

2 型糖尿病易感候选基因在世界不同人群中的多样性比较分析

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摘要: 近 10 年来兴起的全基因组关联分析(Genome-wide association study, GWAS)相关研究结果获得了大量与 2 型糖尿病相关的候选易感基因, 了解这些候选基因在正常人群中的遗传多样性程度以及在不同人群间的遗传差异, 不但有助于阐明 2 型糖尿病的遗传机理, 而且对于今后在特定人群中进行 2 型糖尿病发病机制的深入研究具有指导意义。本研究通过对 GWAS 数据库和相关文献的搜索和整理确定了 170 个与 2 型糖尿病相关的基因或基因区域; 随后基于千人基因组计划的全基因组测序数据对这些候选基因在世界范围内 14 个人群间的遗传多样性进行了比较分析; 进一步确定了在人群间存在显著差异的易感基因, 并分析了这些基因的多样性特征。在所研究的 14 个世界人群中, 2 型糖尿病候选易感基因的遗传多样性与基因组范围的平均水平没有显著差异; 但其中 8 个易感基因 *IL20RA*、*RNMTL1-NXN*、*NOTCH2*、*ADRA2A-BTBD7P2*、*TBC1D4*、*RBM38-HMGB1P1*、*UBE2E2* 和 *PPARD* 在群体间呈现显著差异, 其中最明显的是 *IL20RA* 基因($F_{ST}=0.152$), 该易感基因在非洲人群和非非洲人群间存在显著等位基因频率和单倍型频率差异。14 个人群中易感基因遗传结构差异的主要原因是由于非洲人群与非非洲人群之间的群体遗传结构的不同所造成的。进一步比较东西方人群间的 2 型糖尿病候选基因遗传结构差异, 发现在东西方人群中同样存在明显的群体遗传结构差别, 其中 *DGKB-AGMO* ($F_{ST}=0.173$) 和 *JAZF1* ($F_{ST}=0.182$) 是差异最显著的易感基因。本研究通过对群体间 2 型糖尿病易感基因遗传结构进行比较, 鉴别出一些差异特别显著的易感基因, 对今后 2 型糖尿病易感基因与不同人群间发病率和易感性差异的相关研究提供重要参考。

关键词: 2 型糖尿病; 易感基因; 遗传多样性; 单核苷酸多态性; 世界人群

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A comparative analysis of genetic diversity of candidate genes associated with type 2 diabetes in worldwide populations

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Abstract: Over the last decade, a larger number of type 2 diabetes mellitus (T2DM) susceptible candidate genes have been reported by numerous genome-wide association studies (GWAS). Understanding the genetic diversity of these candidate genes among worldwide populations not only facilitates to elucidating the genetic mechanism of T2DM, but also provides guidance to further studies of pathogenesis of T2DM in any certain population. In this study, we identified 170 genes or genomic regions associated with T2DM by searching the GWAS databases and related literatures. We next analyzed the genetic diversity of these genes (or genomic regions) among present-day human populations by curating the 1000 Genomes Projects phase1 dataset covering 14 worldwide populations. We further compared the characteristics of T2DM genes in different populations. No significant differences of genetic diversity were observed among the 14 worldwide populations between the T2DM candidate genes and the non-T2DM genes in terms of overall pattern. However, we observed some genes, such as *IL20RA*, *RNMTL1-NXN*, *NOTCH2*, *ADRA2A-BTBD7P2*, *TBC1D4*, *RBM38-HMGB1P1*, *UBE2E2*, and *PPARD*, show considerable differentiation between populations. In particular, *IL20RA* ($F_{ST}=0.1521$) displays the greatest population difference which is mainly contributed by that between Africans and non-Africans. Moreover, we revealed genetic differences between East Asians and Europeans on some candidate genes such as *DGKB-AGMO* ($F_{ST}=0.173$) and *JAZF1* ($F_{ST}=0.182$). Our results indicate that some T2DM susceptible candidate genes harbor highly-differentiated variants between populations. These analyses, despite preliminary, should advance our understanding of the population difference of susceptibility to T2DM and provide insightful reference that future studies can rely on.

Keywords: type 2 diabetes mellitus; candidate gene; genetic diversity; single nucleotide polymorphism; worldwide populations

2 型糖尿病(Type 2 diabetes mellitus, T2DM)作为一种典型的多基因影响的代谢性疾病,其快速增长的全球患病率和并发症所带来的高死亡率已成为人类面临的医学难题^[1]。国际糖尿病联合会(The International Diabetes Federation, IDF)于 2015 年发布的最新全球糖尿病相关数据表明,目前全球共有 4.15 亿糖尿病患者,约占到世界人口总数的 5.7%,而到 2040 年全球糖尿病患者总数预计将达到 6.42 亿。虽然 T2DM 是全球面临的共同医学难题,但是其发病率在世界不同国家和人群之间存在较大的差异^[2]。目前还不清楚这种差异是否与人群遗传背景的差异有内在的关系。迄今通过不同人群的 2 型糖尿病全

基因组关联分析所得到的 T2DM 易感基因超过百个^[3]。本次研究主要通过对全球健康人群中 T2DM 易感基因的遗传多样进行研究,以揭示这些基因在人群中是否存在差异,并且探究了 T2DM 易感基因的遗传多样与人群发病率差异是否存在关联,这对于 T2DM 的遗传机制和发病机理研究有着重要的参考价值。

1 材料和方法

1.1 文献和数据库搜寻 T2DM 易感候选基因

本研究挑选的 T2DM 候选基因主要通过搜索 2015 年 8 月 15 日前收录于全球人类基因组关联分析数据库(National Human Genome Research Institute

GWAS Catalog Database^[4])中与 T2DM 相关的基因, 以及搜集 T2DM 基因关联分析研究的众多文献而获得。纳入研究的标准主要有: (1)研究结果正式发表于科学期刊, 且研究样本量超过百人以上; (2)候选基因与 T2DM 在关联分析中的相关性 $P\text{-value} < 1\text{E-}6$; (3)候选基因位置位于常染色体上。通过以上标准从相关数据库和 48 篇研究报道中一共获得 170 个与 T2DM 相关的基因或者基因区域。T2DM 易感基因及参考文献列表详见附表 1

1.2 14 个世界不同人群全基因组测序数据

研究使用的全基因组测序数据来自于 1000 Genomes Projects phase1^[5]。共有来自 14 个不同人群的 1028 个个体数据纳入研究, 其中包括 5 个欧洲人群: 美国犹他州的欧洲裔白种人 85 例(CEU), 意大利托斯卡纳人 98 例(TSI), 英格兰和苏格兰群岛白种人 89 例(GBR), 芬兰白种人 93 例(FIN)和西班牙伊比利亚人群 14 例(IBS); 3 个东亚人群: 中国北京汉族人群 97 例(CHB), 日本东京的日本人 89 例(JPT)和中国南方汉族人群 100 例(CHS); 3 个非洲人群: 尼日利亚的约鲁巴人 88 例(YRI), 科尼亚韦布耶人群 97 例(LWK)和美国西南地区的非洲裔美国人 61 例(ASW); 以及 3 个拉美人群: 美国加利福尼亚州墨西哥裔人群 66 例(MXL), 波多黎各人 55 例(PUR)和哥伦比亚中部哥伦比亚人 60 例(CLM)。通过过滤平均最小等位基因频率小于 0.01 的位点, 最终有 11 545 249 个单核苷酸多态性位点(SNP)纳入后续的研究分析。

1.3 群体遗传结构分析

本研究使用群体分化指数 F_{ST} 作为群体间遗传结构差异的量化工具进行比较。 F_{ST} 是通过比较群体间以及亚群体内部的杂合度来检测不同群体间分离程度的统计量, 其计算值范围为 0~1。 F_{ST} 值越大, 表明群体间分化程度越大, 群体间差异越大。本研究按照 Weir 等^[6]描述的无偏估计方法来计算每个 SNP 位点或区域的 F_{ST} 值。“离群值”(Outlier)是指与整体数据差距较大的一个或几个基因的 F_{ST} 值, 说明这些基因在群体间存在较大的群体遗传结构差别^[7]。由于数据分布类型的不同, 离群值统计策略会有所区别^[8]。由于计算的全基因组所有 SNP 的 F_{ST} 经验

分布在高差异区域产生了明显的拖尾现象, 分布类似于自由度为 2 或 3 的 χ^2 分布, 并且通过 R 软件中的 KS test 假设检验判断了该数据的分布类型^[9]。对于 χ^2 分布的数据, 实验采用 box plot 策略^[10]对于每条染色体确定 F_{ST} 上限离群值以及极限上离群值。大于上限离群值的 SNP 位点被视为“离群”位点, 表示在所研究的人群中该 SNP 位点的群体遗传结构差别较大。

1.4 单倍型多样性分析

单倍型多态性(Haplotype diversity)是常见的衡量遗传多样性的统计量, 反应出所关注区域出现的单倍型种类的多少^[11]。通过比较不同人群的单倍型多态性, 可以估计不同人群在单倍型上的差异^[12]。计算公式如下:

$$H_d = \frac{N}{N-1} \left(1 - \sum x_i^2 \right)$$

N 是指一共有多少种单倍型出现, x_i 是指每种单倍型出现的频率。本研究将全基因组以 2000 bp 为单位划分出不同的窗口, 并衡量每个人群的每个窗口的单倍型多样性, 最终得到不同人群全基因组单倍型多样性的分布。T2DM 候选基因或 SNP 所在窗口的单倍型多样性值即为这些区域或位点的多样性值。最后, 本研究将同一大洲的人群归为一组, 通过 ANOVA 方差分析进行群体间差异比较以及获得相应统计学 P 值。

