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Review Article

Paraoxonase-1: Genetic Variations and Disease Association

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Abstract:

The association between Paraoxonase 1 (PON-1) polymorphisms and diseases has been a subject of extensive research. PON-1 is an enzyme involved in protecting against oxidative stress and inflammation. Numerous studies have investigated the potential links between PON-1 polymorphisms and various diseases, including cardiovascular diseases, diabetes, neurological disorders, liver diseases, and cancer. However, the findings from these studies have been inconsistent and often conflicting. While some studies have reported significant associations between specific PON-1 polymorphisms and increased or decreased disease risk, others have failed to observe consistent patterns. Factors such as study design, sample size, population characteristics, and genetic heterogeneity may contribute to these discrepancies. This review provides a concise overview of the current understanding of the association between PON-1 polymorphisms and diseases based on existing literature.

Introduction

Paraoxonase-1 (PON-1) is an enzyme that is primarily associated with the metabolism and detoxification of organophosphates, including insecticides and nerve agents. It is also involved in the metabolism of other compounds, such as certain drugs and lipid peroxidation products. PON-1 is synthesized in the liver and is found in high concentrations in the bloodstream, where it is associated with high-density lipoprotein (HDL) particles [1]. Genetic variations within the PON-1 gene have been extensively investigated due to their potential implications for enzyme activity and their association with disease susceptibility.

The most well-known genetic polymorphisms in the PON-1 gene are Q192R and L55M, which refer to amino acid substitutions at positions 192 and 55, respectively [2]. These polymorphisms have been the subject of numerous studies exploring their relationship with various diseases and health conditions.

The Q192R polymorphism has been particularly well-studied and is associated with differences in PON-1 enzyme activity. The R allele is generally linked to higher enzymatic activity compared to the Q allele, resulting in increased hydrolysis of certain toxic substrates. Consequently, individuals carrying the R allele may have a greater capacity to detoxify organophosphates and potentially enjoy protection against their harmful effects. Conversely, the Q allele has been associated with decreased enzyme activity, which may have implications for disease susceptibility [3].

The L55M polymorphism has been associated with serum concentration and associated with cardiovascular diseases [4]. This polymorphism while less extensively researched has also attracted attention. Some evidence suggests that the M allele may be associated with reduced PON-1 enzyme activity, although the clinical significance and its impact on disease susceptibility require further investigation.

Understanding the association between PON-1 genetic variations and diseases is of great importance. Extensive research has explored their potential link to various conditions, including cardiovascular diseases, neurodegenerative disorders, cancer, and pesticide-

related toxicity. However, the findings have been inconsistent, and it is evident that the influence of PON-1 genetic variations on disease development is likely to be influenced by numerous factors, such as environmental exposures, lifestyle choices, and interactions with other genetic variants.

While PON-1 genetic variations are just one piece of the puzzle, they hold promise for personalized medicine and the optimization of drug dosing in the field of pharmacogenomics. By exploring the relationship between PON-1 genetic variations and disease associations, researchers aim to elucidate the complex interplay between genetics, environmental factors, and disease susceptibility, paving the way for tailored therapeutic approaches.

In this review, we aim to provide a comprehensive overview of the current understanding regarding PON-1 genetic variation and its association with various diseases. By examining the existing literature and highlighting the key findings, we hope to contribute to the broader understanding of the complex relationship between PON-1 genetic variations and disease susceptibility, ultimately make provision for personalized medicine and improved patient care.

Genetics of PON-1

The genetics of PON-1 involve the study of the gene encoding this enzyme and the variations or polymorphisms within it. The PON-1 gene is located on the long arm of chromosome 7 (7q21.3-22.1) in humans [2]. The PON-1 gene consists of 8 exons, which are the coding regions of the gene that contain the instructions for protein synthesis. These exons are separated by introns, which are non-coding regions of DNA. The PON-1 gene is approximately 7.5 kilobases (kb) in length.

