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

The human GSTZ1 (a member of GSTζ; MIM: 603758) was discovered by a bioinformatics approach and identified in human expressed sequence tag databases.6 7 In mice and humans, GSTζ is expressed in many tissues at a low level.8 It has been reported that, in mice, Gstζ1 deficiency resulted in the generation of a constant level of oxidative stress.8 Several GSTZ1 variant sequences have been identified in humans8 9; two non-synonymous polymorphisms at nucleotide positions 94 (Gla32Lys; rs7975) and 124 (Gly42Arg; rs7972) have been reported10 and a G-1002A polymorphism in the promoter region of GSTZ1 has also been identified.9

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 XRCC1.11 12

Associations between the abovementioned polymorphisms and both schizophrenia and bipolar disorder have been reported.12–16 It has also been shown that the QTc interval in patients with schizophrenia is correlated with the GSTZ1 polymorphism.17 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±SD age 43.5±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.18 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.19

Immediately after blood collection, whole blood was stored at −20°C until use. The PCR conditions for determining XRCC1 and GSTZ1 genotypes and laboratory quality control were the same as those reported previously.9 10 12 14

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 V11.5 (SPSS, Chicago, Illinois, USA).

RESULTS
The mean±SD QTc in our patients was 505±43 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).
Table 1 Mean QTc interval (in ms) in patients with schizophrenia stratified according to their XRCC1 and GSTZ1 genotypes

<table>
<thead>
<tr>
<th>Polymorphisms of XRCC1</th>
<th>Mean (ms)</th>
<th>SD</th>
<th>n</th>
<th>t (df=46)</th>
<th>F (df=2, 45)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>504</td>
<td>48</td>
<td>38</td>
<td>0.155</td>
<td>0.877</td>
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<tr>
<td>Arg/Trp</td>
<td>507</td>
<td>29</td>
<td>10</td>
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</tr>
<tr>
<td>Arg399Gln</td>
<td>485</td>
<td>39</td>
<td>11</td>
<td>1.374</td>
<td>0.264</td>
<td></td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>510</td>
<td>46</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gin/Gln</td>
<td>514</td>
<td>46</td>
<td>7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Polymorphisms of GSTZ1</th>
<th>Mean (ms)</th>
<th>SD</th>
<th>n</th>
<th>t (df=46)</th>
<th>F (df=2, 45)</th>
<th>p Value</th>
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<tr>
<td>G-1002A</td>
<td>502</td>
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<td>30</td>
<td>0.264</td>
<td>0.769</td>
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<tr>
<td>GG</td>
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<td>56</td>
<td>16</td>
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<tr>
<td>GA</td>
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<tr>
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<td>40</td>
<td>28</td>
<td>0.816</td>
<td>0.449</td>
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<tr>
<td>Glu32Lys</td>
<td>516</td>
<td>51</td>
<td>16</td>
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<tr>
<td>Glu/Lys</td>
<td>491</td>
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<tr>
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<td>45</td>
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<td>0.859</td>
<td></td>
</tr>
<tr>
<td>Gly/Gly</td>
<td>509</td>
<td>26</td>
<td>3</td>
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</tbody>
</table>

The mean±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 GSTTI polymorphism was associated with the risk of schizophrenia19 and QTc in these patients.17 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,20 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.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES