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Genome-wide Linkage and Association Analysis of Cardiometabolic Phenotypes in Hispanic Americans

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Abstract

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Linkage studies of complex genetic diseases have been largely replaced by Genome-Wide Association studies (GWAS), due in part to limited success in complex trait discovery. However, recent interest in rare and low-frequency variants motivates reexamination of family-based methods. In this study we investigated the performance of two-point linkage analysis for over 1.6 million SNPs combined with single variant association analysis to identify high impact variants which are both strongly linked and associated with cardiometabolic traits in up to 1 414 Hispanics from the Insulin Resistance Atherosclerosis Family Study (IRASFS). Evaluation of all 50 phenotypes yielded 83 557 000 LOD scores with 9 214 LOD scores ≥ 3.0, 845 ≥ 4.0, and 89 ≥ 5.0, with a maximal LOD score of 6.49 (rs12956744 in the *LAMA1* gene for TNFα receptor 2). Twenty-seven variants were associated with $p < 0.005$ as well as having a LOD score > 4, including variants in the *NFIB* gene under a linkage peak with TNFα receptor 2 levels on chromosome 9. Linkage regions of interest included a broad peak (31Mb) on chromosome 1q with acute insulin response (max LOD = 5.37). This region was previously documented with type 2 diabetes in family-based studies, providing support for the validity of these results. Overall, we have demonstrated the utility of two-point linkage and association in comprehensive genome-wide array-based SNP genotypes.

Keywords

linkage analysis; cardiometabolic; acute insulin response; Hispanic

Introduction

Family-based linkage analysis has largely been supplanted by genome-wide association studies, often using unrelated samples, following the limited success of linkage when applied to complex traits. Family-based analyses, however, have inherent strengths which complement other approaches for identification of contributors to complex phenotypes[1,2]. Such analyses may be especially applicable to identifying low frequency (minor allele frequency [MAF] 0.01–0.05) to rare (MAF < 0.01) alleles with high impact[3–8]. We have implemented approaches in parallel which utilize simple two-point linkage analysis and conventional association analysis to search for genetic variants with meaningful contributions to phenotypic variance of traits. Two-point linkage analysis considers each variant independently, unlike multipoint analysis which integrates the information from multiple variants simultaneously. Therefore, two-point linkage does not have the same issues with inflation due to linkage disequilibrium between markers and can be used to test putatively impactful variants for linkage directly. The combined two-point linkage and association approach has the advantage of being able to directly align SNP results for the two analyses, pinpointing variants which show evidence of both linkage and association at the single SNP level. In prior studies, this has been applied to exome chip data, thus focusing on coding variants[9] and characteristics of a functional SNP[10].

Evaluation of association in the context of linkage has an extensive history[11–13], with association typically utilized to determine whether genetic variants residing under the linkage peak explain the observed signal. We have observed that instances of strong linkage and association together at a single locus (e.g. APOE with ApoB levels, CETP with HDL

levels, ADIPOQ with adiponectin levels)[9,10] represent variants or loci which have a striking impact on phenotype, reflected as explanation of a high proportion of the variance of the trait (3–60%). We have also observed this across a range of minor allele frequencies (1–45%), indicating that this approach can be informative for a full range of genetic variation. Other groups have utilized combined metrics of linkage and association to identify variants with large impact[11]; however, that is a project currently undergoing evaluation separate from these analyses.

Here we have investigated the performance of these approaches in a contemporary genetic dataset consisting of comprehensive genome-wide and exome chip data encompassing 1.6 million SNPs in 90 Hispanic families from the Insulin Resistance Atherosclerosis Family Study (IRASFS). Based on our prior work and recent evidence for the existence of high impact non-coding variants[14], we hypothesize this family-based method is applicable to the search for such variants.

Materials and Methods

Samples and Phenotype Data

The samples used in this study are from the Hispanic cohorts of the Insulin Resistance and Atherosclerosis Family Study (IRASFS)[15]. Briefly, subjects were ascertained on the basis of large family size in San Luis Valley, Colorado and San Antonio, Texas. The sample consisted of 1 425 individuals from 90 families, who were extensively phenotyped, including a frequently sampled intravenous glucose test (FSIGT), measures of blood lipids and inflammatory markers, anthropomorphic measures, as well as fat deposition measures by computed tomography (CT) and dual X-ray absorptiometry (DXA) scans. IRB approval was obtained at all clinical and analysis sites, and all participants provided informed consent.

Genotype Data

SNP genotype data from three genotyping chips were utilized. Illumina OmniExpress and Illumina Omni 1S chips were genotyped as part of the Genetics Underlying Diabetes in Hispanics (GUARDIAN) Consortium (N = 1034 and 1038, respectively)[16], and the Illumina HumanExome Beadchip was genotyped on a larger subset (N = 1414)[9] of the full IRASFS Hispanic cohorts. Genotyping of the Illumina HumanExome BeadChip v1.0 (N = 552) and v1.1 (N = 862) was performed at the Wake Forest Center for Genomics and Personalized Medicine Research, while the Illumina HumanOmniExpress BeadChip and Illumina Omni1S BeadChip were genotyped at the core genotyping laboratory at Cedars-Sinai Medical Center. All genotypes were called separately by genotyping array using GenomeStudio (Illumina, San Diego, CA). Sample and autosomal SNP call rates were ≥0.98 (>0.99 SNP call rates for the OmniExpress and Omni1S chips), and Exome Chip SNPs with poor cluster separation (<0.35) were excluded. All datasets independently underwent Mendelian error checking using PedCheck[17] to detect genotypes discordant in families for Mendelian inheritance, with resolution by removing all inconsistent genotypes. The total number of unique SNPs available for analysis following QC was as follows: 81 559 from the

Exome Chip, 668 758 from OmniExpress and 920 823 from the Omni1S chip, for a total of 1 671 140 SNPs.

Imputation to the 1000 Genomes integrated reference panel (version 2) was performed using genotypes and samples from the OmniExpress dataset (N = 634K genotypes and 1034 individuals) using SHAPEIT[18] for phasing and IMPUTE2[19] for imputation.

Analyses

SNPs were evaluated for both two-point family-based linkage and single SNP association using Sequential Oligogenic Linkage Analysis Routines (SOLAR)[20] separately by genotyping platform. Both analyses used age, sex, body mass index (BMI), and study center as covariates. All phenotypes evaluated were transformed to approximate normality of the residuals if necessary (Supplementary Table 1). Additionally, due to the high impact of a low frequency variant known to influence adiponectin levels in this population[3,10], presence of the variant encoding the G45R missense mutation in *ADIPOQ* (rs200573126) was included as a covariate for analyses involving adiponectin. Visceral adipose tissue area (VAT), visceral to subcutaneous tissue ratio (VSR), waist circumference, and waist-to-hip ratio (WHR) were run both with and without BMI as a covariate. However subcutaneous adipose tissue area (SAT), percent body fat, and body adiposity index (BAI) were not adjusted for BMI. All association analyses included three admixture proportions as covariates. Existing admixture proportion estimates were available from previously genotyped exome chip data; estimates were computed by maximum likelihood estimation of individual ancestries in ADMIXTURE[21] assuming five ancestral populations (K = 5) from exome chip-wide SNP data after pruning for linkage disequilibrium (LD) to produce admixture estimates for the greatest number of samples. Of the five variables considered, three variables were selected as representing the variation in these Hispanic samples, as inclusion of additional postulated ancestral populations began isolating individual pedigrees.

