Toward Precision Medicine: *TBC1D4* Disruption Is Common Among the Inuit and Leads to Underdiagnosis of Type 2 Diabetes

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OBJECTIVE

A common nonsense mutation in *TBC1D4* was recently found to substantially increase the odds of type 2 diabetes in Greenlandic Inuit, leading to exclusively increased postprandial glucose. We investigated the frequency and effect of the *TBC1D4* mutation on glucose metabolism and type 2 diabetes diagnosis among Canadian and Alaskan Inuit.

RESEARCH DESIGN AND METHODS

Exome sequencing of the *TBC1D4* variant was performed in 114 Inuit from Nunavik, Canada, and Sanger sequencing was undertaken in 1,027 Alaskan Inuit from the Genetics of Coronary Artery Disease in Alaskan Natives (GOCADAN) Study. Association testing evaluated the effect of the *TBC1D4* variant on diabetes-related metabolic traits and diagnosis.

RESULTS

The *TBC1D4* mutation was present in 27% of Canadian and Alaskan Inuit. It was strongly associated with higher glucose (effect size +3.3 mmol/L; $P = 2.5 \times 10^{-6}$) and insulin (effect size +175 pmol/L; $P = 0.04$) 2 h after an oral glucose load in homozygote carriers. *TBC1D4* carriers with prediabetes and type 2 diabetes had an increased risk of remaining undiagnosed unless postprandial glucose values were tested (odds ratio 5.4 [95% CI 2.5–12]) compared with noncarriers. Of carriers with prediabetes or type 2 diabetes, 32% would remain undiagnosed without an oral glucose tolerance test (OGTT).

CONCLUSIONS

Disruption of *TBC1D4* is common among North American Inuit, resulting in exclusively elevated postprandial glucose. This leads to underdiagnosis of type 2 diabetes, unless an OGTT is performed. Accounting for genetic factors in the care of Inuit with diabetes provides an opportunity to implement precision medicine in this population.

Precision medicine, as defined by the National Institutes of Health's Precision Medicine Initiative Working Group, aims to tailor health care to individual variability in genes, environment, and lifestyles (1). While oncology has demonstrated some tangible success with precision medicine, few examples exist in other domains of health care (2). Genetic predisposition to disease may vary not only by individual but also by ancestry, and harnessing this information may help health care providers to better understand

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how to approach disease among different ethnicities. This may be particularly relevant in specific populations, such as the Inuit, that have had different natural selection pressures leading to different frequencies of genetic variants.

Moltke et al. (3) recently identified a population-specific nonsense variant in *TBC1D4* which was both common (minor allele frequency [MAF] 17%) and had a large effect on type 2 diabetes risk among the Greenlandic population (homozygote odds ratio [OR] 10.3; $P = 1.6 \times 10^{-24}$ in a recessive model). Specifically, compared with noncarriers, homozygous carriers of the *TBC1D4* p.Arg684.Ter variant had markedly higher concentrations of 2-h plasma glucose (3.8 mmol/L [68 mg/dL]; $P = 2.5 \times 10^{-35}$) and serum insulin (165 pmol/L [24 uIU/mL]; $P = 1.5 \times 10^{-20}$) after an oral glucose tolerance test (OGTT). Conversely, this variant decreased fasting glucose and had little effect on HbA_{1c}. The same effects—although of smaller magnitude—were also observed in heterozygote carriers.

What is not known is whether this variant is present in other Inuit and whether it may, given the exclusive effect on postprandial glucose, influence diagnostic strategies for type 2 diabetes. Such information may have clinical utility given that the prevalence of type 2 diabetes has been increasing dramatically among the Inuit over the past 25 years (4).

Interestingly, the ancestors of the Inuit in Greenland are thought to have migrated from Siberia, across the Central and Eastern Canadian Arctic (5). If the *TBC1D4* nonsense mutation arose earlier along migration routes out of Siberia, this mutation would also be present in North American Inuit. Therefore, in this study we assessed the prevalence of the *TBC1D4* mutation and its effect on diagnostic strategies for type 2 diabetes in the North American Arctic Inuit population.

