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Original Article

COMT Val158Met polymorphism is associated with blood pressure and lipid levels in general families of Bama longevous area in China

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Abstract: To see the possible relationship between COMT Val158Met polymorphism and blood pressure (BP) and serum lipid levels and its putative role in human longevity, we genotyped COMT Val158Met (rs4680) by PCR-RFLP for members from Bama long-lived families (BLF, n = 1538), Bama non-long-lived families (BNLF, n = 600), Pingguo (a county outside Bama region) long-lived families (PLF, n = 538) and Pingguo non-long-lived families (PNLF, n = 403) after anthropometric measures were collected and serum lipid levels were detected. The distribution of genotypes and alleles among four family groups was significantly different (all $P < 0.01$), with GA/AA genotype and minor allele A presenting more frequently in Bama population than Pingguo Population ($P < 0.01$). The systolic blood pressure (SBP), pulse pressure (PP), total cholesterol (TC), triglyceride (TG) and low density lipoprotein-cholesterol (LDL-C) levels of GG genotype carriers were dramatically higher than non-GG carriers in BNLF ($P < 0.05$); the SBP and PP levels of GG carriers were lower ($P < 0.05$) while TC, LDL-C level were higher ($P < 0.01$) than that of non-GG carriers in PLF; no difference in blood pressure and lipids were observed between genotypes in BLF and PNLF ($P > 0.05$). Correlation analyses revealed that COMT Val158Met was mainly correlated negatively with SBP, diastolic blood pressure (DBP) and LDL-C in BNLF and negatively with TC level in BLF, BNLF and PLF. These data suggest that COMT Val158Met polymorphism may have more impact on the modulation of BP and lipid profiles in the average families than in the long-lived families in Bama region. The association between this SNP and other phenotypes (e.g. cognition) and its roles in the longevity in Bama area thus warrant further investigation.

Keywords: COMT, blood pressure, blood lipid, longevity

Introduction

Catechol-O-methyl-transferase (COMT) is an enzyme that catalyses the degradation of catecholamine neurotransmitters including dopamine (DA), norepinephrine, epinephrine, L-dopa and their metabolites and thus inactivate them [1]. It is well established that DA plays essential roles in executive processing, especially in the function of pre-frontal cortex (PFC) [2, 3], and age-related loss of dopaminergic function correlates with cognitive impairment [4].

The gene encoding human COMT is mapped to chromosome 22q11 which spans 27 kb with 6 exons and is the most widely studied member of the neurotransmission-related gene classes [5]. A common functional variant at nucleotide 472 (G > A, rs4680) on exon 4 of human COMT gene results in a valine to methionine substitution at the 158 amino acid (Val158Met) and reduces its thermostability and activity by ~40% [6]. Higher enzymatic activity of COMT may accelerate the degradation of DA and attenuate cognitive performance while lowered COMT activity may perturb DA metabolism and enhance cognitive functionality. For instance, individuals carrying the ancestral Val allele present higher enzymatic activity but perform less well on working memory tests and executive cognition than those with the low activity

Met allele [3, 7]. Patients with Parkinson's disease (PD) and Alzheimer's disease (AD) who exhibit poor cognition are more prevalent of COMT Val allele than average controls [8]. The COMT Val allele is associated with a younger age at onset in men with idiopathic PD [9]. Preclinical trials showed that COMT inhibitors improved working memory and attention in model animals and humans [2, 10]. More intriguingly, this polymorphism has so far only been found in humans, the only species that can develop cognition, a behavioral domain in which humans differ from non-human primates [3]. Together, these observations demonstrate that COMT Val allele correlates strongly with poorer while Met allele with better cognitive performance. In this context, it is therefore reasonable to hypothesize that long-lived populations who preserve good cognition may be endowed a higher COMT Met frequency.

Nevertheless, it is worth noting that COMT has both central and peripheral effect, elevated circulatory COMT may increase peripheral vascular resistance and predisposes individuals to hypertension. In addition, cognition is a considerably complex trait which is not only determined by cerebral structure and volume but also influenced by other factors such as blood and nutrition supply. Hypertension and unfavorable lipid profile may impair cerebral vascular functionality and be associated with poorer cognitive status.

