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GCK-MODY in the US National Monogenic Diabetes Registry: Frequently Misdiagnosed and Unnecessarily Treated

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Abstract

Aims—GCK-MODY leads to mildly elevated blood glucose typically not requiring therapy. It has been described in all ethnicities, but mainly in Caucasian Europeans. Here we describe our United States cohort of GCK-MODY.

Methods—We examined the rates of detection of heterozygous mutations in the *GCK* gene in individuals referred to the US Monogenic Diabetes Registry with a phenotype consistent with GCK-MODY. We also assessed referral patterns, treatment, and demography, including ethnicity, of the cohort.

Results—Deleterious heterozygous *GCK* mutations were found in 54.7% of Registry probands selected for *GCK* sequencing for this study. Forty-nine percent were previously unnecessarily treated with glucose-lowering agents, causing hypoglycemia and other adverse effects in some of the subjects. The proportion of probands found to have a *GCK* mutation through research based testing was similar across each ethnic group. However, together African American, Latino and Asian subjects represented only 20.5% of screened probands and 17.2% of those with GCK-MODY, despite higher overall diabetes prevalence in these groups.

Conclusions—Our data show a high detection rate of GCK-MODY is possible based on clinical phenotype, and that prior to genetic diagnosis, a large percentage are inappropriately treated with glucose-lowering therapies. We also find low minority representation in our Registry, which may be due to disparities in diagnostic diabetes genetic testing, and is an area needing further investigation.

Introduction

GCK-MODY (also known as maturity-onset diabetes of the young type 2, MODY2) has a prevalence of 1 in 1000 individuals [1]. It is due to mutations in the *GCK* gene encoding glucokinase, which catalyzes the conversion of glucose to glucose-6-phosphate, a key step in glucose metabolism and the regulation of insulin secretion. Even small alterations in the

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enzymatic capacity of *GCK* can increase the glucose threshold for glucose stimulated insulin release [2]. Functional assessment of mutations within *GCK* have demonstrated that protein instability or disrupted enzyme kinetics are the primary causes of hyperglycemia [3-5]. Heterozygous inactivating mutations in *GCK* result in mild, persistent and typically asymptomatic fasting hyperglycemia, ranging from 99-144 mg/dL (5.49-7.99 mmol/l) [6]. Pathogenicity of variants is usually determined by extensive family history and/or functional studies [7]. Hundreds of mutations leading to hyperglycemia have been identified within *GCK*, many without formal functional studies, and benign variants have been primarily found within the regions of the protein encoded by the three different tissue specific promoter-derived exons (exons 1 a,b,c) [8, 9].

GCK-MODY is not associated with the significant micro- or macrovascular complications common to other forms of hyperglycemia [10]. Glucose-lowering therapy is not required, except possibly during pregnancy [11]. In pregnancy, it is generally advised that treatment decisions be based on mutation status of the fetus, due to risk of fetal macrosomia in cases where the fetus is unaffected, though there does not appear to be long-term metabolic consequences for unaffected fetuses [12]. GCK-MODY may be a risk factor for pregnancy complications [13]. Outside of pregnancy, treatment can be discontinued in most individuals following genetic diagnosis to confirm GCK-MODY. Misdiagnosis as type 1, type 2 or gestational diabetes and the high costs of commercial genetic testing are barriers to acquiring an accurate diagnosis. We have previously demonstrated the potential economic benefits of genetic testing for the most common forms of monogenic diabetes, including GCK-MODY [14]. Schnyder, et al and Pinelli, et al also demonstrated the cost utility of accurate genetic diagnosis specifically for GCK-MODY [15, 16].

In this study we assess rates of detection of GCK-MODY based on clinical features, demography and treatment patterns of individuals referred for testing and suspected to have GCK-MODY within the US Monogenic Diabetes Registry. Previous descriptions of GCK-MODY have primarily occurred in European populations, including the United Kingdom, France, Italy and Spain, among others [17-20]. Descriptions have mainly reflected Caucasians, in large part owing to the ethnic makeup of the regions under study.

Current national practice guidelines suggest that ethnicity should be a consideration when selecting those for genetic testing [21]. However, there has been concern that ethnic minorities may be underrepresented in MODY registry cohorts [22]. Given the diverse ethnic representation in the United States and the higher burden of diabetes in ethnic minorities, we sought to ascertain the ethnic makeup of those referred for and those with GCK-MODY in the US monogenic diabetes registry.

