Coffee, Genetic Variants, and Parkinson's Disease: Gene–Environment Interactions

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Studies of gene–environment interactions may help us to understand the disease mechanisms of common and complex diseases such as Parkinson's disease (PD). Sporadic PD, the common form of PD, is thought to be a multifactorial disorder caused by combinations of multiple genetic factors and environmental or life-style exposures. Since one of the most extensively studied life-style factors in PD is coffee/caffeine intake, here, the studies of genetic polymorphisms with life-style interactions of sporadic PD are reviewed, focusing on coffee/caffeine intake.

Introduction

INTAKE OF COFFEE, or its major bioactive compound, caffeine, has been linked with protective effects on several diseases such as Parkinson's disease (PD). PD is one of the most common forms of neurodegenerative disorder worldwide, and 1–2% of individuals aged ≥ 65 years are affected.¹ Manifestation of PD is characterized by symptoms related to motor impairment such as resting tremor, bradykinesia, rigidity, and postural instability. These clinical features of PD are known to result primarily from degeneration of dopaminergic neurons in the substantia nigra and the subsequent loss of dopamine in the striatum. Despite it being so widespread, no curative or preventative measures for PD are available today primarily because of the complex nature of PD etiology.

Until recently, PD had long been thought of as a non-genetic disorder, since the majority of PD is idiopathic. However, the development of genetic research in the recent decades has identified several causative genes and improved our understanding of the etiology of PD. Nonetheless, $< 10\%$ of individuals display a Mendelian inheritance pattern, that is, the familial form of PD,² while the sporadic form of PD is more common ($> 85\%$). Sporadic PD is thought to be a multifactorial disorder caused by combinations of multiple genetic and environmental or life-style factors. It is likely that specific variants of a gene—polymorphisms—may increase the risk of developing or progressing the disease, but alone they rarely

dictate disease status in a given individual unless additional factors are present, namely, environmental/life-style factors. Previously, numerous association studies of PD have been conducted on either genetic or environmental factors alone, and the outcomes are often inconsistent among them. One reason that may explain the inconsistency is the presence of gene–environment interactions, which have often been overlooked in previous studies. Coffee/caffeine intake is one such environmental factor that has been associated with PD in many studies, while a few studies have failed to find an association. Therefore, here, the gene–life-style interactions of sporadic PD are discussed, focusing on coffee/caffeine intake.

Genetic Factors

In linkage analysis with familial PD, several causative genes have been identified.² The genes associated with autosomal dominant PD include *SNCA*³ and *LRRK2*,⁴ and those associated with autosomal recessive PD include *parkin*,⁵ *PINK1*,⁶ *DJ-1*,⁷ *ATP13A2*.⁸ Although the findings from studies on these mutations have shed light on the disease mechanisms and have advanced our understanding considerably, these highly penetrant mutations attribute only a small fraction of PD. In the common form of sporadic PD, numerous susceptibility genes have been associated with the disease. However, typically, those susceptibility genes are much more common while the magnitude of the risks is much smaller

compared to the mutations found in familial PD. The large body of PD susceptibility gene data is summarized and constantly updated in the PDGENE database (www.pdgene.org/top_results).

