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Original Article

Familial resemblance for glucose and insulin metabolism indices derived from an intravenous glucose tolerance test in Blacks and Whites of the HERITAGE Family Study

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Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia, is a complex disease primarily caused by impairment in insulin sensitivity (S_I) and insulin secretion. While a strong genetic component for T2DM is well established, there are few reports on racial differences in the magnitude of the genetic effects of T2DM and indices of glucose and insulin metabolism. We report here on the familial resemblance for traits related to glucose metabolism at pre-exercise training levels in 492 members from 99 sedentary White families and 259 members from 108 Black families participating in the multicenter HERITAGE Family Study. All these traits were obtained from the frequently sampled intravenous glucose tolerance test (IVGTT). They include glucose disappearance index (K_g), an overall index for glucose tolerance, acute insulin response to glucose ($AIR_{Glucose}$) which is an index for insulin secretion, and those derived from the minimal model including S_I and the disposition index (DI). DI, derived as the product of S_I and $AIR_{Glucose}$, is a measure of the activity of the B-cells adjusted for insulin resistance. After adjustment for age, sex, and body mass index, the maximal heritability estimates in Blacks (Whites) are $48 \pm 14\%$ ($25 \pm 8\%$) for K_g, $44 \pm 14\%$ ($46 \pm 8\%$) for $AIR_{Glucose}$, $38 \pm 12\%$ ($44 \pm 8\%$) for S_I and $32 \pm 14\%$ ($24 \pm 8\%$) for DI. Interestingly, Blacks have higher heritability for overall glucose tolerance than Whites but there is no race difference in heritability estimates for insulin sensitivity or insulin secretion.

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Type 2 diabetes (T2DM) is a strong risk factor for cardiovascular diseases and is a leading cause of morbidity in the USA and around the world (1, 2). At the time of diagnosis, there is usually no absolute insulin deficiency, and impaired insulin action (insulin resistance) is considered a primary cause (1, 3, 4). However, recent studies also suggest that the influence of glucose on basal insulin to enhance glucose utilization and suppress endogenous glucose production, the so-called glucose effectiveness (5), is of particular importance in T2DM where insulin-dependent glucose uptake mechanisms are dysfunctional.

While the clinical manifestations of T2DM are well documented, the mechanisms underlying the development of the disease and the impairment of its intermediate traits such as insulin secretion, insulin resistance or glucose effectiveness are far from clear. The few published linkage reports on genetic markers for T2DM and its intermediate traits have not yielded a consensus (6–10). Identification of the genetic factors could lead to better understanding of the specific metabolic defects responsible for the disease process. Early results from twin and family studies suggested that there is a strong genetic component for T2DM (11–13). There have also been studies based on surrogate indices for insulin secretion and insulin resistance (low S_I), such as fasting plasma insulin and HOmeostasis Model Assessment (HOMA) insulin resistance index, which show evidence of modest to moderate genetic influences (14–23). However, these insulin resistance indices are reported not to be highly correlated with the index obtained from euglycemic hyperinsulinemic clamp (24), the gold standard for insulin sensitivity measurement, especially in subjects with diabetes or impaired glucose tolerance (IGT) (25). Various indices for β-cell function are also not very accurate unless adjusted for insulin resistance (26). On the other hand, the insulin sensitivity indices derived from the intravenous glucose tolerance test (IVGTT) with minimal model (MINMOD) analysis have produced higher correlations with the index obtained from the clamp technique than the fasting plasma insulin and HOMA insulin resistance index do (27). There have been few genetic studies using these more robust measures from MINMOD (28, 29). One recent paper on Finnish subjects by Watanabe et al. (29) reported significant and moderate heritability estimates for MINMOD insulin sensitivity (S_I), $AIR_{Glucose}$, an acute insulin response to an intravenous glucose challenge, DI, the disposition index derived from the product of S_I and $AIR_{Glucose}$, and the MINMOD glucose effectiveness index (S_G).

We therefore undertook the present study to estimate and compare heritabilities for MINMOD model indices in the HERITAGE Family Study, a multicenter project involving four clinical centers in the USA and Canada. The HERITAGE examined both White and Black populations and investigated potential differences between the two racial groups. The indices were the glucose disappearance index (K_g), an intravenous glucose tolerance index, in addition to $AIR_{Glucose}$, S_I, and DI.

