TPH1 Gene Polymorphism (rs211105) Influences Serotonin and Tryptophan Hydroxylase 1 Concentrations in Acute Pancreatitis Patients

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Research Article

Keywords: AP, polymorphism, acute pancreatitis, rs211105, TPH1, tryptophan hydroxylase 1

Posted Date: June 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-567244/v1

TPH1 gene polymorphism (rs211105) influences serotonin and tryptophan hydroxylase 1 concentrations in acute pancreatitis patients

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Abstract

Background: The role of serotonin and its metabolic pathway in the proper functioning of the pancreas has not been thoroughly investigated yet in the aspect of AP (acute pancreatitis). Tryptophan hydroxylase (TPH) as the rate-limiting enzyme of serotonin synthesis has been considered for possible associations in various diseases. Single-nucleotide polymorphisms (SNPs) in TPH genes have been already described in associations with psychiatric and digestive

system disorders. Aim of this study was to explore association of rs211105 (T/G) polymorphism in TPH1 gene with tryptophan hydroxylase 1 concentrations in blood serum in population of acute pancreatitis patients, and to investigate this association with acute pancreatitis susceptibility. Results: To date, we have found an association between the presence of the T allele at the position rs211105 (OR = 2.47, 95% CI: 0.94-6.50, p = 0.06) under conditions of a decreased AP incidence. For TT and GT genotype in control group, the lowest concentration of TPH was associated with higher serotonin levels (TT: R_s=-0.415, p=0.0018; GT: R_s=-0,457, p=0.0066), while for AP group: the highest levels of TPH among TT genotype were associated with lower levels of serotonin (TT: R_s=-0.749, p=0.0000), and in GG genotype higher levels of TPH were associated with higher levels of serotonin (GG: R_s=-0.738, p=0.037).Conclusions: Here, the new insight of the potential role of selected genetic factor in pancreatitis development was brought. Not only the metabolic pathway of serotonin, but also factors affecting serotonin synthesis may be interesting and important point in acute pancreatitis.

Keywords: AP, polymorphism, acute pancreatitis, rs211105, TPH1, tryptophan hydroxylase 1

1. Introduction

Ischaemia, bile duct obstruction, activation of pancreatic protease as well as proinflammatory cytokines are important components in the etiopathogenesis of acute pancreatitis (AP) [1, 2]. AP may have an unpredictable course. So, there is an urgent need for determination the prognostic symptoms that would enable to identify patients at high risk of severe course [3, 4].Till now, more severe AP has been associated with elder age, obesity, pancreatic necrosis, fluid collection, organ failure and some genetic factors [5]. The role of serotonin and its metabolic pathway in the proper functioning of the pancreas has not been throughly investigated yet in the aspect of AP.

Serotonin (5-HT, 5-hydroxytryptamine) is a monoamine neurotransmiter, synthesized in serotonergic neurons of the central nervous system (CNS), in enterochromaffin cells (EC) present in the gastrointestinal epithelium [6] and also, immune system cells as macrophage, and T cells [7]. However, it is known that the brain-derived serotonin provides only about 5% of total body serotonin, while 95% of serotonin is produced in the peripheral organs, mostly in gut. It became an inspiration for research on serotonin function of multiple physiology aspects [8].

The 2-step enzymatic synthesis pathway starts from dietary L-tryptophan conversion into 5-hydroxy-L-tryptophan (5-HTP) and then to 5-HT by two enzymes: tryptophan hydroxylase (TPH) and ubiquitous aromatic L-amino acid decarboxylase (AADC), respectively (Figure 1). 5-HT is degraded into 5-hydrosyindoleacetic acid by monoamine oxidase A (5-HIAA) [7, 9].

