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M Verma and S I Stone | Novel *HNF1A* variant in HNF1A-MODY

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Identification of a novel hepatocyte nuclear factor-1 alpha (*HNF1A*) variant in maturity onset diabetes of the young type 3 (HNF1A-MODY)

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Summary

We identified an adolescent young woman with new-onset diabetes. Due to suspicious family history, she underwent genetic testing for common monogenic diabetes (MODY) genes. We discovered that she and her father carry a novel variant of uncertain significance in the *HNF1A* gene. She was successfully transitioned from insulin to a sulfonylurea with excellent glycemic control. Based on her family history and successful response to sulfonylurea, we propose that this is a novel pathogenic variant in *HNF1A*. This case highlights the utility of genetic testing for MODY, which has the potential to help affected patients control their diabetes without insulin.

Learning points:

- *HNF1A* mutations are a common cause of monogenic diabetes in patients presenting with early-onset diabetes and significant family history.
- Genetic testing in suspected patients allows for the identification of mutations causing monogenic diabetes.
- First-degree relatives of the affected individual should be considered for genetic testing.
- The use of sulfonylurea agents in patients with HNF1A-MODY can reduce dependence on insulin therapy and provide successful glycemic control.

Background

Most cases of monogenic diabetes (MODY) present at a relatively early age (before 25 years old) and follow an autosomal dominant pattern of inheritance (1). MODY constitutes about 1–5% of diabetes mellitus (DM) cases and is characterized by defects in pancreatic β-cell function and impaired insulin release (2). Mutations in the hepatocyte nuclear factor-1 alpha (*HNF1A*) gene are associated with the development of HNF1A-MODY (monogenic diabetes type 3, MODY 3); however, not all patients with *HNF1A* mutations will have diabetes upon testing (1). HNF1A-MODY patients usually present with polyuria, polydipsia, and glucosuria (1, 3). Diagnosis of MODY depends on genetic testing, which is usually initiated depending on clinical information and biomarkers such as c-peptide and islet autoantibodies (3). Patients with HNF1A-MODY respond well to low-dose sulfonylurea treatment, which can increase glucose-induced insulin secretion (3, 4). This case outlines the diagnosis of HNF1A-MODY in a patient with a novel heterozygous missense variant in the *HNF1A* gene that was identified by genetic testing due to

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significant family history. We highlight the diagnostic process and provide clinical guidance for when to consider genetic testing for monogenic diabetes.

Case presentation

A 13-year-old young woman was admitted with new-onset diabetes. The diagnosis was made in the absence of polydipsia, polyuria, or weight loss and was incidentally found to have dysuria and a urinary tract infection on a urinalysis. During her admission, she was noted to have a strong family history of diabetes (Fig. 1). Particularly, her father (II-2) was also diagnosed with diabetes at age 13. He was initially treated with oral medications for approximately 10 years. He then was without therapy for 7 years with no apparent ill effects. He resumed treatment with insulin at age 30 and continues to take insulin. The proband's paternal grandfather (I-3) was diagnosed with pre-diabetes in his 60s and currently is controlling his blood sugars via a strict low-carbohydrate diet. Neither him nor the paternal grandmother (I-2) was available for genetic testing. The proband has two paternal uncles with a history of diabetes. The brother of the paternal grandmother (I-1) was diagnosed with diabetes in his 30s. He suffered many complications of diabetes including lower extremity amputations. He is now deceased due to complications from his diabetes. The brother of the paternal grandfather (I-4) was diagnosed with diabetes in his 20s. He died at age 71 due to cancer. According to the proband's father, both individuals (I-1 and I-4) demonstrated an atypical diabetes pattern where they would be able to stop insulin for long periods of time. However, their medical records were not able to be verified.

