**FTO Genotype and Type 2 Diabetes Mellitus: Spatial Analysis and Meta-Analysis of 62 Case-Control Studies from Different Regions**

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**Abstract:** Type 2 diabetes mellitus (T2DM) is a global health problem that results from the interaction of environmental factors with genetic variants. Although a number of studies have suggested that genetic polymorphisms in the fat mass and obesity-associated (FTO) gene are associated with T2DM risk, the results have been inconsistent. To investigate whether FTO polymorphisms associate with T2DM risk and whether this association is region-related, we performed this spatial analysis and meta-analysis. More than 60,000 T2DM patients and 90,000 controls from 62 case-control studies were included in this study. Odds ratios (ORs), 95% confidence intervals (CIs) and Moran’s I statistic were used to estimate the association between FTO rs9939609, rs8050136, rs1421085, and rs17817499, and T2DM risk in different regions. rs9939609 (OR = 1.15, 95% CI 1.11–1.19) and rs8050136 (OR = 1.14, 95% CI 1.10–1.18) conferred a predisposition to T2DM. After adjustment for body mass index (BMI), the association remained statistically significant for rs9939609 (OR = 1.11, 95% CI 1.05–1.17) and rs8050136 (OR = 1.08, 95% CI 1.03–1.12). In the subgroup analysis of rs9939609 and rs8050136, similar results were observed in East Asia, while no association was found in North America. In South Asia, an association for rs9939609 was revealed but not for rs8050136. In addition, no relationship was found with rs1421085 or rs17817499 regardless of adjustment for BMI. Moran’s I statistic showed that significant positive spatial autocorrelations existed in rs9939609 and rs8050136. Studies on rs9939609 and rs8050136 focused on East Asia and South Asia, whereas studies on rs1421085 and rs17817499 were distributed in North America and North Africa. Our data suggest that the associations between FTO rs9939609, rs8050136 and T2DM are region-related, and the two single-nucleotide polymorphisms contribute to an increased risk of T2DM. Future studies should investigate this issue in more regions.

**Keywords:** type 2 diabetes mellitus; T2DM; fat mass and obesity-associated; FTO; polymorphism(s); spatial analysis; meta-analysis
1. Introduction

Diabetes is a growing global health problem; more than 300 million people live with diabetes worldwide [1], and the prevalence of diabetes is estimated to rise [2]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, as it accounts for more than 90% of diabetes cases [3]. Although the pathogenesis mechanisms of T2DM have not been clearly defined, a combination of genetic and environmental factors is believed to lead to the disease [4].

The fat mass and obesity-associated (FTO) gene is located on chromosome 16 (16 q12.2), containing nine exons and several single-nucleotide polymorphisms (SNPs) [5]. In 2007, a genome-wide association study (GWAS) searching for type 2 diabetes-susceptibility genes confirmed a common variant (rs9939609) in the FTO gene that predisposes European populations to diabetes [6]. Since then, a large number of studies have focused on the association between FTO polymorphisms, expression and T2DM in different populations [7–10]. Meanwhile, some meta-analyses have been performed to elucidate the relationship between FTO polymorphisms and T2DM risk. For instance, a meta-analysis utilizing data from studies prior to 2010 identified an association between rs9939609 and T2DM in East and South Asians [11]. Additionally, a Norwegian population-based Nord-Trøndelag Health Study (HUNT study) [12], including three cohorts (HUNT, Malmö Diet and Cancer (MDC) and Malmö Preventive Project (MPP)), reported strong association between rs9939609 and T2DM risk in Scandinavians after adjustment for age, sex and body mass index (BMI). Another meta-analysis of association between obesity/BMI-associated loci and T2DM risk [13], using data from studies conducted between 2007 and 2012, revealed that FTO rs9939609 significantly associated with T2DM which also remained significant following adjustment for BMI; Analysis by Vasan et al. [14] has provided evidence that rs9939609 is associated with obesity and T2DM in Asian Indians, with modest attenuation observed when adjusting for BMI. These and the majority of other previous meta-analyses have focused on single population or one FTO loci without consideration of population-specific environmental influences among different regional subgroups. As such, the results of these meta-analyses cannot be generalized to the world.

More recently, geographic information systems (GIS) and spatial analysis are increasingly applied in the investigation of disease spatial pattern, including diabetes [15].

To more comprehensively clarify the association between FTO polymorphisms and T2DM risk, we performed this spatial analysis and meta-analysis to include most, if not all, eligible studies published before January 2017.

2. Materials and Methods

2.1. Search Strategy

Eligible articles were selected by searching up to January 2017 in PubMed and EMBASE using the following keywords: “FTO or fat mass and obesity-associated gene” and “variant or variation or polymorphism” and “type 2 diabetes or type 2 diabetes mellitus or T2D or T2DM”. Articles obtained from the initial search were then screened based on the inclusion criteria described below. Only publications with English language were included. If more than one population was included in a given article, results were considered as separate studies.

2.2. Study Selection Criteria and Data Extraction

The selected studies met all of the following inclusion criteria. The studies had to: (1) evaluate the association between FTO polymorphisms and T2DM risk; (2) have a case–control or cohort design; and (3) provide odds ratios (OR) with a 95% confidence interval (CI) or sufficient data for calculation. From each study, the following information was collected: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the samples; (5) sample size of cases and controls; (6) Hardy–Weinberg equilibrium (HWE) in control groups; and (7) data of SNPs. Data were independently extracted from eligible articles by two authors (YY and HYL) according to the criteria.
described. Discrepancies were resolved by discussion with a third reviewer (SML), and a consensus approach was used.

2.3. Spatial Analysis

The ArcGIS v10.3 software is a GIS tool that has become increasingly prevalent in public health research to understand the spatial pattern of diseases and genetic biodiversity [15]. This software was utilized to depict the geographic distribution of the association studies. R was used to calculate Moran’s I, a statistic for evaluating the spatial autocorrelation [16,17]. By constructing the spatial weight matrix, Moran’s I coefficient can be calculated as follows:

\[ I = \frac{N}{\sum_i \sum_j w_{ij}} \frac{\sum_i \sum_j w_{ij}(X_i - \bar{X})(X_j - \bar{X})}{\sum_i (X_i - \bar{X})^2} \]

\( N \) is the number of spatial units indexed by \( i \) and \( j \); \( X \) is the variable of interest; \( \bar{X} \) is the mean of \( X \); and \( w_{ij} \) is an element of a matrix of spatial weights. In this study, we constructed the spatial weight matrix by making a distance threshold \( h \). If the distance between point \( i \) and point \( j \) is smaller than \( h \), \( w_{ij} \) will be 1. Otherwise, \( w_{ij} \) will be 0. It is worth noting that all diagonal elements of matrix \( w \) are all 0. Monte Carlo simulations were used to test for the significance of Moran’s I.