For validation of performance, genotypes imputed to the 1000 Genomes panel were also evaluated for linkage (and association) in two regions which were selected for their linkage regions as well as being phenotypically of particular interest to our group: chromosome 1 for acute insulin response to glucose (AIR) and chromosome 7 for insulin sensitivity index (S_I). Best guess genotypes from the imputed data were used in the linkage analysis because methods that account for imputation uncertainty have not been developed for linkage. These analyses used the same covariates as previously mentioned.

Results

The goal of this analysis was to test the utility of carrying out a combined linkage and association analysis in a contemporary dataset made up of GWAS (Illumina OmniExpress and Omni1S) and exome chip data encompassing over 1.6 million SNPs. The combined performance was evaluated for a total of 50 quantitative traits from 7 phenotypic groups: Glucose Homeostasis, Adiposity, Lipids, Biomarkers, Hypertension, Liver Enzymes, and Liver Fat, in 90 families from the IRASFS with an average family size of 15.4 individuals. Overall, 83 557 000 LOD scores and association p-values were calculated across the three genotyping sets.

Characteristics of the samples and genotyping are summarized in Table 1. The sample consisted of 1418 individuals from 90 families. Specifically, for the smallest genotyped sample (OmniExpress), sample sizes ranged from 786 (percent body fat) to 1034 (AIR), although larger sample sizes were available for SNPs present on the exome chip (up to 1256 for fibrinogen and ACR). Across all phenotypes, there were 9214 LOD scores greater than or equal to 3, 845 ≥ 4 and 89 ≥ 5. Of the 57 variants with LOD scores greater than 5.0, 27 were linked to TNFα receptor 2 levels, 13 to HDL levels, 5 to AIR, 4 to G45R-adjusted adiponectin levels, and three to BMI-adjusted VAT. While a detailed summary of each trait analysis is impractical, following on our earlier observations[9,10], we have initially focused on the patterns visible in linkage analysis followed by relating these results to association analysis results. In this report, we evaluated linkage and association with 50 cardiometabolic phenotypes (see Supplementary Table 1 for complete listing). Selected phenotypes, namely TNFα receptor 2 levels, high density lipoprotein (HDL) levels, AIR, adiponectin levels (adjusted for G45R, a high impact mutation identified previously in these samples[3,10]), and VAT adjusted for BMI are summarized in Table 1. Overall, 12 phenotypes (from 4 phenotype groups: glucose homeostasis, lipids, adiposity and biomarkers) were represented in this category of LOD > 5.0 results summarized in Table 2, where highest LOD scores are grouped by phenotype and chromosome. A complete summary of LOD scores greater than 5 is presented in Supplementary Table 2.

Evaluation of loci with high LOD scores

The overall maximal LOD score of 6.49 was observed with rs12956744 with the biomarker TNFα receptor 2 levels (Table 3; Figure 1a). This SNP is located in intron 1 (nearer the 5′ end) of *LAMA1* (laminin subunit alpha-1 gene) on chromosome 18. Of note, three additional intronic variants in *LAMA1* were also linked to TNFα receptor 2 levels with LOD > 6, and 9 SNPs overall were linked with LOD > 3 (Table 3). Notably, one SNP (rs28569884) was also associated with TNFα receptor 2 levels (p-value = 5.9×10^{-4}; LOD = 1.06). The variant rs28569884 (in intron 56) is distal to the striking linkage signal (146 kb apart), though there was another LOD score over 4 (rs4395154; LOD = 4.47) just 13 kb away at the 3′ end of the *LAMA1* gene (intron 62). *LAMA1* is a very large gene, with 63 exons and 245 SNPs analyzed. Of these, 11 (4.4%) had nominally significant association (p-value < 0.05) with TNFα receptor 2 levels. Comparatively, 9 variants had LOD scores greater than 3 (3.7%) and 23 variants had LOD scores greater than 1 (9.4%).

A major focus of our laboratory is identifying genetic contributors to metabolic measures of glucose homeostasis. The top linkage result of LOD = 6.47 (Table 4) for AIR was rs28479408, an intronic variant located in *SYCP2L* (synaptonemal complex protein 2-like gene) on chromosome 6 (Figure 1b). Although this variant was not associated with AIR (p-value = 0.71), six other SNPs in this gene were also linked (rs4713044, LOD = 6.10; rs12190237, LOD = 5.58; rs12214063, LOD = 3.58; rs1767771, LOD = 3.42; rs2153159, LOD = 3.31; rs1632103, LOD = 3.15) but not associated (p-values > 0.5) (Table 4).

Strikingly, chromosome 1 had a broad linkage peak for AIR, with a maximal LOD score of 6.37 (rs2252384) in the region between *FAM163A* and *TOR1AIP2* (located at approximately 179 Mb; 1q25.2; Figure 1b; Table 5). Chromosome 1 has a long history of

linkage to diabetes, making this result all the more interesting[22–25]. Here, variants with LOD scores greater than three spanned much of the proximal q arm of the chromosome, with the most concentrated linkage peak residing between 156Mb and 187 Mb, a region encompassing 357 RefSeq genes (1q22–31.1). Focusing on the peak LOD-1 substantially narrowed the region to a very narrow 1.57 Mb. Of the 343 variants within this region with LOD scores greater than 3, 73 of them had p-values less than 0.05, with a best association signal occurring at rs6426957 (Chr1:165988336; p-value = 6.34×10^{-4}, LOD = 3.09, MAF = 0.441; Supplementary Table 3). Notably, many variants within *RASAL2* (RAS protein activator like 2 gene) showed nominal evidence of association ($0.05 > \text{p-value} > 1.42\times10^{-3}$) in addition to linkage (N = 45 of 46 linked [LOD>3] SNPs; Tables 5 and 6). LOD scores at this gene ranged from 3.00–5.38.

Additional linkage results of interest include regions on chromosomes 7 and 12 which were linked to insulin sensitivity index (S_I). Although these regions did not reach the magnitude seen for TNFα receptor 2 and AIR, the consistency of linkage in the region is compelling. On chromosome 7, the highest LOD score (5.11) was seen with rs1024591, an intergenic SNP over 300kb from the nearest gene (a long intergenic non-coding RNA, *LINC01372*) (Supplementary Table 4). The linkage signal on chromosome 12 is made up of two distinct peaks (Figure 1c), one at ~53Mb and the second at ~105 Mb (Supplementary Table 5). The LOD scores seen here are not as striking by magnitude (max LOD for each peak 4.27–4.28), but the consistency of LOD scores over 3 into tight peaks is notable (Supplementary Table 5). The first peak consists of 14 variants with LOD scores over 3, from 50.6–54.5Mb, with multiple variants in the *KRT8* (keratin 8 gene) and *ESPL1* (extra spindle pole bodies like 1, separase) showing evidence for linkage, as well as single variants at the proximal end of the peak in *LIMA1* (LIM domain and actin binding 1 gene), *DIP2B* (disco interacting protein 2 homolog B gene), and *SLC4A8* (solute carrier family 4, sodium bicarbonate cotransporter, member 8 gene). There was no evidence for association among linked variants at this linkage peak, though other, unlinked variants in the region showed nominal association (Supplementary Table 5).

