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Sequence Polymorphisms of *MC1R* Gene and their Association Analysis with Depression and Antidepressant Response

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Abstract

Melanocortin 1 receptor (MC1R) has been shown to be involved in various functions, such as pigmentation, anti-pyretic and anti-inflammatory actions, development of melanoma, susceptibility to UV-induced sun damage, modification of oculocutaneous albinism, development of freckles and mediation of female-specific mechanisms of analgesia. MC1R's natural agonists include α- Melanocyte-stimulating hormone (MSH) and corticotrophin (ACTH1-39), which is an important component of hypothalamic-pituitary-adrenal axis and increased in response to stress. Given the multiple relevant roles of MC1R, we studied whether the *MC1R* gene would be associated with susceptibility to major depressive disorder (MDD) or response to antidepressant treatment. The human *MC1R* gene is highly polymorphic; therefore, we sequenced the entire *MC1R* coding region of 1122 bp in 181 depressed Mexican-American patients and 185 controls. A total of 23 single nucleotide polymorphisms (SNPs, 15 known and eight new) were found within the sequenced region. Among the common SNPs, the non-synonymous SNP rs885479 (R163Q) was associated with the diagnosis of depression ($P = 0.04$). The non-synonymous SNP rs2228479 (V92M) and the synonymous SNP rs2228478 were found to be associated with remission with desipramine treatment. No associations were found for remission with fluoxetine or for the combined sample treated with fluoxetine or desipramine. The frequency of one (H2) of five haplotypes identified was higher in depressed when compared to controls ($P = 0.05$). *In silico* functional analysis indicates that SNPs rs885479 and rs2228479 have significant impact on the protein function. The above results showed that the *MC1R* might associate with MDD and treatment response to desipramine.

Keywords

MC1R; major depression; antidepressant; SNPs; haplotype; association

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Introduction

Major depressive disorder (MDD) is a common and complex gene-environmental disorder clinically characterized by a pervasive low mood, loss of interest in usual activities and diminished ability to experience pleasure (anhedonia), and fatigability. Other key CNS functions such as sleep, appetite, temperature and neuroendocrine regulation, and locomotion, cognition may also be altered. The onset of a depressive episode would require a genetic background of increased susceptibility combined with the presence of stressful life events. Consequently, it has been assumed that genes that exacerbate or buffer the effect of life stressors may contribute to MDD risks. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene has been shown to moderate the influence of stressful life events in depression (Caspi et al., 2003). Given the SSRIs were among the most effective antidepressants, this finding was plausible and regarded as the success of neurotransmitter hypothesis. But following up studies failed to fully replicate this finding (Risch et al., 2009). The meta-analysis showed that stressful life events is a potent risk factor for depression, but 5-HTT genotype was not shown to be a predisposition factor for developing depression either along or interacting with stressful life events (Risch et al., 2009). Several other hypotheses for the mechanism of depression susceptibility have been also proposed, such as the neuroendocrine hypothesis, which studies the role hypothalamic-pituitary axis overactivation and inhibition of counterproductive neurovegetative function in chronic life stress. The neurotrophic hypothesis implicates the role of neurotoxic and neuroprotective effects in depression development, and neurotrophins, such as the brain-derived neurotrophic factor (BDNF) are postulated to have a key role in the pathophysiology of depression and antidepressant action (Groves, 2007). The neuroimmune hypothesis has been concerned with the interactions between the CNS and the immune system. Recently, a possible immune system dysregulation with Th1 activation in depression has been proposed by Wong et al. (Wong et al., 2008). Variants of PSMB4 (proteasome subunit beta type 4) and TBX21 (T-box 21) were associated with MDD and antidepressant treatment (Wong et al., 2008). As a complex trait with both genetic and nongenetic contributory factors, potential new genetic factors associated with susceptibility of MDD are still under vigorous investigation using genome wide association study (GWAS) strategies. Well-designed pharmacogenomic studies require prospective double blind design that is not particularly suitable for GWAS due to the limitation of the number of patients that can be enrolled prospectively. For that reason it is reasonable to propose candidate gene studies of small, but very well characterized pharmacogenomic samples.

