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Frequency and characterization of mutations in genes in a large cohort of patients referred to MODY registry

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Abstract

Objective: There have been few large-scale studies utilizing exome sequencing for genetically undiagnosed maturity onset diabetes of the young (MODY), a monogenic form of diabetes that is under-recognized. We describe a cohort of 160 individuals with suspected monogenic diabetes who were genetically assessed for mutations in genes known to cause MODY.

Methods: We used a tiered testing approach focusing initially on *GCK* and *HNF1A* and then expanding to exome sequencing for those individuals without identified mutations in *GCK* or *HNF1A*. The average age of onset of hyperglycemia or diabetes diagnosis was 19 years (median 14 years) with an average HbA1C of 7.1%.

Results: Sixty (37.5%) probands had heterozygous likely pathogenic/pathogenic variants in one of the MODY genes, 90% of which were in *GCK* or *HNF1A*. Less frequently, mutations were identified in *PDX1, HNF4A, HNF1B,* and *KCNJ11*. For those probands with available family members, 100% of the variants segregated with diabetes in the family. Cascade genetic testing in families identified 75 additional family members with a familial MODY mutation.

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Author Contributions

Emily Breidbart and Wendy K. Chung designed the study. Emily Breidbart carried out the data collection, WES analysis, and wrote the initial draft of this paper. Liyong Deng, Charles LeDuc, and Jiancheng Guo performed and analyzed the Sanger sequencing. Patricia Lanzano coordinated data collection and kept the database. Xiao Fan helped with the WES analysis. Rudy L. Leibel gave input throughout the study and critically reviewed the data. Wendy K. Chung supervised each stage of the research and was the second reviewer of this manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Employment

Wendy K. Chung serves on the scientific advisory board for the Regeneron Genetics Center. Rudolph Leibel serves on the Alkermes medical advisory board and is a consultant to Boehringer-Ingelheim Inc. and Janssen Inc. None of these collaborations had any relationship to this study.

Honorarium

None declared

Statement of Ethics

The study was reviewed and approved by the Institutional Review Board at Columbia University (IRB-AAAA4485). All participants provided written informed consent.

Conclusions: Our study is one of the largest and most ethnically diverse studies using exome sequencing to assess MODY genes. Tiered testing is an effective strategy to genetically diagnose atypical diabetes, and familial cascade genetic testing identified on average one additional family member with monogenic diabetes for each mutation identified in a proband.

Keywords

MODY; diabetes; genetics in diabetes and obesity; molecular genetics

Introduction

Maturity onset diabetes of the young (MODY) is a monogenic form of diabetes caused by mutations in genes important to beta cell function. Monogenic diabetes is most often autosomal dominantly inherited and less commonly autosomal recessively inherited. [1, 2, 3].

MODY accounts for 1–5% of diabetic patients [4, 5]. MODY can present in childhood, adolescence, or adulthood. The majority of individuals with MODY are initially incorrectly diagnosed as having Type 1 or Type 2 Diabetes [1,2]. Patients with MODY typically have a strong family history of diabetes, present with variable degrees of insulin dependency, and have no evidence of beta cell autoimmunity [5]. The majority of patients with apparent monogenic diabetes are not genetically characterized [6]. A study in the UK estimated that 80% of MODY patients had not had molecular genetic testing [7], and genetic testing in the U.S. is likely no more frequent [8]. Limited genetic testing likely reflects lack of awareness of monogenic diabetes, insufficient provider training about accessing and interpreting genetic diagnostic tests, cost of genetic testing, incomplete insurance coverage for genetic testing, and the lack of knowledge about how management is impacted and quality of life improved by a genetic diagnosis [7]. *GCK* and *HNF1A* account for a majority (~ 85%) of MODY cases with a confirmed molecular diagnosis [7]. *GCK* accounted for 32% of molecularly confirmed cases in a large cohort in the United Kingdom [7]. Patients with *GCK* mutations often do not require medication, except during pregnancy when insulin may be offered to prevent fetal overgrowth [3]. Mutations in *HNF1A* are the most common cause of MODY in the UK (52% of molecularly confirmed cases) as well as in other European countries [7, 9–12]. *HNF1A* mutations are associated with a progressive decline in beta cell function and a microvascular and macrovascular risk profile similar to typical type 1 or 2 diabetes [3]. However, *HNF1A* mutation carriers are typically responsive to oral sulfonylurea therapy at a median dose of 80 mg daily or 1.3 mg/kg/day of gliclazide [13–16]. At the time of this writing, there are currently 14 MODY genetic subtypes that have been reported [17]. Exome sequencing (ES) is a highly efficient form of high-throughput genetic analysis, in which more than 95% of the coding DNA of an individual is sequenced. Exome sequencing affords flexibility for gene discovery because all coding regions are sequenced so that additional genes can be assessed in the future. Within the field of endocrinology, exome sequencing has led to significant advancements in our understanding of numerous disorders; however, few large-scale studies utilizing exome sequencing for genetically undiagnosed MODY patients have been performed [18].

