Association of a Common *G6PC2* Variant with Fasting Plasma Glucose Levels in Non-Diabetic Individuals

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Key Words

Blood glucose · Plasma glucose · Fasting plasma glucose · *G6PC2* · Single nucleotide polymorphism · Polymorphism · rs560887

Abstract

Background/Aims: Fasting plasma glucose (FPG) levels correlate with cardiovascular disease and mortality in both diabetic and non-diabetic subjects. *G6PC2* encodes a pancreatic islet-specific glucose-6-phosphatase-related protein and *G6pc2*-null mice were reported to exhibit decreased blood glucose levels. Two recent genome-wide association studies have implicated a role for *G6PC2* in regulation of FPG levels in the general European population and reported the strongest association with the rs560887 SNP. The purpose of this study was to replicate this association in our independent epidemiological samples. **Methods:** DNA samples from non-Hispanic white Americans (NHWs; n = 623), Hispanic Americans (n = 410) and black Africans (n = 787) were genotyped for rs560887 using TaqMan allelic discrimination. **Results:** While no minor allele A of rs560887 was observed among blacks, its frequency was 33% in NHWs and 17.5% in Hispanics. The rs560887 minor allele was associated with reduced FPG levels in non-diabetic NHWs (p = 0.002 under an additive model). A similar trend of association was

observed in non-diabetic Hispanics (p = 0.076 under a dominant model), which was more pronounced in normoglycemic subjects (p = 0.036). **Conclusions:** Our results independently confirm the robust association of *G6PC2*/rs560887 with FPG levels in non-diabetic NHWs. The observed evidence for association in Hispanics warrants further studies in larger samples.

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Introduction

Blood glucose levels are maintained within narrow limits by hormonal and other regulators to prevent the harmful effects of hypo- or hyperglycemia. Acquired factors such as age and obesity appear to contribute to, but cannot fully explain, the inter-individual variation in blood glucose concentration [1]. Fasting plasma glucose (FPG) levels are under significant genetic influence (heritability estimates >25%) and have been shown to correlate with cardiovascular disease and mortality in both diabetic and non-diabetic individuals [2–8].

Glucose-6-phosphatase catalytic 2 gene (*G6PC2*, also known as *IGRP*, on chromosome 2q24.3) encodes a pancreatic islet-specific glucose-6-phosphatase catalytic subunit-related protein. *G6PC2* had initially drawn attention

Table 1. Biometric and quantitative data of 2 non-diabetic US samples; non-Hispanic whites (NHWs) and Hispanics

	NHWs			Hispanics		
	female (n = 328)	male (n = 295)	all ^a (n = 623)	female (n = 208)	male (n = 202)	all ^a (n = 410)
Age, years	52.67 ± 0.64	53.01 ± 0.66	52.83 ± 0.46	50.18 ± 0.87	52.12 ± 0.88	51.13 ± 0.62
BMI, kg/m ²	24.81 ± 0.24	26.27 ± 0.19	25.50 ± 0.16	25.89 ± 0.34	25.55 ± 0.28	25.72 ± 0.22
Fasting glucose, mg/dl ^b	93.35 ± 0.46	98.16 ± 0.47	95.63 ± 0.34	93.26 ± 0.58	97.91 ± 0.62	95.55 ± 0.44
Normal (70–99 mg/dl)	81.7%	60%	71.4%	79.8%	63.2%	71.6%
Impaired (100–125 mg/dl)	18.3%	40%	28.6%	20.2%	36.8%	28.4%
Fasting insulin, μU/ml	10.86 ± 0.38	12.19 ± 0.41	11.49 ± 0.28	13.78 ± 0.59	12.95 ± 0.53	13.37 ± 0.40
Total cholesterol, mg/dl	218.23 ± 2.43	213.74 ± 2.27	216.11 ± 1.67	211.54 ± 2.88	213.89 ± 3.24	212.70 ± 2.16
LDL-C, mg/dl	135.52 ± 2.17	140.39 ± 2.06	137.80 ± 1.51	130.54 ± 2.54	138.18 ± 3.05	134.28 ± 1.98
HDL-C, mg/dl	56.84 ± 0.80	44.00 ± 0.63	50.76 ± 0.57	52.28 ± 0.94	45.23 ± 0.83	48.81 ± 0.65
Triglycerides, mg/dl	130.75 ± 3.41	149.15 ± 4.45	139.45 ± 2.79	142.02 ± 4.52	156.26 ± 5.23	149.03 ± 3.47

Data are unadjusted means ± SE after removal of outliers.