The second linkage peak resides from 101–109Mb on chromosome 12, and included 21 linked variants which represented multiple signals from *CHST11* (carbohydrate (chondroitin 4) sulfotransferase 11 gene), *ACACB* (acetyl-CoA carboxylase beta gene), and *FOXN4* (forkhead box N4 gene), in addition to intergenic variants and genes implicated by a single variant, such as *CMKLR1* (chemerin chemokine-like receptor 1 gene) (Supplementary Table 5). One of these linked variants showed nominal evidence of association, with a p-value of 5.50×10^{-3} (rs11114094 in *SVOP* [SV2 related protein gene]; Table 6; Supplementary Tables 3 and 5), although like the prior peak, other unlinked variants in the linkage region also demonstrated evidence of association.

Variants with evidence of both linkage and association

Utilizing the linkage results as a search tool and prioritizing those with any evidence of association identified 1076 variants with p-values less than 0.05 as well as a LOD score greater than or equal to 3 (Supplementary Table 3). Twenty-seven variants were associated with $p < 0.005$ as well as having a LOD score > 4 (Table 6). *NFIB* was the primary gene

implicated under a linkage peak with TNFα receptor 2 levels on chromosome 9, where there was also evidence of nominal association (p-values on the order of 2×10^{-4}; Figure 1a; Supplementary Table 6). *NFIB*, which encodes nuclear factor I/B, is represented by 293 SNPs (135 from OmniExpress; 157 from Omni 1S, 1 from exome chip), 289 of which were located in introns. Only one coding variant in this gene was polymorphic from the exome chip dataset, this SNP (rs114558598; I24F) was not linked (LOD = −0.005) or associated (p-value = 0.08). Ten common variants (0.27 < MAF > 0.49) within this gene (all intronic) had LOD scores greater than 3. Overall, 68 *NFIB* variants had LOD scores greater than 1, and 24 had LOD scores greater than 2.

LPHN3 on chromosome 4 was a strong signal for LDL levels, with two intronic variants being both linked and associated (rs2343249; LOD = 4.30; p-value = 1.00×10^{-5} and rs9312078, LOD = 3.02; p-value = 8.20×10^{-5}; Table 7; Figure 1d). Both the linkage and association signals were confined to the gene region, with strong LD ($r^2 > 0.8$) between the two top SNPs. There was further support throughout the gene-encoding region for both modest linkage and association with diminishing LD (Supplementary Figure 1). The strongest association result among LOD scores ≥ 3 was with fibrinogen levels; rs1131878 from the OmniExpress chip, LOD = 3.08 and p-value = 1.99×10^{-6} (Supplementary Table 3). This SNP was located within the *UGT2B4* gene, which encodes UDP glucuronosyltransferase 2 family polypeptide B4.

Discussion

This study evaluated the utility of combining two-point linkage with association analysis in a data set comprised of array-based SNP genotyping totaling 1.6 million non-coding and coding variants in a family-based sample of Hispanics with extensive phenotype information. The goal of the study was to evaluate whether GWAS data in the context of linkage adds insight into the genetic origins of cardiometabolic traits, while utilizing association analysis as a follow up to determine likely candidate loci. This builds upon our prior evaluation of combined linkage and association using exome chip data in this cohort[9]. Large-scale linkage analysis of SNP genotyping has been uncommon for complex phenotypes recently. To this end, we evaluated 50 phenotypes (46 distinct traits) related to glucose homeostasis, lipids, blood pressure, adiposity, liver fat and enzymes, and biomarkers. Given the breadth of genotypic data and number of phenotypes, the results are extensive, but some noteworthy observations can be made. Broadly speaking, we believe the markedly denser genotypic dataset reveals many insights into the genetic bases of the traits such as TNFα receptor 2, AIR, and S_I when compared to our prior study using the more limited data from the exome chip.

Relatively dense genotyping data provides visual evidence of linkage similar to conventional multipoint methods. In addition, while exome chip analysis primarily targets models where functional variants are exonic, the GWAS datasets can potentially address other models such as high impact non-coding variants, especially through linkage analysis. Here we have observed few examples where evidence for both linkage and association are apparent. An example is *LPHN3* (Table 7, Supplementary Figure 1), where LOD scores reached 4.30 with a p-value of 1.00×10^{-5}, suggesting a true impact on LDL levels. Given the actual low

density of coverage in GWAS datasets which are designed to cover genomic regions through LD relationships, it is unlikely to capture truly causal variants by chance. The ultimate test of whether this approach will be successful will require whole genome sequencing data. Overall, these results incorporating two-point linkage and association analyses can identify meaningful signals that impact cardiometabolic traits, often in the absence of striking association alone. These conclusions are consistent with our prior work[9,10] in which we have shown that linkage evidence can be relatively strong, but association evidence only appears when the functional variant is also captured. The latter is unlikely in a GWAS dataset. For these reasons, our main focus was on regions with evidence of linkage based on both the power of linkage methods and the "far-sighted" ability of linkage to identify genetic relationships[4–7,9,10].

As noted above, several genomic regions had relatively strong evidence of linkage, but limited association results. Based on our logic, this would suggest the possibility of underlying, as yet unidentified functional variants. Thus, for the strongest linkage with TNF2α receptor levels (LOD = 6.49) we would hypothesize that one or more high impact non-coding variants lie within the linkage region. *LAMA1* is similar to *LAMA5* which has previously been related to TNFRSF1B expression[26], making it plausible for *LAMA1* to be related to TNF2α receptor levels.

Analysis of traits of interest to our laboratory (AIR, S_I) also resulted in notable linkage peaks. It is tempting to scan these linked regions for biologically relevant genes. Genes located under a broad AIR linkage region on chromosome 1 (Figure 1b, Table 5) included *FAM163A*, also known as neuroblastoma derived secretory protein (*NDSP*), *TOR1AIP2*, and *RASAL2. FAM163A* (aka *NDSP*) has been associated in methylation analysis for borderline personality disorder[27] with overexpression observed in neuroblastoma[28,29]. *TOR1AIP2* encodes torsin A interacting protein 2, which is involved in the nuclear envelope[30,31]. Mutations in *TOR1AIP1* have been shown to cause muscular dystrophy[32]. *RASAL2* (RAS protein activator like 2) has been implicated as an obesity susceptibility gene in both Chinese[33] and Mexican populations[34], as well as having a role in the susceptibility of many cancers, including liver[35], thyroid[36], ovarian[37], breast[37,38], and lung[39].

Genes under the S_I linkage peaks also included interesting candidates. On chromosome 12, the most relevant gene with linkage in the distal linkage peak was *CMKLR1* (chemerin chemokine-like receptor 1), which is believed to play a role in glucose homeostasis[40–42], obesity[41,43,44] and diabetes development[45]. Of note, a strong association signal (p-value = 1×10^{-7}) was also seen within this linkage peak in *WSCD2* (WSC domain containing 2; 100Mb from *CMKLR1*) (Figure 1c).

