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Review Article

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Environmental-Genetic Interactions in the Pathogenesis of Parkinson's Disease

Yoshio Tsuboi*
Department of Neurology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan

To date, numerous case-control studies have shown the complexity of the pathogenesis of Parkinson's disease (PD). In terms of genetic factors, several susceptibility genes are known to contribute to the development of PD, including α-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), and glucocerebrosidase (*GBA*). In addition, numerous recent epidemiological studies have shown that several environmental factors are either risk factors for PD or protective factors against PD. Risk factors identified include herbicides and pesticides (e.g., paraquat, rotenone, and maneb), metals (e.g., manganese and lead), head trauma, and well water. In contrast, smoking and coffee/caffeine consumption are known to be protective against PD. A recent finding in this field is that environmental-genetic interactions contribute more to the pathogenesis of PD than do genetic factors or environmental factors alone. In this review, I will discuss how these interactions promote the development of PD.

Key words: Parkinson's disease, environmental factor, genetic factor, environmental-genetic interaction

INTRODUCTION

Multiple factors influence the pathogenesis of sporadic Parkinson's disease (PD). In terms of genetic factors, several susceptibility genes are known to contribute to the development of PD. Environmental factors are also known to be involved. In addition, aging is closely related to the development of PD because of its effects on neurodegenerative disorders. Studies have been conducted to determine the extent to which genetic or environmental factors contribute to the etiology of PD, including twin studies conducted by Tanner in 1999 [1]. In this work, the concordance of PD within pairs of twins was assessed and compared between homozygous and heterozygous twins. The results indicated that no genetic component is involved in cases where the disease begins after the age of 50 years, but that genetic factors are important with PD onset before the age of 50. We have now learned about the complexity of PD pathogenesis. However, studies that are more recent have extended this earlier finding, providing a better understanding of the complexity of PD pathogenesis. A particularly important recent finding in this field is that environmental-genetic interactions contribute more to the pathogenesis of PD than do genetic factors or environmental factors alone.

GENETIC FACTORS RELATED TO PD

Familial forms of PD have been reported by clinicians involved in extensive, long-term studies. The Contursi kindred, which is one of the largest and most intensively investigated families, is an Italian family with an autosomal-dominant form of familial PD [2]. In this group, the clinical features are characterized by an average age for PD onset of 46 years, average duration between disease onset and death of 9 years, and neurological signs of progressive

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*To whom correspondence should be addressed.
TEL: 81-92-801-1011, FAX: 81-92-865-7900
e-mail: tsuboi@cis.fukuoka-u.ac.jp

parkinsonism with good response to levodopa treatment as well as cognitive dysfunction and psychiatric features. These characteristics cannot be distinguished from those of sporadic PD, with the exception of earlier disease onset. In 1997, it was found that all affected individuals in this family have a point mutation in the α-synuclein (*SNCA*) gene [3]. This was the first time that a form of PD caused by a mutation in a single gene had been discovered.

A second intensively investigated family, the Iowa kindred, has another genetic form of PD with a different *SNCA* mutation [4, 5]. Interestingly, in this family, in contrast to the Contursi kindred in which a point mutation is involved, there was triplication of the region containing the *SNCA* gene resulting in a level of expression of the α-synuclein protein that is twice that of normal subjects. The average age for onset of PD in this family is 35 years and the average duration between disease onset and death is 8 years. The clinical features are characterized by relatively rapid progression of PD with good response to levodopa. Furthermore, some of the patients develop cognitive dysfunction, autonomic failure, and myoclonus. Neuropathological analysis of both families with *SNCA* mutations revealed the presence of Lewy bodies. Although cases in these families with *SNCA* mutations were characterized by autosomal-dominant inheritance with high penetrance, they are clinicopathologically similar to sporadic PD with Lewy body pathology, suggesting that the *SNCA* gene contributes to sporadic PD. However, families with a *SNCA* mutation are very rare globally. To date, only five families with *SNCA* gene duplication and one case with gene triplication have been identified in Japan [6-9]. In Korea, only one family with this gene duplication has been identified [10]. In addition, certain polymorphisms located in the *SNCA* promoter region are known to increase susceptibility to sporadic PD [11].

In addition to *SNCA*, the leucine-rich repeat kinase 2 (*LRRK2*) gene was found to play a role in the pathogenesis of both familial and sporadic PD. Family D, from Western Nebraska, USA, is another case of autosomal-dominant familial PD, this time involving the *LRRK2*-R1441C mutation [12]. The clinical characteristics of this family are similar to those of sporadic PD, with diverse neuropathology among family members. A postmortem study revealed strikingly diverse pathologies, including Lewy body PD, diffuse Lewy body disease, nigrostriatal degeneration without distinctive histopathology, and progressive supranuclear palsy-like pathology.