Methods

Study subjects

The HERITAGE Family Study is a multicenter exercise-training study. The main objective of the study was to assess the role of genetic factors in the cardiovascular, metabolic, and hormonal responses to aerobic exercise training in sedentary families. The HERITAGE sampling procedure outlining the inclusion and exclusion criteria has been described in detail elsewhere (30).

Several criteria were used to screen subjects for participation. First, offspring were required to be 17–40 years old and parents were required to be 65 years old or younger in order to reduce pubertal and aging confounding effects. Second, families were required to be sedentary, defined at baseline as not engaging in regular vigorous physical activity over the previous 6 months. Vigorous activity was any activity lasting 30 min or more involving a rate of energy expenditure of 7 METS or more (1 MET equals 3.5 ml O_2 uptake per kg body weight per min and represents the rate of energy expenditure at rest) in individuals ≥ 50 years or 8 METS or more for younger individuals, and occurring more than once a week. Third, individuals with a BMI greater than 40 kg/m^2 were usually excluded because of metabolic abnormalities and difficulties to exercise, unless shown to be capable of exercising on a cycle ergometer. Fourth, individuals with blood pressure levels greater than 159 mmHg systolic and/or 99 mmHg diastolic also were excluded. Fifth, individuals with any condition or disease that was life threatening or that could be aggravated by cycle exercise were excluded (e.g. a malignancy; uncontrolled endocrine and metabolic disorders; definite or possible coronary heart disease; and chronic or recurrent respiratory problems). Finally, individuals requiring lipid lowering, antidiabetics or antihypertensive drugs were excluded.

In all, there were 108 Black and 99 White nuclear families. The sample sizes for the present study were 259 and 492 subjects for Blacks and Whites, respectively. The study protocol had been

previously approved by the Human Subjects Committee at each participating institution. Informed written consent was obtained from each subject.

Measures

All participants underwent a battery of tests both prior to and after completing the 20-week standardized exercise-training program. Results are limited to the baseline (pre-exercise training) evaluation in the present study.

IVGTT protocol. The IVGTT protocol proposed by Walton et al. (31) was closely followed. The IVGTT was performed in the morning after an overnight (12 h) fast. Before their visit, subjects were provided with instructions and details of the procedures they would undergo. Upon arrival at the Clinical Center (by 09:00 h), weight and height were measured and recorded. A nomogram was used to calculate the dosage of intravenous glucose (20 g/m^2 of body surface) and the total volume to be injected (40 ml/m^2), which was aliquoted in syringes of 30 ml. An additional syringe of 10 ml of saline was prepared to rinse the vein after glucose injection. After resting for 15 min in a lying or semi-reclined position, a microperfusion butterfly and/or an indwelling catheter (local option) were inserted into an antecubital vein in each arm for injection and sampling, respectively.

Blood samples were collected through the venous catheter at -15 and 0 min. Then, glucose was injected intravenously via the microperfusion butterfly system or indwelling catheter in the opposite arm over a period of 3 min, followed by the injection of 10 ml of saline or the solute (up to 50 ml) with the indwelling catheter. Blood samples to measure plasma glucose and insulin were taken at 1, 3, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150 and 180 min after the end of the glucose injection in the opposite arm. At each time point, a 5-ml blood sample was collected in an EDTA tube. Samples were kept on ice and after centrifugation of the blood, plasma samples were collected and kept frozen at -80°C until their shipment to the core laboratory in Québec (within a month).

Plasma insulin and glucose measurement. Plasma insulin was measured by radioimmunoassay after polyethylene glycol separation, as described by Desbuquois and Aurbach (32). Polyclonal antibodies, which cross-react more than 90% with proinsulin and presumably its conversion intermediates, were used (33). Therefore, in this study as in others (33, 34), insulin refers to immunoreactive insulin defined as the sum of insulin, proinsulin and split-proinsulin. In the present cohort with normal fasting glucose levels and no history of diabetes, it is estimated that about 10% of the immunoreactive insulin is in the form of proinsulin and its conversion intermediates (34). Insulin levels were treated as missing for three individuals with insulin antibodies, four individuals with extremely low glucose disappearance rate, and one individual with both conditions. The intra- and inter-assay coefficients of variation were 7.7% and 10.3%, respectively. Plasma glucose was enzymatically determined using a reagent kit distributed by Diagnostic Chemicals Ltd.

