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Catechol-O-methyltransferase association with hemoglobin A1c

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Abstract

Aims—Catecholamines have metabolic effects on blood pressure, insulin sensitivity and blood glucose. Genetic variation in catechol-*O*-methyltransferase (*COMT*), an enzyme that degrades catecholamines, is associated with cardiometabolic risk factors and incident cardiovascular disease (CVD). Here we examined *COMT* effects on glycemic function and type 2 diabetes.

Methods—We tested whether *COMT* polymorphisms were associated with baseline HbA_{1c} in the Women's Genome Health Study (WGHS), and Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), and with susceptibility to type 2 diabetes in WGHS, DIAbetes Genetics Replication And Meta-analysis consortium (DIAGRAM), and the Diabetes Prevention Program (DPP). Given evidence that *COMT* modifies some drug responses, we examined association with type 2 diabetes and randomized metformin and aspirin treatment.

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Contribution Statement

Hypothesis: KH, BT, TK, PM, KM, DC.
Analysis: JF, KH, KM, DC, MH, LC, KJ.
Interpretation of results: JF, KH, KM, DC, MH, LC, KJ, BT, TK, GB, PR, DPP.
Manuscript preparation: JF, KH, KM, DC, MH, LC, KJ, BT, TK, GB, PR.

Disclosure Statement

JCF has received consulting honoraria from PanGenX and Pfizer. The other authors have no conflicts to disclose.

Results—*COMT* rs4680 high-activity G-allele was associated with lower HbA_{1c} in WGHS (β = −0.032% [0.012], $p = 0.008$) and borderline significant in MAGIC (β = −0.006% [0.003], $p = 0.07$). Combined *COMT* per val allele effects on type 2 diabetes were significant (OR = 0.98 [0.96–0.998], $p = 0.03$) in fixed-effects analyses across WGHS, DIAGRAM, and DPP. Similar results were obtained for 2 other *COMT* SNPs rs4818 and rs4633. In the DPP, the rs4680 val allele was borderline associated with lower diabetes incidence among participants randomized to metformin (HR = 0.81 [0.65–1.00], $p = 0.05$).

Conclusions—*COMT* rs4680 high-activity G-allele was associated with lower HbA_{1c} and modest protection from type 2 diabetes. The directionality of *COMT* associations was concordant with those previously observed for cardiometabolic risk factors and CVD.

1. Introduction

Diabetes and cardiovascular disease (CVD) frequently co-occur [1] and share risk factors, notably hypertension and obesity [2]. However, genome-wide association studies (GWAS) conducted to examine genetic risk factors for these related diseases have uncovered few specific genes associated with both CVD and diabetes [3].

The catecholamines, epinephrine, norepinephrine, and dopamine, influence cardiometabolic function by their varied effects on insulin, glucose metabolism, vascular tone and heart rate. Epinephrine increases glucose utilization in adipose tissue [4] and temporarily increases blood glucose by increasing hepatic glucose production, suppressing insulin secretion, and inhibiting insulin-stimulated glucose utilization [5]. This process can lead to hyperglycemia, particularly in individuals with diabetes [6]. Dopamine and norepinephrine also participate in glucose metabolism by controlling insulin secretion during glucose stimulation [7], effects that may be reduced in patients with diabetes [8] and obesity [9].

Catechol-*O*-methyltransferase (*COMT*) is a key enzyme in catecholamine metabolism, and is ubiquitously expressed, with high levels in the liver, lungs, kidneys, adrenal glands, brain and erythrocytes [10]. The *COMT* rs4680 functional polymorphism has been associated with cardiometabolic risk factors of abdominal obesity [9], systolic blood pressure [11], triglycerides and most recently, coronary artery disease in the CARDIoGRAMplusC4D consortium and incident CVD in the Women's Genome Health Study (WGHS) [12]. In the WGHS [13], a subset for genetic analysis of the Women's Health Study, a randomized placebo-controlled trial of aspirin and vitamin E for prevention of primary CVD with 10 years of follow-up, *COMT* associated CVD protection was eliminated with randomized allocation to either aspirin or vitamin E, suggesting potential *COMT* gene-drug interactions [12].

