Background
Monogenic diabetes mellitus (DM) is an early-onset, non-autoimmune disease. Genetic diagnosis can personalize patient management and lead to prevention. We describe four generations of DM in one family, caused by a heterozygous mutation in the RFX6 gene. RFX6 (Regulatory Factor X, 6) is essential for the development of the endocrine pancreas. Mutations in RFX6 can cause neonatal (Mitchell-Riley syndrome) as well as childhood DM, intestinal atresia and hepatobiliary abnormalities. Heterozygous mutations in RFX-6 were described as associated with MODY with reduced penetrance.

Patients
Transient, stress hyperglycemia was the first clinical presentation of our patient at the age of 3 years. Non-autoimmune DM was diagnosed at 13 years.

Maternal family history revealed great-grandmother, grandmother and a mother, two aunts and one cousin with DM. They were diagnosed as diabetics in adolescence or young adulthood. Only the patient’s mother was treated by insulin.

Methods
Next generation sequencing (NGS) panels for genes of monogenic DM, using the Trusight One platform (Illumina), was utilized for genetic analysis of the proband.

MODY - 15 genes panel: ABC2, ABP1, A1K, BID, CCN11, CNR1, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLFL1, NEUROD1, PAX4, PDX1, RFX6

Expanded panel of 23 additional genes and phenotypic search

Analysis: In house-data relying on pipeline, and local database of >1500 Israeli population samples.

Sanger sequencing was performed to validate the likely-pathogenic finding and for segregation analysis in the family.

Results
We identified a heterozygous mutation in RFX6 gene (c.781-2_787delinsG affecting intron7/exon 8) in the proband that co-segregated in five family members with DM, and in the patient’s healthy brother and three young cousins. One uncle who carries the mutation has asymptomatic DM. This mutation was previously reported to cause autosomal recessive neonatal diabetes.

NGS sequencing

Sanger

RFX6 gene mutations

Inframe deletion of 9 nucleotides, insertion of G, across intron7/exon 8

Ancestry

Clinical characteristics of patients with heterozygous RFX6 - MODY

Conclusions

- Heterozygous RFX6 mutation was diagnosed as the cause of familial DM
- Genetic evaluation of youth with non-autoimmune DM provides accurate diagnosis and identifies subjects at risk.

Take home messages

- Diabetes mellitus prevalence is increasing
- Accurate family history provides clues to diagnosis
- Investigating the genetic etiology of diabetes is important and may pave the way to cure
- Diagnosing the correct type of diabetes has an impact on: Personalized treatment, accurate prediction of diabetes risk in unaffected carriers and education of the families
- Diagnosis of family at risk can lead to prevention!