Meta-analyses of the association of G6PC2 allele variants with elevated fasting glucose and type 2 diabetes

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Abstract

Objective
To collectively evaluate the association of glucose-6-phosphatase catalytic unit 2 (G6PC2) allele variants with elevated fasting glucose (FG) and type 2 diabetes (T2D).

Design
Meta-analysis

Data sources
PubMed, Web of Knowledge and Embase databases.

Study selection
Full text articles of studies that identified an association of G6PC2 with T2D and elevated FG.

Patient involvement
There was no T2D patient involvement in the analyses on the association of FG with G6PC2, there were T2D patients and non-diabetes patient involvement in the analyses on the association of T2D with G6PC2.

Statistical analysis
Random-effects meta-analyses were used to calculate the pool effect sizes. I² metric and H² tests were used to calculate the heterogeneity. Begg’s funnel plot and Egger’s linear regression test were done to assess publication bias.
Results

Of the 423 studies identified, 21 were eligible and included. Data on three loci (rs560887, rs16856187 and rs573225) were available. The G allele at rs560887 in three ethnicities, the C allele at rs16856187 and the A allele at rs573225 all had a positive association with elevated FG. Per increment of G allele at rs560887 and A allele at rs573225 resulted in a FG 0.070 mmol/l and 0.075 mmol/l higher (β (95% CI) = 0.070 (0.060, 0.079), p = 4.636e-50 and 0.075 (0.065, 0.085), p = 5.856e-48, respectively). With regard to the relationship of rs16856187 and FG, an increase of 0.152 (95% CI: 0.034–0.270; p = 0.011) and 0.317 (95% CI: 0.193–0.442, p = 6.046e-07) was found in the standardized mean difference (SMD) of FG for the AC and CC genotypes, respectively, when compared with the AA reference genotype. However, the G-allele of rs560887 in Caucasians under the additive model and the C-allele of rs16856187 under the allele and dominant models were associated with a decreased risk of T2D (OR (95% CI) = 0.964 (0.947, 0.981), p = 0.570e-4; OR (95% CI) = 0.892 (0.832, 0.956), p = 0.001; and OR (95% CI) = 0.923(0.892, 0.955), p = 5.301e-6, respectively).

Conclusions

Our meta-analyses demonstrate that all three allele variants of G6PC2 (rs560887, rs16856187 and rs573225) are associated with elevated FG, with two variants (rs560887 in the Caucasians subgroup and rs16856187 under the allele and dominant model) being associated with T2D as well. Further studies utilizing larger sample sizes and different ethnic populations are needed to extend and confirm these findings.

Introduction

Fasting plasma glucose (FPG) levels are associated with a risk of type 2 diabetes (T2D) and cardiovascular disease [1]. There is strong evidence suggesting that hyperglycemia is a risk factor in a dose-dependent manner for both micro- and macro-vascular complications in both type 1 and type 2 diabetes [2].

Both genetic and environmental factors contribute to the pathophysiology of T2D [3, 4]. However, the contribution of genetic factors to T2D risk is not well understood. Global knock-out of the glucose-6-phosphatase catalytic unit 2 (G6PC2) gene in mice led to a significant decrease in blood glucose [5]. Previous studies have showed that higher FPG levels within the normal glucose range constitute an independent risk factor for T2D [1, 6]. Considering the genetic risk that might result from G6PC2 alleles, a number of studies have explored the association of G6PC2 with fasting glucose (FG) and T2D in different ethnicities [7–12]. However, individual studies have yielded inconsistent or conflicting findings, possibly caused by limitations associated with an individual study, such as different genetic backgrounds and ethnicity, sample size and so on. Wang H et al [13] have previously performed a meta-analysis on the association of G6PC2 rs560887 with T2D. To expand and evaluate more precisely the relationship between G6PC2 and FG and T2D, we carried out meta-analyses of published studies.

Methods

Search strategy

We included all studies published prior to 4th April of 2017 that reported an association between G6PC2 and T2D and FG. Eligible studies were found by searching the PubMed, Web
of Knowledge and Embase databases for relevant reports. We used the gene name “G6PC2” as search term limited in all fields to retrieve association studies between genetic variants in G6PC2 and FG or T2D. We also reviewed reference lists of the identified publications for additional relevant studies. A literature search was performed on these databases without restriction to regions or publication types. Two investigators (YY.S and YQ.L) independently searched the articles, and disagreements were resolved by discussion.