Serotonin regulates emotional expression, social behaviour, and proliferation of immune system cells, muscle and epithelial cells, and neurons [6, 10, 11]. It is also a chemotactic molecule for such cells as eosinophils, dendritic cells or mast cells [7]. It has been proved that the intracellular content of serotonin correlates positively with insulin secretion rate, and Tph1-deficient mice showed the development of a mild form of diabetes as a result of impaired insulin secretion in pancreas [12]. Almaca et al. [13] found that serotonin is a paracrine signal released by human pancreatic β-cells to regulate glucagon secretion. The effect of serotonin deficiency, the lack of its transporters, receptors or enzymes of the serotonin pathway are implicated in many diseases, including depression, numerous mood swings, emotional instability, schizophrenia and other neurological disorders, and irritable bowel syndrome [14–22].

Because serotonin concentration is regulated by rate-limiting enzyme - TPH, TPH has been considered for possible associations with suicidal behavior [19, 20, 23, 24], irritable bowel

syndrome [18], or depression [25]. Presently, two forms of TPH were identified (TPH1 and TPH2), while TPH2 is expressed mainly in the brain, and TPH1 – in brain and EC cells in the gut [18].

The human TPH1 gene has been cloned and mapped to the chromosome 11p15.3-14 (Gene ID: 7166); it has 11 exons [19, 24] and consists of 444 amino acids [18].

Single-nucleotide polymorphisms (SNPs) have been described in the genes coding the type one and two of tryptophan hydroxylases in associations with psychiatric disorders and suicidal behavior [26–29]. There are few studies investigating the rs211105 polymorphism role in diarrhea-predominant irritable bowel syndrome, and digestive system [18, 21, 22]. However, there are no published data using TPH1 polymorphism rs211105 in correlation to serotonin hydroxylase 1 or serotonin concentrations in blood serum.

In the present study, we investigated association of TPH1 gene polymorphism rs211105 (T/G) with acute pancreatitis and tryptophan hydroxylase 1 concentrations in blood serum. Due to the fact that tryptophan hydroxylase 1 is also expressed in β-cells of pancreas [6], we predict its role in proper pancreas functioning.

2. Material and methods

2.1. Ethics and general information

Specialists recruited the all 198 participants either at the Department of General Surgery and Oncology of the Warmia and Mazury University Hospital in Olsztyn or at the Clinical Department of Trauma-Orthopedic Surgery and Spine Surgery of the Provincial Specialist Hospital in Olsztyn in 2014-2020. All participants were treated according to the Patient Right Protection Act of our institution and international guidelines, and the Local Bioethics Committee approved our study (13/2016; 51/2019).

Peripheral blood samples (5-10 ml) were collected from each patient by medical staff, and all biological material was immediately transported to the laboratory and directly used in analysis or stored at -80°C.

2.2. Controls and AP group characteristic

Our study included 198 individuals (all Caucasian): 107 patients diagnosed with AP (19 females and 88 males; mean age ranging from 28 to 76 years; average 52.4) and 91 healthy people (25 females and 66 males; mean age ranging from 23 to 68 years; average 49.7).

Patients were admitted to the hospital 8-36 hours after the onset of AP symptoms (pain, vomiting, emetic reflex). Comorbidity of chronic circulatory system, liver, kidney or lung diseases caused exclusions from the study. Blood samples were collected from the forearm vein for the panel of biochemical tests twice – upon arrival at the hospital and 48 hours after admission. Up to 2 days, each patient had computed tomography (CT) with contrast performed to detect fluid collections, the extent of inflammation or necrotic changes. APACHE-II (Acute Physiology And Chronic Health Evaluation II) scores were calculated using data from the first 24 h after admission to assess patients' condition. Predicting acute pancreatitis severity and potential complications were based on imaging scales performed 3-4 days after the onset of symptoms, then after 10-12 days treatment.

Table 1 presents the characteristics of both groups.

2.3. Polymorphism rs211105 in TPH1 gene in healthy and AP patients

DNA was isolated from peripheral blood using GeneJET™ Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, Waltham, USA) according to the manufacturer's instructions. Polymorphism rs211105 was assessed by polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) according to method

described by Shiotani et al. [21] with own modifications. Primers for PCR reaction had following sequence:

TPH1HAF caaaagcagaataaagatgcaca; TPH1HAR acctacagggtgagggaagg.

