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Genome-wide scans for heritability of fasting serum insulin and glucose concentrations in hypertensive families

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Abstract *Aims/hypothesis:* The heritability of fasting serum insulin and glucose concentrations in non-diabetic members of multiplex hypertensive families is unknown. *Methods:* We calculated the familial aggregation of fasting serum glucose and insulin concentrations and performed a genome-wide scan to assess whether quantitative trait loci contribute to these phenotypes in 2,412 non-diabetic individuals from 1,030 families enrolled in the Hypertension Genetic Epidemiology Network (HyperGEN) in the Family Blood Pressure Program. *Results:* The heritability (±SE) of fasting serum insulin was 0.47±0.085 in European Americans and 0.28±0.08 in African Americans ($p<0.0001$ for both), after adjusting for age, sex, and BMI. A genome-wide scan for fasting serum insulin yielded a maximum log of the odds (LOD) score of 2.36 on chromosome 5 at 20 cM ($p=0.0004$) in European Americans, and an LOD score of 2.28 on chromosome 19 at 11 cM ($p=0.0004$) in African Americans. The heritability of fasting serum glucose was 0.5109±0.08 in the former and 0.29±0.09 in the latter ($p<0.0003$ for both) after adjusting for age, sex and BMI. A genome-wide scan for fasting serum glucose revealed a maximum LOD score of 2.07 on chromosome 5 at 26 cM ($p=0.0009$) in European Americans. *Conclusions/interpretation:* These analyses demonstrate the marked heritability of fasting serum insulin and glucose concentrations in families enriched for the presence of members with hypertension. They suggest that genes associated with fasting serum insulin concentration are present on chromosomes 19 and 5, and that genes associated with fasting serum glucose concentration are on chromosome 5, in families enriched for hypertension.

Keywords African Americans · Essential hypertension · Fasting blood sugar · Heritability · Linkage analysis · Serum insulin concentration

Abbreviations AA: African American · EA: European American · FBPP: Family Blood Pressure Program · h^2: heritability · HOMA: homeostasis model assessment · HyperGEN: Hypertension Genetic Epidemiology

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Network · IBD: Identity-by-descent · LOD: Log of the odds · NHLBI: National Heart, Lung and Blood Institute · SOLAR: Sequential oligogenic linkage analysis routines

Introduction

Hyperinsulinaemia is a major risk factor for the subsequent development of type 2 diabetes mellitus [1, 2]. Fasting serum insulin concentrations are excellent estimates of insulin resistance and the resulting hyperinsulinaemia in population studies, and have been shown to aggregate in families [3]. Insulin resistance is associated with increased serum triglyceride levels, reduced high-density lipoprotein concentrations and reduced low-density lipoprotein particle size; these metabolic parameters predict increased cardiovascular morbidity and mortality [4, 5].

The heritability (h^2) and roles of inherited and environmental factors in causing hyperglycaemia and elevated serum insulin concentrations among hypertensive subjects remain unknown. In non-hypertensive populations, an adjusted h^2 value of 0.34 for fasting serum glucose [6] and 0.46 for fasting serum insulin concentrations [7] were reported in the Framingham Offspring Study. Similar high familial correlations for these prediabetic measures were reported in Amish families [8], the HERITAGE FAMILY study [9], and Caucasian twins [3]. Elevated serum insulin and glucose concentrations represent an increased risk of developing overt type 2 diabetes mellitus, with increased rates of cardiovascular morbidity and mortality [10].

It is likely that both genetic and environmental factors determine fasting serum insulin and glucose concentrations in hypertensive subjects. The Hypertension Genetic Epidemiology Network (HyperGEN) is a family-based consortium seeking to identify the genes responsible for elevated blood pressure [11]. We performed maximum likelihood variance component linkage analysis of fasting serum glucose and insulin concentrations and homeostasis model assessment (HOMA) to identify loci contributing to the variance of these traits in the non-diabetic relatives of families enriched for the presence of essential hypertension.

