Introduction

Schizophrenia (MIM 181500) is one of the most disabling psychiatric disorders affecting around 24 million people worldwide, with a prevalence ranging from 0.7 to 1.1% and with a lifetime morbidity risk of 0.5-2.7%.[1,2] Schizophrenia affects men and women equally; however, most researchers agree that the onset of schizophrenia in women appears later than in men.[3] Due to its early age of onset and the lifelong disability, schizophrenia is considered as one of the most catastrophic mental illnesses.[4-5] One of the most vital aspects for developing treatment and prevention strategies for schizophrenia is identifying the causes of the disorder. Research over the decades has led us to suggest that the etiology of schizophrenia involves the interplay of complex polygenic influences and environmental risk factors operating on brain maturational processes.

Schizophrenia has long been considered as a disorder involving immune system. Possible role of the immune response system in the pathogenesis of schizophrenia is indicated by several authors and meta-analyzed.[6-10] An immune response shifting from Type 1 to Type 2 is one of the strong propositions supporting the immunoinflammatory origin of schizophrenia.[11,12] Variations in the concentration of cytokines in patients...
with schizophrenia have also been reported. It has been shown that the concentration of cytokines in blood serum in patients suffering from schizophrenia varies depending on whether the patient is in active or resting phase of the disease.

Interleukin (IL)-10, a Th2 cytokine is one of the many cytokines that seems to play a vital role in immune response that is generated in brain. Increased level of cytokine IL-10 in the cerebrospinal fluid of schizophrenics has been reported. Production of cytokine IL-10 is controlled by IL-10 gene located on human chromosome 1 (1q31-q32) in a region reported to be related to schizophrenia in genetic association studies. Given the strong hereditary background of schizophrenia, it is assumed that genetic factors may also underlie immune system deregulation and aberrant cytokine production observed in schizophrenia. IL-10 is secreted by a variety of cells including monocytes/macrophages, T-cells, β-cells, and mast cells. It is responsible for various functions. It shifts the Th1/Th2 balance by downregulating the Th1 responses and by suppression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) secretion. A number of single-nucleotide polymorphisms (SNPs) were reported in the proximal and distal regions of the IL-10 gene. Three promoter polymorphisms (rs1800896-1082A/G, rs1800871-819T/C, and rs1800872-592A/C) are reportedly involved in IL-10 transcription rate, thereby directly affecting its production level. The -1082G, -819C, and -592C (GCC) alleles have been associated with elevated levels of IL-10 production, while ACC and ATA haplotypes exhibit intermediate and low IL-10 gene transcription, respectively. These polymorphisms on IL-10 gene are reported to be linked with susceptibility to the development of schizophrenia. However, data is limited and inconsistent, therefore do not allow drawing unequivocal conclusions. In this study, we aimed to investigate the association between IL-10 gene polymorphisms in promoter region at -1082, -819, and -592 loci and susceptibility to schizophrenia in Saudi cohort.

Materials and Methods

Subjects

The study population was composed of a total of 392 unrelated Saudi subjects including 181 schizophrenia patients recruited from the outpatient psychiatric clinic of Prince Sultan Military Medical City (PSMMC) Riyadh, Saudi Arabia and 211 age- and sex-matched healthy volunteers. The diagnosis of schizophrenia was based on the criteria mentioned in American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR version. This criterion uses the self-reported experience of the patient and reported abnormalities in behavior and a comprehensive clinical assessment by a neuropsychiatrist. To ensure the diagnostic reliability, a systemic search into the case notes of the patients was made. Out of 200 initially selected schizophrenia patients, 19 patients failed to meet explicit stated criteria, hence were excluded and only 181 patients were included in this study. Among the confirmed 181 cases of schizophrenia, there were 53 females and 128 males with mean age of 39 ± 12.5 years and mean disease duration of 9 ± 4.5 years. Age of onset of disease ranged from 19 to 64 years. The female to male ratio of schizophrenia patients in our study was 1:2.5. The control group consisted of 61 females and 150 males with mean age of 36 ± 10 years.

If diagnoses of schizophrenia was confirmed by above mentioned criteria, patients were further assessed for positive and negative symptoms using Positive or Negative Syndrome Scale (PANSS) involving further clinical interview, cognitive testing, motor assessment, and careful review of medical and historical records as described by Kay et al. All the subjects in control group were screened using a questionnaire about the health status and excluded if they had any history of neurological, psychiatric, or medical disorders or had a past or present involvement in substance abuse. Control subjects less than 26-years-old and having first- or second-degree relatives with schizophrenia or any psychiatric disorder were excluded. A number of baseline parameters to rule out any psychotic illness were adopted as described by Johnstone et al. This study was approved by the ethical committee of the hospital and informed consent was obtained from each subject.

