

Maturity-Onset Diabetes of the Young Identified Among Algerian Proband with Early-Onset Diabetes

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Aim: To investigate the prevalence of variants within selected maturity-onset diabetes of the young (MODY)-genes among Algerian patients initially diagnosed with type 1 diabetes (T1D) or type 2 diabetes (T2D), yet presenting with a MODY-like phenotype.

Methods: Eight unrelated patients with early-onset diabetes (before 30 years) and six relatives with diabetes were examined by targeted re-sequencing for variants in genes known to be involved in MODY (*HNFL1A*, *GCK*, *HNFA4A*, *HNFB1B*, *INS*, *ABCC8*, *KCNJ11*). Clinical data for probands were retrieved from hospital records.

Results: A total of 12 variants were identified, of which three were classified as pathogenic and one as a variant of uncertain clinical significance (VUS). Two of the pathogenic variants were found in *GCK* (p.Gly261Arg and p.Met210Lys, respectively) in one proband each and the remaining pathogenic variant was found in *HNFB1B* (p.Gly76Cys) in a proband also carrying the VUS in *HNFL1A* (p.Thr156Met).

Conclusion: Variants in known MODY-genes can be the cause of early-onset diabetes in Algerians diagnosed with T1D or T2D among patients presenting with a MODY-like phenotype; thus, genetic screening should be considered.

Keywords: MODY, type 1 diabetes, early-onset, monogenic diabetes, genes

Introduction

The monogenic form of diabetes called Maturity-Onset Diabetes of the Young (MODY) is a heterogeneous form of diabetes caused by variants in specific genes of which the majority affects insulin secretion.¹ It is characterized by an autosomal-dominant mode of inheritance, onset before 25 years of age and a preservation of insulin secretion with detectable C-peptide outside the “honeymoon” period.²⁻⁴ To date, at least fourteen subtypes of MODY have been found which are caused by variants in genes implicated in pancreatic development, insulin biosynthesis and/or secretion: *HNFA4A* (MODY1), *GCK* (MODY2), *HNFL1A* (MODY3), *PDX1* (MODY4), *HNFB1B* (MODY5), *NEUROD1* (MODY6), *KLF11* (MODY7), *CEL* (MODY8), *PAX4* (MODY9), *INS* (MODY10), *BLK* (MODY11), *ABCC8* (MODY12), *KCNJ11* (MODY13) and *RFX6* (MODY14).^{5,6} These various MODY subtypes differ in clinical manifestation: age of onset, severity of hyperglycemia, risk of complications, response to treatment and associated extrapancreatic manifestations.⁷ *GCK*-MODY patients usually do not require any pharmacological treatment and do not develop comorbidities⁸ whereas carriers of variants in the two transcription factors *HNFL1A* and *HNFA4A*, as well as the two genes (*ABCC8* and *KCNJ11*) encoding a beta-cell K-ATP

channel, are sensitive to sulphonylurea treatment.^{8–10} In contrast, patients carrying variants in the insulin gene (*INS*) will very likely require insulin therapy.¹¹ Therefore, molecular genetic diagnosis is crucial as it anticipates the patient's prognosis and can influence treatment decisions. In addition, a molecular genetic diagnosis can lead to early clinical care of asymptomatic relatives.^{12,13}

Previous studies of the prevalence and etiology of MODY have most commonly been investigated in Caucasians and have shown that MODY represents about 1–2% of diabetes among Europeans¹⁴ with a predominance of MODY2 (*GCK*-MODY) and MODY3 (*HNF1A*-MODY).^{15,16} Studies investigating the prevalence of different forms of diabetes in Algeria are however limited.¹⁷ The prevalence and etiology of MODY may be different in Algeria due to differences in genetic ancestry and the long tradition of consanguine marriages¹⁷ and only one previous study has examined the presence of MODY in Algeria which reported one family with MODY caused by the p.Arg85Trp *GCK* variant.¹⁸ Due to the possibility to target treatment according to the genetic etiology in patients carrying variants within *HNF4A*, *GCK*, *HNF1A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ11*, it is important to establish if variants within these known MODY-genes are the cause of early-onset diabetes in Algerian patients.

