Investigating the Impact of HNF1-A Gene Exon 5 Mutations on Suspected cases of Maturity Onset Diabetes of the Young type three in Egyptian Children

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Abstract

Background: Currently, maturity onset diabetes of the young (MODY) is linked to 1-5% of Diabetes mellitus patients. To determine a MODY diagnosis, predict a probable clinical course and determine the family at risk, and identify a course of treatment, genetic analysis is needed.

Objectives: The Present study aims to detect mutation in exon 5 of hepatocyte nuclear factor -1- alpha (HNF1A) gene in suspected MODY3 cases.

Patients and methods: This case-control study, included 20 Egyptian diabetic patients and 10 healthy children as a control group. All cases were subject to full history taking, complete clinical examination and investigation as serum biomarkers for C-peptide assays, glycated hemoglobin (HbA1c), fasting and 2h post-prandial blood sugar levels, Anti-Gad and Anti-Islet antibodies and genetic analysis for HNF1A gene exon 5 revealed no abnormalities.

Results: The cases group included 9 males and 11 females, their mean age was 13.63±2.74 years, all cases (100%) had a positive family history of DM, and none had neonatal hypo or hyperglycemia and none had previous DKA. All cases were negative for Anti-Gad and Anti-Islet. The mean age on onset of DM was 11.08 ± 2.77 years, the mean duration of DM was 2.2 ± 0.16 years. 5% of cases were treated by oral hypoglycemic, 15 % were treated by insulin and oral hypoglycemic drugs, 15% were managed by healthy lifestyle and 65% of cases treated by insulin with a mean dose 0.34 ± 0.19**.** DNA sequencing of exon 5 reveals a normal exon with no variation detected.

Conclusion: Due to phenotypic similarities, DNA sequencing for 10 Exons of HNF1A gene is advised if negative followed by Glucokinase (GCK), HNF1B, and HNF4A is strongly advised in cases where clinical suspicion of MODY exists.

Keywords: MODY; HNF1-A; Gene Mutations; Exon 5.

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Introduction

MODY, a variant of noninsulin-dependent diabetes mellitus (NIDDM), follows an autosomal dominant inheritance pattern. It is characterized by mild fasting hyperglycemia, with average levels around 7 mmol/L and a median glycated hemoglobin (HbA1C) of 6.5 percent. These elevated blood sugar levels are present from birth and gradually increase as individuals age. In contrast to autoimmune or insulin-resistant conditions, MODY doesn't typically exhibit associated symptoms. Furthermore, individuals with MODY maintain their ability to naturally produce insulin **(Jang, 2020).**

Accurately determining the global incidence of MODY is challenging due to frequent misdiagnosis as diabetes mellitus of type 1 or type 2. Additionally, its rarity leads to variations in occurrence among different populations **(Behl et al., 2022).** Molecular genetic studies on MODY families have revealed that it is not a single condition but rather a diverse condition involving variations in metabolism, genetics, and clinical presentation. These variations result from mutations in a single gene crucial for the proper function of pancreatic beta-cells. Moreover, monogenic diabetes, including MODY, represents the most common form of diabetes mellitus **(Sanyoura et al., 2018).** Currently, MODY-related cases account for approximately 1–5% of all diabetes mellitus cases **(Hoffman et al., 2021).**

Through genetic research, scientists have identified 15 distinct genes responsible for causing MODY, such as the HNF4α gene in MODY1, GCK gene in MODY2, HNF1α-gene in MODY3, and HNF-1β gene in MODY5. Mutations in these genes can predispose individuals to develop MODY **(Oliveira et al., 2020).** The development and activity of pancreatic beta-islet cells are greatly affected by the transcription factor HNF1A. Both endocrine and exocrine cells in the pancreas express HNF1A during the developmental stage. This transcription factor is essential for insulin secretion in response to glucose **(Beysel et al., 2019).**

