A nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin.

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Abstract

Aims
Treatment change following a genetic diagnosis of MODY is frequently indicated but little is known about the factors predicting future success. We conducted the first prospective study determining the impact of a genetic diagnosis in UK patients with \textit{GCK}, \textit{HNF1A} or \textit{HNF4A}-MODY and identified the clinical characteristics predicting success (HbA1c ≤58 mmol/mol) on recommended treatment at 2 years.

Methods
An observational prospective, non-selective study of individuals referred for genetic testing to the Exeter Molecular Genetic Laboratory from Dec 2010-12. Individuals from the UK with \textit{GCK}, \textit{HNF1A}/\textit{HNF4A}-MODY not on recommended treatment at time of genetic diagnosis, diagnosed <30 years and aged <50 years were eligible to participate.

Results
44/58 (75.8\%) individuals changed treatment following the genetic diagnosis. 8 individuals with \textit{GCK}-MODY stopped all diabetes medication without any change in HbA1c (49.5 v 49.5 mmol/mol, p=0.28). 36/49 (73.5\%) with \textit{HNF1A}/\textit{HNF4A}-MODY changed treatment, however only 13/36 (36\%) were managed with diet or sulfonylurea alone at 2 years and had HbA1c ≤58 mmol/mol. These individuals had shorter diabetes duration (median 4.6 v 18.1 years), better HbA1c (58 v 73 mmol/mol) and were slimmer (median BMI 24.2 v 26.0 kg/m\textsuperscript{2}) at time of genetic diagnosis, compared to the individuals (n=23/36) with HbA1c >58 mmol/mol (or <58 mmol/mol requiring additional treatment). 64\% (7/11) individuals with diabetes duration ≤11 years and HbA1c ≤69 mmol/mol at time of genetic test achieved good glycaemic control (HbA1c ≤58 mmol/mol) with diet or sulfonylurea alone compared to none with diabetes duration >11 years and HbA1c >69 mmol/mol at genetic diagnosis.

Conclusions
In \textit{GCK}-MODY treatment cessation was universally successful, with no change in HbA1c \textit{off} treatment. In \textit{HNF1A}/\textit{HNF4A}-MODY shorter diabetes duration, lower HbA1c and BMI at genetic diagnosis predicted successful treatment with sulfonylurea/diet alone, supporting the need for early genetic diagnosis and treatment change. Our study suggests that, in individuals with longer duration of diabetes (>11 years), rather than ceasing current treatment, a sulfonylurea should be added to existing therapy especially in those who are overweight or obese with a high HbA1c.
Keywords
Maturity Onset Diabetes of the Young, Hepatocyte nuclear factor 1 alpha, Hepatocyte nuclear factor 4 alpha, Glucokinase, Sulfonylurea, Genetic testing

Abbreviations (alphabetical order)
Glucokinase (GCK)
Hepatocyte nuclear factor 1 alpha (HNF1A)
Hepatocyte nuclear factor 4 alpha (HNF4A)
Maturity Onset Diabetes of the Young (MODY)
Urinary C-Peptide Creatinine Ratio (UCPCR)

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Introduction
Maturity Onset Diabetes of the Young (MODY) accounts for 3.6% of diabetes diagnosed below 30 years in the UK [1]. Diagnosis of MODY has significant implications for diabetes management. Individuals with GCK-MODY need no treatment [2-5] and those with HNF1A or HNF4A-MODY are optimally treated with low dose sulfonylureas [6-9].

There is significant delay from diabetes diagnosis to correct molecular genetic diagnosis of MODY [3, 10-12]. The majority are initially misdiagnosed with type 1 diabetes (T1D) or type 2 diabetes (T2D) and inappropriately treated [11, 13-17].

Current data on success of transfer to sulfonylurea treatment in HNF1A/HNF4A-MODY following genetic diagnosis are limited and retrospective [10, 18] and, in one case, focused on individuals in a single centre with expertise in monogenic diabetes [9]. There have been no prospective studies of individuals with MODY to assess success of treatment change, glycaemic control and maintenance on recommended treatment following genetic diagnosis in individuals with MODY in non-specialist centres.

Our study aimed to determine the impact of a genetic diagnosis on diabetes treatment in UK patients with GCK, HNF1A or HNF4A-MODY and identify the clinical characteristics which predicted successful management (HbA1c ≤58 mmol/mol) with no treatment in GCK-MODY or sulfonylurea in HNF1A and HNF4A-MODY at 2 years.

Methods
Study Design
This was an observational prospective, non-selective study of all individuals with HNF1A/HNF4A or GCK-MODY identified from routine UK referrals for genetic testing to the Exeter Molecular Genetic Laboratory from December 2010 to December 2012. Ethical approval was granted by the NRES Committee South West - Central Bristol (REC no. 10/H0106/03).