In the present paper, we aim to assess if the presence of pathogenic variants in *HNF4A*, *GCK*, *HNF1A*, *HNF1B*, *INS*, *ABCC* and, *KCNJ11* is the cause of diabetes in Algerian patients with an early onset (before 30 years of age) initially diagnosed with type 1 diabetes (T1D) or type 2 diabetes (T2D), yet, presenting with a MODY-like phenotype.

Patients and Methods

Patients

Our study included eight probands (seven males and one female) diagnosed with T1D except for one patient (P4) initially diagnosed with T2D. In addition, six family members with diabetes (two males and four females) were included (Table S1). In addition to being diagnosed with early-onset diabetes, probands were selected due to suspicion of MODY as they had at least three of the following features: 1) a family history of diabetes mimicking an autosomal-dominant inheritance (Figure 1 and Figure S1), 2) young age at diabetes diagnosis (< 30 years old), 3) diabetes managed with oral hypoglycemic agents (OHA) or low insulin doses (≤ 0.5 U/Kg/J) at least three years after

diagnosis, 4) BMI < 30 kg/m², 5) decreased renal threshold for glycosuria and 6) anti-body negative (when antibodies are measured) (Table 1). The patients were recruited from University Hospital Mustapha Pacha, Central Hospital of Army, Djillali Bounaâma Hospital and Parnet Hospital. Proband were from families without known consanguinity. The present study was approved by the local ethics committee "Algerian National Agency for Research in Health Sciences, ATRSS ex-ANDRS" in compliance with Helsinki declaration (Code number 43-ANDRS-2011). After obtainment of written informed consent from all participants including consent to publish familial case descriptions (from parents for participants under 18 years old), blood samples were collected for biochemical, immunological and genetic studies.

The mean age-of-diagnosis for probands was 22.5 ± 6.2 years old [range 9–27 years old], the diabetes duration was 6.4 ± 3.4 years [range 0.5–10 years] and the mean value of BMI was of 21.7 ± 2.6 kg/m² [range 18–24.7 kg/m²] at the latest examination.

Clinical Data Collection, Biochemical and Immunological Measurements

The family history of diabetes, BMI, age at diabetes diagnosis, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) at diagnosis and treatment history were collected from hospital records. The treatment information included in Table S1 is from the latest examination.

Blood samples were drawn for DNA extraction and measurement of FPG, plasma lipids and HbA1c. Moreover, β cells autoantibodies (Tyrosine phosphatase (IA2) and/or Glutamic Acid Decarboxylase (GAD) autoantibodies) were measured in probands. Endogenous insulin production was assessed in patients by measuring C-peptide concentrations at the last examination.

Assays

Measurement of HbA1c was performed by High-Performance Liquid Chromatography HPLC (Tosoh G8, Japan); plasma glucose, plasma triglycerides, total plasma cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were evaluated on the automatic analyser (BiOLiS 24i, Japan), C-peptide by chemiluminescence Immuno-Assay (LIAISON[®], DiaSorin, Germany) and IA2 and/or GAD auto-antibodies (GADA) by ELISA (*Enzyme-Linked ImmunoSorbent Assay*) (ELISA plate reader, PR 3100. BioRad, USA).

