Title: Improvements in awareness and testing has led to a three-fold increase over 10 years in the identification of monogenic diabetes in the UK

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Abstract

Aims/hypothesis: Maturity Onset Diabetes of the Young (MODY) is a rare monogenic form of diabetes. In 2009, >80% of UK cases were estimated to be misdiagnosed. Since then, there have been a number of initiatives to improve the awareness and detection of MODY including education initiatives (Genetic Diabetes Nurse (GDN) programme), the MODY probability calculator, and targeted next generation sequencing (tNGS). We aimed to examine how the estimated prevalence of MODY, and other forms of monogenic diabetes diagnosed outside the neonatal period, has changed over time and how the initiatives have impacted case finding.

Research design and Methods: UK referrals for genetic testing for monogenic diabetes diagnosed >1y of age from 01/01/1996 to 31/12/2019 were examined. Positive-test rates were compared for referrals reporting involvement of the GDNs/MODY calculator with those that did not.

Results: A diagnosis of monogenic diabetes was confirmed in 3860 individuals, >3-fold higher than 2009 (01/01/1996-28/02/2009; n=1177). Median age at diagnosis in probands was 21y. GDN involvement was reported in 21% of referrals; these referrals had a higher positive-test rate than those without GDN involvement (32% v 23%, p<0.001). MODY calculator usage was indicated on 74% of eligible referrals since 2014; these referrals had a higher positive-test rate than those not using the calculator (33% v 25%, p=0.001). 410 (10.6%) cases were identified through tNGS. Monogenic diabetes prevalence was estimated to be 248 cases/million (double that estimated in 2009 due to increased case-finding).

Conclusions: Since 2009, referral rates and case diagnosis have increased three-fold. This is likely to be the consequence of tNGS, GDN education and the MODY calculator.

Key words: Diabetes, GDN, misdiagnosed, MODY, monogenic, prevalence

Abbreviations:

GDN Genetic Diabetes Nurse, HRA UK Health Research Authority, IQR inter-quartile range, RAS Research Application System, REC Research Ethics Committee, tNGS Targeted next generation sequencing

Maturity onset diabetes of the Young (MODY) is a rare, young-onset, monogenic form of diabetes. Identifying MODY is crucial for the patient as a correct diagnosis can inform optimal treatment, long-term complication risk, risk to other family members, and other aspects of clinical care such as pregnancy management(1).

Based on population screening studies, MODY has been estimated to account for 1-4% of paediatric and young-adult diabetes cases(2-7), varying depending on the genes tested, how pathogenicity of variants is determined, age group of the cohort, and screening criteria chosen. In practice, however, referral of patients for diagnostic genetic testing for MODY is often less systematic and based on clinician opinion, so many of these cases are missed. In the UK, 2009 data (published in 2010) estimated >80% MODY cases were misdiagnosed with significant regional variation in referral rates(8).

Since 2009, more resources have been put into the recognition and awareness of MODY. Education initiatives, such as the Genetic Diabetes Nurse (GDN) project in the UK, have been set up to raise awareness and support local clinicians and patients and their families with testing and changes to treatment and management following a genetic diagnosis (9). The MODY calculator (https://www.diabetesgenes.org/exeter-diabetes-app/), has been developed as a free-to-use clinical tool, accessible worldwide, that provides the probability of a patient having MODY based on their clinical features to help clinicians with decisions on which patients to refer for diagnostic genetic testing(10). In addition, targeted Next Generation Sequencing (tNGS) allows all potential MODY genes and additional monogenic diabetes genes to be sequenced in parallel meaning a greater chance of identifying mutations, particularly in rarer genes, compared with traditional Sanger sequencing which was

limited to testing the common MODY genes in series unless a specific phenotype was recognised(11).

To date, studies have examined the prevalence of MODY, but have not considered how the estimated prevalence may have changed over time as efforts to raise awareness and detection of MODY have improved. We aimed to assess the change in estimated prevalence of MODY, and other monogenic causes for diabetes diagnosed outside of the neonatal period, over time at a national level in the UK by examining all referrals to the two laboratories responsible for all diagnostic genetic testing for monogenic diabetes in the UK. We also examined the potential impact of three initiatives (the GDN project, the MODY calculator, and tNGS) on improving the identification of patients with MODY in routine clinical practice.