Bama long-lived individuals residingalong the midstream of Hongshuihe River in Guangxi Province, P. R. China have emerged as an optimal cohort for human aging/longevity study over the past decades [11]. They had been found to preserve better cognition and daily living activity as compared to age-matched populations from other regions in China [12]. In the current investigation, we genotyped the COMT Val-158Met polymorphism and evaluate the potential correlation with blood pressure and lipid levels for Bama long-lived families with normal cognition to see whether this variant overrepresents in these families and account for the longevity in Bama area by interplaying with common cognitive influencing factors.

Materials and methods

Subjects studied

The study design and the participating families had been described elsewhere [11]. Briefly, 1538 family members from Bama long-lived families residing Bama area along the midstream of Hongshuihe River Basin (Bama, Fengshan, Donglan and Du'an County), Guangxi Zhuang Autonomous Region, P. R. China were enrolled as our target study group (BLF, 870 males and 668 females, aged 61. 8 ± 25. 8 ranging 30-104 years). Family members from three other families living in Bama and out-of-Bama area were recruited as comparison groups: (1) Bama non-long-lived families (BNLF, n = 600, 394 males and 206 females, age 53. 1 ± 23. 5 ranging 30-77 years), who live in the same area as BLF (environment-matched) but without a history of exceptional longevity (no past or current nonagenarian/centenarian in the first, second and third degree relatives); (2) Pingguo long-lived families (PLF, n = 538, 342 males and 196 females, aged 58. 5 ± 25. 5 ranging 30-95 years) from Pingguo, a county which belongs to Youjiang River system and is 200 km away from Bama area (environment-unmatched); (3) Pingguo non-long-lived families (PNLF, n = 403, 258 males and 145 females, aged 48. 5 ± 19. 6 ranging 30-72 years), average families from Pingguo County which have no history of exceptional longevity. These control groups were set to attenuate the potential confounding effect of environmental factors such as dietary habit and lifestyle or ethnic background on our observational variables. All subjects were ethnically Zhuang, apparently healthy and had no evidence of any chronic illness. Participants with a history of myocardial infarction, stroke, hypertension and diabetes were excluded. The current study was approved by the Ethics Committee of Guangxi Medical University. All participants gave their written informed consents after an extensive description of aims of the study.

Epidemiological survey

Information on socio-demographic and lifestyle factors was collected with standardized questionnaires. Anthropometric variables including blood pressure, body height, body weight, waist circumference and body mass index (BMI) were measured or calculated in all groups as described previously [11]. Hypertension was defined as systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg, and/or self-reported anti-hypertensive treatment within 2 weeks prior to the survey [13]. Normal weight, overweight, and obe-

Table 1. Comparison of clinical characteristics among groups ($\bar{x} \pm s$)

Parameters	BLF (n = 1538)	BNLF (n = 600)	PLF (n = 538)	PNLF (n = 403)	F (χ^2)	*P*
Male/female (n)	870/668	394/206	342/196	258/145	20.872	0.001
Age (years)	61.75±25.80	53.12±23.51▲	58.54±25.45▲	48.53±19.60▲,#	77.477	0.000
BMI (kg/m^2)	21.37±3.41	21.41±3.20	21.00±3.14▲	21.63±3.68	3.162	0.024
FPG (mmol/L)	4.75±1.34	4.53±1.09▲	4.41±1.47▲	4.590±1.60	6.007	0.004
SBP (mmHg)	143.45±27.69	137.47±25.33	136.17±27.00▲	129.26±21.56▲,#	11.180	0.000
DBP (mmHg)	86.56±12.10	85.30±11.55	81.67±11.03▲	81.53±11.15▲,#	27.312	0.000
PP (mmHg)	56.89±23.08	52.18±20.74	54.59±22.92	47.73±17.72	1.440	0.229
TC (mmoL/L)	5.16±1.05	5.12±0.98	4.576±0.93▲	4.58±0.98▲,#	60.096	0.000
TG (mmoL/L)	1.06(0.77)	1.08(0.82)	0.94(0.68)▲	0.91(0.79) ▲,#	5.287	0.001
HDL-C (mmoL/L)	1.60±0.43	1.56±0.39	1.57±0.37	1.57±0.40	0.380	0.768
LDL-C (mmoL/L)	2.92±0.92	2.94±0.87	2.42±0.78▲	2.42±0.85▲,#	59.133	0.000