Signal transduction mediated by pro-opiomelanocortin protein (POMC) represents a logical candidate pathway in pharmacogenomic studies of depression. POMC consists of 241 amino acids, which could be classified as three main domains: the central highly conserved ACTH1–39 sequence, with α-MSH at its N-terminus; the C-terminal β-lipotropin, which can be cleaved to generate β-endorphin; and the N-terminus region which contains γ-MSH (Castro and Morrison, 1997; Takahashi et al., 1981). Posttranslational processing of the POMC protein ultimately leads to the generation of various hormones with distinct bioactivities, such as the melanocortins (alpha-, beta-, and gamma-), β-lipotrophin, γ-lipotropin, β-endorphin and ACTH. Melanocortins exert their biological effects by binding

to the smallest family of stimulate G-protein-coupled transmembrane receptors (GPCR), the melanocortin receptors (MCR). Five MCRs have been identified and termed MC1R to MC5R, with various homologous between each other. MC1R is a 317 amino acid protein, expressed in various tissues including melanocytes, macrophage cells, human monocytes, neutrophils, endothelial cells, fibroblasts, mast cells and lymphocytes, as well as in rat and human brains in neurons of the periaqueductal gray substance (Adachi et al., 1999; Andersen et al., 2001; Bhardwaj et al., 1997; Catania et al., 1996; Hartmeyer et al., 1997; Star et al., 1995; Taherzadeh et al., 1999; Xia et al., 1995). Besides α-MSH, ACTH1-39 also can serve as active peptide of MC1R (Abdel-Malek, 2001). Until now, many different functions have been attributed to this receptor, including hair and skin pigmentation, anti-pyretic and anti-inflammatory actions, development of melanoma, susceptibility to UV-Induced sun damage, modification of oculocutaneous albinism, development of freckles and solar lentigines (Bastiaens et al., 2001; Jackson, 1993; King et al., 2003; Nakayama et al., 2006; Rees, 2004; Valverde et al., 1995; Valverde et al., 1996). MC1R also mediates female-specific mechanisms of analgesia through kappa-opioid receptor in mice and humans (Getting, 2006; Mogil et al., 2003). Given the multiple function of MC1R, here we explored whether the polymorphism of the *MC1R* gene are associated with MDD and antidepressant response in Mexican Americans.

Methods

Participants

DNA samples from 280 Mexican-Americans (95 depressed patients and 185 age- and sex-matched health controls) were obtained from previous studies (Licinio et al., 2004; Wong et al., 2006), while 86 depressed Mexican-American samples were newly recruited according to the same criteria described previously (Wong et al., 2006). All the participants had at least three of four biological grandparents of Mexican heritage. Among the depressed participants, 95 individuals were enrolled in a pharmacogenetic study of antidepressant treatment response to desipramine or fluoxetine. This study was approved by the IRBs of the University of California Los Angeles, University of Miami, and John Curtin School of Medical Research, and has been registered in ClinicalTrials.gov (NCT00265292).

Genotyping

Sequencing was used for screening SNPs on the *MC1R* gene for the existing 366 DNA samples. The entire coding region of the *MC1R* gene was amplified using PCR primers MC1R_F (5'-GGC AGC ACC ATG AAC TAA GC -3') and MC1R_R (5'-GGT CAC ACA GGA ACC AGA CC-3') to yield an 1122-nucleotide product containing 5' and 3' flanking sequences. Briefly, amplification was performed in 20 μL reaction volumes, containing 100 ng DNA, 0.2 μM of each primer, 0.2 mM of each dNTP, 1 X PCR buffer, and 1 U of AmpliTaq (Applied Biosystems Inc., Foster City, CA, USA). PCR was initiated at 95°C for 2 min and performed for 35 cycle each consisting of 1 min at 94°C, 1 min at 65°C and 1 min at 72°C. The PCR products were cleaned up using ExoSAP-IT enzyme (USB Corporation, Cleveland, OH). Then, the cleaned PCR products was directly sequenced using ABI BigDye v3.1 sequencing Kit on the ABI 3730xl DNA Analyzer (Applied Biosystems) following the manufacture's protocols. All the PCR products were sequenced in both strands. Primers

used for sequencing include the two PCR primers MC1R_F and MC1R_R, as well as two inner primers MC1R_F2 (5'-CAT CTC CAT CTT CTA CGC ACT G-3') and MC1R_R2 (5'-CGT GCT GAA GAC GAC ACT G-3').

