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Heat-shock protein-70 genes and response to antidepressants in major depression

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Abstract

In the search of predictors of antidepressant efficacy, much interest has recently focused on pro-inflammatory proteins, as they were found to be elevated during major depressives states and decreased by antidepressant drugs. In the present paper we investigated the role of the genes coding for heat-shock-70 family proteins, recently hypothesized to be activated by antidepressants and thus mediate the reduction of pro-inflammatory cytosines.

One hundred and forty two hospitalised patients, affected by major depression and treated with antidepressants drugs for a major depressive episode were evaluated for depressive severity at the baseline and at the discharge and genotyped for five SNPs within the genes HSPA1L, HSPA1A and HSPA1B.

Markers were not individually associated with symptom severity after treatment. Instead, we found a three markers haplotype, including SNPs within HSPA1L and HSPA1A, associated with a poorer response to antidepressant treatment ($p=0.005$). Single markers as well as haplotypes were not associated with other clinical features.

In conclusion, genetic variants within the genes coding for HSP-70 family proteins may affect the action of antidepressants and thus their therapeutic efficacy.

Keywords: Antidepressant; Depression; Genetics; Heat-shock protein; Pharmacogenetics

1. Introduction

Antidepressant drugs efficacy in short-term major depression treatment is, at least partly, under genetic control (Franchini et al., 1998; O'Reilly et al., 1994; Pare et al., 1962; Serretti et al., 1998). A number of pharmacogenetic predictors of antidepressant efficacy have been reported over the last few years (for a review see Serretti et al., 2005) but results are still inconsistent.

A recent field of interest focused the role of pro-inflammatory cytosines (Leonard and Myint, 2006; Muller and Schwarz, 2006) as it is known that in major depression occurs a prolonged elevation of pro-inflammatory cytokines concentration, probably inducing malfunction of noradrenergic and serotonergic neurotransmission in the brain (Muller and Schwarz, 2006). There is evidence that antidepressants reduce the release of pro-inflammatory cytosines, thus some authors have hypothesized that efficacy of treatments may be partly due to this mechanism (for a review see Leonard, 2001).

Heat-shock protein-70 (HSP-70) mediates a highly conserved system of cellular response to a range of insults (Beere and Green,

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Table 1
Characteristics, primer sequences and PCR conditions for pyrosequencing of heat-shock protein gene 5 SNPs

Gene name	Gene size	Chromosomal position of gene	SNP name	Chromosomal position of SNP	Alleles	Heterozygosity
HSPA1L	5411pb	31885375–31890786	rs2227956	31886251	C/T	0.238
			rs2075799	31886508	A/G	0.24
HSPA1A	2382bp	31891316–31893698	rs1043618	31891486	C/G	0.497
			rs562047	31891842	C/G	0.074
HSPA1B	2507bp	31903503–3190610	rs539689	31905566	C/G	0.497

SNP name	Primer sequences	Contents of PCR reaction	PCR conditions
rs2227956	Forward: 5′-AGGGGAGTTCCCTTCAGATCGA-3′ Reverse: 5′-Biotin-AACCATGCGCTCAATCTCCTC-3′ Sequencing primer: 5′-TTCTCAATGTCACAGCCA-3′	DyeMix DNA polymerase (Biostream, Suwon, Korea) 10 μl, forward and reverse primers 0.5 μl each, water 8.5 μl, DNA template 0.5 μl	94 C 5 min, 94 °C 30 s, 67 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs2075799	Forward: 5′-CTGATGGGGGACAAGTCTGAGA-3′ Reverse: 5′-Biotin-TGGGGATGGTGGAGTTGC-3′ Sequencing primer: 5′-GTCCCTGGGGCTGGAG-3′	Dye mix 10μl, forward and reverse primers 0.25μl each, water 9.0μl, DNA template 0.5μl	94 °C 5 min, 94 °C 30 s, 65 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs1043618	Forward: 5′-TCTTCTCGCGGATCCAGTGTT-3′ Reverse:5′-Biotin-TGGTCGTTGGCGATGATCT-3′ Sequencing primer: 5′-AGCCCCCAATCTCAG -3′	Dye mix 10 μl, forward and reverse primers 0.5 μl each, water 8.5μl, DNA template 0.5μl	94 °C 5 min, 94 °C 30 s, 67 °C 30 s, 72 °C 7min (40 cycles)
rs562047	Forward: 5′-AGATCTCCTCGGGGTAGAATGC-3′ Reverse: 5′-Biotin-GCTGATCGGCCGCAAGTT-3′ Sequencing primer: 5′-CGGGGTAGAATGCCTTG-3′	Dye mix 10 μl, forward and reverse primers 0.5 μl each, water 8.5 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 67 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs539689	Forward: 5′-AACAAAGGCCCCTAATCCAC-3′ Reverse: 5′-Biotin-TCATCAGCGGACTGTACCAG-3′ Sequencing primer: 5′-CCTGAGCCCCGAAGCC-3′	Dye mix 10 μl, forward and reverse primers 0.25 μl each, water 9.0 μl, DNA template 0.5 μl	94 °C 5 min, 4 °C 30 s, 65 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)

