The interplay between environmental and genetic factors in Parkinson's disease susceptibility: The evidence for pesticides

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A B S T R A C T

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by dopaminergic neuron loss in the substantia nigra. Although its aetiology remains unknown, accumulating evidence suggests that multiple genetic and environmental factors confer a small to moderate risk of developing PD. Over the past two decades, considerable progress has been made towards understanding the molecular basis of PD. Mutations in a number of genes were found to cause autosomal dominant or autosomal recessive monogenic forms of PD (Xiromerisiou et al., 2010). In addition, several common genetic variants were also identified through candidate gene or genome-wide association studies and meta-analyses to modulate the risk of sporadic PD [data available at PDGene database] (Lill et al., 2012). It is widely believed that an interaction between genetic and environmental factors influences the susceptibility to PD. Human epidemiological studies have implicated pesticides as risk factors of PD and neurodegeneration (Kanavouras et al., 2011) although this association remains controversial. A number of case–control studies as well as prospective studies have shown a positive association between pesticide exposure and increased risk of PD (Ascherio et al., 2006; Frigerio et al., 2006) whereas other studies have failed to demonstrate such an association (Behari et al., 2001; Nuti et al., 2004). A meta–analysis of 19 studies demonstrated a significant association between PD and exposure to pesticides with a combined odds ratio of 1.9 (Priyadarshi et al., 2000). The review by Li et al. (2005) concluded that there was no clear evidence of an exposure–response association, or linking a specific class or individual pesticides to PD, whereas Brown et al. (2006) stated that the weight of evidence was sufficient to conclude that a generic association between pesticide exposure and PD exists (Table 1).

A possible reason for this discrepancy seen in epidemiological studies investigating pesticide exposure and the risk of PD may be related to different susceptibilities of populations to environmental exposures on the basis of their genetic variability. Evidence of pesticide–gene interactions has been provided from studies in animal models and from human genetic association studies (Burbulla and Kruger, 2011). The present review will therefore focus only on current knowledge regarding gene to pesticide interactions in the risk of PD using data from human genetic association studies.
where pesticide exposure was also evaluated. The studies are presented with regard to the main mechanism of the tested genes by which may influence pesticide toxicity. Genetic loci investigated for interaction with pesticides in PD patients include polymorphisms in genes implicated in pesticide metabolism: cytochromes CYP2D6 and CYP1B1, paraaxonase-1 (PON1) genes, in pesticide transport: ATP-Binding Cassette, subfamily B, member 1 (ABCB1) gene, in mitochondrial dysfunction and regulation of oxidative stress: glutathione S-transferases (GSTs), heme oxygenase-1 (HMOX1), nitric oxide synthases (NOS), manganese superoxide dismutase (MnSOD; SOD2), quinone oxidoreductase 1 (NOQ1) genes and in genes that may have direct effects on dopaminergic neurons: dopamine transporter (SLC6A3), α-synuclein gene (SNCA), leucine-rich repeat kinase 2 (LRKK2), brain derived neurotrophic factor (BDNF), PTFE-induced putative kinase 1 (PINK1) genes.