The HNF1A gene, which can be found on chromosome 12q24.31, has 10 exons and an overall span of 23,790 bp. HNF1A encodes a protein of 631 amino acids. In individuals with HNF1A-MODY(MODY3), a correct diagnosis allows for a transition from insulin or metformin to sulfonylureas or meglitinides, resulting in sustained improvements in diabetes management **(Chandran et al., 2020).** Cases with HNF1A allelic variants typically present a strong family history of diabetes, early onset of diabetes (usually before the age of 25), and independence from insulin, as indicated by the presence of C-peptide, even after a prolonged duration of the disease. Most individuals with MODY do not exhibit signs of insulin resistance, and their body mass index falls within the normal range **(Pavić et al., 2018).**

Exon 5, often referred to as the mutational hotspot, shows a high frequency of MODY3 mutations within HNF1α. These mutations are scattered throughout the coding region of the HNF1α gene, with a concentration in exon 5 **(Ghosal et al., 2012).** The aim of this study is to find the mutation in exon 5 of the HNF1 gene in possible instances of MODY3 and study their relationships to clinical characteristics in patients, including age at disease onset, insulin needs, family history and complications.

Patients and methods

This case- control study was conducted in the period between October 2019 and December 2022 and included 20 diabetic patients (9 male and 11 female) aged from 10-18 years following up in the Diabetes Endocrinology & Metabolism Pediatric Unit, Children Hospital, Cairo University and pediatric endocrine unit in Aswan University Hospital and 10 healthy children (5 male and 5 female) as a control group. variants in exon 5 of the HNF1A gene tested in the patients. At pediatric diabetes clinics at Cairo university and Aswan university hospitals, Children who met the criteria for MODY screening conducted a review of clinical, biochemical, phenotypical, and outcomes.

All enrolled patients met the screening requirements, and the conditions for inclusion and exclusion are described below. their guardians provided informed written consent, the Ethical committee number is *19 /9/407.*

Criteria for inclusion: Patients suspected to have MODY3 were included and ranged in age from 10 to 18 years, Positive family history of diabetes in young age in 3 successive generations before 25 years, detectable C-peptide (> 0.2 nmol/L) in presence of hyperglycemia negative for Anti-Gad and Anti-Islet, low insulin dose (less than 0.5 U/kg/day) **(Mayer-Davis et al., 2018)**.

Criteria for exclusion: The study avoids patients with type 2 diabetes, secondary causes of diabetes, previous episodes of diabetic ketoacidosis, and signs of diabetes type 2 (obesity, acanthosis nigricans).

All patients underwent thorough history taking, full clinical examination and anthropometric measurements.

Laboratory investigations: Serum biomarkers for fasting and 2h post-prandial blood sugar levels, mean cholesterol, mean triglyceride, C-peptide assays, HbA1c, Anti-Gad and Anti-Islets are recruited from patient file.

Genetic analysis: The HNF1A gene's exon 5 completed genetic study using DNA sequencing in the way described below: Sample collection and preparation: A clean vacutainer containing "EDTA" was used to draw up three milliliters of venous blood. They underwent the following processes: DNA extraction, DNA concentration measurement, DNA amplification through Polymerase Chain Reaction, detection of amplified products using the primer sequences described in (**Table.1**)., DNA purification, and detection of purified products. They had either immediately treated or stored at - 20 ºC, to undergo additional cleaning, long-Read Capillary Electrophoresis, and DNA cycle sequencing (**Fig.1**).