Parameters calculated. K_g, used as a measure of overall intravenous glucose tolerance, was an estimate of the disappearance rate (%/min) of plasma glucose based on the slope of the line derived from least-squares regression of the natural logarithm of plasma glucose on time from 10 through 60 min during the IVGTT (35). $AIR_{Glucose}$ was computed as the incremental integrated area under the insulin curve for the first 10 min of the IVGTT and used as an index of insulin secretion. S_I was derived from the MINMOD analysis (36). $DI = AIR_{Glucose}S_I$, was used as an index of overall glucose homeostasis.

Statistical analysis

Because of skewed distributions, all four variables were transformed using a natural logarithm prior to the following data analysis.

Age and BMI adjustments. Adjustments for the effects of covariates on K_g, $AIR_{Glucose}$, S_I, and DI were carried out separately in eight sex by generation (fathers, mothers, sons, and daughters) by race groups using a stepwise multiple regression procedure and retaining only significant terms ($\alpha = 0.05$). Age, age^2, age^3 and body mass index (BMI = kg/m^2) were considered in the regression models. Appendix A summarizes the percentages of variance for these indices by age and BMI in the eight groups.

Familial correlation mode. The purpose of the familial correlation analysis is to determine whether there is evidence of familial or genetic factors underlying the variation in each trait (univariate correlation analysis). Significant correlations among siblings and between parents and offspring, but not between spouses, suggest that there are genetic influences on the trait. Significant spouse correlations, in addition to sibling and parent–offspring correlations, indicate that the variation is due to both genes and familial environments.

The general univariate correlation model was based on four groups of individuals – fathers (f), mothers (m), sons (s), and daughters (d), leading to eight interindividual correlations (fm, fs, fd, ms, md, ss, sd, dd). The computer program SEGPATH (37) was used to estimate the familial correlations based on maximum likelihood methods. The statistical method of analysis fits the model directly to the family data, under the assumption that the phenotypes in a family jointly follow a multivariate normal distribution.

Hypothesis tests. The significance of each set of familial correlations is tested by comparing the log-likelihood of a reduced model where some of the correlations are fixed to zero against the log-likelihood obtained from the general model where all familial correlations are estimated. The likelihood ratio test, which is the difference between minus twice the log-likelihoods ($-2\ln L$) under the two models, is distributed as a χ^2. The degrees of freedoms (df) are given by the difference in the number of parameters estimated in the two nested models. A χ^2 with a p-value of less than 0.05 is taken to suggest that the familial correlations set to zero under a null hypothesis are significantly different from zero. In addition to the likelihood ratio test, Akaike's information criterion (AIC) (38), which is $-2\ln L$ plus twice the number of estimated parameters, was used to judge the fit of non-nested models. The best model is indicated by the smallest AIC value. In addition to testing the significance of parent–offspring, sibling, and spouse correlations, five other sex-specific hypotheses were tested. Appendix B gives a detailed description of each model tested along with the parameter constraints and the df. The familial correlation model as implemented in SEGPATH has been published in detail elsewhere (39).

Results

Table 1 presents the means, medians, and SDs of age, BMI, and the unadjusted K_g, $AIR_{Glucose}$, S_I and DI by sex and generation in Blacks and Whites separately. In general, Blacks have higher levels of K_g, $AIR_{Glucose}$, and DI but lower levels of S_I than Whites across the groups; offspring have higher levels of K_g, $AIR_{Glucose}$, and DI than do parents.

The results of the hypothesis tests are summarized in Tables 2 and 3 for Blacks and Whites, separately. We did not find any sex or generation differences in the familial correlations for any of these four traits in either race (model 4, all p-values > 0.05).