2 结果与分析

2.1 世界不同人群全基因组 SNP 位点 F_{ST} 值分布

利用全基因组常染色体 11 545 249 个 SNP 位点, 计算得到 14 个人群每一个 SNP 位点的 F_{ST} 值。全基因组 F_{ST} 平均值为 0.025, 其分布范围是 0~0.85。利用 F_{ST} 衡量世界人群间群体遗传结构的差异, 构建了基因组 F_{ST} 经验分布图, 结果如图 1 所示。所研究的 170 个目的基因共包含 192 214 个 SNP 位点。

由图 1 所示, 全基因组 F_{ST} 经验分布类似于自由度为 2 或 3 的 χ^2 分布, 在群体遗传结构差异较大区域产生了明显的拖尾, 所以本文采用 Box plot 策略对于全基因组“离群”位点进行鉴定。全基因组 SNP 位点 F_{ST} 中位数为 0.0393, 经计算全基因组上限离群值为 0.1494。一共检测得到 698 108 个离群

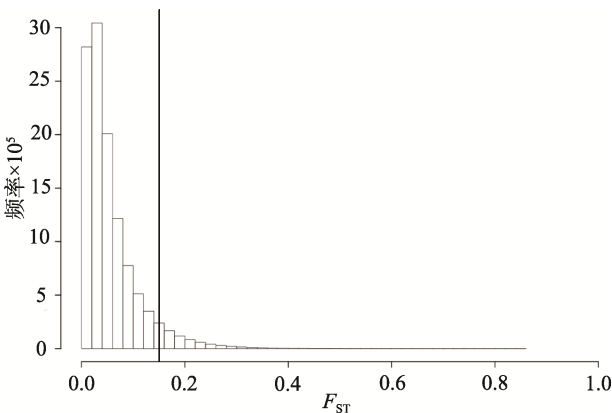


图 1 世界不同人群常染色体 SNP 位点 F_{ST} 经验分布图
Fig. 1 The empirical distribution of SNP F_{ST} of worldwide populations on autosomes
黑色竖线为上限“离群”值。

位点，占全基因组 SNP 位点的 6%。由于不同染色体之间的 SNP 位点总数差别较大，所以按照不同染

色体对于离群位点进行了统计，结果见表 1。

在本研究所关注的 170 个 T2DM 易感基因及基因区域内，共检测到 10 533 个“离群”SNP 位点，占总“离群”SNP 位点的 1.51%。其中 9 号染色体所检测到的 T2DM 易感基因“离群”位点的数目最多，占该染色体“离群”SNP 总数的 5.49%，远远高于其他染色体。在第 2、7、11、16 号染色体上同样检测出较高的 T2DM“离群”位点比例。

进一步使用置换检验从整体角度对 T2DM 基因所包含 SNP 位点的群体差异与非 T2DM SNP 进行比较，在全基因组范围内随机抽取 5000 次与 T2DM 易感基因 SNP 数目相同的位点，利用随机抽取 5000 组数据的中位数制作频数分布图(图 2)。T2DM 易感基因 SNP 位点 F_{ST} 中位数为 0.0391。发现相比于基因组非 T2DM 位点，T2DM 易感基因 SNP 位点的是一组群体差异较小 SNP 位点。

表 1 常染色体 F_{ST} “离群”位点统计表
Table 1 The number of autosomes loci F_{ST} greater than “outliers” cut-off value

染色体	上分界值	离群 SNP 总数	占总体 SNP 位点百分比	T2DM 位点数	占总离群位点百分比
1	0.1514	55 237	6.17%	187	0.34%
2	0.1528	60 268	6.24%	1515	2.51%
3	0.1516	49 714	6.05%	946	1.90%
4	0.1516	50 129	5.97%	131	0.26%
5	0.1452	45 534	6.11%	783	1.72%
6	0.1396	45 893	6.06%	893	1.95%
7	0.1455	40 718	5.99%	964	2.37%
8	0.1525	37 968	5.87%	286	0.75%
9	0.1472	31 283	6.25%	1719	5.49%
10	0.1472	34 525	5.95%	536	1.55%
11	0.1438	34 263	6.00%	774	2.26%
12	0.1491	33 869	6.10%	376	1.11%
13	0.1437	25 134	5.99%	266	1.06%
14	0.1498	22 385	5.86%	131	0.59%
15	0.1578	21 210	6.24%	148	0.70%
16	0.1516	21 069	5.81%	518	2.46%
17	0.1592	18 661	5.92%	24	0.13%
18	0.1454	18 373	5.56%	147	0.80%
19	0.1436	16 273	6.03%	55	0.34%
20	0.1522	16 613	6.42%	66	0.40%
21	0.1482	9687	5.92%	45	0.46%
22	0.1576	9302	5.76%	23	0.25%
合计	0.1494	698 108	6.01%	10 533	1.51%

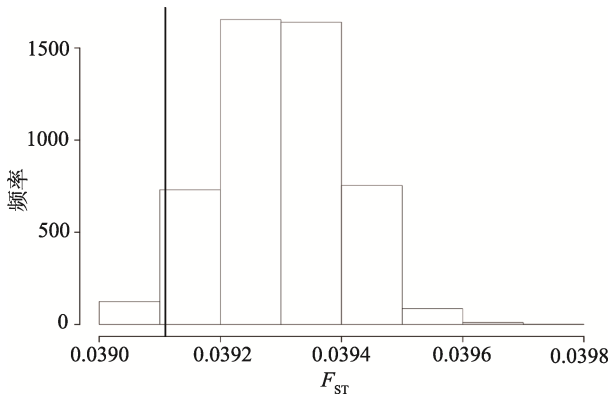


图2 T2DM 候选易感基因整体置换检验结果分布图

Fig. 2 The distribution of permutation test of the whole T2DM candidate genes

黑色竖线为 T2DM 基因中位数。

2.2 世界不同人群 T2DM 易感基因 F_{ST} 分布

以基因为单位, 比较 T2DM 易感基因在世界人群之间的群体遗传差别。利用窗口平移计算策略得到全基因组 24 719 个功能基因的 F_{ST} , 中位数为 0.0554, 分布范围是 0.2287(*SMA4*)~0(*ZNF658B*)。全基因组上限离群值为 0.1235。全基因组功能基因中共有 625 个基因在 14 个人群间 F_{ST} 超过上限离群值。

将挑选的 T2DM 易感基因 F_{ST} 值进行统计, 结果见表 2。在 170 个目的基因或基因区域中, 有 8 个 T2DM 易感基因的 F_{ST} 值大于全基因组上限离群值。其中差别最大的易感基因为 *IL20RA*^[13](Interleukin 20 receptor alpha, F_{ST} =0.1523)。进一步对差异基因的群体遗传结构进行比较, 发现差异基因是由于非洲人群与非非洲人群之间的等位基因频率不同造成的, 结果见表 3。

非洲人群在世界人群中 T2DM 发病率是最低的, 非洲大陆平均发病率仅有 3.2%^[2], 远远低于其他大陆人群。利用皮尔森相关分析(Pearson correlation analysis), 计算差异基因平均等位基因频率和发病率之间的相关性, 两者呈现显著的正相关性(P -value=0.012, Cor =0.65), 说明非洲人群在 T2DM 候选基因中存在独特的群体遗传结构, 可能会影响疾病的发生, 是造成非洲人群极低的 T2DM 发病率的最重要的遗传因素。

进一步对于差异基因的 GWAS 位点的单倍型频率进行比较, 发现前期找到的 8 个差异基因不仅在等位基因频率上存在显著地差异, 而且其中 6 个易

感基因在单倍型多样性上也存在明显差别, 结果见表 4。在 6 个存在单倍型差异的易感基因中, 按照群体地域间分组, 单倍型多态性在不同地区人群之间的差异较大。非洲人群的单倍型多态性是世界人群中最高的, 也证实 T2DM 候选基因在现代人群走出非洲后受到瓶颈效应等因素影响^[14]。值得注意的是, 某些基因在同一地区的不同群体之间的单倍型多样性也存在显著的差异。例如 *PPARD* 基因在拉美人群中遗传多样性差距显著, 这可能与人群混合和迁徙历史有着密切的关系。

2.3 东西方人群 T2DM 易感基因 F_{ST} 分布

在全球人群中, 非洲人群与非非洲人群间 T2DM 易感基因遗传结构差距十分显著, 但是东西方人群作为 T2DM 的主要患病人群^[15], 两种人群之间也可能存在遗传结构差异。由于前期实验并不能清晰地显示东西方人群间 T2DM 易感基因遗传结构区别, 因此下一步研究将会对欧洲人群和东亚人群之间 T2DM 易感基因的遗传结构差异进行比较。首先对于东西方人群的遗传差异计算, 同样采用 F_{ST} 作为量化工具进行研究。对千人基因组计划中的 8 个典型东西方人群进行分析, 其中包括 CEU、TSI、GBR、FIN、IBS、CHB、JPT 和 CHS。

