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Genetic causes of maturity onset diabetes of the young may be less prevalent in American pregnant women recently diagnosed with diabetes mellitus than in previously studied European populations

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Abstract

Context—There are many causes of impaired glucose tolerance in pregnant women. It is unclear whether genetic etiologies are a source of impaired glucose tolerance in pregnant women.

Objective—To prospectively determine the prevalence of maturity onset diabetes of the young (MODY) due to glucokinase (GCK) mutations in an American population of women with recent onset diabetes mellitus and gestational diabetes. We hypothesized that based on America's higher prevalence of gestational diabetes mellitus (GDM) and Type 2 diabetes, there may be an increased prevalence of GK mutations in our population than in previously reported studies from European studies.

Design—Over a three-year period, 72 pregnant women with recently diagnosed diabetes mellitus were prospectively assessed for presence of the most common pathogenic GCK mutations.

Setting—This study was performed in a gestational diabetes clinic in Urban America and a high-risk pregnancy clinic that served the military and their families on an American military base in Germany.

Patients—Seventy-two women; 65 with diagnosis of diabetes mellitus in this pregnancy (GDM/ overt diabetes) and 7 with diagnosis in the last nine years prior to pregnancy were recruited during pregnancy and blood samples were obtained.

Interventions—None.

Main outcome measures—Each study participant's blood sample was analyzed with restriction fragment length polymorphism to assess for mutations in the GCK gene.

Results—There were 38 female and 34 male neonates born at 38 weeks gestation ± 1.2 weeks.

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Declaration of interest

The authors have nothing to disclose.

Mean birth weight was 3351 g $\pm$ 450 g. There were no patients with GCK mutations found in our population 0/72. This prevalence is not greater than that seen in previous a similar study in European women with gestational diabetes, but in fact significantly less ($p = 0.03$).

Conclusion—American women with recently diagnosed diabetes mellitus likely have no higher prevalence of MODY than in previously studied European women with diabetes mellitus and may have a lower prevalence.

Keywords

Gestational diabetes; glucokinase mutation; maturity onset diabetes of the young

Introduction

Maturity onset diabetes of the young (MODY) is a disease in which a clear Mendelian genetic link has been delineated in the literature [1]. MODY's phenotype is characterized by diabetes mellitus with an early age at (20–25 years of age) onset, a primary defect in beta-cell function and autosomal dominant inheritance [2].

There are multiple sub-types of MODY described in the literature [3], each due to a different gene mutation. The glucokinase (GCK) MODY form is manifest by mutations in the *GCK* gene. The *GCK* gene is found on chromosome 7 and consists of 12 exons which encode a 465 amino acid protein. To date, over 200 separate GCK MODY mutations have been reported, mostly in European Caucasians [4–6]. In those found to have a GCK mutation, the clinical phenotype of their disease is such that there is typically a benign lifetime prognosis. The GCK mutation has not been associated with longstanding and more severe forms of diabetes mellitus. The increased insulin resistance of pregnancy may be why women with MODY may be initially classified as having gestational diabetes mellitus (GDM).

GCK is an enzyme that is found in the pancreas, liver, gut and brain. GCK catalyzes the first step in glycogen synthesis and glycolysis, which is the phosphorylation of glucose to glucose-6-phosphate. GCK acts as a glucose sensor where it is found, triggering shifts in cell metabolism commensurate with local glucose levels. This increased insulin response results in mild hyperglycemia.

Universal screening for diabetes is rarely performed in pre- menopausal women, except during pregnancy. At first glance, the diagnoses of GDM and GCK MODY may appear similar based on the mild fasting hyperglycemia delineated on pregnancy screening tests. The prevalence of GCK mutation of MODY varies. Some European authors have reported a prevalence of between 2 and 6% [7-9]. Nonetheless, the differences in the two diagnoses may have significant implications in terms of both lifetime health and maternal/ fetal outcome.

Based on the hypothesis that the clinical characteristics of MODY were similar to that of newly diagnosed gestational or women with overt diabetes, we screened 72 women with gestational and mild pre-gestational diabetes in an American population for the presence of a GCK MODY mutation. We hypothesized that the presence of genetic causes of

hyperglycemia may be associated with higher prevalence of glucose intolerance among American women.

