Influence of the interaction between environmental quality and T102C SNP in the HTR2A gene on fibromyalgia susceptibility

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ABSTRACT

Objectives: This study aimed to investigate the genetic influence of the T102C polymorphism of the 2A serotonin receptor gene (HTR2A) and its interaction with environmental aspects, such as exposure to noise, traffic, climate, and opportunities to acquire new information, physical protection, and security, among others, as possible risk factors for developing fibromyalgia syndrome (FMS). **Methods:** Forty-one FMS patients and 49 controls were evaluated. Environmental factors were evaluated by application of the V domain of the WHOQOL-100 questionnaire. Patients were asked that their answers represented only the periods preceding the onset of symptoms. The T102C variant of the HTR2A gene was determined through PCR/RFLP. **Results:** Among patients, the frequency of carriers of the 102C allele was higher than in controls (76.5% vs. 50%; P = 0.028). The scores of the V domain were lower in patients than in controls, indicating a worst perception of the environmental quality by patients (P < 0.001). The factor "lack of opportunities for acquiring new information and skills" increased the chance of developing FMS by almost 14-fold (P = 0.009). The factor "low quality of social care and health" together with the presence of the 102C allele also increased this chance by more than 90-fold (P = 0.005). However, carriers of the same allele who have high quality social care and health are not at a higher risk to develop FMS. **Conclusion:** These data suggest that these factors may predispose to FMS, especially in carriers of the 102C allele. However, studies with larger samples are required to confirm this hypothesis.

Keywords: quality of life, environment, serotonin, genetic polymorphism, fibromyalgia.

INTRODUCTION

Fibromyalgia syndrome (FMS) represents a set of symptoms and signs of idiopathic origin, characterized by long-lasting generalized musculoskeletal pain. In addition, it is significantly related to several other symptoms ranging from irritable bowel syndrome, fatigue, and migraine to cognitive and psychological disorders.[1–3] Considering that FMS can be mistaken for other conditions, because many of its symptoms can be found in other pathologies, the American College of Rheumatology (ACR), in 1990, established criteria to identify FMS, which consider the presence of generalized pain along with the identification of pain upon pressure in at least 11 of 18 specific points, called tender points.[1,4,5]

The etiology of FMS remains uncertain. Some authors have suggested that it can originate from physical traumas,

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surgical interventions, infectious diseases, emotional stress, traumatic events in childhood, psychophysical violence, sexual abuse, abandonment, wars, occupational stress or hyperactive lifestyle.[2,6–11] Genetic factors may also play an important role in pain transmission or modulation, mainly when influenced by environmental and familial stimuli.[12–14]

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that plays a fundamental role in sleep, pain threshold, vascular constriction and dilation, hunger/satiety and libido dynamics, depression, anxiety, and possibly in obsessive-compulsive disorders.[15–17] A possible contribution of 5-HT to the etiology of FMS has been suggested, not only because of the efficacy of the replacement of 5-HT reuptake inhibitors in chronic pain management, but also due to biological findings, such as low levels of 5-HT in patients with idiopathic pain.[18,19] Thus, the possible association of the single nucleotide polymorphism (SNP) with the 5-HT receptor genes has been frequently supported by several researchers studying patients with FMS, among which the 2A serotonin receptor gene (HTR2A) stands out.

As the environment also influences human health, the group known as WHOQOL (World Health Organization Quality of Life) considers that the definition of quality of life should comprise the individual's perception and his/her relationship with the environment. Thus, an instrument was developed to measure quality of life based on 100 questions: the WHOQOL-100 questionnaire,[20] already validated in Brazil by Fleck.[21] However, so far, no study has applied the WHOQOL-100, or its facets separately, aiming at identifying possible environmental factors predisposing to the development of FMS.

In an attempt to correlate the etiology of FMS with a physiological factor, studies have concentrated efforts not only in the components of the serotoninergic system, but also in factors involving genetic predisposition, behavior, and quality of the environment. However, no study on the gene/environment interaction has been carried out so far. Thus, this study aimed at assessing the interaction between the variability of the HTR2A gene and the perception of the effect of environmental quality on susceptibility to FMS.

PATIENTS AND METHODS

Patients

The individuals assessed belong to Novo Hamburgo, state of Rio Grande do Sul, Brazil, characterized by the predominance of the German colonization. The study sample consisted of 41 females of European descent, mean age 47.93 ± 11.21 years, and clinical diagnosis of FMS confirmed on medical examination, according to the ACR criteria.[5] Patients with cognitive deficit and motor disability were excluded from the study.

