






The Role of *PON1* Variants in Disease Susceptibility in a Turkish Population

Mahmoud Abudayyak¹  Tuğçe Boran¹  Rumeysa Tukul¹ Ezgi Oztas¹  Gül Özhan¹ 

¹Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey

Address for correspondence Gül Özhan, Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey (e-mail: gulozhan@istanbul.edu.tr).

Global Med Genet 2020;7:41–46.

Abstract

Paraoxonase 1 (PON1) enzyme plays a major role in antioxidant defense and protects the cells against reactive species. The most common *PON1* Q192R and L55M polymorphisms are responsible for a wide variation of PON1 activity, which showed an up to 13-fold interindividual variation among the same genotype. *PON1* genotypes were evaluated with the development of pancreatitis, colorectal cancer, and hypothyroidism in a hospital-based, case-control study. Individuals with rs662 G allele had a two-fold risk of developing hypothyroidism. A weak association was found between rs854560 T allele and pancreatitis. The results were preliminary. Further studies with a larger number and detailed biochemical parameters are needed.

Keywords

- ▶ paraoxonase-1
- ▶ hypothyroidism
- ▶ pancreatitis

Introduction

Paraoxonase (PON) is one of the more important antioxidants and antiatherogenic enzymes. It is mainly synthesized in the liver and metabolizes organophosphate, carbamate, aromatic carboxylic acid ester, unsaturated aliphatic ester, cyclic carbonate, and lactone compounds. It plays a significant role in the detoxification of nerve gases such as sarin, soman, and tabun.^{1–3} The *PON* family consists of three genes: *PON1*, *PON2*, *PON3*, with each encoding a unique protein. The *PON* genes, located adjacent to each other on chromosome 7 in humans, show approximately 65% similarity in amino acids.^{4,5} *PON1* stimulates high-density lipoprotein (HDL)-mediated cholesterol flow, protects against oxidative damage, and has peroxidase-like activity. Proteins encoded by the *PON1* and *PON3* are found in the blood circulation,⁶ while the intracellular enzyme encoded by *PON2* is not found in the circulation. However, all the enzymes prevent oxidation of lipids^{7,8} and are important for components of the antioxidant system in humans. Therefore, dysfunction in these enzymes can be associated with some diseases related to oxidative stress such as cancer and cardiovascular disease.⁹

PON1 variation is the most studied member of the *PON* gene family. The coding region of *PON1* has two polymorphic sites, which are leucine (L)/methionine (M) at position 55 (L55M, rs854560) and glutamine (Q)/arginine (R) at position

192 (Q192R, rs662).¹⁰ The rs854560 polymorphism leads to changes in the serum enzyme concentration. *PON1* enzyme concentration is higher in AA genotypes than TT genotypes.^{11–13} The rs662 polymorphism affects substrate specificity of the *PON1* hydrolytic activity. Diazinon, soman, and sarin are hydrolyzed more efficiently in 192Q isoform of the *PON1* enzyme, which is encoded A allele, whereas paraxon is hydrolyzed at a higher rate than 192R isoform of *PON1* enzyme, which is encoded G allele. Also, A allele prevents the accumulation of lipid peroxides more than G allele^{14,15} (–Fig. 1).

PON1 enzymatic activity is also affected by many physiological and pathological factors such as pregnancy, aging, diabetes, and renal disease.¹⁶ *PON1* activity has been found decreased in type 1 and 2 diabetes as well as metabolic syndrome, which could be related with reduced secretion of insulin and decreased ability of HDL.¹⁷ Some researchers reported that *PON1* polymorphisms could be related to diseases associated with oxidative stress-related inflammation like acute pancreatitis and neurodegenerative diseases such as Alzheimer's.^{18,19} Oxidative stress lead to reduction in *PON1* and *PON3* enzymatic activity, while *PON2* enzyme activity increases under oxidative stress conditions.¹⁰

Oxidative stress plays a key role in the pathogenesis of several diseases via numerous pathways. Although thyroid



