Research Paper

Is the Gly82Ser polymorphism in the *RAGE* gene relevant to schizophrenia and the personality trait psychoticism?

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Background: The receptor for advanced glycation end products (RAGE) is the main receptor for S100B, an astrogial proinflammatory mediator that has been suggested to be involved in the pathophysiology of schizophrenia. To further elucidate the possible relevance of inflammation for mental functions, we investigated a functional polymorphism in the gene coding for RAGE in relation to personality traits and susceptibility to schizophrenia. **Methods:** We studied the Gly82Ser polymorphism (rs2070600, 244G>A) in 2 population-based cohorts of middle-aged participants assessed using the Karolinska Scales of Personality. In addition, we compared genotype frequencies between patients with schizophrenia and controls. **Results:** The population-based cohorts included 270 women and 247 men, and the case–control study involved 138 patients with schizophrenia and 258 controls. In the population-based cohorts, 82Ser carriers were found to have significantly higher scores for the psychoticism personality trait comprising the detachment and suspicion subscales. The case–control study revealed that the 82Ser allele was significantly more frequent among patients than controls. **Limitations:** This study was limited by the modest sample size and the use of a self-report measure to assess personality traits. **Conclusion:** Our findings suggest that the proven relation between certain personality traits and schizophrenia can at least to some extent be explained on a genetic level. Also, the activated S100B–RAGE axis may be an underlying cause, not only a consequence, of the disease.

Introduction

The receptor for advanced glycation end products (RAGE) is a multiligand glycoprotein that is upregulated at sites of pathology.[1] The ligands binding to RAGE include advanced glycation end products that arise during certain metabolic conditions and normal aging as well as amyloid fibrils, which make up the amyloid plaques seen in the brains of patients with Alzheimer disease.[2] Other well-studied ligands are the proinflammatory and neurotrophic members of the S100/calgranulin family, S100A12 and S100B, which are secreted mostly by astrocytes in the central nervous system.[3]

Recent studies have reported elevated serum and cerebrospinal fluid (CSF) levels of S100B in patients with schizophrenia, resulting in the hypothesis that astrocytes are either activated, damaged or dysfunctional in these patients.[4–6] The interaction between S100B and RAGE expressed on neurons and glial cells results in activation of NFκB, which in turn induces the secretion of the proinflammatory cytokines interleukin-6 and tumour necrosis factor-α.[7,8] Additionally, activation of RAGE has been shown to increase expression of the receptor itself.[9] Besides the membrane-bound form of RAGE, the receptor is secreted in plasma as a spliced isoform that lacks the transmembrane domain.[10] Soluble RAGE (sRAGE) competes with cell-bound RAGE by binding to the same ligands, but lacks the signalling ability. Soluble RAGE has been recently

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suggested to regulate the detrimental effects of S100B observed in patients with schizophrenia.[6]

Circulating levels of sRAGE have been associated with a nonsynonymous single nucleotide polymorphism (SNP) found in the ligand-binding domain of the receptor that gives rise to the substitution of glycine to serine change at amino acid 82 in the RAGE protein (Gly82Ser, rs2070600, 244G>A).[11] The 82Gly/Gly genotype was reported to be associated with higher plasma levels of sRAGE than the 82Gly/Ser group. A way to study the influence of genes on human behaviour is to study their association with personality traits, which are considered to be partly heritable and stable throughout life.[12] Since certain personality traits are coupled with the risk for psychiatric disorders,[13] it is of interest to study the association between candidate genes and the risk for disease as well as the putative association between the gene and normal behaviour (i.e., personality traits associated with the disorder). We have previously reported that genetic variations within the *S100B* gene are associated with the self-directedness personality trait.[14] This association, coupled with the implications of RAGE and S100B in patients with schizophrenia and the shown relation between inflammation and psychiatric disorders,[15] prompted us to investigate the possible influence of the Gly82Ser SNP on personality traits and examine Gly82Ser genotype frequencies in patients with schizophrenia compared with controls.