**Selection**

The study inclusion criteria were as follows: (1) published in Chinese or English; (2) primary outcomes of T2D or FG were given; (3) either I or II, as follows: (I) provided the odds ratio (OR) with 95% confidence interval (CI) or adequate information about the genotype and allele to calculate the OR and 95% CI for the association of rs568007 and rs16856187 polymorphisms with T2D. (II) provided mean and standard deviation (SD) values of FG and sample size (n) in every genotype for rs16856187, and linear regression coefficients (β) of per-effect allele from linear regression analysis for the association of rs560887 and rs573225 with FG or enough data to calculate them. Studies were excluded if any of the following factors were identified: (1) not an association study for T2D or FG [14–24]; (2) studied other single nucleotide polymorphisms (SNPs) [25–28]; (3) data were not fully available [29–32]; (4) not population-based studies [33–34]; (5) meta-analyses or systematic review [13, 35–40]; (6) duplicate studies [41–43]. For duplicate publications, the study with the most recent and complete information was included.

**Patient involvement**

There was no T2D patient involvement in the analyses on the association of FG with G6PC2; There were T2D patients and non-diabetes patient involvement in the analyses on the association of T2D with G6PC2.

**Data extraction**

Data were extracted and summarized independently by two of the authors. The adjudicating senior authors resolved any disagreement. If the data were unavailable, an attempt was made to contact the corresponding author to request missing data via E-mail. The following information was extracted: (1) study characteristics such as the first author, study name, year published, country; (2) subjects and methods characteristics including sex, mean age, sample size (n), Body Mass Index (BMI), genotyping method and blood samples measured for FG; (3) primary outcomes such as risk allele, risk allele frequency (RAF), OR with 95% CI and their adjustment factors, statistical methods and the \( p \) value of Hardy-Weinberg equilibrium (HWE) test in control group for data on T2D; Mean and SD of FG and sample size (n) in every genotype, and \( \beta \) and their standard error (SE) or 95% CI, \( p \) value for linear regression and their adjustment factors as in previously published studies [44–46], and the \( p \) value of HWE for data on FG. All data were extracted independently by two investigators (YY.S and YQ.L), and discrepancies were resolved by discussion.

**Quality assessment**

The strengthening report of genetic association studies (STREGA) quality score system was used to assess the qualities of all included studies [47]. The STREGA system includes twenty-two quality assessment items with scores ranging from 0 to 22 (S1 Supplement). Studies are classified into three levels based on their scores: low quality (0–12), moderate-high quality...
(13–17), and high quality (18–22). Two authors (XJ.L and DD.Z) independently assessed the quality of included studies. Discrepancies over quality scores were resolved by discussing with all authors and subsequent consensus.

Statistical analysis

In our meta-analyses the included studies on rs560887 and rs573225 used an additive model to assess the genetic effect of G6PC2 polymorphisms [48]. For the studies on rs16856187, an additive model (AA versus AC versus CC) was used for the association of FG, and an allele model (A versus C), dominant model and recessive model were used for the association of T2D. The \( \beta \) value and SEs were used to identify the association of rs560887 and rs573225 \[14, 32, 44\] with FG. SE of the \( \beta \) value was calculated by 95% CI or \( \beta \) value and \( p \) value when SE was not extracted directly from the original literature \[49, 50\]. The SMD was used to analyze the association between rs16856187 and FG. ORs with 95% CIs were assessed to determine the relationship between T2D and rs560887 and rs16856187.

The aggregated results OR and 95% CI, \( \beta \) and 95% CI and SMD were calculated using random-effects meta-analysis. A statistical test for heterogeneity was conducted using the I\(^2\) metric and H\(^2\) tests \[51\]. A I\(^2\) greater than 50% or H\(^2\) greater than 1 was suggestive of substantial between-study heterogeneity \[52–53\]. Sensitivity analyses were performed by omitting each study to identify possible study contributions to the heterogeneity. To evaluate the reliability and stability of our results, Begg’s funnel plot and Egger’s linear regression test were done to assess publication bias \[54, 55\]. We divided the study populations into three ethnic subgroups, including Caucasians, Asians and African-Americans for the relationship between FG and rs560887, and two ethnic subgroups (Caucasians and Asians) for the relationship between T2D and rs560887. All analyses were performed using Stata 12.1 (Stata Corp, College Station, TX, USA).

The HWE for all the subjects of each study was evaluated using \( \chi^2 \) test. For the studies which didn’t include the distributions of genotypes but contained the information on the RAF in both cases and controls, we calculated the frequency of the different genotypes according to the HWE Law, which can be used to calculate the crude ORs and 95% CIs under an additive genetic model. All reported probabilities (\( p \) values) were two-sided, with \( p < 0.05 \) considered statistically significant.

Finally, for a better presentation of the public health relevance, we explored the PAR by taking into account both the pooled per-allele ORs and the pooled RAF (T2D risk allele frequency). PAR was calculated as \( PAR = (X − 1)/X \). Assuming a multiplicative model, \( X = (1 − f)^2 + 2f(1 − f)\gamma + f^2\gamma^2 \), where \( f \) is RAF and \( \gamma \) is their estimated ORs. We calculated the pooled prevalence of each risk allele in various groups using the inverse variance method described previously \[56\].

