Rheumatol Int (2012) 32:417–426
DOI 10.1007/s00296-010-1678-9

ORIGINAL ARTICLE

Candidate gene studies of fibromyalgia: a systematic review and meta-analysis

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Received: 24 June 2010 / Accepted: 14 November 2010 / Published online: 1 December 2010

Abstract The aim of this study was to explore whether the candidate gene polymorphisms contribute to fibromyalgia susceptibility. The authors conducted a meta-analysis on associations between serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) S/L allele, catechol-O-methltransferase (COMT) val158Met, and serotonin 2A (5-HT2A) receptor 102T/C polymorphisms and fibromyalgia susceptibility as determined using the following: (1) allele contrast, (2) recessive, (3) dominant models, and (4) contrast of homozygotes. We also performed a systematic review with available data of the candidate genes. A total of 21 separate comparisons were considered in this systematic review and meta-analysis. Seventeen candidate genes and over 35 different polymorphisms were identified in studies on fibromyalgia susceptibility. Meta-analysis of the 5-HTTLPR S/L allele and COMT val158Met failed to reveal any association with fibromyalgia. However, meta-analysis of the C allele, CC + CT genotype, and CC versus TT genotype of the 5-HT2A receptor 102T/C polymorphism showed significant association with fibromyalgia. The overall OR of the association between the C allele and fibromyalgia was 1.333 (95% CI = 1.053–1.688, $P = 0.017$). The ORs for the CC + CT genotype, and CC versus TT genotype showed the same pattern as that observed for the C allele (OR = 1.541, 95% CI = 1.032–2.303, $P = 0.035$; OR = 1.838, 95% CI = 1.151–2.936, $P = 0.011$). This meta-analysis demonstrates that the 5-HT2A receptor 102T/C polymorphism confers susceptibility to fibromyalgia. In contrast, no association was found between the 5-HTTLPR S/L allele, COMT val158Met, and susceptibility to fibromyalgia.

Keywords Candidate gene · Polymorphism · Fibromyalgia · Meta-analysis

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Introduction

Fibromyalgia is a chronic, generalized pain condition, defined by widespread musculoskeletal pain for more than 3 months and the presence of ≥11 tender point [1]. Fibromyalgia is characterized by persistent widespread pain, fatigue, and sleep disturbance, and often accompanied by a variety of associated symptoms such as irritable bowel syndrome, headache, and mood disorders [2]. Fibromyalgia is considered a disorder of pain regulation and the result of a central nervous system malfunction that causes amplification of pain transmission and interpretation [3]. Although the etiology of fibromyalgia remains unclear, it is believed that genetic and environmental factors may play significant roles in the development of fibromyalgia [4]. Significant familial aggregation, convincing demonstrations of genetic linkages and associations demonstrate an underlying genetic basis for fibromyalgia [5]. Many studies have examined the potential contribution of the candidate gene polymorphisms to fibromyalgia susceptibility, but these studies have produced diverse results [6–23].

Serotonin (5-hydroxytrptamine, 5-HT) is a key neurotransmitter in the central nervous system. The serotonin transporter (5-HTT) gene has been reported to be involved in the pathogenesis of major psychiatric disorders, including anxiety, depression, schizophrenia, and autism

[24]. A 44-bp insertion or deletion in the 5'-flanking promoter region of HTT (5-HTT gene-linked polymorphic region of 5-HTTLPR) creates a short (S) and a long (L) allele. The S and L alleles have 14 and 16 repeat elements, respectively [25]. The short variant designated 'S' is associated with reduced transcriptional efficiency of the 5-HTT gene promoter, resulting in lowered 5-HT reuptake activity compared to the long form (L) variant. The effect of serotonin is mediated by different 5-HT receptor subtypes [26, 27]. The 5-HT2A receptor is located in cortex, caudate nucleus, and all the intestines [28], and it may play a role in the etiology of several neuropsychiatric diseases and pain perception [24]. A silent polymorphism in the 5-HT2A receptor gene is defined by a T to C transition at position 102 [23]. Although the 5-HT2A 102T/C polymorphism does not result in alteration of the amino acid sequence of the protein, a strong association was found between the 102T/C polymorphism and psychiatric illness such as mood disorder and schizophrenia [29]. Catecholamines (norephinephrine, epinephrine, and dopamine) are the sympathetic neurotransmitters. Catechol-O-methyltransferase (COMT) is the major catecholamine-degrading enzyme. COMT has been implicated in the modulation of pain [30]. COMT val158-Met is a single nucleotide polymorphism (SNP), which consists of a G→A transition at codon 158, the results of which is an amino acid change. Val/Val, Val/Met, and Met/Met genotypes are associated with high, intermediate, and low activity of the enzyme, respectively [31].