The control sample consisted of 49 females of European descent, who did not meet the ACR criteria for clinical diagnosis of FMS. All were volunteers and underwent the assessment for clinical symptoms and palpation of the tender points by a physical therapist. Their mean age was 41.48 ± 10.78 years. This research was approved by the Ethics Committee of the Universidade Feevale.

Assessment of quality of life regarding environment

All patients were asked to answer the questions of the V domain of the WHOQOL-100 questionnaire retrospectively, based on the period prior to symptom onset. All individuals in the control group answered the questionnaire about their perception of the environmental quality. However, the group was reminded that the answers should reflect the present time.

The WHOQOL-100 questionnaire was validated in Brazil in 1999[21] and provides a detailed assessment of 25 facets, one of which relates to the overall quality of life. The other 24 facets are distributed into the six following domains: physical health; psychological; level of independence; social relationships; aspects of the environment; and spirituality/religion/personal beliefs. The V domain of the WHOQOL-100 questionnaire relates to environmental issues and comprises 32 questions divided into eight facets as follows: Freedom, physical safety and security; Home environment; Financial resources; Health and social care: accessibility and quality; Opportunities for acquiring new information and skills; Participation in and opportunities for recreation or leisure; Physical environment (pollution, noise, traffic, climate); and Transport. The questions are answered in a Likert-type scale, whose values vary from 0 to 5. The final score of the domain was obtained through the mean of the facets. Scoring was obtained by reverting some questions, when necessary. To compute the scores, we used the syntax files according to the WHO specifications.

Genotyping methods

From all participants, 5 mL of peripheral blood were collected, and DNA was extracted from lymphocytes by using the technique described by Lahiri and Nurnberger.[22] The T102C SNP of the gene of the HTR2A gene (rs6313) was assessed through

PCR-RFLP, described by Warren et al.,[23] by using the enzyme Msp I. The genotypes were determined by separating fragments after agarose gel electrophoresis, staining with ethidium bromide and visualizing under UV. The individuals were classified according to the pattern of bands found: the 102T allele corresponding to a single band of 342 pb; and the 102C allele with two bands of 216 pb and 126 pb. The genotype could be determined in 34 patients and 36 controls.

Statistical methods

The difference in the scores of the V domain of WHOQOL-100 questionnaire between patients and controls was tested using the Mann-Whitney test. To detect the correlation between total score of the V domain of WHOQOL-100 questionnaire and the score of each facet nonparametric Spearman correlation was used. This analysis was performed to detect which facets would contribute most to the total score of the domain. The chi-square test (χ^2) was used to test the difference of the genotype frequencies of HTR2A gene between patients and controls and to test the Hardy-Weinberg equilibrium in both groups, and also in the total sample. The difference in allele frequencies between groups was tested by Fisher exact test, using the InStat program version 3.06. For the χ^2 tests that provided significant results, the residual analysis was performed to determine which groups contributed more strongly to the difference found. That analysis was performed with the WinPepi program version 6.9.

The influence of the interaction between the HTR2A gene and the scores of the V domain of WHOQOL-100 questionnaire on the risk of developing fibromyalgia was tested through multiple logistic regression, in which the independent variables tested were as follows: WHOQOL-100 (scores of the V domain transformed into two categories according to the 50th percentile: high and low scores); SNP in the HTR2A gene (transformed into carriers and non-carriers of the 102C allele); and the variable interaction between both. The modeling method used was the stepwise backward method. The interaction between the HTR2A gene and the scores of the different facets was also tested by inserting eight variables corresponding to the scores of the eight facets, the variant of the HTR2A gene, and all interaction variables, in a total of 17 variables tested initially. The method used was also the stepwise backward, and modeling is shown in Table 1. The Statistical Package for Social Sciences SPSS®, version 16.0, was used for data analysis.

Ethical implications

The present study is in accordance with all ethical principles designated by the Nuremberg Code and Helsinki Declaration, in addition to the Guidelines and Regulatory Norms of the Research Involving Human Beings of the National Health Council (CNS 196/96). Thus, it was approved by the Ethics Committee of the Universidade Feevale (protocol 2.02.02.06.346). Sample collection was only initiated after this approval. All subjects participated voluntarily, received instructions on the development of the study, and provided written informed consent.

