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Genome-wide linkage scans for prediabetes phenotypes in response to 20 weeks of endurance exercise training in non-diabetic whites and blacks: the HERITAGE Family Study

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Abstract *Aims/hypothesis:* Impaired insulin secretion, insulin action, insulin-independent glucose effectiveness, glucose tolerance and the associated abnormalities in insulin and glucose metabolism phenotypes are precursors of type 2 diabetes. Genome-wide multipoint variance component linkage scans were carried out using 654 markers to identify quantitative trait loci for insulin sensitivity, acute insulin response to glucose, disposition index and glucose effectiveness training responses in whites and blacks in the HERITAGE Family Study. *Methods:* These phenotypes were obtained from an IVGTT with the minimal model. The distributions of insulin sensitivity, acute insulin response to glucose and disposition index training responses (post-training minus baseline) were approximately normalised using a square-root transformation. All phenotypes were adjusted for the effects of age, BMI and their respective baseline values within sex and generation by race prior to linkage scans. *Results:* In blacks, a promising linkage with a maximum lod score of 3.1 on 19q (54–62 Mb) for glucose effectiveness training response was found. Six interesting linkages with lod scores of at least 1.0 were found for disposition index training response in whites. They included 1p (30 Mb), 3q (152 Mb), 6p (23–42 Mb), 7q (95–96 Mb), 10p (15 Mb) and 12q (119–126 Mb). *Conclusions/interpretation:* Quantitative trait loci for 20 weeks of endurance exercise training responses in insulin action and glucose metabolism phenotypes were found on chromosome 19q as well as 6p and 7q, with nominal (6p, 7q) but consistent (6p) linkages across the races.

Keywords Acute insulin response to glucose · Disposition index · Exercise training response · Glucose effectiveness · Insulin sensitivity · IVGTT · Minimal model · Quantitative trait loci

Abbreviations AIR_g: acute insulin response to glucose · DI: disposition index · *GYS1*: glycogen synthase 1 gene · LDB: location database · PPAR: peroxisome proliferator-activated receptor · S_I: insulin sensitivity · S_G: glucose effectiveness

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Introduction

Type 2 diabetes is characterised by an elevation in blood glucose in the fasting state and/or following a glucose challenge resulting from insulin resistance and insufficient compensatory insulin secretion by pancreatic beta islet cells. Insulin action, as the insulin sensitivity index (S_I), can be estimated from the frequently sampled IVGTT with minimal model. Other indices include the acute insulin response to glucose (AIR_g, reflecting insulin secretion) and the disposition index ($DI=S_I \times AIR_g$, measuring overall glucose homeostasis and taking account of the hyperbolic relationship between S_I and insulin secretion). Glucose effectiveness (S_G) represents an insulin-independent effect whereby glucose mediates its own disposal from plasma. Impairments in these insulin action and glucose metabolism indices are recognised as prediabetic phenotypes involving pathogenic development and pathogenetic processes of type 2 diabetes. Exercise training improves peripheral S_I and S_G in healthy human subjects [1], and significant improvements in S_I, AIR_g, DI and S_G in response to 20 weeks of endurance exercise training have been observed and reported in the HERITAGE Family Study [2]. Recent investigations in HERITAGE provide further evidence that physiological training responses vary appreciably from person to person, and these individual differences are influenced by genetic factors [3].

Genome-wide linkage scans localising quantitative trait loci for type 2 diabetes and associated traits are numerous. However, there are no scans for such unique traits of glucose and insulin metabolism phenotypes in response to endurance exercise training, except for the baseline values [4] and fasting values [5] in HERITAGE. In this study, S_I, AIR_g, DI and S_G derived from an IVGTT using the Minimal Model Millennium software [6] were obtained before and after 20 weeks of endurance exercise training. Training responses were defined as differences between post-training and baseline values.

We searched for quantitative trait loci that may harbour candidate genes influencing changes in S_I, AIR_g, DI and S_G in response to endurance exercise training in sedentary and non-diabetic whites and blacks.