Individual studies based on small sample sizes have insufficient statistical power to detect positive associations and are incapable of demonstrating the absence of an association. Furthermore, the low statistical powers of individual studies could explain contradictory results. Meta-analysis integrates previous research, and increases statistical power and resolution by pooling the results of independent analyzes [32]. In the present study, we explored whether the candidate gene polymorphisms contribute to fibromyalgia susceptibility by applying a meta-analysis approach and by systematically reviewing available data.

Methods

Identification of eligible studies and data extraction

We performed a search for studies that examined associations between candidate gene polymorphisms and fibromyalgia. MEDLINE citation was used to identify articles in which candidate gene polymorphisms were analyzed in patients with fibromyalgia. Combinations of keywords, such as, 'polymorphism' and 'fibromyalgia' were entered as both Medical Subject Headings (MeSH) and as text words. References in these identified studies were also investigated to identify additional studies not indexed by MEDLINE. Genetic association studies that determined the distributions of the candidate gene polymorphisms in fibromyalgia cases and controls were eligible for inclusion. The study inclusion criteria were the following: (1) published before March 2010; (2) the inclusion of original data; and (3) the provision of enough data to calculate odds ratios (ORs). When a study reported results on different populations, we treated the results obtained separately during the meta-analysis.

The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, number of cases, and controls for the polymorphisms. Allele frequencies were calculated from genotype distributions.

Evaluation of publication bias

Funnel plots are often used to detect publication bias. However, it is a limitation of funnel plotting that a large range of studies with varying sizes and subjective judgments, are required. It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was small. Hence, we evaluated publication bias using Egger's linear regression test [33], which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Evaluations of statistical associations

We performed meta-analyzes using the following: (1) allelic contrast and (2) homozygote contrast, (3) recessive, and (4) dominant models. Point estimates of risks, ORs, and 95% confidence intervals (CI) were calculated for each study. We also assessed within- and between-study variations or heterogeneities using Cochran's Q-statistics, a heterogeneity test that assesses the null hypothesis that, all studies were evaluating the same effect. In addition, we quantified the effect of heterogeneity using I^2 values. I^2 ranges between 0 and 100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than chance [34]. I^2 values of 25, 50, and 75% are referred to as low, moderate, and high estimates. Fixed effects assume that the genetic factors have similar effects on fibromyalgia susceptibility across all investigated studies, and that observed variations between studies are caused by chance alone [32]. The random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [35]. If study groups show no heterogeneity, the fixed and random effects models produce similar results, and if not, the random effects model usually produces wider CIs than the fixed effects model. The random effects model

is used in the presence of significant between-study heterogeneity. Statistical manipulations were undertaken using a Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Results

Studies included in the meta-analysis

Thirty-three studies were identified by electronic or manual searching, and twenty-two were selected for a full-text review based on title and abstract details [5–23, 36–38]. Four studies were excluded because they were reviews [5, 36, 37] or because they did not concern fibromyalgia [38]. Thus, eighteen studies met the inclusion criteria [6–23]. Of these, three studies contained data on two different groups [7, 12, 20]. In the present study, we analyzed these groups independently. Therefore, a total of 21 separate comparisons were considered in this systematic review and meta-analysis. Relevant features of the studies included in the systematic review and meta-analysis are provided in Table 1. Seventeen candidate genes and over 35 different polymorphisms were identified in studies for fibromyalgia susceptibility (Table 2). Candidate gene studies in fibromyalgia encompass 5 5-HTTLPR S/L allele, 5 COMT val158Met, and 3 5-HT2A receptor 102T/C polymorphisms (Table 1). All studies of three polymorphisms showed the genotype and allele frequencies of the polymorphisms except for Cohen et al.'s study giving only allele data [20]. There was one study for adrenergic receptor A1A (ADRA1A) [7], adrenergic receptor B2 (ADRB2) [7], adrenergic receptor B3 (ADRB3) [7], dopamine-D_3-receptor (DRD3) [8], dopamine-D_4-receptor (DRD4) [17], dopamine transporter (DAT) [10], 5-HT2A receptor (rs6311) [11], COMT (rs6269, rs4633, rs4818, rs4680, rs20907, and rs16559) [12], monoamine oxidase-A (MAO-A) [promoter variable number tandem repeat (VNTR), 941G/T] [13], monoamine oxidase-B (MAO-B) [13], endothelial nitric oxide synthase (eNOS) [14], tachykinin NK1 (substance P) receptor (TACR1) [10], alpha-1 antitrypsin (AAT) [10], interleukin-4 (IL-4) [15], 5-HTTLPR (intron2 VNTR) [19], 5-HT receptor 3A, and 3B (HTR3A and 3B) (some SNPs) [16], respectively (Tables 1, 2). We performed a meta-analysis on the association of the polymorphisms with fibromyalgia if there were at least two comparisons.

