

# ICAM G241A Polymorphism and Soluble ICAM-1 Serum Levels: Evidence for an Active Immune Process in Schizophrenia

Holger Krönig Michael Riedel Markus J. Schwarz Martin Strassnig  
Hans-Jürgen Möller Manfred Ackenheil Norbert Müller

Psychiatric Hospital, Ludwig-Maximilian University Munich, Munich, Germany

## Key Words

Schizophrenia · Soluble ICAM-1 serum levels ·  
Single-nucleotide polymorphism · G241A

## Abstract

**Objectives:** We have previously reported reduced serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) in schizophrenic patients. A single-nucleotide polymorphism (SNP) of the ICAM-1 gene was described at position 241. The G→A SNP results in a nonsynonymous amino acid exchange of the ICAM-1 protein, and the A allele was shown to be also associated with several immunological disorders like rheumatoid arthritis. **Methods:** We investigated 70 schizophrenic patients and 128 unrelated healthy control persons regarding the relationship between the serum levels of sICAM-1 and the ICAM-1 G241A polymorphism. **Results:** We were able to replicate our previous finding of reduced sICAM-1 levels in schizophrenia. Healthy control persons carrying the polymorphic A allele showed markedly lower sICAM-1 serum levels than carriers of the homozygous GG wild type ( $p < 0.004$ ). In contrast, no significant difference in the sICAM-1 serum levels were seen regarding the G241A genotype distribution in schizophrenic patients. **Conclusion:** We hypothesize that the biochemical effect of the G241A SNP is masked in schizophrenic patients, indicating a disease-related mechanism leading to reduced levels of sICAM-1 in schizophrenia.

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## Introduction

Schizophrenia is a heterogeneous disorder with a worldwide prevalence of about 1% and a high socioeconomic impact. It is characterized by symptoms such as hallucinations or disorganized thinking, loss of goal-directed behaviors, and deterioration in social role functioning. Direct and indirect costs have been estimated at about USD 4.3 billion/year in the United States [1].

There is no doubt that a hereditary component has to be assumed [2]. Additionally, there is major evidence for the involvement of an immune process in the pathophysiology of the disorder [3]: in vitro lymphocyte stimulation studies showed a reduced production of the proinflammatory, Th1-like cytokines interferon gamma (IFN- $\gamma$ ) or interleukin-2 in cells of schizophrenic patients. Elevated levels of antibody titers directed against a variety of (auto-)antigens were found in serum and cerebrospinal fluid of schizophrenic patients [4–7]. Based on these findings, several authors [8, 9] concluded that there is a reduced cellular immune response in at least a subgroup of schizophrenic patients. This reduced cellular immune response was interpreted as being a reduced activation of the Th1 cells accompanied by a relatively more pronounced activity of Th2 cells [9].

Activation of T cells may require a minimum of two signals by antigen-presenting cells such as macrophages and B cells: the first signal delivered by major histocompatibility complex-peptide complex and a second signal

delivered by cell surface molecules such as the intercellular adhesion molecule-1 (ICAM-1) [10]. The adhesion molecule ICAM-1 is a transmembrane glycoprotein, which belongs to the immunoglobulin superfamily, and contains five tandem immunoglobulin-like domains. The two ligands of ICAM-1 are the integrins LFA-1 (lymphocyte function associated antigen-1, CD11a/CD18) and MAC-1 (macrophage-1 antigen, CD11b/CD18) [11]. LFA-1 and MAC-1 are the binding sites for ICAM-1-mediated activation of lymphocytes and macrophages, respectively.

In a previous investigation [12], we demonstrated significantly decreased serum levels of soluble ICAM-1 (sICAM-1) in schizophrenic patients as compared with healthy controls. Based on these findings, we have investigated the gene coding for ICAM-1 as a candidate gene for schizophrenia [13]. The G→A single-nucleotide polymorphism of the ICAM-1 gene located at position 241 in exon 4 leads to an amino acid (glycine-to-arginine) replacement. This occurs in the binding domain for MAC-1, a region that is important for the function of the ICAM-1 protein. We performed a case-control study in 190 schizophrenic patients and healthy control individuals each, but there was no significant difference of the G241A genotype distribution between the two groups.

In contrast, an increased frequency of the A allele of the G241A polymorphism was described in several disorders which are characterized by an inflammatory process: rheumatoid arthritis [14], Behçet's disease [15], giant cell arteritis [16], or ulcerative colitis [17, 18]. All these diseases are characterized by increased sICAM-1 serum levels [19–22]. These associations indicate a functionality of the polymorphism in the MAC-1-binding site, although experimental data are still lacking [23].