Despite the effects of *COMT* genetic variation on CVD and the extensive role of catecholamines in cardiometabolic processes, the relationship between *COMT*, glycemic function and diabetes has not been well studied. Given the role of catecholamines in glycemic control and *COMT* association with triglycerides and systolic blood pressure in the Women's Health Study [12], we sought to examine *COMT* association with metabolic disease. We examined the association of *COMT* rs4680 and closely linked rs4633 and rs4818 with HbA_{1c} and susceptibility to type 2 diabetes in 2 prospective and 2 cross-

sectional studies: the WGHS [13]; the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), a consortium of GWAS for quantitative glycemic traits in non-diabetic individuals [14]; the DIAbetes Genetics Replication And Meta-analysis consortium (DIAGRAM), a consortium of cross-sectional GWAS for case–control studies of diabetes [15]; and the Diabetes Prevention Program (DPP), a placebo-controlled trial of metformin and lifestyle changes for the prevention of type 2 diabetes in an ethnically diverse cohort of individuals with prediabetes [16]. In addition, based on the biological link between aspirin and type 2 diabetes [17] and the potential relationship between *COMT* and aspirin [12], we performed exploratory analyses to examine *COMT* effects on rates of incident type 2 diabetes among those randomly allocated to metformin (DPP) and aspirin (WGHS) compared to placebo.

2. Research Design and Methods

2.1. Study Populations

WGHS methods were previously described [13]. Briefly, genotyping of rs4680 and rs4818 was performed using Illumina Infinium II and linkage disequilibrium relationships determined from 1000G CEU population. Genotyping quality was >99.6% for rs4680 and rs4818. Rs4633 was imputed using Mach v. 1.0.16. HbA_{1c}, systolic blood pressure (SBP), triglycerides and body mass index (BMI) were measured at baseline. The Institutional Review Board of Brigham and Women's Hospital, Boston, approved all analyses.

DPP methods were previously described [18]. Briefly, genotyping was carried out on a Sequenom platform for participants who gave consent for genetic analysis ($N = 2714$). Subjects were ethnically diverse. Inclusion was limited to subjects with impaired glucose tolerance (elevated fasting blood glucose 5.3–6.9 mmol/L and/or two-hour plasma glucose 7.8–11.0 mmol/L). Data from rs4818 was unavailable.

2.2. Public Domain GWAS

COMT SNP associations with HbA_{1c} and type 2 diabetes were extracted from publically available GWAS summary statistics published by consortium-based inverse variance weighted fixed-effects meta-analyses. MAGIC reported quantitative glycemic trait data including HbA_{1c} from 23 GWAS among individuals with European descent ($N = 46,368$) [14]. Data on all three SNPs were available. DIAGRAM reported a GWAS of type 2 diabetes ("DIAGRAMv3") including 12,171 cases of diabetes and 56,862 controls with whole genome genotyping combined with metabochip data for summary statistics among a maximum of 149,821 subjects, 146,171 with European descent and 3650 with Pakistani descent [15]. Rs4680 and rs4633 data were available for 82,085 and 82,125 subjects respectively. Data for rs4818 was available from the DIAGRAM Trans-ethnic T2D GWAS meta-analysis representing 10,514 cases [19].

2.3. Statistical Analysis

COMT association with HbA_{1c} was analyzed using a similar approach to the one previously reported for 15 CVD biomarkers (including, triglycerides and systolic blood pressure) measured at baseline in the Women's Health Study [12]. Briefly, linear regression was used

