Increased Risk of Myocardial Infarction Among Patients With Type 2 Diabetes Who Carry the Common rs10830963 Variant in the *MTNR1B* Gene

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OBJECTIVE

The common *MTNR1B* single nucleotide polymorphism rs10830963 associates with risk of type 2 diabetes (T2D). Here, we examine the association between this gene variant and the risk of myocardial infarction (MCI) among patients with T2D. MCI is a main cause of death and disability among such individuals.

RESEARCH DESIGN AND METHODS

Data from the UK Biobank cohort were used in order to examine the association between rs10830963 and incidence of MCI (fatal and nonfatal) among 13,655 participants with probable T2D during a follow-up period of 6.8 years.

RESULTS

Assuming an additive genetic model, a positive association was found between the rs10830963 variant in the *MTNR1B* gene and the risk for incident MCI during the 6.8-year follow-up (adjusted hazard ratio per G allele 1.19 [95% CI 1.02, 1.40], $P = 0.03$).

CONCLUSIONS

The rs10830963 polymorphism may be a useful genetic marker for MCI in patients with T2D.

Activation of melatonin receptor 1B (MTNR1B) by the pineal gland hormone melatonin inhibits the release of insulin by pancreatic islets in response to glucose (1,2). This inhibitory effect is particularly strong among carriers of a common variant in the *MTNR1B* gene, rs10830963 (G risk allele; ~30% of the population carry at least one G risk allele). This may also explain the strong association of this single nucleotide polymorphism (SNP) with the risk of type 2 diabetes (T2D) (3). It is noteworthy that melatonin also acts on other organs through MTNR1B, including the heart. Using an experimental myocardial ischemia/reperfusion mouse model, a recent study demonstrated that melatonin-induced activation of MTNR1B on myocardial cells ameliorated myocardial ischemic/reperfusion injury (4). Myocardial infarction (MCI) is a main cause of death and disability among individuals with diabetes (5). For instance, the results of a 5.5-year cohort study involving 1.9 million individuals (of whom 1.8% had T2D) demonstrated a higher risk of nonfatal MCI (adjusted hazard ratio 1.54 [95% CI 1.42, 1.67]) in individuals with T2D than in those without diabetes (6). It is not known, however, whether carrying the minor G allele of rs10830963 modifies the risk of MCI.

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Thus, in this study we examined the association between this gene variant and the risk of MCI among patients with T2D from the UK Biobank cohort.

RESEARCH DESIGN AND METHODS

Study Population

The UK Biobank is a prospective, population-based cohort study that enrolled, from 2006 through 2010, more than 500,000 individuals aged between 40 and 69 years. Participants were recruited from across the U.K. and enrolled at one of the UK Biobank assessment centers. For the current study, 337,083 unrelated individuals of white British ancestry whose genomes passed quality control were initially available, among whom 13,655 were identified as having probable T2D at baseline. The UK Biobank received ethics approval from the National Health Service Research Ethics Service (London, U.K.) (reference 11/NW/0382), and participants gave informed consent.

Assessment of T2D

Participants were classified as having T2D whenever one of two criteria was met: *1*) T2D indicated by using a validated algorithm based on self-reported disease, medication, and a diagnosis of T2D noted in the medical history (for more details regarding the algorithm, see the work by Eastwood et al. [7]). The variables were collected by a questionnaire individuals completed with a touch-screen device and through verbal interviews with a trained nurse from the UK Biobank baseline assessment team. *2*) HbA_{1c} level $\geq$6.5% ($\geq$48 mmol/mol) (8). HbA_{1c} levels in red blood cells were centrally determined by the UK Biobank using high-performance liquid chromatography performed on a Bio-Rad VARIANT II TURBO HbA_{1c} analyzer (9). Individuals with probable type 1 diabetes or probable gestational diabetes mellitus identified by the aforementioned algorithm were excluded from the analysis.