We reinvestigated our schizophrenic patients and healthy controls regarding the relationship between the serum levels of sICAM-1 and the G241A polymorphism to cover two main objectives: (1) Is the previously reported finding of reduced sICAM-1 serum levels in schizophrenic patients reproducible? (2) Is the ICAM-1 G241A genotype related to sICAM-1 serum levels in schizophrenic patients?

## Subjects and Methods

### Subjects

A total of 70 Caucasian patients suffering from schizophrenia (41 males, 29 females; mean age  $31.17 \pm 10.62$  years, age range 17–63 years) were recruited at the Psychiatric Hospital of the University of Munich, including 21 patients from our first study about

sICAM-1 in unmedicated and medicated schizophrenic patients [12] who were reinvestigated for the genetic G241A polymorphism. All patients were at least 8 weeks free from antipsychotics.

In our previous investigation [12], we observed that antipsychotic treatment increases the sICAM-1 levels. Therefore, we reinvestigated for our examination of a possible association between G241A polymorphism and sICAM-1 serum levels only patients with a washout period >2 months.

Diagnoses were established according to the criteria of the DSM-IV by two independent experienced psychiatrists. In 50 of the patients, paranoid schizophrenia was diagnosed (DSM-IV: 295.3x), 11 patients carried a diagnosis of disorganized schizophrenia (DSM-IV: 295.1x), 1 patient was diagnosed as being catatonic schizophrenic (DSM-IV: 295.2x), 2 patients as being undifferentiated schizophrenic (DSM-IV: 295.9x), 1 patient had a schizophreniform disorder (DSM-IV: 295.4x), 2 patients had a residual schizophrenia (DSM-IV: 295.6x), and 3 patients had a schizoaffective disorder (DSM-IV: 295.7x). The mean age at onset was 27.25 years. Thirty-four of the patients were suffering from their first episode of schizophrenia.

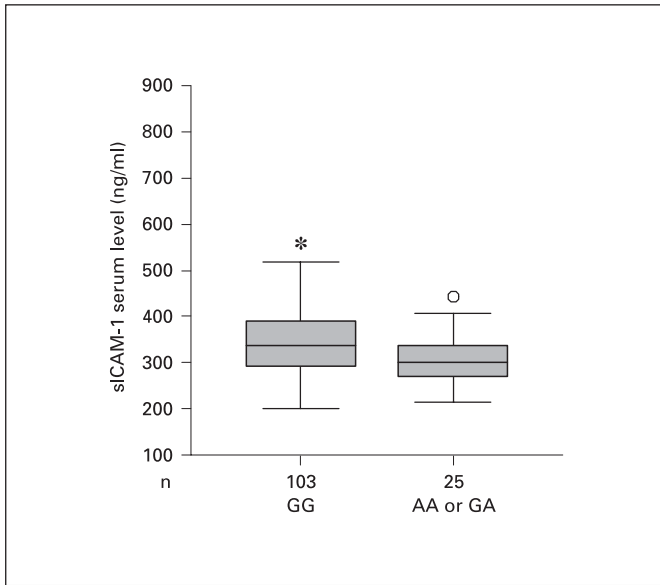
One hundred and twenty-eight healthy Caucasians from the general population (70 males, 58 females; mean age  $30.05 \pm 9.70$  years, age range 18–65 years) were recruited as the control group. All controls were screened for past or present psychiatric illness by interview and by the MMPI-2 [24, 25]. Additionally, they were medically examined, including standard laboratory tests. A history of a psychosis in a first-degree relative was asked for by interviewing the control persons and was considered an exclusion criterion. Physical health was evaluated by extensive examinations, including blood tests to exclude infectious or inflammatory diseases in both study groups.

The study was approved by the local ethics committee, and all patients and controls gave their written informed consent after the aim of the study had been fully explained.

### Methods

The sICAM-1 serum levels were determined by means of a commercially available double sandwich ELISA (Endogen; Pierce Biotechnology, Rockford, Ill., USA). Intra- and interassay variances were <8%. Measurements were done in duplicate. The paired samples of 1 patient were always measured within one assay together with a set of control samples. The laboratory personnel were blinded regarding the source of the samples.

Genomic DNAs from all subjects were prepared from peripheral whole-blood cells using the QIAamp system (Qiagen, Hilden, Germany). Genotyping of the codon G241A of ICAM-1 was performed by the snapshot method using a PTC-200 thermocycler (MJ Research, Watertown, Mass., USA) and a genetic analyzer ABI Prism 310 (Applied Biosystems, Foster City, Calif., USA). In the first step we carried out a PCR. Forward primer: 5'-ACT CCC CCA CAA CTT gTC Ag-3'; reverse primer: 3'-TCA CAC TgA CTg Agg CCT Tg-5'. The PCR was performed with 50 ng DNA in a total volume of 25  $\mu$ l containing 0.25  $\mu$ l AmpliTaqGold, 2.5  $\mu$ l 10 $\times$  PCR mix, 0.625  $\mu$ l of each primer, and 2.5  $\mu$ l dNTPs for 29 cycles of denaturation (95°C), annealing (58°C), and extension (72°C). After restriction with SAP and ExoI, a SNAPshot PCR for both codons was made. SNAPshot primer: ICAM4-S 5'-CCg TTg TCT gTT CCC Tgg AC-3'. The PCR was performed in a total volume of 10  $\mu$ l containing 1.0  $\mu$ l template, 1  $\mu$ l SNAPshot primer, and 5.0  $\mu$ l SNAPshotReadyReaction Premix, annealing temperature