Findings from individual association studies often fail to replicate, as their sample sizes are too small and the genetic influence is limited. Genome-wide association studies (GWAS) are effective strategies to overcome this. GWAS examine genetic polymorphisms in large series of cases versus controls, thereby enabling identification of low-penetrant alleles that are not detectable in linkage studies.² As genotype array platforms used in GWAS can analyze huge number of single nucleotide polymorphisms (SNPs) simultaneously, it is possible to conduct association studies using sets of SNPs that tag most common variants in the genome. Thus, scanning for associations is available even without prior knowledge of function or position of the potential PD susceptibility genes. The outcomes from GWAS for PD in various populations have been published, of which the majority have unequivocally replicated the association of some genetic risk loci, *SNCA*⁹ and *MAPT*.⁹ In addition, *BST1*,¹⁰ *LRRK2*,¹⁰ *PARK16* at Chr1q32,¹⁰ *GAK*,^{11,12} and *HLA-DR*¹² have also been identified as susceptibility loci in sporadic PD. Further risk loci were identified in meta-analysis of multiple GWAS, including *AMSD*, *STK39*, *MCC1/LAMP3*, *SRT11*, and *CCDC62/HIP1R*.¹³ Among these susceptibility genes, *LRRK2* and *SNCA* are also identified as PD-causing genes in autosomal dominant forms.¹⁴ Nonetheless, these GWAS-identified susceptibility variants account for only a fraction of the estimated heritability and still cannot explain the vast majority of PD, which indicates that there are yet uncovered causal contributors to PD, such as gene–gene or gene–environment interactions. In other words, it is likely that presence of these specific gene variants in combination with other such variants (gene–gene) or exposure to certain environmental factors (gene–environment) increases the risk of disease development.

Coffee/Caffeine Intake

Coffee/caffeine intake is one of the most extensively studied environmental or life-style exposures in PD (summarized in Wirdefeldt¹⁵) along with pesticide exposure and cigarette smoking. Caffeine, a main psychoactive compound in the coffee, has been suggested to be neuroprotective, as it functions as an adenosine receptor antagonist. Inverse association between PD and coffee intake (or total caffeine intake deducted from all caffeine-containing food, including coffee) has been reported in a series of case-control studies in various populations,^{16–22} and in some cases, dose-dependent PD protectiveness has also been demonstrated.^{23,24} Several studies have found that the protective effects of coffee/caffeine intake was gender specific^{25,26} suggesting the

influence of estrogen status, that is, protective effects were only found in men or abolished in postmenopausal estrogen use. Moreover, a meta-analysis (including eight case-control and five cohort studies) showed a strong inverse correlation between coffee drinking and PD, and the effect was independent from smoking.²⁷ More recent meta-analysis (including seven cohort studies, two nested case-control studies, 16 case-control studies, and one cross-sectional study) further confirmed the protective effect of coffee/caffeine exposure on PD with 25% risk reduction.²⁸

Gene–Coffee/Caffeine Interactions in PD

To date, a few studies have investigated interactions between coffee/caffeine intake and PD genetic factors (summarized in Table 1). For instance, Gao *et al.* investigated potential gene–environment interactions with SNPs, which were significantly associated with PD in previous GWAS.²⁹ A nested case-control study was conducted within the participants of the National Institutes of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study (584 cases, 1,571 controls). Environmental factors—caffeine intake as well as smoking—were analyzed with SNPs at or near the PD genes, namely, *SNCA*, *MPPT*, *LRRK2*, and *HLA* loci. They found no significant interactions of GWAS SNPs with caffeine intake or smoking. A significant interaction was only found when the combination of caffeine and smoking exposures was analyzed with SNP rs2896905 in *SLC2A13* close to the *LRRK2* gene ($p_{\text{interaction}} \leq 0.0017$ after Bonferroni correction).

Interactions between bone marrow stromal cell antigen 1 (*BST1*) gene and caffeine intake were investigated in a Japanese population.³⁰ SNPs in the *BST1* gene have been associated with PD risk in several case-control studies, GWAS, and meta-analysis of GWAS^{10,31–34} in different populations. However, in the study with 229 sporadic cases and 357 controls, they found only a weak association in PD risk and *BST1*-SNP rs11724635, and no gene–environment interactions with either smoking or caffeine intake, even though these two environmental exposures were identified as strong independent risk factors in the same population.

Another study³⁵ focused on the PD gene–environment interactions in nitric oxide synthase (*NOS*) genes (*NOS1*, *NOS2A*, and *NOS3*) in family-based case-control samples consisting of 337 sporadic PD cases and 389 controls. Eight SNPs in *NOS1* and seven SNPs in *NOS2* were significantly associated with PD in earlier onset families with sporadic PD. The environmental factors analyzed in this study include caffeine intake, cigarette smoking, pesticide exposure, and the use of nonsteroidal anti-inflammatory drugs. Gene–environment interactions were analyzed in a subset of the data with environmental risk factor data available (163 PD cases and 178 controls)

using generalized estimating equations. They found significant interactions of pesticide exposure with *NOS1* and cigarette smoking with *NOS2A*, while only one interaction found between caffeine intake and *NOS2A* was conditional, that is, only when all pairwise interactions were considered and a more stringent significant level was applied ($p_{\text{interaction}}=0.0088$ with a significance level of $p \leq 0.01$).