Subjects and methods

Population Participants in the HyperGEN Network of the Family Blood Pressure Program (FBPP), sponsored by the National Heart, Lung and Blood Institute (NHLBI), were evaluated. HyperGEN study methods have previously been reported [11]. In brief, family members were recruited from five clinical centers (Framingham, MA; Minneapolis, MN; Salt Lake City, UT; Forsyth County, NC; and Birmingham, AL). Participants provided written informed consent and the project was approved by the Institutional Review Boards at all of the institutions. A sibship was ascertained if it had two or more siblings with hypertension (defined as blood pressure ≥140/90 or the use of anti-hypertensive medications), with an age at diagnosis of less than 60 years. Participants reporting a personal history of diabetes mellitus, having a fasting blood glucose concentration of 6.99 mmol/l or higher, or being treated with insulin or oral hypoglycaemic agents were excluded from analyses.

Phenotyping Morning fasting serum samples from study participants were collected in a resting state and run in duplicate for insulin concentration on an automated immunoassay instrument and its ultra-sensitive insulin kit (Beckman Coulter, Fullerton, CA, USA) [12]. The sensitivity of this assay is 0.03 mU/l (0.21 pmol/l) and the dynamic range is 0.03–300 mU/l (0.21–2100 pmol/l). There is zero cross-reactivity with pro-insulin and C-peptide, 30% with bovine insulin, and 97% with porcine insulin.

Serum glucose concentrations were measured using Elan Glucose reagent (hexokinase method) [13]. Assay sensitivity is 0.11–24.98 mmol/l and the detection limit 0.11 mmol/l is documented through the repetitive assay of a diluted serum control. The observed detection limit, calculated as two standard deviations of a 30-replicate within-run precision study, is 0.57 mmol/l and is below the claimed limit of 0.11 mmol/l.

HOMA was calculated as (fasting serum insulin*fasting serum glucose)/22.5.

Genotyping Genotyping was performed by the NHLBI-funded Mammalian Genotyping Service. For additional information regarding the genotyping methods see the website of the Center for Medical Genetics at the Marshfield Medical Research Foundation http://www.research.marshfieldclinic.org/genetics/). The genome screen was performed by means of an automated technique with the scanning fluorescence detector. The Cooperative Human Linkage Center screening set 8, including 387 microsatellite markers spaced approximately every 9 cM throughout the genome, was used, with an average marker heterozygosity of 0.76.

Statistical analysis The distributions of fasting serum insulin and glucose concentrations were positively skewed. The natural logarithm transformed both insulin and glucose to approximate normality and was used for all analyses and model building. Any highly influential outliers were excluded from the analyses after adjusting for covariates. Pedigree and genotype data were screened for possible errors using ASPEX software, version 2.2 [14], MAPMAKER/SIBS, version 2.1 [15], PedCheck, version 1.1 [16], and PREST, version 2.01 [17].

The heritability of serum measures was estimated separately in each race and jointly, using variance component modelling as implemented in SOLAR software, version 2.1.2 [18]. Covariates in the model for fasting glucose were age, sex, BMI, age^2, and age×sex. Covariates in the model for fasting insulin were age, sex, BMI, age^2, age×sex, sex×BMI, and sex×age^2. These were selected using a backward elimination approach allowing for re-entry of eliminated covariates at each step (significance level=0.10 for backward and forward steps). For both analyses, covariates were selected among age, sex, and BMI, age^2, age×sex, age×BMI, sex×BMI, sex×age^2, and BMI×age^2. Centred values were used to

Table 1 Demographic characteristics of HyperGEN study population

Characteristic	African American	Caucasian	Race combined
Sex			
Female	65.6 (836)	52.6 (599)	59.5 (1,435)
Male	34.4 (438)	47.4 (539)	40.5 (977)
Age, years	46.7±12.7 (1,274)	55.8±13.1 (1,138)	51.0±13.7 (2,412)
BMI, kg/m^2	31.8±7.6 (1,274)	29.5±6.1 (1,138)	30.7±7.0 (2,412)
Fasting serum glucose, mmol/l	5.32±1.14 (1,247)	5.42±1.46 (1,109)	5.37±1.30 (2,356)
Fasting serum insulin, mU/l	10.8±11.2 (1,093)	8.0±5.7 (1,078)	9.4±9.0 (2,171)
Hypertension[a]	70.2 (894)	73.6 (838)	71.8 (1,732)

Data listed as means±standard deviation (*n*) for continuous measures and % (*n*) for dichotomous measures

[a]Defined as blood pressure >140/90 mmHg or use of antihypertensive medication

model the effects of continuous covariates, and indicator variables (0/1) were used for discrete covariates. The heritability estimate adjusted for the effects of covariates is reported together with corresponding estimates of standard error, *p* value, and proportion of variance due to covariates. We considered *p* values of 0.05 or less to be significant.