Table 1. Forward and reverse primers sequence for HNF1A gene (exons 5). (Boutin et al, 2001)

	Forward primer (5' to 3')	**Reverse primer (5' to 3')**
HNF1A exon 5	GGCAGACAGGCAGATGGCCTA	GCCTCCCTAGGGACTGCTCCA

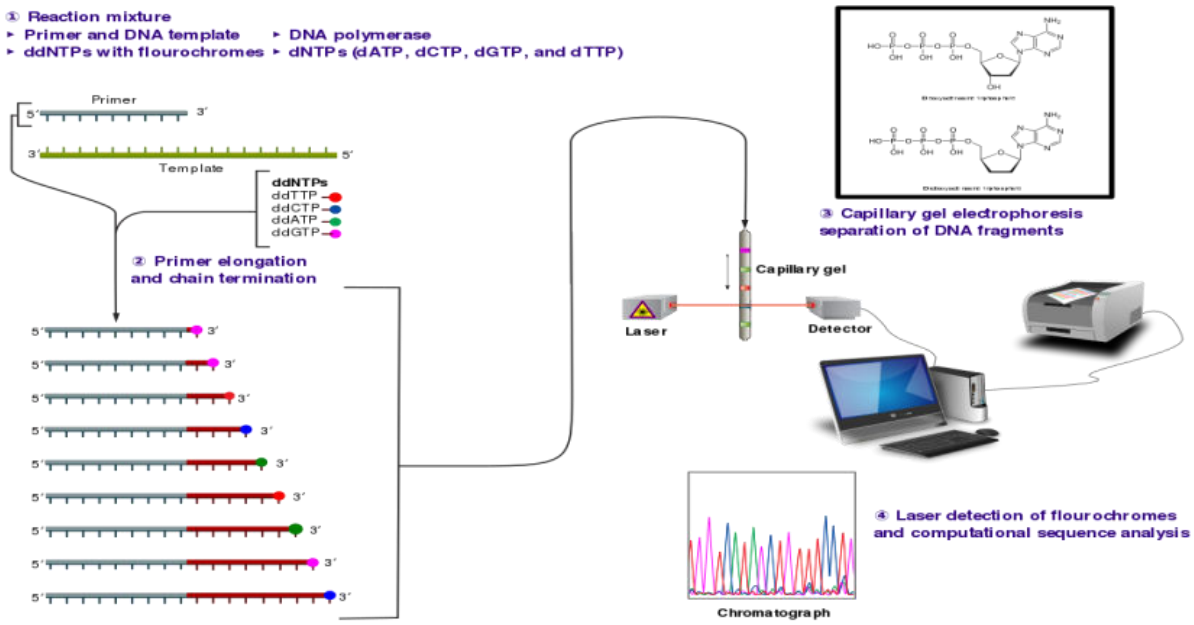

Fig.1. The Sanger (chain-termination) method for DNA sequencing. (Sanger et al, 1977)

Statistical analysis

Statistical Package for Social Science was applied to study, code, and organize the information that was gathered. In order to analyze non-numerical data, descriptive statistics were used, including computing the frequency and percentage as well as the Mean and the standard deviation for parametric numerical data.

For analytical statistics, the Student T-Test was employed to evaluate the statistical significance of differences between the means of the two study groups. Additionally, the Chi-Square test was utilized to investigate the relationship between two qualitative variables. In cases where the expected count was less than 5 in more than 20% of cells, Fisher's exact test was applied.

Statistical significance was evaluated using a p-value, with values less 0.05 being considered significant at the level of confidence of 95%.

Results

The mean age of the studied cases and controls were 13.63±2.74 and 12.50±1.35 years respectively. The percentage of boys and girls were 45% and 55% for cases and 50%: 50% for controls. Three quarters of cases (75%) were from Upper Egypt vs. all controls from upper Egypt (**Table.2**).

Table 2. Studied children demographic and socioeconomic data

Characteristics	Cases (No. 20)		Control (No. 10)		Test of significance #
	No.	%	No.	%	
Mean children age (years)	13.63±2.74		12.50±1.35		P=0.654
Gender					
Male	9	45	5	50	P=0.796
Female	11	55	5	50	

Characteristics	Cases (No. 20)		Control (No. 10)		Test of significance #
	No.	%	No.	%	
Residence					
Upper Egypt	**15**	**75**	**10**	**100**	**P=0.122**
Lower Egypt	**5**	**25**	**0**	**0**	

Regarding pubertal staging, 20% of cases (4 cases) were prepubertal, 80 % (16 cases) were pubertal. The mean height was154.20 ± 12.10 and, mean height SDS was - 0.03 ± 1.09, while mean weight was SDS 0.38 ± 1.0 and, mean BMI SDS 0.49 ± 1.19. Regarding sexual maturity rating, 20% (2 controls) were prepubertal, 80% (8 controls) were pubertal. The mean height was147.80 ± 7.08, the mean height SDS was -0.34 ± 0.72, while mean weight SDS was 0.03 ± 0.6 and mean BMI SDS was 0.36 ± 0.76 (**Table.3**).

