

# Paraoxonase1 and its relationship with Parkinson's disease

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## Abstract

This study reviews current understanding of relationship of paraoxonase1 polymorphisms and activity of paraoxonase1 in Parkinson's Disease (PD). Paraoxonase 1 (PON1) is involved in the detoxification of insecticides and pesticides and metabolisms of these toxins. Two polymorphisms within the gene affect the activity of paraoxonase. In One of them a methionine replaces with leucine at position 54 (M54L) and the other a glutamine change to arginine variant at position 192 (Q192R). There are some evidences show the genetic polymorphisms of PON1 can protect against organophosphates such as paraoxon and diazinon. Results of studies that investigate these associations are controversial. There was no significant association between PON1-1 92Q/R alleles and risk of developing PD and also there is no evidence for an association between PON 1-192 polymorphism and development of PD, however, a study found that the 192R alleles were risk factor for developing PD. These polymorphisms explain only some of the variations in serum PON1 activity; thus, the other critical test of the hypothesis is likely to be whether low serum PON1 activity is associated with Parkinson disease or not. In this review we summarize current knowledge from PON1 association studies regarding the interaction between gene polymorphisms and activity of PON1 with the risk of PD.

## Introduction

Parkinson's disease was first described in 1817 by an English doctor [1], although the reports of possible parkinsonian syndromes dating back many years ago [2,3]. PD is the most common neurodegenerative disorder just after the Alzheimer disease among the elderly [4,5]. Although the median age at onset PD is about 60 years, clinical diagnosis may occur after loss of 30 to 50% of substantia nigra dopaminergic neurons of PD [6]. The PD phenotype may occur only when 60-70% of substantia nigra neurons stop functioning [7]. PD leads to rigidity, slowness of voluntary movement and postural instability [4]. In the advanced stages, cognitive and mood disorders are also common [8].

Diagnosing of PD is typically done by the presence of some intracytoplasmic inclusions, known as "Lewy bodies", which are primarily composed of  $\alpha$ -synuclein protein aggregates [9]. Parkinson disease arise from neuronal loss, which mainly affecting dopaminergic neurons of the substantia nigra [10]. with a prevalence of 5 million individuals world-wide [11]. The Formation of the Parkinson's disease is arisen from a combination of genetic and environmental factors, which likely interact with each other. Epidemiological studies have indicated that environmental factors such as pesticides may increase risk of idiopathic Parkinson's disease (PD) [12]. Environmental factors are apparent causes of the 'sporadic' Parkinson's disease [13,14]. In addition to the environmental factors, sporadic autosomal recessive form of PD a candidate gene (Parkin) on human chromosome 6q25.2-q27 has been identified [15]. The risk in relatives has been reported to be threefold higher than in the general population [16]. In 1985, it was reported that familial susceptibility to PD might be mediated by genetic variability of enzymes involved in the detoxification of neurotoxins [17]. It has been widely believed that polymorphic variations in xenobiotic metabolizing enzymes, such as glutathione transferase, CYPs and paraoxonase, may affect PD risk by altering the detoxification of pesticides and other putative neurotoxins [18-20]. A number of case-control studies and prospective studies have shown a significant association between pesticide exposure and risk of PD [21,22], whereas other studies have failed to demonstrate such association [23,24].

## Paraoxonase1

The Paraoxonase (PON) gene family contains three different members (PON1, PON2 and PON3), and exhibits anti-oxidative characters principally in the blood circulation [25]. Human PON genes share approximately 70% identity at the nucleotide level and approximately 60% identity at the amino acid level [26]. Human PON2 and PON3 lack or have very limited paraoxonase and arylesterase activities, but they are similar to PON1 in that both hydrolyze aromatic and long-chain aliphatic lactones, e.g. [27,28]. PON1 is not found in the blood of fishes, birds and most reptiles. The enzymes also classified by Norman Aldridge [29]. Paraoxonase (PON1; EC 3.1.8.1; formerly EC 3.1.1.2) is a calcium-dependent serum enzyme belonging to the class of A-esterases [29], this enzyme is a protein of 354 amino acids with a molecular mass of 43 kDa [30, 31]. It is a glycoprotein synthesized in the liver and secreted into the blood [32]. Paraoxonase1 in the plasma associated with High-Density Lipoproteins (HDL) [33-35].