Several polymorphisms have been identified within the PON-1 gene, with the two most commonly studied ones being the Q192R and L55M polymorphisms [2]. These polymorphisms affect the activity and function of the PON-1 enzyme. Five polymorphisms have been discovered in the non-coding region of the PON-1 gene in addition to these two in the coding area of the gene [5-7]. Positions 2108 (C/T), 2126 (G/C), 2162 (A/G), 2832 (G/A), and 2909 (C/G) correspond to these.

These genetic variations can influence the individual's susceptibility to various diseases and conditions, particularly those related to oxidative stress, inflammation, and the metabolism of toxic compounds. Different combinations of PON-1 genotypes, which are determined by the presence of specific alleles, may result in varying levels of enzyme activity and thus affect an individual's health outcomes.

PON-1 polymorphisms and disease association

PON-1 polymorphism and cardiovascular diseases

PON-1 polymorphism has been extensively studied in relation to cardiovascular diseases (CVD). Two polymorphisms, Q192R and L55M, have been widely studied in relation to CHD among the many PON-1 polymorphisms. The Q192R polymorphism of the PON-1 gene has received particular attention in cardiovascular research. It is evident that the PON-1 Q192R polymorphism affects the enzyme activity and substrate selectivity [3,8]. Higher PON-1 activity is believed to provide protection against CVD by reducing oxidative stress, inhibiting the oxidation of low-density lipoprotein (LDL) cholesterol, and promoting the clearance of lipid peroxides.

Some studies have suggested that individuals carrying the QQ genotype (homozygous for the Q allele) may have a reduced risk of developing CVD compared to those carrying the QR or RR genotypes [9, 10] while other have opposite findings [11, 12]. Some researches [9, 13] found an association between the presence of allele 55L and atherosclerosis, while others [14, 15] did not. Results of a meta-analysis on potential associations between the risk of CHD and the PON-1 gene polymorphism at locations 108, 55, and 192 were published by Wheeler et al. The presence of PON1 allele 192R PON1 was only marginally associated with CHD [16].

There was no correlation between C-108T and G-909C promoter polymorphism and the presence of CHD in case-control research that evaluated the potential impact of PON-1 status on CHD. Regardless of genotype, the authors found that PON-1 activity and concentration were considerably lower in CHD patients than in the healthy population [13].

Independent of genotype, a decrease in enzyme concentration and activity were seen. Therefore, it was proposed that genotyping analysis and enzyme serum activity assessment may be taken into consideration as potential indicators of CHD [17].

PON-1 polymorphism and Alzheimer's disease (AD)

Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment. The association between PON-1 polymorphism and AD has also been a subject of investigation, although the research in this area is still ongoing, and the findings have been inconsistent.

Some studies have suggested a potential link between PON-1 polymorphisms and the risk of developing AD. A correlation between AD and variations in the PON gene cluster in Caucasians and African Americans has already been established [18]. Particularly, there was convincing evidence of a link between the SNP-C161T and AD in both ethnic groups, with the T-allele having detrimental consequences [18]. In contrast, no correlation with AD was discovered in a study that

examined the same SNP in an Italian case-control sample [19]. According to another study, a heterozygous methionine allele of the L55M polymorphism raises the risk of AD in men. It's interesting to note that homozygous people with the QQ and MM genotypes have longer lifespan and develop AD at a later age [20].

A meta-analysis on the association between PON genes and Alzheimer's disease was done by Nie et al. [21] comprising fifteen studies that involved five SNPs. The investigation revealed that A allele of the PON-1 rs705379 polymorphism was positively related to AD in the Caucasian population, and the GG genotype significantly reduced AD risk in Caucasians, according to the authors' findings. They also noted that the SS genotype of PON-2 S311C polymorphism had a significant association with Alzheimer's disease in the studied population [21]. A meta-analysis is constrained by the calibre of the studies included; more thorough research is needed to clarify the function of PON-1 in AD.

It is important to note that AD is a complex multifactorial disease influenced by multiple genetic and environmental factors. The role of PON-1 polymorphisms in AD development is likely to be influenced by other genetic variations, lifestyle factors, and interactions with other genes involved in AD pathogenesis.

