Identifying Glucokinase Monogenic Diabetes in a Multiethnic Gestational Diabetes Mellitus Cohort: New Pregnancy Screening Criteria and Utility of HbA_{1c}

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OBJECTIVE

Glucokinase monogenic diabetes (GCK–maturity-onset diabetes of the young [MODY]) should be differentiated from gestational diabetes mellitus (GDM) because management differs. New pregnancy-specific screening criteria (NSC) have been proposed to identify women who warrant *GCK* genetic testing. We tested NSC and HbA_{1c} in a multiethnic GDM cohort and examined projected referrals for *GCK* testing.

RESEARCH DESIGN AND METHODS

Using a GDM database, 63 of 776 women had a postpartum oral glucose tolerance test suggestive of GCK-MODY. Of these 63 women, 31 agreed to undergo *GCK* testing. NSC accuracy and HbA_{1c} were examined. Projected referrals were calculated by applying the NSC to a larger GDM database (*n* = 4,415).

RESULTS

Four of 31 women were confirmed as having GCK-MODY (prevalence ~0.5–1/100 with GDM). The NSC identified all Anglo-Celtic women but did not identify one Indian woman. The NSC will refer 6.1% of GDM cases for *GCK* testing, with more Asian/Indian women referred despite lower disease prevalence. Antepartum HbA_{1c} was not higher in those with GCK-MODY.

CONCLUSIONS

The NSC performed well in Anglo-Celtic women. Ethnic-specific criteria should be explored.

Glucokinase monogenic diabetes (GCK–maturity-onset diabetes of the young [MODY]) results from heterozygous mutations in the glucokinase (*GCK*) gene. Fasting hyperglycemia, typically 5.5–8.0 mmol/L (1), is present from birth but often is subclinical and may first be detected during routine screening for gestational diabetes mellitus (GDM). It is important to differentiate GCK-MODY from standard GDM because the management of GDM, in particular intensive glycemic control, may adversely affect the fetus of a pregnant woman with GCK-MODY (2,3). In contrast to GDM, which is associated with a greatly increased risk for subsequent diabetes, women with GCK-MODY, and their affected offspring, have a low prevalence of diabetes complications and do not require treatment outside of pregnancy (4–6).

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Performing universal *GCK* genetic testing in women with GDM is not currently practicable. Standard screening criteria (SSC) to preselect cases that should undergo *GCK* testing are well established for the nonpregnant population (fasting glucose 5.5–8.0 mmol/L and an increment of <4.6 mmol/L between fasting and 2-h glucose on an oral glucose tolerance test [OGTT]). The sensitivity of SSC for detecting GCK-MODY outside of pregnancy is >98% (7).

New pregnancy-specific screening criteria (NSC) (fasting glucose ≥5.5 mmol/L on antepartum OGTT and prepregnancy BMI <25 kg/m^2) have been proposed (4). The NSC were derived from a predominantly Anglo-Celtic population (4). Their applicability to other ethnicities is unknown. In addition, HbA_{1c} reference ranges for nonpregnant women with GCK-MODY were recently developed (8). Antepartum HbA_{1c}, a measure of glycemic exposure over time, may differentiate GCK-MODY from standard GDM.

The specific aims of our study of a multiethnic GDM cohort were to *1*) estimate the prevalence of GCK-MODY; *2*) examine the performance of the NSC; *3*) calculate the projected referrals for *GCK* testing, by ethnicity, using the NSC; and *4*) examine the utility of HbA_{1c} in differentiating GCK-MODY from standard GDM.

RESEARCH DESIGN AND METHODS

Participants

GDM diagnostic practices at the Royal Prince Alfred Hospital (RPAH) have previously been described (9). Of 776 women in the RPAH GDM database, 63 had a postpartum OGTT (2008–2012) highly suggestive of GCK-MODY on the basis of SSC. Of those 63 women, 31 agreed to undergo genetic testing. The study was approved by the Sydney Local Health District Ethics Review Committee.

