Diagnosis of non-autoimmune paediatric diabetes by targeted next generation sequencing(NGS): findings in two families with rare mono- and digenic forms of diabetes

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BACKGROUND AND OBJECTIVES

Nearly 10% of paediatric onset cases of diabetes are auto-antibodies negative. After exclusion of the most prevalent MODY (MODY 2, 3 and 5), patients are often diagnosed as type 2 diabetes. Our hypothesis was that rare monogenic forms of diabetes could be under-diagnosed.
We report here on two informative families with negative auto-antibodies childhood-onset diabetes cases and clinical and biological presentation not informative for T2D.

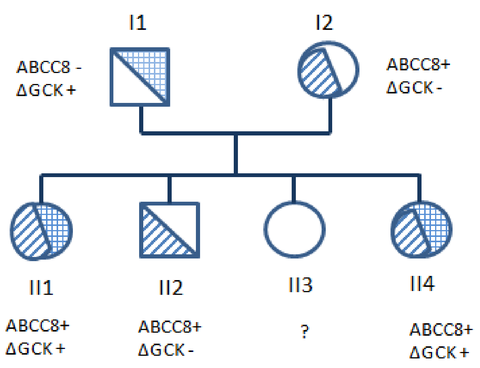
METHODS

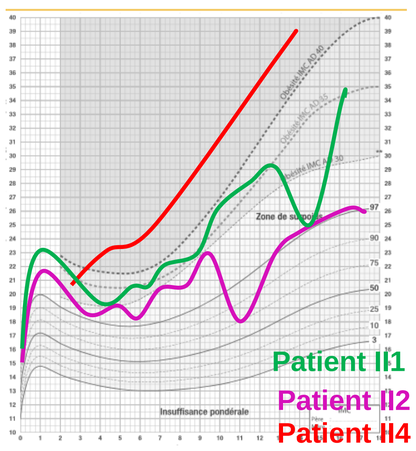
Next generation sequencing (NGS) analysis of a panel of genes (*GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *ABCC8*, *KCNJ11*, *INS)* with a role in insulin secretion was applied to 2 index cases. Segregation analysis was subsequently performed by Sanger sequencing and quantitative PCR (MLPA) in relatives.

RESULTS

First family

- Index case II1: diagnosis in childhood
- Brother and a sister diagnosed at 10 and 15 years
- All are auto-antibody negatives for diabetes.
- Family history of “T2D”
- Variable phenotype and evolution (see table below).





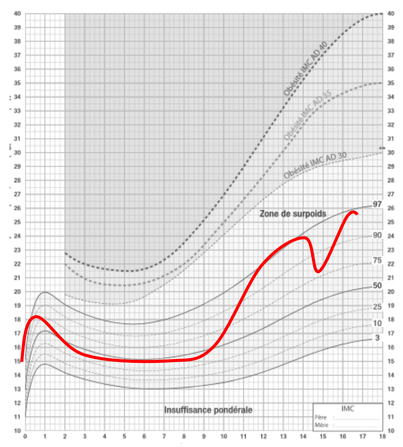
Patient	Genotype		Sex	Age of diagnosis	Circumstances of diagnosis	BMI max before diagnosis (adult equivalent)	Acanthosis nigricans	HBA1c (%)	Therapeutics	Results
	ABCC8	ΔGCK								
I1	-	+	M	-	-	-	-	-	-	-
I2	+	-	F	20				8,4	OAD+ Insulin	
II1	+	+	F	13	Screening	26	No	7,2	Diet only	HbA1c between 6 and 7
II2	+	-	M	15	SPUPD, HGT>3g/L	35	Yes	14	OAD+ Insulin	HbA1c always >12%, adherence problems
II3	?	?	F	18	Screening	-	-	6,5	No treatment since diagnosis	HbA1c remains 6,5%
II4	+	+	F	12	Screening	40 (since age of 4)	No	8,2	Metformin + diet	HbA1c remains >7,5%, lost of follow during 3 years : HbA1c 10%

Genetic testing (NGS):
- deletion of the glucokinase gene (paternal inheritance)
- mutation in the ABCC8 gene (maternal inheritance)
- or both (II1 and II4)

helps understand the heterogeneity of clinical presentation and evolution in family members

Second family

- Index case : 15 years old girl
- Consanguineous parents
- Father diagnosed with T2D at 44 years with normal BMI (17 kg/m^2), well controlled with oral therapy
- Born small for gestational age
- Overweight with acanthosis nigricans
- HbA1c = 14% at diagnosis
- No ketosis



- Low dose of insulin initually (4 U/d) in association with metformin
- Well controlled 6 month after diagnosis (HbA1c = 6,8%) with diet and Metformin.
- All diabetes antibodies negative (GAD, IA2, IAA, ICA, ZnT8).
- 3 sisters with normal fasting blood glucose level, her 2 brothers refused the blood sample
- No argument for a MODY 3, 5 or 7 (abdominal ultrasound).

Genetic testing (NGS):
- novel pathogenic missense mutation in the insulin gene also present in the father : c.85C>T exon 2

CONCLUSIONS

NGS appears as an essential tool to identify rare causes of monogenic diabetes. The two case reports highlight its importance for the etiological diagnosis of atypical forms of diabetes, to allow an accurate diagnosis and an appropriate management.

The authors have nothing to disclose.

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Diabetes
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