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Paraoxonase-1 (PON1) rs662 Polymorphism and Its Association with Serum Lipid Levels and Longevity in the Bama Zhuang Population

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Background: The present study was performed to identify the association of PON1 rs662 polymorphism with serum lipid levels and human longevity in the Bama Zhuang population.

Material/Methods: PON1 genotypes were determined by Taqman SNP Genotyping Assays in 110 long-lived inhabitants (longevity group, aged 90–110 years), 110 healthy inhabitants in Bama County (control 1 group, aged 43–82 years) and 110 healthy inhabitants in Nandan County (control 2 group, aged 28–82 years) without family history of longevity.

Results: BMI (body mass index) and TG (serum total triglyceride) level were lower in the longevity group than in the two control groups, while the contents of serum LDL-c (low-density lipoprotein cholesterol) and HDL-c (high-density lipoprotein cholesterol) and the levels of SBP (systolic blood pressure) and DBP (diastolic blood pressure) in the longevity group were higher than in the two control groups ($p<0.01$). Significant differences in the frequencies of three genotypes (GG, AG, and AA) were observed between the longevity group and control 2 group ($\chi^2=15.190$, $p=0.001$). The minor allele frequency (MAF) of rs662 was significantly higher in the longevity group than in the two control groups. The levels of HDL-c in the longevity group were different among the three genotypes ($p<0.05$). The levels of TG for GG and GG+AG genotypes were significantly different, while the levels of TC (total cholesterol) and HDL-c for AG and GG+AG genotypes were significantly different among the three groups ($p<0.05$). Serum lipid parameters were correlated with several environmental factors, including age, gender, DBP, SBP, and BMI. The association of PON1 rs662 polymorphism and serum lipid levels was different among the three groups.

Conclusions: PON1 polymorphism might be one of the genetic factors of longevity in the Bama Zhuang population. The PON1 rs662 SNP (single nucleotide polymorphism) was associated with serum HDL-c levels in the longevity group.

MeSH Keywords: Aryldialkylphosphatase • Lipids • Longevity • Polymorphism, Genetic

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Background

The paraoxonase gene family includes at least three members: PON1, PON2, and PON3 [1]. PON1 is the most studied and best known member of the paraoxonase family [2]. The PON1 gene is located in the long arm of chromosome 7 (q21-q22) in humans and is known to be polymorphic [3,4]. In addition, PON1 is a 43-45 kDa glycoprotein, synthesized in the liver and secreted in blood [5,6]. PON1 is associated with coronary artery disease, stroke, Alzheimer's disease, chronic renal failure, metabolic syndrome, chronic liver impairment [7–10], and dermatosis such as psoriasis and systemic lupus erythematosus (SLE) [11,12]. In addition to the aforementioned diseases, PON1 is also involved in ageing and longevity [13,14]. Furthermore, studies have shown that the elevation of cholesterol is an important risk factor for coronary heart disease, which might contribute to human ageing and longevity [15,16].

Longevity and ageing are complex traits, resulting from the interaction between multiple genetic and environmental factors [17]. Studies of human twins suggest that genetic factors determine 15–30% of longevity traits [18]. PON1 is one of the longevity genes identified; other genes includes APOE, GSTT1, IL-6, IL-10, FOXO3a, and SIRT6 [19,20]. Because PON1 is a serum HDL-bound enzyme that catalyzes the hydrolysis of organic phosphates and lipid peroxides and protects LDLs from oxidation [21], PON1 plays an antioxidant role in lipid metabolism. These actions of PON1 exert a protective effect on the early progression of cardiovascular disease and atherosclerosis [22].