Additional genes included *LIMA1* (LIM domain and actin binding 1, also known as *EPLIN* and *SREPB3*), a tumor suppressor; *DIP2B* (disco interacting protein 2 homolog B), replicated as a susceptibility locus for colorectal cancer[46]; and *SLC4A8*, a sodium bicarbonate transporter, which may have a role in regulation of blood pressure with some variants in this gene having been previously implicated[47,48]. Further, *KRT8* (keratin 8, type II) which is overexpressed in human liver disease, resides under the linkage peak on 12q[49].

The linkage region on chromosome 7 contained only one putative gene, *LOC102723427*, about which there is no known information.

The most intriguing signal lies in *LPHN3* and was both linked and associated with LDL levels at two separate variants. This gene encodes latrophilin 3 (recently renamed as *ADGRL3*[50]; adhesion G protein-coupled receptor L3), which is related to latrotoxin, the toxin produced by the black widow spider[51]. There is evidence suggesting a role for latrophilin 3 (among other latrophilins) in binding to fibronectin leucine-rich transmembrane (FLRT) family members, which has been shown to promote the development of glutamatergic synapses[52,53]. Additionally, genetic variants in *LPHN3* have been associated reproducibly with attention deficit hyperactivity disorder (ADHD) and other psychiatric conditions[54–56]. *LPHN3* is also being investigated as a pharmacogenetic target[57]. Despite the lack of biological evidence directly supporting the link between *LPHN3* variants and LDL cholesterol levels, cholesterol is crucially important in the brain, and further study may elucidate a mechanism by which genetic variants in *LPHN3* impact plasma LDL levels.

We previously reported *CETP* (cholesterol ester transfer protein) linkage and association with HDL levels in exome chip data from this Hispanic sample[9]. Linkage of *CETP* in this dataset was stronger with LOD scores of up to 5.43, an increase of 1.14 over the previous top signal (Table 6; Supplementary Table 2).The addition of GWAS data implicated additional linked variants (LOD > 5, N = 4) proximal to the coding region, perhaps occluding interpretation of the functional impact of this linkage result.

Here we assessed the impact of SNP density to provide insight into linkage relationships with the conclusion that dense SNP maps do reveal additional insight. We have extended this query further by evaluation of imputed genotype data in regions of particular interest due to evidence of strong linkage with glucose homeostasis-related phenotypes. Three regions were selected based on substantial linkage evidence and a particular interest in glucose homeostasis: chromosome 1 with AIR and chromosomes 7 and 12 with S_I. Utilization of imputed data increases the number of markers capturing the region by 22–fold (18 411 directly genotyped markers, 406K imputed markers). The maximal LOD score from the imputed AIR region was 6.45 at rs2252384 (the same SNP implicated in the directly genotyped data; Supplementary Figure 2). The slight increase in LOD score (6.37 to 6.45) can likely be attributed to more complete information following imputation of missing genotypes. For chromosome 7 with S_I, a new best SNP rs2530421 had the maximum LOD score of 5.53 (compared to the prior best LOD of 5.11 at rs1024591). The imputed best SNP lies very near the original peak linkage, providing little additional guidance in refining the causal variant(s), given the high degree of correlation between the top linked SNPs (r^2 = 0.937). Evaluation of another linked region (chromosome 12 with S_I) also showed some limited improvement in linkage signals, but linkage signals were only modestly increased, as could be expected due to the information carried by these imputed markers being wholly derived from the genotyped markers which had already been informative. Thus, inclusion of imputed genotypes marginally improved the maximal LOD scores when evaluated in this small number of examples. However, the improvements did not further refine the regions of interest (Supplementary Figure 2).

In conclusion, we have built upon our previous analysis of combined two-point linkage and association[9] and evaluated utility of the approach in a dataset comprised of comprehensive genome-wide array-based SNP genotypes. As seen previously, there were few examples in this data where linkage and association both provided striking evidence at the same locus, which, based on our prior analysis[10], would implicate a likely ungentoyped causal variant. However, the GWAS plus exome chip design identified multiple additional regions of linkage which were not seen in exome chip analysis alone. Positive, strong evidence of association with SNPs was not observed, suggesting that functional variants, if they are indeed captured by the linkage signal, have not been identified. To truly test the broad utility of this approach, whole genome sequencing data will be necessary which will incorporate the full spectrum of variant frequencies.

The authors declare no conflicts of interest related to this publication. Supplementary information is available at the Journal of Human Genetics website.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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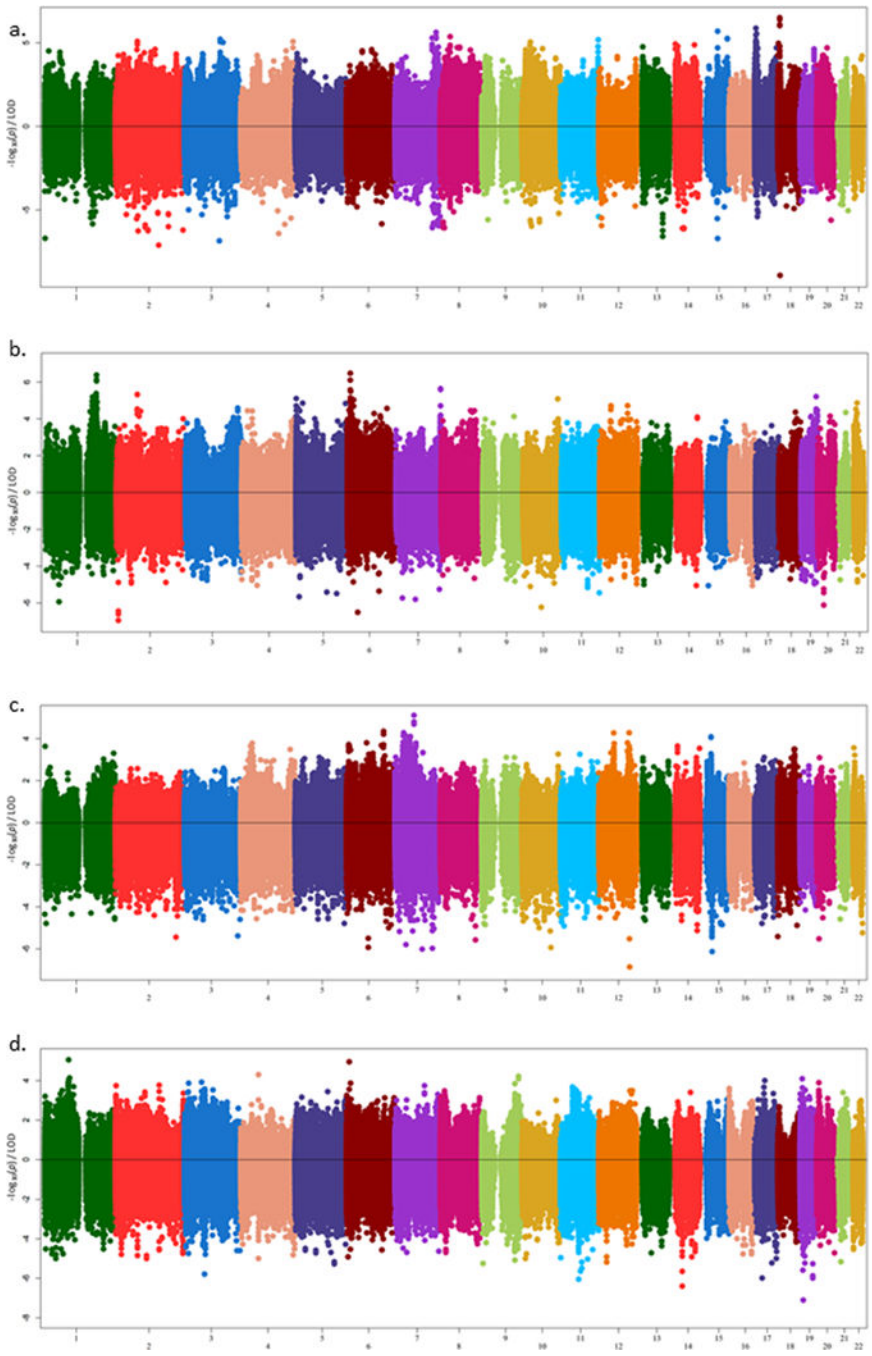

Figure 1.