2001) and several studies showed a protective role of HSP-70 in various models of nervous system injury (Chang et al., 2004; Kelly and Yenari, 2002; Rajdev and Sharp, 2000; Yenari et al., 1999). The synthesis of HSP-70 induced by insults concomitantly inhibit the production of cytosines (Hall, 1994); thus abnormal functioning of HSP-70 was hypothesized underlying altered stress in major depression: in fact a deletion in HSP-70 mRNA, resulting in the non-synthesis of the protein, was found in a group of major depression patients (Shimizu et al., 1996).

The effect of antidepressants in reducing pro-inflammatory cytosines, which is a possible mechanism underlying their therapeutic efficacy, may be mediated by the activation of HSP-70 (Guest et al., 2004), thus the genes coding 70-kDa heat-shock family proteins (HSP-70) are of extreme interest in the response and efficacy of antidepressant treatments.

The human HSPA multigene family encodes several highly conserved 70-kDa proteins with structural and functional properties in common, but which vary in their inducibility in response to metabolic stress. In the class III region of the major histocompatibility complex on 6p21.3 was identified a duplicated HSP-70 locus (Sargent et al., 1989), named HSPA1A and HSPA1B. Both encode identical 641-amino acid proteins but the 3′ untranslated regions of these genes are divergent. Northern blot analysis of HeLa cell RNA detected an approximately 2.4-kb HSPA1B transcript that was expressed at elevated levels following heat shock. Sargent et al. also identified a region with similarity to HSPA1A located approximately 4 kb telomeric to HSPA1A; this homologous region has been defined as a gene of the HSP-70 family (HSPA1L) (Milner and Campbell, 1992).

In the present paper we investigated a set of polymorphisms, within the mentioned HSPA1A, HSPA1B and HSPA1L genes, in association with the response to antidepressant treatment, in a sample of patients affected by Major depressive disorder.

2. Methods

2.1. Sample

One hundred and forty-two patients affected by Major depressive disorder (MDD) were enrolled in this study. Diagnosis of MDD was based on the consensus between two board-certified psychiatrists according to the DSM-IV criteria (American Psychiatric Association, 1994). The patients were assessed using a Structured Clinical Interview, DSM-IV Axis I disorders-Clinical Version (First et al., 1995) and patients having comorbidity Axis I disorder other than MDD were excluded. Patients included in the sample were all hospitalised and treated for a major depressive episode, with antidepressants (ADs), for at least more than two weeks (mean: 29.4±15.9 days). Concurrent psychotropic drugs were not allowed, except for benzodiazepines. Subjects with neurological and concurrent medico-surgical illness were also excluded from the study.

According to these criteria, the present sample was mainly composed by females (73%) with a mean age at onset of 41.5± 15.2. Mean age of patients at the current hospitalisation was 43.3±15.33 years. All subjects were biologically unrelated, native Korean descendants residing in Korea. Written informed consent was provided by the subjects after being explained the purpose and method of the study. The institutional review board of Kangnam St. Mary's Hospital approved the study that was conducted in accordance with the Declaration of Helsinki.

2.2. Treatments and response assessment

During hospitalisation, patients were treated with ADs (paroxetine=63, fluoxetine=7, venlafaxine=24, mirtazapine=24, dothiepin=9, trazodone=2, missing=13) at standard therapeutic doses (paroxetine: 20–40 mg, fluoxetine: 20–40 mg, venlafaxine: 150–225 mg, mirtazapine: 30–60 mg, dothiepin: 150–225, trazodone: 400–600 mg) and anti-anxiety drugs (93.5%): alprazolam (n=41, median dosage: 1.5 mg/die), lorazepam (n=81, median dosage: 3 mg/die), clonazepam (n=8 median dosage: 3 mg/die).