Genotyping

The *MTNR1B* rs10830963 SNP (chromosome 16, intron variant) was directly genotyped with the Affymetrix UK

Table 1—Baseline characteristics of the population with T2D, stratified by rs10830963 genotype

		rs10830963 Genotype			
Characteristics	Total population (n = 13,655)	CC (n = 6,805)	CG (n = 5,689)	GG (n = 1,161)	*P* value
Time at risk, years	93,099	46,474	38,745	7,880	—
Age, years	60.2 ± 6.7	60.2 ± 6.7	60.1 ± 6.7	60.2 ± 6.8	0.71*
Sex					0.22#
Female	5,300 (38.8)	2,621 (38.5)	2,249 (39.5)	430 (37.0)	
Male	8,355 (61.2)	4,184 (61.5)	3,440 (60.5)	731 (63.0)	
BMI, kg/m^2	31.9 ± 5.9	32.0 ± 6.0	31.9 ± 5.9	31.7 ± 5.7	0.40*
Region of test center					0.08#
England	12,004 (87.9)	5,988 (88.0)	5,007 (88.0)	1,009 (86.9)	
Wales	677 (5.0)	315 (4.6)	287 (5.0)	75 (6.5)	
Scotland	974 (7.1)	502 (7.4)	395 (6.9)	77 (6.6)	
Townsend index	−0.9 ± 3.3	−0.9 ± 3.3	−0.9 ± 3.3	−0.9 ± 3.2	0.78*
Systolic BP, mmHg	145.5 ± 18.3	145.4 ± 18.2	145.5 ± 18.5	145.8 ± 17.8	0.69*
BP-lowering medication					0.62#
Yes	8,018 (58.7)	4,017 (59.0)	3,313 (58.2)	688 (59.3)	
No	5,637 (41.3)	2,788 (41.0)	2,376 (41.8)	473 (40.7)	
Cholesterol-lowering medication					0.14#
Yes	9,372 (68.6)	4,724 (69.4)	3,863 (67.9)	785 (67.6)	
No	4,283 (31.4)	2,081 (30.6)	1,826 (32.1)	376 (32.4)	
Smoking status					0.01#
Current	5,986 (43.8)	2,883 (42.4)	2,567 (45.1)	536 (46.2)	
Former	6,099 (44.7)	3,134 (46.1)	2,474 (43.5)	491 (42.3)	
Never	1,477 (10.8)	735 (10.8)	615 (10.8)	127 (10.9)	
Missing data	93 (0.7)	53 (0.8)	33 (0.6)	7 (0.6)	
Alcohol intake frequency					0.35#
Daily or almost daily	2,222 (16.3)	1,131 (16.6)	930 (16.3)	161 (13.9)	
Three or four times per week	2,268 (16.6)	1,118 (16.4)	936 (16.5)	214 (18.4)	
One or two times per week	3,347 (24.5)	1,668 (24.5)	1,375 (24.2)	304 (26.2)	
One to three times per month	1,762 (12.9)	858 (12.6)	751 (13.2)	153 (13.2)	
Special occasions only	2,397 (17.6)	1,210 (17.8)	996 (17.5)	191 (16.5)	
Never	1,644 (12.0)	809 (11.9)	697 (12.3)	138 (11.9)	
Missing data	15 (0.1)	11 (0.2)	4 (0.1)	0 (0.0)	
Sleep duration, h/day	7.2 ± 1.3	7.2 ± 1.3	7.2 ± 1.3	7.2 ± 1.3	0.58*
HbA_{1c}, % (mmol/mol)	7.0 ± 3.4 (52.9 ± 14.1)	7.0 ± 3.5 (53.1 ± 14.3)	7.0 ± 3.4 (52.8 ± 14.1)	7.0 ± 3.4 (52.9 ± 13.5)	0.64*
Incident MCI					0.16#
Yes	360 (2.6)	164 (2.4)	158 (2.8)	38 (3.3)	
No	13,295 (97.4)	6,641 (97.6)	5,531 (97.2)	1,123 (96.7)	

Data are n (%) or mean ± SD unless otherwise specified. BP, blood pressure. #Based on the χ^2 test. *Based on ANOVA.

Biobank Lung Exome Evaluation (UK BiLEVE) Axiom array or the Applied Biosystems UK Biobank Axiom array. Quality control and imputation were conducted centrally by using the Haplotype Reference Consortium (UK10K) and 1000 Genomes Project phase 3 reference panels. Testing for Hardy-Weinberg equilibrium revealed that the SNP did not deviate from the expected genotype proportion. The minor allele frequency of the rs10830963 G risk allele was 29.3%. An additive genetic model was assumed when analyzing the effects of this gene variant on the risk of incident MI in this study.

