Published in final edited form as:

Pediatr Diabetes. 2015 May ; 16(3): 227–233. doi:10.1111/pedi.12150.

Identifying monogenic diabetes in a pediatric cohort with presumed type 1 diabetes

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Abstract

Objective—Monogenic diabetes (MD) is rare and can often be confused with type 1 diabetes (T1D) in a pediatric cohort. We sought to determine clinical criteria that could optimally identify candidates for genetic testing of two common forms of MD that alter therapy: *glucokinase* (*GCK*) and *hepatocyte nuclear factor 1 alpha* (*HNF1α*).

Research design and methods—We performed a retrospective chart review of 939 patients with a presumed diagnosis of T1D, 6 months–20 yr of age, and identified four clinical criteria that were unusual for T1D and could warrant further evaluation for MD: (i) negative pancreatic autoantibodies, (ii) evidence of prolonged endogenous insulin production, or (iii) strong family history of diabetes in multiple generations. One hundred and twenty-one patients were identified as having one or more of these high-risk clinical criteria and were offered screening for mutations in *GCK* and *HNF1α*; 58 consented for genetic testing.

Results—Of 58 patients with presumed T1D who underwent genetic testing, four were found to have *GCK* and one had *HNF1α*. No patients with only one high-risk feature were found to have MD. Of 10 patients who had two or more high risk criteria, five had MD (50%).

Conclusion—A high frequency of MD from mutations in *GCK/HNF1α* may be identified among pediatric diabetic patients originally considered to have T1D by performing genetic testing on those patients with multiple clinical risk factors for MD.

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Author contributions

R. G. G. wrote the manuscript, collected the clinical data, and assisted with the genetic experiments. W. K. C. reviewed/edited the manuscript and supervised the genetic experiments. L. D. performed the genetic experiments. R. G. reviewed/edited the manuscript. M. P. G. wrote and reviewed the manuscript.

Preliminary data was presented as an abstract for the American Diabetes Association 70th Scientific Sessions Annual Meeting in Orlando, Florida.

Keywords

diabetes mellitus type 1; genetic testing; MODY; pediatrics

Monogenic diabetes (MD) may be misdiagnosed as T1D in children. MD is rare and is reported to range between 1 and 5% of all cases of diabetes (1-5). The overall prevalence of MD is between 0.17 and 0.2 cases per 100 000 (6, 7). Identifying MD in a cohort of pediatric patients with T1D can be challenging and most often is pursued when patients have atypical characteristics of type 1 or type 2 diabetes. Identification of patients with MD can alter therapy and provide the ability to accurately predict the risk of diabetes in other family members.

The 2009 ISPAD Clinical Practice Consensus Guidelines on diagnosing and treating MD in pediatrics reported that the following clinical criteria may suggest a diagnosis of MD: (i) neonatal onset, (ii) diabetes in a parent, (iii) evidence of a low exogenous insulin requirement, and (iv) negative pancreatic autoantibodies (8). Absence of high-risk HLA alleles for T1D has also been used as a potential indicator of MD (9-11), but this expensive test is infrequently performed outside of a research setting.

Several studies screening for MD among children and adolescents with T1D have been published (9-15). Moller et al. examined 39 Danish type 1 diabetes (T1D) patients with an affected first-degree relative who had no high-risk HLA haplotypes and found that 10% of them had a mutation in the *hepatocyte nuclear factor type 1 alpha* (*HNF1α*) gene (MODY3) (9). Interestingly, one of the probands had a positive GAD antibody titer, suggesting that islet autoantibody positivity does not exclude a patient from having MD (9). Kawasaki et al. identified that 7% of patients in an antibody-negative T1D cohort were found to have *HNF1α* mutations. In contrast to the previous study, in this series all probands with mutations had a high-risk HLA haplotype (10). Lambert et al. sought to determine the prevalence of *HNF1α* mutations in a cohort of families with multiple (at least three) generations of family members with diabetes (11). They found that a strong family history alone was not predictive of *HNF1α* gene mutations, but instead suggest that a 'step-wise approach' using both family history and negative pancreatic autoantibodies could effectively screen for *HNF1α* gene mutations. Rubio-Cabezas et al. examined a cohort of 25 patients with antibody-negative T1D, looking for mutations in either *KCNJ11* or insulin genes if the diabetes began as a neonate, or *HNF1α* or *HNF4α* genes in patients with an older age of onset. Rubio-Cabezas showed that two of the 25 patients had insulin gene mutations causing MD (12). Autoantibody negativity alone was not a good predictor of *HNF1α* or *HNF4α* mutations (*GCK* was not tested in this study.). Urinary C-peptide creatinine ratio has been proposed as a useful and non-invasive biomarker in distinguishing adult patients with *HNF1α* and *HNF4α* from patients with long-standing (>5 yr duration) T1D (16). To date, this has not been validated in children and will not be helpful in a patient with newly diagnosed diabetes who may still have pancreatic beta cell reserve.