Genes that encode proteins directly involved in caffeine metabolism and caffeine functions, such as *CYP1A2* and *ADORA2A*, have been studied for the gene-coffee/caffeine interactions on PD risk. *CYP1A2* gene encodes cytochrome P450 CYP1A2, and caffeine is primarily catabolized in the liver by this enzyme. Not surprisingly, two separate meta-analyses of GWAS^{36,37} found that sequence variants at the *CYP1A1-CYP1A2* region in chromosome 15q24 were associated with coffee consumption. Furthermore, it was found that a SNP in *CYP1A2*, rs762551 (A to C substitution), altered metabolic rate of caffeine, where C carriers are considered slow caffeine metabolizers while A carriers are rapid metabolizers.³⁸ Another caffeine-related gene, *ADORA2A* encoding adenosine A2A receptor, has been investigated in several studies in relation to the coffee/caffeine effects, since caffeine is a competitive antagonist of the receptor. In several animal models, caffeine's antagonistic effect on the adenosine A2A receptor was neuroprotective.³⁹⁻⁴³ The question is whether these caffeine-related genes have any impact on the risk of PD by itself and/or interactions with the coffee/caffeine intake.

In a study conducted on 446 sibling pairs (case with unaffected sibling) and 158 unrelated pairs (case with unrelated control), none of the SNPs examined (*ADORA2A*: rs5751876 or rs3032740; *CYP1A2*: rs35694136 or rs762551) were associated with PD risk.⁴⁴ In the same study, no significant interactions were observed for lifetime coffee drinking with either *ADORA2A* or *CYP1A2* SNPs.

Likewise, another association study (418 cases, 468 race-, sex-, and age-matched controls) found no main effect of *CYP1A2* rs762551 on the onset of PD or the interactions with caffeine.⁴⁵

A nested case-control study⁴⁶ within the participants of the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) examined gene-caffeine interaction for the genes involved in caffeine metabolism, *CYP1A2* and *NAT2*, with PD risk. Additionally, they also analyzed genetic variants in the estrogen receptor genes, *ESR1* and *ESR2*, since previous studies have reported gender specific PD protective effects of caffeine.^{25,26} In the study (298 cases: 159 females, 139 males; 1,285 age-, sex-, and DNA source-matched controls: 724 females, 561 males), *CYP1A2* rs762551 was associated with a marginally increased risk of PD only in women with an adjusted relative risk (RR) of 1.34 [95% CI 1.02-1.78]. However, there was no caffeine

interaction with the *CYP1A2* polymorphism or with the *NAT2* status (rs1799931, rs1801280, and rs1799930; classified as slow/fast acetylators) for PD risk. Similar to the caffeine-related genes, only a marginal association was found in the polymorphisms of estrogen receptors (*ESR1*: rs3798577 and *ESR2*: rs1255998) with PD susceptibility only in woman. There was, however, a statistical significance in a three-way interaction with caffeine, postmenopausal hormone use, and an *ESR2* SNP on PD risk ($p=0.05$).