Subjects & Methods

Monogenic Diabetes Registry

Subjects with known or suspected monogenic diabetes were consented for participation in the IRB-approved Monogenic Diabetes Registry (<http://monogenicdiabetes.uchicago.edu>) [23]. For all available time points, key data were gathered and included clinical and family information, ethnicity, age, weight, hemoglobin A1c (HbA1c) and medication information

collected using surveys and medical records. Genetic testing was done commercially by the supervising clinicians or on a research basis. The following criteria were used to select probands for research genetic testing for GCK-MODY: chronic mild fasting hyperglycemia (100-140 mg/dl, 5.55-7.75 mmol/l) and HbA1c 5.6-7.8% (38-62 mmol/mol) plus a linear three generation family history of hyperglycemia or diabetes mellitus or BMI less than 30 kg/m² in adults and BMI below the 95th percentile in children and age at diagnosis less than 30 years.

Sanger sequencing was performed for all coding exons and tissue specific promoter regions and 20 bp of flanking intronic sequences of *GCK*.

With the participant's consent, research-based genetic testing results were conveyed to their supervising clinician. All participants were encouraged to seek confirmatory clinical genetic testing through their primary care providers. Supervising clinicians and participants were given access to published data on outcomes after treatment discontinuation in confirmed case of GCK-MODY, showing that treatment does not alter HbA1c [11].

Results

Monogenic Diabetes Registry

The clinical details of all subjects are shown in Table 1. To date, a total of 1,235 families with known or suspected monogenic diabetes have been consented for participation in the Monogenic Diabetes Registry. For this study, we selected 117 probands with a phenotype consistent with GCK-MODY for research-based sequencing of *GCK*. A deleterious heterozygous mutation in *GCK* was found in 64 (54.7%) of these. A further 18 probands had a pre-existing genetic diagnosis of GCK-MODY at registration. Testing was offered to first degree relatives of positive index cases.

The Registry now follows 200 individuals (111 families) with hyperglycemia due to *GCK* mutations. We report on 157 of those individuals (82 probands). Initial genetic testing was performed on a research basis in 82.8% of subjects. Of 61 mutations identified through the Registry, ten (16.4%) were novel (Supplementary Table 1). Probands found to have pathogenic mutations within *GCK* were younger at clinical diagnosis of hyperglycemia compared to those who were *GCK* negative.

The majority of subjects with GCK-MODY were referred by physicians (79.7%), with the remainder discovering the study through Internet searching. The probands' supervising clinicians were primarily subspecialists with 75.6% of subjects under the care of pediatric or adult endocrinologists. Excluding insulin used solely during pregnancy, almost half of subjects (49.0%) were treated with at least one glucose-lowering agent for a minimum of 3 months. There were 27 reports of adverse effects to medications; hypoglycemia was the most commonly reported adverse effect (Table 2). Supervising clinicians were advised that pharmacotherapy could invariably be safely discontinued. The majority of subjects (79.2%) discontinued drug therapy as a direct result of genetic testing, whereas 3 subjects chose to continue on drug therapy. As expected for GCK-MODY, there was no difference in follow-

up Hb1Ac of individuals after discontinuing pharmacotherapy following genetic diagnosis (Table 1).

The median time between clinical diagnosis of hyperglycemia and genetic testing results in probands was 2.8 years (assessed only in the 71 probands diagnosed after 1992, when *GCK* mutations were established as a cause of MODY) [24]. A minority (6.1%) of probands reported no family history of hyperglycemia. There were 263 first-degree relatives of probands identified with hyperglycemia. Of the 123 relatives that have undergone genetic testing, 117 (95.1%) have been found to share the proband's mutation.

Families referred to the registry with a GCK-MODY phenotype were predominantly Caucasian. The ethnic distribution of the registry was compared with US population estimates and diabetes-specific ethnic distribution to identify which groups may be underestimated (Table 3). African American, Latino and Asian subjects made up only 6.0%, 6.8% and 7.7% respectively, of Registry probands with a GCK-MODY phenotype, despite these groups having a higher prevalence of diabetes within the US population as a whole (12.8%, 13.2% and 9% respectively) [25]. The proportion of probands found to have a *GCK* mutation through research based testing was similar across each ethnic group.

Discussion

Misdiagnosing GCK-MODY as other forms of diabetes is frequent [26]. This study demonstrates that a high detection rate is possible if candidates for genetic testing are chosen based on clinical phenotype and supports similar findings in studies outside of the US [27]. Variable awareness of genetic forms of diabetes and unequal consideration of and access to genetic testing are potential reasons that the majority of monogenic diabetes goes unrecognized [17].

