Comparison of Environmental and Genetic Factors for Parkinson's Disease between Chinese and Caucasians

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Key Words

Parkinson's disease · Chinese · Caucasian · Prevalence · Environmental factors · Genetics

Abstract

This review paper compares the differences in prevalence, and environmental and genetic risk factors for Parkinson's disease between Chinese and Caucasian subjects. Comparison of age-specific prevalence between Chinese people and Caucasians suggests that the prevalence is lower in the Chinese (at least in the past), although the prevalence rate in China appears to be rising. Distinctions in environmental risk factors and genetic factors are discussed. The difference in prevalence may be due to distinctions in environmental and genetic risk factors as well as the complex interaction between these environmental and genetic factors, although discrepancies in methodology for prevalence surveys can also be an explanation.

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Introduction

Parkinson's disease (PD) is a relatively common neurodegenerative disease among the elderly in all countries and ethnic groups. With the substantial increase in longevity of the world's population, there is a growing need to obtain better epidemiologic data of relevance for this disease. Zhang and Roman [1] in their review of worldwide occurrence of PD have found that the prevalence of the disease is lowest in China, Japan and Africa and highest amongst Western industrialised nations, especially United States and Europe. The cause for this difference is not yet clarified, although well documented.

Previously, studies of PD had concentrated mainly on epidemiologic aspects including frequency (prevalence and incidence) and environmental risk factors. With the advances of genetics, specific mutations including *α-synuclein* and *parkin* genes have been discovered. Moreover, the polymorphism of many candidate genes have also been investigated. Some of the more commonly studied ones are cytochrome P-450 CYP2D6, monoamine oxidase (MAO) and dopamine transporter (DAT). The hypotheses behind candidate genes are that certain commonly occurring genetic variations may increase the risk of PD due to their influence on potential PD-causing pathways. The potential PD-causing pathways include

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xenobiotic metabolism and transport, oxidative phosphorylation, dopamine metabolism and utilization, free radical scavenging and ubiquitin pathways. Although the results from various studies have been inconsistent, the hypotheses behind their investigations have been interesting. The contribution of both genetics and environment to the development of PD has been further reiterated in a recent study [2].

Recently, genetic studies of some of these candidate genes for PD have been carried out in Chinese people with mostly negative results. Although methodological and diagnostic differences might have caused biases, it seems plausible that the differences between the Chinese and Caucasians may be real, and that these genetic differences along with differences in environmental factors may have accounted for the lower frequency of PD amongst mainland Chinese subjects. As far as we are aware, there has been no critical review of the above issues. Therefore, a review and comparison of the epidemiology, highlighting important similarities and differences of environmental and genetic risk factors for PD between Caucasian and Chinese subjects is timely. The review will also explore some aspects of genetic and environmental interactions.

Methods of the Review

Relevant articles from 1985 to 2002 were searched using Medline and Embase. Key terms used included 'Parkinson's disease', 'prevalence', 'epidemiology', 'genetics' and 'risk factors'. From the obtained literature and its references, further articles were reviewed if they were thought to be relevant.

Prevalence Studies

While comparison of prevalence may provide useful clues to the aetiology, the accuracy of prevalence estimation needs to be considered. Prevalence is affected by the incidence of the disease, survival after diagnosis, utilisation of healthcare, confounding factors and methodological issues such as difference in study design and diagnostic criteria [3, 4]. Bearing in mind these difficulties, we attempt to compare age-specific prevalence from studies using the more accurate method of door-to-door survey (see first 8 studies in table 1). The difference is most distinct between the mainland Chinese and Caucasians. The Taiwanese live in an intermediate industrialised environment and have intermediate prevalence.

Since age is the most consistent risk factor of PD, prevalence studies with published age-specific prevalence were selected (table 1). It is not possible to be certain that the differences are not due to chance, as none of these studies provided confidence intervals for the age-specific prevalence estimates. However, the point estimate of prevalence for the mainland Chinese is substantially lower than that for Caucasians, particularly when door-to-door surveys are compared. Surveys relying on reports from general practitioners or medical registries may underestimate the prevalence because of inability to identify patients with early disease. However, even in these surveys (see studies 9–13 in table 1), the prevalence is higher in Caucasians than in the mainland Chinese (door-to-door surveys).