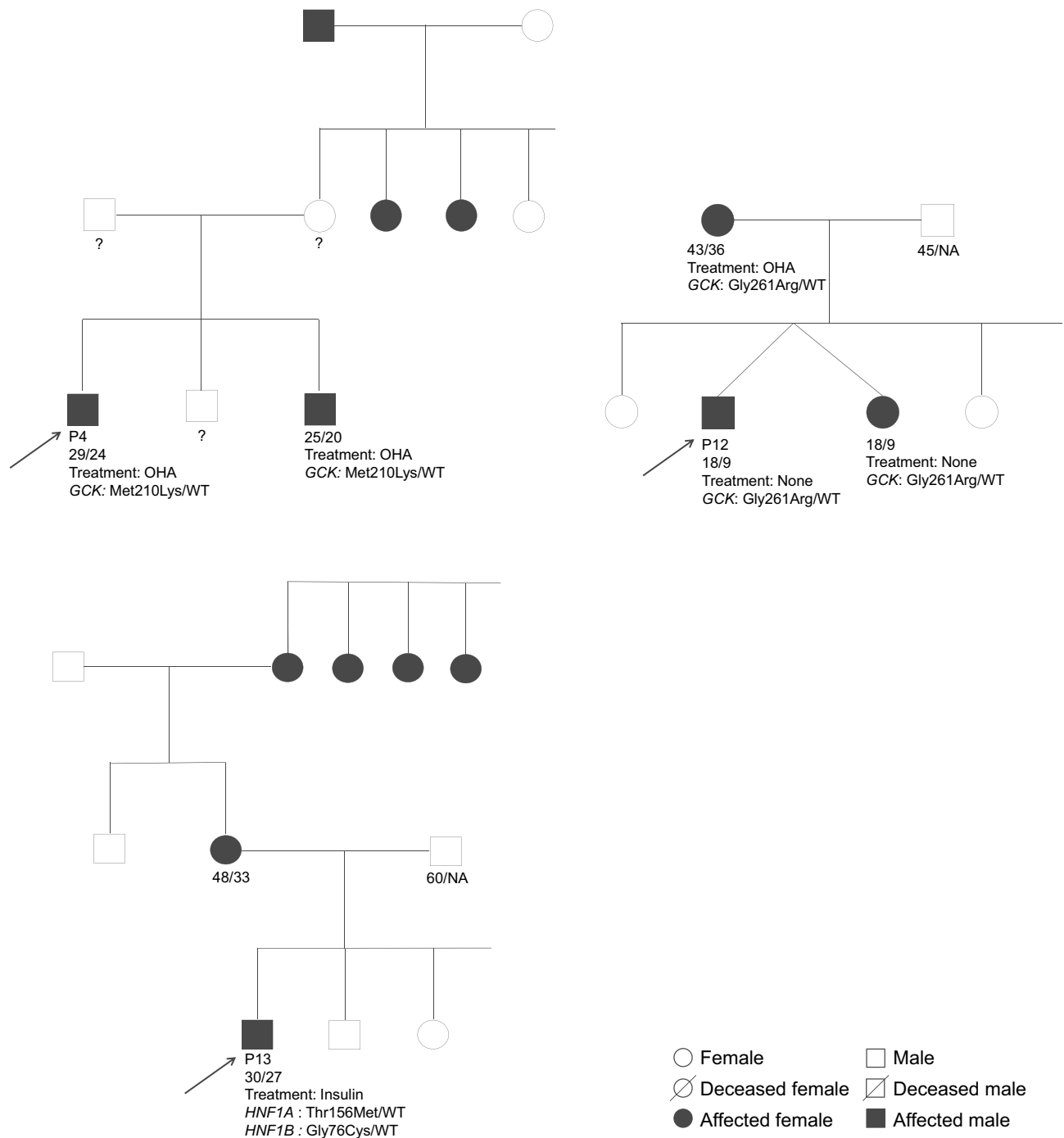


Figure 1 Pedigrees of the families 4, 12 and 13 where pathogenic variants were identified.

Notes: The P-numbers indicate subjects undergone genetic investigation and the numbers below indicate the age at the last examination/age at diabetes onset (years). Squares represent males and circles indicate females. Black symbols indicate subjects with manifested diabetes and white symbols indicate healthy or non-investigated members. The arrow indicates the proband. Abbreviations: WT, wild-type allele; NA, not applicable.

Screening for HNF1B Alterations

For patients having *HNF1B* variants, additional measurements were performed, including serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ -glutamyl transferase (GGT), serum uric acid, creatinine and potassium, measured on a Cobas 400⁺ Analyser.

