SUPPLEMENTARY MATERIAL

A loss-of-function splice acceptor variant in *IGF2* is protective for type 2 diabetes

Running Title: *IGF2* loss-of-function type 2 diabetes protective variant.

The SIGMA T2D Genetics Consortium

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Supplementary Figure legends

Supplementary Figure 1: Genotype integration and imputation strategy. The sample was divided into two cohorts according to the technologies used to ascertain the genetic variants. A subset of the samples (Dataset 1) was genotyped on the OMNI2.5 (*1*)and exome chip arrays. Dataset 2 was also ascertained by whole-exome sequencing and was used as a Mexican specific reference panel (*2*). We imputed both the variants of the whole-exome-sequencing Mexican specific reference panel and the 1000G (phase 3, release June 2014) variants into the samples that did not have whole-exome sequencing information. We only imputed 1000G (phase 3) variants into the samples that had whole-exome sequencing, OMNI2.5 and exome chip genotypes. We then performed the association testing separately of each dataset and meta-analyzed both results.

Supplementary Figure 2: Characterization of the *IGF2-INS-TH* locus. Regional plot is shown for the *IGF2-INS-TH* and *KCNQ1*, without conditioning (a). Conditioning on rs139647931 and rs2237897 *KCNQ1* variants revealed two additional independent signals, rs4929965 and rs149483638 (b). 95% credible set when conditioning on the two *KCNQ1* variants and rs4929965 reveals the splice acceptor site variant (rs149483638) as top variant (c). 95% credible set when conditioning on rs149483638 and the *KCNQ1* variants (d). Point colors indicate the R-squared with the index SNP, marked in purple.

Supplementary Figure 3: Synthetic association plot. Whole-exome sequencing data from 3,732 individuals was integrated with OMNI2.5 and exome array genotypes as described in Supplementary Figure 1. All the variants with minor allele frequency (MAF)<0.001 were removed from the analysis. Low-frequency variants (0.001<MAF<0.05) were sequentially added into the model starting from the most significant variant. The first line represents the odds ratio (OR) and the 95% confidence interval for the association of the rs149484648 variant. Each of the following lines represent the estimated OR and 95% confidence interval of the rs149483638 after adding, in a sequential manner each of the low-frequency variants into the model. As shown in the plot, the rs149483638 association was did not disappear when adding up to 50 low-frequency variants into the model, which suggest that this signal is not driven by the presence of low-frequency variants strongly associated with the disease.

Supplementary Figure 4: Forest plot for the meta-analysis of rs10770141 variant, near *TH*. Odds ratios for the meta-analyses are represented with a diamond.

Supplementary Figure 5. Gene expression of isoform 2, as measured by expression of exon 2 of *IGF2* across tissues and cell lines. Expression across T2D- relevant tissues extracted from GTEx (left panel). Gene expression was also analyzed in different embryonic cell lines, including embryonic cell-line derived pancreatic precursors (right panel). *human embryonic stem cells presented here were included among the cell lines approved by NIH in 2010 to preempt the use of federal funds to generate new cell lines from human embryos.

Supplementary Figure 6. Expression level of *IGF2* in human pancreatic progenitors and other tissues. RNA-seq data showing the expression of *IGF2* isoforms in various adult human tissues (lung, muscle, adrenal, heart, adipose, breast, colon, brain, prostate and kidney), hESC-derived cell lines (mesenchymal, mesendoderm, trophoblast and neuronal progenitors) and hESC-derived pancreatic progenitors. The yellow box highlights the location of the *IGF2* exon of interest, which is highly expressed in human pancreatic progenitors, as opposed to most other tissues and cell lines. All tracks are scaled to a maximum of 20 RPKM.

Supplementary Figure 7. The dosage of the T2D protective A allele was not correlated with expression of total *IGF2* expression (as measured by expression levels of the exon 3) in liver (**a**) and in adipose tissue (**b**) nor was total circulating IGF2 (c). The expression of all IGF2 (as measured by exon 3 expression) was not correlated with T2D status (d) or HbA1c in non-diabetic individuals (**e**).

Supplementary Figure 8. Association of human homozygous "knockouts" for isoform 2 of *IGF2* (AA homozygous) with other diseases or clinical outcomes. While "homozygous knock-outs" were associated with ~40% reduced risk for T2D, there was no evidence of increased risk for other diseases in individuals homozygous for the A allele.

Supplementary Note (online)

Detailed description of study participants

Diabetes in Mexico Study (DMS):

Individuals were enrolled in the study, recruited from two tertiary level institutions (IMSS and ISSSTE) located in Mexico City. The diagnosis of T2D was made based on ADA criteria. 811 unrelated healthy subjects older than 45 years and with fasting glucose levels below 100 mg/dL were classified as controls. 569 unrelated individuals, older than 18 years, with either previous T2D diagnosis or fasting glucose levels above 125 mg/dL were included as T2D cases. Individuals with fasting glycemia between 100-125 mg/dL were excluded. Informed consent was obtained from all participants. The study was conducted with the approval of the Ethics and Research Committees of all institutions involved. Genomic DNA was purified from whole blood samples using a modified salting-out precipitation method (Gentra Puregene, Qiagen Systems, Inc., Valencia, CA, USA).

Clinical history of these individuals was manually reviewed and incidence of difference diseases was used for the phenome-wide association analysis.

Mexico City Diabetes Study (MCDS):

The Mexico City Diabetes Study is a population based prospective investigation. All 35-64 years of age men and non-pregnant women residing in the study site (low income neighborhoods equivalent to 6 census tracks with a total population of 15,000 inhabitants) were interviewed and invited to participate in the study. We had a response rate of 67% for the initial exam. Diagnostic criteria for type 2 diabetes were recommended by the ADA. Fasting glucose 126 mg/dL or more or 2 hr post 75 gr of glucose load 200 or more. If a participant was diagnosed as diabetic by a physician and was under pharmacologic therapy for diabetes he was considered as diabetic regardless the blood glucose levels. The study was conducted with the approval of the Ethics and Research Committees

of all institutions. Informed consent was obtained from all participants. Genomic DNA was extracted from whole blood using the QIAmp 96 DNA Blood Kit (12) (Qiagen, Cat. No. 51162).

Multiethnic Cohort (MEC):

The MEC consists of 215,251 men and women in Hawaii and Los Angeles, and comprises mainly five self-reported racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians and European Americans (3). Between 1993 and 1996, adults between 45 and 75 years old were enrolled by completing a 26-page, self-administered questionnaire asking detailed information about dietary habits, demographic factors, level of education, personal behaviors, and history of prior medical conditions (e.g., diabetes). Potential cohort members were identified through Department of Motor Vehicles drivers' license files, voter registration files and Health Care Financing Administration data files. In 2001, a short follow-up questionnaire was sent to update information on dietary habits, as well as to obtain information about new diagnoses of medical conditions since recruitment. Between 2003 and 2007, we re-administered a modified version of the baseline questionnaire. All questionnaires inquired about history of diabetes, without specification as to type (1 vs. 2). Between 1995 and 2004, blood specimens were collected from ~67,000 MEC participants at which time a short questionnaire was administered to update certain exposures, and collect current information about medication use.

Cohort members in California are linked each year to the California Office of Statewide Health Planning and Development (OSHPD) hospitalization discharge database, which consists of mandatory records of all in-patient hospitalizations at most acute-care facilities in California. Records include information on the principal diagnosis plus up to 24 other diagnoses (coded according to ICD-9), including T1D and T2D. In Hawaii cohort members have been linked with the diabetes care registries for subjects with Hawaii Medical Service Association (HMSA) and Kaiser Permanente Hawaii (KPH) health plans (~90% of the Hawaii population has one of these two plans). Information from these additional databases has been utilized to assess the percentage of

T2D controls (as defined below) with undiagnosed T2D, as well as the percentage of identified diabetes cases with T1D rather than T2D. Based on the OSHPD database <3% of T2D cases had a previous diagnosis of T1D. We did not use these sources to identify T2D cases because they did not include information on diabetes medications, one of our inclusion criteria for cases (see below).