Markov chain Monte Carlo methods were used to estimate race-specific multipoint IBD matrices as implemented in the LOKI software package, version 2.4.7 [19]. Variance component multipoint and bivariate linkage analysis as implemented in SOLAR software, version 2.1.2 [18], was performed to detect and localise quantitative trait loci that influence variation in fasting serum insulin and glucose concentrations, using lodadj to account for slight departures from normality. This approach has been described in detail [20–22].

Results

Genotype data were available from 2,589 individuals in 805 recruited families who participated in the FBPP. Eight subjects were excluded due to fasting serum glucose concentrations above 6.99 mmol/l (six AA, two EA). After correcting family relationships based upon the genetic data, 1,030 distinct pedigrees (613 of whom were African American) were used in the analysis. After exclusion of all influential outliers, 2,412 of the genotyped individuals who were nondiabetic had measurements of fasting serum insulin and/or glucose concentrations. The mean age (±SD) of these individuals was 51.0±3.7 years, 59.5% (*N*=1,435) were women, 53% were AA (*N*=1,279), and a majority were hypertensive (71.7%) and had a mean BMI (±SD) of 30.70±6.98 kg/m^2 (Table 1). Participants had a mean fasting serum glucose concentration

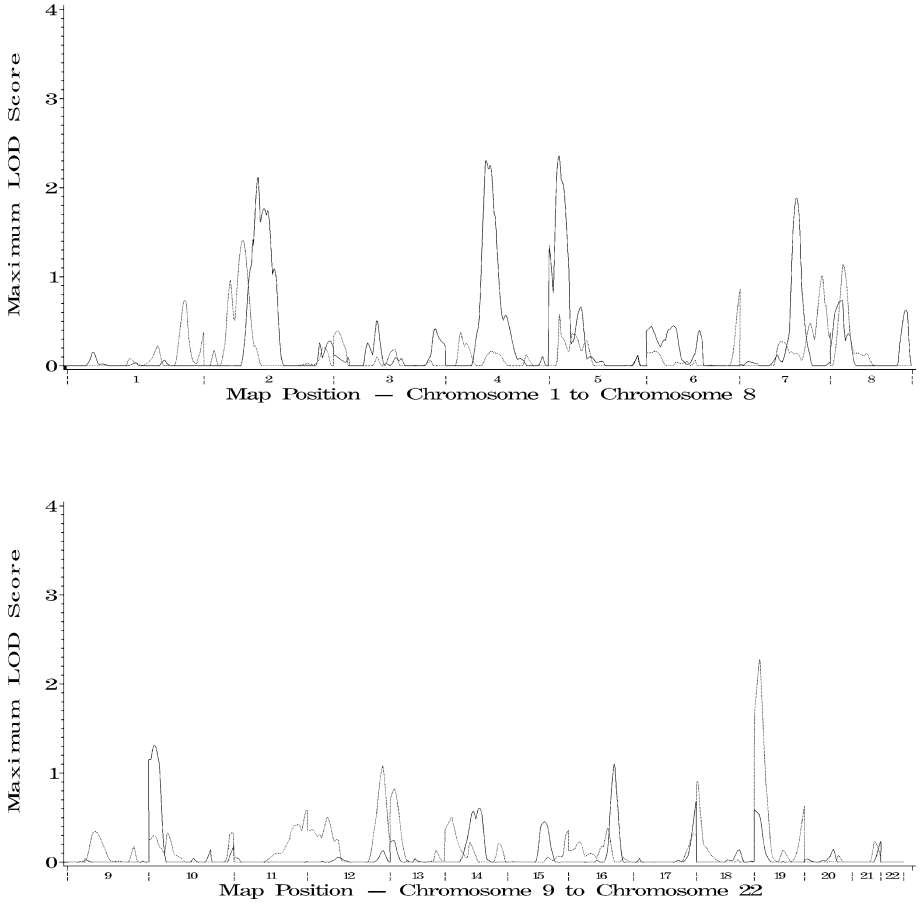

Fig. 1 Genome scan plots for fasting serum insulin concentrations. *Dotted line* African Americans; *solid line* Caucasians

Table 2 Linkage results: fasting insulin, glucose, HOMA analysis and bivariate analysis