Methods

The study was performed in clinics that served women with pre-existing and GDM. Seventy-two pregnant women were recruited for participation in our study. The study sites were located in Cleveland, OH, at MetroHealth Medical Center, Case Western Reserve University and at an American Military Hospital that served American military and their Families at Landstuhl Regional Medical Center, Landstuhl, Germany.

Exclusion criteria were as follows: diabetes diagnosis for greater than 10 years prior to pregnancy and poor glycemic control documented prior to pregnancy. Inclusion criteria were as follows: mild type 2 diabetes (overt) diagnosis made in pregnancy or within 10 years prior to pregnancy. The diagnosis of GDM was made after screening glucose greater than 135 mg/dl was made on a 50 g glucose challenge test, the diagnosis of GDM was made when there were two or more abnormal values on the 100 g 3 h oral glucose tolerance test using the Carpenter/Coustan criteria. All patients gave their written informed consent to participation and in our study, and the Institutional Review Boards in both institutions approved this study. A maternal blood sample was obtained at the time of entry into our study. We obtained buffy coat samples as well. The buffy coat samples were and were assessed for presence of the GCK gene mutation at the Centre for Molecular Genetics at Royal Devon and Exeter Hospital, Exeter, UK. Genomic DNA was extracted from peripheral lymphocytes using procedures previously described by Ellard et al. [9].

Results

We assessed the baseline demographics of the study population as listed below. We also assessed baseline maternal glycemic metabolic characteristics. Finally, we evaluated the neonatal birth weight and length (Table 1).

There were none of the most common GCK mutations found in our study population. We assessed the prevalence of the MODY mutation amongst our population (0/72) and compared it to that prevalence previously noted in a similar European study (6%) [8]. Utilizing the Fishers exact test, there was less prevalence in the American group ($p = 0.03$).

Discussion

We were unable to detect the most commonly found GCK mutations amongst our study group. Our population was racially diverse and included subjects from an urban American environment and an American Military base. The lack of the GCK mutations is significantly different than has been reported in previous studies of similar size in the Italy, Spain and the United Kingdom [4–9].

Unlike many other studies, which were comprised of relatively homogeneous ethnic groups, our study included multiple race/ethnicities. Most European populations that were screened included “local” populace. The authors in these studies attributed these findings to the

founder effect. Our negative study continues to highlight the possible effects of regional differences in terms of genetic prevalence of mutation.

Another factor that was likely related to the lack of finding any GCK mutations in our patients was the clinical heterogeneity of our study population. Soon after initiating our study, Ellard et al. [10] have put forth “best practice guidelines” for molecular genetic diagnosis of MODY in gestational diabetes. These criteria are as follows: mild fasting hyperglycemia (5.5–8 mmol/l) that is persistent before/during and after the pregnancy, an increment of <4.6 mmol/l on at least one OGTT (either during or after pregnancy) and a parent with type 2 diabetes.

There were limitations to our study. As stated above, our study was conducted in our outpatient pregnancy diabetes clinic. We did not follow our patients postpartum for fasting hyperglycemia. Furthermore, we did not select women based on their family history but solely based on their history of recently diagnosed diabetes mellitus.

Many authors have commented on the difficulty of assessing a true MODY prevalence within the population [11], namely, the cost of assessment and the prevalence of multiple confounders due to regional genetic differences. We would also submit that the increase in obesity and dietary preferences among certain populations may, in effect, dampen the prevalence of genetic etiologies in terms of diabetes, thereby lessening its overall prevalence. More work is necessary to determine the interplay between genetics and the environment vis-à-vis the diagnosis of diabetes mellitus.

The presence of MODY and subsequent vertical transmission to the fetus has previously been shown to have potential of having significant effects on fetal weight [12, 13]. The weight variation is due to the shared aberrance in the homeostatic glucose set point amongst MODY carriers.

Recently the presence of MODY in pregnant women and their fetuses was demonstrated to have important clinical implications [14]. That is, the gestational management of maternal hyperglycemia was altered by CVS confirmation of vertical passage of MODY to the fetus. In both cases, fetal weight was within normal limits even though maternal hyperglycemia was not treated with glycemic agents.

