Original Article
https://doi.org/10.9758/cpn.2021.19.1.46
Clinical Psychopharmacology and Neuroscience 2021;19(1):46-52
pISSN 1738-1088 / eISSN 2093-4327

Possible Modulatory Role of ARC Gene Variants in Mood Disorders

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Objective: The genetic background of mood disorders is gradually emerging through the use of large multicenter samples but a detailed phenotyping is complementary in elucidating the role of modulating variants.
Methods: In the present paper we focused on the possible modulatory effects of ARC gene variants on two independent mood disorder samples of European (n = 246 bipolar disorder) and Korean (n = 132 bipolar disorder; n = 242 major depressive disorder [MDD]) ancestry.
Results: No result survived Bonferroni correction, however we evidenced promising trend toward possible association between ARC gene variants and mood disorder phenotypes. In particular, we evidenced weak correlations of ARC single nucleotide polymorphisms with depressive symptoms severity (evaluated through Hamilton depression rating scale scores) in the MDD Korean (rs7465272) and European (rs11167152) samples. Additionally rs10110456 was found to be related to Family History, while rs7465272 was related to suicide risk in the Korean sample. Finally, rs7465272 was associated with body mass index in the European sample.
Conclusion: Overall, ARC gene variants may have a partial role in modulatory effect on treatment efficacy or phenotypes of mood disorders. Further studies, on larger samples may provide a better understanding on the role of ARC gene variants in the symptom severity and treatment outcomes in patients with mood disorders.

KEY WORDS: ARC gene; Depressive disorder; Bipolar disorder; Mood disorder.

INTRODUCTION

Mood disorders have a large societal burden, therefore are the focus of healthcare research since their direct and indirect costs [1]. The main concern around mood disorders is the lack of a definite treatment. The actual drug therapy frequently fails to show a complete efficacy; partial responders and non-responders are, in fact, commonly observed in clinical practice [2]. The main reason explaining this partial efficacy ultimately lie in the complex background behind mood disorders. Both environmental and genetic factors concur to drugs' efficacy inter-individual variation. In particular, the biological background is an important research focus since it may provide new targets for drugs development and biomarkers to pre-emptive test drugs' efficacy [3].

Many investigations were performed with the aim of identifying the biological processes involved in the development of mood disorders [4-8]. Despite the years of research, this field remain pretty active and provided many promising candidate genes for further testing and profiling. In fact, most recent studies on very large samples evidence a number of modulating gene variants [9]. This fact is a normal occurrence given the polygenetic nature of mood disorders and the consequential low effect of each variant toward the phenotype.

Received: June 20, 2019 / **Accepted:** July 29, 2019
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Among the genes showing an interesting link with psychiatric disorders there is ARC (activity regulated cytoskeleton associated protein) [10-12]. In particular, its potential association with Mood Disorders and antidepressant efficacy was already hinted in a previous work by our group [13]. ARC is an early onset gene that encodes for a protein likely to be involved in the regulation of the actin cytoskeleton [14,15] and microtubules [16]. ARC was demonstrated to be essential for the maintenance of dendritic spines density and morphology [17,18] and seems to be significantly involved in mood disorders mechanics. In particular, it was hypothesized that some drugs may elicit their effects through the control on ARC expression, and the consequent modulation of neuroplasticity and neurotransmission processes [12].

In this paper we focused on ARC and in particular on the role of 4 single nucleotide polymorphisms (SNPs), namely rs10110456, rs11167152, rs7465272, rs10097505, on treatment efficacy In this paper our aim was to further contribute to the literature regarding ARC role in mood disorders, in particular we evaluated the same SNPs we investigated in a precedent work [13] in two samples of moderate size and of different ethnicity. At the same time, we attempted to find possible similarities between two genetically distinct populations.