Molecular Analysis

Genomic DNA was extracted from peripheral whole blood by standard methods.¹⁹ DNA concentration and purity were determined using a NanoDrop (MaestroNano Spectrophotometer, MAESTROGEN Technologies, TAIWAN) and adjusted to 100ng/ μ L. Targeted regions,

Table 1 Clinical and Laboratory Characteristics of the Eight Probands

Trait	Mean ± SD	Range
Men/women	7/1	–
Age at examination (years)	28.9 ± 5.36	18.0–37.0
Age at diagnosis (years)	22.5 ± 6.23	9.00–27.0
Duration of diabetes (years)	6.44 ± 3.42	0.50–10.0
BMI (kg/m ²)	21.7 ± 2.6	18.0–24.7
Fasting plasma glucose (mmol/l)	8.49 ± 3.66	4.77–15.8
HbA1c (%)	7.56 ± 2.81	5.30–12.8
HbA1c (mmol/mol)	54.4 ± 28.67	34.4–116.4
C-peptide (nmol/l)	0.47 ± 0.26	0.22–1.01
Triglycerides (mmol/l)	1.11 ± 0.32	0.77–1.70
Total cholesterol (mmol/l)	4.34 ± 0.87	3.18–5.65
LDL-cholesterol (mmol/l)	2.85 ± 1.05	1.28–4.01
HDL-cholesterol (mmol/l)	1.13 ± 0.39	0.77–1.70
Treatment at last examination(Diet/OHA/Insulin/Insulin + OHA)	1/1/4/2	-

including the coding regions and exon/intron boundaries of the *HNF4A*, *GCK*, *HNF1A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ11* genes, were captured and sequenced using the Illumina HiSeq2000 Analyzer as described.²⁰ Obtained results were analyzed for sequence variations using the SeqScape Software (Applied Biosystems) by comparison with published reference sequences (NM_175914, NM_000162, NM_000545.5, NM_000458.2, NM_000207.2, NM_000352 and NM_000525). Variants were classified as being either pathogenic, likely pathogenic, variants of uncertain significance (VUS) or benign, based on the standards and guidelines from American Collee of Medical Genetics and Genomics and the Association for Molecular Pathology.²¹ This classification is based on 1) the location and function of variant, 2) minor allele frequency (MAF) in both the Gnomad database²² and a Middle Eastern reference population,²³ 3) previous information of variants being involved in MODY,^{24–26} 4) predicted functionality based on changes in thermostability²⁵ or CADD score (<http://cadd.gs.washington.edu/info>) and 5) information of the prevalence of variants in house database of approximately 6000 Danish population-based non-diabetic individuals²⁷ in which the above genes were sequenced.

Results

Clinical Description of Probands

Clinical and biochemical characteristics of the probands are summarized in [Table 1](#) and immunological data are presented in [Table S1](#).

A total of 12 variants were found in *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ11*. Eight variants were classified as benign, three as pathogenic, and one as a VUS ([Table 2](#)). The identified pathogenic variants have previously been found in MODY families.^{24,28}

Family 4

The proband in family 4 (P4) was heterozygous for the pathogenic substitution c. 629T>A in the *GCK* gene, resulting in the p.Met210Lys variant. This patient was diagnosed with diabetes incidentally at age 24 years old, after pre-employment medical checkup that revealed a fasting plasma glucose of 7.11 mmol/l. Subsequent blood glucose monitoring showed that fasting plasma glucose and post-prandial glucose reached 8.89 mmol/l and 11.11 mmol/l, respectively. The patient P4 was initially treated with metformin and then with gliclazide 80 mg twice a day. However, the treatment at the latest examination was 850 mg metformin 3 times a day. HbA1c values ranged between 6.70% (49.7 mmol/mol) and 7.21% (55.3 mmol/mol). A recent oral glucose tolerance test (OGTT) (performed in 2019) showed fasting plasma glucose levels of 8.55 mmol/l and levels of 7.83 mmol/l 120 min after glucose intake.