Patient Characteristics
Individuals were eligible to participate if: i) genetic testing confirmed HNF1A, HNF4A or GCK-MODY, ii) they were not on recommended treatment at time of genetic diagnosis and iii) they had been diagnosed with diabetes <30 years and were <50 years at time of genetic testing. Treatment was considered 'non-recommended' if those with HNF1A/HNF4A-MODY were treated with medication other than sulfonylureas and those with GCK-MODY were taking any diabetes therapy.

61 individuals referred from across the UK fulfilled eligibility criteria. 58/61 were contactable and agreed to participate (39 HNF1A-MODY, 10 HNF4A-MODY, 9 GCK-MODY) (Figure 1). There were 41 females, median age at diagnosis of diabetes was 17 [IQR 13-21] years, BMI 24.8 [IQR 21.9-28.2], duration of diabetes at genetic diagnosis 10 [IQR 2-20] years and baseline HbA1c 59.5 mmol/mol [IQR 50-73]. At time of genetic diagnosis 50 individuals (86.2%) were insulin treated (43 HNF1A/4A, 7 GCK) and 8 (13.8%) were taking metformin alone (6 HNF1A/4A, 2 GCK). Of those on
insulin, 46 were on insulin alone and 4 took metformin in addition. BMI for children under the age of 19 was adjusted to adult equivalent using the Child Growth Foundation Reference Standards [19].

Follow up and treatment:
Individuals were telephoned at baseline (time of genetic test result), 3, 6, 12 and 24 months. Self-reported diabetes treatment was recorded. Hba1c was measured at baseline (prior to treatment change), 3, 6 and 12 months from ‘finger prick’ blood samples collected at home and posted to the Blood Sciences laboratory at the Royal Devon and Exeter NHS Foundation Trust. Hba1c results at 24 months were accessed from the patient’s local laboratory. Genetic reports included a statement indicating recommended treatment for GCK, HNF1A and HNF4A-MODY but all decisions regarding diabetes management after genetic diagnosis were made by local clinicians.

Statistical analysis
Non-parametric tests (Mann-Whitney test for continuous variables, Chi squared/Fisher’s exact test for categorical variables) were used to compare characteristics of treatment groups. Wilcoxon matched-pairs signed-ranks test was used to compare Hba1c before and after the genetic diagnosis. In two individuals, a single Hba1c value was imputed assuming a linear trend between two available Hba1c points. Analysis was conducted using Stata/SE 14 (StataCorp LLC, Texas, USA).

Results
44/58 individuals (75.8%) changed treatment following the genetic diagnosis (Fig. 1). 14 individuals (24.2%) did not change treatment and were not followed up. Reasons for continuing previous treatment were: pregnancy (n=3), patient choice (n=5), clinical choice (n=5) this included patients with retinopathy and nephropathy or concomitant confirmed T1D (n=1, GAD antibody positive, urine C-peptide creatinine ratio 0.12 nmol/mol) (Fig. 1).

8 individuals with GCK-MODY, (including 7 previously insulin treated), stopped all diabetes treatment post genetic diagnosis irrespective of diabetes duration (median 1.8 years, IQR 0.6-7.2) and BMI (median 19.8 kg/m², IQR 17.9-22.7). Hba1c remained the same at median 1.25 years (IQR 1-2) follow up without any treatment (49.5 mmol/mol [IQR 47-52]) v 49.5 [IQR 47- 50.5], p=1) (Supp. Fig 1).

36/49 (73.5%) individuals with HNF1A/HNF4A-MODY changed treatment post genetic diagnosis (Fig. 1). Of these, 21/36 (58%) were treated with diet (n=3) or sulfonylurea alone (n=18) at 2 years. 13/21 (62%) of these individuals had Hba1c ≤58 mmol/mol at 2 year follow up (Table 1).

We next compared clinical characteristics of the 13 individuals on sulfonylurea/diet alone achieving Hba1c ≤58 mmol/mol with the 23 individuals with Hba1c >58 mmol/mol (n=22) or ≤58 mmol/mol on additional treatment (n=1) at 2 year follow up (Table 1). The individuals with Hba1c ≤58 mmol/mol on sulfonylurea/diet alone at 2 years had shorter diabetes duration (median 4.6 v 18.1 years), were slimmer
(median BMI 24.2 v 26.0 kg/m²), and had better HbA1c (58 v 73 mmol/mol) at transfer compared to those with HbA1c >58 mmol/mol or the single individual with HbA1c <58 mmol/mol on additional treatment (Table 1). There was no difference in genetic aetiology in these groups. Those on sulfonylurea/diet alone at 2 years improved HbA1c from median 58 mmol/mol pre-genetic diagnosis to 46 mmol/mol post genetic diagnosis, p=0.001, in contrast to the other group where HbA1c increased (73 v 77 mmol/mol, p=0.03) (Table 1). Individuals in the latter group who were taking sulfonylurea were on maximum recommended dose (gliclazide 160 mg twice a day).