Location		HOMA[a]		Fasting insulin[a]		Fasting glucose[a]		Bivariate[b]	
Marker	CHR	AA	EA	AA	EA	AA	EA	AA	EA
D2S441 / D2S1394	2	1.08 @ 80.0	0.50 @ 98.0	1.41 @ 78.0	1.42 @ 99.0	1.90 @ 96.0 (86.0, 107.0) 0.0014[c]	0.00 @ 96.0	1.24 @ 96.0	0.65 @ 99.0
D2S1790	2	0.31 @ 106.0	1.03 @ 109.0	0.22 @102.0	2.12 @ 109.0 (95.0, 137.0) 0.0007[c]	1.41 @ 103.0	0.00 @ 109.0	0.55 @ 106.0	1.12 @ 108.0
D4S3243	4	0.12 @ 94.0	2.46 @ 81.0 (72.0, 103.0) 0.0003[c]	0.17 @ 92.0	2.30 @ 81.0 (73.0, 104.0) 0.0004[c]	0.00 @ 86.0	0.00 @ 81.0	0.63 @ 96.0	1.17 @ 81.0
D5S817 / D5S2845	5	0.33 @ 20.0	2.00 @ 19.0 (11.0, 38.0) 0.0010[c]	0.58 @ 20.0	2.36 @ 20.0 (11.0, 37.0) 0.0004[c]	0.00 @ 24.0	2.07 @ 26.0 (21.0, 38.0) 0.0009[c]	0.72 @ 21.0	3.11 @ 26.0 (21.0, 38.0) 0.0002[c]
D7S821 / D7S1799	7	0.41 @ 114.0	0.68 @ 115.0	0.14 @ 112.0	1.88 @ 115.0 (103.0, 125.0) 0.0015[c]	0.20 @ 110.0	0.00 @ 111.0	0.10 @ 116.0	1.86 @ 111.0 (102.0, 126.0) 0.0034[c]
D7S559	7	1.69 @ 182.0 (156.0, –) 0.0024[c]	0.09 @ 180.0	0.37 @ 182.0	0.04 @ 182.0	0.27 @ 180.0	0.00 @ 182.0	0.16 @ 182.0	0.00 @ 182.0
D9S1838	8	1.69 @ 25.0 (6.0, 36.0) 0.0024[c]	0.38 @ 24.0	1.14 @ 25.0	0.73 @ 23.0	0.02 @ 24.0	0.03 @ 24.0	1.40 @ 25.0	0.26 @ 24.0
D9S1838	9	0.0 @ 164.0	0.12 @ 162.0	0.00 @ 164.0	0.00 @ 164.0	0.00 @ 164.0	1.84 @ 164.0 (152.0,–) 0.0016[c]	0.24 @ 164.0	1.79 @ 164.0 (154.0,–) 0.0041[c]
D10S1213 / D10S1248	10	73.0 @ 171.0	0.73 @ 171.0	0.33 @ 168.0	0.17 @ 170.0	0.00 @ 160.0	1.51 @ 160.0 (146.0,–) 0.0040[c]	0.28 @ 170.0	1.14 @ 161.0
D11S912	11	0.11@ 146.0	0.0 @ 135.0	0.34 @ 136.0	0.00 @ 136.0	0.61 @ 143.0	0.00 @ 136.0	1.55 @ 135.0 (120.0,–) 0.0077[c]	0.00 @ 135.0
D13S1493 / D13S894	13	0.73 @ 10.0	0.26 @ 8.0	0.82 @ 9.0	0.25 @ 8.0	1.30 @ 17.0	0.19 @ 30.0	1.51 @ 12.0 (–,54.0) 0.0084[c]	0.02 @ 8.0
D13S325 / D13S788	13	0.02 @ 42.0	0.0 @ 42.0	0.00 @ 42.00	0.00 @ 42.0	1.81 @ 42.0 (–,50.0) 0.0018[c]	0.12 @ 38.0	1.62 @ 43.0 (–,50.0) 0.0064[c]	0.09 @ 36.0
D13S317 / D13S793	13	0.11 @ 70.0	0.10 @ 54.0	0.00 @ 64.0	0.01 @ 62.0	0.82 @ 79.0	1.64 @ 64.0 (54.0,77.0) 0.0028[c]	1.38 @ 83.0	1.65 @ 65.0 (55.0,80.0) 0.0058[c]
D18S877	18	15.0 @ 36.0	0.00 @ 46.0	0.01 @ 46.0	0.00 @ 46.0	1.70 @ 46.0 (28.0,59.0) 0.0024[c]	0.00 @ 46.0	1.23 @ 46.0	0.00 @ 46.0
D19S1034	19	2.26 @ 11.0 (–,22.0) 0.0006[c]	0.63 @ 0.0	2.28 @ 11.0 (–,20.0) 0.0004[c]	0.59 @ 2.0	0.55 @ 5.0	0.00 @ 10.0	2.46 @ 11.0 (–,18.0) 0.0008[c]	0.13 @ 2.0