Differences in the stringency of diagnostic criteria can affect prevalence. Anderson et al. [5] demonstrated that the difference in reported age-specific prevalence between Argentina and India disappears when the same diagnostic criteria are applied. However, when the same diagnostic criteria are applied, the difference between China and Argentina remains.

The magnitude of differences in incidence contributing to the difference in prevalence is difficult to assess because of the paucity of incidence studies.

Difference in survival after diagnosis is unlikely to contribute significantly to age-specific prevalence comparison, although mortality in patients with PD increases with age [6]. Using the same methodology, a prevalence study of the Inuits in Greenland showed that the age-specific prevalence of PD is higher among the Inuits than the Danish despite a shorter life expectancy of 10 years [7].

Differential utilisation of health services is a problem for the comparison of prevalence studies which select potential cases from medical databases or registries, and medical practitioners, but not for door-to-door studies. This is not a major issue for the comparison between the Chinese and Caucasians because the Chinese prevalence is obtained from door-to-door surveys.

Environmental Factors

With increased age, the risk of PD increases, which may be related to the longer exposure to neurotoxins and/or natural attrition of neurons. Furthermore, the ageing brain may be more susceptible to injury, as supported by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and mice studies [8, 9]. The age-specific prevalence of PD is 5- to 10-fold lower in mainland China when

Table 1. Comparison of prevalence between Chinese and Caucasians

Reference	Year of survey	Country	Age-specific prevalence (per 100,000)				Crude prevalence	Method
			50–60	60–70	70–80	80+		
Li et al. [45]	1983	China (urban population)	92	145	615 ^a	–	44	door-to-door, 2 stages
Wang et al. [89]	1986	China (29 provinces)	22.5	89.4	157.6	132	14.6	door-to-door, 2 stages
Wang et al. [10]	1992	Taiwan (farming population)		780	1,750	2,540		door-to-door, 1 stage, pilot study
Wang et al. [11]	1993	Taiwan (Kinmen, farming population)	273	535	565	1,839	119	door-to-door, 1 stage
Chen et al. [12]	1993	Taiwan (Ilan)	122.5	546.7	819.7	2,197.8	367.9	door-to-door, 2 stages
De Rijk et al. [89]	1990's	France, Italy, the Netherlands, Spain (pooled results from 5 studies)	–	625	1,768	3,498	–	door-to-door
De Rijk et al. [90]	1990's	European, pooled results from Sweden, France, the Netherlands, Italy, Spain and Germany	–	565	1,666	2,813	–	door-to-door
Morgante et al. [91]	1987	Sicily	115.6	430.2	1,212.5	236.7	167.4	door-to-door, 2 stages
Scharag et al. [92]	1997	UK (London)	109	342	961	1,265	119	computerised records of general practices
Errea et al. [93]	1992	Spain	100.2	435.6	953.3	973.1	220.6	hospital records, GP, psychiatrist and physicians identifying
Dias et al. [94]	1992	Portugal	36 ^d	169 ^d	513 ^d	660 ^d	105	GP reporting
Milanov et al. [95]	1999	Bulgaria	70.5 ^c	388.9 ^c	1,524.4 ^c	3,456.2 ^c	168.5 ^c	hospital record registry
Mayeux et al. [96]	1989	USA (New York)	125.2 ^b	438.0 ^b	1,352.8 ^b	846.7 ^b	178.3 ^b	community registry, neurologist diagnosis

^a Aged ≥ 70.^b Recalculated prevalence rates of Caucasian only and age intervals are different: 45–64, 65–74 and ≥ 85.^c Recalculated combined prevalence of 2 populations.^d Age intervals: 45–54, 55–64, 65–74, ≥ 75.

compared with Europe, although the prevalence rate in more developed ethnic Chinese regions such as Taiwan [10–12] and Hong Kong is higher (prevalence rate = 188 per 100,000) [13]. Some critics argue that the relative low prevalence of PD in the Chinese may be due to lower life expectancy. However, Zhang and Roman [1] found a lower prevalence in the Chinese even after age adjustment in comparison with Caucasians, indicating that other factors such as environment and/or genetics may play a role. Recent findings of an increased prevalence in regional Chinese populations may reflect an increase in accumu-

lated exposure to environmental toxins or alternatively improved access to health care and better diagnostic awareness.