在本文研究的东西方人群中, 东西方人群全基因组 24 719 个功能基因 F_{ST} 中位数是 0.0443, 分布范围是 0.257(*SLC45A2*)~0(*SMN2*), 上限离群值是 0.1283。全部功能基因中有 725 个基因大于上限离群值。所关注的 170 个 T2DM 基因中, 有 12 个基因(基因区域)大于上限离群值。东西方人群间差别最大的基因分别是 *DGKB-AGMO*^[16](F_{ST} =0.1731)和 *JAZF1*^[17,18](F_{ST} =0.1822), 结果详见表 4。说明在东西方人群中的确同样存在显著遗传差异的 T2DM 易感基因, 这些基因可能影响东西方人群 T2DM 的发病过程。

3 讨 论

T2DM 是目前世界上患病人数最多的代谢类疾病, 是继肿瘤、心脑血管疾病之后第三大严重威胁人类健康的慢性非传染性疾病, 具有高致死率、高致残率和高医疗花费的特征, 并成为当前世界各国共同面对的公共健康问题^[19]。但是 T2DM 具体的发

表 2 世界不同人群 2 型糖尿病候选基因 F_{ST} 计算结果
Table 2 T2DM candidate gene F_{ST} between the worldwide populations

染色体	起始位置	终止位置	rsID	基因位置	基因	F_{ST-14}	F_{ST-8}	P 值	OR (95% CI)	GWAS 研究人群
1	50906934	51425936	rs17106184	50909985	<i>FAF1</i>	0.0754	0.0573	4.00E-09	1.11 (1.07-1.16)	EUR, EA, SA
1	92145899	92371559	rs111165354	92194322	<i>TGFBR3</i>	0.0836	0.1222	4.00E-06	1.20 (1.11-1.29)	SA
1	94994731	95139725	rs7542900	95070041	<i>F3-PGBD4P7</i>	0.0786	0.0669	6.00E-06	1.16 (1.09-1.25)	AA
1	120454175	120612317	rs10923931	120517959	<i>NOTCH2</i>	0.1420	0.0292	4.00E-08	1.13 (1.08-1.17)	EUR
1	207627644	207663240	rs17045328	207652176	<i>CR2</i>	0.0507	0.0578	7.00E-06	1.38 (1.20-1.59)	SEA
1	214141277	214214847	rs2075423	214154719	<i>PROX1</i>	0.0502	0.0439	2.00E-06	1.07 (1.04-1.10)	SEA
1	214098091	214214847	rs340874	214159256	<i>LINC00538-PROX1</i>	0.0740	0.0450	7.20E-10	1.07 (1.05-1.09)	EUR
1	219347172	219800000	rs2820446	219748818	<i>LYPLAL1</i>	0.0731	0.0758	2.30E-06	1.06 (1.04-1.09)	EUR, EA, SA, ME
1	228870823	228882416	rs6426514	228880115	<i>RHOJ</i>	0.0488	0.0187	2.00E-06	1.51 (1.27-1.59)	PS
1	233119881	233431459	rs12027542	233340154	<i>PCNXL2</i>	0.0773	0.0491	4.00E-07	1.41 (1.23-1.61)	SEA
2	640000	677439	rs10190052	646674	<i>TMEM18</i>	0.0341	0.0340	2.00E-07	1.06 (1.04-1.08)	EUR, EA, SA, ME
2	3751181	3895000	rs11677370	3841420	<i>DCDC2C</i>	0.0707	0.0686	3.00E-06	1.35 (1.19-1.53)	SEA
2	27719470	27746556	rs780094	27741237	<i>GCKR</i>	0.0437	0.0312	1.30E-09	1.19 (1.11-1.29), 1.06 (1.04-1.08)	SA, EUR
2	43457975	43823113	rs7578597	43732823	<i>THADA</i>	0.0926	0.0867	1.00E-09	1.15 (1.06-1.12)	EUR
2	60500000	60780633	rs243088	60568745	<i>BCL11A</i>	0.0924	0.1225	2.30E-06	1.03 (0.89-1.20)	EUR, EA, SA, ME
2	58747888	60614580	rs243021	60584819	<i>FLJ30838-MIR4432</i>	0.1196	0.1470	3.00E-15	1.08 (1.06-1.10)	EUR
2	105654482	105859924	rs6712932	105837598	<i>MRPS9-GPR45</i>	0.0502	0.0775	6.00E-06	0.66 (0.55-0.79)	EUR
2	135213329	135615443	rs6723108	135479980	<i>TMEM163-MIR5590</i>	0.0892	0.1149	2.70E-09	1.66 (1.41-1.96)	EUR
2	151324709	152042675	rs7560163	151637936	<i>RND3-FABP5P10</i>	0.0694	0.0655	7.00E-09	1.33 (1.19-1.49)	AA
2	161128661	161350318	rs7593730	161171454	<i>RBMS1</i>	0.0556	0.0530	4.00E-08	1.11 (1.06-1.16), 0.90 (0.86-0.93)	EUR
2	165430250	165544287	rs3923113	165501849	<i>EIF3EP3-SNORA70F</i>	0.0866	0.1448	1.00E-08	1.19 (1.11-1.29), 1.09 (1.06-1.13)	SA
2	165349322	165698678	rs13389219	165528876	<i>GRB14-COBL1</i>	0.0881	0.1042	1.00E-08	1.07 (1.05-1.10)	EUR
2	169757749	169766510	rs560887	169763148	<i>G6PC2</i>	0.0616	0.0528	8.50E-122	NR	EUR
2	227007509	227044778	rs7578326	227020653	<i>LOC646736</i>	0.0809	0.0461	5.00E-20	1.11 (1.08-1.13)	EUR
2	226896033	227663506	rs2943640	227093585	<i>IRSI</i>	0.1225	0.1458	7.00E-09	1.09 (1.05-1.13)	EUR
2	226265601	227523509	rs2943641	227093745	<i>NYAP2-MIR5702</i>	0.1225	0.1458	9.00E-12	1.19 (1.13-1.25)	EUR
2	230222344	230579286	rs1861612	230522398	<i>DNER</i>	0.0837	0.0833	7.00E-08	1.29(NR)	India
3	12045833	12299981	rs13081389	12289800	<i>SYN2-GSTM5P1</i>	0.0826	0.0604	2.00E-07	1.15 (1.10-1.21)	EUR

续表 2

染色体	起始位置	终止位置	rsID	基因位置	基因	F_{ST-14}	F_{ST-8}	P 值	OR (95% CI)	GWAS 研究人群
3	12329348	12475855	rs1801282	12393125	<i>PP4RG</i>	0.1034	0.0530	2.00E-06	1.16 (1.10–1.23), 1.14 (1.08–1.20), 1.14 (1.08–1.20)	EUR, EA
3	23198000	23632296	rs6780569	23198484	<i>UBE2E2</i>	0.1251	0.0480	4.37E-09	1.18 (1.12–1.25)	EA
3	54952380	55515426	rs358806	55313400	<i>LRTM1-WNT3A</i>	0.0871	0.0997	3.00E-06	0.86 (0.75–0.97)	EUR
3	63996224	64088807	rs831571	64048297	<i>PSMD6; PRICKLE2-AS1</i>	0.0968	0.0380	8.00E-11	1.09 (1.06–1.12)	EA
3	64670545	64997143	rs4607103	64711904	<i>ADAMTS9-AS2</i>	0.0775	0.1109	1.00E-08	1.09 (1.06–1.12)	EUR
3	102153858	102960078	rs2063640	102203045	<i>ZPLD1-NDUFA4P2</i>	0.0800	0.0536	3.00E-06	1.23 (1.13–1.34)	SEA
3	123001142	123135189	rs11717195	123082398	<i>ADCY5</i>	0.0779	0.0956	2.00E-08	1.15 (0.98–1.36)	EUR, EA, SA, ME
3	142375738	142432505	rs3773506	142431000	<i>PLS1</i>	0.0512	0.0389	9.00E-06	1.81 (1.39–2.35)	India
3	170714136	170744768	rs11920090	170717521	<i>SLC2A2</i>	0.0571	0.0248	8.00E-13	1.01 (0.99–1.04)	EUR
3	179512746	179692008	rs7630877	179661318	<i>PEX5L</i>	0.0643	0.0817	7.00E-06	1.32 (1.17–1.49)	SEA
3	185361526	185542827	rs1374910	185531661	<i>IGF2BP2</i>	0.0517	0.0344	9.00E-16	1.13 (1.09–1.17), 1.12 (1.07–1.18), 1.14 (1.11–1.18)	EUR, EA
3	186648314	186796341	rs16861329	186666461	<i>ST6GAL1</i>	0.0803	0.0721	3.80E-08	1.09 (1.06–1.12)	SA
3	187780000	188608460	rs16862964	187792711	<i>LPP</i>	0.1032	0.1359	6.00E-09	1.07 (1.04–1.09)	EUR, EA, SA
4	1243228	1333936	rs7656416	1254535	<i>CTBP1-AS1; MAEA</i>	0.0611	0.0872	1.00E-08	1.15 (1.1021.21)	EA
4	1303230	1333936	rs6815464	1309901	<i>MAEA</i>	0.0611	0.0808	2.00E-20	1.13 (1.10–1.16)	EA
4	6270000	6304992	rs4689388	6270056	<i>WFS1</i>	0.0834	0.0569	2.00E-09	1.09 (1.06–1.13)	EUR
4	46911252	46970000	rs2055942	46968050	<i>GABRA4-COX7B2</i>	0.0284	0.0208	1.00E-06	NR	Arab
4	122589151	122686340	rs7659604	122665514	<i>ANX45-TMEM155</i>	0.0950	0.0450	9.00E-06	1.35 (1.19–1.54)	EUR
4	153520000	153601317	rs6813195	153520475	<i>TMEM154</i>	0.0944	0.0261	4.00E-14	1.08 (1.05–1.11)	EUR, EA
4	164445449	164534776	rs3792615	164532801	<i>MARCH1</i>	0.0732	0.0365	9.00E-06	1.93 (1.45–2.59)	India
5	53180613	53606403	rs702634	53271420	<i>ARL15</i>	0.0899	0.1289	7.00E-09	1.06 (1.04–1.09)	EUR, EA, SA
5	55395506	56191978	rs459193	55806751	<i>ANKRD55-MAP3K1</i>	0.0938	0.1063	6.00E-09	1.08 (1.05–1.11)	EUR
5	56100899	56191978	rs10461617	56104308	<i>RPL26P19-MAP3K1</i>	0.0485	0.0797	4.00E-06	1.20 (1.11–1.29)	SA, EUR
5	76382622	76444176	rs4457053	76424949	<i>ZBED3-AS1</i>	0.0843	0.0855	3.00E-12	1.08 (1.06–1.11)	EUR
5	89312437	89705603	rs12518099	89546109	<i>MIR3660-CETN3</i>	0.1170	0.0351	7.00E-07	1.16 (1.10–1.22)	EUR
5	123972609	124180805	rs6595551	124139895	<i>ZNF608</i>	0.0618	0.0590	6.00E-06	2.63 (1.72–4.01)	EA
5	154870705	156194798	rs170533082	155394230	<i>PP1GPI-SGCD</i>	0.0954	0.1034	4.00E-07	1.49 (1.28–1.73)	India
6	4142000	4146332	rs3916765	4142696	<i>LOC102725019; HLA-DQA2</i>	0.0819	0.0545	1.00E-06	1.3 [1.19–1.42]	EUR