The Bama Zhuang population, located in the Hongshui River Basin, Guangxi, has emerged as a known group for studying longevity, as the group has had a relatively consistent genetic background over the past few decades [23,24]. Many efforts have been made to identify the environmental and genetic factors involved in the longevity of the population residing in the Bama region, but the specific mechanisms are still not clear. The association between T(-107)C, Q192R, and L55M PON1 polymorphisms and plasma or serum lipid levels in humans has been studied in several previous works [19,25,26], but the relationship of PON1 polymorphism of rs662 and plasma or serum lipid levels in the longevity study participants has not been reported. In this study, we examined the relationship between the rs662 polymorphism of PON1 and the serum lipid profiles in the longevity group and two control groups to further explore the longevity in Bama nonagenarians/centenarians of the ethnic Zhuang population.

Material and Methods

Study population

In our study, all the participants were ethnic Zhuang from Guangxi Zhuang Autonomous Region, the People's Republic of China. Longevity was defined as living to 90 years of age or older. In this study, the longevity group included 110 individuals (27 males and 83 females, age range 90–110 years) and 110 unrelated participants (40 males and 70 females, age range 43–82 years) as the control 1 group (environment fit) from Bama County. There were 110 individuals included as the control 2 group (40 males and 70 females, age range 28–82 years) from Nandan County, which is about 160 kilometers from Bama County (environmentally unmatched). No long-lived family members were reported in the control 1 and control 2 groups. We selected long-lived family members if they had at least two siblings meeting the following inclusion criteria: (1) age 90 years or older, and (2) participant with one or more living brothers or sisters who satisfied the first criterion. The age of the participants was certificated officially through an identity card or residence registration booklet, and the accounts of their offspring and other important socio-demographic events. All participants were healthy and had no evidence of diseases associated with atherosclerosis, coronary heart disease, or diabetes. The participants were not taking medications known to affect serum lipid levels (for example statins or fibrates, beta-blockers, diuretics, or hormones). The study was approved by the ethics committee of Guangxi Medical University. Three hundred and thirty participants were enrolled in the study after obtaining written informed consent. The study was performed in accordance with the tenets of the Declaration of Helsinki. Weight and height were measured and body mass index (BMI) was calculated as the weight (in kilogram) divided by the square of height (in meters), kg/m^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a standard mercury sphygmomanometer.

Biochemical analysis

Blood samples were collected from each participant after an overnight fast. A venous fasting blood sample of 5 mL was obtained from each participant. About 3 mL of blood sample was used to determine serum lipid levels. The levels of total triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were determined by standard enzymatic methods with commercially available kits.

Genotyping

For genotype analysis, genomic DNA was extracted from 2 mL of whole blood in ethylenediaminetetraacetic (EDTA) tubes by

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Table 1. A comparison of general characteristics and serum lipid levels between the longevity and two control groups.

Parameter	Longevity (n=110)	Control 1 (n=110)	Control 2 (n=110)	χ^2(t)	p
Gender (m/f)	27/83	40/70	40/70	4.675	0.097
Age (years)	95.47±5.10	72.68±9.38	49.13±14.19	562.293	0.000
WC (cm)	74.49±8.13	72.72±6.99	78.29±8.72	14.022	0.000
SBP (mmHg)	145.36±23.11	139.30±26.85	116.34±17.31	49.796	0.000
DBP (mmHg)	80.62±11.55	78.93±13.36	74.75±10.65	7.067	0.001
BMI (kg/m2)	18.63±2.84	19.53±2.69	21.97±3.18	38.792	0.000
TC (mmol/L)	4.91±1.08	4.65±0.97	4.86±1.06	1.988	0.139
FBG (mmol/L)	5.89±2.02	5.79±1.57	5.99±1.51	0.383	0.682
TG (mmol/L)	1.53±1.00	1.52±1.04	2.04±0.76	10.734	0.000
HDL-c (mmol/L)	1.57±0.83	1.33±0.75	1.07±0.26	15.950	0.000
LDL-c (mmol/L)	2.78±0.71	2.68±0.78	2.42±0.64	7.721	0.001

Values are given as means ±SD. BMI – body mass index; WC –waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; TG – serum total triglyceride; TC – serum total cholesterol; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol.