The discovery of *LRRK2* mutations in familial PD was an epoch-defining event, highlighting that genetic factors are much more important in the etiology of PD than had previously been believed. This is because the *LRRK2* mutation is very common in familial and sporadic PD patients in certain groups. For example, it is known that the *LRRK2*-G2019S mutation is present at high frequency in cases of familial and sporadic PD in Caucasian populations, particularly in North Africa [13-16]. Approximately 40% of North African cases of sporadic and familial PD have the *LRRK2*-G2019S mutation. There are no apparent differences in the clinical features between PD with the *LRRK2* mutation and sporadic PD. The age at onset and cardinal symptoms of PD are identical between those with either sporadic or familial PD [17]. In contrast, in Asian populations, few patients have the *LRRK2*-G2019S mutation. However, it is known that *LRRK2* G2385R is a polymorphism that conveys susceptibility to PD in Asians [18, 19]. Again, there are no differences in the clinical features between PD with and without the *LRRK2*-G2385R polymorphism. In addition, several polymorphisms in the *LRRK2* gene are known to convey susceptibility to sporadic PD.

Another example of susceptibility to sporadic PD is that individuals who are heterozygous for the glucocerebrosidase (*GBA*) gene mutation show greater susceptibility to PD [20, 21].

In general, younger age at onset is observed in most patients with the familial form of PD, but no other specific clinical features can distinguish familial from sporadic cases. In addition, not all patients have a positive family history, either because inheritance is recessive or low penetrance of a dominant mutation. Hence, a positive family history is an unreliable sign for distinguishing between "genetic" and "non-genetic" forms of PD.

ENVIRONMENTAL FACTORS RELATED TO PD

What roles do environmental factors play in the pathogenesis of PD? MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was identified as the first exogenous chemical that could lead to the development of a human neurodegenerative disease. This discovery occurred in 1983 when MPTP was accidentally created as a byproduct of synthetic opioid production. Four individuals developed marked parkinsonism after intravenous MPTP administration [22]. MPTP is a neurotoxic precursor to 1-methyl-4-phenylpyridinium (MPP+), which causes permanent symptoms of PD by destroying dopaminergic neurons in the substantia nigra. A neuropathological study revealed selective neurodegeneration in the nigrostriatal pathway in individuals who had been exposed to MPTP [23]. These cases illustrate that exogenous materials can cause human neurodegenerative disease, although the exact mechanism is not clear. In addition to MPTP, numerous recent epidemiological studies have shown that several other environmental factors are either risk factors for PD or protective factors against PD. Identified risk factors include

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herbicides and pesticides (e.g., paraquat, rotenone, and maneb), metals (e.g., manganese and lead), head trauma, and well water. In contrast, smoking and coffee/caffeine consumption are known to be protective against PD. Those who currently smoke are protected to a greater extent against PD than those who previously or never smoked. In addition, the duration of smoking is more important than smoking intensity for protection against PD. Furthermore, consumption of coffee/caffeine has been shown to be protective against PD in a dose-dependent manner.

In a study based on the Honolulu Asian Aging Study, 8,004 male Japanese immigrants were enrolled between 1965~1968 in Hawaii [24]. During an average follow-up period of 30 years, PD developed in 102 cases. From these data, the relationships between smoking and coffee consumption and the onset of PD were assessed. In the non-smoking group, coffee consumption showed a clear inverse relationship to the development of PD. In addition, the group of current smokers showed a low incidence of PD. These findings indicated that higher coffee/caffeine intake is associated with a significantly lower incidence of PD and that this effect appeared to be independent of smoking.

ENVIRONMENTAL-GENETIC INTERACTIONS WITH PD

More recent studies indicated that environmental-genetic interactions play significant roles in the development of PD. An example is related to cytochrome P450 (CYP) 2D6, one of the CYP superfamilies of enzymes, which metabolizes several xenobiotics in the liver, including organophosphate pesticides, the herbicide atrazine, and MPTP. In general, the activity of *CYP2D6* has been genetically determined; to date, alleles *1 and *2 convey normal function, alleles *3, *4, and *5 result in a loss of function, and allele *10 results in decreased activity [25].

So-called "poor metabolizers," those showing deficient enzymatic activity of *CYP2D6*, are more common in Caucasians (5%) than in Asian populations (0.2%). However, the existence of a relationship between a polymorphism in the *CYP2D6* gene and PD remains controversial. Most studies have failed to find evidence that variants of this gene convey susceptibility to PD. However, careful studies of the interaction between a genetic polymorphism of *CYP2D6* and pesticide exposure revealed that the combination of the poor metabolizer genotype and pesticide exposure results in a significantly increased risk of developing PD compared with normal metabolizers without pesticide exposure with a maximum relative risk of 8.14 [26, 27].