### 1.1. Pesticides metabolism

CYP2D6, CYP1B1 genes: Several xenobiotics, including organophosphate compounds, triazine (atrazine), carbamates (carbaryl, maneb, ziram) and MPTP are metabolized at least in part by cytochrome (CYP) P450 enzyme CYP2D6 (Neafsey et al., 2009). There is a considerable variability in CYP2D6 enzymatic activity among individuals which is mainly determined by genetic variants. Several polymorphisms of CYP2D6 gene were found to influence the enzyme’s production and activity resulting in increased, normal, intermediate or absent (poor metabolizers) metabolism of substrates (Zhou, 2009). The frequency of CYP2D6 poor metabolizers is around 5–10% amongst Caucasians. The most common polymorphism that accounts for approximately 75% of CYP2D6 poor metabolizer status in Caucasian populations is CYP2D6*4 (C>G, rs3892057). This polymorphism causes an aberrant mRNA splicing at intron3/exon4 boundary resulting in a frame shift and an early termination (Gough et al., 1990). CYP2D6*4 AA homozygotes were found to lack enzyme activity, whereas the other genotypes have normal CYP2D6 activity. Elbaz et al. (2004) first provided evidence that CYP2D6*4 homozygosity interacts with pesticide exposure in the risk of developing PD. Their study included a population of 190 PD patients and 419 matched controls with a high prevalence of pesticide exposure for gardening or professional use. The authors did not find any effect of CYP2D6*4 polymorphism on PD risk in the absence of pesticide exposure. However, among individuals exposed to pesticides, poor metabolizers (CYP2D6*4 AA homozygotes) had an approximately twofold increase in PD risk [odd ratio (OR), (95% confidence intervals, CI): 3.28 (1.16–9.27)] compared to normal metabolizers [OR (95%CI): 1.5, (0.92–2.43)]. Similar findings were described in another case control association study of 393 PD cases and 389 healthy controls (Deng et al., 2004). In this study apart from CYP2D6*4, the authors genotyped two additional polymorphisms,
the CYP2D6 (A2549del) and CYP2D6*5 (CYP2D6del), that also contribute to metabolic rate phenotypes. Poor metabolizers again were at increased risk of PD only if highly exposed to pesticides [OR (95% CI): 8.41 (1.01–69.76)]. In addition in this level of pesticide exposure heterozygotes of the CYP2D6*4, CYP2D6*3 and CYP2D6*5 were also at increased risk of PD [OR (95% CI): 3.27 (1.21–8.80)]. However, other studies have found no significant interaction between pesticide exposure and CYP2D6 gene polymorphisms in the risk of PD (Chan et al., 1998; Dick et al., 2007). Dick et al. (2007) carried out a large European multicenter study on 767 PD patients and 1989 controls in which they genotyped for a number of polymorphisms relevant for xenobiotic metabolism. The majority of gene-environment analyses including CYP2D6 polymorphism did not show significant interaction effects. The role of the Val432Leu polymorphism in another cytochrome P450 enzyme gene, the CYP1B1, which is also implicated in pesticide metabolism, was also investigated in this study but no significant interactions were reported (Dick et al., 2007).

It is therefore currently unclear whether genetically determined poor metabolizers are susceptible to PD as a result of their impaired ability to inactivate and detoxify pesticides or other environmental neurotoxins that cause neurodegeneration and PD. On the contrary it is also possible that high rate metabolizers again may be at increased risk of neurodegeneration when CYP enzymes metabolize environmental substrates, otherwise nontoxic, into bioactive toxic compounds.

Paraaxonase-1 gene: Paraaxonase-1 (PON1) is a serum calcium-dependent esterase enzyme that is synthesized primarily in the liver and released into the bloodstream, where it is bound to high-density lipoproteins (HDLs). It catalyzes the hydrolysis of the active metabolites (oxons) of some organophosphates (OP) including parathion, diazinon and chlorpyrifos (Costa et al., 2012). Genetic variations in PON1 gene were found to influence the serum enzyme levels, protein stability or its catalytic efficiency. One of the most widely studied PON1 SNPs is the coding synonymous Leu/Met polymorphism at position 55 in exon 3 (rs854560) (Androutsopoulos et al., 2011; Belin et al., 2012; Hadjigeorgiou et al., 2007; Kokouva et al., 2012; Zintzaras and Hadjigeorgiou, 2004). The M allele of this polymorphism was linked to decreased expression, enzyme levels and activity as well as protein stability (Costa et al., 2012; Garin et al., 1997; Leviev et al., 2001; Leviev and James, 2000) irrespective of other PON1 variants (O'Leary et al., 2005). The possibility that individuals carrying this polymorphism may be more susceptible to the neurotoxic effects of organophosphates leading to PD was tested in a recent case-control study of 351 PD cases and 635 controls living near agricultural areas with substantial use of organophosphates (Manthripragada et al., 2010). It was found that residential exposure to chlorpyrifos or to high levels of diazinon increase the risk of PD regardless of PON1 L55M genotypes [OR (95% CI): 1.56 (1.02–2.40), 1.55 (1.05–2.30), respectively]. However, individuals carrying the MM genotype (low PON activity) were at a greater risk of PD when exposed to chlorpyrifos [OR (95% CI): 2.61 (1.25–5.44)] or to diazinon [OR (95% CI): 2.24 (1.12–4.48)]. The interaction of chlorpyrifos with MM genotype was more pronounced in the cases of earlier PD onset (<60 years) [OR (95% CI): 5.30 (1.71–16.44)]. However with regards to parathion, the study did not detect any interaction with PON1 L55M polymorphism in the risk of PD possibly because hydrolysis by PON1 seems not to be the primary pathway of paraxon (the active metabolite of parathion) detoxification (Li et al., 2000). The joint effects of PON1 L55M polymorphism with organophosphates was also investigated in two other studies but no significant association was reported (Dick et al., 2007; Fong et al., 2005). Overall, PON1 variants may represent a potential biomarker of identifying individuals susceptible to organophosphorus neurotoxicity leading to neurodegeneration and PD.