In the MEC, diabetic cases were defined using the following criteria: (a) a self-report of diabetes on the baseline questionnaire, 2nd questionnaire or 3rd questionnaire; and (b) self-report of taking medication for T2D at the time of blood draw; and (c) no diagnosis of T1D in the absence of a T2D diagnosis from the OSHPD (California Residents). Controls were defined as: (a) no self-report of diabetes on any of the questionnaires while having completed a minimum of 2 of the 3 (~80% of controls returned all 3 questionnaires); and (b) no use of medications for T2D at the time of blood draw; and (c) no diabetes diagnosis (type 1 or 2) from the OSHPD, HMSA or KPH registries. To preserve DNA for genetic studies of cancer in the MEC, subjects with an incident cancer diagnosis at time of selection for this study were excluded. Controls were frequency matched to cases on sex, ethnicity and age at entry into the cohort (5-year age groups) and for Latinos, place of birth (U.S. vs. Mexico, South or Central America), oversampling African American, Native Hawaiian and European American controls to increase statistical power. Many of the T2D variants have also been evaluated in studies of cancer in the MEC which allowed for inclusion of additional controls who met the criteria above.

Altogether, this study included 2,231 T2D cases and 2,607 controls of Latin American ethnicity. Informed consent was obtained from all participants. The study was conducted with the approval of the Ethics and Research Committees of all institutions. Genomic DNA extraction was done using Qiagen from buffy coat.

UNAM/INCMNSZ Diabetes Study (UIDS):

IGF2 loss-of-function T2D protective variant

Cases were recruited at the outpatient diabetes clinic of the Department of Endocrinology and Metabolism of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). All Mexican-mestizo individuals were invited to participate in the study. Diagnosis of type 2 diabetes was done following the American Diabetes Association criteria, i.e., fasting plasma glucose values ≥126 mg/dL, current treatment with a hypoglycemic agent, or casual glucose values ≥200 mg/dL.

Control subjects were recruited from a cohort of adults aged 45 years or older among government employees, blue collar workers and subjects seeking for attention in medical units for any condition besides those considered as exclusion criteria (see below). Normoglycemic status was defined as having a fasting plasma glucose concentration < 100 mg/dL and no previous history of hyperglycemia, gestational diabetes or use of metformin.

Patients were interviewed following a standardized questionnaire; it included the medical history, a previously validated, three days food record and a physical activity registry. In addition a blood sample (after 9-12 hours of fasting) was obtained. The questionnaire included demographic, socio-economic and medical history of the patients and their family. Blood pressure, height, waist circumference and weight must be measured in the same visit. For taking blood pressure, systolic and diastolic pressure were recorded using a mercury sphygmomanometer; subjects remained seated and at rest for five minutes before measuring.

Inclusion criteria: Men or women aged 25 years or older, with BMI greater than 20 but lower than 40 kg/m2.

Exclusion criteria: Diabetes, coronary heart disease, stroke, transient ischemic attack, lower limb amputations, alcoholism (more than 10 servings of alcohol per week) or any disease that in opinion of the researcher may limit life expectancy to less than 2 years. Subjects that planned to move out of town permanently during the next three years were also excluded. Pregnant women,

individuals with drug addictions, the use of systemic corticosteroids in pharmacologic doses (intravenous, oral or injectable, including injections in the joints) were exclusion criteria also. Replacement dosage of systemic corticosteroids (up 7.5 mg/day of prednisone or 30 mg/day of hydrocortisone or its equivalent; as well as inhaled or topical corticosteroids) was allowed into the study. Other exclusion criteria were: active liver disease (defined as AST (SGOT) or ALT (SGPT) > 2.0x upper limit of the normal range, alkaline phosphatase (ALK-P) > 1.5x upper limit of the normal range or total bilirubin > 1.5x upper limit of the normal range), significant renal dysfunction (defined as serum creatinine > 1.7 upper limit of the normal range or nephrotic syndrome), any history of malignancy (except for basal cell skin carcinoma) and uncontrolled depression or psychosis.

Informed consent was obtained from all participants. The study was conducted with the approval of the Ethics and Research Committees of all institutions. Genomic DNA was extracted from whole blood using the QIAmp 96 DNA Blood Kit (12) (Qiagen, Cat. No. 51162).

Pima Native Americans

Diabetes was diagnosed by 1997 American Diabetes Association criteria; details for this cohort have been described previously (4). rs149483638 was analyzed in 3,199 full heritage Pima Indians selected from a longitudinal study (4). These individuals included 1,847 women and 1,352 men; mean age at examination was 40.6 (±16.5) years, and 1519 individuals (47%) had diabetes. The frequency of the A allele of rs149483638 was 0.149 (0.169 in non-T2D and 0.135 in T2D). Mean (SD) age was 40.8 (16.4) (49.5 [13.0] for affected, 33.0 [14.4] for unaffected). Mean (SD) age at onset for affected was 35.9 (12.5). Mean (SD) maximum BMI observed in the longitudinal study was 37.6 (8.7) (38.9 [8.7] for affected; 36.3 [8.5] for unaffected). Mean (SD) fasting glucose: 134.1 (69.0) mg/dL (181.1 [78.5] for affected; 94.1 [9.6] for unnaffeted).

IGF2 loss-of-function T2D protective variant

Genotypes were assessed by the BeadXpress system (Illumina, San Diego, CA) according to the manufacturer's instructions. The association between genotype and diabetes was assessed under an additive model by logistic regression model with control for age, sex, birth year, and proportion of Amerindian ancestry (estimated using 45 ancestry informative markers). The model was fit by the generalized estimating equation method to account for familial dependence among siblings.

The Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples T2D-GENES Consortium (T2D-GENES):

All the exons were sequenced in 12,294 additional individuals as part of the whole-exome sequencing studies performed through the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) consortia. Individuals were selected spanning 5 ethnicities: European (the FUSION study (5)[FUSION], the METSIM study (6)[METSIM], KORA-gen (7)[KORA], the WTCCC/UKT2D consortium (8; 9)and the UK Adult Twin Registry (10)[UKT2D], as well as Ashkenazi individuals recruited from the metropolitan New York region (11)[Ashkenazim] and small number of individuals from the Finnish [Botnia] and Swedish [Malmo] prospective cohorts used for the initial sequencing experiment (12-19)), African-American (the Jackson Heart Study (JHS) cohort [JHS] as well as additional individuals recruited from North Carolina, South Carolina, Georgia, Tennessee, or Virginia (20)[WFS]), South Asian (the London Life Sciences Prospective Population Study (LOLIPOP) (21; 22)[LOLIPOP] and Singapore Indian Eye Study (SINDI) (23)[Singapore Indians]), East Asian (the Korean Association REsource (KARE) (24)[KARE] as well as the Singapore Diabetes Cohort Study (SDCS) and Singapore Prospective Study Program (25-27)[Singapore Chinese]), and Hispanic (the San Antonio Family Heart Study (FHS) (28), the San Antonio Family Diabetes/Gallbladder Study (SAFDGS) (29), the Veterans Administration Genetic Epidemiology Study (VAGES) (30), the Family Investigation of Nephropathy and Diabetes (FIND) (31), San Antonio component [San Antonio], and individuals from Starr County, TX (32)[Starr

County]). Data generation and processing was performed in an identical fashion as for the initial sequencing experiment, although target capture was performed with the Agilent SureSelect Human All Exon platform rather than a custom hybrid capture array.

Diabetes in Mexico Study 2 (DMS2):

This cohort included 1228 unrelated volunteers from different ethnic groups along Mexico (Tarahumara, Yaqui, Mayo, Mixteco, Náhuatl, Otomí, Chinanteco, Mixe, Zapoteco, Mazateco, Totonaco, Huasteco, Maya, Kanjobal, Mame, Poptijacalteco, Kaqchikel, Tojolabal, Chontal, Huave). Inclusion criteria were that they identified themselves as indigenous, both parents and their four grandparents speak the same native language and were born in the same community. The diagnosis of T2D was made based on ADA criteria. Seven hundred eighty-three unrelated healthy subjects older than 45 years and with fasting glucose levels below 100 mg/dL were classified as controls. Four hundred forty-five unrelated individuals, older than 18 years, with either previous T2D diagnosis or fasting glucose levels above 125 mg/dL were included as T2D cases. Individuals with fasting glucose levels between 100-125 mg/dL were excluded. Informed consent was obtained from all participants. The study was conducted with the approval of the Ethics and Research Committees of all institutions involved. Genomic DNA was purified from whole blood samples using a modified salting-out precipitation method (Gentra Puregene, Qiagen Systems, Inc., Valencia, CA, USA). Genotyping of the rs149483638 variant was performed using a custom TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) and genotype of each sample was assigned automatically by SDS 2.3 software (Applied Biosystems, Foster City, CA, USA). For the genotyping quality control, 5% of samples were randomly selected and measured in duplicates. TaqMan probes: Allele ‘C’ VIC-CAAACTCTCCA[G]GAGATG. Allele ‘T’ FAM-CAAACTCTCCA[A]GAGATG. 5 Positive controls were added to all plates and verified that their genotype matched the expected.

Association analyses were performed by logistic regression adjusting for age, BMI, gender ant the

first two principal components derived from a panel of 96 ancestry informative markers (33).

Clinical history of these individuals was manually reviewed and incidence of difference diseases was used for the phenome-wide association analysis.

San Antonio Mexican American Family Studies (SAMAFS):

Genotypes for rs11564732, which showed an r2=0.89 with rs149483638 in our discovery sample, was carried out using the MassARRAY system (Sequenom, San Diego, CA). Variant assay primers were designed using Sequenom's online assay design tool in conjunction with their MassARRAY Assay Designer v4.0 software, to amplify ~100bp surrounding the variant for amplification in the MassEXTEND reaction. The MassARRAY Matrix Liquid Handler was used for automated preparation of reaction products which were then spotted onto 384-sample SpectroCHIP arrays using the MassARRAY Nanodispenser chip spotting station. Spotted arrays were loaded into the MassARRAY Analyzer 4 and sample genotypes determined by measuring the migration times, within a vacuum for each base at a specific locus (MALDI-TOF MS). Analysis of spectra and generation of genotypes was conducted using Sequenom's TyperAnalyzer software v4.0.21. Samples were from three Mexican American family studies from San Antonio, Texas: San Antonio Family Heart Study (28)(SAFHS); San Antonio Family Diabetes/Gallbladder Study (29)(SAFDGS); and the Veterans Administration Genetic Epidemiology Study (30). These studies are referred to as the San Antonio Mexican American Family Studies (SAMAFS). The rs11564732 genotypic data were available for 2,980 SAMAFS individuals (Mean age [± SD]=49.9 ± 15.6; Mean BMI [± SD]=32.3 ± 8.2; Females=61%; T2D=40%).

The association analysis was carried out using FBAT, assuming the additive model and using the residuals resulting from regressing out age, age^2 and BMI (34).

Diabetes Prevention Program

IGF2 loss-of-function T2D protective variant

The DPP enrolled 3,234 US participants at high risk of developing diabetes (on the basis of overweight, increased fasting glucose and impaired glucose tolerance) and randomised them to placebo, metformin 850 mg twice daily or a lifestyle intervention aimed at ≥7% weight loss and ≥150 min of physical activity per week; a fourth arm of 585 participants initially randomised to troglitazone was terminated early because of concerns with hepatotoxicity (35). The main endpoint was development of diabetes confirmed by OGTT. The trial was conducted at 27 centers, all of which obtained individual Institutional Review Board approval. The DPP showed that participants treated with metformin or with a lifestyle intervention were 31% or 58% less likely to develop diabetes after an average of 3 years of follow-up, respectively (35). The 3,548 DPP participants presented here (2,994 who completed the trial in the placebo, metformin or lifestyle arms, plus 554 originally randomised to troglitazone) provided informed consent specific to genetic investigation. The distribution of self-reported ethnicities among participants in this genetic study was 56.4% white, 20.2% African American, 16.8% Hispanic, 4.3% Asian and 2.4% American Indian. The mean age was 51 years and mean BMI was 34.0 kg/m^2.

rs149483638 was genotyped as part of the Human Core Exome genotyping array from Illumina at the Genomics Platform at the Broad Institute. Genotyping and calling was performed as described below. Genotyping of rs149483638 was completed with high quality on the Human Core Exome genotyping arrays (99.9% call rate). The association between the outcome variables and the marker was tested using multivariable mixed model regression. All models were adjusted for age at randomization, sex, study site, and population stratification using principal components derived only from Hispanic and Amer-Indian subjects. Clinic was entered into the model as a random effect. In additional models, waist was added in addition to these covariates. Because of the low frequency of the minor allele in the other ethnic groups, only self-reported Hispanics (n=538) and American Indians (n=78) are included in the analysis. These two groups were analyzed together and then tested in stratified models as only the Hispanic group has individuals homozygous for the rare

allele. Given the possibility that variants in *IGF2* exhibit a parent-of-origin effect, besides the additive model (per allele effect) we also tested the homozygous extremes model (comparing CC vs TT) in order to reduce the noise of heterozygous subjects in cases parent-of-origin is present.

The natural log of ISI and the IGR was used in the analysis because their distributions are skewed. Because these hypotheses represent confirmation of previous findings (and thus possess a high prior probability), a P value of 0.05 was considered statistically significant. Insulin sensitivity index (ISI), the reciprocal of insulin resistance by homeostasis model assessment, was calculated as 22.5/[fasting insulin x (fasting glucose/18.01)]. The mean ISI values were compared at baseline.

The Insulin Index was defined as [(insulin at 30 min) – (insulin at 0 min)]/[(glucose at 30 min) – (glucose at 0 min)]. The mean Ins Index values were compared at baseline.

Resource for Genetic Epidemiology Research on Adult Health and Aging (GERA)

GERA cohort data was obtained through dbGaP under accession phs000674.v1.p1 (36). The Resource for Genetic Epidemiology Research on Aging (GERA) Cohort was created by a RC2 "Grand Opportunity" grant that was awarded to the Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH) and the UCSF Institute for Human Genetics (AG036607; Schaefer/Risch, PIs). The RC2 project enabled genome-wide SNP genotyping (GWAS) to be conducted on a cohort of over 100,000 adults who are members of the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC), and participating in its RPGEH. The resulting GERA cohort is 42% male, 58% female, and ranges in age from 18 to over 100 years old with an average age of 63 years at the time of the RPGEH survey (2007). The sample is ethnically diverse, generally well-educated with above average income. Approximately 69% of the participants are married or living with a partner. Length of membership in KPNC averages 23.5 years. UCSF and RPGEH investigators worked with the genomics company Affymetrix to design four custom microarrays for genotyping each of the four major race-ethnicity groups included in the GERA

Cohort, described in detail in Hoffmann et al., 2011a and 2011b. Following genotyping and quality control procedures, and after removal of invalid, discordant, or withdrawn samples, about 103,000 participants were successfully genotyped. The resulting genotypic data were linked to survey data and data abstracted from the electronic medical records. As described below, all RPGEH participants were mailed new consent forms with explicit discussion of the placement of data in the NIH-maintained dbGaP. About 77% of participants returned completed consent forms, resulting in a final sample size of 78,486 participants in the GERA Cohort with data for deposit into dbGaP.

A subset of Hispanic individuals (1064 cases and 4832 controls) from the GERA cohort, as potential carriers of the rs149483638 variant were separately QCed and analyzed. All genotyped datasets separately underwent the same 3-step quality control protocol using PLINK and included 2 stages of SNP removal and an intermediate stage of sample exclusion.

The exclusion criteria for genetic markers consisted on: proportion of missingness ≥ 0.05, Hardy-Weinberg Equilibrium p-value $\leq 1x10^{-20}$ for all the cohort. Only for the GERA cohort we considered a MAF of 0.001 as exclusion criteria because of the large sample size of this dataset. This protocol for genetic markers was performed twice, before and after sample exclusion.

For the individuals, we considered the following exclusion criteria: gender discordance, subject relatedness (pairs with ≥ 0.125 from which we removed the individual with the highest proportion of missingness), variant call rates ≥ 0.02 and population structure showing more than 4 standard deviations within the distribution of the study population according to the first seven principal components.

The presence of up to 18 medical conditions besides T2D was taken into account for the phenome-wide association analysis. The description of ICD9 codes that are included in each of the medical conditions can be found here (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd004308).

We performed a two-stage imputation procedure, which consisted in pre-phasing the genotypes into whole chromosome haplotypes followed by imputation itself. The pre-phasing was performed using the SHAPEIT2 (37)tool, IMPUTE2 for genotype imputation and the SNPTEST (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html#introduction) tool for association testing. GWIMp-COMPSs can incorporate the contribution of several reference panels, and in this work we used 1000 Genomes (1000G) Phase3 haplotypes (October, 2014) (38). Association testing was performed by additive logistic regression using SNPTEST, and adjusting for the 7 derived principal components, age, and body mass index.

Exome chip SNP genotyping and quality control

The Genomics Platform at the Broad Institute (Cambridge, MA) received, QC'd and tracked DNA samples for Exome array processing. The exome array was designed in order to cover rare and low-frequency coding variants identified through whole-exome sequencing studies of 12,031 individuals from different populations including 362 individuals of Hispanic ancestry.

The samples were plated into 96-well plates that included a quality control sample for processing on the Illumina HumanExome BeadChip (Illumina, Inc. San Diego, CA) using manufacturer's protocols. The arrays were scanned using Illumina iScans. Genotypes were called using three different calling algorithms: Illumina GenCall, Z-call (39) and Birdsuite (http://www.broadinstitute.org/science/programs/medical-and-population-genetics/birdsuite/birdsuite-0).

Clusters were fit using the Birdseed algorithm to each genotyping plate independently. Genotypes with confidence below 99.9% were excluded from analysis (e.g. considered "missing" or "no-call" genotypes). Samples with low numbers of non-reference alleles (< ~20,000, depending on the cohort), low call rate (<99.3%) or unusually high heterozygosity (> ~0.05, depending on the cohort) were removed from subsequent analysis; thresholds were chosen based on visual inspection of the

sample distributions. Variants with low call rate (<99.2%) or mean confidence for alternative genotype calls (<99%) were also excluded from subsequent analysis.

RNA isolation from frozen tissue samples

RNA was extracted via the miRNeasy Mini Kit from Qiagen. This kit combines a phenol/guanidine-based lysis and a silica-membrane based purification. Tissue specimens were prepared and cut to 20-25 mg on a dry ice bath, then placed in 2 mL processing tubes containing QIAzol lysis reagent and a steel bead. Tubes were then placed in the TissueLyser for 5 min at 25Hz to lyse and homogenize the samples.

After homogenizing, tubes were incubated at room temperature for 5 min. 140 µl chloroform was then added to each tube containing homogenate. Samples incubated at room temperature for 2-3 min and were centrifuged at 12,000xg/4C for 15 min.

After centrifugation, the samples separated into 3 phases: an upper, colorless aqueous phase containing RNA, a white interphase, and a lower, red organic phase. The upper aqueous phase was carefully transferred to a new 1.5mL eppendorf tube (~350 µL). 525 µL of 100% ethanol was added to this phase and mixed thoroughly by pipetting up and down several times.

The entire sample, including any precipitate, was pipetted into RNeasy mini spin columns and then centrifuged for 15 s at 8000xg in order to collect and discard the flow-through.

350 µL Buffer RWT was pipetted into the RNeasy Mini spin column and centrifuged for 15s at 8000xg to wash. The flow-through was again discarded.

80 µL of DNase I diluted with buffer RDD was pipetted directly onto each column membrane and incubated at room temp for 15 minutes.

350 µL Buffer RWT was then pipetted onto the DNase I remaining on the RNeasy Mini spin column and centrifuged for 15s at 8000xg, flow through discarded

700 µL Buffer RWT was then added to the RNeasy Mini spin column, centrifuged for 15s at 8000xg, and the flow through discarded.

500µL Buffer RPE was then pipetted onto the RNeasy Mini spin column and centrifuged for 15s at 8000xg. The flow through was again discarded Again 500 µL Buffer RPE was pipetted onto the RNeasy Mini spin column and centrifuged for 2 min at 8000xg.

The RNeasy Mini spin columns were then placed into new 2mL collection tubes and centrifuged at full speed for 1 min. This allowed the membrane to fully dry out, ensuring no ethanol was carried over during RNA elution.

For each sample, the RNeasy Mini spin column was transferred to a new 1.5 ml eppendorf tube. 20 µL RNase-free water was then added directly to the spin column membrane. The tubes were then centrifuged for 1 min at 8000xg to elute the RNA. This step was then repeated a second time.

The RNA samples were then capped and incubated at 65˚C × 5 minutes to denature the RNA and then chilled immediately on wet ice for 2-3 minutes.

Supplementary text (online)

Fine mapping and credible set analysis of IGF2-INS-TH locus

In order to better characterize both the primary and the secondary signal, we performed a credible set analysis of the two regions, after integrating the exome chip results with Omni 2.5 Illumina array genotypes that were available for the majority of the samples (1), and exome-sequencing data that was available for 41% of the samples (2)genotyped by exome-chip. We imputed both exome-seq and 1000G (phase 3, release June 2014) variants into the samples that did not have whole-exome sequencing information, and only 1000G (phase 3) variants into the samples that had whole-exome sequencing, OMNI2.5 and exome chip genotypes. We then performed the association testing separately of each dataset and meta-analyzed both results (Supplementary Figure 1). We used this

data as input to perform the credible set analysis, following the previously described methodology (40). The splice site variant (rs149483638) ranked first according to its posterior probability, being the one with the highest prior of being the causal variant (Supplementary Figure 2).

When conditioning for these two *KCNQ1* variants and the rs149483638 in order to identify secondary signals, we identified another independent association with rs10770141 (OR=1.14; $p=3\times10^{-4}$) located at the promoter region of TH gene. This variant was previously reported in a gene-centric meta-analysis (41). When meta-analyzing our data with those of this study, rs10770141 resulted in a novel GWAS significant signal, which was independent of the first splice-site variant in *IGF2* (OR=1.08 (1.05-1.11); $p=1.1\times10^{-9}$) (Supplementary Figure 1).

We also used the fraction of the dataset for which we had exome-sequencing data in order to discard if rare variants with a strong effect size are the cause of a "synthetic association" (42), i. e. that rare variants with large effect size, are responsible for the association signal found in the common variant (rs149483638). For this purpose, we performed multiple regression analyses introducing the rare variants as covariates, to test if this caused a loss of the association signal in rs149483638. This analysis confirmed that we were not in front of a synthetic association, as at least 31 rare variants had to be excluded in order to dilute the signal of the rs149483638 variant (Supplementary Figure 3).

Credible set analysis

The credible set analysis were constructed as described in (40). Briefly, for each association analyses results, we computed an approximate Bayes factor for each variant,

$$r = \frac{0.04}{se^2 + 0.04}$$

$$z = beta/se$$

IGF2 loss-of-function T2D protective variant

$$abf = \frac{\sqrt{(1-r)}}{\exp\left(-r \times \frac{z^2}{2}\right)}$$

assuming that the prior on beta is Gaussian and variance 0.04. Then, a posterior probability for each variant was computed dividing the ABF by the total number of variants in the region. Then the cumulative posterior probability was computed and all the variants in the 95% credible set interval were selected and included in the credible set. Assuming that we had two independent signals in the *IGF2* region, we computed a first credible set conditioning on the two *KCNQ1* T2D associated variants (rs139647931 and rs2237897) and the rs4929965, and a second credible set conditioning on rs149483638 variant and the two *KCNQ1* T2D associated variants (rs139647931 and rs2237897). We selected all the variants that showed an r-squared higher than 0.1 with the top variants in each of the regions to compute the credible set analysis.