RESEARCH DESIGN AND METHODS

To test whether the *TBC1D4* variant is indeed specific to Greenland or is shared by other Arctic populations, we assayed the p.Arg684Ter single nucleotide polymorphism in two distinct North American circumpolar populations. The first consisted of 114 Inuit from Nunavik in Northern Quebec, Canada (the Eastern North American Arctic), and the second of 1,027 individuals from a cohort study of Alaskan Inuit, called the Genetics of Coronary Artery Disease in Alaskan Natives (GOCADAN) study (6) (the Western North American Arctic).

Inuit from Nunavik were recruited originally for the purposes of a research project assessing genetic determinants of fatty acid metabolism (7). While that study did not include type 2 diabetes status or metabolic traits, it was used to quantify the prevalence of the *TBC1D4* variant in Nunavik.

Informed consent for the current study was obtained from all participants. The *TBC1D4* variant (rs61736969, a nonsense polymorphism in *TBC1D4* that is also called p.Arg684Ter or c.2050C>T) was assayed using exome sequencing (see the Supplementary Data for a detailed description of the exome sequencing).

We next tested the effect of this variant on glucose metabolism in the GOCADAN study (6). This longitudinal, population-based study, conducted between October 2000 and April 2004, aimed to investigate the genetic determinants of cardiovascular disease among 1,214 Inuit from several coastal villages in the Norton Sound region of Western Alaska. All individuals older than 18 years residing in this region were invited to participate. Testing included a physical examination, laboratory determinations, and measures of subclinical disease (described in detail elsewhere [6]). Specifically, type 2 diabetes status was determined by self-report, medication use, and fasting glucose screening (Accu-Chek Advantage). A urine sample was collected and blood samples were taken when fasted and 2 h after a standard 75-g OGTT (Glutol; Paddock Laboratory Inc., Minneapolis, MN). Participants were excluded from the OGTT if they were already considered as having type 2 diabetes according to the following criteria: having known type 2 diabetes and requiring insulin, or using oral hypoglycemic agents with two recorded glucose values >13.9 mmol/L or a fasting blood glucose value >12.5 mmol/L.

For the purposes of this study, we used Sanger sequencing on the *TBC1D4* variant in 1,027 GOCADAN participants (51 self-reported cases with type 2 diabetes and 976 controls) with available DNA samples. PCR and Sanger sequencing of the resulting amplicons were performed using established protocols (see the Supplementary Data for a detailed description of the method).

For comparison purposes, we queried the MAFs of the *TBC1D4* variant in different ancestral populations with available data in phase 3 of the 1000 Genomes Project (8).

Next, we conducted a genetic association study of the GOCADAN cohort, applying both additive and recessive genetic models to test for associations between the *TBC1D4* variant and reported type 2 diabetes status, as well as 14 traits related to type 2 diabetes (fasting and 2-h plasma glucose concentrations at OGTT, fasting and 2-h serum insulin concentrations at OGTT, Gutt insulin sensitivity index [$ISI_{0,120}$] (9), serum HbA_{1c}, triglycerides, total serum cholesterol, LDL cholesterol, HDL cholesterol, albuminuria, BMI, percentage fat mass, and waist circumference). For these quantitative traits, the association testing was done only in participants without diabetes. To evaluate the association between the *TBC1D4* variant and type 2 diabetes status, we used the full data set (both patients with diabetes and those without diabetes). Because of skewed values for some traits, we performed additional association tests after a rank-based inverse normal transformation (10) of the values to ensure normality. The measured genotype association method used for the association testing was implemented in the Sequential Oligogenic Linkage Analysis Routines software program (available from https://www.nitrc.org/projects/se_linux; described in detail elsewhere [11]). Finally, we accounted for multiple testing by applying a Bonferroni correction (12), dividing the α level (0.05) by the number of traits tested ($n = 14$). We recognize that this correction is overly conservative because many of the traits are highly correlated.

To compare the risk of underdiagnosis of prediabetes and type 2 diabetes among *TBC1D4* carriers and noncarriers, we applied the 2010 American Diabetes Association criteria (13) to the sample of patients with available OGTT values in order to classify them into 3 groups: type 2 diabetes, prediabetes, or neither. Specifically, type 2 diabetes was diagnosed if at least one of the following four criteria is present: *1*) $HbA_{1c} \geq 6.5\%$ (48 mmol/mol); *2*) fasting plasma glucose ≥ 7 mmol/L (126 mg/dL); *3*) 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during 75-g OGTT; or *4*) random plasma glucose ≥ 11.1 mmol/L (200 mg/dL). Prediabetes was diagnosed if at least one of the following three criteria was present: *1*) fasting plasma glucose between 5.6 and 6.9 mmol/L (100 and 125 mg/dL); *2*)

2-h plasma glucose in 75-g OGTT between 7.8 and 11.0 mmol/L (140 and 199 mg/dL); or *3*) HbA_{1c} between 5.7% and 6.4% (39 and 46 mmol/mol).