to evaluate SNP associations with HbA_{1c} assuming a standard additive genetic model according to dose of coding alleles. DPP data were not included in the HbA_{1c} analysis because of bias introduced by the inclusion criteria which required subjects to have an HbA_{1c} >6%. Cox proportional hazards models were used to test association between each SNP and incidence of type 2 diabetes. Models were adjusted for age. WGHS models were also adjusted for obesity (using BMI >30), systolic blood pressure (SBP), triglycerides and HbA_{1c} at baseline. As the population of the WGHS was racially homogenous (23,294 women of European ancestry) no adjustment was made for race/ethnicity. DPP models were also adjusted for sex and race/ethnicity using principal components. Coding allele-drug interactions for each SNP were tested by significance of Cox model terms corresponding to the product of SNP genotype (0, 1, or 2 encoded alleles) and indicator variable (s) for drug allocation (0 = placebo, 1 = drug). Hardy–Weinberg equilibrium was assessed by an exact test. Consistent with MAGIC and DIAGRAM meta-analyses, fixed effects meta-analysis using inverse variance weighting was performed to estimate overall SNP estimates for HbA_{1c} and type 2 diabetes using Comprehensive Meta-Analysis Version 2 (Biostat™, NJ).

3. Results

There was considerable variability in *COMT* allele frequencies across the cohorts (Table 1) consistent with racial heterogeneity at this locus reported in the literature [20]. Rs4680 and rs4633 were in Hardy–Weinberg equilibrium in the WGHS and DPP, the two studies with available individual level data. In the WGHS linkage disequilibrium among rs4680 and rs4818 was ($r^2 = 0.70$; $D' = 1.00$) in participants of European descent.

3.1. COMT and HbA_{1c}

The three COMT SNPs examined, rs4680, rs4818 and rs4633 are known to have functional effects on enzymatic activity or gene expression and have been reported previously to affect a range of clinical phenotypes [10]. The directionality of *COMT* associations was concordant with those previously observed for cardiometabolic risk factors and CVD. The coded alleles at all three *COMT* SNPs were significantly associated with lower baseline levels of HbA_{1c} in the WGHS (Table 2). This association was essentially the same in models adjusted for obesity (BMI >30) or systolic blood pressure but slightly attenuated when adjusted for triglyceride levels (Table 3). Rs4680 was borderline and rs4818 non-significantly associated with HbA_{1c} in MAGIC. The effects of rs4680 and rs4633 were significant when the studies were combined in a meta-analysis. By contrast, in MAGIC, no significant association was observed between rs4633 and fasting glucose ($p = 0.47$), 2-h glucose levels ($P = 0.89$), or fasting insulin ($P = 0.37$), (Table 4).

3.2. COMT and Type 2 Diabetes

In the WGHS, the association of *COMT* rs4818 with type 2 diabetes was significant (Table 5). Rs4680 and rs4633 were borderline significant and directionally concordant with the effects on HbA_{1c}. In DIAGRAM, associations with type 2 diabetes were significant for rs4818 but non-significant for rs4633 and rs4680. The associations were directionally concordant with the diabetes associations in the WGHS. Controlling for obesity (BMI >30) in the WGHS age-adjusted models did not modify the association between *COMT* and Type

II diabetes (Table 6). Adjustment with systolic blood pressure, triglycerides and HbA_{1c} resulted in a slight attenuation of the *COMT* effects. Combining the WGHS effects with those in DPP, in a fixed-effects meta-analysis yielded significant estimates of the association of type 2 diabetes for all 3 SNPs (Table 5).

3.3. COMT and Drug Treatment Outcomes

In DPP, statistically significant hazard ratios were found in the metformin treatment arm for both rs4680 and rs4633 (Table 7). By contrast, no rs4680 or rs4633 effects on diabetes incidence were observed among those allocated to placebo (Table 7). This potential difference in treatment effects however, was not found to be statistically significant for either rs4680 (P-interaction = 0.16) or rs4633 (P-interaction = 0.11). In models stratified by race/ethnicity, significant hazards remained for the rs4633 marker in the African American group only (Table 8). No *COMT* gene-drug effects were found in the WGHS for randomized allocation to aspirin v. placebo (Table 7).

4. Discussion

Given the role of catecholamines in glycemic control and *COMT* association with cardiometabolic risk factors of systolic blood pressure, triglycerides and incident CVD, *COMT* is a plausible candidate locus for association with measures of glycemic function and type 2 diabetes. Here we show modest, nominally significant and directionally consistent associations between *COMT*, HbA_{1c} and type 2 diabetes across multiple cohorts.