Power calculations

Power to detect a genetic association was estimated using the QUANTO program version 1.2.4. For the association study with FG, we had an estimated power of more than 99.99% to detect a minimal per-allele effect at \( \beta \) of 0.070 mmol/l for rs560887 and 0.075 mmol/l for rs573225 under an additive model, depending on an allele frequency of 0.76 and 0.67. For the association study with T2D, we had an estimated power of 97.58% to detect an OR of 0.967 for rs560887 under the prevalence of 8.8% \[57\] under an additive model, and 98.78%, 64.23% and 10.01% power to detect genetic effects at an OR of 0.960, 0.892 and 0.923 for rs16856187 under allele, dominant and recessive model, respectively. A \( p \) value <0.05 was considered statistically significant (two-tailed).
Results

Literature search results

Through literature searches a total of 423 articles from PubMed (National Center for Biotechnology Information), Web of Knowledge and Embase databases were identified up to 4th April 2017. A flow chart of study selection in the meta-analyses is shown in Fig 1. There were 52 articles included after duplicates were removed and following the screening of the titles and abstracts. As shown in S2 Supplement, 31 full-text articles were excluded. Overall, 21 articles were eligible and included (see study inclusion flowchart in Fig 1[7–12, 58–72]). Of these, 5 articles covered the loci rs560887 for FG and T2D, 3 articles covered the loci rs16856187 for FG and T2D, 2 articles covered the loci rs560887 and rs573225 for FG, 8 articles covered the loci rs560887 for FG, and 3 articles covered the loci rs560887 for T2D, respectively (Tables 1 and 2). In total, 18 studies comprising 69120 cases (62492 for rs560887, 6628 for rs16856187), 126483 non-diabetic controls (119627 for rs560887, 6856 for rs16856187), and 35 studies...
### Table 1. Characteristics of the studies on the association of two SNPs with T2D.

| First Author        | Study name          | Country (Ethnicity) | Year published | FG-raising allele (frequencies) | Case | Control | STREGA score | HWE | rs560887 | rs16856187 |
|---------------------|---------------------|---------------------|----------------|--------------------------------|------|---------|-------------|-----|----------|-----------|
| Bouatia-Naji et al. | European            | France (Caucasian)  | 2008           | G (0.70)                       | 2792 | 62.2    | 50.4        | N   | Yes      | √         |
| Reiling et al.      | New Hoorn Study     | The Netherlands (Caucasian) | 2009 | G (0.692)                       | 2628 | 55      | 64          | N   | Yes      | √         |
| Rose et al.         | Inter99             | Denmark (Caucasian)  | 2009           | G (0.689)                       | 1963 | 61.6    | 60.5        | N   | Yes      | √         |
| Takeuchi et al.     | Japanese            | Japan (Asian)       | 2009           | G (0.971)                       | 5629 | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | Sri Lankan          | Sri Lanka (Asian)   | 2009           | G (0.907)                       | 599  | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | DGI                 | Finland, Sweden (Caucasian) | 2009 | G (NA)                          | 1464 | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | KORA                | Germany (Caucasian)  | 2009           | G (NA)                          | 433  | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | Rotterdam           | The Netherlands (Caucasian) | 2009 | G (NA)                          | 1178 | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | WTCCC T2D           | UK (Caucasian)      | 2009           | G (NA)                          | 1924 | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | CCC                 | UK (Caucasian)      | 2009           | G (NA)                          | 512  | NA      | NA          | N   | Yes      | √         |
| Takeuchi et al.     | ADDITION/ELY        | Europe (Caucasian)  | 2009           | G (NA)                          | 852  | NA      | NA          | N   | Yes      | √         |
| Dupuis et al.       | MAGIC               | Europe (Caucasian)  | 2010           | G (0.70)                        | 40655| NA      | NA          | N   | Yes      | √         |
| Rees et al.         | UKADS               | South Asian (Asian) | 2011           | G (0.82)                        | 857  | 45.3    | 56.9        | N   | Yes      | √         |
| Rees et al.         | DGP                 | South Asian (Asian) | 2011           | G (0.84)                        | 821  | 52.4    | 54.6        | N   | Yes      | √         |
| Al-Daghri et al.    | RIYADH COHORT       | Saudi Arabia (Caucasian) | 2017 | G (0.81)                        | 185  | 52.0    | 59.4        | N   | Yes      | √         |
| Hu et al.           | Shanghai            | China (Asian)       | 2008           | C (0.285)                       | 1876 | 52.4    | 61.2        | N   | Yes      | √         |
| Hu et al.           | Shanghai            | China (Asian)       | 2010           | C (0.294)                       | 3410 | 54.9    | 60.33       | N   | Yes      | √         |
| Tam et al.          | Hong Kong           | China (Asian)       | 2010           | C (0.298)                       | 1342 | 40.5    | 44.5        | N   | Yes      | √         |

NA = not available; √ represents this SNP was studied; HWE = Hardy-Weinberg equilibrium; No represents p value of HWE less than 0.05, Yes represents p value of HWE more than 0.05; Europe represents the country from Europe.