Methods

Personality trait study participants

The 2 population-based cohorts, one consisting of middle-aged women and the other of middle-aged men, investigated in this study were originally recruited from the National Population Register for studies on obesity, anthropometrics and cardiovascular risk factors. Clinical data and further details on these 2 cohorts have been reported previously.[16,17] At the time of investigation, no exclusions owing to somatic or psychiatric disease were made in either cohort. We obtained blood samples from all women and men for genotyping. All volunteers gave their informed consent, and the study protocol was approved by the ethical committee at the University of Gothenburg.

Personality assessment

The participants in both cohorts were assessed using the Karolinska Scales of Personality (KSP).[18] This inventory consists of a self-report questionnaire that has been widely used in studies involving biologic correlates of personality traits.[14,18–20] Previous studies have investigated the validity and reliability of the KSP questionnaire and found that interindividual variations were both stable and partly heritable for several of the subscales.[19,21] The KSP is based on 135 items forming 15 subscales that can further be classified into 4 factors covering different dimensions of temperament: extraversion (comprising the impulsiveness and monotony avoidance subscales), neuroticism (comprising the somatic anxiety, muscular tension, psychic anxiety, psychasthenia, inhibition of aggression, guilt and socialization subscales), psychoticism (comprising the detachment and suspicion subscales) and nonconformity (comprising the verbal aggression, indirect aggression, irritability and social desirability subscales).[22] The KSP factors and subscales are standardized to adjust for age and sex using normative data to have a mean of 50 and standard deviation (SD) of 10 (i.e., T-scores).

Case–control study participants

We recruited all patients with schizophrenia in the northwestern part of Stockholm County, and they have been described in detail previously.[23,24] All reviews of hospital case notes, interviews and diagnostic formulations were performed by psychiatrists trained in Sweden.

The case–control cohort could be divided into 2 groups. The first group consisted of patients recruited from psychiatric clinics in northwestern Stockholm County who were assessed for lifetime psychiatric diagnosis using the DSM-III-revised and for geographic origin using data from hospital case notes, clinical and/or structured interviews and parish register data. Further assessments were made with regards to clinical subtraits and subdiagnosis of schizophrenia based on the DSM-III-revised. The second group was recruited in a similar way, with the following differences: in addition to the Structured Clinical Interview for DSM-III-revised, patients were assessed using the psychosis module of the Schedules for Clinical Assessment in Neuropsychiatry. Evaluations of lifetime diagnosis were conducted by reviewing hospital records using DSM-IV, not DSM-III-revised, as the diagnostic tool. However, investigations of the comparability of the 2 diagnostic systems showed good agreement in the present sample.[23] Identification of geographic origin in the second group was based on interview data only.

We selected participants based on diagnosis and race, and we excluded participants with an unknown subdiagnosis or one that was not included among the 5 subclassifications of schizophrenia (i.e., 295.1–3, 295.6 and 295.9). We defined age at onset of schizophrenia as the patient's age at the time of the first appearance of psychotic symptoms; one of us (E.G.J.) assessed age at onset by reviewing the patients' lifelong psychiatric medical records.

The controls were selected randomly from among the 1090 participants of the Kungsholmen project, which consisted of people aged 75 years and older living in Stockholm, Sweden.[25] All participants in the case–control study provided informed consent, and the study was approved by the Ethics Committee of the Karolinska Hospital and the Karolinska Institutet.

Genotyping

Human genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen). The studied polymorphism was analyzed using polymerase chain reaction (PCR) as the amplifying step, followed by genotype determination by pyrosequencing.