There are clinical tools available to aid diabetes care providers with selection of appropriate patients for genetic testing, but it is unclear if physicians are widely familiar with these screening aids [16, 28]. Although most individuals with GCK-MODY within the Registry were under the care of endocrinologists, the majority did not have a genetic diagnosis at referral. This, coupled with rates of unnecessary treatment, implies that endocrinologists may not be adept at recognizing this uncommon form of diabetes and/or procuring commercial genetic testing. Low numbers of referring physicians outside of endocrinology suggests these problems are exacerbated in non-specialists. The rising incidence of diabetes in the US is not being met with a concomitant rise in clinical endocrinologists [29]. This will result in more patients primarily receiving care for diabetes from primary care clinicians. Our data suggest that efforts must be made to ensure that all healthcare providers supervising diabetes treatment recognize the cardinal clinical features that should prompt *GCK* genetic testing.

The majority of participants in this study had research-based genetic testing rather than clinical/commercial testing. The delays in securing an accurate molecular genetic diagnosis in monogenic diabetes are multifactorial, but the high costs of commercial testing and failure of insurance providers to routinely cover testing costs are significant contributors [30].

Genetic testing for the most common monogenic diabetes causes has historically been based on Sanger sequencing of multiple genes in a sequential manner. Less time consuming and potentially less costly next-generation diabetes gene panels may improve access to testing [31-33]. Additionally, decreased health care expenditures for those with confirmed GCK-MODY relative to those misdiagnosed with other diabetes types that require pharmacological intervention should prompt increased access to and insurance coverage of genetic testing. Our data clearly demonstrate that finding a *GCK* mutation in a patient also has implications for other family members. While mutations can occur spontaneously, those mutations will be inherited in subsequent generations in an autosomal dominant manner. The mild hyperglycemia that is a feature of heterozygous *GCK* mutations allows identification of family members who should undergo genetic testing.

Our data show frequent inappropriate use of drug therapy in patients with GCK-MODY in the US. Subjects reported adverse effects, most commonly hypoglycemia, from these unnecessary medications. Similar to other studies, glycemic control of individuals after cessation of pharmacotherapy following genetic diagnosis did not change [11]. Our previous studies show that genetic testing for MODY diagnosis may be cost-effective in appropriately selected patients due to cost-savings from genetically-driven management [14]. The impact of a genetic diagnosis on quality of life has not been firmly established, but studies demonstrating the rarity of any significant diabetes related complications and the safe withdrawal of drug treatment without a worsening of hyperglycemia suggest a positive effect [10]. Additional studies are needed to assess cost and quality-of-life benefits for MODY diagnosis.

The majority of Registry participants with a GCK-MODY phenotype self-identified as Caucasian and there was underrepresentation of a number of ethnic minorities when compared to the greater US population and ethnicity-specific diabetes rates. GCK-MODY has been described in ethnically diverse populations, but has been mainly studied in European populations. Prevalence data is lacking in ethnic minorities and there is not clear data to support or refute ethnic-specific differences in GCK-MODY prevalence. However, the low referral rate of ethnic minorities and the equivalent relative frequency of GCK-MODY causing mutations across races in our cohort would suggest that GCK-MODY may be similarly prevalent in ethnic minorities as in Caucasians. These data suggest that GCK-MODY (and likely other forms of monogenic diabetes), may frequently go under-recognized in populations (Latino, African American and Asian) that have a high burden of type 2 diabetes as demonstrated by our Registry and previous studies [34]. The reasons for underrepresentation of minorities within the Registry are likely to be multifaceted. Reasons may include differing awareness and perceptions of diagnostic diabetes genetic testing as well as decreased self and/or physician referral to the Registry for ethnic minorities as compared to non-Hispanic whites in the US. This may be influenced by current national practice guidelines, which include ethnicity as a consideration when identifying monogenic diabetes [21]. Future studies are needed to address equity in diabetes precision medicine for GCK-MODY and other forms of monogenic diabetes.

Limitations

Other series have shown a higher rate of GCK-MODY diagnosis in a pediatric population compared to adult populations [34, 35]. Our relatively young cohort may have improved the ability to recognize those appropriate for *GCK* testing. However, other groups have also demonstrated the feasibility of identifying GCK-MODY using simple clinical criteria while accounting for age [28].