2.4. Statistical Analysis

The strength of association between FTO SNPs and T2DM risk was expressed as a pooled OR and 95% CI. A z-test was performed to evaluate the significance of the pooled OR (\( p < 0.05 \) was considered statistically significant). The \( \chi^2 \)-test-based Q test and I\(^2 \) were performed to assess the heterogeneity of the studies. A value of \( I^2(\%) > 50\% \) or \( p \leq 0.10 \) indicated significant heterogeneity. A random-effects model (DerSimonian–Laird method) [18] was used to determine the pooled OR in the presence of heterogeneity; otherwise a fixed-effects model (Mantel–Haenszel method) [19] was used. Subgroup analyses were performed by region. Sensitivity analyses were performed to assess the stability of the combined results by excluding the studies with unknown HWE in controls. Publication bias was evaluated by Begg’s test [20] and Egger’s test [21] (\( p < 0.05 \) was considered statistically significant). Data analyses were conducted using STATA 12.0 (Stata-Corp LP, College Station, TX, USA).

3. Results

3.1. Study Characteristics and Quality

A total of 202 potentially relevant papers were identified from PubMed and EMBASE. After reading the title and abstract, 148 articles were excluded because they addressed topics that did not match the inclusion criteria. The full texts of the remaining 54 articles were carefully screened. We excluded five meta-analyses or reviews, three articles that explored the association between FTO polymorphisms and gestational diabetes, two articles that did not include the full text, and three papers with insufficient data. In total, 41 articles met the inclusion criteria. A flow chart describing the article selection for our meta-analysis is shown in Figure 1. Of the articles included, 29 studies investigated rs9939609, 26 studies explored rs8050136, four studies investigated rs1421085 and three studies explored rs17817499. Other SNPs that were assessed in only one study were not analyzed. The detailed characteristics of the included studies are shown in Table 1.
Figure 1. Study selection flow chart based on preferred reporting items for spatial analysis and meta-analysis.

Table 1. Characteristics of the included studies.

| First Author     | Year | Region          | Sample Size | Risk Allele Frequency | HWE | Ref. |
|------------------|------|-----------------|-------------|-----------------------|-----|------|
| Phani            | 2016 | South Asia      | 518 518     | 0.54 0.59             | NA  | [7]  |
| Xiao             | 2016 | East Asia       | 879 895     | 0.341 0.295           | yes | [22] |
| Xiao             | 2015 | East Asia       | 849 873     | 0.336 0.292           | yes | [8]  |
| Shen             | 2015 | East Asia       | 81 80       | 0.125 0.106           | yes | [9]  |
| Al-Sinani        | 2015 | West Asia       | 992 294     | 0.48 0.435            | yes | [23] |
| Xiao             | 2016 | East Asia       | 879 895     | 0.341 0.295           | yes | [22] |
| Xiao             | 2015 | East Asia       | 849 873     | 0.336 0.292           | yes | [8]  |
| Shen             | 2015 | East Asia       | 81 80       | 0.125 0.106           | yes | [9]  |
| Al-Sinani        | 2015 | West Asia       | 992 294     | 0.48 0.435            | yes | [23] |
| Bazzi            | 2014 | South Asia      | 81 95       | 0.525 0.542           | yes | [10] |
| Kalnina          | 2013 | Europe          | 974 1075    | 0.501 0.438           | yes | [26] |
| Ali              | 2013 | South Asia      | 1583 1317   | 0.362 0.304           | yes | [27] |
| Binh             | 2012 | East Asia       | 98 251      | 0.255 0.181           | yes | [28] |
| Iwata            | 2012 | East Asia       | 722 758     | 0.206 0.182           | yes | [29] |
| Rees(COBRA)      | 2011 | South Asia      | 385 1281    | 0.336 0.294           | yes | [30] |
| Rees(UKADS/DGP)  | 2011 | South Asia      | 1568 1177   | 0.329 0.298           | yes | [30] |
| Huang            | 2011 | East Asia       | 591 1200    | 0.299 0.305           | yes | [31] |
| Chauhan          | 2011 | South Asia      | 2361 2755   | 0.35 0.34             | yes | [32] |
| Cruz             | 2010 | North America   | 519 547     | 0.252 0.212           | yes | [33] |
| Bressler (African-American) | 2010 | North America   | 655 2685    | 0.463 0.483           | yes | [34] |
| Bressler (white) | 2010 | North America   | 988 9915    | 0.465 0.443           | yes | [34] |
| Liu              | 2010 | East Asia       | 1774 1984   | 0.136 0.117           | yes | [35] |
| Jaynik           | 2009 | South Asia      | 1453 1361   | 0.353 0.3               | yes | [36] |
| Legry            | 2009 | Europe          | 283 2601    | 0.456 0.42             | yes | [37] |
| Sanghera         | 2008 | South Asia      | 513 353     | 0.363 0.31             | yes | [38] |
| Horikawa         | 2008 | East Asia       | 1849 1578   | 0.209 0.205           | yes | [39] |
| Chang            | 2008 | East Asia       | 735 726     | 0.132 0.127           | yes | [40] |
| Omori            | 2008 | East Asia       | 1621 1053   | 0.209 0.195           | yes | [2]  |
| Horikoshi        | 2007 | East Asia       | 864 864     | 0.216 0.192           | yes | [41] |
| Zeggini.         | 2007 | Europe          | 5681 8284   | 0.435 0.394           | yes | [42] |
| Frayling         | 2007 | Europe          | 3757 5346   | NA NA                 | yes | [6]  |
Table 1. Cont.

