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# Association between T102C 5-HT2A receptor gene polymorphism and 5-year mortality risk among Brazilian Amazon riparian elderly population

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## Abstract

**Objective:** Serotonin (5-HT) is a pleiotropic molecule that exerts several functions on brain and peripheral tissues via different receptors. The gene for the 5-HT2A receptor shows some variations, including a T102C polymorphism, that have been associated with increased risk of neuropsychiatric and vascular disorders. However, the potential impact of 5-HT2A imbalance caused by genetic variations on the human lifespan has not yet been established.

**Methods:** We performed a prospective study involving an Amazon riparian elderly free-living population in Maués City, Brazil, with a 5-year follow-up. Out of a cohort of 637 subjects selected in July, 2009, we genotyped 471 individuals, including 209 males (44.4%) and 262 females (55.6%), all averaging 72.3 ± 7.8 years of age (ranging from 60 to 100 years).

**Results:** The T102C-SNP genotypic frequencies were 14.0% TT, 28.0% CC, and 58.0% CT. From 80 elderly individuals who died during the period investigated, we observed significantly ($P = .005$) higher numbers of TT carriers (27.3%) and CC carriers (21.2%), compared to heterozygous CT carriers (12.5%). Cox-regression analysis showed that association between the T102C-SNP and elderly survival was independent of age, sex, and other health variables.

**Conclusions:** Our findings strongly suggest that imbalance in 5-HT2A may cause significant disturbances that lead to an increased susceptibility to death for individuals who are over 60 years of age.

  

## 1 | INTRODUCTION

Similar to many regulatory molecules, serotonin or 5-hydroxytryptamine (5-HT) exerts pleiotropic functions in the body (Marston, Garfield, & Heisler, 2011). These functions include neurotransmission related to appetite, cognition perception, and mood. In addition, serotonin has important actions on some peripheral tissues such as platelet aggregation, smooth muscle contraction and intestinal motility (Kawai and Rosen, 2010; Seyedabad, Fakhfouri, Ramezani, Mehr, & Rahimian, 2014). The extensive functional role of serotonin is mediated by several 5-HT receptor subtypes that are encoded by distinct nuclear genes (McCorvy and Roth, 2015).

Reduction of serotonin levels as well as the expression of several 5-HT2A receptors occurs during the aging process (Mattson, Maudsley, & Martin, 2004). Decreases in 5-HT2A receptors have been associated with some chronic age-related diseases such as dementia, osteoporosis, gastrointestinal disorders, and immune dysfunctions. Serotonin is an important molecule and evidence showed that age-related changes in serotonin systems are important risk factors for several dysfunctions and morbidities, including cardiovascular diseases (Fidalgo, Ivanov, & Wood, 2013). Moreover, aging-related decline in serotonin function has been associated with change in sleep, sexual behavior, and mood. The main impact of age on serotonin involves changes in its receptors, including gene and protein expression, as well as binding affinity of the 5-HT2A receptor (Hoekzema et al., 2011).

Therefore, 5-HT2 receptors are of significant clinical interest because of their potential involvement in mediating the effects of serotonin (Fidalgo et al., 2013). However, it is still not clear whether serotonin and 5-HT2A receptors play a role in the human lifespan or longevity (Fidalgo et al., 2013).

A major difficulty in assessing the influence of serotonin on human longevity may be due to the broad and dual actions of several of its receptors on body functions. This is the case for the 5-HT2A receptor, an important G protein-coupled receptor that mediates the effects of 5-HT in brain, mainly in the cerebral cortex, basal ganglia, hippocampus, thalamus, cerebellum and hypothalamus. 5-HT2A is also peripherally distributed and has been implicated in several physiological functions, including vascular smooth muscle contraction, extravascular smooth muscle contraction, and platelet aggregation; the latter being directly associated with vascular disorders. For these reasons, 5-HT2A antagonists have been used to treat certain cardiovascular diseases (Nagatomo, Rashid, AbulMuntasir, & Komiyama, 2004). However, the 5-HT2A that is highly expressed in the prefrontal cortex area plays an important role in cognitive regulation of emotion, and its dysfunction has been implicated in many psychiatric disorders including schizophrenia, mood, anxiety, obsessive-compulsive and eating disorders. 5-HT2A receptor dysfunction is also implicated in Alzheimer disease and psychosis associated with Parkinson's disease (Aznar and Klein, 2013; Berger, Gray, & Roth, 2009; Mestre, Zurowski, & Fox, 2013; Salmon, 2007).

