KCNQ1 rs2237892 Polymorphism: Searching for any Prognostic Parameter to Predict Cardiac Events in Diabetic Population?

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Abstract

Background and objectives: KCNQ1 encodes a protein for a voltage-gated potassium channel in heart and pancreatic islets. Several polymorphisms within KCNQ1 like rs2237892 are associated with type 2 diabetes mellitus. Despite lots of studies on polymorphisms association with the disease; there is still a lack of data for predicting parameters associated with adverse cardiac complications. In this study, the association of TT and CC variants of rs2237892 with cardiovascular events intensity and onset time was examined. Methods: We planned an experimental cohort study in which 256 diabetic subjects during a 24 month period evaluated. Participants underwent thorough clinical and para-clinic investigations to detect cardiovascular events including myocardial infarction, hypertension and arrhythmias. DNA extraction and amplification was done and genotyping performed according to standard methods. Results: We found 47 patients with rs2237892; twenty-six (55.3%) showed TT variant and the remaining had CC variant (44.7%). The mean frequency of cardiac events among TT and CC variants were 0.430 and 0.664 and eta coefficient of association between two variants and cardiac events frequency found as 0.54 and 0.536, respectively. The mean hazard time for cardiac events was nearly 20 percent longer in the case of TT variants. Conclusions: We found a weak association between variants and cardiovascular events with no statistically meaningful effect on the rate of events. Those with TT variants will be affected, about 20 percent later than the other variant (99% CI, lower 9.671, upper 15.329). This finding may work as a key to monitor such events in patients.

Original Article

1. Introduction

Type 2 diabetes mellitus (T2DM) has become a serious health problem all over the world. It has been determined that T2DM is a multifactorial disease in which interaction between environmental and genetic factors causes disease. During recent decade, after the advent of genome wide association studies (GWAS), several T2DM susceptibility loci have been discovered. As a result of these studies, it has been identified that several polymorphisms within KCNQ1 gene are associated with T2DM [1-10]. One of these polymorphisms that its association with T2D has been well documented is rs2237892 [1-4, 7-11].

KCNQ1 (potassium voltage-gated channel KQT-like sub-family, member 1) is located at chromosome 11p15.5, and mainly encodes a protein for a voltage-gated potassium channel which plays a key role in the repolarization phase of the cardiac action potential [12-14]. Mutations in this gene lead to cardiac long QT syndrome, atrial fibrillation and Lange-Nielsen cardio-auditory syndrome [13-17]. Apart from myocardial tissue, KCNQ1 is also expressed in pancreatic islets, and a blockade of the KvLQT1 channel with KCNQ1 inhibitors 293B, may increase insulin secretion [18].

Determining T2DM genes architectures offer some hopes that the findings will pave the way for better understanding of T2DM pathogenesis and disease complications. Such a fundamental understanding will lead to development of novel therapeutics which help physicians treat the disease effectively rather than just control its progression. Despite lots of studies about KCNQ1 association with T2DM among different populations throughout the world; there is still a lack of data to determine the predicting factors for adverse cardiac complications, hence we decided to conduct the present study to evaluate the association of rs2237892 with T2DM adverse cardiac complications.

In this study, we examined the association of TT and CC variants of rs2237892 within KCNQ1 with prevalent clinical complications of T2DM i.e. cardiovascular events including myocardial infarction (MI), hypertension (HTN) and cardiac arrhythmias.
Methods

Study Population

After applying exclusion criteria including diabetic neuropathy, diabetic foot ulcer, macro-albuminuria and hyper/hypo thyroidism, 256 patients with type 2 diabetes from a population study in Iran, between January 2010 and August 2012, included in our study who underwent routine check-up in Taban Diabetes and Health polyclinic in Tehran. They had been diagnosed based on World Health Organization (WHO) type 2 diabetes diagnostic criteria: the venous fasting plasma glucose (FPG) value \( \geq 7.0 \text{ mmol/l} \) (126mg/dl), or the plasma glucose value \( \geq 11.1 \text{ mmol/l} \) (200 mg/dl), 2 hours after a 75g oral load of glucose (2hpp).

Clinical examination

All participants underwent thorough clinical examination and review of systems, and also electrocardiography by two expert cardiologists. Patients were categorized into two groups of cardiac events involved and non-involved persons based on a series of clinical and laboratory landmarks such as signs and symptoms, electrocardiograms (ECG) (ST segment elevation), cardiac markers (troponin I and CK-MB), angiograms (coronary artery stenosis > 60%), previous coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). In addition, patients who had systolic blood pressure \( \geq 140 \text{ mmHg} \), or diastolic blood pressure \( \geq 90 \text{ mmHg} \) [19], or both of them in two visits, or took anti-hypertensive medications considered as cardiac event involved group. Patients who had symptoms such as palpitation, syncope, or family history of sudden death, or took specific medication, were assessed for supra-ventricular and ventricular arrhythmia by ECG and continuous ambulatory ECG. Any kind of supra-ventricular and ventricular arrhythmia included in this study, based on ACC/AHA/ESC guidelines [20, 21].