Subjects, materials and methods

HERITAGE was designed to investigate the role of the genotype in cardiovascular, metabolic and hormonal responses to aerobic exercise training, and the contribution of exercise training to changes in type 2 diabetes and cardiovascular disease risk factors. In general, subjects in the 20-week training programme were required to be in good health. All subjects had been sedentary at baseline for at least 6 months prior to study entry [7]. Age was ≤65 years for parents and ≥17 years for offspring. Subjects with uncontrolled endocrine and metabolic disorders or diabetes were excluded from participation. Resting blood pressure was ≤159/99 mm Hg. None of the subjects took medications to control hypertension or for dyslipidaemia. BMI had to be less than 40 kg/m^2. However, several subjects with their BMI slightly higher than 40 kg/m^2 were approved for participation by supervising physicians, because they were considered to be in good health and able to exercise. HERITAGE design, protocol, population, inclusion and exclusion criteria are described elsewhere [7].

A total of 441 subjects from 98 white families and 187 subjects from 90 black families had complete data. Sample size descriptions are given in Table 1 for whites and Table 2 for blacks. The Institutional Review Boards at five participating centres of HERITAGE approved the study protocol. Written informed consent was obtained from each participant.

The training programme has been described elsewhere [8]. Each subject was administered a comprehensive battery of tests prior to the 20-week training programme, including an IVGTT. Subjects then completed 60 sessions of endurance exercise on cycle ergometers that were computer-controlled to maintain the subjects' heart rates at levels associated with fixed percentages of their baseline maximal oxygen uptake. The full test battery, including the IVGTT, was administered again after completion of the training programme. The IVGTT protocol [9] has been detailed previously [4]. It was performed in the morning after overnight fasting for 12 h. Blood samples to measure plasma glucose and insulin were taken 1, 3, 5, 10, 15, 20, 30, 45, 60, 75, 90,

Table 1 Basic characteristics of whites

Variable[a]	Number Fathers	Mean	SD	Number Mothers	Mean	SD
Age (years)	89	53.5[b]	5.3	76	52.2[b]	5.2
BMI (kg/m^2)	89	28.3[b]	4.5	76	27.5[b]	4.9
Baseline S_I	89	3.24[b,c]	3.09	75	4.90[c]	3.26
Response S_I	89	0.27	2.64	74	−0.17	2.56
Baseline AIR_g	89	654[c]	569	76	496[b,c]	324
Response AIR_g	89	−59	343	76	−19	153
Baseline DI	89	1,679[b,c]	1,586	75	2,213[c]	1,781
Response DI	89	82	1,361	74	−186	1,277
Baseline S_G	89	1.45	0.66	76	1.61	0.89
Response S_G	89	0.10[b]	0.86	76	−0.04	0.89
Variable	Sons			Daughters		
Age (years)	138	25.5[b]	6.2	138	25.6[b]	6.3
BMI (kg/m^2)	138	25.8[b,c]	4.9	138	23.8[b,c]	4.5
Baseline S_I	138	4.36[b]	2.57	135	4.69	2.86
Response S_I	136	0.61	2.73	135	0.12	2.70
Baseline AIR_g	138	785[b]	630	138	630[b,c]	432
Response AIR_g	138	−58	355	138	−13	249
Baseline DI	138	2,618[b]	1,738	135	2,514	1,615
Response DI	136	328	2,026	135	71	1,760
Baseline S_G	138	1.60	0.87	138	1.78	0.90
Response S_G	138	0.35[b]	1.19	138	0.13	1.27

[a]Units: S_I, 10^{-4} min^{-1}/μU/ml; AIR_g, pmol/l×10 min; S_G, 100 min^{-1}
[b]Differences in means are significant ($p<0.05$) for father–son or mother–daughter comparisons
[c]Differences in means are significant ($p<0.05$) for spouse or sibling comparisons

Table 2 Basic characteristics of blacks

Variable[a]	Number Fathers	Mean	SD	Number Mothers	Mean	SD
Age (years)	17	49.2[b,c]	7.8	30	45.9[b,c]	6.1
BMI (kg/m^2)	17	26.8	4.6	30	29.4	5.3
Baseline S_I	16	2.74	3.38	30	2.98	2.84
Response S_I	16	0.11	2.31	30	0.12	2.70
Baseline AIR$_g$	17	706[b,c]	452	30	1,595[b]	2,164
Response AIR$_g$	17	6	385	30	−150	626
Baseline DI	16	2,052	3,232	30	3,469	4,312
Response DI	16	−172	2,452	30	504	3,834
Baseline S_G	17	1.66[c]	1.14	30	1.85	1.05
Response S_G	17	−0.09	0.99	30	0.17	1.52
Variable	Sons			Daughters		
Age (years)	59	28.6[c]	6.7	81	27.8[c]	8.1
BMI (kg/m^2)	59	27.5	5.2	81	27.8	6.4
Baseline S_I	59	2.63	1.86	81	2.77	2.15
Response S_I	57	0.59	1.79	81	0.32	2.01
Baseline AIR$_g$	59	1,743[c]	1,443	81	1,813	1,376
Response AIR$_g$	59	−163	700	81	−37	505
Baseline DI	59	3,569	3,083	81	4,002	3,209
Response DI	57	388	3,046	81	456	3,004
Baseline S_G	59	1.94[c]	1.14	81	2.15	1.28
Response S_G	59	0.32	1.79	81	0.32	1.57

[a]Units: S_I, 10^{-4} min^{-1}/μU/ml; AIR$_g$, pmol/l×10 min; S_G, 100 min^{-1}
[b]Differences in means are significant (p<0.05) for spouse or sibling comparisons
[c]Differences in means are significant (p<0.05) for father–son or mother–daughter comparisons

120, 150 and 180 min after the end of the glucose injection in the opposite arm.

Plasma insulin was measured by radioimmunoassay after polyethylene glycol separation [10]. Polyclonal antibodies that cross-react more than 90% with proinsulin, and presumably its conversion intermediates, were used [11, 12]. The intra- and interassay coefficients of variation were 7.7 and 10.3%, respectively. Plasma glucose was enzymatically determined using a reagent kit distributed by Diagnostic Chemicals (Oxford, CT, USA). AIR$_g$ was computed as the incremental integrated area under the insulin curve for the first 10 min of the IVGTT. S_I, AIR$_g$, DI and S_G were all derived from the Minimal Model Millennium software [6].

S_I, AIR$_g$ and DI exercise training responses were skewed and were approximately normalised using a square-root transformation. S_I, AIR$_g$, DI and S_G exercise training responses were adjusted for the effects of age, age^2, age^3, BMI and their respective baseline values (to assess genetic determinants on these exercise training response phenotypes independently of the effects of their baseline levels) within each of the sex by generation groups, separately by race, in both the mean and the variance using a stepwise multiple regression procedure. For each of the regressions, only terms that were significant at the 5% level were retained. Finally, each of the adjusted variables was standardised (mean of 0, SD of 1) within sex×generation groups, separately by race.

PCR conditions and genotyping methods have been described previously [13]. Incompatibilities of Mendelian inheritance were checked, and markers showing incompatibilities (between 5 and 10% depending on marker) were retyped completely from PCR reaction to the genotyping. Microsatellite markers were mainly selected from the Marshfield panel version 8a (http://www.marshfieldclinic.org/geneticsresearch). Map locations in location database (LDB) composite units were derived from the Location Database of Southampton, UK (http://www.cedar.genetics.soton.ac.uk/public_html). The LDB units were obtained by integrating different types of data (genetic linkage maps, radiation hybrid maps, physical maps, cytogenetic data, and mouse homology) into a single map. The data were obtained from the Internet, published sources, and the Wessex Human Genetics Institute. Here, LDB units were used to perform linkage scans, and the physical distance in Mb, obtained from the National Center for Biotechnology Information physical map, build 34.3, was used to present scan results.

Multipoint linkage analyses were performed using the variance components model as implemented in the computer program SEGPATH [14, 15]. Under this model, a phenotype is under the influence of the additive effects of a trait locus (g), a residual familial background modelled as a pseudopolygenic component (G_R), and a residual non-familial component (r). The effects of the trait locus and the pseudopolygenic component on the genotype are quantified by the heritabilities h_g^2 and h_r^2 respectively. Allele-sharing probabilities at each marker location for each sib pair were estimated using the multipoint approach in the computer program MAPMAKER/SIBS [16], and were entered into the SEGPATH model. Other parameters in the model include spouse resemblance (u), additional sibling resemblance (b) and the phenotype means and variances. The linkage hypothesis is tested by restricting h_g^2=0. A likelihood ratio test contrasting the null versus the alternative hypotheses is asymptotically distributed as a 50:50 mixture of a χ^2 with 1 degree of freedom and a point mass at zero [17]. The lod score is computed as $\chi^2/(2\times\log_e 10)$.

Results

Means and SD for S_I, AIR$_g$, DI and S_G exercise training responses, together with the baseline values, separately by sex and generation groups, are presented in Table 1 for whites and Table 2 for blacks. Favourable and significant (p<0.05) exercise training responses have been observed in both races and have been reported elsewhere [2]. Significant (p<0.05) racial differences in means of the exercise training response phenotypes were not found within each of the sex×generation groups.