The coffee-caffeine interactions of *ADORA2A* and *CYP1A2* genotypes were further investigated in a consortium study,⁴⁷ Parkinson's Epidemiology and Genetic Association Studies in the United States (PEGASUS), which combined DNA and risk factor data from five population-based case-control studies (1,325 cases, 1,735 age- and sex-matched controls). Unlike the other studies, they found PD protective effects of two *ADORA2A* polymorphisms (rs71651683, a 5' transcription start region variant, and rs5996696, a promoter region variant). Logistic regression analysis showed that rs71651683 was inversely associated with PD risk with an odds ratio (OR) of 0.51 [95% CI 0.33-0.80], permutation adjusted $p=0.015$. Likewise, an inverse association of rs5996696 with PD risk was also found (AC and CC genotypes vs. AA wild type; OR=0.76 [95% CI 0.13-1.01], permutation adjusted p for trend=0.04). However, these variants showed no interactions with coffee intake. For *CYP1A2* polymorphisms (rs762551, rs2472304, and rs2470890), the same study found no overall associations with PD risk, which is similar to the reports from others. However, they found that the coffee-PD association was strongest in individuals with homozygous for variant allele in either rs762551 or rs2470890. The effect of coffee consumption (ever vs. never) in the subjects with rs762551 homozygous for the variant allele was adjusted OR=0.33 [95% CI 0.16-0.68], $p_{\text{interaction}}=0.05$, while that of rs2470890 homozygous for the variant allele was adjusted OR=0.43 [95% CI 0.27-0.69], $p_{\text{interaction}}=0.04$.

The coffee-*CYP1A2* interactions on PD were also analyzed by Hill-Burns *et al.*⁴⁸ in the NeuroGenetic Research Consortium (NGRC) consisting of 1,458 PD cases and 931 controls. This study, however, did not replicate the gene-coffee interaction in any of CYP SNPs rs762551, rs2472304, or rs2470890, even though they used the same model as Popat *et al.*,⁴⁷ namely, adjusted for age and sex only and stratified the subjects into ever or never coffee users. Hill-Burns' study took into account that both population structure and smoking status are potential confounders, as noted also by Mellick and Ross.⁴⁹ The adjustment for the study population is particularly important because the frequency of certain risk-modifying genetic variants (e.g., *LRRK2* variants) is highly ethnicity dependent.⁴⁹ Therefore, in the study, the genetic mixture of the population was relatively homogeneous, where all the subjects were Caucasian of

TABLE 1. GENE-COFFEE/CAFFEINE INTERACTIONS IN PARKINSON'S DISEASE

<i>Reference</i>	<i>Gene</i>	<i>Description</i>	<i>SNPs</i>	<i>Interactions with coffee/caffeine</i>	<i>Case/control</i>
Gao 2012 ²⁹	<i>SNCA</i>	Consistently associated in PD GWAS	rs11931074 rs3857059 rs2736990 rs393152 rs17563986 rs199533	Not significant	584/1571
	<i>MAPT</i>	Consistently associated in PD GWAS	rs11564162 rs2896905 rs1491923 rs3129882	Not significant	
	<i>LRRK2</i>	Consistently associated in PD GWAS	rs11724635	Not significant	
Miyake 2012 ³⁰	<i>HLA</i>	Consistently associated in PD GWAS	27 SNPs	Not significant	229/357
Hancok 2008 ³⁵	<i>BST</i>	Consistently associated in PD GWAS	rs944725	Not significant	163/178
	<i>NOS1</i> <i>NOS2A</i>	Encoding a nitric oxide synthase isoform Encoding a nitric oxide synthase isoform		Significant with stratified generalized estimating equations $p_{\text{interaction}} = 0.0088$; OR and CI not shown	
Tan 2007 ⁴⁵	<i>NOS3</i> <i>CYP1A2</i>	Encoding a nitric oxide synthase isoform Encoding CYP1A2 enzyme, primary metabolizer of caffeine	5 SNPs rs762551	Not significant	418/468
Facheris 2008 ⁴⁴	<i>ADORA2A</i> <i>CYP1A2</i>	Encoding an adenosine receptor isoform, Caffeine is an antagonist of the receptor Encoding CYP1A2 enzyme, primary metabolizer of caffeine	rs3032740 rs35694136 rs762551	Not significant	565/565 455/455 391/391
Palacios 2010 ⁴⁶	<i>CYP1A2</i> <i>NAT2</i> <i>ESR1</i>	Encoding CYP1A2 enzyme, primary metabolizer of caffeine Encoding NAT2 enzyme, metabolizer of caffeine Encoding an estrogen receptor isoform	rs762551 rs1799931 rs1801280 rs1799930 rs3798577	Not significant Not significant Marginally significant in women with likelihood ratio tests $p_{\text{interaction}} = 0.07$; RR[95%CI] = 1.05[0.82–1.34] Marginally significant in women with likelihood ratio tests $p_{\text{interaction}} = 0.07$; RR[95%CI] = 0.81[0.54–1.22]	159/724
	<i>ESR2</i>	Encoding an estrogen receptor isoform	rs1255998		

