Multigenerational inheritance and clinical characteristics of three large pedigrees with early-onset type 2 diabetes in Jamaica

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ABSTRACT

Objective. *To document the existence and clinical characteristics of three large families with multigenerational inheritance of early-onset type 2 diabetes in Jamaica.*

Methods. *Three probands from large families with multigenerational inheritance of early-onset type 2 diabetes in at least three generations were detected at the University Hospital of the West Indies in Jamaica. Each proband at the time of diagnosis was ≤ 25 years of age, was lean, and did not require insulin therapy. Clinical, metabolic, and genetic assessments were undertaken to profile the diabetes in the three families.*

Results. *Three pedigrees—BK, SU, and CA—consisting of 38, 48, and 113 members, respectively, with multigenerational inheritance of early-onset type 2 diabetes in at least three generations, were investigated. The mean age at diagnosis of the three pedigrees was 31.5 ± 2.9 years, with 10 persons detected below 25 years of age. Findings suggestive of overweight, insulin resistance, low insulin secretion, dyslipidemia, and mild intra-abdominal obesity were present. Islet cell antibodies and sequence variants in* MODY1 *to* –6 *genes were absent.*

Conclusions. *Large families demonstrating multigenerational inheritance of diabetes and other characteristics consistent with early-onset type 2 diabetes are present in the Jamaican population.*

Key words Inheritance patterns; diabetes mellitus, type 2; pedigree; Jamaica.

Categories of diabetes in the young include early-onset type 2 diabetes, maturity-onset diabetes of the young (MODY), and type 1 immune-mediated diabetes (1).

Early-onset type 2 diabetes is characterized by insulin resistance, obesity, the onset of diabetes before age 40 years, and the occasional presence of autosomal dominant inheritance (1, 2). Autosomal dominant inheritance of diabetes mellitus is defined as the presence of diabetes mellitus in at least three generations with only one parent in the first generation having diabetes mellitus (3). Doria et al. (4) reported on families with early-onset type 2 diabetes occurring before 35 years of age with autosomal dominant inheritance.

In the etiologic classification of diabetes mellitus, MODY is now not classified as type 2 diabetes but rather as a specific type of diabetes with genetic defects in beta cell function (5). MODY is a group of heterogeneous monogenic disorders in which there are six mutated genes known as *MODY1* to *–6*, low insulin secretion, normal body mass

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index (BMI), and the onset of diabetes before the age of 25 years (6–13).

While large families with autosomal dominant inheritance of diabetes in the young have been reported in other countries (7, 8, 14, 15), the existence of these families in Jamaica has not been previously documented.

We report here three large Jamaican families in which diabetes in the young has been inherited in multigenerations rather than in a purely autosomal dominant fashion and displays mixed characteristics of early-onset type 2 diabetes and MODY.

MATERIALS AND METHODS

The study was conducted in Jamaica at the University Hospital of the West Indies. Previously, 698 Jamaican pregnant women with a family history of diabetes occurring before age 35 had been evaluated for the prevalence of gestational diabetes, the results of which were published (16). Three of these women belonged to large families with a family history of subjects with diabetes mellitus who do not need insulin, even though the diabetes was diagnosed before the age of 25 years and in which there is multigenerational inheritance of diabetes mellitus. Members of these three families were invited to participate in this study. The criteria for including the probands in the study were age of onset of diabetes before 25 years, having three or more generations affected by diabetes, diabetes being diagnosed on the paternal or maternal side only, and not requiring insulin therapy for more than 6 months after the diagnosis of diabetes.

A detailed pedigree was obtained from each proband by using a questionnaire. The response was cross-checked with family members who were invited to participate in the study. A special effort was made to recruit the partners of diabetic members of the pedigree, so that the metabolic state of these partners could help shed light on that of their offspring. Each participant was subjected to clinical, laboratory, and molecular genetic assessments. Individuals below 16 years of age from nondiabetic parents were not included in the study. The pedigrees were matched by age, sex, BMI, and ethnicity with control subjects who were healthy volunteers from the University of the West Indies in Jamaica.

