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ORIGINAL PAPER

Association of GA genotype of SNP rs4680 in *COMT* gene with psoriasis

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Abstract

Psoriasis is a multigene and multifactorial skin disease with heterogeneous genetic inheritance. Mental disorders participate in the development of psoriasis as predisposing factors; a correlation of dermatological diseases with pathological anxiety and stress was shown. Meanwhile, there are no studies describing molecular mechanisms of the linkages between psycho-emotional disorders and skin diseases. The aim of this study is to find the associations between SNP in genes *COMT* (rs4680), *DBH* (rs141116007), *CCKAR* (rs1800857) and *CCKBR* (rs1805002), and psoriasis. Patients were selected according to the 10th revision of International Classification of Diseases (L-40). The sample size was 88 patients. The size of the control sample (population control) was 365 people. Genotyping was performed using PCR-RFLP and real-time PCR. Statistical analysis was performed using WinPepi software. Identification of complex genotypes was performed by the Monte Carlo method using APSampler 3.6.1 algorithm. Among the studied genes, only GA genotype of *COMT* gene is significantly associated with psoriasis [$\chi^2 = 19.163$ ($p = 1.3E{-}5$), F (p) $= 1.2E{-}5$, OR 3.47 (CI 99% = 1.61–7.91)]. At the moment, the functional significance of this phenomenon is difficult to explain.

Keywords Psychodermatology · Psoriasis · Genes · *COMT* · *DBH* · *CCKAR* · *CCKBR* · Polymorphism · Genotyping · Genetic associations

Introduction

Psoriasis is a common, chronic inflammatory skin disease with a complex etiology involving genetic risk factors and environmental triggers [11, 13]. It is also characterized as a common dermatologic disorder with psychiatric comorbidity [23]. Among concomitant to psoriasis pathologies, heart and vessel disorders most often occur [27]. Psoriasis is a multigene and multifactorial disease with heterogeneous genetic inheritance [7]. It is common for psoriasis to have disorders in keratinocyte proliferation and differentiation malfunctions, caused by autoimmune response of T lymphocytes and macrophages against skin cells [23].

It has been repeatedly stated that mental illnesses (disorders) are involved in the development of psoriasis as predisposing factors, and the correlation of dermatological diseases with pathological anxiety and stress was shown [12].

In recent years, a new scientific and medical branch called psychodermatology was developed [19]. Psychodermatological approach implies treating psycho-emotional disorders (anxiety, depression, stress, etc.) at first and then the skin manifestations treatment [29]. The attribution of psoriasis to the category of psychosomatic skin diseases is based on vast clinical material, which allows tracing the relationship between stress, depressions and dermatosis [6, 22]. In addition to the time dependency between the influence of emotional stress and appearance of skin pathology symptoms, parallelism between the severity, prevalence, intensity of the disease and the psycho-emotional disorders intensity is often observed [3]. According to studies [23], patients with

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psoriasis suffer from psychiatric and psychological symptoms which are incommensurable to skin lesions.

However, there are no studies describing the molecular mechanisms of linkages between psychosomatic diseases and skin diseases. Therefore, the purpose of our work had become conducting molecular genetic research of the links and relationships between anxiety, stress and psoriasis.

The aim of this study was to find associations of psoriasis with SNP in genes *COMT* (rs4680), *DBH* (rs141116007), *CCKAR* (rs1800857) and *CCKBR* (rs1805002), which are involved in the pathogenesis of panic disorder [2, 18] as well as identify the combination of alleles of studied genes (complex genotypes) associated with psoriasis.

Materials and methods

Patients and samples

The blood samples of patients with psoriasis were obtained from VG Korolenko City Clinical Hospital № 14 (Russia, Moscow). Patients with a diagnosis of psoriasis, living in Moscow or the Moscow region were selected in accordance with the 10th revision of International Classification of Diseases (L-40). The sample size was 88 patients. For a control was used DNA samples extracted from whole blood of unsurveyed residents of Moscow and the Moscow region ($n = 365$); the blood sampling was performed at the Moscow station of blood transfusion. All patients participating in the study were aware of the objectives of the work and had signed «informed consent». The study was conducted according to the Declaration of Helsinki Principles (1964).

Molecular genetic analysis

DNA was isolated from 200 µl of whole blood using Magna™ DNA Prep 200 («Isogen», Russia) extraction kit. The fluorescent probes (TaqMan probe for SNP rs4680 in the gene *COMT*) and primers were synthesized by «DNA synthesis», LLC (Russia) for all substitutions. Fluorescent dyes VIC and FAM, and quencher BHQ1 were used for the production of labeled primers of TaqMan probes. The nucleotide sequences of the primers are described in Table 1.