RESULTS

Considering the data obtained from the means of all facets of the V domain of the WHOQOL-100 questionnaire of patients and controls, the patients with FMS reported environmental conditions in the period previous to the disease as significantly worse than those in the control group ($P < 0.001$; Figure 1).

Regarding the eight facets of the V domain of the WHOQOL-100 questionnaire, the assessment provided by FMS patients was significantly worse than that provided by controls, except for the first facet, which relates to physical safety and security. Although the patients had physical safety and security indices worse than those of controls, the preoccupation with these factors was common to all sample studied (Figure 2).

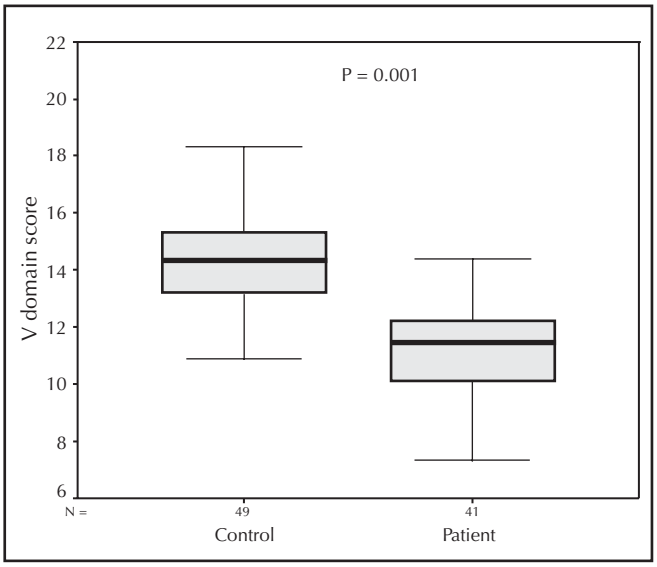

Figure 1
Scores of the V domain of the WHOQOL-100 questionnaire in patients with FMS (11.48 ± 2.15) and controls (14.43 ± 1.96), calculated from the means of all facets.

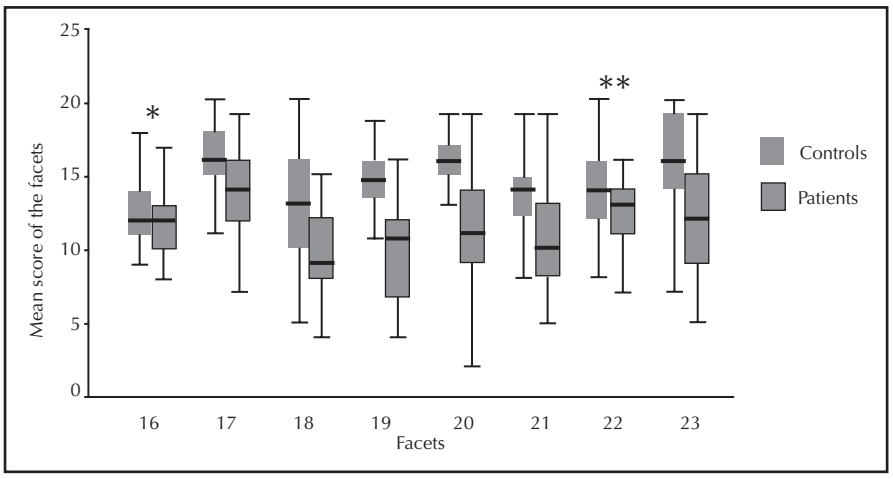

Figure 2
Boxplot of the scores obtained in each facet, comparing patients with FMS and controls.

*P = 0.299; **P = 0.008; others, P = 0.001.

From left to right: facet 16 – Physical safety and security; facet 17 – Home environment; facet 18 – Financial resources; facet 19 – Health and social care: accessibility and quality; facet 20 – Opportunities for acquiring new information and skills; facet 21 – Participation in and opportunities for recreation and leisure; facet 22 – Physical environment; facet 23 – Transport.