Table 3. Anthropometric data and pubertal staging of the studied children

Characteristics	Cases (No. 20)	%	Control (No. 10)	%	Test of significance
Tanner staging					
Prepubertal	4	20	2	20	P=1.000
Pubertal	16	80	8	80	
Mean height (cm)	154.20 ± 12.10		147.80 ± 7.08		P=0.437
Mean height (SDS)	- 0.03 ± 1.09		-0.34 ± 0.72		P=0.332
Mean weight (kg)	51.60 ± 11.87		47.00 ± 7.59		P=0.511
Mean weight (SDS)	0.38 ± 1.07		0.03 ± 0.60		P=0.188
Mean BMI (kg/m^2)	21.52 ± 2.06		21.12 ± 1.96		P=0.837
Mean BMI (SDS)	0.49 ± 1.19		0.36 ± 0.76		P=0.445

* Significant (p<0.05)

The mean fasting blood sugar was significantly higher in the cases group (96.05±17.53 mg/dl) than in the controls (81.20±9.27 mg/dl), p=0.042. The mean postprandial blood sugar was statistically higher in cases group (151.65 ± 16.43 mg/dl) compared to controls (137.00 ± 4.69 md/dl), p<0.001. The mean HbA1c in the cases group (8.23±1.56) was statistically higher than in the controls (4.49±0.45), p=0.001. Regarding the mean levels of TG, c-peptide, and cholesterol (in mg/dl), there was no significant difference between diabetic patients and control group (**Table.4**).

Table 4. Laboratory data of the studied children

Characteristics	Cases		Control		Test of significance
	No. (20)	%	No. (10)	%	
Mean fasting blood sugar(mg/dl)	96.05± 17.53		81.20 ± 9.27		P= 0.042*
Mean post prandial blood sugar (mg/dl)	151.65 ± 16.43		137.00 ± 4.69		P<0.001*
Mean cholesterol level (mg/dl)	94.05 ± 9.84		86.20 ± 8.34		P= 0.651
Mean Triglyceride level(mg/dl)	111.65 ± 14.76		95.90 ± 10.83		P= 0.277
Mean HbA1c% (Glycated	8.23 ± 1.56		4.49 ± 0.45		P= 0.001

Characteristics	Cases		Control		Test of significance
	No. (20)	%	No. (10)	%	
heamoglobin)					
Mean c- peptide (ng/ml)	0.85 ± 0.64		1.66 ± 0.18		P= 0.061

* Significant (p<0.05)

All cases have a family history of diabetes mellitus, and none of the cases had neonatal hypoglycemia or hyperglycemia or previous DKA. All cases were negative for Anti-Gad and Anti-Islet. The mean age of onset of DM was 11.08 ± 2.77 years, the mean duration of DM was 2.2 years. 10% had neuropathy, none of cases had acanthosis nigricans or lipodystrophy. 5% of cases were treated by oral hypoglycemic, 15 % were treated by insulin and oral hypoglycemic drugs, 15% were managed by healthy life style and 65% of cases treated by insulin with a mean dose 0.34 ± 0.19(**Table.5**).