Another example of environmental-genetic interactions relates to solute carrier family 6 member 3 (*SLC6A3*), which is a dopamine transporter gene, the polymorphism of which is potentially associated with the development of PD. To date, *SLC6A3* variants, including 5' A clade and 3' variable number of tandem repeats 9-repeat allele, have been shown to be related to PD onset [28]. However, it has also been shown that the combination of a number of risk alleles of the *SLC6A3* gene and pesticide exposure is significantly associated with the risk of developing PD [29]. In the California Central Valley Study, the relationship between the *SLC6A3* gene and pesticide exposure was re-evaluated, reinforcing the findings of a previous study. The combination of a risk allele and exposure to paraquat and maneb was associated with a greater risk of PD compared with possession of the risk allele alone [30].

The next example of environmental-genetic interactions relates to the monoamine oxidases (MAO), which are enzymes that catalyze the oxidation of monoamines in the brain. In the case of *MAO* in particular, *MAO-B* gene polymorphisms are known to be risk factors for PD [31]. Because these *MAO* genes are located adjacently on the X chromosome in humans, the roles that these genes play in PD may be different in males and females. Upon investigation of the inverse relationship between smoking and

Table 1. Environmental-genetic interactions in Parkinson's disease

Gene	Genotype	Environmental factor	Odds ratio or p value	Ref.
CYP2D6	Poor metabolizer	Pesticide exposure	4.76, 8.41	26, 27
SLC6A3	5' A clade, 3' VNTR 9-repeat allele	Pesticide	5.66	29
		Paraquat, and maneb exposure	4.53 for both paraquat and maneb exposure	30
MAO-B	Intron 13 genotype G	Smoking in men	0.27 (p=0.02 for trend)	33
Glutathione S-transferase	CC genotype at GSTP1-114	Smoking dose	2.2 for diazinon, 2.6 for chlorpyrifos	34
Paraoxonase 1	Leu-Met 55 polymorphism MM genotype	Diazinon, chlorpyrifos	0.51 for rs71651683	35
ADORA2A	rs71651683, a 5' variant rs5996696, a promoter	Caffeine	0.37 for rs5996696 (CC genotype compared with AA wild-type genotype)	36
CYP1A2	Slow metabolizer: rs762551, rs2470890	Caffeine	(p=0.05 interaction) for rs762551 (p=0.04 interaction) for rs2470890	36

PD, it was found that the combination of smoking and a single nucleotide polymorphism (i.e., the *A→G* substitution 36 bases upstream of the exon 14 boundary: genotype G) in the *MAO-B* intron 13 is more protective against PD only in males [32, 33].

As another example of genetic-environmental interactions, glutathione S-transferase (GST) is related to the antioxidation and detoxification of endogenous and xenobiotic substrates. Among *GST* gene polymorphisms, a homozygous CC genotype at GSTP1-114 is known to be protective against PD, especially in heavy smokers [34].

Organophosphates are recognized as neurotoxins and have been identified as environmental risk factors for PD in some studies. The genotype of paraoxonase 1 (PON1) has been shown to determine the level of susceptibility to the detrimental effects of organophosphate exposure, including the insecticides diazinon and chlorpyrifos. It has been speculated that those with *PON1* variants that elicit low enzyme activity might be at higher risk of suffering detrimental effects upon exposure to organophosphates. In a previous study, the relationship between *PON1* polymorphisms and exposure to the organophosphate diazinon was examined. It was found that individuals with the homozygous MM genotype for the *PON-1* Leu-Met 55 polymorphism are more susceptible to the detrimental effects associated with diazinon exposure [35].

It is known that caffeine protects neurons against degeneration by blocking adenosine receptor A2A (ADORA2A). In addition, caffeine is primarily metabolized by CYP1A2, which indicates that CYP1A2 enzyme activity might influence neuroprotection in PD patients. Furthermore, a very recent report revealed an association between certain *ADORA2A* polymorphisms and the development of PD [36]. It was concluded that two *ADORA2A* polymorphisms were inversely associated with PD risk. In contrast, the association between coffee intake and PD was strongest among slow metabolizers of caffeine who were homozygous carriers of certain CYP1A2 polymorphisms.

CONCLUSIONS

Many studies have reported associations between genetic polymorphisms and PD. Even if such studies fail to generate significant results, some genes might be found to have significant roles if their interactions with environmental factors are examined (Table 1). Recent studies have revealed that certain interactions promote the development of PD: between the *CYP2D6* and *SLC6A3* genes and insecticide exposure; between the *MAO-B* and *GST* genes and smoking; between the *ADORA2A* and *CYP1A2* genes and caffeine consumption; and between the *PON-1* gene and organic phosphate exposure. It is thought that prevention of PD and personalized medicine to treat this disease may be established in the future by the extensive genotyping of individuals and the consideration of particularly relevant environmental parameters.

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