续表 2

染色体	起始位置	终止位置	rsID	基因位置	基因	F_{ST-14}	F_{ST-8}	P 值	OR (95% CI)	GWAS 研究人群
6	7252213	7281375	rs9502570	7258617	<i>SSRI-RREB1</i>	0.0504	0.0602	1.00E-09	1.09 (1.04-1.14)	EUR, EA, SA
6	20534687	21232634	rs9465871	20717255	<i>CDK4L1</i>	0.0713	0.0795	7.00E-20	1.20 (1.14-1.26), 1.38 (1.25-1.52)	EUR, EA
6	31132114	31138451	rs3130501	31136453	<i>POU5F1</i>	0.0208	0.0237	4.20E-09	1.07 (1.04-1.09)	EUR, EA, SA
6	35310334	35395968	rs7744392	35322763	<i>PP4RD</i>	0.1251	0.0521	3.00E-06	NR	EA
6	37787306	38122399	rs9470794	38106844	<i>ZFAND3</i>	0.0632	0.0691	2.00E-10	1.12 (1.08-1.16)	EA
6	39282236	39285000	rs1535500	39284050	<i>KCNK16-KCNK17</i>	0.0398	0.0141	2.00E-08	1.13 (1.08-1.19), 1.08 (1.05-1.11)	EA
6	43737945	43973694	rs9472138	43811762	<i>VEGFA-C6orf223</i>	0.0900	0.0608	4.00E-06	1.06 (1.04-1.09)	EUR
6	71276624	71298606	rs1048886	71289189	<i>C6orf57</i>	0.1027	0.0335	3.00E-08	1.26 (1.14-1.39)	India
6	126660934	127000000	rs4273712	126964510	<i>C6orf173 (CENPW)</i>	0.0983	0.1133	3.00E-06	1.07 (1.04-1.10)	EUR
6	133138357	133189998	rs7769051	133146796	<i>SNORA33-HMGB1P13</i>	0.0588	0.0421	2.00E-06	1.28 (1.16-1.42)	AA
6	137221108	137366317	rs6937795	137291281	<i>IL20RA</i>	0.1523	0.0422	7.00E-06	1.06 (1.03-1.09)	EUR
6	139935578	140526463	rs642858	140273647	<i>ATP5F1P6-MIR3668</i>	0.0612	0.0848	2.00E-06	1.35 (1.19-1.53)	India
6	148663728	148873184	rs6930576	148704954	<i>SASH1</i>	0.0536	0.0615	7.00E-07	1.31 (1.18-1.45)	AA
7	13900000	14030327	rs7795991	13900731	<i>ETV1</i>	0.0442	0.0516	7.00E-07	1.05 (1.03-1.07)	EA
7	14184673	15601640	rs2191349	15064309	<i>DGKB-AGMO</i>	0.1123	0.1731	1.10E-08	1.06 (1.04-1.08)	EUR
7	16889636	16890425	rs1525739	16889812	<i>LOC100287613</i>	0.0641	0.0520	6.00E-06	NR	EUR
7	27870192	28220437	rs849135	28196413	<i>JAZF1</i>	0.1095	0.1822	5.00E-14	1.10 (1.07-1.13)	EUR
7	30691558	30739719	rs2284219	30714436	<i>CRHR2</i>	0.0780	0.0662	8.00E-06	1.05 (1.03-1.08)	EUR
7	36892510	37025871	rs741301	36917995	<i>ELMO1</i>	0.0452	0.0347	8.00E-06	2.67 (1.71-4.16)	EA
7	44183870	44253893	rs4607517	44235668	<i>GCK-YKT6</i>	0.0497	0.0321	5.00E-08	1.07 (1.05-1.10)	EUR
7	100487614	100493592	rs7636	100490077	<i>ACHE</i>	0.0650	0.0483	5.00E-06	1.85 (1.42-2.41)	EA
7	127010353	127225654	rs6467136	127164958	<i>ZNF800-GCCI</i>	0.0782	0.0705	5.00E-11	1.11 (1.07-1.14)	EA
7	127233688	127255780	rs10229583	127246903	<i>FSCN3-P4X4</i>	0.0782	0.0705	2.00E-10	1.14 (1.09, 1.19)	EA
7	127812802	127897682	rs791595	127862802	<i>MIR129-LEP</i>	0.0773	0.0461	3.00E-13	1.17 (1.12-1.22)	EA
7	130417381	130561569	rs972283	130466854	<i>KLF14-MIR294</i>	0.0531	0.0258	2.00E-10	1.07 (1.05-1.10)	EUR
8	21549529	21771205	rs17428041	21711431	<i>GFR2-DOK2</i>	0.0973	0.0833	2.00E-07	0.67 (NR)	EUR
8	41510743	41522804	rs516946	41519248	<i>ANK1</i>	0.0290	0.0158	2.50E-10	1.10 (1.06-1.15), 1.09 (1.06-1.12)	EUR
8	95938199	95961615	rs896854	95960511	<i>TP53INP1</i>	0.0423	0.0139	1.00E-09	1.06 (1.04-1.09)	EUR
8	118147336	118188953	rs11558471	118185733	<i>SLC30A8</i>	0.0618	0.0517	2.00E-14	1.15 (1.10-1.21)	EUR