In Blacks, the hypotheses of 'no sibling and parent–offspring correlations' (model 5) were all rejected, while the 'no spouse correlation' hypothesis (model 6) was not rejected for K_g, $AIR_{Glucose}$, and S_I. Based on these likelihood ratios tests and AIC tests, the best model for K_g, $AIR_{Glucose}$ and S_I was a single familial correlation (parent–offspring = sibling) and no spouse resemblance (model 8). For DI, the significance of sibling and parent–offspring correlations were marginal based on the likelihood ratio. However, according to the AIC, model 8 was also the most parsimonious model for DI.

In Whites, the hypotheses of 'no sibling and parent–offspring correlations' were also all rejected, while 'no spouse correlation' hypothesis

Table 1. Characteristics (mean (median) ± SD) of study variables among 492 Whites and 259 Blacks from the HERITAGE Family Study by sex and generation groups

Variable	Black fathers (n = 21–22)	Black mothers (n = 45–46)	Black sons (n = 77)	Black daughters (n = 113–114)
Age (years)	48.9 (47.3) ± 7.20	46.3 (44.8) ± 6.64	27.4 (27.0) ± 7.19	27.6 (26.6) ± 7.67
BMI (kg/m^2)	27.5 (26.6) ± 5.45	29.5 (28.6) ± 5.26	27.5 (26.7) ± 5.75	27.8 (25.9) ± 7.07
K_g (%/min)	1.41 (1.12) ± 0.73	1.70 (1.59) ± 0.72	1.91 (1.77) ± 0.73	2.02 (1.90) ± 0.67
$AIR_{glucose}$ (pM × 10 min)	497 (489) ± 340	756 (558) ± 588	1 078 (805) ± 845	959 (816) ± 570
S_I ($\times 10^{-5}$ min^{-1}/pM)	2.90 (1.85) ± 3.12	2.86 (2.05) ± 2.26	3.25 (2.15) ± 3.99	2.70 (2.17) ± 1.80
DI	1 373 (811) ± 1 809	1 812 (1310) ± 1 644	2 580 (1953) ± 2870	2 349 (2 116) ± 1 451
	White fathers (n = 96)	White mothers (n = 86)	White sons (n = 152–154)	White daughters (n = 155–156)
Age (years)	53.5 (51.9) ± 5.22	52.1 (50.7) ± 5.12	25.4 (24.6) ± 6.05	25.2 (24.1) ± 6.15
BMI (kg/m^2)	28.3 (27.0) ± 4.39	27.6 (26.1) ± 4.80	25.6 (24.4) ± 4.84	23.7 (22.5) ± 4.47
K_g (%/min)	1.35 (1.23) ± 0.52	1.57 (1.47) ± 0.57	1.63 (1.52) ± 0.55	1.84 (1.73) ± 0.58
$AIR_{glucose}$ (pM × 10 min)	349 (262) ± 269	306 (279) ± 191	451 (342) ± 346	366 (296) ± 236
S_I ($\times 10^{-5}$ min^{-1}/pM)	3.36 (2.44) ± 2.85	4.93 (3.79) ± 3.68	4.31 (3.60) ± 2.62	4.94 (4.27) ± 3.29
DI	1 041 (809) ± 942	1 365 (1 062) ± 1159	1 540 (1 302) ± 1055	1 529 (1 266) ± 954

K_g indicates glucose disappearance index; $AIR_{Glucose}$, acute insulin response; S_I, insulin sensitivity based on MINMOD model; DI, disposition index; BMI, body mass index.

Table 2. Results of hypothesis tests for univariate familial correlation analyses of age, sex, and BMI adjusted glucose metabolism-related indices among 259 Blacks from the HERITAGE Family Study

