Published in final edited form as:
Diabet Med. 2010 September ; 27(9): 1074–1079. doi:10.1111/j.1464-5491.2010.03072.x.

A common variant of *NOS1AP* is associated with QT interval duration in a Chinese population with Type 2 diabetes

J. Lu, **C. Hu**, **W. Hu**[*], **R. Zhang**, **C. Wang**, **W. Qin**, **W. Yu**, **K. Xiang**, **W. Jia**, and **the International Type 2 Diabetes 1q Consortium**
Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Clinical Center of Diabetes, Shanghai, China

[*]Department of Electrocardiography, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

Abstract

Aims—Electrocardiographic ventricular repolarization QT parameters are independent risk factors for cardiovascular events and sudden cardiac death in diabetic patients. The aim of the study was to investigate the association of polymorphisms of the nitric oxide synthase 1 adaptor protein (NOS1AP) gene with QT interval in Chinese subjects with or without Type 2 diabetes.

Methods—Three single nucleotide polymorphisms (SNPs) (rs10494366, rs12143842 and rs12029454) were genotyped in 1240 Type 2 diabetic patients (631 men and 609 women) and 1196 normal controls (433 men and 763 women). Individuals with overt diseases other than diabetes were excluded. Heart-rate corrected QT interval (QTc) was determined by standard 12-lead ECG and Bazett formula. Sex-pooled analysis and sex-specific analysis for genotype–phenotype association were both conducted.

Results—In the diabetic group, the rs12143842 T allele was associated with a 3.87-ms (P = 0.014, empirical P = 0.039) increase in QTc duration for each additional allele copy, while rs10494366 and rs12029454 exhibited no significant association with QTc. We found no evidence of association for the three SNPs in subjects with normal glucose regulation. No significant SNP-gender and -diabetes affection interaction was observed.

Conclusions—The genetic variant rs12143842 in *NOS1AP* is associated with QT interval duration in a Chinese population with Type 2 diabetes. Future studies in different populations are needed to validate this finding and to evaluate the impact of *NOS1AP* variants on cardiovascular events and sudden cardiac death in diabetic patients.

Keywords

NOS1AP; QT interval; single nucleotide polymorphism

Introduction

The QT interval duration is a non-invasive electrocardiographic measurement of the ventricular repolarization process with an estimated heritability of approximately 35% [1,2]. An abnormally prolonged QT interval duration is the feature of long-QT syndrome, which is

Correspondence to: Weiping Jia, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai, 200233, China. wpjia@sjtu.edu.cn.

Competing interests
Nothing to declare.

characterized by life-threatening arrythmias and sudden cardiac death [3]. Although various mutations of genes encoding for ion channels have been identified to be responsible for long- and short-QT syndromes [4,5], genetic determinants for QT variation in general population remain to be further elucidated.

With the rapidly rising incidence and prevalence in recent years, Type 2 diabetes has become a major threat toward a global epidemic. Evidence suggests that electrocardiographic ventricular repolarization QT parameters are independent risk factors for cardiovascular events and sudden cardiac death in patients with diabetes [6-8]. Therefore, study of the determinants of ventricular repolarization in diabetic patients may provide valuable insight into the mechanisms underlying adverse cardiovascular events and sudden cardiac death in diabetic patients

NOS1AP, encoding the nitric oxide synthase 1 adaptor protein, has been found to regulate neuronal nitric oxide synthase (nNOS) activation through the interaction with the nNOS PDZ domain [9]. Furthermore, the acute inhibition or chronic genetic disruption of nNOS was reported to have an effect on cardiac contractility *in vitro* and suggested a role for nNOS in the regulation of calcium fluxes [10]. In 2006, a multistage genome-wide association study (GWAS) identified an association between QT interval and common variations of *NOS1AP* [11] and this association has been replicated in several independent populations [12-14]. However, these studies were restricted to subjects of non-Asian descent, warranting a replication in an Asian sample. Thus, we carried out the current study to test for the association of *NOS1AP* with QT interval duration in Chinese subjects with or without Type 2 diabetes.