AA African American, *EA* European American, *CHR* chromosome

[a]Significant results reported as maximum LOD score @ location in centiMorgans (LOD-1 interval) empirical *p* value

[b]Significant results reported as maximum LOD score @ location in centiMorgans (LOD-1 interval) *p* value

[c]LOD-1 support interval and *p* values for maximum LOD scores above 1.5

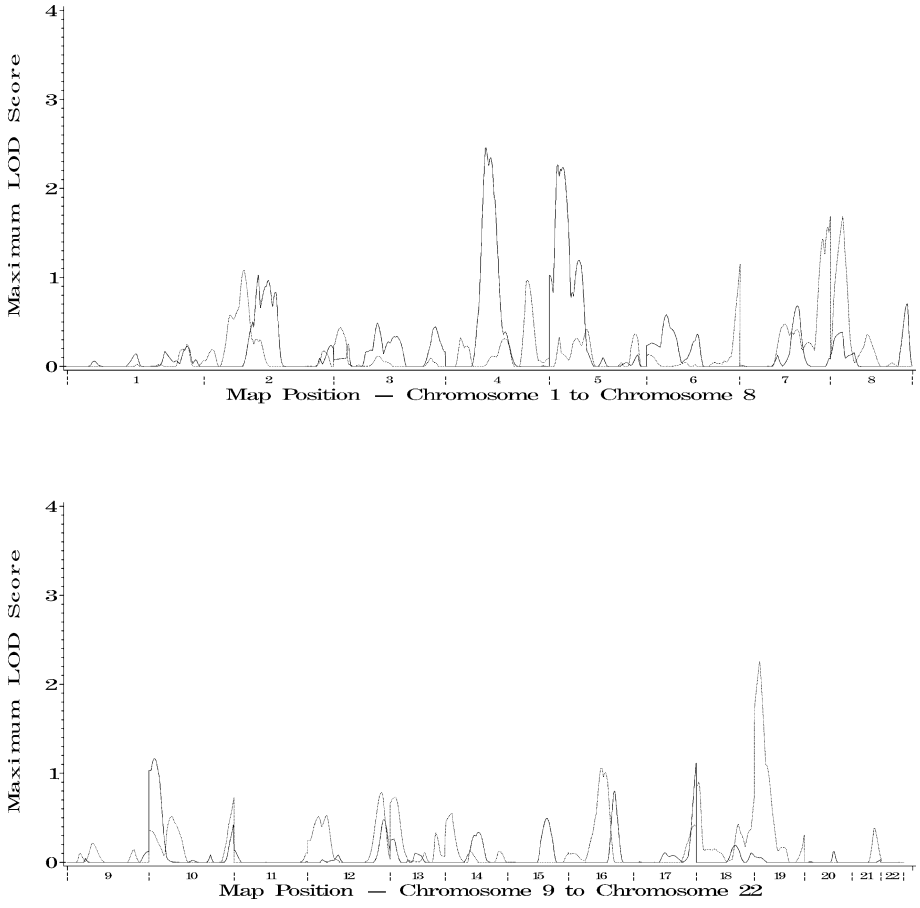

Fig. 2 Genome scan plots for HOMA. *Dotted line* African Americans; *solid line* Caucasians

of 5.37±1.30 mmol/l and a mean fasting serum insulin concentration of 9.40±9.0 mU/l. Among these 2,412 individuals, there were 1,329 sibling pairs (513 AA), 610 avuncular pairs (190 AA), 156 half-sibling pairs (144 AA), 185 first cousins (54 AA), and 2 EA monozygotic twins. The mean family size with insulin and/or glucose data was 2.34 members (AA 2.09, EA 2.73).