Opposed plots showing LOD scores from the two-point linkage (upper portion) and log-transformed p-values for association (lower portion) results across all arrays for (a.) TNFα receptor 2 levels, (b.) Acute Insulin Response (AIR). (Note the broad linkage peak on Chromosome 1, and the strong linkage also on Chromosome 6), (c.) Insulin Sensitivity Index (S_I) (Of particular note are the signals on chromosomes 7 and 12.), and (d.) Low Density Lipoprotein (LDL) levels. (Note the signals on chromosome 4, contributed by

LPHN3 and chromosome 19, which represents the *APOE* locus, evaluated in our previous publication with Apolipoprotein B levels.)

Table 1

Demographic characteristics of the IRASFS Hispanic samples with selected phenotypes.

Characteristic	Exome Chip (81 559 variants)		Omni Express (668 758 variants)		Omni 1S (920 823 variants)	
Samples[1]	1 414		1 034		1 038	
Age (years)	1 263	42.75 (18–81)	1 034	40.63 (18–81)	1 038	40.61 (18–81)
% Female	823	58.3 % F	609	58.90%	612	58.90%
BMI (kg/m^2)	1 253	28.88 (16–58)	1 027	28.28 (16–58)	1 027	28.28 (16–58)
% T2D[2]	187	13.20%	0	0%	0	0%
AIR (pmol*mL-1*min-1)	1 035	761.86 (−80.9–4 313.7)	1 034	760.29 (−80.9–4 313.7)	1 038	759.21 (−80.9–4 313.7)
TNFα receptor 2 (ng/mL)	982	7.05 (2.38–30.00)	821	6.79 (2.38–30.00)	824	6.79 (2.38–30.00)
Fibrinogen (mg/dL)	1 256	265.74 (113–591)	1 032	259.37 (113–506)	1 036	259.61 (113–506)
Cholesterol (mg/dL)	1 255	177.94 (74–348)	1 031	176.12 (74–311)	1 035	176.17 (74–311)
HDL (mg/dL)	1 254	43.82 (18–125)	1 030	43.58 (18–100)	1 034	43.60 (18–100)
LDL (mg/dL)	1 242	109.17 (31–218)	1 022	109.04 (31–213)	1 026	109.06 (31–213)
Triglycerides (mg/dL)	1 252	124.57 (18–836)	1 030	118.30 (18–836)	1 034	118.31 (18–836)
ACR (mg/g)	1 256	53.55 (1.63–3 903.92)	1 032	19.63 (1.93–1 459.68)	1 036	19.58 (1.93–1 459.68)
Percent Body Fat	943	33.95 (10.10–55.03)	786	33.51 (10.10–51.78)	789	33.52 (10.10–51.78)
VAT (cm^2)	1 206	114.02 (10.04–382.56)	994	106.56 (10.04–363.34)	998	106.52 (10.04–363.34)
VSR	1 164	0.38 (0.07–1.63)	963	0.36 (0.07–1.56)	967	0.36 (0.07–1.56)

Data presented as mean (range) or percent.

[1] From 90 pedigrees, not entirely overlapping.

[2] at baseline

Table 2

Summary of linkage results for phenotypes with at least one variant with LOD >4.

Phenotype	LOD > 5	LOD > 4	LOD > 3
Acute Insulin Response (AIR)	24	180	1 335
Insulin Sensitivity Index (S_I)	1	17	247
Disposition Index (DI)		8	101
Metabolic Clearance Rate of Insulin (MCRI)		6	100
Total Cholesterol	1	16	269
High Density Lipoprotein (HDL)	13	129	1 202
Low Density Lipoprotein (LDL)	1	9	191
Apolipoprotein B (ApoB)		9	291
Triglycerides	4	18	151
Systolic Blood Pressure (SBP)		1	48
Diastolic Blood Pressure (DBP)		1	24
Albumin/Creatinine Ratio (ACR)		3	169
Adiponectin (adjusted)	13	96	621
C-Reactive Protein (CRP)		5	84
Fibrinogen		16	341
TNFα Receptor 2 (TNF2)	27	259	2 458
Retinol Binding Protein 4 (RBP4)		1	20
Body Mass Index (BMI)	1	11	100
Body Adiposity Index (BAI)		4	66
Percent Body Fat	1	18	159
Waist Circumference		2	32
Waist-to-Hip Ratio (WHR)		1	10
Subcutaneous Adipose Tissue (SAT)	1	7	151
Visceral Adipose Tissue (adj. for BMI)		1	63
Visceral-to-Subcutaneous Ratio (VSR)	1	8	138
Visceral-to-Subcutaneous Ratio (VSR; adj. for BMI)	3	9	141

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Phenotype	LOD > 5	LOD > 4	LOD > 3
Liver Density		4	123
Inverse Normalized Liver		2	47
Gamma Glutamyl Transpeptidase (GGT)		6	126

Boldface indicates phenotypes with a LOD score >5.

Table 3

Selected *LAMA1* results with TNFα receptor 2 protein levels (LOD>1 and/or P-value <0.01)