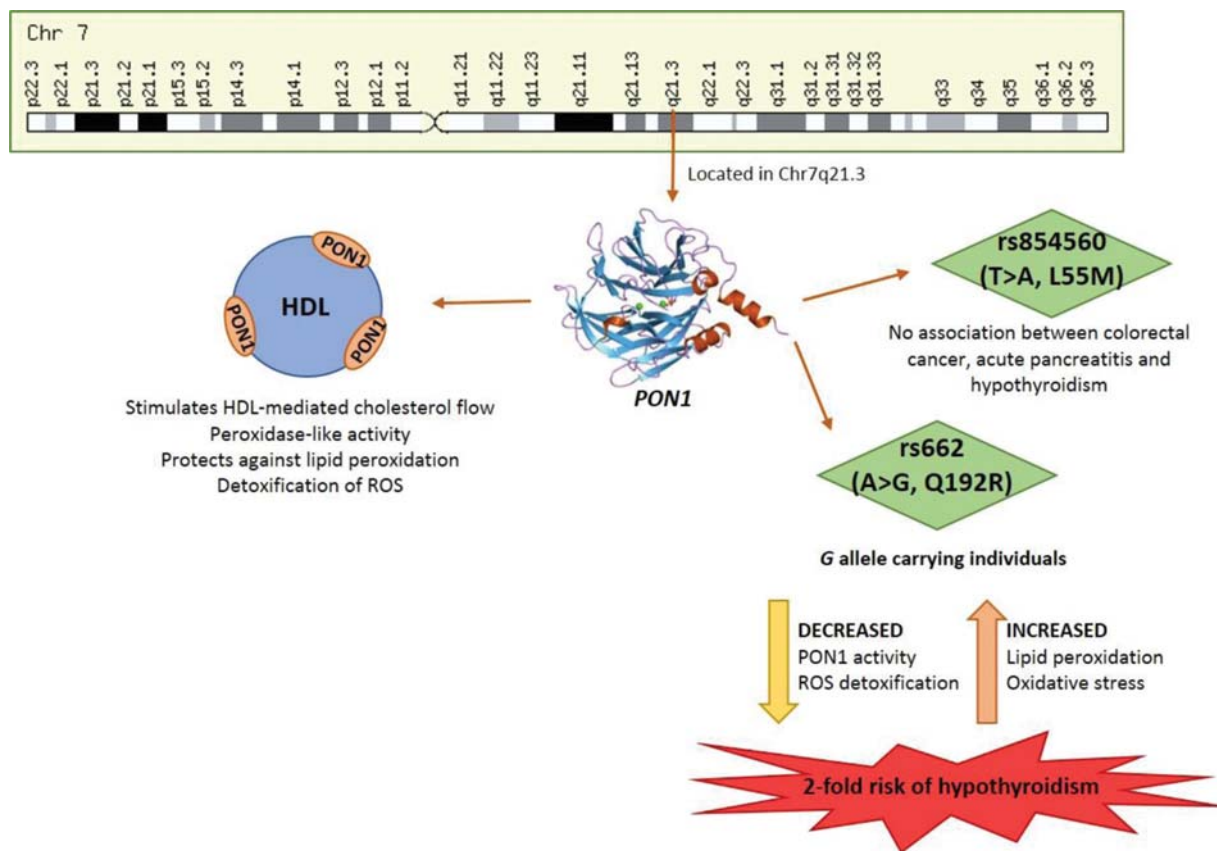


Fig. 1 Relation between the rs854560 and rs662 polymorphisms of *PON1* and disease development.

hormones mainly regulate protein, vitamin and antioxidant enzymes synthesis and degradation, they also play a role in reactive oxygen species (ROS) production.²⁰ ROS are highly reactive molecules that mainly attack membrane lipids, and inadequate removal of ROS could result in lipid peroxidation, metabolic dysfunctions, damaged macromolecules and eventually cell death.

Since *PON1*, a known antioxidant, has a peroxidase-like activity, it could prevent oxidative stress in hypothyroidism. However, several reports indicated elevated oxidative stress parameters^{21,22} and decreased *PON1* activity²³ in hypothyroid patients. It is well-known that increased level of ROS is related to many cancers including colorectal cancers. *PON1* enzyme is a phase 1 detoxification enzyme with a wide range of substrate specificity. Therefore, *PON1* enzyme activities may alter ROS production or the rate of chemical metabolism, and this may influence the risk of colorectal cancer.²⁴ Acute pancreatitis is an inflammatory disease mediated by cytokines, bioactive lipids, and oxidative stress.²⁵ Paraonase activity is regulated by interleukin-1 and tumor necrosis factor- α ²⁶; besides oxidative response, *PON1* may also be a part of the inflammatory response.