the Chelex-100 method [27]. The extracted DNA was stored at –20°C until analysis. The PON1 rs662 polymorphism was detected by the Applied Biosystems 7500 Real-Time PCR System. Polymerase chain reaction (PCR) amplification for each polymorphism was performed in a volume of 10 μL with 1 μL of genomic DNA, 0.25 μL of Assay-on- Demand SNP Genotyping Assay Mix (40×) (Applied Biosystems Co., Ltd. US), 3.75 μL ddH_2O, and 5 μL TaqMan Universal PCR Master Mix, No AmpErase UNG (2×). The cycling conditions were: predenaturation at 95°C for 10 minutes, followed by 43 cycles of denaturation at 92°C for 15 seconds, annealing at 60°C for 1 minute, and a terminal extension step of 72°C for 5 minutes. The fluorescence yield for the two different dyes was measured to obtain the allelic discrimination plot and identify individual genotypes (SDS 2.3 software, Applied Biosystems) following PCR.

Statistical analysis

Data analyses were conducted using SPSS 16.0. Continuous variables were presented as mean ±SDs. We used analysis of variance (ANOVA) to compare continuous variables (such as BMI, TC, TG, HDL-c, and LDL-c) and the chi-square test to compare categorical variables. The Hardy-Weinberg equilibrium was assessed using the Pearson's chi-square test. Allele and genotype frequencies were calculated directly. Differences in genotype and allele frequencies among the groups were estimated by the chi-square test. P values were subjected to Bonferroni's correction (p=0.05/number of comparisons), yielding a new p value (p<0.017, number of comparisons=3). The differences of serum lipid levels with different PON1 genotypes were evaluated using analysis of co-variance (ANCOVA). In order to assess the association between PON1 polymorphism and serum lipid levels, multiple linear regression analysis was performed. A p<0.05 on a two-tailed test was considered statistically significant.

Results

General characteristics and serum lipid levels

A summary of demographic and biochemical characteristics of the longevity and the control groups are provided in Table 1. The BMI was lower in the longevity group than the two control groups. Serum concentrations of LDL-c and HDL-c and SBP and DBP in the longevity group were significantly higher than in the two control groups (p<0.01). The waist circumference and TG level were different (p=0.000) among the three groups; the maximum waist circumference and TG level were observed in the control 2 group. No statistically significant differences in gender, fasting blood glucose (FBG), or TC levels were found among the three groups.

Hardy-Weinberg equilibrium test of different populations

Three PON1 genotypes (GG, AG, AA) were detected and their genotype distributions in all participants were consistent with the Hardy-Weinberg equilibrium (p>0.05) (Table 2).

Genotypic and allelic frequencies

GG was the dominant genotype in the control 1 and control 2 groups, with a frequency of 0.536 and 0.636, respectively.

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Table 2. Chi-square Test of Hardy-Weinberg equilibrium of PON1 rs662.

Group	n	GG	AG	AA	χ^2	p
Longevity	110	43	51	16	0.019	0.990
Control 1	110	59	42	9	0.155	0.926
Control 2	110	70	35	5	0.054	0.973
Total	330	172	128	30	0.759	0.684

Table 3. Genotypic frequency of the PON1 polymorphism, n (%).

Group	n	Genotype n(%)			χ^2	p
		GG	AG	AA		
Longevity	110	43 (39.1)	51 (46.4)	16 (14.5)	5.341[a]	0.069
Control 1	110	59 (53.6)	42 (38.2)	9 (8.2)	2.717[b]	0.257
Control 2	110	70 (63.6)	35 (31.8)	5 (4.6)	15.190[c]	0.001
Total	330	172 (52.1)	128 (38.8)	30 (9.1)	15.646[d]	0.004

[a] Longevity *vs.* control 1; [b] control 1 *vs.* control 2; [c] longevity *vs.* control 2; [d] total χ^2 value; $p<0.017$ indicates statistical significance.

Table 4. Distribution of alleles and MAF in PON1 rs662.