Polymerase chain reaction (PCR) amplification

Genomic DNA was extracted from the blood of schizophrenia patients and controls using the QIAamp®DNA mini kit (Qiagen, USA). IL-10 gene was amplified using amplification refractory mutation systems (ARMS)-PCR methodology to detect any polymorphism involved at various loci viz: -592, -819, and -1082. The sets of primers used to amplify various types of polymorphism were as reported earlier.

PCR amplification was carried out in Ready-To-Go PCR Beads (Amersham Biosciences, USA). Reaction consisted of 10 temperature cycles of denaturation for 15 s at 94°C, annealing for 50 s at 55°C, and extension for 40 s at 72°C. Then 25 cycles of denaturation for 20 s at 94°C, annealing for 50 s at 59°C, and extension for 50 s at 72°C. Final extension was performed at 72°C for 7 min. A positive control was included in the PCR assay by amplification of the human growth hormones (HGH) gene. Electrophoresis of the PCR product was performed.
in 1.5% agarose gel, stained with ethidium bromide, and photographed.

Statistical analysis

The differences in genotype and allele frequencies between patients and controls were analyzed with the Fisher’s exact test. $P \leq 0.05$ was considered significant. The strength of the association of disease with respect to a particular genotype/allele was expressed with the odds ratio interpreted as relative risk (RR). The strength of the association of disease with respect to a particular genotype/allele was expressed with odds ratio interpreted as RR following the method of Woolf as described by Schallreuter et al.$^{[31]}$ RR indicates how many times more frequent a disease is in the positive subjects compared with allele/genotype-negative subjects. It is calculated for a genotype/allele that is increased or decreased in psoriasis patients compared to the frequency in normal Saudi subjects. RR was calculated using the following formula:

$$RR = \frac{a \times d}{b \times c}$$

a = Number of patients expressing the allele or genotype

b = Number of patients without allele or genotype expression

c = Number of controls expressing the allele or genotype

d = Number of controls without allele or genotype expression

The etiologic fraction (EF) indicates the hypothetical genetic component of the disease. EF values of >0.00-0.99 are significant. It is calculated for positive associations (RR > 1) using the following formula proposed by Savejgaard et al.$^{[32]}$

$$EF = \frac{(RR - 1)f}{RR}, \text{ where } f = \frac{a}{a + b}$$

Preventive fraction (PF) indicates the hypothetical protective effect of one allele/genotype for a disease. It is calculated for negative associations (RR < 1) using the following formula.$^{[32]}$ Values of < 1.0 indicate the protective effect of an allele/genotype against the manifestation of disease.

$$PF = \frac{(1 - RR)f}{RR (1 - f) + f}, \text{ where } f = \frac{a}{a + b}$$

Results

The demographic features of the participants are summarized in [Table 1]. The results of SNP for IL-10 G (-1082) A, IL-10 C (-592) A, IL-10 C (-819) T, and corresponding genotypes using ARMS-PCR method are summarized in [Tables 2-4].

The frequency of -1082GG genotype was found to be significantly lower ($P = 0.027$) in schizophrenia patients (2.21%) as compared to controls subjects (7.53%). On the contrary, the frequency of heterozygous genotype GA was significantly higher ($P = 0.0002$) in patients (91.71%) as compared to control subjects (75.27%), whereas frequency of homozygous AA genotype was lower in patients (6.08%) as compared with controls (12.20%). These results indicate that genotype -1082GA is susceptible to schizophrenia (RR = 3.636, EF = 0.393) while genotypes GG and AA are resistant to schizophrenia (RR = 0.278, PF = 0.363 and RR = 0.311, PF = 0.362 respectively, [Table 2].

The frequency of -819 CC genotype was significantly higher ($P = 0.05$) in the schizophrenia patients (51.93%)

| Table 1: Demographic features of patients/controls |
|-----------------------------------------------|
| Number of patients 181                        |
| Gender F:M=53:128 (1:2.5)                     |
| Age of patients mean 39±12.5 (range 26-74 years) |
| Age of onset mean 29±12.5 (range 19-64 years)  |
| Duration of disease mean 9±4.5                |
| Type of schizophrenia:                        |
| With negative symptoms: 94 (52.22%)           |
| With positive symptoms:86 (47.78%)            |
| Number of controls 211                        |
| Gender F:M=61:150 (1.2.5)                     |
| Age mean 36±10 (range 26-60 years)            |

| Table 2: Genotype and allele frequencies of interleukin-10 (-1082G/A) variants in schizophrenia patients and matched controls |
|----------------------------------------------------------|
| Genotype/allele | Schizophrenia (N = 181) | Control (N = 186) | P-value | RR | EF*/PF |
|-----------------|--------------------------|------------------|---------|----|--------|
|                 | N | Frequency (%) | N | Frequency (%) |       |       |       |
| GG              | 4 | 2.21            | 14 | 7.53            | 0.02$^*$ | 0.278 | 0.363 |
| GA              | 166 | 91.71         | 140 | 75.27         | <0.001$^*$ | 3.636 | 0.393$^*$ |
| AA              | 11 | 51.13         | 31 | 12.20        | <0.001$^*$ | 3.636 | 0.362 |
| G-allele        | 174 | 48.07         | 168 | 45.16         | 0.45 | 1.124 | 0.056$^*$ |
| A-allele        | 188 | 51.13         | 204 | 54.84         | 0.45 | 0.889 | 0.056 |