The h^2 of serum insulin was 0.47±0.08 in EAs and 0.28± 0.08 in AAs (p<0.0001 for both), after controlling for the significant main and interactive effects of age, sex and BMI. An additional 33% and 31% of the variance in EAs and AAs, respectively, was due to measured covariates. Figure 1 contains the univariate genome-wide scan results for fasting erum insulin concentration in EAs and AAs. A maximum LOD score of 2.36 was observed on chromosome 5 at 20.0 cM (marker D5S817/D5S2845, p=0.0004), with lesser peaks of LOD 2.30 on chromosome 4 (81 cM, marker D4S3243) and 2.12 on chromosome 2 (109 cM, marker D2S1790) in EAs, and 2.28 on chromosome 19 (11 cM, marker D19S1034) in AAs, p<0.0007 for all (Fig. 1). Table 2 contains the results of the genome scan for fasting serum insulin (as well as for HOMA, fasting serum glucose and the bivariate analysis), reporting maximum LOD scores of more than 1.5, position, LOD-1 interval and p value in AAs and EAs (see symbols and footnotes) and maximum LOD scores with position in all other scans in proximity to the significant results. The results of the HOMA genome scan are presented in Fig. 2 and Table 2. Similar regions of linkage were observed for fasting serum insulin concentrations on chromosomes 4 and 5 in EAs and on chromosome 19 in AAs.

The h^2 of serum glucose concentration was 0.51±0.08 in EAs and 0.29±0.09 in AAs (p≤0.0003 for both), after controlling for the significant main and interactive effects of age, sex, and BMI. An additional 22% and 20% of the variance in EAs and AAs, respectively, was due to measured covariates. The univariate genome-wide scan results for fasting serum glucose are depicted in Fig. 3. A maximum LOD score of 2.07 was observed on chromosome 5 at 26.0 cM (marker D5S817/D5S2845, p=0.0009) in EAs and a lesser peak was observed on chromosome 2: LOD 1.90 at 96.0 cM (marker D2S441/D2S1394), p<0.0014 in AAs (Fig. 3; Table 2).

In AAs, the genetic correlation between fasting serum glucose and insulin was nonsignificant (p=0.37), while the environmental correlation was r_E=0.46±0.07 (p<0.0001). In EAs, the genetic correlation between fasting serum glucose and insulin was also nonsignificant (p=0.86), while the environmental correlation was r_E=0.35±0.10 (p=0.0007). These data suggest that the primary genetic determinants of fasting serum glucose concentration are different from those that contribute to the variation in fasting serum insulin concentration. A bivariate genome-wide scan for loci contributing to both fasting serum glucose and insulin concentrations in both races demonstrated eight regions with maximum LOD scores above 1.5 (four in AAs and four