One approach to investigate the impact of serotonin with altered function on the human lifespan involves the analysis of polymorphisms in the 5-HT2A receptor gene. The T102C SNP occurring in this gene can produce three genotypes: TT, CC, and TC. Previous studies have described an association between the CC genotype, that shows 20% less receptor density on cell membranes, and neuropsychiatric disorders such as schizophrenia (Ni, Lu, Wu, Chen, Yi, & Zhang, 2013; Vaquero-Lorenzo et al., 2006), psychotic symptoms in Alzheimer's patients (Fehér et al., 2013), and alcohol and tobacco addiction (Jakubczyk et al., 2012; Prado-Lima et al., 2004; Ramos-Neto et al., 2014; Wrzosek et al., 2012). Dysfunctions of the 5-HT2A receptor also include brain diseases such as migraine headaches, anxiety, and mental depression (Fidalgo et al., 2013).In addition, problems with 5-HT2A can cause cardiovascular diseases related to platelet aggregation and abnormal vascular smooth muscle cell physiology (Machida, Iizuka, & Hirafuji, 2013). In the vascular system, serotonin induces proliferation and migration via 5-HT2A receptors activation and causes both enhancement of prostaglandin I2 production and reduction of nitric oxide (NO) by suppressing inducible NO syntheses (Machida et al., 2013). In a recent study, Lairez, Cognet, & Schaak, (2013) showed that a selective blockade of 5-HT2A receptors prevented the development of cardiac hypertrophy in mice. Another investigation by Nelson, Harrod, & Lamping, (2012) suggested that both 5HT-2A and 5HT-2B receptors contribute to serotonin-induced vascular dysfunction in diabetes.

Due to their relevance to nervous and cardiovascular diseases, 5-HT2A receptors have been targeted for the development of pharmacological drugs, including selective serotonin reuptake inhibitors, to treat some psychiatric disorders such as depression. However, epidemiological evidences suggest that the use of these drugs can cause important physiological alterations in bone, thereby increasing the risk of fracture (Eom, Lee, Ye, Park, & Cho, 2012).

Considering specifically the T102C-SNP, some investigations described the relationship between the CC genotype or C allele and schizophrenia (Ni et al., 2013; Vaquero-Lorenzo et al., 2006), suicidal behavior (González-Castro et al., 2013), alcohol dependence, impulsivity of alcohol dependent-patients (Jakubczyk et al., 2012; Wrzosek et al., 2012), and relapse after alcohol dependency treatment (Jakubczyk et al., 2012). Associations between CC genotype and smoking (Prado-Lima et al., 2004) and nicotine dependence level (Ramos-Neto et al., 2014) were also reported. The CC genotype was reported to be associated with Alzheimer's disease (Fehér et al., 2013) and the occurrence of hallucinations,

delusions, psychosis, and aberrant motor behavior in Alzheimer's patients (Pritchard et al., 2008). A link between the C allele or CC genotype with metabolic disturbances was also previously reported. Choi et al. (2005) studied serum lipid profiles of 646 Korean subjects carrying different T102C-SNP genotypes and found a strong correlation between the CC genotype and lower levels of total cholesterol and HDL-cholesterol than in subjects carrying the TT or CT genotype.

By contrast, the TT genotype has been associated with some common disorders in elderly subjects such as urinary incontinence (Noronha et al., 2010; Schwanke et al., 2007). An interaction between the T allele of T102C-SNP and endothelin-1 variant with hypertension in a Japanese sample was also described by Yamamoto, Jin, & Wu, (2006) as well as an association between the TT genotype and non-fatal acute myocardial infarction (Yamada et al., 2000). Other studies have described an association between the TT genotype and nonfatal acute myocardial infarction (Yamada et al., 2000), urinary incontinence (Noronha et al., 2010; Schwanke et al., 2007) or hypertension (Yamamoto et al., 2006). Irrespective of phenotypes, individuals with the allele T of the polymorphism of the 5HT2A gene showed greater regional brain volumes in the left inferior temporal and left inferior occipital gyri in a study of patients with recent onset schizophrenia, compared to healthy control subjects (Vijayakumari et al., 2015). Moreover, Jobim, Prado-Lima, Schwanke, Giugliani, & Cruz (2008) investigated the genotype distribution in three age groups and showed a high frequency of TT in people between 45 and 64 years of age. In addition, a consistent increase in CC frequency was observed in elderly subjects ($\geq$ 65 years old), when compared with younger age groups.

However, whether serotonin 5-HT2A receptor dysfunction has any impact on the human lifespan is still not clear. More specifically, when considering the T102C-SNP, the genotype that increases the susceptibility to risk of death in the elderly is not known. Is it the CC type that is associated with neurological disorders or TT that is linked to cardiovascular and peripheral dysfunctions such as urinary incontinence? To address this question, we performed a longitudinal investigation in a partially isolated riparian elderly human population living in Maués City, located in the Amazon rainforest region of Brazil that is accessible only by boat or plane.

## 2 | MATERIALS AND METHODS

### 2.1 | Samples and data collection

To evaluate the potential impact of the T102C-SNP on the human lifespan, we analyzed an Amazon riparian elderly population living in Maués City, located in the Amazon rainforest region of Brazil. This city is partially isolated due to limited accessibility that reduces the use of specialized health services and advanced medical treatments. The investigation described here is part of a project previously approved by the Ethics Committee of the University of Amazonas State. Details of the study were previously published by Maia-Ribeiro et al. (2013). Briefly, an epidemiological study was performed in order to analyze health and functional fitness factors in the riparian elderly assisted by the Family Health Program (FHP) developed by the Brazilian Health Ministry in Maués City, Amazonas. This city was chosen because it is geographically located in the middle of the Amazon region and is inhabited by a riverine population living in a small urban area and spread across more than 170 riverbanks communities. The research program was started in 2009, when this city had 1% of its population over 80 years of age, whereas most cities of Amazonas State had less than 0.5% of the oldest population group ($>$ 80 years). Moreover, in Maués, 92% of population was included in the FHP.