1.2. Pesticide transport

ATP-binding cassette, subfamily B, member 1 gene (ABCB1): ABCB1 gene encodes for a large transmembrane protein the multidrug resistance protein 1 (MDR1), which acts as an ATP-dependent efflux pump for a wide variety of endogenous substances, drugs and xenobiotics. Among other tissues, MDR1 is highly expressed in endothelial cells of blood–brain–brain barrier preventing thus the accumulation of molecules in the brain and speeding up their removal. Mouse knockout for the ABCB1 gene exhibited nearly 100-fold increased accumulation of the neurotoxic pesticide ivermectin compared to wild type (Schinkel et al., 1994). Several pesticides have been shown to be capable of binding and/or inhibiting MDR1 protein that may explain their accumulation into the brain. In a recent gene-pesticide interaction association study on ABCB1 gene the authors focused on two polymorphisms that were reported to alter the expression and activity of MDR1 protein: the G2677A/T (Ala893Ser/Thr; rs2032582) and the C3435T (Ile1140Le; rs 1045642). The study included 207 PD cases and 482 controls characterized by an increased prevalence of pesticide exposure for gardening or professional use (Dutheil et al., 2010). Each polymorphism was not found to influence the risk of PD. However, males homozygous for the variant alleles of G2677A/T polymorphism and reported professional exposure to organochlorine insecticides showed a trend towards increased risk of PD [OR (95% CI): 3.5 (0.9–14.50)]. When the analysis performed among the PD cases only, a significant interaction was detected between homozygosity for the variant alleles and organochlorine exposure in the risk of PD for each polymorphism [OR (95% CI): G2677A/T: 5.4 (1.1–27.5), C3435T: 4.1 (1.0–17.0)]. In addition after using the cumulative lifetime exposure hours as a measure of pesticide exposure, instead of the categorical variable ever/never exposed, the interaction between G2677A/T polymorphism and organochlorine exposure continued to remain significant (p value: 0.005). In another study in 415 PD cases and 184 controls a significant interaction between pesticide exposure and T allele of the C3453T polymorphism was revealed [OR (95% CI): 4.744 (1.009; 22.306), whereas no such effect was noticed for G2677A/T polymorphism (Zschiedrich et al., 2009). Similarly, in a study of 107 PD patients and 103 controls, carriers of T allele of C3453T polymorphism were at increased risk of PD when exposed to pesticides [OR (95% CI): 4.9 (1.7–14.6) (Drozdzik et al., 2003)]. These studies suggest that genetic vulnerability in pesticides transport and elimination may predispose neurons to the toxic effects of pesticides leading to neurodegeneration.