Amplification was performed using HS Taq DNA polymerase kit («Evrogen», Russia) in accordance with the manual. PCR was executed using a T100™ Thermal Cycler (Bio-Rad, USA). PCR mixture «qPCRmix-HS» («Evrogen», Russia) was used for a real-time PCR. Genotyping by real-time PCR was performed twice, using CFX-96 real-time PCR detection system (Bio-Rad, USA).

DNA cleavage was performed with restriction endonucleases («SibEnzyme», Russia) in accordance with the manufacturer's prescriptions. The PCR products were analyzed the following way: endonuclease PstI (3 h incubation at 37 °C) was used for analyzing SNP rs1800857 (*CCKAR*), and endonuclease Bst4CI (3 h incubation at 65 °C)—for analyzing SNP rs1805002 (*CCKBR*). The sizes of PCR-RFLP products are GG—150 bp, 87 bp; GA—237 bp, 150 bp, 87 bp; AA—237 bp. For Ins/Del polymorphism in *DBH* gene, the PRC fragments length was Ins—120 bp and Del—101 bp.

Separation of PCR-RFLP products was performed in 2% agarose gel. Molecular weight marker M50 (50–500 bp, «Laboratory Isogen», Russia) was used. Electrophoresis was performed at 10–12 V/cm for 45–60 min. The gel was photographed in the short-wave UV light with the use of iuVCR system attached to a computer.

Bioinformatics tools

DNA variant rs1800857 was analyzed with the splicing prediction program Human Splicing Finder [5]. For reconstruction of signaling pathways, the program PathwayStudio 9.0 with ResNet12 database (Elsevier LLC) was used.

Table 1 Nucleotide sequences of the primers used in the study and PCR conditions

Gene SNP	Primer sequences	PCR conditions
COMT rs4680	F: 5′-ATCAACCCCGACTGTGCCG-3′ R: 5′-CCAGGTCTGACAACGGGTCA-3′ G: VIC-TCGCTGGCGTGAAGGAC-BHQ1 A: FAM-ATTTCGCTGGCGATGAAGGAC-BHQ1	95 °C – 1′, (95 °C – 30″, 63 °C – 1′, 72 °C – 1′)*40c
DBH rs141116007	F: 5′-AATCAGGCACATGCACCTCC-3′ R: 5′-GGCCCTGAGGAATCTTACAGG-3′	95 °C – 3′, (95 °C – 20″, 57 °C – 10″, 72 °C – 15″)*40c
CCKAR rs1800857	F: 5′-ATCGTGGGTCCAGTGATGT-3′ R: 5′ GGCTCCTTTGCTGTGATTGT-3′	95 °C – 3′, (95 °C – 30″, 63 °C – 15″, 72 °C – 20″)*40c
*CCKBR*rs 1805002	F: 5′-CTGGCAGTCAGCGACCTCCT-3′ R: 5′-CACAAGCATCAGTGGGACTTC-3′	95 °C – 3′, (95 °C – 20″, 62 °C – 15″, 72 °C – 20″)*40c

Statistical analysis

Hardy–Weinberg equilibrium test in the patient samples and the control samples was performed using Pearson criterion (χ^2 test).

To assess the associations of SNPs, Fisher's two-tailed test and Pearson criterion (χ^2 test) were used; all calculations were performed in WinPepi software [1]. The results with p value less than 0.05 ($p < 0.05$) were considered reliable. The mode of inheritance was determined using Akaike information criterion (AIC).

The search for combinations of alleles and/or genotypes (complex genotypes) associated with the development of psoriasis was performed by the Monte Carlo algorithm in APSampler v.3.6.0.1 [9]. The reliability of complex genotype associations with psoriasis was verified by Fisher's two-tailed test, with subsequent validation of the results using the standard permutational test. The strength of association was expressed in odds ratio (OR) with confidence interval (CI) 95%. The differences between comparable frequencies were considered reliable if permutation Westfall–Young p value was less than 0.05.

