Genetic Variants in ST8SIA2 gene influence treatment outcome in treatment resistant depression: a European multicenter study

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INTRODUCTION:

Major depressive disorder (MDD) is the most common neuropsychiatric disease and although many people are affected by treatment resistance and lots of studies have focused on this topic, there are still not enough reliable markers to predict treatment response and resistance. As shown by our group the 5-HT1A receptor plays a fundamental role in MDD, modulating treatment response to SSRI and ECT [1]. Interestingly, the sialyltransferase 8B gene (ST8SIA2), being essential for the polysialylated form of the neural cell adhesion molecule (PSA-NCAM), is closely linked to the 5-HT1A receptor [2]. Furthermore serotonergic innervation controls PSA-NCAM activity in the hippocampus with antidepressants increasing its level. SSRIs and PSA-NCAM thereby enhance neuronal plasticity, an important factor in antidepressant treatment as recently proposed by our group [3]. Additionally ST8SIA2 has been associated with mood disorders and treatment resistant depression and hence is a promising candidate gene for treatment resistance and response in MDD.

Therefore here we investigated the role of ST8SIA2 in treatment resistant depression. The impact of 8 SNPs covering this gene *(rs2290492, rs3759917, rs3784723, rs4777989, rs8035760, rs11632521, rs11853992, rs17522085)* **and their resulting haplotypes on treatment outcome phenotypes was analyzed.**

SNP	rs2290492	rs3759917	rs3784723
Alleles	CC CT TT	GG GT TT	CC CT TT
Subjects	232 92 13	10 99 231	2 18 300
SNP	**rs4777989**	**rs8035760**	**rs11632521**
Alleles	AA AG GG	AA AT TT	AA AG GG
Subjects	98 132 66	9 74 253	83 139 68
SNP	**rs11853992**	**rs17522085**	
Alleles	AA AG GG	CC CT TT	
Subjects	201 119 20	249 75 5	

Table 1.
Alleles of the SNPs analyzed and their corresponding subject numbers (total numbers).

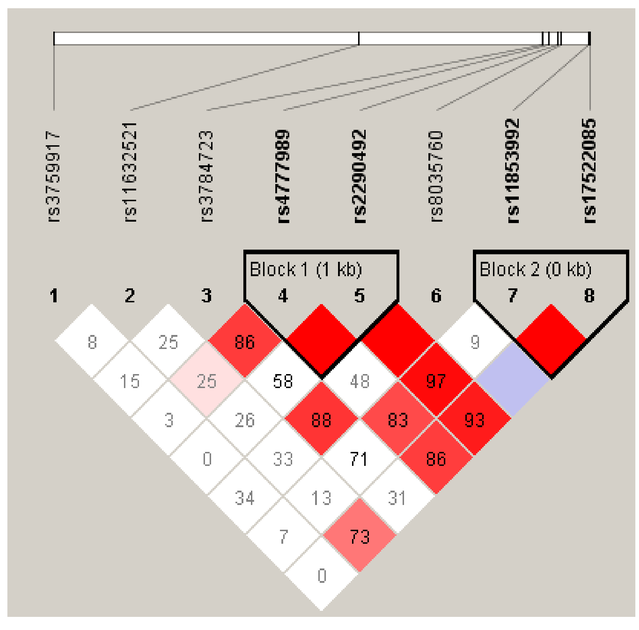

Figure.
Linkage Disequilibrium of all 8 SNPs analysed via HaploView. Complete LD was found for SNPs rs4777989 and rs2290492 as well as rs11853992 and rs17522085.

METHODS:

The patients were derived from the TRD1 European multicenter study on treatment resistant depression. Of the 346 patients genotyped for ST8SIA2, some were featured in other work of the multicenter study group. After collection of venous blood samples the DNA was isolated using phenol-chloroform extraction procedure. Genotypes were obtained by Sequenom iPLEX-assay (Sequenom, Cambridge, MA) from Cogenics (Morrisville, NC). Linkage disequilibrium (LD) and Hardy Weinberg equilibrium (HW) were analyzed using Haploview4.2. Statistical tests were performed using 'R' software. For single SNPs associations with resistance or response were performed using Fisher's exact test, contrasting Response Vs Non-Response and Resistance Vs Non-Resistance. Haplotypes were analyzed via the Haplo.Stats package for 'R' using haplo.em, haplo.score and haplo.score.slide, comparing Response, Non-Response and Resistance. Results were corrected for multiple testings.

RESULTS:

All SNPs were in HD, and LD was detected for rs4777989 and rs2290492 and for rs11853992 and 17522085. The fisher test for resistance vs. nonresistance did not show significant effects. The fisher test investigating response vs. nonresponse showed associations of the C allele of rs3784723 (p=0.01) and of the G-allele of rs4777989 (p=0.04) with treatment response. An association of rs2290492 did not withstand correction for multiple testings.

For haplotype analysis sliding windows of 3 SNPs were used, showing significant global p values for haplotypes starting at SNP 1, 2 and 3 (SNPs were numbered as listed in the introduction). We therefore used SNP 1-5 (rs2290492, rs3759917, rs3784723, rs4777989, rs8035760) comprised in these windows for haplotype association. The haplotype C-T-C-G-A was associated with treatment response (p=0.04), in accordance to the single marker association tests.

A) SNP Analysis

SNP	Response Vs Non-Response	SNP	Response Vs Non-Response
rs2290492	p = 0.031	*rs8035760*	n.s.
rs3759917	n.s.	*rs11632521*	n.s.
rs3784723	**p = 0.0006**	*rs11853992*	n.s.
rs4777989	**p = 0.0025**	*rs17522085*	n.s.

B) Haplotype Analysis

Sliding Windows	Global simulated p-value	Sliding Windows	Global simulated p-value
SNP 1-3	**p = 0.02**	*SNP 4-6*	p = 0.80
SNP 2-4	**p = 0.04**	*SNP 5-7*	p = 0.07
SNP 3-5	**p = 0.03**	*SNP 6-8*	p = 0.06

Haplotype SNP1-5	Simulated p-value	*Frequencies:* Resistants	Non-Responders	Responders
C – T – C – G – A	**p = 0.0059**	*0.0063*	*0.0189*	*0.0508*

Table 2. Associations withstanding correction for multiple testing (p=0.0031 for SNP, p=0.0063 for haplotype analysis) are bolded.
A) Results of the fishertest used for SNP analysis of Response Vs Non-Response.
B) Results of the haplotype analysis. Sliding scores over 3 SNPs showed associations for SNP 1-5. Haplotype analysis using SNP 1-5 showed association of haplotype C-T-C-G-A with treatment outcome, beeing significantly more frequent in responders. (Corrected p = 0.0063)

CONCLUSIONS:

This is the first study investigating genetic polymorphisms within ST8SIA2 in treatment resistant depression and treatment response. It further affirms the proposed role of ST8SIA2 in the serotonergic system and depression. Our results point toward an impact of a haplotype comprising 5 SNPs on response to various antidepressants. Two of these SNPs also showed effects in single marker association tests. Thus our study elaborates the connection of ST8SIA2 to MDD and the serotonergic system and provides new data on genetics in treatment response.

References:

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Acknowledgements:
No potentil conflict of interest**.**