Then we compared the ratio of *TBC1D4* carriers to noncarriers who would have been diagnosed as having prediabetes and type 2 diabetes only by a 2-h OGTT. The OR of missed diagnosis of type 2 diabetes was calculated using the Fischer exact method (14,15) as applied in the epitools package of the R statistical software package (R Foundation for Statistical Computing, Vienna, Austria).

The study of Nunavik Inuit was approved by the Nunavik Nutrition and Health Committee and Comité d'éthique de la recherche du Centre hospitalier de l'Université de Montréal. The GOCADAN study was approved by the ethics review board at Norton Sound Health Corporation and all relevant institutional review boards. The analysis investigating the risk of type 2 diabetes underdiagnosis among GOCADAN participants was approved by the research ethics committee of the Jewish General Hospital of Montreal.

RESULTS

A map detailing the locations of the participating Nunavik and Alaskan Inuit cohorts appears in Fig. 1. Exome sequencing of the p.Arg684Ter variant (rs61736969, a nonsense polymorphism in *TBC1D4* c.2050C>T) in the cohort of 114 Nunavik Inuit individuals (63 men and 51 women; mean age 52 years) revealed that the variant was present. Of the 114 sequenced samples, 10 were removed from the analysis because of high levels of admixture (see the Supplementary Data for a definition of the admixture). The genotyping of the C/T variant in the remaining 104 samples from Nunavik revealed an allele frequency of 16.3% for the T allele (the nonsense polymorphism) (Supplementary Table 1).

Sanger sequencing of the p.Arg684Ter variant in the GOCADAN cohort also revealed the presence of the rs61736969 C/T variation, a nonsense mutation. The estimated allele frequency of the T allele among the sample of 1,027 individuals was 13.2% (Supplementary Table 1).

We next assessed the allele frequencies of the *TBC1D4* variants among different ancestral populations in phase 3 of the 1000 Genomes Project (8). The *TBC1D4* c.2050C>T variant had a MAF of 0% in Europeans, 0.6% in Latinos, 0% in African Americans, 0% in East Asians, and 0% in South Asians, and a global MAF of ~1%. It is important to state that rs61736969 is a triallelic variant. There exists in individuals of African ancestry an alternate allele that has a MAF of 3.6% and is not the same allele as the one found in Inuit.

A detailed description of the metabolic traits assayed for the entire GOCADAN cohort, and separately for carriers, noncarriers, and nongenotyped participants, appears in Table 1. The results of the association between the *TBC1D4* p.Arg684Ter variant and these metabolic traits for both the additive and recessive genetic models are reported in Table 2. When comparing homozygous carriers without diabetes of the variant with carriers of other genotypes, we found that homozygous carriers have increased concentrations of 2-h plasma glucose (β = +3.3 mmol/L; $P = 2.5 \times 10^{-6}$) and 2-h serum insulin concentrations (β = +175 pmol/L; P = 0.04) after an OGTT. Homozygous carriers also demonstrated decreased peripheral insulin sensitivity, as estimated by the $ISI_{0,120}$ ($\beta = -1.36$ SDs; P = 0.001). Heterozygous carriers without diabetes also showed an increase in 2-h plasma glucose (β = +0.5 mmol/L; $P = 2.8 \times 10^{-4}$). There was no discernible effect on fasting plasma glucose or serum insulin concentrations and HbA_{1c} in homozygotes without diabetes when applying a recessive model of transmission. Consistent with results found by Moltke et al. (3), heterozygote carriers without diabetes had lower fasting glucose and insulin concentrations ($\beta = -0.13$ mmol/L; $P = 2.2 \times 10^{-4}$ and $\beta = -9$ pmol/L; $P = 7 \times 10^{-4}$, respectively). When analyzing a group of 26 individuals with type 2 diabetes who were not using any medications for type 2 diabetes and had undergone an OGTT, we found that homozygous carriers of the *TBC1D4* variant displayed a higher 2-h plasma glucose concentration than noncarriers (β = +14 mmol/L; P = 0.02), but there was no significant association with 2-h serum insulin and fasting glucose and insulin concentrations among these individuals (Supplementary Table 2).