BLF, Bama long-lived families; BNLF, Bama non-long-lived families; PLF, Pingguo long-lived families; PNLF, Pingguo non-long-lived families; BMI, body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The quantitative variables were presented as mean ± standard deviation and the values of TG were presented as median (interquartile range). As compared to BLF, ▲indicates P<0.05; comparison between PNLF and HNLF, #indicates P<0.05.

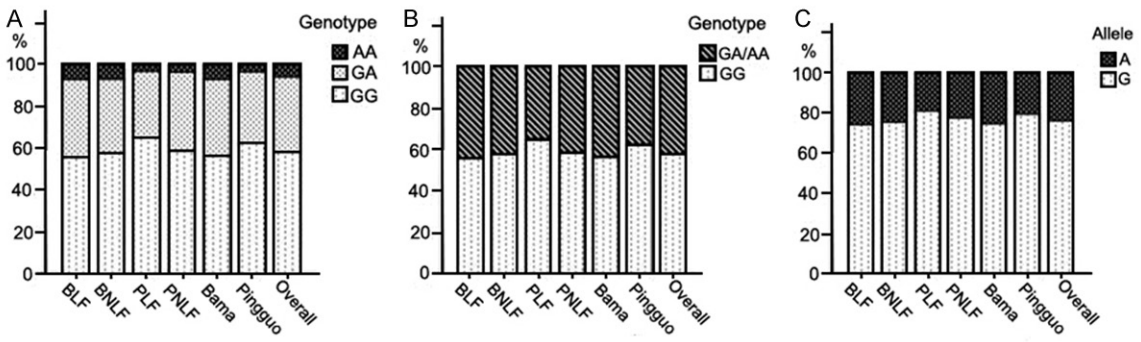

Figure 1. A. Comparison of genotypes among groups, $x^2 = 24.901$, $P = 0.000$, between regions, $x^2 = 19.904$, $P = 0.000$; B. Comparison between combined genotypes (GA/AA) and GG genotype among groups, $x^2 = 15.139$, $P = 0.002$, between region, $x^2 = 10.288$, $P = 0.001$; C. Comparison of allele among groups, $x^2 = 21.010$, $P = 0.000$, between regions, $x^2 = 17.337$, $P = 0.000$.

sity were defined as BMI < 24, 24 to 28, and > 28 kg/m^2, respectively [14].

Biochemical measurements

An overnight fasting venous blood sample of 8 mL was drawn by venipuncture from each subject, 4 mL of which was collected in a glass tube for serum separation and subsequent lipid determination while the remaining was transferred to an anticoagulant tube (4.80 g/L citric acid, 14.70 g/L glucose, and 13.20 g/L trisodium citrate) for DNA extraction. Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels were measured by enzymatic methods with commercially available kits as also previously described [11]. Individuals with TC > 5.17 mmol/L and/or TG > 1.70 mmol/L were defined as dyslipidemia [15].