Table 1
Multiple logistic regression analysis: modeling through the backward method

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
-2 log probability	24.6	24.6	25.2	28.3	29.2	29.8	30.3	31.4	31.8	32.0	32.8	33.0	33.7	37.2
X^2	55.8	55.8	55.2	52.2	51.3	50.6	50.1	49.0	48.7	48.4	47.6	47.4	46.7	43.2
R^2x100	82.2	82.2	81.6	78.9	78.0	77.4	76.9	75.8	75.5	75.2	74.4	74.2	73.5	69.8
OR														
HTR2A[a]	0.0	0.0	0.0	0.002	0.05	0.13	0.30	0.12	0.16	0.21	0.22	0.19	0.196	0.343
Facet 16	0.076	0.076	0.059	1.72	1.0	1.71	3.67	3.81	3.02	3.32	1.56	VE	VE	VE
Facet 17	201.9	201.9	202.8	10.53	21.4	17.8	11.21	3.44	4.20	4.49	5.66	6.59	5.93	VE
Facet 18	6.0	6.03	6.3	0.07	0.14	0.08	0.10	0.10	0.16	0.26	VE	VE	VE	VE
Facet 19	0.007	0.007	0.003	0.128	0.13	0.17	0.37	0.87	0.88	0.90	0.45	0.37	0.31	0.57
Facet 20	15.6	15.6	67.5	45.5	14.5	13.73	9.8	6.94	5.12	5.08	5.64	5.78	**10.06**	**13.73**
Facet 21	13.4	13.4	11.6	5.21	4.3	6.59	4.99	2.74	2.0	VE	VE	VE	VE	VE
Facet 22	0.59	0.59	0.86	3.38	1.27	4.68	3.56	2.00	VE	VE	VE	VE	VE	VE
Facet 23	1.54	1.54	0.79	3.69	11.06	9.32	7.31	6.62	6.0	4.96	2.34	2.39	VE	VE
HTR2A × Facet 16	6×10^8	5×10^9	$3{,}307 \times 10^3$	66.44	13.6	5.76	VE	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 17	0.0	0.0	0.0	0.006	0.013	0.023	0.069	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 18	0.001	0.0	0.0	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 19	5×10^{10}	5×10^{11}	6×10^8	**11,055.6**	**2,349.9**	**1,462.4**	**478.8**	**288.97**	**220.2**	**214.7**	**306.2**	**345.28**	**547.15**	**261.14**
HTR2A × Facet 20	436.7	4,148.9	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 21	0.002	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 22	19,639.5	185,301.9	144.9	17.0	8.8	VE	VE	VE	VE	VE	VE	VE	VE	VE
HTR2A × Facet 23	3×10^7	2×10^8	319,104.4	31.3	VE	VE	VE	VE	VE	VE	VE	VE	VE	VE

VE: variable excluded from the model.[a] Genotypes were encoded as "0" (genotype TT) and "1" (subjects with the C allele).[b] Scores of the facets were encoded as "0" and "1" according to the 50th percentile of each facet.
OR values in bold are significant ($P < 0.05$).

Table 2
Genotype and allele frequencies of the T102C SNP in the HTR2A gene in the total sample (patients with FMS and controls)

Genotypes	Total sample (n = 70)	Patients (n = 34)	Controls (n = 36)	P
TT	37.1% (26)	23.5% (08)[1]	50.0% (18)	
TC	42.9% (30)	56.0% (19)[1]	30.5% (11)	0.052
CC	20.0% (14)	20.5% (07)	19.4% (07)	
TT	37.1% (26)	23.5% (08)	50% (18)	0.028
C+	62.9% (44)	76.5% (26)	50% (18)	
Alleles[2]				
102T	59.0%	51.5%	65.3 %	0.12
102C	41.0%	48.5%	34.7%	

[1]Residual analysis: P < 0.05.

[2] Fisher's exact test.

The non-parametric Spearman correlation between the total score of the V domain of the WHOQOL-100 questionnaire and the score of each facet and question has shown the following facets as those that had the strongest influence on total score of the V domain of the WHOQOL-100 questionnaire, in all participants: facet 20 – opportunities for acquiring new information and skills (rho = 0.845; P < 0.001); facet 18 – financial resources (rho = 0.828; P < 0.001); and facet 21 – participation in and opportunities for recreation and leisure (rho = 0.782; P < 0.001). Those that have the least influenced were as follows: facet 16 – physical safety and security (rho = 0.642; P < 0.001); and facet 22 – physical environment (rho = 0.490; P < 0.001).

Table 2 shows the allele and genotypic frequencies of the samples investigated by genotyping of the T102C SNP (rs6313) of the serotonin receptor gene HTR2A. The comparison of the genotypic frequencies has shown that homozygosity for the 102T allele is significantly rarer in patients with FMS than in controls (P < 0.05), while heterozygosity is more common in these patients (P < 0.05). In addition, when grouped according to homozygosity or heterozygosity of the allele, those with the 102C allele were more often found among patients with FMS as compared to controls (P = 0.028).