| First Author Year Region | Sample Size | Risk Allele Frequency | HWE Ref. |
|--------------------------|-------------|-----------------------|----------|
|                          | T2DM Control T2DM Control |
| T2DM Control T2DM Control |
| rs8050136               |             |                       |          |
| Xiao 2016 East Asia     | 879 895     | 0.313 0.275           | yes [22] |
| Xiao 2015 East Asia     | 849 873     | 0.308 0.274           | yes [23] |
| Shen 2015 East Asia     | 88 80       | 0.114 0.106           | yes [24] |
| Al-Sinani 2015 West Asia| 992 294     | 0.458 0.425           | yes [25] |
| Chang 2014 East Asia    | 1502 1518   | 0.127 0.124           | yes [26] |
| Almawi 2013 West Asia   | 995 1195    | 0.487 0.551           | yes [27] |
| Qian 2013 East Asia     | 2898 3262   | 0.127 0.103           | yes [28] |
| Gamboa 2012 North America| 1027 990   | 0.194 0.2              | yes [29] |
| Ivata 2012 East Asia    | 724 763     | 0.205 0.183           | yes [30] |
| Chauhan 2011 South Asia | 1106 1800   | 0.35 0.34             | yes [31] |
| Ramya 2011 South Asia   | 1001 851    | 0.14 0.107            | yes [32] |
| Han 2010 East Asia      | 1007 995    | 0.13 0.11             | yes [33] |
| Almawi(2015) West Asia  | 992 294     | 0.458 0.425           | yes [34] |
| Bressler(White) 2010 North America| 657 2728 | 0.425 0.44            | yes [35] |
| Bressler(White) 2010 North America| 984 9783 | 0.44 0.402            | yes [36] |
| Wang 2010 East Asia     | 1165 1136   | 0.134 0.119           | yes [37] |
| Liu 2010 East Asia      | 1748 2015   | 0.139 0.117           | yes [38] |
| Hu 2010 East Asia       | 1849 1785   | 0.13 0.118            | yes [39] |
| Rong 2009 North America | 1472 1825   | 0.151 0.136           | yes [40] |
| Lee 2008 East Asia      | 886 501     | 0.129 0.14             | yes [41] |
| Ng(HK) 2008 East Asia   | 1481 1530   | 0.156 0.136           | yes [42] |
| Ng(SNUH) 2008 East Asia | 761 632     | 0.138 0.122           | yes [43] |
| Ng(KHGS) 2008 East Asia | 799 1516    | 0.124 0.118           | yes [44] |
| Omori 2008 East Asia    | 1616 1060   | 0.208 0.194           | yes [45] |
| Horikoshi 2007 East Asia| 857 861     | 0.238 0.2              | yes [46] |
| Zeggini 2007 Europe     | 4207 4111   | 0.44 0.39             | yes [47] |
| Scott 2007 Europe       | 2339 2401   | 0.406 0.381           | yes [48] |

rs1421085

| Cauchi(Morocco) 2012 North Africa | 1193 1095 | 0.395 0.356 | yes [55] |
| Cauchi(Tunisia) 2012 North Africa | 1446 942  | 0.41 0.407 | yes [56] |
| Bressler(White) 2010 North America| 657 2725 | 0.084 0.112 | yes [34] |

rs17817499

| Almawi 2013 West Asia | 995 1195 | 0.517 0.557 | yes [44] |
| Bressler(White) 2010 North America| 989 9893 | 0.451 0.41  | yes [34] |

T2DM, Type 2 diabetes mellitus; HWE, Hardy–Weinberg equilibrium; COBRA, Control of Blood Pressure and Risk Attenuation; UKADS/DGP, UK Asian Diabetes Study/Diabetes Genetics in Pakistan; HK, Hong Kong; SNUH, Seoul National University Hospital; KHGS, Korean Health and Genome Study.

3.2. Region-Related Associations Exist between rs8050136, rs9939609 and T2DM

For rs8050136, a total of 33,889 T2DM cases and 45,490 controls were included in the final data analysis. The overall results showed a significant association between rs8050136 and T2DM risk (OR = 1.14, 95% CI 1.10–1.18, p (<z test) < 0.001, I^2 = 37.4%) (Table 2, Figure 2a), with the association remaining statistically significant after adjustment for BMI (OR = 1.08, 95% CI 1.03–1.12, p (<z test) < 0.001, I^2 = 27.1%) (Table 2, Figure 2b). To more clearly understand the association between rs8050136 and T2DM in different regions, we performed the subgroup analyses by region. Consequently, without BMI adjustment, a significant association between rs8050136 and T2DM was uncovered in East Asia (OR = 1.15, 95% CI 1.10–1.20), West Asia (OR = 1.17, 95% CI 1.05–1.29) and Europe (OR = 1.19, 95% CI 1.14–1.25) (Table 2, Figure 3a), with no such association in North America (OR = 1.06, 95% CI 0.93–1.19) or South Asia (OR = 1.19, 95% CI 0.91–1.48). After adjustment for BMI, significant association was only observed in East Asia (OR = 1.13, 95% CI 1.05–1.20) (Table 2, Figure 3b).
Figure 3b). More importantly, as seen in Figure 4, the majority of studies on rs8050136 were distributed in East Asia. Several other studies were scattered throughout Europe, Northern America, South Asia and West Asia. More data for these regions may be required to detect an association.

Table 2. Meta-analysis of fat mass and obesity-associated (FTO) single-nucleotide polymorphisms (SNPs) and T2DM risk.

| SNP       | No. of Study (T2DM/Control) | Without BMI Adjustment | With BMI Adjustment | | |
|-----------|-----------------------------|------------------------|---------------------|---|---|
|           |                            | OR (95% CI)            | p<sub>z</sub><sup>a</sup> | I<sup>2</sup>% | P<sub>H</sub><sup>b</sup> | OR (95% CI) | p<sub>z</sub><sup>a</sup> | I<sup>2</sup>% | P<sub>H</sub><sup>b</sup> |
| All       |                            |                        |                     |              |                      |                        |                     |              |                      |
| rs9939609 | 29 (32771/50161)           | 1.15 (1.11–1.19)       | 0                   | 53.2         |                      | 1.11 (1.05–1.17)       | 0                   | 56.1         | 0.003                   |
| rs8050136 | 26 (33889/45490)           | 1.14 (1.10–1.18)       | 0                   | 37.4         | 0.032                | 1.08 (1.03–1.12)       | 0                   | 27.1         | 0.151                   |
| rs1421085 | 4 (4285/16279)             | 1.05 (0.91–1.21)       | 0.48                | 80.6         | 0.001                | 1.02 (0.88–1.19)       | 0.755               | 78.2         | 0.003                   |
| rs17817499| 3 (2634/15482)             | 1.09 (0.93–1.28)       | 0.271               | 82.7         | 0.003                | 1.05 (0.90–1.23)       | 0.539               | 80           | 0.007                   |
| East Asia |                            |                        |                     |              |                      |                        |                     |              |                      |
| rs9939609 | 11 (10063/10262)           | 1.11 (1.05–1.17)       | 0                   | 19.5         | 0.257                | 1.11 (1.02–1.20)       | 0                   | 0            | 0.535                   |
| rs8050136 | 15 (19109/19422)           | 1.15 (1.10–1.20)       | 0                   | 0            | 0.789                | 1.13 (1.05–1.20)       | 0                   | 0            | 0.531                   |
| North America |                        |                        |                     |              |                      |                        |                     |              |                      |
| rs9939609 | 3 (2162/14790)             | 1.11 (0.89–1.32)       | 0                   | 85.4         | 0.001                | 1.02 (0.81–1.22)       | 0                   | 85.7         | 0.008                   |
| rs8050136 | 4 (4140/17082)             | 1.06 (0.93–1.19)       | 0                   | 74.1         | 0.009                | 1.03 (0.97–1.10)       | 0                   | 69.9         | 0.019                   |
| Europe    |                            |                        |                     |              |                      |                        |                     |              |                      |
| rs9939609 | 4 (10695/17306)            | 1.18 (1.14–1.22)       | 0                   | 0            | 0.49                 | 1.11 (0.93–1.29)       | 0                   | 75.6         | 0.043                   |
| rs8050136 | 2 (8020/10685)             | 1.19 (1.14–1.25)       | 0                   | 46.5         | 0.172                | NA                    | NA                  | NA           | NA                      |
| South Asia |                        |                        |                     |              |                      |                        |                     |              |                      |
| rs9939609 | 10 (8859/9152)             | 1.19 (1.10–1.29)       | 0                   | 58.6         | 0.01                 | 1.19 (1.06–1.31)       | 0                   | 69.7         | 0.01                   |
| rs8050136 | 2 (2107/2651)              | 1.19 (0.91–1.48)       | 0                   | 68           | 0.077                | 1.06 (0.94–1.18)       | 0                   | 0            | 0.808                   |
| West Asia |                            |                        |                     |              |                      |                        |                     |              |                      |
| rs8050136 | 2 (1987/1489)              | 1.17 (1.05–1.29)       | 0                   | 0            | 0.76                 | 1.12 (0.98–1.25)       | 0                   | 0            | 0.369                   |