Based on the significant role of *PON1* in oxidant-antioxidant balance, the present study aimed to evaluate the relationship between *PON1* polymorphism and disease susceptibility in a small-sized patient population with hypothyroidism, colorectal cancer, and pancreatitis.

Material and Methods

Sample Collection

The study was conducted as a cross-sectional study with Turkish participants recruited from Istanbul University Medical Faculty between February 2017 and March 2018. The effects of the *PON1* polymorphisms on hypothyroidism, colorectal cancer, and pancreatitis susceptibility were evaluated among a total of 200 participants who volunteered. Fifty patients with secondary hypothyroidism caused by total thyroidectomies; 50 patients with histopathologically confirmed colorectal cancer; and 50 patients clinically diagnosed with mild or severe acute pancreatitis were included. Fifty ethnic, age and gender-matched controls who had no history of these conditions were selected randomly from hospital patients. The sample size was proper to evaluate the relationship between selected single nucleotide polymorphisms (SNPs) and diseases based on power analysis (<http://osse.bii.a-star.edu.sg>). The study was approved by the ethical committee of Istanbul University (2017/1370) and performed in accordance with the Helsinki Declaration of 1975. All participants were provided informed consent. Demographic and anthropometric factors (ethnicity, age, body mass index [BMI, kg/cm²]) were assessed using a short questionnaire.

Genotyping

Genomic DNA was extracted from venous blood samples by High Pure PCR Template Preparation Kit (Roche, Germany) and

Table 1 Reference sequences of custom-designed LightSNiP assay probes

LightSNiP	Reference sequence	Melting temperatures
rs662 (575A > G)	TCACTATTTCTTgACCC CTACTTAC [A/g] ATCCTgggAgATg TATTTgggTTTA	52.56 °C for allele [G] 60.28 °C for allele [A]
rs854560 (163T > A)	AgCCAgTCCATTAagg CAgTATCTCCA[A/T] gTCTTCAGAgCCAag TTTCTgCCAgA	60.23 °C for allele [A] 65.50 °C for allele [T]

Abbreviation: rs: reference SNP number; alleles in the square brackets indicates the polymorphisms.

kept at 4°C. Genotyping was performed on real-time PCR platform (LightCycler 480, Roche, Germany) using LightCycler FastStart DNA Master HybProbe and Roche LightSNiP assay probes (Roche, Germany) according to the manufacturer's instructions. In a final volume of 20 µL reaction mix per sample, the following mixtures was added: 1X FastStart DNA Master Mix, 2 mM MgCl₂, 0.2 µM LightSNiP HybProbe, appropriate amount of PCR grade water, and 500 ng DNA sample. In each run, sterile water and a known genotyped sample were used as negative and positive controls, respectively, to achieve 100% concordance. Details of custom-designed LightSNiP assay probes were summarized in ►Table 1.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (Version 20, Chicago, USA). The Hardy–Weinberg Equilibrium (HWE) analysis was performed to compare the observed and expected genotype frequencies of subject by using the Chi-squared (χ²) test. Data comparisons were done by using Fisher's exact test. The odds ratios (OR) and 95% confidence intervals (CI) were estimated to

evaluate the association between cases and controls. A two-tailed value of *p* < 0.05 was considered a statistically significant difference.

Results

In the present study, two SNPs of the *PON1*, rs662 and rs854560, were genotyped in a Turkish population. The cases and controls were evaluated to determine the effects of *PON1* polymorphisms on hypothyroidism, colorectal cancer, and pancreatitis susceptibility. All participants were Caucasian, and the characteristics of the studied population were summarized in ►Table 2. Gender distribution was almost the same in all groups except hypothyroidism where females had a representation of 91%. In disease groups, patients who were ≥ 50 years old represented at least 61.3% of cases, whereas the control group was relatively young with volunteers who are ≥ 50 years old accounting for 44.5%. Nonsmokers represented at least 60% of all patients; however, approximately one third of the patients were overweight. As shown in ►Table 3, the genotype distribution was found to be consistent with the HWE among all participants (*p* > 0.05), indicating that the studied population was randomized and unbiased. The minor allele frequencies of the studied SNPs were found notably similar to Europeans^{15,17,27}; however, highly different from Asians.^{28,29}

The dominant model was used to evaluate whether *PON1* polymorphisms increase the risk of hypothyroidism, colorectal cancer, or pancreatitis. The genotype distributions, allele frequencies and estimated ORs with 95% CI among all cases and controls are summarized in ►Table 4. The genotyping analysis based on a dominant model showed that individuals with G allele of rs662 had an approximately two-fold risk of developing hypothyroidism (OR = 2.05; 95% CI = 1.05 to 3.97; *p* = 0.047). In addition, it was observed that individuals with T allele of rs854560 had an approximately 1.5-fold risk of developing

Table 2 Demographic and anthropometric factors of cases and controls

Variable	Percentile (%)			
	Control (n = 50)	Hypothyroidism (n = 50)	Colorectal cancer (n = 50)	Pancreatitis (n = 50)
Gender				
Male	44.4	8.2	59.4	51.3
Female	55.6	91.8	40.6	48.7
Age				
≥ 50	44.5	78.6	61.3	72.9
< 50	55.5	21.4	38.7	27.1
BMI				
□ 25	18.6	31.8	30	48.6
> 25	81.4	68.2	70	51.4
Smoking status				
Nonsmoking	62.9	86.4	90	59.4
Smoking	37.1	13.6	10	40.6

Abbreviation: BMI, body mass index (kg/m²).

Table 3 Genotype distribution of rs662 and rs854560 in the Turkish population

SNPs	Genotypes	Observed (n)	Expected (n)	χ^2	p-Value
rs662 (575A > G)	A/A	109	103	4.13	0.134
	A/G	69	54		
	G/G	22	16		
rs854560 (163T > A)	A/A	83	79	4.09	0.167
	T/A	85	93		
	T/T	32	28		

Abbreviations: n, number of subjects; rs, reference SNP number; SNPs, single nucleotide polymorphisms; χ^2 , Chi-square. Note: $p < 0.05$, significance level.

Table 4 Genotype distributions and allele frequencies of *PON1* polymorphisms among cases and controls

Subject (n)	rs662 (575A > G)						OR (95% CI)	p-Value
	Genotype distributions (n)			Allele frequencies		A versus any G		
	AA	AG	GG	A	G			
Controls (50)	26	17	7	0.69	0.31			
Hypothyroidism (50)	34	14	2	0.82	0.18	2.05 (1.05–3.97)	0.047	
Colorectal cancer (50)	26	14	10	0.66	0.34	0.87 (0.48–1.57)	0.762	
Pancreatitis (50)	23	24	3	0.70	0.30	1.05 (0.57–1.91)	1.000	
Subject (n)	rs854560 (163T > A)						OR (95% CI)	p-Value
	Genotype distributions (n)			Allele frequencies		A versus any T		
	AA	TA	TT	A	T			
Controls (50)	20	23	7	0.63	0.37			
Hypothyroidism (50)	20	20	10	0.60	0.40	0.88 (0.49–1.55)	0.771	
Colorectal cancer (50)	17	23	10	0.57	0.43	0.78 (0.44–1.37)	0.471	
Pancreatitis (50)	26	19	5	0.71	0.29	1.44 (0.79–2.60)	0.292	

Abbreviations: 95% CI, 95% confidence intervals; n, number of subjects; OR, odds ratio; rs, reference SNP number. Note: $p < 0.05$, significance level.

pancreatitis (OR = 1.44; 95% CI = 0.79 to 2.60); however, the association did not reach statistical significance ($p = 0.292$).

