



Genetic testing clarifies diagnosis and treatment in a family with both *HNF1A* and type 1 diabetes

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Introduction

Making a diagnosis of diabetes may be straightforward when blood glucose levels reach the levels indicated by the World Health Organization (WHO), with a fasting blood glucose ≥ 7.0 mmol/L (126 mg/dl) or two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl).¹ However, the classification of the actual type of diabetes may not always be obvious and there is increasing recognition of specific types of diabetes which may also present during childhood or adolescence. The complexity of the disease process is demonstrated by multiple clinical phenotypes, including autoimmune diabetes masquerading as type 2 diabetes in young adults² and this is likely to increase with escalating obesity in children. Increasing obesity in children may make identifying the true diabetes phenotype more challenging and increase the need for additional non-genetic investigations.

The WHO and the American Diabetes Association classification of diabetes is based on the aetiology of the disease, with type 1 diabetes due to a primary destruction of the beta cells, which is autoimmune (type 1A) or unknown (type 1B) – type 2 being diabetes with no known aetiology, although it is characterised by a combination of resistance to insulin action and inadequate compensatory response to insulin secretion.³ Other specific types of diabetes have also been identified such as those caused by genetic defects of beta-cell function, e.g. maturity onset diabetes of the young (MODY). Ensuring the appropriate diagnosis therefore

ABSTRACT

Confirming a diagnosis of diabetes may often be straightforward but identifying the actual type of diabetes may not always be obvious, particularly in those with a family history of diabetes. Use of non-genetic tests, such as pancreatic antibodies, may assist in the classification of diabetes but is not routine practice. The introduction of molecular genetic testing may confirm a diagnosis of monogenic diabetes but may be considered by some health care professionals to be expensive and unnecessary, particularly if treatment change is unlikely. However, a positive genetic result may lead to successful transfer from insulin to sulphonylurea treatment in many cases with improvements in glycaemic control and quality of life.

This paper describes a family with diabetes diagnosed below the age of 22 years in three individuals, and the confirmation of both *HNF1A* and type 1 diabetes within the family. This case highlights the importance of both genetic and non-genetic tests in confirming a diagnosis. Copyright © 2009 John Wiley & Sons.

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KEY WORDS

monogenic diabetes; *HNF1A*; sulphonylurea sensitivity; genetic testing; GAD antibodies

indicates the need to identify the presence of an autoimmune destructive process in the case of type 1 diabetes, or a specific genetic cause in those with genetic defects of beta-cell function in the case of patients with MODY. The need to make the differential diagnosis is clearly important as the treatment requirements are different. Those with type 1 diabetes require insulin for survival, those with type 2 are typically treated first line with metformin or other oral agents, and in those with *HNF1A* diabetes low dose sulphonylureas are the first line treatment.

Type 1 diabetes accounts for approximately 5–10% of all cases of diabetes⁴ but over 95% of cases of diabetes in children. Type 1 diabetes is one of the most frequent chronic diseases in children and adolescents (0.1–0.2%). In contrast, *HNF1A* diabetes accounts for only 1–2% of all diabetes. Therefore the most likely type of diabetes diagnosed in

children based purely on frequency is type 1 diabetes.

MODY, which is caused by a change in a single gene (monogenic), accounts for 1–2% of diabetes, or approximately 20 000 to 40 000 of cases in the UK. It is characterised by three key features: (1) a young age of diagnosis (<25 years in at least one family member); (2) autosomal dominant inheritance of the diabetes (e.g. diabetes passed down from an affected parent); and (3) non-insulin dependent diabetes or measurable c-peptide at least three years after diagnosis. The most common cause of monogenic diabetes is a mutation in the *HNF1A* gene.⁵ *HNF1A* diabetes is frequently misdiagnosed as type 1 diabetes due to its presentation with marked hyperglycaemia in slim adolescents and young adults.^{6–10} Misdiagnosis also occurs due to inadequate history taking and unfamiliarity with the inheritance of monogenic diabetes.¹⁰ Identifying

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monogenic diabetes is important as this has implications for treatment.¹¹

Patients with *HNFI1A* diabetes are especially sensitive to the glucose lowering effect of sulphonylureas which are the pharmacological treatment of choice.^{8,12–16} Those with *HNFI1A* diabetes can be successfully treated with low dose sulphonylureas, with good glycaemic control¹⁷ and increased quality of life.¹⁸ Patients with *HNFI1A* diabetes are also known to have a low renal threshold for glucose,^{19,20} and glycosuria usually precedes the development of diabetes in *HNFI1A* mutation carriers.²⁰