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes by using standard methods. The COMT Val158Met polymorphism was genotyped by PCR-RFLP method using endonuclease Nla III for digestion as described by Lachman et al [16]. To ensure the reliability of genotyping, six randomly selected DNA samples (two for each genotype) were sequenced and the sequencing results were all in line with that of genotyping. Laboratory technicians who

Table 2. Impact of COMT Val158Met genotype on BP and lipid levels in different groups

Group/genotype	n	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Overall								
GG	1785	139.48±26.57	85.00±12.01	54.47±22.15	5.02±1.04	1.01 (0.69)	1.59±0.40	2.81±0.89
GA+AA	1294	138.72±27.13	84.52±11.71	54.19±22.22	4.91±1.04	1.04 (0.74)	1.57±0.42	2.73±0.93
F/Z		0.196	0.215	0.798	5.722	-0.231	0.931	4.563
p		0.658	0.643	0.372	0.017	0.818	0.335	0.033
Bama region								
GG	1199	142.50±27.25	86.68±12.15	55.82±22.87	5.19±1.03	1.07 (0.83)	1.60±0.40	2.95±0.89
GA+AA	939	140.77±27.03	85.58±11.67	55.18±22.10	5.09±1.03	1.06 (0.71)	1.58±0.44	2.89±0.92
F/Z		0.744	2.593	0.000	5.171	-0.906	0.989	2.116
p		0.388	0.107	0.994	0.023	0.365	0.320	0.146
Pingguo region								
GG	586	133.11±23.89	81.48±10.89	51.63±20.28	4.65±0.96	0.91 (0.67)	1.57±0.39	2.51±0.82
GA+AA	355	133.28±26.70	81.72±11.37	51.56±22.36	4.45±0.93	0.94 (0.76)	1.57±0.39	2.28±0.79
F/Z		2.929	0.411	2.707	5.740	-0.111	0.069	10.583
p		0.087	0.522	0.100	0.017	0.912	0.792	0.001
BLF								
GG	853	143.57±27.57	86.95±12.08	56.63±23.17	5.19±1.04	1.04 (0.80)	1.61±0.41	2.93±0.89
GA+AA	685	143.29±27.85	86.07±12.12	57.22±22.99	5.11±1.07	1.08 (0.74)	1.58±0.45	2.91±0.95
F/Z		0.150	1.324	1.339	1.275	-0.432	1.531	0.089
p		0.699	0.250	0.247	0.259	0.665	0.216	0.765
BNLF								
GG	346	139.90±26.31	86.02±12.33	53.88±22.05	5.21±1.02	1.15 (0.83)	1.56±0.38	3.00±0.88
GA+AA	254	134.19±23.58	84.31±10.33	49.87±18.62	5.02±0.91	1.03 (0.63)	1.56±0.40	2.86±0.86
F/Z		4.775	1.087	3.976	8.513	-2.316	0.108	7.205
p		0.029	0.298	0.049	0.004	0.021	0.743	0.007
PLF								
GG	350	135.29±24.91	81.17±10.94	54.12±20.90	4.69±0.93	0.91 (0.67)	1.58±0.39	2.54±0.78
GA+AA	188	137.82±30.37	82.40±11.12	55.43±26.23	4.34±0.89	1.03 (0.69)	1.56±0.35	2.22±0.76
F/Z		4.543	0.744	4.128	11.724	-0.305	1.168	11.929
p		0.034	0.389	0.043	0.001	0.761	0.280	0.001
PNLF								
GG	236	129.99±22.03	81.93±10.81	48.06±18.82	4.59±1.00	0.92 (0.68)	1.55±0.39	2.47±0.86
GA+AA	167	128.24±20.90	80.96±11.63	47.27±16.10	4.56±0.97	0.91 (0.97)	1.59±0.42	2.35±0.82
F/Z		0.059	0.016	0.148	0.020	0.130	0.340	1.038
p		0.809	0.900	0.701	0.888	0.896	0.560	0.309

performed genotyping were blinded to clinical and biochemical data.

Statistical analyses

Levels of the quantitative variables are presented as mean ± SD (TG levels are presented as medians and interquartile due to skewed distribution). Allelic and genotypic frequencies were calculated directly. Hardy-Weinberg equilibrium was computed for the expected genotype distribution using the standard goodness-of-fit test. Difference in genotype and allele distribution between the groups was estimated by using the chi-square test. The statistical evaluation for the categorical variables was based on the calculation of the Student t-test. The association of COMT genotypes with blood pressure and serum lipid variables was evaluated using analysis of covariance (ANCOVA). Multiple logistic analyses with stepwise modelling were used to evaluate the association of blood pressure and serum lipid levels with genotypes (GG = 1, GA = 2, AA = 3) and several environment factors. In all hypothesis tests, two-tailed values of $P<0.05$ were considered statistically significant. All data were analyzed using the statistical software package SPSS 16.0 (SPSS Inc, Chicago, IL).