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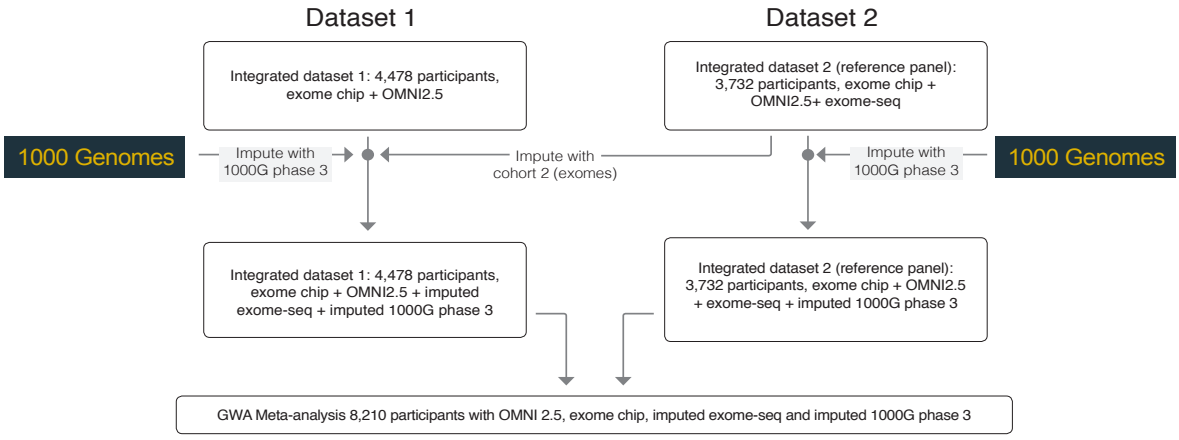
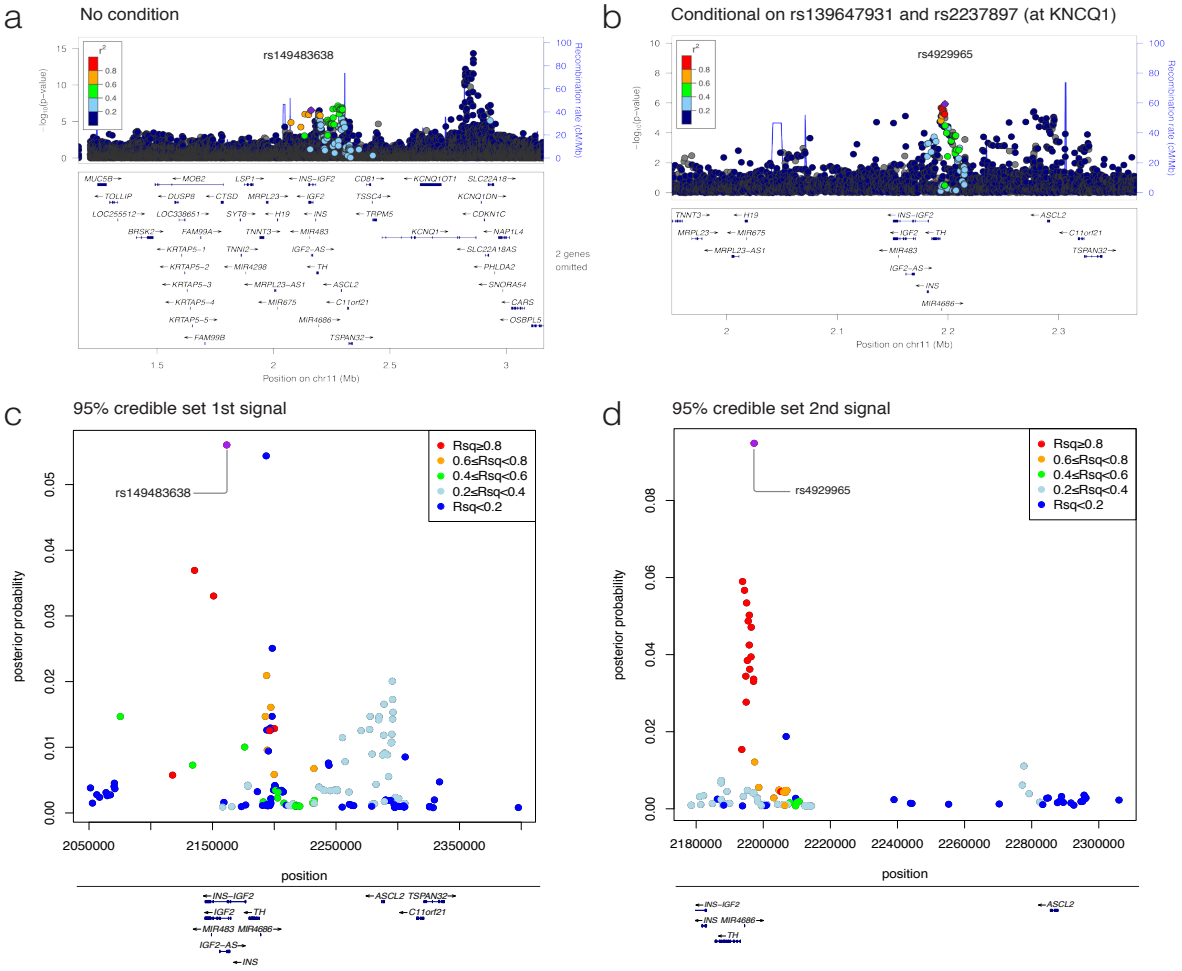
Supplementary Figure 1