No study has published criteria that have been able to reliably identify candidates at high risk for MD in a population of patients thought to have T1D. Given the expense of genetic testing, there is a need to clinically identify patients with a high likelihood of having the two

most common forms of MD before performing genetic sequencing. *GCK* accounts for 10–60% of MD cases and is most prevalent in French and Italian families, whereas *HNF1α* accounts for 20–65% of MD cases most often in families from Great Britain (5). The clinical impact of a diagnosis of MD is significant. Depending on the type of MD, molecular classification may allow for discontinuation of insulin and transition to an oral agent, as in the case of patients with mutations in *HNF1α* who can usually achieve euglycemia with sulfonylurea therapy. Patients found to have mutations in *GCK* who may be on small doses of insulin, can discontinue insulin and be maintained on diet alone. It may also help to identify family members at risk for diabetes and inform management of diabetes in family members, allow for informed reproductive options during pregnancy, and provide important prognostic information regarding risk of future diabetic complications.

We hypothesized that pediatric patients with MD resulting from mutations in *GCK* or *HNF1α* can be identified among a cohort of patients thought to have T1D using clinical data that are easily accessible to physicians. The aim of this study was to develop a reliable, cost-effective predictive tool using readily available clinical data to identify these two common forms of MD in a population of children originally diagnosed with T1D.

Methods

Using retrospective chart review, we identified all pediatric patients with presumed T1D diagnosed by a pediatric endocrinologist on clinical grounds, aged 6 months–20 yr, who were seen at the Naomi Berrie Diabetes Center over a 12 month period. Exclusion criteria included cystic fibrosis-related diabetes, diabetes secondary to pancreatectomy, and patients with features suggestive of type 2 diabetes (including BMI >85th percentile and evidence of insulin resistance). Because we were only interested in patients whose presentation was consistent with T1D, we also excluded patients with forms of MD that have distinguishable clinical features (i.e., neonatal diabetes, lipodystrophic diabetes, Wolfram syndrome, mitochondrial disorders). If more than one child in a family had T1D, only the proband (sibling who was first diagnosed) was included in the study. The ethnic composition of the entire pediatric cohort included 74% Caucasian, 12% Hispanic, 10% African-American, and 2% Asian patients. From this cohort of presumed T1D patients, we identified a subpopulation of patients who had at least one of the following three clinical criteria that we considered unusual for autoimmune T1D and hypothesized that their presence would make MD more probable: (i) negative pancreatic autoantibodies, (ii) hemoglobin A1c (HbA1c) less than or equal to 7.0% and an insulin requirement of 0.5 U/kg/day or less more than 1 yr after diagnosis suggesting persistent endogenous insulin production, or (iii) at least three consecutive generations of family members with diabetes mellitus. All patients with one or more high-risk clinical criteria were offered genetic sequencing for mutations in *GCK* and *HNF1α* either at an in-person visit or by telephone.

The following clinical data were collected for 939 patients with presumed T1D: age at diagnosis, presence of pancreatic autoantibodies [GAD 65, islet cell antigen 512 (ICA), and insulin autoantibody (IAA) if drawn within 1 wk of starting insulin treatment], HbA1c, history of diabetic ketoacidosis, treatment regimen, medical history, and family history.

Antibody positivity was determined by the laboratory performing the test. We did not use a specific titer threshold for each antibody.