Multiple regression analysis (Table 3) enabled to test the presence of interactions between the scores of the V domain of the WHOQOL questionnaire and polymorphism of the HTR2A gene. One could observe that women with scores lower than 13 in facet 20 ("opportunities for acquiring new information and skills") have 13.7-fold more chance of developing FMS than those with scores greater than that value (P = 0.009). In addition, a significant interaction was detected between the genetic variant and scores of facet 19 ("health and social care: accessibility and quality") (P = 0.005), showing that the influence of polymorphism is much stronger in women with lower scores in facet 19.

That interaction was interpreted by using logistic regression parameters (Table 3) and regression equation, and the calculations yielded an OR of 90.02 for those women, who, in addition to having the 102C allele, also have low scores in facet 19. On the other hand, in the group of the same genotype, but with higher values in facet 19, the OR calculated was 0.34, indicating protection for women with the risk genotype who score high for facet 19.

Table 3
Multiple logistic regression assessing the joint influences on FMS

	OR (95% CI)	P	Beta
HTR2A[1]	0.34 (0.037–3.21)	0.35	-1.07
Facet 19[2] – Health and social care: accessibility and quality	0.57 (0.05–6.14)	0.65	-0.56
Facet 20[3] – Opportunities for acquiring new information and skills	**13.7 (1.92–97.9)**	**0.009**	**2.62**
Facet 19 × HTR2A	**261.14 (5.24–13,021.5)**	**0.005**	5.57
Interpretation of the interaction facet 19 × HTR2A		**Beta calculated**	**OR calculated**
Subjects with the 102C allele **(beta HTR2A = 1)** and LOW scores in facet 19 **(beta HTR2A × facet 19 = 1)** = (-1.07) + 5.57		**4.5**	**90.02**
Subjects with the 102C allele **(beta HTR2A = 1)** and HIGH scores in facet 19 **(beta HTR2A × facet 19 = 0)** = -1.07		**-1.07**	**0.34**

[1]Encoded as 0 (genotype TT) and 1 (subjects with the C allele).

[2]Encoded according to the 50th percentile as 0 (scores greater than 12) and 1 (scores lower than 12).

[3]Encoded according to the 50th percentile as 0 (scores greater than 13) and 1 (scores lower than 13).

DISCUSSION

Quality of life assessment has gained importance as a measure to analyze the results of medical treatments.[21] In fact, patients with FMS experiment low quality of life as compared with the general population, because the FMS has a negative impact on patients' quality of life, involving personal, familial and social aspects, and strongly correlating with pain intensity, fatigue and decreased functional capacity. Burckhardt et al.[24] have assessed the quality of life of women with FMS and have compared their data with those of women with rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, insulin-dependent diabetes, and healthy controls. Their results have shown that patients with FMS have the lowest quality of life indices. Other studies of patients with FMS have shown that pain is the worst aspect related to the low quality of life reported by patients.[25–27]

Such studies have aimed only at assessing how much the disease and its treatment influence the quality of life of patients, associating the results with clinical aspects or comparing them with healthy individuals or patients with other diseases. All these approaches have concluded that the use of the WHOQOL-100 questionnaire as an instrument for clinical follow-up is very interesting to assess symptoms. To date, however, there is no record of the use of that questionnaire as a tool to assess predisposing factors. In other words, there is no record of the use of that questionnaire as a means of answering how quality of life could influence the development of FMS and/or its symptoms, as shown in this study. Aiming at assessing which environmental factors could influence the development of symptoms in patients with FMS, the V domain of the WHOQOL-100 questionnaire, which relates to questions about the environment and the individual's perception about the surrounding world, was used.

Financial problems, few opportunities for recreation, leisure and acquisition of new information were the factors that most influenced the questionnaire score among patients with FMS, even before developing the syndrome. This observation results from both the statistically significant difference between patients with FMS and controls and the correlation of the questions with the total score of the V domain of the WHOQOL-100 questionnaire. Likewise, Valeikiene et al.[28] have reported a correlation in facet 21 ("participation in and opportunities for recreation and leisure") between patients with Parkinson's disease and osteoarthritis. Thus, these results have suggested that individual preoccupations with financial difficulties and mainly the lack of leisure activities and learning opportunities can be factors related to the development of chronic syndromes such as FMS. Unfortunately, only the influence of each facet separately can be compared, since no other study published so far has assessed the relationship between each facet of the V domain and any pathology.