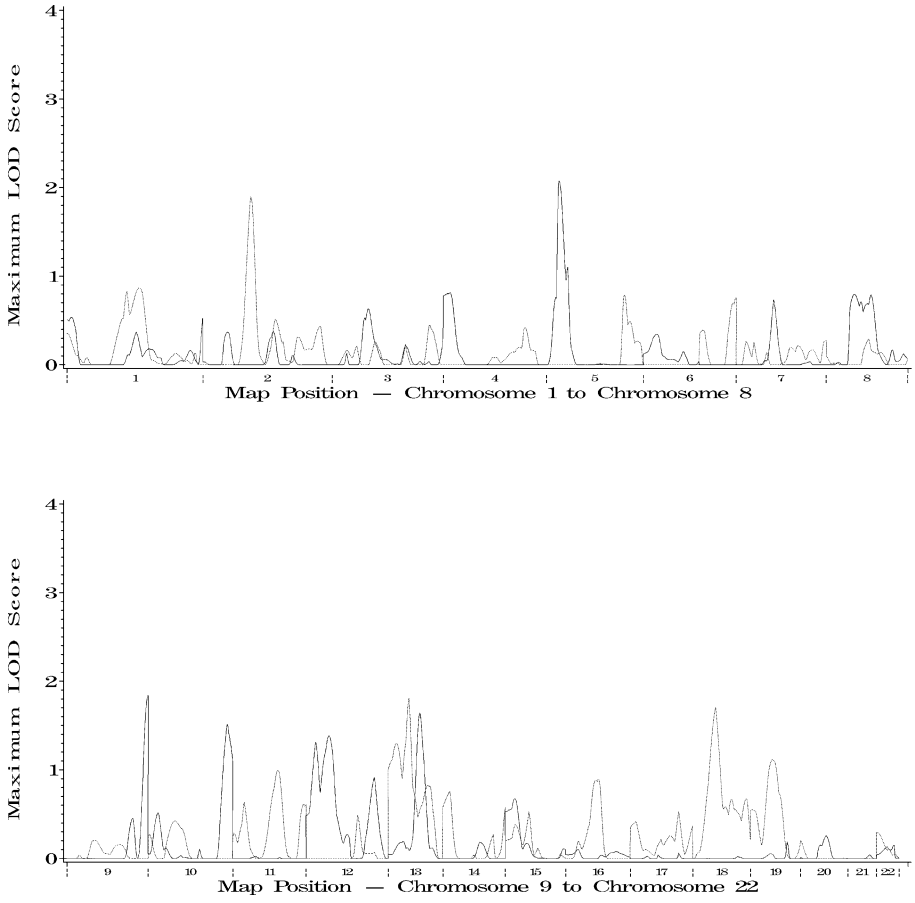

Fig. 3 Genome scan plots for fasting serum glucose concentrations. *Dotted line* African Americans; *solid line* Caucasians

in EAs). These regions are depicted, separately by race, in Fig. 4 and Table 2.

Discussion

This report is the first to reveal that inherited factors appear to play important roles in the regulation of fasting serum insulin and glucose concentrations in hypertensive, nondiabetic AAs and Caucasians. The heritability of fasting serum insulin and glucose concentrations remained highly significant even after controlling for the effects of significant covariates. The marked heritability of fasting serum glucose and insulin concentrations appears consistent with other reports in Framingham [6, 7], Amish [8], and HERITAGE families [9]. Additionally, the genome scans in AAs and EAs provided suggestive evidence that genes regulating fasting serum insulin concentrations and insulin sensitivity (HOMA) were present on chromosomes 19, 7, 5, 4 and 2, and genes regulating fasting glucose concentration were present on chromosomes 2, 5, 9, 13 and 18. In general, the linkage peaks for fasting insulin, HOMA and fasting glucose differed by ethnic group (see Table 2). Race-combined analyses added little, as results were driven by a single ethnic group (data not shown). Although the bivariate genome scan demonstrated several regions with suggestive evidence for linkage, these results were probably driven by linkage to either fasting serum insulin or fasting serum glucose concentrations alone, based on the low genetic correlation observed between these measures.

Several genome-wide scans have been performed in nondiabetic families evaluated for prediabetic phenotypes and in multiplex type 2 diabetes families. Regions of linkage in several reports overlap with those observed in this HyperGEN analysis. On chromosome 19, linkage was detected at 18 cM for fasting insulin in Pima Indians (LOD 1.33) [23], and for type 2 diabetes and glucose intolerance in young-onset French families at 36 cM (LOD 1.26) [24]. Linkage with fasting glucose, and combined fasting and non-fasting glucose, was detected on chromosome 5 at 0 cM in the Framingham Offspring Study (LOD 1.09) [6], and Framingham Heart Study (LOD 1.65) [25]. The HyperGEN fasting serum glucose scan loci on chromosome 13 are near reported loci for related phenotypes in 580 Finnish families from the FUSION Study [26], i.e., 2-h insulin (LOD 2.86 at 65 cM) and insulin secretion (insulin/glucose) (LOD 1.37 at 62 cM), and loci for type 2 diabetes in AAs with earlier age at diagnosis (p<0.006 at 76 cM) [27] and Japanese families (LOD 0.94, 79 cM) [28]. Linkage for these phenotypes resides within, or near, the peaks where we found evidence for linkage to fasting insulin (chromosomes 19 and 5) and fasting glucose (5 and 13) in the univariate analyses. Therefore, the regions identified in the HyperGEN genome scan as influencing fasting serum insulin and glucose concentrations may reflect genes that also play major roles in susceptibility to diabetes mellitus