Meta-analysis of the association between the 5-HTTLPR, COMT, and 5-HT2A receptor polymorphism and fibromyalgia

The summary of meta-analysis for the candidate gene polymorphisms with fibromyalgia is shown in Table 3. Meta-analysis was performed for the 5-HTTLPR S/L allele [6, 19, 20, 22], COMT val158Met [8, 9, 11, 12], and 5-HT2A receptor 102T/C polymorphisms [11, 21, 23]. Meta-analysis of the SS genotype (recessive effect), SS and SL genotype (dominant effect), SS versus LL genotype, and S allele of 5-the HTTLPR revealed no association with fibromyalgia (Fig. 1). And meta-analysis of the MM genotype, the MM and MV genotypes, the MM versus the VV genotype, and of the M allele of the COMT failed to reveal any association with fibromyalgia.

In contrast, meta-analysis of the C allele, CC + CT genotype, and CC versus TT genotype of the 5-HT2A receptor 102T/C polymorphism showed significant association with fibromyalgia (Figs. 1, 2). The overall OR of the association between the C allele and fibromyalgia was 1.333 (95% CI = 1.053–1.688, $P = 0.017$). The ORs for the CC + CT genotype, and CC versus TT genotype showed the same pattern as that observed for the C allele (OR = 1.541, 95% CI = 1.032–2.303, $P = 0.035$; OR = 1.838, 95% CI = 1.151–2.936, $P = 0.011$). Meta-analysis of the CC versus CT + TT genotype also showed the same trend as that shown by the 5-HT2A receptor 102T/C polymorphism C allele (OR = 1.380, 95% CI = 0.961–1.981, $P = 0.081$).

Candidate gene studies involved in the susceptibility to fibromyalgia

Among the candidate gene studies of the fibromyalgia except for 5-HTTLPR S/L allele, COMT val158Met, and 5-HT2A receptor 102T/C polymorphisms, the ADRB2 AC haplotype ($P = 0.04$), ADRB2 AC haplotype ($P = 0.05$), ADRA1A rs1383914 ($P = 0.01$), COMT rs4818 ($P = 0.001$), DRD4 exon3 VNTR ($P = 0.034$), and MAO-A allele3 ($P = 0.033$) showed a significant association with fibromyalgia. However, other gene polymorphisms such as ADRB3, DRD3, DAT, 5-HT2A receptor (rs6311), COMT (rs6269, rs4633, rs4818, rs4680, rs20907, and rs16559), MAO-B, eNOS, TACR1, AAT, IL-4, 5-HTTLPR (intron2 VNTR), HTR3A, and 3B (some SNPs) did not reveal any association with fibromyalgia susceptibility.

Heterogeneity and publication bias

There was no between-study heterogeneity during the meta-analyzes of the 5-HT2A receptor polymorphisms. Some heterogeneity was found in the meta-analyzes of the C versus T allele of the COMT and the SS versus SL + LL of the 5-HTTLPR. Egger's regression test showed no evidence of publication bias in this meta-analysis of the polymorphisms (Egger's regression test P values >0.1). The distributions of the genotypes in normal control groups were consistent with the H–W equilibrium, except for the studies by Tander et al. [11] and Cohen-2 et al. [20]

Table 1 Characteristics of individual studies included in the systematic review and meta-analysis