Farming and rural living are generally regarded as risk factors of PD in westernised countries [14, 15]. On the contrary, there is no association with PD in mainland China [16, 17]. However, in a Taiwanese study, Liou et al. [18] found that rural living and farming (especially rice growing) as well as the use of herbicides/pesticides were associated with a greater risk of PD in univariate analysis. After multiple logistic regression, occupational use of her-

Table 2. A comparison of the studies reporting environmental risk factors and PD in Caucasians and Chinese

Reference	Rural living	Well water drinking	Farming	Pesticides	Coffee
Hernan et al. [35] (Caucasian, meta-analysis)	–	–	–	–	0.69 (0.59–0.8)
Priyadarshi et al. [19] (USA, meta-analysis)	2.17 (1.54–3.06)	1.44 (0.92–2.24)	1.72 (1.20–2.46)	2.16 (1.95–2.39)	
Tanner et al. [16] (mainland China)	0.57 (0.33–0.98)	0.74 (0.41–1.32)	–	–	
Wang et al. [17] (mainland China)	0.76 (0.49–1.18)	0.59 (0.36–0.95)	–	–	
Chan et al. [20] (Hong Kong)	1.0 (0.995–1.01)	1.04 (0.70–1.54)	0.92 (0.59–1.43)	1.80 (0.90–3.58)	
Liou et al. [18] (Taiwan)	2.04 (1.23–3.38)	1.07 (0.19–5.98)	1.81 (1.25–2.64)	3.32 (1.59–6.94)	

Figures are ORs, with 95% CIs in parentheses.

bicides/pesticides (OR = 6.7, 95% CI 2.62–17.21) and paraquat were the only significant factors. Rural living and farming may be complex and hybrid factors made up of many other variables. Pesticide and herbicide usages are only two. Well water drinking is another. The reason for the difference between westernised countries and mainland China may be explained by different farming practices in rural areas. The relative low usage of pesticides and herbicides (neurotoxins) by mainland Chinese farmers (at least in the past, and it may still be the case in some areas) may contribute to the difference. Although not universal, there is a general consensus that exposure to pesticides and herbicides are risk factors for PD [19]. This is certainly the case in Caucasians (table 2). In a recently published study from Hong Kong [20], pesticide usage amongst Chinese farmers, albeit infrequent, has been found to be significantly associated with increased risk of PD in females (OR = 6.84, 95% CI = 1.90–24.7). The usage of toxic farming substances such as herbicides and pesticides in Taiwan and Hong Kong may indeed explain the higher prevalence found amongst these Chinese populations when compared with the mainland. The conversion of MPTP by MAO type B (MAOB) to MPP⁺, which has chemical similarities to commonly used herbicides including paraquat, lends support to an association of PD with herbicide/pesticide exposure. Epidemiologic studies that use multiple logistic regression supported that most variables such as rural dwelling and farming are variables dependent on pesticide/herbicide exposure [21, 22] Wang et al. [17] found that well water drinking was associated

with reduced risk of PD in China. This is in contradiction to other findings that well water drinking is a risk factor in the West [14]. These differences again may be explained by pesticide and herbicide usages in farming practice. These chemicals used by farmers may find their ways to underground water and hence cause contamination of well water in westernised countries. This contrasts with the infrequent usage of such chemicals by mainland Chinese farmers, and therefore resulting in possibly ‘cleaner’ underground water.