<sup>a</sup> p value for z-test; <sup>b</sup> p value for χ²-test based Q test; BMI, body mass index; OR, odds ratio; CI, confidence interval; NA, not available.
Figure 2. Meta-analysis for the associations between rs8050136 and Type 2 diabetes mellitus (T2DM) risk: (a) without; and (b) with adjustment for body mass index (BMI).
Figure 2. Meta-analysis for the associations between rs8050136 and Type 2 diabetes mellitus (T2DM) risk: (a) without; and (b) with adjustment for body mass index (BMI).

Figure 3. The stratified analysis results of rs8050136 grouped by region: (a) without; and (b) with adjustment for BMI.

Figure 4. Geographic distribution of selected studies exploring the association between rs8050136 and T2DM risk. Blue bars indicate T2DM patients while pink bars indicate controls; the height of bars is proportional to sample size. Studies in black text represent those that showed a significant association between the SNP and T2DM risk. Studies in red text indicate no significant association.
For rs9939609, a total of 32,771 T2DM cases and 50,161 controls were included in the meta-analysis. The overall results indicated that rs9939609 was significantly associated with an increased risk of T2DM (OR = 1.15, 95% CI 1.11–1.19, \( p \) (z-test) < 0.001, \( I^2 = 53.2\% \)) (Table 2, Figure S1a). After adjustment for BMI, the association remained statistically significant (OR = 1.11, 95% CI 1.05–1.17, \( p \) (z-test) < 0.001, \( I^2 = 56.1\% \)) (Table 2, Figure S1b). Due to the heterogeneity that existed between studies, we performed stratified analyses grouped by region. In the subgroup analyses, similar results were found in East Asia (without BMI adjustment: OR = 1.11, 95% CI 1.05–1.17; with BMI adjustment: OR = 1.11, 95% CI 1.02–1.20) and South Asia (without BMI adjustment: OR = 1.19, 95% CI 1.06–1.31), whereas no such association existed between rs9939609 and T2DM in North America (without BMI adjustment: OR = 1.11, 95% CI 0.89–1.32; with BMI adjustment: OR = 1.02, 95% CI 0.81–1.22) (Table 2, Figure S2). Additionally, in Europe, a significant association between rs9939609 and T2DM was observed without BMI adjustment (OR = 1.18, 95% CI 1.14–1.22), whereas no association was uncovered with BMI adjustment (OR = 1.11, 95% CI 0.93–1.29). Similar to the distributions of rs8050136 studies, the geographic distribution of researches on rs9939609 were concentrated in East Asia and South Asia, where the association was found to be significant.

As illustrated in Figure 5, when the spatial scale was smaller than 1,000,000 meters, there was significant positive spatial autocorrelation in terms of both rs9969309 and rs8050136. It turned out that in relative small spatial scale (\( h < 1,000,000 \) meters), the studies with significant correlations tended to be clustered, which indicated that the correlation between rs9969309 and rs8050136, and T2DM risk was strongly associated with the geographic factors. With the \( h \) increasing, Moran’s \( I \) showed no positive spatial autocorrelation of these two SNPs and T2DM risk, which meant we cannot reject the null hypothesis of completed spatial randomness. Our results follow Tobler’s first law of geography: “Everything is related to everything else, but near things are more related than distant things” (pp.236, [56]). It seemed that in Asia, there was a strong positive-positive (significant-significant) spatial autocorrelation while in Europe there may be some negative-negative (non-significant-non-significant) spatial autocorrelation. In North America, the spatial autocorrelation was not significant, maintaining a relatively random spatial pattern.
3.3. Sensitivity Analyses

To assess the stability of the combined results obtained by excluding studies of unknown HWE in controls [7,25], a sensitivity analysis was conducted (Figure S5). The analysis confirmed that the rs9939609 polymorphism conferred a predisposition to T2DM.

3.4. Assessment of Publication Bias

To evaluate the publication bias, we performed Begg’s test and Egger’s test. The results showed that there was no publication bias for the associations between the four FTO polymorphisms and T2DM risk (p > 0.05 for Begg’s test and Egger’s test) (Table S1).

4. Discussion

Our meta-analysis and spatial analysis are based on a large sample size, including over 60,000 and 90,000 subjects for rs9939609 and rs8050136, respectively, spanning regions across Asia, Europe and Northern America. In line with previous meta-analyses of Asian populations [14,36,45], we further demonstrated a strong association between rs9939609 and rs8050136, and T2DM regardless of adjustment for BMI (Table 2, Figures 2 and 3, Figures S1 and S2). Notably, the associations are region-related.

Indeed, some statistics such as Moran’s I [16,17], and local indicators of spatial autocorrelation (LISA) [57] can be used to quantitatively study spatial autocorrelation. However, due to obstacles including the modifiable areal unit problem (MAUP) (i.e., some papers only provide a country location while some papers have the city location) and the low data volume, it is difficult to perform spatial statistics for rs1421085 and rs17817499 to further explore the spatial pattern. Nevertheless, our data.
still indicate the geographic factor may play an important role in the correlations between T2DM risk and rs8050136 (Figures 4 and 5), rs9939609 (Figure 5).

Initially, the articles we reviewed contained more than 10 types of FTO SNPs in T2DM patients and controls, but we eventually chose the four most common SNPs, namely rs9939609, rs8050136, rs1421085 and rs17817499. All four SNPs are located in intron 1 of the FTO gene, a region of strong linkage disequilibrium [40]. Some studies have found no direct connection between the variants and FTO expression or function [9], while other studies have suggested that variants of FTO play an important role in regulating body weight and fat mass by influencing food intake [6]. A recent report revealed that SNPs in FTO could influence obesity by altering the expression of the adjacent genes IRX3 and RPGRIP1L [58]. Although mechanisms regarding how these noncoding variants affect T2DM are not yet clear, Smemo et al. have demonstrated that variants within FTO can form long-range functional connections with IRX3, representing a determinant of body mass and composition [59]. Additionally, recent studies have suggested hepatic FTO contributes to glucose homeostasis [60–62], indicating that FTO may play a role in the regulation of carbohydrate metabolism.

