Research Letter

South Asian individuals with diabetes who are referred for MODY testing in the UK have a lower mutation pick-up rate than white European people.

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Abbreviations

SA South Asian
WE White European

Key Words

Glucokinase, Hepatic nuclear factor 1 alpha, Hepatic nuclear factor 4 alpha, MODY, South Asian

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To the Editor: Maturity onset diabetes of the young (MODY) is an autosomal dominantly inherited form of diabetes that has been extensively described in white populations, but diagnosed with lower frequency in other ethnic groups. Mutations in the GCK, HNF1A and HNF4A MODY genes have been reported in a variety of ethnic groups [1–3], but there are few data on prevalence in non-white ethnic groups. MODY was first reported in a UK South Asian (SA) cohort in a systematic survey of childhood diabetes[4]. A 2006 study revealed a lower
than expected frequency of referrals for MODY testing in the UK SA population [5]. The frequency and characteristics of MODY in non-white European populations is important for the precise diagnosis of young-onset diabetes.

We undertook a retrospective analysis of UK referrals for MODY testing to determine if referrals for individuals of SA origin had increased since that reported in the 2006 study and to investigate the pick-up rate and clinical features of MODY mutations in this population. The UK MODY database, held centrally at the Royal Devon and Exeter National Health Service (NHS) Foundation Trust, is populated prospectively from a standardised request proforma that includes ethnicity. Proband referrals (>1 year old at diagnosis) from 1996 to November 2015, in whom sequencing for mutations in the most common MODY genes (HNF1A, HNF4A, HNF1B or GCK) was requested, were selected. Only variants classified as pathogenic or likely pathogenic were included. Assignment of pathogenicity was based on UK best practice guidelines [6]; including findings from established variant/mutation database and literature searches, details of familial cosegregation and identification of clinical features characteristic of the MODY gene mutation. Additionally, data from in silico prediction models (SIFT, PolyPhen2, AlignGVGD, Grantham distance accessed using AlaMut Visual 2.7, Interactive Biosoftware, Rouen, France) were used, along with details of amino acid species conservation and predictions of effects on splicing. Finally, variants in the Exome Aggregation Consortium [7] and 1000 genomes [8] databases with a minor allele frequency >0.01, were excluded.

Ethnicity was categorised as white European (WE) or SA based on UK census classification[9]. The SA group included people from India, Pakistan and Bangladesh or in whom ethnic origin was stated to be ‘Asian’ and excluded mixed ethnicity.

A total of 4688 proband referrals were identified and ethnicity was recorded in 4010 cases. White European referrals accounted for 3472 of 4010 (86.6%). 293 cases referred were in people of SA ethnicity (7.3%), and 81 referrals (2.0%) were from African or Caribbean backgrounds (see table 1).

1180 probands had MODY mutations, with a mutation pick-up rate of 25.2% (1180/4688). The mutation pick-up rate was 29.1% (1011/3472) in the WE group and 12.6% (37/293) in the SA group (p<0.001) (see Table 1). The pick-up rate in children (≤12 years) referred for testing did not differ between ethnic groups; 32.6% in WE vs 26.7% in SA children, p=0.356 (data not shown).

Phenotypes of those with and without confirmed MODY mutations are displayed in Table 2. Generally, SA MODY patients with GCK mutations were diagnosed earlier than WE patients (6.5 vs 20 years, p<0.0001), however, when only considering diagnosis in children under 12 years old, there was no significant difference in age at diagnosis. Referrals from both ethnic
groups had similar proportions of a history of parental diabetes and were equally likely to be non-insulin dependent.

In both SA and WE individuals, the HNF1A / HNF4A MODY phenotypes were similar across all variables reported except for HbA1c, which was higher in the SA group (8.6% [70 mmol/mol] vs 7.2% [55 mmol/mol], p=0.004; see Table 2).

SA people in whom no MODY mutations were found were younger at diagnosis (19 years vs 25 years, p<0.0001) and had a shorter duration of diabetes, compared with WE individuals. BMI was similar across both ethnic groups (WE, 25.3 vs SA 25.0 kg/m², p=0.217). However, SA people were more likely to have a parent affected with diabetes (83.6% vs 68.2%, p<0.0001) and were more likely not to be treated with insulin at referral (60.2% vs 50.6%, p=0.006), when compared with WE individuals (see Table 2).

