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REVIEW

Polymorphism in candidate genes: implications for the risk and treatment of idiopathic Parkinson's disease

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ABSTRACT
Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder for which no restorative or neuroprotective therapy is available. Interest has recently been directed to association studies on polymorphisms of various genes, mainly those related to dopamine metabolism and transport, and their effect on response to PD, which includes primarily levodopa and dopaminomimetics. Approximately 15–20% of patients with PD do not respond to levodopa, and the majority of those who do respond develop adverse fluctuations in motor response, primarily levodopa-induced dyskinesias. This review summarizes the influence of polymorphisms in various genes on the relative risk of IPD and on levodopa efficacy. It focuses on the importance of well-designed polymorphism studies that include large samples of patients with IPD and tightly matched controls and use identical methodologies. Valid data on such polymorphisms might increase the efficacy of levodopa, decrease its side effects, and reduce the occurrence of levodopa-induced dyskinesias. They might also provide a novel diagnostic tool for PD.
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Introduction

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disease for which no restorative or neuroprotective therapy is available. It is characterized by continuous cell loss in the nigrostriatal system — about 10% per year by positron-emission tomography (PET).[1,2] In recent years, evidence highlighting the importance of the interaction between environmental factors and genetics has prompted a large number of association studies on the role of gene polymorphisms in the relative risk of IPD. Candidate genes were selected on the basis of the current understanding of the pathophysiology of IPD and include mainly genes that are linked to dopamine synthesis, transport, and degradation, detoxification of xenobiotics and other toxins in dopaminergic neurons and mitochondrial metabolism, and also genes that encode for essential transcription factors or neurotrophic factors involved in the development of the mesencephalic dopaminergic system. In addition, a number of association studies suggested that functional polymorphisms might affect the phenomenon of

'levodopa-nonresponse' and levodopa-induced motor fluctuations, mainly levodopa-induced dyskinesia.

The aim of the present review was to summarize the polymorphism-association studies on IPD performed to date, with emphasis on the influence of polymorphisms in dopamine-related genes on the efficacy of levodopa. We searched the Medline database (PubMed) from January 1954 to January 2004 using the key words 'PD', 'polymorphism', and 'levodopa'. The search was augmented by a review of the references cited in the articles identified. Only studies with two or more independent investigations of a specific gene, or gene-family polymorphism in patients with clinically and/or pathologically well-diagnosed IPD and matched (age, gender, and ethnicity) controls (healthy or without clinical evidence of neurodegeneration disease), were included. The genes whose polymorphisms have already been studied in relevance to IPD risk and genes that should be examined were summarized in Table 1. The genes that have been studied were subdivided into those confirmed via meta-analysis, and those that were not confirmed by meta-analysis. The genes that were not confirmed by meta-analysis were further divided into those which fulfilled the Lohmueller *et al* criteria for replication in meta-analysis,[3] and those which did not (see Table 1). This review addresses some of the difficulties in interpreting of the results and provides recommendations for designing novel polymorphism-association studies in the future.

Genetic variations with potential effect on PD risk: dopamine metabolism

Dopamine receptors

The dopamine receptors are one of the most studied groups for polymorphism and IPD risk. There are five types. The D1 receptors include types D1 (DRD1) and D5 (DRD5) and the D2 receptors include types D2 (DRD2), D3 (DRD3), and D4 (DRD4). All are located in the striatum and are primarily involved in the dopaminergic response in PD.[4,5] The D2 receptors mediate the motor effects of central dopamine stimulation. The genes for the five receptors are found on four separate chromosomes.[6–10] Each type contains seven transmembrane domains with a unique binding site formed by the external loops of the protein.[11]

DRD2: There are nine studies on DRD2 polymorphism in PD. Of the three studies that investigated the 141C Ins/Del and Ser311/Cys311 variants,[12–14] two showed a significant difference in allelic frequencies between patients with PD and control subjects, whereas the third failed to find any such association.[12] The first two studies[13,14] also examined the A1 allele of the TaqIA polymorphism, and the B1 allele of the TaqIB polymorphism, and found that they were more frequent in patients with PD than in control subjects: Patients carrying the A1 or B allele had an increased risk of developing PD. Two other studies of the same polymorphism did not find any association with PD,[15,16] with or without the combination of genotypes for intron 13 of

Table 1 Candidate genes that might confer idiopathic Parkinson's disease susceptibility

Genes that have been studied			
Genes confirmed via well-designed meta analysis	*Genes that were not confirmed via well-designed meta analysis*		*Genes that have not been studied*
	Fulfilled criteria for replication in meta-analysis*	*Did not fulfill criteria* for replication in meta-analysis*	
DRD4	DRD2	DRD5	Neurotransmitters (eg, glutamate, GABA, etc) and Neuropeptides (eg, substance p, enkephalin, etc).
DAT	UCH-L1	DBH	Dopamine-signaling molecules (eg, CDK5, DARPP-32, etc).
COMT	BDNF	GDNF	Other enzymes (eg, GC) necessary for synthesis of critical cofactors for dopamine metabolism (eg, BH4, etc).
MAO-B	α-Synuclein	MAO-A	Other neurotrophic factors (eg, NGF, FGF, TGF, etc).
CYP450 Ezymes	Nurr-1	TH	Other transcription factors (eg, En1, Pitx3, Lmx1b, etc).
ND2	ND3	Parkin	Other linkage-derived genes (eg, PARK3-PARK8, etc).
NAT2		Catalase	Other antioxidant factors and enzymes (glutathione, GRX, GPX, etc).
APO-E4		SOD	
GST		AADC	

**P*-value of less than 0.001 for initial positive studies or less than 0.01 when the results are replicated independently by two studies.[3]
AADC = aromatic amino acid decarboxylase; *APO E4* = apolipoprotein E4; *BDNF* = brain derived neurotrophic factor; *BH4* = tetrahydrobiopterin; *CDK5* = cyclin-dependent kinase 5; *COMT* = catechol-*O*-methyltransferase; *CYP450* = cytochrome *P*450; *DARPP-32* = AMP-regulated phosphoprotein of 32 kDa; *DAT* = dopamine transporter; *DBH* = dopamine β hydroxylase; *DR* = dopamine receptor; *EN* = engrailed gene; *FGF* = fibroblast growth factor; *GABA* = γ-amino butyric acid; *GC* = GTP cyclohydrolase I; *GDNF* = glial-derived neurotrophic factor; *GRX* = glutathione reductase; *GPX* = glutathione peroxidase; *GST* = glutathione transferase; *Lmx1b* = LIM-homodomain transcription factor 1B; *MAO* = monoamine oxidase; *ND2/3* = NADH dehydrogenase subunit-2/3 gene; *NAT2* = *N*-acetyltransferase 2; *NGF* = nerve growth factor; *Nurr-1* = nuclear receptor related-1; *Pitx3* = pituitary homeobox 3; *SOD* = superoxide dismutase; *TH* = tyrosine hydroxylase; *TGF* = transforming growth factor; *UCH-L1* = ubiquitin carboxyl-terminal hydrolase L1.

monoamine oxidase B (MAO-B),[16] the dopamine-deactivating enzyme. nor was there an association of smoking and PD risk with the presence of these polymorphisms.

The remaining four studies examined the polymorphic dinucleotide repeat in the second intron of the DRD2 gene,[17–20] but only two of them[18,20] found a significant association between this polymorphism and PD in Caucasians.

Together, these findings imply that the DRD2 polymorphism might be involved in the risk of PD, but more studies and well-designed meta-analysis are needed for verification (see also Table 1).

DRD4: Five studies examined the 48 base-pair tandem repeat polymorphism in exon 3 of the DRD4 gene.[12,17,21–23] Only one reported a significant association, namely, a higher rate of repeat numbers 6–7 in PD patients ($n=95$) those controls ($n=47$) in the Chinese population.[23]

These results, together with the meta-analysis performed by Tan *et al*,[24] suggest that the DRD4 does not play a major role in PD (see Table 1).

Dopamine transporter

The dopamine transporter (DAT) is normally present in the terminals of neurons originating in the substantia nigra. It has been shown to confer 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) toxicity to non-neuronal cell cultures by allowing uptake of the 1-methyl-4-phenylpyridinium ion [MPP(+)].[25] The DAT gene contains a variable number tandem repeat (VNTR) in the 3′-untranslated region. Between three and 11 copies of this 40-bp repeat element are found in normal populations.[26] Of the five early studies that examined this polymorphism in the DAT gene,[12,18,27–29] the Australian study[28] showed an association of the 11-copy allele with a 10-fold increase in the risk of IPD. In the studies conducted more recently, the rare 11-copy allele was found to occur more often in PD patients in the Korean population[30] and in Chinese patients ($n=171$[31] and $n=180$[32]) compared to control subjects ($n=128$[31] and $n=85$[32], respectively). However, these findings were not confirmed in two other studies,[33,34] which revealed that the homozygote 10-copy genotype of VNTR may confer protection against PD, but only in males.[34]

Four studies examined the 1215A/G polymorphism located in exon 9,[35–38] but only two of them, both from Japan, noted a significant decrease in the 1215G polymorphism in patients with PD compared to controls.[35,36]

Overall, the results so far, including the meta-analysis performed,[24] concerning the DAT polymorphism and the risk of PD remain equivocal.

Tyrosine hydroxylase

The tyrosine hydroxylase (TH) gene encodes for the rate-limiting enzyme in catecholamine synthesis. The two control studies conducted to date on the involvement of functional polymorphisms of the TH gene in the pathogenesis of PD found no significant allelic or genotypic association of IPD with the Val 81Met polymorphism.[39,40] Although only two studies were performed, TH polymorphism does not seem to be involved in IPD susceptibility.

Dopamine beta hydroxylase

Two studies examined the correlation of dopamine hydroxylase (DBH) gene and polymorphism with susceptibility to PD.[41,42] The first failed to show any significant association.[41] The other one, however, found that the allelic frequency of A2 allele and the genotypic frequency of A2/A2 genotype of the DBH gene were significantly higher in PD patients in the Shanghai Chinese Han population ($P<0.01$), and that the risk of suffering from PD increased in individuals with the A2 allele. At the same time, the allelic frequency of the A1 allele and the genotypic frequency of the A1/A2 genotype were significantly lower in PD patients ($P<0.01$).[42]

DBH is an enzyme that catalyzes the reaction of dopamine to adrenaline. Therefore, it seems reasonable to suggest that polymorphism in this enzyme might alter its activity and reduce dopamine levels in the brain. However, neurons that express TH and DBH are defined as noradrenergic neurons only,[43] and therefore the relevance of this polymorphism and PD risk is doubtful.

Monoamine oxidase (MAO)

The monoamine oxidase (MAO) enzyme oxidizes various physiologically and pathologically important monoamine neurotransmitters and hormones, such as dopamine, noradrenaline, adrenaline, and serotonin. There are two types of MAO — type A (MAO-A) and type B (MAO-B) — each with different bioactivities.

