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CLINICAL QUESTION

Who should have genetic testing for maturity-onset diabetes of the young?

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Summary

Maturity-onset diabetes of the young (MODY) is a clinically heterogeneous group of monogenic disorders characterized by autosomal dominant inheritance of young-onset, non-insulin-dependent diabetes. The genes involved are important in beta cell development, function and regulation and lead to disorders in glucose sensing and insulin secretion. Heterozygous *GCK* mutations cause impaired glucokinase activity resulting in stable, mild hyperglycaemia that rarely requires treatment. *HNF1A* mutations cause a progressive insulin secretory defect that is sensitive to sulphonylureas, most often resulting in improved glycaemic control compared with other diabetes treatment. MODY owing to mutations in the *HNF4A* gene results in a similar phenotype, including sensitivity to sulphonylurea treatment. *HNF1B* mutations most frequently cause developmental renal disease (particularly renal cysts) but may also cause MODY in isolation or may cause the renal cysts and diabetes syndrome (RCAD syndrome). Mutations in *NEUROD1*, *PDX1* (*IPF1*), *CEL* and *INS* are rare causes of MODY. MODY is often misdiagnosed as type 1 or type 2 diabetes. However, a correct genetic diagnosis impacts treatment and identifies at-risk family members. Thus, it is important to consider a diagnosis of MODY in appropriate individuals and to pursue genetic testing to establish a molecular diagnosis.

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Introduction

Monogenic diabetes, caused by single gene mutations, accounts for approximately 2% of all diabetes cases.[1] The most prevalent phenotype is maturity-onset diabetes of the young (MODY). MODY is characterized by dominant inheritance of early-onset (typically before 25 years of age), non-insulin dependent diabetes. The term MODY describes a heterogeneous group of disorders caused by mutations in genes important to beta cell development, function and regulation, glucose sensing, and in the insulin gene itself. Mutations in at least eight different genes can cause MODY.[2] The expected clinical course, complications and associated extra-pancreatic features vary based upon the underlying molecular genetic defect (Table 1).[3] The majority of MODY cases go undiagnosed owing to frequent misclassification as either type 1 or type 2 diabetes.[4] Correctly identifying MODY has important implications for treatment, surveillance of complications and associated extra-pancreatic disorders, and identification of affected and at-risk family members. Thus, it is important that clinicians appreciate the impact of a correct molecular diagnosis of monogenic diabetes.

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Distinguishing MODY from type 1 and type 2 diabetes

Maturity-onset diabetes of the young should be considered in any individual carrying a diagnosis of either type 1 or type 2 diabetes with atypical features for these polygenic disorders (Fig. 1). This includes the absence of pancreatic autoantibodies (type 1B) at the time of diagnosis or evidence of continued endogenous insulin outside of the honeymoon period in type 1 diabetes. A diagnosis of type 2 diabetes in a young individual who is not significantly overweight or who lacks hallmarks of insulin resistance, including acanthosis nigricans or elevated fasting insulin, should be questioned.[5] The presentation of MODY-related diabetes can be delayed for decades beyond the original definition of onset before age 25. Diabetes in two or more consecutive generations in a pattern consistent with autosomal dominant inheritance should prompt consideration of MODY (but spontaneous *de novo* cases occur). Dominant inheritance in a person classified with type 1 diabetes is particularly important, as an affected parent is uncommon (seen in 2–4%).[6] However, distinguishing type 2 diabetes from MODY on the basis of family history can be more problematic. Patients with type 2 diabetes and MODY are nearly equally as likely to have a parent with diabetes. However, two or more consecutive generations of diabetes (with young onset in at least one family member) and the absence of metabolic features (significant obesity or features of insulin resistance) is most suggestive of MODY.[7] There are additional features unique to MODY subtypes that can prompt consideration of monogenic diabetes.

Table 1. Genes involved in maturity-onset diabetes of the young (MODY)