The study was approved by the Faculty of Medical Sciences, University Hospital of the West Indies, Mona Ethics Committee; informed consent was obtained from subjects after the nature of the study was explained to them.

Medical history

Participants completed an interviewer-administered questionnaire to determine details about their history of diabetes at diagnosis, hospitalization, diabetic-related complications, medications, any comorbid disease, and diabetes-related complications of ischemic heart disease, peripheral vascular disease, diabetic retinopathy, and peripheral neuropathy. Ischemic heart disease was defined as a history consistent with angina pectoris and peripheral vascular disease as symptoms of claudication.

Anthropometric measurements

Height was measured to the nearest centimeter, and weight was measured to the nearest 0.1 kilogram. The BMI was calculated as the weight in kilograms divided by the square of the height in meters.

Waist circumference was measured midway between the anterior-superior iliac crest and the lower ribs. Hip circumference was measured at the widest part of the hip and the maximum circumference of the buttocks. The waist/hip ratio (WHR) was calculated as the waist measurement divided by the hip measurement. Blood pressure was measured with an aneroid sphygmomanometer after the patient had been sitting for at least 5 minutes.

Diabetic retinopathy was evaluated by direct fundoscopy and peripheral neuropathy assessed by using the vibration sensation to a 128-hertz tuning fork at the dorsum of the terminal phalanx.

Laboratory assessments

Fasting blood samples were taken for glucose, hemoglobin A1c, triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine, uric acid, insulin, and C-peptide. Subjects without known diabetes mellitus were administered a 75-gram, 2-hour oral glucose tolerance test according to World Health Organization (1999) criteria (17). Diabetes mellitus was defined as fasting plasma glucose > 7.0 millimoles per liter of blood (mmol/L) and a 2-hour plasma glucose ≥ 11.1 mmol/L or a previous diagnosis of diabetes with ongoing treatment with oral agents and/or insulin. Impaired fasting glucose was defined as fasting plasma glucose > 6.1 and 2-hour plasma glucose < 7.8 mmol/L. Impaired glucose tolerance was defined as a fasting plasma glucose < 7.0 mmol/L and 2-hour plasma glucose ≥ 7.8 mmol/L and ≤ 11.1 mmol/L.

Hemoglobin A1C was assessed by an affinity chromatography method (Sigma Diagnostics). Total cholesterol was evaluated by an enzymatic method (Abbott Diagnostics) and high density lipoprotein cholesterol was determined in the supernate after precipitating the other lipoproteins with phosphotungstic acid (Sigma Diagnostics). Triglyceride was assessed by an enzymatic method (Abbott Diagnostics). Creatinine was estimated by the alkaline picrate method. Insulin and C-peptide were determined by chemiluminescent methods (Diagnostic Products Corporation). Islet cell antibodies were determined by indirect immunofluorescence using 4-micrometer cryostat sections of rhesus monkey pancreas (Innova Diagnostics) as substrate. The manufacturer's instructions were followed when commercially prepared reagents were used.

Insulin resistance and beta cell function were calculated by homeostasis model assessment (HOMA) (18). This model was based on the assumption that a healthy subject of normal weight and < 35 years old has an insulin resistance of 1 and a beta cell function of 100%.

Genetic studies. The probands with a family history consistent with early-onset multigenerational type 2 diabetes, along with two affected family members, were screened for sequence variants in the *MODY* genes by polymerase chain reaction (PCR) single-strand conformation analysis (19). Genomic DNA was prepared from peripheral blood by phenol-chloroform extraction. A genome scan was performed by means of PCR and automated fragment analysis, as described by Irving et al. (16). Each individual was genotyped for approximately 425 microsatellite markers with a mean distance between markers of < 10 centimeters. The failure rate averaged across all markers was < 3%. Mutations in glu-