In ethnic terms, besides the Sateré-Maués natives who first colonized Maués' area, the region is currently inhabited by riverine people named Caboclos. Caboclos are a Portuguese-speaking mestizo people thought of as a 'quasi-ethnic' group and recognized as the historical peasantry of the Amazon (Antoinnete, 2006). The group known as peasants is defined in a variety of ways and in the Brazilian Amazon region, peasants, and peasantry are inherently problematic terms. The Caboclos can be traced back about 300 years, when they originated as a disenfranchised Native Amerindian population. This group occupied the depopulated floodplains after the ravages of disease brought by the arrival of Europeans. The native people mixed with European settlers, primarily Portuguese, and adopted a form of social organization that reflected their Amerindian and European ancestors (Krieger et al., 1965). Locally, Caboclos are referred to as riparian, riverine or river-side dwellers. Genetically, the Caboclos living in Maués probably have a similar ethnic contribution as other western riverine Amazonian populations (Ferreira et al., 2002).The genetic contribution frequencies of Amerindians, Europeans and Africans to the ethnic composition of the studied populations were $0.44 \pm 0.064$, $0.35 \pm 0.069$, and $0.21 \pm 0.046$, respectively (Ferreira et al., 2002).

Our investigation began in 2009 when the total population of Maués was estimated at 45,285 people, including 21,094 living in a small urban area and the remaining 24,190 living in about 175 communities distributed along river tributaries. Elderly individuals ($\geq$60 years old) represented about 6.49% ($n = 2{,}939$) of the total population. An initial cross-sectional investigation was performed with 1805 subjects (male/female = 937/869) representing 61% of Maués´ elderly population. This investigation estimated the prevalence of the main chronic degenerative diseases in this population. This initial evaluation was performed using a structured interview that collected information about demographic

variables (i.e., education, income, marital status, occupation), lifestyle (e.g., smoking habits), CVD risk factors (i.e., hypertension, type 2 diabetes, obesity, dyslipidemia and metabolic syndrome), history of previous chronic diseases (including CVD morbidities and hospitalization within the preceding year), and use and quantity of daily medication. Additionally, anthropometric measures were collected, including body mass index, (BMI in $Kg/m^2$) and waist circumference, all of which were used to diagnosed obesity in the sample population. The sample consisted in elderly persons living in the urban and riverine/rural areas. Since access to Maués samples is very difficult for researchers to obtain, a complementary investigation was performed using a sub-sample of elderly living in the urban area. In this second expedition, blood samples were collected from participants. Considering an estimated frequency of minor allele of 15%, the 95% confidence interval (CI) and 3% estimation of error was calculated for the inclusion of at least of 459 subjects in genotype analysis. However, as Maués is hard to access and the blood samples needed to be transported to the southern Brazilian region for analysis, we only examined 637 subjects. Moreover, due the logistics of blood sample transport from the Amazon rainforest to the laboratory that performed the genetic analysis, it was only possible to genotype 471 elderly subjects because of sample degradation issues.

## 2.2 | Biochemical and gene polymorphism analysis

To perform the biochemical and genetics analysis, peripheral blood was collected by venipuncture (20 mL). The blood samples were collected in lithium-heparin and EDTA and were subsequently frozen and stored at −4°C. Blood tests were performed and the results were compared among elderly carriers of different T102C-SNP genotypes. These test include: (1) glucose, total cholesterol, HDL-c, LDL-c, and triglycerides; (2) total cholesterol, HDL-c, TG, uric acid and glucose (determined by enzymatic colorimetric methods using commercial kits); (3) total cholesterol Cod-Ana Labtest (Cat.76, Lagoa Santa, Brazil), HDL-c precipitant Labtest (Cat.13, Lagoa Santa, Brazil), TG Gpo-Ana, Glucose PAP Labtest (Lagoa Santa, Brazil). LDL-c was determined according to the Friedwald equation, that is, (LDL-c) = (TG) − (HDL-c + TG/5). From these results, subjects were diagnosed with hypercholesterolemia (total cholesterol ≥ 240 mg/dL); hypertriglyceridemia (triglycerides ≥ 150 mg/dL); and with lower HDL-cholesterol levels (HDL≤ 45 mg/mL).

Blood samples collected in EDTA were transferred to the Biogenomic Lab at the University Federal of Santa Maria, RS, Brazil, and used to determine T102C-SNPs (Prado-Lima et al., 2004). Genotyping of the T102C polymorphism was done using Thermo Scientific Phusion Blood Direct PCR Kit, which is designed to perform PCR directly from whole blood with no prior DNA extraction or sample preparation. Reactions were carried out in a 25-μL volume, containing 100 ngof genomic DNA and 10pmol of each primer (5′-TGTGCTACAAGTTCTGGCTT-3′) and (5′-GTGCAG TTTTTCTCTAGGG-3′) (Choi et al., 2005). The PCR products were digested with HpaII restriction enzyme. The 102T allele PCR products remained uncut, with a single DNA band of 342 bp, whereas the 102C allele showed two bands of 216 and 126 bp.

