E-text paper 2

Phase I reactions (mainly catalyzed by cytochrome P450 enzymes) may produce reactive intermediates, thereby causing a bioactivation of parent compounds. Reactive metabolites may be inactivated during the biosynthetic phase of metabolism, through reactions catalyzed by glutathione S-transferases and other enzymes, depending on the nature of the electrophilic group. The relative amounts of activation and detoxification will determine whether a chemical is toxic. Because both genetic and environmental factors influence the levels of enzymes that metabolically activate and detoxify chemicals, they can also influence the risk of adverse effects.

One of the most extensively studied genes is cytochrome P450 2D6 (*CYP2D6*) that codes for a phase I enzyme that metabolises a wide range of drugs. One meta-analysis concluded that the "Poor Metaboliser" phenotype shows a modest but significantly increased odds ratio for PD.[2] CYP1B1 is another inducible phase I enzyme, highly expressed in human brainstem, which metabolises a broad range of xenobiotics.[3] (See E Table 1 for gene frequencies). The amino acid substitution $Val_{432}Leu$ (*CYP1B1*3* allele) [4] may modulate the enzyme activity toward different substrates, including benzo[a]pyrene.[5]

Paraoxonase 1 (PON1) hydrolyses organophosphate pesticides and two polymorphisms have been described, at codons 55 and 192 respectively, that affect metabolic activity.[6]

The glutathione S-transferases are a family of enzymes involved in phase II

metabolism. Homozygous gene deletions of *GSTM1* and *GSTT1* lead to the absence of their respective enzymes in about 50% and 20% of Caucasians. *GSTM1* genotype may modify the natural history of PD with *GSTM1 positive* subjects having PD onset later than *GSTM1 null*.[7] De Palma et al. found an excess of PD among subjects bearing a *GSTT1 null* genotype.[8] The *GSTM3* gene has a three base pair deletion in intron 6, [9] and it is hypothesised that the transcription of the wildtype (A) and the variant (B) allele are differently regulated.

Two polymorphisms of the *GSTP1* gene have been characterised, in exon 5 ($Ile_{105}Val$) and exon 6 ($Ala_{114}Val$). Menegon et al. found an excess of PD among pesticide exposed subjects bearing at least one variant *GSTP1* allele.[10]

NAD(P)H: quinone oxidoreductase (NQO1), also termed diaphorase, is an inducible enzyme which catalyses the two-electron reduction of quinones, using NAD(P)H as co-factor. A functional $C_{609}T$ polymorphism of the *NQO1* gene, leading to abolition of enzyme activity in homozygous mutants, occurs among Caucasians with a frequency of about 10%.[11] The polymorphism may modify the risk of PD modulating the production of toxic quinones deriving from dopamine auto-oxidation. In addition, NQO1 can catalyse the reduction of coenzyme Q to a form that prevents mitochondrial complex I inhibition by rotenone,[12] a naturally occurring pesticide used to induce neurodegeneration in a rodent model of the disease.

The genes coding for the enzymes monoamine oxidase A and B are located on the X chromosome. Monoamine oxidases A and B catalyse the oxidative deamination of dopamine to 3,4-dihydroxyphenylacetaldehyde, producing H_2O_2 as a reaction by-

product.[13] Polymorphisms in *MAO-A* have been linked to an increased risk of PD in some studies [14] although these findings have been inconsistent.

Manganese superoxide dismutase (SOD2) is an important antioxidant enzyme in the human brain. A polymorphism in the mitochondrial targeting sequence may affect localisation and transport of SOD2 to mitochondria.[15] Mitochondrial oxidative stress has been implicated in the pathogenesis of PD and so the *SOD2* gene may also increase an individual's susceptibility to PD development. The amino acid substitution, $Val_{9}Ala$, has been associated with an increased risk of PD in one Japanese study.[15]

Microsomal epoxide hydrolase (EPHX1) cleaves reactive epoxides to form transhydrodiols and is known to be polymorphic in Caucasians. The amino acid substitution in exon three ($Tyr_{113}His$) results in reduced enzyme activity, whereas the $His_{139}Arg$ in exon 4 leads to increased activity in vitro. Ahmadi *et al.* found an almost four-fold increased risk of PD in subjects homozygous for the low activity variant. [7] The dopamine transporter (DAT1) is involved in the uptake of compounds such as the neurotoxin MPP_{+} into dopaminergic neurones.[16] The $A_{1215}G$ polymorphism in exon 9 of the *DAT1* gene has been associated with decreased susceptibility to PD in one Japanese study.[17]

Dopamine receptor D2 (*DRD2*) polymorphisms may be involved in reinforcing the action of nicotine. Smoking is negatively associated with Parkinson's disease.[18] DRD2 polymorphisms may modify the risk of smoking [19] and hence that of PD. N-acetyltransferase 2 (NAT2) is involved in the metabolism of a number of xenobiotics including drugs. The *NAT2* slow acetylator genotype has been associated with an increased risk of familial PD.[20]