Discussion

Genetic polymorphism studies contribute to the generation and identification of gene maps related to various diseases such as cancer, development of new drugs by targeting proteins encoded by specific genes, elucidation of molecular basis of different responses of individuals to drugs, and determination of the factors to be considered in drug selection in treatment. The importance of genetic differences in recent years has attracted the attention of researchers.^{30,31} *PON1* activity shows different distribution in different ethnic groups. The guanine exchange of cytosine at position 55 in the 3rd exon (rs854560) and the adenine thymine change at position 192 in the 4th exon (rs662) are the most important gene variants in *PON1* activity. The C/G nucleotide change at position 55 leads to the change of leucine to methionine (Leu55Met, L55M, rs854560) in amino acid sequence, while the changes from glutamine to arginine (Gln192Arg, Q192R, rs662) appear as a result of A/T nucleotide change at position 192.^{32–34}

There are some studies related to *PON1* polymorphism in the Turkish population. In a study conducted on a group of individuals with cardiovascular disease, the G allele frequency of *PON1* rs662 was higher in the patient group, but no statistically significant difference was found than the healthy individuals.³⁵ In another study, the relation between cardiovascular diseases and *PON1* rs662 and rs854560 polymorphisms was investigated. The T allele frequency of *PON1* rs854560 was higher in the patient group. It is stated that rs854560 polymorphism can be considered as a risk factor for the development of cardiovascular disease among the Turkish population.²⁷ A study was conducted to determine *PON1* rs662 and rs854560 polymorphisms distribution in diabetic patients with complications and the changes in enzyme activity. Individuals with TT genotypes of rs854560 and with AA genotypes of rs662 were seen very frequently in type 2 diabetes group; also, enzyme activity was found to be lower in the patients' group.³⁶ In another study conducted in diabetic patients, a significant relationship between the two polymorphisms and the disease was determined. *PON1* enzyme, which is heterozygote for rs662, was found to be three times more

effective in the occurrence of complications; also, it was found to be more effective in relation to the risk of diabetic complications.³⁷

It is well-known that higher levels of oxidative stress are one of the main causes for cancer development. In normal conditions, *PON1* activity protects the organisms against oxidative stress via ROS detoxification. *PON1* activity is highly variable during pathogenesis and its complex regulation involves both genetic and environmental factors. It can be expected that variations on *PON1* gene may cause alterations on the *PON1* activity; and, decreased *PON1* activity may cause cancers. Stevens et al³⁸ observed no association between prostate cancer and *PON1* rs662 and rs854560 polymorphisms; however, when they combined these SNPs, they suggested that men with *PON1* genotypes face an increased risk of contracting aggressive prostate cancer. On the other hand, Antognelli et al³⁹ found that rs662 AG and rs854560 TA/TT genotypes had a significantly higher risk of prostate cancer. Most research works have been focused on the effects of *PON1* polymorphisms in breast cancer; however, they have yielded conflicting results. According a meta-analysis conducted by Saadat,⁴⁰ G allele of rs662 was associated with decreased risk of breast cancer, whereas both TA and TT genotypes of rs854560 were associated with increased risk of breast cancer. It is reasonable to expect that *PON1* polymorphisms, due to their lipid peroxidation scavenging activity, may influence colorectal cancer development as well. Similar to Van der Logt et al,²⁴ our results indicated that in *PON1* rs662 and rs854560 polymorphisms have no effect on colorectal cancer susceptibility.

Considering the crucial role of *PON1* in the regulation of the oxidative stress and inflammation, it might be involved in the pathophysiology of acute pancreatitis. Unal et al⁴¹ showed significantly decreased *PON1* activity and positive correlation to HDL level, with significantly increased malondialdehyde levels in acute pancreatitis among Wistar albino rats. Since genetic variations may result in altered activity of *PON1*, Verlaan et al⁴² investigated *PON1* variants as a modifying factor of chronic pancreatitis. It was observed that allele frequencies of *PON1* rs854560 did not differ between chronic pancreatitis patients and controls, whereas it was found in subgroup analysis that *PON1* rs662 A allele was significantly higher in idiopathic chronic pancreatitis patients compared with controls. Our results are the first in the literature which showed that individuals with T allele of rs854560 had an approximately 1.5-fold risk of developing acute pancreatitis; however, the association did not reach statistical significance.