A program in a thermo cycler was as follows: initial denaturation: 94°C for 3 min, proper denaturation: 94°C for 30 s, attaching the starters at the temperature 61°C for 30 s, synthesis: 72°C for 30 s, final synthesis: 72°C for 5 min, number of cycles: 40, cooling: 4°C. There was 25 µl of the mixture of DreamTaq™ Green Master Mix (Thermo Scientific, Waltham, USA), specific starters, the DNA matrix and molecularly pure water (Sigma-Aldrich, Saint Louise, USA). The yield and specificity of PCR products were evaluated after electrophoresis in 1.5% agarose gel (Promega, Madison, USA) and staining with GelGreen (Biotium, Fremont, USA). Next, FastDigest® BsuRI (HaeIII) (Thermo Scientific, Waltham, USA) enzyme was added to the *TPH1* rs211105 PCR products and then digested according to manufacturer's instruction. For genotyping a 2.5% agarose gel was used (Figure 1). To confirm proper genotyping, 30 randomly chosen samples was genotyped one more time after proper genotyping.PCR-RFLP products were: TT (324 bp), GG (75, 249 bp), and GT (324, 249, 75 bp).

2.4. Tryptophan hydroxylase 1 concentration

TPH1 concentration has been determined using Human Tryptophan 5-hydroxylase 1 ELISA kit according to the manufacturer's instruction (Wuhan EIAab Science Co., China). The analysis was performed in duplicate at 37°C with gentle shaking (250 rpm) in microplate incubator (SkyLine ELMI Shaker DTS-4, Riga, Lithuania).

In brief, TPH1 content was measured in the following order: 100 µL of Samples, Blank, and Standards in range of concentration 0.312 – 20 ng/mL were added into microtiter strips and incubated for 2 hours. Then, liquids were removed and 100 µL of Detection reagent A working solution was pipetted. Incubation was carried out for 1 hour, after that microplate was rinsed

three times with Wash Buffer, and 100 µl of the Detection reagent B working solution was added. After 1-hour incubation rinsing the microplate with Wash Buff-er was performed as previously, and 100 µL of Substrate Solution was added to each well. After a 15-minute incubation, 50 µL of Stop Solution was pipetted to the microplate. The absorbance was measured at a wave-length of λ= 450 nm using an ELISA reader (BiogenetAsys UVM 340, Cambridge, UK).

2.5. Serotonin concentration

The analysis was performed in duplicate using Serotonin ELISA kit according to the manufacturer's instruction (LDN, Labor Diagnostika NORD, Nordhorn, Germany), and described by Cieślińska et al. [30]. All steps of the ELISA were carried out at RT (room temperature) with gentle shaking (250 rpm) in microplate incubator (SkyLine ELMI Shaker DTS-4, Riga, Lithuania).

The first step was the acetylation of the samples by mixing: 25 µL of serum, standards or controls with 500 µL of acylation buffer, and 25 µL of acylation reagent. After a 15-minute incubation, acetylated samples were pipetted into the 96-well plate. In addition, 100 µl of the serotonin antiserum was also added into all wells, and incubation was carried out for 30 minutes. After three washes of the plate with Wash Buffer, 100 µl of the conjugate was added, and incubated for 15 minutes. Then, 100 µL of substrate was pipetted, and after 15 minutes stop solution was added. The absorbance was measured at a wavelength of λ= 450 nm using an ELISA reader (BiogenetAsys UVM 340, Cambridge, UK). The concentration range of the standard curve was 10.2 – 2500 ng/mL.

2.6. Statistical analysis

The frequency distribution of common risk factors for AP are presented as the mean. The genotype distribution among subjects was analyzed for Hardy-Weinberg equilibrium (HWE) using the chi-square test, and genotype and SNP allele frequencies were compared in AP patients and control groups by Fisher's test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analysis and used to compare both, allele frequencies in controls and AP patients, and allele frequencies between females and males. The risk of AP development was estimated via wild-type genotype and wild/mutant versus the mutant-type genotypes. Serotonin and tryptophan hydroxylase concentration results have been presented as a mean ± standard error. The mean values in Control and AP groups were compared using ANOVA and Student's t-test. Sperman rank order correlation analysis was used to estimate the relationship between analyzed parameters. Statistical analysis was calculated on Statistica 13.1 (TIBCO Software Inc., Paolo Alto, CA, USA) and GraphPad Prism 6 software (GraphPad Software Inc., San Diego, CA, USA), with ≤ 0.01 P-value as a statistically significant factor. Statistical analyses were described in our previous work [30].