In India, Khanna et al.,[29] by use of the WHOQOL-100 questionnaire, have reported that physical and psychological factors are seriously compromised in patients with systemic lupus erythematosus (SLE). However, the domains related to social and environmental factors did not significantly correlate with the active status of the disease in patients with SLE. Comparatively, the mean score of the V domain of the WHOQOL-100 questionnaire of patients with FMS was 11.48 ± 2.15, while that of patients with SLE was greater (14.1), apparently showing a higher influence of environment on the FMS. Van Houdenhove et al.[30] have suggested that a hyperactive lifestyle might be one of the factors making people more vulnerable to the development of FMS, also contributing to the disease onset and perpetuation. These authors have explained that individuals with a more active lifestyle are at a higher risk of physical overload through neglecting attitudes involving musculoskeletal wear and tear and sleep deprivation. Certain characteristics of personality, such as obsessive-compulsive disorders, perfectionism, excessive work and tendency towards self-sacrifice, seem related to that hyperactive lifestyle. Thus, our findings along with some studies published on the issue seem to indicate that a low environmental quality influences the development of FMS.

In addition to the environmental influence, another subjacent mechanism of FMS is its relation to disorders in the 5-HT transmission and metabolism. This hypothesis is based on studies showing that 5-HT levels are decreased in patients with FMS as compared to controls. Furthermore, low 5-HT levels have been inversely correlated with clinical measures of pain perception.[17,31] Serotonin plays an important role in several neuropsychiatric disorders through the regulation of serotoninergic pathways, influencing the pain threshold by means of interaction with P substance, potentiating the endogenous effects of endorphin. Low 5-HT levels decrease pain thresholds, allowing more pain to be felt in the central nervous system and disrupting the repairing process of deep sleep,[17,32] characteristics commonly found in patients with FMS. In addition, many authors have suggested that genetic factors might be involved in the etiology of FMS.[33–35] Such studies, however, are few and conflicting, but, due to the physiological questions involved, 5-HT-related genes are good candidates to research.

Gürsoy et al.[33] have managed to relate the 102TT genotype of the HTR2A gene to psychiatric symptoms of FMS, but not to the syndrome itself, in a population in Turkey.

Tander et al.[34] have also found no significant differences between Turkish patients and healthy individuals regarding this variant. On the other hand, Bondy et al.[35] have detected a decreased genotypic frequency of 102TT homozygosity and increased 102C allele frequency in patients of German origin with FMS, a population whose ethnical composition is similar to that of the present study, and for which the risk allele for FMS would be the same detected in our findings. However, in that German population investigation, pain severity was significantly greater in the 102TT genotype of the T102C SNP of the HTR2A receptor gene in patients with FMS, as compared to controls.[35] The only study developed in Brazil has assessed a population of the central region of the country and has detected no significant relationship of this SNP with fibromyalgia. Because multiple interactions of several systems and neurotransmission pathways might be involved in the process of susceptibility to fibromyalgia, in addition to polygenic interactions and influence of environmental factors,[36] this type of analysis should be performed in each population of different ethnicity.

The T102C polymorphism alters neither the expression nor the structure of the HTR2A receptor, meaning that its involvement with FMS is indirect. A binding unbalance might exist with the true functional variant, which might be part of the promoter region or other regulatory regions of the gene. Recent evidence has shown that the total levels of both mRNA of the HTR2A gene and receptors are lower in healthy individuals with the 102CC genotype than in those with the 102TT genotype.[16,37] Data on the risk related to FMS and its different psychiatric manifestations and symptoms of pain are controversial, thus further investigation is necessary to confirm the association of the 102C allele with FMS found in the present study for the southern Brazilian population, and also to assess whether that relation exists in different population groups.

Considering the multifactorial etiology of the FMS, the influences investigated in the present study might interact with each other. Data derived from the multivariate analyses (Table 3) allowed the recognition that the low scores in facet 19 ("health and social care: accessibility and quality") increase the chances of developing FMS, especially when interacting with the gene investigated. Thus, in the sample studied, individuals with the 102C allele of the HTR2A gene and whose scores in facet 19 are also low have the highest chances of developing the pathology; these values range from 90- to almost 150-fold more chance of developing FMS, according to the genotype of the HTR2A gene. However, if only one of these variables is altered, i.e., presence of the 102TT genotype for this gene, or if there is not much preoccupation with these factors, protection is granted.