Genetic Testing

GCK promoter, coding regions, and intron–exon boundaries of exons 1a–10 were sequenced using BigDye Terminator version 3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and analyzed on a 3730xl DNA Analyzer (Applied Biosystems) using Sequencing Analysis Software version 5.2 (Applied Biosystems) and Mutation Surveyor version 4.0.6 (Soft Genetics, State College, PA). The pathogenicity of *GCK* variants was determined by reviewing published reports of *GCK* mutations (10) and prediction software. *GCK* mutations were cross-validated by the Molecular Genetics Laboratory at the Royal Devon and Exeter National Health Service Foundation Trust.

Multiplex ligation-dependent probe amplification was performed using SALSA MLPA P241-D2 MODY mix-1 probemix and EK1 reagent kit (MRC-Holland, Amsterdam, the Netherlands) to identify partial or whole *GCK* deletions not identified through sequencing alone. Data were analyzed using Gene Mapper Software version 5.0 (Applied Biosystems).

Statistical Analysis

Statistical analyses were performed with NCSS software (NCSS LLC, Kaysville, UT). Ethnic group comparisons were analyzed using the χ^2 test. Continuous, nonpaired data were analyzed using a two-sample *t* test or the Mann-Whitney *U* test. A *P* value <0.05 was considered statistically significant.

The NSC were tested using *1*) confirmed GCK-MODY cases to determine their applicability; *2*) the GDM cohort (*n* = 776) to calculate the sensitivity and specificity of the NSC in differentiating GCK-MODY from standard GDM; and *3*) a larger GDM database (*n* = 4,415) to calculate projected referrals for *GCK* testing.

RESULTS

Prevalence of GCK-MODY

Of 776 cases, 4 were confirmed GCK-MODY, giving a minimum prevalence of 0.5 in 100 cases of GDM. Four of 31 high-risk women (12.9%) had GCK-MODY. Assuming a similar proportion among the remaining high-risk women who were unavailable for testing, the estimated prevalence of GCK-MODY was 1 in 100 cases of GDM. Ethnic-specific prevalence rates were ~1.4–2.7 per 100 (3–6 per 220) for Anglo-Celtic women and ~1–1.9 per 100 (1–2 per 103) for Indian women. The study group was ethnically diverse: 39% were Anglo-Celtic, 26% Southeast Asian, and 16% Indian.

Performance of the NSC

When applied to confirmed GCK-MODY cases, the NSC identified all Anglo-Celtic women. One Indian woman, however, had a higher BMI and would not have been detected. Prepregnancy BMI was not different between GCK-MODY and GDM cases.

When the NSC were applied to the GDM cohort, 33 of 776 women proceeded to genetic testing to identify ~3–6 patients with GCK-MODY. Using the minimum prevalence, the sensitivity of the NSC was 75% and the specificity was 96.1%.

Projected Referrals for *GCK* Genetic Testing Using the NSC

When the NSC were applied to the larger GDM database, 6.1% of patients would be eligible for genetic testing, reduced from 14.2% using the SSC (Table 1). Only 3.2% of Anglo-Celtic women would be tested, reduced from 15.3%. At least twice as many Southeast Asian (8.0%) and Indian (7.5%) women would be referred.

Utility of HbA_{1c}

Antepartum HbA_{1c} was not significantly different between the groups with GCK-MODY (5.6 ± 0.4% [38 ± 4 mmol/mol]) and GDM (5.3 ± 0.4% [34 ± 4 mmol/mol]; *P* = 0.9). Only 2 of 4 women with GCK-MODY had an antepartum HbA_{1c} ≥5.6% (38 mmol/mol), the lower limit of the nonpregnant GCK-MODY reference range (8).

CONCLUSIONS

This study demonstrated that, in this multiethnic GDM cohort, *1*) the prevalence of GCK-MODY was ~0.5–1 in 100; *2*) the NSC would have detected all Anglo-Celtic women with GCK-MODY but not the single Indian woman with GCK-MODY; *3*) the application of the NSC will halve the need for genetic testing, with a preferential reduction for referred Anglo-Celtic women; and *4*) antepartum HbA_{1c} has limited value in differentiating GCK-MODY from standard GDM.