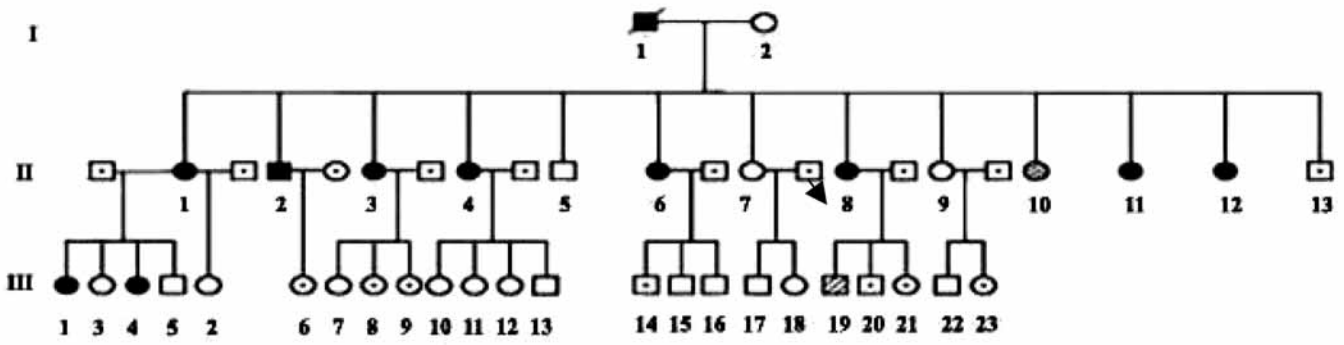
cokinase, hepatocyte nuclear factor (HNF)-1α, HNF-1β, HNF-4α, insulin promoter factor (IPF)-1, and Neuro-D1 genes linked with early-onset autosomal type 2 diabetes were searched for by means of a double-gradient, denaturing gradient gel electrophoresis. This procedure was followed by direct sequencing of the products of the PCR that were amplified from the exons, flanking introns, and minimal promoters of glucokinase, HNF-1α, HNF-1β, HNF-4α, IPF-1, and Neuro-D1 genes.

Statistical analysis. Data are presented as mean ± standard error of the mean. Mean data were compared by using the unpaired *t*-test. Statistics were computed with SPSS 11.5 (SPSS Inc., Chicago, Illinois, United States). A significant difference between groups is present when $P < 0.05$. Checks for linkage with markers D7S2846 and D7S1818 flanking the glucokinase locus, D12S395 flanking the HNF-1α locus, D20S478 and D20S481 flanking the HNF-4α locus, D17S1293 flanking the HNF-1β locus, and D17S1391 flanking the Neuro-D1 locus were done by parametric linkage analysis.