However, the data relating to the period prior to the development of the pathology can be influenced by the subjective evaluation of each individual studied and might not represent the true environmental status of the subject in the period. According to some specialists, there is the hypothesis that patients who have non-objective diseases, such as FMS, can idealize their pre-morbid lifestyle as compared with the current.[30] However, if that was the case, one might expected that the patients would have increased scores in the V domain of the WHOQOL questionnaire. In that same context, other comorbidities, such as depression, might be influencing the results. Among patients with FMS, depressive disorders are the most frequent psychiatric comorbidities, reaching prevalence from 20% to 80%. Thus, patients with higher scores of depression might consider their environment worse than reality, leading to a reduction in these scores. Since the HTR2A gene might also be related to depression in these patients, it might be an explanation for the interaction detected.

Unfortunately, to date, this type of interaction regarding FMS has not been tested in the worldwide literature, and, thus, cannot be compared to our data. However, it should be clear that the present study has a large limitation, which is the small sample size. This is noticed especially when assessing the magnitude of the confidence intervals of these OR (Table 3). Thus, although our data should not be neglected because of this limitation, they should only serve as the basis for a hypothesis of interaction between gene and environment, which should be further tested.

Finally, it is suggested that FMS gathers a set of characteristics that reflect a diversity of causes. Because of the high frequency of aggregation to psychiatric disorders, the pathways leading to pain exacerbation in FMS can involve aspects both psychological and physiological. In addition, it should be considered that environmental and behavioral factors, as well as genetic predisposition, might play very significant roles in the onset of the symptoms of the FMS. Similarly to that which occurs with any multifactorial characteristic, the T102C SNP in the HTR2A receptor gene may have a small effect on the metabolism of 5-HT, when assessed in isolation, suggesting that other genes might also be involved in the etiopathogenesis of the FMS. New studies on this issue should create perspectives for the better understanding of the promotion and perpetuation mechanisms of the FMS. These challenges represent a key element for better understanding this complex syndrome, and can serve as a basis for prevention and better therapeutic management of pain in these patients.