Phenotype	Affected gene; gene symbol	Clinical features
HNF4A-MODY (MODY1)	Hepatocyte nuclear factor 4-alpha; *HNF4A*	Progressive insulin secretory defect with presentation in adolescence or early adulthood Possible history of neonatal macrosomia and/or neonatal hypoglycaemia in propositus or family member Low HDL, lipoprotein A1, and lipoprotein A2 Sensitive to sulphonylureas
GCK-MODY (MODY2)	Glucokinase; *GCK*	Congenital stable, mild hyperglycaemia (fasting glucose typically ranges from 5·5 to 8 mmol/l) Small incremental increase between fasting and 2 h glucose on OGTT (usually <3·5 mmol/l) Hemoglobin A_{1c} typically ≤59 mmol/mol Microvascular complications are rare
HNF1A-MODY (MODY3)	Hepatocyte nuclear factor 1-alpha; *HNF1A*	Progressive insulin secretory defect with presentation in adolescence or early adulthood Low renal glucose threshold Low hsCRP levels Large incremental increase between fasting and 2 h glucose on OGTT Increased HDL Sensitive to sulphonylureas
PDX1-MODY (*IPF1*) (MODY4)	Pancreatic duodenal homeobox 1; *PDX1* (insulin promoter factor 1; *IPF1*)	Rare, diabetes appears to be mild
HNF1B-MODY (MODY5)	Hepatocyte nuclear factor 1-beta; *HNF1B*	Progressive diabetes, often with renal disease Renal and genitourinary abnormalities, pancreatic atrophy, exocrine pancreatic dysfunction Hyperuricaemia, gout, and abnormal liver function tests may occur
NEUROD1-MODY(MODY6)	Neurogenic differentiation 1; *NEUROD1*	Rare
CEL-MODY	Carboxyl-ester lipase; *CEL*	Pancreatic atrophy, exocrine pancreatic dysfunction
INS-MODY	Insulin; *INS*	Rare
Other rare causes	See text	
ABCC8	ATP-binding cassette, subfamily C, member 8	More commonly causes of permanent or transient neonatal diabetes, *ABCC8* and *KCNJ11* are also associated with neonatal hyperinsulinaemic hypoglycaemia
KCNJ11	Potassium channel, inwardly rectifying, subfamily J, member 11	
UPD6	Paternal uniparental isodisomy of chromosome 6q24	

GCK MODY

Glucokinase catalyses glucose conversion to glucose-6-phosphate, the first step in glycogen storage and glycolysis. By this mechanism, glucokinase acts as the glucose sensor of the beta cell linking insulin secretion to elevations in serum glucose. It is also expressed in the liver, where the MODY mutations can result in reduced hepatic glycogen synthesis and increased hepatic glucose production resulting in moderately elevated morning blood sugars. Heterozygous inactivating mutations in *GCK* raise the set point for insulin secretion in response to increased blood sugar. *GCK* mutations result in stable, mild fasting hyperglycaemia with a threshold for glucose-stimulated insulin release typically 6·6–7·2 mmol/l.[2,8] The haemoglobin A1c rarely exceeds 53–59 mmol/mol. Complications are rare, and generally glucokinase-related diabetes does not require any therapy. Moreover, treatment with insulin or oral hypoglycaemic agents does not change overall glycaemia.

GCK mutations are the most frequent monogenic cause of diabetes in asymptomatic children with persistent mild hyperglycaemia or glycosuria. In a study of 59 children with confirmed asymptomatic hyperglycaemia, 59% had *GCK* mutations.[9] Such children are typically found during routine child health examinations or during evaluation for an unrelated complaint. Family history often reveals 'borderline' diabetes or gestational diabetes in parents and grandparents. However, there may be no family history of impaired fasting glucose or diabetes as affected individuals are generally asymptomatic and may never come to medical attention. Testing parents will reveal a mildly elevated blood glucose in the parent carrying the *GCK* mutation, except in cases of *de novo* mutations.

GCK mutations should also be considered in women diagnosed with gestational diabetes with continued hyperglycaemia after delivery in the absence of risk factors for type 2 diabetes. The incidence of *GCK* mutations in this population ranges from 5% to as high as 80% depending on the stringency of prescreening criteria.[10,11] Women with *GCK* mutations are commonly treated with insulin during pregnancy to avoid foetal macrosomia. However, the optimal treatment of *GCK* diabetes during pregnancy is uncer-