SNP	Chr	Position	Chip	N	MAF	LOD	P-value	Beta Value	Standard Error	Variance
rs4395154	18	6942805	OmniExpress	820	0.46	**4.47**	0.25	0.016	0.014	0.001
rs2016639	18	6943264	OmniExpress	821	0.431	**3.46**	0.2	−0.018	0.014	0.002
rs17439137	18	6951060	OmniExpress	821	0.235	1.07	0.77	−0.005	0.016	0
rs8086875	18	6951710	Omni1S	821	0.208	1.15	0.36	0.015	0.017	0.0008
rs8088218	18	6951971	Omni1S	820	0.21	1.62	0.32	0.017	0.017	0.001
rs12454596	18	6953989	OmniExpress	821	0.446	1.85	0.73	0.005	0.014	0.0002
rs949215	18	6955676	OmniExpress	821	0.25	1.18	0.96	0.001	0.016	0
rs28569884	18	6956111	Omni1S	821	0.058	1.06	**5.94E-04**	−0.098	0.029	0.015
rs509497	18	6957193	OmniExpress	821	0.393	1.29	**0.04**	0.028	0.014	0.005
rs633691	18	6967089	OmniExpress	821	0.419	**3.18**	0.085	0.024	0.014	0.0044
rs11873205	18	6979621	Omni1S	818	0.13	1.54	**0.0072**	−0.055	0.021	0.0113
rs538815	18	6982443	OmniExpress	821	0.202	1.69	0.5	−0.011	0.017	0.0003
rs619106	18	7011413	OmniExpress	821	0.291	0.03	**0.042**	−0.032	0.015	0.009
rs67268419	18	7013648	Omni1S	820	0.077	1.74	0.74	−0.009	0.025	0.0006
rs541928	18	7034932	Omni1S	821	0.153	2.05	0.49	0.013	0.019	0
rs7240767	18	7070642	OmniExpress	821	0.468	0	**0.029**	−0.03	0.014	0.0058
rs7228959	18	7076464	OmniExpress	821	0.49	0	**0.044**	−0.027	0.014	0.0047
rs16951199	18	7080135	OmniExpress	815	0.068	0	**0.017**	−0.064	0.027	0.0081
rs11081298	18	7085706	Omni1S	820	0.466	2.91	0.94	−0.001	0.014	0.0001
rs12606163	18	7096977	OmniExpress	807	0.485	**4.78**	0.11	0.022	0.014	0.0038
rs972038	18	7102036	Omni1S	816	0.171	0.07	**0.046**	−0.036	0.018	0.0103
rs12955222	18	7102427	OmniExpress	821	0.482	**4.53**	0.13	0.02	0.013	0.0038
rs12956744	18	7102706	Omni1S	821	0.407	**6.49**	**0.03**	0.03	0.014	0.0071
rs12959835	18	7103146	Omni1S	820	0.408	**6.38**	**0.034**	0.029	0.014	0.0068
rs1462780	18	7105988	OmniExpress	820	0.019	0	**0.034**	−0.103	0.049	0.0072
rs34433741	18	7108999	Omni1S	820	0.415	**6.07**	0.089	0.023	0.014	0.0031
rs4798533	18	7109571	Omni1S	819	0.282	1.52	0.82	−0.003	0.015	0.0002

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SNP	Chr	Position	Chip	N	MAF	LOD	P-value	Beta Value	Standard Error	Variance
rs12454984	18	7109652	Omni1S	821	0.404	**6.02**	0.15	0.02	0.014	0.0019
rs984355	18	7114212	OmniExpress	821	0.217	2.55	0.36	0.016	0.017	0

Boldface indicates LOD scores > 3 or p-values < 0.05.

Table 4

Chromosome 6 AIR linkage peak with linked (LOD>3) and/or associated (p-value <0.05) variants.

SNP	Chr.	Position	Chip	N	MAF	Gene	LOD	P-value	Beta Value	Standard Error	Variance
rs12208366	6	10383410	Omni1S	1 034	0.146		**3.43**	0.578	0.39	0.701	0
rs480965	6	10387251	OmniExpress	1 033	0.142		**3**	0.546	0.419	0.695	0
rs533558	6	10395572	OmniExpress	1 033	0.406		**3.55**	0.122	−0.771	0.499	0.002
rs79025376	6	10400618	Omni1S	1 033	0	*TFAP2A*	0	**5.06E-03**	−27.514	9.816	0.008
rs78497087	6	10471612	Omni1S	1 032	0.356		**3.39**	0.813	0.123	0.518	0
rs491803	6	10477438	Omni1S	1 033	0.331		**3.31**	0.885	0.075	0.521	0
rs9466917	6	10606584	Omni1S	1 033	0.492	*GCNT2*	**3.32**	0.89	0.069	0.501	0
rs3798704	6	10615268	Omni1S	1 034	0.494	*GCNT2*	**3.33**	0.923	0.048	0.5	0
rs1233887	6	10739432	OmniExpress	1 033	0.36		**3.1**	0.714	−0.187	0.51	0
rs518954	6	10791859	OmniExpress	1 029	0.278	*MAK*	**3.1**	0.184	0.727	0.546	0.003
rs12214063	6	10855738	Omni1S	1 032	0.213	*SYCP2L*	**3.58**	0.753	−0.195	0.62	0
rs1767771	6	10857646	Omni1S	1 034	0.473	*SYCP2L*	**3.42**	0.685	−0.203	0.499	0
rs1632103	6	10862649	Omni1S	1 034	0.478	*SYCP2L*	**3.15**	0.558	−0.293	0.5	0
rs2153159	6	10887932	Omni1S	1 033	0.36	*SYCP2L*	**3.31**	0.969	−0.02	0.506	0
rs4713044	6	10911282	OmniExpress	1 033	0.182	*SYCP2L*	**6.1**	0.951	−0.039	0.63	0
rs28479408	6	10912131	Omni1S	1 034	0.177	*SYCP2L*	**6.47**	0.712	−0.236	0.64	0
rs12190237	6	10922638	OmniExpress	1 031	0.164	*SYCP2L*	**5.58**	0.775	0.188	0.66	0
rs6457131	6	11227328	OmniExpress	1 029	0.207	*NEDD9*	**3.24**	0.919	0.061	0.604	0
rs55813531	6	11238023	Omni1S	1 031	0.185	*NEDD9*	**5.14**	0.274	0.698	0.639	0.002
rs17496723	6	11238633	Omni1S	1 031	0.413	*NEDD9*	1.2	**7.89E-03**	−1.323	0.498	0.004
rs9468690	6	11239119	OmniExpress	1 033	0.455	*NEDD9*	0.86	**7.86E-03**	−1.316	0.495	0.005
rs9461574	6	11239518	OmniExpress	1 033	0.492	*NEDD9*	1.94	**5.77E-03**	−1.354	0.49	0.006
rs12209631	6	11242203	OmniExpress	1 028	0.175	*NEDD9*	**3.08**	0.0873	1.134	0.662	0.005
rs6908326	6	11247387	OmniExpress	1 033	0.204	*NEDD9*	2.97	**5.11E-03**	1.683	0.6	0.009
rs10947066	6	11253969	Omni1S	1 034	0.264	*NEDD9*	**4.34**	**0.0468**	1.117	0.562	0.007
rs10947067	6	11253990	Omni1S	1 033	0.265	*NEDD9*	**4.25**	**0.0481**	1.113	0.563	0.006
rs6457197	6	11254692	Omni1S	1 028	0.496	*NEDD9*	**3.72**	**0.0165**	−1.176	0.491	0.01

SNP	Chr.	Position	Chip	N	MAF	Gene	LOD	P-value	Beta Value	Standard Error	Variance
rs6457202	6	11255770	Omni1S	1 033	0.445	*NEDD9*	**4.29**	**8.71E-03**	1.324	0.505	0.013
rs7766626	6	11256000	OmniExpress	1 031	0.371	*NEDD9*	**3.73**	**0.0152**	1.206	0.496	0.01
rs210903	6	11724542	OmniExpress	1 031	0.271	*C6orf105*	**3.93**	0.954	−0.032	0.561	0
rs4713831	6	11726626	OmniExpress	1 014	0.298	*C6orf105*	**4.12**	0.726	0.189	0.541	0
rs210897	6	11729299	Omni1S	1 034	0.282	*C6orf105*	**5.49**	0.893	0.075	0.557	0
rs114551218	6	11736145	Omni1S	1 030	0.003	*C6orf105*	0	**3.48E-03**	13.077	4.476	0.014
rs210890	6	11740036	OmniExpress	1 032	0.162	*C6orf105*	**3.13**	0.552	0.4	0.673	0
rs12204492	6	11774626	OmniExpress	1 032	0.424	*C6orf105*	**3.62**	0.376	−0.431	0.487	0.001
rs2235384	6	11776631	OmniExpress	1 031	0.205	*C6orf105*	**3.02**	0.481	0.419	0.594	0

Boldface indicates LOD scores > 3 or p-values < 0.05.