Monoamine oxidase A (MAO-A)

Three of the nine existing of MAO-A polymorphism in PD examined the (GT)*n* dinucleotide repeat in intron 1 of the MAO-A locus on the X chromosome.[18,44,45] One found that the polymorphic 122 allele appeared three times more frequently in patients with PD ($n=91$) than in control subjects ($n=129$).[44] The second study reported that 119 allele appeared 10 times more frequently in men with PD ($n=30$) compared with control subjects ($n=102$).[45] The third study did not find any association.[18]

Two separate studies, of which one examined the (GT)*n* dinucleotide repeat in intron 2 of MAO-A locus on the X chromosome, and the other examined the RLFP with *Eco*RV polymorphism, found no differences in the distributions of any MAO-A alleles between PD patients and controls.[46,47]

A very recent work found that PD patients had higher frequencies of the G allele and the GG genotype, and lower frequencies of the TT genotype, than controls. When patients were divided into two groups by age of onset, significant differences in the allelic and genotypic frequencies were observed only between the early-onset PD subgroup and the control group; when patients were grouped by sex, a significant difference was observed only between the male PD subgroup and the male controls.[48] By contrast, three other recent studies failed to observe any

such differences in the allelic or genotypic frequency of MAO-A.[16,49,50]

Monoamine oxidase B (MAO-B)

In all, 17 Seventeen studies examined the MAO-B polymorphism. Of them, 10 focused on the G/A polymorphism in intron 13 of the gene, of which four reported a significant positive association with PD in Caucasian and Japanese populations;[47,51–53] the others found no association.[33,46,54–57]

The remaining seven studies examined the (GT)*n* dinucleotide repeat in intron 2 of the gene. Two studies found that the frequency of alleles 186 and 188 or 180 was higher in PD patients in relevance to controls in Caucasian and Australian populations, respectively.[44,58] The remaining investigations did not find any positive association between the presence of the polymorphism and either PD[18,46,59] or the interaction of PD with smoking.[57,60]

According to these and other results,[24] it seems that MAO-A polymorphism and the G/A polymorphism in intron 13 of the MAO-B genes are not associated with IPD susceptibility, while the >188 bp allele of MAO-B polymorphism might confer IPD susceptibility (see Table 1). Some of the between-study differences may be due, in part, to differences in methodologies and in the polymorphisms studied.

Catechol-O-methyltransferase (COMT)

One of the most studied enzymes in patients with PD is catechol-*O*-methyltransferase (COMT). COMT inactivates neurotransmitters, hormones, potentially toxic metabolites, and xenobiotics containing a catechol moiety by enzymatic methylation.[61–63] Its activities include the catalyzation of levodopa degradation to 3-*O*-methyldopa (3-OMD) in the periphery and brain. IT also catalyzes dopamine degradation to 3-methyoxythyramine (3-MT), and degradation 3,4,-dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA).

Eight studies investigated the G to A (108 Val to 108 Met) substitution in exon 4 of the COMT gene, a common amino-acid polymorphism that results in low efficacy of the enzyme. Three found that the frequency of the 108Val allele is higher in PD patients than controls in the Japanese[64,65] and Taiwanese[52] populations, and is augmented by the MAO-B G intron 13 polymorphism. However, these findings were not confirmed in studies of IPD patients in Caucasian,[66] Chinese,[67] Finnish,[68,69] and American[33] populations, and therefore a conclusion regarding the association of COMT to IPD risk cannot be made (see Table 1).

Xenobiotic metabolizing enzymes

Cytochrome P450 system enzymes

Researchers have postulated that certain enzymes in the cytochrome *P*450 (CYP) system provide a protective mechanism from environmental neurotoxins.[70] Several reviews and meta-analysis were performed to determine whether there is an association between cytochrome *P*450 polymorphisms (CYP2D6, CYP1A1, CYP2C9, CYP2C19, CYP1A2, and CYP2E1) and the risk of PD.[71–76]

The most studied is the CYP2D6 gene, which encodes for the enzyme debrisoquine 4-hydroxylase that metabolizes a wide range of drugs, including MPTP, and has a number of functional polymorphisms.[77,78] However, the findings were inconclusive. Although two meta-analyses[72,74] reported a significant association of the poor-metabolizer genotype with PD, the other two did not reveal any significant association.[73,75] In research conducted since the publication of these meta-analyses, no association was found between CYP2D6 polymorphism and the risk of PD.[79–86]

CYP2E1 is an ethanol-inducible enzyme apparently involved in the activation of neurotoxicants that increase oxidative stress (OS), a well-known contributory factor in the pathogenesis of PD.[87] Three studies found no significant differences between PD patients and controls in the distribution of either allelic or genotype frequencies of CYP2E1,[88,89] suggesting that there is no association between this gene and IPD.

Findings for the CYP1A1 polymorphism were inconclusive. In two studies, the authors found that the relative risk of PD was higher in the CYP1A1 m2 alleles and the CYP1A1 m1m2 and m2m2 genotypes,[89,91] but these results were not confirmed by two other studies.[83,92]

Overall, these results do not suggest any association between the cytochrome *P*450 enzymes examined to date and the risk of IPD (see Table 1).

Glutathione s-transferases

As mentioned above, OS is widely thought to contribute significantly to the pathogenesis of PD.[87] Given the role of glutathione S-transferases (GSTs) in the conjugation of electrophiles and protection against reactive oxygen species, researchers have suggested that genes encoding the GSTs are good candidates for association studies of PD.[93] Seven studies investigated the role of the GST polymorphisms (GSTM1, GSTT1, GSTP1, and GSTZ1) in the pathogenesis of IPD. Three found that polymorphisms of the GSTM1 and GSTT1 loci resulting from complete gene depletions increased susceptibility to PD.[93–95] One of these studies further examined the presence of null genotypes of GSTM1, GSTT1, and two polymorphisms of mEPHX in subjects with PD, and found raised levels of homozygosity of the histidine (H) 113 isoform of mEPHX.[95] Analysis of the allele frequencies yielded an increased frequency of the H-allele in these patients. Furthermore, a significantly elevated median age of onset of PD was found among the GSTM1 gene carriers compared to the PD patients with GSTM1 null genotypes.[95] The remaining four studies did not confirm these results, and did not find any association between GST polymorphisms and the risk of PD.[96–99] The variability of these findings precludes a definitive conclusion regarding the association of GST polymorphism with IPD risk.

N-acetyl transferase

Seven studies examined the *N*-acetyl transferase-2 (NAT2) polymorphism. Of the four that focused on polymorphisms of NAT2 in chromosomes 8p21.3–23.1, all reported a higher frequency of the slow acetylator genotype in PD[81,98,100] or in young-onset PD.[101] However, the remaining studies, which investigated three mutant alleles M1, M2, and M3 of NAT-2, did not find any differences in allelic frequencies or genotypic distributions between patients with IPD and age-matched controls from the Netherlands,[102] Europe,[103] and the US.[104] Although Tan *et al*[3] reported that the slow acetylator genotype of NAT2 is associated with IPD risk, findings of recent studies raise doubts concerning this issue.

Other related genes

Apolipoprotein E

Apolipoprotein E (ApoE) is an important factor in plasma lipid metabolism and a component of several plasma lipoprotein–lipid particles. In all, 25 studies examined the C/T transition converting codon 112 from cysteine (E3) to arginine (E4) in PD patients. Four of them showed that the E4 allele occurred more often in demented[105,106] and nondemented[107,108] PD patients, but the others did not find any positive associations.[69,109–130] Two additional studies examined the C/G-T/A transition converting codon 158 from arginine (E3) to cysteine (E2), and found that E4 allele E4 had a higher frequency in young[131] and demented[132] PD patients. Taken together, the results of these studies raise doubts as to the association between Apo-E and PD risk.

Mitochondrial genes

Several mitochondrial polymorphisms have been reported in the literature, including the G5460A at mtDNA-encoded reduced nicotinamide adenine dinucleotide dehydrogenase (NADH) 2 (ND2) of complex I and A4336G at the $tRNA^{Gln}$ gene. In a study of the G5460A missense mutation in the ND2 subunit gene of NADH dehydrogenase, a three-fold higher frequency was noted in patients with PD (4/21) compared to controls (5/77).[133] These results were not replicated in later studies.[134,135] Another study found the mtDNA (A4336G) mutation in two of 23 PD patients and none of 100 age-matched controls ($P<0.05$).[136] No differences in the frequency of the A4336G polymorphism were noted between IPD patients and controls.[133,135,137,138] A recent study examined the ND3 of complex I enzyme and found that individuals with a specific haplogroup (J or K) demonstrated a significant decrease in risk of PD as opposed to individuals carrying the most common haplogroup (H). Furthermore, a specific single-nucleotide polymorphism (SNP) that defines the J and K haplogroups, 10398G, was strongly associated with this protective effect.[139] These results suggest that ND3 is an important factor in PD susceptibility and could help explain the role of complex I in PD expression; however, more studies and meta-analysis are needed to confirm these data (see also Table 1).

Neurotrophic factors

Brain-derived neurotrophic factor (BDNF) Two studies found that homozygosity for the V66M polymorphism of the brain-derived neurotrophic factor (BDNF) gene occurs more frequently in patients with PD than in unaffected controls.[41,140] However, three other studies conducted in Swedish[141] and Japanese populations did not confirm these results.[142,143]

Glial-derived neurotrophic factor (GDNF) In the only study on glial-derived neutrophic factor (GDNF), a potent survival factor for nigrostriatal dopaminergic neurons was found in one of 30 PD patients. However, the alteration did not change the predicted amino-acid sequence, and it was also found in one of 20 patients without PD.[143]

Further studies and meta-analysis are needed before we can draw conclusions concerning the effect of neurotrophic factors, and especially genetic variations in BDNF, on the risk of IPD (see also Table 1).

Antioxidant enzymes

Antioxidant enzymes are very important in regulating the OS level in cells.[87] Low levels of these enzymes might increase OS and aggravate PD. Indeed, many studies have reported an aberrant OS metabolism within the substantia nigra and other dopaminergic regions of the brain in patients with PD.[87] In one investigation for the possible link between an antioxidant enzyme polymorphism and the risk for PD, the genes encoding for three free-radical detoxifying enzymes were screened: copper/zinc superoxide dismutase, manganese superoxide dismutase (SOD2), and catalase. The authors found an amino-acid substitution (glycine to aspartic acid) in exon 9 of the catalase gene in one PD patient; the same patient also showed a decrease in red blood cell catalase activity.[145] Although similar results were obtained in another study,[146] later investigations did not find any genetic differences in the distributions of allelic frequencies of SOD2 between PD patients and controls.[147–149] The interpretation of these inconclusive results is problematic.

Linkage-derived candidate genes

Alpha-synuclein This is a presynaptic protein highly and broadly expressed in the brain, but its normal function is unknown. It is also called non-amyloid β component precursor (NACP) because of its localization in amyloid plaques in Alzheimer's disease. Mutations of the alpha-synuclein gene have been shown to be relevant in some rare cases of autosomal dominant PD. Among the nine association studies performed to date, only four found significant results for the polymorphism of the promoter region of the alpha-synuclein gene (NACP-Rep1) in German,[131] American,[150,151] and Japanese[152] populations; the remaining studies from Japan,[153] Ireland,[154] Singapore,[155] Germany,[156] and Italy[157] found no differences from controls. More studies and meta-analysis are needed in order to determine

unequivocally whether the alpha-synuclein gene polymorphism is associated with IPD risk (see also Table 1).

Parkin Mutations in the parkin gene, an E3 protein–ubiquitin ligase, are known to cause autosomal recessive, early-onset PD. However, the role of polymorphisms in this gene in the risk of IPD was not investigated until recently. In all, 11 studies so far have examined three polymorphisms in the parkin gene: G/A transition in exon 4 (S167N), C/T transition in exon 10 (R366W), and G/C transition in exon 10 (V380L). Seven found that at least one of these polymorphisms was associated with the risk of PD in Japanese,[158,159] American,[160,161] Chinese,[162] French,[163] and Australian[164] populations. The rest found that the allelic or genotypic frequencies of S167N, R366W, and V380L were similar in patients with PD and nonaffected controls in Finnish,[69] Taiwanese-Chinese,[165] Spanish,[166] and American[167] populations.

