

Differential diagnosis: Identifying people with monogenic diabetes

Maggie Shepherd, Sylvia Miles, Jackie Jones,
Kate Morel, Sian Ellard, Andrew Hattersley

Article points

1. Monogenic diabetes is often misdiagnosed, leading to inappropriate treatment.
2. Maturity-onset diabetes of the young (MODY) is characterised by autosomal dominant inheritance, young age of onset (<25 years in at least one family member) and non-insulin-dependent diabetes.
3. Hepatocyte nuclear factor 1 alpha is the most common cause of MODY and those affected are extremely sensitive to low-dose sulphonylureas.
4. Hepatocyte nuclear factor 4 alpha MODY in either parent can cause macrosomia and neonatal hypoglycaemia.

Key words

- Maturity-onset diabetes of the young
- Monogenic diabetes
- HNF1A
- HNF4A
- HNF1B

Authors' details can be found at the end of this article.

Maturity-onset diabetes of the young (MODY) is initially misdiagnosed in 90% of cases, resulting in inappropriate advice and treatment. Lack of familiarity with the key characteristics of MODY – autosomal dominant inheritance, young age of diagnosis (<25 years) and non-insulin-dependent diabetes – contribute to this misclassification. Confirmation by molecular genetic testing of the MODY subtype is important as it enables correct treatment choices and follow-up of family members, and can explain a range of clinical features. Genetic diabetes nurses work across the UK to increase awareness of monogenic diabetes and provide support and follow-up for families during genetic testing and treatment change. This article describes three families identified with MODY and highlights implications of the diagnosis, including treatment change and family follow-up. The use of non-genetic tests to aid differential diagnosis is also discussed. Increased awareness of the features of monogenic diabetes will enable DSNs to identify possible cases.

Monogenic diabetes is diabetes caused by a mutation in a single gene. It accounts for 1–2% of UK diabetes (Owen and Hattersley, 2001) but is frequently misdiagnosed because of its presentation in slim adolescents (Lehto et al, 1997; Møller et al, 1998; Hathout et al, 1999; Shepherd, 2001; Lambert et al, 2003). This leads to inappropriate treatment in many cases.

Maturity-onset diabetes of the young (MODY) is characterised by autosomal dominant inheritance, young age of onset (<25 years in at least one family member) and non-insulin-dependent diabetes (Stride and

Hattersley, 2002; *Table 1*). Mutations that cause MODY have been identified in at least six genes, and most of these have associated clinical features. For example, hepatocyte nuclear factor 1 alpha (HNF1A) and hepatocyte nuclear factor 4 alpha (HNF4A) MODY are associated with sensitivity to low-dose sulphonylureas, the pharmacological treatment of choice (Pearson et al, 2000; 2003), and hepatocyte nuclear factor 1 beta (HNF1B) is associated with renal cysts and diabetes (Bingham et al, 2001), which may help to predict the most likely genotype. Lack of familiarity with these characteristics and unawareness of the importance of family history

are contributory factors in the misclassification of diabetes in these cases.

DSNs have a role in identifying potential MODY cases: confirming age of diagnosis <25 years and diabetes in one parent can indicate the potential for further investigation. The autosomal dominant nature of MODY means that one would expect to find an affected parent in 90% of cases (Shields and Ellard, personal communication); in contrast, at diagnosis only 10% of those with type 1 diabetes are likely to have a parent affected.

Measuring pancreatic antibodies or urinary C-peptide creatinine ratio (UCPCR) in people diagnosed with diabetes <25 years of age and having a parent with diabetes may aid differential diagnosis and indicate whether genetic testing would be appropriate. Pancreatic antibodies are present in 70–96% of those with type 1 diabetes when measured close to diagnosis (Sabbah et al, 2000). Glutamic acid decarboxylase (GAD) 65 and islet antigen 2 (IA2) levels can be measured by the molecular genetic laboratory at the Royal Devon and Exeter NHS Foundation Trust.