The incidence of type 2 diabetes is rising in young people, predomi-

nantly due to increasing obesity, and these patients frequently have one or more parent affected. There is an increased incidence in high prevalence racial groups and they frequently have other features associated with insulin resistance such as acanthosis nigricans (Table 1).²¹

The use of non-genetic tests to aid accurate diagnosis, such as islet cell antibodies (ICAs) and glutamic acid decarboxylase (GAD) antibodies, are not routinely performed in clinical practice in the UK.¹⁰ In patients with diabetes, the presence of autoantibodies can help define the aetiology of the disease (Table 1)²¹ and aid classification as type 1 diabetes.²² The

uptake of pancreatic antibody testing across the UK is varied and is only performed in a small number of laboratories, causing practical difficulties for those requesting testing. Accuracy of antibody results also differs depending on the assay used.² Many paediatric teams routinely test a range of pancreatic antibodies but this is not standard practice across the UK.

ICAs are strongly associated with the development of type 1 diabetes.² ICAs are present in >85% of children at diagnosis but these decline over time with only 20% present four to six years post-diagnosis.²³ ICAs are the most sensitive antibodies in

Table 1. Factors to consider in differentiating between type 1 diabetes, monogenic diabetes and young onset type 2 diabetes in those diagnosed between 10 and 30 years. (Adapted from ISPAD Consensus Guidelines, 2006)²¹

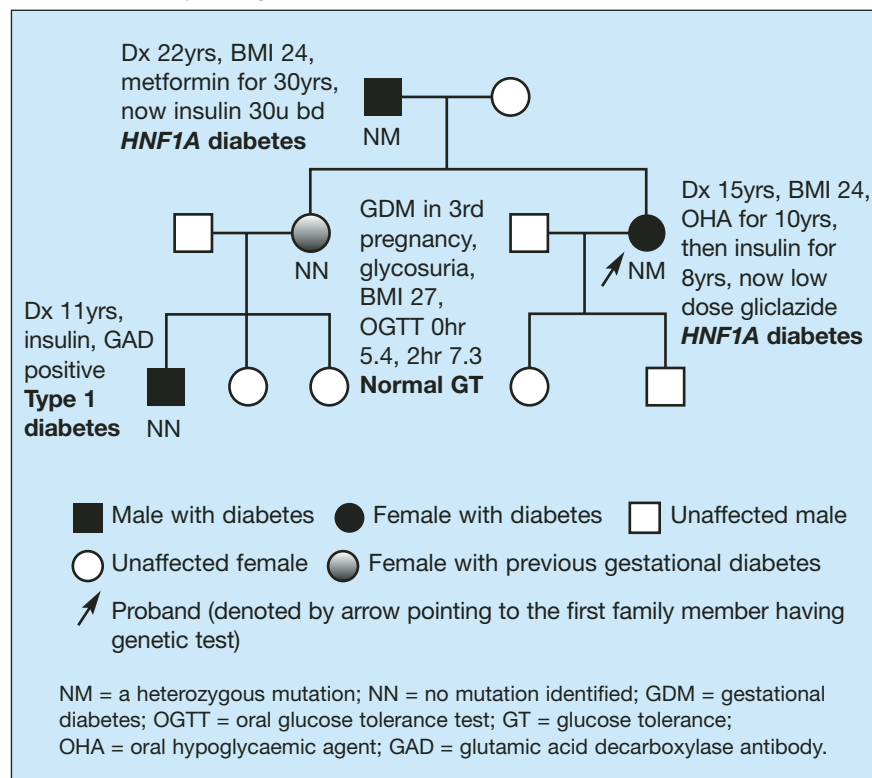
	Type 1	<i>HNFI1A</i> MODY	Young onset type 2
Age at diagnosis	Mainly childhood to young adults	Often post-pubertal	Usually pubertal or later
Onset	Most often acute/rapid	Variable	Variable, from slow/mild to severe
Parent with diabetes	<2–4%	99%	80%, but may have 2 parents affected
BMI/obesity	Usually slim/normal (but reflects background population)	Usually slim/normal (but reflects background population)	Obesity frequent
Ethnic group	Frequent in Caucasians	Frequent in Caucasians	Increased incidence in high prevalence racial groups
Insulin dependent	Yes	No	No
Ketosis prone	Yes, common	Uncommon in MODY	Uncommon
Measurable c-peptide >5 years post-diagnosis	No	Yes, normal levels	Yes, may be high indicating insulin resistance
Antibody positive	80–95% of cases positive at diagnosis	No (population prevalence, i.e. 1–2% of cases positive)	No (population prevalence, i.e. 1–2% of cases positive)
Frequency (% of all diabetes in European white populations)	90%	1–2%	10%
Frequency (% of all diabetes in high prevalence populations)	60–70%	1–2%	30–40%
Acanthosis nigricans	No	No	Yes