We also assessed the combined effect of diabetes duration and HbA1c at genetic diagnosis to predict optimal glycemia control with diet/sulfonylurea alone in patients with HNF1A/HNF4A-MODY. We divided the cohort by median diabetes duration (≤11 yr v >11 yr) and median HbA1c at genetic diagnosis (≤69 v >69 mmol/mol) (Fig. 2). 10/18 (55%) with shorter diabetes duration achieved optimal control compared to 3/18 (17%) with longer diabetes duration (p=0.03). Similarly, 10/18 (55%) with lower HbA1c at genetic diagnosis achieved optimal control compared to 3/18 (17%) with higher HbA1c at genetic diagnosis (p=0.03). 7/11 (64%) patients with shorter diabetes duration and lower HbA1c at genetic diagnosis achieved optimal control but none of the patients (0/11) with longer duration and higher HbA1c at genetic diagnosis achieved HbA1c ≤58 mmol/mol with diet/sulfonylurea alone (p=0.02). Similar results were seen for diabetes duration and BMI at genetic diagnosis (Suppl. Fig. 2).

Discussion
This national prospective, non-selective study demonstrates that most patients commence the recommended treatment after a genetic diagnosis is confirmed. However, in HNF1A/4A-MODY two-thirds were on diet or sulfonylurea alone at 2 years and just 36% achieved good glycemic control (≤58 mmol/mol) needed to avoid diabetes complications. Our study suggests that successful treatment with diet/sulfonylurea alone was most likely in those with HNF1A/HNF4A-MODY who had shorter duration, normal BMI and better HbA1c at time of genetic diagnosis. All those with GCK-MODY could stop insulin or oral hypoglycaemic agents without deterioration in glycemic control, as previously shown [5].

Improvement in glycemic control in HNF1A/HNF4A-MODY is needed to prevent diabetes complications. Patients with HNF1A/HNF4A-MODY are at increased, or at least the same, risk of developing diabetes related complications compared to other diabetes subtypes [20, 21]. Our study showed that despite successful transfer to recommended treatment, only one third of patients achieved HbA1c ≤58 mmol/mol on sulfonylurea/diet alone. Lack of optimal glycemic control in our study may result from clinical inertia or limited experience managing HNF1A/HNF4A-MODY by local clinicians and previous advice advocating trial of sulfonylureas even in those with long standing diabetes [10]. The lack of standardised treatment guidelines for individuals needing additional second line therapy may also contribute to suboptimal glycemic control. Our results are similar, albeit lower, than previous studies where around 50-62% attained HbA1c ≤58 mmol/mol with sulfonylurea therapy alone [9,
The difference in the results may be due to difference in duration of diabetes at genetic diagnosis in these two studies.

Progressive loss of pancreatic β-cell function is a feature of HNF1A/HNF4A-MODY, resulting in increasing glyemia and increasing treatment requirements over time [22]. Successful treatment change and achieving good glycemic control is more likely to be achieved if the genetic diagnosis is made early. Prompt transfer to sulfonylureas, enabling optimal glycemia soon after diabetes diagnosis may reduce the risk of future complications in HNF1A/4A-MODY as seen with type 1 and type 2 diabetes [23, 24]. If individuals are transferred to optimal treatment early it may be easier to achieve good control and maintain it. This is reflected by the data that patients with lower HbA1c at genetic diagnosis are more likely to achieve good glycaemic control at 2 years. Contrary to this, patients with higher HbA1c at genetic diagnosis rarely achieved good glycemic control with sulfonylurea alone. As a consequence of these data we now recommend that a sulfonylurea should be added to existing treatment, rather than replacing it, in HNF1A/HNF4A-MODY patients with longer diabetes duration (11 >years), especially in those with higher HbA1c at genetic diagnosis and BMI >25 kg/m².

We identified that higher HbA1c at genetic diagnosis and BMI were associated with reduced success on sulfonylurea treatment in HNF1A/HNF4A-MODY. Similar results have also been seen in a previous retrospective study [9]. In our data, raised BMI at genetic diagnosis markedly reduced success of sulfonylurea therapy in those with a longer duration of diabetes. This is likely to reflect the impact of increased insulin resistance in those with more severe beta cell dysfunction. These data raise the question whether weight loss may aid glycaemic control in patients with HNF1A/HNF4A-MODY.