**Fig. 1.** Serum levels of sICAM-1 in relation to the ICAM-1 G241A genotype (wild-type GG versus heterozygous or homozygous A allele) in healthy controls. Outliers are indicated by \* and °.  $p = 0.004$ .

60°C. Afterwards, a restriction was performed, and the SNAPshot PCR products were sequenced by means of the ABI Prism 310 genetic analyzer.

#### Statistics

Statistical analyses were performed using SPSS for windows. The results are reported as mean values  $\pm$  SD. We used the t test for independent samples and the  $\chi^2$  test. Since the differences between schizophrenic patients and healthy controls regarding serum sICAM-1 levels have already been described, we used the one-tailed t test.

## Results

The two groups did not differ concerning their age ( $t = 0.754$ , d.f. = 196,  $p = 0.452$ ) or gender ( $\chi^2 = 0.277$ , d.f. = 1,  $p = 0.599$ ). The schizophrenic patients showed markedly lower serum levels of sICAM-1 ( $305.51 \pm 106.1$  ng/ml) than the healthy controls ( $337.70 \pm 79.60$  ng/ml; one-tailed  $t = 2.219$ , d.f. = 112.25,  $p = 0.014$ ; table 1).

The two groups did not differ regarding their ICAM-1 G241A genotype distribution ( $\chi^2 = 0.277$ , d.f. = 1,  $p = 0.599$ ; table 2). Both groups were in Hardy-Weinberg equilibrium (schizophrenic patients:  $\chi^2 = 1.127$ , d.f. = 2,  $p = 0.569$ ; controls:  $\chi^2 = 0.356$ , d.f. = 2,  $p = 0.837$ ). Since

**Table 1.** Serum levels of sICAM-1 in schizophrenic patients and healthy controls

| Group                  | sICAM-1, ng/ml      |
|------------------------|---------------------|
| Schizophrenic (n = 70) | $305.51 \pm 106.06$ |
| Controls (n = 128)     | $337.68 \pm 79.58$  |

**Table 2.** Observed genotype distribution of the ICAM-1 G241A polymorphism in schizophrenic patients and healthy controls, additionally the Hardy-Weinberg equilibrium by the expected genotypes is shown

|               | ICAM-1 G241A |    |    |          |    |    |
|---------------|--------------|----|----|----------|----|----|
|               | observed     |    |    | expected |    |    |
|               | GG           | GA | AA | GG       | GA | AA |
| Schizophrenic | 52           | 18 | 0  | 53       | 16 | 1  |
| Controls      | 103          | 23 | 2  | 102      | 24 | 1  |

**Table 3.** Serum levels of sICAM-1 (ng/ml) in relation to the ICAM-1 G241A genotype in schizophrenic patients and healthy controls (mean  $\pm$  SD)

| Group         | GG                              | GA/AA                           |
|---------------|---------------------------------|---------------------------------|
| Schizophrenic | $297.97 \pm 107.52$<br>(n = 52) | $327.31 \pm 101.46$<br>(n = 18) |
| Controls      | $345.75 \pm 82.73$<br>(n = 103) | $304.45 \pm 54.70$<br>(n = 25)  |

homozygosity for the polymorphic A allele was extremely rare, we further combined the AA and GA genotypes for comparison with the homozygous wild type (GG). The 241A allele frequency was 12.9% in the patients and 10.5% in the controls, while the G allele was found in 87.1% of the patients and in 89.5% of the controls.

Statistical comparison of the sICAM-1 serum levels in healthy controls unraveled significantly lower levels showing the polymorphic A allele than in those presenting the homozygous GG wild type (two-tailed  $t = 3.027$ , d.f. = 54.124,  $p = 0.004$ ; table 3, fig. 1). In contrast, no significant differences in the sICAM-1 serum levels were seen

regarding the G241A genotype distribution in schizophrenic patients (two-tailed  $t = 1.012$ , d.f. = 68,  $p = 0.315$ ; table 3).