Among the rest of the type 2 diabetes–related traits, we found a marginal decrease in BMI, waist circumference, and percentage fat mass values among heterozygotes without diabetes (Table 2) and a lower BMI among heterozygote carriers with diabetes ($\beta = -5.9$ kg/m^2; $P = 1.7 \times 10^{-2}$) (Supplementary Table 2). However, we caution that these results require further replication in additional cohorts. After Bonferroni correction for multiple testing, the P value cutoff for statistical significance decreased to 3.5×10^{-3}. At this overly conservative threshold, all of our results remained significant, except for percentage fat mass and BMI. We observed consistent results when testing the association of the p.Arg684Ter variant with inverse normalized traits (Supplementary Tables 3 and 4). No association was found between the p.Arg684Ter variant and type 2 diabetes status among the 51 cases and 976 controls in the GOCADAN cohort in either the additive or recessive models (Supplementary Table 5).

Finally, we investigated how many *TBC1D4* carriers and noncarriers with

Figure 1—Map of the Arctic showing the regions of sampling for the Quebec Inuit (Nunavik) and GOCADAN (Norton Sound) cohorts.

Table 1—Characteristics of the entire GOCADAN cohort (metabolic traits) and specifically in *TBC1D4* variant carriers, noncarriers, and nongenotyped participants

Trait	Noncarriers (n = 771)		Heterozygote carriers (n = 241)		Homozygote carriers (n = 15)		Nongenotyped participants (n = 187)		All participants (n = 1,214)	
	Participants (n)	Mean (SD)	Participants (n)	Mean (SD)	Participants (n)	Mean (SD)	Participants (n)	Mean (SD)	Participants (n)	Mean (SD)
Fasting plasma glucose (mmol/L)	771	5.3 (1.1)	240	5.1 (1.1)	15	5.0 (0.9)	133	5.2 (0.6)	1,159	5.2 (1.0)
2-h plasma glucose (mmol/L)	573	5.2 (1.9)	156	5.6 (2.3)	6	8.9 (3.5)	92	5.6 (2.2)	827	5.3 (2.0)
Fasting serum insulin (pmol/L)	768	65.1 (52.2)	241	52.2 (33.4)	15	50.2 (26.8)	130	67.2 (51.6)	1,154	62.5 (48.8)
2-h serum insulin (pmol/L)	570	205.6 (234.0)	156	210.0 (193.4)	6	350.4 (300.4)	91	227.1 (228.5)	823	209.9 (226.8)
HbA_{1c} (%)	770	5.5 (0.5)	241	5.4 (0.4)	15	5.5 (0.3)	132	5.4 (0.3)	1,158	5.4 (0.5)
HbA_{1c} (mmol/mol)	770	36.0 (5.1)	241	35.0 (4.8)	15	37.0 (3.3)	132	35.0 (3.6)	1,158	36.0 (4.9)
$ISI_{0,120}$ (mg × L^2/mmol × mU × min)	566	115.4 (53.9)	156	110.1 (53.1)	6	71.9 (47.7)	88	104.6 (46.0)	816	113.1 (53.1)
Fasting serum triglyceride (mmol/L)	771	1.5 (1.1)	239	1.4 (0.6)	15	1.7 (0.6)	131	1.4 (0.9)	1,156	1.5 (1.0)
Fasting serum total cholesterol (mmol/L)	771	5.2 (1.1)	239	5.2 (1.0)	15	5.5 (1.2)	131	5.3 (1.1)	1,156	5.2 (1.0)
Fasting serum LDL cholesterol (mmol/L)	771	3.0 (0.9)	239	3.0 (0.9)	15	3.1 (1.0)	131	3.1 (0.9)	1,156	3.0 (0.9)
Fasting serum HDL cholesterol (mmol/L)	771	1.5 (0.5)	239	1.6 (0.5)	15	1.6 (0.3)	131	1.6 (0.5)	1,156	1.5 (0.5)
Albuminuria (mg/g)	739	0.1 (0.3)	234	0.0 (0.2)	15	0.1 (0.3)	129	0.1 (0.2)	1,117	0.1 (0.2)
Waist circumference (cm)	709	88.0 (13.3)	227	84.2 (11.4)	12	87.8 (6.8)	169	88.7 (13.2)	1,117	87.3 (13.0)
BMI (kg/m^2)	717	27.5 (5.7)	229	26.4 (5.2)	12	26.5 (3.3)	174	27.9 (5.6)	1,132	27.3 (5.6)
Fat mass (%)	711	38.1 (8.2)	226	37.0 (8.3)	12	32.1 (6.2)	172	37.4 (8.8)	1,121	37.7 98.3)
Type 2 diabetes, n (%)										
Self-reported	21 (2.7)		6 (2.5)		3 (20)		3(1.6)		33 (2.7)	
Diagnosed	24 (3.1)		7 (2.9)		1(6.7)		2 (1.1)		38 (3.1)	