RESULTS

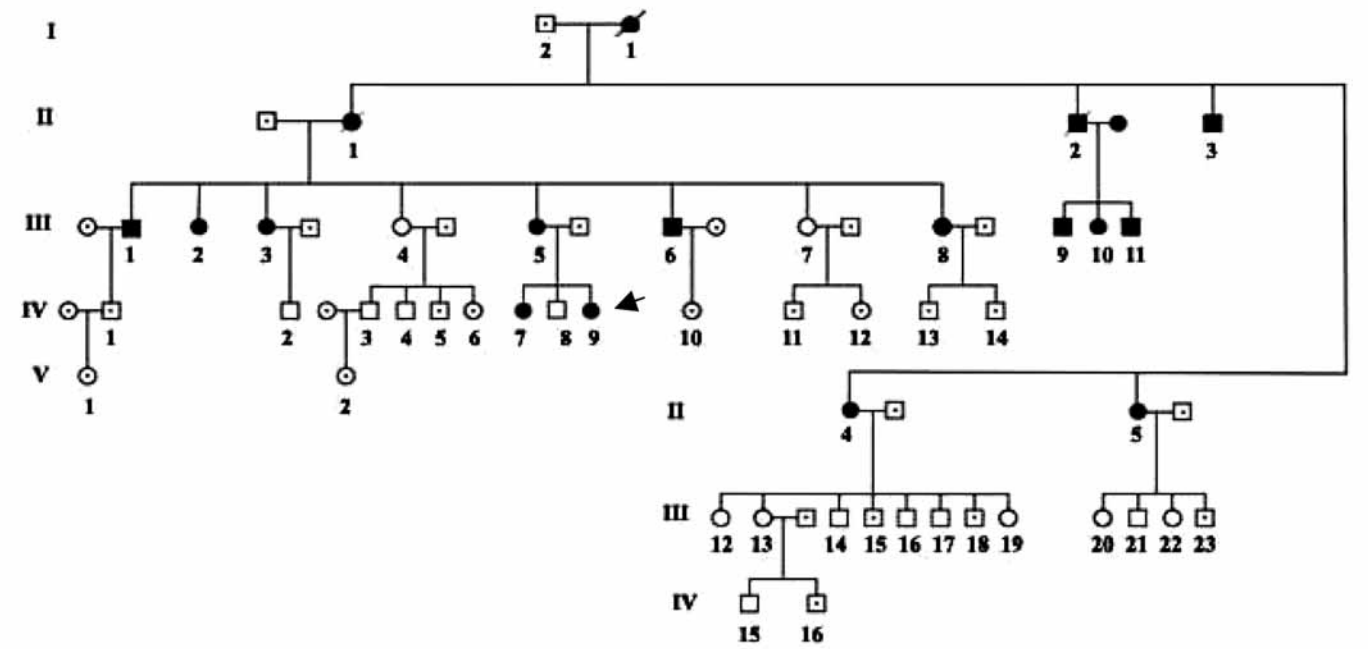
The three pedigrees—BK, SU, and CA—consisted of 38, 48, and 113 members, respectively, and were classified as large families (Figures 1–3). There were three generations in the BK pedigree, and the SU and CA pedigrees had five generations. Fifty-two males and 76 females were studied; 71 members were not stud-

FIGURE 1. Jamaican BK pedigree showing three generations with multigenerational inheritance of early-onset type 2 diabetes, Jamaica, 2000–2003[a]



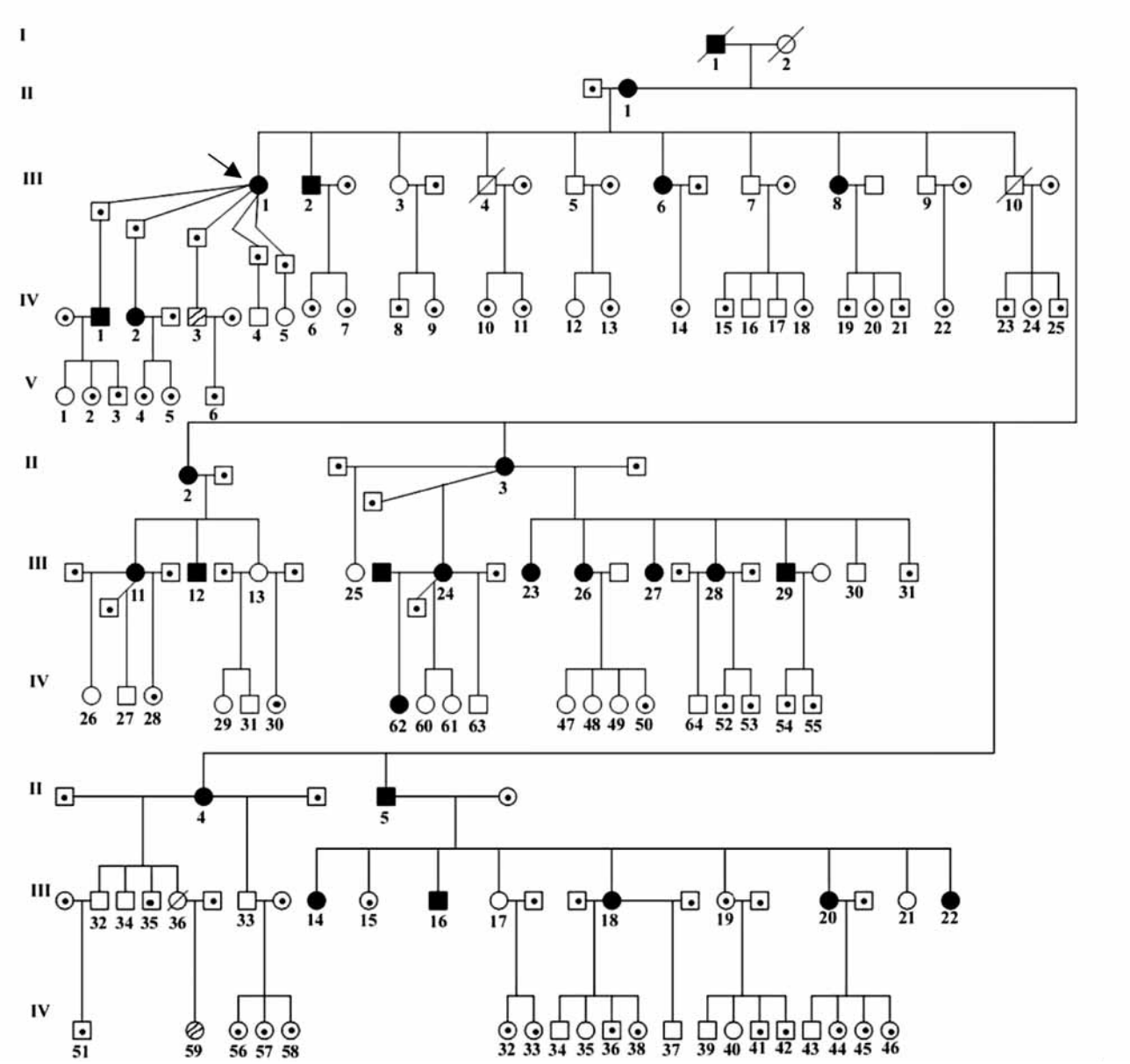
[a] Roman numeral = generation number; numbers below symbols = patient numbers with that generation; square = male; circle = female; slash = deceased; closed symbol = diabetes; diagonal shading = glucose intolerance; open symbol = normoglycemia; center dot = not tested; arrow = proband.