Differences in dietary habits may partly be responsible for the difference in the prevalence of PD. However, there is considerable difficulty in accurately recording dietary intake, thus making it difficult to be certain of the results of ascertainment of specific dietary factors in PD. In a recent large community-based study by de Rijk et al. [23], vitamin E (an antioxidant) consumption has been found to be significantly lower among PD patients. This result is also shared by Tanner et al. [24] and further supported by experimental evidence of reduced putamen F-dopa uptake in PET scans amongst patients with vitamin E deficiency [25]. However, a protective effect of vitamin E consumption has not been found in other reports [26–28]. Other studies also suggest that vitamin E consumption, through diet or supplementation, does not provide significant protective effect [29–31]. Similarly, no significant differences between cases and controls in dietary intake of vitamin E were found in a Chinese study [20]. While the issue is contentious whether dietary factors are indeed important, the vegetable-rich diet of the Chinese which

Fig. 1. A theoretical model illustrating interplay between environmental and genetic factors of PD.

contains substantial amount of antioxidants and vitamin E may potentially explain the lower prevalence of PD in this racial group.

Interestingly, beverage consumption of tea amongst the Chinese [20] as well as coffee drinking amongst Caucasians [32–35] have been found to be protective against PD. Tea drinking was found to be a protective factor for PD in the Hong Kong Chinese [19] in univariate analysis. However, results amongst Caucasian studies are mixed. An American study has found tea to be protective [36], whilst a French study has demonstrated the reverse [37], and another prospective American study has found reduced risk for men but not women [38]. Consumption of herbal tea and fruits from the Annonaceae family containing neurotoxic alkaloids was found to be associated with atypical parkinsonism and progressive supranuclear palsy in the French West Indies [39]. Perhaps the type of tea and its additional content are important factors in determining the association of tea with PD. Coffee intake has been inversely associated with PD in some studies [31, 32] but disputed by others [36, 40]. The differences may be due to methodological variations. The inverse relationship found in a recent prospective longitudinal study in Hawaii has lent weight in supporting the finding given the strength of its design. While the protective effect of tea may be explained by its potent antioxidant property, another alternative explanation may be that both tea and coffee contain similar protective micronutrients, such as caffeine. Caffeine given to mice with pharmacologically induced dopamine depletion can prevent akinesia [41]. Chen et al. [42] also found that caffeine may be protective against MPTP toxicity via the inactivation of the adenosine receptor A_{2A} .

Smoking has been consistently, although not universally, reported to be a protective factor [13]. One large-scale prospective study even reported a modest dose-response relationship [43]. The protective effect of smoking may be confounded by the possibility that people who smoke have greater mortality than those who do not [44]. However, the consistency of the inverse relationship and the supporting evidence of protective effects of nicotine on MPTP-induced cell loss in the substantia nigra [45] of mice strengthen the protective hypothesis. The effect of smoking is likewise shared by some [19], but not all [13], Chinese studies. A confounding factor for the role of smoking in Chinese patients with PD is the male:female ratio (3.7:1), which is much higher than that seen in Western communities [46]. Given that smoking is extremely rare in Chinese women with PD, an inverse association with smoking would contradict the higher PD prevalence in Chinese men. This raises the question of whether smoking exerts a true biologic protective effect. Another possible explanation could be due to sex-related risk of PD. For instance MAOB (X-linked) G-A polymorphism has been associated with increased risk in both Caucasians [47] and Chinese subjects [48, 49]. A Taiwanese study [48] has found that males with the MAOB polymorphism are at high risk compared with females.

Genetic Factors

Unlike the environmental factors, genetic factors have been consistently associated with increased disease risk [50], although this may reflect shared exposures and/or biased recalls in addition to a true genetic predisposition or cause. Twin studies have shown that early-onset PD is

largely genetic, while late-onset PD has a large environmental component [51]. To date, *α -synuclein* (chromosome 2) gene defect in Caucasians and *parkin* (chromosome 6) gene defect in the Japanese as well as Caucasians have been identified as causes of early-onset disease. Linkage analyses have identified many more genetic defects in Caucasians including chromosomes 1, 2 and 4 in Caucasians [52] and chromosome 12 in the Japanese [53]. Genomic screening also found at least 4 loci to be significant for later-onset PD (17q, 8p, 5q and 9q) [54].

