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Angiogenin variation and Parkinson's disease

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Genetic studies have highlighted an overlap in risk factors for amyotrophic lateral sclerosis (ALS) and parkinsonism.[1, 2] A recent study by van Es and colleagues has shown that variation in the ALS gene, Angiogenin (*ANG*), is more frequent in Parkinson's disease (PD) patients than controls; the study showed that *ANG* variants were present in 0.46% of ALS, 0.45% of PD and 0.04% of controls.[3, 4] In the present study we sequenced *ANG* in our PD patient-control series to assess the mutation burden in patients and risk of disease.

We employed the Mayo Clinic Florida Caucasian PD patient-control series. This series contains 630 patients with PD and 676 healthy control subjects matched by age. All patients were examined and observed longitudinally by a movement disorders neurologist and diagnosed with PD according to published criteria. Unrelated control individuals were free of personal or familial history suggestive of parkinsonism. We performed bidirectional DNA sequencing on all exons of the *ANG* gene. The ethical review boards at each institution approved the study, and all participants provided informed consent.

We identified four coding non-synonymous *ANG* variants in our patients with PD (0.63%) and zero in our controls (Table). Of the four variants, two are novel (c.70G>C; p.A-1P and c.302A>C; p.Q77P) and were not observed in the large study by van Es and colleagues. The other two known variants were p.K17I and p.K60E, after removing p.K17I from the analysis the frequency remained 0.47% which matches the findings of van Es et al. Table 1 displays variation observed in the *ANG* gene and the frequency of both common and rare variants. Statistical association for common variants was performed and a significant association with disease risk and rs11701 was observed (uncorrected P-value 0.01). Interestingly, association of SNP rs11701 with risk of ALS first nominated *ANG* as gene for ALS.[5]

The study of van Es et al. has demonstrated the important role rare variants play in the individual risk of susceptibility to PD. Further studies are warranted to characterize patients with PD who carry rare variants in *ANG* and identify if there are clinicopathologic correlates that distinguish carriers from typical late-onset sporadic PD patients. As we move towards an era of individualized medicine it will be crucial to determine the frequency of rare variants and elucidate their influence on disease risk. The feasibility of genetic testing for such rare variants will need to be addressed in the long term.

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Table 1

Angiogenin variants identified by sequencing in US case/control series

The association between common *ANG* variation and PD was evaluated using a logistic regression model adjusted for age (age at diagnosis for patients and age at blood draw for controls) and gender, where odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. We examined association under an additive model. For exploratory analysis P-values ≤ 0.05 were considered statistically significant and analyses were performed using PLINK (http://pngu.mgh.harvard.edu/purcell/plink/)

				US Controls					US Cases						
Chromosome: BP	**SNP**	**Amino Acid**	**major/minor allele**	**Major (%)**	**Het (%)**	**(%)**	**Total**	**MAF**	**Major (%)**	**Het (%)**	**Minor (%)**	**Total**	**MAF**	**OR (95% CI)**	**p value**
14:21152357	rs117466368		**G/C**	643(95.1)	33(4.9)	0(0)	676	0.024	600(95.2)	30(4.8)	0(0)	630	0.024	0.87(0.52,1.46)	0.60
14:21152402	rs117787610		**C/T**	652(96.4)	24(3.6)	0(0)	676	0.018	608(96.5)	22(3.5)	0(0)	630	0.017	0.87(0.48,1.59)	0.66
14:21152406	rs117053048		**T/C**	642(95.0)	34(5.0)	0(0)	676	0.025	600(95.2)	30(4.8)	0(0)	630	0.024	0.85(0.51,1.42)	0.53
14:21152535	rs45591635		**G/T**	644(95.3)	31(4.6)	1(0.1)	676	0.024	599(95.1)	31(4.9)	0(0)	630	0.025	0.91(0.55,1.51)	0.72
14:21152553	rs113950902		**C/G**	676(100)	0(0)	0(0)	676	0.000	629(99.8)	1(0.2)	0(0)	630	0.001	NA	NA
14:21152604	rs28589507		**C/A**	531(78.6)	128(18.9)	17(2.5)	676	0.120	497(78.9)	124(19.7)	9(1.4)	630	0.113	0.92(0.72,1.16)	0.47
14:21152699	rs45525731		**A/C**	646(95.6)	30(4.4)	0(0)	676	0.022	600(95.2)	30(4.8)	0(0)	630	0.024	0.95(0.56,1.61)	0.85
14:21152895	rs117978329		**T/C**	644(95.3)	32(4.7)	0(0)	676	0.024	600(95.2)	30(4.8)	0(0)	630	0.024	0.89(0.53,1.5)	0.66
14:21152938	IVS1+27		**C/T**	625(92.5)	51(7.5)	0(0)	676	0.038	574(91.1)	55(8.7)	1(0.2)	630	0.045	1.22(0.82,1.82)	0.33
14:21161794	c.70G>C	A-1P	**G/C**	676(100)	0(0)	0(0)	676	0.000	629(98.8)	1(0.2)	0(0)	630	0.001	NA	NA
14:21161844	rs121909536	K17I	**A/T**	676(100)	0(0)	0(0)	676	0.000	629(98.8)	1(0.2)	0(0)	630	0.001	NA	NA
14:21161973	rs17560	K60E	**A/G**	676(100)	0(0)	0(0)	676	0.000	629(98.8)	1(0.2)	0(0)	630	0.001	NA	NA
14:21162025	c.302A>C	Q77P	**A/C**	676(100)	0(0)	0(0)	676	0.000	629(98.8)	1(0.2)	0(0)	630	0.001	NA	NA
14:21162053	rs11701		**T/G**	565(83.6)	103(15.2)	8(1.2)	676	0.088	483(76.7)	136(21.6)	11(1.7)	630	0.125	1.40(1.08,1.80)	0.01
14:21162248	Exon2 + 81	3'UTR	**A/C**	676(100)	0(0)	0(0)	676	0.000	629(98.8)	1(0.2)	0(0)	630	0.001	NA	NA