Life Changing Decisions Due to Etiological Genetic Diagnosis in Families of Children with Maturity Onset Diabetes of the Young (MODY)

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Background: Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of disorders characterized by pancreatic beta-cell dysfunction, and usually referred to monogenic forms of diabetes mellitus to distinguish them from the more common type 1 (T1D) or type 2 diabetes (T2D). Fourteen different MODY genetic subtypes have been identified so far. Making a definite diagnosis is very challenging because of similar or overlapping clinical phenotypes between diabetes subtypes. Nevertheless, distinction within childhood diabetes spectrum is crucial as optimal treatments are different, with the possibility of treating some MODY subtypes with oral agents and some can even be managed without any medication. Accurate diagnosis is significant to probands as well as to other family members. It is estimated that up to 1-2% of those diagnosed with gestational diabetes, T1D or T2D have MODY.

Aim: The objective of our work was to create a genetic characterization of our patients.

Patients and Methods: We established a collaboration between the Pediatric Endocrinology unit in Edmond and Lilly Safra Children's Hospital, Israel and the Integrative Genomics and Modelling of Metabolic Diseases research laboratory at EGID (Lille, France).

Sixteen probands with suspected MODY based on clinical evaluation were rigorously selected for a comprehensive genetic analysis of all known monogenic diabetes genes using next-generation sequencing (NGS) and Illumina HiSeq equipment (LIGAN-PM platform at EGID, Lille, France). After human genome alignment, quality controls and variant calling, candidate rare mutations were fully annotated and filtered, and criteria for mutation pathogenicity from the *American College of Medical Genetics* guidelines were used to score the identified mutations as pathogenic or likely pathogenic for MODY.

Results: The genetic diagnosis rate in the clinically suspected MODY patients was 68.7% (11/16).

In 11 patients, we identified pathogenic/likely pathogenic mutations in *GCK* (7 cases), *HNF1A* (2 cases), *APPL1* (one case with a nonsense mutation) and in *WFS1* (one case with a homozygous mutation) (Table 1, Figure 1).

The *WFS1* missense mutation was previously reported in four cases, 2 of them presenting with signs of Wolfram syndrome and one with monogenic diabetes.

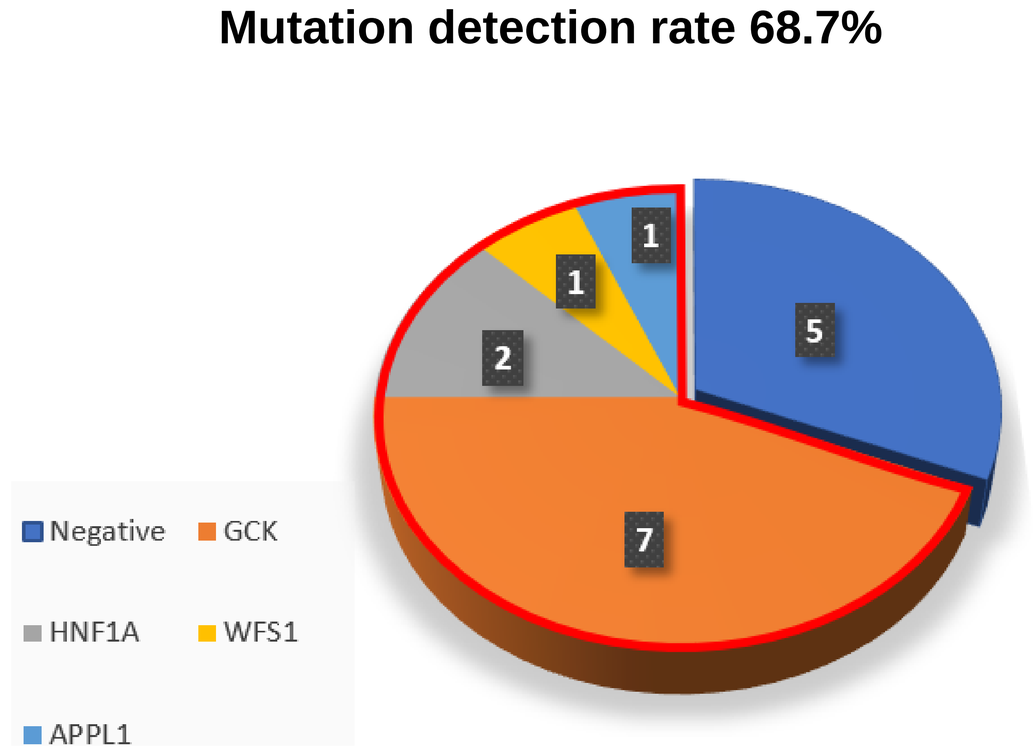
As a result of the genetic confirmation of MODY mutation, insulin treatment was withheld in two children; in 4 adults insulin treatment was discontinued, (one of them was on insulin pump); and antidiabetic oral medication was discontinued in one adult.

Genetic counseling was given to family members.

Table 1 - Clinical and genetic characteristics of the cohort

Gender	Age at diagnosis (years)	Family history	Mutation	Previously reported
F	9	Yes, Father (since age of 40 yrs)	GCK p.G246E	Yes
M	30	Yes, (Mother, daughter)	GCK c.1019+8 G/C	No
F	11	Yes, paternal branch	GCK c.1019+8 G/C	No
F	11		HNF1A p.R271W	Yes
M	16	Yes, paternal branch		
F	4	Grandfather (paternal side)		
M	17	Father/IFG, consanguinity? 7 sibs*	WFS1 p.R558C	Yes
M	17	no information	HNF1A p.R203S	Yes
M	10	Yes, Mother (worsening during pregnancy)		
M	8			
F	9	Mother w/MODY2	GCK p.A173P	No, but p.A173S reported as MODY2 mutation
F	6	Father (IFG)	APPL1	
M	16	Father, cousin	GCK p.G178W	Yes
F	14	Mother's sister	GCK p.A384T	Yes
M	8	Maternal branch (2 cousins w/IFG)		
F	17	Father/sister	GCK p.G246E	Yes

Figure 1 - Genetic distribution of the cohort



Conclusion: Our study confirms that a comprehensive NGS analysis guided by a thorough clinical evaluation is an accurate powerful approach to make a precision diagnosis in monogenic diabetes.

Distinction between monogenic diabetes and other forms of diabetes enabled us to individualize an adequate treatment.

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ESPE European Society for Paediatric Endocrinology