In general, age accounted for little variance in the exercise training responses (<10% in DI [white sons], AIR$_g$ [black daughters] and S_G [black mothers]). In contrast, the baseline values were significant predictors of the exercise training responses in both races for most groups, accounting for 20–50% of the variance (except baseline AIR$_g$ in

Table 3 Summary of multipoint linkage scan results with lod scores ≥1.0 in whites and blacks

Phenotype	Chromosome	Marker	Distance (Mb)	Lod score
Whites				
DI	1p35.1	D1S1622	29.813	1.2
DI	3q25.2	D3S1279	152.346	1.2
DI	6p22.1	D6S1660	23.422	1.1
DI	6p22.1	D6S299	24.033	1.2
DI	6p21.31	TNF	31.647	1.1
DI	6p21.1	D6S1017	41.724	1.0
DI	7q21.3	PON1–D7S821	94.549–95.670	1.2–1.4
DI	10p13	D10S191	14.564	1.1
DI	12q24.31	D12S395	118.600	1.0
DI	12q24.33	D12S2078	126.314	1.1
Blacks				
S_G	1p31.2	D1S476	57.609	1.1
S_G	1q44	D1S304–D1S2682	238.330–245.028	1.1–1.7
S_G	2p22.1–p21	D2S2247–D2S2374	27.278–35.684	1.3–1.5
DI	6p22.1	D6S2239	26.182	1.0
S_G	10p12.33	D10S197	26.531	1.0
S_G	10q23.1–q23.2	D10S541–D10S2470	89.656–92.029	1.0–1.4
S_G	12q13.11–q13.13	D12S1661–D12S1604	46.893–52.014	1.0–1.3
DI	13q14.3	D13S788	49.691	1.0
AIR_g	15q15.3	D15S117	56.196	1.0
S_G	15q26.2	IGF1R	96.927	1.0
AIR_g	18q12.3	D18S535	36.401	1.1
S_G	19q13.33–q13.43	GYS1–D19S254	54.164–62.359	1.8–3.1*
S_I	20q13.12	D20S43–D20S481	42.885–44.454	1.0–1.1
S_I	22q11.23–q12.3	D22S264–D22S421	19.098–24.277	1.0–1.1

*Genome-wide false discovery rate or empirical *p* value is 0.05 at this locus, and empirical *p* values at the remaining marker sites are non-significant (i.e. empirical *p* values >0.05)

white mothers and black men). After transformation and adjustment of the data, both skewness (0.34–0.66) and kurtosis (−0.10 to 1.20) for all the exercise training response phenotypes across races became acceptable.

The mean (±SD) heterozygosities for 654 markers used in this study were 0.72±0.15 in whites and 0.76±0.16 in blacks, with an average intermarker spacing of 2.6 Mb. Residual genetic heritabilities for all the four training response phenotypes, as expected in dissecting other complex traits, were modest to moderate, the estimates ranging from 10% in whites to 20–30% in blacks. All linkage results with lod scores ≥1.0 are summarised in Table 3. They include cytogenetic regions of 1p, 1q, 2p, 3q, 6p, 7q, 10p, 10q, 12q, 13q, 15q, 18q, 19q, 20q and 22q. All autosomal linkage scan results are presented for whites in Fig. 1a and for blacks in Fig. 1b. In addition, linkage analysis results on chromosome 6 are depicted in Fig. 2a for whites and Fig. 2b for blacks; those on chromosome 7 are depicted in Fig. 3a for whites and those on chromosome 19 are depicted in Fig. 3b for blacks. The strongest linkage is on 19q (54–62 Mb) for S_G exercise training response in blacks with promising lod scores ≥1.75 [18] at four markers. These markers include the human skeletal muscle glycogen synthase (*GYS1*) gene locus (54 Mb, lod score 1.8), D19S601 (57 Mb, lod score 2.1), D19S589 (58 Mb, lod score 2.0) and D19S254 (62 Mb, lod score 3.1).

