# Whole-Exome Sequencing in Children with Suspected Maturity-Onset Diabetes of the Young (MODY)

Mustafa Tosur[1], Claudia Soler-Alfonso[2], Katie M Chan[2], Michael M Khayat[3], Shalini N Jhangiani[3], Ahmad Refaey[4], Donna Muzny[3], Richard A Gibbs[3], Ashok Balasubramanyam[5], Maria J Redondo[1], Aniko Sabo[3]

[1] Department of Pediatrics, Section of Diabetes and Endocrinology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA; [2] Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA ; [3] Human Genome Sequencing Center, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [4] University of Houston, Houston, TX, USA; [5] Baylor College of Medicine, Division of Diabetes, Endocrinology and Metabolism, Houston, TX, USA

## Introduction

- The yield of commercial gene panels for MODY has been reported as low as 27% suggesting the presence of un-identified gene variants in MODY.
- We aimed to study novel genetic factors of MODY.

## Methods

- We identified 10 probands who had clinical characteristics suggestive of MODY but had negative genetic test results in a commercial MODY panel.
- We performed whole-exome sequencing (WES) in probands and their parents.
- In each trio, we prioritized rare protein-altering variants in 70 neonatal diabetes and MODY candidate genes.

## Results

**Table 1: Baseline Characteristics**

| | |
|---|---|
| Mean age at diagnosis | 10 (± 3.8) years |
| Gender | 6 F / 4 M |
| Race/ethnicity (n) | 4 non-Hispanic white<br>5 Hispanic<br>1 Asian |
| Negative islet autoantibodies | 100% |
| Family history of diabetes | 90% |
| Previously assigned diabetes types (n) | 7 type 1 diabetes (T1D)<br>2 unknown<br>1 ketosis-prone diabetes |
| Negative MODY gene panel | 100% |

### Patient 1: *de novo* variant in *INS*

- c.94G>A, p.Gly32Ser
- *De novo* status confirmed by Sanger sequencing
- Previously diagnosed with autoantibody negative T1D at 3 y/o
- Has not been previously reported in MODY but multiple individuals with neonatal diabetes[1]

### Patient 1: *de novo* variant in *INS*

- Same and an alternative amino acid change reported as pathogenic in ClinVar
- Absent in population databases (gnomAD)
- Multiple computational tools predict deleterious effect
- Likely Pathogenic


### Patient 2: frameshift deletion in *RFX6*

- c.2650delC, p.Gln884AsnfsTer57
- Previously diagnosed with autoantibody negative T1D at 12 y/o
- The variant inherited from the mother, who was diagnosed with diabetes of unknown etiology at 25 y/o
- Heterozygous protein-truncating variants in *RFX6* have been reported in individuals with MODY[2]

## Conclusions

- We identified two new MODY cases, with a novel variant not previously associated with MODY in one of them, using WES in children who were initially diagnosed with T1D.
- Our study demonstrates clinical utility of exome sequencing in atypical cases of diabetes suspected of MODY.

## Acknowledgements

- Funded by Mike Hogg Fund
- Supported by Human Genome Sequencing Center at Baylor College of Medicine

## Bibliography

1. Stoy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A. 2007;104(38):15040-4.
2. Patel KA, Kettunen J, Laakso M, Stancakova A, Laver TW, Colclough K, et al. Heterozygous RFX6 protein truncating variants are associated with MODY with reduced penetrance. Nat Commun. 2017;8(1):888.