Results

General clinical characteristics

The comparison of basic demographic and clinical data between BLF and other referent

Table 3. Impact of COMT genotype on BP and lipids in different families stratified by gender

Group/genotype		n	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
BLF									
Male	GG	485	138.26±22.67	87.33±11.46	50.93±18.91	5.19±1.07	1.10 (1.01)	1.59±0.44	2.85±0.93
	GA+AA	385	137.99±23.09	86.08±11.31	51.90±18.08	5.05±1.06	1.11 (0.90)	1.58±0.51	2.80±0.94
	F/Z		0.963	1.577	4.214	3.013	-0.866	0.005	0.340
	p		0.327	0.209	0.040	0.083	0.387	0.942	0.560
Female	GG	368	150.77±31.73	86.42±12.86	64.35±26.03	5.19±1.00	0.99 (0.61)	1.64±0.36	3.03±0.82
	GA+AA	300	150.36±31.85	86.05±13.14	64.31±26.67	5.20±1.08	1.04 (0.64)	1.59±0.35	3.05±0.94
	F/Z		0.143	0.352	0.010	0.000	-1.862	3.153	0.015
	p		0.705	0.553	0.922	0.982	0.063	0.076	0.904
BNLF									
Male	GG	230	137.80±25.22	87.27±12.49	50.53±20.77	5.11±0.94	1.22 (0.86)	1.53±0.38	2.88±0.84
	GA+AA	164	131.51±18.89	84.37±10.25	47.15±13.79	4.98±0.93	1.04 (0.84)	1.52±0.41	2.83±0.90
	F/Z		5.548	6.225	1.216	2.805	-1.865	0.027	0.616
	p		0.019	0.013	0.271	0.095	0.062	0.870	0.433
Female	GG	116	144.14±28.03	83.51±11.67	60.63±23.09	5.40±1.14	1.07 (0.81)	1.62±0.37	3.25±0.92
	GA+AA	90	139.07±29.83	84.22±10.52	54.84±23.47	5.08±0.87	0.95 (0.52)	1.64±0.38	2.93±0.76
	F/Z		0.970	0.392	2.268	5.296	-1.409	0.083	8.484
	p		0.326	0.532	0.134	0.022	0.159	0.774	0.004
PLF									
Male	GG	218	134.24±21.20	81.96±10.02	52.28±18.48	4.78±0.93	1.01 (0.90)	1.53±0.39	2.58±0.81
	GA+AA	124	134.62±24.73	84.23±11.35	50.39±20.04	4.33±0.90	1.07 (1.03)	1.55±0.38	2.15±0.74
	F/Z		0.928	4.974	0.121	19.797	-0.765	0.356	22.769
	p		0.336	0.026	0.728	1.17E-5	0.445	0.551	2.74E-6
Female	GG	132	137.28±30.75	79.67±12.42	57.61±24.57	4.52±0.90	0.76 (0.44)	1.66±0.36	2.47±0.74
	GA+AA	64	144.33±38.86	78.67±9.69	65.67±33.59	4.36±0.88	0.91 (0.41)	1.57±0.31	2.36±0.79
	F/Z		2.286	0.311	4.878	1.447	-1.735	2.879	0.739
	p		0.132	0.578	0.029	0.231	0.083	0.092	0.391
PNLF									
Male	GG	157	128.09±20.75	83.11±11.12	44.98±18.34	4.59±1.05	1.00 (0.94)	1.48±0.37	2.47±0.94
	GA+AA	101	126.77±19.23	82.23±11.97	44.53±14.35	4.62±0.99	0.95 (1.17)	1.55±0.43	2.33±0.87
	F/Z		1.014	0.002	1.335	0.511	-0.278	2.781	0.776
	p		0.315	0.962	0.249	0.475	0.774	0.097	0.379
Female	GG	79	133.69±24.038	79.63±9.84	54.06±18.41	4.59±0.89	0.84 (0.43)	1.69±0.40	2.49±0.70
	GA+AA	66	130.42±23.14	79.08±10.91	51.35±17.73	4.48±0.94	0.81 (0.52)	1.64±0.40	2.37±0.75
	F/Z		0.403	0.101	0.362	0.207	-0.155	0.302	0.541
	p		0.527	0.751	0.548	0.650	0.877	0.583	0.463