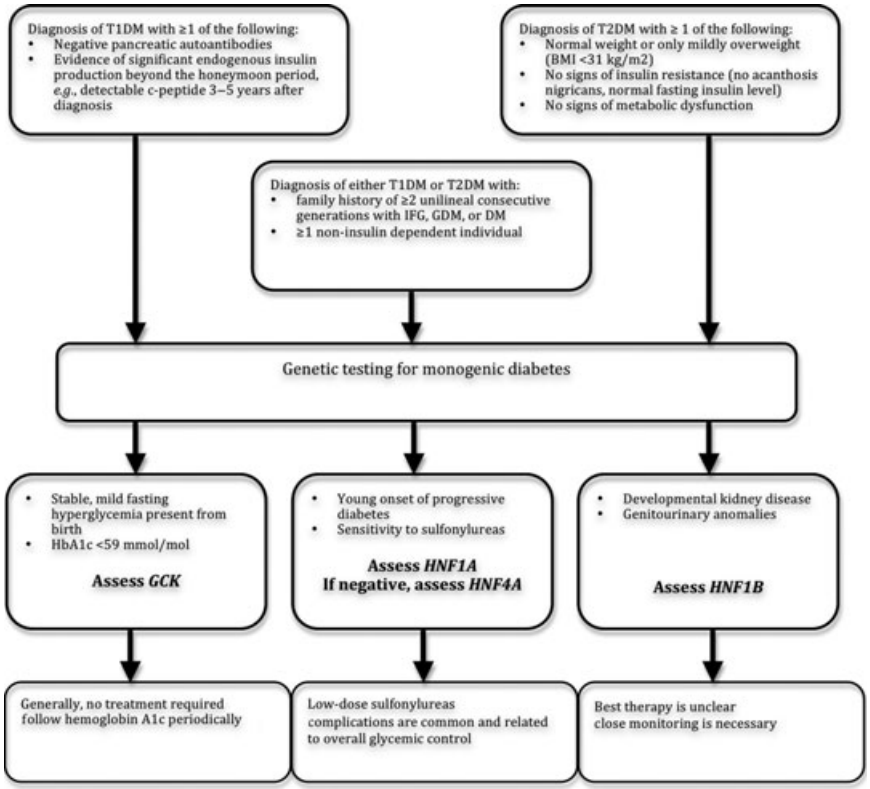

Fig. 1 Approach to genetic testing in suspected monogenic diabetes.

tain and largely depends on whether the foetus also carries a glucokinase mutation, as this is the main determinant of birth weight. Additionally, one study showed no difference in birth weight of infants born to mothers with *GCK* mutations treated with either insulin or diet during pregnancy.[12] Reassuringly, studies suggest that the offspring of mothers with *GCK* mutations do not demonstrate any negative affects on beta cell function as a result of exposure to mild maternal hyperglycaemia.[13]

People with *GCK* mutations can develop marked insulin resistance with type 2 diabetes secondary to typical risk factors of obesity, sedentary lifestyle and genetic susceptibility. This can worsen glycaemia and precipitate pharmacologic therapy.

HNF1A and *HNF4A* MODY

HNF1A and *HNF4A* encode transcription factors important to pancreatic development and beta cell differentiation and function. Diabetes caused by mutations in these genes follows a similar clinical picture with progressive beta cell failure. Microvascular complications are common and are related to overall glycaemic control. *HNF1A* and *HNF4A* mutations cause MODY that is often particularly sensitive to low-dose sulphonylurea therapy. Sensitivity to sulphonylureas has been demonstrated in *HNF1A*-MODY[14] and reported in *HNF4A*-MODY, but not established by randomized trials.[15]

Mutations in *HNF1A* are the most common cause of MODY, responsible for 52% of monogenic diabetes in the large UK series.[4] Mutations in *HNF1A* are highly penetrant. Diabetes develops by age 25 years in 63% of mutation carriers and by age 50 years in 94%.[7] *HNF1A* mutations also result in a low renal threshold for glucose; thus, glycosuria is commonly found in mutation carriers even at relatively normal blood glucose levels.[16] Sulphonylureas are the treatment of choice in *HNF1A* diabetes.[14] In one study, 70% of individuals with a genetic diagnosis of *HNF1A* diabetes successfully switched from insulin to sulphonylurea treatment and remained off insulin at a median of 39 months with good glycaemic control.[17] Individuals with diabetes caused by *HNF1A* mutations have also been shown to have a 5·2-fold greater response to sulphonylureas than to metformin for reduction in fasting plasma glucose.[14]

Diabetes caused by *HNF4A* mutations accounts for ∼10% of MODY.[4] In a study of subjects with a clinical phenotype of *HNF1A* diabetes but negative genetic testing for *HNF1A* mutations, 29% were found to have mutations in the *HNF4A* gene.[16] *HNF4A* mutations caused a similar clinical phenotype as *HNF1A* diabetes characterized by progressive insulin secretory defects, diabetes onset before 25 years and a sensitivity to sulphonylureas.[15] *HNF4A* mutations can paradoxically cause foetal macrosomia and transient neonatal hypoglycaemia.[18] A personal or family history of these diagnoses should raise suspicion of *HNF4A*-MODY.