PON-1 polymorphism and Diabetes mellitus

The association between PON-1 polymorphism and diabetes mellitus, particularly type-2 diabetes mellitus (T2DM), has been investigated in several studies.

Genotyping of the PON-1 L55M and Q192R polymorphisms was done in 293 healthy people and 287 patients with T2DM.Comparing T2DM patients to healthy people, it was shown that the frequency of the genotypes QR/RR and LM/MM was significantly greater. Additionally, the risk of having diabetes increased up to 1.68 times for patients with the R allele and up to 2.24 times for those with the M allele. Higher body mass index (BMI), elevated cholesterol, triglycerides, LDL, fasting serum insulin, and HOMA-IR were all linked to the QR/RR and LM/MM genotypes [22].

Several studies have investigated the association between PON-1 polymorphisms and diabetic complications, such as diabetic nephropathy (kidney disease), retinopathy (eye disease), and cardiovascular disease. Variable results have been found in studies examining the association between PON-1 polymorphisms and diabetic complications. According to Flekac et al., L55M and Q192R polymorphisms are related to macroangiopathy in diabetic patients [23].Individuals with PON1-55 MM and PON1-192QQ genotypes tend to have poorer diabetes control compared to those with LL and RR genotypes. Patients with the LL genotype had better diabetes control than those with the MM genotype, and vice versa ($P < 0.05$). The L55M polymorphism, rather than the Q192M polymorphism, was an independent determinant for beta-cell function in glucose tolerant according to Chiu et al. [24]. The PON1-R192 variant being identified in the Turkish population as an independent genetic risk factor for the development of problems in diabetes more than three times [25] and RR genotype may be a risk factor for cardiac problems in type 2 diabetes patients [26]. According to Mackness et al. [27], the LL genotype is associated with the onset of diabetic retinopathy.

PON-1 polymorphism and Cancer

Several studies have investigated the association of PON-1 polymorphism and cancer risk. A meta-analysis that examined 30 publications investigated the association between the PON-1 Q192R polymorphism and the risk of cancer by Zhang et al.[28], explored the significance of the genetic variant Q192R in cancer susceptibility because PON-1 polymorphisms have been linked to various forms of cancer.

The investigators did a thorough review of the literature, and their meta-analysis looked at 30 papers with a total of 8,112 cases and 10,037 controls. The results showed that the PON-1-192 R allele was linked to a lower risk of all cancers when compared to the 192 Q allele; however, when the results were broken down by cancer type, it was found that the risk of specific cancer subtypes varied between heterozygous, homozygous, dominant, and recessive models [28].It is generally known that oxidative stress and elevated levels of free radicals might raise the likelihood of developing cancer; as a result, more research is needed to completely understand the antioxidant capabilities of the genetic variations of PON-1.

According to another meta-analysis on the relationship between PON-1 genetic polymorphisms and breast cancer susceptibility, the presence of the R allele on the polymorphism Q192R was linked to a lower risk of breast cancer. On the other hand, PON-1-55LM and PON-1-55MM genotypes were both linked to higher risk [29]. In fact, those with the MM and QQ genotypes had reduced levels of PON-1, which may impair their ability to eliminate dietary carcinogens and inflammatory oxidants, increasing the likelihood of developing breast cancer [29]. This serves as evidence that studying PON-1 genotype in addition to PON-1 activity is important.

PON-1 polymorphism and Parkinson's disease (PD)

Parkinson's disease is a neurodegenerative disorder that primarily affects the movement and coordination of an individual. Some studies suggest that certain PON-1 gene polymorphisms may be associated with an increased risk of developing PD. The L55M

polymorphism was reported to affect various symptoms of PD development in research with 246 patients with PD who were exposed to organophosphates [30]. The M54 allele increases vulnerability to PD in a Russian population, according to Akhmedova et al. [31]. Swedish case-control research provided additional support of this relationship. In compared to healthy controls, Japanese PD patients had a statistically significant increase in the R192 allele, according to Kondo and Yamamoto [32]. However, other studies have failed to find a significant association between PON-1 polymorphism and Parkinson's disease [33-35].