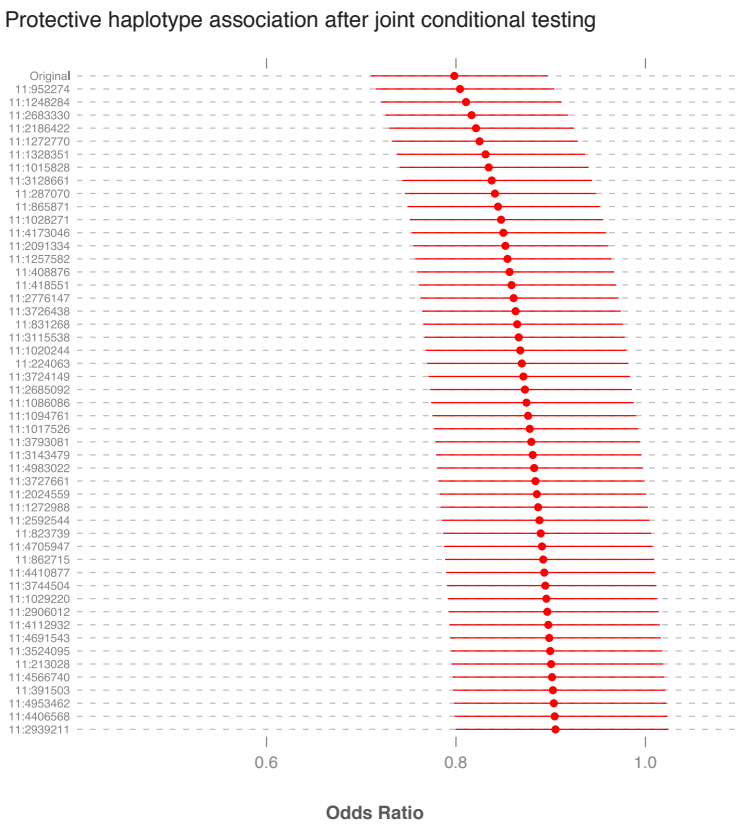


Supplementary Figure 2

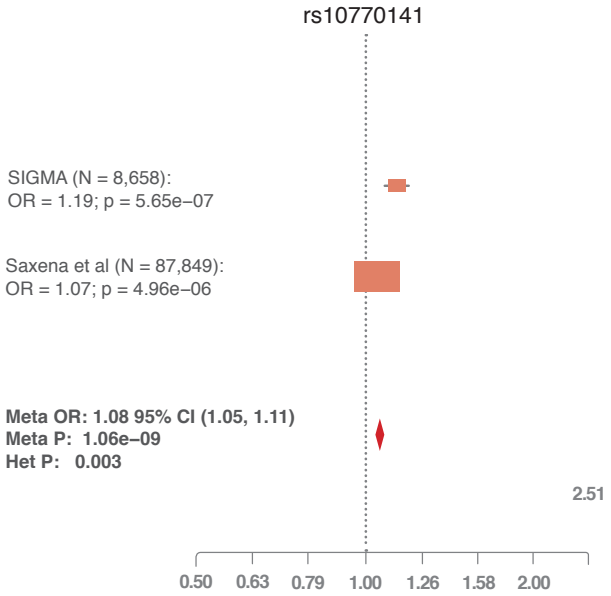


SUPPLEMENTARY DATA

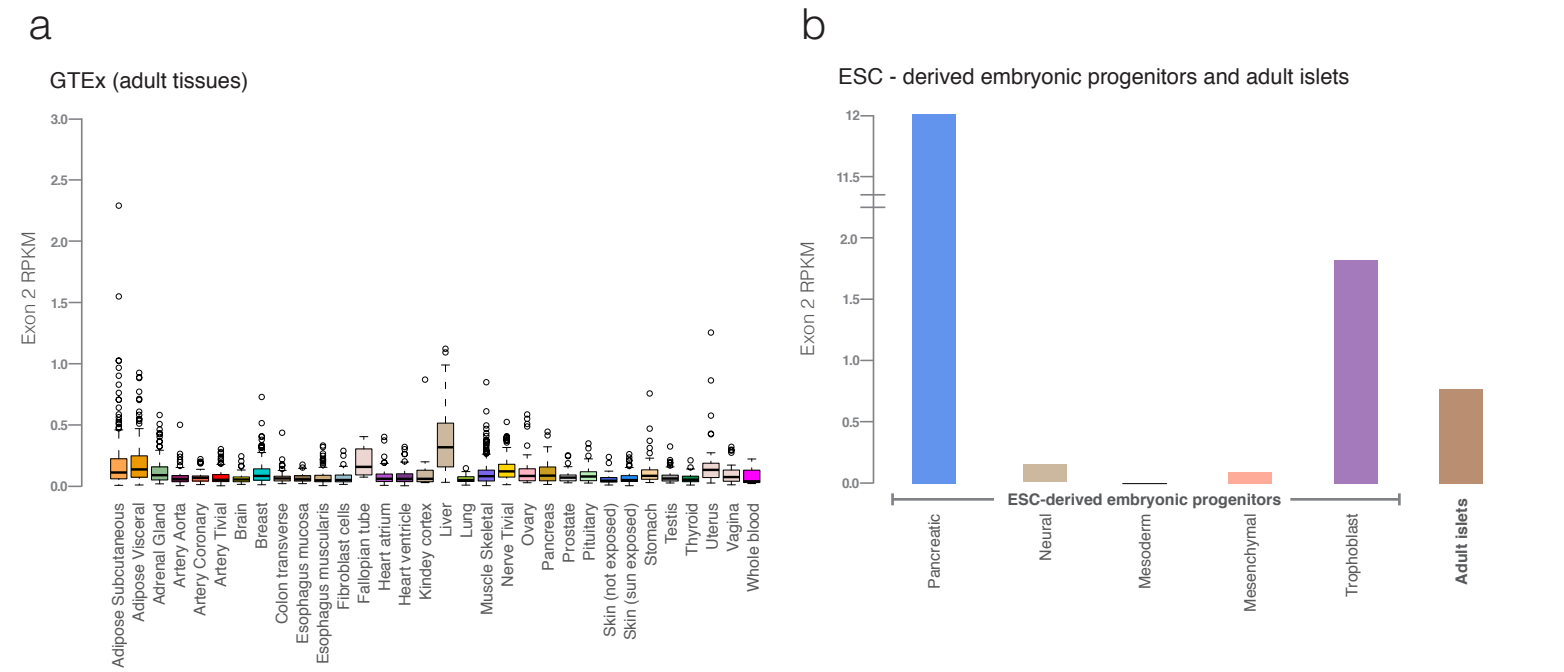
Supplementary Figure 3



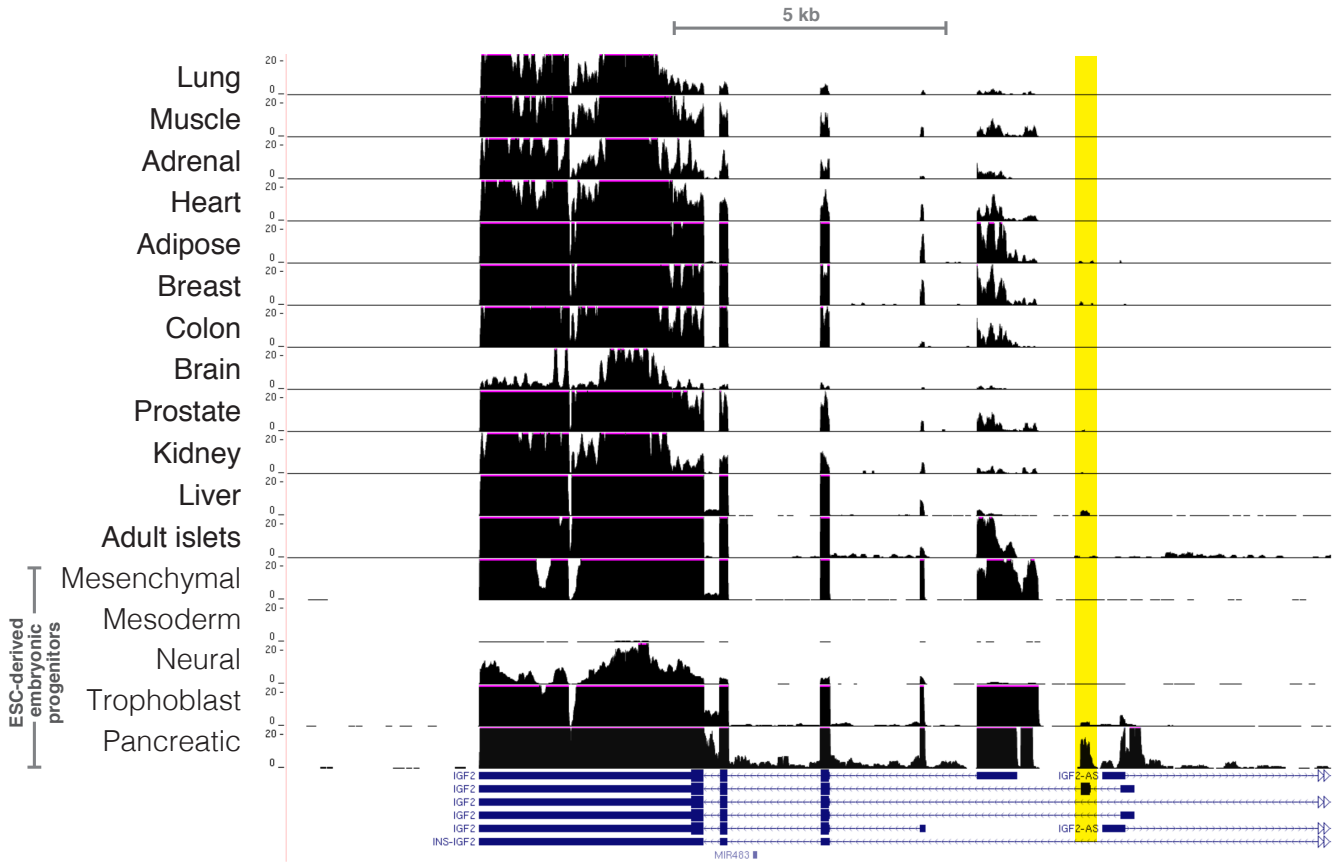
Supplementary Figure 4



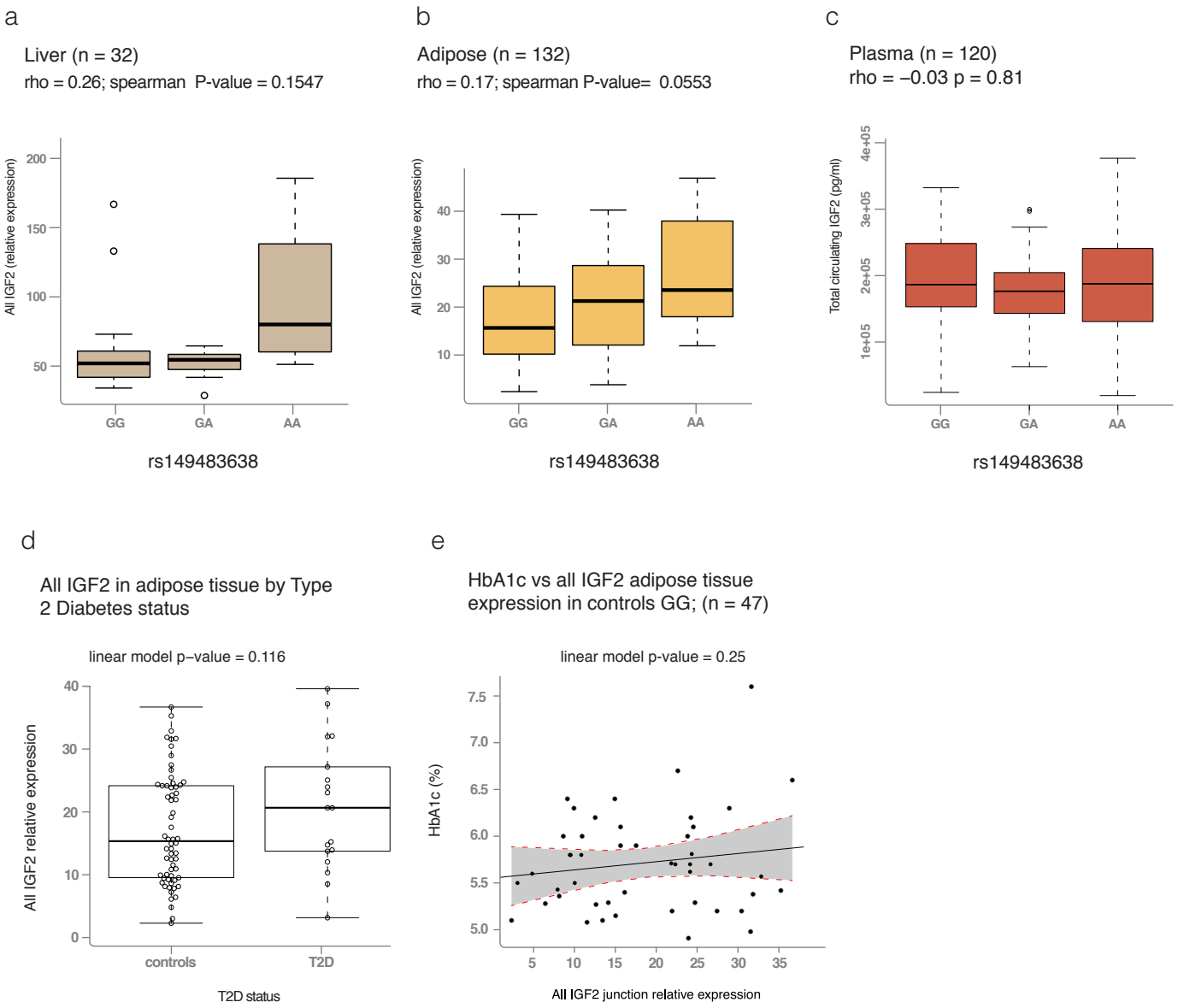
Supplementary Figure 5



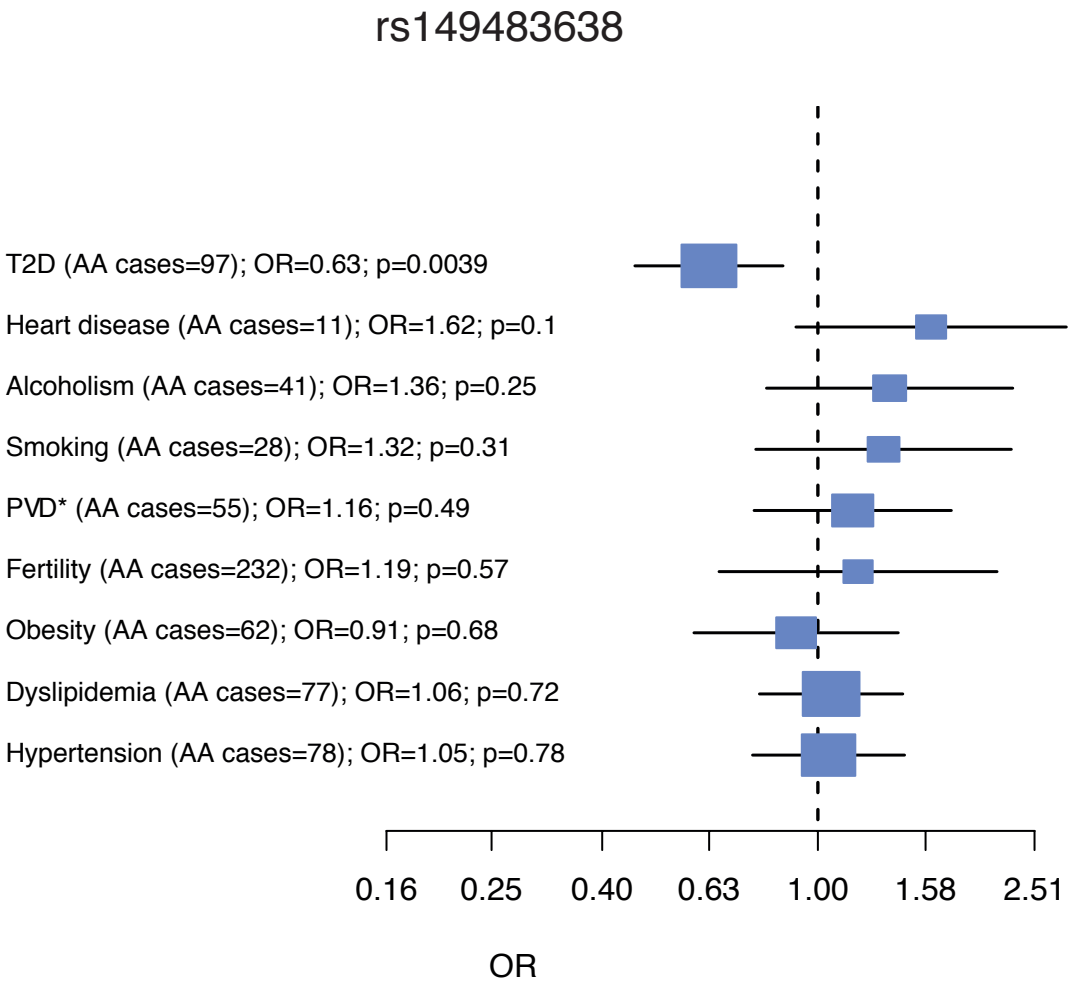
Supplementary Figure 6



Supplementary Figure 7



Supplementary Figure 8



Supplementary Table 1: Top hits identified by exome chip association analysis. Odds ratios and p-values where derived by Wald's test, after adjusting for BMI, the first 10 principal components to adjust for population stratification and body mass index (BMI), age and sex. Directional consistency with previous studies is also represented.

rsid	Chr	Position	Closest Gene	Consequence	Reference Allele	Alternative Allele	MAF Affected	MAF Unnaffected	Number Effective Samples	Odds Ratio Wald Test adjusted	*p*-value Wald Test corrected	Odds ratio directionally consistent?
rs7903146	10	114758349	*TCF7L2*	intron variant	C	T	0.24	0.20	8622	1.38	4.76E-17	+
rs7901695	10	114754088	*TCF7L2*	intron variant	T	C	0.25	0.22	8622	1.31	5.03E-13	+
rs4506565	10	114756041	*TCF7L2*	intron variant	A	T	0.25	0.22	8617	1.31	6.63E-13	+