The gen of this protein is collocated on the long arm of chromosome 7 between q21.3 and q22.1 with other members of its family [36,37]. Regarding the roles of organophosphates in etiology of PD, PON1 is the main means of protection of the nervous system against the neurotoxicity of organophosphates [38,39]. PON1 has two activities; one paraoxonase activity that breakdown paraoxon, a toxic metabolite of the parathion and the other activity is arylesterase that breakdown phenyl acetate to phenyl lactate [32]. Mammal serum paraoxonase is also hydrolyze the active metabolite of other OPs insecticides,

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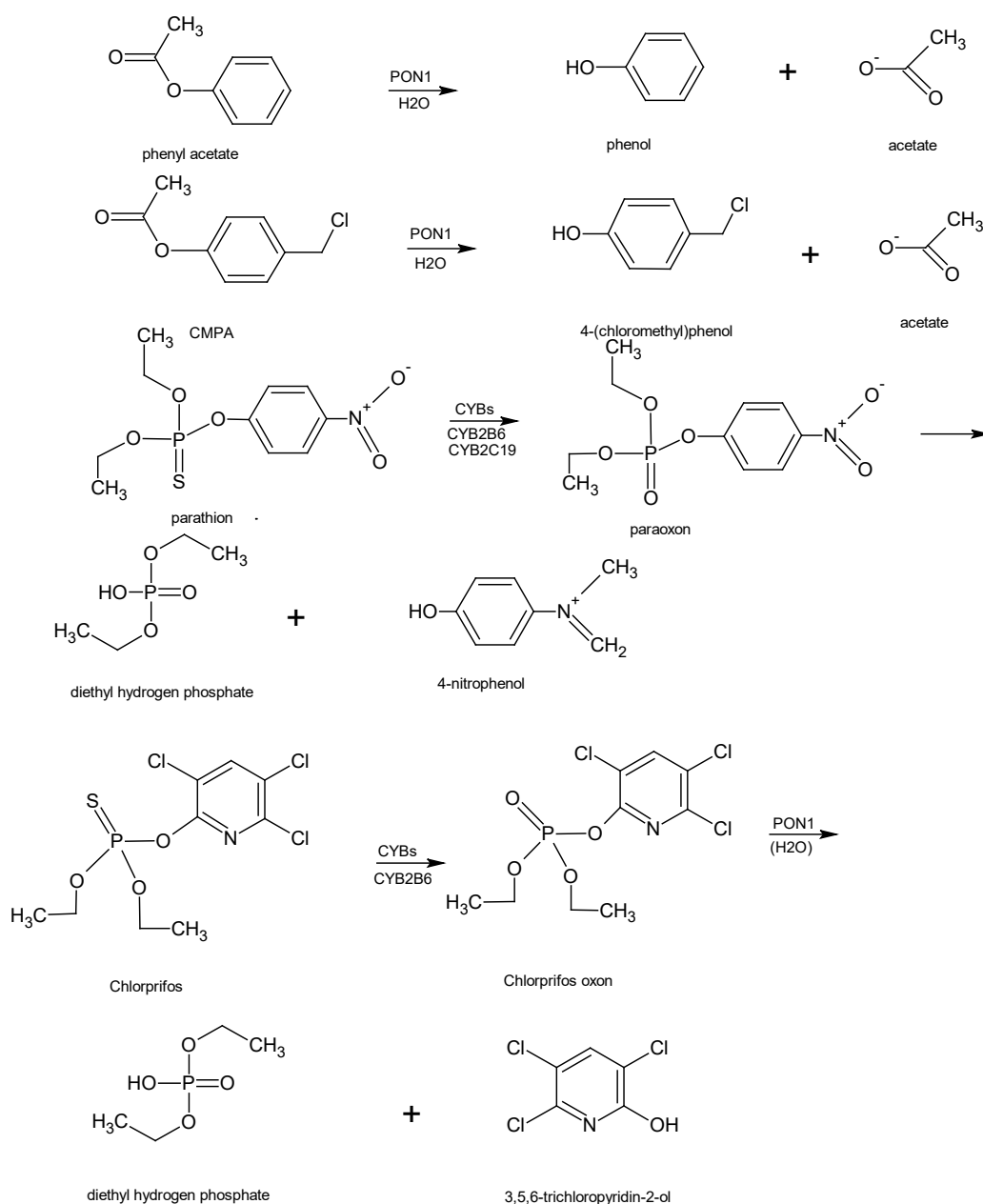
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such as chlorpyrifos, diazinon, and of nerve toxins such as sarin and soman [40]. Lactone-containing drugs-spirolactone, mevastatin, simvastatin, and lovastatin have been identified as substrates for PON1 [41]. Such aldehydes can also be hydrolyzed by PON1. Figure 1 point to the metabolisms of the some organophosphate by PON1. On the other hand this enzyme contain a histidine aminoacid at position (115, 134, 155 and 243) and cysteine at the (42, 248 and 353) position, in active site. This histidine is essential for esterase activity and cysteine is essential for hydrolase activity, thus zinc or nickel may bind to histidine. Other metals (e.g. mercury) or smoking extract constituents may interact with Cysteine (Cys) [42]. PON1 variants may represent a biomarker for identifying individuals susceptible to organophosphorus neurotoxicity leading to neurodegeneration and PD [43]. On the other hand this enzyme has been shown to be inactivated by oxidative stress and many antioxidative nutrients [25].