Biochemical assessment

Laboratory measurements included fasting plasma glucose, 2hpp blood glucose, HbA1c and troponin I, CK-MB. Venous blood samples were obtained after an overnight fasting and analyzed at Taban laboratory. HbA1c was measured using the latex immuno-agglutinin method.

DNA extraction and genotyping

DNA extraction was performed from blood samples and genotyping of rs2237892 segment of KCNQ1 was done according to standard sequencing methods [6]. Genotype distributions obeyed the Hardy-Weinberg equilibrium \( (P>0.05) \) and genotyping reactions were performed on an ABI 7900 genetic analyzer using 2\,ul of genomic DNA (10 ng/\,ul), according to manufacturers’ instructions.

Statistical analyses

All data were analyzed by using the SPSS15 software. The central index of mean and dispersion index of standard deviation (STD) were calculated. Analyses of cardiac events involved patients for continuous data and categorical variables in different groups according to the TT and CC variants within KCNQ1 were determined by one-way ANOVA. Two-tailed P-values less than 0.05 were considered significant.

Results

The characteristics of study individuals including 256 patients with T2DM have been shown briefly in Table 1.

Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patients’ metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>256</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>21-62 (43.21±0.5)</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>129 / 127</td>
</tr>
<tr>
<td>Mean duration of disease involvement (Years)</td>
<td>14.3±2.4</td>
</tr>
<tr>
<td>FPG *</td>
<td>119-251(192.9±21.6)</td>
</tr>
<tr>
<td>HbA1c mean measures (%)</td>
<td>10.621±1.4</td>
</tr>
<tr>
<td>Mean BMI a (Kg /m²)</td>
<td>28.91±2.74</td>
</tr>
</tbody>
</table>

Table 2- Cardiovascular events frequency among TT and CC variants of rs2237892

<table>
<thead>
<tr>
<th>Findings</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events in TT variant</td>
<td>11</td>
<td>0.430</td>
<td>0.23868</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardiovascular events in CC variant</td>
<td>17</td>
<td>0.664</td>
<td>0.27915</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Statistical analyses of the ANOVA for the association of variants and cardiovascular events revealed weak CC and TT variants association with cardiovascular events, with Eta measure of association of 0.54 and 0.536, respectively. Also, the mean hazard time to appear a cardiovascular event for the CC variant and TT variant were 10.5 and 12.68 months (99% CI, lower 9.671 and upper 15.329), respectively (Fig. 1).
In our study we included 256 patients with type 2 diabetes from a population study in Iran underwent thorough the clinical examination and review of systems, and also electrocardiography. We tried to evaluate any association with the two different TT and CC variants of the rs2237892 and major cardiovascular events including MI and HTN and cardiac arrhythmias.

We found that there was a weak association with both variants and cardiovascular events frequency (0.54 and 0.536, respectively) during a follow-up period of 24 months, and also there was no statistically meaningful effect on the rate of cardiac events like MI and HTN and cardiac arrhythmias in study population.

There was only a difference among two genotypes of TT and CC for the times predicted for the patients to be involved with the cardiovascular events (10.5 versus 12.68 months). We showed that those who have TT variants will be affected by cardiovascular events, statistically about 20 percent later than individuals whose genotype were CC variant (99% CI, lower 9.671 and upper 15.329).

**Conclusion:**

The purpose of this study was to determine the presence of any association between TT and CC variants of the rs2237892 and major cardiovascular events including MI and HTN and cardiac arrhythmias. Based on this study, no statistically significant association was found between these two variants and cardiac events after a 24-month follow-up. On the other hand, no absolute predictor parameter was found to determine precisely the onset or intensity of such events in our study population. Perhaps the results showed that patients with TT variants may develop cardiac events approximately 20 percent later than those with CC variant, although additional investigations with bigger sample size are needed to emphasize this finding. Our study may be complementary to the other authors’ data which may be important key to monitor the unwanted cardiovascular events in different diabetic patients, hence, it would serve as a suitable due to check more clinical and laboratory parameters in diabetic patients as probable predictors of adverse complications.

**Ethical standards**

The present study was approved by the ethical committee of Taban Diabetes and Health polyclinic.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Acknowledgments**

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**References**