Of note, the overall heterogeneity of rs9939609 increased slightly after BMI adjustment (I^2 = 53.2%, p < 0.001 without BMI adjustment vs. I^2 = 56.1%, p = 0.003 with BMI adjustment) (Table 2), suggesting that BMI may not primarily account for heterogeneity. To this end, we performed additional subgroup analyses by region and found that heterogeneity still existed in the group of North America and South Asia independent of BMI adjustment. We then excluded each study in South Asia and North America and performed subgroup analyses, respectively. When omitting studies by Fawwad et al. or Chauhan et al. in South Asia, as well as Bressler et al. (African-Americans) in North America [24,32,34], the heterogeneity disappeared in the South Asian (I^2 = 34.6%, p = 0.141 and I^2 = 37.2%, p = 0.121) and North American (I^2 = 0.0%, p = 0.667) subgroups, respectively, without BMI adjustment (Table S2). Of note, the heterogeneity showed no change by removing other studies in South Asian or North American subgroup. Alternatively, only removing the study by Ali et al. [27], heterogeneity in the South Asian subgroup also attenuated sharply (I^2 = 20.3%, p = 0.288) after adjustment for BMI (Table S2). These results demonstrated that these studies mentioned above were the main source of heterogeneity in South Asia and North America. Unlike rs9939609, owing to the low data volume of the studies, the heterogeneity in rs1421085 and rs17817499 showed no change by subgroup analyses.

BMI is widely considered as a confounder of T2DM risk. In this study, the overall associations between the four SNPs and T2DM risk were not affected by BMI adjustment. (Table 2), indicating that the overall associations were BMI-independent. Nevertheless, in Europe for rs9939609 and West Asia for rs8050136, the BMI adjustment altered the associations (Table 2). In agreement with previous reports [11,12], our data showed that rs9939609 was also associated with T2DM risk somewhat independently of BMI in East and South Asia as well as in Europe. Interestingly, different regions showed different associations between rs9939609 and rs8050136, and T2DM risk, demonstrating that the associations were region-dependent. Generally, a race/ethnicity population might live in the same region in most of the non-immigrant countries. Thus, our results might reflect the influence of different races/ethnicities to some extent.

The rs9939609 was the first SNP discovered within the FTO gene that showed a strong association with BMI and as such is the most widely investigated SNP of FTO [63]. Additionally, the A allele of rs9939609 is known to indicate a predisposition to obesity, T2DM, polycystic ovary syndrome (PCOS) and some cancers [41,64,65]. Our results of rs9939609 are not only consistent with earlier reports [11–14], but also include more recent studies with greater geographical coverage [7–9,22,23,34] (Table 2, Figure S2), providing stronger evidence for these associations. Similarly, rs8050136 was also found to function as a susceptible SNP to rs9939609-related diseases. Unlike rs9939609 and rs8050136, studies on rs1421085 and rs17817499 are scarce, and have limited regional coverage; lack of association maybe due to smaller sample size and less studies involved.

The study we present here still possesses several limitations. First, a large proportion of the studies focused on Asian populations, with European and Northern American populations only
accounting for a small part. Second, there were relatively few studies on rs1421085 and rs17817499, which may lead to bias in negative results (Table 2, Figures S3 and S4). Lastly, except for BMI, we used genotype data without considering other possible confounders (such as age and sex) or gene–gene and gene–environment interactions. Although BMI is widely used to measure obesity, it has been suggested that different criteria (not necessarily > 30) may be used in different ethnic populations. Adiposity (or specific distribution of fat) rather than body weight (or BMI) may play a critical role in the regulation of insulin sensitivity and the development of diabetes. This may lead to an inconsistency in the effect of BMI on the association between FTO variants and T2DM risk. Therefore, further studies that adjust for more concomitant factors and cover more regions should be conducted.

5. Conclusions

The spatial analysis and meta-analysis showed that the associations between genetic polymorphisms in FTO and T2DM are region-related and that shedding light on spatial variations can provide new insights into well-established relationships. The rs9939609 and rs8050136 SNPs contributed to an increased risk of T2DM, which could provide new solutions for T2DM prevention and therapy. This study presented an initial step in spatial analysis for genetic and regional factors in the development of diabetes, although more work remains to be done before we can understand the impact of genetics, environment, geography, BMI and fat distribution on diabetes as well as how these associations may vary across space.

Supplementary Materials: The following can be found online at www.mdpi.com/2073-4425/8/2/70/s1, Table S1. Publication bias of FTO SNPs; Table S2. Heterogeneity for rs9939609 in South Asia and North America subgroups after excluding each study; Figure S1. Meta-analysis for the associations between rs9939609 and T2DM risk (a) without and (b) with adjustment for body mass index (BMI); Figure S2. The stratified analysis results of rs9939609 grouped by region (a) without and (b) with adjustment for body mass index (BMI); Figure S3. Meta-analysis for the associations between rs1421085 and T2DM risk (a) without and (b) with adjustment for body mass index (BMI); Figure S4. Meta-analysis for the associations between rs17817499 and T2DM risk (a) without and (b) with adjustment for body mass index (BMI); Figure S5. Sensitivity analysis of rs9939609 by excluding studies with an unknown Hardy-Weinberg equilibrium (HWE) in controls.

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References

1. Kleinberger, J.W.; Pollin, T.I. Personalized medicine in diabetes mellitus: Current opportunities and future prospects. *Ann. N. Y. Acad. Sci.* **2015**, *1346*, 45–56. [CrossRef] [PubMed]
2. Omori, S.; Tanaka, Y.; Takahashi, A.; Hirose, H.; Kashiwagi, A.; Kaku, K.; Kawamori, R.; Nakamura, Y.; Maeda, S. Association of *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8*, and *KCNJ11* with susceptibility to type 2 diabetes in a Japanese population. *Diabetes* **2008**, *57*, 791–795. [CrossRef] [PubMed]
3. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In standards of medical care in diabetes—2015. *Diabetes Care* **2015**, *38* (Suppl. S1), S8–S16.
4. O’Rahilly, S.; Barroso, I.; Wareham, N.J. Genetic factors in type 2 diabetes: The end of the beginning? *Science* **2005**, *307*, 370–373. [CrossRef] [PubMed]
5. Dina, C.; Meyre, D.; Gallina, S.; Durand, E.; Korner, A.; Jacobson, P.; Carlsson, L.M.; Kiess, W.; Vatin, V.; Lecoeur, C.; et al. Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nat. Genet.* **2007**, *39*, 724–726. [CrossRef] [PubMed]
6. Frayling, T.M.; Timpson, N.J.; Weedon, M.N.; Zeggini, E.; Freathy, R.M.; Lindgren, C.M.; Perry, J.R.; Elliott, K.S.; Lango, H.; Rayner, N.W.; et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007, 316, 889–894. [CrossRef] [PubMed]