The brother of P4 ([Figure 1](#)) was also heterozygous for this *GCK* variant. At diagnosis, fasting plasma glucose levels of 6.89 mmol/l were found with subsequent

Table 2 Variants Identified in MODY-Genes and Their Pathogenicity Classification

Variant	Amino Acid Position	MAF (Gnomad ²²)	MAF (GME ²³)	Classification According to ACMG ²¹
<i>GCK</i>	M210K	0.0004%	0%	Pathogenic
	G261R	0.0004%	0%	Pathogenic
<i>HNF4A</i>	I441V	0.03%	2%	Benign
<i>HNF1B</i>	G76C*	0.055%	0.2%	Pathogenic
<i>HNF1A</i>	I27L	35%	43%	Benign
	T156M*	0.007%	0%	VUS
	S487N	35%	42%	Benign
<i>ABCC8</i>	V1572I	5%	9%	Benign
	A1369S	63%	73%	Benign
<i>KCNJ11</i>	K23E	64%	73%	Benign
	L270V	4%	4%	Benign
	V337I	64%	73%	Benign

Note: *Variants found in the same proband.

Abbreviations: ACMG, American Collee of Medical Genetics and Genomics; GME, Greater Middle East.

measures at fasting and 2-h glucose of 7.78 mmol/l and 7.72 mmol/l, respectively.

Family 12

The proband from family 12 (P12) (Figure 1) was carrying two variants: Ile441Val in *HNF4A* (c.1321A>G) and Gly261Arg in *GCK* (c.784G>A). Only the *GCK* Gly261Arg variant is considered pathogenic. Genetic screening of additionally two family members with diabetes from family 12 (twin sister and mother) revealed that both were carriers of the *GCK* Gly261Arg variant but not the *HNF4A* Ile441Val.

The proband of this family was born at term from non-consanguineous parents with a birth-weight of 2.95 kg. He was lethargic during infancy. In 2010 (aged 9 years old) he was admitted to the hospital for surgical intervention for hernia, and a routine laboratory test was performed which revealed impaired fasting glucose and subsequently an HbA1c value of 7.0% (53.0 mmol/mol). Insulin therapy was immediately initiated with 4x2U/day and this dosage was preserved for 8 years. The proband's blood glucose was measured over a period of 8 years and HbA1c levels ranged between 5.4% (35.5 mmol/mol) and 7.0% (53.0 mmol/mol) and random blood glucose ranged between 4.94 and 8.89 mmol/l. During a routine visit in 2018, the patient revealed that insulin therapy had not been taken regularly for approximately one year. Yet, his fasting plasma glucose level was below 8.05 mmol/l, post-prandial values stayed below 11.11 mmol/l and fasting fingertip blood glucose values ranged between 4.17 and 7.22 mmol/l. His most recent HbA1c value was 5.5% (36.6 mmol/mol). In addition to diabetes, the patient experienced four epileptic seizures between 2017 and 2018. Three of these experienced while treated with insulin and during the most severe attack, hypoglycemia was detected with a value of 2.22 mmol/l.

The proband's twin sister was also diagnosed with diabetes in 2010 with an HbA1c value of 7.0% (53.0 mmol/mol). Thus, insulin treatment was initiated with a dosage of 4 x 2U/day. After insulin omission, her fingertip blood glucose ranged between 5.44 and 7.94 mmol/l and her random blood glucose ranged between 6.39 and 8.33 mmol/l, except for one measure of 9.78 mmol/l during illness. Her most recent HbA1c value is 6.0% (42.1 mmol/mol). The proband's mother was diagnosed with diabetes in 2011 and OHA treatment (metformin, glimepiride) was initiated. She has remained on this treatment regime as she has obtained a good glycemic control, with HbA1c values below 7.0% (53.0 mmol/mol). The proband's father, elder and younger

sisters all have fingertip blood glucose levels within the normal range (4.17 to 5.00 mmol/l).