METHODS

Samples

European (EU) sample

Two-hundreds and forty-six (246) patients affected by Bipolar Disorder were recruited in the 'Psy Pluriel' center, Centre European de Psychologie Médicale and the Department of Psychiatry of Erasme Hospital in Brussels. A detailed description of the sample has been reported elsewhere [19]. In brief, the Clinical Outcome Measures for Bipolar Disorder (COPE-BD) project enrolled patients that met the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for a diagnosis of Bipolar type I/II disorders. A structured examination tool was used to assess socio-demographic characteristics, psychiatric antecedents, diagnosis, current and previous treatments of subjects. Lifetime and current diagnosis, course of illness and comorbidities were assessed through the Mini-International Neuropsychiatric Interview (MINI) [20].

Korean (KOR) sample

One-hundred and thirty-two (132) patients diagnosed with BD and two-hundreds and forty-two (242) patients diagnosed with major depressive disorder (MDD) for a total of 374 subjects were recruited in the Department of Psychiatry of Seoul St. Mary's Hospital. The diagnosis were performed according to DSM-IV criteria [20] for bipolar disorder and major depressive disorder, respectively. For this sample, three-hundred and twenty-six (326) controls were also available at the same site. Controls were recruited among hospital staff and non-psychiatric hospital patients, who did not satisfied criteria for current or past psychiatric disorder. Recruitment details and exclusion criteria were previously reported [21,22]. All patients had to be eligible for pharmacological treatment. Patients and controls were evaluated for psychiatric disorders by MINI [20]. Other characteristics of included subjects were collected through a structured interview and review of clinical charts.

The local ethical committees approved the study procedures, and all the subjects were included after they had signed an informed consent (approval no. HC10TISI0031 and OM021).

Main Evaluations

Response to antidepressant treatment, remission and resistance to treatments (primary outcomes) were defined according to the previous research [23]. Briefly, response to treatment is defined as a $\geq$ 50% improvement of HDRS scores from baseline to endpoint; remission as a HDRS score of $\leq$ 7 at the endpoint; resistance as non-response to at least two adequate consecutive antidepressant trials (including the present) [23]. All subjects were treated in a naturalistic setting.

Selection of Polymorphisms and Genotyping

The following criteria were applied to select polymorphisms: 1) reported prevalence of at least 5% for the variant allele among Caucasians (data from http://hapmap.ncbi.nlm.nih.gov/); 2) previous evidence of possible modulation effect. Among eligible polymorphisms, the choice was performed taking into account previous findings in literature. The list of genotyped polymorphisms is shown in Supplementary Table 2 (available online). SNPs showing genotyping rate $<$ 80% were included in the analyses, however the obtained results were considered as sugges-

tive only.

Genomic DNA was purified with an automated workstation (Maxwell; Promega, Fitchburg, MA, USA) and checked for quality and quantity by a small scale spectrophotometer (NanoDrop; Thermo Fisher Scientific Inc., Waltham, MA, USA). Genotyping was performed using restriction fragment length polymorphism, allele-specific oligonucleotide and melting curve analysis on Applied BioSystems 7500 Real-Time PCR system (Thermo Fisher Scientific Inc.). Genotyping was performed according to the manufacturer's standard protocols. Forward and reverse primers' sequences are available upon request.

Statistical Analyses

Hardy-Weinberg Equilibrium (HWE) and Linkage Disequilibrium (LD) were tested through Haploview 3.2 software for Windows (https://www.broadinstitute.org/haploview/haploview) [24]. Haplotypes' analysis was performed in "R" environment (http://cran.r-project.org/), using the statistics package "haplo.score".

The statistical analyses for single SNPs (ANOVA, ANCOVA, Multinomial Logistic Regression, Repeated Measures ANOVA) were performed through the use of IBM SPSS package for windows ver. 23.0 (http://www.ibm.com/analytics/us/en/technology/spss/). Genotypes and dominance/recessive models were tested. Bonferroni correction was applied to minimize false-positive risk derived from multiple testing. We took in consideration the number of SNPs tested for significance (4) in the main analysis. Significance was considered for $p < 0.05/4 = 0.0125$.