FIGURE 2. Jamaican SU pedigree showing five generations with multigenerational inheritance of early-onset type 2 diabetes, Jamaica, 2000–2003[a]



[a] Roman numeral = generation number; numbers below symbols = patient numbers with that generation; square = male; circle = female; slash = deceased; closed symbol = diabetes; diagonal shading = glucose intolerance; open symbol = normoglycemia; center dot = not tested; arrow = proband.

FIGURE 3. Jamaican CA pedigree showing five generations with multigenerational inheritance of early-onset type 2 diabetes, Jamaica, 2000–2003[a]



[a] Roman numeral = generation number; numbers below symbols = patient numbers with that generation; square = male; circle = female; slash = deceased; closed symbol = diabetes; diagonal shading = glucose intolerance; open symbol = normoglycemia; center dot = not tested; arrow = proband.

ied for various reasons, which included being deceased, being younger than 16 years of age and having nondiabetic parents, being unavailable at the time of the study, and declining to participate in the study. Partners from outside the family generally participated in the study when the spouse was affected and also appreciated the investigation. More females than males had diabetes: 72% and 28%, respectively. Of the subjects with diabetes mellitus (diabetic group in Table 1) 11 were diagnosed during the study. Twenty-eight were diagnosed with diabetes before the age of 35 years, and 10 of them were diagnosed below 25 years of age. The mean age at diagnosis was 31.5 ± 2.9 years. Forty male and 50 female control subjects were also investigated (control group). The BMI, WHR, serum triglyceride, and systolic and diastolic pressures were significantly lower in the control group than in the nondiabetic group ($P < 0.05$). Comparison of the nondiabetic group with the diabetic group showed there was no difference in the WHR, but the diabetic group had higher blood pressures, was more insulin resistant, was overweight, and had higher fasting plasma glucose, total cholesterol, and triglyceride levels than the nondiabetic group (insulin resistance, $P < 0.01$; fasting plasma glucose, $P < 0.001$; total cholesterol, $P < 0.03$; triglyceride, $P < 0.001$). There were no significant differences in the high density lipoprotein cholesterol, low density lipoprotein cholesterol, and serum creatinine levels between these two groups (Table 1).