$ISI_{0,120}$, Gutt insulin sensitivity index.

available 2-h OGTT results would have been diagnosed with prediabetes or type 2 diabetes only by meeting the 2-h OGTT diagnostic criterion. This is clinically relevant because the variant leads to increased 2-h OGTT but decreased fasting glucose, with no change in HbA_{1c}. Among the *TBC1D4* carriers, 50 had type 2 diabetes or prediabetes, of whom 16 (32%) would have been diagnosed only by using the 2-h OGTT (30% of heterozygote carriers and 50% of homozygote carriers) (Table 3). By contrast, failure to perform a 2-h OGTT would have missed a diagnosis of type 2 diabetes or prediabetes in 16 of 203 noncarriers (8%) (Table 3). The odds of missing a diagnosis of type 2 diabetes or prediabetes was 5.4 (95% CI 2.5–12) when comparing carriers with noncarriers. Table 3 describes the rate of missed diagnoses of type 2 diabetes and prediabetes separately. Supplementary Table 6 provides the prevalences of prediabetes and type 2 diabetes in the subsample of GOCADAN participants with available OGTT results, according to their number of *TBC1D4* variant copies.

CONCLUSIONS

Genetic disruption of *TBC1D4* is present in approximately 27% of Inuit across the North American Arctic and results in a high rate of missed diagnoses of type 2 diabetes and/or prediabetes unless 2-h OGTTs are performed. This is because *TBC1D4* disruption is associated with an elevation in postprandial glucose and decreases fasting glucose, while having no effect on HbA_{1c}. This suggests that since 2-h OGTTs are rarely performed in clinical practice (16), diagnostic strategies for type 2 diabetes and prediabetes in the Inuit should now always include OGTT and/or genotypic risk stratification. These findings demonstrate an opportunity to apply the principles of precision medicine.

The findings confirm and extend the main findings from Moltke et al. (3) among Greenlandic Inuit to the North American Inuit. While effect sizes and directions of the *TBC1D4* mutation were similar in our populations, the uncertain effect on type 2 diabetes risk in our population may be a result of the relatively small number of participants with type 2 diabetes in the GOCODAN cohort (51 cases/976 controls in the GOCADAN cohort vs. 220 cases/1,810 controls in the Greenlandic cohort).

Table 2—Association of the *TBC1D4* variant with metabolic traits in individuals without diabetes from the GOCADAN cohort