Patients were evaluated at the intake and at the discharge, with the 10-items Montgomery-Åsberg Depression rating scale (MADRS) (Montgomery and Asberg, 1979) and the Clinical Global Impression scale (CGI) (Guy, 1976) by expert psychiatrists blind to genetic status, to detect symptomatic change during AD treatment. MADRS score at baseline was 39.1±6.4 and 26.3±5.9 at the discharge; CGI scores were 4.4±0.7 at baseline and 2.5±0.8 at discharge. Response to treatment was defined by final scores for MADRS and CGI and by percent reduction of scores from baseline, as this latter index is more sensitive to symptomatologic change when the response rate is low (Leucht et al., 2006), as it was in our sample.

2.3. Genetic analysis

Genomic DNA was extracted from the patients' whole blood samples, using a DNA extraction kit (Accuprep Genomic DNA extraction kit, Bioneer, Korea). Five SNPs (rs2227956 C/T, rs2075799 A/G, rs1043618 C/G, rs562047 C/G, rs539689 C/G) were selected based on public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/).

PCR primers (Bioneer, Korea) and sequencing primers (Bioneer, Korea) used for the Pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software (Biotage AB, Sweden) and one primer of each primer set was biotinylated. Information of SNPs, PCR primers and sequencing primers are listed in Table 1. DNA templates of subjects were amplified in PTC 200 thermal cycler (Bio-Rad Laboratories, U.S.A.) using each primer sets for 5 SNPs. Biotinylated PCR products were immobilized onto streptavidin-coated beads (37 μl of binding buffer, 3 μl of streptavidin sepharose beads, Amersham, Sweden) and incubating at room temperature for 10 min. The beads were transferred to a filter plate and liquid was removed by vacuum filtration (Biotage AB, Sweden). DNA was purified by washing in ethanol for 5 s, denatured in 0.2 M NaOH for 5 s, and washed with washing buffer (10 mM Tris-acetate) for 5 s. The immobilized single-stranded template was washed, then transferred to a PSQ 96 Plate and annealed with the sequencing primers using 0.4 μl of sequencing primers and 100 μl of annealing buffer (20 mM Tris-acetate, 2 mM Mg-acetate) and incubating at 90 °C for 2 min. Substrates, enzymes, and dNTPs from the SNP Reagent Kits (Biotage AB, Sweden) were added to a cartridge according to amounts specified by Pyrosequencing Assay Design Software (Biotage AB, Sweden). The 5 SNPs were genotyped using PSQ 96MA Pyrosequencer and SNP Software (Biotage AB, Sweden). Details are presented in Table 1.

2.4. Alleles frequencies, Hardy–Weinberg equilibrium and linkage disequilibrium between markers

Rs2227956, rs1043618 and rs539689 alleles frequencies were similar to that reported on the public database on http://www.ncbi.nlm.nih.gov/SNP/, for Asian populations (rs2227956*C: 9.8%, rs1043618*C: 25.7%, rs539689: 69.0%). The frequency of rs562047*C (90.5%), not reported in Asians, was similar to that reported in Caucasians (94.0%). The frequency of the rs2075799*A allele (3.2%) was lower than the one reported for Asians (15%) but similar to the one reported for Europeans (4.2%). Overall, in this Korean sample, only rs2227956 deviated from allele frequency distribution in Caucasian but consistently with the distribution in Asian populations (29% in Caucasians vs. 10% in Asiatic populations).

In this sample all polymorphisms were in Hardy–Weinberg equilibrium (rs2227956 p=0.51, rs2075799 p=1.0, rs1043618 p=0.87, rs562047 p=0.91, rs539689 p=1.0). The two SNPs within HSPA1L were not in significant full Linkage Disequilibrium (LD) (D'=1, LOD=0.13), while SNPs within the HSPA1A were in strong significant LD (D'=0.82, LOD=6.38). Being all SNPs very close, we also analyzed LD among markers in different genes and we observed a full LD between rs2227956 (HSPA1L) and rs539689 (HSPA1B), between rs2075799 (HSPA1L) and rs1043618 (HSPA1A), between rs2075799 (HSPA1L) and rs539689 (HSPA1B) (Fig. 1).