## 2.3 | Mortality data collection

From five-year follow-up, the project started to evaluate potential environmental, biochemical and genetic variables associated with mortality in riparian elders. Therefore, the data for different T102C-SNP genotypes were compared with the mortality information from official death records (dates and specific causes of death). The mortality data were obtained from the Municipal Health Department of Maués City registry. Deaths were computed monthly, beginning one month after the start of the study and over a period of 60 months (duration of the study).

## 2.4 | Statistical analysis

All statistical analyses were performed using the SPSS/PC statistical package, version 19.0 (SPSS, IL). An initial analysis was performed to evaluate the potential association between different T102C-SNP genotypes, age and other health and lifestyle variables using One-way analysis of variance followed by Bonferroni *post hoc* test. This post hoc analysis allows differences in sample number among the different genotypes, and has been used in previous genetic epidemiological studies such as by Prado-Lima, Cruz, Schwanke, Netto, & Licinio, (2006), Manica-Cattani et al. (2010), and Duarte et al. (in press). Quantitative variables, such as age, that were significantly different among genotypes were categorized using the values found in 75th percentiles. The categorization was performed to estimate the risk or protective value (95% of CI) associated with each genotype and/or allele. Case-control studies, comparing for example the genotype frequencies between young adults and elderly groups, can have several epidemiological and genetic population biases. To evaluate if the T102C-5HT-2A is related with survival, a second analysis was performed in the similar way as previously described by Da Cruz et al (2003). In this analysis, the mortality of riparian elderly carrying different T102C-SNP genotypes was examined during the 60-month follow-up using the Kaplan-Meier method. From these results, we determined the genotype combination associated with increased mortality risk (TT × CC and TC; CC

**TABLE 1** Baseline Characteristics by T102C-5 HT2A SNP Among Elderly Caboclos. Maues. Brazil. 2009

| | Genotypes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TT ($n = 66$) | | | CT ($n = 273$) | | | CC ($n = 132$) | | | |
| | | 95% CI | | | 95% CI | | | 95% CI | | |
| Variables | Mean ± SD | Lower | Upper | Mean ± SD | Lower | Uppper | Mean ± SD | Lower | Upper | *P* |
| Age (years) | 69.8 ± 6.9 | 66.9 | 72.6 | 72.5 ± 7.6 | 71.5 | 73.2 | 72.9 ± 8.4 | 70.8 | 73.3 | 0.03 |
| Waist circumference (cm) | 88.7 ± 16.0 | 86.1 | 92.8 | 87.8 ± 14.4 | 86.9 | 90.0 | 88.9 ± 12.5 | 84.7 | 89.1 | 0.337 |
| BMI (Kg/m2) | 25.4 ± 4.4 | 24.5 | 26.7 | 25.8 ± 4.5 | 24.7 | 25.7 | 24.5 ± 5.7 | 24.4 | 25.8 | 0.728 |
| SBP (mmHg) | 128.4 ± 26.1 | 124.8 | 137.9 | 129.4 ± 27.7 | 126.1 | 132.1 | 129.3 ± 25.2 | 123.0 | 131.7 | 0.594 |
| DBP (mmHg) | 72.8 ± 12.6 | 70.1 | 77.1 | 73.1 ± 14.9 | 71.5 | 74.7 | 73.8 ± 12.9 | 69.2 | 73.8 | 0.476 |
| Glucose (mg/dL) | 123.9 ± 48.2 | 110.5 | 132.6 | 123.6 ± 51.5 | 114.6 | 124.6 | 117.2 ± 30.32 | 105.2 | 119.3 | 0.356 |
| Cholesterol total (mg/dL) | 199.9 ± 48.4 | 186.3 | 214.4 | 210.7 ± 56.4 | 200.8 | 213.5 | 204.5 ± 44.8 | 200.0 | 217.9 | 0.578 |
| Triglycerides (mg/dL) | 158.4 ± 69.2 | 145.7 | 197.76 | 161.9 ± 107.4 | 154.4 | 178.0 | 165.4 ± 82.2 | 147.4 | 180.6 | 0.785 |
| LDL-cholesterol (mg/dL) | 136.8 ± 40.9 | 115.4 | 143.8 | 145.4 ± 51.6 | 127.7 | 141.1 | 143.5 ± 47.3 | 113.7 | 131.9 | 0.134 |
| HDL-cholesterol (mg/dL) | 48.5 ± 32.4 | 66.4 | 77.5 | 49.9 ± 44.2 | 69.2 | 74.4 | 51.6 ± 37.6 | 69.3 | 76.4 | 0.896 |

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. Genotypes groups were compared by Two-Way ANOVA followed by *post hoc* Bonferroni test. * = significant difference at $P < .05$ in relation to other genotypes..

× TT and TC or CT × CC and TT). We also examined the potential effects of different intervening variables (sex, age, chronic disease, polypharmacy or use of multiple medications, socioeconomic and cultural factors, lifestyle, and self-rated health) on the mortality results using a multivariate Cox proportional hazards method (Backward Wald). To perform this analysis, variables that present in univariate tests with a $P$ value $< .20$ were included in the multivariate equation. Considering that the number of deceased individuals was low, more than multivariate analysis was performed including genotype, age, and two additional predictors. All data are presented as means ± SD (standard deviation) for continuous variables, or as numbers and percentages, for categorical variables. In all analyses, $P < .05$ was used to indicate statistical significance.