Model	df	K_g			$AIR_{Glucose}$		
		χ^2	p	AIC	χ^2	p	AIC
1. General model	0	–	–	16.00	–	–	16.00
2. No sex difference in offspring	4	3.06	0.55	11.06	1.23	0.87	9.23
3. No sex difference in parents and offspring	5	3.39	0.64	9.39	4.25	0.51	10.25
4. No sex and generation difference	6	3.44	0.75	7.44	4.64	0.59	8.64
5. No sibling and parent–offspring correlations	7	18.20	0.01	20.20	17.02	0.02	19.02
6 No spouse correlations	1	0.01	0.94	14.01	0.12	0.72	14.12
7. All correlations are equal	7	5.57	0.59	7.57	6.01	0.54	8.01
8. All sibling and parent correlations are equal and no spouse correlation	7	3.55	0.83	5.55*	4.68	0.70	6.68*
		S_I			DI		
1. General model	0	–	–	16.00	–	–	16.00
2. No sex difference in offspring	4	5.89	0.21	13.89	4.99	0.29	12.99
3. No sex difference in parents and offspring	5	5.93	0.31	11.93	5.00	0.42	11.0
4. No sex and generation difference	6	10.30	0.11	14.30	5.04	0.54	9.04
5. No sibling and parent–offspring correlations	7	19.68	<0.01	21.68	11.49	0.12	13.49
6. No spouse correlations	1	0.01	0.92	14.01	0.06	0.80	14.06
7. All correlations are equal	7	10.72	0.15	12.72	5.53	0.60	7.53
8. All sibling and parent correlations are equal and no spouse correlation	7	9.40	0.22	11.40*	5.04	0.66	7.04*

* The most parsimonious model. K_g, glucose disappearance index; $AIR_{Glucose}$, acute insulin response; S_I, insulin sensitivity based on MINMOD; DI, disposition index.

was not rejected for K_g, $AIR_{Glucose}$, and S_I. Based on these hypothesis tests and the AIC, the most parsimonious model was the 'all correlation are equal' model (model 7) for K_g, a single familial correlation and no spouse resemblance (model 8) for $AIR_{Glucose}$ and S_I. For DI, the pattern was similar to that in Blacks. The model 8 was the most parsimonious model.

When the 'no sibling correlations' and 'no parent–offspring correlations' hypotheses were examined separately, the conclusion did not differ from when these two hypotheses were tested in the same model.

Table 4 summarizes the familial correlations and heritability estimates from the most parsimonious models for both Blacks and Whites. The heritability estimates were $48 \pm 14\%$ for K_g, $44 \pm 14\%$ for $AIR_{Glucose}$, $38 \pm 12\%$ for S_I, and $32 \pm 14\%$ for DI in Blacks. In Whites, the corresponding heritability estimates were $25 \pm 8\%$ for K_g, $46 \pm 8\%$ for $AIR_{Glucose}$, $44 \pm 8\%$ for S_I, and $24 \pm 8\%$ for DI, respectively. Based on the maximum likelihood test ($p < 0.05$) and the comparison of the means and standard errors (SEs), the heritability is significantly different across races only for K_g (higher in Blacks than Whites).

Discussion

T2DM is a complex disease that is likely due to multiple genes with modest effects, rather than one or a small number of genes with large effect (40). Moreover, because of the heterogeneity of the pathophysiological mechanisms underlying this disorder, linkage analyses have so far not produced the same results in all studies (7–9). Linkage and association studies using intermediate phenotypes such as indices of β-cell function, insulin resistance, and glucose effectiveness could potentially generate useful leads. However, an important issue is how to measure these phenotypes and to verify they aggregate in families. Fasting insulin and HOMA insulin resistance index are not very reliable in subjects with T2DM and IGT (25). The indices for insulin secretion and resistance derived from IVGTT with MINMOD have offered more reliable results. To the best of our knowledge, there has been only one report on heritability estimates for MINMOD insulin secretion, insulin sensitivity, and glucose effectiveness performed in Finnish families with T2DM (29). The present findings of significant and moderate heritability estimates in both Black and White HERITAGE populations are comparable with the results from the earlier study, suggesting that these observations apply over different ethnic populations.