Subjects and methods

Subjects

We recruited 1240 unrelated patients with Type 2 diabetes mellitus whose details were included in the Shanghai Diabetes Institute inpatient database and 1196 controls who participated in the Shanghai Diabetes Study [15]. All participants were of Han Chinese ancestry and resided in Shanghai or nearby regions. Diabetes was defined according to the 1999 WHO criteria (fasting plasma glucose ≥ 7.0 mmol/l and/or 2 h plasma glucose ≥ 11.1 mmol/l). Type 1 diabetes and mitochondrial diabetes were excluded by clinical, immunological (individuals with GAD and/or protein tyrosine phosphatase IA-2 antibodies were excluded) and genetic methods (mitochondrial $tRNA^{LEU(UUR)}$ A3243G mutation carriers were excluded). The control subjects had normal glucose tolerance, defined as a fasting plasma glucose level of < 6.1 mmol/l and a 2-h 75-g oral glucose tolerance test plasma glucose level of < 7.8 mmol/l. Individuals with malignancy, mental disorders, history of ketoacidosis, history of acute or chronic myocardial infarction or severe kidney or liver diseases were excluded from our study. The study protocol was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. All participants gave informed consents prior to the study.

Clinical measurements

All subjects underwent a detailed clinical investigation. Anthropometric parameters included height, weight and blood pressure. HbA_{1c} was also obtained using the Bio-Rad Variant II haemoglobin testing system (Bio-Rad Laboratories, Hercules, CA, USA).

The 12-lead electrocardiograph (ECG) was obtained with a GE Marquette digital recording system (GE Healthcare, Waukesha, WI, USA) according to standard procedures. As heart rate could affect QT interval measurement, we utilized the widely used Bazett formula to obtain heart-rate corrected QT interval (QTc). At least one 12-lead ECG was performed on

each participant until a clear measurement of QTc was made. Based on ECG data, we excluded individuals with myocardial infarction, bundle branch block, artrio-ventricular conduction defects, atrial fibrillation or QRS > 120 ms, as these conditions may alter ventricular repolarization and subsequent QT interval measurement.

SNP selection and genotyping

Three SNPs in *NOS1AP* (rs10494366, rs12143842 and rs12029454), previously reported to be associated with QT-interval [11,16-18], were selected. rs10494366, rs12143842 and rs12029454 are located in intron 1, the 5' region and intron 2 of *NOS1AP*, respectively. To date, no function has been reported for these SNPs. Genotyping was performed by primer extension of multiplex products with detection by matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy using a MassARRAY platform (MassARRAY Compact Analyzer; Sequenom, San Diego, CA, USA). The call rates for rs10494366, rs12143842 and rs12029454 were 98.36, 99.59 and 98.23%, respectively. The concordance rates based on 100 duplicate pairs were 100% for all these SNPs.

Statistical analysis

Allele frequencies for each SNP were calculated by gene counting. Genotype frequency distribution was tested for Hardy–Weinberg equilibrium with a χ^2-test. Pairwise linkage disequilibrium was determined by calculating $|D'|$ and r^2 using Haploview (version 3.32). For analysis of genotype–phenotype association, a linear regression model adjusting for age, gender and HbA_{1c} (diabetic subjects only) was employed under an additive genetic model. Correction of multiple testing on genotype association after adjusting confounders was performed using PLINK (version 1.05) through 10 000 permutations. Sex-pooled analysis and sex-specific analysis were both conducted. A two-tailed *P*-value of < 0.05 was considered statistically significant. The statistical analyses were performed using SAS for Windows (version 8.0; SAS Institute, Cary, NC, USA).

For the three SNPs genotyped in the current study, both our diabetic and control samples had over 80% power to detect a genetic effect of 4.4 ms, which was reported previously [16], at the significance level of 0.05.

Results

The characteristics of the participants (1240 patients and 1196 controls) at baseline are summarized in Table 1. Not unexpectedly, there were significant differences of age, BMI, blood pressure and QTc between Type 2 diabetic patients and normal controls.

The minor allele frequencies for rs10494366, rs12143842 and rs12029454 were 36.6, 34.4 and 28.9%, respectively. All three SNPs conformed to the Hardy–Weinberg equilibrium and these SNPs were in low linkage disequilibrium (Table 2).