Statistical analysis

Maximum likelihood estimates of haplotype frequencies were calculated in control, depressed, remitter, and non-remitter groups using the program Haploview (v4.1) (Barrett et al., 2005). The statistical significance of the genotype/allele/haplotype frequency variables between the depressed patient and control group as well as the antidepressant drug response was evaluated by chi-square test with Yates correction for small numbers.

In silico functional analysis

The functional impact of the coding SNPs on the protein was estimated by PANTHER software, which calculates the subPSEC (substitution position-specific evolutionary conservation) score based on an alignment of evolutionarily related proteins with known functional information (Brunham et al., 2005; Thomas et al., 2006). The probability that a given variant will cause a deleterious effect on protein function, $P_{deleterious}$, was estimated as a function of the subPSEC score. PANTHER subPSEC scores are continuous values ranged from 0 (neutral) to about −10 (most likely to be deleterious). The subPSEC score of −3, which corresponds to a $P_{deleterious}$ of 0.5, is the cutoff point for functional significance (Brunham et al., 2005).

Results

We sequenced 1122 bp of the entire MC1R coding region in 181 depressed Mexican-American patients and 185 health controls. Totally, 23 SNPs (15 known SNPs in the NCBI dbSNP database and eight new SNPs) have been found within the region sequenced (Table 1). The frequency of individuals with at least one SNP is 76.3% (n = 138) and 73.5% (n = 136) in depressive and control group, respectively. Fifteen non-synonymous SNPs result in protein amino acid variations, and seven SNPs have the minor frequency higher than 1%. The minor allele frequency of four common SNPs, rs1805005, rs2228479, rs885479, and rs2228478, is 5.7%, 5.9%, 30.8%, and 11.6% in the control group (Table 1 and 2). Among them, the SNP rs885479, with the highest minor allele frequency in the study population, has been found to be associated with depression ($P = 0.04$).

We also found that two SNPs, rs2228479 and rs2228478, were associated with desipramine response (Table 2). The frequency of allele A at SNP rs2228479 is 12% in the remitter group, which is significantly higher than that in the nonremitter group (0%) when treated with desipramine. Similarly, the frequency of G allele at SNP rs2228478 is 20% in the remitter group, which is significantly higher than that in the nonremitter group (2.9%) when treated with desipramine. No association was found for remission at all the SNPs when treated with fluoxetine, or considering both fluoxetine and desipramine.

Five major haplotypes have been found in the study population, which make up 93.1% of the entire study population (Table 3). We defined the haplotypes as H1 to H5 based on their frequency from high to low. Their frequencies are 49.4%, 31.8%, 4.9%, 4.6%, and 2.4%,

respectively. Among the five haplotypes, the frequency of H2 is 33.2% in the depressed group, and 28.4% in the control group. The statistical test for the frequency difference of H2 between is on the critical significant point, $P = 0.05$.

In silico functional analysis of the non-synonymous SNPs associated with depression and desipramine response was performed. The subPSEC scores ($P_{deleterious}$) of SNPs rs885479 (R163Q) and rs2228479 (V92M) are −4.27401 (0.78143) and −4.54511 (0.82421), respectively. The subPSEC scores indicate that both SNPs have significant impact on the protein function.

Discussion

The frequencies of A allele at SNP rs885479 are 37.3% and 30.8% respectively in the depressed and control group, which are lower than in Asians (63.3% in Chinese and 75.6% in Japanese, respectively) and higher than in Africans (0%) and Caucasians (7.5%) according to the HapMap database (http://www.hapmap.org/). The frequency of T allele at SNP rs1805005 is 5.7% in the studied population, which is lower than that of Caucasians (10.0%) and higher than that of Asians (0%) and Africans (0%; http://www.hapmap.org/). Although the Mexican Americans are considered a recent mixed population from three major ethnic groups: Spaniard, Africans and Native Americans (Hanis et al., 1991), our data showed that there is no significant evidence of stratification in the studied population (Dong et al., 2009). Therefore, this Mexican-American population is appropriate for a case-control association study. The *MC1R* allele frequencies are consistent with the gene admixture between Mexican Americans and other ethnic groups.

