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An attempt to replicate interaction between coffee and *CYP1A2* gene in connection to Parkinson's disease

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Popat *et al.* [1] recently reported evidence for interaction between Cytochrome P450 1A2 (*CYP1A2*) genotype and coffee on the risk of developing Parkinson's disease (PD). This finding is particularly intriguing because caffeine consumption is inversely associated with risk of developing PD, and *CYP1A2* is involved in metabolism of caffeine. Popat *et al.* also suggested that the coffee–PD association was strongest among homozygous carriers of the slow-metabolizer *CYP1A2*_rs762551_CC genotype.

In an accompanying editorial [2] Mellick and Ross point out that caffeine-metabolism genes have not been found to associate with PD in genome-wide studies. Were the genes missed because coffee and interaction were not in the analytical model?

Considering the high potential significance of this observation, we attempted to replicate it using 1458 persons with PD and 931 controls from the NeuroGenetics Research Consortium (NGRC), all Caucasian of European Origin, with detailed life-time coffee consumption data [3] and genotyped using Illumina HumanOmni1-Quad_v1-0_B genotyping array [4]. rs2472304 was genotyped, rs762551 and rs2470890 were imputed with high accuracy (imputation-information-score>0.98) [5]. The study was approved by Institutional Review Boards.

We first tested interaction under the same model as Popat *et al.* adjusting for age and sex while stratifying coffee-consumption as ever/never (Table 1). In addition, we reanalyzed the data with coffee stratified as high/low (defined at median), which is a more sensitive measure for NGRC due to high coffee-consumption and few non-coffee-drinkers in NGRC. We also tried models where principal components and smoking were added as covariates.

As noted by Mellick and Ross [3] both population structure (genetic mixtures) and smoking could confound these results. Inclusion of principal components corrects for population structure in European-Americans due to Jewish/non-Jewish ancestry and European country-of-origin [4]. Inclusion of smoking as a covariate helps assess if results are affected by the correlation between smoking and coffee-drinking, and the inverse association of smoking with PD [3]. Unfortunately, we did not replicate the reported interactions under any of the models, nor did we find a stronger PD-coffee association among slow-metabolizers (Table 1).

Acknowledgments

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Table 1

Test results for SNPxCoffee interaction and genotype-specific PD-coffee association

	P values for CoffeexSNP interaction on PD risk						E/N Coffee-PD association by rs762551 genotype				H/L Coffee-PD association by rs762551 genotype			
	rs762551		rs2472304		rs2470890		AA		AC		AA		AC	
	E/N	H/L	E/N	H/L	E/N	H/L	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Popat et al. [1] N=1325 cases, 1735 controls Replication in NGRC N=1458 cases, 931 controls	0.05		0.07		0.04		0.61 (0.45–0.81)	0.9 (0.66–1.23)			0.33 (0.16–0.68)			
NGRC adjusted only for sex and age as Popat et al.	0.46	0.80	0.47	0.72	0.46	0.69	0.75 (0.52–1.07)	1.01 (0.70–1.46)			0.90 (0.39–2.05)	0.65 (0.50–0.85)	0.58 (0.43–0.76)	1.25 (0.65–2.40)
NGRC adjusted for sex, age, PC1, PC2 *	0.46	0.81	0.49	0.71	0.48	0.67	0.73 (0.51–1.05)	1.00 (0.69–1.45)			0.87 (0.38–2.00)	0.65 (0.50–0.85)	0.58 (0.44–0.77)	1.26 (0.65–2.42)
NGRC adjusted for sex, age, smoking	0.47	0.79	0.48	0.72	0.47	0.70	0.83 (0.58–1.21)	1.06 (0.73–1.55)			0.82 (0.36–1.90)	0.70 (0.53–0.91)	0.59 (0.44–0.78)	1.14 (0.58–2.22)
NGRC adjusted for sex, age, and PC1, PC2, smoking	0.49	0.80	0.50	0.70	0.50	0.68	0.82 (0.57–1.19)	1.06 (0.73–1.54)			0.81 (0.35–1.87)	0.70 (0.53–0.91)	0.59 (0.44–0.79)	1.15 (0.58–2.25)

Minor allele frequencies in controls were similar in Popat et al and our replication data set: 0.29 and 0.29 for rs762551, 0.36 and 0.34 for rs2472304, 0.36 and 0.34 for rs2470890. SNPxCoffee interaction P values, and odds ratios (OR) and their 95% confidence intervals (CI) for genotype-specific association of coffee with PD, are shown for each SNP as reported by Popat et al and calculated in NGRC data. Coffee consumption was dichotomized as ever/never (E/N), as in Popat et al, and also as high/low (H/L), dividing at median consumption in controls. High/low is more appropriate for NGRC because very few of our subjects never drank coffee. CC genotype, slow metabolizer, was reported by Popat et al as having strongest PD-coffee effect, that was not the case in NGRC.

* PC1 and PC2 are principal components that differentiate genetic variation according to Jewish/non-Jewish ancestry and European country of origin