The goal of this study was to determine the frequency of mutations in 13 known MODY genes in 160 probands referred with suspected monogenic diabetes.

Methods

From 2002-2016, 307 probands were referred to the Columbia University MODY registry by their endocrinologist for testing for suspected monogenic diabetes; 362 affected and unaffected family members were also assessed. All participants provided informed consent and the study was approved by the Institutional Review Board at Columbia University (IRB-AAAA4485).

We reviewed the medical records and pedigrees of all probands enrolled in this registry. Eligibility criteria to our study were hyperglycemia or diagnosis of diabetes, family history of at least one other family member, and no documented positive autoantibodies.

Patients with age of onset <1 year of age were excluded as this age of diagnosis could represent neonatal diabetes (19). Probands with only anti-GAD antibodies were not excluded as the prevalence of anti-GAD antibodies in MODY has been well-described [20, 21]. Insulin antibodies after insulin administration and exposure were allowed, as insulin therapy for >2 weeks can generate insulin antibodies; if insulin antibodies were present prior to insulin therapy, proband was excluded. As a small number of patients did not have documentation of antibodies submitted by their providers, we did include those who had 2 generations or more of diabetes in their family. Additionally, to enable detection of *de novo* or recessively inherited mutations, probands without a family history of diabetes were included only if their referring endocrinologist provided formal documentation of negative autoantibody status (22, 23). A total of 160 probands met inclusion criteria for the study.

Most recent HbA1c(s) was noted. When more than one HbA1c was available, the highest number was recorded. Ancestry was participant-reported.

Body mass index (BMI) was calculated by patient's age in years and months, and then categorized according to CDC criteria as underweight, normal, overweight, and obese based on their BMI for age [24]. We did not exclude patients who were overweight or obese, as obesity has been described in association with several forms of MODY [25, 26].

Probands were initially Sanger sequenced for all coding exons and at least 15 bp of adjacent intronic sequence for *GCK* and *HNF1A*. Individuals without likely pathogenic or pathogenic variants in *GCK* or *HNF1A* and enrolled family members went onto exome sequencing as previously described [27].

Variant Annotation

Exome sequencing data were generated and processed as previously described [27]. Variants were annotated using Annovar [28] and filtered for variants with an allele frequency of < 0.1% in ExAC. Variants were classified by ACMG/AMP criteria [29]. All likely pathogenic/pathogenic variants detected by exome sequencing were confirmed by Sanger sequencing in the proband and tested for segregation in any available family members.

Results

Cohort Characterization

Out of the 307 probands referred to the registry, a total of 160 met eligibility criteria for this study. Clinical characteristics of the probands are provided in Table 1. Seventy-nine probands were singletons and 81 probands had one or more family members in the study. The mean age of onset was 19.3 years, median 14 years. There were approximately equal numbers of males and females. Mean HbA1c was 7.1%. More than half of the probands (57.5%) had a normal BMI. The majority of participants were of European ancestry (53.1%), followed by Latina (23.8%) and Asian (10.6%). Antibody status was reported in 74% of patients. Antibodies recorded included islet cell antibody, insulin antibody, GAD antibody, and zinc transporter 8 antibody. Of those probands with reported antibodies, the majority of probands had three or more negative antibodies (36.1%).