## Discussion

Based on the previously reported finding of markedly reduced sICAM-1 serum levels in schizophrenic patients, we investigated the possible relationship between a ICAM-1 gene variant and sICAM-1 serum levels in schizophrenic patients and in healthy controls. The first goal was to confirm our previous finding of reduced sICAM-1 levels in schizophrenia, the second was to possibly explain the altered sICAM-1 serum levels by the ICAM-1 genotype.

First of all, we were able to replicate our previous finding of reduced sICAM-1 levels in schizophrenia. Secondly, we found a marked relationship between ICAM-1 G241A genotype and sICAM-1 levels in healthy control persons, but not in schizophrenic patients.

We report strong evidence of the involvement of the ICAM-1 gene G241A polymorphism in the immune function. Healthy controls presenting the polymorphic A allele showed significantly lower sICAM-1 serum levels as compared with homozygous carriers of the GG genotype. This is in accordance with results of a recently published study, investigating the relationship between sICAM-1 serum levels and ICAM-1 G241A single-nucleotide polymorphism [26]. Moreover, the allele frequencies of our controls are similar to those reported in other healthy populations [27].

The G241A polymorphism leads to a nonsynonymous nucleotide exchange that results in a nonconservative amino acid replacement. Since this occurs in the binding domain for MAC-1, a region that is important for the adhesion and activation of macrophages and monocytes, so it has to be suggested that the function of the polymorphism could be related to MAC-1 binding. Thus, the affinity of ICAM-1 to MAC-1 may be reduced, and elevated sICAM-1 levels may reflect an increased expression of membrane-bound ICAM-1. This hypothesis is consistent with the significantly increased frequency of the 241A allele in Th1/immune-system-related diseases like rheumatoid arthritis [14], Behçet's disease [15], giant cell arteritis [16], and ulcerative colitis [17, 18]. Moreover, elevated sICAM-1 serum levels have been described in all of these disorders [19–22]. However, the direct correlation between ICAM-1 genotype and sICAM serum levels has not been studied in these disorders until now.

The soluble form of ICAM-1 consists of the complete extracellular domain of the adhesion molecule and can be found in serum/plasma and cerebrospinal fluid [28, 29]. Principally, there are two ways of sICAM-1 production: differential mRNA splicing or proteolytic cleavage of the membrane-bound form [30, 31]. sICAM-1 was considered a significant and specific marker of the course of inflammatory disorders, including multiple sclerosis [32–35]. Therefore, sICAM-1 was expected to correlate with the expression of the membrane-bound form [36]. Recent results demonstrate an increase of sICAM-1 serum concentrations during effective IFN- $\beta$  therapy of multiple sclerosis [37]. These findings indicate the dependence of sICAM-1 level modulation on additional factors.

Our finding presented herein gives further evidence for the functionality of the ICAM-1 G241A polymorphism. Moreover, it demonstrates one of the factors that have the potency to influence the levels of sICAM-1.

We did not find any relationship between genotype and sICAM-1 levels in the group of schizophrenic patients. On the other hand, we were able to replicate our former finding of reduced sICAM-1 serum levels in schizophrenic patients. Thus, the reduced sICAM-1 expression in schizophrenia appears to be caused by a disease-related process. This process seems to mask the genotype-dependent sICAM-1 expression, as observed in healthy persons. One of the most consistent immunological finding in schizophrenia is a reduced in vitro production of the Th1 cytokine IFN- $\gamma$  [38–41]. IFN- $\gamma$  has been shown to enhance the cellular ICAM-1 expression and the release of sICAM-1 in epithelial cells [42]. Therefore, lower sICAM-1 levels in schizophrenic patients may be related to a reduced IFN- $\gamma$  signal.

There are two possible explanations for this phenomenon: The reduced IFN- $\gamma$  signal may either be caused by a genetic variant of the IFN- $\gamma$  gene or any other gene related to the IFN- $\gamma$  signal. On the other hand, there may be an active disease process in schizophrenia, characterized by a reduced Th1 activation. Redirection of the Th1/Th2 dysbalance might then serve as a new therapy strategy in schizophrenia. The latter is in accordance with results of a recent study, investigating the effect of immunomodulation in schizophrenia: based on the Th2 hypothesis, we have carried out a clinical trial with the aim to redirect the Th1/Th2 imbalance. Cyclooxygenase-2 inhibitors are known to reverse the Th2 predominance by inducing the production of Th1-like cytokines and inhibiting the production of Th2-like cytokines in noninflammatory conditions [43, 44]. We, therefore, used the cyclooxygenase-2 inhibitor celecoxib in a double-blind,



placebo-controlled study, including a total of 50 schizophrenic patients. Indeed, we could demonstrate the therapeutic efficacy of cyclooxygenase inhibition [45].

Further investigation of the mechanism underlying the altered immune response in schizophrenic patients will thus help to understand the pathophysiology of schizophrenia and to find new targets for immunomodulating treatment in schizophrenia.

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