A recent study of 100 people with type 1 diabetes and 500 people with MODY found positive antibodies (either GAD65, IA2 or both) in 82% of those with type 1 diabetes within 6 months of diagnosis compared with less than 1% of those with MODY, indicating that positive antibodies are highly predictive of

type 1 diabetes (McDonald, 2010, submitted for publication).

C-peptide and endogenous insulin are produced in equimolar amounts, and UCPCR has been shown to be a stable and reproducible measure of insulin production (Bowman et al, 2010). UCPCR can be measured on a post-meal urine sample, which can be posted to the laboratory, making it an easy test to perform. UCPCR <0.2 nmol/mmol indicates total insulin deficiency, typically seen in people with type 1 diabetes 5 years after diagnosis, so the test can be used to differentiate between MODY and type 1 diabetes after this period of time (Besser et al, 2010).

This article presents three case studies of people identified with monogenic diabetes and highlights implications of the molecular genetic diagnosis for treatment and family follow-up.

Case 1

John* presented with diabetes at 19 years of age. He had a blood glucose level of 19 mmol/L, 2+ ketonuria, BMI 22 kg/m², polydipsia and lethargy. He was considered to have type 1 diabetes and was managed on insulin aspart 4 units three times daily, insulin detemir 8 units once daily; HbA_{1c} level 8.8% (73mmol/mol) and home blood glucose level 7–11 mmol/L. The possibility of MODY was raised 2 years later.

His mother had been diagnosed during pregnancy at age 24, and following her second

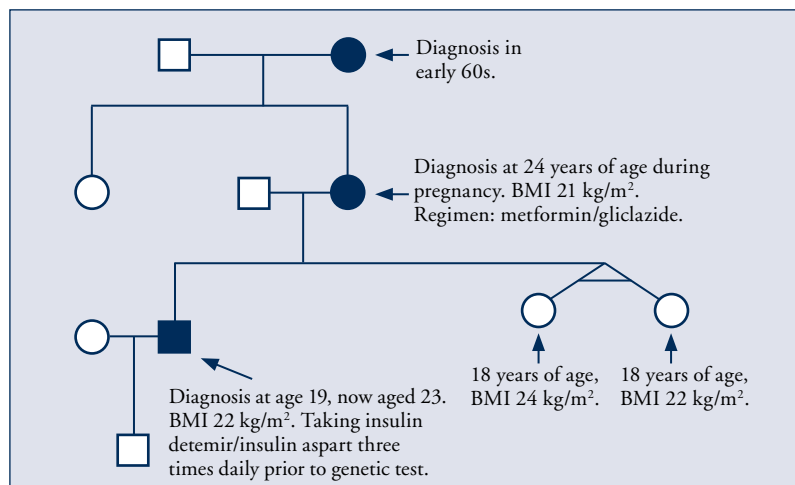
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1. DSNs have a role in identifying potential maturity-onset diabetes of the young (MODY) cases: confirming age of diagnosis <25 years and diabetes in one parent can indicate the potential for further investigation.
2. The autosomal dominant nature of MODY means that one would expect to find an affected parent in 90% of cases, compared with only 10% of those with type 1 diabetes.
3. C-peptide and endogenous insulin are produced in equimolar amounts, and urinary C-peptide creatinine ratio has been shown to be a stable and reproducible measure of insulin production.

Table 1. The three key features that may suggest possible maturity-onset diabetes of the young (MODY) in insulin-treated individuals.

Key features (all three need to be present)	Additional details	Notes
Autosomal dominant inheritance of diabetes.	One parent will also have diabetes and the diabetes may be traced back through the three or more generations with the diabetes being inherited from parent to child.	Monogenic diabetes does not “skip” a generation.
Young age of onset.	Diabetes diagnosed <25 years of age in at least one family member.	Age at diagnosis of diabetes may be variable in other family members through the generations.
Non-insulin-dependent diabetes.	People may have been treated with insulin from diagnosis but will have measurable C-peptide >5 years post-diagnosis.	Other patients may be on diet or tablet treatment, clearly indicating non-insulin dependence.
Other features may be present in addition to the three key features, e.g. sensitivity to sulphonylureas, macrosomia and neonatal hypoglycaemia or renal cysts.		