Our study has limitations. The treatment decisions were made via local clinicians and were not standardised. We did not collect data regarding changes in BMI over time and any effect this had on treatment requirements, which has previously been shown to negatively affect glycemia [9]. It was not appropriate to use multiple regression analysis of factors predicting successful long-term treatment with sulfonylurea alone to identify the relative contribution of each factor due to the small size of our study. Despite these limitations, our study provides the first national prospective data regarding treatment change post genetic diagnosis in non-specialised centres across the UK.

In summary, our national prospective study identified that the majority of individuals changed treatment following a genetic diagnosis of MODY. Those with GCK-MODY were able to stop all diabetes treatment with no deterioration in HbA1c. In HNF1A/HNF4A-MODY only two thirds were maintained on sulfonylurea/diet alone at 2 years and just 36% of those achieved HbA1c ≤58 mmol/mol two years post genetic diagnosis. Shorter diabetes duration, lower HbA1c and BMI at genetic diagnosis predicted successful treatment in HNF1A/4A-MODY with sulfonylurea/diet alone, supporting the need for early genetic diagnosis and treatment change.
Acknowledgements
We are grateful to the patients who took part in this study and the clinicians involved in their care.

Funding
This work presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-041], a parallel funding partnership between the Wellcome Trust and the Department of Health; and was supported by the National Institute for Health Research (NIHR) Exeter Clinical Research Facility. MS, BS and MH are supported by the NIHR Exeter Clinical Research Facility. K.A.P. has a postdoctoral fellowship funded by the Wellcome Trust (110082/Z/15/Z). S.E. and A.T.H. are Wellcome Trust Senior Investigators (WT098395/Z/12/Z), ATH is an NIHR Senior Investigator. ERP is a Wellcome Trust New Investigator. The views expressed are those of the author(s) and not necessarily those of the Wellcome Trust, Department of Health, the NHS, or the NIHR.

Duality of interest
There are no conflicts of interest to disclose.

Contribution statement
All authors contributed to the concept, design, acquisition of data or analysis and interpretation of data and drafting / revising the article and final approval of the article.

References
Figure 1. Flowchart indicating recruitment, treatment at genetic diagnosis and 2 year post genetic diagnosis.

SU, Sulfonylurea; MF, Metformin; Ins, Insulin; OHA, oral hypoglycaemic agents
Table 1. Characteristics of patients with HNF1A/HNF4A-MODY at genetic diagnosis and at 2 year follow up. OHA, Oral hypoglycaemic agents. Data are median (interquartile range) for continuous variables and n (%) for categorical variables.

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<th>Eligible</th>
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<td>n=23</td>
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</tr>
<tr>
<td>Duration of diabetes</td>
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</tr>
<tr>
<td>BMI</td>
<td>0.02</td>
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<td>HbA1c on genetic test</td>
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</tr>
<tr>
<td>Insulin + Metformin</td>
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<td>Metformin</td>
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<th>At 2 year follow up</th>
<th>n (%)</th>
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<td>HbA1c &lt;58mmol/mol</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Insulin + Metformin</td>
<td>2 (13%)</td>
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<tr>
<td>Metformin</td>
<td>6 (26%)</td>
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</table>

61 confirmed MODY not on recommended treatment at genetic test, diagnosed <30yrs, aged <50yrs (39 HNF1A, 10 HNF4A, 9 GCK)
Figure 2. The effect of duration of diabetes and HbA1c at genetic diagnosis on ability to achieve good glycaemic control with diet/sulfonylurea alone at 2 years post genetic diagnosis in patients with HNF1A/HNF4A-MODY. HbA1c and duration of diabetes were divided into two groups by the median value of the HNF1A/HNF4A-MODY cohort (n=36).
Supplementary Fig 1: HbA1c of individuals with GCK-MODY before and after the post genetic diagnosis. The graph shows the HbA1c for the individuals with GCK-MODY (n=8) before the genetic diagnosis on treatment and after stopping the treatment for median 1.5 years (IQR 1-2, range 0.25 to 3 years) following the genetic diagnosis. Median HbA1c is highlighted with black rectangle.

Supplementary Fig 2. The effect of duration of diabetes and BMI at genetic diagnosis on ability to achieve good glycaemic control with diet/sulfonylureas alone at 2 years post genetic diagnosis in patients with HNF1A/HNF4A-MODY. Duration of diabetes were divided into two groups by the median value of the HNF1A/HNF4A-MODY cohort (n=36).