Table 5. Clinical data of the studied cases

Characteristics	Number (N. 20)	%
Positive family history of DM	20	100
Negative history of previous DKA	20	100
Negative history of neonatal hypo/ hyperglycemia	20	100
Mean onset of DM (years)	11.08 ± 2.77	
Mean duration of DM (years)	2.2 ± 0.16	
Clinical examination Acanthosis nigricans Neuropathy Lipodystrophy	 0 2 0	 0 10 0
Negative Anti-Gad	20	100
Management of D.M Insulin Oral hypoglycemic Insulin and oral hypoglycemic drugs Healthy lifestyle	 13 1 3 3	 65 5 15 15
Mean insulin dose	0.34 ±0.19	

The result of genetic sequencing of exon 5: revealed no abnormalities.

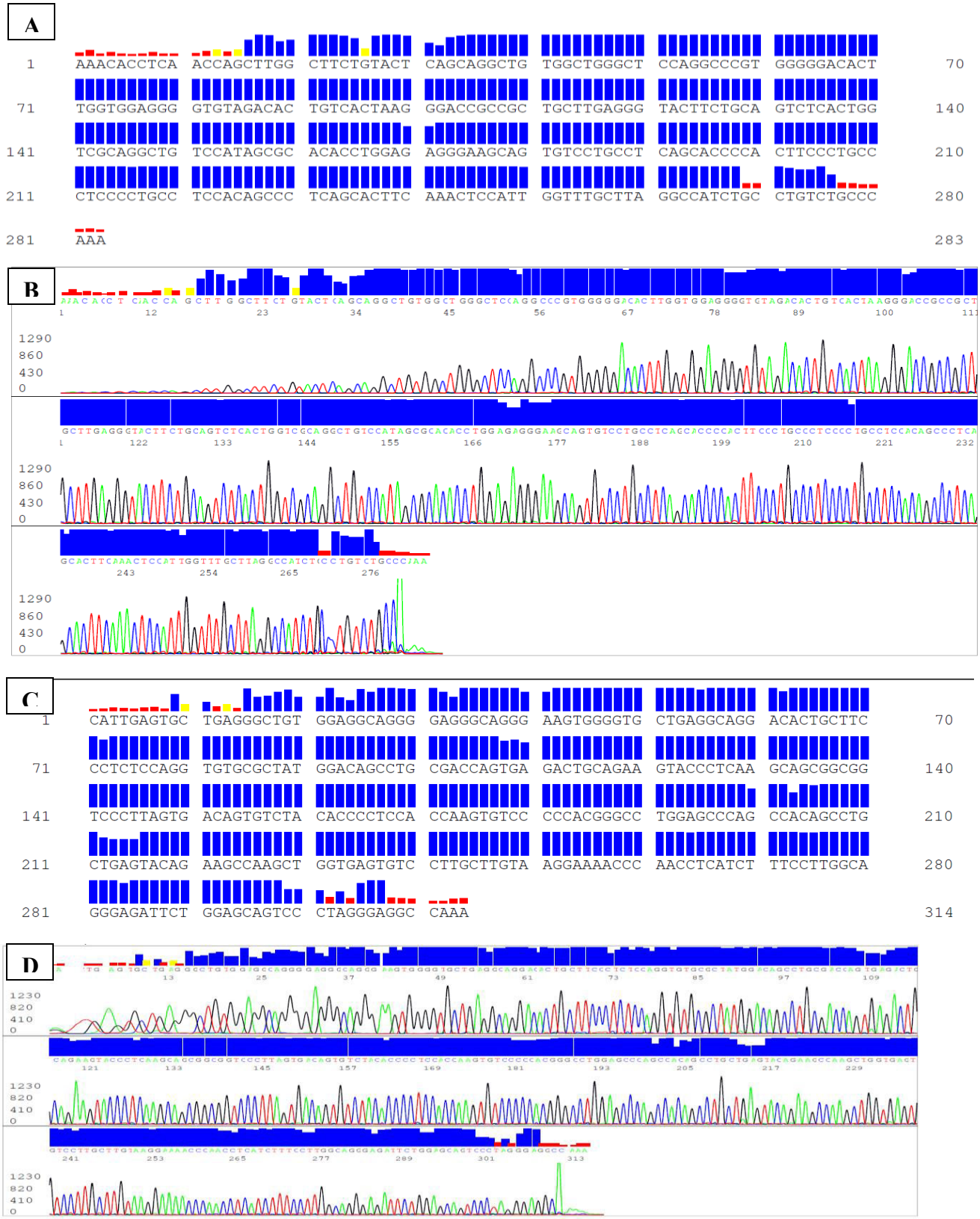

Fig.2. Forward (A &B) and Reverse DNA (C &D) sequencing of exon 5

Discussion

This case control study, included 20 Egyptian diabetic patients aged from 10-18 years and 10 healthy children as a control group. The cases group included 9 males and 11 females, their mean age was 13.63±2.74 years, 75% of cases were from Upper Egypt and 25% were from Lower Egypt. There was no statistical difference between cases and control regarding personal characters.

The cases group included 9 males and 11 females, this was in line with the findings of **Katashima et al.** (2021) in Japan, who enrolled 45 (17 males and 28 females) unrelated diabetic persons who were clinically diagnosed as cases of MODY. They investigated the presence of HNF4 and GCK genetic variants in juvenile study population with onset of DM before the age of seventeen years old. In contrast to the work of **Trhanint et al. (2022)**, who evaluated young adults with diabetes at the genetic and clinical levels in Moroccan households. Twenty patients were included in the analysis, with men making up 60% of the group.

In the current study, the mean age was 13.63±2.74 years, this was in the same way with **Al-Kandari et al. (2021),** who conducted research on mutations among patients diagnosed with MODY in a nation where DM is an epidemic disease. Similarly, in the study by **Katashima et al. (2021)**, the mean age at the time of diagnosis was 10.5±3.3 years. In contrast to **Trhanint et al. (2022)**, who noted that the individuals' ages ranged anywhere from 13 to 19 years on average (range: 5–31 years old).