Figure 1. Family tree indicating autosomal dominant inheritance of diabetes. Square=male; circle=female.



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1. People with hepatocyte nuclear factor 1 alpha (HNF1A) mutations are prone to complications of diabetes, and a history of early myocardial infarction in these families is common.
2. The finding that John was producing C-peptide (using the urinary C-peptide creatinine ratio test) was consistent with maturity-onset diabetes of the young (MODY) but did not rule out type 1 diabetes as it could have been in the honeymoon period.
3. Testing negative for antibodies also supported a non-autoimmune type of diabetes.
4. Confirmation of HNF1A MODY in John's family enabled him to stop insulin treatment and improve glycaemic control on sulphonylureas, and allowed appropriate testing and counselling of other family members.

pregnancy was treated with oral blood glucose-lowering agents. Her BMI is now 21 kg/m² and she was treated with gliclazide 40 mg daily and metformin 500 mg three times a day; HbA_{1c} level 9.5% (80 mmol/mol). John's maternal grandmother was diagnosed with diabetes in her early 60s, indicating autosomal dominant inheritance within the family (Figure 1).

SM made contact with the family to confirm the clinical details and family history, and sent blood and urine samples from John and his mother to the molecular genetic laboratory at the Royal Devon and Exeter NHS Foundation Trust. John tested negative for GAD and IA2 pancreatic antibodies, supporting a non-autoimmune cause of diabetes. A postprandial urine sample with a UCPCR of 1.14 nmol/mmol 3.5 years post-diagnosis established that John was still producing insulin.

Genetic testing confirmed that both John and his mother had HNF1A MODY. Consequently John's insulin was stopped and he was transferred to gliclazide 20 mg daily. His glycaemic control improved and his home blood glucose levels were 4–8 mmol/L. He has no hypoglycaemia and his quality of life has improved: "I was anxious about stopping insulin as I was told I needed it to survive. It's fantastic not to have to inject and the worry of hypos has gone."

His mother's dose of gliclazide was increased to 80 mg twice daily in addition to metformin, with good effect. The possibility of predictive genetic

testing is being discussed with John's twin sisters and maternal aunt. John has a young son and is aware that he has a 50% chance of inheriting the same genetic change but has decided not to pursue genetic testing at this stage.

HNF1A summary

HNF1A mutations are the most common cause of UK MODY (Frayling et al, 2001). HNF1A MODY is characterised by a beta-cell defect and usually presents in slim adolescents or young adults and is consequently often misdiagnosed as type 1 diabetes (Lehto et al, 1997; Møller et al, 1998; Hathout et al, 1999; Shepherd, 2001; Lambert et al, 2003).

Individuals with HNF1A MODY are particularly sensitive to low-dose sulphonylureas, the pharmacological treatment of choice (Pearson et al, 2000; 2003), and have improved glycaemic control and quality of life on this treatment (Shepherd et al, 2003; 2009).

People with HNF1A mutations are prone to the complications of diabetes, and a history of early myocardial infarction in these families is common (Steele et al, 2010).

The finding that John was producing C-peptide (using the UCPCR test) was consistent with MODY but did not rule out type 1 diabetes as it could have been in the honeymoon period. Testing negative for antibodies also supported a non-autoimmune type of diabetes. Confirmation of HNF1A MODY in this family enabled John to stop insulin treatment and improve glycaemic control on sulphonylureas, and allowed appropriate testing and counselling of other family members.

