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No Association of *DNM3* with age of onset in Asian Parkinson's disease

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Abstract

Background: Genetic variability in *DNM3* have been shown to modify age of onset of Parkinson's disease (PD) among *LRRK2* Gly2019Ser carriers in North African Arab-Berber populations. In Asian populations, the Gly2019Ser mutation is rare or absent but two other *LRRK2* variants Gly2385Arg and Arg1628PPro increase PD risk. We aim to determine if the *DNM3* locus is associated with age of PD onset in both carriers and non-carriers of *LRRK2* risk variants in Asians.

Methods: We analyzed the association of *DNM3* rs2421947 genotypes with age of PD onset in 3,645 Chinese samples, of which 369 carry at least one of two Asian *LRRK2* risk variants.

Results: *DNM3* rs2421947 genotypes were not associated with PD age of onset in Chinese samples. We observed no heterogeneity in the effect of rs2421947 between the Asian *LRRK2* risk variant carriers and non-carriers.

Conclusions: *DNM3* rs2421947 is not associated with age of PD onset in *LRRK2* risk variant carriers and non-carriers in Chinese. Further studies in other Asian populations will be of interest.

Introduction

A recent study by Trinh et al [1] demonstrated that genetic variability within *DNM3*, tagged by rs2421947, modifies the age of onset of PD among *LRRK2* Gly2019Ser carriers in the North African Arab-Berber population, with homozygotes for the G allele having a younger age of onset compared to heterozygotes or homozygotes for the C allele. They supported their findings using genome-wide linkage and association studies, and replicated the findings in other North African and European Gly2019Ser carriers.

The highly penetrant Gly2019Ser mutation is not found in Asian Populations; instead, two other lower-penetrance *LRRK2* risk variants, Gly2385Arg and Arg1628Pro, each present in 1-5% of East Asian populations, have been shown to increase risk of PD by up to two-fold [2]. It is unknown if *DNM3* variants are associated with age of onset in Asian PD patients, with or without *LRRK2* risk variants. Here, we examine the effect of *DNM3* rs2421947 on the age of onset in 677 Chinese PD patients and 2,968 controls from Singapore, out of which 369 carry Gly2385Arg and/or Arg1628Pro.

Results

Given that the three reported *DNM3* SNPs, rs2421947, rs742510 and rs2206543, are in high linkage disequilibrium ($r^2 = 0.87-1$) across African, European and Asian populations, we chose to focus our analysis on rs2421947 as the tag SNP for that locus. This variant showed no association with PD risk in our GWAS of 779 cases and 13,227 controls (19.3% in cases, 18.5% in controls, OR=1.05, 95% CI=0.92-1.19, P=0.49) [3].

We first tested genotypes of *DNM3* rs2421947 in the 677 Chinese PD patients for association with their documented age of onset (see Methods in Supplementary Information). 88 of the 677 patients carried at least one of the two low-penetrance *LRRK2* risk variants (34 carried

Gly2385R only, 50 carried Arg1628Pro only and 4 carried both). The age of PD onset was not significantly different between the 88 carriers and the 589 non-carriers (Table 1; t-test $P=0.64$, Mann Whitney $P=0.65$). *DNM3* rs2421947 genotypes were not significantly associated with age of onset as a quantitative trait in all PD samples, in *LRRK2* risk variant carriers or non-carriers (Table 1). We next examined 2,968 non-affected individuals with complete genotype and age information available, of which 281 carried at least one *LRRK2* risk variant (142 carried Gly2385Arg only, 136 carried Arg1628Pro only and 3 carried both). The age distribution was not significantly different between the carriers and 2,687 non-carriers (Table 1; t-test $P=0.19$, Mann Whitney $P=0.15$).