Discussion

The strongest linkage evidence was found on 19q13 in the *GYS1* gene locus to D19S254 (54–62 Mb) for S_G exercise training response in blacks (but not in whites), with a maximum lod score of 3.1. HERITAGE and several other studies previously reported linkages in this region for type 2 diabetes and associated risk factors. At D19S589 (58 Mb, lod score 2.0, for S_G exercise training response), there are at least four findings in the literature that are in agreement. They include linkages for a principal component score (lod score 2.1, primarily percentage body fat, plasma HDL cholesterol and triglycerides) and for fasting insulin (lod score 1.6), both in HERITAGE whites [5, 19], for familial combined hyperlipidaemia in Dutch families (lod score 1.3) [20], and for 2-h glucose in Pima Indians (lod score 1.1) [21]. Moreover, linkages in this region have also been reported in the Framingham Offspring Study (D19S178, 49 Mb, lod score 1.8) for 2-h insulin, in Finnish families (D19S412-D19S867, 52–55 Mb, highest lod score 2.8) for an empirical insulin-resistance index and in multiplex familial type 2 diabetes families (D19S178; *GSY1* gene locus, 49–54 Mb, highest lod score 3.2) for plasma triglycerides [22–24]. Recently, two groups reported linkages at this region for type 2 diabetes, one in a subset of the Japanese population with age at diagnosis younger than 45 years

