Updated prevalence of monogenic diabetes in Australia: Fremantle Diabetes Study Phase 2

To the Editor: Based on Fremantle Diabetes Study Phase 2 (FDS2) data, we reported in this Journal that the prevalence of maturity-onset diabetes of the young (MODY) and permanent neonatal diabetes in an urban Australian population was 0.24% and 0.12%, respectively, of people diagnosed with diabetes.[1] A further FDS2 participant among those identified as probably having MODY by clinical risk prediction was the only one with a novel heterozygous missense variant (Ala161Thr) in the *KCNJ11* gene which encodes the pore-forming KIR6.2 subunit of the pancreatic β-cell adenosine triphosphate-dependent potassium channel.[2] This variant was not considered to be a cause of MODY at the time of our publication in 2017,[1] but evidence has since emerged that it is a pathogenic activating mutation. It has been identified in two other patients with neonatal diabetes diagnosed before 9 months of age who were responsive to sulfonylurea therapy, and in another diagnosed at 14 years of age who was glutamic acid decarboxylase and islet antigen 2 antibody negative, and had a low (5th percentile) type 1 genetic risk score,[3] a body mass index of 21, a stimulated serum C-peptide concentration of 289 pmol/L (fasting range, 260–1030 pmol/L) 11 years after diagnosis, and a family history of non-insulin-requiring diabetes in her brother and mother (both diagnosed at 18 years of age) and maternal uncle and grandfather (unpublished data, Molecular Genetics Laboratory, Royal Devon and Exeter NHS Foundation Trust).

Our patient with this novel MODY mutation was also diagnosed with diabetes at 14 years of age. At 19 years of age, she was glutamic acid decarboxylase and islet cell antibody negative, and had a body mass index of 28.7 and a serum C-peptide concentration of 660 pmol/L with a simultaneous plasma glucose level of 8.2 mmol/L. Her glycated haemoglobin level was 6.8% (51 mmol/mol) on metformin monotherapy. She remained well controlled on metformin at FDS2 assessments at 23 and 25 years of age (glycated haemoglobin ≤ 6.4% or ≤ 46 mmol/mol), but subsequently progressed to requiring insulin.

Patients with diabetes due to an activating *KCNJ11* gene mutation have a defect in insulin secretion and, in most cases, can be treated successfully with sulfonylurea. This includes those who have been treated with insulin previously (our FDS2 participant has recently been offered this transition).[4] Activating variants in the *KCNJ11* gene are likely to cause permanent neonatal diabetes, MODY or transient neonatal diabetes that remits and can subsequently relapse during the teenage years.[5] Each of our participant's offspring will have a 50% risk of inheriting this variant and thus developing neonatal and/or later onset diabetes.

This new variant means that MODY prevalence has increased to 0.29% of people diagnosed with diabetes, or 107 per million of the Australian population, compared with 0.24% or 89 per million in our original publication.[1] All MODY and permanent neonatal diabetes cases in the FDS2 cohort were people of European ancestry,[1] and the participant newly identified with MODY was of Eurasian background.

The present case illustrates the clinical and genetic heterogeneity of monogenic diabetes. The discovery of new variants allows improved understanding of the pathophysiology and treatment of diabetes in young people.

Timothy ME Davis[1]
Ashley E Makepeace[2]
Kirsten Peters[1]
Kevin Colclough[3]
Wendy A Davis[1]

1 University of Western Australia, Perth, WA.
2 Fiona Stanley Hospital, Perth, WA.
3 Molecular Genetics Laboratory, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

tim.davis@uwa.edu.au

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