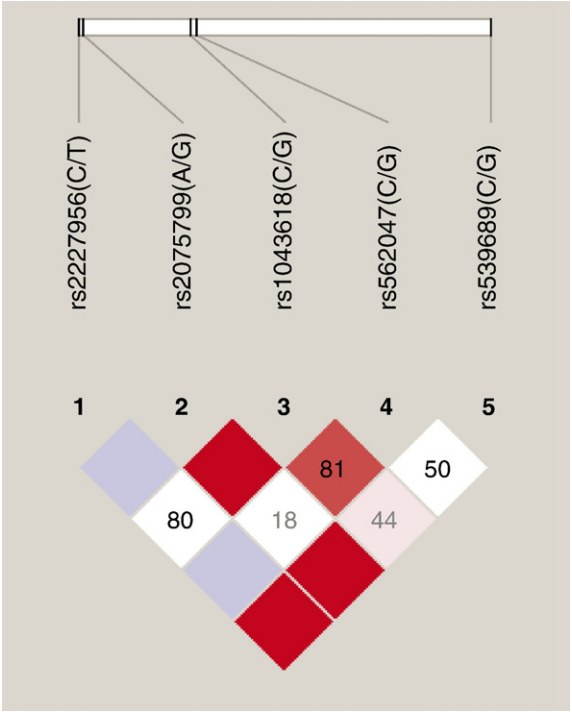

Fig. 1. Linkage disequilibrium among five markers within HSPA1L (rs2227956, rs2075799), HSPA1A (rs1043618, rs562047) and HSPA1B (rs539689) (see text for details).

2.5. Statistical analysis

Haploview 3.2 was used to generate a linkage disequilibrium map and to test for Hardy–Weinberg equilibrium. Single genotypes associations with MADRS and CGI scores were analyzed by the analysis of variance (ANOVA); when including covariates or other factors, the analysis of covariance (ANCOVA) and the multivariate analysis of co-/variance (MANOVA/MANCOVA) were employed. Baseline scores were included as covariates plus the clinical variables associated with genotypes. Associations with other clinical variables in the sample were performed by the ANOVA or the Chi-square test. The "R" software ("A Programming Environment for Data Analysis and Graphics" Version 2.2.1) was employed to analyze haplotypes with both discrete and continuous traits and to include covariates. Permutation (50,000 permutations) was used to estimate the global significance of the results for haplotype analyses and confirm the expectation–maximization values. Results were considered significant with an alpha level lower than 0.01 (Bonferroni correction for five markers). With this level of significance, for single marker allele analyses, in our sample we had a power of 0.80 to detect a medium effect size of $d=0.44$, which corresponded to a difference of approximately 2.7 MADRS points between two alleles and corresponded to an explained variance of about 4.8% (Cohen, 1988).

3. Results

3.1. Clinical correlates of response to antidepressant treatment

Reductions of MADRS and CGI scores from baseline to the discharge were not associated with any clinical feature we considered in the present work: sex (respectively: $p=0.34$, $p=0.44$), age ($p=0.19$, $p=0.96$), age at onset ($p=0.24$, $p=0.97$), family history for psychiatric disorders ($p=0.90$, $p=0.34$), suicide attempt ($p=0.81$, $p=0.64$), antidepressant administered ($p=0.82$, $p=0.58$) and dosage for each type (all p values >0.05), anti-anxiety treatment ($p=0.51$, $p=0.20$) and dosage for each type (all p values >0.05), duration of treatment ($p=0.22$). Reduction of MADRS scores was only marginally dependent from baseline depressive severity ($p=0.015$), while reduction of CGI scores was more consistently related to initial global severity ($p>0.0001$).

3.2. Association analysis between markers and response to antidepressant treatment

Analyzing percent reduction in MADRS scores from baseline to discharge, we found the HSPA1A rs1043618 SNP marginally associated, with carriers of the G variant showing a lower percent reduction. However, genotype analysis did not confirm the association (Table 2). Carriers of the rs539689 C allele and C/C genotype for the HSPA1B gene, showed medium final higher scores at the MADRS. However, when including baseline scores as covariates in the ANCOVA, result was not significant (main effect of alleles: $p=0.061$; main effect of the genotype: $p=0.14$). No any association was observed with CGI scores (data not showed, all p value >0.01).