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Table 2. Characteristics of the studies on the association of three SNPs with fasting glucose.

| First Author | Study name          | country (Ethnicity) | Year published | n     | Age (SD), year | Sex | BMI (SD), kg/m² | STREGA score | HWE | rs560887 | rs573225 | rs16856187 |
|--------------|---------------------|---------------------|----------------|-------|----------------|-----|----------------|--------------|-----|----------|----------|-----------|
| Reiling et al. | New Hoorn Study    | The Netherlands (Caucasian) | 2009          | 2225  | 53 (7)         | 46  | NA             | 17           | Yes | G (0.693) |          |           |
| Prokopenko et al. | CoLaus          | Switzerland (Caucasian) | 2009          | 5000  | 52.46 (10.72)/53.84 (10.73) | 46  | 26.36 (3.84)/24.94 (4.63) | 14           | Yes | G (0.72)  |          |           |
| Prokopenko et al. | Framingham        | USA (Caucasian)     | 2009          | 6479  | 45.9 (11.5)/46.0 (11.6) | 46.0 | 27.7 (4.2)/25.9 (5.5) | 14           | Yes | G (0.70)  |          |           |
| Prokopenko et al. | Rotterdam         | The Netherlands (Caucasian) | 2009          | 2058  | 63.8 (5.5)/64.2 (6.1) | 43  | 25.9 (2.8)/26.3 (3.8) | 14           | Yes | G (0.69)  |          |           |
| Prokopenko et al. | Sardinia          | Italy (Caucasian)   | 2009          | 4305  | 44.08 (18.10)/43.19 (17.3) | 43.8 | 26.15 (4.11)/24.75 (5.03) | 14           | Yes | G (0.63)  |          |           |
| Takeuchi et al. | Japanese           | Japan (Asian)      | 2009          | 4813  | 48.8 (12.3)     | 58.2 | 22.9 (3.2)     | 17           | Yes | G (0.97)  |          |           |
| Takeuchi et al. | Sri Lankan         | Sri Lankan (Asian)  | 2009          | 2319  | 51.8 (8.1)      | 45.9 | 23.9 (4.3)     | 17           | No  | G (0.91)  |          |           |
| Chambers et al. | Indian Asian       | India (Asian)      | 2009          | 5089  | 53.9 (10.6)     | 85   | 26.8 (4.2)     | 13           | Yes | G (0.85)  |          |           |
| Chambers et al. | European whites    | Finland (Caucasian) | 2009          | 4462  | 31             | 47.6 | 24.6 (4.2)     | 13           | Yes | G (0.69)  |          |           |
| Bouatia-Naji et al. | Haguenau         | France (Caucasian) | 2010          | 1201  | 22.27 (3.95)    | 48.1 | 22.63 (4.15)   | 15           | Yes | G (NA)    | A (NA)   |           |
| Bouatia-Naji et al. | DESIR            | France (Caucasian) | 2010          | 3483  | 46.87 (9.99)    | 46.5 | 24.29 (3.57)   | 15           | Yes | G (NA)    | A (NA)   |           |
| Bouatia-Naji et al. | NFBC86           | Finland (Caucasian) | 2010          | 4372  | 16 (0)         | 48.9 | 21.27 (3.56)   | 15           | Yes | G (NA)    | A (NA)   |           |
| Bouatia-Naji et al. | Obese children   | France (Caucasian) | 2010          | 476   | 10.89 (3.14)    | 47.9 | 28.42 (6.13)   | 15           | Yes | G (NA)    | A (NA)   |           |
| Ramos et al. | HUFS               | Africa (African-American) | 2010          | 927   | 46.1 (12.6)/46.9 (13.5) | 42   | 28.3 (6.9)/31.4 (8.7) | 14           | Yes | G (0.957) |          |           |
| Rennström et al. | GLACIER           | Sweden (Caucasian) | 2010          | 1630  | 52.3 (8.8)      | 39.8 | 25.9 (4.1)     | 15           | Yes | G (0.71)  |          |           |
| Dupuis et al. | MAGIC              | Europe (Caucasian) | 2010          | 76558 | NA             | NA   | NA             | 10           | Yes | G (0.70)  |          |           |
| Barker et al. | FRENCH controls    | France (Caucasian) | 2011          | 634   | 11.9 (2.4)/11.9 (2.2) | 48.9 | 17.5 (2.2)/17.7 (2.5) | 14           | Yes | G (0.70)  |          |           |
| Barker et al. | EYHS               | Denmark, Estonia (Caucasian) | 2011          | 1934  | 11.9 (2.9)/12.0 (2.9) | 46.3 | 18.4 (2.8)/18.5 (3.1) | 14           | Yes | G (0.70)  |          |           |
| Barker et al. | FRENCH cases       | France (Caucasian) | 2011          | 581   | 11.2 (2.9)/10.8 (3.4) | 45.1 | 29.9 (6.4)/29.4 (6.6) | 14           | Yes | G (0.70)  |          |           |
| Barker et al. | Raine              | Australia (Caucasian) | 2011          | 1045  | 14.1 (0.2)/14.1 (0.2) | 52.2 | 21.2 (4.2)/21.9 (4.2) | 14           | Yes | G (0.70)  |          |           |
| Barker et al. | ALSPAC             | UK (Caucasian)      | 2011          | 1736  | 15.4 (0.3)/15.4 (0.3) | 51.0 | 20.9 (3.3)/21.7 (3.7) | 14           | Yes | G (0.70)  |          |           |
| Rees et al. | South Asians       | Pakistan (Asian)   | 2011          | 1163  | 56.3 (10.8)     | 52.9 | 24.3 (5.0)     | 15           | Yes | G (0.84)  |          |           |