MODY = maturity onset diabetes of the young.

children younger than 10 years at diagnosis; however, they are difficult to test and are therefore not often used in the clinical setting. GAD antibodies are present in 70–80% of type 1 cases in Caucasians at diagnosis but can still be identified in approximately 45% 12 years after diagnosis.²³ Insulinoma antigen (IA2) antibodies have been reported in 32–75% of patients with newly diagnosed type 1 diabetes.²⁴ IA2 are usually the latest antibodies to appear and so are not very sensitive in young children. Insulin autoantibodies (IAAs) are the first antibodies to appear during the destruction process so usually present in young children, but the positivity declines with age. Antibody results may be considered inconclusive in some cases as approximately 20% of people with type 1 diabetes may be antibody negative.²⁵ There is a newly described antibody ZnT8 that is present in a significant proportion of children previously diagnosed as having antibody negative type 1 diabetes,²⁶ but this is not currently available for clinical use. Testing for a range of antibodies is recommended to enhance disease prediction²² as the presence of multiple antibodies has the highest positive predictive value for type 1 diabetes.²

Measurement of c-peptide can also aid differential diagnosis but only three years or more following diagnosis as insulin production may continue in those with type 1 diabetes during the honeymoon period. Presence of c-peptide does vary with age, with <5% of those diagnosed <15 years having a c-peptide within the normal range two years post-diagnosis compared to 46% of those diagnosed between 15 and 34 years.²⁷

Making an accurate diagnosis is important as it has long-term consequences for treatment and counselling regarding risk to other siblings and future children. Increasing awareness of monogenic diabetes and the possibility of genetic testing can ensure accurate diagnosis and appropriate treatment, and this may be achieved through a variety of means. This paper discusses a case of familial diabetes identified following the publication of an article written for a women's magazine.

Figure 1. Family pedigree


Case report

Joan, the mother of an 11-year-old boy who had recently been diagnosed with diabetes, contacted the Exeter monogenic team, having read an article in *Yours* magazine. The family history corresponded with the three key characteristics of monogenic diabetes (Figure 1). For this reason, the case was examined further to clarify the possibility of a specific genetic type of diabetes.

Joan's father was diagnosed with diabetes aged 22 years during a medical performed prior to his application to join the Territorial Army. Glycosuria was identified but he reported no symptoms at this time. He was treated with metformin for nearly 30 years before being transferred to insulin when he had chicken pox. He is now aged 64 years and is of normal weight with a BMI of 24. He had been taking insulin for the past 14 years and was treated with Novomix 30/70 30u pre-breakfast and Novomix 50/50 30u pre-evening meal, equating to 0.78u/kg/day. He achieves good glycaemic control with an HbA_{1c} of 6.2%.

Joan had gestational diabetes detected during her third pregnancy at around 28 weeks' gestation

following a steroid injection to promote development of the fetus's lungs. She was asked to monitor her own blood glucose levels during this time, which remained below 10mmol/L, and no treatment was given. She continued to have glycosuria post-delivery but did not have a post-natal oral glucose tolerance test (OGTT). Her current BMI is 27.

Joan's son, Ben, was diagnosed with type 1 diabetes at the age of 11 years in the summer of 2008, having presented with a short history of polydipsia, polyuria, lethargy and weight loss. He had vomited and was complaining of abdominal pain. His blood glucose was 19.6mmol/L on admission and he had ketones in his urine. He was commenced on insulin immediately. His weight was just below the 50th centile (34kg) and height between the 50th and 75th centiles (1.45m). He has two younger sisters who are unaffected.

Joan's sister, Clare, was diagnosed with diabetes at 15 years after repeated urine infections, and glycosuria was identified. She was treated with low dose sulphonylureas for 10 years, gliclazide 40mg twice daily, although she does not recall any discussions about her type of diabetes at this time. She



was transferred to insulin at the age of 25 years during her first pregnancy. She remained on insulin post-delivery as she wanted to have another baby. Following delivery of her second child, it was felt that her blood glucose control was inadequate and she was advised to stay on insulin. She was initially treated on a twice daily regimen but found her glycaemic control was poor and converted to a basal bolus regimen. She had been taking Humalog 6+6+10u and Lantus 14u. She reported a most recent HbA_{1c} of 7.4%. Her BMI was 26. Clare had tested the blood glucose levels of her two children at home and identified random glucose of 9.8mmol in her seven-year-old daughter and 5–6mmol in her five-year-old son.