3. Results

3.1. Polymorphism rs211105 in TPH1 gene

At the rs211105 polymorphic site the frequency of alleles T and G were determined in healthy individuals and in those diagnosed with AP in our study population.

Three genotypes (TT, GT and GG) were identified in the whole study population (Control and AP). Of the total 198 participants, 108 had genotype TT, 79 had GT and 11 had GG. The observed genotype frequencies at rs211105 polymorphic site of TPH1 gene in Controls ($\chi 2$ =

197 0.73, p=0.39) and AP patients ($\chi 2$ = 0.11, p=0.74) conformed to the Hardy-Weinberg
198 equilibrium. This suggests no unexpected population stratification and no sampling bias.

199 Table 2 shows the genotype distributions, allele frequencies and associations between genotype
200 at rs211105 polymorphic site and AP incidence. We determined an association between the
201 presence of the T allele at the position rs211105 (OR = 2.47, 95% CI: 0.94-6.50, p = 0.06) of
202 the tryptophan hydroxylase 1 gene under conditions of a decreased AP incidence. We also noted
203 that in AP group in comparison to Control group genotype GG at the position rs211105 is more
204 frequent than GT (OR=2.01, 95%CI: 0.49-8.16, p=0.32) and TT (OR=2.67, 95%CI: 0.67-10.59,
205 p=0.16).

206

207 **3.2. Tryptophan hydroxylase 1 concentration in serum**

208 Average TPH1 concentration in Control group was 12.8 ng/ml (SDE = 0.09), and in AP
209 group 16.5 ng/ml (SDE = 0.41) with statistically significant difference (p<0.0001). Figure 2
210 presents tryptophan hydroxylase 1 concentration according to TPH1 rs211105 (T/G) genotype
211 in both control and AP groups. The highest difference was found between the control and AP
212 groups with GG genotype (12.7 ng/ml, SDE = 1.97). Tryptophan hydroxylase 1 (TPH)
213 concentrations in serum (ng/ml) in correlation to genotype at are presented in Figure 3.

214 Spearman's rank order showed, that in control group with TT and GT genotype at
215 polymorphic site of rs211105 in TPH1 gene, the lowest concentration of TPH was associated
216 with higher serotonin levels (TT: R_s=-0.415, p=0.0018; GT: R_s=-0,457, p=0.0066). In examined
217 group, highest levels of TPH among TT genotype were associated with lower levels of serotonin
218 (TT: R_s=-0.749, p=0.0000), and in GG genotype higher levels of TPH were associated with
219 higher levels of serotonin (GG: R_s=-0.738, p=0.037).

220

4. Discussion

Pancreatic β cells are the main factor regulating glucose and lipid homeostasis by the insulin action. These hormones' production is controlled by nutrients (mainly glucose), the nervous system, and hormones [8]. There are studies showing that pancreatic β cells are also capable of serotonin production, and enzymes required for serotonin synthesis, which includes TPH1 and TPH2 [8, 31, 32].

It has been known that combined genetic, metabolic and environmental, factors contribute to the development and re-occurrence of acute and chronic pancreatitis [33]. To the best of our knowledge, this is the first examination and association of TPH1 gene polymorphism rs211105 and serotonin and tryptophan hydroxylase concentrations in patients diagnosed with acute pancreatitis.

The present study involved 198 individuals: 91 Controls and 107 AP patients. The results of laboratory parameters determined prior to analysis are presented in Table 1. Higher levels than accepted reference points for bilirubin, ALT and AST were determined in the AP patients (1.9 mg/dL, 155.7 IU/L and 155.2 IU/L, respectively). AP patients also had increased amylase activity, significantly higher lipase activity indicating pancreatic dysfunction. Their additional high $p < 0.001$ CRP level demonstrates the ongoing inflammation.