## 3 | RESULTS

From the 637 people included in the 2009 cohort, it was possible to analyze the T102C-SNP genotypes of 471 elderly (subgroup) subjects who represented 74% of the initial sample. Of this subgroup, 442 (or 93.8%) people were born in Maués or neighboring communities; with 209 (44.4%) males and 262 (55.6%) females. The mean age of the 471 elderly individuals was 72.3 ± 7.8 years (ranging from 60 to 100 years). The T102C-SNP genotypic frequencies were 14.0% TT ($n = 66$), 28.0% CC ($n = 132$) and 58.0% CT ($n = 273$). The allelic frequencies were C = 0.577 and T = 0.423. The test sample was not in Hardy-Weinberg equilibrium since it showed an excess of heterozygous subjects (frequency expected = 230.1 vs. frequency observed = 273), compared to homozygous subjects, $P < .05$. The genotypic frequencies were not influenced by sex/gender.

Comparisons across phenotypic trait baselines are presented in Tables 1 and 2. As shown in Table 2, the comparison of baseline characteristics among subjects carrying different T102C-SNP genotypes showed similar health and lifespan patterns at the moment of inclusion in the study (July 2009), except for their ages. The C allele carriers presented a higher mean age than did the TT subjects ($P = .021$).

Eighty elderly subjects died during the period from July 2009 to July 2014. The T102C-SNP genotype frequencies were calculated between living and deceased subjects and we observed significantly ($P = 0.005$) higher numbers of deceased TT-carriers (27.3%) and CC-carriers (21.2%), when compared with heterozygous CT-carriers (12.5%). The relative risk for TT- and CC-carriers who died was 2.127 times higher (95% CI = 1.306–3.464) than for CT-carrying elderly subjects. The Kaplan-Meir survival curve (Figure 1) confirmed that subjects with TT and CC genotypes were more likely to die than subjects with a CT genotype. The mean survival time for each genotype was 50.4 ± 2.0 months for TT, 51.7 ± 1.5 months for CC and 55 ± 1.0 months for CT. The survival of heterozygous CT individuals was significantly higher ($P = .007$) than both the homozygous TT and CC (Figure 1).

**TABLE 2** Characteristic baselines comparison among riparian elder carrying different T102C-SNP genotypes

| Variables | | TT % (n) | CT % (n) | CC % (n) | *P* |
|---|---|---|---|---|---|
| Gender (%) | Males | 49.2 (32) | 44.9 (122) | 45.1 (59) | 0.979 |
| | Females | 50.8 (34) | 55.1 (150) | 54.9 (73) | |
| Age (%) | 60–75 years | 57.8 (38) | 31.1 (85) | 34.1 (45) | 0.001 |
| | $\geq$ 75 years | 42.4 (28) | 68.9 (188) | 65.9 (87) | |
| Hypertension (%) | | 51.5 (34) | 49.1 (134) | 42.4 (56) | 0.356 |
| Diabetes mellitus 2 (%) | | 18.2 (12) | 13.2 (36) | 10.4 (14) | 0.331 |
| Obesity ($\geq$ 30 kg/m$^2$) (%) | | 13.6 (9) | 12.5 (34) | 8.3 (11) | 0.398 |
| Metabolic syndrome (%) | | 16.7 (11) | 12.2 (33) | 16.8 (22) | 0.36 |
| Hypercholesterolemia (%) | | 20 (13) | 24.3 (66) | 23.6 (31) | 0.798 |
| Hypertriglyceridemia (%) | | 50.9 (34) | 42.4 (115) | 50 (66) | 0.24 |
| HDL $\leq$ 45 mg/dL (%) | | 2.2 (1) | 8.7 (24) | 7.6 (10) | 0.334 |
| Cardiovascular diseases (%) | | 9.1 (6) | 9.2 (25) | 5.3 (7) | 0.389 |
| Hospitalization last 6 months (%) | | 13.6 (9) | 12.9 (35) | 16.7 (22) | 0.593 |
| Daily medicine intake (%) | | 50 (33) | 53.1 (145) | 49.2 (65) | 0.736 |
| Smoking habit (%) | | 10.6 (7) | 12.5 (34) | 12.1 (16) | 0.918 |
| Regular exercise (%) | | 42.8 (28) | 40.7 (111) | 40.9 (54) | 0.966 |

Considering different T102C-genotypes, their frequencies varied by age group. In the 60–69 age group, the frequencies were TT = 10.8%, CC = 9.3% and CT = 5.7%. In the 70–79 years-old deceased, the distribution was TT = 19.0%, CC = 16.7%, and CT = 13.3%. In the group > 80 years-old deceased, the distribution was TT = 33.3%, CC = 35.5% and CT = 28.6%. A complementary survival analysis was performed considering the three different age groups (Figure 2). As expected, a higher frequency of deceased individuals in the oldest-old group was observed in all elderly carrieŕs for all T102C-genotypes. However, the CT-group showed a lower frequency of mortality in the group with 70–79 years old.