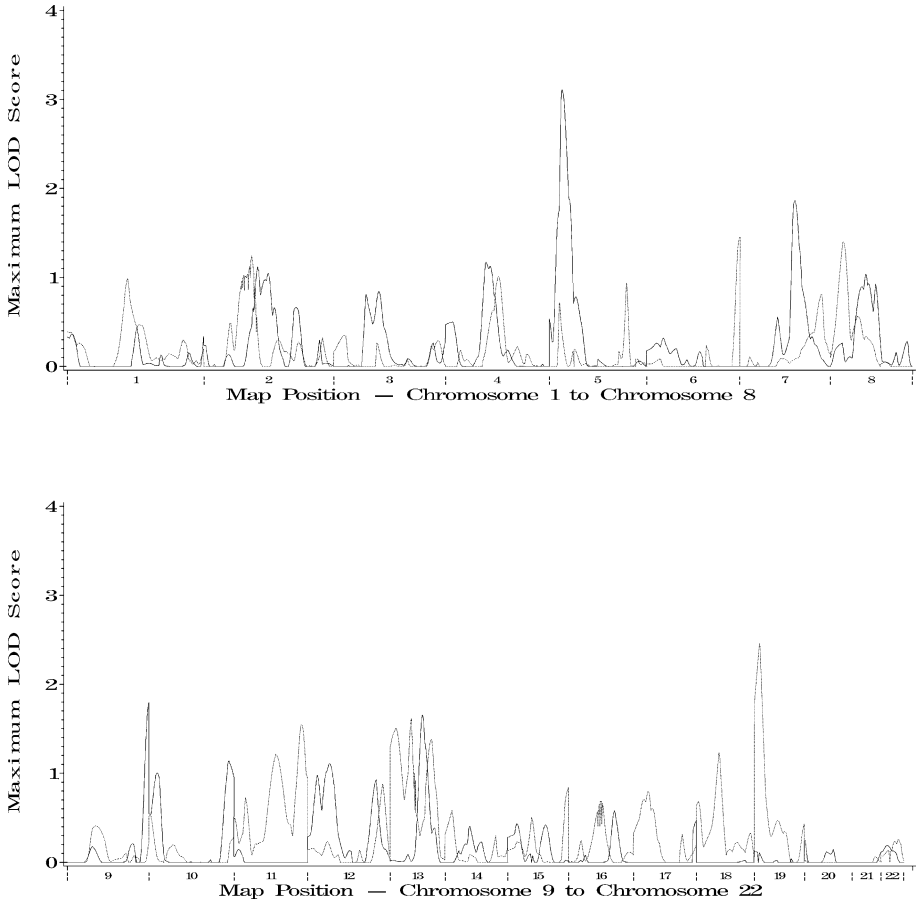

Fig. 4 Genome scan plots for bivariate analysis of fasting serum glucose and insulin concentrations. *Dotted line* African Americans; *solid line* Caucasians

and/or related phenotypes. Our data are unique, however, in that they are from a biracial population enriched for the presence of essential hypertension.

Fasting serum glucose concentrations clearly fluctuate in individuals with insulin resistance and in those with diabetes mellitus. In addition, little is known about the natural history of insulin resistance among treated and untreated hypertensive subjects. These difficulties are encountered in all cross-sectional studies. The overlapping regions of linkage observed for the diabetes-related phenotypes in Pima [23] and Finnish [26] families, and the Framingham Offspring [6] and Heart Studies [25], support the existence of genes affecting fasting serum insulin concentrations on chromosomes 19 and 5 and fasting serum glucose on chromosome 13.

In conclusion, this report analysed the heritability of fasting serum insulin and glucose concentrations in non-diabetic members of multiplex hypertensive families. Elevated serum insulin concentrations and fasting blood sugars (insulin resistance) are well recognised risk factors for the development of heart attack and stroke. The heritabilities of fasting serum insulin and glucose concentrations were significant after controlling for the main and interactive effects of age, sex, and BMI. Additionally, suggestive evidence for genetic linkage to fasting serum insulin concentrations and insulin sensitivity (HOMA) were detected on chromosomes 19, 5, 4, and 2; and suggestive evidence for linkage to fasting serum glucose concentrations was detected on chromosomes 2, 5, 9, 13, and 18. These results suggest that the genes regulating susceptibility to insulin resistance, hyperglycaemia and diabetes-related phenotypes may reside in these regions and play an important role in the observed familial aggregation of cardiovascular disease. It is important that additional large, family-based analyses in hypertensive cohorts attempt to reproduce these results and identify the causative genes.

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