Studies (Ref)	Country/ Ethnicity	Numbers		Studied polymorphisms	Findings (SNP associated with FM)
		FM	Control		
Potvin et al. 2010 [6]	Canada	48	50	5-HTTLPR S/L allele	NS
Vargas-Alarcon-1 et al. 2009 [7]	Mexican	78	48	ADRA1A (rs574584, rs138914, rs1048191, rs573542), ADRB2 (rs1042713, rs1042714), ADRB3 (rs4994)	ADRB2 AC haplotype ($P = 0.04$)
Vargas-Alarcon-2 et al. 2009 [7]	Spanish	78	71	Same as above	ADRB2 AC haplotype ($P = 0.05$) ADRA1A rs1383914 ($P = 0.01$)
Potvin et al. 2009 [8]	Canada	37	36	DRD3 Ser9Gly, COMT rs4680	NS
Cohen et al. 2009 [9]	Israel	209	152	COMT val158Met (rs4680)	$P = 0.004$
Ablin et al. 2009 [10]	Israel	87	200	TACR1 1354G/C, DAT VNTR, AAT glutamic acidlysine E342 K mutation	NS
Tander et al. 2008 [11]	Turkey	80	91	5-HT2A receptor rs6311, rs6313 (102T/C), COMT rs4680	NS
Vargas-Alarcon-1 et al. 2007 [12]	Mexican	57	33	COMT rs6269, rs4633, rs4818, rs4680, rs20907, rs16559	Rs4818 ($P = 0.001$), rs4680 ($P = 0.023$)
Vargas-Alarcon-2 et al. 2007 [12]	Spanish	78	80	Same as above	NS
Gursoy et al. 2008 [13]	Turkey	107	90	MAO-A promoter VNTR, MAO-B intron13 G/A	MAO-A allele3 ($P = 0.033$)
Alasehirli et al. 2007 [14]	Turkey	96	79	eNOS Glue298Asp (G894T)	NS
Su et al. 2007 [15]	Taiwan	62	100	MAO-A 941G/T, IL-4 intron3 VNTR	NS
Frank et al. 2004 [16]	Germany	96	312	HTR3A, HTR3B; some SNPs	NS
Buskila et al. 2004 [17]	Israel	81	458	DRD4 exon3 VNTR	DRD 7 repeat ($P = 0.034$)
Gursoy et al. 2003 [18]	Turkey	61	61	COMT rs4680	LL + LH ($P = 0.024$)
Gursoy 2002 [19]	Turkey	53	60	5-HTTLPR S/L, intron2 VNTR	NS
Cohen-1 et al. 2002 [20]	Arab	48	54	5-HTTLPR S/L	5-HTTLPR S/L ($P = 0.001$)
Cohen-2 et al. 2002 [20]	Jewish	51	497	5-HTTLPR S/L	5-HTTLPR S/L ($P = 0.024$)
Gursoy et al. 2001 [21]	Turkey	58	58	5-HT2A receptor 102T/C	NS
Offenbaecher et al. 1999 [22]	Germany	62	110	5-HTTLPR S/L	5-HTTLPR SS ($P = 0.046$)
Bondy et al. 1999 [23]	Germany	168	115	5-HT2A receptor 102T/C	5-HT2A receptor 102TT ($P = 0.023$)

Ref reference, *FM* fibromyalgia, *SNP* single nucleotide polymorphism, *5-HTTLPR* serotonin transporter (5-HTT) promoter region, *NS* not significant, *S/L allele* short/long allele, *TACR* tachykinin NK1 (substance P) receptor, *DAT* dopamine transporter, *AAT* alpha-1 antitrypsin, *ADR* adrenergic receptor, *DRD3* dopamine-D_3-receptor, *5-HT2A* 5-hydroxytryptamine (serotonin) 2A, *COMT* catechol-O-methyltransferase, *val158Met* codon 158 with valine-to-methionine transition, *MAO* monoamine oxidase, *5-HTR3A* 5-HT receptor 3A, *5-HTR3B* 5-HT receptor 3B, *VNTR* variable number tandem repeat, *eNOS* endothelial nitric oxide synthase, *IL-4* interleukin-4, *DRD4* dopamine-D_4-receptor

Deviation from the H–W equilibrium among controls implies potential bias during control selection, or genotyping errors, but excluding this study that did not produce H–W equilibrium among controls, did not materially affect our results.

Discussion

Candidate gene studies require large samples to achieve adequate statistical power and replicable results [39]. Nonetheless, a lot of published candidate gene studies in fibromyalgia have used relatively small samples. This meta-analysis and systematic review revealed the paucity of data about the association of candidate gene polymorphisms with fibromyalgia.