Table 5

Broad linkage region on Chromosome 1 with Acute Insulin Response: Variants with LOD >4.5

SNP	Chr.	Position	Chip	N	MAF	Gene	LOD	P-value	Beta Value	Standard Error	Variance Explained (association)
rs12047043	1	164625696	OmniExpress	1 029	0.225	*AX748175*	**4.95**	0.16	0.832	0.594	0.005
rs4657367	1	164627551	OmniExpress	1 033	0.225	*AX748175*	**4.72**	0.15	0.857	0.591	0.005
rs4656475	1	166004063	Omni1S	1 032	0.14	Intergenic	**4.66**	0.38	0.635	0.721	0.001
rs6662013	1	166042658	Omni1S	1 034	0.247	*FAM78B*	**5.19**	0.71	−0.21	0.565	0
rs6680174	1	166459849	OmniExpress	1 033	0.266	Intergenic	**4.73**	0.33	0.544	0.553	0.001
rs1476076	1	167794511	Omni1S	1 031	0.467	*ADCY10*	**4.74**	0.81	−0.113	0.48	0
rs203849	1	167849414	OmniExpress	1 033	0.484	*ADCY10*	**4.62**	0.43	−0.395	0.5	0.002
rs4656148	1	168179545	Omni1S	1 031	0.273	Intergenic	**4.87**	0.42	0.427	0.535	0
rs11589732	1	168585289	OmniExpress	1 033	0.228	Intergenic	**5.00**	0.86	0.106	0.582	0
rs7474070	1	171050589	OmniExpress	1 033	0.22	Intergenic	**4.86**	0.11	−0.959	0.597	0.003
rs16863990	1	171055570	OmniExpress	1 032	0.193	Intergenic	**5.09**	0.15	−0.929	0.644	0.003
rs12402693	1	171057312	OmniExpress	1 032	0.193	Intergenic	**5.16**	0.14	−0.947	0.643	0.003
rs12404183	1	171058946	OmniExpress	1 026	0.212	Intergenic	**4.59**	0.21	−0.754	0.603	0.002
rs1800822	1	171076935	OmniExpress	1 029	0.201	*FMO3*	**4.62**	0.3	−0.637	0.613	0.002
rs2281002	1	171080629	OmniExpress	1 033	0.189	*FMO3*	**4.79**	0.12	−1.005	0.646	0.004
rs909529	1	171082896	OmniExpress	1 033	0.201	*FMO3*	**4.72**	0.078	−1.103	0.624	0.004
rs6659102	1	176535567	OmniExpress	1 032	0.149	*PAPPA2*	**4.66**	0.91	−0.082	0.685	0
rs7540152	1	176656255	OmniExpress	1 033	0.13	*PAPPA2*	**4.53**	0.73	0.256	0.731	0
rs791031	1	176667810	OmniExpress	1 030	0.129	*PAPPA2*	**4.60**	0.82	0.165	0.734	0
rs11583320	1	178042145	OmniExpress	1 029	0.221	Intergenic	**4.52**	**5.63E-03**	1.597	0.576	0.006
rs964993	1	178062359	OmniExpress	1 033	0.188	*LOC100302401*	**4.67**	**1.89E-03**	1.988	0.639	0.007
rs10913506	1	178092233	OmniExpress	1 033	0.186	*RASAL2*	**4.93**	**1.52E-03**	2.019	0.636	0.008
rs10798604	1	178254568	OmniExpress	1 029	0.174	*RASAL2*	**4.96**	**0.033**	1.38	0.648	0.004
rs77603205	1	178279051	Omni1S	1 033	0.173	*RASAL2*	**4.52**	**0.021**	1.504	0.652	0.005
rs10913550	1	178408795	OmniExpress	1 033	0.174	*RASAL2*	**5.16**	**0.027**	1.435	0.65	0.004
rs9803679	1	178410425	OmniExpress	1 033	0.174	*RASAL2*	**5.21**	**0.027**	1.435	0.65	0.004
rs2017349	1	178419417	OmniExpress	1 033	0.259	*RASAL2*	**5.38**	0.07	1.034	0.57	0.004

SNP	Chr.	Position	Chip	N	MAF	Gene	LOD	P-value	Beta Value	Standard Error	Variance Explained (association)
rs12073428	1	178427933	OmniExpress	1 030	0.157	*RASAL2*	**4.98**	**7.40E-03**	1.829	0.682	0.006
rs1008495	1	178458708	OmniExpress	1 029	0.19	Intergenic	**4.73**	0.065	1.134	0.613	0.004
rs2252384	1	179785891	OmniExpress	1 033	0.242	Intergenic	**6.37**	0.095	−0.937	0.561	0.004
rs2794579	1	179787027	OmniExpress	1 033	0.243	Intergenic	**6.12**	0.09	−0.965	0.568	0.004
rs1148821	1	179795505	OmniExpress	1 033	0.24	Intergenic	**6.05**	0.095	−0.945	0.566	0.004
rs2804699	1	181322837	Omni1S	1 026	0.351	Intergenic	**4.91**	0.49	0.353	0.515	0
rs2804694	1	181331833	Omni1S	1 033	0.332	Intergenic	**4.55**	0.53	0.333	0.531	0.001

Boldface indicates LOD scores > 3 or p-values < 0.05.