From these results, a complementary analysis of percentile distribution identified 74.7 years as the 75th percentile among TT subjects. For this reason, the sample was categorized in two groups: elderly < 75 and $\geq$ 75 years old. These age groups were used in the subsequent analysis (Table 1).

A multivariate Cox regression analysis was performed to determine the potential influence of different factors, that is, obesity, diabetes, gender, etc., on the relationship between the T102C-SNP of the 5-HT2A gene receptor and mortality of the riparian elderly. The results presented in Table 3 show that the association between the high survival rate and the CT genotype was independent of sex, age, and any of the other health factors examined.

Although we were also interested in knowing the cause of mortality, most elderly subjects who died did not receive medical assistance and it was not possible to ascertain the primary cause of death ($n$ = 60, 79.4%). However, ten subjects died due to cardiac failure, three by respiratory diseases, one by renal failure, one by hepatic failure, two by diabetes complications, two by gastrointestinal disorders, and one by senility. Due to the few number of elderly for whom the cause of death was known, we did not perform a correlative analysis between the cause of death and T102C-SNP.

## 4 | DISCUSSION

Our results indicated that heterozygous (CT) subjects exhibited a significantly higher chance of survival after five years than elderly subjects with either of the homozygous genotypes (TT and CC). Another important finding was that the association between CT genotype and high survival was independent of sex and age in the moment that the cohort was selected (i.e., July 2009). Furthermore, the longevity of CT-carriers was also not influenced by many health determinants.

Several recent studies failed to find a link between the T102C-SNP and neuropsychiatric or cardiometabolic

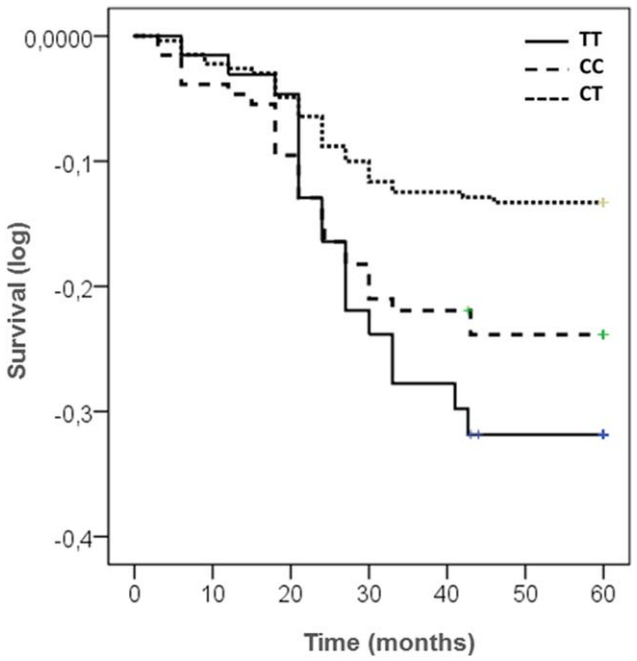


**FIGURE 1** Kaplan-Meier survival curve for mortality of Amazon riverine elderly subjects carrying different T102C-SNP genotypes of the 5-HT2A gene receptor: TT, CC and TC. The survival time of CT-carriers was significantly ($P = .007$) higher than that of homozygous carriers (TT and CC). Vertical scale logarithms (0, −0.1, −0.2, −0.3, and −0.4) correspond to non-constant declines in the estimated percent surviving (100%, 90%, 82%, 74%, and 67%), respectively

disorders (Peng, Yu, Su, & Luo, 2014; Yildiz et al., 2013; Zhao et al., 2014). These inconsistencies suggest that some environmental, ethnic, or genetic factors may play important roles in the association between the T102C-SNP and the chronic disorders studied thus far. For example, in a previous investigation performed by our research team, we found an association between tobacco use and the CC genotype in a southern Brazilian population (Prado-Lima et al., 2004). However, in this study, we did not find any association between smoking habit and the T102C-SNP in the riparian elderly population. However, the number of smokers in the riparian elderly sample in the present study was very low ($n = 57$) and may be the reason for the lack of a significant relationship between the T102C-SNP and tobacco use.

In the present investigation, we conducted a prospective analysis of an elderly population above 60 years of age. We found a higher number of CC and CT subjects, and our sample was not in Hardy-Weinberg equilibrium, as it contains an excess of heterozygous individuals. Our findings suggest the involvement of some, yet unknown, evolutionary factor(s), genetic and environmental. Considering that most elderly born in Maués and nearby regions always lived in this geographical area, the impact of migration(s) on genotype frequencies is likely to be minimal. However, when we followed-up the subjects for five years, it was evident that CT subjects exhibited a higher survival time than homozygous subjects. However, after performing a multivariate analysis, we did not find a significant influence of age, sex, or any prevalent morbidity commonly found in elderly populations. Unfortunately, due to the low number of elderly who died with medical assistance, it was not possible to perform a correlative analysis between the cause of mortality and T102C-SNP genotypes. Nonetheless, it is possible to infer that heterozygosity confers some kind of resistance to elderly