(Continued)
| First Author | Study name | country (Ethnicity) | Year published | n   | Age (SD), year | Sex | BMI (SD), kg/m² | STREGA score | HWE | rs560887 | rs573225 | rs16856187 |
|-------------|------------|---------------------|---------------|-----|----------------|-----|----------------|--------------|-----|----------|----------|------------|
| Torvik et al. | CAU | European-Americans (Caucasian) | 2012 | 2349 | 62.5 (10.3) | 46.8 | 27.5 (4.9) | 16 | Yes | G (0.72) |           |           |
| Torvik et al. | CHN | China (Asian) | 2012 | 664 | 61.7 (10.4) | 48.6 | 23.8 (3.3) | 16 | Yes | G (0.97) |           |           |
| Torvik et al. | AFA | Africa (African-American) | 2012 | 1366 | 61.8 (10.2) | 45.1 | 29.8 (5.6) | 16 | No  | G (0.93) |           |           |
| Torvik et al. | HIS | Hispania (Caucasian) | 2012 | 1171 | 60.7 (10.3) | 48.0 | 29.0 (4.8) | 16 | Yes | G (0.86) |           |           |
| Baerenwald et al. | DESIR cohort | France (Caucasian) | 2013 | 4220 | NA | NA | NA | 17 | Yes | G (0.695) | A (0.670) |           |
| Zheng et al. | Caucasians | Caucasus (Caucasians) | 2015 | 336 | 13.9 | 38.7 | NA | 15 | Yes | G (0.723) |           |           |
| Zheng et al. | Hispanics | Hispania (Caucasian) | 2015 | 205 | 12.6 | 45.6 | NA | 15 | Yes | G (0.834) |           |           |
| Zheng et al. | African-Americans | Africa (African-American) | 2015 | 211 | 13.4 | 40.8 | NA | 15 | Yes | G (0.934) |           |           |
| Horikoshi et al. | 1000G | Europe (Caucasian) | 2015 | 40091 | 57.9 | 43.0 | NA | 10 | Yes | G (0.69) |           |           |
| Langlois et al. | Mexican children and adolescents | Mexico (mixed) | 2016 | 1421 | 9.25 (2.07) | 53.1 | 19.67 (4.22) | 18 | Yes | G (0.913) |           |           |
| Tam et al. | Healthy Adults | China (Asian) | 2010 | 583 | 41.4 (10.5) | 45.5 | 22.9 (3.3) | 19 | Yes | A (0.303) |           |           |
| Tam et al. | Healthy Adolescents | China (Asian) | 2010 | 1061 | 15.4 (1.9) | 45.3 | 19.9 (3.5) | 19 | Yes | A (0.299) |           |           |
| Hu et al. | Shanghai | China (Asian) | 2008 | 1800 | 57.35 (12.35) | 41.3 | 23.57 (3.25) | 19 | Yes | A (0.303) |           |           |

NA = not available; √ represents this SNP was studied
HWE = Hardy-Weinberg equilibrium
No represents p value of HWE less than 0.05, Yes represents p value of HWE more than 0.05
Europe represents the country from Europe,mixed represents a multi-ethnic nation.

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containing 187,968 non-diabetic participants (13,752 for rs573225 and rs560887, 17,077 for rs560887 and 3,444 for rs16856187) were included. The meta-analyses were carried out according to the “Meta-analysis on Genetic Association Studies” statement (S3 Supplement).

Association of rs560887, rs573225 and rs16856187 polymorphisms with FG

Meta-analysis estimates of SNP associations with FG are presented in Table 3. Under an additive model [48], a nominally significant positive association with FG was observed: per increment of additional G allele at rs560887 in \( G6PC2 \), FG was 0.070 mmol/l (95% CI: 0.060, 0.079, \( p = 4.635 \times 10^{-50} \)) higher, with heterogeneity observed (I\(^2\) = 72%, 95% CI: 60%, 80%; H\(^2\) = 2.56).