续表 2

染色体	起始位置	终止位置	rsID	基因位置	基因	$F_{ST}-14$	$F_{ST}-8$	P 值	OR (95% CI)	GWAS 研究人群
8	128958804	129598078	rs1561927	129568078	TMEM75	0.0805	0.1076	1.00E-07	1.06 (1.04–1.09)	EA
8	134048972	134243932	rs4527850	134196849	SLA- <i>WISPI</i>	0.0870	0.1095	2.00E-06	1.23 (1.13–1.34)	PS
9	3824127	4294000	rs10814916	4293150	GLIS3	0.0832	0.0798	2.00E-14	1.10 (1.07–1.13)	EA
9	8314245	10612723	rs649891	10430602	PTPRD	0.1170	0.1567	9.00E-10	1.57 (1.36–1.82)	EA
9	21994789	22452472	rs7018475	22137685	CDKN2B- <i>AS1:DMRTA1</i>	0.1165	0.1017	7.80E-15	1.18 (1.13–1.24), 1.25 (1.17–1.32)	EUR, EA
9	27948083	29212998	rs824248	28772700	LINGO2	0.0747	0.0686	8.00E-06	1.18 (1.07–1.26)	MEXICAL
9	81905000	82341796	rs17791513	81905590	TLE4	0.0804	0.0339	3.00E-08	1.21 (1.13–1.31)	EUR
9	81651269	82006955	rs13292136	81952128	KRT18P24- <i>CHCHD2P9</i>	0.0975	0.1190	2.80E-08	1.11 (1.07–1.15)	EUR
9	84198597	84534842	rs2796441	84308948	TLE1- <i>FAM75D5</i>	0.1021	0.1252	5.40E-09	1.07 (1.05–1.10)	EUR
9	93589701	94124206	rs773506	93975471	SYK- <i>AUH</i>	0.0796	0.0918	6.00E-06	1.32 (1.18–1.49)	AA
9	112403067	112713756	rs1327796	112526289	PALM2	0.0726	0.0701	3.00E-06	1.13 (1.08–1.20)	EA
9	113127528	113489959	rs10980508	113419759	SVEP1- <i>RPS21P5</i>	0.0693	0.0844	1.00E-06	NR	ME
9	139249251	139254057	rs11787792	139252148	GP5M1	0.0447	0.0305	2.00E-10	1.15 (1.10–1.20)	EA
10	12237960	12620822	rs12779790	12328010	CDC123- <i>MIR4480</i>	0.0803	0.0706	1.00E-08	1.13 (1.08–1.18)	EA, EUR
10	70883907	70932616	rs1802295	70931474	VPS26A	0.0539	0.0530	4.00E-08	1.08 (1.05–1.12)	SA
10	71390002	71500000	rs2812533	71452285	C10orf35	0.0483	0.0644	5.00E-06	1.07 (1.04–1.09)	EA
10	80828791	81076285	rs12571751	80942631	ZMIZ1	0.0798	0.0779	1.00E-10	1.09 (1.06–1.13), 1.08 (1.05–1.10)	EUR
10	89623194	89778532	rs10788575	89768584	PTEN	0.0299	0.0261	9.00E-06	1.06 (1.03–1.08)	EA
10	94211440	94356609	rs6583826	94347830	IDE- <i>RPL11P4</i>	0.0704	0.0401	7.00E-06	1.18 (1.10–1.27)	SEA
10	94449680	94819251	rs5015480	94465559	HHEX- <i>EXOC6</i>	0.0946	0.0988	1.20E-14	1.15 (1.11–1.19), 1.13 (1.09–1.17)	EUR, EA
10	112836789	113083160	rs10885122	113042093	ADRA24- <i>BTBD7P2</i>	0.1340	0.0760	3.00E-16	1.04 (1.01–1.07)	EUR
10	114710008	114927436	rs11196205	114807047	TCF7L2	0.0902	0.1250	2.00E-51	1.40 (1.35–1.46), 1.25 (1.19–1.32), 1.40 (1.34–1.46), 1.37 (1.31–1.43)	EUR, EA, SA, AA
10	120967196	121215131	rs10886471	121149403	GRK5	0.0741	0.0551	7.00E-09	1.12 (1.08–1.16)	EA
10	124151818	124195000	rs10510110	124192430	PLEKHA1	0.0472	0.0360	1.00E-07	1.05 (1.03–1.07)	EA
10	132890654	133109984	rs10741243	132947962	TCERG1L	0.0654	0.0765	5.00E-06	1.75 (1.38–2.23)	India
11	2482683	2870340	rs2237897	2858546	KCNQ1	0.0904	0.1073	2.00E-42	1.26 (1.14–1.40), 1.42 (1.34–1.49)	EA, EUR
11	11203355	11261722	rs2722769	11228374	HMGV1P22- <i>MTNDS2P1</i>	0.0565	0.0620	2.00E-06	1.35 (1.19–1.54)	AA
11	17406795	17410206	rs5219	17409572	KCNJ11	0.0725	0.0215	5.00E-11	1.14 (1.09–1.20), 1.14 (1.10–1.19)	EUR, EA
11	41557675	43290919	rs9300039	41915366	RPLP23- <i>HNRNPKP3</i>	0.1208	0.1427	6.00E-08	1.25 (1.15–1.37)	EUR

续表 2

染色体	起始位置	终止位置	rsID	基因位置	基因	$F_{ST} - 14$	$F_{ST} - 8$	P 值	OR (95% CI)	GWAS 研究人群
11	45868668	45904799	rs111605924	45873091	<i>CRY2</i>	0.0622	0.0970	1.00E-14	1.04 (1.02-1.06)	EUR
11	47290926	47351582	rs79444584	47336320	<i>MADD</i>	0.0591	0.0655	2.00E-18	1.01 (0.99-1.03)	EUR
11	61567096	61584529	rs174550	61571478	<i>FADS1</i>	0.0427	0.0257	2.00E-15	1.04 (1.02-1.06)	EUR
11	72396113	72433403	rs1552224	72433098	<i>ARAP1</i>	0.0389	0.0494	1.00E-22	1.13 (1.08-1.19), 1.14(1.11-1.17)	EUR
11	92085261	92715948	rs1387153	92673828	<i>FAT3-MTNR1B</i>	0.0933	0.0581	8.00E-15	1.09 (1.06-1.11)	EUR
11	92702788	92715948	rs10830963	92708710	<i>MTNR1B</i>	0.0551	0.0476	8.00E-13	1.11 (1.06-1.16), 1.09 (1.06-1.12)	EUR
11	108093558	108300000	rs11212617	108283161	<i>ATM-C11orf65</i>	0.0363	0.0218	3.00E-09	1.35 (1.22-1.49)	EUR
11	129407732	129729898	rs7107217	129473690	<i>RPS27P20-TMEM45B</i>	0.0843	0.0652	3.00E-07	1.18 (1.10-1.27)	AA
12	51347781	51364289	rs12304921	51357542	<i>HIGD1C</i>	0.0465	0.0741	7.00E-06	2.50 (1.53-4.09)	EUR
12	55038374	55197407	rs1153188	55098996	<i>DCD-VDAC1P5</i>	0.0698	0.0907	2.00E-07	1.08 (1.05-1.11)	EUR
12	66111799	66220754	rs2358944	66117558	<i>PCNPP3-RPSAP52</i>	0.1086	0.1242	4.00E-06	1.08 (1.05-1.11)	AA
12	66151799	66220754	rs1531343	66174894	<i>RPSAP52</i>	0.1086	0.0509	3.60E-09	1.10 (1.07-1.14)	EUR
12	66212000	66309307	rs2261181	66212318	<i>HMG42</i>	0.1086	0.0216	4.00E-08	1.16 (1.10-1.23)	EUR
12	71518876	71980088	rs7961581	71663102	<i>TSPAN8-LGR5</i>	0.0922	0.1154	7.00E-06	1.28 (1.11-1.49)	EUR
12	102811453	102876000	rs35767	102875569	<i>IGF1</i>	0.0408	0.0500	3.00E-08	1.04 (1.01-1.07)	EUR
12	121401640	121410095	rs7305618	121402932	<i>RPL12P33; HNF1A-AS1</i>	0.0443	0.0316	2.00E-08	1.16 (1.08-1.24)	HIS
12	121416548	121440314	rs12427353	121426901	<i>HNF1A</i>	0.0443	0.0512	4.00E-06	1.12 (1.07-1.18)	EUR
12	121458094	121477045	rs7957197	121460686	<i>OASL</i>	0.0373	0.0604	2.40E-08	1.07 (1.05-1.10)	EUR
12	123640042	123717785	rs1727313	123640853	<i>MPHOSPH9</i>	0.1185	0.0509	1.00E-08	1.06 (1.04-1.08)	EUR, EA, SA
13	23755059	23899304	rs9552911	23864657	<i>SGCG</i>	0.0776	0.0669	2.00E-08	0.67 (0.58-0.77)	PS
13	26780904	26796028	rs10507349	26781528	<i>RNF6</i>	0.0503	0.0313	2.00E-07	1.06 (1.04-1.08)	EA
13	75858799	76056250	rs61736969	7589521	<i>TBC1D4</i>	0.1316	0.0949	1.60E-24	NR	EUR
13	76445174	76857948	rs1929752	76812217	<i>FLJ33379</i>	0.0472	0.0668	3.10E-06	1.17 (1.10-1.25)	SA, EUR
13	80055258	80915086	rs1359790	80717156	<i>NDFIP2-SPRY2</i>	0.0680	0.0647	6.00E-09	1.10 (1.05-1.14), 1.15 (1.10-1.20)	EUR, EA
14	101003483	101201467	rs730570	101142890	<i>BEGAIN-DLK1</i>	0.1051	0.1422	8.00E-06	1.21 (1.12-1.31)	HIS, EUR
15	38780301	38857007	rs7403531	38822905	<i>RASGRP1</i>	0.0769	0.0532	4.00E-09	1.10 (1.06-1.13)	EA
15	62359175	62457482	rs111071657	62433962	<i>C2CD4A-C2CD4B</i>	0.0536	0.0528	9.00E-14	1.13 (1.09-1.18)	EA
15	77713242	77777945	rs7119	77777632	<i>HMG20A</i>	0.0218	0.0233	7.00E-11	1.09 (1.06-1.12), 1.14 (1.09-1.19)	SA, EUR
15	77713242	77924869	rs7177055	77832762	<i>HMG20A-LINGO1</i>	0.0757	0.0323	4.60E-09	1.08 (1.05-1.10)	EUR