According to these results and the criteria presented by Lohmueller *et al*,[3] the association of the parkin gene and IPD risk is uncertain.

Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) This peptide belongs to the de-ubiquitinating enzyme family. A missense mutation in this gene was found to cause PD in a German family. Recent studies of the S18Y polymorphism of the UCH-L1 gene noted an association with IPD risk in Japanese,[41,140,168,169] American,[170] German,[171] and French[172] populations. However, two other studies, from Australia[173] and China,[174] did not, though it was suggested that the S18Y polymorphism might be a weak protective factor against early-onset PD.[174]

These results indicate that the presence of the S18Y polymorphism of the UCH-L1 gene might be associated with a reduced risk of IPD. Additional studies and meta-analysis are still required (see also Table 1).

Transcription factors

Nuclear receptor related-1 (Nurr1) This is a member of the steroid/thyroid hormone nuclear receptor superfamily that is predominantly expressed in the midbrain, substantia nigra, and ventral tegmental area. Studies in knockout Nurr1 mice indicate that this hormone receptor is essential for the development and differentiation of midbrain dopamine neurons.[175] Therefore, a polymorphism in this gene may well be related to PD risk. One study on the BseRI restriction site of the Nurr1 gene found a homozygous 7048G7049 polymorphism in intron 6 (NI6P) which had a significantly higher frequency in patients with sporadic PD than in healthy control subjects. The clinical features of the homozygous PD patients were similar to those of typical PD.[175] Although these results were replicated by a recent study,[176] two other recent studies of several independent polymorphisms in the sixth and seventh introns in a Swedish[177] and Singaporean[178] population did not find a significant genotype or allelic association with PD. Further research is warranted to determine whether a polymorphism in this gene or other genes encoding for transcription factors involved in the development of the mesencephalic dopaminergic system, such as engrailed gene (En1), Pituitary homeobox 3 (Pitx3), and LIM-homodomain transcription factor 1B (Lmx1b), are associated with the risk of IPD (see also Table 1).

Genetic variations with a potential effect on levodopa response

Levodopa-induced motor fluctuations in Parkinson's disease

The administration of dopamine precursors, particularly levodopa, is the gold standard of treatment for PD. As levodopa is degraded to dopamine by peripheral aromatic amino-acid decarboxylase (AADC), which does not pass the blood–brain barrier (BBB), it has to be co-administered with an AADC inhibitor (carbidopa or benserazide).

The majority of patients respond well to levodopa, at least during the early years of therapy, with individual differences in the degree of symptom improvement. The failure to respond in approximately 15–20% of patients[4] could be the result of population pharmacokinetic and pharmacodynamic heterogeneity in various genes, or misdiagnosis of another parkinsonian syndrome, such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) as PD. Furthermore, even in good, stable responders, levodopa control of motor symptoms gradually diminishes after 2–5 years.[179] About 70% of patients ultimately develop a variety of adverse, incapacitating motor manifestations (motor fluctuations and dyskinesias) in response to levodopa treatment.[180] Peak-dose dyskinesias (PDDs) are the most common pattern of levodopa-induced dyskinesia occurring before the fifth year of treatment,[4,181] in an estimated 30–80% of chronically treated PD patients.[181–183] PDDs appear during the period of maximal relief of parkinsonian symptoms. They are predominantly choreic in nature, and commonly affect the face, neck, and limbs.[184] When they manifest early in the course of the disease, PDDs are related to peak levodopa concentrations and may be reduced by lowering the treatment dose. Later, however, they occur at levodopa doses needed to induce an anti-parkinsonian effect. These findings suggest that the pharmacologic mechanisms that mediate dyskinesias may differ from those mediating the therapeutic effect of levodopa.[185] Although studies on predictors of the development of dyskinesias have shown discordant results,[4,186,187] several risk factors, such as duration of levodopa treatment, disease duration, female sex, young age at onset, and lower tremor scores at baseline, have been identified. These factors, however, only partially account for the appearance of PDD during levodopa treatment, because a considerable proportion of PD patients present never acquire PDD. Thus, a genetic predisposition probably plays a role as well.

Peripheral pharmacokinetics of levodopa

The plasma elimination half-life of levodopa is quite short (about 2 h), which explains the short duration of action (2–3 h) in patients with advanced disease.[188] Therefore, several strategies are used in order to increase the amount of levodopa passing the BBB or to delay the breakdown of dopamine in the brain, such as co-administration of selegi-

line (deprenyl) or rasagiline or other MAO inhibitors. In addition, the peripheral concentration of levodopa can be increased by inhibiting COMT production with entcapone. Figure 1 depicts a suggested polymorphism model of various dopamine-related genes that may affect the response to levodopa. A polymorphism in the gene encoding for AADC might reduce its activity, thereby reducing dopamine levels in the periphery and brain. In addition, polymorphisms in genes encoding for MAO-B and COMT might increase their activity, leading to a reduction in levodopa and, consequently, in dopamine levels in the periphery and brain.

Pharmacogenomics of levodopa

The mechanisms underlying the fluctuations in response to levodopa are only partially understood. They involve, at least in part, polymorphisms in genes that affect levodopa's pharmacodynamic and pharmacokinetic properties (Tables 2,3).

Pharmacodynamics: dopamine receptors

Oliveri *et al*[20] were the first to address the possibility that polymorphisms in the genes for DRD1 and DRD2 could be implicated in the appearance of PDD after long-term levodopa use. They found that the frequencies of the 13 and 14 alleles of the DRD2 gene polymorphism were higher in nondyskinetic than in dyskinetic PD patients. The risk reduction of developing PDD for PD patients carrying at least one of the 13 or 14 alleles was 72% with respect to PD subjects who did not carry these alleles.[20]

Another study investigated the association between DRD2 and DRD3 gene polymorphisms and the risk of developing motor fluctuations in PD.[189] The authors found that the TaqIA polymorphism located in the DRD2 gene may influence the risk of developing 'wearing off' motor fluctuations. No such association was found for the DRD3 *Bal*I and *Msp*I polymorphisms.[189]

Together, these studies support the hypothesis that certain individuals are predisposed to the more frequent motor complications of long-term levodopa use, and that the

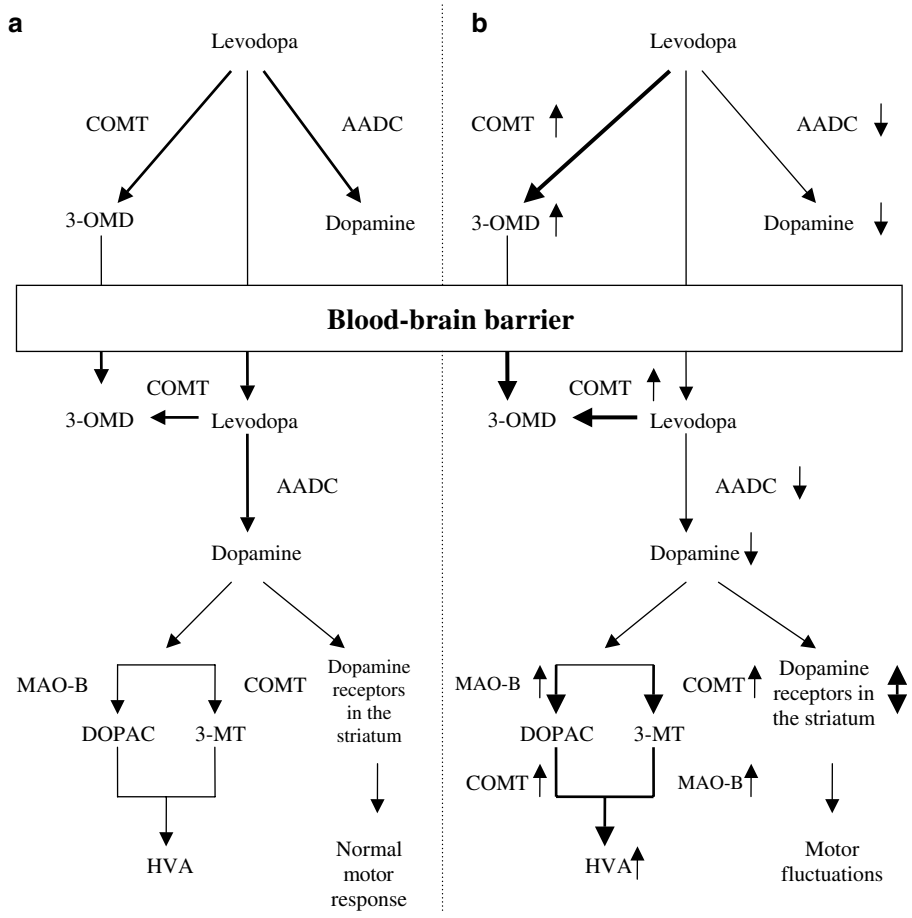

Figure 1 Suggested polymorphism model of various dopamine-related genes that might affect the action of levodopa in levodopa-responsive (a) and levodopa-nonresponsive (b) patients. AADC – aromatic amino–acid decarboxylase; COMT – catechol-*O*-methyltransferase; DOPAC – 3,4-dihydroxyphenylacetic acid; HVA – homovanillic acid; MAO-B – monoamine oxidase type B; 3-MT – 3-methoxytyramine. 3-OMD – 3-*O*-methyl-dihydroxy-phenylalanine.

Table 2 Dopamine-related gene polymorphisms in levodopa treatment

Study	*Race*	*Type and site of polymorphism*	*PD (no.)*	*Controls (no.)*	*Association Yes/No*	*Results*	*Statistics*
Oliveri *et al*[19]	Caucasian	Dinucleotide repeat in second intron of *DRD2*, chromosome 11q22–23	136	224	Yes	15 allele more frequent in parkinsonian patients than controls. Frequency of the 13 and 14 alleles higher in nondyskinetic than dyskinetic PD patients.	χ^2 test or Fisher's exact test under the assumption of Hardy–Weinberg equilibrium.
Makoff *et al*[188]	Caucasian	–141C/del and the Taq IA RFLP which is a C/T base change 10.5 kb 3′ to the end of DRD2	84[a]	71[b]	Yes	Association with late-onset hallucinations and C allele of the Taq IA polymorphism, 10.5 kb 3′ to DRD2	SPSS program and χ^2 test
Goetz *et al*[189]	Caucasian	DRD1, DRD2, DRD3, DRD4, and APOE	44[a]	44[b]	No	No association between hallucinations and the genes examined	Mantel–Haenszel tests for genotypes
Kaiser *et al*[191]	Caucasian	DRD2, DRD3, DRD4 and DAT	183	—	Yes (DAT)	Patients with psychosis or dyskinesia carried the 9 copy allele 40–bp VNTR of the DAT more frequently than nonafflicted patients	Pearson's χ^2 test or Fisher's exact test; Mann–Whitney *U* test
Wang *et al*[187]	Chinese	DRD3 BalI and MspI and DRD2 TaqIA	140	140	Yes (DRD2)	Genotypic distribution of DRD2 TaqIA polymorphism was significantly different in motor fluctuators and nonmotor fluctuators	Yates-corrected χ^2 test or Fisher's exact test
Wang *et al*[190]	Chinese	DRD5 T978C	120	110	No	Overall allelic and genotypic frequencies did not differ significantly between PD patients and controls	Student's *t*-test or Mann–Whitney rank sum test, χ^2 test

[a]Hallucinators.
[b]Non-hallucinators.