Despite the considerable overlap between cardiometabolic risk factors and coincidence of diabetes and CVD, few genetic variants have been shown to be associated with both diseases [3]. Our findings of a modest association with type 2 diabetes are consistent with a recent study that reported a small protective effect of the rs4680 high-activity G allele in a Southern Chinese case/control study [21]. However our results differ from a case/control study of men with obesity in Denmark in which the *COMT* rs4680 GG-genotype was associated with impaired glucose tolerance or type 2 diabetes [9]. These differences may in part be attributed to the heterogeneity in the racial/ethnic, gender and disease states of these cohorts. Adjusting our WGHS models for obesity did not modify the *COMT* association with type 2 diabetes suggesting that these effects do not lie on the same causal pathway. However, there was mild attenuation observed with triglycerides in models of HbA_{1c}.

The contrasting *COMT* effects between HbA_{1c} and fasting and 2-h glucose in the MAGIC database may likely be related to the differences in the health status of the cohorts studied here. Further the glycemic gap is similar to other studies that showed that interindividual differences in HbA_{1c} do not necessarily correspond with differences in glycemia and may reflect differences in hemoglobin glycation per se [22,23]. In spite of the directional concordance, the association of high-activity *COMT* alleles with lower levels of glycated hemoglobin may be unrelated to type 2 diabetes and more a function of epinephrine mediated increases in glucose production [5,6] being greater in people genetically predisposed to have lower-activity *COMT*. Therefore replication of these findings is warranted to determine if they signify a true genetic effect and point towards an underlying biological process relevant to diabetes risk.

The search for genetic variants that modify the response to treatment with metformin has focused on candidate gene analyses of metformin transporter genes [24]. The list of drugs that appear to be modified by *COMT* including aspirin, vitamin E [12] and quercetin [25] is growing. Although we found that *COMT* was associated with metformin outcomes in the DPP, the interaction effect was not significant and it remains to be seen if this effect has any relevance to clinical treatment outcomes.

The strengths of this study derive from the large, prospective design of the WGHS with 10-years follow-up. In addition, MAGIC and DIAGRAM are large consortia constituted from populations with a wide variety of demographic characteristics. However, WGHS only examined adult Caucasian women, while other groups, including MAGIC, were more diverse in age and gender, which may explain the difference in HbA_{1c} effect estimates observed between these two studies. Other differences include the generally good health of WGHS participants compared with DPP participants who at baseline were “prediabetic” or had blood sugar levels above normal but not sufficiently elevated to be diagnosed with diabetes. Given the significant interaction discovered between aspirin and *COMT* in the context of CVD [12], lack of data on the use of these drugs in the DPP, MAGIC, or DIAGRAM may also be a limitation.

Catechol-*O*-methyltransferase (*COMT*) is emerging as an important disease and pharmocogenomic hub with important links to cardiovascular disease [12] as well as a cancer [26] and neurological disease [27]. To fully appreciate and potentially leverage *COMT* effects for the development of precision medicines, it is important to understand the scope of these effects in prevalent and chronic diseases such as type 2 diabetes. The potential effects of *COMT* genotype on HbA_{1c} and type 2 diabetes reported here are consistent with the cardiometabolic protection reported for *COMT* effects on hypertension, triglycerides and incidence of cardiovascular disease. Thus these findings are hypothesis generating and further investigation is necessary to understand the complete relationship between *COMT* genotype, type 2 diabetes, and its treatment.

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Table 1

COMT SNPs and coded allele frequencies in each of the study cohorts. Allele frequencies from the 1000 Genomes are included as a reference

Study	Study type	Cohort	N	Coded allele frequency		
				Rs4680	Rs4633	Rs4818
WGHS	RCT	Unselected (women)	23,294	G (0.46)	C (0.46)	G (0.39)
MAGIC	GWAS meta-analysis	Unselected cohorts	46,368	G (0.52)	C (0.52)	G (†)
DIAGRAM	GWAS meta-analysis	Impaired glucose function	82,085	G (†)	C (†)	C (†)
DPP	RCT	Unselected cohorts	2714	G (0.56)	C (0.55)	†
1000 Genomes [1]				G (0.63)	C (0.63)	G (0.70)

† Data not available in database.