^a Including subjects with missing data or outliers for some of the variables.

^b SI conversion factor for fasting glucose (from mg/dl to mmol/l): divide by 18 or multiply by 0.0555. SI conversion factors for other quantitative traits can be found at http://jama.ama-assn.org/content/vol295/issue1/images/data/103/DC6/JAMA_auint_si.dtl.

as a major autoantigen for T cells that play an essential role in the development of type 1 diabetes in non-obese mice and humans [9–11]. *G6pc2*-null mice exhibit a mild metabolic phenotype with decreased blood glucose levels but unchanged insulin, glucagon, glycerol and cholesterol concentrations [12]. Recently, 2 genome-wide association studies (GWAS) have implicated a role for *G6PC2* in contributing to inter-individual variation in FPG levels in the general population [13, 14]. Both GWAS reported *G6PC2*/rs560887 [G>A, minor allele frequency (MAF) = 0.30 in Europeans] as the SNP most strongly associated with FPG levels among non-diabetic Europeans.

As replication of new findings by independent groups in independent samples is crucial for establishing the genetic associations for complex diseases, we sought to replicate the association of *G6PC2*/rs560887 with FPG levels in independent samples of non-Hispanic white (NHW) and Hispanic Americans. We also tried to assess the effect of rs560887 in black Africans, but the SNP turned out to be monomorphic in our sample.

Subjects and Methods

Subjects

The study samples consisted of 623 NHWs and 410 Hispanics who were non-diabetic unrelated Americans from the San Luis Valley Diabetes Study, a population-based case-control study of type 2 diabetes (T2D) in the San Luis Valley, Southern Colorado

[15–18]. A standard oral glucose tolerance test and World Health Organization criteria (www.who.int/topics/diabetes_mellitus/en/) were used to identify the subjects with normal glucose tolerance, impaired glucose tolerance [2-hour oral glucose tolerance test plasma glucose levels of 140–199 mg/dl (7.8–11 mmol/l)], or previously unknown diabetes. Individuals with FPG levels below 100 mg/dl (5.6 mmol/l) were considered normoglycemic, those with levels of 100–125 mg/dl (5.6–6.9 mmol/l) were considered to have impaired fasting glucose, and those with levels of 126 mg/dl (7 mmol/l) and above were considered to have diabetes [19]. Non-diabetic individuals [blood glucose levels below 126 mg/dl (7 mmol/l)] included normoglycemic subjects as well as those with impaired glucose levels. The present study included a subset of non-diabetic participants; although some individuals had impaired fasting glucose, all subjects had normal glucose tolerance test results. The demographic features and characteristics of NHWs and Hispanics are presented in table 1. Detailed information on the black African sample (from Benin City, Nigeria), from which 787 individuals were included in this study, can be found elsewhere [20]. The study was approved by the University of Pittsburgh Institutional Review Board.

Laboratory Methods

Blood samples were drawn after overnight fasting. Glucose concentration was determined using glucose oxidase method and total immunoreactive insulin concentration using double-antibody radioimmunoassay [15–18]. Total cholesterol, HDL cholesterol, and triglycerides were measured using enzymatic methods, and LDL cholesterol was calculated by the Friedewald equation when triglyceride levels were less than 400 mg/dl (4.5 mmol/l) [15–18].