RESULTS

Data regarding the samples under investigation are summarized in Supplementary Table 1 (available online). Supplementary Figure 1 and Table 2 (available online) reports results of Linkage and Hardy−Weinberg Equilibrium tests on the samples under investigation. Of note, rs1116715 and rs1009750 resulted not in equilibrium in the European sample. Also, in the same sample rs1011045 showed a genotyping rate < 85% thus decreasing the power of analyses on this SNP. The genotype distribution between European and MDD Korean samples are significantly different, reflecting the overall distribution observed in larger population studies (Hapmap).

Primary Outcome

None of the analyzed SNPs either in single or in haplotypic analyses resulted associated with treatment outcomes.

Secondary Data

Analyses on MDD-KOR subsample evidenced some associations with rs7465272 and symptoms severity at baseline (HDRS.B). Correlation of some ARC haplotypes, namely rs11167152-rs7465272 and rs7465272-rs10097505, with Symptom Severity (calculated as HDRS score at Baseline) was observed in the MDD-KOR subsample. In the same sample the haplotype rs10110456-rs11167152-rs7465272 (which shares two SNPs with one of the previously reported) resulted associated with symptoms improvement.

No other haplotypes resulted significant based on our analyses. Regarding exploratory analyses on other characteristics, our analyses evidenced weak associations with suicide risk and family history. In particular, rs10110456 was correlated with Family History while rs7465272 as related to suicide risk. However, none of these associations survived Bonferroni correction. No significant data was obtained on the whole KOR sample nor in the BPD-KOR subsample.

Analyses on BPD-EU sample evidenced an association of rs111667152 with symptoms severity at baseline. Also, rs7465272 was associated with body mass index (BMI). These associations did not survive Bonferroni correction.

All the details regarding the data obtained are reported in Table 1 (single SNP analyses) and Table 2 (haplotype analyses).

DISCUSSION

In this paper we focused on ARC possible influence on treatment efficacy and other clinical features in two samples of different ethnicity. The reason for this choice is based on previous research on possible associations of this gene with antidepressant efficacy (in particular with response and remission outcomes for rs10110456 and rs11167152) [13]. Unfortunately, despite the previous data, ARC variants do not seem to have any effect on treatment efficacy according to our principal data. We cannot exclude the possibility of the effect being not strong enough to be detected in our samples. ARC variants, how-

Table 1. Overall summary of data obtained on investigated samples

Gene	SNP	Variable[a]	Test type[b]	*p* value	Analysis details	Confidence interval
MDD-Korean						
ARC	rs10110456	Family history	Dominant model (GG vs. GA/AA)	0.036	Not A vs. A: B = 0.725, SE = 0.341, *p* = 0.033, OR = 2.064	1.059−4.024
	rs7465272	Suicidal ideation	Recessive model (AA vs. TA/TT)	0.045	Not T vs. T: B = 1.023, SE = 0.493, *p* = 0.038, OR = 2.783	1.058−7.317
	rs7465272	HDRS at baseline	Dominant model (TT vs. TA/AA)	0.027	A μ = 23.925, SE = 0.703	22.539−25.310
					Not A = 21.831, SE = 0.621	20.608−23.054
			Genotype	0.038	AA μ = 25.842, SE = 1.659	22.573−29.111
					TA μ = 23.506, SE = 0.775	21.978−25.033
					TT μ = 21.831, SE = 0.620	20.609−23.053
BPD-European						
ARC	rs7465272	BMI at baseline	Genotypic	0.020	AA μ = 31.087, SE = 2.115	26.920−35.254
					TA μ = 25.121, SE = 1.052	23.047−27.195
					TT μ = 24.534, SE = 1.063	22.441−26.628
			Recessive model (AA vs. TA/TT)	0.006	T μ = 24.830, SE = 0.746	23.360−26.301
					Not T μ = 31.087, SE = 2.111	26.928−35.247
	rs11167152	HDRS at baseline	Genotypic	0.047	CC μ = 15.044, SE = 0.800	13.465−16.624
					GC μ = 12.295, SE = 1.144	10.036−14.555
					GG μ = 11.879, SE = 1.321	9.270−14.488
			Recessive model (CC vs. GC/GG)	0.014	G μ = 12.117, SE = 0.863	10.414−13.820
					Not G μ = 15.044, SE = 0.798	13.469−16.620