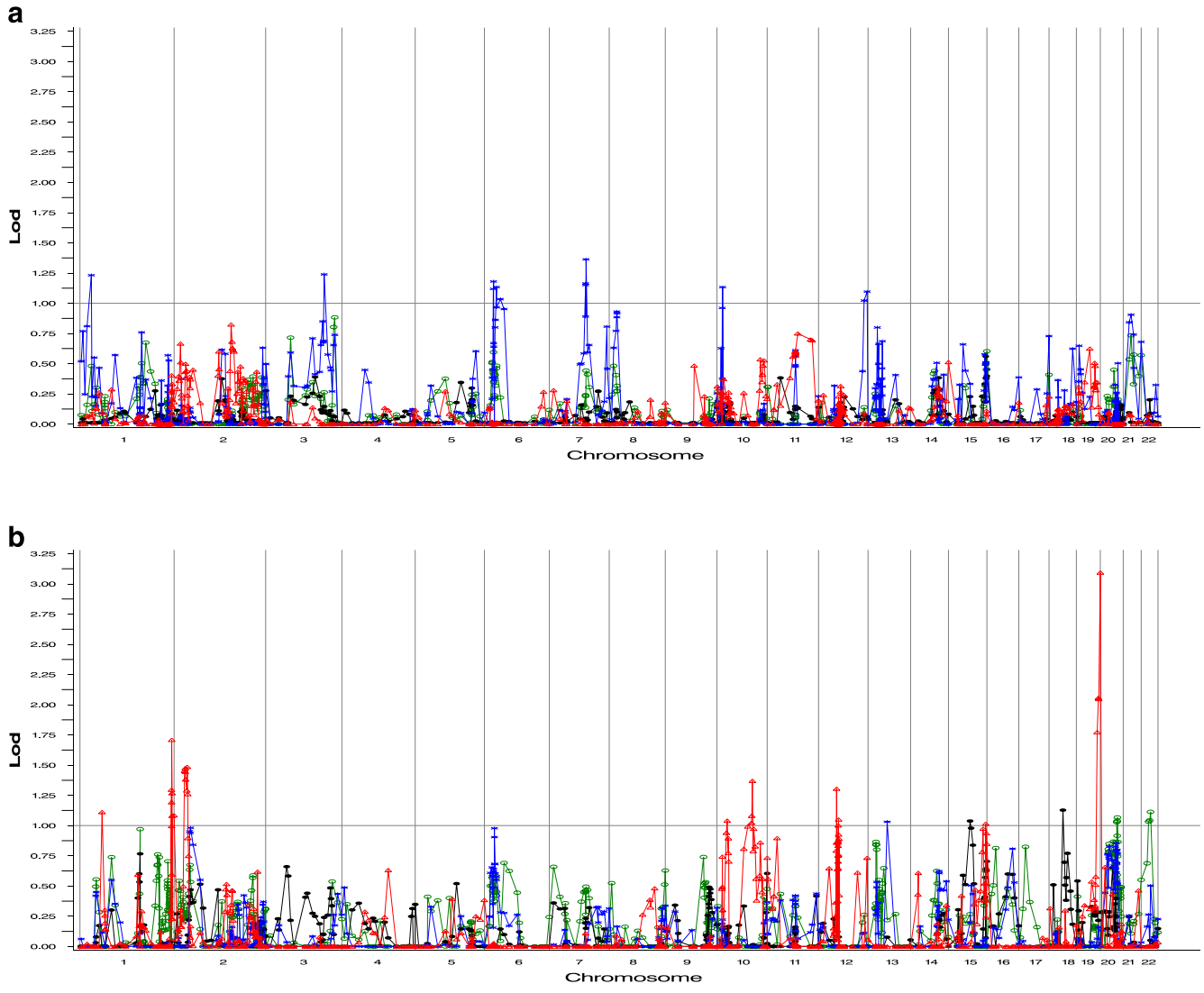

Fig. 1 Multipoint linkage scan results on all autosomes for S_I (*green circles*), AIR_g (*black dots*), DI (*blue stars*) and S_G (*red triangles*) exercise training responses among whites (**a**) and blacks (**b**). Lod score of horizontal reference line is 1.0 for interesting linkages

(D19S571, 58 Mb, lod score 1.7), and the other one in a Dutch population (D19S246–D19S601, 56–57 Mb, highest lod score 1.3) [25, 26]. Follow-up studies on 19q13 to search for type 2 diabetes susceptibility genes or genes linked to glucose–insulin–lipid metabolism, particularly in response to endurance exercise training, are strongly justified.

S_G represents the ability of glucose itself to mediate its own disposal from plasma, independently from the dynamic changes due to basal insulin. It involves both the autoregulatory effect of hepatic glucose output and peripheral glucose utilisation. Although S_G is different from S_I, it is also important in the assessment of glucose tolerance [27]. Decreased S_G levels may predict the development of type 2 diabetes; controversially, others [28] found an opposite association of increased S_G levels with type 2 diabetes using 20 normoglycaemic first-degree relatives of type 2 diabetes patients against 20 matched controls. The storage of glucose as glycogen in human skeletal muscles is frequently impaired in patients with type 2 diabetes and their non-diabetic relatives, partially because of impaired activation of the *GYS1* gene by insulin [29]. The *GYS1* gene, here linked with S_G exercise training response, encodes glycogen synthase, a key enzyme in glucose storage. GYS1 associations with type 2 diabetes and insulin resistance have been suggested [30] but not confirmed [31]. Insulin stimulates GYS1 mRNA expression, and impaired stimulation of *GYS1* gene expression by insulin in type 2 diabetes is thought to be secondary to chronic hyperglycaemia [32]. Exercise of large muscle masses is one of the most efficacious modes to prevent the development of insulin resistance by reducing skeletal muscle stores of glycogen and triglycerides [33]. Studies designed to clarify the effects of sequence variation in the *GYS1* gene on S_G exercise training response are practicable. Finally, and cautiously, given that S_I is associated insulin activation of muscle GYS1 activity, the fact that our linkage finding at the *GYS1* gene locus for S_G but not for S_I in blacks but not in whites