According to some researchers, both hypo- and hyperthyroidism are associated with low-density lipoprotein (LDL) oxidation.^{43,44} Yavuz et al⁴⁵ reported iatrogenic thyroid hormone excess might affect thyroid hormone excess on *PON1* activity. Also, it was reported that dyslipidemia in thyroid diseases and lipid oxidation, due to oxidative stress, played an important role in the pathogenesis of thyroid diseases. Several studies^{20,23,46} revealed that serum *PON1* activity was significantly decreased in hypothyroidism. Although the mechanism is unclear, several possible mechanisms, which involve increased ROS production and oxidative stress, are suggested.⁴⁷ Since the Q to R (A > G) substitution of *PON1* rs662 forms more

active *PON1* with higher capacity of detoxification,³⁹ individuals carrying A allele should be less vulnerable to oxidative stress products and lipid peroxidation. Our results showed that individuals carrying G allele of rs662 had an approximately two-fold risk of developing hypothyroidism (OR = 2.05; 95% CI = 1.05 to 3.97; $p = 0.047$). In accordance to recent knowledge, it can be suggested that *PON1* rs662 polymorphisms had a substantial effect on hypothyroidism pathogenesis.

Conclusion

The present study is a comprehensive cross-sectional study, and the first study regarding the effects of *PON1*, an oxidative stress-related gene, and polymorphisms on disease susceptibility in a Turkish population diagnosed with colorectal cancer, hypothyroidism or pancreatitis. There are limited studies about the effects of *PON1* polymorphisms on common diseases; thus, it is believed that preliminary results of this study will elucidate the relation. In the present study, a substantial association between *PON1* G allele of rs662 and hypothyroidism and a weak association between *PON1* T allele of rs854560 and pancreatitis were identified. No effect of both *PON1* variants was observed on colorectal cancer development. Considering the lack of data, further studies with larger number of hypothyroidism patients and detailed biochemical parameters are needed.

Funding

This work was funded by the Research Fund of Istanbul University (Project No. TLO- 2018-27696).

Conflict of Interest

None declared.

Acknowledgment

The authors would like to thank all the participants who volunteered.

References

- 1 Bařkol G, Kõseođlu K. Paraoxanase: biochemical features, functions and clinical importance. *Erciyes Med J* 2004;26:75-80
- 2 Harel M, Aharoni A, Gaidukov L, et al. Structure and evolution of the serum paraoxanase family of detoxifying and anti-atherosclerotic enzymes. *Nat Struct Mol Biol* 2004;11(05):412-419
- 3 Ařkar TK, Bũyũkleblebici O. Paraoxanase: A new biochemical marker of oxidant-antioxidant status in atherosclerosis. In: Lushchak V, ed. *Oxidative Stress-Molecular Mechanisms and Biological Effects*. Intech Open, London; 2012:145-154
- 4 Draganov DI, La Du BN. Pharmacogenetics of paraoxanases: a brief review. *Naunyn Schmiedeberg's Arch Pharmacol* 2004;369(01):78-88
- 5 Ng CJ, Shih DM, Hama SY, Villa N, Navab M, Reddy ST. The paraoxanase gene family and atherosclerosis. *Free Radic Biol Med* 2005;38(02):153-163
- 6 Rochu D, Chabrière E, Masson P. Paraoxanase-1 and its interactions with HDL: molecular structures of *PON1* and HDL. In: *The HDL Handbook*. Cambridge: Academic Press; 2010:99-131
- 7 Ng CJ, Wadleigh DJ, Gangopadhyay A, et al. Paraoxanase-2 is a ubiquitously expressed protein with antioxidant properties and is capable of preventing cell-mediated oxidative modification of low density lipoprotein. *J Biol Chem* 2001;276(48):44444-44449