It has been known that serotonin has an important role in the development of experimental colitis pathogenesis, and causes secretion of proinflammatory mediators in immune system. The regulation of 5-HT and 5-TH expressing cells is closely correlated with inflammation the formation of inflammation, which is characteristic in many diseases of the digestive system [7]. In energy metabolism the crucial role play insulin, glucagon, and serotonin, whose concentration is regulated by glucose in the human body [31]. We have shown statistically significant correlation between genotype of TPH gene and levels of serotonin.

The serotonin level in the control group is higher than in the AP group. The TPH level in the control group remains at the levels of 11-14.2 ng/ml, while spread of TPH concentrations in the AP group is much higher. With a lower concentration of TPH in the control, a high concentration of serotonin is still maintained, while in the AP group - despite a high concentration of TPH, serotonin levels are lower (Figure 2).

In AP group, TT genotype was linked to higher TPH concentration and lowest serotonin levels (Rs=-0.75, p=0.0000) in comparison to control group, where TT and GT genotype subgroups had higher serotonin levels despite of low TPH concentrations (TT: R_s=-0.415, p=0.0018; GT: R_s=-0.457, p=0.0066). Only in the AP group of patients with GG genotype, serotonin concentration is on average higher than in the control. It has been known that the intracellular content of serotonin correlates positively with insulin secretion, which is the main factor conditioning normal glycemia [12]. Thus, we anticipate that low level of serotonin in patients with acute pancreatitis could possibly affect the disruption in the synthesis of insulin, which resulted in a pathological glucose concentration. This is an interesting issue because of the simultaneous and significant differences in the content of glucose in both groups ($p > 0.05$), which we have determined. Average glucose concentration in Control group was 85.6 (±12.1) mg/dL, and in AP group 127.4 (±33.9) mg/dL. In our study, serotonin concentration is negatively correlated with TPH1 concentration, which was 12.8 ng/ml (SE = 0.09) in the control group and 16.5 ng/ml (SE = 0.41) in the AP group. Examined group with TT genotype and higher TPH levels were negatively associated with serotonin concentration (in comparison to control (TT: R_s=-0.750, p=0.0000)). TPH is closely related to serotonin synthesis, what has been described by many researchers [7, 34]. The inhibition of serotonin production using a specific inhibitor of TPH1 decreases the severity of trinitrobenzene sulfonic acid-induced colitis in mice, indicating that the enzymatic regulation of HT-5 synthesis may influence on the development of improved the therapeutic strategies in inflammatory disorders [35]. We showed

that despite the high TPH1 concentration in the AP group, the patients had a lower serotonin concentration compared to control (Figure 2). It is suggested that our results are in conflict with the general mechanism that the synthesis of serotonin from tryptophan is enzymatically regulated by tryptophan hydroxylase in a positive correlation. It should be noted, that our research included analysis of concentration TPH 1, and not its activity. Presumably, a high concentration of enzyme is not always correlated with high catalytic activity, which we described in our previous studies on the role of dipeptidyl peptidase-4 (DPPIV; EC 3.4.14.5) in autism spectrum disorders [36].

Our current results determine the relationship between serotonin and TPH-1 levels with genetic factors, including the polymorphism rs211105 in TPH1 gene in healthy and AP patients. We showed that three genotypes (TT, GT and GG) were identified in both groups. Of the total 198 participants, 108 had genotype TT, 79 had GT and 11 had GG. Table 2 shows distribution of genotypes and alleles frequencies. We have determined that genotype GG at the position rs211105 in AP group is more frequent than GT (OR=2.01, 95%CI: 0.49-8.16, p=0.32) and TT (OR=2.67, 95%CI: 0.67-10.59, p=0.16) in comparison to Control group. In the current study, we have also found an association between the presence of the T allele at the position rs211105 (OR = 2.47, 95% CI: 0.94-6.50, p = 0.06) of the tryptophan hydroxylase 1 gene under conditions of a decreased AP incidence. Thus, the difference in both, TPH1 concentration and polymorphism rs211105 in TPH1 gene may indicate the role of this enzyme in the availability of serotonin in human body and the probable impact on the development of diseases associated with glucose metabolism. This issue is highlighted by Katsumata et al. [22], showed that the group of patients with diarrhea predominant irritable bowel syndrome showed a significant correlation between the TPH1 rs211105 T/T genotype and lower scores for role physical and mental health, and higher scores for indigestion and diarrhea. The TT/GT/GG genotypes were: 48/13/1 (0.88 for T and 0.12 for G alleles), and 46/18/0 (0.86 for T and 0.14 for G alleles) for