Case 2

Rose* was born at 38 weeks' gestation (birth weight 4.2 kg) and presented with neonatal hypoglycaemia (blood glucose level 0.4 mmol/L), which required treatment with diazoxide and chlorthiazide for 6 months. Her family was contacted by JJ as part of a study of families with macrosomia and neonatal hypoglycaemia to collect DNA samples and a detailed family history.

Rose's father, David*, BMI 30 kg/m², was diagnosed with diabetes at 39 years and treated

with sulphonylureas. Rose's paternal aunt was diagnosed with diabetes at 17 years on routine screening, treated with diet for 4 years and then started insulin, which has continued ever since (Figure 2). Neither of David's parents is known to be affected. Rose has two siblings, who had birth weights of 3.4 kg and 4.4 kg at term, and neither had neonatal hypoglycaemia.

Genetic testing in Rose and David confirmed HNF4A MODY. Macrosomia and neonatal hypoglycaemia, as seen in Rose, have recently been shown to be features of HNF4A mutations (Pearson et al, 2007). Inheritance of this mutation means that Rose would be expected to develop diabetes later in life. She currently has normal glucose tolerance: oral glucose tolerance test (OGTT) 0 min, 3.5 mmol/L; 120 min, 4.9 mmol/L. David is taking gliclazide 160 mg and metformin 1000 mg twice daily. His UCPCR is 2.17 nmol/mmol, indicating that he is producing insulin [now] but may progress to insulin injection in the future.

David's sister is undergoing genetic testing which, if positive, would indicate that she could transfer from insulin to sulphonylureas. David's parents are being tested for undiagnosed diabetes as the autosomal dominant inheritance of MODY suggests that one of them would also be affected. Rose's siblings are having genetic counselling and predictive genetic testing to determine whether they have also inherited an affected copy of the HNF4A gene.

HNF4A summary

HNF4A and HNF1A mutations result in a similar diabetic phenotype, but HNF4A MODY is also characterised by hyperinsulism in utero, leading to macrosomia (birth weight >4 kg) in 56% of cases, and neonatal hypoglycaemia in around 10–15% of cases (Pearson et al, 2007). The hypoglycaemia is transient, but in some cases persists beyond the first year. In adolescence or adulthood there is progression to beta-cell failure and diabetes in early adulthood. Sulphonylureas can also be used in HNF4A (Pearson et al, 2005).

Identification of an HNF4A mutation is important for both males and females planning a pregnancy, since there is a risk of macrosomia

(and neonatal hypoglycaemia) regardless of which parent is affected. Additional scans and early delivery may be indicated to reduce the risk of complications during delivery. In this case the genetic diagnosis allowed follow-up of other family members and the provision of advice regarding diabetes treatment and management of future pregnancies.

Case 3

Anna* was diagnosed in 1993, aged 33 years, with "type 1 diabetes", confirmed by OGTT: 0 min, 7.3 mmol/L; 120 min, 17.6 mmol/L. Her HbA_{1c} level was 8.8% (73 mmol/mol) and her BMI was 23 kg/m². She was commenced on isophane insulin 10 units and 8 units twice daily.

Shortly before her diabetes was confirmed, hyperglycaemia had been noted when she was investigated for recurrent miscarriages. These investigations indicated a bicornate uterus. Her first child, Neil*, was born in 1995 at 33 weeks' gestation, birth weight 1.29 kg. He was taken to the special care baby unit (SCBU) and found to have proximal renal tubular acidosis; renal ultrasound scan (USS) indicated small kidneys with at least two cysts. Anna was identified with nephrocalcinosis in 1996 and renal USS showed that both her kidneys were slightly small and irregular. Anna had a second son 7 years later, born at 36 weeks' gestation, birth weight 1.93 kg.