Table 3 Other dopamine-related gene polymorphisms in levodopa treatment

Study	Race	Type and site of polymorphism	PD (no.)	Controls (no.)	Association Yes/No	Results	Statistics
Fujii *et al*[192]	Japanese	Four polymorphic sites of CCK gene (-196G/A, -45C/T, 1270C/G, 6662C/T) found in PD patients and controls	116	95	Yes	Significant difference in distributions of three identified genotypes at the -45 locus	χ^2 test with Bonferroni correction
Wang *et al*[193]	Chinese	CCK 45C/T, CCK-A receptor 779T>C and CCK-B receptor 1550G>A gene	160	160	Yes (45C/T)	Only CCK CT/TT genotype associated with 4.429-fold increased risk of visual hallucinations	Yates-corrected χ^2 test or Fisher's exact test
de la Fuente-Fernandez *et al*[194]	Caucasian	APOE epsilon 4	17[a]	88[b]	Yes	APOE epsilon 4 associated with visual hallucinations	χ^2 test and logistic regression models
Reilly *et al*[195]	Caucasian	Average plasma concentration ratio of 3-O-methyldopa to levodopa	14	—	Yes	Patients with the higher erythrocyte COMT activity had less favorable clinical responses to levodopa	—
Rivera-Calimlim *et al*[196]	CaucasianVs. Filipinos	Average erythrocyte concentration of COMT levels in patients taking L-dopa	?	?	No	Filipinos were prescribed substantially lower doses than Caucasians, and more Filipinos developed dyskinesia at comparable doses of levodopa.	?
Chong *et al*[197]	Caucasian	Examination of two codominant alleles for the COMT gene	24	—	No	No significant correlation between genotype and improvement in UPDRS score	Student's *t*-test, linear models approach
Lee *et al*[198]	Korean	Investigation of COMT genotypes	73	49	No	No significant difference in distribution of COMT genotypes	ANOVA

[a]Hallucinators.
[b]Non-hallucinators.

DRD2 gene may play a pivotal role in this genetic susceptibility. Interestingly, both studies found that the DRD2 gene was involved in the development of different types of motor complications, namely, wearing off and PDD. These results suggest that the DRD2 gene might play a pivotal role[20,189] in the genetic susceptibility to the motor complications induced by levodopa in PD, but this should be further examined.

Polymorphism in dopamine-related genes and L-DOPA adverse events

The first of two studies on hallucinations in IPD compared the frequency of polymorphisms in the DRD2 and DRD3 genes between patients who had drug-induced hallucinations and those who did not. Two polymorphisms close to DRD2 and one in DRD3 were studied. Findings were negative for the whole group of hallucinating patients, but there was an association of late-onset hallucinations with the C allele of the TaqIA polymorphism 10.5 kb 3′ to DRD2. This polymorphism may be in linkage disequilibrium with a mutation in DRD2 or a nearby gene that predisposes patients to drug-induced hallucinations later in the course of IPD.[190]

Similar results were obtained in a study that examined the frequency of dopamine receptor genetic variants (DRD1, DRD2, DRD3, DRD4) and Apo-E alleles in patients with PD with and without chronic visual hallucinations.[191]

DRD5 Wang *et al*[192] used a case–control design to investigate whether the DRD5 T978C polymorphism is associated with the risk of developing motor fluctuations in PD. No differences in overall allelic and genotypic frequencies were noted between motor fluctuators and nonfluctuators. Further study is needed to determine if this or other DRD5 polymorphisms are associated with susceptibility to PD or with the risk of developing motor fluctuations in PD.

DAT Another recent study examined whether polymorphisms in the dopamine receptor genes and the DAT gene are predictors of adverse effects of levodopa. Only the nine-copy allele 40-bp VNTR of the DAT proved to be a predictor of psychosis or dyskinesia.[193]

These results suggest that DRD2 polymorphism might influence the response of levodopa and contribute to levodopa-induced motor fluctuations (see also Table 2).

Cholecystokinin (CCK) This is a peptide that modulates the release of dopamine and dopamine-related behaviors in the mesolimbic pathway. Two studies investigated the effect of CCK gene polymorphism on PD risk.[194,195] The first analyzed genetic variations in the coding and promoter regions of the gene and identified four polymorphic sites (G 196A, C45 T, C1270G, C6662 T). There was a significant difference in the distributions of three of the genotypes at the −45 locus between 116 PD patients ($n = 116$) and age-matched control subjects ($n = 95$), and between PD patients with and without hallucinations.[194] The other study investigated the association of polymorphisms in CCK and its two receptors (specifically, CCK C45T, CCK-A receptor T779C and CCK-B receptor G1550A) with PD in 160 Chinese patients and an equal number of controls matched for age, gender, ethnic origin, and area of residence. None of the gene polymorphisms were correlated with risk of PD, although the CCK CT/TT genotype was associated with a 4.429-fold increased risk of visual hallucinations in PD. Separate analysis of the CCK-A-receptor and B-receptor polymorphisms yielded no link with hallucinations in PD; however, a combined effect was found in the hallucinating patients who harbored both the CCK CT/TT and CCK-A receptor TC/CC genotypes. Furthermore, PD patients with this genotype had a 5.922-fold increased risk of developing visual hallucinations.[195]

These results suggest that the CCK - C45T polymorphism might influence vulnerability to hallucinations in PD patients treated with levodopa (see also Table 3).

ApoE An additional study examined whether the Apo-epsilon 4 allele is a risk factor for drug-induced hallucinations in nondemented patients with PD. In all, 76% of the patients who harbored the allele had visual hallucinations compared with 23% of those who did not. Treatment with dopamine agonists also contributed to an increased risk of hallucinations.[196] The authors concluded that nondemented PD patients with the ApoE epsilon 4 allele have a high risk of developing drug-induced visual hallucinations. More research is needed in order to validate these results (see also Table 3).

Pharmacokinetics

Catechol-O-methyltransferase (COMT)

As previously mentioned, one of the ways to increase the peripheral concentration of levodopa is to inhibit COMT with drugs such as tolcapone. However, patients with PD have a variable response to this medication, and a subset of patients develop severe side effects, such as diarrhea. The variable response may be explained by a polymorphism in the COMT gene, which changes the response to both tolcapone and levodopa (Figure 1). Indeed, SNP at nucleotide 1947 in the COMT gene has been found to encode for low and high activity, resulting in low-, medium-, and high-activity genotypes.

Early studies reported that COMT activity in erythrocytes of patients with PD is an important determinant of response to levodopa.[197,198] However, these authors based their findings on only self-reported subjective improvement and did not measure the objective motor response. In addition, no genetic differences were evaluated owing to technological restrictions at the time.

In a more recent study of the relationship between this genotypic variation and the clinical effects of tolcapone changes in levodopa doses and in scores on the United Parkinson Disease Rating Scale (UPDRS), part III (motor subscale) wsa analyzed periodically after the administration of tolcapone. Genotype analysis was performed on seven patients in whom treatment was complicated by diarrhea. Using a linear model approach that adjusted for severity of PD, tolcapone dose, and initial differences in baseline scores, the authors failed to find a significant correlation between

genotype and improvement in UPDRS score. There was also no significant difference in the change in daily levodopa intake by COMT genotype, and no relationship between diarrhea and COMT genotype.[199]

The second recent study investigated COMT genotypes in relation to levodopa response in 73 Korean patients with PD. Findings were compared with 49 control subjects. No significant differences were observed in the distribution of the COMT genotypes among the three groups, and in motor response (evaluated by time to peak response), duration and magnitude of response in the motor part of the UPDRS, and tapping or walking.[200]

These studies indicate that the genetic variants of the COMT enzyme investigated so far do not determine the response to tolcapone or levodopa in PD (see also Table 3).

Conclusions and future strategies

In recent years, the growing interest in the interactions between genetic and environmental factors has prompted a great number of association studies. These offer a potentially powerful approach to identify genetic variants that influence susceptibility to IPD. Candidate genes have been suggested on the basis of our knowledge of the pathophysiology of PD and include mainly genes related to dopamine metabolism and transport, detoxification of xenobiotics and other toxins in dopaminergic neurons, mitochondrial metabolism, and genes that encode for essential transcription factors or neurotrophic factors involved in the development of the mesencephalic dopaminergic system (see Table 1). However, out of 30 genes studied so far, only the MAO-B >188 bp allele showed significant association with IPD in meta-analysis[24] and only six genes (DRD2, ND3, BDNF, α-Synuclein, UCHL1, and Nurr-1) showed significant association with IPD in several studies and fulfilled the Lohmueller criteria for replication in meta-analysis[3] (see Table 1). In addition, only the DRD2 polymorphism appears to influence the response of levodopa and contribute to levodopa-induced motor fluctuations (see also Table 2).

Potential reasons for these mixed results might be related to differences in the polymorphisms studied in the same gene, and differences in sample sizes, ethnic groups, and methodologies, which make the synthesis of independent studies almost impossible. Additional potential contributors are population stratification, biological credibility of the gene-disease association, and gene-gene interactions. Furthermore, the inconsistencies may be due to false-positive or false-negative results, or true variability in association among different populations. Therefore, in order to increase the reliability of future studies, well-designed trials, with large samples[24] and tightly matched controls should be performed,[3,24] using similar statistical, diagnostic, and molecular methods to enable comparisons, extrapolations, and synthesis of the results from independent individual studies on meta-analysis. In addition, the criteria to be predictive of replication on meta-analysis should be set at a *P*-value of less than 0.001 for initial positive studies or less than 0.01 when the results are replicated independently by two studies.[3] Furthermore, future studies should also examine novel polymorphisms that might be associated with IPD risk, such as neurotransmitters, for example, enkephalin and neuropeptides, and other dopamine-related genes (eg, dopamine-signaling molecules and dopamine-related transcription factors). We suggest that the results of association studies on polymorphism of different PD-related genes be assembled in a universal genedatapool in order to facilitate planning of future strategies.

The combination of more association studies with further studies of the molecular mechanism of levodopa 'nonresponders' and levodopa-induced motor fluctuations might improve PD pharmacotherapy and serve as a novel diagnostic tool for PD.