## Paraoxonase1 polymorphism

Studies have shown PON1 polymorphisms generated variable susceptibility to different diseases. As mentioned earlier PON1 have Two common coding polymorphisms, a leucine to methionine substitution at position 54 (L54M, rs854560) and a glutamine to arginine substitution at position 192 (Q192R, rs662), which influence the PON1 activity [44-46]. The PON 1 L55M polymorphism has been associated with variability in PON1 concentration and PON1 activity in plasma [46-48]. whereas the PON1 Q 192 R polymorphism has been shown to affect only the activity of PON1 [49]. The PON1 polymorphisms affect the catalytic abilities of this enzyme. The R allele at position 192 hydrolyzes paraoxon faster than the Q allele but hydrolyzes diazoxon slowly. Then, homozygotes for the B allele are poor metabolizer of organophosphate such as diazoxon, soman and sarin.



**Figure 1.** Metabolisms of the organophosphate by paraoxonase 1

The plasma concentration of the enzyme in M allele at position 54 is lower from L54 allele. Thus, R192 and L54 might be markers of higher activity of PON1 [46,50-54]. In other words, plasma of homozygous individuals for the wild-type Leu-allele of the rs854560 polymorphism has higher PON1 mRNA, protein and higher PON1 activity than homozygous for Met-allele carriers, while heterozygous carriers have intermediate mRNA, protein levels [48,55]. Several previous studies showed the association of one or both of these polymorphisms with PD. Akhmedova et al. reported that the M54 allele increase susceptibility to PD in a Russian population [56]. A further evidence for this association was shown in a Swedish case-control study. Kondo and Yamamoto described a significant increase of the R192 allele in PD patients from Japan in comparison to healthy controls [15]. However, some studies indicated there is no an association between PON1 polymorphisms an Parkinson's disease [57]. The aim of the present study includes investigation of both the M54L and the R192Q allele, genotype and haplotype distribution in PD patients and healthy subjects. In addition to these polymorphisms, some investigators have recently detected polymorphic mutations in the promoter region of PON1 gene, in particular, the T(107)C promoter polymorphism has been shown to affect PON1 gene expression and enzymatic activity [58]. Table 1 summarizes the evidence for an association between PON1 L55M and Parkinson's disease. Moreover, another study showed the association of R192Q allele with PD.

