

# Association between QTc of patients with schizophrenia and five genetic polymorphisms of *GSTZ1* and *XRCC1*

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## ABSTRACT

**Background** Several antipsychotic agents are known to prolong the QT interval. A study was undertaken to find the possible influence of polymorphisms of *GSTZ1* (MIM: 603758) and *XRCC1* (MIM: 194360) on the rate-corrected QT interval (QTc) in patients with schizophrenia.

**Methods** The study was carried out on 48 inpatients with schizophrenia. The patients were diagnosed with chronic schizophrenia according to structured clinical interviews using SCID-I (clinician version) to confirm and document DSM-IV diagnosis. Measurements of the QT and RR intervals were recorded using a magnifying grid on lead II. The QTc was calculated according to Bazett's formula. A PCR-based method was used to determine the *GSTZ1* and *XRCC1* genotypes.

**Results** Statistical analysis showed that there was no association between the study polymorphisms of *GSTZ1* and *XRCC1* and QTc.

**Conclusions** *GSTZ1* is not associated with QTc in patients treated with antipsychotic drugs.

## INTRODUCTION

Genetic factors are involved in the QT interval length on the ECG.<sup>1–2</sup> However, it is known that the rate-corrected QT interval (QTc) is influenced by various environmental parameters including medication.<sup>3–5</sup> A number of drugs including several antipsychotic agents are known to prolong the QT interval in a dose-dependent manner.<sup>3–4</sup>

The human *GSTZ1* (a member of GST $\zeta$ ; MIM: 603758) was discovered by a bioinformatics approach and identified in human expressed sequence tag databases.<sup>6–7</sup> In mice and humans, GST $\zeta$  is expressed in many tissues at a low level.<sup>8</sup> It has been reported that, in mice, *Gstz1* deficiency resulted in the generation of a constant level of oxidative stress.<sup>8</sup> Several *GSTZ1* variant sequences have been identified in humans<sup>8–9</sup>; two non-synonymous polymorphisms at nucleotide positions 94 (Glu32Lys; rs7975) and 124 (Gly42Arg; rs7972) have been reported<sup>10</sup> and a G-1002A polymorphism in the promoter region of *GSTZ1* has also been identified.<sup>9</sup>

The x-ray repair cross-complementing 1 protein (XRCC1; MIM: 194360) plays an important role in DNA single-strand break repair in cells. Two polymorphisms at codons 194 (Arg194Trp; rs 1799782) and 399 (Arg399Gln; rs 25487) have been reported in human XRCC1.<sup>11</sup>

Associations between the abovementioned polymorphisms and both schizophrenia and bipolar disorder have been reported.<sup>12–16</sup> It has also been

shown that the QTc interval in patients with schizophrenia is correlated with the *GSTZ1* polymorphism.<sup>17</sup> In the present study the association between QTc in patients with schizophrenia and polymorphisms of *XRCC1* and *GSTZ1* was investigated.

## MATERIALS AND METHODS

This study was performed in Shiraz, southern Iran. Forty-eight inpatients with schizophrenia from Ibn-Sina and Razi Hospitals, Shiraz University of Medical Sciences of mean  $\pm$  SD age  $43.5 \pm 9.4$  years participated in the study. The patients were diagnosed as having chronic schizophrenia according to clinical interview using SCID-I (clinician version) to confirm and document a diagnosis of DSM-IV, as described previously.<sup>18</sup> The patients were receiving conventional antipsychotic drugs such as perphenazine, trifluoperazine, chlorpromazine, thioridazine and haloperidol. None were receiving antidepressants.

Measurements of the QT and RR intervals were recorded using a magnifying grid on lead II because the T wave is often well-defined in this lead. Two independent observers who were blinded to the genotypes of the patients determined the duration of the QT interval, which was recorded for three consecutive beats through lead II. The QTc was calculated using Bazett's formula in which the QT interval is adjusted for heart rate by dividing it by the square root of the RR interval.<sup>19</sup>

Immediately after blood collection, whole blood was stored at  $-20^{\circ}\text{C}$  until use. The PCR conditions for determining *XRCC1* and *GSTZ1* genotypes and laboratory quality control were the same as those reported previously.<sup>9–10–12–14</sup>

The Kolmogorov-Smirnov test was applied in order to show the normal distribution of QTc. To evaluate an association between the suggested independent variables and QTc, the independent Student t test and/or one-way analysis of variance were used. Statistical analysis was performed using the Statistical Package for Social Sciences V.11.5 (SPSS, Chicago, Illinois, USA).

## RESULTS

The mean  $\pm$  SD QTc in our patients was  $505 \pm 45$  ms, which is significantly increased compared with normal controls. This value is exceedingly high given that 500 ms is the threshold to stop medications due to the substantial risk of a torsades des pointes arrhythmia about this value. Using the Kolmogorov-Smirnov test, the QTc showed a normal distribution ( $Z=0.690$ ,  $p=0.728$ ).



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**Table 1** Mean QTc interval (in ms) in patients with schizophrenia stratified according to their *XRCC1* and *GSTZ1* genotypes

Polymorphisms	Mean (ms)	SD	n	t (df=46) F (df=2, 45)	p Value
Polymorphisms of <i>XRCC1</i>					
Arg194Trp					
Arg/Arg	504	48	38	0.155	0.877
Arg/Trp	507	29	10		
Arg399Gln					
Arg/Arg	485	39	11	1.374	0.264
Arg/Gln	510	46	30		
Gln/Gln	514	46	7		
Polymorphisms of <i>GSTZ1</i>					
G-1002A					
GG	502	40	30	0.264	0.769
GA	507	56	16		
AA	524	9	2		
Glu32Lys					
Glu/Glu	500	40	28	0.816	0.449
Glu/Lys	516	51	16		
Lys/Lys	491	51	4		
Gly42Arg					
Gly/Gly	504	46	45	0.178	0.859
Gly/Arg	509	26	3		

The mean $\pm$ SD QTc in our patients according to their genotypes of *XRCC1* and *GSTZ1* polymorphisms are shown in table 1. Statistical analysis using the independent Student t test and/or one way analysis of variance showed that there was no association between the polymorphisms of *GSTZ1* and *XRCC1* and QTc.

## DISCUSSION

We have previously found that the *GSTT1* polymorphism was associated with the risk of schizophrenia<sup>18</sup> and QTc in these patients.<sup>17</sup> The present results indicate that *GSTZ1*, which is another detoxifying glutathione S-transferase (GST) enzyme, is not associated with QTc in patients treated with antipsychotic drugs.

As ethnicity may influence the observed associations in multifactorial traits,<sup>20</sup> replication of this study in other countries is recommended. The main limitations of our study are the small sample size, lack of stratification of patients according to drug intake and the lack of measurement of plasma concentrations of antipsychotic drugs and/or their active metabolites.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Ethics approval was obtained from the Institutional Review Board of Shiraz University.

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