When the study population was divided into three ethnic subgroups, pooled \( \beta \) (95% CI) and \( p \) were [0.075 (0.068, 0.081) mmol/l, \( p = 4.06 \times 10^{-118} \)], [0.054 (0.020, 0.088) mmol/l, \( p = 0.002 \)] and

| Table 3. Meta-analyses of \( G6PC2 \) polymorphisms and FG or T2D. |
|-----------------------------|-----------------------------|
| **SNP/FG-raising allele**   | **Association of \( G6PC2 \) polymorphism with FG** | **Association of \( G6PC2 \) polymorphism with T2D** |
| number of studies | \( n \) | \( \beta \) (ADD) (95% CI) | \( p \) | I\(^2\) (95% CI) | \( H^2 \) | number of studies | \( n \) (case/control) | OR (95% CI) | \( p \) | I\(^2\) (95% CI) | \( H^2 \) |
| rs560887/G (overall) 32 | 184,524 | 0.070 (0.060,0.079) | 4.635e-50 | 72 (60.80) | 2.56 | 15 | 24278/67043 | 0.967 (0.932,1.003) | 0.076 | 39 (0.67) | 0.42 |
| Caucasians | 23 | 78,334 | 0.075 (0.068,0.081) | 4.06e-118 | 37 (38.73) | 0.58 | 11 | 16372/58538 | 0.964 (0.947,0.981) | 0.570e-4 | 0 (0.60) | 0.00 |
| Asians | 5 | 14,048 | 0.054 (0.020,0.088) | 0.002 | 46 (0.80) | 0.85 | 4 | 7906/8505 | 1.120 (0.940,1.334) | 0.205 | 66 (0.88) | 2.06 |
| African-Americans | 3 | 2504 | 0.018 (0.004,0.031) | 0.010 | 0 (0.90) | 0.00 | - | - | - | - | - |
| Mexico | 1 | 1,421 | 0.120(0.002,0.238) | 0.046 | - | - | - | - | - | - | - |
| rs16856187/C allele model#, (A vs C) | 3 | 3,444 | - | - | - | - | - | - | - | - | - |
| Additive model# | - | - | - | - | - | - | - | - | - | - | - |
| AC vs AA | - | - | 0.152 (0.034,0.270) | 0.011 | 58 (0.88) | 1.36 | - | - | - | - | - |
| CC vs AA | - | - | 0.317 (0.193,0.442) | 6.046e-07 | 0 (0.90) | 0.00 | - | - | - | - | - |
| Dominant model, (AC+CC) vs AA | - | - | - | - | - | - | - | - | - | - | - |
| Recessive model, CC vs (AC+AA) | - | - | - | - | - | - | - | - | - | - | - |
| rs573225/A | 5 | 13,752 | 0.075 (0.065,0.085) | 5.856e-48 | 0 (0.79) | 0.00 | - | - | - | - | - |
| * indicate standardized mean differences (SMD) of AC vs AA and CC vs AA genotypes in rs16856187, respectively. 
# indicate additive model for FG, allele model for T2D, respectively. 
\( p \): significance test of effect size (\( \beta \)) = 0 or effect size (OR) = 1.

FG = fasting glucose; T2D = type 2 diabetic.
\( \beta \) represents linear regression coefficients for the association of \( G6PC2 \) polymorphism with FG.
OR represents odds ratio for the association of \( G6PC2 \) polymorphism with T2D.
ORs for rs560887 were calculated with logistic regression adjusted for different adjustment factors.
ORs for rs16856187 were calculated using \( \chi^2 \) tests.

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[0.018 (0.004, 0.031) mmol/l, \(p = 0.010\)] in Caucasians, Asians and African-Americans, respectively (Fig 2). Heterogeneity was observed \([I^2 = 37\%, 95\% CI: 38\%, 73\%; H^2 = 0.58], (I^2 = 46\%, 95\% CI: 0, 80%; H^2 = 0.85), (I^2 = 0, 95\% CI: 0, 90%; H^2 = 0.00)\) in Caucasians, Asians and African-Americans, respectively.

In the association of rs16856187 with FG under the additive model, an additive trend of 0.152 (0.034, 0.270) and 0.317 (0.193, 0.442) increased in SMD of FG for AC and CC genotypes was found when compared to the AA reference genotype, respectively. Heterogeneity was observed \((I^2 = 58\%, 95\% CI: 0, 88%; H^2 = 1.36)\) for AC vs AA while no heterogeneity was observed \((I^2 = 0, 95\% CI: 0, 90%; H^2 = 0.00)\) (Fig 3).