Here we found that among the four common SNPs, rs1805005, rs2228479, rs885479, and rs2228478 (Table 1 and 2), the SNP rs885479 (G→A, R163Q) has been found to be associated with depression ($P = 0.04$). We also found two SNPs, rs2228479 (G→A, V92M) and rs2228478 (A→G, T314T), were associated with remission with desipramine (Table 2). The SNP rs2228479 (V92M), together with the changes at codons 84 and 95, has been supposed to alter the alpha-helix structure of the second transmembrane domain (Valverde et al., 1995), thereby affecting the function of MC1R. *In silico* functional analysis reveal that both SNPs associated with depression and desipramine response have significant functional impact on MC1R. The variants of MC1R were reported to be associated with fear of dental pain, anxiety regarding dental care and avoidance of dental care (Binkley et al., 2009). MC1R could mediate female-specific mechanisms of analgesia through kappa-opioid receptor in mice and humans (Getting, 2006; Mogil et al., 2003). Desipramine, a tricyclic antidepressant, is also used to treat cocaine and alcohol dependence, neuropathic pain and attention deficit disorder (Gawin et al., 1989). Desipramine was shown to mediate analgesia by blocking norepinephrine reuptake in diabetic neuropathy (Canciani et al., 2006). There was no association with remission with fluoxetine, or with response in the combined sample of patients treated with fluoxetine and desipramine. Fluoxetine, which blocks serotonin uptake, has not been shown to be no more effective than placebo for the relief of pain (Max et al., 1992). It is therefore possible that the MC1R may be involved in the remission of depression treated by desipramine through the pain pathway. Risk of depression in women

was estimated to be twice as much as that in man (Weissman et al., 1996); this might be intrinsically connected with female-specific mechanisms of analgesia mediated by MC1R.

The natural agonists melanocortin and ACTH of MC1R are derived from the same polypeptide POMC. ACTH is an important component of the hypothalamic-pituitary-adrenal axis and is often produced in the anterior lobe of the pituitary gland in response to biological stress, or produced from cells of immune system (T cells, B cells and macrophages) as a response to stimuli that go along with stress (including CRH). Therefore, there is also a possibility that MC1R might have a role in susceptibility to depression through the hypothalamic-pituitary-adrenal axis responses either to stress or to immune regulation, or through other unknown pathways.

Here, we report the novel association of the variants of *MC1R* with depression and with response to the antidepressant desipramine. Possibly due to the relatively small sample size, the association was modestly significant. Replication in larger samples will be needed to confirm the reported associations here. Since these variants were predicted to have functional effects on protein, confirmation with specific experiments evaluating the pharmacological activity of these variants would be worthy of further study.