This study is the first to explore the characteristics of individuals of SA ethnicity who have been referred for MODY testing using data from the largest MODY diagnostic service in the UK. It demonstrates a lower pick-up rate of MODY mutations in people of SA ethnicity. In our analysis, SA people accounted for markedly more referrals than previously reported in 2006 (7.3% vs 0.5%) [5]. Whilst this broadly reflects the UK population demographics, because of the higher prevalence of type 2 diabetes in SA people it is suggested that this is still lower than expected [9]. The detection rate for MODY mutations was lower in the SA group than in WE referrals. However, when a mutation was not detected, SA referrals were more likely to meet the clinical criteria for MODY than WE individuals. This may demonstrate a referral bias favouring SA cases that more stringently meet the clinical criteria. However, the results also show that these criteria are not sensitive for the separation of MODY from young-onset type 2 diabetes in this population. For example, SA people without mutations had higher BMIs than those with confirmed MODY mutations, suggesting that the low MODY detection rate in this group may have resulted from a higher prevalence of young-onset, familial diabetes.

When analysing the SA group as a whole, the best predictors differentiating those with MODY (mutations in all genes) from those without a mutation, were a lower BMI and age at onset; BMI was lower in the SA group with MODY mutations than those without mutations (MODY, 21.4 kg/m² and no MODY, 25.0 kg/m², p=0.001, data not shown), but BMI was generally higher and non-significantly different in the no mutation group when compared with WE people (25.0 vs 25.3 kg/m², respectively). The lower BMI and age at diagnosis in SA referrals was primarily observed in the GCK mutation group and not seen in the HNF1A / HNF4A mutation or ‘no mutation’ groups. It is likely that these findings reflect a lower referral rate
in adults and children over 12 years old since the mutation pick-up rate in both ethnic groups was similar in children under 12 years.

There is limited evidence to support that SA individuals have a lower prevalence of MODY, with only one previous study suggesting fewer GCK mutations occurred in Indian children [10], however, this study may have been underpowered since the estimated minimum prevalence of MODY (in a predominantly white population) has recently been demonstrated to be 1 in 1000 cases[11]. Thus, it is more likely that the lower mutation pick-up rate in SA individuals compared to WE individuals observed in our study reflects higher prevalence of younger-onset type 2 diabetes, which is supported by our analysis demonstrating similar mutation pick-up rates between ethnic groups in pre-pubertal children.

Our data highlight the need to consider the optimum method for identifying cases of MODY in people of non-white European ethnicity. Approaches such as the MODY probability calculator [12] need to be validated in non-white populations as our data suggest that MODY cases may be more sensitively identified using lower cut-offs for age at diagnoses and BMI. Referrals for MODY testing in the SA population have increased considerably but may still be under-representative of the general UK population. Meanwhile, despite meeting referral criteria more stringently, the lower MODY mutation pick-up rate for SA individuals suggests that these criteria are not sensitive for separating MODY from younger-onset type 2 diabetes in the UK SA population.

Further work is required in unselected cohorts, to develop ethnic-specific criteria that facilitate the identification of MODY from type 2 diabetes in SA people with young-onset diabetes.

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**Contribution statement:** SM & AT designed the study. SM collated the data, carried out the analysis and drafted the manuscript. BS assisted with study design and provided support with analysis. KC assisted with data acquisition. DJ, NO, SE and AH provided supervision, assisted
with interpretation of analysis and revised the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

Guarantor

AH is the guarantor of this work

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### Table 1  Breakdown of proband referrals for MODY genetic testing and MODY pick-up rate by ethnic group.