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Table 2

Meta-analysis of COMT SNP * association with I HbA_{1c} (%) in WGHS and MAGIC

Study	rs4680	rs4633	rs4818
	β [SE], *p*-value	β [SE], *p*-value	β [SE], *p*-value
WGHS	−0.032 [0.012], *p* = 0.008	−0.034 [0.012], *p* = 0.005	−0.029 [0.012], *p* = 0.016
MAGIC	−0.006 [0.003], *p* = 0.07	−0.007 [0.003], *p* = 0.04	−0.006 [0.007], *p* = 0.4
Fixed	−0.008 [0.003], *p* = 0.01	−0.009 [0.003], *p* = 0.007	−0.012 [0.006], *p* = 0.05

* Rs4680 coded allele = G(val), reference allele = A(met); rs4633 coded allele = C, reference allele = T; rs4818 coded allele = G, reference allele = C.

Table 3

Age-adjusted Cox proportional hazard models of COMT rs4680, rs4633, rs4818 effects on HbA_{1c} in the WGHS adjusted for obesity (BMI >30), systolic blood pressure (SBP) or triglycerides

	Rs4680		Rs4633		Rs4818	
	β [SE]	*p*	β [SE]	*p*	β [SE]	*p*
Age-adjusted	−0.031 [0.012]	0.008	−0.034 [0.012]	0.005	−0.029 [0.012]	0.02
BMI > 30	−0.030 [0.012]	0.01	−0.033 [0.012]	0.006	−0.028 [0.012]	0.02
SBP	−0.027 [0.012]	0.02	−0.030 [0.012]	0.01	−0.025 [0.012]	0.04
Triglycerides	−0.023 [0.010]	0.03	−0.024 [0.010]	0.02	−0.018 [0.010]	0.09
Fully-adjusted	−0.020 [0.010]	0.05	−0.022 [0.010]	0.04	−0.015 [0.011]	0.16

Table 4

COMT rs4633 association with measures of blood glucose in MAGIC

Outcome measure	N	β, *P*-value
Fasting glucose	133,010	−0.002, $p = 0.47$
2-h glucose	42,854	−0.002, $p = 0.89$
Fasting insulin	108,557	−0.002, $p = 0.37$

Table 5

Meta-analysis of COMT SNP association with type 2 diabetes in WGHS, DIAGRAM and DPP

Study	Rs4680*	Rs4633*	Rs4818*
	HR [95% CI], *p*-value	**HR [95% CI], *p*-value**	**HR [95% CI], *p*-value**
WGHS	0.92 [0.84–1.00], $p = 0.06$	0.91 [0.84–1.00], $p = 0.05$	0.89 [0.81–0.98], $p = 0.017$
DIAGRAM	0.98 [0.96–1.01], $p = 0.12$	0.98 [0.96–1.01], $p = 0.13$	0.94 [0.88–1.01], $p = 0.035$
DPP	0.95 [0.84–1.06], $p = 0.35$	0.96 [0.84–1.09], $p = 0.51$	Not available
Fixed	0.98 [0.96–0.998], $p = 0.03$	0.98 [0.96–1.00], $p = 0.04$	0.92 [0.87–0.98], $p = 0.005$

*Rs4680 coded allele = G(val), reference allele = A(met); rs4633 coded allele = C, reference allele = T; rs4818 coded allele = G, reference allele = C.