1.3. Mitochondrial dysfunction and oxidative stress

Glutathione S-transferase genes: Glutathione S-transferases (GSTs) are a family of membrane-bound and cytosolic enzymes that catalyze the conjugation of reduced glutathione (GSH) with reactive electrophilic compounds derived from xenobiotic agents, toxic endogenous substrates or reactive species of oxidative stress (Hayes and Pulford, 1995). Apart from the enzymatic activities, GSTs bind to cytotoxic substances and thus serve as transport proteins preventing the interaction between these ligands and cellular molecules (Litwack et al., 1971). The GSTs may also have direct neuroprotective effects via inhibition of the c-Jun N-terminal kinase 1 (JNK1) in the mitogen-activated protein (MAP) kinase pathway, a kinase involved in stress response, neuronal apoptosis and death (Adler et al., 1999; Leppa and Bohmann, 1999). There are a number of cytosolic GSTS isoforms with functional differences that exhibit genetic variations. The possibility of joint effects of GSTS polymorphisms and pesticide use was first tested in a small group of 95 PD patients and 95 controls (Menegon et al., 1998). Out of this group 39 patients and 26 controls reported exposure to
pesticides for more than 6 months before the onset of PD. The authors investigated the effects of the following polymorphisms: GSTM1 deletion, GSTT1 deletion, GSTP1 *1104Val* and *Ala114Val* and GSTT1 (*Lys32Glu*, *Arg42Gly*). The study revealed that the distribution of GSTP1 genotypes were significantly different among cases and controls exposed to pesticides (*p* = 0.009). Another recent study also tested pesticide-GSTs interaction in a Japanese population of 238 PD patients and 370 controls with about 50% of them reporting either home or professional pesticide use (Kiyohara et al., 2010). In total seven GSTs polymorphisms of 5 isoforms were tested: GSTM1 deletion, GSTT1 deletion, rs1695 of GSTP1, rs4925 and rs11191972 of GSTO1, rs156697 and rs2297235 of GSTO2. However, none of these polymorphisms were found to interact with pesticide use in the risk of PD. In contrast, another study in 7 SNPs of GSTP1 gene including the non-synonymous Ile104Val and Ala114Val polymorphisms revealed a joint effect with pesticide use in the age of PD onset (Wilks et al., 2006). In particular, in 278 male PD patients (104 of whom reported residential and occupational use of herbicides respectively) three SNPs (rs749174, rs1871042, rs947895) were found to interact with herbicide use in the age of PD onset (*p* < 0.05). In addition, haplotype analysis of the 7 studied SNPs revealed two haplotype blocks. Using one SNP of each block [rs1799811 (Ala114Val) and rs762803] the authors detected a haplotype (major allele of rs1799811 and minor allele of rs762803) that was associated with earlier PD onset by 7.93 years in the occupationally herbicide exposed group (*p* = 0.008) and a later onset of PD by 2.82 years in the non-exposed group (*p* = 0.048). In another study in 767 PD and 1989 European controls the authors investigated the effect of GSTM1 deletion, GSTT1 deletion, GSTM3 (a 3-bp insertion/deletion in intron 6) and GSTP1 (Ile104Val and Ala114Val) polymorphisms. The study showed that individuals heavily exposed to solvents (but not to pesticides) were at increased risk of PD when null homozygous in GSTM1 gene [OR (95%CI): 2.34 (1.08–4.62)] (Dick et al., 2007). Taken together, the above mentioned genetic association studies provide some evidence, although not consistent, for interaction between pesticide exposure and GSTs variants in the risk of developing PD and the age of disease onset.

**Heme oxygenase-1 gene:** Heme oxygenase (HOX1) is an enzyme that catalyzes heme degradation and release of carbon monoxide and free iron. HOX1 has also antioxidant properties and is upregulated in response to oxidative damage induced by various insults including pesticides. PD animal models treated with MPTP exhibited oxidative stress and increased expression of HOX1 in striatum (Fernandez-Gonzalez et al., 2000). Possible interaction between pesticides and HOX1 gene polymorphism was tested in a study of 237 PD patients and 203 controls (Infante et al., 2011). The authors studied a polymorphism in the promoter region of the gene (−413, rs2071746) that alters its transcriptional activity. Although the study did not detect any significant effect on PD risk for either the promoter polymorphism or pesticide exposure, when both these factors were combined a significant joint effect was detected [OR (95%CI): 5.49 (1.17–25.6)]. It is therefore possible that those individuals with genetically defective antioxidant response may be at increased risk of PD when exposed to toxic compounds such as pesticides.

**Nitric oxide synthase gene:** Nitric oxide synthases (NOS) are a family of enzymes that catalyze the production of the reactive free radical nitric oxide (NO) which is implicated in several physiological and pathological processes. There are three NOS isoforms encoded by different genes: the neuronal NOS (nNOS) encoded by NOS1, the inducible (iNOS) encoded by NOS2A and the endothelial (eNOS) encoded by NOS3 gene. Excessive NO has been implicated in loss of dopaminergic neurons that characterizes PD. The effect of NOS genes on PD risk in relation to pesticides was reported as part of a large association study in a sub-population of 178 cases and 178 relative and controls (Hancock et al., 2008). In order to capture most of the genetic variability across the three genes the authors selected 27 common and tagging SNPs of NOS1 gene, 17 NOS2A gene SNPs and 5 NOS3 gene SNPs. The study revealed an interaction of pesticides with NOS1 intronic rs12829185 [OR (95%CI): 3.12 (1.71–5.71)], the intronic rs10774910 [OR (95%CI): 1.58 (1.03–3.54)] and the rs2688286 [OR (95%CI): 3.52 (1.78–6.95)] located in the 3′ untranslated region of NOS1 gene. The data from this study implicate another component of oxidative stress the NO production that may interact with pesticides exposure in the development of PD.