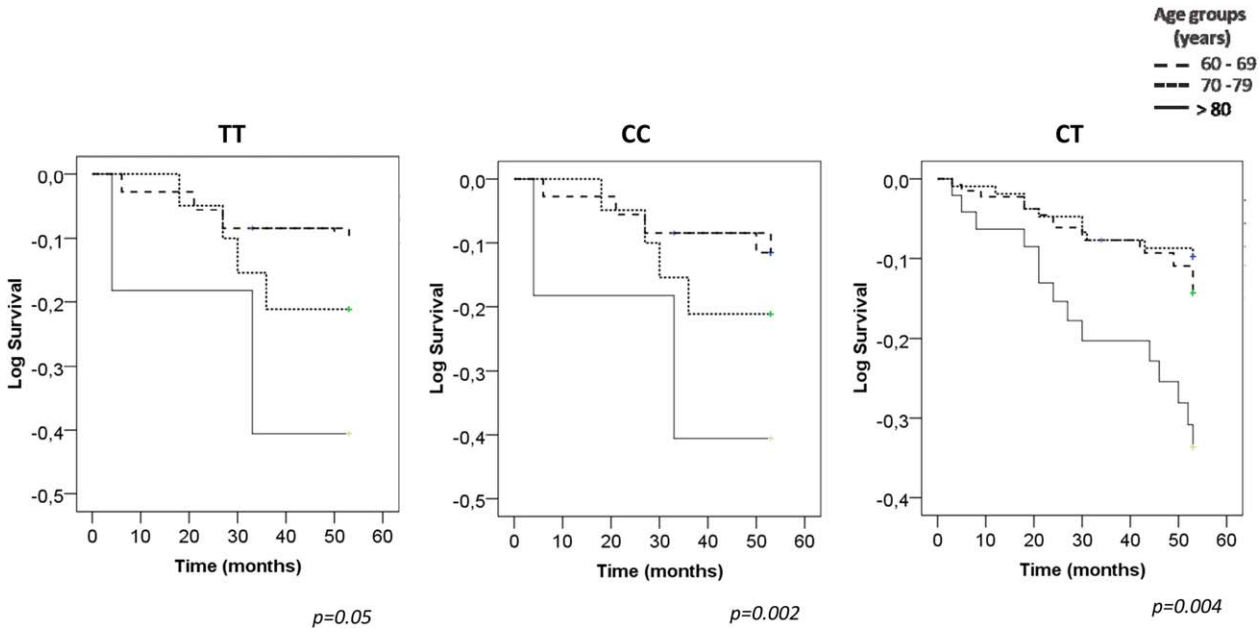


**FIGURE 2** Kaplan-Meier survival curve for mortality of Amazon riverine elderly subjects with different age groups considering each T102C-SNP genotypes of the 5-HT2A gene receptor: TT, CC, and TC. In all groups, higher frequency of oldest-old (>80 years) mortality was observed. However, in heterozygous higher elderly with intermediary age (70–79 years) showed similar survival frequency than younger elderly group (60–69 years). Vertical scale logarithms (0, −0.1, −0.2, −0.3, and −0.4) correspond to non-constant declines in the estimated percent surviving (100%, 90%, 82%, 74%, and 67%), respectively

**TABLE 3** Association between high survival rate and the CT genotype

| Variables | Wald | Risk | 95%CI | *P* |
|---|---|---|---|---|
| **First Model** | | | | |
| CT genotype | 9.878 | 2.046 | 1.309–3.197 | 0.002[a] |
| Age (>75 years) | 2.993 | 0.647 | 0.396–1.059 | 0.084 |
| Sex (male) | 1.387 | 1.303 | 0.839–2.025 | 0.239 |
| Previous chronic morbidities | 0.180 | 0.890 | 0.518–1.527 | 0.672 |
| **Second Model** | | | | |
| CT genotype | 10.020 | 2.058 | 1.316–3.217 | 0.002[a] |
| Age (> 75 years) | 3.520 | 1.659 | 0.968–2.844 | 0.066 |
| Daily intake medicine | 0.028 | 2.061 | 1.319–3.221 | 0.867 |
| Hospitalization (last year) | 0.408 | 0.804 | 0.421–1.570 | 0.523 |

[a]Multivariate analysis was performed by Cox PH model.

people, probably due the maintenance of 5-HT2A receptor balance that is a key component of several functions of neural and peripheral tissues. In fact, the frequency of heterozygous subjects was higher than expected. Therefore, we checked the location where each elderly subject was born and we found that almost all of them (>95%) were born in Maués or in neighboring rainforest cities. Thus, the potential contribution of migrations in skewing our findings by bringing in new alleles or genotypes is highly unlikely.