### Sources of variation in PON1 activity

PON1 activity has been shown to be regulated both genetically and by post translational modifications [59,60]. PON1 diurnal activity is quite constant. Serum paraoxonase activity significantly decreased with age ( $r = 0.38$ ;  $p = 0.0001$ ); however, its arylesterase activity and its concentration in the serum did not change significantly by aging. Thus, the decrease in PON1 activity may contribute to the increased susceptibility of HDL to oxidation; decreased in detoxification of organophosphates because of aging and oxidative damage. In newborns, PON1 activity until 6 months age is very low, suggesting that newborns can be significantly more sensitive to poisoning by pesticide than adults [50]. In rats, no differences were found in plasma and liver PON1 activity between 3- and 24-month-old animals [61]. Recent investigations have reported a progressive decrease in PON1 activity in elderly humans. More over many other factors can affect the PON1 activity and concentration. Some factors such as Dietary cholesterol, alcohol use, and vitamin C associate with an increase in AREase activity. And others like iron and folic acid can decrease AREase activity [62]. Triolein supplementation maybe increase the serum PON1 activity; whereas fish oil reduce this enzyme and tripalmitin not affect it [63]. The effects of various dietary fats on PON1 status have been evaluated in rats. Interestingly, PON1 activity in mice and humans can be increases with feed Oleic acid [64,65], others studies shows that Aspirin

use associated with high serum levels of paraoxonase activity [66] and synthesis of the PON1 protein as well as activity reduced by glycation of this enzyme [60].

In addition to PON activity, PON1 concentration change with genetic polymorphisms. Experimental evidence showed that serum activity in healthy subjects is directly related to protein concentration. Homozygous BB individuals have higher PON1 concentrations than homozygous AA. Moreover, heterozygous AB individuals have an intermediate level. It was shown the 55 polymorphism also affected the PON1 concentration. However it could not be found such effects in healthy population [67]. Considering the role of PON1 in PD, the concentration and activity of this enzyme can be different in Parkinson's patients and healthy subjects. Serum PON1 activity were significantly lower in patients than in healthy individuals and this different would be expected based on age alone [7]. Aryl esterase activity of the PON1 protein was significantly higher in PD. healthy subjects suggesting that paraoxonase activity of PON1, but not aryl esterase activity of PON1, is causally involved in the progression of PD [7].

### Other disease association with PON 1

PON1 activity can be regulated genetically and environmentally [60]. One of the most important roles of the PON1 is protection of LDL and HDL against oxidation induced by copper ions as well as by other free radicals [68]. This protection of PON1 is most probably related to the hydrolyzing of some activated lipids [69] and other lipid peroxide products [68] which are produced during the acute phase response. PON1 activity has been demonstrated decrease by LPS (lipopolysaccharide) [70] or TNF  $\alpha$  /IL -1B explosion but increase with IL-6 [71]. Regarding the roles of these factors, activity of PON1 can be changed in different inflammatory and infectious diseases. PON1 activity has been observed decrease in the serum of patients diagnosed with chronic hepatitis [72], rheumatoid arthritis [73], multiple sclerosis [74], diabetes mellitus [75], atherosclerosis, Alzheimer dementia and cancers [76-79]. Also decrease in PON1 activity levels were reported in radiology workers exposed to long-term (>5 years) ionizing radiation [80].

### Prostate and ovarian cancers

These types are the most common cancers in developed countries. The serum paraoxonase eliminates carcinogenic radicals [81,82]. A study in Finnish man found a new common mutation in the coding region of the PON1 gene, termed I102V, that was strongly associated with an increased risk of prostate cancer also PON1 polymorphism were significantly associated with epithelial ovarian cancer [83,84].

### Myocardial infarction

PON1 activity in patients who have survived a myocardial infarction was reported to be lower [85,86].

### Diabetes

Presence of PON1-55 MM and PON1-192 QQ genotypes related with weaker diabetes control than RR genotypes. other studies like this emphasized above findings [87,88].