Studies have been done on roles of polymorphism of the genes in the serotoninergic, catecholaminergic, and dopaminergic systems in fibromyalgia. We combined the evidence on the association of the 5-HTTLPR S/L allele, COMT val158Met, and 5-HT2A receptor 102T/C polymorphisms and susceptibility of fibromyalgia. The results of this meta-analysis provide evidence of an association of the 5-HT2A receptor 102T/C polymorphisms with

Table 2 All candidate gene polymorphisms studied in fibromyalgia

Genes	Gene names	Polymorphisms	Studied numbers	Chromosomal location	References
5-HTTPLR	Serotonin transporter (5-HTT) promoter region	S/L allele	5	17q11.1–q12	[6, 19, 20, 22]
		Intron2 VNTR	1		[19]
COMT	Catechol-*O*-methyltransferase	rs6269	1	22q11.2	[12]
		rs4633	1		[12]
		rs4818	1		[8, 9, 11, 12]
		rs4680 (val158Met)	5		[12]
		rs20907	1		[12]
		rs16559	1		
5-HT2A receptor	5-hydroxytryptamine (serotonin) 2A receptor	rs6311	1	13q14–q21	[11]
		rs6313 (102T/C)	3		[11, 21, 23]
ADRA1A	Adrenergic receptor alpha-1-A	rs574584	1	8p21–p11.2	[7]
		rs138914	1		[7]
		rs1048191	1		[7]
		rs573542	1		[7]
ADRB2	Adrenergic receptor beta-2	rs1042713	1	5q31–q32	[7]
		rs1042714	1		[7]
ADRB3	Adrenergic receptor beta-3	rs4994	1	8p12–p11.2	[7]
DRD3	Dopamine-D_3-receptor	Ser9Gly	1	3q13.3	[8]
DRD4	Dopamine-D_4-receptor	VNTR	1	11p15.5	[17]
DAT	Dopamine transporter	VNTR	1	5p15.3	[10]
MAO-A	Monoamine oxidase A	Promoter VNTR	1	Xp11.3	[13]
		941G/T	1		[13]
MAO-B	Monoamine oxidase B	Intron13 G/A	1	Xp11.23	[13]
eNOS	Endothelial nitric oxide synthase	Glue298Asp (G894T)	1	7q36	[14]
TACR1	Substance P receptor	1354G/C	1	2p12	[10]
AAT	Alpha-1 antitrypsin	E342K	1	14q32.1	[10]
IL-4	Interleukin-4	Intron3 VNTR	1	5q31.1	[15]
HTR3A	5-HT receptor 3A	Exon 1 -42C/T	1	11q23.1	[16]
		30C/T	1		[16]
		Exon 2 97G/A	1		[16]
		Exon 3 IVS3 +7A/C	1		[16]
		Exon 6 576G/A	1		[16]
		Exon 9 1377G/A	1		[16]
HTR3B	5-HT receptor 3B	Exon 1 -102_-100delAAG	1	11q23.1	[16]
		Exon 4 IVS4 +12G/A	1		[16]
		+11C/T	1		[16]
		Exon 5 386A/C	1		[16]
		Exon 6 IVS6 +72A/G	1		[16]
			1		[16]

5-HTTLPR serotonin transporter (5-HTT) promoter region, *NS* not significant, *S/L allele* short/long allele, *TACR* tachykinin NK1 (substance P) receptor, *DAT* dopamine transporter, *AAT* alpha-1 antitrypsin, *ADR* adrenergic receptor, *DRD3* dopamine-D_3-receptor, *5-HT2A* 5-hydroxytryptamine (serotonin) 2A, *COMT* catechol-O-methyltransferase, *val158Met* codon 158 with valine-to-methionine transition, *MAO* monoamine oxidase, *5-HTR3A* 5-HT receptor 3A, *5-HTR3B* 5-HT receptor 3B, *VNTR* variable number tandem repeat, *eNOS* endothelial nitric oxide synthase, *IL-4* interleukin-4, *DRD4* dopamine-D_4-receptor

fibromyalgia susceptibility. However, in this meta-analysis, no association was found between the 5-HTTLPR S/L allele and COMT val158Met polymorphism and fibromyalgia.

Serotonin is a neurotransmitter that participates in many physiological processes such as sleep, appetite, thermoregulation, pain perception, hormone secretion, and sexual behavior [24]. Dysregulation of the serotonergic system

Table 3 Meta-analysis of candidate gene polymorphisms and fibromyalgia association