Research design and Methods

We examined data on referrals and cases from the two laboratories in the UK responsible for all national diagnostic genetic testing for monogenic diabetes. The MODY diagnostic service within the Exeter Genomics Laboratory at the Royal Devon and Exeter NHS Foundation Trust provides monogenic diabetes testing for England, Wales and Northern Ireland. Referral details of all patients who undergo monogenic diabetes testing at the Exeter Genomics Laboratory are recorded within an in-house database. Scotland has offered a separate service for Scottish residents since 2016 through the East of Scotland Regional Genetics Service and provided data on referrals and cases for this study.

We examined all UK patients with diabetes diagnosed >=1 year of age that were referred to these services for monogenic diabetes testing from 01/01/1996 to 31/12/2019, 10 years and 10 months after the previous study that reported patients

detected on 28/2/2009. In the previous study over 99% of the patients reported had mutations in the 4 commonest MODY genes (GCK, HNF1A, HNF4A, and HNF1B). For this previous study they were tested by Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) (for gene deletions) and so testing would typically be initially based on phenotype and serially tested rather than parallel testing. In 2013 targeted next generation sequencing (tNGS) was introduced to the Exeter Genomics Laboratory as a routine testing option where multiple known monogenic diabetes genes are tested in parallel. Here, in line with updated testing criteria, we tested cases for variants (including gene deletions) in 28 known monogenic diabetes genes (*ABCC8, CEL, CISD2, GATA4, GATA6, GCK, HNF1A, HNF1B, HNF4A, INS, INSR, KCNJ11, LMNA, MAFA, NEUROD1, PAX6, PCBD1, PDX1, PLIN1, POLD1, PPARG, RFX6, SLC19A2, SLC29A3, TRMT10A, WFS1, ZBTB20, and ZFP57*) and the mitochondrial DNA variant m.3243A>G by targeted next generation sequencing as described previously(11). The classification of variant pathogenicity in both laboratories is assessed in line with the 2015 American College of Genetics and Genomics guidelines(12), or, prior to these being introduced in 2017, according to an in house framework. Cases with variants of uncertain clinical significance are not included. Only referrals for genetic testing where the patient presented with diabetes were included so HNF1B-associated renal disease and HNF4A hyperinsulinism were excluded from the data cohort.

Case and referral rates were calculated by region. Regional and national population data from mid-2019 was obtained from the UK Office for National Statistics.(13)

Due to local research interest, the Exeter region (EX postcode area, population size 547,511 (UK Census 2011)(14)) has the highest referral rate and so was used to

calculate a minimum prevalence of monogenic diabetes and estimate the number of missing cases in the UK.

Genetic diabetes nurses

The GDN project was set up in 2002 and has provided training for 62 diabetes specialist nurses to gain specialist knowledge in genetic forms of diabetes. GDN involvement in a referral is recorded on the Exeter laboratory's patient's diagnostic referral form and recorded on their referrals database. This information is not available for the Scottish laboratory. Positive-test rates of GDN and non-GDN associated referrals were compared (using Chi-squared), as well as number of family members followed up. Regional GDN activity was calculated based on GDN-person-time in post (so 2 GDNs in post for 12 months would class as 24 months GDN person-time). Regional GDN activity was correlated with cases identified per million population, summarised with the Pearson correlation coefficient.

MODY calculator

The MODY calculator was launched in 2012 (https://www.diabetesgenes.org/exeter-diabetes-app). Since August 2014, for referrals to the Exeter laboratory, the referring clinician reports if they have used the MODY calculator on the diagnostic referral form. This information is not available for referrals to the Scottish laboratory. The number of eligible referrals (diagnosed between 1 and 35, of white ethnicity (the calculator has not been validated for use in other ethnicities and older ages), and using the post August 2014 diagnostic referral form for MODY) that reported using the MODY calculator was recorded and positive-test rates were compared between those who reported using the calculator and those who did not using Chi-Squared.

Ethics Committee approval: This project analysed anonymised data based on referrals to the MODY diagnostic services in Exeter and Dundee. Only aggregate data were shared between sites. On the Integrated Research Application System (IRAS) application form, the project filter questions identified Research Ethics Committee (REC) approval was not required as this piece of work was classed under "Research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) is generally excluded from REC review, provided that the patients or service users are not identifiable to the research team in carrying out the research". The UK Health Research Authority (HRA)'s online tool for assessment of need for ethical approval was completed and confirmed REC review was not needed.