**Manganese superoxide dismutase, quinone oxidoreductase 1 genes:** The manganese superoxide dismutase (MnSOD; SOD2) is an important antioxidant enzyme of mitochondria that catalyzes the conversion of superoxide radicals into oxygen and hydrogen peroxide. There is a common polymorphism in the −9 codon of MnSOD signal peptide causing a Valine to Alanine substitution. This amino acid transition is reported to have functional consequences on the structure of the mitochondria-targeting sequence leading to impaired MnSOD protein trafficking and activity (Grasbon-Frodil et al., 1999). Quinone oxidoreductase 1 (NQO1) is a cytosolic enzyme that catalyzes the two-electron reduction of quinoid compounds utilizing NAD(P)H as co-factor, preventing thus the formation of reactive oxygen species. A non-synonymous functional polymorphism of NQO1 gene (C609T, Pro187Ser) has been described to affect significantly the enzymatic activity (Kuehl et al., 1995). The above mentioned polymorphisms were investigated in 153 PD patients and 155 healthy controls for possible interaction with occupational pesticide exposure. The study showed that carriers of Ala(-9) MnSOD or 187Ser NQO1 polymorphisms were at increased risk of PD only when exposed to pesticides [OR (95%CI): 2.49 (1.18–5.26) and 2.42 (1.16–4.76), respectively] (Fong et al., 2007). However, no equivalent findings were detected in another study of 767 PD and 1989 controls for the same polymorphisms (Dick et al., 2007).

In general, one of the main mechanisms of pesticide toxicity that may lead to the development of PD is mitochondrial dysfunction and induction of oxidative stress. Individuals carrying specific genetic variants may be more or less vulnerable to the toxic effects of pesticides leading to oxidative damage of dopaminergic neurons. However, given the conflicting results in different studies focused on subsets of genes and the fact that numerous enzymes are involved in these processes, association studies should include all relevant genes and be conducted in larger populations with high frequencies and levels of pesticide exposure in order to detect significant gene-pesticide interactions.

1.4. **Neuronal toxicity**

**Dopamine transporter (SLC6A3) gene:** The dopamine transporter protein (DAT) is responsible for the active reuptake of dopamine from the synapse back into pre-synaptic terminals that terminates the dopaminergic neurotransmission. It is possible that DAT may be the gateway of neurotoxins and pesticides into the dopaminergic neurons (Edwards, 1993) although there is still no conclusive evidence regarding the mechanisms involved in the selective loss of dopaminergic neurons after pesticide exposure (Richardson et al., 2005). The effect of SLC6A3 gene polymorphism in combination with pesticide use was examined in a case-control study of 293 cases and 395 controls (Kelada et al., 2006). In a search for risk alleles in the highly variation diverse promoter region the authors, out of 22 SNPs, constructed two evolutionary clades (A and B) that were found to affect gene expression. In addition, from the 3′-untranslated region, a well-known variable number of tandem repeat (VNTR) polymorphism was selected for the study as a risk allele for PD. None of these regions separately was associated...
with increased risk for PD. However, after combining both regions the authors detected that possession of two or more risk alleles was associated with a modestly increased risk of PD [OR (95%CI): 1.58 (1.03–2.40)]. More importantly, this association was stronger among male individuals exposed to pesticides [OR (95%CI): 5.66 (1.73–18.53)] suggesting a significant 5LCA63 risk alleles-pesticide interaction. Using the same approach and risk alleles, a dose dependent effect was reported in a recent study of 324 incident PD patients and 334 population controls (Ritz et al., 2009). Among individuals living close to areas of high use of both parquat and maneb, carriers of one susceptibility allele had a 3-fold increase in the risk of PD [OR (95%CI): 2.99 (0.88–10.2)] which rose to 4.5-fold in carriers of two or more risk alleles [OR (95%CI): 4.53 (1.70–12.1)].

\textit{a-Synuclein gene (SNCA)}: Fibrillar a-synuclein (a-syn) aggregates in the form of intraneuronal Lewy body inclusions appear to be central in the pathogenesis of PD. SNCA gene missense mutations or gene multiplication causes autosomal dominant PD (Xiropermisou et al., 2010). A microsatellite polymorphism in the promoter of SNCA gene (REP1, D4S3481) that alters gene expression, was linked to the development of sporadic PD (Xiropermisou et al., 2010). Pesticides were found to directly accelerate the rate of a-syn fibrillation (Uversky et al., 2001). In addition, a-syn transgenic animal models of PD exposed to pesticides exhibited increased a-syn pathology suggesting combined interaction (Gao and Hong, 2011). In a rural population of 333 PD cases and 336 population controls the SNCA REP1 polymorphism was investigated for combined effects with residential pesticide exposure assessed from the proximity of individuals’ homes to agriculture fields, where substantial amounts of pesticides were applied. With regards to joint effects on PD risk and age of onset, the degree of interaction did not reach statistical significance, possibly due to the small number of individuals in the category of high level of paraquat exposure combined with longer repeat polymorphism (Gatto et al., 2010). A previous study in 833 cases and 833 case-unaffected siblings and unrelated controls also failed to detect any interaction between SNCA REP1 polymorphism and self-reported pesticide exposure (Brighina et al., 2008).