Table 2. Adjusted^a mean values $\pm$ SE of quantitative metabolic traits among three *G6PC2*/rs560887 genotypes in 2 non-diabetic US populations; non-Hispanic whites (NHWs) and Hispanics

	NHWs				Hispanics			
	<i>G6PC2</i> /rs560887 genotypes				<i>G6PC2</i> /rs560887 genotypes			
	GG	GA	AA	p value ^e	GG	GA	AA	p value ^f
Genotype count ^b	270	291	61		278	109	16	
Fasting glucose, mg/dl ^c	96.50 $\pm$ 0.49	95.50 $\pm$ 0.45	92.94 $\pm$ 1.00	0.002	96.02 $\pm$ 0.46	94.34 $\pm$ 0.87	95.33 $\pm$ 2.11	0.076
Fasting insulin, μ U/ml ^d	11.95 $\pm$ 0.45	11.23 $\pm$ 0.34	10.66 $\pm$ 0.66	0.199	13.15 $\pm$ 0.39	13.99 $\pm$ 0.68	11.98 $\pm$ 0.76	0.267
Total cholesterol, mg/dl	218.59 $\pm$ 2.43	214.10 $\pm$ 2.36	216.74 $\pm$ 4.95	0.363	213.90 $\pm$ 2.69	206.94 $\pm$ 3.53	229.06 $\pm$ 10.75	0.378
LDL-C, mg/dl	140.72 $\pm$ 2.30	134.88 $\pm$ 2.08	140.39 $\pm$ 4.63	0.317	134.72 $\pm$ 2.49	130.00 $\pm$ 3.28	152.07 $\pm$ 10.11	0.668
HDL-C, mg/dl ^d	51.00 $\pm$ 0.74	50.63 $\pm$ 0.73	50.15 $\pm$ 1.48	0.737	49.23 $\pm$ 0.73	47.92 $\pm$ 1.09	48.12 $\pm$ 2.67	0.379
Triglycerides, mg/dl ^d	135.49 $\pm$ 3.73	145.45 $\pm$ 4.32	130.51 $\pm$ 7.19	0.644	150.59 $\pm$ 3.97	146.35 $\pm$ 6.98	144.28 $\pm$ 12.53	0.339
BMI ^d , kg/m ²	25.33 $\pm$ 0.23	25.50 $\pm$ 0.23	26.36 $\pm$ 0.57	0.145	25.59 $\pm$ 0.25	26.19 $\pm$ 0.47	25.37 $\pm$ 0.77	0.368

^a BMI adjusted for 'gender, age and smoking' and all other traits adjusted for 'gender, age, BMI and smoking'.

^b Including subjects with missing data or outliers for some of the variables.

^c SI conversion factor for fasting glucose (from mg/dl to mmol/l): divide by 18 or multiply by 0.0555. SI conversion factors for other quantitative traits can be found at [http://jama.ama-](http://jama.ama-assn.org/content/vol295/issue1/images/data/103/DC6/JAMA_auinst_si.dtl)

[assn.org/content/vol295/issue1/images/data/103/DC6/JAMA_auinst_si.dtl](http://jama.ama-assn.org/content/vol295/issue1/images/data/103/DC6/JAMA_auinst_si.dtl).

^d Natural log-transformed before analysis.

^e p value under the additive model, adjusted for the same covariates used for adjusting the mean values.

^f p value under the dominant model, adjusted for the same covariates used for adjusting the mean values.

Genotyping

DNA samples were genotyped for rs560887 using a TaqMan SNP genotyping assay (C____323082_10; Applied Biosystems, Foster City, Calif., USA) and end-point fluorescence readings were performed on an ABI Prism 7900HT instrument (Applied Biosystems). The overall genotype call rate was 99.8% in NHWs, 98.3% in Hispanics, and 98.5% in blacks. The discrepancy rate was 0% in all samples for 10% random repeats.

Statistical Methods

Allele and genotype frequencies were determined by direct counting. Deviation of the observed genotype frequencies from those predicted by Hardy-Weinberg equilibrium was evaluated using the χ^2 goodness-of-fit test. Dependent quantitative variables with skewed distributions were transformed (using log transformation) to reduce the effects of non-normality. After initial removal of extreme outliers, additional outliers falling outside of the transformed mean $\pm$ 3.5 SD range were excluded in each population, separately in males and females. This excluded a maximum of 4 values for any trait in any population sample. Analysis of variance and linear regression were used to test for the effects of genotypes on the quantitative traits transformed (if necessary) and adjusted for 4 covariates (gender, age, BMI and smoking) included in the model. When BMI was treated as a dependent variable, 3 covariates (gender, age, and smoking) were used in the model. Genotype associations were tested under the 'additive' model in NHWs in order to replicate the findings of original GWAS in Europeans. Due to the smaller size of the Hispanic sample, the tests were performed under the 'dominant' model in this sample. All computations were performed using the R statistical software (version 2.3.1; www.r-project.org). Because we were test-

ing a specific hypothesis regarding the relationship between the *G6PC2* genotypes and FPG levels and other metabolic traits, a nominal p value of less than 5% was considered as evidence of association.