groups was summarized in **Table 1**. The SBP, DBP, BMI, FPG, TC, TG, LDL-C levels of BLF were similar with that of local BNLF controls but were significantly higher than that of non-local counterparts. This might be ascribed to the higher mean age of BLF. No difference was found on pulse pressure and HDL-C levels among the four groups.

Genotype and allele distribution

None of the genotypic and allelic distributions deviated significantly from that predicted by the Hardy-Weinberg equilibrium ($P > 0.05$). The frequencies of minor allele (A, Met) and its homozygotic (AA) and heterozygotic (GA, Val/Met) genotype of BLF were almost identical to that of BNLF (25.88%, 7.22% and 37.32% vs. 24.67%, 7.00% and 35.33%) but markedly higher than that of Pingguo groups (**Figure 1A-C**). However, these differences did not maintain through sex stratification (data not shown).

Genotype and blood pressure and serum lipids

As shown in **Table 2**, in the overall, Bama and Pingguo population, no impact of COMT Val-

Table 4. Relationship between blood pressure and relative factors in different families

BP	Relative factor	B	Std. error	Beta	t	*P*
BLF						
SBP	Age	0.646	0.023	0.616	28.210	0.000
DBP	Age	0.178	0.018	0.380	9.835	0.000
	TC	0.964	0.314	0.083	3.067	0.002
BP	Age	0.479	0.025	0.541	18.907	0.000
	Genotype	2.568	1.002	0.056	2.563	0.010
BNLF						
SBP	Age	0.702	0.037	0.651	18.874	0.000
	Genotype	-4.953	1.738	-0.095	-2.849	0.005
DBP	Age	0.120	0.021	0.249	5.833	0.000
	Sex	-3.829	0.969	-0.159	-3.952	0.000
	Genotype	-2.436	0.921	-0.104	-2.645	0.008
	LDL-C	1.490	0.569	0.110	2.617	0.009
PP	Age	0.540	0.029	0.614	18.634	0.000
PLF						
SBP	Age	0.735	0.035	0.680	20.814	0.000
	TG	14.344	3.736	0.133	3.840	0.000
DBP	Age	0.169	0.020	0.379	8.634	0.000
PP	Age	0.535	0.032	0.577	16.536	0.000
	TG	13.611	3.444	0.147	3.952	0.000
	HDL-C	4.836	2.120	0.078	2.281	0.023
PNLF						
SBP	Age	0.532	0.046	0.491	11.672	0.000
DBP	Age	0.184	0.035	0.310	5.251	0.000
	TG	8.021	2.152	0.191	3.728	0.000
PP	Age	0.509	0.039	0.552	13.189	0.000

158Met polymorphism on SBP, DBP and PP was detected (P > 0.05 for all), however, when it came to lipids, the TC and LDL-C levels of A allele carriers (GA/AA) were remarkably lower than non-A carriers (GG) (P < 0.05 for each). When analyzed according to families, no difference was observed on blood pressure and lipid levels between the mutant (GA/AA) and the ancestral genotype (GG) in BLF and PNLF, which persisted after sex stratification. However, GA/AA genotype dramatically lowered SBP, PP, TC, TG and LDL-C levels in BNLF while raised SBP in PLF. When gender was taken into account, the impact of GA/AA genotype on blood pressure in BNLF mainly existed in males while its impact on lipids mainly existed in females. In PLF, GA/AA genotype was associated with elevated DBP and lowered TC and LDL-C in males while with higher PP in females (**Table 3**). Together, in Bama population, the influence of COMT Val158Met polymorphism on blood pressure and lipid levels predominantly in average families rather than long-lived families.