(continued)

TABLE 1. CONTINUED

<i>Reference</i>	<i>Gene</i>	<i>Description</i>	<i>SNPs</i>	<i>Interactions with coffee/caffeine</i>	<i>Case/control</i>
Popat 2011 ⁴⁷	<i>CYP1A2</i>	Encoding CYP1A2 enzyme, primary metabolizer of caffeine	rs762551 rs2470890	Significant with logistic regression using likelihood ratio test $p_{\text{interaction}} = 0.05$; OR [95%CI] = 0.33[0.16–0.68] $p_{\text{interaction}} = 0.04$; OR [95%CI] = 0.43[0.27–0.69] Not significant	925/1249
	<i>ADORA2A</i>	Encoding adenosine receptor subtype, caffeine is an antagonist of the receptor	rs5751876 rs3032740 rs5996696		
Hill-Burns 2011 ⁴⁸	<i>CYP1A2</i>	Encoding CYP1A2 enzyme, primary metabolizer of caffeine	rs762551	Not significant	1458/931
Hamza 2011 ⁵¹	<i>GRIN2A</i>	Encoding GRIN2A, subunit of NMDA glutamate receptor	rs4998386 and neighboring SNPs	Significant with joint test for GWAS and interaction study followed by stratified GWAS (heavy vs. light coffee-drinkers) $p_{\text{pooled}} = 7 \times 10^{-8}$; OR _{pooled} = 0.51, SE = 0.06	2472/2848
Yamada-Fowler 2014 ⁵²	<i>GRIN2A</i>	Encoding GRIN2A, subunit of NMDA glutamate receptor	rs4998386	Significant with logistic regression using likelihood ratio test $p_{\text{joint effect}} = 0.002$, OR[95%CI] = 0.38[0.20–0.70] $p_{\text{interaction}} < 0.001$, OR[95%CI] = 0.998[0.991–0.999]	193/377

GWAS, genome-wide association studies; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

European origin, unlike the PEGASUS⁴⁷ cohort, which had diversity in ethnic backgrounds, including African Americans, Asians, white Hispanics, and white non-Hispanics. Furthermore, they conducted additional analysis using principle components that differentiate genetic variation according to Jewish/non-Jewish ancestry and European country of origin as covariates along with smoking status. However, under any of the models, the study found no gene–coffee interactions or a stronger PD–coffee association in slow caffeine metabolizers.

Later, Popat *et al.*⁵⁰ acknowledged the possible confounding effects of smoking or population stratification on the *CYP1A2*–PD association and the coffee–*CYP1A2* interactions in the PEGASUS population, but re-analysis of the data after adjusting for smoking and race/ethnicity indicated that they were unlikely to be the cause of disagreement between the studies. The authors pointed out that the lack of replication may be the true heterogeneity between the study designs, including subject collection (population vs. clinic based), and variations in the exposure assessment instrument. Nonetheless, the PD associations with *ADORA2A* variant and the *CYP1A2*–caffeine interaction need to be cautiously viewed,^{49,50} since the functions of the variant found to be statistically significant in the study are unknown (*ADORA2A* rs5996696), whereas in the genetic variants with physiologically relevant phenotype (*CYP1A2* slow caffeine metabolizers), interaction was not adjusted for multiple comparisons, and a weaker effect was seen in heterozygotes.