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Table 1

MC1R genotype and allele frequencies in Mexican Americans

Order	SNP	Chromosome Position	Allele	Phenotype	Depressed patient			Control		
					Genotype (N = 181)			Genotype (N = 185)		
					Major/Major	Major/Minor	Minor/Minor	Major/Major	Major/Minor	Minor/Minor
1	New	88513294	G→A	G43R	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
2	rs1805005	88513345	G→T	V60L	163 (90.1)	18 (9.9)	0 (0)	165 (89.2)	19 (10.3)	1 (0.5)
3	New	88513416	G→A	S83S	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
4	rs1805006	88513419	C→A	D84E	180 (99.4)	1 (0.6)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
5	rs2228479	88513441	G→A	V92M	167 (92.3)	13 (7.2)	1 (0.6)	164 (88.6)	20 (10.8)	1 (0.5)
6	rs34158934	88513451	C→T	T95M	180 (99.4)	1 (0.6)	0 (0)	185 (100)	0 (0)	0 (0)
7	New	88513476	C→T	A103A	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
8	rs3212364	88513485	G→A	L106L	180 (99.4)	1 (0.6)	0 (0)	183 (98.9)	2 (1.1)	0 (0)
9	New	88513500	G→A	A111A	177 (97.8)	4 (2.2)	0 (0)	182 (98.4)	3 (1.6)	0 (0)
10	rs11547464	88513592	G→A	R142H	179 (98.9)	2 (1.1)	0 (0)	183 (98.9)	2 (1.1)	0 (0)
11	rs1805007	88513618	C→T	R151C	181 (100)	0 (0)	0 (0)	183 (98.9)	2 (1.1)	0 (0)
12	rs1110400	88513631	T→C	I155T	180 (99.4)	1 (0.6)	0 (0)	182 (98.4)	3 (1.6)	0 (0)
13	rs1805008	88513645	C→T	R160W	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
14	**rs885479** *	88513655	G→A	R163Q	**79 (43.6)**	**69 (38.1)**	**33 (18.2)**	**91 (49.2)**	**74 (40)**	**20 (10.8)**
15	rs3212366	88513753	T→C	F196L	180 (99.4)	1 (0.6)	0 (0)	185 (100)	0 (0)	0 (0)
16	New	88513866	G→A	Q233Q	180 (99.4)	1 (0.6)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
17	New	88513910	G→A	Q248D	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
18	New	88513970	C→G	P268R	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
19	New	88513987	G→A	G274S	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
20	rs1805009	88514047	G→C	R294P	177 (97.8)	3 (1.7)	1 (0.6)	183 (98.9)	2 (1.1)	0 (0)
21	rs3212367	88514067	C→T	F300F	181 (100)	0 (0)	0 (0)	184 (99.5)	1 (0.5)	0 (0)
22	rs2228478	88514109	A→G	T314T	155 (85.6)	25 (13.8)	1 (0.6)	146 (78.9)	35 (18.9)	4 (2.2)
23	rs3212368	88514133	G→A	3'UTR	177 (97.8)	4 (2.2)	0 (0)	180 (97.3)	5 (2.7)	0 (0)

* This SNP is significantly associated with depression ($P = 0.04$).

Table 2

Four common MC1R mutations and status of remission

SNP	Test	Non-remitter (NR) Vs Remitter (R), Desipramine+Fluoxetine					Non-remitter (NR) Vs Remitter (R), Desipramine					Non-remitter (NR) Vs Remitter (R), Fluoxetine				
		NR	R	χ^2	df	*P*	NR	R	χ^2	df	*P*	NR	R	χ^2	df	*P*
rs1805005 (V60L)	ALLELIC	5/61	6/102	0.28	1	0.60	2/32	3/47	0.00	1	0.98	3/29	3/55	0.59	1	0.44
rs2228479 (V92M)	ALLELIC	1/65	7/101	2.3	1	0.13	0/34	6/44	4.39	1	**0.04** *	1/31	1/57	0.19	1	0.67
rs885479 (R163Q)	ALLELIC	28/38	37/71	1.17	1	0.28	16/18	14/36	3.2	1	0.07	12/20	23/35	0.04	1	0.84
rs2228478 (T314T)	ALLELIC	3/63	13/95	2.75	1	0.10	1/33	10/40	5.18	1	**0.02** *	2/30	3/55	0.05	1	0.83

*The SNPs are associated with desipramine response ($P < 0.05$).

Table 3

MC1R haplotypes from 23-locus (SNP1–23)[a] and depression status in Mexican Americans

Haplotype	Sequence [b]	Frequency	Case, Control Ratios	χ^2	*P* value
H1	GGGCGCCGGGCTCGTGGCGGCAG	0.494	174.1:187.9, 187.4:182.6	0.477	0.4898
H2	GGGCGCCGGGCTC**A**TGGCGGCAG	0.318	127.3:237.4, 105.3:264.7	3.397	**0.0500**
H3	G**T**GCGCCGGGCTCGTGGCGGCAG	0.049	16.5: 345.5, 19.2: 350.8	0.152	0.6965
H4	GGGC**A**CCGGGCTCGTGGCGGC**G**G	0.046	14.0: 348.0, 20.0: 350.0	0.978	0.3227
H5	GGGCGCCGGGCTCGTGGCGGC**G**G	0.024	6.3: 355.7, 11.4: 358.6	1.365	0.2400

[a] See Table 1 for definitions of the SNP1–23, and the haplotype is from 5' to 3' in MC1R.

[b] The SNPs shown in bold and underlined in the haplotype are different ones compared with most common haplotype H1.