The estimated prevalence of GCK-MODY in GDM, and the sensitivity and specificity of the NSC, are consistent with those in previous studies (4,11). In this study, one Indian woman with GCK-MODY did not satisfy the BMI criterion and would not have been detected. Unlike the study by Chakera et al. (4), we did not find a difference in prepregnancy BMI between the GCK-MODY and GDM groups. While BMI has historically helped differentiate MODY from other types of diabetes, it may become less useful as background rates of obesity increase among all ethnicities (12).

Table 1—Projected referrals for *GCK* genetic testing in a multiethnic GDM cohort using the NSC compared with the SSC applied in pregnancy

	Projected referrals for *GCK* testing using SSC, *n* (%)	Projected referrals for *GCK* testing using NSC, *n* (%)	Reduction in referrals using NSC compared with SSC, %
GDM cohort (*n* = 4,415)	627 (14.2)	271 (6.1)	57
Ethnic breakdown			
Anglo-Celtic (*n* = 960)	147 (15.3)	31 (3.2)	79
European (*n* = 449)	71 (15.8)	16 (3.6)	77
Southeast Asian (*n* = 1,796)	185 (10.3)*	143 (8.0)*	22
Indian (*n* = 453)	73 (16.1)	34 (7.5)*	53
Arabic (*n* = 234)	39 (16.7)	14 (6.0)	64
Aboriginal (*n* = 52)	11 (21.2)	1 (1.9)	99
Islander (*n* = 126)	44 (34.9)*	2 (1.6)	99
Other (*n* = 345)	57 (16.5)	30 (8.7)*	47

*$P < 0.003$ for the difference between these ethnic groups and Anglo-Celtic women.

Our study assessed the projected impact of the NSC on various ethnic groups using an ethnically diverse database. We demonstrated that the NSC would reduce referrals of Anglo-Celtic women for *GCK* testing by ~80% but would refer substantially more Southeast Asian and Indian women despite lower disease prevalence.

This is, to our knowledge, the first study to investigate antepartum HbA_{1c} in GCK-MODY. No difference between the GCK-MODY and GDM groups was demonstrated. Given that only half of the GCK-MODY group had an antepartum HbA_{1c} within the nonpregnant GCK-MODY reference range, this reference range does not seem to discriminate adequately between GCK-MODY and standard GDM during pregnancy.

A major strength of our study is its unique design. A difficulty in studying GCK-MODY is that, because of its low population prevalence, a prospective study would take several years to identify a sufficient number of women with GCK-MODY (13). Our study design maximized the yield of GCK-MODY by preselecting from a GDM database women whose postpartum OGTT was highly suggestive of GCK-MODY based on well-substantiated SSC. Our detection rate (12.9%) is consistent with another multiethnic GDM cohort (14) and validates our approach.

Our study has important clinical implications. One of the main issues with MODY is that >80% of cases are undiagnosed, in part because of the financial cost of genetic testing (13). The targeted application of the NSC is predicted to halve the number of GDM cases tested for GCK-MODY, reducing the economic burden of *GCK* testing. Our data support adoption of the NSC for use in Anglo-Celtic women with GDM. Ethnic-specific screening criteria should be explored.

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Author Contributions. V.L.R. wrote the manuscript, conceived of and designed the study, performed recruitment and genetic testing, acquired and analyzed data, and interpreted the results. M.H. reviewed and edited the manuscript, conceived of and designed the study, assisted with genetic testing, acquired and analyzed data, and interpreted the results. J.P. and D.K.Y. reviewed and edited the manuscript, conceived of and designed the study, and interpreted the results. S.C. and B.M. reviewed the manuscript and assisted with genetic testing. L.M. and M.C. reviewed the manuscript and analyzed data. G.P.R. and J.W. reviewed and edited the manuscript, conceived of and designed the study, assisted with recruitment and genetic testing, acquired and analyzed data, and interpreted the results. V.L.R., G.P.R., and J.W. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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