diarrhea-predominant irritable bowel syndrome patients and controls, respectively. Obtained in our research frequency results are also convergent to Gizatullin et al. [25], who showed the rs211105 frequency of T allele 0.75 (G 0.25) in control group and 0.78 in major depression patients (G 0.22), and Andreou et al. [26] in healthy volunteers – with 0.23 frequency for G allele.

Conclusions

The etiology and the course of AP are still insufficiently examined. Here, the new insight of the potential role of selected genetic factor in pancreatitis development was brought. Not only the metabolic pathway of serotonin, but also factors affecting serotonin synthesis may be interesting and important point in acute pancreatitis.

Declaration section

Ethics approval and consent to participate: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Commission at the University of Warmia and Mazury (no. 13/2016; 51/2019). An informed consent was obtained from all participants. The raw data did not contain any personal identifying information that can be linked to particular individuals, and was anonymised before its use.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author (Anna Cieślińska, e-mail: anna.cieslinska@uwm.edu.pl) on reasonable request.

Competing interests: All authors declare that they don't have any competing financial or non-financial interest.

Funding: This research received no external funding.

Authors' contributions: J.S.: study conception, data collection, drafting, review and editing of the manuscript, funding acquisition. E.F.: data collection, drafting, laboratory testing, review and editing of the manuscript. A.C.: data collection, analysis and interpretation, laboratory testing, drafting, review and editing of the manuscript. ML, D.R., and H.J.S: study conception and design, review and editing of the manuscript. N.K and K.W.: data collection. J.P. and E.K. : study conception and design. All authors read and approved the final manuscript.

Acknowledgements: The authors sincerely thank all the patients who participated in this study.