| Ethnic Group                    | n    | %    | MODY mutation (n) | Pick-up rate (%) |
|--------------------------------|------|------|-------------------|------------------|
| All groups                     | 4688 |      | 1180              | 25.2             |
| Individuals with known ethnicity | 4010 |      | 1083              | 27.0             |
| White                          | 3472 | 86.6 | 1011              | 29.1             |
| South Asian                    | 293  | 7.3  | 37                | 12.6***          |
| African-Caribbean              | 81   | 2    | 8                 | 9.9              |
| Middle Eastern                 | 47   | 1.2  | 5                 | 10.6             |
| South East Asian               | 21   | 0.5  | 6                 | 28.6             |
| Mixed /Other                   | 96   | 2.4  | 16                | 16.7             |
| All Non-white ethnic groups    | 538  | 13.4 | 72                | 13.4             |

Statistical analysis was carried out using a \( \chi^2 \) test on the two largest ethnic groups; White and South Asian.  
***\( p<0.001 \) vs white individuals
Table 2  Clinical characteristics of referrals with GCK or HNF1A / HNF4A MODY mutations and those without MODY mutations, analysed by ethnic group.

| MUTATION STATUS | No Mutation | GCK | HNF1A / HNF4A |
|-----------------|-------------|-----|---------------|
| Variable        | WE          | SA  | WE            | SA  | WE            | SA  | p value |
| Total (n)       | 2387        | 256 | 358           | 17  | 545           | 15  | 0.054   |
| Age at diagnosis (years) | 25 (16–35) | 19 (14–30) | <0.0001*** | 20 (14–28) | 6.5 (4.5–15) | <0.0001* | 18.5 (15–25) | 16 (14–20) | 1.000   |
| Age at diagnosis in children <12 years (years) | 9 (6–11) | 11 (7–11.5) | 0.012* | 8 (5–10) | 5 (3–7) | 0.079 | 11 (9–12) | 11 (8–12) | 1.000   |
| Current Age (years) | 35 (25–47) | 28 (19–36) | <0.0001*** | 29 (19–39) | 13 (6–17) | 0.0044** | 37 (26–48) | 25 (20–48) | 0.108   |
| Duration of diabetes (years) | 7 (2–14) | 4 (2–9) | <0.0001*** | 6 (2–11) | 2 (0–5) | 0.0045** | 14 (6–27) | 11 (6–28) | 0.658   |
| BMI (kg/m²) in patients aged>16 years | 25.3 (22.4–29.6) | 25.0 (23.0–28.2) | 0.217 | 22.1 (20.1–25.0) | 19.7 (18.0–20.3) | 0.02* | 24.1 (22.0–27.0) | 24.0 (21.1–24.6) | 0.246   |
| Fasting glucose (mmol/l) | 7.4 (6.1–10.1) | 7.9 (6.5–10.7) | 0.223 | 6.7 (6.3–7.3) | 6.9 (6.5–7.1) | 0.918 | 7.8 (6.3–9.9) | 7.3 (6.7–8.2) | 0.638   |
| HbA1c (%) | 7.4 (6.3–9.1) | 7.8 (6.7–9.7) | 0.0065* | *6.4 (6.1–6.7) | 6.6 (6.5–6.9) | 0.04* | 7.2 (6.3–8.4) | 8.6 (8.1–8.8) | 0.004** |
| HbA1c (mmol/mol) | 57 (45–76) | 62 (50–83) | 0.0065* | *46 (43–50) | 49 (48–52) | 0.04* | 55 (45–68) | 70 (65–73) | 0.004   |
| Meets all three clinical criteria (%) | 14.8 | 31.3 | <0.0001*** | 43.5 | 85.7 | 0.002** | 44.7 | 50 | 0.736   |
| Diagnosed <25 years (%) | 43.4 | 58.6 | <0.0001*** | 61.5 | 94.1 | 0.006** | 72.1 | 93.3 | 0.069   |
| Currently non-insulin treated (%) | 50.6 | 60.2 | 0.006** | 89.7 | 92.3 | 0.762 | 65.7 | 69.2 | 0.794   |
| History of parental diabetes (%) | 68.2 | 83.6 | <0.0001*** | 83.5 | 93.8 | 0.274 | 89.9 | 92.9 | 0.720   |

Data are presented as medians and interquartile ranges or %

aCalculated using cases where the data set for all parameters is complete

Statistical analysis was carried out using Mann-Whitney U / \( \chi^2 \) tests

*\( p<0.05, ** \( p<0.01, *** \( p<0.001 \)