α -Synuclein Gene

Recently, the missense mutation G209A in exon 4 resulting in an exchange of an alanine to a threonine at position 53 of the amino acid sequence (Ala53Thr) has been found in the Italian Contursi kindred [55] and some unrelated Greek families. This promises an exciting era into the molecular basis of PD. A second *α -synuclein* mutation associated with PD has recently been described by Kruger et al. [56]. This variant is characterised by a cytosine to guanine transversion at nucleotide position 88 of the coding sequence (exon 3) leading to a change at position 30 of the amino acid sequence (Ala30Pro). *α -Synuclein* is a precursor to constituents of Alzheimer's disease plaques and is found in Lewy bodies, the eosinophilic inclusion bodies, which are the defining neuropathological characteristics of PD. The function of *α -synuclein* is unknown, although it is thought to be involved in neuronal plasticity and may mediate binding between structural proteins [57].

However, the G209A (Ala53Thr) mutation is rare and is not found in other large familial [58, 59] or sporadic [60] PD patients. Similarly, search amongst the Chinese for this rare mutation has failed to reveal anything positive in a study in Hong Kong [61] and 2 studies in Taiwan [62, 63]. The study from Hong Kong and the study from Taiwan [63] have also failed to show Ala30Pro mutation.

Parkin

The *parkin* gene was first described amongst juvenile-onset PD in Japan [64]. *Parkin* is a 465 amino acid protein that contains a ubiquitin homologous domain in its amino terminus and two RING finger domains in its carboxy terminus. Proteins with RING finger domains have a ubiquitin ligase function, thus linking *parkin* to the ubiquitin-proteasome system [65]. It is postulated that *parkin* interacts with substrate proteins and by acting as a ubiquitin ligase is involved in their degradation. Furthermore, *parkin* has been found to interact with *α -synuclein* [66]. It is postulated that mutated forms of *parkin* cannot

bind to the glycosylated isoform of *α -synuclein*, resulting in its accumulation and potential cytotoxicity [67]. The lack of Lewy bodies in juvenile-onset PD is consistent with the inability of the ubiquitin-proteasome pathway to form ubiquitinated aggregates of *α -synuclein*.

A number of different homozygous point mutations, gene deletions and multiplications have been detected in patients with *parkin* gene mutations [64, 68]. In a study of 73 families with early-onset (age <45 years) PD in Caucasians, 49% had *parkin* mutations [68]. In comparison, among 100 patients with sporadic PD and age of onset <45 years, *parkin* mutations were detected in 70% of them, presenting at age <20 years, but only 3% presented at age >30 years. Likewise, the *parkin* gene is well documented in the Japanese and is also found in the Hong Kong Chinese [unpubl. data]. Hence, as compared with *α -synuclein*, *parkin* gene mutation is a more common hereditary cause of PD.

Candidate Genes

In general, the hypotheses behind candidate genes are characterised by genetic polymorphism that leads to lessened or abolished enzyme activity, and by fixed expression or homozygous allelic deletion (a theoretical correspondence between genotype and phenotype). The most commonly studied genes are those involved in oxidative stress through the generation of free radicals (phase I enzymes) or involved in scavenging (phase II enzymes). An example of a phase I enzyme is CYP2D6. Of all the candidate genes, CYP2D6, a debrisoquine hydroxylase gene, has received the widest attention. This cytochrome enzyme is responsible for the metabolism of various xenobiotics such as haloperidol and toxins such as MPTP, thus making it a plausible candidate gene for PD. Barbeau et al. [69] first suggested the possibility of failure of the enzyme debrisoquine hydroxylase to detoxify neurotoxin may be a predisposing factor to PD. Smith et al. [70] later found that the poor metaboliser phenotype had a 2.54-fold increase in the risk of PD. However, recent genetic research efforts in this gene have produced conflicting results [71]. Several meta-analyses have come up with different conclusions: McCann et al. [72], weakly associated; Christensen et al. [73], weakly associated, and Rostami-Hodjegan et al. [74], no association.