The Gly82Ser polymorphism is located in exon 3 of the gene coding for RAGE. The primers that were used were 5′-ATT TGG ATC CCC GTC ACT CT-3′ as the forward and 5′-biotin-GCC TGG CAC CGG AAA ATC-3′ as the reverse primer. The PCR step was performed using HotstarTaq polymerase (Qiagen) and GeneAmp PCR System 9700 (Applied Biosystems). We used a total volume of 20 μL containing 0.3 μM of primers, 1.5 mM of $MgCl_2$, about 50 ng of DNA and 200 μM of each deoxyribonucleotide triphosphate. An initial 15-minute denaturation step at 95°C was followed by 41 cycles of 15 seconds at 95°C, 30 seconds at 62°C and 15 seconds at 72°C. Once the cycles were completed, the reaction was incubated at 72°C for 7 minutes and then left at 4°C. The PCR product was genotyped using a Pyrosequencer PSQ 96 and the PSQ 96 SNP Reagent Kit (Qiagen). To identify the polymorphism, we used 15 pmol of the sequencing primers 5′-CGT GTC CTT CCC AAC-3′. We used a total of 20 μL of PCR product for pyrosequencing in accordance with the manufacturer's instructions.

Statistical analysis

The association between KSP T-scores and genotype was assessed using an independent samples *t* test. The interaction between sex and genotype was assessed with personality traits as the dependent variable in a linear regression.

We compared genotype frequencies between patients with schizophrenia and controls using the Fisher exact test (1-tailed), and we tested homogeneity between odds ratios (ORs) using the Breslow–Day statistic. The possible influence of the Gly82Ser genotype on age at onset of schizophrenia was investigated using an independent samples *t* test (1-tailed).

Deviation from Hardy–Weinberg equilibrium for the Gly82Ser allele was assessed using Haploview (version 4.2). Power analyses in terms of effect-size calculations were assessed in all cohorts using the G*Power software. We performed the statistical analyses using SPSS Statistics for Mac, version 18.0.0. We considered results to be significant at $p < 0.05$, and *p* values are nominal except when explicitly stated as corrected.

Results

Personality trait study participants

The 2 population-based cohorts comprised 270 women aged 42 years and 247 men aged 51 years. The KSP questionnaires were returned by 204 women and 153 men; however, 26 women and 20 men left some questions blank, which resulted in missing values in their personality profiles.

Case–control study participants

We recruited 173 patients with schizophrenia to participate in the study. Of these, 137 patients were assessed using the DSM-III-revised, reviews of hospital case notes, clinical and/or structured interviews and parish register data. Further assessments were made with regards to clinical subtraits and subdiagnosis of schizophrenia based on DSM-III-revised. The remaining 36 patients were assessed using the Structured Clinical Interview for DSM-III-revised and the Schedules for Clinical Assessment in Neuropsychiatry. In addition, evaluations of lifetime diagnosis were conducted using the DSM-IV, rather than the DSM-III-revised, as a diagnostic tool.

The mean age of all 173 patients was 43.7 (SD 16.5) years. We excluded 32 patients with an unknown subdiagnosis or one that was not included among the 5 subclassifications of schizophrenia. One patient with ancestors from Sudan was also excluded, resulting in a sample of 140 white European patients (53 women and 87 men) with a mean age of 44.9 (SD 16.7) years. The age at onset of schizophrenia was available for 136 patients: mean 24.2 (SD 7.6) years.

We recruited 258 controls (109 women and 149 men) for participation in the study. Their mean age was 80.5 (SD 4.6) years and they were all white Europeans.

Genetic characteristics

Of the 270 participants in the female personality trait cohort, 250 were homozygous and 20 were heterozygous for the 82Gly allele. None was found to be homozygous for the 82Ser variant. In the male personality trait cohort, 220 participants were homozygous and 22 were heterozygous for the 82Gly allele, and 1 was homozygous for the 82Ser variant. In the statistical analysis, this latter participant was grouped with those who were heterozygous for the 82Gly allele. Genotyping of 4 samples in the male cohort failed owing to lack of DNA. Power calculations revealed that with a 5% significance level and 80% power, we would be able to detect an overall mean difference between the genotype groups as low as Cohen's $d = 0.54$.

Compared with carriers of the 82Gly/Gly genotype, the presence of the 82Ser variant was found to be associated with significantly higher scores in the psychoticism factor of the KSP (Table 1 and Fig. 1) in the combined population. Analysis of the subscales comprising this factor revealed significantly higher scores in detachment and suspicion for 82Ser carriers. When stratifying for sex, significant outcomes were seen only among women. However, we did not find any significant effect of interactions between sex and genotype on personality traits when analyzing the combined group.