续表 2

染色体	起始位置	终止位置	rsID	基因位置	基因	F_{ST-14}	F_{ST-8}	P 值	OR (95% CI)	GWAS 研究人群
15	80351909	80478924	rs11634397	80432222	<i>ZFAND6-FAH</i>	0.0718	0.1181	2.00E-09	1.06 (1.04–1.08)	EUR
15	90373830	90456222	rs2028299	90374257	<i>AP3S2; C15orf38-AP3S2</i>	0.0539	0.0523	1.90E-11	1.10 (1.07–1.13)	SA
15	91509267	91557881	rs12899811	91544076	<i>PRC1</i>	0.1064	0.1594	6.00E-07	1.09 (1.04–1.13)	EA
16	24741048	24837547	rs17177078	24810681	<i>TNRC6A</i>	0.0566	0.0717	5.00E-06	NR	EUR
16	53737874	54148379	rs11642841	53845487	<i>FTO</i>	0.0858	0.1010	1.30E-12	1.17 (1.12–1.22)	EUR, SA
16	57546089	57570477	rs8052123	57563671	<i>CCDC102A</i>	0.0645	0.0560	5.00E-06	1.06 (1.04–1.08)	EA
16	75237993	75258822	rs7202877	75247245	<i>CTRB2-CTRBI</i>	0.0488	0.0401	3.50E-08	1.12 (1.07–1.16)	EUR
16	78859149	79634622	rs17797882	79406918	<i>RPS3P7-MAF</i>	0.1045	0.1227	9.00E-07	1.08 (1.05–1.12)	EA
16	81478774	81745367	rs16955379	81489373	<i>CMIP</i>	0.0677	0.0600	3.00E-07	1.08 (1.05–1.12)	EA
17	685512	767351	rs623323	700020	<i>RNMTL1-NXXN</i>	0.1454	0.0706	4.00E-06	1.28 (1.15–1.42)	SA
17	2207247	2228553	rs391300	2216258	<i>SRR</i>	0.0777	0.0799	3.00E-09	1.28 (1.18–1.39)	EA
17	6939393	6943440	rs312457	6940393	<i>SLC16A13</i>	0.0580	0.0384	8.00E-13	1.20 (1.14–1.26)	EA
17	6943440	6947242	rs75493593	6945087	<i>SLC16A11-SLC16A13</i>	0.0483	0.0384	5.00E-15	1.25 (1.18–1.23)	MEXICAL
17	36046433	36105096	rs4430796	36098040	<i>HNF1B</i>	0.1068	0.0355	2.00E-11	1.13 (1.07–1.09), 1.19 (1.13–1.25)	EUR, EA
18	2916991	2949000	rs10460009	2948029	<i>LPIN2-LOC727896</i>	0.0607	0.0806	9.00E-06	1.35 (1.18–1.54)	SA
18	6941742	7117813	rs8090011	7068462	<i>LAMA1</i>	0.1180	0.0687	8.00E-09	1.22 (1.12–1.3)	EUR
18	57838564	58040001	rs12970134	57884750	<i>MC4R</i>	0.0579	0.0617	1.20E-08	1.08 (1.05–1.11)	EUR
19	19349057	19657468	rs10401969	19407718	<i>CILP2</i>	0.0554	0.0318	7.00E-09	1.13 (1.09–1.18)	EUR
19	33877854	34012799	rs3786897	33893008	<i>PEPD</i>	0.0804	0.0484	3.50E-07	1.17 (1.10–1.24), 1.10 (1.07–1.14)	EA
19	39574944	39602128	rs472265	39580737	<i>PAPL</i>	0.0641	0.0183	9.00E-06	1.39 (1.20–1.61)	India
19	46150000	46185717	rs8108269	46158513	<i>GIPR</i>	0.0565	0.0773	5.00E-06	1.06 [1.02–1.11]	EUR
20	42935196	42979432	rs6017317	42946966	<i>FITM2-R3HDM1</i>	0.0479	0.0622	1.00E-11	1.09 (1.07–1.12)	EA
20	42984441	43053276	rs4812829	42989267	<i>HNF4A</i>	0.0573	0.0791	3.00E-10	1.13 (1.08–1.19), 1.09 (1.06–1.12)	SA
20	55966453	56084386	rs328506	56029604	<i>RBM38-HMGB1P1</i>	0.1261	0.0858	2.00E-06	1.11 (1.06–1.15)	PS
21	33245627	33651376	rs2833610	33385186	<i>HUNK-MIS18A</i>	0.0899	0.0850	4.00E-06	1.17 (1.09–1.24)	SA
22	31644347	31673624	rs2106294	31645759	<i>L1MK2</i>	0.0654	0.1098	4.00E-06	1.75 (1.39–2.22)	AA
22	44220386	44258378	rs470089	44248504	<i>SULT4A1</i>	0.0395	0.0414	9.00E-06	NR	EUR

F_{ST-14} : 目的基因在 14 个人群的 F_{ST} 计算结果; F_{ST-8} : 目的基因在东西方 8 个人群 F_{ST} 计算结果; EUR: 欧洲人群; SA: 南亚人群; EA: 东亚人群; India: 印度人群; PS: 旁遮普族人群; MEXICAL: 墨西哥人群; HIS: 西班牙人群; AA: 美国黑人; Arab: 阿拉伯人

表 3 世界人群 T2DM 差异基因平均等位基因频率分布
Table 3 Distribution of mean allele frequency of T2DM differential gene in the world populations

差异基因	人群														F_{ST}
	CEU	TSI	GBR	FIN	IBS	CHB	JPT	CHS	YRI	LWK	ASW	MXL	PUR	CLM	
<i>IL20RA</i>	0.379	0.380	0.354	0.368	0.357	0.433	0.452	0.418	0.878	0.830	0.779	0.402	0.414	0.408	0.1523
<i>RNMTL1-NXN</i>	0.881	0.879	0.865	0.862	0.871	0.832	0.850	0.848	0.505	0.540	0.582	0.849	0.835	0.840	0.1454
<i>NOTCH2</i>	0.787	0.778	0.756	0.749	0.805	0.813	0.813	0.799	0.530	0.514	0.593	0.748	0.727	0.757	0.1420
<i>ADRA2A-BTBD7P2</i>	0.515	0.510	0.508	0.508	0.500	0.500	0.500	0.500	0.830	0.791	0.734	0.545	0.527	0.533	0.1340
<i>TBC1D4</i>	0.591	0.615	0.573	0.538	0.536	0.526	0.508	0.505	0.915	0.905	0.852	0.602	0.659	0.592	0.1316
<i>RBM38-HMGB1P1</i>	0.971	0.969	0.972	0.973	0.946	0.925	0.927	0.938	0.616	0.637	0.693	0.947	0.914	0.958	0.1261
<i>UBE2E2</i>	0.653	0.689	0.699	0.669	0.607	0.626	0.694	0.653	0.196	0.250	0.279	0.795	0.605	0.683	0.1251
<i>PPARD</i>	0.974	0.954	0.978	0.987	0.893	0.964	0.983	0.990	0.565	0.552	0.684	0.951	0.859	0.942	0.1251
人群患病率(%)	0.108	0.051	0.047	0.06	0.077	0.098	0.057	0.098	0.023	0.024	0.038	0.158	0.121	0.1	~

注：同一底纹代表同一大陆人群。

表 4 世界群体间差异基因单倍型多样性统计表
Table 4 Haplotype diversity of differential gene between the worldwide populations

差异基因	SNP	人群														P 值
		CEU	TSI	GBR	FIN	IBS	CHB	JPT	CHS	YRI	LWK	ASW	MXL	PUR	CLM	
<i>IL20RA</i>	13	0.386	0.399	0.411	0.369	0.389	0.302	0.203	0.341	0.484	0.513	0.385	0.270	0.312	0.355	0.005
<i>RNMTL1-NXN</i>	17	0.324	0.469	0.407	0.396	0.455	0.316	0.362	0.240	0.454	0.349	0.466	0.393	0.355	0.469	0.114
<i>NOTCH2</i>	3	0.275	0.240	0.293	0.315	0.198	0.128	0.087	0.176	0.510	0.509	0.491	0.362	0.314	0.290	0.001
<i>ADRA2A-BTBD7P2</i>	9	0.288	0.294	0.337	0.358	0.370	0.356	0.344	0.304	0.321	0.313	0.519	0.288	0.369	0.312	0.599
<i>TBC1D4</i>	13	0.588	0.612	0.592	0.542	0.638	0.342	0.438	0.424	0.607	0.658	0.691	0.575	0.674	0.624	0.001
<i>RBM38-HMGB1P1</i>	9	0.655	0.655	0.662	0.668	0.619	0.499	0.318	0.447	0.625	0.668	0.675	0.627	0.646	0.656	0.001
<i>UBE2E2</i>	8	0.639	0.636	0.595	0.604	0.624	0.580	0.647	0.545	0.644	0.724	0.734	0.711	0.704	0.679	0.005
<i>PPARD</i>	12	0.202	0.170	0.126	0.093	0.140	0.331	0.297	0.367	0.415	0.434	0.319	0.059	0.231	0.254	0.005

注：同一底纹代表同一大陆人群。

表 5 东西方人群遗传结构差异基因等位基因频率
Table 5 Mean allele frequency of T2DM differential gene between the Eastern and Western

差异基因	人群									F_{ST}
	CEU	TSI	GBR	FIN	IBS	CHB	JPT	CHS		
<i>JAZF1</i>	0.635	0.623	0.639	0.647	0.642	0.699	0.713	0.706		0.1822
<i>DGKB-AGMO</i>	0.641	0.627	0.633	0.637	0.641	0.413	0.421	0.408		0.1731

注：同一底纹代表同一大陆人群。

病机制并未得到明确的研究结论。经研究表明，T2DM 的发生与遗传以及环境等因素密切相关^[20]。自 2007 年起，高通量基因分型及测序技术大量地运用在不同人群 T2DM 关联分析中，检测出上百个与 T2DM 相关联的易感候选基因。本研究的目的是比较 T2DM 易感基因在世界人群之间的遗传结构多样性，对将来进行 T2DM 易感基因生物功能方面的研

究有着重要参考价值，甚至对于以后的基因治疗、个性化药物开发等研究都具有非常重要的意义。
首先本研究所关注的 170 个 T2DM 易感基因(基因区域)的整体遗传多样性水平与世界人群全基因组的多样性水平无明显差距。通过置换检验发现 T2DM 易感基因的群体间整体遗传结构与非 T2DM 基因遗传结构相比，拥有更小的群体间遗传结构差