One hundred and twenty-one patients had 1 of the clinical criteria suggestive of MD. At least one pancreatic autoantibody measurement was available in 456 of the patients and 95 patients had negative autoantibodies (21%). Twenty-one patients (5%) had criteria suggestive of persistent insulin secretion. Eleven patients (2%) had a family history of diabetes in three or more consecutive generations (2%). Ten patients (2% patients) met more than one criterion. Of 118 patients offered testing for MD, 58 patients consented to genetic testing as part of a research protocol approved by the Columbia University IRB. Of these 58, 38 had only negative antibodies, 7 had low insulin requirement alone, and 3 had multiple generations of diabetes. Ten additional subjects met more than one of the inclusion criteria (Fig. 1).

Consented patients had 5 mL of whole blood drawn for genetic sequencing of *GCK* and *HNF1 α* mutations. Genomic DNA was isolated from peripheral leukocytes by cell lysis of whole blood followed by DNA extraction and precipitation. Each patient's DNA was amplified by polymerase chain reaction for the coding regions and splice sites (primers and conditions available upon request) and sequenced by dideoxysequencing. Specimens were sequenced at GENEWIZ (GENEWIZ, Inc. South Plainfield, NJ, USA). Sequences were then analyzed by comparison to the reference template using NCBI's Basic Local Alignment Search Tool (BLAST) on the National Center for Biotechnology Information (NCBI) gene website (NM_000162.3 for *GCK* and NM_000545.5 for *HNF1 α*).

Post hoc analysis was performed between group of patients with MD and those without mutations. Chi-squared and Fisher's exact tests were used to identify differences of clinical characteristics between these two groups.

Results

Five patients were identified to have mutations associated with MD among the 58 patients who underwent genetic testing (8.6% of patients). Table 1 lists the high-risk clinical criteria in each patient with MD and the genetic mutation identified. All five patients with MD had negative pancreatic autoantibodies. Four patients were found to have *GCK* mutations and one had an *HNF1 α* mutation.

The relationship between diagnosis of MD and number of clinical characteristics identified as unusual for T1D in patients with at least one clinical characteristic is shown in Table 2. Among our 58 patients undergoing genetic testing, 48 were tested because of only one clinical feature considered unusual for T1D. None of the patients with only one clinical feature was found to carry a mutation in *GCK* or *HNF1 α* . In contrast, 10 of our 58 patients underwent genetic testing because of the presence of 2 or more clinical features considered unusual for T1D. In this group of 10 patients, 5 (50%) were found to have MD by genetic testing.

The clinical characteristics of the patients with MD are compared to the patients with presumed T1D in Table 3. Age at diagnosis, presence of autoimmune disease, and indices of

glucose control did not differ among the two groups. There was no history of diabetic ketoacidosis (DKA) in the MD group while 12 of 53 patients with presumed T1D had a history of DKA. The mean age of diagnosis of diabetes was 7 yr in the MD patients (range: 1–10 yr) and 8 yr of age in the non-MD patients (range: 1–17 yr). None of the five MD patients had a second autoimmune disease, compared to 10 of 53 (19%) non-MD patients. Among the non-MD patients, five had autoimmune thyroiditis, three patients had celiac disease, one had ulcerative colitis, and one had vitiligo. One of the 5 (20%) MD patients reported having a first-degree family member with autoimmune disease (hypothyroidism). Seventeen of 53 non-MD patients (32%) had a first-degree family member with autoimmunity. The most often reported autoimmune disease was thyroid (in eight family members), followed by T1D (in seven family members). The average HbA1C at the time of diagnosis for the *GCK* patients was 6.6% (range: 5.9–7.9%), 8.8% for the *HNF1α* patient, and for the patients with presumed T1D was 10.3% (range: 5.5–15.3%). The average most recent HbA1c for the *GCK* patients was 6.2% (range: 5.8–6.5%), 6.4% for the *HNF1α* patient, and for the patients with presumed T1D was 7.4% (range: 5.3–13.8%).

The treatment regimen for the patients with MD was variable depending on the genetic mutation. The patient with *HNF1α* had negative antibodies and an HbA1c at diagnosis of 8.8% and was started on insulin. She is Caucasian; her family history is unknown because she was adopted at birth. She remained on insulin for the first year after diagnosis, and then it was discontinued with normal blood sugars. When her HbA1c rose above 6% she underwent genetic testing and oral glimepiride was initiated with preservation of good glycemic control.