In diabetic patients, the SNP rs12143842 was significantly associated with QTc under an additive genetic model adjusting for age, sex and HbA_{1c}, with each copy of the minor allele (T) prolonging QTc by 3.87 ms ($P = 0.014$, empirical $P = 0.039$) (Table 3). There was a 3.05-ms difference in QTc for each additional minor allele (A) for rs12029454 ($P = 0.039$). However, the significance was not retained after correction for multiple comparisons (empirical $P = 0.11$). With respect to rs10494366, no evidence for association was found in this study ($P = 0.18$, empirical $P = 0.42$) (Table 3). As women had a longer QTc than men, we further investigated the gender-specific effect of *NOS1AP* SNPs on QTc. When age and HbA_{1c} were taken as covariates, rs12143842 was associated with a 5.46-ms increase of QTc in women ($P = 0.018$), even after adjustment for multiple testing (empirical $P = 0.049$). By

comparison, the association did not reach statistical significance in men ($P = 0.42$, empirical $P = 0.76$) (Table 4). No significant gender–SNP interaction was observed ($P = 0.24$).

In the control group, the association for rs12029454 with QTc was not significant, although a trend towards association after adjusting for age and sex (β = 2.63 ms for each copy of minor allele A, $P = 0.054$) was observed. We found no evidence of association for rs10494366 ($P = 0.30$) and rs12143842 ($P = 0.65$) (Table 3). In addition, separation of gender revealed no significant association (Table 4).

As we found the statistically significant result only in the diabetic group, a test for the SNP–diabetes affection interaction was conducted after cases and controls were pooled. Although not significant, rs12143842 showed a trend towards interaction with diabetes status ($P = 0.057$) (Table 5).

Discussion

In the present study, three SNPs were tested for the association with QTc duration in a cohort of 1240 subjects with Type 2 diabetes and 1196 individuals with normal glucose regulation. In the diabetic group, rs12143842 was associated with increased QT interval duration in the entire group and in women, while rs10494366 and rs12029454 exhibited no significant genetic effect. In the control group, we observed no evidence of association with QT interval for the three SNPs, with rs12029454 showing a marginal association.

rs10494366 was first identified in an attempt to find genetic variants modulating cardiac repolarization [11], and its association with QT interval was validated in several subsequent population-based studies [12-14], indicating that this association is not a false-positive result, at least in European populations. However, we did not observe the same effect either in our Chinese diabetic sample or in the normal control group. Considering that we had over 80% power to detect a genetic effect of 4.4 ms previously reported in the Rotterdam Study [16] in both the diabetic and the normal control group, this result might likely reflect the difference in genetic architecture between the European and the Asian populations. In contrast, rs12143842 was associated with a significant increase of QT-interval duration in our study, consistent with two population-based studies [16,18]. rs12143842 is located in the 5’ region of *NOS1AP* and has no known function. In fact, the fine mapping in the initial study concerning the association between *NOS1AP* and QT interval indicated that the most likely location of the underlying functional variant is in the 5’ region of *NOS1AP*. Functional studies are therefore warranted to clarify whether rs12143842 could regulate the transcription. Alternatively, there might be a true causal SNP that is in linkage disequilibrium with rs12143842.

It is notable that we observed a stronger genetic effect of *NOS1AP* variants on QT interval in the diabetic group than in the control group. Intriguingly, a synergistic interaction of diabetes and *NOS1AP*, probably because of a reduced repolarization reserve of diabetes [19,20], was suggested by Lehtinen *et al*. [21]. In their study, the strength of the effect of *NOS1AP* variants on QT was larger in diabetic patients than in the total sample of diabetic and non-diabetic subjects, which is consistent with the pattern of our findings. A test for the SNP–diabetes affection interaction was also conducted in our study. Although not significant, a trend toward interaction was observed ($P = 0.057$) and future studies of larger sample are needed to clarify this issue.

Several community-based studies found that women were more susceptible to drug-induced ventricular arrhythmia than men [22-24] and that women with long-QT syndrome are at higher risk than men of cardiac arrest and sudden cardiac death [25,26], raising the possibility that genetic factors may modify cardiac repolarization in a gender-specific

manner. This was further supported by a genome-wide association scan in three European populations, in which a stronger association in females was observed [27]. Similar to these findings, we found evidence of an association between *NOS1AP* and QT interval only in women, supporting the difference of QT biology in the two genders. However, no significant gender–SNP interaction was observed, probably underpowered because of the limited samples of each gender in our diabetic sample.

There are several lines of evidence that prolonged QT interval predisposed diabetic patients to sudden cardiac death and cardiovascular diseases [6-8]. Specifically, a study conducted in 192 Chinese diabetic patients revealed that women with prolonged QT interval have a 2.8-fold greater rate of cardiovascular disease as compared with those with a normal QT interval [28]. Interestingly, the International Type 2 Diabetes 1q Consortium showed that one of the nominal associations with Type 2 diabetes was located in the *NOS1AP* gene. Although this association was not replicated in additional samples of European descent, a significant effect of common *NOS1AP* variants on the susceptibility to Type 2 diabetes was observed recently in a Chinese population [29]. Our findings, together with these observations, suggest that women carrying the risk-conferring polymorphisms of *NOS1AP* may be more prone to cardiovascular events and sudden cardiac death, a finding which needs to be further investigated in the future.