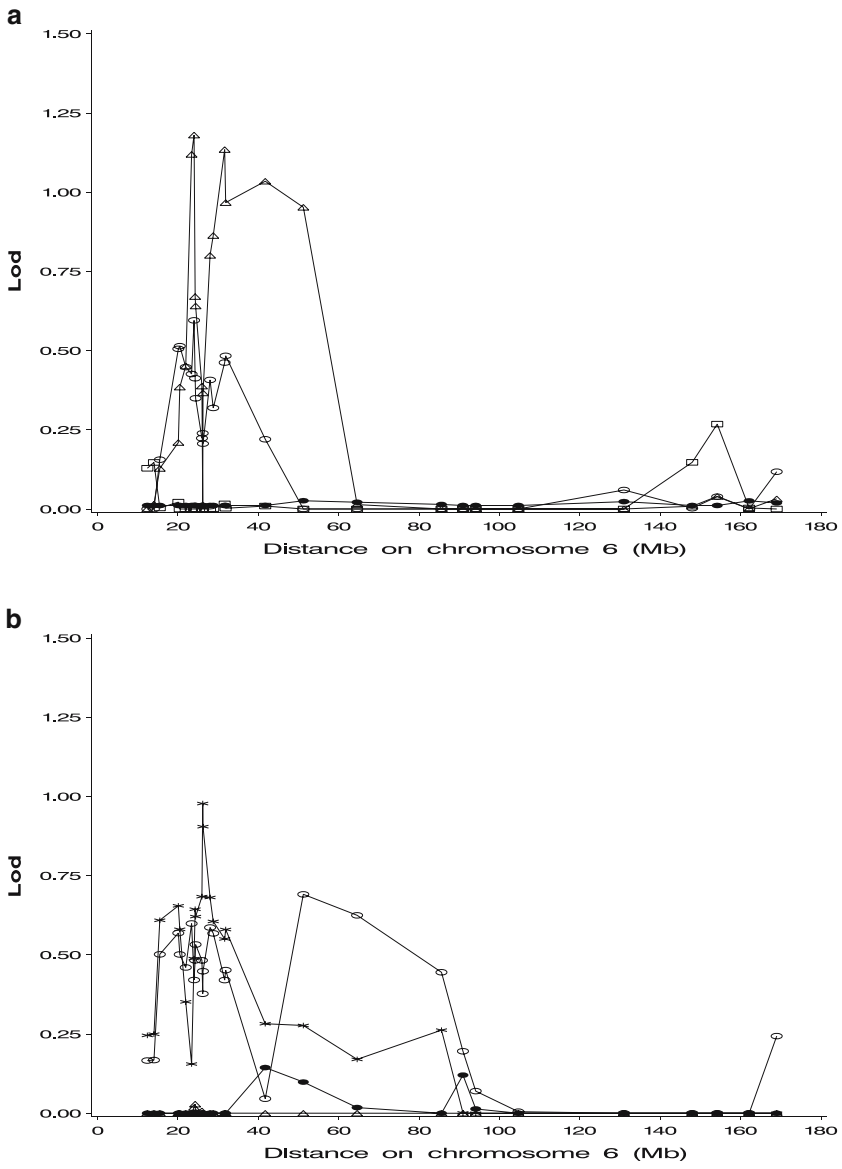

Fig. 2 Multipoint linkage analysis results on chromosome 6 for S_I (*circles*), AIR_g (*dots*), DI (*stars*) and S_G (*triangles*) exercise training responses in whites (**a**) and blacks (**b**)

suggests that validations and replications from other independent studies should be strongly encouraged.

Interestingly, all nominal linkages especially found in whites were for the DI exercise training response. DI, S_I and AIR_g are non-independent traits. DI is a measure reflecting the balance between insulin secretion and insulin action on the disposition of glucose. In other words, DI is an index of insulin secretion adjusted for insulin sensitivity. Thus, finding stronger results for DI than for AIR_g alone should not be surprising. The best replicated region across races for DI exercise training response was 6p, with a lod score of 1.2 at D6S299 (24 Mb) in whites and of 1.0 at D6S2239 (26 Mb) in blacks. Previously, an interesting linkage in this region was found for baseline S_I (D6S2439, 27 Mb, lod score 1.7) in HERITAGE [4]. We propose that a quantitative trait locus in this region may harbour gene(s) that influence DI exercise training response with pleiotropic effects on baseline S_I. Two previous studies reported quantitative trait loci at D6S276 (24 Mb, lod score 2.1) for type 2 diabetes in Chinese Hans [34] and D6S273 (32 Mb, lod score 1.8) for fasting glucose in Pima Indians [21]. Candidate genes surrounding this locus include the *TNFα* (32 Mb), *BAT2* (32 Mb), *HLA-DQB1* (33 Mb), *PPARD* (35 Mb) and *GLP1R* (39 Mb) genes. TNF-α is an inflammatory cytokine with a wide range of anti-tumour and immune functions. Its role in the development of insulin resistance has been established [35]. The *BAT2* gene is within the human major histocompatibility complex class III region. Its product is associated with the age at onset of type 1 diabetes, and possibly with the inflammatory process of pancreatic beta cell destruction during the development of type 1 diabetes. The *HLA-DQB1* gene product specifies the autoimmune response against insulin-producing islet cells that leads to type 1 diabetes. Peroxisome proliferator-activated receptor (PPAR)-δ is ubiquitous, and belongs to one of the transcription factors of the superfamily of nuclear receptors. PPARs are major regulators of lipid and glucose metabolism and insulin sensitivity [36]. Glucagon-like peptide 1, a