7. Phani, N.M.; Vohra, M.; Rajesh, S.; Adhikari, P.; Nagri, S.K.; D’Souza, S.C.; Satyamoorthy, K.; Rai, P.S. Implications of critical PPARγ2, ADIPOQ and FTO gene polymorphisms in type 2 diabetes and obesity-mediated susceptibility to type 2 diabetes in an Indian population. Mol. Genet. Genomics 2016, 291, 193–204. [CrossRef] [PubMed]

8. Xiao, S.; Zeng, X.; Quan, L.; Zhu, J. Correlation between polymorphism of FTO gene and type 2 diabetes mellitus in Uygur people from Northwestern China. Int. J. Clin. Exp. Med. 2015, 8, 9744–9750. [PubMed]

9. Shen, F.; Huang, W.; Huang, J.T.; Xiong, J.; Yang, Y.; Wu, K.; Jia, G.F.; Chen, J.; Feng, Y.Q.; Yuan, B.F.; et al. Decreased N6-methyladenosine in peripheral blood rna from diabetic patients is associated with FTO expression rather than ALKBH5. J. Clin. Endocrinol. Metab. 2015, 100, E148–E154. [CrossRef] [PubMed]

10. Bazzi, M.D.; Nasr, F.A.; Alanazi, M.S.; Alamri, A.; Turjoman, A.A.; Moustafa, A.S.; Alfadda, A.A.; Pathan, A.A.; Farine, N.R. Association between FTO, MC4R, SLC30A8, and KCNQ1 gene variants and type 2 diabetes in Saudi population. Genet. Mol. Res. 2014, 13, 10194–10203. [CrossRef] [PubMed]

11. Li, H.; Kilpelainen, T.O.; Liu, C.; Zhu, J.; Liu, Y.; Hu, C.; Yang, Z.; Zhang, W.; Bao, W.; Cha, S.; et al. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia 2012, 55, 981–995. [CrossRef] [PubMed]

12. Hertel, J.K.; Johansson, S.; Sonestedt, E.; Jonsson, A.; Lie, R.T.; Platou, C.G.; Nilsson, P.M.; Rukh, G.; Midtbjell, K.; Hveem, K.; et al. FTO, type 2 diabetes, and weight gain throughout adult life: A meta-analysis of 41,504 subjects from the Scandinavian HUNT, MDC, and MFP studies. Diabetes 2011, 60, 1637–1644. [CrossRef] [PubMed]

13. Xi, B.; Takeuchi, F.; Meirhaeghe, A.; Kato, N.; Chambers, J.C.; Morris, A.P.; Cho, Y.S.; Zhang, W.; Mohlke, K.L.; Kooper, J.S.; et al. Associations of genetic variants in/near body mass index-associated genes with type 2 diabetes: A systematic meta-analysis. Clin. Endocrinol. 2014, 81, 702–710. [CrossRef] [PubMed]

14. Vasan, S.K.; Karpe, F.; Gu, H.F.; Brismar, K.; Fall, C.H.; Ingelsson, E.; Fall, T. FTO genetic variants and risk of obesity and type 2 diabetes: A meta-analysis of 28,394 Indians. Obesity 2014, 22, 964–970. [CrossRef] [PubMed]

15. Hipp, J.A.; Chaline, N. Spatial analysis and correlates of county-level diabetes prevalence, 2009–2010. Prev. Chronic Dis. 2015, 12, E08. [CrossRef] [PubMed]

16. Moran, P.A. The interpretation of statistical maps. J. R. Stat. Soc. 1947, 10, 243–251.

17. Moran, P.A. A test for the serial independence of residuals. Biometrika 1950, 37, 178–181. [CrossRef] [PubMed]

18. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. Control. Clin. Trials 1986, 7, 777–88. [CrossRef] [PubMed]

19. Mantel, N.; Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 1959, 22, 719–748. [PubMed]

20. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994, 50, 1088–1101. [CrossRef] [PubMed]

21. Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629–634. [CrossRef] [PubMed]

22. Xiao, S.; Zeng, X.; Fan, Y.; Su, Y.; Ma, Q.; Zhu, J.; Yao, H. Gene polymorphism association with type 2 diabetes and related gene-gene and gene-environment interactions in a Uygur population. Med. Sci. Monit. 2016, 22, 474–487. [PubMed]

23. Al-Sinani, S.; Woodhouse, N.; Al-Mamari, A.; Al-Shafiee, O.; Al-Shafae, M.; Al-Yahyaee, S.; Hassan, M.; Jaju, D.; Al-Hashmi, K.; Al-Abri, M.; et al. Association of gene variants with susceptibility to type 2 diabetes among Omanis. World J. Diabetes 2015, 6, 358–366. [CrossRef] [PubMed]

24. Fawwad, A.; Siddiqui, I.A.; Zeeshan, N.F.; Shahid, S.M.; Basi, A. Association of snp rs9939609 in FTO gene with metabolic syndrome in type 2 diabetic subjects, recruited from a tertiary care unit of Karachi, Pakistan. Pak. J. Med. Sci. 2015, 31, 140–145. [PubMed]

25. Raza, S.T.; Abbas, S.; Ahmad, A.; Ahmed, F.; Zaidi, Z.H.; Mahdi, F. Association of glutathione-s-transferase (GSTM1 and GSTT1) and FTO gene polymorphisms with type 2 diabetes mellitus cases in Northern India. Balk. J. Med. Genet. 2014, 17, 47–54.
26. Kalnina, I.; Zaharenko, L.; Vaivade, I.; Rovite, V.; Nikitina-Zake, L.; Peculis, R.; Fridmanis, D.; Geldnere, K.; Jacobsson, J.A.; Almen, M.S.; et al. Polymorphisms in FTO and near TMEM18 associate with type 2 diabetes and predispose to younger age at diagnosis of diabetes. *Gene* 2013, 527, 462–468. [CrossRef] [PubMed]

27. Ali, S.; Chopra, R.; Manvati, S.; Singh, Y.P.; Kaul, N.; Behura, A.; Mahajan, A.; Sahajpal, P.; Gupta, S.; Dhar, M.K.; et al. Replication of type 2 diabetes candidate genes variations in three geographically unrelated Indian population groups. *PLoS ONE* 2013, 8, e58881. [CrossRef] [PubMed]

28. Binh, T.Q.; Phuong, P.T.; Nhung, B.T.; Thoang, D.D.; Lien, H.T.; Thanh, D.V. Association of the common FTO-rs9939609 polymorphism with type 2 diabetes, independent of obesity-related traits in a Vietnamese population. *Gene* 2013, 513, 31–35. [CrossRef] [PubMed]