Genotype frequencies from the case–control study are shown in Table 2. We were unable to genotype 2 samples in the patient group. Power calculations revealed that with a 5% significance level and 80% power we would be able to detect an OR of 2.4 and an earlier age of onset (Cohen's $d = 0.63$) among 82Ser carriers compared with participants homozygous for 82Gly.

Compared with Gly homozygotes the 82Gly/Ser genotype was associated with an increased risk for schizophrenia (OR 2.4, 95% confidence interval 1.2–4.9; Table 2). When stratifying for sex, the increased risk was significant only in men, but a test of homogeneity of the OR in men (3.7) and women (1.4) did not reveal any significant differences ($p = 0.24$). Part of the difference could be explained by the discrepancies in

genotype frequencies between the sexes in the control group. Using the entire control group, we found ORs of 2.7 and 1.9 for men and women, respectively. The Gly82Ser polymorphism was not found to significantly affect the age of onset in the patient group, but when men and women were analyzed separately, male carriers of the 82Ser variant showed a borderline significance of earlier age at onset of disease compared with the 82Gly/Gly group (Table 3). There was no significant effect of the interaction between sex and genotype on age at onset when analyzing the combined group ($p = 0.39$).

The distribution of the genotypes did not differ significantly from the Hardy–Weinberg equilibrium in either of the cohorts (all $p > 0.05$).

Discussion

In the present study, the 82Ser allele of the gene coding for RAGE was associated with higher scores in psychoticism and its detachment and suspicion subscales compared with Gly homozygotes in a merged sample of 2 population-based cohorts, 1 male and 1 female. Moreover, a case–control study revealed that the 82Ser allele increased the susceptibility to schizophrenia and was potentially associated with an earlier age of onset in male patients.

A high score in the detachment subscale is characterized by the lack of closeness and warmth in personal relationships.[26] This trait may also include social isolation, apathy and lack of intimate friendships, all of which are featured among the negative symptoms of schizophrenia.[26,27] Suspicion is included among the positive symptoms of schizophrenia and has been reported to be a useful predictor in determining the risk of conversion to psychosis.[28] With the present findings in mind, we suggest that the Gly82Ser polymorphism influences normal variability in personality, which in turn, along with additional risk factors, renders certain individuals susceptible to psychopathology. This theory finds support from the current literature on RAGE and its ligands.

Functional studies of the Gly82Ser polymorphism have found that it affects the structure of the receptor protein, which in turn influences the degree by which it is cleaved by certain proteases.[11] The 82Ser allele has been reported to diminish this proteolysis, which may explain why this allele has been associated with lower plasma levels of sRAGE. This isoform of RAGE competes with cell-bound receptors for the same ligands but lacks the signalling ability and has been suggested to regulate the detrimental effects of S100B in patients with schizophrenia.[6] Consistent with these findings, another study demonstrated that the 82Ser allele increases proinflammatory induction followed by the interaction of, for example, S100B with RAGE, and the 82Ser allele was further postulated to enhance mechanisms underlying inflammatory diseases.[29] Recently, 2 independent studies showed an association between the 82Ser allele and the risk for Alzheimer disease.[2,30] Interestingly, cognitive deficits[31] and neuronal atrophy[32] are suggested to be prevalent in patients with schizophrenia, and it is thus possible that the Gly82Ser polymorphism is a common denominator for cognitive impairment.

In line with the proinflammatory actions of the S100B–RAGE axis, emerging evidence is implicating elevated levels of neuroinflammatory mediators in the psychopathology of various psychiatric diseases, including depression and schizophrenia.[33] Patients with schizophrenia have, for example, increased serum and CSF levels of S100B.[4,5,34,35] Negative symptoms have been found to correlate with increasing S100B serum levels.[4] Several studies have reported associations between personality traits and inflammation;[36] for instance, we have shown that genetic variations in *S100B*[14] and in genes related to the innate immune system[37] influence personality traits. Although numerous studies show an interaction between neurotransmission and inflammation,[38–40] one cannot rule out the possibility that immune molecules themselves, via unknown mechanisms, are determinants for mental functions.