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REFERENCES

1 Morrish PK, Sawle GV, Brooks DJ. The rate of progression of Parkinson's disease: a longitudinal [18F] DOPA PET study. In: Battistin L, Scarlato G, Caraceni T *et al* (eds). *Advances in Neurology*, Vol 69 Lippincott-Raven Publishers: Philadelphia (PA) 1996; pp 427–431.
2 Leenders KL. Pathophysiology of movement disorders studied using PET. *J Neural Transm Suppl* 1997; **50**: 39–46.
3 Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 2003; **33**: 177–182.
4 Cardoso F, Jankovic J. Dystonia and dyskinesia. *Psychiatr Clin North Am* 1997; **20**: 821–838.
5 Turjanski N, Lees AJ, Brooks DJ. *In vivo* studies on striatal dopamine D1 and D2 site binding in L-dopa-treated Parkinson's disease patients with and without dyskinesias. *Neurology* 1997; **49**: 717–723.
6 Grandy DK, Marchionni MA, Makam H, Stofko RE, Alfano M, Frothingham L *et al.* Cloning of the cDNA and gene for a human D2 dopamine receptor. *Proc Natl Acad Sci USA* 1989; **84**: 9762–9766.
7 Sunahara RK, Niznik HB, Weiner DM, Stormann TM, Brann MR, Kennedy JL *et al.* Human dopamine D1 receptor encoded by an intronless gene on chromosome 5. *Nature* 1990; **347**: 80–83.
8 Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB *et al.* Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 1991; **350**: 610–614.
9 Tiberi M, Jarvie KR, Silvia C, Falardeau P, Gingrich JA, Godinot N *et al.* Cloning, molecular characterization and chromosomal assignment of a gene encoding a second D1 receptor subtype: differential expression pattern in rat brain compared with the D1A receptor. *Proc Natl Acad Sci USA* 1991; **88**: 7491–7495.
10 Le Coniat M, Sokoloff P, Hillion J, Martres MP, Giros B, Pilon C *et al.* Chromosomal localization of the human D3 dopamine receptor gene. *Hum Genet* 1991; **87**: 618–620.
11 Schwartz JC, Giros B, Martres MP, Sokoloff P. The dopamine receptor family: molecular biology and pharmacology. *Semin Neurosci* 1992; **4**: 99–108.
12 Higuchi S, Muramatsu T, Arai H, Hayashida M, Sasaki H, Trojanowski JQ. Polymorphisms of dopamine receptor and transporter genes and Parkinson's disease. *J Neural Transm* 1995; **10**: 107–113.
13 Oliveri RL, Annesi G, Zappia M, Civitelli D, De Marco EV, Pasqua AA *et al.* The dopamine D2 receptor gene is a susceptibility locus for Parkinson's disease. *Mov Disord* 2000; **15**: 127–131.

14 Grevle L, Guzey C, Hadidi H, Brennersted R, Idle JR, Aasly J. Allelic association between the DRD2 TaqI A polymorphism and Parkinson's disease. *Mov Disord* 2000; **15**: 1070–1074.
15 Comings DE, Comings BG, Muhleman D, Dietz G, Shahbahrami B, Tast D *et al.* The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA* 1991; **266**: 1793–1800.
16 Costa-Mallen P, Costa LG, Smith-Weller T, Franklin GM, Swanson PD, Checkoway H. Genetic polymorphism of dopamine D2 receptors in Parkinson's disease and interactions with cigarette smoking and MAO-B intron 13 polymorphism. *J Neurol Neurosurg Psychiatry* 2000; **69**: 535–537.
17 Nanko S, Ueki A, Hattori M, Dai XY, Sasaki T, Fukuda R *et al.* No allelic association between Parkinson's disease and dopamine D2, D3, and D4 receptor gene polymorphisms. *Am J Med Genet* 1994; **54**: 361–364.
18 Plante-Bordeneuve V, Taussig D, Thomas F, Said G, Wood NW, Marsden CD *et al.* Evaluation of four candidate genes encoding proteins of the dopamine pathway in familial and sporadic Parkinson's disease: evidence for association of a DRD2 allele. *Neurology* 1997; **48**: 1589–1593.
19 Pastor P, Munoz E, Obach V, Marti MJ, Blesa R, Oliva R *et al.* Dopamine receptor D2 intronic polymorphism in patients with Parkinson's disease. *Neurosci Lett* 1999; **273**: 151–154.
20 Oliveri RL, Annesi G, Zappia M, Civitelli D, Montesanti R, Branca D *et al.* Dopamine D2 receptor gene polymorphism and the risk of levodopa-induced dyskinesias in PD. *Neurology* 1999; **53**: 1425–1430.
21 Wan DC, Law LK, Ip DT, Cheung WT, Ho WK, Tsim KW *et al.* Lack of allelic association of dopamine D4 receptor gene polymorphisms with Parkinson's disease in a Chinese population. *Mov Disord* 1999; **14**: 225–229.
22 Kronenberg MF, Menzel HJ, Ebersbach G, Wenning GK, Luginger E, Gollner M *et al.* Dopamine D4 receptor polymorphism and idiopathic Parkinson's disease. *Eur J Hum Genet* 1999; **7**: 397–400.
23 Ricketts MH, Hamer RM, Manowitz P, Feng F, Sage JI, Di Paola R *et al.* Association of long variants of the dopamine D4 receptor exon 3 repeat polymorphism with Parkinson's disease. *Clin Genet* 1998; **54**: 33–38.
24 Tan EK, Khajavi M, Thornby JI, Nagamitsu S, Jankovic J, Ashizawa T. Variability and validity of polymorphism association studies in Parkinson's disease. *Neurology* 2000; **55**: 533–538.
25 Kitayama S, Shimada S, Uhl GR. Parkinsonism-inducing neurotoxin MPP+: uptake and toxicity in nonneuronal COS cells expressing dopamine transporter cDNA. *Ann Neurol* 1992; **32**: 109–111.
26 Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW *et al.* Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics* 1992; **14**: 1104–1106.
27 Leighton PW, Le Couteur DG, Pang CC, McCann SJ, Chan D, Law LK *et al.* The dopamine transporter gene and Parkinson's disease in a Chinese population. *Neurology* 1997; **49**: 1577–1579.
28 Le Couteur DG, Leighton PW, McCann SJ, Pond S. Association of a polymorphism in the dopamine-transporter gene with Parkinson's disease. *Mov Disord* 1997; **12**: 760–763.
29 Mercier G, Turpin JC, Lucotte G. Variable number tandem repeat dopamine transporter gene polymorphism and Parkinson's disease: no association found. *J Neurol* 1999; **246**: 45–47.
30 Kim JW, Kim DH, Kim SH, Cha JK. Association of the dopamine transporter gene with Parkinson's disease in Korean patients. *J Korean Med Sci* 2000; **15**: 449–451.
31 Wang J, Liu Z, Chen B. Association between genetic polymorphism of dopamine transporter gene and susceptibility to Parkinson's disease. *Zhonghua Yi Xue Za Zhi* 2000; **80**: 346–348.
32 Zhang L, Shao M, Xu Q, Dong X, Yang J, Li Y *et al.* Association between dopamine transporter gene polymorphism and Parkinson's disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2001; **18**: 431–434.
33 Goudreau JL, Maraganore DM, Farrer MJ, Lesnick TG, Singleton AB, Bower JH *et al.* Case–control study of dopamine transporter-1, monoamine oxidase-B, and catechol-*O*-methyl transferase polymorphisms in Parkinson's disease. *Mov Disord* 2002; **17**: 1305–1311.
34 Lin JJ, Yueh KC, Chang DC, Chang CY, Yeh YH, Lin SZ. The homozygote 10-copy genotype of variable number tandem repeat dopamine transporter gene may confer protection against Parkinson's disease for male, but not female patients. *J Neurol Sci* 2003; **209**: 87–92.
35 Morino H, Kawarai T, Izumi Y, Kazuta T, Oda M, Komure O *et al.* A single nucleotide polymorphism of dopamine transporter gene is associated with Parkinson's disease. *Ann Neurol* 2000; **47**: 528–531.
36 Nishimura M, Kaji R, Ohta M, Mizuta I, Kuno S. Association between dopamine transporter gene polymorphism and susceptibility to Parkinson's disease in Japan. *Mov Disord* 2002; **17**: 831–832.
37 Kimura M, Matsushita S, Arai H, Takeda A, Higuchi S. No evidence of association between a dopamine transporter gene polymorphism (1215A/G) and Parkinson's disease. *Ann Neurol* 2001; **49**: 276–277.
38 Lin CN, Liu HC, Tsai SJ, Liu TY, Hong CJ. Association study for Parkinson's disease and a dopamine transporter gene polymorphism (1215A/G). *Eur Neurol* 2002; **48**: 207–209.
39 Plante-Bordeneuve V, Davis MB, Maraganore DM, Marsden CD, Harding AE. Tyrosine hydroxylase polymorphism in familial and sporadic Parkinson's disease. *Mov Disord* 1994; **9**: 337–339.
40 Kunugi H, Kawada Y, Hattori M, Ueki A, Otsuka M, Nanko S. Association study of structural mutations of the tyrosine hydroxylase gene with schizophrenia and Parkinson's disease. *Am J Med Genet* 1998; **81**: 131–133.
41 Momose Y, Murata M, Kobayashi K, Tachikawa M, Nakabayashi Y, Kanazawa I *et al.* Association studies of multiple candidate genes for Parkinson's disease using single nucleotide polymorphisms. *Ann Neurol* 2002; **51**: 133–136.
42 Zhao XP, Xie HJ, Tang GM, Zhao WW, Xu L, Su JJ *et al.* Dopamine beta hydroxylase gene polymorphism and Parkinson's disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2003; **20**: 238–240.
43 Goridis C, Rohrer H. Specification of catecholaminergic and serotonergic neurons. *Nat Rev Neurosci* 2002; **3**: 531–541.
44 Hotamisligil GS, Girmen AS, Fink JS, Tivol E, Shalish C, Trofatter J *et al.* Hereditary variations in monoamine oxidase as a risk factor for Parkinson's disease. *Mov Disord* 1994; **9**: 305–310.
45 Nakatome M, Tun Z, Shimada S, Honda K. Detection and analysis of four polymorphic markers at the human monoamine oxidase (MAO) gene in Japanese controls and patients with Parkinson's disease. *Biochem Biophys Res Commun* 1998; **247**: 452–456.
46 Nanko S, Ueki A, Hattori M. No association between Parkinson's disease and monoamine oxidase A and B gene polymorphisms. *Neurosci Lett* 1996; **204**: 125–127.
47 Kurth JH, Kurth MC, Poduslo SE, Schwankhaus JD. Association of a monoamine oxidase B allele with Parkinson's disease. *Ann Neurol* 1993; **33**: 368–372.
48 Jiang XH, Yang H, Yang JF, Dong XM, Xu QY, Chen B. Relationship between the Fnu4HI site polymorphism of monoamine oxidase A gene and Parkinson's disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2003; **20**: 211–214.
49 Xie H, Wang X, Hao Y, Tang G, Xu L, Wu Q *et al.* The EcoR V polymorphism of human monoamine oxidase A is not associated with idiopathic Parkinson's disease in a Shanghai Han population. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2002; **19**: 329–331.
50 Takehashi M, Tanaka S, Masliah E, Ueda K. Association of monoamine oxidase A gene polymorphism with Alzheimer's disease and Lewy body variant. *Neurosci Lett* 2002; **327**: 79–82.
51 Costa P, Checkoway H, Levy D, Smith-Weller T, Franklin GM, Swanson PD *et al.* Association of a polymorphism in intron 13 of the monoamine oxidase B gene with Parkinson's disease. *Am J Med Genet* 1997; **74**: 154–156.
52 Wu RM, Cheng CW, Chen KH, Lu SL, Shan DE, Ho YF *et al.* The COMT L allele modifies the association between MAOB polymorphism and PD in Taiwanese. *Neurology* 2001; **56**: 375–382.
53 Shao M, Liu Z, Tao E, Chen B. Polymorphism of MAO-B gene and NAD(P)H: quinone oxidoreductase gene in Parkinson's disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2001; **18**: 122–124.
54 Morimoto Y, Murayama N, Kuwano A, Kondo I, Yamashita Y, Mizuno Y. Association analysis of a polymorphism of the monoamine oxidase B gene with Parkinson's disease in a Japanese population. *Am J Med Genet* 1995; **60**: 570–572.
55 Ho SL, Kapadi AL, Ramsden DB, Williams AC. An allelic association study of monoamine oxidase B in Parkinson's disease. *Ann Neurol* 1995; **37**: 403–405.
56 Hwang WJ, Lai ML, Tsai TT, Lai MD. Genetic polymorphism of monoamine oxidase B and susceptibility of Parkinson's disease. *Zhonghua Yi Xue Za Zhi (Taipei)* 1997; **60**: 137–141.

