SUPPLEMENTAL MATERIALS

METHODS

Subject Recruitment. Participation in BetaGene is restricted to Mexican Americans with fasting glucose <126 mg/dl (7 mM) from families of a proband with GDM diagnosed within the previous 5 years. Probands are identified from the patient populations at Los Angeles County/USC Medical Center, OB/GYN clinics at local hospitals, and the Kaiser Permanente health plan membership in Southern California. Probands qualify for participation if they (a) are of Mexican ancestry (both parents and ≥3/4 of grandparents Mexican or of Mexican descent), (b) have a confirmed diagnosis of GDM within the previous 5 years, (c) have glucose levels associated with poor pancreatic β-cell function and a high risk of diabetes when not pregnant (1), (d) have no evidence of β-cell autoimmunity by GAD-65 testing, and (e) have available for study either 2 non-diabetic siblings and 3 non-diabetic first cousins from a single nuclear family or at least five siblings. Using information from the proband to determine preliminary eligibility, siblings and cousins are invited to participate, as are available parents and connecting uncles and aunts. GDM probands, siblings and cousins have extensive phenotyping for diabetes-related traits (below) and form the basis for the primary analysis of this report.

Clinical Protocols. Phenotyping for BetaGene was performed on two separate visits to the General Clinical Research Center. Visit 1 consists of a physical examination, DNA collection, and a 75 g oral glucose tolerance test (OGTT) with blood samples obtained before and 30, 60, 90, and 120 min after glucose ingestion. Fasting blood samples were also collected for lipid measurements. Participants who had fasting glucose <126 mg/dl on the OGTT were invited for Visit 2, which consisted of a DEXA scan for determination of body fat and an insulin-modified intravenous glucose tolerance test (IVGTT) performed as previously described (4). Probands, their siblings, and their cousins undergo the full phenotyping protocol, while parents, uncles, aunts, spouses, and offspring had only a physical exam, fasting glucose measurement, and DNA collection.

Prioritizing Disease Genes by Analysis of Common Elements

The "Prioritizing Disease Genes by Analysis of Common Elements" (PDG-ACE) algorithm is a JAVA-based bioinformatic tool developed by the National Center for Integrative Biomedical Informatics (https://portal.ncibi.org/portal). In the search for novel complex relationships among disease-related genes, PDG-ACE identifies common over-represented biomedical keywords extracted from NCBI Entrez Gene records describing genes at hypothesized disease-related loci. Biomedical keywords used in the analysis are derived from MeSH, OMIM, and directly from Entrez Gene. Significance of over-representation is established by permutation testing and correction is made for testing multiple hypotheses. In testing the algorithm, expected multi-gene influences are found in documented gene/gene interactions used as positive controls, while no significant influences are seen in randomly selected gene pairs used as negative controls. To date, multi-gene influences have been identified in the etiology of complex diseases ranging from type 2 diabetes mellitus, to breast cancer, to bipolar disorder.

TABLE S1. Correlation among QTs. Pair-wise Pearson's correlation coefficient (p-value) are computed among QTs from the BetaGene Study.

	BMI (kg/m^2)	Fasting Glucose [mM]	2-hour Glucose [mM]	Fasting Insulin [pM]	30' D Insulin [pM]	2-hour Insulin [pM]	S_G [$\times 10^{-2}$ min^{-1}]	S_I [$\times 10^{-3}$ min^{-1} per pM]	AIR [pM ×10 min]	Disposition Index
BMI (Kg/m^2)	1.0									
Fasting Glucose [mM]	0.29 (<0.001)	1.0								
2-hour Glucose [mM]	0.28 (<0.001)	0.49 (<0.001)	1.0							
Fasting Insulin [pM]	0.57 (<0.001)	0.41 (<0.001)	0.32 (<0.001)	1.0						
30' DInsulin [pM]	0.23 (<0.001)	-0.06 (0.2298)	-0.17 (<0.001)	0.49 (<0.001)	1.0					
2-hour Insulin [pM]	0.38 (<0.001)	0.18 (<0.001)	0.41 (<0.001)	0.66 (<0.001)	0.44 (<0.001)	1.0				
S_G [$\times 10^{-2}$ min^{-1}]	-0.26 (<0.001)	-0.32 (<0.001)	-0.39 (<0.001)	-0.25 (<0.001)	0.02 (0.6967)	-0.29 (<0.001)	1.0			
S_I [$\times 10^{-3}$ min^{-1} per pM]	-0.50 (<0.001)	-0.14 (0.0023)	-0.15 (0.0012)	-0.49 (<0.001)	-0.41 (<0.001)	-0.49 (<0.001)	0.35 (<0.001)	1.0		
AIR [pM ×10 min]	0.25 (<0.001)	-0.18 (<0.001)	-0.24 (<0.001)	0.36 (<0.001)	0.62 (<0.001)	0.29 (<0.001)	0.19 (<0.001)	-0.36 (<0.001)	1.0	
Disposition Index	-0.22 (<0.001)	-0.40 (<0.001)	-0.49 (<0.001)	-0.16 (<0.001)	0.22 (<0.001)	-0.19 (<0.001)	0.55 (<0.001)	0.24 (<0.001)	0.57 (<0.001)	1.0