Table 2 Genotype frequencies of studied SNPs presented in percentage (%) and χ^2 value for Hardy–Weinberg equilibrium

Gene, SNP	Genotype	Patients	H–W χ^2	Control	H–W χ^2
DBH rs141116007		$n = 88$	0.49	$n = 355$	4.38
	II	27.3%		36.1%	
	ID	53.4%		43.4%	
	DD	19.3%		20.6%	
CCKAR rs1800857		$n = 88$	0.13	$n = 363$	0.05
	TT	76.1%		74.9%	
	TC	22.7%		23.4%	
	CC	1.1%		1.7%	
CCKBR rs1805002		$n = 88$	7.08	$n = 362$	15.85
	GG	84.1%		83.4%	
	GA	12.5%		13.8%	
	AA	3.4%		2.8%	
COMT rs4680		$n = 88$	26.26	$n = 192$	0.02
	AA	10.2%		27.1%	
	AG	77.3%		49.5%	
	GG	12.5%		23.4%	

Results

Detected genotypes frequencies are shown in Table 2. The deviation from Hardy–Weinberg equilibrium was revealed only for two SNPs: *CCKBR* rs1805002—control samples and *COMT* rs4680—patient samples.

Allele frequencies and statistical analysis of their association with psoriasis are shown in Table 3.

For all of the SNPs, allele frequencies were about the same in patient and control samples. No associations of most of the studied SNPs with psoriasis were found. The analysis of genotype frequencies revealed significant association only for SNP in *COMT* gene (rs4680, c.472G > A, p.Val158Met). Dominant inheritance mode was shown for A allele rs4680 (Table 4).

The search of polygenic associations, which would predict an individual's predisposition to multifactorial diseases, was carried out using APSampler v.3.6.0.1 software. Two significantly associated complex genotypes and alleles were found (permutation Westfall–Young p value < 0.01). The results are shown in Table 5.

The results of polygenic analysis revealed two genotypes associated with psoriasis with reliability $p_{perm} < 0.01$. The first genotype is a combination of *COMT* heterozygote (rs4680:GA) and a deletion in *DBH* gene (Ins/Del19:D). The second is *COMT* heterozygote (rs4680:GA) itself.

It is clear that effect of the deletion in *DBH* (Ins/Del19:D) gene is minimal because the difference in OR value is small (3.50 with deletion and 3.47 without deletion).

For verification of our results, a statistical test of association between GA heterozygote and GG + AA homozygotes of *COMT* gene using WinPepi software was conducted. The

Table 3 Allele frequencies of studied SNPs and data on association of these alleles with psoriasis

Gene, SNP		Patients (%)	Control (%)	χ^2, p	F (p)	OR	CI 95%
DBH rs141116007	I	54	57.7	0.818	0.395	0.86	0.61–1.21
	D	46	42.3	0.366		1.17	0.82–1.65
CCKAR rs1800857	T	87.5	86.6	0.092	0.901	1.08	0.65–1.86
	C	120.5	13.4	0.762		0.93	0.54–1.54
CCKBR rs1805002	G	90.3	90.3	0.00	1.000	1.00	0.56–1.87
	A	9.7	9.7	0.997		1.00	0.54–1.77
COMT rs4680	A	48.9	51.8	0.423	0.525	0.89	0.61–1.29
	G	51.1	48.2	0.515		1.13	0.78–1.63

χ^2, p chi square and p value, F (p) Fisher's two-tailed test, p value, *OR* odds ratio, *CI 95%* confidence interval 95%

results are $\chi^2 = 19.163$ ($p = 1.3E{-}5$), F (p) $= 1.2E{-}5$, OR 3.47 (CI 99% = 1.61–7.91). Thus, the association between GA *COMT* heterozygote with psoriasis was found.

Discussion

The products of genes researched in this work are responsible for the release of (*CCKAR*), regulate the reuptake (*CCKBR*) of dopamine, and are responsible for its degradation (*COMT* and *DBH*). The data on the role of the studied SNPs and their influence on the function of gene products are summarized in Table 6.

In our study the statistical tests revealed an association with psoriasis only for the *COMT* gene, which encodes catechol-*O*-methyltransferase. The heterozygous genotype GA is associated with psoriasis. According to the study of the Turkish population [8], AA genotype, which leads to a decrease of the *COMT* enzyme activity, is significantly associated with psoriasis. According to the results of the Chinese study, no connection between *COMT* gene and psoriasis was found [10]. However, other authors showed an increase in activity of the soluble form of the enzyme in patients with psoriasis [21, 28]. An increase of the enzyme activity increases the degradation of catecholamines: dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline).

