer's disease (AD) and cerebrovascular pathology.

LOCUS	AD Pathology	Gross Infarcts	Microscopic Infarcts
PARK16	0.123 (0.076, 0.108)	-0.345 (0.406, 0.396)	0.236 (0.448, 0.599)
STK39	0.015 (0.030, 0.628)	0.069 (0.162, 0.670)	0.011 (0.170, 0.949)
ACMSD	-0.021 (0.101, 0.832)	-0.148 (0.540, 0.785)	0.616 (0.582, 0.290)
MCCC1	0.027 (0.027, 0.315)	-0.022 (0.146, 0.879)	0.166 (0.159, 0.296)
NMD3	-0.019 (0.022, 0.389)	-0.050 (0.117, 0.669)	-0.097 (0.123, 0.432)
SNCA	0.004 (0.023, 0.869)	0.110 (0.125, 0.380)	-0.201 (0.131, 0.124)
GAK	-0.002 (0.030, 0.949)	-0.232 (0.157, 0.141)	-0.109 (0.166, 0.511)
BST1	0.020 (0.020, 0.320)	-0.110 (0.107, 0.306)	-0.029 (0.113, 0.800)
FAM47E	-0.001 (0.020, 0.953)	0.074 (0.108, 0.494)	0.086 (0.114, 0.452)
HLA-DRB5	-0.021 (0.020, 0.289)	-0.011 (0.108, 0.918)	0.123 (0.115, 0.285)
GPNMB	-0.011 (0.020, 0.592)	0.129 (0.110, 0.239)	0.063 (0.115, 0.588)
FGF20	0.010 (0.022, 0.659)	-0.039 (0.116, 0.739)	0.119 (0.125, 0.337)
CCDC62	0.042 (0.051, 0.412)	0.164 (0.274, 0.550)	-0.183 (0.289, 0.526)
LRRK2	-0.039 (0.025, 0.121)	0.168 (0.136, 0.214)	-0.002 (0.141, 0.990)
SETD1A	-0.002 (0.019, 0.930)	-0.084 (0.105, 0.425)	0.181 (0.112, 0.106)
MAPT	0.008 (0.024, 0.730)	0.136 (0.125, 0.276)	0.149 (0.131, 0.254)
SREBF1	-0.002 (0.024, 0.922)	-0.163 (0.126, 0.198)	-0.160 (0.133, 0.227)
RIT2	-0.031 (0.021, 0.136)	0.066 (0.111, 0.551)	-0.179 (0.120, 0.136)

Based on linear (global AD pathology) or logistic (gross or microscopic infarcts) regression models examining the relation of postmortem indices to PD SNP genotypes. Estimates (SE, p-value) are based on the effect of increasing dosage of the SNP reference allele, after adjustment for age at death and gender.