Results

The rs560887 genotype frequencies were in Hardy-Weinberg equilibrium and the frequency of the minor allele A was 33% in NHWs (similar to that previously reported for Europeans in the literature and dbSNP; www.ncbi.nlm.nih.gov/sites/entrez?db=snp) and less common (17.5%) in Hispanics. Data from 775 successfully genotyped black Africans did not show any example of allele A, suggesting that if it exists in this population, its frequency is extremely low. It is unlikely that heterozygotes in black Africans were overlooked as a result of technical issues since the TaqMan genotype clusters were compact and well-separated. Among the 3 submissions in the dbSNP, 2 submitters reported a MAF of 0 or 0.8% in 'black Africans' while 1 reported a higher MAF of 4.3% in 'black Americans'; the latter is most likely due to Caucasian admixture.

Table 2 summarizes the association analysis results for FPG levels and other quantitative metabolic traits in

'non-diabetic' NHWs and Hispanics. *G6PC2*/rs560887 minor allele was significantly associated with reduced FPG levels in NHWs after adjusting for gender, age, BMI and smoking ($p = 0.002$ under an additive model; major allele homozygote = 0, heterozygote = 1, minor allele homozygote = 2). The effect size of rs560887 was small and explained only $\sim 1.4\%$ of the variation in FPG levels. Both the direction and size of this effect were consistent with GWAS in Europeans. We observed a similar relationship between *G6PC2*/rs560887 and FPG levels in 'non-diabetic' Hispanics, however, it was not statistically significant (adjusted $p = 0.076$ under a dominant model; major allele homozygotes vs. heterozygotes + minor allele homozygotes). When the association with FPG levels was tested in only 'normoglycemic' subjects (by excluding non-diabetic individuals with impaired fasting glucose levels; table 1), it did not improve in NHWs (data not shown), however, it became modestly significant in Hispanics (adjusted $p = 0.036$ under the dominant model; adjusted mean values $\pm$ SE were 91.54 ± 0.37 for GG vs. 90.18 ± 0.51 for GA + AA). Using the same genetic models (additive in NHWs and dominant in Hispanics), we next tested whether *G6PC2*/rs560887 was associated with other quantitative traits in non-diabetic NHWs and Hispanics. We did not observe a significant association with BMI, fasting insulin levels or lipid measurements in either sample.

Discussion

Epidemiological studies suggested a relationship between blood glucose levels and risk for cardiovascular disease and all-cause mortality in both diabetic and non-diabetic subjects [2–8]. A systematic overview and meta-analysis of non-diabetic cohort studies revealed a graded relationship between glucose levels and cardiovascular risk, extending below the diabetic threshold [6]. A U-shaped relation between glucose levels and mortality was reported [7]; that is, both high (diabetes or impaired glucose levels) and low [<70 or 80 mg/dl (3.9 or 4.4 mmol/l)] FPG levels were associated with increased mortality risk from cardiovascular disease and all causes. The DECODE study [8] also reported increased mortality risk with both high and very low glucose concentrations. These observations highlight the importance of investigating not only the genetic determinants of T2D but also those involved in regulation of FPG levels in non-diabetic individuals.