Table 4 Genotype combination frequencies of studied SNPs in patients with psoriasis and control samples and the results of association study

Gene, SNP	Genotypes	Patients (%)	Control (%)	χ^2, p	F (p)	OR	CI 95%	Model
DBH rs141116007	II	27.3	36.1	2.414	0.133	0.67	0.38–1.14	dom.
	ID + DD	72.7	63.9	0.120		1.50	0.88–2.64	
CCKAR rs1800857	TT	76.1	74.9	0.055	0.891	1.07	0.61–1.94	dom.
	CT + CC	23.9	25.1	0.814		0.94	0.52–1.65	
CCKBR rs1805002	AA	3.4	2.8	0.106	0.725	1.24	0.21–4.96	rec.
	GG + GA	96.6	97.2	0.745		0.80	0.20–4.65	
COMT rs4680	GG	10.2	27.1	**10.062**	**1.6E−3**	0.31	0.13–0.67	dom.
	AA + GA	89.8	72.9	**1.5E−3**		**3.26**	**1.48–7.91**	

Significant association in bold

χ^2, p chi square and p value, F (p) Fisher's two-tailed test, p value, *OR* odds ratio, *CI 95%* confidence interval 95%, *Model* model of inheritance: *dom*. dominant, *rec*. recessive

Table 5 The results of search of alleles and genotypes associated with psoriasis (APSampler v.3.6.0.1 software)

Complex genotypes	Patients (%)	Control (%)	F (p)	OR	CI (95%)	p_{Bonf}	FDR	p_{perm}
*COMT*_rs4680:G, A; *DBH*_ rs141116007:D	58	28	2.54E−06	3.50	2.06–5.95	< 0.001	0.00	< 0.001
*COMT*_rs4680:G, A	77	49	7.16E−06	3.47	1.96–6.16	< 0.001	0.00	< 0.001

χ^2, p chi square and p value, F (p) Fisher's two-tailed test, p value, *OR* odds ratio, *CI 95%* confidence interval 95%, p_{Bonf} p value, Bonferroni correction, p value, p_{perm} p value after permutational test (Westfall–Young)

Table 6 Studied SNPs and their role in gene/protein functions

Gene, SNP, description	Function
DBH, rs141116007 NG_008645.1:g.249_267del19	Homozygotes Del/Del and Ins/Ins have, respectively, low and high level of *DBH* activity in plasma [4], Ins/Del heterozygotes have medium level of activity
CCKAR, rs1800857 NM_000730.2:c.113-5T > C	Does not affect the main splicing site, but creates two sites (splicing enhancer and splicing silencer) and defects in exon and intron identification elements and splicing regulatory sequence. This may affect splicing efficiency and *CCKAR* expression (Human Splicing Finder analysis results)
CCKBR, rs1805002 XM_005253211.1:c.373G > A XP_005253268.1:p.Val125Ile	Changes amino acid sequence of receptor (in the second extracellular loop) which may lead to changes in receptor–ligand affinity [17]
COMT, rs4680 NM_001135161.1:c.472G > A XP_005261286.1:p.Val158Met	People with AA (Met/Met) genotype show three–four times higher enzyme activity than those with GG (Val/Val) genotype [20]

However, other authors note an increased plasma concentration of epinephrine in the blood of patients diagnosed with psoriasis [16]. Epinephrine causes the accumulation of cAMP in the patient's skin [15], which is probably one of the pathological molecular mechanisms—cAMP is important in the development of the inflammatory response.

Information about the role of genes *CCKAR, CCKBR* and *DBH* in the pathogenesis of psoriasis is not found in the literature.

Results of polygenic analysis also showed a significant influence of gene polymorphism *COMT* (rs4680) in the development of psoriasis. The carrying of both alleles of rs4680 in combinations with Del allele of *DBH* gene forms the strongly associated pattern (OR = 3.50).

The participation in complex genotypes of minor wild-type alleles was shown for *CCKAR* and *CCKBR* genes. This indicates their insignificant contribution to the pathogenesis of psoriasis. Meanwhile, the D allele of *DBH* gene is a part of complex genotypes, increasing the impact of the *COMT* gene GA genotype. This indicates its importance in the pathogenesis of psoriasis. However, it is not associated with disease by itself, and exerts its effect only in complex genotypes.