It should be noted that the present estimates of heritability based on familial correlations are the maximal estimates, and also may include effects due to familial environmental factors especially when there are significant spouse correlation in addition to significant parent–offspring and sibling

Table 3. Results of hypothesis tests for univariate familial correlation analyses of age, sex, and BMI adjusted glucose metabolism-related indices among 492 Whites from the HERITAGE Family Study

Model	df	K_g			$AIR_{Glucose}$		
		χ^2	p	AIC	χ^2	p	AIC
1. General model	0	–	–	16.00	–	–	16.00
2. No sex difference in offspring	4	7.69	0.10	15.69	3.26	0.51	11.26
3. No sex difference in parents and offspring	5	8.23	0.14	14.23	5.29	0.38	11.29
4. No sex and generation difference	6	11.14	0.08	15.14	6.36	0.38	10.36
5. No sibling and parent–offspring correlations	7	23.79	<0.001	25.79	41.88	<0.01	43.88
6. No spouse correlations	1	1.13	0.29	15.13	0	0.96	14.00
7. All correlations are equal	7	11.42	0.12	13.42*	10.53	0.16	12.53
8. All sibling and parent correlations are equal and no spouse correlation	7	11.59	0.12	13.59	6.51	0.48	8.51*
		S_I			DI		
1. General model	0	–	–	16.00	–	–	16.00
2. No sex difference in offspring	4	1.45	0.84	9.45	2.30	0.68	10.30
3. No sex difference in parents and offspring	5	3.04	0.69	12.05	2.31	0.80	8.31
4. No sex and generation difference	6	3.55	0.74	7.55	2.32	0.89	6.32
5. No sibling and parent–offspring correlations	7	41.68	<0.01	43.68	13.07	0.07	15.07
6 No spouse correlations	1	0.84	0.36	14.84	0.08	0.77	13.10
7. All correlations are equal	7	6.03	0.54	8.03	3.09	0.88	5.09
8. All sibling and parent correlations are equal and no spouse correlation	7	4.22	0.75	6.22*	2.41	0.93	4.41*

* The most parsimonious model. K_g, glucose disappearance index; $AIR_{Glucose}$, acute insulin response; S_I, insulin sensitivity based on MINMOD; DI, disposition index.

correlations. Physical activity and diet are two possible major environmental factors contributing to the individual differences in these indices for glucose and insulin metabolism (41, 42).

We found that there is racial difference in the heritability for K_g, an overall index of intravenous glucose tolerance. Although the Black–White differences in means and prevalences do not directly translate into Black–White differences in heritability estimates for the traits in this study, a higher heritability could partly explain why Blacks have higher prevalence of T2DM than Whites (1). Black–White differences in insulin secretion and clearance have been observed as early as in adolescent (43). However, we did not find any differences in heritability estimates for S_I, $AIR_{Glucose}$, and DI in the present investigation. Impaired insulin secretion, insulin resistance and low S_G appear to be the three major factors contributing to the development of impaired glucose tolerance and T2DM. Therefore, a higher heritability for K_g but not S_I and $AIR_{Glucose}$ in Blacks than in Whites suggests that Blacks might have higher heritability estimates for S_G. It is also likely that Blacks might have higher inheritance for insulin clearance than Whites.

Previous studies have suggested that the DI, which reflects insulin secretion corrected for insulin resistance, can give a more accurate estimate of β-cell function (26, 44). We examined the heritability for this disposition index and found lower estimates than those for $AIR_{Glucose}$ in both Blacks and Whites, which is in accordance with the findings by Watanabe et al. (29). This could largely be due to the fact that $AIR_{glucose}$ includes heritability for insulin resistance, which is factored out by the DI, and suggest that the inheritance of DI be independent of S_I inheritance.

Adiposity is an important covariate for glucose and insulin metabolic indices (45). After adjustment for percent body fatness, an index of adiposity, a previous study on Pima Indians resulted in lower heritability estimates for diabetes-related traits (20). However, our comparison of heritability estimates with and without BMI adjustment (results not reported) did not reveal any significant differences. This finding is in agreement with the findings from the study by Watanabe et al. in a Finnish population (29). Since the Pima Indians have higher adiposity levels than the Whites and Blacks in the HERITAGE Family Study, adiposity may have had greater effects on diabetes-related traits in former subjects. This effect of adiposity levels on glucose and insulin metabolism has been proposed before (46, 47).