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Figures

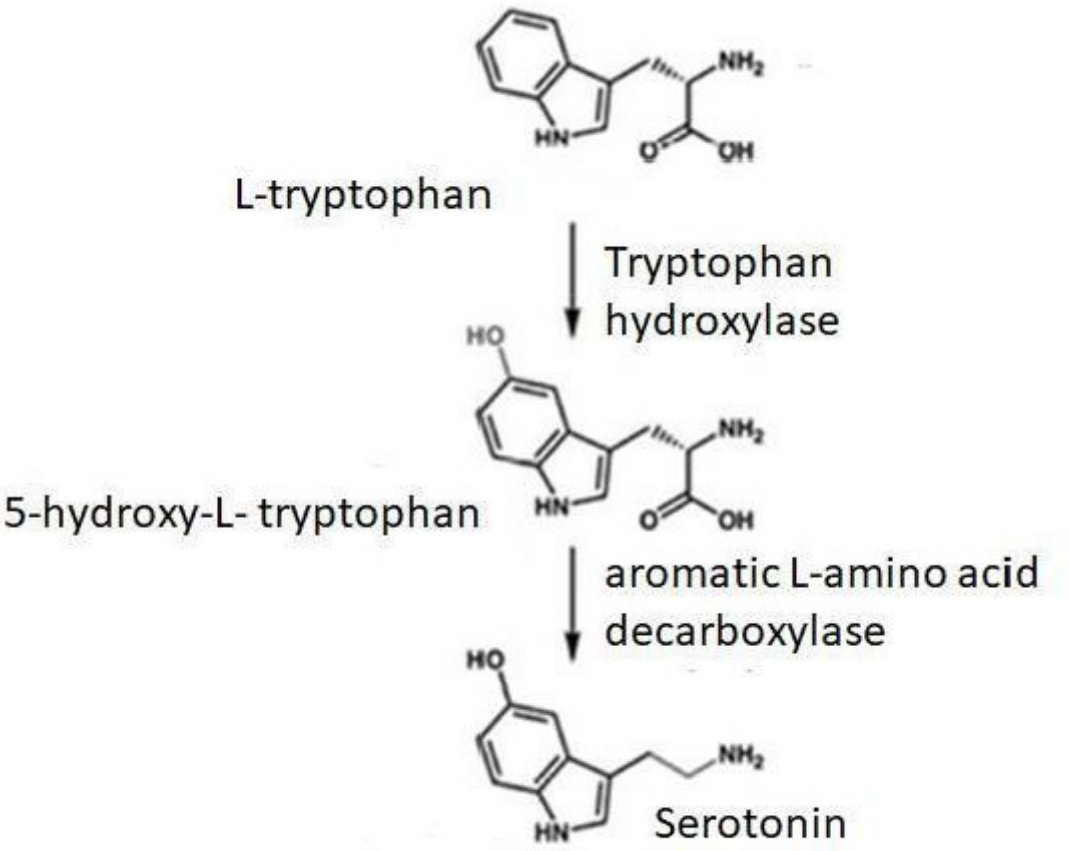

Figure 1

Scheme of serotonin synthesis from L-tryptophane (based on El-Merahbi et al. [8] modified)

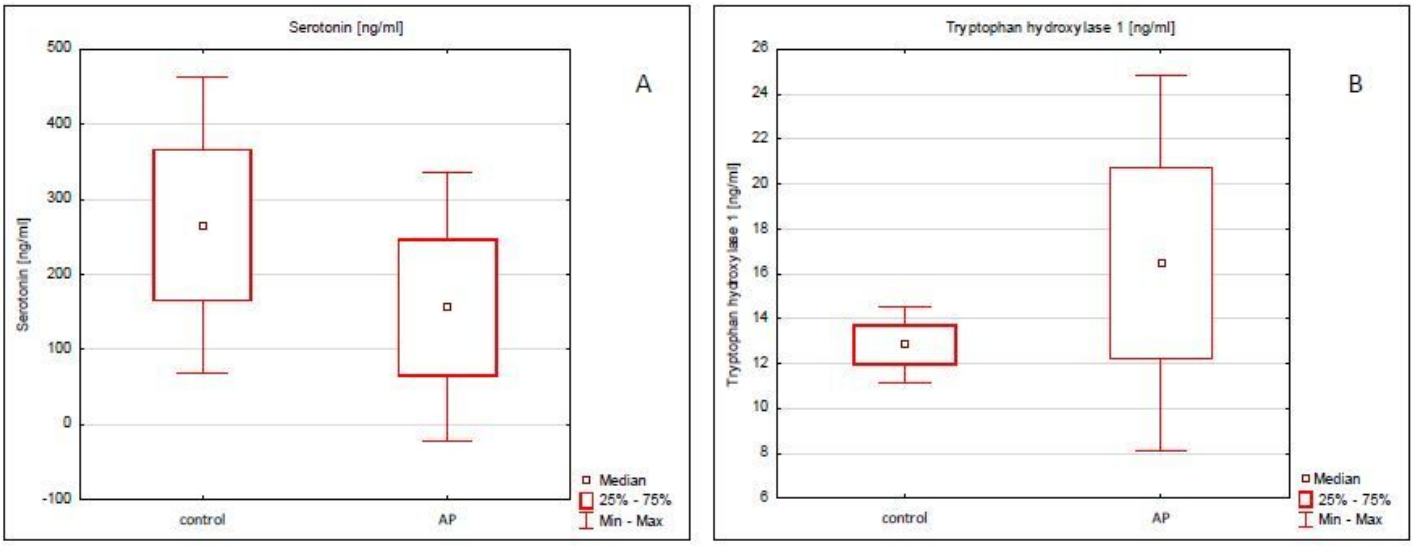

Figure 2

Serotonin (A) and tryptophan hydroxylase 1 (TPH) (B) concentrations in serum (ng/ml) in control and AP groups.