To explain the linkage between complex genotypes associated with psoriasis, we made a brief scheme of signaling pathways involving studied genes (Fig. 1). Identified complex genotypes associated with psoriasis are characterized by high activity of *COMT* and low activity of *DBH*. Receptors of cholecystokinin *CCKAR* and *CCKBR* are not changing their functionality. Thus, the lack of *DBH* was apparently compensated by the excessive activity of *COMT*. However, this leads to low synthesis of norepinephrine and epinephrine which in combination with the excessive activity of *COMT* leads to a lack of these molecules in the body of patients. The obtained scheme is in concordance with the data obtained in other studies [21, 28] with respect to increased activity of *COMT* in patients with psoriasis, but does not correspond to reported increase of epinephrine in patients [14, 16]. Meanwhile, we showed the comorbidity of psoriasis and restless leg syndrome, which is caused by a dopamine deficiency and can be corrected by preparations based on dihydroxyphenylalanine (levodopa) [26].

The association of GA genotype of *COMT* gene with psoriasis found in our study has no direct explanation of its functional activities. It is possible that patients with AA genotype are more likely to suffer from the dopaminergic hyperfunction (Parkinson's disease, restless leg syndrome, and others.), and as a result they are observed in neurological clinics instead of dermatological.

Another possible explanation of that association is that there may be a genetic linkage between the studied substitute and a marker for psoriasis. However, adjacent genes *TXNRD2, RPL8P5, ARVCF, MIR4761, TANGO2, MIR3618* and *DGCR8* have nothing to do with psoriasis.

The most interesting hypothesis, which could explain the effect of the GA heterozygote of the *COMT* gene on the pathogenesis of psoriasis, from our point of view, is the possibility of changing the activity of the heterodimer. Thus, it was shown that *COMT* enzyme can exist in three forms: a monomer, a membrane-bound monomer and a dimer [26]. The structure of proteins *COMT* 158Val and *COMT* 158Met is different, which results in different affinity to substrates [25] and different stability of the enzyme [24]. Perhaps the heterodimer has an affinity for other substrates. Thus, patients with psoriasis have an increased excretion of adrenaline in stressful situations [14]. Perhaps affinity for

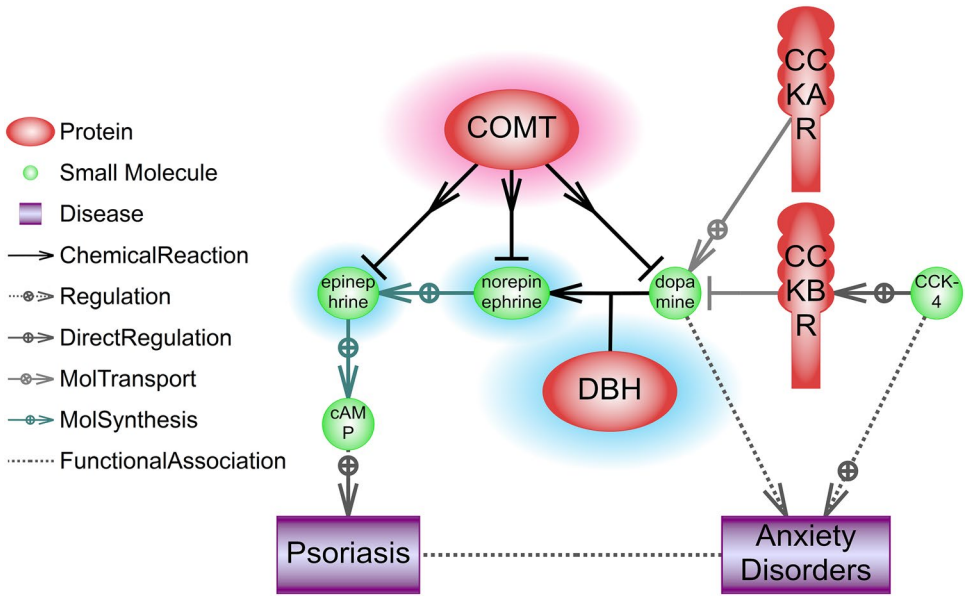

Fig. 1 Scheme of the regulation of dopamine release and degradation which includes investigated genes. Red—the excess of molecules or increased activity of the enzyme. Blue—reduction in the number of molecules and decreased activity of the enzyme. Legend is on the figure. The description is in the text. The scheme was made using PathwayStudio10 software (Elsevier LLC)

adrenaline becomes lower, which contributes to its accumulation in patients. Perhaps the affinity to other *COMT* substrates changes.

Conclusion

We found the association of the GA genotype of *COMT* gene with psoriasis. At the moment, it is difficult to explain the functional significance of this phenomenon. We hope that the answer will be received in a further study of the role of polymorphisms of genes encoding enzymes of neurotransmitter systems in the pathogenesis of psoriasis, which is undoubtedly associated with pathological anxiety and stress.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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