Polymorphism was found to be extremely rare in the Chinese in 2 association studies [75, 76]. Only 3 mutant alleles (G1934A) were found amongst 207 Chinese PD patients and 227 controls in the larger study [75]. All of the mutant alleles were heterozygous, one was in a PD patient and the two others were controls. No single base

Table 3. Some candidate genes and their association with PD in Caucasians and Chinese subjects (*)

Gene	Author/year	Case/control	Association	Possible mechanism
CYP2D6 (G1934A and 2637 deletion)	McCann et al. [72]/1977 Christensen et al. [73]/1998 Rostami-Hodjegan et al. [74]/1998 *Chan et al. [20]/1998 *Lo et al. [76]/1998	1.133/1.950 207/227 53/94	yes (meta-analysis) (1.7) no (meta-analysis) no (meta-analysis) no no	detoxify neurotoxin
MAOB	Tan et al. [77]/2000 Mellick et al. [78]/2000 *Chan et al. [49]/2003 *Wu et al. [82]/2001	204/285 176/227 224/197	meta-analysis (2.58) no 1.47 (non-tea drinker) 2.07 (↑ by COMT polymorphism)	activate neurotoxin
DAT-1 (11-copy allele)	Tan et al. [77]/2000 *Leighton et al. [79]/1997	526/638 203/230	no no	transport neurotoxin
NAT-2	Tan et al. [77]/2000 *Chan et al. [83]/2003	792/912 99/912	meta-analysis (1.36) yes (5.53)	detoxify neurotoxin
GST-P1 GST-M1&T1	Menegon et al. [86]/1998 Bandmann et al. [97]/1997	95/95 100/100	no (yes ¹) no	detoxify neurotoxin
COMT	Xie et al. [81]/1997 *Wu et al. [82]/2001	70/62 224/197	no no	
DRD4	*Wan et al. [80]/1999	101/105	no	dopaminergic post-synaptic transmission
tRNAGlu	Tan et al. [77]/2000	288/459	meta-analysis (3.0)	mitochondrial function

The Caucasian results (except CYP2D6) are based on the meta-analysis by Tan et al. [77]. Figures in parentheses are ORs.

¹ Only becomes statistically significant if analysis restricted to a small subset of subjects exposed to pesticides.

deletion at position 2637 in exon 5 was detected in any of the subjects. In the smaller study in Taiwan [76], no differences in allele or genotype frequencies of C188T, G1934A and G4268C polymorphism were detected upon comparison of PD patients (n = 53) with normal controls (n = 94). Again G1934A allele was found to be extremely rare. Preliminary evidence suggests that CYP2D6 is unlikely to play a significant role in the pathogenesis of PD in the Chinese.

The polymorphisms of various other genes have been put forward as putative factors. These genes are often involved in the metabolism of potential neurotoxins, dopamine transportation or antioxidant defences. Some of the examples include MAO types A (MAOA) and B (MAOB), DAT-1, dopamine receptor gene (D₂, D₃, D₄), catechol-*o*-methyltransferase (COMT), manganese superoxide dismutase, N-acetyltransferase 2 (NAT-2) and glutathione transferases (phase II enzymes which are involved in scavenging electrophilic reactive intermediates). Results of studies of these candidate genes in Cau-

casians using allele association methods varied. This may be in part due to sample bias in some studies or because in many studies, sample sizes were small, therefore subject to a lack of power to discern small differences in a lot of the candidate genes. Recently, a review of case-control candidate gene studies and meta-analysis of individual gene polymorphism [77] has found significant associations with PD in polymorphisms of NAT-2, MAOB and GSTT1, but not in others such as dopamine receptors (DRD2 and DRD4), DAT, MAOA and COMT. In their conclusion, the authors stressed that although significant association does not imply a causal relationship between the presence of the polymorphisms and PD pathogenesis, their pathophysiologic significance should be studied further.