In the association of rs573225 with FG, a nominally significant positive association with elevated FG was observed: per increment of A allele at rs573225 in G6PC2, FG was 0.075 mmol/L higher (\(\beta = 0.075; 95\% CI: 0.065–0.085, p = 5.856e-48\), with no heterogeneity observed \((I^2 = 0, 95\% CI: 0, 79%; H^2 = 0.00)\) (Fig 4).

**Association of rs568007 and rs16856187 polymorphisms with T2D**

In the overall estimate, no association was detected between the rs568007 and risk of T2D (OR = 0.967; 95% CI: 0.932–1.003; \(p = 0.076\), with low heterogeneity \((I^2 = 39\%, 95\% CI: 0, 67%; H^2 = 0.42)\). In Asians, rs568007 also had no association with risk of T2D (OR = 1.120; 95%CI: 0.940–1.334; \(p = 0.205\)) (Fig 5). Conversely, in the Caucasian subgroup we found a significant association between the FPG-raising G-allele and decreased risk of T2D (OR = 0.964;
95% CI: 0.947–0.981; \( p = 0.570 \times 10^{-4} \), with no heterogeneity observed (\( I^2 = 0 \), 95% CI: 0, 60%; \( H^2 = 0.00 \)). When both the pooled RAF and the pooled per-allele OR were taken into account, the presence of each risk allele would be associated with a 5.4%, 5.3% and 18.3% increase in incidence of T2D according to the PAR estimate in total sample, Caucasian and Asians subgroup, respectively.

**Fig 3.** Forest plot for the association of rs16856187 with FG under the additive model.

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95% CI: 0.947–0.981; \( p = 0.570e^{-4} \), with no heterogeneity observed (\( I^2 = 0 \), 95% CI: 0, 60%; \( H^2 = 0.00 \)). When both the pooled RAF and the pooled per-allele OR were taken into account, the presence of each risk allele would be associated with a 5.4%, 5.3% and 18.3% increase in incidence of T2D according to the PAR estimate in total sample, Caucasian and Asians subgroup, respectively.

**Fig 4.** Forest plot for the association of rs573225 with FG under the additive model. Pooled \( \beta \) for the additive genetic model was shown under a random-effects model. Square sizes were proportional to weight of each study in the meta-analysis.

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Under the allele model, the association between the rs16856187-C allele and decreased risk of T2D was significant (OR = 0.892; 95% CI: 0.832–0.956; \( p = 0.001 \)) with low heterogeneity among studies (\( I^2 = 35, 95\% \text{ CI}: 0, 79\%; H^2 = 0.50 \)) (Fig 6A). Under the dominant model (AC+CC vs AA), a significant negative association was detected (OR = 0.923; 95% CI: 0.892–0.955; \( p = 5.301e-6 \)) with no heterogeneity among studies (\( I^2 = 0, 95\% \text{ CI}: 0, 90\%; H^2 = 0.00 \)) (Fig 6B). Under the recessive model (CC vs AC+AA), no significant association was detected (OR = 0.960; 95% CI: 0.827, 1.115; \( p = 0.596 \)) with high heterogeneity among studies (\( I^2 = 80, 95\% \text{ CI}: 35%, 94%; H^2 = 3.28 \)) (Fig 6C). Results under the allele and dominant model indicated that the FPG-raising C-allele might be associated with a decreased risk of T2D. When both the pooled RAF (rs16856187-A allele) and the pooled per-allele OR were taken into account, the presence of each A-allele would be associated with a 6.5%, 4.6% and 2.3% increase in incidence of T2D according to the PAR estimate under allele, dominant and recessive model, respectively.

Publication bias, sensitivity test

Visual inspection of funnel plots for the primary outcomes did not show distinct asymmetry, and based on Begg’s funnel plots (S1 Fig) and Egger’s linear regression, no publication bias was observed (all \( p > 0.1 \)). In the sensitivity test (S2 Fig), the leave-one-out influential analyses did not show any major change in the primary outcome, indicative of a good stability of results.

Discussion

To the best of our knowledge, this is the most comprehensive meta-analyses on the evaluation of the associations between G6PC2 SNPs and FG and T2D. Our meta-analyses include the
most SNPs in G6PC2 on the associations of these SNPs with FG and T2D studied to date. In these meta-analyses, we analyzed three SNPs (rs560887, rs16856187 and rs573225) in the G6PC2 gene for an effect on FG and two SNPs (rs560887 and rs16856187) for an association with T2D. We found that all three SNPs were associated with elevated FG level in participants with normal glucose regulation, and rs560887 in the Caucasians subgroup and rs16856187 under allele and dominant model were all associated with T2D. However, no associations with T2D risk were found for G at rs560887 in overall and Asians populations, which is consistent with a meta-analysis published in 2013[13]. Compared with this previous study, our study contained greater sample sizes in the Caucasians subgroup (number of case/control were 47673/97909 and 54586/111122 for previous and current studies,

Fig 6. Forest plot for the association between G6PC2 rs16856187 and T2D under the allele (A), dominant (B) and recessive (C) model.