The engagement of RAGE with its ligand S100B has been implicated in developmental processes.[41] On one hand, nanomolar levels of S100B have been proposed to protect neurons and promote their survival during development as well as to facilitate neurite extension via activation of RAGE. On the other hand, micromolar levels of S100B exert toxic effects on neurons by inducing neuronal apoptosis via mechanisms involving RAGE-dependent overproduction of reactive oxygen

Table 1: Gly82Ser genotype and Karolinska Scales of Personality factor scores* in 2 population-based cohorts of women and men and in the combined sample

	All			Women			Men		
KSP factor	82Gly/Gly	82Gly/Ser + Ser/Ser	*p* value (corrected)†	82Gly/Gly	82Gly/Ser	*p* value (corrected)†	82Gly/Gly	82Gly/Ser + Ser/Ser	*p* value
No.	296–324‡	27–29‡		170–186‡	16		126–136‡	11–13‡	
Extraversion	52.6 (8.2)	49.9 (11.1)	0.10	52.3 (7.8)	49.4 (7.8)	0.15	52.9 (8.7)	50.5 (14.5)	0.38
Neuroticism	48.4 (6.4)	47.7 (7.3)	0.60	48.6 (7.2)	47.0 (8.6)	0.41	48.0 (5.2)	48.5 (5.6)	0.74
Psychoticism	47.7 (9.2)	53.0 (10.1)	0.004 (0.016)	47.8 (9.0)	54.1 (11.5)	0.010 (0.040)	47.5 (9.4)	51.5 (8.0)	0.17
Detachment	45.0 (10.4)	50.6 (10.6)	0.007	44.4 (10.2)	52.4 (12.3)	0.004	45.9 (10.7)	48.29 (7.7)	0.45
Suspicion	50.4 (10.9)	55.6 (11.9)	0.017	51.3 (10.7)	55.8 (13.1)	0.11	49.3 (11.2)	55.4 (10.7)	0.07
Nonconformity	48.6 (6.3)	48.3 (7.3)	0.78	50.3 (7.0)	49.2 (8.9)	0.57	46.4 (4.6)	47.2 (4.6)	0.58

KSP = Karolinska Scales of Personality; SD = standard deviation
*The KSP scores are reported as mean T-scores. All data are reported as mean (and standard deviation).
†The *p* values are Bonferroni-corrected for the 4 main factors tested.
‡The KSP questionnaires of 26 women and 20 men were incomplete, resulting in missing values in their personality trait profiles and varying *n* values. We obtained *p* values using an independent samples *t* test (2-tailed).

species. Since neurobiologic factors in the developing brain have been suggested to be of relevance to the personality of an individual,[42] and since schizophrenia is suggested to be a neurodevelopmental disorder[43] our results may indicate that the influence of the studied polymorphism on mental functions occurs early in life. This suggestion is supported by the fact that personality traits are both heritable and relatively stable throughout life.[12] Despite the preliminary nature of the current finding with regards to age at onset and genotype, the results lend further support for the hypothesis that immune molecules are affecting the developing brain, as it is likely that a variant that causes susceptibility to schizophrenia via neurodevolopmental processes also speeds up the onset of disease. The apparent sex differences demonstrated in the different parts of this study must be considered with caution, as no significant differences in effect sizes were found for either of the analyzed variables.