The clinical course of the *GCK* patients was more variable and will be referred to here as GCK-1, GCK-2, GCK-3, and GCK-4. GCK-1 was an 11-month-old Caucasian boy diagnosed after his diabetic mother noted him to have polyuria. His HbA1c was 6.4%. With negative pancreatic autoantibodies and a strong family history of diabetes (mother and maternal grandfather), he was referred for genetic testing. GCK-2, of mixed Caucasian/Hispanic descent, had elevated fasting blood glucose on routine screening and an HbA1c of 6.3%. He had negative pancreatic antibodies and a multigenerational family history of diabetes. He screened positive for *GCK* and after cascade testing was performed, his younger sister (asymptomatic with positive GAD-65 autoantibody) and mother were also found to have the same mutation. GCK-3 had elevated fasting blood sugars that were tested by family members given their strong family history of diabetes of unclear etiology. He had negative pancreatic autoantibodies and was referred for genetic testing. His mother, maternal aunt, and maternal grandmother, all Caucasian, were all found to have the same mutation. GCK-4, of Hispanic descent, had an HbA1c of 7.9% at diagnosis, in the setting of a respiratory viral illness and was started on insulin briefly that was weaned off within several weeks. He was 9-years-old at diagnosis, was not obese, and had no evidence of acanthosis nigricans or puberty on his physical exam. Remaining off insulin with euglycemia and with negative antibodies, he was referred for genetic testing. Cascade testing revealed *GCK* mutations in his mother and brother. All *GCK* patients have maintained good glycemic control with diet and exercise alone.

Discussion

Identifying patients with MD in the pediatric population, in whom T1D is often the presumptive diagnosis, can be challenging. Reliable screening criteria with a significant pre-test probability of identifying patients with MD are needed. Clinicians would be greatly aided by these screening criteria to help identify patients who may have a monogenic form of diabetes so they may be referred for genetic testing.

We used three readily available clinical criteria to identify those patients in our cohort with presumed T1D who would be offered genetic testing for MD. We reasoned that the following clinical characteristics were unusual in T1D and may be more probably found in MD: no evidence of pancreatic autoimmunity; low insulin requirement with a low HbA1c outside of the honeymoon phase; and a multigenerational family history of diabetes. We performed genetic sequencing of *GCK* and *HNF1α* in 58 patients and found four of them to have a mutation in *GCK* and one had a mutation in *HNF1α*. All of the patients with MD had two or more clinical characteristics, including negative pancreatic autoantibodies.

There were no significant differences between the patients with MD and those with presumed T1D in: age at diagnosis, HbA1c at diagnosis and most recent HbA1c, or presence of autoimmune diseases in proband or family members. Prior studies have documented a high rate of thyroid autoimmunity (thyroiditis: 25–27% prevalence) and gastrointestinal autoimmunity (celiac disease: 5–8% prevalence) in patients with T1D (17, 18). In addition, 20–30% of relatives of patients with T1D also have a history of an autoimmune disease, including T1D (17, 19). It is possible that we failed to see an increase in autoimmunity in the probands and family members in the patients with presumed T1D compared to the MD patients because of the small numbers studied. However, it is also important to point out that the presence of autoimmunity in the probands or family members does not exclude MD.

None of our MD patients had a history of DKA. Twelve percentage of our non-MD patients ever had DKA in the past. This is less than the DKA frequency of 20–30% in newly diagnosed T1D patients that is often cited (20, 21).

It is standard practice at our diabetes center to test all new-onset diabetes patients for GAD antibody, ICA antibody and IAA (the latter if they are naïve to exogenous insulin). Antibody negativity alone can be a good first step in deciding if a patient has MD, but other factors need to be considered. Conversely, 1% of patients with mutations in *GCK*, *HNF1α*, or *HNF4α* can have positive autoantibodies, specifically GAD antibody (22). The presence of pancreatic autoantibodies should not exclude a patient who fits other clinical criteria from a work-up of MD if a strong evidence of autosomal dominant inheritance is found, because the discovery of an MD mutation could be advantageous for other family members.