Haplotypes in HSPA1L and HSPA1A markers were not associated with final MADRS scores (HSPA1L: Global stat. = 4.72 $df=3$ $p=0.19$; HSPA1A: Global stat. = 3.54 $df=3$ $p=0.32$). However, when analyzing haplotypes including all five markers (as the three genes are strictly close), we observed a trend of association (Global stat. = 15.01 $df=8$ $p=0.059$); sliding windows analysis revealed a major contribution from rs2227956 (HSPA1L), rs2075799 (HSPA1L) and rs1043618 (HSPA1A) (Global stat. = 11.73 $df=4$ $p=0.019$, Sim. $p=0.020$), with the T–G–G haplotype significantly associated with higher final scores. By including baseline scores as covariate in the model, result for the T–G–G haplotype was even stronger (Stat. = 2.65 $p=0.0080$, Sim. $p=0.0079$). As well, analyzing percent reduction from baseline, the T–G–G haplotype showed a trend of association with a lower response to treatment (Global stat. = 7.90 $df=4$ $p=0.095$, Sim. $p=0.039$) (Table 3). Duration of treatment was not different between haplotypes ($p=0.74$) and the effect of T–G–G haplotype was not influenced by it (effect

Table 2
Association analysis between markers with final MADRS scores and percent reduction of MADRS scores from baseline (MADRS = Montgomery–Åsberg Depression rating scale)

Genes	Markers	Alleles	Final MADRS	p value	% reduction MADRS	p value	Genotypes	Final MADRS	p value	% reduction MADRS	p value
HSPA1L	rs2227956	C ($n=29$)	24.3±5.7	$p=0.05$	34.6±11.3	$p=0.27$	C/C ($n=2$)	22.5±6.4	0.17	31.8±9.6	0.45
		T ($n=255$)	26.6±5.8		31.9±12.7		C/T ($n=25$)	24.6±5.8		35.1±11.8	
							T/T ($n=115$)	26.8±5.8		31.6±12.8	
	rs2075799	A ($n=9$)	26.2±5.9	$p=0.25$	32.3±12.7	$p=0.70$	A/A ($n=0$)	–	0.24	–	0.69
		G ($n=275$)	28.6±5.0		30.6±8.8		G/A ($n=9$)	28.6±5.0		30.6±8.8	
							G/G ($n=133$)	26.2±5.9		32.3±12.8	
HSPA1A	rs1043618	C ($n=73$)	26.7±5.8	$p=0.11$	34.8±12.6	$p=0.04$	C/C ($n=10$)	26.8±5.8	0.22	36.7±14.7	0.14
		G ($n=211$)	25.4±5.9		31.3±12.5		C/G ($n=53$)	26.1±5.8		34.0±12.0	
							G/G ($n=79$)	26.8±5.8		30.4±12.6	
	rs562047	C ($n=257$)	26.5±5.8	$p=0.21$	32.0±12.5	$p=0.47$	C/C ($n=115$)	26.6±5.8	0.19	31.8±12.4	0.45
		G ($n=27$)	25.0±6.1		33.9±13.5		C/G ($n=27$)	25.0±6.1		33.9±13.5	
							G/G ($n=0$)	–		–	
HSPA1B	rs539689	C ($n=196$)	26.9±5.8	$p=0.02$	31.4±12.5	$p=0.13$	C/C ($n=68$)	27.7±5.5	0.03	30.2±12.2	0.17
		G ($n=88$)	25.1±5.9		33.9±12.7		C/G ($n=60$)	25.0±6.1		34.3±12.7	
							G/G ($n=14$)	25.3±5.6		32.9±13.2	

Table 3
Association analysis between rs2227956–rs2075799–rs1043618 haplotypes and final MADRS scores (MADRS = Montgomery–Åsberg Depression rating scale) (see text for details)

3-markers haplotypes	Haplotypes Frequency	Final MADRS		% reduction MADRS	
		Statistics	*p* values	Statistics	*p* values
T–G–C	0.225	−2.15	0.031	2.27	0.023
C–G–G	0.099	−1.97	0.049	0.96	0.33
T–A–C	0.028	1.13	0.26	−0.66	0.51
T–G–G	0.644	2.79	0.005	−2.53	0.011

of haplotype including duration of treatment as covariant: Stat. = 2.72 $p=0.006$; interaction between haplotype and time in the ANCOVA: $p=0.73$).