In the present study, the mean height SDS was - 0.03 ± 1.09. While the mean weight SDS was 0.38 ± 1.07, the mean BMI was 21.52 ± 2.06. Tanner staging was prepubertal in 4 cases (20%) and pubertal in 16 cases (80%). Our results were in agreement with **Haliloglu et al. (2016),** who reported that all patients had normal body weight with the exception of one patient who was overweight, and that the mean BMI was 17.2 ±1 9 kg/m2 (14.5 ±21. 2 kg/m2).While in the study by **Trhanint et al. (2022)** , 21.24 kg/M2 was the average BMI (range,13–30 kg/M^2).

In the current study, the mean fasting blood sugar (96.05± 17.53 mg/dl) was statistically higher in cases group. The mean postprandial blood sugar was 151.65 ± 16.43 mg/dl. The mean HbA1c was 8.23 ± 1.56. There was no statistical difference between cases and control regarding the mean cholesterol level (mg/dl), mean TG level or mean c-peptide levels. In accordance with, **Al-Kandari et al. (2021),** the mean HbA1c for the index patients was 8.26%.

According to the findings of the research conducted by **Haliloglu et al**., (2016), the average levels of glucose in the blood during fasting (FBG) and after two hours of testing were 123± 14 mg/dl (107–157 mg/dl) and 181 ± 30 mg/dl (136–247 mg/dl), respectively. At the time of presentation, the patient's HbA1c level was 5.9–7.6%.

In the current study, all cases (100%) had a positive family history of DM. Our results were in agreement with **Katashima et al. (2021),** who reported that the incidence of a family history of diabetes in children with MODY was 100%, and 73.3% (33/45) spanned three generations. Similarly, **Corrales et al. (2010)** reported that all patients with MODY 2 & MODY 3 had family history of DM. **Zubkova et al. (2018),** included 312 patients (162 boys and 150 girls) aged 3 months to 25 years with suspected MODY, Twenty mutations

were detected in the HNF1A gene (MODY3) in 19 (6.1%) probands. A hereditary history of DM was present in 15 (78.9%) families.