Treatment modalities varied among both groups. All four of the *GCK* mutation patients are managed with diet alone with excellent glycemic control. The one patient with an *HNF1α* mutation is on a sulfonylurea with euglycemia. The majority of non-MD patients remain on basal/prandial insulin; however there are several exceptions. Three non-MD patients are on basal insulin only. These patients were originally diagnosed with T1D (all antibody-negative) but then had a prolonged honeymoon phase (>1 yr) during which time they were

completely weaned off prandial insulin. One additional patient is a lean Caucasian teenager diagnosed with T1D after random elevated fasting blood sugar without DKA 7 yr ago (HbA1c was initially 6.1%). He also has autoimmune thyroiditis and a family history of autoimmune hypothyroidism and vitiligo. He has a sister with diabetes and a mother with diabetes, both of whom are lean. He had been on basal insulin intermittently over the past several years, which was self-discontinued for concern of hypoglycemia. He now maintains good glycemic control with an HbA1c of 6.5% or less.

There are several limitations to this study. The cohort of patients analyzed is a sample of convenience and does not truly represent all patients who met criteria for entry into the study. Patients not included either refused genetic analysis, had moved away, transferred to another provider, or were unavailable to come to the diabetes center for testing. Because we did not test all T1D patients at our center, we are unable to draw conclusions regarding overall prevalence of MD in our pediatric cohort. We also only tested patients for GAD, ICA, and IAA antibodies, as this is considered standard for all new-onset diabetes patients at our institution. It is well-known that antibody titers are variable throughout the course of the disease, and we may be missing type 1a diabetes patients because of transiently low antibodies. For this reason, we repeated GAD and ICA titers on all patients with negative antibodies to confirm their absence. It is also possible that we may be misclassifying several patients as without type 1a diabetes because we did not measure islet cell antibody and zinc-transporter antibodies. Another limitation is that we only tested all patients for the two most common forms of MD: *GCK* and *HNF1α*. It is possible that we may have missed some patients with rarer forms of MD, i.e., *HNF4a* and *INS*. We were only able to perform sequencing for these two genes, not deletion analysis. Finally, because this was a cross-sectional analysis, we were unable to follow these patients over time to see how their diabetes evolved and determine optimal therapeutic modalities.

This study confirms that a subset of patients misclassified as having T1D can be identified as having increased probability of *GCK* or *HNF1α* using routinely collected clinical criteria. These three criteria are best assessed collectively rather than individually, and can help to determine which patients are good candidates for molecular genetic testing which may provide improved prognostic information and assist with refining therapy.

Acknowledgments

Dr Gandica is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We gratefully acknowledge the contributions of the patients. This work was supported by DK065522, DK52431, DK26687, and DK63608.

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Fig. 1. Recruitment flow chart showing all potential patients and how patients were selected for genetic testing.

Table 1

Clinical criteria identified in patients diagnosed with monogenic diabetes

Patient	Pancreatic autoantibody	Low insulin requirement	HbA1c	7% >12 months post-diagnosis	DM in 3 generations	Extra-pancreatic illness	Gene	Mutation(s)
1	Negative		No		Yes	No	<i>GCK</i>	Gly299Arg
2	Negative		Yes		Unknown	No	<i>HNF1α</i>	IVS1 + 1 G>A
3	Negative		No		Yes	No	<i>GCK</i>	Val182Met
4	Negative		No		Yes	No	<i>GCK</i>	Arg185Ter
5	Negative		Yes		No	No	<i>GCK</i>	Arg340Lys

DM, diabetes mellitus; HbA1c, hemoglobin A1c.

Table 2

Likelihood of diagnosis of monogenic diabetes when pediatric patients with presumed T1D are offered genetic testing when at least one high-risk clinical characteristic was present

	Monogenic diabetes diagnosis	Presumed T1D diagnosis
1 clinical characteristic present	0	48
2 clinical characteristics present	5	5

T1D, type 1 diabetes.

Table 3

Comparison of clinical characteristics of subjects with monogenic diabetes and those with presumed T1D

	<i>GCK</i> subjects (n = 4)	<i>HNF1α</i> subject (n = 1)	Presumed T1D (n = 53)	p value
Mean age at diagnosis (yr)	6.5	10	9	NS
Autoimmune disease in proband (%)	0	0	19%	NS
Autoimmune disease in first-degree relative (%)	25%	Unavailable	34%	NS
History of DKA (%)	0	0	12%	NS
Mean HbA1c % at diagnosis (range)	6.6% (5.9–7.9)	8.8%	10.2 (5.5–15.3)	NS
Mean most recent HbA1c % (range)	6.2% (5.8–6.5)	6.4%	7.4 (5.4–13.8)	NS

DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; T1D, type 1 diabetes.