Group	G	A	MAF	χ^2	*p*	OR	95% CI
	n (%)	n (%)					
Longevity	137 (62.3)	83 (37.7)	0.377	5.480	0.019[a]	1.616	1.080–2.417
Control 1	160 (72.7)	60 (27.3)	0.273	2.814	0.093[b]	1.458	0.937–2.269
Control 2	175 (79.5)	45 (20.5)	0.205	15.909	0.000[c]	2.356	1.538–3.608
Total	472 (71.5)	188 (28.5)	0.285	16.348	0.000[d]	–	–

[a] Longevity *vs.* control 1; [b] control 1 *vs.* control 2; [c] longevity *vs.* control 2; [d] total χ^2 value; $p<0.017$ suggests statistical significance; OR – odds ratio; 95% CI – 95% confidence interval.

However, AG was the dominant genotype in the longevity group, with a frequency of 0.464. The frequency of the GG genotype was obviously higher than other genotypes in all participants. We observed significant differences in the frequencies of the three genotypes (GG, AG, and AA) between the longevity and control 2 group (χ^2=15.190, p=0.001) (Table 3). The allelic frequencies of PON1 rs662 are shown in Table 4. The frequency of G and A alleles were 0.715 and 0.285, respectively. The MAF of rs662 in PON1was significantly higher in the longevity group than in the two control groups (χ^2=16.348, p=0.000).

Genotypes and serum lipid levels

The levels of HDL-c in the longevity group, but not in the two control groups, were different among the three genotypes ($p<0.05$) (Table 5A). The levels of TG for GG and GG+AG genotypes were significantly different, while the levels of TC and HDL-c for AG and GG+AG genotypes were significantly different ($p<0.05$) among the three groups (Table 5B).

Risk factors for serum lipid parameters

Serum lipid parameters were associated with a few environmental factors, including age, gender, DBP, SBP, and BMI (Table 6).

Discussion

In our study, serum LDL-c, serum HDL-c, SBP, and DBP levels in the longevity group were significantly higher than in the two control groups. The highest TG levels were observed in the control 2 group. These aforementioned characteristics were consistent with other geriatric studies [28,29]. The differences could not totally be explained by higher average age

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Table 5A. Genotype of the rs662 polymorphism and serum lipid levels in the longevity and two control groups.

rs662	n	TC (mmol/L)	TG (mmol/L)	HDL-c (mmol/L)	LDL-c (mmol/L)
Longevity					
AA	16	4.66±1.18	1.35±0.73	1.42±0.61	2.64±0.74
AG	51	4.97±0.90	1.55±1.08	1.80±0.97	2.75±0.61
GG	43	4.94±1.25	1.56±1.02	1.37±0.63	2.87±0.80
F-value	–	0.723	0.371	3.963	0.953
P-value	–	0.488	0.691	0.022	0.389
GG+AG	94	4.96±1.07	1.56±1.04	1.60±0.86	2.80±0.70
AA	16	4.66±1.18	1.35±0.73	1.42±0.61	2.64±0.74
F-value	–	1.454	0.739	1.122	1.081
P-value	–	0.231	0.392	0.292	0.301
Control 1					
AA	9	5.22±0.94	1.99±0.81	1.48±0.42	2.91±1.26
AG	42	4.49±0.92	1.52±0.91	1.34±0.99	2.64±0.78
GG	59	4.67±1.00	1.46±0.77	1.31±0.57	2.66±0.69
F-value	–	2.435	0.985	0.225	0.492
P-value	–	0.093	0.377	0.799	0.613
GG+AG	101	4.60±0.97	1.48±0.83	1.32±0.77	2.66±0.73
AA	9	5.22±0.94	1.99±0.81	1.48±0.42	2.91±1.26
F-value	–	3.721	1.908	0.445	0.952
P-value	–	0.056	0.170	0.506	0.332
Control 2					
AA	5	4.86±2.07	2.41±1.62	0.94±0.12	2.55±1.01
AG	35	4.90±1.07	1.93±0.61	1.08±0.26	2.42±0.69
GG	70	4.83±0.99	2.06±0.74	1.08±0.26	2.41±0.58
F-value	–	0.138	0.914	0.634	0.179
P-value	–	0.871	0.404	0.532	0.836
GG+AG	105	4.86±1.01	2.02±0.70	1.08±0.26	2.41±0.62
AA	5	4.86±2.07	2.41±1.62	0.94±0.12	2.55±1.01
F-value	–	0.003	1.367	1.265	0.285
P-value	–	0.959	0.245	0.263	0.594