- 8 Camps J, Marsillach J, Joven J. The paraoxonases: role in human diseases and methodological difficulties in measurement. *Crit Rev Clin Lab Sci* 2009;46(02):83–106
- 9 Abelló D, Sancho E, Camps J, Joven J. Exploring the role of paraoxonases in the pathogenesis of coronary artery disease: a systematic review. *Int J Mol Sci* 2014;15(11):20997–21010
- 10 Aviram M, Rosenblat M. Paraoxonases 1, 2, and 3, oxidative stress, and macrophage foam cell formation during atherosclerosis development. *Free Radic Biol Med* 2004;37(09):1304–1316
- 11 Garin MC, James RW, Dussoix P, et al. Paraoxonase polymorphism Met-Leu54 is associated with modified serum concentrations of the enzyme. A possible link between the paraoxonase gene and increased risk of cardiovascular disease in diabetes. *J Clin Invest* 1997;99(01):62–66
- 12 Leviev I, Deakin S, James RW. Decreased stability of the M54 isoform of paraoxonase as a contributory factor to variations in human serum paraoxonase concentrations. *J Lipid Res* 2001;42(04):528–535
- 13 Mackness M, Mackness B. Human paraoxonase-1 (PON1): gene structure and expression, promiscuous activities and multiple physiological roles. *Gene* 2015;567(01):12–21
- 14 Davies HG, Richter RJ, Keifer M, Broomfield CA, Sowalla J, Furlong CE. The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin. *Nat Genet* 1996;14(03):334–336
- 15 Mackness MI, Arrol S, Mackness B, Durrington PN. Alloenzymes of paraoxonase and effectiveness of high-density lipoproteins in protecting low-density lipoprotein against lipid peroxidation. *Lancet* 1997;349(9055):851–852
- 16 Li HL, Liu DP, Liang CC. Paraoxonase gene polymorphisms, oxidative stress, and diseases. *J Mol Med (Berl)* 2003;81(12):766–779
- 17 Tarcin O, Yavuz DG. Paraoxonase 1 activity in endocrine diseases. *Turk J Endocrinol Metab* 2011;15:33–38
- 18 Kondo I, Yamamoto M. Genetic polymorphism of paraoxonase 1 (PON1) and susceptibility to Parkinson's disease. *Brain Res* 1998;806(02):271–273
- 19 Scacchi R, Gambina G, Martini MC, Broggio E, Vilardo T, Corbo RM. Different pattern of association of paraoxonase Gln192->Arg polymorphism with sporadic late-onset Alzheimer's disease and coronary artery disease. *Neurosci Lett* 2003;339(01):17–20
- 20 Sarandöl E, Taş S, Dirican M, Serdar Z. Oxidative stress and serum paraoxonase activity in experimental hypothyroidism: effect of vitamin E supplementation. *Cell Biochem Funct* 2005;23(01):1–8
- 21 Costantini F, Pierdomenico SD, De Cesare D, et al. Effect of thyroid function on LDL oxidation. *Arterioscler Thromb Vasc Biol* 1998;18(05):732–737
- 22 Dumitriu L, Bartoc R, Ursu H, Purice M, Ionescu V. Significance of high levels of serum malonyl dialdehyde (MDA) and ceruloplasmin (CP) in hyper- and hypothyroidism. *Endocrinologie* 1988;26(01):35–38
- 23 Baskol G, Atmaca H, Tanriverdi F, Baskol M, Kocer D, Bayram F. Oxidative stress and enzymatic antioxidant status in patients with hypothyroidism before and after treatment. *Exp Clin Endocrinol Diabetes* 2007;115(08):522–526
- 24 Van Der Logt EM, Janssen CH, Van Hooijdonk Z, et al. No association between genetic polymorphisms in NAD(P)H oxidase p22phox and paraoxonase 1 and colorectal cancer risk. *Anticancer Res* 2005;25(2B):1465–1470
- 25 Franco-Pons N, Marsillach J, Joven J, Camps J, Closa D. Serum paraoxonase undergoes inhibition and proteolysis during experimental acute pancreatitis. *J Gastrointest Surg* 2008;12(05):891–899
- 26 Kumon Y, Nakauchi Y, Suehiro T, et al. Proinflammatory cytokines but not acute phase serum amyloid A or C-reactive protein, downregulate paraoxonase 1 (PON1) expression by HepG2 cells. *Amyloid* 2002;9(03):160–164
- 27 Aynacioglu AS, Cascorbi I, Mrozikiewicz PM, Nacak M, Tapanyigit EE, Roots I. Paraoxonase 1 mutations in a Turkish population. *Toxicol Appl Pharmacol* 1999;157(03):174–177