Results

Overview

MODY cases and referrals across the UK

A total of 3,860 cases of monogenic diabetes outside the neonatal period were genetically confirmed in the UK (Table 1) compared to 1,177 in 2009, a 3.3-fold increase in 10.83 years. The number of cases and referrals has increased across all regions since the 2010 paper(8) (Figure 1). There was still considerable regional variation in the number of cases identified across the UK (Supplementary Figure 1 shows maps with revised scales) ranging from 24.3 per million of the population in Northern Ireland to 113.3 in the South West of England (Table 1). The number of cases identified was highly correlated to the proband referral rate of a region (r=0.9). Scotland and the South West had the highest rates of proband referrals in the UK

(both ~250 cases per million population; Table 1). Northern Ireland maintained the lowest rate of referral at 67.1 referrals per million of the population. The majority of cases were diagnosed as adults: 63% (1924/3035) cases that reported age at diagnosis were diagnosed >18 years, with the median (IQR) age at diagnosis of cases at 21 (15, 31) years.

Yearly referrals and cases

Referrals and confirmed cases of monogenic diabetes have been increasing year on year (Fig 2a) while the positive test-rate for probands has been stable at around 23% (Fig 2b). Since the 2010 report, there has been a four-fold increase in the number of probands that have been referred for testing (n=8537 v 2072) and the number of confirmed cases in the UK has more than trebled (3860 v 1177 for all cases including family members; 2083 v 564 for probands alone).

Family member referrals

Most probands (54%) had at least 1 family member referred (median 3 per family). Of the 3190 UK family members, 1821 recorded having diabetes on the request form and 86% (1562/1821) of these patients were diagnosed with monogenic diabetes.

Genetic Diabetes Nurse Network

Genetic Diabetes Nurses (GDN) involvement was recorded on 21% (1821/7981) of proband referrals to the Exeter laboratory, ranging from 8% to 38% across the different regions (supplementary table 1 and supplementary figure 2). Referrals associated with a GDN had a higher positive test rate than those without (32% v 23%, $p<0.001$). Proband cases referred by a GDN (588/2011 (29%)) were more likely to have

additional family members referred for testing compared to cases with no GDN involvement (58% v 51%, p=0.007). Regions with higher GDN activity (as measured by person-time in post) were associated with a higher number of confirmed cases of monogenic diabetes (Fig 3) (r=0.86, p<0.001).

MODY calculator

There were 1657 referrals to the Exeter Laboratory from August 2014 (the date when recording on diagnostic referral forms began) to 31st December 2019 that were eligible for the MODY calculator (diagnosed with diabetes between the ages of 1 and 35 and White ethnicity). Of these referrals, 1224 (74%) reported using the calculator on the diagnostic request form, ranging from 56% to 87% across the different regions (supplementary table 1 and supplementary figure 2). Referrals reporting a MODY probability score had a higher positive test rate than those without (33% v 25%, p=0.001).

To what extent has the testing of additional genes improved the number of cases found?

Supplementary Figure 3 shows the distribution of genetic causes found for the 3860 confirmed monogenic diabetes cases in the UK. The four most common genes (*GCK, HNF1A, HNF4A, HNF1B*) accounted for 89.4% of cases. In the original study a total of 1,177 cases of MODY were identified with >99% having mutations in *GCK, HNF1A, HNF4A, & HNF1B*. The use of tNGS testing greatly increased the testing of all genes but particularly the rarer causes. A total of 410/3860 cases (10.6% of all cases) had causes other than the most common 4 MODY genes detected through tNGS testing. The full breakdown of genetic causes identified is given in Supplementary Table 2.

Twenty-two rarer causes were found, of which the most common were the mitochondrial DNA variant m.3243A>G (4.5%) and mutations in the *ABCC8* gene (1.8%). 40 patients had biallelic mutations causing a recessively inherited subtype of monogenic diabetes. Of these, 4 were homozygous for a mutation as a result of known consanguinity.

Prevalence

In 2009 we estimated that there were 108 cases of monogenic diabetes per million population, which would lead to an estimate of 7214 cases in the UK population and therefore, now with 3860 cases identified, only 46% would be missing.

However, the finding of new cases suggests this past prevalence was an underestimate. An updated prevalence of monogenic diabetes in the UK was calculated based on data from the Exeter area where there is the most testing and the most awareness (as defined by the EX-postcode region of the UK, population size 547,511). 136 cases of monogenic diabetes have been identified in the EX postcode region (105 having mutations in genes included in the original study) leading to a prevalence of 248 cases per million of the population. Based on this prevalence and extrapolating to the whole UK population, this would suggest there is a minimum of 16,566 cases of monogenic diabetes in the UK. Of these estimated total UK cases, 3,860 (23%) have been identified through genetic testing suggesting 77% remain undiagnosed.

Discussion

Over the last 10 years the referral rates and detection of monogenic diabetes cases outside the neonatal period has improved across the UK, with more than a three-fold increase in the number of cases detected since 2009. The referral rate has consistently increased, and we have shown measures that have been introduced such as the GDNs and the MODY calculator have led to better positive test rates.