		Additive model			Recessive model		
Trait	Patients (*n*)	β	95% CI	*P* value	β	95% CI	*P* value
Fasting plasma glucose (mmol/L)	976	−0.13	−0.19 to −0.06	**2.21×10^{-4}**	−0.08	0.08–0.08	0.33
2-h plasma glucose (mmol/L)	709	0.50	0.23–0.77	**2.87×10^{-4}**	3.31	0.70–4.68	**2.50×10^{-6}**
HbA_{1c} (%)	975	−0.03	−0.07 to 0.01	0.10	0.13	0.08–0.28	0.10
HbA_{1c} (mmol/mol)	975	−0.3	−0.8 to 0.1	0.10	1.4	0.9–3.1	0.10
Fasting serum insulin (pmol/L)	974	−9.00	−14.20 to −3.79	**7.03×10^{-4}**	−6.84	10.83–14.39	0.53
2-h serum insulin (pmol/L)	706	13.8	−20.16 to 47.85	0.43	175.28	88.65–349.03	**0.05**
$ISI_{0,120}$ (SD)	703	−0.15	−0.31 to 0.01	0.07	−1.36	−2.18 to −0.53	**1.21×10^{-3}**
Fasting serum HDL cholesterol (mmol/L)	974	0.02	−0.05 to 0.08	0.64	0.09	0.13–0.35	0.46
Fasting serum LDL cholesterol (mmol/L)	974	0.01	−0.12 to 0.13	0.93	0.09	0.26–0.60	0.73
Fasting serum triglyceride (mmol/L)	974	−0.08	−0.20 to 0.04	0.18	0.32	0.25–0.80	0.20
Fasting serum total cholesterol (mmol/L)	974	0.00	−0.13 to 0.14	0.98	0.35	0.28–0.89	0.21
Waist circumference (cm)	919	−2.85	−4.70 to −0.99	**2.47×10^{-3}**	−0.10	4.11–7.98	0.98
Fat mass (%)	921	−0.99	−1.73 to −0.25	**0.01**	−0.61	1.64–2.60	0.71
BMI (kg/m^2)	931	−0.83	−1.63 to −0.04	**0.04**	−0.86	1.79–2.64	0.63
Albuminuria (mg/g)	939	0.27	−0.06 to 0.60	0.11	3.38	3.31–9.86	0.31

Results are shown for an additive and a recessive genetic model. The number of patients for each trait includes those with genotype data for the specific variant and phenotypic data for the specific trait. β is the effect size (change in the trait expressed in its unit of measurement if one copy of the effect allele is present) estimated using untransformed values. All *P* values <0.05 are considered statistically significant and appear in boldface. $ISI_{0,120}$, Gutt insulin sensitivity index.

There is a plausible pathophysiologic explanation for the abovementioned findings. TBC1D4 acts as a mediator of insulin-stimulated glucose uptake through GLUT4 mobilization (17). Murine experiments have shown that knocking down Tbc1d4 causes a significant decrease in basal plasma glucose and insulin-stimulated glucose uptake in muscle and adipose tissue (18) In humans, these findings are supported by a case report of familial postprandial hyperinsulinemia associated with a *TBC1D4* variant (19).

Carrying a mutation that solely increases postprandial glucose may influence type 2 diabetes complications. Interestingly, postprandial glucose seems to be a better predictor of cardiovascular disease and all-cause mortality than fasting glucose, and this association is linear (20,21). Specifically, postprandial glucose >7.8 mmol/L has been associated with all-cause mortality (22), and postprandial glucose >10.0 mmol/L has been associated with microvascular complications and myocardial infarctions (23). Some of these studies found that these effects of postprandial glucose occurred in addition to effects from fasting glucose and HbA_{1c}. These findings and others have prompted the American and Canadian Diabetes Associations to include OGTT as part of the diagnostic criteria for type 2 diabetes (13,24). However, all the above-mentioned studies have been done in non-Inuit populations, leaving open the possibility that the impact of postprandial hyperglycemia might be different in Inuit carrying the *TBC1D4* variant.

Our findings suggest that the *TBC1D4* variant is relatively common among the Eastern Canadian Nunavik Inuit and the Alaskan Inuit and potentially in other Arctic populations. These findings are clinically relevant given the increasing prevalence of diabetes in these populations (6,25,26). With an expected allele frequency of approximately 14%, we anticipate that 2% of the North American Inuit population are

Table 3—Classification of *TBC1D4* variant carriers and noncarriers according to their type 2 diabetes and prediabetes status and their diagnostic criteria for type 2 diabetes

	T2D or prediabetes			T2D		Prediabetes	
Criteria for T2D diagnosis	Only 2-h glucose (OGTT)	FG and/or HbA_{1c}	T2D and prediabetes cases diagnosed only by OGTT (%)	Only 2-h glucose (OGTT)	FG and/or HbA_{1c}	Only 2-h glucose (OGTT)	FG and/or HbA_{1c}
TBC1D4 noncarriers	16	187	8	7	11	9	176
TBC1D4 heterozygote carriers	14	32	30	4	3	10	29
TBC1D4 homozygote carriers	2	2	50	1	0	1	2
TBC1D4 carriers (homozygote + heterozygote)	16	34	32	5	3	11	31