\textit{LRRK2, BDNF genes}: Leucine-rich repeat kinase 2 (LRRK2) is a large protein kinase with multiple domains, localized predominantly in the cytoplasm but also associated with the mitochondrial outer membrane. Mutations in the LRRK2 gene were found to cause familial PD (PARK8) (Paisan-Ruiz et al., 2004). Pathogenic mutations may increase LRRK2 kinase activity, which appears to mediate neuronal toxicity (Greggio et al., 2006). In a recent study, possible interaction between LRRK2 SNPs and pesticide use was investigated. A population of 453 PD cases and 291 controls were genotyped for 6 coding LRRK2 SNPs: G1624C, R1628P, K1637K, S1647T, E2108E, G2385R. The study revealed that the S1647T polymorphism, which alters the folding structure of the protein, was associated with increased risk of PD only in individuals exposed to pesticides (Lin et al., 2011). The same study reported a similar interaction between pesticide use and the V66M polymorphism of BDNF (brain derived neurotrophic factor) (Lin et al., 2011), a neurotrophic factor that protects dopaminergic neurons from oxidative insults.

\textit{PINK1 gene}: PTEN-induced putative kinase 1 (PINK1) is a ubiquitous serine/threonine-protein kinase that localizes to mitochondria, where it is believed to defend against oxidative stress and protect neurons from mitochondrial dysfunction. Mutations in PINK1 gene cause PARK6, an autosomal recessive early-onset PD (Valente et al., 2004). In a preliminary study of 48 early onset PD patients and 61 controls, a polymorphism in exon 2 splicing region of PINK1 gene (IVS1–7 A/G, rs2298298) in conjunction with exposure to environmental risk factors (including pesticide use) were associated with earlier onset of PD (Godeiro et al., 2010). Also, another study in 453 PD cases and 291 controls showed a trend towards combined effects of pesticide use and a non-synonymous PINK1 gene SNP (Ala340Thr, rs3738136), [OR (95%CI): 7.39 (0.85–64.09), p = 0.07] (Lin et al., 2011).

2. Potential confounders

The epidemiological evidence of gene–pesticide interactions associated with PD is currently inconsistent and subject to limitations, for example with regard to case definition. Also, most of the studies in the literature are case–control studies and recall bias is known as an important limitation which is further complicated by effects of age and possibly of the disease.

A potential source of bias in many studies is the absence of validated exposure assessments. The vast majority of studies rely on self-reports using questionnaires and there is the potential for misclassification, particularly if individuals associate their disease with pesticide exposure. Most studies do not attempt to validate exposure estimations, e.g. through occupational or biomonitoring. Few studies analyze exposure by frequency or duration of use, or by specific chemicals. Although most studies adjust for age and sex, there is often no adjustment for other potentially confounding factors, in particular smoking which is the environmental factor most consistently associated with a reduction in the risk of developing PD (Wirdzelfeldt et al., 2011). In addition, exposure to other environmental factors such as living in a rural area, well water use, farming, exposure to farm animals or living on a farm point out the problem of confounding factors.

Given these limitations there is a need for larger, prospective studies with adequate exposure measurements, ideally through biomonitoring, which consider a range of gene–environment interactions.

3. Conclusions

Multiple genetic and environmental risk factors are known to confer susceptibility to the development of PD. Each factor individually may have a minor effect, whereas their interaction may prove sufficient to cause PD. It is therefore possible that separate study of genetic or environmental factors may not detect significant interactions which may account, at least in part, for the inconsistent findings in the environmental and genetic association studies.

Human genetic association studies that tested for interaction between genes and pesticides’ exposure in the risk of PD have provided some evidence that genetic susceptibility either in metabolism, elimination and transport of pesticides or in the extent of mitochondrial dysfunction, oxidative stress and neuronal loss may increase the risk of individuals of developing PD when they are exposed to pesticides. However, this evidence is currently limited and conflicting, and it is therefore important that these interactions are considered in future studies which may provide a better understanding of the pathogenic mechanisms of PD.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References