A new strategy for post-GWAS analysis called genome-wide association and interaction study (GWAIS) was proposed by Hamza *et al.* based on the concept that inclusion of environmental factors can help identify genes that are missed in GWAS.⁵¹ Each SNP's main effect on PD risk found in GWAS plus its interaction with caffeine intake was analyzed using the data of NGRC in the discovery data set (1,458 cases, 931 controls). The study revealed a strong PD association and caffeine interactions with *GRIN2A* that encodes an NMDA-glutamate-receptor subunit involved in the brain's excitatory neurotransmission. The *GRIN2A* SNPs interacting with caffeine were rs4998386 and the neighboring SNPs. Further analysis with additional three data sets consisting of 2,472 cases and 2,848 controls (the total of four cohorts) found that among heavy coffee drinkers, rs4998386_T (minor allele) carriers had lower PD risk than rs4998386_CC carriers with OR=0.51, $p=7 \times 10^{-8}$, SE=0.06 (TC to CC excluding rare heterogeneous TT genotype).

Later, the coffee/caffeine–*GRIN2A* interactions on PD were replicated in an independent study conducted by the authors' group.⁵² *GRIN2A* SNP rs4998386 and its interaction with caffeine intake on PD was studied in a patient–control study in an ethnically homogenous population in southeastern Sweden (193 cases, 377 controls). An association was observed between rs4998386 and PD with

OR=0.61 [95% CI 0.39–0.96], $p=0.03$, under a model excluding rare TT genotypes. There was also a strong significance for joint effects of gene and coffee drinking on PD risk (TC heavy caffeine vs. CC light caffeine: OR=0.38 [95% CI 0.20–0.70], $p=0.002$) and a gene–caffeine interaction (OR=0.998 [95% CI 0.991–0.999], $p<0.001$). Overall, the results support the findings of Hamza *et al.*⁵¹ and provide additional evidence to indicate PD protective effects of coffee/caffeine intake, as well as the interaction with glutamate receptor genotypes.

Conclusions

Studies of gene–environment interactions may help us to understand the disease mechanisms of common and complex diseases such as PD. Previous findings of PD association studies, including several GWAS as well as meta-analysis of GWAS, indicate that a single genetic or environmental factor alone cannot fully explain the etiology of PD. Instead, a complex interplay between an individual's genetic make-up and environmental exposure is likely to be the cause of PD. Thus, several interactions between genes and environmental factors, which have a significant impact on PD risk, have been reported (summarized in Tsuboi⁵³), for instance, *CYP2D6* with pesticides^{54,55} and MAO-B with smoking.⁵⁶

Here, studies were reviewed on the interactions between genes and a well-established PD associated lifestyle factor—coffee/caffeine intake. Overall, it appears that either the PD GWAS genes (i.e., genes consistently associated in PD GWAS studies) or caffeine metabolism/function-related genes (e.g., *ADORA2A* and *CYP1A2*) are not strongly linked to the coffee/caffeine effects on PD. Interestingly, however, a strong gene–coffee/caffeine interaction on PD susceptibility was found in an NMDA-glutamate-receptor subunit gene, *GRIN2A*, which has not been revealed in previous PD GWAS or candidate gene association studies. Since overexcitation of NMDA-glutamate-receptor is linked to the glutamate excitotoxicity, the result may be relevant for the disease mechanism of PD.

Nevertheless, whether caffeine *per se* is directly involved in the putative PD connection with NMDA-receptor-glutamate-excitotoxicity is unclear. One weakness in most studies on PD gene–caffeine interaction is that they deducted the numerical value of caffeine consumption from the coffee intake data, or, if not, the sum of coffee and the other caffeine-containing beverages. The resulting estimation of caffeine intake data appears to be reflecting mainly “coffee consumption.” It is often assumed that coffee's effects on health are derived from its primary psychoactive chemical compound, caffeine. However, it should be noted that coffee also contains other bioactive compounds such as beta-carboline alkaloids, which function as monoamine oxidase inhibitors.⁵⁷ and it is possible that these compounds in coffee are the

true causative agents for PD protection. Therefore, the gene-coffee/caffeine interaction results should be interpreted with caution.

Author Disclosure Statement

No competing financial interests exist.

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