Investigation

When the patient presented to her primary care provider, her chief complaint was dysuria. She did not have any known history of polydipsia, polyuria, or weight loss. A urinalysis revealed blood and leukocyte esterase in the urine confirming a urinary tract infection. However, she also was noted to have glucose in her urine. This prompted chemistries to be drawn demonstrating blood glucose of 250 mg/dL and bicarbonate of 30 mEq/L. Her hemoglobin A1c was 9.0%. Due to her age, she was initially given a diagnosis of type 1 DM (T1DM) and admitted to St. Louis Children's Hospital for diabetes education. Her screening labs for hypothyroidism demonstrated an elevated thyroid-stimulating hormone (TSH) of 7.28 with a normal free T4. However, her TSH normalized when repeated a few months after diagnosis. Diabetes autoantibodies were drawn and negative for islet cell autoantibodies (ICA),

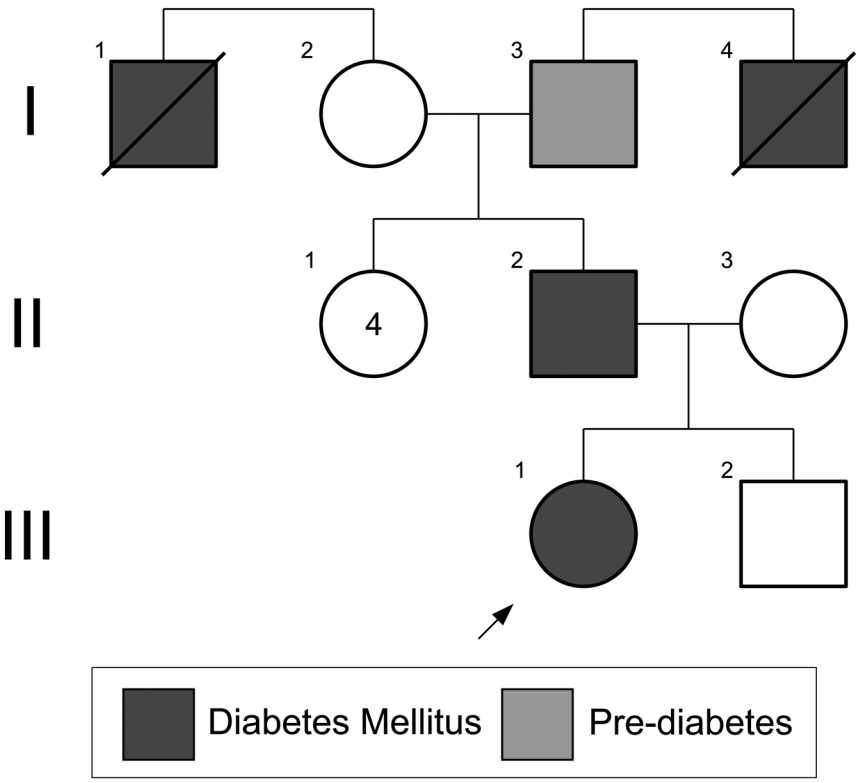

Figure 1
The family pedigree chart illustrating individuals affected by early- or adult-onset diabetes. The proband is indicated by an arrow. Individual II-2 developed diabetes at 13 years old and was treated with oral medication for 10 years. He had no treatment for 7 years and began insulin at 30 years old, which he continues today. He has a history of hypertension and high cholesterol and was confirmed to have a c.811C>G; p.Arg271Gly mutation in *HNF1A*. Individual III-1 (the proband described here) developed diabetes at 13 years old and was confirmed to have a c.811C>G; p.Arg271Gly mutation in *HNF1A*.

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glutamic acid decarboxylase autoantibodies (GAD-65), and insulin autoantibodies (IAA). Given her negative diabetes autoantibodies and atypical diabetes history of the patient's father, we ordered genetic testing for monogenic diabetes (Athena Diagnostics Monogenic Diabetes (MODY) Five Gene Evaluation (*GCK*, *HNF4A*, *IPF1*, *HNF1A*, *HNF1B*), Test code 885).