Partial or whole gene deletions of *GCK* make up a minority of cases of GCK-MODY, but may be missed using Sanger sequencing alone because deletions longer than the PCR amplicons are not detected due to a lack of amplification [36]. Multiplex ligation-dependent probe amplification is a better technique to identify large deletions and gene rearrangements, but this technique was not used in our study [37]. Thus, despite a high detection rate, a minority of *GCK* mutations due to deletions may have been missed in our cohort.

Conclusions

Our data show a high detection rate of GCK-MODY based on clinical phenotype is possible within a US population. This study provides evidence that GCK-MODY is frequently misdiagnosed and inappropriately treated, which leads to unnecessary healthcare costs. Targeted testing leads to a high rate of detection in family members of an affected individual. We also demonstrate that GCK-MODY may be under-recognized in ethnic minorities, potentially contributing to inequities in personalized genetic medicine in diabetes and to overall diabetes care disparities. Efforts must be directed toward recognition of monogenic diabetes and access to genetic testing, with particular attention to equitable utilization of genetic testing resources for the estimated 310,000 affected US Americans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The guarantors, D.C. and R.N. conceptualized and designed the study, wrote the manuscript and researched data. C.B., S.B., J.D., and E.T., researched data and reviewed/edited the manuscript. J.H., L.P. and S.G. contributed to the discussion and reviewed/edited the manuscript.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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Table 1
U.S. Mongenic Diabetes Registry Participants Selected for GCK Testing

	GCK-positive Subjects	GCK-negative Probands
<i>n</i>	157 (82 probands)	53
Female	85 (54.1%)	33 (62.3%)
Birth weight	3062g (2839-3374g)	3333g (2910-3520g)
HbA1c prior to genetic testing	6.4% (6.2-6.7%) / 46 mmol/mol (44-50 mmol/mol)	6.1% (5.9-6.4%) / 43 mmol/mol (41-46 mmol/mol)
HbA1c post genetic diagnosis	6.3% (6.1-6.5) / 45 mmol/mol (43-48)	n/a
Pharmacotherapy (>3 months duration)		
None/ Not reported	80 (51.0%)	38 (71.7%)
At least one agent	77 (49.0%)	15 (28.3%)
More than one agent	20 (12.7%)	2 (3.8%)
Metformin	38 (24.2%)	4 (11.3%)
Insulin	33 (21.0%)	5 (9.4%)
Sulfonylurea	17 (10.8%)	3 (5.7%)
Proband age at hyperglycemia diagnosis	14.0 yrs (7.3-26.8yrs)	23.2 yrs. (10.0-31.8 yrs)
Proband time to genetic diagnosis	2.8 yrs (1.1- 6.2 yrs)	n/a
Proband's supervising clinician		
Pediatric Endocrinologist	34 (41.4%)	24 (45.3%)
Adult Endocrinologist	28 (34.2%)	26 (49.0%)
Family Medicine	8 (9.8%)	2 (3.8%)
Internist	5 (6.1%)	1 (1.9%)
Pediatrician	5 (6.1%)	0
Obstetrician	2 (2.4%)	0

Data are median (interquartile range), n (%).

Table 2
Medication Adverse Effects in GCK-positive Subjects

Medication Type	Hypoglycemia (symptomatic and/or confirmed)	Gastrointestinal symptoms	Other*
Insulin (n=33)	11 (33%)	-	1 (3%)
Metformin (n=38)	3 (7.8%)	9 (24%)	1 (2.6%)
Sulfonylurea/Glinides (n=17)	7 (41%)	1 (6%)	1 (5.8%)

Data are number and percent reporting symptom out of total number treated with each type of medication.

* allergy to insulin, malaise with sulfonyllurea, weight loss with sulfonylurea

Table 3
Ethnic distribution of Registry probands with a GCK phenotype but without an established genetic cause at registrations

Ethnic Group	Probands	GCK-positive	2013 US population	Diabetes in the US* [18]
All	117	54.7% (64)		
Caucasian	67.5% (79)	57.0% (45)	62.6%	7.6%
Latino	6.8% (8)	50.0% (4)	15.1%	12.8%
African American	6.0% (7)	57.1% (3)	13.9%	13.2%
Asian	7.7% (9)	44.4% (4)	6%	9.0%
American Indian and Alaskan	0	0	2%	15.9
Native				
Native Hawaiian and Other	0	0	0.4%	n/a
Pacific Islander				
Unreported/Mixed	12.0% (14)	50.0% (7)	n/a	n/a

* Age-adjusted percentage of people aged 20 years and older