Correlation analyses

Multiple linear regression analyses showed that COMT Val158Met correlated positively with PP in BLF while negatively with SBP and DBP in BNLF, i.e., A-allele carries tended to have higher PP in BLF but lower SBP and DBP in BNLF. No any correlation was observed between blood pressure and COMT polymorphism in the two Pinguo groups.

On lipids, COMT Val158Met correlated with TC and LDL-C inversely in BNLF and PL, with A allele carriers tending to produce less TC and LDL-C. An absence of association was noted this polymorphism and lipids in BLF and PNLF (**Tables 4**, **5**).

Discussion

In the current study, the frequency of the minor A allele of the COMT gene at +158 locus in the overall population studied is around 0. 24, similar to that of other Chinese healthy populations (e.g. Shanghai Hans, 0. 25; Southwestern Hans, 0. 21), Japanese population (0.32) and even American blacks (0.32), but profoundly lower than that of Caucasians (German, 0.52) [17-21], indicating a geographical-specific allelic distribution pattern worldwide. The underlying mechanism for this great discrepancy and its implication has yet to be elucidated. Further stratification analyses by gender and region showed that the frequency of mutant COMT genotypes (GA/AA) of BLF is statistically analogous to that of local general families, but significantly higher than that of out-of-Bama populations. The overrepresentation of an allele in Bama population seems to implicate that if it acts as an advantage factor it may be a genetic contribution to the longevity in the area; by contrary however, if it is a deleterious variant there may be other unknown buffering variants to counteract its unfavorable effect [22].

COMT 158Met has not only been linked to a reduced COMT activity and an increased cere-

Table 5. Relationship between serum lipid parameters and relative factors in different families

	Lipid parameters	Relative factor	B	Std. error	Beta	t	*P*
BLF							
	TC	DBP	0.008	0.002	0.092	3.195	0.001
		Age	0.010	0.001	0.243	7.005	0.000
	TG	None					
	HDL-C	None					
	LDL-C	Age	0.008	0.001	0.227	7.943	0.000
		DBP	0.005	0.002	0.064	2.263	0.024
BNLF							
	TC	Age	0.006	0.002	0.154	3.536	0.000
		Genotype	-0.210	0.083	-0.105	-2.527	0.012
		Sex	0.214	0.088	0.104	2.446	0.015
		DBP	0.010	0.004	0.112	2.542	0.011
	TG	Sex	0.065	0.027	0.127	2.428	0.016
		Genotype	-0.039	0.020	-0.078	-1.975	0.049
	HDL-C	None					
	LDL-C	Age	0.010	0.002	0.271	5.131	0.000
		Sex	0.358	0.090	0.202	3.979	0.000
		DBP	0.008	0.003	0.108	2.475	0.014
PLF							
	TC	Genotype	-0.354	0.078	-0.182	-4.515	0.000
		Age	0.010	0.002	0.264	6.453	0.000
	TG	PP	0.002	0.001	0.175	3.389	0.001
		Age	-0.002	0.001	-0.150	-2.553	0.011
	HDL-C	Age	0.004	0.001	0.239	5.528	0.000
	LDL-C	Age	0.008	0.001	0.242	5.748	0.000
		Genotype	-0.320	0.069	-0.193	-4.621	0.000
PNLF							
	TC	Age	0.008	0.002	0.168	3.435	0.001
	TG	Sex	-0.094	0.025	-0.164	-3.720	0.000
		DBP	0.003	0.001	0.144	3.144	0.002
	HDL-C	Age	0.005	0.001	0.247	5.031	0.000
	LDL-C	Age	0.011	0.003	0.259	4.557	0.000