29. Iwata, M.; Maeda, S.; Kamura, Y.; Takano, A.; Kato, H.; Murakami, S.; Higuchi, K.; Takahashi, A.; Fujita, H.; Hara, K.; et al. Genetic risk score constructed using 14 susceptibility alleles for type 2 diabetes is associated with the early onset of diabetes and may predict the future requirement of insulin injections among Japanese individuals. *Diabetes Care* 2012, 35, 1763–1770. [CrossRef] [PubMed]

30. Rees, S.D.; Islam, M.; Hydrie, M.Z.I.; Chaudhary, B.; Bellary, S.; Hashmi, S.; O’Hare, J.P.; Kumar, S.; Sanghera, D.K.; Chaturvedi, N.; et al. An FTO variant is associated with type 2 diabetes in South Asian populations after accounting for body mass index and waist circumference. *Diabet. Med.* 2011, 28, 673–680. [CrossRef] [PubMed]

31. Huang, W.; Sun, Y.; Sun, J. Combined effects of FTO rs9939609 and MC4R rs17782313 on obesity and BMI in Chinese Han populations. *Endocrine* 2011, 39, 69–74. [CrossRef] [PubMed]

32. Chauhan, G.; Tabassum, R.; Mahajan, A.; Dwivedi, O.P.; Mahendran, Y.; Kaur, I.; Nigam, S.; Dubey, H.; Varma, B.; Madhu, S.V.; et al. Common variants of FTO and the risk of obesity and type 2 diabetes in Indians. *J. Hum. Genet.* 2011, 56, 720–726. [CrossRef] [PubMed]

33. Cruz, M.; Valladares-Salgado, A.; Garcia-Mena, J.; Ross, K.; Edwards, M.; Angeles-Martinez, J.; Ortega-Camarillo, C.; de la Pena, J.E.; Burguete-Garcia, A.I.; Wacher-Rodarte, N.; et al. Candidate gene association study conditioning on individual ancestry in patients with type 2 diabetes and metabolic syndrome from Mexico City. *Diabetes Metab. Res. Rev.* 2010, 26, 261–270. [CrossRef] [PubMed]

34. Bressler, J.; Kao, W.H.; Pankow, J.S.; Boerwinkle, E. Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in Whites and African-Americans in the ARIC study. *PLoS ONE* 2010, 5, e10521. [CrossRef] [PubMed]

35. Liu, Y.; Liu, Z.; Song, Y.; Zhou, D.; Zhang, D.; Zhao, T.; Chen, Z.; Yu, L.; Yang, G.; et al. Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the Asian population. *Obesity* 2010, 18, 1619–1624. [CrossRef] [PubMed]

36. Yajnik, C.S.; Janipalli, C.S.; Bhaskar, S.; Kulkarni, S.R.; Freathy, R.M.; Prakash, S.; Mani, K.R.; Weedon, M.N.; Kale, S.D.; Dhar, M.K.; et al. FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia* 2009, 52, 247–252. [CrossRef] [PubMed]

37. Legry, V.; Cottel, D.; Ferrell, R.E.; Nath, S.K.; et al. Effect of an FTO polymorphism on fat mass, obesity, and type 2 diabetes mellitus in the French MONICA study. *Metabolism* 2009, 58, 971–975. [CrossRef] [PubMed]

38. Sanghera, D.K.; Ortega, L.; Han, S.; Singh, J.; Ralhan, S.K.; Wander, G.S.; Mehra, N.K.; Mulvihill, J.J.; Ferrell, R.E.; Nath, S.K.; et al. Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: *PPARG2* (Pro12Ala), *IGF2BP2*, *TCF7L2* and FTO variants confer a significant risk. *BMC Med. Genet.* 2008, 9, 59. [CrossRef] [PubMed]

39. Horikawa, Y.; Miyake, K.; Yasuda, K.; Enya, M.; Hirota, Y.; Yamagata, K.; Hinokio, Y.; Oka, Y.; Iwasaki, N.; Iwamoto, Y.; et al. Replication of genome-wide association studies of type 2 diabetes susceptibility in Japan. *J. Clin. Endocrinol. Metab.* 2008, 93, 3136–3141. [CrossRef] [PubMed]

40. Chang, Y.C.; Liu, P.H.; Lee, W.J.; Chang, T.J.; Jiang, Y.D.; Li, H.Y.; Kuo, S.S.; Lee, K.C.; Chang, L.M. Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. *Diabetes* 2008, 57, 2245–2252. [CrossRef] [PubMed]

41. Horikoshi, M.; Hara, K.; Ito, C.; Shoijima, N.; Nagai, R.; Ueki, K.; Froguel, P.; Kadowaki, T. Variations in the *HHEX* gene are associated with increased risk of type 2 diabetes in the Japanese population. *Diabetologia* 2007, 50, 2461–2466. [CrossRef] [PubMed]
42. Zeggini, E.; Weedon, M.N.; Lindgren, C.M.; Frayling, T.M.; Elliott, K.S.; Lango, H.; Timpson, N.J.; Perry, J.R.; Rayner, N.W.; Freathy, R.M.; et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 2007, 316, 1336–1341. [CrossRef] [PubMed]

43. Chang, Y.C.; Liu, P.H.; Yu, Y.H.; Kuo, S.S.; Chang, T.J.; Jiang, Y.D.; Nong, J.Y.; Hwang, J.J.; Chuang, L.M. Validation of type 2 diabetes risk variants identified by genome-wide association studies in Han Chinese population: A replication study and meta-analysis. *PloS ONE* 2014, 9, e95045. [CrossRef] [PubMed]

44. Almawi, W.Y.; Nemr, R.; Keleshtian, S.H.; Echtay, A.; Saldanha, F.L.; AlDoseri, F.A.; Racoubian, E. A replication study of 19 GWAS-validated type 2 diabetes at-risk variants in the Lebanese population. *Diabetes Res. Clin. Pract.* 2013, 102, 117–122. [CrossRef] [PubMed]

45. Qian, Y.; Liu, S.J.; Lu, F.; Li, H.Z.; Dong, M.H.; Lin, Y.D.; Du, J.B.; Lin, Y.; Gong, J.H.; Jin, G.F.; et al. Genetic variant in fat mass and obesity-associated gene associated with type 2 diabetes risk in Han Chinese. *BMC Genet.* 2013, 14, 86. [CrossRef] [PubMed]

46. Gamboa-Melendez, M.A.; Huerta-Chagoya, A.; Moreno-Macias, H.; Vazquez-Cardenas, P.; Ordonez-Sanchez, M.L.; Rodriguez-Guillem, R.; Riba, L.; Rodriguez-Torres, M.; Guerra-Garcia, M.T.; Guillen-Pineda, L.E.; et al. Contribution of common genetic variation to the risk of type 2 diabetes in the Mexican Mestizo population. *Diabetes* 2012, 61, 3314–3321. [CrossRef] [PubMed]