Beta cell function was lower in the diabetic subjects ($P < 0.01$). The fasting serum insulin and fasting C-peptide

TABLE 1. Clinical characteristics of three Jamaican pedigrees (BK, SU, and CA) with early-onset type 2 diabetes and a control group, Jamaica, 2000–2003

Parameter	Diabetic group (n = 58)[a]	Nondiabetic group (n = 70)	Control group (n = 90)	P_1[b]	P_2[c]
Male/female ratio	16/42	36/34	40/50	N/A	N/A
Age at time of study (years)	39.7 ± 3.4	26.4 ± 2.4	25.7 ± 0.9	0.001[d]	0.17
Age at time of diagnosis (years)	31.5 ± 2.9	N/A[e]	N/A	N/A	N/A
Fasting plasma glucose (millimoles/liter)	10.2 ± 1.4	5.0 ± 0.2	5.2 ± 0.1	0.001	0.26
Plasma glucose after 2 hours (millimoles/liter)	17.6 ± 2.7	5.6 ± 0.1	5.0 ± 0.1	0.001	0.27
Hemoglobin A1C (%)	11.3 ± 1.3	6.0 ± 0.2	5.3 ± 0.7	0.001	0.25
Fasting serum insulin) (milliunits/liter)	7.2 ± 2.3	10.6 ± 1.5	8.7 ± 0.5	0.05	0.18
Fasting C-peptide (nanograms/milliliter)	1.6 ± 0.5	2.1 ± 0.3	1.3 ± 0.4	0.05	0.05
Insulin resistance	3.1 ± 0.1	2.3 ± 0.2	1.9 ± 0.1	0.01	0.06
Beta cell function (%)	21.4 ± 10.4	141.0 ± 33.1	101.0 ± 5.7	0.01	0.05
Islet cell antibody	Negative	Negative	Negative	N/A	N/A
Body mass index (kilograms/meter squared)	28.3 ± 1.5	23.3 ± 1.6	20.5 ± 0.1	0.01	0.05
Waist/hip ratio	0.91 ± 0.06	0.92 ± 0.08	0.81 ± 0.03	0.31	0.05
Total cholesterol (millimoles/liter)	5.3 ± 0.3	4.7 ± 0.6	3.8 ± 0.6	0.03	0.24
High density lipoprotein cholesterol (millimoles/liter)	1.1 ± 0.1	1.3 ± 0.1	1.44 ± 0.3	0.32	0.31
Low density lipoprotein cholesterol (millimoles/liter)	2.8 ± 0.5	2.8 ± 0.2	2.38 ± 0.6	0.41	0.32
Triglycerides (millimoles/liter)	2.8 ± 0.5	1.6 ± 0.3	0.97 ± 0.4	0.01	0.05
Serum creatinine (micromoles/liter)	70.8 ± 6.4	72.1 ± 6.1	44.5 ± 11.8	0.24	0.001
Systolic pressure (millimeters of mercury)	121.8 ± 3.8	116.4 ± 2.3	105 ± 8.6	0.02	0.001
Diastolic pressure (millimeters of mercury)	82.2 ± 2.1	77.4 ± 0.01	69.5 ± 8.5	0.01	0.02

Note: Data are presented as mean ± standard error of the mean.
[a] n, number in group.
[b] P_1, significant value of diabetic group versus nondiabetic group.
[c] P_2, significant value of nondiabetic group versus control group.
[d] $P < 0.05$ is significant between groups.
[e] N/A, not applicable.

groups differed significantly in diabetic and nondiabetic subjects (fasting serum insulin, $P < 0.05$; fasting C-peptide, $P < 0.05$). A test for islet cell antibodies was negative. Parametric linkage analysis yielding logarithmic scores ranging from –0.10 to –10.80 with no evidence of linkage heterogeneity and mutation screening (19) ruled out diabetes associated with *MODY1* to *–6* genes. No diabetic member with acanthosis nigricans was detected and no major diabetic complications were present.