bral DA level which is favorable of the maintenance of better cognition, but also to a higher risk of hypertension due to a spontaneous elevation of peripheral DA concentration. For instance, systolic and diastolic pressure had been found to be raised in Met/Met COMT homogenous individuals in Taiwanese females and Sweden and Japanese middle-aged males as compared to the other two genotypes, which was interpreted by a lowered degradation of DA and catechol estrogen and their resultant peripheral synaptic levels [7, 23]. By investigating the impact of COMT rs4680 on blood pressure and its association with daily intake of salt and calories, Htun et al observed that Japanese middle-aged men carrying COMT Met/Met genotype displayed higher systolic and diastolic pressure levels and higher incidence rate of hypertension than who carried Val/Val and Val/Met genotypes [24]. These ob-servations had found their support in animal models, in which hypertensive rats exhibited higher COMT activity than normotensive rats [25], and COMT knockout mice were more resistant to salt-induced hypertension than genetically normal mice [26]. Nevertheless, Hagan et al noted almost opposite results in Norwegian population: enhanced instead of reduced COMT activity correlated with hypertension, Val/Val rather than Met/Met homogenous genotype presented more frequently in SBP-elevated subjects [27]. In the current study, after adjustment for age, we found that although the blood pressure level of BLF was significantly higher than that of geographic- and non-geographic-matched controls, it lacked distinct association with COMT Val158Met polymorphism, while in BNLF, Met allele was found to be related to lowered SBP and DBP, particularly in men. These divergent finding may be attributed to the different genetic background, sample size, sex ratio, age range of the enrolled subjects across studying populations [28]. Assuming that COMT Met is indeed correlated with hypertension, COMT inhibitor entacapone may be a therapeutic strategy, but its elusive anti-hypertensive effect has not been established [29]. Thus, there is no clear consensus on the association between COMT rs4680 and hypertension to date. We have no appropriate explanation for the higher blood pressure in BLF currently; a long-term longitudinal follow-up is thus warranted.

Very little data was available as far as the association between COMT Val158Met polymorphism and lipid profile is concerned, most of which were mainly based on population models

of some disorders. For instance, Almeida and colleagues did not reveal any impact of this variant on lipid levels in Brazilian perimenopausal women [30]. Patients with chronic renal disorders who carried COMT 158Met presented lowered LDL-C level [19]. Schizophrenia sufferers complicated with metabolic syndrome (MS) who harbored COMT 158Met documented an elevated TG and homocysteine (Hcy) level in females but not in males [17]. This modulation of TG and Hcy was believed to be the outcome of the interactions between COMT 158Met and MTHFR 677C/T, a common variant on methylene tetrahydrofolate reductase (MTHFR) gene [31]. Works from other research group had also shown that COMT might involve in the metabolism of Hcy in that COMT activity positively correlated with serum Hcy level while COMT inhibitor lowered Hcy level [32]. In addition, COMT might affect human appetite and eating behavior via dopaminergic pathway, entailing preschool children a predilection to palatable oily food and resultant hyperlipidemia and obesity [33]. To our knowledge, this is the first family-based study to evaluate the association of COMT Val158Met and lipid profiles in the general population and long-lived subjects, unraveling overall a reverse correlation between COMT Val158Met and TC and LDL-C. This correlation, however, might be affected by family and gender in that it no longer remained in BLF through family and gender stratification, indicating a limited impact, if any, of COMT Val158Met on lipid modulation in long-lived families. The relatively higher lipid levels in BLF might be attributed to its higher proportion of the oldest olds who had less molar teeth and preferred myofiber-free fatty pork [11].

In sum, although presented more frequently in Bama area, COMT 158Met mainly modulate blood pressure and lipid levels in general families rather than long-lived families. The limited impact of this polymorphism on blood pressure and lipid parameters may imply that there are other unveiled variants which might interplay with each other and shape the age-related traits and the survival status in Bama longevous area. Its possible links with other phenotypes (e.g. cognition) and contributions to the longevity in Bama region deserve further exploration.

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Disclosure of conflict of interest

None.

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