Genetic testing identified a heterozygous missense variant in the *HNF1A* gene–NM_000545.4:c.811C>G; p.Arg271Gly (Table 1). It is located in exon 4 and the homeodomain of the DNA binding region of the *HNF1A* gene (5). This mutation could not be found in the gnomAD or dbSNP databases but was reported in the Human Genome Mutation Database (HGMD) in association with MODY. The p.Arg271 residue at this position is highly conserved across species and *in silico* analysis (SIFT and PolyPhen) predicts this variant to be pathogenic. In addition, a CADD score of 25.1 indicates that the variant is predicted to be highly deleterious. Currently, it is classified as a variant of unknown significance (VUS) by the reporting clinical laboratory according to ACMG guidelines for the interpretation of sequence variants. Two other missense mutations at the same codon position (R271W and R271Q) have been reported to be associated with MODY (6). Both of these variants have also been reported as pathogenic in the ClinVar database. Genetic testing of the patient's father revealed the same *HNF1A* variant. Unfortunately, the grandparental generation was unavailable for genetic testing.

Treatment

The genetic results led to a diagnosis of HNF1A-MODY. The patient's transition from detemir (insulin) to glyburide (sulfonylurea) is outlined in Fig. 2. The patient was given a half dose of detemir at night (0 h), followed by 1.25 mg glyburide at breakfast (10 h) (Fig. 2). Detemir was held at night (19 h) and the patient was able to achieve adequate glycemic control on glyburide alone, as evidenced by her low blood sugar at 40 h (Fig. 2). Her HbA1c improved to 6.2% within 3 months. She achieved adequate glycemic control with 0.625 mg glyburide twice daily. Most recently, she required a dose adjustment to 0.625 mg in the morning and 1.25 mg in the evening.

Table 1 *In silico* analysis of *HNF1A* mutation in exon 4.

HGNC symbol	HFN1A
Dominant transcript	NM_000545.4
DNA change	c.811C>G
Genomic DNA change	g.15719C>G
Alteration location	chr12:121432064C>G
Amino acid change	R271G
SIFT	Predicted NOT tolerated
PolyPhen	Probably damaging
CADD score	25.1

Outcome and follow-up

The genetic diagnosis led to the patient stopping insulin and being maintained on oral glyburide. Her HbA1c levels have remained adequate even without regular blood sugar monitoring. The patient continues to be followed by our care team.

It was concluded that mutation of the *HNF1A* gene was inherited in an autosomal dominant inheritance pattern with incomplete penetrance. The patient's father underwent targeted family testing and was found to have the same genetic mutation. He was referred to the adult endocrinology department and added adjunctive treatment for glyburide, in addition to his regular dosing of insulin. Genetic testing was also recommended for the patient's brother.

Discussion

We report a case of HNF1A-MODY that was diagnosed through the identification of a novel *HNF1A* variant using genetic testing. In this case, an accurate diagnosis of HNF1A-MODY led to the patient's treatment being changed from insulin to an oral sulfonylurea agent. This allowed the patient to maintain appropriate glycemic control without the need for insulin which significantly improved her quality of life. This case is an example of how a correct genetic diagnosis of monogenic diabetes can shape clinical management and help to optimize treatment (2).

Sulfonylureas are now considered first-line therapy for patients with *HNF1A*-MODY (MODY 3) as it allows patients to achieve excellent glycemic control (7). Hypoglycemia may occur, especially in patients with preserved β cell function, and can be addressed by introducing smaller doses of sulfonylureas during initial treatment (7, 8). Sulfonylureas aid in the secretion of insulin, specifically by binding to the sulfonylurea receptor subunit of the K-ATP channel and triggering depolarization of pancreatic β cells (8). In cells with *HNF1A* mutations, sulfonylureas can bypass the existing β cell defects to produce an adequate insulin secretory response (8). In the present case, the patient will require long-term follow-up to ensure that her glycemic control continues.