DISCUSSION

We have described three diabetic families with diabetic members that had some characteristics consistent with that of both MODY and early-onset type 2 diabetes. The probands developed diabetes before the age of 25 years, did not require insulin therapy at the time of diagnosis, and demonstrated multigenerational inheritance in at least three generations (1, 13, 16).

In the second generation, 100% of the members in the SU and CA pedigrees and 69% in the BK pedigree were diagnosed with diabetes mellitus. These percentages are greater than the 50% expected from an autosomal dominant gene and therefore not in conformity with pure mendelian inheritance. Our finding supports that of other researchers (20, 21), who also found abnormality in the mode of autosomal dominant inheritance in their studies. Although autosomal dominant inheritance is expected in MODY (22), Mohan et al. (23) noted that only 27% of MODY patients have definite autosomal dominant inheritance and that in 73% the mode of inheritance was not clear. Early-onset type 2 diabetes is associated with 45% to 80% of patients having at least one parent with diabetes and the family may have a history of diabetes over several generations (1), as demonstrated by the pedigrees in this study.

Late-onset type 2 diabetes could also play a role here in determining the numbers of siblings in the older generations with diabetes, especially generation two in these three pedigrees. In addition, environmental and lifestyle factors could have an impact on the members of the pedigrees, resulting in increased penetrance of diabetes mellitus as postulated by Beaty et al. (24). The impact of aging, environmental factors, and lifestyle factors could have influenced the prevalence of diabetes in these three large pedigrees and hence caused blurring of a typical autosomal dominant inheritance, which was not apparent when we investigated smaller families (16).

These three pedigrees are insulin resistant, overweight, and dyslipidemic and they show multigenerational inheritance of diabetes mellitus. These characteristics are inconsistent with MODY but consistent with early-onset type 2 diabetes. No known *MODY* genes were detected in the pedigrees. Doria et al. in 1999 (4) described 29 pedigrees that had the characteristics of early-onset type 2 diabetes in which none of the then known *MODY* genes was detected. That study, however, did not mention how many diabetic members were present in each generation to address specifically the mode of inheritance of the diabetes that was described as autosomal dominant.

The average age at diagnosis of the three pedigrees was 31.5 ± 2.9 years, similar to the findings of Kim et al. (6). Early researchers of MODY (20, 22) proposed the age of diagnosis of diabetes mellitus to characterize this disease to be below the age of 25 years. Although we discovered 10 affected members of the pedigrees with diabetes diagnosed before the age of 25 years, the presence of insulin

resistance and overweight in the three pedigrees mitigate against them being classified as MODY. Eighteen other affected members were diagnosed between the ages of 25 and 35 years, and this finding implies that young members of the pedigrees with the genotype responsible for diabetes, but hitherto phenotypically normal, have the potential to develop diabetes up to age 35 years.

Although the characteristics of these three pedigrees put them in the categories of both MODY (6–13) and early-onset type 2 diabetes (1), the pedigrees appear to qualify more for early-onset type 2 diabetes. Furthermore, based on the findings of this study, the mode of inheritance demonstrated by these three pedigrees could be more accurately described as multigenerational rather than purely autosomal dominant.

We have used HOMA as proposed by Matthews et al. (18) to determine insulin resistance and beta cell function. We are aware of the limitations of the use of HOMA, but there is good correlation between estimates of insulin resistance and beta cell function derived from HOMA and the euglycemic or minimal model assessments (25, 26). Bobova et al. (25) and Song et al. (27) proposed that HOMA can therefore be considered suitable in large-scale epidemiologic studies, as it is less costly and less invasive.

The results of the control group with respect to insulin resistance and beta cell function revealed that even in the normal population there is some insulin resistance and related overfunctioning of the beta cells based on interpretation of HOMA. The diabetic group in this study showed significantly higher insulin resistance and significantly lower beta cell function than the nondiabetic and control groups. In the presence of insulin resistance, hyperinsulinemia is the initial response of the body to maintain normoglycemia, but with increasing duration of diabetes mellitus hyperinsulinemia converts to hypoinsulinemia through low beta cell function (1), which could explain the findings with the diabetic individuals in this study.