$^*$Statistically significant; N = Number of subjects, RR = Relative risk, EF = Etiological fraction, PF = Preventive fraction.
compared to controls (41.71%), while CT showed a reverse pattern with lower frequency (38.12%) in schizophrenia patients as compared to 48.34% in controls ($P = 0.05$). The frequency of homozygous TT genotype was similar in both schizophrenia and control samples (9.95%). The CT genotype is more common among the healthy controls indicating that the 819 CT genotype may have a protective effect on the susceptibility to schizophrenia ($RR = 0.66$, $PF = 0.17$), whereas CC genotype appears to be susceptible to schizophrenia ($RR = 1.51$, $EF = 0.17$) [Table 3].

The frequency of -592 CC genotype was significantly higher in schizophrenia patients as compared to controls (51.93 vs 41.71%, $P = 0.05$), while CA genotype was found to be significantly lower ($P = 0.05$) in schizophrenia patients (38.12%) compared to control subjects (48.34%). The frequency of homozygous AA genotype was similar both schizophrenia and control samples (9.95%). The higher frequency of CA genotype among the healthy controls indicated that the individuals with -592CA genotype are protected against schizophrenia ($RR = 0.66$, $PF = 0.17$), while CC genotype at position -592 of IL-10 are susceptible to schizophrenia ($P = 0.05$, $RR = 1.51$, and $EF = 0.17$) [Table 4].

Upon stratification of subjects into gender and with positive or negative symptoms, no significant difference was found in distribution of alleles and genotypes of all the three polymorphisms either with sex of patients or schizophrenia with positive or negative symptoms [Tables 5 and 6].

**Discussion**

In the present study, intermediate IL-10 producer genotype -1082 G/A showed positive association with schizophrenia as 91.71% of the patients have this genotype as compared to 75.27% of control subjects.
saying that individuals having 1082 G/A genotype are more prone to schizophrenia. Similarly, another study showed that intermediate IL-10 producer genotype -1082 GA is susceptible to schizophrenia in Taiwanese. Almoguera et al. reported a significant association of IL-10-1082A allele with Spanish schizophrenia females. Contrary to these, significantly increased frequency of G allele was reported in the schizophrenia group in Chinese, Chinese, and Italians. By contrast, the association between the schizophrenia and the presence of 1082G has not been found in Korean and Turkish populations.

The frequency of IL-10-819CC was significantly higher, whereas the frequency of IL-10-819CT, was significantly lower in schizophrenia patients compared to healthy controls. The genotype -819 CC has been reported to be a high producer of IL10, whereas CT and TT as intermediate and low producer, respectively. These findings further indicated that genotypes associated with intermediate-high production of IL-10 are more prevalent in schizophrenia patients. The genotypes of IL-10- (592), being in linkage disequilibrium with the genotypes of IL-10- (819) followed the pattern similar to those for frequencies of -819 in schizophrenia patients and healthy controls. The frequency of IL-10-592CC was also significantly higher in schizophrenia patients compared to healthy controls. However, contradictory reports are available from different ethnicities on the association between schizophrenia and IL-10-592C/A polymorphism. It has been reported as the statistically significant polymorphism in Chinese and Turkish patients with schizophrenia. On the other hand, -592 C/A polymorphism had no association with both allele and genotype distributions in Italian and Korean schizophrenia patients.

The genotypes of IL-10-1082GA, -819CC, and -592CC (ACC haplotype): known to be associated with intermediate production of IL-10 are more prevalent in our schizophrenia patients indicating the possible association with susceptibility of schizophrenia which is supported by the finding that the schizophrenia patients show statistically significant increased expression of IL-10 as compared to controls. Considering IL-10 gene promoter haplotypes, GCC in Italians, and Chinese, whereas GTA in Turkish, and Chinese population, both associated with high IL-10 production, have also been linked to schizophrenia. It seems that IL-10 might correlate to schizophrenia based on the hypotheses of Th2-like immunity shift of susceptible allele carrier.

There was no significant association of IL-10 polymorphisms with positive or negative symptoms of schizophrenia in our study. However, recently Sun et al. reported that the interaction of the promoter of IL-10 rs1800872 and dopamine beta-hydroxylase (DBH) rs72393728 polymorphism is significantly associated with the PANSS general score, and suggested that the interaction of their variants may play a role in psychopathology of the general symptoms on PANSS in schizophrenic patients in a northern Chinese Han population.