Two recent GWAS reported an association of small effect size ($\sim 1\%$) between the *G6PC2*/rs560887 SNP and reduced FPG levels in the general European population [13, 14]. The first GWAS [13] evaluated 392,935 SNPs in a discovery sample of 654 'normoglycemic' French subjects and was able to replicate the strongest association observed with FPG levels (*G6PC2*/rs560887; $p = 4 \times 10^{-7}$ adjusted for age, gender and BMI under the additive model) in additional French and Finnish samples. The second GWAS [14] investigated the SNPs from 2 genome-wide scans in a total of 5,088 'non-diabetic' individuals from Finland and Sardinia (Italy) and found a strong association between FPG levels and a SNP (rs563694) that resides between *G6PC2* and *ABCB11* ($p = 3.5 \times 10^{-7}$). The same study [14] was able to confirm the significant association of rs563694 in 6 of 7 follow-up samples of mixed European descent. Subsequent genotyping/analyses of the *G6PC2*-*ABCB11* region by the second GWAS [14] also revealed that *G6PC2*/rs560887 [in high linkage disequilibrium (LD) with rs563694; $D' = 0.99$, $r^2 = 0.84$] showed the strongest association with fasting glucose (meta $p = 2.8 \times 10^{-10}$). Interestingly, rs560887 did not show evidence of association with T2D in either GWAS [13, 14], leading the authors to hypothesize that either the genetic determinants of FPG levels in physiological states are different than those associated with T2D risk or the effect of *G6PC2* variation on T2D susceptibility is too small to be easily detected.

Our results in 'non-diabetic' NHWs support the findings of recent GWAS with a significant association (adjusted $p = 0.002$ under the additive model) of *G6PC2*/rs560887 with FPG levels in the same direction (minor allele A associated with reduced FPG levels). Consistent with GWAS, the effect size of rs560887 was small and accounted for only $\sim 1.4\%$ of inter-individual variation in FPG levels. Although it was not statistically significant, we observed a similar trend of association in 'non-diabetic' Hispanics (adjusted $p = 0.076$ under the dominant model), which was more pronounced and modestly significant when analyzed only in 'normoglycemic' subjects after excluding non-diabetic individuals with impaired fasting glucose levels (adjusted $p = 0.036$ under the dominant model). It is important to note that we had less power to detect the association in Hispanics due to the smaller sample size (410 Hispanics vs. 623 NHWs) and lower MAF of rs560887 (17.5% in Hispanics vs. 33% in NHWs). In addition, there may be LD structure differences between the two ethnic groups; such that the true causative genetic variant(s) may be in high LD with rs560887 in NHWs but in low LD in Hispanics. Consis-

tent with recent GWAS and mouse studies, we did not detect significant association with BMI, fasting insulin levels, or lipid measurements in either population, suggesting that the observed association with FPG levels is independent of these traits. GWAS also concluded that the effect of the *G6PC2* variation on FPG levels might be independent from adiposity-induced insulin resistance.

The rs560887 SNP is located close to the acceptor splice-site in the third intron of *G6PC2* and predicted to affect pre-mRNA splicing by alternative usage of exon 4 [13, 14]. Due to tissue-specific expression of various *G6PC2* splice forms [21], the pancreatic RNA samples from individuals with different rs560887 genotypes (which are not readily available) would be necessary to directly test the latter hypothesis.

In conclusion, our results independently confirm the robust association of *G6PC2*/rs560887 (or another tightly linked, yet undiscovered variant) with FPG levels in non-diabetic NHWs and further support the relevance of the glucose phosphorylation pathway to blood glucose homeostasis in the general population. Although additional GWAS and meta-analysis increasingly support the association of *G6PC2*/rs560887 with FPG levels in individuals of European descent [22], our results further extend this observation to the Hispanic population by providing evidence for association that warrants replication in larger

samples due to lower MAF of rs560887 in this population. The small effect sizes of *G6PC2*/rs560887 and other relevant genetic variants in *GCKR*, *GCK* and *MTNR1B* [22] suggest that the majority of genetic factors that regulate FPG levels remain to be identified. The absence (or very low MAF) of this SNP in our black African sample supports the presence of additional common variants (in *G6PC2* and/or other genes) that contribute to blood glucose regulation in individuals from various ethnic origins. In fact, the rs560887 variant is also rare among Asians and a recent study demonstrated that another *G6PC2* variant common in Chinese was associated with FPG levels in this population [23]. Resequencing of *G6PC2* in selected individuals with upper and lower range of FPG levels may help to determine the extent to which common and rare variation of *G6PC2* explains the variation in FPG levels and whether rs560887 is the most important *G6PC2*-linked genetic determinant of glucoregulation.

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