Genes	Polymorphism	No. of studies	Test of association			Test of heterogeneity			
			OR	95% CI	*P* value	Model	*Q*	*P* value	I^2
5-HTTLPR	S vs. L	5	1.106	0.889–1.376	0.367	F	6.55	0.161	38.9
	SS vs. SL + LL	5	1.508	0.788–2.848	0.206	R	12.2	0.016	67.2
	SS + SL vs. LL	5	0.854	0.610–1.196	0.357	F	6.49	0.165	38.4
	SS vs. LL	5	1.277	0.839–1.944	0.254	F	5.21	0.266	23.2
COMT	M vs. V	5	0.973	0.650–1.457	0.894	R	14.9	0.005	73.3
	MM vs. MV + VV	4	1.060	0.645–1.740	0.819	F	0.916	0.016	0
	MM + MV vs. VV	4	1.271	0.874–1.848	0.209	F	0.38	0.944	0
	MM vs. VV	4	0.946	0.538–1.665	0.848	F	0.85	0.836	0
5-HT2A receptor	C vs. T	3	1.333	1.053–1.688	0.017	F	0.04	0.980	0
	CC vs. CT + TT	3	1.380	0.961–1.981	0.081	F	1.24	0.536	0
	CC + CT vs. TT	3	1.541	1.032–2.303	0.035	F	1.17	0.557	0
	CC vs. TT	3	1.838	1.151–2.936	0.011	F	0.02	0.987	0

5-HTTLPR serotonin transporter (5-HTT) promoter region, *COMT* catechol-O-methyltransferase, *5-HT2A* 5-hydroxytryptamine (serotonin) 2A, *F* fixed effect model, *R* random effect model

has been related in many psychiatric diseases. Fibromyalgia is associated with decreased levels of serotonin and serotonin metabolites in serum and the central nervous system, as well as with a decreased rate of serotonin transport into the cerebrospinal fluid [40, 41]. This meta-analysis failed to show an association of the 5-HTTLPR S/L polymorphism with fibromyalgia susceptibility, but our study found an association of the 5-HT2A receptor 102T/C polymorphisms with fibromyalgia susceptibility, suggesting the serotonergic system may play a role in the pathogenesis of fibromyalgia. We found an association of the C allele, CC + CT genotype, and CC homozygosity of the 5-HT2A receptor 102T/C polymorphism with fibromyalgia. In human postmortem studies, the production of 5-HT2A receptors in temporal cortex was about 20% less for the C allele than for the T allele [42]. The 102T/C polymorphism is located in exon 1 near the gene's promoter, and so may have some role in gene regulation [29]. Since the C allele of the 5-HT2A receptor 102T/C polymorphism has less activity, it may have some role in fibromyalgia.

Studies examining the association between COMT and fibromyalgia have largely focused on a functional polymorphism in exon 4 that leads to an amino acid substitution (valine→methioinin) [31]. This polymorphism has been shown to affect COMT enzyme activity, such that homozygosity for the valine allele shows 3–4 times greater activity than homozygosity for the methionine allele. A functional polymorphism in the promoter region of the 5-HTTLPR is one of the most frequently studied genetic markers in fibromyalgia [36]. Despite the potential relevance of these functional polymorphisms to fibromyalgia [25], this meta-analysis failed to detect a significant association of the COMT val158Met polymorphism and the 5-HTTLPR S/L polymorphism with fibromyalgia susceptibility. Because genetic studies in fibromyalgia have been carried out in small numbers of patients, this meta-analysis cannot rule out the possibility that the COMT val158Met polymorphism and the 5-HTTLPR S/L allele play a role in fibromyalgia susceptibility. Larger studies are necessary to clarify the role of the candidate genes in the pathogenesis of fibromyalgia.

While some gene polymorphisms including the ADRB2 [7], ADRA1A [7], COMT rs4818 [12], DRD4 [17], and MAO-A allele3 [13] showed a significant association with fibromyalgia, other gene polymorphisms such as ADRB3 [7], DRD3 [8], DAT [10], 5-HT2A receptor (rs6311) [11], COMT (rs6269, rs4633, rs4818, rs4680, rs20907, and rs16559) [12], MAO-B [13], eNOS [14], TACR1 [10], AAT [10], IL-4 [15], 5-HTTLPR (intron2 VNTR) [19], HTR3A, and 3B (some SNPs) [16] was not associated with fibromyalgia. However, there is insufficiency evidence to conclude whether the polymorphisms are associated with fibromyalgia susceptibility, because there was only one study about the association of the polymorphisms with fibromyalgia, respectively.