Table 6

Age-adjusted Cox proportional hazard models of COMT rs4680, rs4633, rs4818 effects on type 2 diabetes in the WGHS adjusted for obesity (BMI >30), systolic blood pressure (SBP), triglycerides and hemoglobin A1c (HbA1c)

	Rs4680		Rs4633		Rs4818	
	HR [SE]	***p***	**HR [SE]**	***p***	**HR [SE]**	***p***
Age-adjusted	0.92 [0.046]	0.06	0.91 [0.046]	0.05	0.89 [0.047]	0.017
BMI >30	0.91 [0.046]	0.04	0.91 [0.047]	0.03	0.88 [0.048]	0.011
SBP	0.94 [0.046]	0.17	0.93 [0.047]	0.13	0.91 [0.048]	0.06
Triglycerides	0.93 [0.046]	0.13	0.93 [0.046]	0.11	0.91 [0.047]	0.06
HbA1c	0.96 [0.046]	0.36	0.96 [0.046]	0.38	0.92 [0.047]	0.11

Table 7

COMT association with treatment response to metformin in the DPP and aspirin in the WGHS

Study	SNP	HR [95% CI], *p*-value	HR [95% CI], *p*-value	$p_{\text{Interaction}}$
DPP		Metformin (n = 896)	Placebo (n = 909)	
	Rs4680	0.81 [0.65–1.00], p = 0.05	0.99 [0.82–1.18], p = 0.90	0.16
	Rs4633	0.76 [0.60–0.97], p = 0.03	1.02 [0.84–1.23], p = 0.90	0.11
WGHS		Aspirin (n = 5812)	Placebo (n = 5811)	
	Rs4680	0.87 [0.73–1.04], p = 0.12	1.05 [0.87–1.25], p = 0.60	0.15
	Rs4633	0.88 [0.73–1.05], p = 0.16	1.05 [0.88–1.26], p = 0.60	0.14
	Rs4818	0.88 [0.74–1.05], p = 0.16	1.01 [0.83–1.21], p = 0.90	0.30

Table 8

Cox proportional hazard models of COMT rs4680 and rs4633 effects on type 2 diabetes by treatment arm in the DPP stratified by race

	Placebo (*n* = 909)				Metformin (*n* = 896)				Lifestyle (*n* = 909)			
All ethnicities	**HR**	**Conf. limits**		***P* val**	**HR**	**Conf. limits**		***P* val**	**HR**	**Conf. limits**		***P* val**
Rs4633	1.02	0.84	1.23	0.85	0.76	0.60	0.97	0.03	1.09	0.84	1.41	0.53
Rs4680	0.99	0.82	1.18	0.88	0.81	0.65	1	0.05	1.04	0.82	1.33	0.73
Caucasians	***n* = 499**				***n* = 512**				***n* = 492**			
Rs4633	1.11	0.85	1.45	0.43	0.85	0.61	1.24	0.37	1.04	0.74	1.47	0.82
Rs4680	1.22	0.95	1.56	0.12	0.87	0.65	1.16	0.35	0.97	0.71	1.32	0.84
African American	***n* = 192**				***n* = 184**				***n* = 178**			
Rs4633	1.08	0.70	1.64	0.74	0.55	0.33	0.94	0.03	1.11	0.63	1.96	0.71
Rs4680	0.79	0.55	1.15	0.22	0.68	0.43	1.07	0.10	1.44	0.78	2.65	0.25
Hispanic	***n* = 152**				***n* = 145**				***n* = 162**			
Rs4633	1.05	0.65	1.69	0.84	0.84	0.48	1.49	0.56	0.99	0.52	1.85	0.97
Rs4680	0.937	0.61	1.44	0.77	0.823	0.49	1.37	0.46	0.84	0.46	1.53	0.57
Asian/Pac Is	***n* = 38**				***n* = 33**				***n* = 49**			
Rs4633	0.50	0.22	1.16	0.11	1.23	0.38	0.4	0.73	2.37	0.09	50.0	0.61
Rs4680	0.48	0.21	1.08	0.08	1.02	0.37	2.83	0.97	0.53	0.12	2.33	0.40
American Indians	***n* = 28**				***n* = 22**				***n* = 28**			
Rs4633	0.65	0.21	2.00	0.46	0.35	0.07	1.82	0.21	NA			
Rs4680	0.52	0.17	1.55	0.24	0.52	0.13	2.06	0.35	NA			