Genetic Analysis

One-hundred and sixty probands were genetically analyzed by Sanger and then reflexive exome sequencing. Of the 160 probands, 60 had a likely pathogenic/pathogenic heterozygous variant in one of the known MODY genes (Table 2 and Supplemental Table 1). No individual had more than one such mutation. For those probands with additional available family members, all of the variants segregated with diabetes in the family. This cascade genetic testing resulted in a total of 135 individuals (60 probands and 75 relatives) identified with a likely pathogenic/pathogenic variant in a known MODY gene. None of the implicated mutations were *de novo* or recessively inherited. Eighteen of the sixty mutations were caught by whole exome sequencing. Twenty (33%) of these mutations are novel and are not reported in the literature or in ClinVar (Table 3). The two most implicated genes in probands were *GCK* (45) and *HNF1A* (11). Genes with a low frequency of mutations included *PDX1, KCNJ11, HNF4A,* and *HNF1B*. The majority (62.5%) of probands had no identifiable mutation in a known MODY gene.

Discussion

Our study is one of the largest investigations using cascade targeted and then exome sequencing for monogenic diabetes to date [30–33]. It is also one of the most ethnically diverse as the registry was based in a large urban medical center with referrals from all over the country. In our series of atypical diabetes patients, *GCK* and *HNF1A* were the genes most implicated. *GCK* was the most commonly identified gene in this cohort and was four times more frequent than *HNF1A* mutations. Large European series have found a higher frequency of mutations in *HNF1A* relative to *GCK* [7, 9–12]. However, several recent series in the United States, Germany, Austria and Spain have noted a similar distribution of mutations across genes as we observed [23, 34–35]. Perhaps because routine lab testing in healthy individuals including pregnant women is performed more frequently in the United States, asymptomatic or more mildly affected individuals may be more readily diagnosed at younger ages in the US [3]. In addition, since the average age of onset was <20 years in our cohort, our data is consistent with studies showing that in pediatric populations, GCK is the most commonly implicated MODY gene (36–38).

Interestingly, nine patients in our cohort had positive GAD antibodies, and one had a likely pathogenic mutation in GCK. This illustrates that the presence of GAD antibodies alone does not exclude a diagnosis of MODY. Neither of the two probands who tested positive for insulin antibodies far in their course of treatment had MODY mutations. Furthermore, there were 11 probands who had an obese BMI in our cohort. Five of these probands had a likely pathogenic/pathogenic variant, 3 in GCK and 2 in HFN1A. Of the 22 probands with an overweight BMI, 11 of them had a likely pathogenic/pathogenic variant (6 GCK, 4 HNF1A, 1 KCNJ11). This highlights the importance of not eliminating consideration of a MODY diagnosis based on weight, especially in a society with significant childhood obesity; 18.5% of 2–19 year olds in the United States are obese and 16.6% are overweight based on recent NHANES data. (38). This echoes the findings of recent studies that have warned against using obesity as a strict exclusion criterion (23, 25–26). Lastly, of the 7 patients with no known family history of diabetes, none were found to have a mutation in a MODY gene, which emphasizes the significance of family history in consideration of MODY diagnosis.

To identify mutations in both known and novel genes for diabetes and to minimize reporting variants of uncertain significance, we recommend a two-step process to first assess *GCK* and *HNF1A* and then use exome sequencing for individuals with suspected monogenic diabetes. Over 90% of the mutations we identified were in *GCK* and *HNF1A* and can be readily assessed by either targeted Sanger or next-generation sequencing. Limiting the first tier of testing maximizes the diagnostic yield, minimizes the cost, and minimizes the burden of variants of uncertain significance. Individuals strongly suspected of having monogenic diabetes who are interested in comprehensive genomic analysis can then reflex onto exome sequencing to identify mutations in rare genetic causes of diabetes or to identify novel genetic causes. Over half of our probands do not have mutations in known diabetes genes and are currently being assessed for DNA sequence variants in potentially novel diabetes genes.