异,说明 T2DM 易感基因在世界人群范围内是一组更为保守的功能基因,其中大多数候选基因在不同人群中的基因序列甚至所编码蛋白的结构都是十分类似的。例如 *POU5F1* 基因(*POU Class 5 Homeobox 1*)是与 T2DM 十分相关的易感基因(P -value < 4.2E-9),并且同时在欧洲、南亚及东亚人群中都得到了 GWAS 验证^[13],以往的研究已表明 *POU5F1* 基因所表达的功能蛋白与干细胞是否分化相关^[21]。*POU5F1* 在世界人群中并没有存在明显的人群结构差异。以 *POU5F1* 为代表的这类与 T2DM 十分相关、并且在多个群体中得到关联验证、同时在世界人群中无独特群体遗传结构的易感基因,应首先作为目的基因进行 T2DM 生物过程等相关后续研究。

虽然 T2DM 易感基因整体水平在全球 14 个人群中并无明显群体结构差异,但还是存在某些易感基因在群体间显示出遗传结构差异。在 170 个候选基因中,*IL20RA*、*RNMTL1-NXN*^[22]、*NOTCH2*^[17]、*ADRA2A-BTBD7P2*^[16]、*TBC1D4*^[23]、*RBM38-HMGB1P1*^[22]、*UBE2E2*^[24]和 *PPARD*^[25]等 8 个易感基因存在明显的世界人群遗传结构差异,分别是 F_{ST} 值排在全基因组功能基因前 3%(表 3)。首先,这 8 个候选基因全部筛选自单一群体的 GWAS 研究结果,所以群体遗传背景差异可能是造成易感基因关联分析结果不同的主要原因。进一步研究发现,这 8 个候选基因最主要的差异是由于非洲人群和非非洲人群之间的等位基因频率不同造成的。非洲人群的独特的群体遗传结构很可能是造成非洲人群比其他人群 T2DM 发病率低的原因之一。造成这种差异原因可能是由于现代人类祖先人群走出非洲后^[14],在受到瓶颈效应以及自然选择压力的影响下,致使 T2DM 易感基因的群体遗传结构产生变化,从而影响疾病的发生。例如影响人类肤色表型的相关基因 *SLC24A5*^[26]就在世界人群遗传结构差异极大($F_{ST}=0.1681$)。

东西方人群作为世界 T2DM 主要的患者群体,两群体间本就存在明显的外观及群体遗传差异^[27],例如对人瞳孔颜色影响最大的基因 *OCA2*^[28],在东西方人群中就存在极大的群体遗传结构的不同($F_{ST}=0.2018$)。根据 Study of Women's Health Across the Nation 研究显示,不同人群在胰岛 β 细胞功能及胰岛素敏感性方面存在差异,与欧洲人群相比,

东亚人群显示出更为明显的胰岛素敏感性降低和胰岛 β 细胞功能减退,即东亚人群的胰岛素敏感性和胰岛素分泌均比欧洲人群低^[29,30]。因此实验进一步针对东西方人群 T2DM 易感基因群体结构进行分析,在 8 个东西方人群中,有 12 个候选基因存在东西方遗传结构差别,其中 *DGKB-AGMO* 和 *JAZF1* 的差别程度在全基因组的前 0.7%,该易感基因发现于欧洲人群的 GWAS 分析^[16,18]。已有研究表明 *DGKB* (*Diacylglycerol kinase beta 90 kDa*)与胰岛素应答相关,并且很可能是造成胰岛 β 细胞功能障碍产生的遗传因素^[31]。同时 Li 等^[32]通过动物模型实验,证实 *JAZF1*(*JAZF zinc finger 1*)基因与肝脏胰岛敏感性有着十分密切的关系。因此这 2 个差别易感基因很可能与东西方人群胰岛素分泌和胰岛素敏感性差别相关。造成东西方人群存在显著遗传差异的原因,有可能是在人类祖先离开非洲大陆后在东西方不同环境和迁徙历史的影响下造成的,同时也受到近期人群之间基因交流的影响^[33],导致人群之间的地理距离与群体遗传结构存在相关性,在相同地区生活的人群遗传结构更为相似,因而相似遗传结构可能影响 T2DM 在同一区域人群的患病过程及发病率,而对于距离较远的人群影响不同。

本研究同时从等位基因频率和单倍型多样性等方面证实,T2DM 易感基因在不同人群中存在独特的人群遗传结构,而且人群独特的遗传背景可能是造成易感基因在不同人群中的关联性差异^[34],也可能造成基因功能产生差别,因此在今后的基因生物学功能研究以及大数据易感基因筛查及治疗的相关研究中,都需要考虑人群遗传结构多样性的影响,从而对于不同人群实验制定方案应该是不同的。

本研究通过对 14 个世界人群的 T2DM 易感基因的遗传多样性进行研究,揭示出 T2DM 易感基因的遗传结构在不同人群间的确存在差异,并且这种差异可能与 T2DM 在不同人群中发病率的改变具有一定的相关性,这对于 T2DM 的遗传机制和发病机理研究有着重要的意义,同时在今后相关的 T2DM 群体遗传研究中对于遗传结构差异应予以充分考量。

附录:

附表见网络电子版 www.chinagene.cn。

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附表 1 T2DM 易感基因相关参考信息

No	染色体	起始位置	终止位置	基因	Pubmed ID
1	1	50906934	51425936	<i>FAF1</i>	24509480
2	1	92145899	92371559	<i>TGFBR3</i>	23209189
3	1	94994731	95139725	<i>F3-PGBD4P7</i>	22238593
4	1	120454175	120612317	<i>NOTCH2</i>	18372903
5	1	207627644	207663240	<i>CR2</i>	21490949
6	1	214141277	214214847	<i>PROX1</i>	24509480
7	1	214098091	214214847	<i>LINC00538-PROX1</i>	20081858 25344220
8	1	219347172	219800000	<i>LYPLAL1</i>	24509480
9	1	228870823	228882416	<i>RHOU</i>	23300278
10	1	233119881	233431459	<i>PCNXL2</i>	21490949
11	2	640000	677439	<i>TMEM18</i>	24509480
12	2	3751181	3895000	<i>DCDC2C</i>	21490949
13	2	27719470	27746556	<i>GCKR</i>	20081858
14	2	43457975	43823113	<i>THADA</i>	18372903
15	2	60500000	60780633	<i>BCL11A</i>	24509480
16	2	58747888	60614580	<i>FLJ30838-MIR4432</i>	20581827
17	2	105654482	105859924	<i>MRPS9-GPR45</i>	17668382
18	2	135213329	135615443	<i>TMEM163-MIR5590</i>	23209189
19	2	151324709	152042675	<i>RND3-FABP5P10</i>	22238593
20	2	161128661	161350318	<i>RBMS1</i>	20418489
21	2	165430250	165544287	<i>EIF3EP3-SNORA70F</i>	21874001
22	2	165349322	165698678	<i>GRB14-COBL1</i>	22885922
23	2	169757749	169766510	<i>G6PC2</i>	20081858
24	2	227007509	227044778	<i>LOC646736</i>	20581827
25	2	226896033	227663506	<i>IRS1</i>	22885922 24509480
26	2	226265601	227523509	<i>NYAP2-MIR5702</i>	19734900
27	2	230222344	230579286	<i>DNER</i>	24101674
28	3	12045833	12299981	<i>SYN2-GSTM5P1</i>	20581827 18372903
29	3	12329348	12475855	<i>PPARG</i>	18372903
30	3	23198000	23632296	<i>UBE2E2</i>	20818381
31	3	54952380	55515426	<i>LRTM1-WNT5A</i>	17554300
32	3	63996224	64088807	<i>PSMD6;PRICKLE2-AS1</i>	22158537
33	3	64670545	64997143	<i>ADAMTS9-AS2</i>	19734900
34	3	102153858	102960078	<i>ZPLD1-NDUFA4P2</i>	21490949
35	3	123001142	123135189	<i>ADCY5</i>	20081858
36	3	142375738	142432505	<i>PLS1</i>	21490949
37	3	170714136	170744768	<i>SLC2A2</i>	20081858
38	3	179512746	179692008	<i>PEX5L</i>	21490949
39	3	185361526	185542827	<i>IGF2BP2</i>	17463248 20581827 18711366
40	3	186648314	186796341	<i>ST6GAL1</i>	21874001
41	3	187780000	188608460	<i>LPP</i>	24465431
42	4	1243228	1333936	<i>CTBP1-AS1;MAEA</i>	22456796
43	4	1303230	1333936	<i>MAEA</i>	22158537
44	4	6270000	6304992	<i>WFS1</i>	19734900 20581827
45	4	46911252	46970000	<i>GABRA4-COX7B2</i>	23937595