- 28 Zama T, Murata M, Matsubara Y, et al. A 192Arg variant of the human paraoxonase (HUMPONA) gene polymorphism is associated with an increased risk for coronary artery disease in the Japanese. *Arterioscler Thromb Vasc Biol* 1997;17(12):3565–3569
- 29 Sanghera DK, Saha N, Kamboh MI. The codon 55 polymorphism in the paraoxonase 1 gene is not associated with the risk of coronary heart disease in Asian Indians and Chinese. *Atherosclerosis* 1998;136(02):217–223
- 30 Özhan G, Topal P, Alpertunga B. Flavin-containing monooxygenase 3 gene polymorphisms in Turkish population. *Toxicol Mech Methods* 2012;22(06):461–465
- 31 Arici M, Özhan G. The genetic profiles of CYP1A1, CYP1A2 and CYP2E1 enzymes as susceptibility factor in xenobiotic toxicity in Turkish population. *Saudi Pharm J* 2017;25(02):294–297
- 32 Akçay YD, Sagin FG, Sendağ F, Oztekin K, Sozmen EY. Effects of estrogen-only therapy on LDL oxidation in women with hysterectomy: does paraoxonase genotype play a role? *Maturitas* 2006;53(03):325–332
- 33 Gupta N, Gill K, Singh S. Paraoxonases: structure, gene polymorphism & role in coronary artery disease. *Indian J Med Res* 2009;130(04):361–368
- 34 Humbert R, Adler DA, Disteché CM, Hassett C, Omiecinski CJ, Furlong CE. The molecular basis of the human serum paraoxonase activity polymorphism. *Nat Genet* 1993;3(01):73–76
- 35 Zargari M, Sharafeddin F, Mahrooz A, Alizadeh A, Masoumi P. The common variant Q192R at the paraoxonase 1 (PON1) gene and its activity are responsible for a portion of the altered antioxidant status in type 2 diabetes. *Exp Biol Med (Maywood)* 2016;241(14):1489–1496
- 36 Ergun MA, Yurtcu E, Demirci H, et al. PON1 55 and 192 gene polymorphisms in type 2 diabetes mellitus patients in a Turkish population. *Biochem Genet* 2011;49(1-2):1–8
- 37 Altuner D, Suzen SH, Ates I, Koc GV, Aral Y, Karakaya A. Are PON1 Q/R 192 and M/L 55 polymorphisms risk factors for diabetes complications in Turkish population? *Clin Biochem* 2011;44(5-6):372–376
- 38 Stevens VL, Rodriguez C, Talbot JT, Pavluck AL, Thun MJ, Calle EE. Paraoxonase 1 (PON1) polymorphisms and prostate cancer in the CPS-II Nutrition Cohort. *Prostate* 2008;68(12):1336–1340
- 39 Antognelli C, Mearini L, Talesa VN, Giannantoni A, Mearini E. Association of CYP17, GSTP1, and PON1 polymorphisms with the risk of prostate cancer. *Prostate* 2005;63(03):240–251
- 40 Saadat M. Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis. *Cancer Epidemiol* 2012;36(02):e101–e103
- 41 Unal E, Uzun H, Kusaslan R, et al. Serum paraoxonase (a high-density lipoprotein-associated lipophilic antioxidant) activity and lipid profile in experimental acute pancreatitis. *Pancreas* 2005;31(01):84–87
- 42 Verlaan M, Harbers EG, Pap A, Jansen JB, Peters WH, Drenth JP. Paraoxonase 1-192Q allele is a risk factor for idiopathic chronic pancreatitis. *Mol Diagn* 2005;9(01):9–15
- 43 Duntas LH. Thyroid disease and lipids. *Thyroid* 2002;12(04):287–293
- 44 Sundaram V, Hanna AN, Koneru L, Newman HA, Falko JM. Both hypothyroidism and hyperthyroidism enhance low density lipoprotein oxidation. *J Clin Endocrinol Metab* 1997;82(10):3421–3424
- 45 Yavuz DG, Yüksel M, Deyneli O, Ozen Y, Aydin H, Akalin S. Association of serum paraoxonase activity with insulin sensitivity and oxidative stress in hyperthyroid and TSH-suppressed nodular goitre patients. *Clin Endocrinol (Oxf)* 2004;61(04):515–521
- 46 Azizi F, Raiszadeh F, Solati M, Etemadi A, Rahmani M, Arabi M. Serum paraoxonase 1 activity is decreased in thyroid dysfunction. *J Endocrinol Invest* 2003;26(08):703–709
- 47 Aviram M, Rosenblat M, Billecke S, et al. Human serum paraoxonase (PON 1) is inactivated by oxidized low density lipoprotein and preserved by antioxidants. *Free Radic Biol Med* 1999;26(7-8):892–904