33% of the mutations we identified in known MODY genes were novel. Because treatment, follow-up, and prognosis vary among MODY molecular subtypes, genetic diagnosis has management implications for the patient and family. *GCK* mutation carriers generally do not need treatment, and molecular diagnosis often leads to discontinuation of unnecessary medications. Conversely, *HNF1A, HNF4A,* and *KCNJ11* mutation carriers are responsive to sulfonylureas and thus, mutation carriers can transition off insulin or less effective oral antidiabetic agents to an easier and more targeted treatment once the diagnosis is made [39]. Correct genetic diagnosis also enables screening for associated conditions. *HNF1B* mutations for example are associated with kidney and urinary tract anomalies, so identification of a *HNF1B* mutation warrants screening for renal cysts, chronic kidney disease, and genital tract malformations.

Identification of a monogenic cause of diabetes in a proband led to testing of 143 family members and identification of 75 mutation-positive and 68 mutation-negative family members. This targeted cascade genetic testing within families provides a cost-effective strategy to risk-stratify family members and tailor diabetes screening and management within the family.

Limitations of our study include not having DNA on family members from all probands with which to test segregation, although we did have family members for 67% of probands assessed.

In summary, we present a simple, efficient, tiered strategy to genetically assess monogenic diabetes. We believe that this simple strategy should be used in clinical settings to provide accurate genetic diagnoses that allow tailored, less burdensome, and more effective treatment and cost-efficient identification of at-risk family members. In addition, we recommend that obesity and overweight as well as GAD antibody status do not exclude consideration of a MODY diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing Interests

The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Table 1:

Clinical characteristics of Probands (N=160)

	Age of onset
Mean (STDEV)	19.3 y (13.6 y)
	Age at Enrollment
Mean (STDEV)	24.2 y (16.1 y)
	Family Status
Singleton	79 (49.4%)
1 or more family members	81 (50.6%)
	Gender N (%)
Male N (%)	84 (52.5%)
Female N (%)	76 (47.5%)
	HbA1c (%)
Mean (STDEV)	7.1% (1.8%)
	BMI category
Normal (18.5–24.9 kg/m^2) N (%)	92 (57.5%)
Overweight (25-29.9 kg/m^2) N (%)	22 (13.8%)
Obese (>30 kg/m^2) N (%)	11 (6.9%)
Underweight (<18.5 kg/m^2)	1 (0.6%)
Unknown N (%)	34 (21.3%)
	Ancestry
Asian N (%)	17 (10.6%)
Black N (%)	5 (3.1%)
European N (%)	85 (53.1%)
Latina N (%)	38 (23.8%)
Other N (%)	3 (1.9%)
Two or more races N (%)	12 (7.5%)
	Antibody Status
Reported	119 (74.3%)
	Reported Negative Antibodies by Count
One N (%)	13 (10.9%)
Two N (%)	37 (31.1%)
Three or more N (%)	43 (36.1%)
Negative but unspecified N (%)	26 (21.9%)

Table 2:

Distribution of mutations among the MODY Genes (160 probands genetically assessed)

	GCK	***HNF1A***	***HNF4A+***	***PDX1***	***KCNJ11***	***HNF1B***
Total number of probands	45 (28.1%)	11 (6.9%)	1 (.6%)	1 (.6%)	1 (.6%)	1 (.6%)
Total number of additional family members identified with mutations	68	4	0	0	3	0

Table 3:

Novel Mutations

Gene	Exon	Nucleotide change	Amino acid change
GCK	exon7	c.G814T	p.E272X
GCK	exon4	c.A388G	p.I130V
GCK	exon6	c.A625C	p.T209P
GCK	exon7	c.A860C	p.Q287P
GCK	exon9	c.T1121C	p.V374A
GCK	exon2	c.A167C	p.K56T
GCK	exon3	c.290dupG	p.G97fs
GCK	exon8	c.T989G	p.F330C
GCK	exon6	c.A614G	p.D205G
GCK	exon9	c.G1225C	p.D409H
GCK	exon6	c.C660A	p.C220X
GCK	exon9	c.C1148G	p.S383W
GCK	exon5	c.565insTATC	p.K190YfsTer8
GCK	exon9	p.K190YfsTer8	p.S375Y
GCK	exon4	c.A388G	p.I130V
HNF1A	exon1	c.G214T	p.D72Y
HNF1A	exon10	c.T1885G	p.S629A
HNF1B	exon4	c.A913G	p.K305E
HNF4A	exon3	c.A376T	p.K126X
PDX1	exon1	c.93delC	p.S31fs