rs12243326	10	114788815	*TCF7L2*	intron variant	T	C	0.19	0.17	8622	1.31	6.23E-11	+
rs2237892	11	2839751	*KCNQ1*	intron variant	C	T	0.26	0.29	8622	0.80	2.46E-10	+
rs13342692	17	6946287	*SLC16A11*	missense variant	T	C	0.35	0.29	8622	1.24	4.75E-10	+
rs117767867	17	6946330	*SLC16A11*	missense variant	C	T	0.33	0.27	8620	1.22	7.33E-09	+
rs149483638	11	2161530	*INS-IGF2*	splice acceptor variant	C	T	0.17	0.18	8622	0.80	1.36E-07	novel
rs849134	7	28196222	*JAZF1*	intron variant	A	G	0.32	0.37	8622	0.84	2.63E-07	+
rs864745	7	28180556	*JAZF1*	intron variant	T	C	0.32	0.37	8610	0.85	3.97E-07	+
rs1635852	7	28189411	*JAZF1*	intron variant	T	C	0.32	0.37	8611	0.85	6.49E-07	+
rs2184898	10	119418104	*EMX2*	-	G	A	0.25	0.23	8613	1.20	1.12E-06	novel
rs2237895	11	2857194	*KCNQ1*	intron variant	A	C	0.47	0.43	8622	1.16	2.86E-06	+
rs1421085	16	53800954	*FTO*	intron variant	T	C	0.23	0.21	8621	1.18	1.48E-05	+
rs1558902	16	53803574	*FTO*	intron variant	T	A	0.23	0.21	8621	1.18	1.59E-05	+

SUPPLEMENTARY DATA

Supplementary Table 2. Quantitative trait association results for rs149483638 in the discovery cohorts. P-values and effect sizes, and standard error of rs149483638-G allele with quantitative traits in non-diabetic individuals are represented.