Family 13

The proband in family 13 (P13) is a carrier of both a heterozygous pathogenic missense variant in *HNF1B*, (c. 226G>T; Gly76Cys) and the variant in *HNF1A* (c.467C>T; Thr156Met) with an uncertain clinical significance. The mother, maternal grandmother and maternal grandmother's sisters are all diagnosed with diabetes (Figure 1); however, DNA and clinical information is available only for the proband.

Before diabetes onset, the proband was obese (BMI=31.7 kg/m²). He was diagnosed with diabetes at age 27, after manifesting polyuria, polydipsia, marked weight loss (~40 Kg) and ketosis. Diabetes was diagnosed based on a blood sample revealing a random blood glucose of 33.05 mmol/l. Insulin treatment was initiated. At age 29 years old (nearly 3 years after diabetes diagnosis), he was admitted to the hospital after suffering from asthenia and incoercible vomiting accompanied by ketosis. The patient's weight was now 55 kg with a BMI of 18.4 kg/m². Biochemical analyses revealed hypokalemia (2.5 mmol/l), increased bilirubin and liver enzymes levels (ALT, AST and GGT), negativity for GADA (Table 3), a fasting C-peptide level of 0.83 basal and 1.12 nmol/l after glucagon stimulation. In order to elucidate the etiology of the incoercible vomiting, an abdominal pelvis ultrasound and computed tomography (CT) scan was performed and the obtained imaging showed the nutcracker syndrome (Wilkie syndrome) and nephrolithiasis,

Table 3 Results of Biochemical Investigation of Proband P13

Parameters	Measurement Results		Reference Ranges
	At Hospital Admission	At Follow-Up	
FPG (mmol/l)	7.00	5.88	3.88–6.10
Creatinine (mg/l)	4.00	5.00	7.00–12.0
Serum uric acid(mg/l)	32.0	23.8	36.0–77.0
AST (U/L)	57.0	21.0	10.0–50.0
ALT (U/L)	146	10.0	10.0–50.0
GGT (U/L)	113	NA	8.00–61.0
ALP (U/L)	69.0	140	< 125
CRP (mg/l)	0.1	0.70	< 5.00
Bilirubin (mg/l)	19.0	NA	< 10.0
Direct bilirubin (mg/l)	11.0	NA	< 2.00
Indirect bilirubin (mg/l)	8.00	NA	< 8.00

Abbreviations: ALP, alkaline phosphatase; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ -glutamyl transpeptidase; NA, not available.

without any renal, pancreatic or urogenital tracts malformations.

Discussion

The present study demonstrates the presence of the monogenic form of diabetes, MODY, in three out of eight (38%) Algerian North-African patients with early-onset diabetes. In our cohort, the majority of patients were initially diagnosed with T1D based on their young age at diabetes onset and a normal BMI, demonstrating the risk of MODY being misclassified as T1D and underlining the importance of genetic screening. The pathogenic variants identified have all previously been observed in MODY families^{24,28,29} and are therefore not specific to the Algerian population.

Two probands carrying pathogenic variants within *GCK* were identified and both were diagnosed incidentally and not due to the presence of diabetes symptoms. This is of little surprise, as diabetes caused by variants in *GCK* is characterized by only mildly elevated levels of plasma glucose.³⁰ Several of the carriers had received insulin treatment, yet *GCK*-MODY patients are not responsive to oral hypoglycaemic agents such as sulphonylurea or metformin or low-dose insulin³¹ nor do they require treatment as *GCK*-MODY is not associated with progression or risk of comorbidities. Thus, cessation of treatment is recommended to the carriers of pathogenic *GCK* variants identified in the present study.

The *GCK* variant Met210Lys variant found in family P4 has previously been associated with diabetes, impaired glucose tolerance or impaired fasting glucose among related Norwegian subjects by altering glucokinase kinetic parameters.³² This is comparable to the clinical presentation in the identified family.