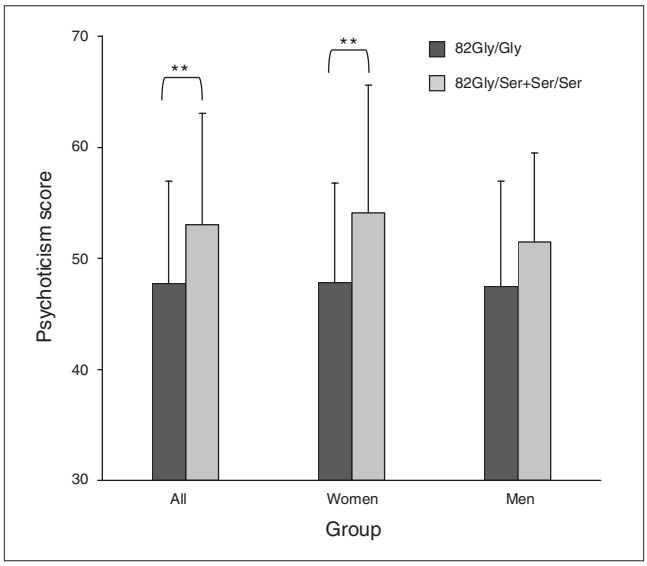

Fig. 1: Mean and standard deviations of Gly82Ser genotype and psychoticism scores (Karolinska Scales of Personality)[18] in 2 population-based cohorts of middle-aged women and men and in the combined sample. ** $p \leq 0.01$ (uncorrected).

Moreover, our findings may elucidate the known comorbidity between schizophrenia and type 2 diabetes.[44] It is conceivable to hypothesize that polymorphisms in RAGE may be a shared feature; carbonyl stress, such as accumulation of advanced glycation end products, has been suggested to be a link to the development of schizophrenia[45] and has also been implicated in other conditions, such as diabetes.[46] The inflammatory state seen in people with schizophrenia may also be relevant for the increased risk of cardiovascular diseases noticed in these patients.[47]

Limitations

The current study had some limitations. In the personality trait study, limitations included the selection process, the limited number of assessed participants and the use of a self-report measure. The limitations in the case–control study included the modest cohort size and population stratifications; however, to minimize the possibility of the latter, we ensured that both patients and controls were of the same race (i.e., white European), were unrelated and were recruited from the same area of Sweden. An additional limitation was the difference in age between patients and controls. Although unlikely, we cannot presently exclude the possibility that the 82Ser allele is associated with lower life expectancy, and therefore is less common in the older control group, rather than in patients with schizophrenia specifically.

Conclusion

The existing literature on RAGE, coupled with the present findings, allows us to speculate on the possibility that 82Ser carriers have increased RAGE signalling, leading to increased

Table 2: Genotype frequencies (%) of the RAGE Gly82Ser polymorphism in controls and patients with schizophrenia and in the combined sample

Genotype*	Controls			Patients			*p* value†		
	All	Women	Men	All	Women	Men	All	Women	Men
No.	258	109	149	138	53	85			
82Gly/Gly	242 (93.8)	100 (91.7)	142 (95.3)	119 (86.2)	47 (88.7)	72 (84.7)	0.011	0.36	0.006
82Gly/Ser	16 (6.2)	9 (8.3)	7 (4.7)	19 (13.8)	6 (11.3)	13 (15.3)			

*No individual in the patient or the control group was found to have the genotype 82Ser/Ser.
†We obtained *p* values using a Fisher exact test (1-tailed).

Table 3: The RAGE Gly82Ser polymorphism and age at onset in patients with schizophrenia

Measure	All		Women		Men		*p* value†		
	82Gly/Gly	82Gly/Ser	82Gly/Gly	82Gly/Ser	82Gly/Gly	82Gly/Ser	All	Women	Men
No.	116	18	45	5	71	13			
Age at onset, yr*	24.5 (7.9)	22.1 (5.6)	25.5 (9.3)	25.9 (5.1)	23.9 (6.9)	20.6 (5.3)	0.10	0.46	0.05

*All data are reported as mean (and standard deviation). Data on the age at onset was missing for 3 women and 1 man.
†We obtained *p* values by independent samples *t* test (1-tailed).

secretion of inflammatory mediators, which in turn may influence mental brain functions through developmental processes and/or neurotoxicity. We can also speculate that RAGE- and S100B-mediated inflammation may be of importance for the etiology of schizophrenia as opposed to merely being elevated as a consequence of disease. Further studies underlying the nature of the possible influence of this SNP on mental processes are warranted.

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