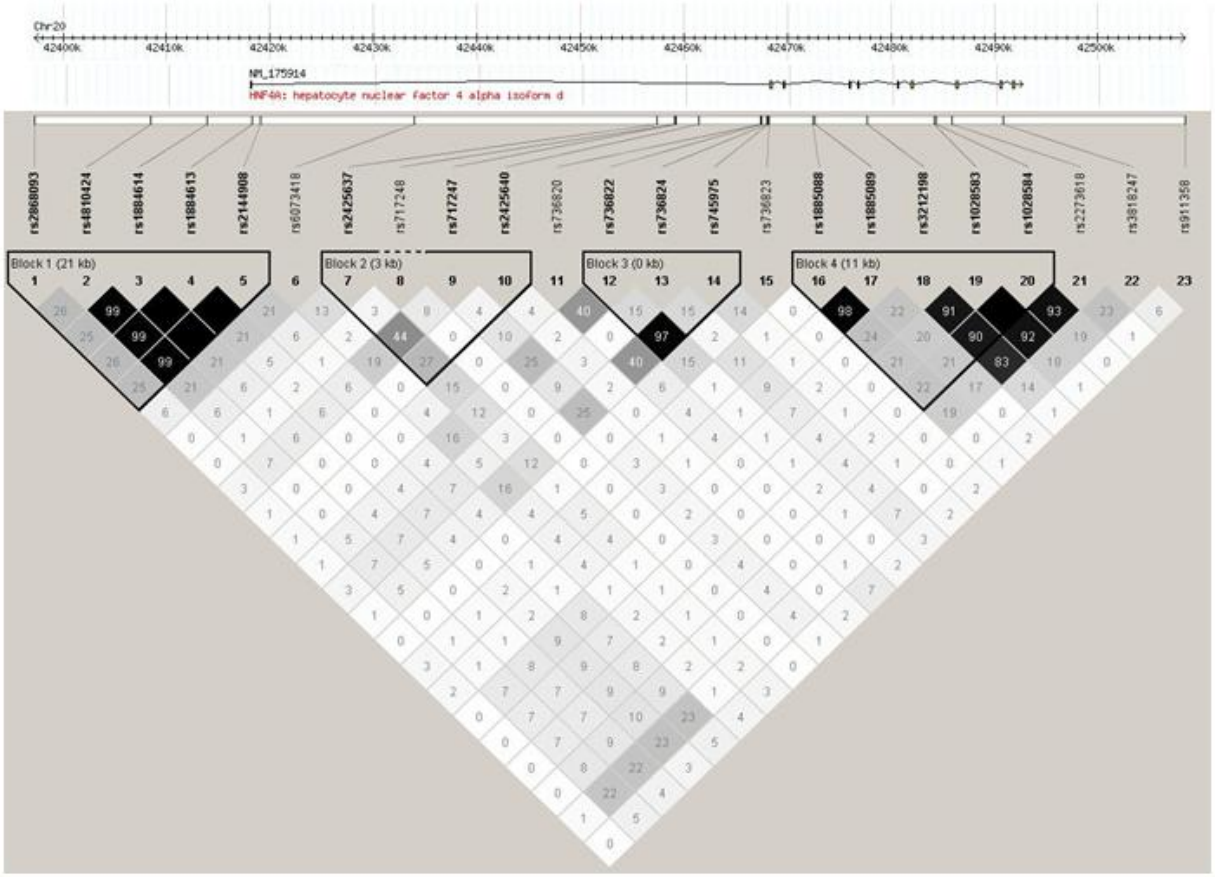
TABLE S2. Univariate association results in BetaGene. Uncorrected p-values for the test of association between rs1801282 or rs2144908 and QTs are shown.

	PPARG (Pro12 Ala) rs1801282		*HNF4A* rs2144908	
	Age, Sex	Age, Sex, and BMI	Age, Sex	Age, Sex, and BMI
BMI	0.3757		0.4444	
Body Fat	0.4341		0.8257	
WHR	0.9892		0.7440	
Fasting Glucose	0.3939	0.4811	0.8225	0.5917
2 hr Glucose	0.4385	0.5384	0.8089	0.9645
Fasting Insulin	0.1764	0.3199	0.3869	0.5929
30’ DInsulin	0.6662	0.5388	0.4597	0.6187
2-hour Insulin	0.5818	0.3741	0.4968	0.6576
Total Cholesterol	0.2363	0.2475	0.2723	0.2609
HDL Cholesterol	0.0943	0.1167	0.7050	0.6369
Triglycerides	0.0440	0.0505	0.2999	0.2379
S_G	0.7544	0.6513	0.2591	0.3214
S_I	0.4324	0.6382	0.1689	0.3361
AIR	0.7757	0.6051	0.4916	0.3230
DI	0.4589	0.5342	0.0888	0.1151

SUPPLEMENTARY FIGURE LEGEND

Figure S1. *HNF4A* Pair-wise Linkage Disequilibrium and Haplotype Block Structure in IRAS FS. LD and haplotype block structure estimated for the 23 *HNF4A* SNPs genotyped in the IRAS FS Mexican American families. Haplotype blocks were determined using the method of Gabriel as implemented in Haploview V3.2. LD is displayed as pair-wise r^2 values, where white indicates $r^2 = 0$, varying shades of grey indicate $0 < r^2 < 1$, and black indicates $r^2 = 1$.

FIGURE S1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42430k
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42460k
42470k
42480k
42490k
42500k
NM_175914
HNF4A: hepatocyte nuclear factor 4 alpha isoform d
rs2868093
rs4810424
rs1884614
rs1884613
rs2144908
rs6073418
rs2425637
rs717248
rs717247
rs2425640
rs736820
rs736822
rs736824
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