of the long-lived individuals. In this study, our main concern was whether and to what extent the polymorphism of PON1 rs662 was involved in the modulation of blood lipids and longevity profiles in the ethnic Zhuang population.

The present study showed that the genotypic and allelic frequencies of rs662 in diverse participants were different. These results suggest that the prevalence of the PON1 rs662 SNP may exhibit an age-related difference. Although the selected gene locus of PON1 was different, our results showed that PON1 is an age-related gene. Our study results are similar

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Table 5B. Genotype of the rs662 polymorphism and serum lipid levels in the longevity and two control groups.

Group	n	TC (mmol/L)	TG (mmol/L)	HDL-c (mmol/L)	LDL-c (mmol/L)
GG					
Longevity	43	4.94±1.25	1.56±1.02	1.37±0.63	2.87±0.80
Control 1	59	4.67±1.00	1.46±0.77	1.31±0.57	2.66±0.69
Control 2	70	4.86±2.07	2.41±1.62	0.94±0.12	2.55±1.01
F-value	–	0.849	3.781	2.173	1.122
P-value	–	0.430	0.025	0.117	0.328
AG					
Longevity	51	4.97±0.90	1.55±1.08	1.80±0.97	2.75±0.61
Control 1	42	4.49±0.92	1.52±0.91	1.34±0.99	2.64±0.78
Control 2	35	4.90±1.07	1.93±0.61	1.08±0.26	2.42±0.69
F-value	–	3.165	2.528	4.080	0.948
P-value	–	0.046	0.084	0.019	0.390
AA					
Longevity	16	4.66±1.18	1.35±0.73	1.42±0.61	2.64±0.74
Control 1	9	5.22±0.94	1.99±0.81	1.48±0.42	2.91±1.26
Control 2	5	4.83±0.99	2.06±0.74	1.08±0.26	2.41±0.58
F-value	–	0.580	1.842	1.914	0.298
P-value	–	0.567	0.179	0.168	0.744
GG+AG					
Longevity	94	4.96±1.07	1.56±1.04	1.60±0.86	2.80±0.70
Control 1	101	4.60±0.97	1.48±0.83	1.32±0.77	2.66±0.73
Control 2	105	4.86±1.01	2.02±0.70	1.08±0.26	2.41±0.62
F-value	–	3.263	5.679	6.157	1.876
P-value	–	0.040	0.004	0.002	0.155

to the results reported from a meta-analysis [30]. Our study showed that the levels of HDL-c in the longevity group were highest in the AG genotype because PON1 and serum high-density lipoprotein (HDL-c) are closely linked together. At the same time, this trend was not shown to be significant in the two control groups, which indicated that the level of HDL-c was related to age. The current study demonstrated that the G allele carriers in the longevity population had higher serum HDL-c and TC levels than the control populations. There were significant differences of the levels of HDL-c and TG between the longevity group and the control 2 group. The participants of the longevity and the control 2 groups had different living environments and different genetic backgrounds. The participants from the Bama region mainly ate cornmeal porridge, and there was less environmental pollution in the Bama region compared to Nandan region. Other studies have shown that the rise of HDL-c and the decline of TG can reduce cardiac-cerebral vascular disease in the elderly [31,32]. Our data indicated that the raising of HDL-c and decreasing of TG were due to rs662 SNP and environmental factors related to longevity.

Long-life populations rarely suffer from age-related chronic diseases such as coronary heart disease, atherosclerosis, and stroke. Many chronic diseases have an association with

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Table 6. Association between serum lipid parameters and relative factors in the participants.