HNF1B MODY

Mutations in *HNF1B* most often cause hereditary developmental renal disease, particularly cystic disease. *HNF1B* mutations can also cause isolated diabetes or diabetes associated with kidney disease

[renal cysts and diabetes (RCAD) syndrome]. Urogenital tract anomalies and atrophy of the pancreas may also occur.[19] As *HNF1B* mutations will not necessarily cause diabetes in all carriers, the pedigree of dominantly inherited diabetes typical of MODY may be absent in *HNF1B* diabetes. However, the co-segregation of diabetes and developmental kidney disease in an individual and within a pedigree identifies individuals likely to have *HNF1B* diabetes.

Additional MODY subtypes

Maturity-onset diabetes of the young caused by mutations in *PDX*, *NEUROD1*, *CEL* and *INS* (also a rare cause of type 1B diabetes) is very rare.[1,20,21] These MODY genes are not commonly assessed for mutations unless testing for the more common causes of MODY is negative and clinical suspicion for MODY is very high. Several gene mutations usually considered to cause neonatal diabetes can also present with a MODY-like picture, including relapsed diabetes following transient neonatal diabetes owing to mild *KCNJ11* mutations and uniparental disomy 6 (UPD6). *ABCC8* mutations can also rarely cause MODY.[22] Additionally, 10–20% of patients with a classic MODY phenotype do not have a mutation in any of the known MODY genes.[23]

Clinical investigation

When MODY is suspected, a limited laboratory evaluation should be carried out to ensure appropriate selection of patients for genetic testing.[24] In individuals carrying a diagnosis of type 1 diabetes, pancreatic autoantibodies should be obtained prior to pursuing genetic testing if not carried out at the time of diagnosis. It is our general practice to assess for GAD 65, IA-2 and islet cell antibodies. Insulin antibodies can also be assessed in individuals not yet on insulin treatment. Negative autoantibodies do not exclude a diagnosis of type 1 diabetes if the duration of diabetes has been substantial at the time of testing. Additionally, 5–30% of type 1 diabetes will be autoantibody negative even at the time of initial diagnosis.[25] However, positive antibodies nearly always imply type 1 diabetes, with rare exceptions (a few patients with *KCNJ11* neonatal diabetes have pancreatic autoantibodies[26]). Additionally, endogenous insulin production should be assessed via c-peptide with paired glucose to demonstrate that the serum glucose is high enough to prompt endogenous insulin secretion.

In individuals diagnosed with type 2 diabetes, fasting glucose, insulin and c-peptide can be informative as MODY lacks the insulin resistance that is characteristic of type 2 diabetes, often manifested as hyperinsulinaemia and high-normal c-peptide. An oral glucose tolerance test (OGTT) can also be considered and may show a pattern characteristic of certain MODY types (Table 1).[27]

Recently, urinary c-peptide creatinine ratio has been shown to be useful in further discriminating possible *HNF1A*-MODY and *HNF4A*-MODY from type 1 diabetes, when diabetes duration has been 5 years or more.[28] Additionally, low hsCRP can help distinguish *HNF1A*-MODY from type 1 and type 2 diabetes.[29] These diagnostic tools may facilitate selection of patients for genetic testing.

Diagnostic and predictive genetic testing

Molecular genetic testing should be pursued in individuals fitting a clinical phenotype of MODY using Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. A list of laboratories that perform genetic testing is available at http://www.genetests.org. Most laboratories will report both pathologic mutations and common polymorphisms. Thus, care must be taken in interpreting results and may require consultation with physicians with expertise in monogenic diabetes (one can consult http://www.monogenicdiabetes.org and http://www.diabetesgenes.org).[30] In the case of *GCK* diabetes, once a mutation is established, at-risk family members can be screened with fasting blood glucose measurement. Those found to have hyperglycaemia can be offered diagnostic genetic testing to confirm presence of a *GCK* mutation.[27] With other causes of MODY, family members with diabetes can be offered diagnostic genetic testing to determine if they carry the pathologic mutation, typically at substantially lower costs than propositus testing. Additionally, predictive genetic testing can be offered to unaffected relatives after appropriate genetic counselling.

Conclusions

A molecular diagnosis of monogenic diabetes alters management and identifies affected and at-risk family members. Thus, genetic testing should be pursued in all patients meeting a clinical diagnosis of maturity-onset diabetes of the young. Moreover, such patients should be followed longitudinally through registries to facilitate our understanding of the unique features and best treatment of each genetic cause of maturity-onset diabetes of the young. Patients with suspected and confirmed diagnoses of monogenic diabetes can be directed to our website at http://www.monogenicdiabetesregistry.org to consider participation in our IRB-approved studies of monogenic diabetes.

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