Our analysis has some limitations. First, the number of studies and the number of subjects in the studies included in the meta-analysis were small. This may have not enough power to explore the association between the candidate gene polymorphisms and fibromyalgia. We also could not perform the ethnic-specific meta-analysis to detect associations in ethnic groups due to limited data. Second, it would have been interesting to examine whether the candidate gene polymorphisms are associated with clinical features of

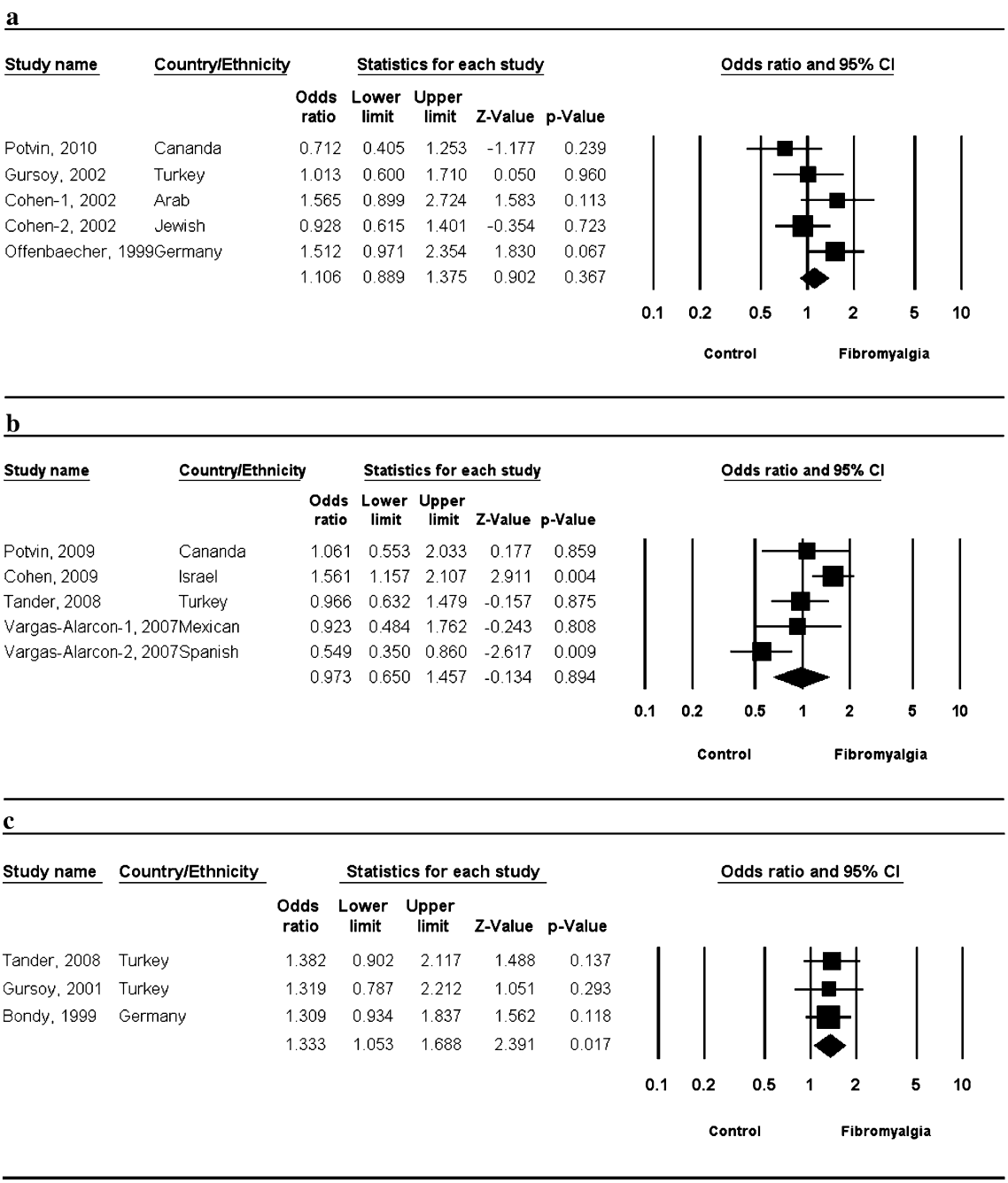

Fig. 1 ORs and 95% CIs of individual studies and pooled data for the association between the 5-HTTLPR polymorphism S allele (**a**), COMT val158Met polymorphism Met allele (**b**), and 5-HT2A receptor C/T polymorphism C allele (**c**) and fibromyalgia

fibromyalgia, but this was not possible due to the limited data available. Third, publication bias may have affected the meta-analysis, as some studies with negative results may not have been published or may have been missed.

In conclusion, this meta-analysis of published data demonstrates that the 5-HT2A receptor 102T/C polymorphism confers susceptibility to fibromyalgia. In contrast, this meta-analysis failed to find the association between the 5-HTTLPR S/L allele, COMT val158Met, and susceptibility to fibromyalgia. Given the small number of studies presently available, additional research including large number of patients and controls is required to conclude the association of the candidate gene polymorphisms with fibromyalgia.