We then used Kaplan Meier analyses to compare how age of PD onset varies with rs2421947 genotypes in all 3,645 cases and controls. Given the lower frequency of the C allele in our Chinese population (19.2%) compared to that reported in Trinh et al (39-46%) [1], we compared patients who are GG homozygotes against patients who are either CC homozygotes or CG heterozygotes. We observed no significant association between rs2421947 genotypes and age of PD onset (Table 1). Similar results were obtained when we analyzed only PD cases (Table 1). The same analysis showed no association in the 369 *LRRK2* risk variant carriers and the 3,276 non-carriers (Table 1, Figure 1) and there was no heterogeneity observed between carriers and non-carriers (Table 1; $P_{het}=0.16$, $I^2=47.5\%$).

Discussion

Unlike Trinh et al [1] we did not observe a significant association between *DNM3* rs2421947 and PD onset in our Chinese samples, whether or not they carry at least one of the

two Asian *LRRK2* risk variants. *DNM3* rs2421947 genotypes were also not correlated with age of PD onset in our Chinese patients.

It is important to note that the penetrance of the Asian *LRRK2* risk variants Arg1628Pro and Gly2385Arg is very much lower, with smaller risk odds ratios (OR~1.5-2) [2] compared the Gly2019Ser variant (OR~17.6) [4]. The Asian risk variants also affect a different domain of the *LRRK2* protein. It is therefore difficult for us to compare the effects of *DNM3* variants in *LRRK2* Gly2019Ser mutation carriers with that of Gly2385Arg and Arg1628Pro risk variant carriers. Notably, a recent study by Fernández-Santiago et al also found that *DNM3* rs2421947 was not associated with PD age of onset in 329 Gly2019Ser carriers in Spain [5], suggesting further studies are needed to confirm this association outside the Arab-Berber population.

Given the relatively small number of *LRRK2* risk variant carriers, we are not able to fully assess if there are more subtle differences in the effects of rs2421947 between carriers of each variant. Another important limitation of our study is the young age of the non-affected individuals, with just 66 of the 281 *LRRK2* carriers (23.5%) at 60 years or older. A longitudinal study to follow-up on these risk variant carriers will be meaningful to dissect genetic modifiers that are associated with the penetrance and age of onset of PD.

Nonetheless, our findings suggest that the *DNM3* locus is not associated with age of onset in Chinese PD patients, whether or not they carry *LRRK2* risk variants. More comprehensive studies will be needed to identify genetic modifiers in other regions of the genome that modify the age of PD onset in Chinese and other Asian populations.

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Figure Legends

Figure 1. Kaplan Meier analysis of age of Parkinson's disease (PD) onset in a) 369 *LRRK2* risk variant carriers and b) 3,276 non-carriers in Chinese samples by *DNM3* rs2421947 genotype comparing GG homozygotes with CC homozygotes and CG heterozygotes. Hazard ratios (HR) with 95% confidence intervals and log-rank test P values are indicated on each plot.

Table 1.

Age distribution and association tests results for *DNM3* rs2421947 with age of PD onset in all Chinese samples, carriers of LRRK2 risk variants Gly2385Arg and/or Arg1628Pro and non-carriers.

Analysis	All samples 677 cases 2,968 controls	<i>LRRK2</i> carriers 88 cases 281 controls	Non-carriers 589 cases 2,687 controls
Mean (median) age in years			
Age of cases	68.1 ± 10.2 (69)	67.2 ± 9.2 (68.5)	68.2 ± 10.3 (70)
Age of onset in cases	63.7 ± 10.3 (64)	63.3 ± 8.8 (64.5)	63.8 ± 10.5 (64)
Age of controls	50.2 ± 14.2 (50)	49.1 ± 13.8 (49)	50.3 ± 14.2 (50)
Correlation with age of onset in cases			
Beta (G allele)	-0.22	-0.04	-0.27
Linear regression P	0.76	0.98	0.74
Kaplan-Meier analysis on PD onset			
Hazard ratio (95% CI)	1.03 (0.88-1.21)	0.78 (0.50-1.20)	1.08 (0.91-1.28)
Cox-Mantel Log-rank P	0.70	0.23	0.36
Kaplan-Meier analysis on age of onset (Cases only)			
Hazard ratio (95% CI)	1.01 (0.86-1.18)	0.91 (0.59-1.40)	1.02 (0.86-1.21)
Cox-Mantel Log-rank P	0.92	0.84	0.79