Earlier published reports and present study indicate that IL-10 promoter polymorphisms may enhance the vulnerability of schizophrenia and many diseases, while may also exert a protective effect against others. It has been confirmed by the twin and family studies that ~75% of the variations in IL-10 production is genetically determined. Furthermore, there are intrapopulation differences in the genetic control of IL-10 production by various alleles of the promoter region. Hence, the share of the promoter polymorphism may be different depending on the population.

The exact mechanism by which IL-10 affects the susceptibility/pathogenesis of schizophrenia is far from clear. It participates in the regulation of the immune response at several levels. IL-10 regulates the inflammatory response, by inhibiting proinflammatory Th1 cytokines production, and it is constitutively expressed during fetal brain development in humans. IL-10 cytokine downregulates the expression of major histocompatibility complex (MHC) class I and II molecules. It also has potent stimulatory effects on B lymphocytes, resulting in increased production of immunoglobulin and DNA replication. Some immune-stimulating effects of IL-10 have been documented, where it induces activated B cells to secrete large

### Table 6: Comparison of frequencies of interleukin-10 (-1082G/A) variants in female and male schizophrenia patients

| Genotype/allele | Female (N = 53) | Male (N = 128) | P-value | RR |
|-----------------|-----------------|----------------|---------|----|
|                 | Frequency (%)    | Frequency (%)  |         |    |
| GG              | 1               | 3              | 0.99    | 0.80 |
| GA              | 49              | 117            | 1.00    | 1.15 |
| AA              | 3               | 8              | 1.00    | 0.90 |
| G-allele        | 51              | 123            | 0.99    | 1.00 |
| A-allele        | 55              | 133            | 0.99    | 1.00 |

N = Number of subjects, RR = Relative risk

### Notes
- Table 6: Comparison of frequencies of interleukin-10 (-1082G/A) variants in female and male schizophrenia patients
- Frequency of IL-10-819CC was significantly higher, whereas the frequency of IL-10-819CT, was significantly lower in schizophrenia patients compared to healthy controls.
- The genotype -819 CC has been reported to be a high producer of IL10, whereas CT and TT as intermediate and low producer, respectively.
- These findings further indicated that genotypes associated with intermediate-high production of IL-10 are more prevalent in schizophrenia patients.
- The genotypes of IL-10-1082GA, -819CC, and -592CC (ACC haplotype): known to be associated with intermediate production of IL-10 are more prevalent in our schizophrenia patients indicating the possible association with susceptibility of schizophrenia.
- Considering IL-10 gene promoter haplotypes, GCC in Italians, and Chinese, whereas GTA in Turkish, and Chinese population, both associated with high IL-10 production, have also been linked to schizophrenia.
- There was no significant association of IL-10 polymorphisms with positive or negative symptoms of schizophrenia in our study.
- Earlier published reports and present study indicate that IL-10 promoter polymorphisms may enhance the vulnerability of schizophrenia and many diseases, while may also exert a protective effect against others.
- The exact mechanism by which IL-10 affects the susceptibility/pathogenesis of schizophrenia is far from clear. It participates in the regulation of the immune response at several levels.
amounts of IgG, IgA, and IgM and in combination with IL-4 results in the secretion of four immunoglobulin isotypes. Thus, increased levels of IL-10 may also play a role in the amplification of humoral responses in some diseases as suggested by Rousset et al. [60]

There is evidence of the role of IL-10 in the neurodevelopmental abnormalities found in schizophrenia. [64] It has been suggested that the genetically determined differences in IL-10 production could lead to behavioral abnormalities in the adulthood after prenatal immune challenge or innate immune imbalances. It has also been pointed out that not only an excess of proinflammatory cytokines, but also an imbalance between both classes of cytokines during development might alter normal brain functions in adult life. [64]

The immune system have been linked to schizophrenia, through candidate-gene, [24, 25, 35] pathway-based, [38] and genome-wide association, [65] approaches that have produced evidence of the immune system involvement in schizophrenia. The present study addresses the significant association of IL-10 promoter polymorphisms with Saudi schizophrenia patients as a case-control study.

**Conclusion**

In conclusion, our results of IL-10 polymorphism in schizophrenia suggested that GA genotype at -1082 position together with CC genotypes at positions -592 and -819 of IL-10 genemight be susceptible to the development of schizophrenia. The genotypes 592 CA, 819 CT, 1082 GG, and 1082 AA of IL-10 gene, maybe protective against schizophrenia in Saudi test population. To our knowledge, this is the first study that examined IL-10 polymorphism in schizophrenia patients from Arabian ethnicity. However, further studies are warranted to investigate IL-10 polymorphisms in larger population samples as well as in schizophrenia affected families.

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