Table 1 reports the nominally significant ($p < 0.05$) data obtained from analyses on the samples under investigation.
SNP, single nucleotide polymorphism; MDD, major depressive disorder; BPD, bipolar disorder. BMI, body mass index; HDRS, Hamilton depression rating scale. B, unstandardized regression weight; SE, standard error; OR, odds ratio, μ, mean. Both Recessive and Dominant Models were tested for each SNP under investigation. Model is defined as dominant or recessive depending on the wild type form of the SNP. Dominant model: Mutated form tested for dominant effect. Recessive model: Mutated form tested for recessive effect. Wild type definition was based on the most common allele of a SNP on European population according to PubMed SNP database.
[a]Indicates the variable tested for association. [b]Indicated the type of model tested for association.

Table 2. Results obtained from Haplotypic analyses on Korean-MDD sample

Hap-freq	Hap-score	*p* value	Sim *p* value	Haplotypes		
HDRS score at baseline						
Global = 0.039		Max−Stat = 0.016				
				rs11167152	rs7465272	
0.731	−248029.000	0.01*	0.013	c	t	
0.256	249388.000	0.01*	0.012	c	a	
Global = 0.048		Max−Stat = 0.030				
				rs7465272	rs10097505	
0.486	−161532.000	0.106	0.108	t	g	
0.252	−0.523	0.601	0.598	t	a	
0.258	253307.000	0.01*	0.012	a	g	
HDRS score Improvement at baseline						
Global = 0.019		Max−Stat = 0.043				
				rs10110456	rs11167152	rs7465272
0.405	−237403.000	0.02	0.015	a	c	t
0.311	0.330	0.742	0.75	g	c	a
0.284	222629.000	0.03	0.024	g	c	t

MDD, major depressive disorder; Hap-freq, Haplotype frequency; Hap-score, Haplotype score; sim, simulation; SNP, single nucleotide polymorphism; HDRS, Hamilton depression rating scale.
*$p < 0.0125$.

ever, may influence symptoms severity at baseline. Interestingly, rs11167152 resulted associated with symptoms severity at baseline in both EU- (single SNP analysis) and MDD-KOR (included in a haplotypic block) samples. Hinting for a possible role of this SNP in depressive severity regardless of the diagnosis and ethnic-related differ-

ences of the genetic background. It has to be noted, though, that data on rs11167152 in the EU-sample can only be considered as exploratory, since this SNP resulted not in HW-equilibrium and the genotyping rates were slightly lower than the 85% threshold. According to in silico analysis of rs11167152 through the Human Splicing Finder (HSF) prediction software (http://www.umd.be/HSF3) [25], the G > C variation create a silencer consensus sequence and at the same time remove a potential enhancing site (for SF2/ASF protein). Both events may influence ARC expression. Rs11167152 also slightly alter a splice site sequence, but, according to in silico data, not enough to influence splicing. It also should be noted that the location of rs11167152 is on the 3'downstream of ARC, as such no splicing events should occur at this location likely making this alteration not influent. Likewise, rs7465272 T > A variation, which as associated with symptoms severity in the KOR-only MDD subsample, potentially decreases the expression of ARC through the creation of a silencer consensus sequence. Rs7465272 was associated with Symptoms' severity in Korean subjects but not in the European ones. However, in the latter MDD subsample it was found to be associated with body mass index. Unfortunately, we were not able to compare BMI data with the Korean one since BMI was not collected from MDD patients (only on BPD ones). From our analyses we found two sets of haplotypes seemingly associated with symptoms severity at baseline in the MDD-KOR subsample. They are rs11167152, rs7465272 and rs7465272, rs10097505. The CA and AG haplotype, respectively were both associated with an higher symptoms severity. Interestingly enough, according to in silico analyses, each of the alleles included in this haplotype are likely to cause the down regulation of ARC expression. From a functional point of view, the potential down-regulation caused by the described alterations leads to a decreased availability of the encoded protein. As such, a reduced ARC expression is likely related to a more severe symptomatology at baseline. Another haplotype within ARC, the rs10110456, rs11167152, rs7465272 GCT haplotype, resulted associated with higher improvement in the sample under analysis. In this case, the link between the evidenced effect on improvement and the biological alterations caused by alleles is less clear. Indeed, rs11167152 C allele promote the down regulation, while rs7465272 T allele has the opposite effect (in silico predictions). The role of rs10110456 G allele is less clear. Overall, our data suggest a possible implication of lower levels of ARC with symptoms phenotype. The importance of ARC levels was described in literature: Interestingly, increased expression of *Arc* can be triggered by 5-HT [26] and this action may be behind 5-HT involvement in the action of antidepressant drugs [27]. Further, it was evidenced an increase of *Arc* mRNA levels after pharmacological treatment in specific regions of the brain (cingulate and orbital areas of the frontal cortex by 34% and 46% respectively) [27].