In 2005, Anna and Neil were referred for genetic testing by KM as she was aware of the clinical history, following information about

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1. Hepatocyte nuclear factor 4 alpha (HNF4A) and HNF1A mutations result in a similar diabetic phenotype, but HNF4A maturity-onset diabetes of the young (MODY) is also characterised by hyperinsulism in utero, leading to macrosomia (birth weight >4 kg) in 56% of cases, and neonatal hypoglycaemia in around 10–15%.
2. Identification of an HNF4A mutation is important for both men and women planning a pregnancy, since there is a risk of macrosomia (and neonatal hypoglycaemia), regardless of which parent is affected.
3. Additional scans and early delivery may be indicated to reduce the risk of complications during delivery.

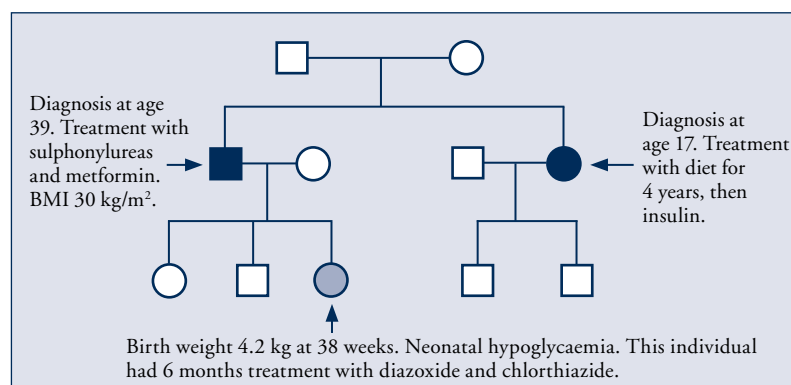


Figure 2. Family tree indicating macrosomia and neonatal hypoglycaemia in child of parent with diabetes. Square=male; circle=female.

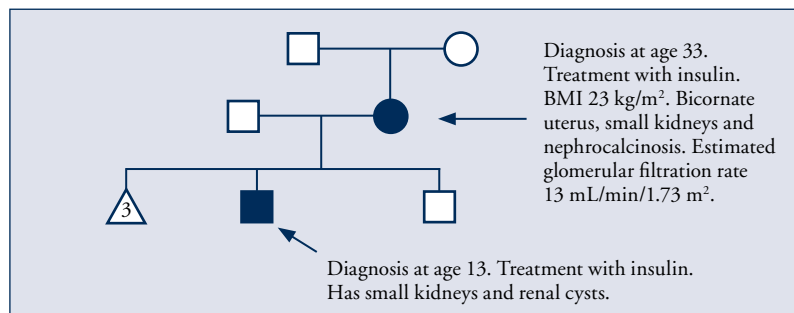


Figure 3. Family tree indicating diabetes and renal problems. Square= male; circle= female; triangle= miscarriages.

specific subtypes of monogenic diabetes at the genetic diabetes nurse study days. Both Anna and Neil were found to have an HNF1B mutation (Figure 3).

Neil developed diabetes at 13 years and is on biphasic insulin aspart 20 units twice daily; his HbA_{1c} level is 8.5–9.2% (69–77 mmol/mol). Anna is on insulin aspart 4 units once daily with her evening meal and insulin glargine 12 units at breakfast; her HbA_{1c} level is 7.6% (60 mmol/mol). Anna and Neil are both under the care of the renal team and Anna’s creatinine level is 319 µmol/L (44–80 µmol/L) and estimated glomerular filtration rate (eGFR) is 13 mL/min/1.73 m². She has been referred to the pre-transplant team and has decided to undergo peritoneal dialysis when required.

HNF1B summary

HNF1B mutations cause renal cysts and diabetes syndrome (Bingham et al, 2001). The renal abnormalities are early onset, often detected in utero and can include a wide range of developmental diseases, most of which are characterised by some type of cyst formation (Bingham et al, 2002; Carbone et al, 2002). Renal function varies from normal to dialysis and some patients have required renal transplants (Bingham et al, 2001).

The diabetes typically develops after the renal disease and the age of diabetes diagnosis is variable: mean age 16 years, range 10–61 years (Bingham et al, 2001). The diabetes is characterised by beta-cell dysfunction, and insulin injections are usually required. Other features, such as low birth weight, uterine malformations and gout, may be present (Bingham et al, 2001; Iwasaki, et al 2001; Edghill et al, 2006).