57 Herman MA, Checkoway H, O'Brien R, Costa-Mallen P, De Vivo I, Colditz GA *et al.* MAOB intron 13 and COMT codon 158 polymorphisms, cigarette smoking, and the risk of PD. *Neurology* 2002; **58**: 1381–1387.
58 Mellick GD, Buchanan DD, McCann SJ, James KM, Johnson AG, Davis DR *et al.* Variations in the monoamine oxidase B (MAOB) gene are associated with Parkinson's disease. *Mov Disord* 1999; **14**: 219–224.
59 Mellick GD, Buchanan DD, Silburn PA, Chan DK, Le Couteur DG, Law LK *et al.* The monoamine oxidase B gene GT repeat polymorphism and Parkinson's disease in a Chinese population. *J Neurol.* 2000; **247**: 52–55.
60 Tan EK, Chai A, Lum SY, Shen H, Tan C, Teoh ML *et al.* Monoamine oxidase B polymorphism, cigarette smoking and risk of Parkinson's disease: a study in an Asian population. *Am J Med Genet* 2003; **120**: 58–62.
61 Kopin I. Catecholamine metabolism: basic aspects and clinical significance. *Pharmacol Rev* 1985; **37**: 334–364.
62 Smit N, Pavel S, Kammeyer A, Westerhof W. Determination of catechol-*O*-methyltransferase activity in relation to melanin metabolism using high performance liquid chromatography with fluorimetric detection. *Anal Biochem* 1990; **190**: 286–291.
63 Mannisto P, Ulmanen I, Lundström K, Taskinen J, Tenhunen J, Tilgmann C *et al.* Characteristics of catechol-*O*-methyltransferase (COMT) and properties of selective COMT inhibitors. *Prog Drug Res* 1992; **39**: 291–350.
64 Kunugi H, Nanko S, Ueki A, Otsuka E, Hattori M, Hoda F *et al.* High and low activity alleles of catechol-*O*-methyltransferase gene: ethnic difference and possible association with Parkinson's disease. *Neuroscience Lett* 1997; **221**: 202–204.
65 Yoritaka A, Hattori N, Yoshino H, Mizuno Y. Catechol-*O*-methyltransferase genotype and susceptibility for Parkinson's disease in Japan. *J Neural Transm* 1997; **104**: 1313–1317.
66 Hoda F, Nicholl D, Bennett P, Arranz M, Aitchison KJ, al-Chalabi A *et al.* No association between Parkinson's disease and low-activity alleles of catechol-*O*-methyltransferase. *Biochem Biophys Res Commun* 1996; **228**: 780–784.
67 Xie T, Ho SL, Li LS, Ma OC. G/A1947 polymorphism in catechol-*O*-methyltransferase (COMT) gene in Parkinson's disease. *Mov Disord* 1997; **12**: 426–427.
68 Syvanen AC, Tilgmann C, Rinne J, Ulmanen I. Genetic polymorphism of catechol-*O*-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. *Pharmacogenetics* 1997; **7**: 65–71.
69 Eerola J, Launes J, Hellstrom O, Tienari PJ. Apolipoprotein E (APOE), parkin and catechol-*O*-methyltransferase (COMT) genes and susceptibility to sporadic Parkinson's disease in Finland. *Neurosci Lett* 2002; **330**: 296–298.
70 Daly AK, Cholerton S, Armstrong M, Idle JR. Genotyping for polymorphisms in xenobiotic metabolism as a predictor of disease susceptibility. *Environ Health Perspect* 1994; **102**(Suppl 9): 55–61.
71 Landi MT, Ceroni M, Martignoni E, Bertazzi PA, Caporaso NE, Nappi G. Gene–environment interaction in parkinson's disease. The case of CYP2D6 gene polymorphism. *Adv Neurol* 1996; **69**: 61–72.
72 McCann SJ, Pond SM, James KM, Le Couteur DG. The association between polymorphisms in the cytochrome P-450 2D6 gene and Parkinson's disease: a case–control study and meta-analysis. *J Neurol Sci* 1997; **153**: 50–53.
73 Rostami-Hodjegan A, Lennard MS, Woods HF, Tucker GT. Meta-analysis of studies of the CYP2D6 polymorphism in relation to lung cancer and Parkinson's disease. *Pharmacogenetics* 1998; **8**: 227–238.
74 Christensen PM, Gotzsche PC, Brosen K. The sparteine/debrisoquine (CYP2D6) oxidation polymorphism and the risk of Parkinson's disease: a meta-analysis. *Pharmacogenetics* 1998; **8**: 473–479.
75 Persad AS, Stedeford T, Tanaka S, Chen L, Banasik M. Parkinson's disease and CYP2D6 polymorphism in Asian populations: a meta-analysis. *Neuroepidemiology* 2003; **22**: 357–361.
76 Riedl AG, Watts PM, Jenner P, Marsden CD. P450 enzymes and Parkinson's disease: the story so far. *Mov Disord* 1998; **13**: 212–220.
77 Barbeau A, Cloutier T, Roy M, Plasse L, Paris S, Poirier J. Ecogenetics of Parkinson's disease: 4-hydroxylation of debrisoquine. *Lancet* 1985; **2**: 1213–1216.
78 Daly AK, Steen VM, Fairbrother KS, Idle JR. CYP2D6 multiallelism. *Methods Enzymol* 1996; **272**: 199–210.
79 Woo SI, Kim JW, Seo HG, Park CH, Han SH, Kim SH *et al.* CYP2D6*4 polymorphism is not associated with Parkinson's disease and has no protective role against Alzheimer's disease in the Korean population. *Psychiatry Clin Neurosci* 2001; **55**: 373–377.
80 Harhangi BS, Oostra BA, Heutink P, van Duijn CM, Hofman A, Breteler MM. CYP2D6 polymorphism in Parkinson's disease: the Rotterdam Study. *Mov Disord* 2001; **16**: 290–293.
81 Maraganore DM, Farrer MJ, Hardy JA, McDonnell SK, Schaid DJ, Rocca WA. Case–control study of debrisoquine 4-hydroxylase, N-acetyltransferase 2, and apolipoprotein E gene polymorphisms in Parkinson's disease. *Mov Disord* 2000; **15**: 714–719.
82 Chida M, Yokoi T, Kosaka Y, Chiba K, Nakamura H, Ishizaki T *et al.* Genetic polymorphism of CYP2D6 in the Japanese population. *Pharmacogenetics* 1999; **9**: 601–605.
83 Nicholl DJ, Bennett P, Hiller L, Bonifati V, Vanacore N, Fabbrini G *et al.* A study of five candidate genes in Parkinson's disease and related neurodegenerative disorders. European Study Group on Atypical Parkinsonism. *Neurology* 1999; **53**: 1415–1421.
84 Joost O, Taylor CA, Thomas CA, Cupples LA, Saint-Hilaire MH, Feldman RG *et al.* Absence of effect of seven functional mutations in the CYP2D6 gene in Parkinson's disease. *Mov Disord* 1999; **14**: 590–595.
85 Sabbagh N, Brice A, Marez D, Durr A, Legrand M, Lo Guidice JM *et al.* CYP2D6 polymorphism and Parkinson's disease susceptibility. *Mov Disord* 1999; **14**: 230–236.
86 Payami H, Lee N, Zareparsi S, Gonzales McNeal M, Camicioli R, Bird TD *et al.* Parkinson's disease, CYP2D6 polymorphism, and age. *Neurology* 2001; **56**: 1363–1370.
87 Gilgun-Sherki Y, Melamed E, Offen D. Oxidative stress-induced neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. *Neuropharmacology* 2001; **40**: 959–975.
88 Wu RM, Cheng CW, Chen KH, Shan DE, Kuo JW, Ho YF *et al.* Genetic polymorphism of the CYP2E1 gene and susceptibility to Parkinson's disease in Taiwanese. *J Neural Transm* 2002; **109**: 1403–1414.
89 Wang J, Liu Z, Chen B. Association between cytochrome *P*-450 enzyme gene polymorphisms and Parkinson's disease. *Zhonghua Yi Xue Za Zhi* 2000; **80**: 585–587.
90 Wang J, Liu Z, Chan P. Lack of association between cytochrome *P*450 2E1 gene polymorphisms and Parkinson's disease in a Chinese population. *Mov Disord* 2000; **15**: 1267–1269.
91 Takakubo F, Yamamoto M, Ogawa N, Yamashita Y, Mizuno Y, Kondo I. Genetic association between cytochrome *P*450IA1 gene and susceptibility to Parkinson's disease. *J Neural Transm Gen Sect* 1996; **103**: 843–849.
92 Chan DK, Mellick GD, Buchanan DD, Hung WT, Ng PW, Woo J *et al.* Lack of association between CYP1A1 polymorphism and Parkinson's disease in a Chinese population. *J Neural Transm* 2002; **109**: 35–39.
93 Stroombergen MCMJ, Waring RH. Determination of glutathione *S*-transferase μ and θ polymorphisms in neurological disease. *Hum Exp Toxicol* 1999; **18**: 141–145.
94 De Palma G, Mozzoni P, Mutti A, Calzetti S, Negrotti A. Case–control study of interactions between genetic and environmental factors in Parkinson's disease. *Lancet* 1998; **352**: 1986–1987.
95 Ahmadi A, Fredrikson M, Jerregard H, Akerback A, Fall PA, Rannug A *et al.* GSTM1 and mEPHX polymorphisms in Parkinson's disease and age of onset. *Biochem Biophys Res Commun* 2000; **269**: 676–680.
96 Menegon A, Board PG, Blackburn AC, Mellick GD, Le Conuteur DG. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. *Lancet* 1998; **352**: 1344–1346.
97 Rahbar A, Kempkes M, Muller T, Reich S, Welter FL, Meves S *et al.* Glutathione *S*-transferase polymorphism in Parkinson's disease. *J Neural Transm* 2000; **107**: 331–334.
98 Harada S, Fujii C, Hayashi A, Ohkoshi N. An association between idiopathic Parkinson's disease and polymorphisms of phase II detoxification enzymes: glutathione S-transferase M1 and quinone oxidoreductase 1 and 2. *Biochem Biophys Res Commun* 2001; **288**: 887–892.
99 Kelada SN, Stapleton PL, Farin FM, Bammler TK, Eaton DL, Smith-Weller T *et al.* Glutathione *S*-transferase M1, T1, and P1 polymorphisms and Parkinson's disease. *Neurosci Lett* 2003; **337**: 5–8.