No any association was observed between haplotypes and CGI scores (baseline: $p=1.00$; final: $p=0.45$, percent reduction: $p=0.70$), as well as with other clinical variables, such as age at onset ($p=0.57$), family history for psychiatric disorders ($p=0.46$), suicide attempt ($p=0.14$).

4. Discussion

Heat-shock proteins-70 (HSP-70) gene polymorphisms have been associated with some neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (Clarimon et al., 2003; Wu et al., 2004). Regarding other mental disorders, in a previous paper, for the first time we reported an association between HSPA1B and Schizophrenia (Pae et al., 2005). Recently, we also obtained positive results in depression (unpublished data) and bipolar disorder (unpublished data).

The functional significance of HSP-70 gene polymorphisms in the pathogenesis of different diseases is not certain. HSP-70 proteins mediate the response to cellular insults (Hall, 1994) and have been found to play a key role in the neuronal integrity, which is related to the pathogenesis of different psychiatric disorders (Dong et al., 2005; Yu et al., 2005). In depression also there is evidence of an involvement of neuronal plasticity; cytokines have been found elevated in severe depressive illness and following stressor exposure (Muller and Schwarz, 2006). Thus, depressive illness may be considered a disorder of neuroplasticity other than being associated with neurochemical imbalances (Hayley et al., 2005).

To our knowledge, this is the first paper reporting an association, though small in explained variance, between genes coding for HSP-70 and response to antidepressant treatment. It has been suggested that antidepressants reduce the release of cytokines (Leonard, 2001), probably enhancing the activity of HSP-70. There is in fact evidence of an increased expression of HSP-70 following the administration of antidepressants, thus the synaptic rearrangement induced by HSP-70 proteins may be the mechanism underlying the therapeutic effect of antidepressants (Guest et al., 2004).

In this paper we reported the haplotype T–G–G (rs2227956, rs2075799, rs1043618) within the HSPA1L and HSPA1A genes, associated with a more severe depressive symptomatology at the end of treatment, thus with a poor response to antidepressants. We may hypothesize that these variants lead to a lower expression of HSP-70 or to less active protein forms, an effect mild for each variant but detectable with the joint analysis. In depressed patients, the lower activation of HSP-70 in response to antidepressants would result in the persistence of brain altered neurotransmission and, thus, in the persistence of clinical depression. However, further studies are needed to understand the mechanisms of activation of HSP-70, it's interaction with antidepressant drugs and it's involvement in depressive states (Guest et al., 2004).

In the present study a concern may regard the discrepancy between single markers and haplotypes analyses, as the three SNPs associated in the haplotype analysis, were not individually associated with response to antidepressants. Further, while rs1043618 and rs2075799 were in full Linkage Disequilibrium (LD), rs2227956 and rs2075799 obtained LOD scores too low to be actually informative of LD, thus we cannot strictly assume the combination of the three markers as a block.

Other limitations of the present study are linked to the sample. Firstly the relatively small sample size lacking of genomic control is liable for stratification bias, however Korean population is considered genetically homogenous (Cavalli Sforza, 1994) and no patients from other regions were included in the study. The power of our sample was sufficient to detect effects of variance explained up to 4.8%, although this is a good result, smaller effects could have been missed. Multiple testing may lead to false positive findings, and this should be considered in the present paper where 5 SNPs were tested, however we applied a Bonferroni correction to limit this bias. Further, the present sample should not be considered representative of the general depressed population as the initial severity was rather high (Zimmerman et al., 2004) and the improvement during antidepressant treatment was rather mild, this may be the cause why we did not observe a difference in the less sensitive CGI scores. The small improvement observed could be due to the heterogeneous use of antidepressants and, at least for some of them, also suggests the possibility of an unspecific effect. This prevented us from performing categorical analyses since no one of the subjects reached euthymia during treatment (Zimmerman et al., 2004). In fact the 50% improvement was observed in a very small part of the sample. This could be due to the selection of the sample in the direction of severely depressed inpatients; in fact although they were not resistant depressives, only most severe cases were admitted in the hospital. Finally, heterogeneous antidepressant treatments and the lack of a replication sample represent other limitations of the study.

In conclusion, we observed an interesting association between genes coding for HSP-70, an important family of proteins exerting a protection role in cellular survival and plasticity, and antidepressant response in mood disorders. Notwithstanding the limitations of the study and the need for independent confirmation, this could be a further step toward an individualized therapy.

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