Because insulin resistance/low insulin sensitivity is central component of syndrome X or the insulin resistance (48) and the there is indication of common genetic mechanism for different components of this syndrome (49), the present findings of mod-

Table 4. Parsimonious familial correlations ± SE and heritability estimates for four glucose metabolism-related indices among 492 Whites and 259 Blacks from the HERITAGE Family Study

Relationship	K_g	$AIR_{Glucose}$	S_I	DI
Blacks				
Spouse	0	0	0	0
Parent–offspring	0.24 ± 0.07	0.22 ± 0.07	0.19 ± 0.06	0.16 ± 0.07
Sibling	[0.24]	[0.22]	[0.19]	[0.16]
h^2	48 ± 14%	44 ± 14%	38 ± 12%	32 ± 14%
Whites				
Spouse	0.13 ± 0.04	0	0	0
Parent–offspring	[0.13]	0.23 ± 0.04	0.22 ± 0.04	0.12 ± 0.04
Sibling	[0.13]	[0.23]	[0.22]	[0.12]
h^2	25 ± 8%	46 ± 8%	44 ± 8%	24 ± 8%

The correlations between brackets mean that they were set equal to the preceding correlations without brackets for this trait. K_g, glucose disappearance index; $AIR_{Glucose}$, acute insulin response; S_I, insulin sensitivity based on MINMOD; DI, disposition index. Maximal heritability $h^2 = (r_{sibling} + r_{parent-offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2r_{spouse}r_{parent-offspring})$, where r represents the interindividual correlations.

erate but significant heritability of insulin sensitivity measured by a more accurate method in this large family-based study would provide basis for better understanding of the pathogenesis of this syndrome. It is also worth mentioning that this current study subjects were selected from a healthy sedentary population. Cautions should be exercised when the present findings are applied to other populations.

In conclusion, there is significant and moderately high heritability for IVGTT-derived phenotypes related to T2DM. Interestingly, Blacks have higher heritability for overall glucose tolerance than Whites but there is no race difference in heritability estimates of insulin sensitivity and insulin secretion, suggesting that there is likely a difference in the genetic etiology between Blacks and Whites for other factors involved in glucose homeostasis, e.g. glucose effectiveness. In addition, although BMI is a significant covariate for these glucose metabolism-related traits, BMI adjustments have no effect on familial resemblance for these traits.

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Appendix A

The percentage of variance explained by age and BMI for four glucose metabolism-related traits by sex and generation groups in Blacks and Whites in the HERITAGE Family Study

Variables	Blacks				Whites			
	Fathers (%)	Mothers (%)	Sons (%)	Daughters (%)	Fathers (%)	Mothers (%)	Sons (%)	Daughters (%)
K_g	25.8 (age)	8.2 (BMI)	NS	10.8 (age^2)	21.7 (BMI) 7.2 (age)	NS	NS	6.2 (age^3)
$AIR_{Glucose}$	26.8 (age)	10.9 (age)	12.2 (BMI) 9.6 (age^3)	NS	NS	NS	12.0 (BMI)	10.7 (BMI) 7.4 (age^2)
S_I	38.8 (BMI)	25.4 (BMI)	26.1 (BMI)	14.5 (BMI)	37.3 (BMI) 2.6 (age)	21.4 (BMI)	34.4 (BMI) 3.0 (age)	20.6 (BMI) 3.9 (age)
DI	15.2 (BMI)	17.4 (BMI)	11.0 (age^3)	4.0 (age^3)	18.4 (BMI) 9.5 (age)	10.4 (BMI)	3.7 (BMI)	NS

K_g, glucose disappearance index; $AIR_{Glucose}$, acute insulin response; S_I, insulin sensitivity based on MINMOD model; DI, disposition index; BMI, body mass index; NS, none of these variables were significant predictors.

Appendix B

Summary of hypothesis tests

Model	df	Parameter constrained
1. General model	0	All eight correlations estimated
2. No sex difference in offspring	4	fs = fd, ms = md, ss = dd = sd
3. No sex difference in parents and offspring	5	fs = fd = ms = md, ss = dd = sd
4. No sex and generation difference	6	fs = fd = ms = md = ss = dd = sd
5. No sibling and parent–offspring correlations	7	ss = dd = sd = fs = fd = ms = md = 0
6. No spouse correlations	1	fm = 0
7. All correlations are equal	7	fm = fs = fd = ms = md = ss = dd = sd