The simultaneous study of BPD and MDD subjects may be biased, given the apparently different nature of the two diseases. However, literature data confirm the existence of an overlapping genetic background [28]. Supported by this data, we performed our analyses in both BPD and MDD subjects in order to evidence any commonalities between the two different populations. EU subsample suffers of some limitations including HWE disequilibrium for two of the investigated SNPs, namely rs11167152 and rs1009750. Further, rs10111045 and rs11167152 genotyping rates were inferior to the 85% threshold. As such the obtained results regarding the above SNPs should be carefully interpreted, and should be considered as suggestive. The somewhat limited number of subjects involved as well as the different ethnicity may pose a limit for the detection of weak influences and replication of data due to a dissimilar genetic background, respectively. Further, EU sample was collected in a cross sectional way, therefore biases may have influenced the outcome definition.

According to our main analyses, we did not find significant associations involving ARC polymorphisms with treatment outcomes in either of the investigated samples. Thus, we did not replicate our previous findings on rs10110456 and rs11167152 ARC SNPs [13]. We did detect some data indicating ARC polymorphisms being able to influence symptoms severity at baseline in both samples. In particular, rs7465272 alone and in haplotypic combination with rs11167152 or rs10097505, showed a significant association with symptoms severity at baseline in the Korean sample. rs11167152 was also the only SNP associated with symptoms severity in the European sample. Further, haplotype rs10110456-rs11167152-rs7465272 resulted associated with symptoms improvement in the Korean sample. Finally, exploratory data evidenced a possible influence of rs7465272 variants on the BMI of depressed subjects in the European sample.

Overall, we found some weak correlations in our analyses, the most suggestive one being the rs11167152 association with symptoms severity in both samples regardless of the ethnic-related genetic differences. Unfortunately, as explained before in the limit section, rs11167152 genotyping evidenced some issues in the EU-sample. The other correlations we found were evidenced only in one or the other sample under investigation. ARC variants do not seem to modulate treatment efficacy or their effect is not strong enough to be detected in our limited sample. These variants, though, may explain a certain degree of difference on symptoms severity on subjects before treatment, especially regarding rs11167152. This hypothesized effect is likely related to ARC expression, with lower levels being associated to a more severe phenotype. Further studies, on larger samples may aid for a better evaluation of ARC role in MDD severity.

■ Acknowledgments

All authors thank the patients for their participation in this study. This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HC10TISI0031). All the authors listed meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this work. They have given their approval for this version to be published and take responsibility for the integrity of the data reported in the work. All authors declare that they have no conflict of interest.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Concetta Crisafulli, Alessandro Serretti. Recruitment (EU): Laura Mandelli, Daniel Souery, Julien Mendlewicz, Alessandro Serretti. Recruitment (KOR): Soo-Jung Lee, Sheng-Min Wang, Changsu Han, Ashwin Patkar, Prakash Masand, Chi-Un Pae. Statistical Analyses: Marco Calabrò, Concetta Crisafulli, Laura Mandelli. First Draft & Revision: Marco Calabrò, Laura Mandelli, Concetta Crisafulli, Alessandro Serretti

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