Another possibility is that the homozygous subjects present a higher risk of dying than heterozygous subjects. Despite the fact that there are few investigations on the potential association between the T102C 5-HT2A polymorphism and chronic diseases, two reports suggest a potential link between this polymorphism with myocardial infarction (Coto et al., 2003; Yamada et al., 2000). The potential risk of a person with a TT-genotype developing myocardial infarction may be related to the role of the 5-HT2A receptor in vascular smooth muscle contraction, platelet aggregation and thrombus formation as well as coronary artery spasms. Accordingly, selective 5-HT(2A) antagonists may have a significant potential in the treatment of cardiovascular diseases (Machida et al., 2013; Nagatomo et al., 2004). However, the CC-genotype has been associated with several life style risk behaviors such as alcoholism and smoking. (Jakubczyk et al., 2013; Prado-Lima et al., 2004) as well as suicide attempts (Vaquero-Lorenzo et al., 2008). Taken together, these findings may explain the higher presence of heterozygous subjects in the elderly population examined in the present study. Unfortunately, because of logistic limitations, it was not possible to evaluate the distribution of the T102C 5-HT2A gene polymorphisms in younger subjects in the Maués population. Despite this limitation, and because of the longitudinal approach of our study, the high frequency of heterozygous subjects in the elderly population is unexpected and underscores the need for further investigations, including those involving younger subjects.

The results described here add to the understanding of the roles of serotonin and its receptors, specifically 5-HT2A, in the human lifespan. Because most of the elderly investigated here had low access to specialized health services, their health status could potentially interfere with and skew our results. A previous investigation performed by Maia-Ribeiro et al. (2013) in this same cohort described functional, gait/balance and health variables of these riparian elderly with and without history of falls. Their results suggested that falls experienced by these elderly were strongly associated with accidents due to environmental conditions related to daily life. Together, these observations show that, in general, the elderly investigated here had a satisfactory health and functional conditions at the moment they were included in our study (i.e., in July, 2009).

A second phase of the study was implemented to identify potential environmental, biochemical and genetic factors that could affect the lifespan of these riparian elderly. A recent investigation performed by Silva et al. (2015) found an interesting association between mortality risk and high levels of oxidized proteins, including advanced oxidation protein products (AOPP) derived from oxidation-modified albumin, as well as fibrinogen and lipoproteins. Elderly subjects with AOPP $\geq$ 60 mmol/L showed a higher risk of death than subjects with low AOPP levels (Silva et al., 2015). In addition to this biochemical marker, the T102C-SNP is another factor that seems to significantly affect the survival of the riparian elderly subjects.

Some methodological constraints related to this study need to be considered. The sample size analyzed here could be considered low in comparison with other population genetic studies examining the association between age and gene polymorphism or age-related chronic diseases and gene polymorphisms. However, the total elderly population of Maués was 2900 subjects and half of these people lived in areas not accessible for clinical and blood data collection. Moreover, most elderly present similar socioeconomic, cultural and lifestyle patterns that decrease the variation that could influence the observed results. Another factor that could influence the results is related to the initial mean age of subjects carrying different T102C-SNPs. In fact, C allele subjects presented a mean age that was higher than TT subjects. To minimize the potential influence of this factor in the survival analysis, the initial age was included in all multivariate equations. The results confirmed that this variable did not affect the observed genotype-related survival.

Another important consideration is the ancestry of the sample population. In fact, Brazilian populations are ethnically heterogeneous according to the geographic regions. This question was investigated by Saloum de Neves Manta et al. (2013) who evaluated the genetic ancestry of approximately 1,300 Brazilians characterized by 46 autosomal Ancestry Informative Markers (AIMs). In addition, 798 individuals from twelve Brazilian populations representing the five geographical macro-regions of Brazil were genotyped, including a Native American community and a rural Amazonian community. The results showed that the rural Amazonian community had a significantly greater proportion of Native American ancestry than other ethnic origins (African: 0.074, European = 0,168, and Native American = 0.758). Despite the fact that we did not assess the genetic ancestry of the elderly people in our study, we can consider that the ancestral description by Saloum de Neves Manta et al. (2013) also apply to the Maués region. To try and minimize this methodological pitfall, and considering also the potential impact of migratory movements that occurred in Amazonia since the 1970s when we designed our study, we avoided analyzing the association between gene and lifespan by a case-control protocol that was used in several studies. Instead, we opted to perform a longitudinal study. For this reason, we believe that our finding of an association between the T102C-SNP and survival is unlikely to be due to chance or other intervenient genetic variables.

Moreover, it is important to point out that, in general, it is difficult to find a robust association and impact of just one SNP on elderly survival. However, in the case of the T102C-SNP, previous studies performed in different populations indicate alterations in the concentration of HT-2A receptors and association with chronic diseases and age-related dysfunctions, that could affect the lifespan (Choi et al., 2005; Coto et al., 2003; Fehér et al., 2013; Jakubczyk et al., 2012, 2013; Lairez et al., 2013; Noronha et al., 2010; Prado-Lima et al., 2004; Schwanke et al., 2007; Yamada et al., 2000).

We did not disregard the possibility that our findings could mask other influences of genetic background, which for some reason, affected the survival rate. While it is impossible to know at this moment how other markers could influence the association described here, the T102C-SNP seems to be a possible candidate to mark mortality risk in the elderly. We understand that independent studies performed in other populations need to be carried out to observe if this finding is universal or not.

Absent of additional investigations, we cannot generalize the association between the T102C-SNP 5-HT2A receptor and longevity of other human populations. Nonetheless, our results strongly suggest that a 5-HT2A genetic imbalance may cause significant disturbances that lead to an increased susceptibility to death for individuals who are over 60 years of age.

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