REFERENCES

REFERÊNCIAS

1. Chakrabarty S, Zoorob R. Fibromyalgia. Am Fam Physician 2007; 76(2):247–54.
2. Fietta P, Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. Acta Biomed 2007; 78(2):88–95.
3. Ablin JN, Cohen H, Buskila D. Mechanisms of disease: genetics of fibromyalgia. Nat Clin Pract Rheumatol 2006; 2(12):671–8.
4. Silva LC, Abreu AC, Pelegrino RS, Coelho OS. O valor da contagem de pontos dolorosos no diagnóstico clínico da fibromialgia. Rev Bras Reumatol 1997; 37(6):317–22.
5. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 33(2):160–72.
6. Ribeiro LS, Coelho AM, Pádua AFM, Dias LL, Azevedo DC, Moura FM *et al*. Fibromyalgia and hepatitis C virus chronic infection: lack of association in two samples. Rev Bras Reumatol 2007; 47(2):97–105.
7. Ribeiro LS, Proietti FA. Fibromyalgia and infectious stress: possible associations between fibromyalgia syndrome and chronic viral infections. Rev Bras Reumatol 2005; 45(1):20–9.
8. Ferucci E, Collier DH. Fibromyalgia: diagnosis and treatment. Prim Care Case Rev 2002; 5(3):101–8.
9. Mehendale AW, Goldman MP. Fibromyalgia syndrome, idiopathic widespread persistent pain or syndrome of myalgic encephalomyelopathy (SME): what is its nature? Pain Pract 2002; 2(1):35–46.
10. Staud R, Domingo M. Evidence for abnormal pain processing in fibromyalgia syndrome. Pain Med 2001; 2(3):208–15.
11. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury: a controlled study of 161 cases of traumatic injury. Arthritis Rheum 1997; 40(3):446–52.
12. Lee YH, Choi SJ, Ji JD, Song GG. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. Rheumatol Int 2010; 11:10–9.
13. Buskila D. Genetics of chronic pain states. Best Pract Res Clin Rheumatol 2007; 21(3):535–47.
14. Souza EJR, Nogueira-Machado JA, Silva FCL, Chaves MM, Costa DC. Avaliação da produção de espécies reativas de oxigênio por granulócitos de sangue periférico de pacientes com fibromialgia primária. Rev Bras Reumatol 2003; 43(6):337–42.
15. Giordano J, Schultea T. Serotonin 5-HT(3) receptor mediation of pain and anti-nociception: implications for clinical therapeutics. Pain Physician 2004; 7(1):141–7.
16. Sanders-Bush E, Fentress H, Hazelwood L. Serotonin 5-HT2 receptors: molecular and genomic diversity. Mol Interv 2003; 3(6):319–30.
17. Juhl JH. Fibromyalgia and the serotonin pathway. Altern Med Rev 1998; 3(5):367–75.
18. Wolfe F, Russell IJ, Vipraio G, Ross K, Anderson J. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. J Rheumatol 1997; 24(3):555–9.
19. Russell IJ. Neurohormonal aspects of fibromyalgia syndrome. Rheum Dis Clinics North Am 1989; 15(1):149–68.
20. The WHOQOL Group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995; 41(10):1403–9.
21. Fleck MPA. The World Health Organization instrument to evaluate quality of life (WHOQOL-100): characteristics and perspectives. Ciênc Saúde Coletiva 2000; 5(1):33–8.
22. Lahiri DK, Nurnberger JI Jr. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 1991; 19(19):5444.
23. Warren JT Jr, Peacock ML, Rodriguez LC, Fink JK. A MspI polymorphism in the hyman serotonin receptor gene (HTR2): detection by DGGE and RFLP analysis. Hum Mol Genet 1993; 2(3):338.
24. Burckhardt CS, Clark SR, Bennett RM. Fibromyalgia and quality of life: a comparative analysis. J Rheumatol 1993; 20(3):475–9.
25. Becker RM, Silva VK, Machado FS, Santos AF, Meireles DC, Mergener M *et al*. Interação entre qualidade do meio ambiente, estresse e a variação do gene APOE na determinação da suscetibilidade à fibromialgia. Rev Bras Reumatol 2010; 50(6):617–30.
26. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health Qual Life Outcomes 2008; 6:8.
27. Pagano T, Matsutani LA, Ferreira EA, Marques AP, Pereira CA. Assessment of anxiety and quality of life in fibromyalgia patients. São Paulo Med J 2004; 122(6):252–8.
28. Valeikiene V, Ceremnych J, Alekna V, Juozulynas A. Differences in WHOQOL-100 domain scores in Parkinson's disease and osteoarthritis. Med Sci Monit 2008; 14(4):CR221–7.

29. Khanna S, Pal H, Pandey RM, Handa R. The relationship between disease activity and quality of life in systemic lupus erythematosus. Rheumatology (Oxford) 2004; 43(12):1536–40.
30. van Houdenhove B, Neerinckx E, Onghena P, Lysens R, Vertommen H. Premorbid "overactive" lifestyle in chronic fatigue syndrome and fibromyalgia. An etiological factor or proof of good citizenship? J Psychosom Res 2001;51(4):571–6.
31. Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Krüger M, Schoeps P *et al*. Possible association of fibromyalgia with a polymorphism in serotonin transporter gene regulatory region. Arthritis Rheum 1999; 42(11):2482–8.
32. Graeff FG. Serotonergic systems. Psychiatr Clin North Am 1997; 20(4):723–39.
33. Gürsoy S, Erdal E, Herken H, Madenci E, Alaşehirli B. Association of T102C polymorphism of the 5-HT2A receptor gene with psychiatric status in fibromyalgia syndrome. Rheumatol Int 2001; 21(2):58–61.
34. Tander B, Gunes S, Boke O, Alayli G, Kara N, Bagci H *et al*. Polymorphisms of the serotonin-2A receptor and catecol-O-methyltransferase genes: a study on fibromyalgia susceptibility. Rheumatol Int 2008; 28(7):685–91.
35. Bondy B, Spaeth M, Offenbaecher M, Glatzeder K, Stratz T, Schwarz M *et al*. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. Neurobiol Dis 1999; 6(5):433–9.
36. Matsuda JB, Barbosa FR, Morel LJ, França SDEC, Zingaretti SM, da Silva LM *et al*. Serotonin receptor (5-HT 2A) and catechol-O-methyltransferase (COMT) gene polymorphisms: triggers of fibromyalgia? Rev Bras Reumatol 2010; 50(2):141–9.
37. Lane HY, Liu YC, Huang CL, Hsieh CL, Chang YL, Chang L *et al*. Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. J Psychiatry Neurosci 2008; 33(1):47–53.