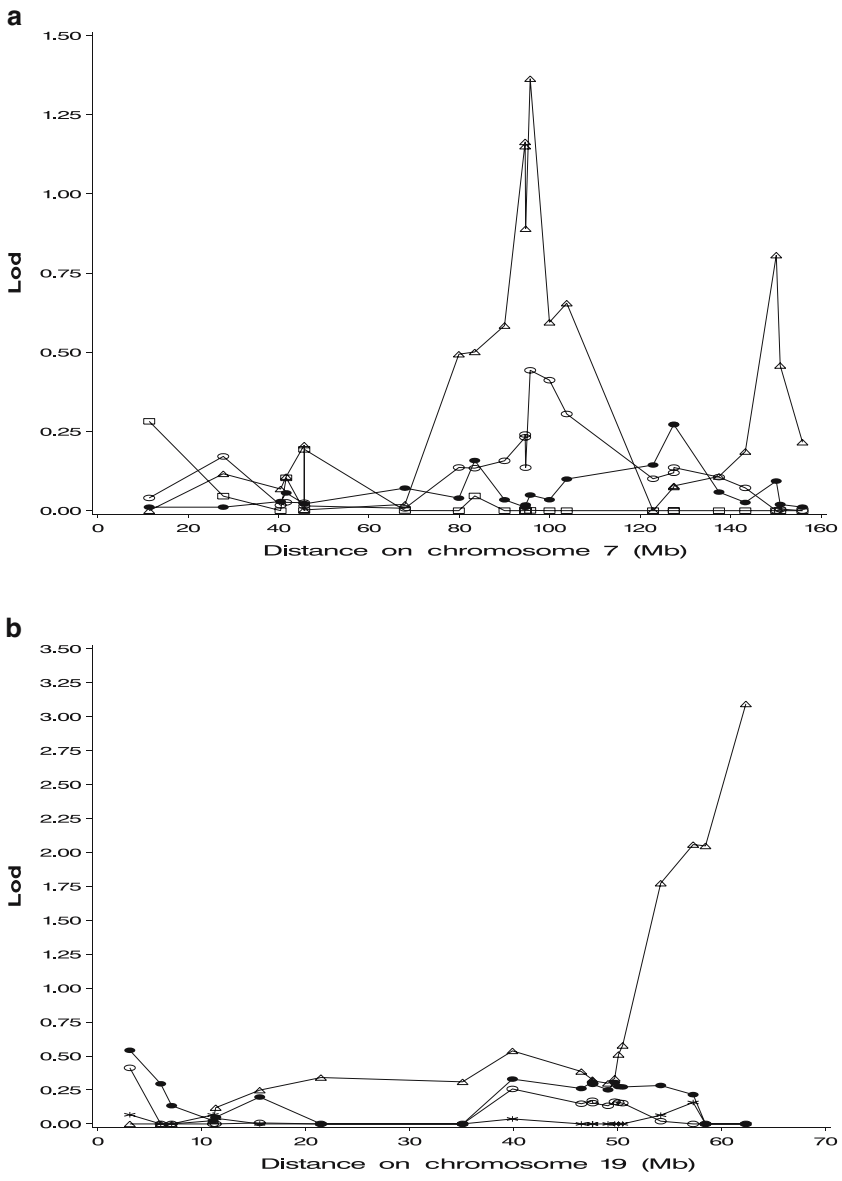

Fig. 3 Multipoint linkage analysis results on chromosome 7 for S_I (*circles*), AIR_g (*dots*), DI (*stars*) and S_G (*triangles*) exercise training responses in whites (**a**) and on chromosome 19 for these phenotypes in blacks (**b**)

hormone derived from the preproglucagon molecule, and secreted by intestinal L cells, is the most potent stimulator of glucose-induced insulin secretion. It has potential for the treatment of type 2 diabetes because of its glucose-dependent insulinotropic and glucagonostatic properties [37]. Though the magnitude of the linkage signals on 6p is not striking, consistencies across whites and blacks and across several other cohorts at this locus warrant further studies.

Among the linkages on 1p, 3q, 7q, 10p and 12q in whites and 1p, 2p, 10, 12q, 13q, 15q, 18q, 20q and 22q in blacks, that on 7q at the *PON1* gene locus D7S821 (95–96 Mb, highest lod score 1.4) for DI exercise training response in whites was supported by two previous findings. They include one at the *PON1* gene locus (lod score 1.4) for fasting insulin exercise training response in HERITAGE whites [4], and one at D7S1799 (103 Mb, *Z* score 1.9) for type 2 diabetes in Pima Indian sib pairs [38].

In conclusion, our genomic scans for glucose and insulin metabolism phenotypes in response to endurance exercise training yielded three quantitative trait loci of interest. A promising locus for S_G exercise training response was identified on 19q13 at the *GYS1* locus; the *GYS1* gene regulates glycogen storage in skeletal muscles. Two possible loci on 6p and 7q were captured for DI exercise training responses, accompanied by consistent findings for relevant traits across other studies.

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