There have been a number of population-based research studies that have aimed to determine the prevalence of MODY, but these have been largely carried out in paediatric cohorts(2-6). In contrast, our study examined monogenic diabetes cases identified through all routine diagnostic referrals at a national level, and importantly had no restriction on age; over half of the cases in our cohort were diagnosed as adults. Therefore, our study gives a clear indication of not only the minimum prevalence but also the extent to which patients with monogenic diabetes may be misdiagnosed in routine clinical practice across all ages.

Our minimum prevalence estimate is higher than previously thought, and this reflects both the continuing increase in referral rates, and the introduction of tNGS; the more we have looked for cases, the more we have found, and the more we have realised are still missing. Our data suggest that despite the improved detection of MODY across the UK more than three quarters of UK cases are still misdiagnosed (with type 1 or 2 diabetes) and considerable regional variation in referral rates remains. There are many possible reasons for this variability in use of genetic testing for monogenic diabetes but historically this could be due to the funding model for testing (£650 per test, recharged to the requesting organisation for referrals to the Exeter laboratory) meaning certain organisations may be more willing than others to pay for this service.

However, in Scotland funding has always been central, and a change to central funding for genomic testing was introduced in England during 2020/2021 which is predicted to increase future referral rates. A further reason for regional variability in referral rates could be differences in awareness of MODY/monogenic diabetes across the country. The GDN project has improved awareness with a correlation between regional GDN time in post and cases in that region, but the reach of GDNs is still limited in certain areas.

Involvement of both the GDNs and the MODY calculator were found to be frequently indicated on diagnostic referral forms. In both cases, the use of these initiatives was associated with a better positive-test rate, suggesting they are helpful in targeting testing at more appropriate patients and ensuring resources are not unnecessarily used on those highly unlikely to have a monogenic cause for their diabetes. The GDN project has shown how increased awareness, education and support for identifying patients with monogenic diabetes can have real benefits and is a model that could be adopted in other countries around the world. The MODY calculator can be easily accessed online and on smartphones for free worldwide (https://www.diabetesgenes.org/exeter-diabetes-app/). Both can be a real help to clinicians who may not have had specialist training in monogenic diabetes with what can be challenging decisions on who to refer for diagnostic molecular genetic testing.

In addition to the initiatives aimed at clinicians to improve referral rates for MODY and monogenic diabetes, since 2013, targeted next generation sequencing has been introduced which has helped ensure more cases are picked up at the diagnostic testing stage. More than 10% of cases had rarer monogenic causes identified through

tNGS, which is in contrast to <1% as identified in our previous report(8) where testing was carried out by Sanger sequencing specific genes.

Clinical implications

The fact that 77% of monogenic cases outside the neonatal period are still estimated to be misdiagnosed indicates that further work is crucially needed to identify these missing cases. The initiatives to improve awareness and diagnosis that we describe are easy to implement but to encourage wide take up, these approaches need to be introduced into guidelines and taken up at a national level to have real impact. Use of the MODY calculator is now proposed in the National Health Services's National Genomic Test Directory's Testing Criteria for Rare and Inherited Disease(15) and such criteria could be introduced for other diagnostic laboratories worldwide. In England, we are also now working with NHS England and the regional Genomic Medicine Service Alliances with plans to train and identify a monogenic diabetes lead consultant and diabetes specialist nurse in every NHS Trust in England through a targeted approach and virtual training. In addition to the initiatives we describe, screening approaches using C-peptide and islet autoantibodies are also helpful in insulin treated patients(6; 7). In line with this, national C-peptide screening in Scotland has recently been introduced which will help not only with diagnosis of MODY, but also with better classification of diabetes more broadly, and the impact of this at a population level will be of considerable interest.

A correct genetic diagnosis is crucial for the patient and can significantly improve their quality of life. The specific genetic cause diagnosed can inform the most appropriate treatment: insulin injections are essential for patients with Type 1 diabetes (the most common young-onset form of diabetes), whereas patients with the most common

forms of monogenic diabetes can be treated with an oral-based sulfonylurea treatment (for HNF1A/HNF4A MODY)(16-18) or require no pharmacological treatment at all (for GCK MODY)(19). Testing is also important as a positive result has implications for family members or future offspring who may also require treatment, and can also inform future complication risk(20; 21) and pregnancy management(22; 23).

Limitations

This study focuses on data collected from an internal database that has been transcribed from referral forms. Clinical information can be missing on referral forms meaning we may have missed some patients, but this is likely to be minimal as the key criteria of diabetes status and country of origin are nearly always reported, particularly for probands.