The second *GCK* variant identified in family P19, Gly261Arg, has been reported in patients with the clinical features of MODY from different populations^{33–41} and has previously been described in a homozygous state in patients with neonatal diabetes.^{42,43} Furthermore, functional studies performed by Gidh-Jain et al (1993)⁴⁴ and Davis et al (1999)⁴⁵ of this variant have revealed that it affects kinetic parameters. Thus, the phenotype of the twin sister and the mother of proband 12, is consistent with *GCK*-MODY phenotype, which is characterized by fasting plasma glucose levels ranging between 5.5 and 8.5 mmol/l, as previously established by the ISPAD consensus guidelines (International Society for Pediatric and Adolescent Diabetes).⁴⁶ Discontinuation of therapy will therefore be initiated.

The Gly76Cys variant in *HNF1B* was present in proband P13. The clinical presentation of proband P13 is consistent with the presence of a pathogenic *HNF1B*-MODY variant by the presence of fluctuant elevation of ALAT, ASAT, GGT and ALP and frequent hypokalemia.⁴⁷ This variant has previously been reported in a fetus with bilateral multicystic dysplasia from North African parents⁴⁸ and in two probands with renal anomalies.⁴⁹ This patient was also a carrier of an *HNF1A*-MODY variant of unknown clinical significance; thus, whether the presence of low CRP concentrations⁵⁰ within this patient is a consequence of the *HNF1A* variant, is uncertain. As DNA was not available from the parents, it was not possible to establish whether the two variants cosegregate with diabetes, and thus causality could not be further examined. Based on the genetic diagnosis, the recommended treatment for this patient is sulphonylurea or insulin.⁵¹

Previous studies examining the prevalence of MODY, have for the majority been performed among Caucasians.¹⁶ However, it is of great importance to investigate other populations as they may identify deviating prevalences as well as clinical characteristics. Studies of *HNF1A* have found that 9% of South Asian MODY patients⁵¹ and 5% of Korean MODY patients are carriers of causal *HNF1A* variants, whereas 14% have been found in Japanese pediatric patients.^{52,53} For *GCK*, a prevalence of 2.5% were found in Korean MODY patients in contrast to 23% among Japanese pediatric patients.^{52–53} Thus, genetic investigation of different ethnicities is key.

The misdiagnosis observed in the present study has also previously been observed. In a study among patients stringently defined as T1D diabetes, nearly 8% had monogenic diabetes variants.⁵⁵ Another study investigating the prevalence of MODY variants in antibody-negative children with diabetes found that 4.1% of these children were carrying pathogenic MODY-variants.⁵⁶ These studies, as well as the present study, illustrate the importance of considering genetic testing in early-onset diabetes to initiate an appropriate intervention.

The limitation of the current study is the small number of included patients. This allows only the conclusion that common forms of MODY exist in Algerian patients with early-onset diabetes. In the present study, more than one third of the patients carried MODY variants; however, whether this prevalence is representative for a larger population cannot be determined.

Conclusion

Pathogenic variants in genes linked to common forms of MODY could explain the etiology of early-onset diabetes among Algerian patients; thus, sequencing of these genes should be considered, as the correct diagnosis can instigate accurate intervention and early diagnosis in family members.

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Author Contributions

FB, APG, TH, RR and CTB contributed to the conception and design of the study. MA, SAA, AEG, FB, BO, FL, AC and AB examined and performed the clinical evaluation of the patients in each family. FB prepared the genomic DNA samples. FB and APG performed the analysis and all authors contributed to the interpretation of data. SA and LY performed biochemical analysis and interpretation of the data. FB and APG drafted the article. Literature search was performed by FB and APG and figures were prepared by FB and APG. All authors have agreed on the journal, critically revised the manuscript, contributed to the discussion and take responsibility and are accountable for the contents of the article. The final version of the paper was read and approved by all authors.

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Disclosure

The authors declare that they have no conflicts of interest.

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