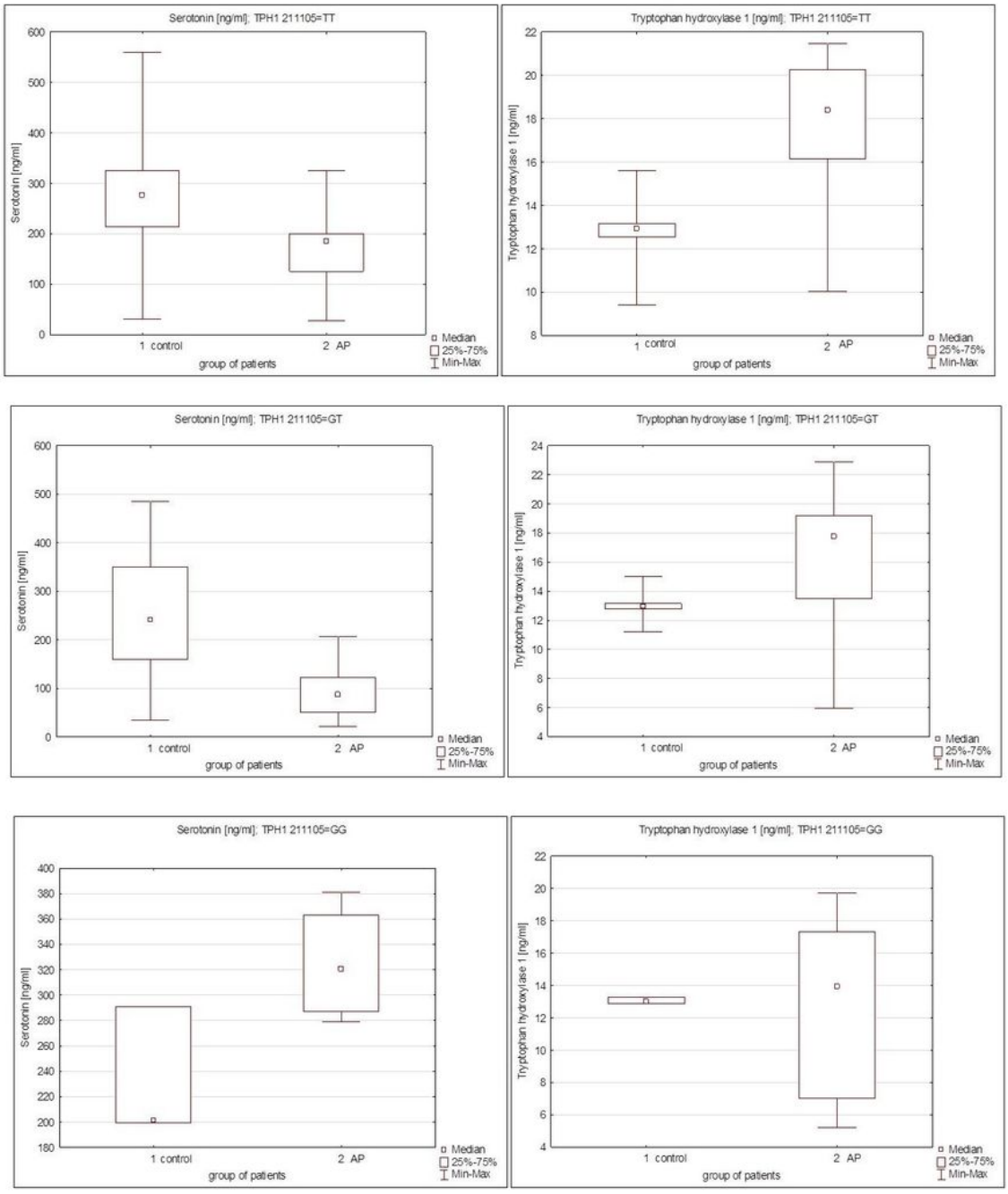

Figure 3

Serotonin and tryptophan hydroxylase 1 (TPH) concentrations in serum (ng/ml) in correlation to TPH rs 211105 TT, GT and GG genotype in control and AP group.