The discovery of an *HNF1A* mutation in an individual can have important implications for other family

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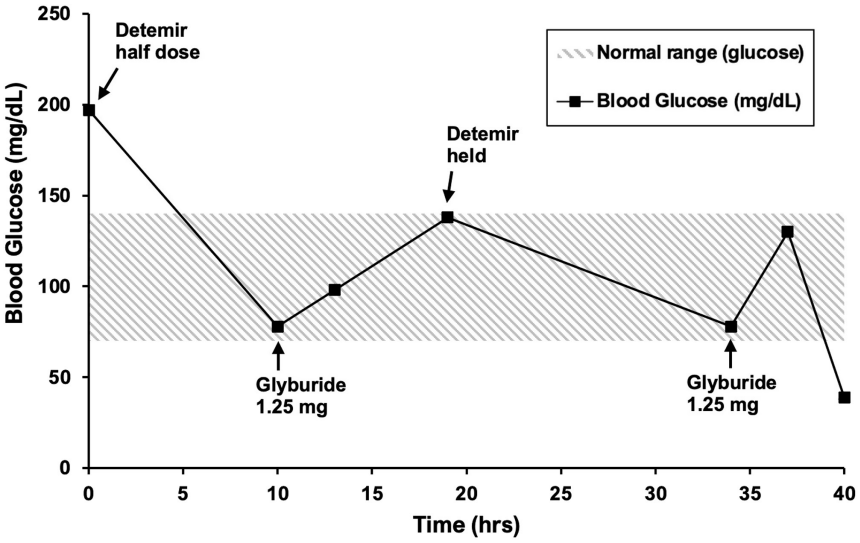

Figure 2
The normal range of glucose is shaded in gray. Detemir (insulin) was held, and adequate glycemic control was achieved with 1.25 mg of glyburide, a type of sulfonylurea.

members. In this case, the patient's diagnosis led to her father undergoing targeted genetic testing and being identified with the same mutation. This allowed him to receive adjunctive treatment to better manage his diabetes. In addition, genetic testing was recommended for the patient's brother, who has a 50% chance of having the mutation (9). Predictive genetic testing can play an important role in monitoring and promptly diagnosing mutation carriers (9). In suspected cases of monogenic diabetes, a family history of diabetes presenting in an autosomal dominant pattern of inheritance remains an important clue in identifying individuals for testing.

Next-generation DNA sequencing (NGS) has facilitated testing by making it possible to test for all MODY genes using a targeted panel (2, 3). Despite the wide availability of genetic testing, there remain challenges in the diagnosis of monogenic diabetes (2). First, challenges exist in the ability to identify patients due to the lack of exclusive clinical criteria for MODY (2, 3). In comparison to type 1 and 2 diabetes, there exists an overlap in the age of onset, family history, and treatment with MODY patients (3). These overlapping features have contributed to the frequent misdiagnosis of monogenic diabetes (2).

Additional challenges are posed by the genetic test itself. The cost of the genetic test and the ability to obtain insurance coverage poses an additional barrier (2, 10). Although genetic panels are useful in clinical diagnosis and identifying novel variants contributing to MODY, the results must be interpreted with discretion to differentiate disease-causing variants from normal variants (2). However, the presence of genetic databases and *in silico* analysis of genes have enhanced the ability of clinicians to assess variant frequency and pathogenicity (2).

In clinical practice, a balance between cost-effectiveness and identification can be achieved through a more rigorous screening criterion (2). This includes considering results of pancreatic autoantibodies, family history of diabetes, BMI, age of onset, and endogenous insulin secretion to determine the need for genetic testing (2). In particular, biomarkers such as negative autoantibody results and C-peptide >200 pmol/L can be used as a useful indicator of whether to pursue genetic testing for MODY (3). Patients with monogenic diabetes present unique challenges in diagnosis which must be adequately addressed by clinicians.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details was obtained from the patient.

Author contribution statement
M V and S S contributed to the conception and design of this manuscript. All authors reviewed and approved the final manuscript.

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