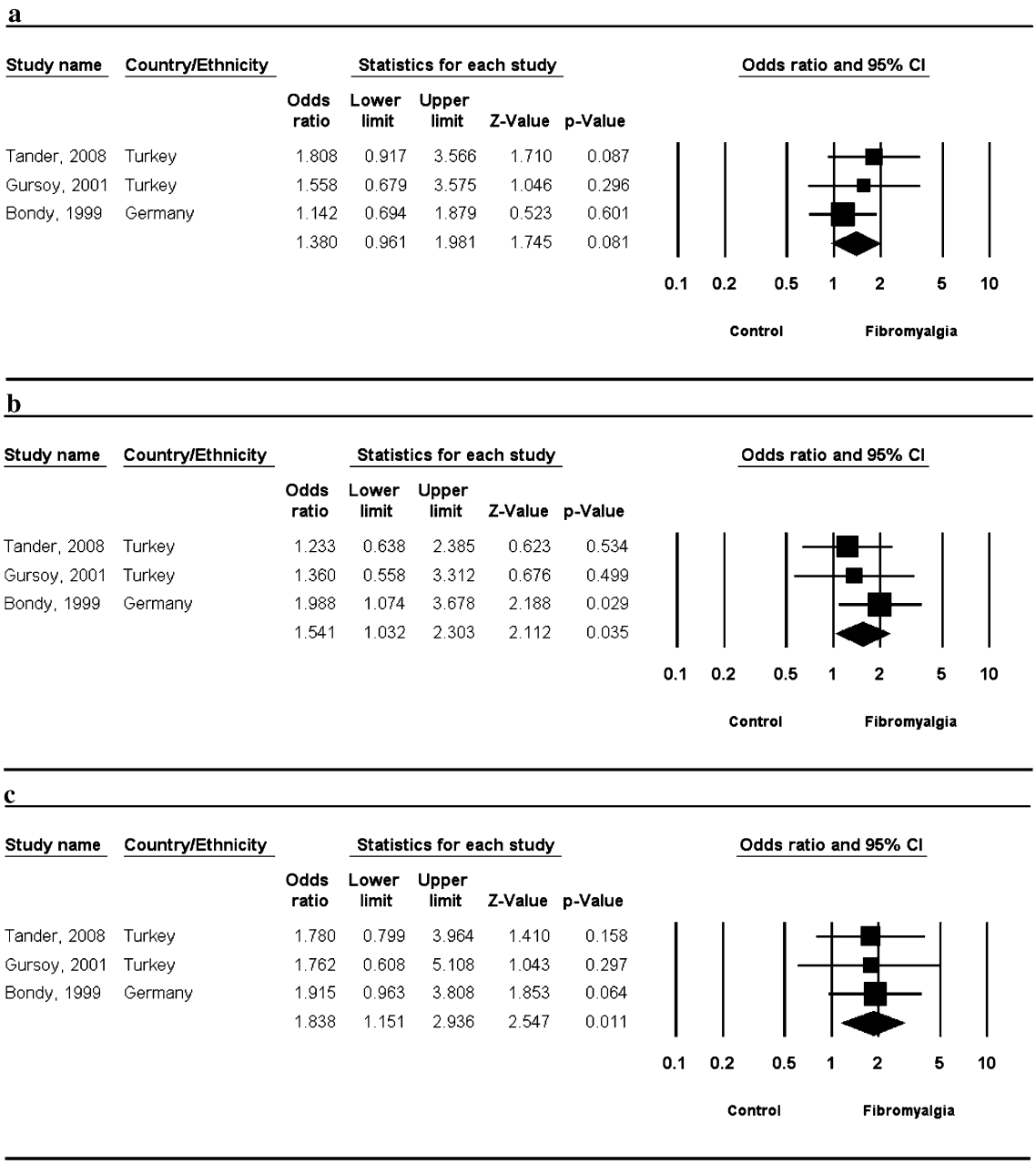

Fig. 2 ORs and 95% CI of individual studies and pooled data for the association between the 5-HT2A receptor C/T polymorphism [CC vs. CT + TT (**a**), CC + CT vs. TT (**b**), CC vs. TT (**c**)] and fibromyalgia

Acknowledgments This study was supported by a Korea University Grant.

Conflict of interest We have no financial and non-financial conflicts of interest.

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