Trait	Effective sample size	MAF	additive *p*-value	additive beta	additive S.E. beta
Fasting Glucose	2215	0.2043	0.3	0.0057	0.0053
Fasting Insulin	1515	0.2071	0.8	-0.0100	0.0381
2-hour glucose challenge	535	0.1998	0.3	0.0413	0.0392
Glycated Hemogoglobin	544	0.1998	0.1	0.0649	0.0418
Cholesterol	2210	0.2043	0.5	0.0249	0.0348
LDLC	1522	0.2066	0.9	-0.0050	0.0427
HDLC	1597	0.2053	0.8	-0.0105	0.0437
TG	2210	0.2043	0.8	0.0396	0.0297
BMI	4364	0.1862	0.2	0.0382	0.0272

LDLC: low-density lipoprotein cholesterol, HDLC: High-density lipoprotein cholesterol, TG: Triglycerides, BMI: Body Mass Index

Supplementary Table 3. Variants in linkage disequilibrium with rs149483638 (R-squared higher than 0.5) and their predicted functional impact

						Variant Effect Predictor (most severe consequence)		
rsid	**chr:position(bp)**	**Allele1**	**Allele2**	**R-squared with top variant**	**postProb**	**Consequence**	**IMPACT**	**SYMBOL**
rs149483638	chr11:2161530	T	C	1.000	0.056	splice_acceptor_variant	HIGH	IGF2
rs144656014	chr11:2135474	A	G	0.823	0.037	intergenic_variant	MODIFIER	-
rs11564732	chr11:2150895	T	C	0.852	0.033	3_prime_UTR_variant	MODIFIER	IGF2
rs10840490	chr11:2193817	C	G	0.619	0.021	upstream_gene_variant	MODIFIER	TH | MIR4686
rs34779113	chr11:2197234	G	GC	0.625	0.016	regulatory_region_variant	MODIFIER	TH | MIR4686
rs10840489	chr11:2192798	T	C	0.602	0.015	intron_variant	MODIFIER	TH | MIR4686
rs146043837	chr11:2075378	A	C	0.550	0.015	intergenic_variant	MODIFIER	-
rs187839678	chr11:2200156	T	C	0.841	0.013	regulatory_region_variant	MODIFIER	-
rs192912194	chr11:2196425	A	G	0.854	0.013	upstream_gene_variant	MODIFIER	TH | MIR4686
rs10840491	chr11:2194390	A	G	0.630	0.010	regulatory_region_variant	MODIFIER	TH | MIR4686
rs140996354	chr11:2232137	T	C	0.703	0.007	regulatory_region_variant	MODIFIER	-
rs11042982	chr11:2199963	C	G	0.603	0.006	regulatory_region_variant	MODIFIER	-
rs80089797	chr11:2117677	T	C	0.826	0.006	intergenic_variant	MODIFIER	-
rs6578993	chr11:2201163	T	C	0.595	0.003	intergenic_variant	MODIFIER	-
rs11043001	chr11:2203045	A	G	0.569	0.003	intergenic_variant	MODIFIER	-
rs7126800	chr11:2202668	A	C	0.586	0.002	intergenic_variant	MODIFIER	-
rs7925375	chr11:2191155	T	C	0.531	0.002	intron_variant	MODIFIER	TH | MIR4686
rs12224088	chr11:2217358	C	G	0.507	0.001	intergenic_variant	MODIFIER	-
rs147580690	chr11:2216970	CA	C	0.515	0.001	regulatory_region_variant	MODIFIER	-

Supplementary Table 4. Association results for each of the cohorts and meta-analysis using both inverse-variance fixed effects model and sample size model.

Dataset	N	OR (95% CI)	p-value
SIGMA	8,658	0.8 (0.74-0.87)	$1.14x10^{-7}$
Pima	3,199	0.68 (0.57-0.81)	$1.09x10^{-05}$
SAFS*	2,982	Z = -2.3	0.021
T2D-GENES-HS	1,924	0.89 (0.7-1.13)	0.326
DMS2	1,228	0.71 (0.58-0.88)	0.001
GERA	5,896	0.82 (0.64-1.05)	0.11
DPP*	616	HR=0.76 (0.49-1.20)	0.24

	OR (95%CI)	Z-score	P-value
METAL (IVFE)	0.78 (0.73-0.84)	-	$5.61x10^{-14}$
METAL (SAMPLE SIZE)	-	-7.53	$4.78x10^{-14}$

*SAFS where analyzed by a family-based association test (FBAT) and where not included in the inverse-variance fixed effects meta-analyses. Since diabetes incidence in the DPP was computed by Hazard Ratios (HR), the results from the DPP were only included in the sample size meta-analysis.

Supplementary Table 5. Family-based association analysis in the San Antonio Families Study

Marker	Allele	afreq	fam#	S-E(S)	Var(S)	Z	*p*
rs11564732**	A	0.13	283	-35.259	234.871	-2.301	0.02

*Residuals where computed after regressing out the age+age^2+BMI.
**rs11564732* was used as a proxy for rs149483638 (Rsq= 0.85, 10.6 kb). A allele in rs11564732 co-segregates with the T allele in rs149483638

Supplementary Table 6. Association of human knockouts for isoform 2 of *IGF2* (AA homozygous) with other diseases or clinical outcomes.

Clinical Outcome	OR	Odds Ratio (95%CI)	P	HetTest	cohorts tested*	total AA cases	total AA controls	total GG cases	total GG controls
T2D Status	0.63	0.63 (0.46-0.86)	0.0039	0.19	DMS1+DMS2+GERA	97	195	1534	4873
Dyslipidemia	1.06	1.06 (0.78-1.43)	0.72	0.69	DMS1+DMS2+GERA	77	210	3096	3281
Fertility	1.19	1.19 (0.66-2.14)	0.57	0.82	DMS1+DMS2	232	24	914	263
Heart disease	1.62	1.62 (0.91-2.87)	0.1	0.24	DMS1+DMS2+GERA	11	273	1200	5133
Hypertension	1.05	1.05 (0.76-1.44)	0.78	0.029	DMS1+DMS2+GERA	78	210	2970	3427
Obesity	0.91	0.91 (0.59-1.41)	0.68	0.13	DMS1+DMS2	62	178	320	644
Peripheral Vascular Disease	1.16	1.16 (0.76-1.76)	0.49	0.078	DMS1+DMS2	55	192	241	856
Smoking	1.32	1.32 (0.77-2.27)	0.31	0.79	DMS1+DMS2	28	220	182	923

*The results were meta-analyzed, when possible with all the available cohorts with that clinical outcome available. Association analyses were corrected for age, BMI, and sex, and the first two principal components to correct for population stratification. Inverse-variant fixed effects meta-analysis was performed. Only clinical conditions with at least 10 AA carriers are presented.

Supplementary table 7. Association of rs149483638 variant with other diseases assessed in the Genetic Epidemiology Research on Aging (GERA). Effect sizes are considering the A allele as effect allele.

Clinical condition	cases (n)	controls (n)	cases MAF	controls MAF	p-value	OR
Varicose veins	259	5637	0.07	0.06	0.506	1.15
Cancer	1127	4769	0.04	0.06	0.522	0.92
Cardiovascular disease	1300	4596	0.05	0.06	0.844	0.98
Depression	887	5009	0.05	0.06	0.954	0.99
Dermathophytosis	997	4899	0.07	0.06	0.760	1.03
Type 2 diabetes	8,227	12,966	0.17	0.18	$5.6x10^{-14}$	0.78
Dyslipidemia	3149	2747	0.06	0.06	0.701	0.96
Hemorrhoids	974	4922	0.06	0.06	0.500	1.08
Hernia abdominopelvic cavity	557	5339	0.06	0.06	0.388	1.15
Hypertensive Disease	2921	2975	0.06	0.06	0.988	1.00
Insomnia	390	5506	0.05	0.06	0.876	1.03
Iron deficiency anemias	299	5597	0.07	0.06	0.277	1.23
Irritable bowel syndrome	362	5534	0.04	0.06	0.006	0.53
Macular Degeneration	225	5671	0.04	0.06	0.616	0.86
Osteoarthritis	1961	3935	0.05	0.06	0.705	1.04
Osteoporosis	450	5446	0.05	0.06	0.810	0.96
Psychiatric: any	1154	4742	0.06	0.06	0.439	1.09
Peripheral Vascular Disease	347	5549	0.05	0.06	0.834	1.05
Acute reaction to stress	662	5234	0.06	0.06	0.591	1.08

* Association analyses were corrected for age, BMI, and sex, and the first two principal components to correct for population stratification. For type 2 diabetes, the meta-analysis results of the discovery and replication cohorts are presented.

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