Data are *n* unless otherwise indicated. The numbers of individuals with only abnormal 2-h plasma glucose on the OGTT (according to the American Diabetes Association criteria for type 2 diabetes [T2D] and prediabetes) represent cases of missed T2D or prediabetes diagnoses. FG, fasting glucose.

homozygous and 25% are heterozygous for the *TBC1D4* variant. Among the possible public health implications of this finding, we speculate that ascertainment of the *TBC1D4* variant could serve as a useful screening test to predict patients with prediabetes and type 2 diabetes with pronounced insulin resistance and exclusively abnormal postprandial glucose concentrations.

The clinical relevance of these findings is magnified since 2-h OGTTs are rarely performed in clinical practice; type 2 diabetes and prediabetes are generally diagnosed using fasting glucose, random glucose, and HbA_{1c} (13,24,27). Although the frequency of OGTT among the Inuit population has not been reported, a population-based registry of laboratory tests for type 2 diabetes diagnosis in Ontario, Canada (16), showed that over 20 years (1995–2005) there was a 28% increase in fasting glucose tests, which were prescribed for 37% of adults without known type 2 diabetes in 2005. During the same period, the percentage of HbA_{1c} tests also increased from 1.7% in 1995 to 6.0%. Remarkably, less than 1% of this population underwent OGTT testing in any year between 1995 and 2005, although OGTT has been recommended for type 2 diabetes screening by the Canadian Diabetes Association since 2003 (24). Thus current clinical practice would miss an important proportion of the Inuit population with type 2 diabetes unless OGTTs are performed.

We did not observe a significant increase of missed type 2 diabetes diagnoses without OGTT among *TBC1D4* carriers, likely because of the small sample of patients with type 2 diabetes and OGTT values (n = 26) in the GOCADAN cohort; nevertheless, we found a sevenfold increase of the odds of missing a diagnosis of prediabetes. Considering that *TBC1D4* carriers with prediabetes and diabetes (27% of the Inuit population) have a fivefold increase in their combined risk to remain undiagnosed (or a 32% chance to remain undiagnosed) without measuring 2-h glucose, performing OGTTs for these Inuit individuals seems to be of clinical relevance. Given that performing an OGTT as a screening test for type 2 diabetes and prediabetes can be particularly cumbersome in the Inuit population, genetic screening for the *TBC1D4* mutation might represent a clinically useful alternative, especially if the cost-effectiveness of this approach is shown. Homozygous and heterozygous carriers could then be further investigated by OGTTs. Of note, genetic screening tests for colon cancer have been successfully implemented in the Quebec Inuit population (28).

An important limitation of this study was that the degree of admixture of the Inuit population studied could not be quantified. Moltke et al. (3) showed an important influence of admixture on the MAF of the *TBC1D4* variant among Greenlandic Inuit, but the degree of admixture among the GOCADAN population cannot be likewise assessed because of a lack of dense genotyping. Nonetheless, this does not change the clinical relevance of these findings, since an important proportion of the North American Inuit population carries the *TBC1D4* variant.

Detecting the presence of the *TBC1D4* variant in the Inuit population might be important not only for diagnostic purposes but also for therapeutic decision making. *TBC1D4* carriers represent a subgroup of patients with type 2 diabetes who may be good candidates for specific pharmacologic treatments. This is because the mechanism of action of *TBC1D4* could suggest a better response of carriers to insulin sensitizers (29,30) than to other first-line type 2 diabetes oral antihyperglycemic drugs, such as sulfonylureas. However, this hypothesis should be tested in clinical trials. Finally, our findings could be applied in pharmacologic research, as *TBC1D4* may represent a potential drug target for type 2 diabetes.