PON-1 polymorphism and non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease is a condition characterized by the accumulation of fat in the liver in the absence of excessive alcohol consumption. It is closely associated with obesity, insulin resistance, and metabolic syndrome. The development and progression of NAFLD involve complex interactions between genetic and environmental factors.

MV Milaciu et. al. [36] evaluated the status of PON-1 gene polymorphism L55M, Q192R and C108T in 81 patients with NAFLD and 81 healthy controls. The L55M polymorphism showed the largest intergroup variation, with the heterozygous variant LM found in 58% of the NAFLD patients and only in 33.3% of the control patients. In comparison to the control group, the frequency of the M allele was noticeably greater in the NALFD group. The pattern makes it quite evident that the M allele and NAFLD are associated. However, the available research on this topic is still limited, and further studies are needed to establish a clear association between PON-1 polymorphism and NAFLD.

Other diseases

A comprehensive review and meta-analysis of PON gene polymorphisms with ischemic stroke was carried out by Liu et al. [37]. The meta-analysis comprised 28 papers. The R allele or RR genotype of the PON-1 Q192R polymorphism was associated with an elevated risk for ischemic stroke in the general population, but no other genetic variations of the PON gene were shown to significantly increase the risk of ischemic stroke [37]. Since the quality of the studies included in the meta-analysis and systematic review is not strong, no general conclusions can be drawn from this research.

The L55M polymorphism reduces paraoxonase activity by lowering the concentration of this enzyme in the blood. Breast cancer incidence was 57% higher and invasive breast cancer incidence was 85% higher in women with the MM genotype for this polymorphism [38].

There may be a relationship between PON-1 Q192R polymorphism and depression, according to research on the correlation of PON-1 Q192R polymorphism with depression in a random sample of 3266 British women [39].

Three PON-1 enzyme polymorphisms—L55M, R192Q, and T-107C—were examined and linked to mortality in research involving 1,932 Danish people aged 47 to 93 [40]. The evaluation of the genotypic and haplotypic distribution among the various age groups came to the conclusion that there was no difference. However, compared to people with the 192QQ homozygous genotype, people with the 192RR homozygous genotype had a decreased survival rate, which was particularly noticeable in women. Nevertheless, Caliebe et al.'s meta-analysis [41], which included 9580 people from different populations, did not find a connection between the R allele and life expectancy.

Conclusion and future prospective

The studies investigating the association between PON-1 polymorphisms and diseases have provided mixed and sometimes conflicting results. While some studies have reported significant associations between specific PON-1 polymorphisms and increased or decreased risk of certain diseases, others have found no significant associations or inconsistent findings. The discrepancies in the literature may be attributed to differences in study design, sample size, population characteristics, and genetic heterogeneity.

Nevertheless, certain trends have emerged from the available evidence. Some PON-1 polymorphisms, such as Q192R and L55M, have been frequently studied in relation to diseases such as cardiovascular diseases, diabetes, and cancer. However, the impact of these polymorphisms on disease risk appears to be influenced by various factors, including ethnic background, environmental factors, and gene-gene or gene-environment interactions.

The mechanisms through which PON-1 polymorphisms influence disease susceptibility are still not fully understood. It is believed that these polymorphisms may affect PON-1 enzyme activity, stability, or expression levels, thereby influencing oxidative stress, inflammation, lipid metabolism, and other relevant pathways implicated in disease development and progression. However, further research is needed to elucidate these mechanisms and establish casual relationships.

The future prospects for research on PON-1 polymorphism and disease association involve functional characterization, gene-environment interactions, diverse population studies, multi-gene interactions, mechanistic investigations, and potential therapeutic implications. Continued exploration in these areas will

contribute to a deeper understanding of the relationship between PON-1 polymorphisms and diseases, leading to improved risk assessment, personalized medicine, and novel therapeutic approaches.

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