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respectively). Association of G at rs560887 with T2D and FG in Caucasians is similar to individuals of European descent in the MAGIC study [OR (95% CI): 0.97 (0.95–0.99), β (SE): 0.075 (0.003) mmol/l, respectively] [70].

There may be some reasonable explanations for these differences between ethnic groups. First, the gene-gene interactions and different environmental factors may affect susceptibility to the genetic variant and diabetes [73, 74]. Second, the sample size for Asian populations may be too small. Third, a previous study has reported that Asian subgroups have unique risk-factor profiles for developing diabetes, which differ from other populations [75]. Thus, further investigations on Asian populations are needed to replicate the observed association with type 2 diabetes. We will explore the association of G6PC2 with T2D in the Chinese population in the near future.

G6PC2 belongs to the G6PC family of proteins, which catalyze the dephosphorylation of glucose-6-phosphate to glucose [76]. Thus, glucose-6-phosphatase activity could control glucose metabolism and insulin secretion [76]. However, carriers of the G allele at rs560887 in Caucasians subgroup and A allele at rs16856187 in allele and dominant model all displayed a lower risk of type 2 diabetes and a higher risk of elevated FPG level, which is inconsistent with these previous studies [1, 6]. The mechanism linking the SNP rs560887-A to reduced G6PC2 activity might be connected to the relative expression of the full-length active protein [23, 77]. Studies have shown that heightened beta-cell sensitivity to glucose and a lowered glucose set-point for insulin secretion are early steps toward β cell apoptosis [78]. Recent reports in individuals of European descent also demonstrated a strong association between G6PC2 variants and insulin secretion [32]. The allele that decreased FPG was also found to lower beta cell function [65]. However, carriers of G at G6PC2 rs560887 displayed a higher risk of type 2 diabetes and a higher FPG level in Asians. It is unclear whether ethnic differences in beta cell function [79, 80] contributed to the different results. Moreover, our relatively small sample size of Asians may also limit our ability to reach a reliable conclusion.

In addition, we also found that the presence of T at rs13387347, A at rs2232316, G at rs492594, A at rs483234, T at rs3755157 and C at rs478333 in G6PC2 among Asians were correlated with a higher risk of T2D [10, 65, 69]. Meanwhile, C at rs478333 in adolescents, T at rs3755157 and A at rs483234 among Asians displayed a higher FG level. However, T at rs13387347 displayed a lower FG level [10, 65, 69]. Due to a lack of data, a meta-analysis was not completed for these SNPs, yet they still provide evidence for the association of G6PC2 with FG and T2D.

This study shows that β value (linear regression coefficient) rather than SMD for the association of FG with G6PC2 SNPs (rs560887 and rs573225) when pooled, which was not seen in the previous studies. This is currently the most comprehensive meta-analyses on G6PC2.

Some limitations in our meta-analyses should be mentioned. First, our results on FG and T2D were based on slightly different adjusted estimates. Second, the studies included in the analyses may be insufficient to allow firm conclusions. Thus, potential publication bias is likely to exist, in spite of the lack of evidence for this obtained from our statistical tests. The power to detect bias is limited, particularly for moderate amounts of bias or meta-analyses based on a small number of small studies [81]. Third, heterogeneity is also a potential problem, with estimates of zero or even just low heterogeneity being a concern since heterogeneity is very likely present but undetected [82]. Finally, the sample size for rs16856187 is small, and the estimate of the effect of rs16856187 on FG may be imprecise. Therefore, further study is necessary to confirm this finding.

Supporting information

S1 Supplement. STREGA reporting recommendations, extended from STROBE statement. (DOC)
S2 Supplement. Full-text articles excluded with reasons.

S3 Supplement. Meta-analysis on Genetic Association Studies checklist.

S4 Supplement. PRISMA 2009 checklist.

S1 Fig. Funnel plot of publication bias for the association of rs560887 (A), rs16856187 (CC vs AA) (B) and (AC vs AA) (C), rs573225 (D) with FG, rs560887 (E), rs16856187 under allele (F), dominant (G) and recessive (H) with T2D, respectively.

S2 Fig. Sensitivity tests for the association of rs560887 (A), rs16856187 (CC vs AA) (B) and (AC vs AA) (C), rs573225 (D) with FG, rs560887 (E), rs16856187 under allele (F), dominant (G) and recessive (H) with T2D, respectively.

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Author Contributions

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Funding acquisition: LLL.

Investigation: YYS XJL DDZ.

Methodology: YYS YQL JJW.

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Resources: CJW LLL.

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Supervision: LLL.

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Visualization: YYS.

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Writing – review & editing: LLL LY JZZ JJF.

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