A limitation of the study resides in the lack of exposure data of QT-prolonging or-shortening drugs. However, no anti-diabetic drugs were proved to be QT prolonging or shortening according to the QT Drugs website (http://www.Qtdrug.org/) and participants with overt diseases other than diabetes, which would require additional drug therapies, were excluded from the study cohort; thus, we had minimized the bias to a great extent. In addition, electrolyte disturbances that may explain QT alteration were not investigated in our study and these deserve to be taken into consideration in the future.

In summary, we have further validated the association of *NOS1AP* with QT interval in a Chinese diabetic cohort. Attempts with larger sample size are needed to clarify whether these findings are specific to the diabetic patients or whether they are common in the general Chinese population. In addition, future studies will also be required to characterize the influence of *NOS1AP* variants on cardiovascular events and sudden cardiac death, especially in diabetic women.

Acknowledgments

This work was supported by grants from the Project of National Natural Science Foundation of China (NSFC) (30630061 and 30800617), the National 973 Program of China (2006CB503901), the National 863 Program of China (2006AA02A409), the Major Program of Shanghai Municipality for Basic Research (08dj1400601), the Shanghai Key Laboratory of Diabetes Mellitus (08DZ2230200) and the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (U01-DK58026 and R01-DK073490). We thank all the participants of this research. We thank all nursing and medical staff at Shanghai Clinical Center for Diabetes for their dedication in this study.

Abbreviations

NOS1AP	nitric oxide synthase 1 adaptor protein
QTc	heart-rate corrected QT interval
SNP	single nucleotide polymorphism

Reference

1. Hong Y, Rautaharju PM, Hopkins PN, Arnett DK, Djousse L, Pankow JS, et al. Familial aggregation of QT-interval variability in a general population: results from the NHLBI Family Heart Study. Clin Genet. 2001; 59:171–177. [PubMed: 11260226]
2. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, et al. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: The Framingham Heart Study. Heart Rhythm. 2005; 2:277–284. [PubMed: 15851319]
3. Goldenberg I, Zareba W, Moss AJ. Long QT syndrome. Curr Probl Cardiol. 2008; 33:629–694. [PubMed: 18835466]
4. Schimpf R, Borggrefe M, Wolpert C. Clinical and molecular genetics of the short-QT syndrome. Curr Opin Cardiol. 2008; 23:192–198. [PubMed: 18382206]
5. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation. 2000; 102:1178–1185. [PubMed: 10973849]
6. Cardoso CR, Salles GF, Deccache W. Prognostic value of QT interval parameters in type 2 diabetes mellitus: results of a long-term follow-up prospective study. J Diabetes Complications. 2003; 17:169–178. [PubMed: 12810239]
7. Rana BS, Lim PO, Naas AA, Ogston SA, Newton RW, Jung RT, et al. QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. Heart. 2005; 91:44–50. [PubMed: 15604334]
8. Whitsel EA, Boyko EJ, Rautaharju PM, Raghunathan TE, Lin D, Pearce RM, et al. Electrocardiographic QT interval prolongation and risk of primary cardiac arrest in diabetic patients. Diabetes Care. 2005; 28:2045–2047. [PubMed: 16043757]
9. Jaffrey SR, Snowman AM, Eliasson MJ, Cohen NA, Snyder SH. CAPON: a protein associated with neuronal nitric oxide synthase that regulates its interactions with PSD95. Neuron. 1998; 20:115–124. [PubMed: 9459447]
10. Ashley EA, Sears CE, Bryant SM, Watkins HC, Casadei B. Cardiac nitric oxide synthase 1 regulates basal and beta-adrenergic contractility in murine ventricular myocytes. Circulation. 2002; 105:3011–3016. [PubMed: 12081996]
11. Arking DE, Pfeufer A, Post W, Kao WH, Newton-Cheh C, Ikeda M, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nat Genet. 2006; 38:644–651. [PubMed: 16648850]
12. Aarnoudse AJ, Newton-Cheh C, de Bakker PI, Straus SM, Kors JA, Hofman A, et al. Common NOS1AP variants are associated with a prolonged QTc interval in the Rotterdam Study. Circulation. 2007; 116:10–16. [PubMed: 17576865]
13. Post W, Shen H, Damcott C, Arking DE, Kao WH, Sack PA, et al. Associations between genetic variants in the NOS1AP (CAPON) gene and cardiac repolarization in the old order Amish. Hum Hered. 2007; 64:214–219. [PubMed: 17565224]
14. Tobin MD, Kahonen M, Braund P, Nieminen T, Hajat C, Tomaszewski M, et al. Gender and effects of a common genetic variant in the NOS1 regulator NOS1AP on cardiac repolarization in 3761 individuals from two independent populations. Int J Epidemiol. 2008; 37:1132–1141. [PubMed: 18511491]
15. Jia WP, Pang C, Chen L, Bao YQ, Lu JX, Lu HJ, et al. Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. Diabetologia. 2007; 50:286–292. [PubMed: 17180353]
16. Eijgelsheim M, Aarnoudse AL, Rivadeneira F, Kors JA, Witteman JC, Hofman A, et al. Identification of a common variant at the NOS1AP locus strongly associated to QT-interval duration. Hum Mol Genet. 2009; 18:347–357. [PubMed: 18927126]
17. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. Nat Genet. 2009; 41:399–406. [PubMed: 19305408]

18. Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. Nat Genet. 2009; 41:407–414. [PubMed: 19305409]
19. Lengyel C, Virag L, Biro T, Jost N, Magyar J, Biliczki P, et al. Diabetes mellitus attenuates the repolarization reserve in mammalian heart. Cardiovasc Res. 2007; 73:512–520. [PubMed: 17182020]
20. Roden DM. Taking the 'idio' out of 'idiosyncratic': predicting torsades de pointes. Pacing Clin Electrophysiol. 1998; 21:1029–1034. [PubMed: 9604234]
21. Lehtinen AB, Newton-Cheh C, Ziegler JT, Langefeld CD, Freedman BI, Daniel KR, et al. Association of NOS1AP genetic variants with QT interval duration in families from the Diabetes Heart Study. Diabetes. 2008; 57:1108–1114. [PubMed: 18235038]
22. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health. 1998; 7:547–557. [PubMed: 9650155]
23. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. J Am Med Assoc. 1993; 270:2590–2597.
24. Yap YG, Camm AJ. Drug-induced QT prolongation and torsades de pointes. Heart. 2003; 89:1363–1372. [PubMed: 14594906]
25. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, et al. Long QT syndrome in adults. J Am Coll Cardiol. 2007; 49:329–337. [PubMed: 17239714]
26. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007; 49:240–246. [PubMed: 17222736]
27. Marroni F, Pfeufer A, Aulchenko YS, Franklin CS, Isaacs A, Pichler I, et al. A genome-wide association scan of RR and QT interval duration in 3 European genetically isolated populations: the EUROSPAN project. Circ Cardiovasc Genet. 2009; 2:322–328. [PubMed: 20031603]
28. Ko GT, Chan JC, Critchley JA, Cockram CS. Cardiovascular disease in chinese type 2 diabetic women is associated with a prolonged QTc interval. Int J Cardiol. 2000; 76:75–80. [PubMed: 11121599]
29. Hu C, Wang C, Zhang R, Ng MC, Bao Y, So WY, et al. Association of genetic variants of NOS1AP with type 2 diabetes in a Chinese population. Diabetologia. 53:290–298. [PubMed: 19937226]