Table 6

Variants with LOD score >4 and p-value <0.005

SNP	Chr	Position	N	MAF	Trait	Gene	Variant	LOD	P-value	Beta Value	Variance
rs17109504	1	83468851	965	0.2363	ApoB	.–.	unknown	4.08	3.99E-03	0.182	0.005
rs10919343	1	170224982	1 032	0.205	AIR		unknown	4.32	0.003	1.86	0.012
rs10494510	1	178074581	1 030	0.187	AIR	*RASAL2*	intron	4.08	0.002	1.98	0.007
rs6670912	1	178082410	1 033	0.187	AIR	*RASAL2*	intron	4.28	0.0014	2.04	0.007
rs4440820	1	178088698	1 034	0.186	AIR	*RASAL2*	intron	4.18	0.0015	2.03	0.008
rs12071903	1	178095804	1 034	0.187	AIR	*RASAL2*	intron	4.22	0.0014	2.041	0.007
rs10798597	1	178108248	1 032	0.185	AIR	*RASAL2*	intron	4.01	0.0019	1.996	0.007
rs10157702	1	178109045	1 033	0.186	AIR	*RASAL2*	intron	4.28	0.0019	1.99	0.007
rs10913513	1	178135941	1 034	0.186	AIR	*RASAL2*	intron	4.08	0.0018	2.002	0.007
rs2343249	4	62419426	1 017	0.3033	LDL	*LPHN3*	intron	4.3	1.00E-05	−0.324	0.027
rs13245847	7	38596983	821	0.431	TNF2	*AMPH*	intron	4.14	5.20E-05	−0.056	0.019
rs723968	9	14154231	820	0.2701	TNF2	*NFIB*	intron	4.11	1.28E-03	−0.05	0.012
rs7044402	9	14157468	821	0.2966	TNF2	*NFIB*	intron	4.19	9.05E-04	−0.049	0.012
rs16931436	9	14185939	821	0.2716	TNF2	*NFIB*	intron	4.09	1.58E-03	−0.049	0.013
rs10756748	9	16327712	1 029	0.313	HDL		unknown	4.1	0.0027	−0.039	0.013
rs1939523	11	132599003	821	0.2954	TNF2	*OPCML*	intron	4.01	3.13E-03	−0.046	0.006
rs73202582	12	92044537	954	0.138	Adiponectin	*0*	unknown	4.15	0.0019	−0.091	0.02
rs9596564	13	33508797	1 029	0.2755	Triglycerides	*PDS5B (243392)-KL (81403)*	unknown	4.13	4.68E-03	−0.08	0.011
rs11158243	14	20473910	821	0.316	TNF2		unknown	4.92	0.0037	−0.046	0.014
rs11643893	16	16285847	784	0.425	Percent Fat	*ABCC6*	intron	4.03	0.0034	−0.891	0.018
rs11076039	16	54450940	1 024	0.466	HDL		unknown	5.43	0.0011	−0.039	0.007
rs11645463	16	54456353	1 030	0.47	HDL		unknown	5.06	0.0049	−0.033	0.004
rs5882	16	57016092	1 020	0.46	HDL	*CETP*	Missense V422I	4.29	4.91E-04	0.042	0.012
rs12602333	17	10169293	821	0.1681	TNF2	*GAS7 (245974)-MYH13 (34889)*	unknown	4.65	3.32E-03	−0.051	0.012
rs17745091	17	52938797	785	0.498	Percent Fat		unknown	5.01	1.80E-04	1.156	0.014
rs2332308	17	52944373	784	0.4802	Percent Fat	*.-TOM1L1 (33678)*	unknown	4.03	2.44E-04	1.141	0.01
rs75500748	22	48739692	819	0.093	TNF2		unknown	4.21	2.70E-04	0.084	0.022

Table 7

LPHN3 Linkage and Association with LDL levels

SNP	Chr	Position	Chip	N	MAF	LOD	P-value	Beta Value	Standard Error	Variance
rs17828264	4	62079015	Omni1S	1 021	0.5	1.17	0.44	−0.051	0.066	0
rs17090416	4	62098937	OmniExpress	1 022	0.279	1.42	0.65	−0.034	0.074	0
rs1505682	4	62111856	OmniExpress	1 022	0.315	1.44	0.22	−0.089	0.073	0.001
rs1505670	4	62115243	Omni1S	1 021	0.475	1.26	0.69	−0.027	0.067	0
rs13140257	4	62128750	Omni1S	999	0.321	1.66	**0.037**	−0.152	0.073	0.003
rs11723103	4	62128825	Omni1S	1 019	0.375	1.33	0.052	−0.137	0.07	0.004
rs1505663	4	62132090	OmniExpress	1 022	0.229	0.15	**7.90E-03**	0.213	0.08	0.003
rs1505664	4	62132345	OmniExpress	1 020	0.371	1.42	**0.05**	−0.137	0.07	0.004
rs67050759	4	62135455	Omni1S	1 019	0.496	1.49	0.12	−0.105	0.068	0.003
rs74329144	4	62136292	Omni1S	1 022	0.055	1.02	0.076	0.263	0.148	0.002
rs77082869	4	62254565	Omni1S	1 021	0.015	0.00	**1.77E-03**	0.896	0.287	0.013
rs10008278	4	62366666	OmniExpress	1 018	0.092	1.28	0.096	0.2	0.12	0.003
rs904243	4	62406445	OmniExpress	1 021	0.164	0.75	**6.49E-04**	−0.312	0.091	0.018
rs7656189	4	62411676	OmniExpress	1 020	0.408	0.74	**4.07E-03**	0.2	0.069	0.013
rs9312078	4	62412292	OmniExpress	1 015	0.331	**3.02**	**8.20E-05**	−0.282	0.071	0.022
rs56905501	4	62413961	Omni1S	1 018	0.392	0.69	**2.98E-03**	0.207	0.07	0.014
rs7688741	4	62416470	Omni1S	1 022	0.383	1.46	**2.11E-04**	−0.262	0.071	0.019
rs2132074	4	62416499	OmniExpress	1 021	0.392	0.64	**1.86E-03**	0.216	0.069	0.014
rs2343249	4	62419426	OmniExpress	1 017	0.303	**4.30**	**1.00E-05**	−0.324	0.073	0.027
rs958862	4	62434848	OmniExpress	1 018	0.341	1.87	**3.60E-04**	−0.258	0.072	0.02
rs10018746	4	62445246	Omni1S	1 021	0.5	0.97	**4.19E-03**	0.192	0.067	0.013
rs11941524	4	62446484	Omni1S	1 022	0.5	0.86	**4.17E-03**	0.192	0.067	0.013
rs2172802	4	62453209	Exome	1 012	0.45	0.50	**6.37E-03**	0.184	0.067	0.01
rs17239080	4	62455462	OmniExpress	1 022	0.374	2.02	**2.32E-03**	−0.212	0.069	0.014
rs11131334	4	62457454	OmniExpress	1 017	0.379	2.11	**4.84E-03**	−0.195	0.069	0.011
rs1497901	4	62461940	OmniExpress	1 021	0.359	2.07	**1.77E-03**	−0.221	0.07	0.013
rs2343250	4	62472682	Omni1S	1 022	0.36	2.09	**1.59E-03**	−0.224	0.071	0.013

SNP	Chr	Position	Chip	N	MAF	LOD	P-value	Beta Value	Standard Error	Variance
rs10001410	4	62474229	OmniExpress	1 019	0.47	0.91	**3.89E-03**	−0.199	0.069	0.016
rs1497921	4	62526281	OmniExpress	1 022	0.356	0.64	**3.19E-03**	−0.204	0.069	0.014
rs66614141	4	62550335	Omni1S	1 022	0.326	1.45	**1.35E-04**	−0.268	0.07	0.02
rs6843311	4	62568688	OmniExpress	1 022	0.363	0.61	**5.25E-03**	−0.194	0.069	0.014
rs11734607	4	62693692	OmniExpress	1 021	0.453	0.24	**2.44E-03**	0.204	0.067	0.015
rs4860106	4	62850522	OmniExpress	1 021	0.422	1.13	0.71	0.025	0.068	0
rs1510921	4	62895592	OmniExpress	1 017	0.241	0.26	**4.00E-03**	0.223	0.077	0.007
rs6827266	4	62902162	Omni1S	1 020	0.437	0.08	**5.00E-03**	0.188	0.067	0.004
rs62306380	4	62908281	Omni1S	1 022	0.239	0.23	**3.55E-03**	0.225	0.077	0.007

Boldface indicates LOD scores > 3 or p-values < 0.05.