Results

Genetic testing was performed initially on Clare as her characteristics of a young age of diagnosis yet non-insulin dependence with a parent also affected corresponded with a diagnosis of monogenic diabetes. The *HNFI1A* gene was sequenced because it was considered the most likely gene to be affected as it is the most common cause of MODY, and is characterised by sensitivity to sulphonylureas – as seen in Clare who had previously been treated with low dose sulphonylureas.

Molecular genetic testing identified a novel missense mutation, S432Y in exon 6 of the *HNFI1A* gene in Clare and her father. Clare was consequently able to stop her insulin after 18 years on this treatment and transferred to 40mg gliclazide once daily initially. Regular home blood glucose monitoring was advised during this transfer and phone support was provided by MS. Blood glucose levels of 8.6–14.2mmol were achieved on the first day following transfer and continued between 4.6mmol and 12.5mmol over the next few days. Doses were increased to gliclazide 40mg pre-breakfast and 20mg pre-evening meal and she is now stabilised on 80mg pre-breakfast and 40mg pre-evening meal. Her home monitoring indicates blood glucose values of 5–10mmol and most recent HbA_{1c} three months after transfer to sulphonylureas remained at 7.4%.

Clare's glycaemic control was maintained on sulphonylureas and she felt there was less fluctuation in her blood glucose levels; her quality of life improved. She lost approximately half a stone in weight as a result of not eating as frequently which she previously did to avoid hypoglycaemia. Her BMI is now 24. She described the impact of changing treatment on her life: *'Taking insulin was something that was always at the front of my mind. I was constantly worrying about having a hypo whilst being out and injecting four times a day was painful 90% of the time. Injecting was like a cloud hanging over me. Being on tablets has given me a new lease of life and I feel a great burden has been lifted off my shoulders. I really do feel like a different person. My tests are far more stable than they ever were on insulin. Being on tablets is like a dream come true.'*

The possibility of transferring to sulphonylureas was discussed with Joan's father; however, due to the duration of his diabetes – 42 years – it was felt the likelihood of this being successful was slim, as *HNFI1A* diabetes is characterised by a progressive beta-cell function. He had good glycaemic control on insulin but was keen to try transferring to sulphonylureas. He subsequently commenced a trial of 80mg gliclazide twice daily but blood glucose control deteriorated despite an increase in doses and he recommenced his previous insulin regimen.

An HbA_{1c} and OGTT were requested for Joan in view of her persistent glycosuria. These were performed by her local GP. The OGTT indicated normal glucose tolerance with fasting blood glucose of 5.4mmol/L, and two-hour value of 7.3mmol/L; her HbA_{1c} of 5.9% was in the normal range. These results indicated she did not have diabetes. It was therefore not surprising to find that Joan had not inherited the *HNFI1A* mutation.

Joan's son, Ben, was tested simultaneously for the *HNFI1A* mutation and was also found to be negative, indicating a diagnosis of type 1 diabetes. This was confirmed by a positive GAD antibody result performed in Exeter of 71.6u/ml (a positive result >5u/ml confirming an autoimmune, type 1 cause of his diabetes). His most recent

HbA_{1c} was 7.9%. He is currently treated with Novorapid pre-meals and Levemir 10u pre-bed. Although insulin treatment remained necessary for Ben, his parents were grateful to have his diagnosis of diabetes investigated. His mother reported *'feeling a lot better. [The diagnosis] has sunk in and things could be worse. We just want to get Ben more stable, and are taking each day as it comes. I am so pleased for my sister and it has changed her life.'*

The risk of Clare's children having inherited the same change in the *HNFI1A* gene is a 50% risk for each child. The possibility of predictive genetic testing for both children was raised, along with the option of monitoring for glycosuria once a year. Clare and her husband decided to pursue genetic counselling and predictive genetic testing so they would know one way or the other whether the children had inherited the affected gene. OGTTs were also performed on both children. The older child had a fasting value of 4.4mmol/L and a two-hour value of 12.7mmol/L, indicating the presence of diabetes in keeping with the pattern of progressive beta-cell dysfunction.²⁸ The second child had a fasting value of 4mmol/L and two-hour value of 6mmol/L. Predictive genetic testing identified that both children had inherited the affected *HNFI1A* gene requiring follow up by their diabetes team.

Discussion

This paper reports a family with both *HNFI1A* and type 1 diabetes and indicates the importance of both non-genetic and genetic tests in families with possible monogenic diabetes. It also highlights the importance of identifying the family member most likely to have a monogenic cause of their diabetes in whom genetic testing should be performed initially.