Our assessment of the likely impact of GDN involvement or usage of the MODY calculator is limited by the data available. Both are indicated by a box on the diagnostic request form and this can also be missed. Furthermore, we have no way of knowing of any potential patients that may not have been referred following involvement of either of these initiatives. Referrals were not tested for all genes and not all patients are tested via tNGS, typically in cases where a specific gene is suspected(24). This means that we cannot rule out that those without a positive test on the database do not have an, as yet undiagnosed, genetic cause.

Conclusions

Since 2009, referral rates and the number of cases diagnosed with monogenic diabetes outside the neonatal period have increased more than three-fold.

Improvements in referrals and diagnosis of cases is likely to be due to the introduction of better education and awareness through initiatives such as the GDNs and MODY calculator and targeted next generation sequencing testing more genes. Despite this, there are still 77% of cases estimated to be undiagnosed or misdiagnosed in the UK and wide variation in referral rates across the country, so further work in disseminating knowledge is needed to ensure more patients obtain the right diagnosis and the optimal care for their diabetes.

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Contribution statement: LP collated data, analysed data, and drafted the manuscript. KC runs the Exeter monogenic diabetes diagnostic service and helped with access to data and writing of the manuscript. MH helped review and edit the manuscript. JM collated data from the Scottish monogenic diabetes diagnostic service and reviewed and edited the manuscript. EP provided data from the Scottish monogenic diabetes diagnostic service and reviewed and edited the manuscript. SE led the genomics testing laboratory in Exeter and helped review and draft the manuscript, AH helped

design the study and review and draft the manuscript. BS designed the study, analysed data, and helped with the writing of the manuscript. LP and BS have verified the underlying data.

Conflict of interest: None

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Table 1 Regional variation in referrals for genetic testing for MODY and diabetic cases with a confirmed diagnosis of MODY from 01/01/1996 to 31/12/2019

Geographical factors		Probands				Relatives	Cases*	
Country/ Region	Population	Referrals (n)	Referrals per million	With mutation (*n*)	Pick-up rate (%)†	Diabetic relatives with mutation (*n*)	Total cases (*n*)	Total cases per million
Scotland	5,463,300	1369	250.6	265	19.4	178	443	81.1
Wales	3,152,879	255	80.9	69	27.1	60	129	40.9
Northern Ireland	1,893,667	127	67.1	23	18.1	23	46	24.3
England	56,286,961	6,781	120.5	1,724	25.4	1479	3,203	56.9
English regions								
East	6,236,072	571	91.6	154	27.0	145	299	47.9
South East	9,180,135	1,163	126.7	346	29.8	280	626	68.2
South West	5,624,696	1,402	249.3	312	22.3	325	637	113.3
London	8,961,989	1,019	113.7	246	24.1	145	391	43.6
West Midlands	5,934,037	461	77.7	120	26.0	122	242	40.8
East Midlands	4,835,928	393	81.3	115	29.3	99	214	44.3
Yorkshire/Humber	5,502,967	543	98.7	153	28.2	121	274	49.8
North East	2,669,941	448	167.8	92	20.5	59	151	56.6
North West	7,341,196	781	106.4	186	23.8	183	369	50.3
Unknown		5		2		37	39	
UK total	66,796,807	8,537	127.8[c]	2,083	24.4 ‡	1,777	3,860	57.8 ‡

Proband referral rates and confirmed cases were calculated per million of regional population

*Probands +relatives

†Minimum % pick-up rate, based on number of probands with mutations identified per all proband referrals for region specified

‡Values averaged

Figure legends

Figure 1: Maps of the UK showing regional variations for referrals for MODY testing (per million population) (in green) and cases diagnosed with monogenic diabetes diagnosed outside the neonatal period (per million population) (in blue) for a) 1996-28/02/2009 and b) 01/03/2009-31/12/2019. Same scale as in original 2010 study(8) used for both.

Figure 2: (a) Cumulative frequency of proband referrals (green) and proband cases (blue) of monogenic diabetes from 1996-2019 at the Exeter Genomics Laboratory. (b) yearly proband positive-test rate of monogenic diabetes. Positive-test rate was calculated as the proportion of positive cases out of all referrals in that year.

Figure 3: Association between GDN involvement and confirmed cases across the UK. Each point represents a region of the UK with GDN person-time in months on the x axis against cases diagnosed with confirmed MODY per million population on the y axis. Association determined using Pearson correlation coefficient ($r=0.86$, $p<0.001$).