Studies of other candidate genes in Chinese subjects have been infrequent and limited by small sample sizes. Results so far have been negative for CYP2D6 [75, 76], DAT [79], dopamine receptor D₄ [80] and COMT [81]. Mixed results have been reported for MAOB [49, 78, 82].

Also, NAT-2 with a slow acetylator genotype was found to be strongly associated with PD in the Chinese (OR = 5.53; CI = 3.08–9.92) [83].

It is important to stress that a positive association in a candidate gene study does not imply a causal relationship between the presence of polymorphism and PD pathogenesis. Other possible reasons for a positive association such as linkage equilibrium ought to be considered. A summary of allelic association studies and functions of some of the important candidate genes studied in Caucasians and Chinese subjects so far is listed in table 3.

Interactions between Environmental Factors and Candidate Genes

Interaction studies have been infrequent in both Caucasians and the Chinese. Despite the small number of reports available, there is evidence to date to suggest that nature and nurture do interact. Caucasian studies have shown that genetic polymorphism of MAOB modifies the association of smoking and PD in that smoking may increase the risk of association with PD in one genotype, but may reduce the risk in another [84, 85]. Similarly, Menegon et al. [86] have found that glutathione transferase polymorphism interacts with pesticide in increasing the risk of PD, and de Palma et al. [87] have observed that the protective effect of smoking was lost among patients with the genotype GSTM1*0. Such interactions have been reported in the Chinese as well [49]. Chan et al. [49] have found that the protective effect of tea drinking masked the increased risk of PD associated with the MAOB polymorphism in the Chinese. Interestingly, a Taiwanese study has also found that MAOB polymorphism increased the risk of PD in the Taiwanese Chinese and that the effect was enhanced by the COMT polymorphism. MAOB is located on the X-chromosome, and although the G-A polymorphism occurs in an intron and therefore does not directly alter the amino acid sequence of the enzyme, linkage disequilibrium with other genes may confer the susceptibility. These early studies suggest that genetic-environmental interactions probably occur in both Caucasians and the Chinese.

Conclusion

Comparison of genetic and environmental risk factors between populations can help to clarify issues such as the importance of environmental factors and the contribu-

tions of genetic factors in different populations. From the above comparison, it appears that in the past, the mainland Chinese probably has a lower rate of exposure to putative environmental risk factors for PD as compared with the West. However, in the more industrialised Chinese populations in Taiwan and Hong Kong, the prevalence rates appear to be of intermediate values. The rural environment and farming practices in mainland China, at least in the past, had not been associated with increased risk of PD. This is most likely due to the lower usage of pesticides/herbicides. This may have implication for farming practices in the West.

Smoking as a protective factor cannot be recommended, even if its effect is truly biological, since the harm outweighs the benefits. On the other hand, interesting findings of tea and coffee drinking may be worthy of further investigations.

The recent discovery of the *parkin* gene in both Caucasians and Asians has major influences on the understanding of the genetic contribution to juvenile parkinsonism. It seems that the *parkin* gene is a significant factor across different ethnic backgrounds. In contrast, the polymorphism of candidate genes and their relationships with sporadic PD remain unclear. One of the problems with allele association studies has been the neglect of simultaneous consideration of genetic and environmental interactions. If a candidate gene has effects in only a small subset of people and the occurrence of the polymorphism is infrequent, then the overall effects will be weak or non-significant within a larger population. CYP2D6 in the Chinese is a good example. Other important aspects in genetic studies that can contribute to the varying results between studies include differences in control allele frequencies and linkage disequilibrium. There are certainly major differences in the frequencies of polymorphism of candidate genes between Caucasians and Chinese subjects; again CYP2D6 is a perfect example. In addition to the differences in environmental risk factors and distribution of genetic polymorphisms, the interaction between these environmental and genetic factors may be an area that needs further exploration in order to better understand the pathogenesis of PD.

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