续附表 1

No	染色体	起始位置	终止位置	基因	Pubmed ID
46	4	122589151	122686340	<i>ANXA5-TMEM155</i>	17554300
47	4	153520000	153601317	<i>TMEM154</i>	24509480
48	4	164445449	164534776	<i>MARCH1</i>	21490949
49	5	53180613	53606403	<i>ARL15</i>	24509480
50	5	55395506	56191978	<i>ANKRD55-MAP3K1</i>	22885922
51	5	56100899	56191978	<i>RPL26P19-MAP3K1</i>	23209189
52	5	76382622	76444176	<i>ZBED3-AS1</i>	20581827
53	5	89312437	89705603	<i>MIR3660-CETN3</i>	19734900
54	5	123972609	124180805	<i>ZNF608</i>	24465431
55	5	154870705	156194798	<i>PIGP1-SGCD</i>	23300278
56	6	4142000	4146332	<i>LOC102725019;HLA-DQA2</i>	23386860
57	6	7252213	7281375	<i>SSR1-RREB1</i>	24509480
58	6	20534687	21232634	<i>CDKAL1</i>	20581827 19401414 17463249 18372903 17463248 17460697 22693455
59	6	31132114	31138451	<i>POU5F1</i>	24509480
60	6	35310334	35395968	<i>PPARD</i>	23137000
61	6	37787306	38122399	<i>ZFAND3</i>	22158537
62	6	39282236	39285000	<i>KCNK16-KCNK17</i>	22158537
63	6	43737945	43973694	<i>VEGFA-C6orf223</i>	18372903
64	6	71276624	71298606	<i>C6orf57</i>	21490949
65	6	126660934	127000000	<i>C6orf173(CENPW)</i>	24509480
66	6	133138357	133189998	<i>SNORA33-HMGB1P13</i>	21150874
67	6	137221108	137366317	<i>IL20RA</i>	24509480
68	6	139935578	140526463	<i>ATP5F1P6-MIR3668</i>	21490949
69	6	148663728	148873184	<i>SASH1</i>	21150874
70	7	13900000	14030327	<i>ETV1</i>	24509480
71	7	14184673	15601640	<i>DGKB-AGMO</i>	20081858
72	7	16889636	16890425	<i>LOC100287613</i>	23386860
73	7	27870192	28220437	<i>JAZF1</i>	18372903 20581827
74	7	30691558	30739719	<i>CRHR2</i>	24509480
75	7	36892510	37025871	<i>ELMO1</i>	17653210
76	7	44183870	44253893	<i>GCK-YKT6</i>	20081858
77	7	100487614	100493592	<i>ACHE</i>	21490949
78	7	127010353	127225654	<i>ZNF800-GCC1</i>	22158537
79	7	127233688	127255780	<i>FSCN3-PAX4</i>	23532257
80	7	127812802	127897682	<i>MIR129-LEP</i>	23945395
81	7	130417381	130561569	<i>KLF14-MIR29A</i>	20581827
82	8	21549529	21771205	<i>GFRA2-DOK2</i>	24974787
83	8	41510743	41522804	<i>ANK1</i>	22885922 22456796
84	8	95938199	95961615	<i>TP53INP1</i>	20581827
85	8	118147336	118188953	<i>SLC30A8</i>	19401414 20581827 20081858
86	8	128958804	129598078	<i>TMEM75</i>	24509480
87	8	134048972	134243932	<i>SLA-WISP1</i>	23300278
88	9	3824127	4294000	<i>GLIS3</i>	22961080 22158537 20081858
89	9	8314245	10612723	<i>PTPRD</i>	20174558

续附表 1

No	染色体	起始位置	终止位置	基因	Pubmed ID
90	9	21994789	22452472	<i>CDKN2B-AS1;DMRTA1</i>	22293688 18372903 20581827 21573907 19401414 17463248
91	9	27948083	29212998	<i>LINGO2</i>	24590345
92	9	81905000	82341796	<i>TLE4</i>	24509480
93	9	81651269	82006955	<i>KRT18P24-CHCHD2P9</i>	20581827
94	9	84198597	84534842	<i>TLE1-FAM75D5</i>	22885922
95	9	93589701	94124206	<i>SYK-AUH</i>	22456796
96	9	112403067	112713756	<i>PALM2</i>	22456796
97	9	113127528	113489959	<i>SVEP1-RPS21P5</i>	23386860
98	9	139249251	139254057	<i>GPSM1</i>	23945395
99	10	12237960	12620822	<i>CDC123-MIR4480</i>	20862305 22961080 18372903
100	10	70883907	70932616	<i>VPS26A</i>	21874001
101	10	71390002	71500000	<i>C10orf35</i>	24509480
102	10	80828791	81076285	<i>ZMIZ1</i>	22885922
103	10	89623194	89778532	<i>PTEN</i>	24509480
104	10	94211440	94356609	<i>IDE-RPL11P4</i>	21490949
105	10	94449680	94819251	<i>HHEX-EXOC6</i>	17463249 22693455
106	10	112836789	113083160	<i>ADRA2A-BTBD7P2</i>	20081858
107	10	114710008	114927436	<i>TCF7L2</i>	17554300 17463249 20581827
108	10	120967196	121215131	<i>GRK5</i>	22961080
109	10	124151818	124195000	<i>PLEKHA1</i>	24509480
110	10	132890654	133109984	<i>TCERG1L</i>	24190949
111	11	2482683	2870340	<i>KCNQ1</i>	21799836 20174558 18711367 18711366
112	11	11203355	11261722	<i>HMGNI1P22-MTND5P21</i>	22238593
113	11	17406795	17410206	<i>KCNJ11</i>	17463248 17453249
114	11	41557675	43290919	<i>RPL9P23-HNRNPKP3</i>	17463248
115	11	45868668	45904799	<i>CRY2</i>	21747906
116	11	47290926	47351582	<i>MADD</i>	20081858
117	11	61567096	61584529	<i>FADS1</i>	20081858
118	11	72396113	72433403	<i>ARAP1</i>	20581827
119	11	92085261	92715948	<i>FAT3-MTNR1B</i>	20581827
120	11	92702788	92715948	<i>MTNR1B</i>	20081858
121	11	108093558	108300000	<i>ATM-C111orf65</i>	21186350
122	11	129407732	129729898	<i>RPS27P20-TMEM45B</i>	22238593
123	12	51347781	51364289	<i>HIGD1C</i>	17554300
124	12	55038374	55197407	<i>DCD-VDACIP5</i>	18372903
125	12	66111799	66220754	<i>PCNPP3-RPSAP52</i>	21150874
126	12	66151799	66220754	<i>RPSAP52</i>	20581827
127	12	66212000	66309307	<i>HMGA2</i>	24509480
128	12	71518876	71980088	<i>TSPAN8-LGR5</i>	17554300 20581827 18372903
129	12	102811453	102876000	<i>IGF1</i>	20081858
130	12	121401640	121410095	<i>RPL12P33;HNF1A-AS1</i>	21573907
131	12	121416548	121440314	<i>HNF1A</i>	24509480
132	12	121458094	121477045	<i>OASL</i>	20581827
133	12	123640042	123717785	<i>MPHOSPH9</i>	24509480

续附表 1

No	染色体	起始位置	终止位置	基因	Pubmed ID
134	13	23755059	23899304	<i>SGCG</i>	23300278
135	13	26780904	26796028	<i>RNF6</i>	24509480
136	13	75858799	76056250	<i>TBC1D4</i>	25043200
137	13	76445174	76857948	<i>FLJ35379</i>	23209189
138	13	80055258	80915086	<i>NDFIP2-SPRY2</i>	20862305
139	14	101003483	101201467	<i>BEGAIN-DLK1</i>	21573907
140	15	38780301	38857007	<i>RASGRP1</i>	22961080
141	15	62359175	62457482	<i>C2CD4A-C2CD4B</i>	20818381 20081858 20862305 21747906
142	15	77713242	77777945	<i>HMG20A</i>	21874001 21490949
143	15	77713242	77924869	<i>HMG20A-LINGO1</i>	22885922
144	15	80351909	80478924	<i>ZFAND6-FAH</i>	20581827
145	15	90373830	90456222	<i>AP3S2;C15orf38-AP3S2</i>	21874001
146	15	91509267	91557881	<i>PRC1</i>	20581827
147	16	24741048	24837547	<i>TNRC6A</i>	23386860
148	16	53737874	54148379	<i>FTO</i>	20581827 17463249 22693455
149	16	57546089	57570477	<i>CCDC102A</i>	23137000
150	16	75237993	75258822	<i>CTRB2-CTRB1</i>	22885922
151	16	78859149	79634622	<i>RPS3P7-MAF</i>	22158537
152	16	81478774	81745367	<i>CMIP</i>	22158537
153	17	685512	767351	<i>RNMTL1-NXN</i>	23300278
154	17	2207247	2228553	<i>SRR</i>	20174558
155	17	6939393	6943440	<i>SLC16A13</i>	23945395
156	17	6943440	6947242	<i>SLC16A11-SLC16A13</i>	24390345
157	17	36046433	36105096	<i>HNF1B</i>	22961080
158	18	2916991	2949000	<i>LPIN2-LOC727896</i>	21490949
159	18	6941742	7117813	<i>LAMA1</i>	22693455
160	18	57838564	58040001	<i>MC4R</i>	22885922
161	19	19349057	19657468	<i>CILP2</i>	24509480
162	19	33877854	34012799	<i>PEPD</i>	22158537
163	19	39574944	39602128	<i>PAPL</i>	21490949
164	19	46150000	46185717	<i>GIPR</i>	24509480
165	20	42935196	42979432	<i>FITM2-R3HDML</i>	22158537
166	20	42984441	43053276	<i>HNF4A</i>	21874001
167	20	55966453	56084386	<i>RBM38-HMGB1P1</i>	23300278
168	21	33245627	33651376	<i>HUNK-MIS18A</i>	21490949
169	22	31644347	31673624	<i>LIMK2</i>	21150874
170	22	44220386	44258378	<i>SULT4A1</i>	23386860