In summary, genetic disruption of *TBC1D4* is common across the North American Inuit and leads to a higher postprandial glucose. Type 2 diabetes and prediabetes should be assessed in the population using OGTT, either after genotypic risk stratification or by testing the entire at-risk population.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
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References

1. Hudson KLR, Patrick-Lake B, Burchard EG, et al.; Precision Medicine Initiative (PMI) Working Group. *The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine*. Bethesda, MD, National Institutes of Health, 2015
2. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–795
3. Moltke I, Grarup N, Jørgensen ME, et al. A common Greenlandic TBC1D4 variant confers muscle insulin resistance and type 2 diabetes. Nature 2014;512:190–193
4. Jørgensen ME, Bjeregaard P, Borch-Johnsen K. Diabetes and impaired glucose tolerance among the inuit population of Greenland. Diabetes Care 2002;25:1766–1771
5. Helgason A, Pálsson G, Pedersen HS, et al. mtDNA variation in Inuit populations of Greenland and Canada: migration history and population structure. Am J Phys Anthropol 2006;130:123–134
6. Howard BV, Devereux RB, Cole SA, et al. A genetic and epidemiologic study of cardiovascular disease in Alaska natives (GOCADAN): design and methods. Int J Circumpolar Health 2005;64:206–221
7. Zhou S, Xiong L, Xie P, et al. Increased missense mutation burden of fatty acid metabolism related genes in Nunavik Inuit population. PLoS One 2015;10:e0128255
8. Abecasis GR, Altshuler D, Auton A, et al.; 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing [published correction appears in Nature 2011;473:544]. Nature 2010;467:1061–1073
9. Gutt M, Davis CL, Spitzer SB, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract 2000;47:177–184
10. Blangero J, Goring HH, Kent JW Jr, et al. Quantitative trait nucleotide analysis using Bayesian model selection. Hum Biol 2005;77:541–559
11. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 1998;62:1198–1211
12. Gelman A, Hill J, Yajima M. Why we (usually) don't have to worry about multiple comparisons. J Res Educ Eff 2012;5:189–211
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
14. Mehta CR, Patel NR. A hybrid algorithm for Fishers exact test in unordered rxc contingency-tables. Commun Stat Theory Methods 1986;15:387–403
15. Clarkson DB, Fan YA, Joe H. A remark on algorithm-643 - Fexact - an algorithm for performing Fishers exact test in R X C contingency-tables. ACM Trans Math Software 1993;19:484–488
16. Wilson SE, Lipscombe LL, Rosella LC, Manuel DG. Trends in laboratory testing for diabetes in Ontario, Canada 1995–2005: a population-based study. BMC Health Serv Res 2009;9:41
17. Sano H, Kane S, Sano E, et al. Insulin-stimulated phosphorylation of a Rab GTPase-activating protein regulates GLUT4 translocation. J Biol Chem 2003;278:14599–14602

18. Wang HY, Ducommun S, Quan C, et al. AS160 deficiency causes whole-body insulin resistance via composite effects in multiple tissues. Biochem J 2013;449:479–489
19. Dash S, Sano H, Rochford JJ, et al. A truncation mutation in TBC1D4 in a family with acanthosis nigricans and postprandial hyperinsulinemia. Proc Natl Acad Sci U S A 2009;106:9350–9355
20. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61–69
21. Sorkin JD, Muller DC, Fleg JL, Andres R. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. Diabetes Care 2005;28:2626–2632
22. Cavalot F, Pagliarino A, Valle M, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diabetes Care 2011;34:2237–2243
23. Sarwar N, Gao P, Seshasai SR, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in Lancet 2010;376:958]. Lancet 2010;375:2215–2222
24. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2003;27(Suppl. 2):S10–S13
25. Carter EA, MacCluer JW, Dyke B, et al. Diabetes mellitus and impaired fasting glucose in Alaska Eskimos: the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. Diabetologia 2006;49:29–35
26. Pelletier C, Dai S, Roberts KC, Bienek A, Onysko J, Pelletier L. Report summary. Diabetes in Canada: facts and figures from a public health perspective. Chronic Dis Inj Can 2012; 33:53–54
27. Simmons RK, Echouffo-Tcheugui JB, Griffin SJ. Screening for type 2 diabetes: an update of the evidence. Diabetes Obes Metab 2010;12: 838–844
28. Li L, Hamel N, Baker K, et al. A homozygous PMS2 founder mutation with an attenuated constitutional mismatch repair deficiency phenotype. J Med Genet 2015;52:348–352
29. Della-Morte D, Palmirotta R, Rehni AK, et al. Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors. Pharmacogenomics 2014; 15:2063–2082
30. Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the promise of insulin sensitization in type 2 diabetes. Cell Metab 2014;20:573–591