Lipid parameters	Risk factor	Unstandardized Coefficient	Std. error	Standardized Coefficient	t	*p*-value
All participants						
TC	Diastolic blood pressure	0.018	0.006	0.206	2.969	0.003
	Gender	0.277	0.124	0.124	2.230	0.026
HDL	Age	0.006	0.002	0.177	2.611	0.009
LDL	Age	0.006	0.002	0.164	2.446	0.015
	Gender	0.269	0.084	0.174	3.181	0.002
	Diastolic blood pressure	0.010	0.004	0.176	2.571	0.011
The longevity and control 1 groups						
TC	Gender	0.353	0.156	0.157	2.257	0.025
	Diastolic blood pressure	0.016	0.007	0.194	2.287	0.023
TG	BMI	0.067	0.029	0.184	2.321	0.021
LDL	Gender	0.310	0.113	0.192	2.753	0.006
	Diastolic blood pressure	0.011	0.005	0.177	2.072	0.039
Longevity group						
TC	Age	–0.043	0.020	–0.204	–2.213	0.036
	Gender	0.535	0.243	0.214	2.207	0.030
HDL	Age	–0.037	0.016	–0.228	–2.356	0.020
LDL	Age	–0.028	0.013	–0.201	–2.082	0.040
Control 1 group						
TC	Diastolic blood pressure	0.022	0.009	0.300	2.363	0.020
HDL	Systolic blood pressure	0.008	0.004	0.293	2.288	0.024
LDL	Gender	0.332	0.159	0.206	2.087	0.039
	Diastolic blood pressure	0.015	0.007	0.266	2.098	0.038
Control 2 group						
LDL	BMI	0.057	0.027	0.285	2.117	0.037

high blood lipid levels [33], whereas PON1 is closely related to HDL-c. Our results suggest that rs662 polymorphisms of PON1 can affect the blood lipids levels of long-living individuals, and carrying the G allele may be a protective factor for longevity. This may be possible because PON1 plays an antioxidant role in lipid metabolism [34] and has a protective effect on progression of cardiovascular disease and atherosclerosis [35,36].

Lipid level's relation to longevity is complex, and phenotypes cannot be interpreted with single gene polymorphism. It is speculated that the influence of PON1 rs662 on lipid metabolism may be limited, similar to other lipid regulating genes such as phosphodiesterase 3A (*PDE3A*) rs7134375 [37], rs2954029 of the Tribbles homolog 1 (TRIB1) gene [38] and MLXIPL/TBL2 rs17145738 [39]. Although the effect of a sole gene can be small, multiple genes can produce larger effects. These effects can be influenced by environmental factors such as diet, lifestyle, and the interactions of other lipid-related genes and environment by undetected pathways. In addition, people are exposed to different ways of life and different environments can change the effects of the genetic variation on blood lipids.

The present study showed that serum lipid profiles were related to age, gender, BMI, DBP, and SBP in the longevity group

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and the two control groups. Our results suggest that environmental factors are also important to serum lipid levels. Diet and lifestyles vary widely in different populations. Longevity is mainly associated with easily digestible plant-based foods, such as whole grains or corn with less fat and animal protein, and the intake of multiple small meals. However, younger individuals are more inclined to eat animal foods, which contain an abundance of saturated fatty acids. Thus, these findings may help identify susceptibility genes, suggest changes to unhealthy lifestyles, and reduce the impact of hyperlipidemia on people's health.

Our study had two main limitations. First, the small sample size and the lack of information on eating habits and life history may affect the interpretation of the results. Second, we studied the association of genetic polymorphisms with serum lipid levels and human longevity, but gene functional studies were not performed in our study.

Conclusions

PON1 polymorphism might be one of the genetic factors of longevity in the Bama Zhuang population. The PON1 rs662 SNP was associated with serum HDL-c levels in the longevity group.

Conflict of interest

The authors declare that they have no conflict of interest.

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