Although the molecular genetic diagnosis did not alter treatment in this case, it did provide an explanation for the clinical features (diabetes, renal problems and bicornate uterus), which had previously been considered separate entities. It also enabled predictive genetic testing for Neil’s younger brother, who was found to be unaffected.

Discussion

The use of non-genetic tests, such as UCPCR and pancreatic antibodies, may also be useful in identifying those in whom genetic testing is most appropriate, and can help to differentiate monogenic diabetes from type 1 and type 2 diabetes. UCPCR is most useful in differentiating between type 1 and MODY more than 5 years post-diagnosis (Besser et al, 2010). Antibodies are best measured close to diagnosis; although they frequently persist beyond diagnosis, they do decline over time (Borg et al, 2000; Sabbah et al, 2000).

DSNs have a key role in identifying patients who may have monogenic diabetes. Identification of individuals diagnosed with diabetes, who have an affected parent, should alert DSNs to consider the use of pancreatic antibodies or UCPCR to help differentiate between type 1 diabetes and MODY. Those who are antibody negative and UCPCR positive (5 years post-diagnosis) could be referred to their local genetic diabetes nurse (or the Exeter team) to discuss the possibility of genetic testing.

Conclusion

Increasing awareness of the key features of MODY, namely autosomal dominant inheritance, young age of onset (<25 years in at least one family member) and non-insulin-dependent diabetes, among healthcare professionals can highlight people who may benefit from genetic testing.

The cases described in this article highlight the importance of identifying monogenic diabetes. Confirmation by molecular genetic testing can lead to transfer from insulin injections to sulphonylurea tablets in some cases, with improvements in glycaemic control and quality of life. The genetic diagnosis can

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1. Non-genetic tests, such as urinary C-peptide creatinine ratio (UCPCR) and pancreatic antibodies, may be useful in identifying those in whom genetic testing is most appropriate, and can help differentiate monogenic diabetes from type 1 and type 2 diabetes.
2. UCPCR is most useful in differentiating between type 1 diabetes and maturity-onset diabetes of the young (MODY) more than 5 years post-diagnosis.
3. Pancreatic antibodies are best measured close to diagnosis; although they frequently persist beyond diagnosis, they do decline over time.
4. Identification of people with diabetes, who have an affected parent, should prompt DSNs to consider the use of pancreatic antibodies or UCPCR to differentiate between type 1 diabetes and MODY.

also allow appropriate follow-up of other family members, including explanations of risk and other associated features. ■

* Names have been changed to ensure anonymity.

Authors

Maggie Shepherd is Honorary Clinical Senior Lecturer, Peninsula Medical School, Exeter; Sylvia Miles is Genetic Diabetes Nurse, Sherwood Forest Hospital Foundation Trust, Nottingham; Jackie Jones is Genetic Diabetes Nurse, Cornwall and Isles of Scilly PCT; Kate Morel is Genetic Diabetes Nurse, Brighton and Sussex University Hospitals NHS Trust; Sian Ellard is Professor of Molecular Genetics, Peninsula Medical School, Exeter; Andrew Hattersley is Professor of Molecular Medicine and Consultant Physician, Peninsula, Medical School, Exeter.

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“Confirmation of a diagnosis of monogenic diabetes by molecular genetic testing can lead to transfer from insulin injections to sulphonylurea tablets in some cases, with improvements in glycaemic control and quality of life.”

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Further information on genetic testing

For further information about genetic testing, details of the samples required and the costs of UCPCR, pancreatic antibodies (GAD65 and IA2) and genetic tests, visit www.diabetesgenes.org

If you have patients who fit the criteria described in this article and would like to discuss them in more detail, please email MS on m.h.shepherd@exeter.ac.uk or your local genetic diabetes nurse (details on the website).