100 Bialecka M, Gawronska-Szklarz B, Drozdzik M, Honczarenko K, Stankiewicz J *et al.* N-acetyltransferase 2 polymorphism in sporadic Parkinson's disease in a Polish population. *Eur J Clin Pharmacol* 2002; **57**: 857–862.
101 Agundez JAG, Jimenez-Jimenez FJ, Luengo A *et al.* Slow allotypic variants of the NAT2 gene and susceptibility to early-onset Parkinson's disease. *Neurology* 1998; **51**: 1587–1591.
102 Harhangi BS, Oostra BA, Heutink P, van Duijn CM, Hofman A, Breteler MM. N-acetyltransferase 2 polymorphism in Parkinson's disease: the Rotterdam study. *J Neurol Neurosurg Psychiatry* 1999; **67**: 518–520.
103 Nicholl DJ, Bennett P. Acetylator genotype and Parkinson's disease. *Lancet* 1998; **351**: 141–142.
104 Van der Walt JM, Martin ER, Scott WK, Zhang F, Nance MA, Watts RL *et al.* Genetic polymorphisms of the N-acetyltransferase gene and risk of Parkinson's disease. *Neurology* 2003; **60**: 1189–1191.
105 Arai H, Muramatsu T, Higuchi S, Sasaki H, Trojanowski JQ. Apolipoprotein E gene in Parkinson's disease with or without dementia. *Lancet* 1994; **343**: 889.
106 Arai H, Higuchi S, Sasaki H. Apolipoprotein E genotype and cerebrospinal fluid tau protein: implications for the clinical diagnosis of Alzheimer's disease. *Gerontology* 1997; **43**(Suppl 1): 2–10.
107 Inzelberg R, Paleacu D, Chapman J, Korczyn AD. Apolipoprotein E and Parkinson's disease. *Ann Neurol* 1998; **44**: 294.
108 Tang G, Xie H, Xu L, Hao Y, Lin D, Ren D. Genetic study of apolipoprotein E gene, alpha-1 antichymotrypsin gene in sporadic Parkinson disease. *Am J Med Genet* 2002; **114**: 446–449.
109 Hardy J, Crook R, Prihar G, Roberts G, Raghavan R, Perry R. Senile dementia of the lewy body type has an apolipoprotein E epsilon 4-allele frequency intermediate between controls and Alzheimer's disease. *Neurosci Lett* 1994; **182**: 1–2.
110 Rubinsztein DC, Hanlon CS, Irving RM, Goodburn S, Evans DG, Kellar-Wood H *et al.* Apo E genotypes in multiple sclerosis, Parkinson's disease, schwannomas and late-ons*et al*zheimer's disease. *Mol Cell Probes* 1994; **8**: 519–525.
111 Harrington CR, Louwagie J, Rossau R, Vanmechelen E, Perry RH, Perry EK *et al.* Influence of apolioprotein E genotype on senile dementia of the Alzheimer and Lewy body types: significance for etiological theories of Alzheimer's disease. *Am J Pathol* 1994; **145**: 1472–1484.
112 Marder K, Maestre G, Cote L, Mejia H, Alfaro B, Halim A *et al.* The apolipoprotein E4 allele in Parkinson's disease with and without dementia. *Neurology* 1994; **44**: 1330–1331.
113 Benjamin R, Leake A, Edwardson JA, McKeith IG, Ince PG, Perry RH *et al.* Apolioprotein E genes in Lewy body and Parkinson's disease. *Lancet* 1994; **343**: 1565.
114 Koller WC, Glatt SL, Hubble JP, Paolo A, Troster AI, Handler MS *et al.* Apolipoprotein E genotypes in Parkinson's disease with and without dementia. *Ann Neurol* 1995; **37**: 242–245.
115 Ibarreta D, Gomez-Isla T, Portera-Sanchez A, Parrilla R, Ayuso MS. Apolipoprotein E genotype in Spanish patients of Alzheimer's or Parkinson's disease. *J Neurol Sci* 1995; **134**: 146–149.
116 Martinoli MG, Trojanowski JQ, Schmidt ML, Arnold SE, Fujiwara TM, Lee VM *et al.* Association of apoplipoprotein epsilon 4 allele and neuropathologic findings in patients with dementia. *Acta Neuropathol* 1995; **90**: 239–243.
117 Poduslo SE, Riggs D, Rolan T, Schwankhaus J. Apolipoprotein E and B alleles in Parkinson's disease. *Neurosci Lett* 1995; **194**: 145–147.
118 Morris CM, Massey HM, Benjamin R, Leake A, Broadbent C, Griffiths M *et al.* Molecular biology of APO E alleles in Alzheimer's and non-Alzheimer's dementias. *J Neural Transm Suppl* 1996; **47**: 205–218.
119 Helisalmi S, Linnaranta K, Lehtovirta M, Mannermaa A, Heinonen O, Ryynanen M *et al.* Apolioprotein E polymorphism in patients with different neurodegenerative disorders. *Neurosci Lett* 1996; **205**: 61–64.
120 Whitehead AS, Bertrandy S, Finnan F, Butler A, Smith GD, Ben-Shlomo Y. Frequency of the apolipoprotein E epsilon 4 allele in a case–control study of early onset Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1996; **61**: 341–351.
121 Egensperger R, Bancher C, Kosel S, Jellinger K, Mehraein P, Graeber MB. The apolioprotein E epsilon 4 allele in Parkinson's disease with Alzheimer lesions. *Biochem Biophys Res Commun* 1996; **224**: 484–486.
122 St. Clair D. Apolipoprotein E gene in Parkinson's disease, Lewy body dementia and Alzheimer's disease. *J Neural Transm* 1997; **51**(Suppl): 161–165.
123 Ballering LAP, Steffens-Nakken HM, Esselink RAJ, De Vos RAI, Jansen Steur ENH, Vermes I. Apolipoprotein E genotype in patients with neurodegenerative diseases. *Clin Biochem* 1997; **30**: 405–411.
124 Wakabayashi K, Kakita A, Hayashi S, Okuizumi K, Onodera O, Tanaka H *et al.* Apolioprotein E E4 allele and progression of cortical Lewy body pathology in Parkinson's disease. *Acta Neuropathol* 1998; **95**: 450–454.
125 Mattila PM, Koskela T, Roytta M, Lehtimaki T, Pirttila TA, Ilveskoski E *et al.* Apolipoprotein E epsilon4 allele frequency is increased in Parkinson's disease only with co-existing Alzheimer pathology. *Acta Neuropathol (Berl)* 1998; **96**: 417–420.
126 Fuente-Fernandez RDL, Sellers A, Beyer K, Lao JI. Apolioprotein E genotypes and age at onset of Parkinson's disease. *Ann Neurol* 1998; **44**: 294–295.
127 Oliveri RL, Nicoletti G, Cittadella R, Manna I, Branca D, Zappia M *et al.* Apolipoprotein E polymorphisms and Parkinson's disease. *Neurosci Lett* 1999; **277**: 83–86.
128 Hao Y, Xie H, Xu L. Association between polymorphism of alpha 1-antichymotrypsin and apolipoprotein E gene and Parkinson's disease in Shanghai Hans. *Zhonghua Yi Xue Za Zhi* 2001; **81**: 1172–1175.
129 Khan N, Graham E, Dixon P, Morris C, Mander A, Clayton D *et al.* Parkinson's disease is not associated with the combined alpha-synuclein/apolipoprotein E susceptibility genotype. *Ann Neurol* 2001; **49**: 665–668.
130 Parsian A, Racette B, Goldsmith LJ, Perlmutter JS. Parkinson's disease and apolipoprotein E: possible association with dementia but not age at onset. *Genomics* 2002; **79**: 458–461.
131 Kruger R, Vieira-Saecker AM, Kuhn W, Berg D, Muller T, Kuhnl N *et al.* Increased susceptibility to sporadic Parkinson's disease by a certain combined α-synuclein/apolipoprotein E genotype. *Ann Neurol* 1999; **45**: 611–617.
132 Bon MAM, Jansen Steur ENH, de Vos RAI, Vermes I. Neurogenetic correlates of Parkinson's disease: apolipoprotein-E and cytochrome *P*450 2D6 genetic polymorphism. *Neurosci Lett* 1999; **266**: 149–151.
133 Kosel S, Lucking CB, Egensperger R, Mehraein P, Graeber MB. Mitochondrial NADH dehydrogenase and CYP2D6 genotypes in Lewy-body parkinsonism. *J Neurosci Res* 1996; **44**: 174–183.
134 Ikebe S, Tanaka M, Ozawa T. Point mutations of mitochondrial genome in Parkinson's disease. *Mol Brain Res* 1995; **28**: 281–295.
135 Bandmann O, Sweeney MG, Danial SE, Marsden CD, Wood NW. Mitochondrial DNA polymorphisms in pathologically proven Parkinson's disease. *J Neurol* 1997; **24**: 262–265.
136 Egensperger R, Kosel S, Schnopp NM, Mehraein P, Graeber MB. Association of the mitochondrial tRNA(A4336G) mutation with Alzheimer's and Parkinson's diseases. *Neuropathol Appl Neurobiol* 1997; **23**: 315–321.
137 Shoffner JM, Brown MD, Torroni A, Lott MT, Cabell MF, Mirra SS *et al.* Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients. *Genomics* 1993; **17**: 171–184.
138 Brown MD, Shoffner JM, Kim YL, Jun AS, Graham BH, Cabell MF *et al.* Mitochondrial DNA sequence analysis of four Alzheimer's and Parkinson's disease patients. *Am J Med Genet* 1996; **61**: 283–289.
139 Van der Walt JM, Nicodemus KK, Martin ER, Scott WK, Nance MA, Watts RL *et al.* Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. *Am J Hum Genet* 2003; **72**: 804–811.
140 Toda T, Momose Y, Murata M, Tamiya G, Yamamoto M, Hattori N *et al.* Toward identification of susceptibility genes for sporadic Parkinson's disease. *J Neurol* 2003; **250**(Suppl 3): III40–III43.
141 Hakansson A, Melke J, Westberg L, Shahabi HN, Buervenich S, Carmine A *et al.* Lack of association between the BDNF Val66Met polymorphism and Parkinson's disease in a Swedish population. *Ann Neurol* 2003; **53**: 823.
142 Hong CJ, Liu HC, Liu TY, Lin CH, Cheng CY, Tsai SJ. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in Parkinson's disease and age of onset. *Neurosci Lett* 2003; **353**: 75–77.
143 Masaki T, Matsushita S, Arai H, Takeda A, Itoyama Y, Mochizuki H *et al.* Association between a polymorphism of brain-derived neurotrophic factor gene and sporadic Parkinson's disease. *Ann Neurol* 2003; **54**: 276–277.