The nondiabetic group had significantly higher beta cell function of 150% with significantly higher insulin resistance compared with the control group. In using HOMA, the 150% beta cell function could be interpreted to mean overfunctioning and indicate that some of the nondiabetic individuals are already in their prediabetic state. Both the diabetic and nondiabetic groups had WHR values consistent with mild abdominal obesity—a phenotypical sign of insulin resistance.

All the diabetic members were treated initially with oral hypoglycemic agents and none of them developed ketosis, which is similar to the findings of other investigators (4, 20). However, some of the diabetic members are now on insulin alone or in combination with oral hypoglycemic agents. Kim et al. (6) proposed that diabetes in a member of a pedigree should be considered non-insulin dependent when hyperglycemia is managed without insulin for at least 2 years after diagnosis.

Our previous report on multigenerational type 2 diabetes in small families where the probands have gestational diabetes (16) is reinforced by the findings of this study of three large pedigrees. As the prevalence of adult type 2 diabetes in Jamaica is high (28), a more detailed assessment of the family history of patients with diabetes needs to be done to uncover the existence of this subset of diabetic patients with multigenerational inheritance of diabetes in Jamaica. This approach could improve the early diagnosis of diabetes mellitus in the relatives of probands, thus minimizing the chronic complications of diabetes mellitus and the socioeconomic costs of treating these complications.

The limitations of this study include the use of HOMA instead of the euglycemic model assessment, and it was justified earlier. In addition, recruitment of family members was challenging.

This study confirms that there are large families in the Jamaican population with multigenerational inheritance of diabetes and with diabetes presenting at an early age, having no known MODY genes, and demonstrating clinical characteristics that could partly be ascribed to early-onset type 2 diabetes or MODY. The recognition of this aspect of diabetes in the region would be of immense value in the differential diagnosis of diabetes in the young.

We recommend that during clinical assessment of patients with diabetes mellitus a detailed family history be taken. Where there is multigenerational inheritance of diabetes, all members of the family above 16 years of age should be assessed for diabetes. Children below the age of 16 years with diabetic parents should also be evaluated for diabetes mellitus.

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RESUMEN

Herencia multigeneracional y características clínicas de la diabetes tipo 2 de inicio temprano en tres árboles genealógicos grandes de Jamaica

Objetivo. Documentar la presencia de herencia multigeneracional de la diabetes de tipo II de inicio temprano en tres familias jamaiquinas grandes y describir sus características clínicas.

Métodos. En el Hospital Universitario de West Indies en Jamaica, se detectaron tres probandos de familias grandes en las que se observó herencia multigeneracional de la diabetes tipo 2 de inicio temprano en al menos tres generaciones. Al momento del diagnóstico, cada probando tenía ≤ 25 años de edad, era delgado y no necesitó insulinoterapia. Se emprendieron estudios clínicos, metabólicos y genéticos con el fin de determinar las características particulares de la diabetes que presentan estas tres familias.

Resultados. Se investigaron tres árboles genealógicos —BK, SU y CA— conformados por 38, 48 y 113 miembros, respectivamente. Cada árbol presentaba herencia multigeneracional de diabetes tipo 2 de inicio temprano en al menos tres generaciones. En los tres árboles genealógicos, la media de la edad al momento del diagnóstico fue de 31,5 ± 2,9 años y 10 personas tenían menos de 25 años. Se observaron signos indicativos de sobrepeso, resistencia insulínica, baja secreción de insulina, dislipidemia y obesidad intrabdominal leve. No se hallaron anticuerpos contra las células de los islotes ni variantes en la secuencia de los genes *MODY1* a *MODY6*.

Conclusiones. Algunas familias grandes de la población jamaiquina presentan herencia multigeneracional de la diabetes y otras características indicativas de diabetes tipo 2 de inicio temprano.

Palabras clave Patrón de herencia; diabetes mellitus tipo 2; linaje; Jamaica.