Outcome

Incident MCI (fatal and nonfatal) was algorithmically defined by the UK Biobank Outcome Adjudication Group. The algorithm for ascertaining MCI after baseline assessment used data from linked hospital admissions and death registries. MCIs prior to baseline assessment were detected either through linked hospital admission records or on the basis of participant self-report. Individuals were excluded if they had had an MCI, ischemic stroke (algorithmically defined), or coronary artery disease (defined by coronary artery bypass, coronary angioplasty, or coronary angiogram reported during the verbal interview) prior to the baseline assessment. The date of the last recorded MCI in the released data (21 February 2016) was used as the censoring date for the participants if no death, outcome, or earlier loss to follow-up ($n = 23$) had been recorded.

Potential Confounders

The following potential confounders were included in the analysis: participants' age, sex, and BMI; the Townsend index reflecting socioeconomic status; systolic blood pressure; use of blood pressure–lowering medications (yes/no); use of cholesterol-lowering medications (yes/no); smoking status (current, former, and never); alcohol intake frequency (six categories ranging from never to daily or almost daily); and daily self-reported sleep duration (hours). We also adjusted our analysis for region of the test center and genetic principal components of ancestry (first 10 columns).

Statistical Analysis

The association between the rs10830963 genotype and incident MCI was estimated by using Cox proportional hazards regression and assuming an additive genetic model. Time at risk was calculated from the date of the baseline investigation to the date on which the first MCI (nonfatal or fatal) was detected, the date of death unrelated to MCI, or the date of the last follow-up (21 February 2016), whichever came first. The primary analysis was adjusted for participants' sex and age (model 1). Model 2 was additionally adjusted for participants' BMI, the Townsend index, systolic blood pressure, use of blood pressure–lowering medications, use of cholesterol-lowering medications, smoking status, alcohol intake frequency, and sleep duration, as well as for region of the test center and genetic principal components of ancestry. In the final model (model 3), we also adjusted for the HbA_{1c} value measured at baseline. Proportional hazards assumptions were confirmed by using Kaplan-Meier survival curves. Baseline comparisons between participants with and those without T2D were performed by using one-way ANOVA or the χ^2 test. Overall, a two-sided P value less than 0.05 was regarded as statistically significant. Analyses were performed with Stata software version 15.1 (StataCorp, College Station, TX).

RESULTS

Characteristics of the T2D cohort, stratified by rs10830963 genotype, are shown in Table 1. In total, the investigated cohort had been at risk for 93,099 years. Genotype distribution of rs10830963 was 49.8% for CC, 41.7% for CG, and 8.5% for GG. During the average 6.8-year observation period, 360 patients with T2D (2.6% of the cohort) had an incident MCI.

Assuming an additive genetic model, the Cox regression analysis revealed a positive association between the rs10830963 variant in the *MTNR1B* gene and the risk of experiencing an incident MCI during the 6.8-year follow-up (model 1: adjusted hazard ratio per G allele 1.17 [95% CI 1.00, 1.37], $P = 0.05$; model 2: 1.19 [1.02, 1.39], $P = 0.03$; model 3: 1.19 [1.02, 1.40], $P = 0.03$).

CONCLUSIONS

Our study, which is based on a large cohort of patients with T2D, demonstrates that those carrying the minor G allele of rs10830963 may have a greater risk for MCI compared with those without the minor G allele. The association between the rs10830963 variant in the *MTNR1B* gene and incident MCI remained significant when adjusted for HbA_{1c}. This suggests that the observed association between this gene variant and MCI may not be simply related to impaired glycemic control, which itself can cause cardiovascular complications such as increased carotid intima-media thickness (10). Altogether, our findings suggest that the rs10830963 polymorphism may be a useful genetic marker for diabetologists to identify patients with T2D who have a high risk of experiencing MCI. Importantly, our results were based on a cohort of patients of white British ancestry who had T2D. Thus, our findings must be confirmed in populations with T2D among other ethnicities. Mechanistic studies using, for example, heart biopsy specimens from human donors will help evaluate whether the rs10830963 polymorphism alters the cardioprotective properties of melatonin through MTNR1B.

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