As accessibility to genetic testing increases in frequency and decreases in cost, it is imperative that more research occurs to assess populations for presence of monogenic forms of diabetes. Suggestions for future studies include assessing populations of women with gestational diabetes with strict criteria as set forth by Ellard et al. [9]. Alternatively, one could retrospectively assess postpartum patients with the diagnosis of gestational diabetes, appropriate glycemic control in pregnancy and subsequent neonates born with weight that is normal or small for gestational age. In these mother–infant pairs, it is possible that the presence of monogenic diabetes could affect both lifetime management and that of future pregnancies. In summary, GCK mutations amongst pregnant women with diabetes are more likely to be found in women with a set phenotype as described by Ellard et al. Furthermore, delineating gravidas with MODY can have important maternal and fetal implications.

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References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010; 33:S62–9. [PubMed: 20042775]
2. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity onset diabetes of the young. *N Engl J Med*. 2001; 345:971–80. [PubMed: 11575290]
3. Weedon MN, Frayling TM. Insights on pathogenesis of type 2 diabetes from MODY genetics. *Curr Diab Rep*. 2007; 7:131–8. [PubMed: 17425917]
4. Tinto N, Zagari A, Capuano M, et al. Glucokinase gene mutations: structural and genotype-phenotype analyses in MODY children from South Italy. *PLoS One*. 2009; 3:e1870. [PubMed: 18382660]
5. Estalella I, Rica I, Perez de Nanclares G, Spanish MODY Group. Mutations in GCK and HNF-1 explain the majority of cases with clinical diagnosis of MODY in Spain. *Clin Endocrinol (Oxf)*. 2007; 67:538–46. [PubMed: 17573900]
6. Barrio R, Bellanne-Chantelot C, Moreno JC. Nine novel mutations in maturity onset diabetes of the young (MODY) candidate genes in 22 Spanish Families. *J Clin Endocrinol Metab*. 2002; 87:2532–9.
7. Zouali H, Vaxillaire M, Lesage S. Linkage analysis and molecular scanning of glucokinase gene in NIDDM families. *Diabetes*. 1993; 42:1238–45. [PubMed: 8349034]
8. Saker PJ, Hattersley AT, Barrow B. High prevalence of a missense mutation of the glucokinase gene in gestational diabetic patients due to a founder-effect in a local population. *Diabetologia*. 1996; 39:1325–8. [PubMed: 8932999]
9. Ellard S, Beards F, Allen LIS. A high prevalence of glucokinase mutations in gestational diabetic subjects selected by clinical criteria. *Diabetologia*. 2000; 43:250–3. [PubMed: 10753050]
10. Ellard S, Bellanné-Chantelot C, Hattersley AT, European Molecular Genetics Quality Network (EMQN) MODY group. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. *Diabetologia*. 2008; 51:546–53. [PubMed: 18297260]
11. Misra S, Dornhorst A. Gestational diabetes mellitus: primum non nocere. *Diabetes Care*. 2002; 35:1811–13. [PubMed: 22923681]
12. Hattersley AT, Beards F, Ballantyne E, et al. Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet*. 1998; 19:268–70. [PubMed: 9662401]
13. Spyer G, Hattersley AT, Sykes JE, et al. Influence of maternal and fetal glucokinase mutations in gestational diabetes. *Am J Obstet Gynecol*. 2001; 185:240–1. [PubMed: 11483936]
14. Chakera AJ, Carleton VL, Ellard S. Antenatal diagnosis of fetal genotype determines if maternal hyperglycemia due to a glucokinase mutation requires treatment. *Diabetes Care*. 2012; 35:1832–4. [PubMed: 22773699]

Table 1

Demographics of study subjects (n = 72).

Maternal:	
Age (years)	29.4 ± 5.9
Weight (kg)	96.20 ± 30.35
Race/ethnicity	
African American	20
Caucasian	41
Hispanic	8
Asian	2
Other	1
BMI	33.84 ± 7.96
Fasting glucose (mg/dL)	86 ± 16
Diabetes mellitus	
Gestational diabetes	65
Pre-existing	7
Hemoglobin A1c	5.5 ± 0.6
GA at delivery (weeks)	37.6 ± 1.8
HOMA-IR	86.48 ± 85.22
Fasting C-peptide (pmol/L)	957.3 ± 571.1
Fasting Insulin (mU/ml)	42.1 ± 46.1
Fetal/neonatal	
Birthweight (g)	3251 ± 547
Length (cm)	48.8 ± 2.5
Glucokinase mutations:	0/72

Values are ± SD.