In the context of a monogenic disorder, it is unusual to find individuals within the same family with the same clinical diagnosis – in this case diabetes – but without the genetic mutation. When this does occur, this is known as a phenocopy which indicates a different cause of disease (or diabetes) from that of other family members with the genetic mutation. Phenocopies are rare but



the importance of confirming the diagnosis is highlighted in this case where there were two different causes of diabetes existing within the family.

Measuring c-peptide could have been helpful in Clare prior to genetic testing to determine whether or not she was producing insulin of her own. However, this was not considered necessary in this case as Clare clearly fitted the criteria for monogenic diabetes and had been sensitive to low dose sulphonylureas, suggesting a likely diagnosis of *HNF1A* diabetes.

Molecular genetic diagnosis confirmed an *HNF1A* mutation in Clare and her father. In Clare's case, the molecular genetic diagnosis enabled her to transfer successfully from insulin to sulphonylureas with improvements in quality of life and glycaemic control. Interestingly, her father had been treated for years with metformin but had never been treated with sulphonylureas; the reason for his transfer to insulin prior to the addition of sulphonylureas is not understood but this was the treatment given in his case. The majority of patients with *HNF1A* diabetes can successfully transfer from insulin treatment without deterioration in glycaemic control.¹⁷ A long duration of diabetes does not preclude transfer to sulphonylureas, although such transfer is less likely to be successful in those with diabetes of long duration.¹⁷

The confirmation of a genetic cause of her diabetes also enabled Clare and her husband to pursue predictive genetic testing for their two children aged seven and five years. Due to the age of the children, this was carried out through their local clinical genetics service to ensure appropriate genetic counselling. Both children would have an OGTT performed in order to determine their current status prior to predictive genetic testing.

The youngest age at which *HNF1A* diabetes has previously presented is four years of age, and families with *HNF1A* diabetes may choose to monitor unaffected family members by checking for glycosuria post-meals on an annual basis as this precedes the development of diabetes. If 'unaffected' family members develop symptoms or are found to have glycosuria, then this should ideally be

Key points

- Use of non-genetic tests to aid accurate diagnosis, such as pancreatic antibodies, may assist in the classification of diabetes but is not routine practice
- The need to make the differential diagnosis in diabetes is clearly important as the treatment requirements are different
- A positive genetic test result of *HNF1A* diabetes may lead to successful transfer from insulin to sulphonylurea treatment in many cases with improvements in glycaemic control and quality of life
- Phenocopies are rare, but the importance of confirming the diagnosis is highlighted in this case where there were two different causes of diabetes within the family
- More information about monogenic diabetes and genetic testing is available from www.diabetesgenes.org

followed up by an OGTT. Fasting blood glucose values are the last to be altered in *HNF1A* diabetes and therefore testing fasting blood glucose alone may be unhelpful in this situation. It has previously been shown that subjects with *HNF1A* mutations have normal fasting plasma glucose and are classified as having diabetes by a raised two-hour plasma glucose during OGTT.²⁸ This can be explained as the insulin secretion rate in *HNF1A* mutation carriers is only reduced when plasma glucose levels exceed 8mmol/L.²⁹ This emphasises the need to carry out an OGTT when screening for diabetes in these families. Other families with *HNF1A* diabetes have chosen to undergo genetic counselling and predictive testing for their young children as they have a need for certainty and prefer to know 'one way or another'. These families have felt it enabled them to better prepare for the inevitable development of diabetes.³⁰

Some professionals may consider molecular genetic testing inappropriate, particularly if treatment change is unlikely. However, this case highlights the importance of genetic testing in all family members with diabetes. This case also emphasises the importance of molecular genetic testing prior to a trial of sulphonylureas; although some may consider this approach rather than genetic testing, clearly those with type 1 diabetes would not respond and the process of trying could be extremely dangerous. Ben's parents were finding it difficult to adjust to his diagnosis of type 1 diabetes; however, they were reassured that he undoubtedly did require insulin and was not

receiving this treatment unnecessarily. Between 3% and 30% of people with type 1 diabetes will have absent pancreatic islet autoantibodies when measured at diagnosis^{23,31,32} and, if testing occurs at this time, it can be useful to test a range of antibodies to increase the chance of a positive result; however, this was not necessary in this case as Ben tested positive to GAD antibodies.

Molecular genetic testing is appropriate in cases where a diagnosis of monogenic diabetes is suspected with the presence of a young age of diagnosis, an autosomal dominant inheritance of diabetes, and non-insulin dependence – particularly when treatment changes may be possible. More information about monogenic diabetes and genetic testing is available from www.diabetesgenes.org.

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Conflict of interest statement

There are no conflicts of interest.

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