47. Ramya, K.; Radha, V.; Ghosh, S.; Majumder, P.P.; Mohan, V. Genetic variations in the *FTO* gene are associated with type 2 diabetes and obesity in South Indians (cures-79). *Diabetes Technol. Ther.* 2011, 13, 33–42. [CrossRef] [PubMed]

48. Han, X.; Luo, Y.; Ren, Q.; Zhang, X.; Wang, F.; Sun, X.; Zhou, X.; Ji, L. Implication of genetic variants near *SLC30A8, HHEX, CDKAL1*, *CDKN2A/B*, *IGF2BP2*, *FTO*, *TCF2*, *KCNQ1*, and *WFS1* in type 2 diabetes in a Chinese population. *BMC Med. Genet.* 2010, 11, 81. [CrossRef] [PubMed]

49. Wen, J.; Ronn, T.; Ohsson, A.; Yang, Z.; Lu, B.; Du, Y.; Groop, L.; Ling, C.; Hu, R. Investigation of type 2 diabetes risk alleles support *CDKN2A/B*, *CDKAL1*, and *TCF7L2* as susceptibility genes in a Han Chinese cohort. *PloS ONE* 2010, 5, e9153. [CrossRef] [PubMed]

50. Hu, C.; Zhang, R.; Wang, C.; Wang, J.; Ma, X.; Lu, J.; Qin, W.; Hou, X.; Wang, C.; Bao, Y.; et al. *PPARG*, *KCNJ11, CDKAL1*, *CDKN2A-CDKN2B, IDE-KIF11-HHEX*, *IGF2BP2*, and *SLC30A8* are associated with type 2 diabetes in a Chinese population. *PloS ONE* 2009, 4, e7643. [CrossRef] [PubMed]

51. Rong, R.; Hanson, R.L.; Ortiz, D.; Wiedrich, C.; Kobes, S.; Knowler, W.C.; Bogardus, C.; Baier, L.J. Association analysis of variation in *FTO, CDKAL1, SLC30A8, HHEX, EXT2, IGF2BP2, LOC387761,* and *CDKN2B* with type 2 diabetes and related quantitative traits in Pima Indians. *Diabetes* 2009, 58, 478–488. [CrossRef] [PubMed]

52. Lee, Y.H.; Kang, E.S.; Kim, S.H.; Han, S.J.; Kim, C.H.; Kim, H.J.; Ahn, C.W.; Cha, B.S.; Nam, M.; Nam, C.M.; et al. Association between polymorphisms in *SLC30A8, HHEX, CDKN2A/B, IGF2BP2, FTO, WFS1, CDKAL1, KCNQ1* and type 2 diabetes in the Korean population. *J. Hum. Genet.* 2008, 53, 991–998. [CrossRef] [PubMed]

53. Ng, M.C.Y.; Park, K.S.; Oh, B.; Tam, C.H.T.; Cho, Y.M.; Shin, H.D.; Lam, V.K.L.; Ma, R.C.W.; So, W.Y.; Cho, Y.S.; et al. Implication of genetic variants near *TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2*, and *FTO* in type 2 diabetes and obesity in 6719 Asians. *Diabetes 2008,* 57, 2226–2232. [CrossRef] [PubMed]

54. Scott, L.J.; Mohlke, K.L.; Bonnycastle, L.L.; Willer, C.J.; Han, S.J.; Moffatt, M.; Duren, W.L.; Stringham, H.M.; Chines, P.S.; Jackson, A.U.; et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 2007, 316, 1341–1345. [CrossRef] [PubMed]

55. Cauchi, S.; Ezzidi, I.; El Achhab, Y.; Mtiraoui, N.; Chaieb, L.; Salah, D.; Nejjari, C.; Labrune, Y.; Yengo, L.; Beury, D.; et al. European genetic variants associated with type 2 diabetes in North African Arabs. *Diabetes Metab.* 2012, 38, 316–323. [CrossRef] [PubMed]

56. Tobler, A.W.R. A computer movie simulation urban growth in Detroit region. *Econ. Geogr.* 1970, 46, 234–240.

57. Anselin, L. Local indicators of spatial association LISA. *Geogr. Anal.* 1995, 27, 93–115. [CrossRef]

58. Almawi, W.Y.; Nemr, R.; Keleshtian, S.H.; Echtay, A.; Saldanha, F.L.; AlDoseri, F.A.; Racoubian, E. A replication study of 19 GWAS-validated type 2 diabetes at-risk variants in the Lebanese population. *Diabetes Res. Clin. Pract.* 2013, 102, 117–122. [CrossRef] [PubMed]

59. Smemo, S.; Tena, J.J.; Kim, K.H.; Gamazon, E.R.; Sakabe, N.J.; Gomez-Marin, C.; Aneas, I.; Credidio, F.L.; Sobreira, D.R.; Wasserman, N.F.; et al. Obesity-associated variants within *FTO* form long-range functional connections with *IRX3*. *Nature* 2014, 507, 371–375. [CrossRef] [PubMed]
60. Bravard, A.; Vial, G.; Chauvin, M.A.; Rouille, Y.; Bailleul, B.; Vidal, H.; Rieusset, J. FTO contributes to hepatic metabolism regulation through regulation of leptin action and SAT3 signalling in liver. *Cell Commun. Signal.* **2014**, *12*, 4. [CrossRef] [PubMed]

61. Guo, F.; Zhang, Y.; Zhang, C.; Wang, S.; Ni, Y.; Zhao, R. Fatmass and obesity associated (FTO) gene regulates gluconeogenesis in chicken embryo fibroblast cells. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **2015**, *179*, 149–156. [CrossRef] [PubMed]

62. Mizuno, T.M.; Lew, P.S.; Luo, Y.; Leckstrom, A. Negative regulation of hepatic fat mass and obesity associated (Fto) gene expression by insulin. *Life Sci.* **2017**, *170*, 50–55. [CrossRef] [PubMed]

63. Speakman, J.R. FTO effect on energy demand versus food intake. *Nature* **2010**, *464*, E1. [CrossRef] [PubMed]

64. Cai, X.; Liu, C.; Mou, S. Association between fat mass- and obesity-associated (FTO) gene polymorphism and polycystic ovary syndrome: A meta-analysis. *PLoS ONE* **2014**, *9*, e86972. [CrossRef] [PubMed]

65. Li, G.; Chen, Q.; Wang, L.; Ke, D.; Yuan, Z. Association between FTO gene polymorphism and cancer risk: Evidence from 16,277 cases and 31,153 controls. *Tumour. Biol.* **2012**, *33*, 1237–1243. [CrossRef] [PubMed]

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