### Lung cancer

It has been emerged the serum PON1 activity in patients with LC compared to healthy individuals is found to be significantly lower [89].

### Breast cancer

The L55M polymorphism, make lowers paraoxonase activity by decreasing the amount of this enzyme present in blood. women with

**Table 1.** Genetic association studies about the co-relation of PON1 polymorphism and PD risk

Study	PD Patients	Controls	PD Susceptibility
Kondo et al. [15]	166	252	Increased risk for MM
Akhmedova et al. [56]	117	207	Increased risk for MM
Carmine et al. [102]	114	127	Increased risk for MM
Clarimon et al. [5]	144	135	No influence
Fong et al. [57]	125	162	No influence
Đurić et al. [103]	106	7	Increased risk for MM
Dick et al. [104]	767	1989	No influence
Manthripragada et al. [20]	351	363	Increased risk for MM
Wingo et al. [105]	566	719	No influence

the MM genotype for this polymorphisms had a 57% higher incidence of breast cancer and an 85% higher incidence of invasive breast cancer [90].

### Rheumatoid Arthritis (RA)

It was shown that increased amount of ROS in plasma may be a sign of rheumatoid arthritis. Baskol et al. reported that increased ROS levels in RA might result in decreased antioxidant PON1 activity [91].

### Cirrhosis

Studies found that PON1 activity was lower in patients with cirrhosis than in those with hepatitis. This reduction in activity of PON1 was considered as a consequence of an altered synthesis and/or secretion of HDL. Alterations of the structure and circulatory levels of HDL was attributed to the hepatic LCAT activity which is frequently affect by chronic liver diseases [92,93].

### Atherosclerosis

Animal models demonstrated that PON1 deficiency was related to a susceptibility of LDL and HDL to oxidation and atherosclerosis development [94,95].

### Coronary artery disease

Studies indicate that PON1 in human is significantly associated with CAD risk [96,97] and its activity is lower among individuals and populations with CAD.

### Depression

A study of the association of paraoxonase1 Q192R polymorphism with depression among a random sample of 3266 British women, suggested that there was an association of PON1 Q192R polymorphism with symptoms of depression [98].

### Other disease

The studies of PON1 polymorphism, activity or levels found a relationship between PON1 with Age-Related Macular Degeneration (AMD). The mechanism(s) for PON1-mediated protection against AMD remains to be determined. A study supported a role for the Q192R polymorphism in decreasing susceptibility to AMD [99]. Saeed et al. found a significant association of variants in the Paraoxonase gene cluster and sporadic ALS in Gulf War veterans [100]. Finally, Paraoxonase activity showed an inverse association only with sperm concentration, and arylesterase activity was not associated with any semen quality parameter [101].

### Conclusion

Multiple genetic and environmental risk factors are known to increase susceptibility to the development of PD. Each factor individually may have a minor effect however their interaction may prove sufficient to cause PD. Over the past few years, an increasing number of studies have attempted to identify paraoxonase1 relationship with PD. Our analysis shows that people work with organophosphates are at significantly increased risk of PD. The association of organophosphates with PD may be related to PON1. PON1 would thus seem worthy of further study as an etiologic factor in the development of PD and perhaps other diseases. To date, accepted that both PON1 L55M and PON1 Q192R polymorphisms have been unequivocally associated with PD. Our review of the results of former studies shows that paraoxonase1 polymorphism may have influence on PD development. And also, it suggests that paraoxonase activity but not aryl esterase activity of PON1

is causally involved in the progression of PD. The authors of this review concluded that there was a significant association of the PON1-55 MM + LM genotype with the risk of PD than the LL genotype and there was only a study for association between the polymorphism of PON1-192 and PD. However, some studies suggested that the M54L and Q192R polymorphisms were not major risk factors for PD. Also, we found that factors which increase paraoxonase activity; such as aspirin and oleic acid may reduce risk of PD. The roles of PON1 in PD is controversial, there is an essential need of future studies which provide a better understanding of roles of the PON1 in PD and pathogenic mechanisms of this disease.

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