144 Wartiovaara K, Hytonen M, Vuori M, Paulin L, Rinne J, Sariola H. Mutation analysis of the glial cell line-derived neurotrophic factor gene in Parkinson's disease. *Exp Neurol* 1998; **152**: 307–309.
145 Parboosingh JS, Rousseau M, Rogan F, Amit Z, Chertkow H, Johnson WG *et al.* Absence of mutations in superoxide dismutase and catalase genes in patients with Parkinson's disease. *Arch Neurol* 1995; **52**: 1160–1163.
146 Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. *Biochem Biophys Res Commun* 1996; **226**: 561–565.
147 Grasbon-Frodl EM, Kosel S, Riess O, Muller U, Mehraein P, Graeber MB. Analysis of mitochondrial targeting sequence and coding region polymorphisms of the manganese superoxide dismutase gene in German Parkinson disease patients. *Biochem Biophys Res Commun* 1999; **255**: 749–752.
148 Farin FM, Hitosis Y, Hallagan SE, Kushleika J, Woods JS, Janssen PS *et al.* Genetic polymorphisms of superoxide dismutase in Parkinson's disease. *Mov Disord* 2001; **16**: 705–707.
149 Hughes AJ, Dniel SE, Kilford L, Lees AJ. Accuracy of the clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; **55**: 181–184.
150 Tan EK, Matsuura T, Nagamitsu S, Khajavi M, Jankovic J, Ashizawa T. Polymorphism of NACP-Rep1 in Parkinson's disease: an etiologic link with essential tremor? *Neurology.* 2000; **54**: 1195–1198.
151 Farrer M, Maraganore DM, Lockhart P, Singleton A, Lesnick TG, de Andrade M *et al.* Alpha-synuclein gene haplotypes are associated with Parkinson's disease. *Hum Mol Genet.* 2001; **10**: 1847–1851.
152 Mizuta I, Nishimura M, Mizuta E, Yamasaki S, Ohta M, Kuno S. Meta-analysis of alpha synuclein/ NACP polymorphism in Parkinson's disease in Japan. *J Neurol Neurosurg Psychiatry* 2002; **73**: 350.
153 Izumi Y, Morino H, Oda M, Maruyama H, Udaka F, Kameyama M *et al.* Genetic studies in Parkinson's disease with an alpha-synuclein/NACP gene polymorphism in Japan. *Neurosci Lett* 2001; **300**: 125–127.
154 Ross OA, Awayn NH, McWhinney D, Maxwell LD, El-Agnaf OM, Barnett YA *et al.* A novel polymorphic triplet repeat in intron five of the alpha-synuclein gene: no evidence of expansion or allelic association with idiopathic Parkinson's disease in the Irish. *Neuroreport* 2002; **13**: 1621–1625.
155 Tan EK, Tan C, Shen H, Chai A, Lum SY, Teoh ML *et al.* Alpha-synuclein promoter and risk of Parkinson's disease: microsatellite and allelic size variability. *Neurosci Lett* 2003; **336**: 70–72.
156 Holzmann C, Kruger R, Saecker AM, Schmitt I, Schols L, Berger K *et al.* Polymorphisms of the alpha-synuclein promoter: expression analyses and association studies in Parkinson's disease. *J Neural Transm* 2003; **110**: 67–76.
157 Spadafora P, Annesi G, Pasqua AA, Serra P, Ciro Candiano IC, Carrideo S *et al.* NACP-REP1 polymorphism is not involved in Parkinson's disease: a case–control study in a population sample from southern Italy. *Neurosci Lett* 2003; **351**: 75–78.
158 Wang M, Hattori N, Matsumine H, Kobayashi T, Yoshino H, Morioka A *et al.* Polymorphism in the parkin gene in sporadic Parkinson's disease. *Ann Neurol.* 1999; **45**: 655–658.
159 Satoh J, Kuroda Y. Association of codon 167 Ser/Asn heterozygosity in the parkin gene with sporadic Parkinson's disease. *Neuroreport* 1999; **10**: 2735–2739.
160 West AB, Maraganore D, Crook J, Lesnick T, Lockhart PJ, Wilkes KM *et al.* Functional association of the parkin gene promoter with idiopathic Parkinson's disease. *Hum Mol Genet* 2002; **11**: 2787–2792.
161 Lincoln SJ, Maraganore DM, Lesnick TG, Bounds R, de Andrade M, Bower JH *et al.* Parkin variants in North American Parkinson's disease: cases and controls. *Mov Disord.* 2003; **18**: 1306–1311.
162 Peng R, Gou Y, Yuan Q, Li T, Latsoudis H, Yuan G *et al.* Mutation screening and association analysis of the parkin gene in Parkinson's disease patients from South-West China. *Eur Neurol.* 2003; **49**: 85–89.
163 Lucking CB, Chesneau V, Lohmann E, Verpillat P, Dulac C, Bonnet AM *et al.* Coding polymorphisms in the parkin gene and susceptibility to Parkinson disease. *Arch Neurol* 2003; **60**: 1253–1256.
164 Mellick GD, Buchanan DD, Hattori N, Brookes AJ, Mizuno Y, Le Couteur DG *et al.* The parkin gene S/N167 polymorphism in Australian Parkinson's disease patients and controls. *Parkinsonism Relat Disord* 2001; **7**: 89–91.
165 Hu CJ, Sung SM, Liu HC, Lee CC, Tsai CH, Chang JG. Polymorphisms of the parkin gene in sporadic Parkinson's disease among Chinese in Taiwan. *Eur Neurol* 2000; **44**: 90–93.
166 Mata IF, Alvarez V, Garcia-Moreira V, Guisasola LM, Ribacoba R, Salvador C *et al.* Single-nucleotide polymorphisms in the promoter region of the PARKIN gene and Parkinson's disease. *Neurosci Lett.* 2002; **329**: 149–152.
167 Oliveira SA, Scott WK, Nance MA, Watts RL, Hubble JP, Koller WC *et al.* Association study of Parkin gene polymorphisms with idiopathic Parkinson disease. *Arch Neurol.* 2003; **60**: 975–980.
168 Zhang J, Hattori N, Leroy E, Morris HR, Kubo S, Kobayashi T *et al.* Association between a polymorphism of ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) gene and sporadic Parkinson's disease. *Parkinsonism Relat Disord* 2000; **6**: 195–197.
169 Satoh J, Kuroda Y. A polymorphic variation of serine to tyrosine at codon 18 in the ubiquitin C-terminal hydrolase-L1 gene is associated with a reduced risk of sporadic Parkinson's disease in a Japanese population. *J Neurol Sci* 2001; **189**: 113–117.
170 Maraganore DM, Farrer MJ, Hardy JA, Lincoln SJ, McDonnell SK, Rocca WA. Case–control study of the ubiquitin carboxy-terminal hydrolase L1 gene in Parkinson's disease. *Neurology* 1999; **53**: 1858–1860.
171 Wintermeyer P, Kruger R, Kuhn W, Muller T, Woitalla D, Berg D *et al.* Mutation analysis and association studies of the UCHL1 gene in German Parkinson's disease patients. *Neuroreport* 2000; **11**: 2079–2082.
172 Elbaz A, Levecque C, Clavel J, Vidal JS, Richard F, Correze JR *et al.* S18Y polymorphism in the UCH-L1 gene and Parkinson's disease: evidence for an age-dependent relationship. *Mov Disord* 2003; **18**: 130–137.
173 Mellick GD, Silburn PA. The ubiquitin carboxy-terminal hydrolase-L1 gene S18Y polymorphism does not confer protection against idiopathic Parkinson's disease. *Neurosci Lett* 2000; **293**: 127–130.
174 Wang J, Zhao CY, Si YM, Liu ZL, Chen B, Yu L. ACT and UCH-L1 polymorphisms in Parkinson's disease and age of onset. *Mov Disord* 2002; **17**: 767–771.
175 Xu PY, Liang R, Jankovic J, Hunter C, Zeng YX, Ashizawa T *et al.* Association of homozygous 7048G7049 variant in the intron six of Nurr1 gene with Parkinson's disease. *Neurology* 2002; **58**: 881–884.
176 Zheng K, Heydari B, Simon DK. A common NURR1 polymorphism associated with Parkinson disease and diffuse Lewy body disease. *Arch Neurol* 2003; **60**: 722–725.
177 Carmine A, Buervenich S, Galter D, Jonsson EG, Sedvall GC, Farde L *et al.* NURR1 promoter polymorphisms: Parkinson's disease, schizophrenia, and personality traits. *Am J Med Genet* 2003; **120**: 51–57.
178 Tan EK, Chung H, Zhao Y, Shen H, Chandran VR, Tan C *et al.* Genetic analysis of Nurr1 haplotypes in Parkinson's disease. *Neurosci Lett* 2003; **347**: 139–142.
179 Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* 1977; **1**: 345–349.
180 Fahn S. Fluctuations of disability in Parkinson's disease: pathopysiological aspects. In: Marsden CD, Fahn S (eds). *Movement Disorders*. Butterworth Scientific: London 1982; pp 123–145.
181 Nutt JG. Levodopa-induced dyskinesia: review, observations, and speculations. *Neurology* 1990; **40**: 340–345.
182 Peppe A, Dambrosia JM, Chase TN. Risk factors for motor response complications in L-dopa-treated parkinsonian patients. *Adv Neurol* 1993; **60**: 698–702.
183 Blanchet PJ, Allard P, Gregoire L, Tardif F, Bedard PJ. Risk factors for peak dose dyskinesia in 100 levodopa-treated parkinsonian patients. *Can J Neurol Sci* 1996; **23**: 189–193.
184 Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord* 1994; **9**: 2–12.
185 Mouradian MM, Heuser IJ, Baronti F, Fabbrini G, Juncos JL, Chase TN. Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol* 1989; **25**: 523–526.

186 Wu M, Brudzynski SM, Mogenson GJ. Functional interaction of dopamine and glutamate in the nucleus accumbens in the regulation of locomotion. *Can J Physiol Pharmacol* 1993; **71**: 407–413.
187 Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Broe GA *et al.* Age at onset: the major determinant of outcome in Parkinson's disease. *Acta Neurol Scand* 1995; **92**: 455–463.
188 Nutt JG, Woodward WR, Carter JH, Trotman TL. Influence of fluctuations of plasma large neutral amino acids with normal diets on the clinical response to levodopa. *J Neurol Neurosurg Psychiatry* 1989; **52**: 481–487.
189 Wang J, Liu ZL, Chen B. Association study of dopamine D2, D3 receptor gene polymorphisms with motor fluctuations in PD. *Neurology* 2001; **56**: 1757–1759.
190 Makoff AJ, Graham JM, Arranz MJ, Forsyth J, Li T, Aitchison KJ *et al.* Association study of dopamine receptor gene polymorphisms with drug-induced hallucinations in patients with idiopathic Parkinson's disease. *Pharmacogenetics* 2000; **10**: 43–48.
191 Goetz CG, Burke PF, Leurgans S, Berry-Kravis E, Blasucci LM, Raman R *et al.* Genetic variation analysis in Parkinson disease patients with and without hallucinations: case–control study. *Arch Neurol* 2001; **58**: 209–213.
192 Wang J, Liu ZL, Chen B. Dopamine D5 receptor gene polymorphism and the risk of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Neurosci Lett* 2001; **308**: 21–24.
193 Kaiser R, Hofer A, Grapengiesser A, Gasser T, Kupsch A, Roots I *et al.* L-dopa-induced adverse effects in PD and dopamine transporter gene polymorphism. *Neurology* 2003; **60**: 1750–1755.
194 Fujii C, Harada S, Ohkoshi N, Hayashi A, Yoshizawa K, Ishizuka C *et al.* Association between polymorphism of the cholecystokinin gene and idiopathic Parkinson's disease. *Clin Genet* 1999; **56**: 394–399.
195 Wang J, Si YM, Liu ZL, Yu L. Cholecystokinin, cholecystokinin-A receptor and cholecystokinin-B receptor gene polymorphisms in Parkinson's disease. *Pharmacogenetics* 2003; **13**: 365–369.
196 de la Fuente-Fernandez R, Nunez MA, Lopez E. The apolipoprotein E epsilon 4 allele increases the risk of drug-induced hallucinations in Parkinson's disease. *Clin Neuropharmacol* 1999; **22**: 226–230.
197 Reilly DK, Rivera-Calimlim L, Van Dyke D. Catechol-*O*-methyltransferase activity: a determinant of levodopa response. *Clin Pharmacol Ther* 1980; **28**: 278–286.
198 Rivera-Calimlim L, Reilly DK. Difference in erythrocyte catechol-*O*-methyltransferase activity between Orientals and Caucasians: difference in levodopa tolerance. *Clin Pharmacol Ther* 1984; **35**: 804–809.
199 Chong DJ, Suchowersky O, Szumlanski C, Weinshilboum RM, Brant R, Campbell NR. The relationship between COMT genotype and the clinical effectiveness of tolcapone, a COMT inhibitor, in patients with Parkinson's disease. *Clin Neuropharmacol* 2000; **23**: 143–148.
200 Lee JJ, Chang CK, Liu IM, Chi TC, Yu HJ, Cheng JT. Genotypes of catechol-*O*-methyltransferase and response to levodopa treatment in patients with Parkinson's disease. *Neurosci Lett* 2001; **298**: 131–134.