Table 1

The clinical characteristics of the study sample

	Characteristics	Type 2 diabetes (*n* = 1240)	Control subjects (*n* = 1196)
Total	Age (years)	60.9 ± 12.44	49.04 ± 13.95*
	BMI (kg/m^2)	24.22 ± 3.47	23.73 ± 3.14*
	Systolic blood pressure (mmHg)	135.66 ± 18.58	122.9 ± 17.66*
	Diastolic blood pressure (mmHg)	81.23 ± 10.11	76.89 ± 10.08*
	HbA_{1c} (mmol/l)	9.11 ± 2.36	5.58 ± 0.35*
	QTc (ms)	411.03 ± 37.82	396.58 ± 32.76*
Men	*n*	631	433
	Age (years)	58.8 ± 13.0	49.8 ± 15.6
	BMI (kg/m^2)	24.11 ± 3.33	23.67 ± 3.05
	Systolic blood pressure (mmHg)	133.65 ± 18.07	126.02 ± 18.17
	Diastolic blood pressure (mmHg)	81.71 ± 10.32	78.96 ± 10.77
	HbA_{1c} (mmol/l)	9.22 ± 2.44	5.58 ± 0.34
	QTc (ms)	400.73 ± 33.97	390.06 ± 31.2
Women	*n*	609	763
	Age (years)	63.0 ± 11.5†	48.61 ± 12.92
	BMI (kg/m^2)	24.33 ± 3.60	23.76 ± 3.18
	Systolic blood pressure (mmHg)	137.68 ± 18.86†	121.13 ± 17.13‡
	Diastolic blood pressure (mmHg)	80.71 ± 9.86	75.72 ± 9.47‡
	HbA_{1c} (mmol/l)	9.00 ± 2.28	5.58 ± 0.36
	QTc (ms)	421.72 ± 38.64†	400.26 ± 33.07‡

Continuous variables are presented as mean ± SD.

QTc, heart-rate corrected QT interval.

*$P < 0.05$ compared with diabetic patients.

†$P < 0.05$ compared with diabetic men.

‡$P < 0.05$ compared with men with normal glucose regulation.

Table 2

The pairewise linkage disequilibrium of the single nucleotide polymorphisms genotyped in the *NOS1AP* region

|*D'*| / r^2	rs10494366	rs12143842	rs12029454
rs10494366		0.44	0.26
rs12143842	0.04		0.34
rs12029454	0.02	0.08	

|*D'*| above the diagonal line and r^2 below the diagonal line.

Table 3

Association analysis of the three single nucleotide polymorphisms (SNPs) and heart-rate corrected QT intervals (QTc) in diabetic and non-diabetic subjects

	SNP	QTc (ms)			β (SE)	*P*-value*	Empirical *P*
		AA	Aa	aa			
Type 2 diabetes	rs10494366	409.68 ± 36.28	412.14 ± 40.14	413.82 ± 35.36	1.31 (1.53)	0.39	0.73
	rs12143842	409.75 ± 38.04	410.39 ± 37.04	420.83 ± 39.38	3.87 (1.57)	0.014	0.039
	rs12029454	410.66 ± 39.13	408.95 ± 37.00	418.86 ± 36.84	3.05 (1.54)	0.039	0.11
Control	rs10494366	397.24 ± 33.99	397.49 ± 31.49	392.87 ± 30.35	1.42 (1.36)	0.30	0.64
	rs12143842	396.44 ± 32.38	397.34 ± 33.08	394.41 ± 33.6	0.65 (1.42)	0.65	0.97
	rs12029454	394.46 ± 32.76	398.04 ± 33.74	398.36 ± 29.87	2.63 (1.36)	0.054	0.15

AA, major allele homozygotes; Aa, heterozygotes; aa, minor allele homozygotes.

**P* was adjusted for age, sex and HbA_{1c} (case group only).

Table 4

Sex-specific association analysis of the three single nucleotide polymorphisms (SNPs) and heart-rate corrected QT intervals (QTc) in diabetic and non-diabetic subjects

	SNP	Men			Women		
		β (SE)	*P*-value*	Empirical *P*	β (SE)	*P*-value*	Empirical *P*
Type 2 diabetes	rs10494366	0.54 (2.06)	0.79	0.99	3.35 (2.43)	0.17	0.57
	rs12143842	1.73 (2.12)	0.42	0.76	5.46 (2.31)	0.018	0.049
	rs12029454	4.32 (2.01)	0.032	0.69	2.06 (2.33)	0.38	0.78
Control	rs10494366	0.22 (2.19)	0.92	0.99	2.02 (1.73)	0.24	0.56
	rs12143842	0.32 (2.32)	0.89	0.81	1.20 (1.79)	0.50	0.92
	rs12029454	3.80 (2.13)	0.076	0.21	1.96 (1.76)	0.26	0.57

*P was adjusted for age and HbA_{1C} (diabetic group only).

Diabet Med. Author manuscript; available in PMC 2011 September 1.

Table 5

Test for single nucleotide polymorphism–diabetes affection interaction in the pooled sample

Interaction with Type 2 diabetes	β	se	*t*	*P*
rs10494366	2.39	2.04	1.17	0.24
rs12143842	4.05	2.12	1.91	0.057
rs12029454	0.57	2.06	0.28	0.78