In the current study, none of cases had neonatal hypo or hyper glycaemia. None of patients had previous DKA. Similarly, **Johansson et al. (2017),** reported that patients with MODY 3 presents without history of ketosis. While in the study by **Zubkova et al. (2018),** At the disease onset, Three (15.8%) patients had classical signs of diabetes and high hyperglycemia had ketosis in onset. Ketosis is generally believed to be untypical of monogenic forms of DM. However, several studies (in particular, the first description of MODY3 in Russia have demonstrated that the presence of ketosis in onset does not exclude MODY.

In the current study, all cases were negative for Anti-Gad and Anti-Islet. In the same way, **McDonald et al. (2011),** 5/508 (less than 1%) individuals with maturity-onset diabetes in the young and 80/98 (82%) patients with Type 1 diabetes were found to have GAD and/or IA-2 antibodies, respectively.

In the current study, the mean age of the onset of DM was 11.08 ± 2.77 years, the mean duration of DM was 2.2± 16 years. In the same way, **Al-Kandari et al. (2021),** who studied the identification of MODY mutations in a Kuwaiti population noticed the mean age of diabetes diagnosis was 10.02 years. Similarly, **Zubkova et al. (2018),** reported that the median age of DM diagnosis in patients with MODY 3 was 10.6 years.

In the current study, 10% had neuropathY, none of cases had acanthosis nigricans, jaundice, or lipodystrophy. This was comparable with **Bhat et al. (2022),** who reported that a considerable number of MODY patients in their study were found to have microvascular complications. Diabetic peripheral neuropathy was the most frequent complication observed in 14% of patients which was unrelated to duration of DM. Diabetic retinopathy and nephropathy was observed in 1.7% and 1.5% patients respectively.

In the current study, 5% of cases were treated by oral hypoglycemic, 15 % were treated by insulin and oral hypoglycemic drugs, 15% were managed by healthy lifestyle and 65% of cases treated by insulin with a mean dose 0.34 ± 0.19. Our results were comparable with **Johansson et al. (2017),** reported that 10/25 of patients were treated by Insulin, 7/25 were treated by Sulfonylurea and 5/25 were treated by diet only. While in the study by **Zubkova et al. (2018),** they reported that at the disease onset, 8 (42.1%) patients started Insulin at a dose of 0.6 U/kg/day (0.06-3); of these, the highest doses (1.1 and 3 U/kg/day) were used in two young children who manifested with a typical clinical picture of diabetes and high hyperglycemia; during treatment, insulin was discontinued in one patient because of hypoglycemia. Metformin at a dose of 500—1,000 mg/day was prescribed to 4 (21.1%) patients; a diet was recommended to 7 (36.8%) patients. By the time of molecular genetic testing, 9 patients received Insulin at a dose of 0.48 U/kg/day (0.2; 1.2); 5 patients received Metformin at a dose of 500—2,000 mg/day; 5 patients had no treatment. After molecular genetic confirmation of the diagnosis, 7 patients receiving Insulin and 5 patients receiving Metformin were successfully switched to pathogenetic therapy with sulfonylurea (SU) drugs: 4 patients received Glibenclamide at a dose of

5.25—7.5 mg/day, and 8 patients received Gliclazide at a dose of 30—60 mg/day. Insulin was continued in 2 patients with an early diagnosis of diabetes due to high insulin requirements (1.1—1.2 U/kg/day) and a low level of endogenous insulin. In addition, **Corrales et al. (2010)** reported that 50% of patients were treated by oral antidiabetics, 30% were treated with Insulin and oral antidiabetics, 20% of patients were treated with insulin only, while none of patients were treated with diet only. And **Zhao et al. (2022)** reported that 35.5% (95% CI: 31.3-40.0) of patients were prescribed with insulin, 40.3% (95% CI: 32.4-48.6) were prescribed with oral hypoglycemic drugs, and 9.5% (95% CI: 5.4-16.2) were administered with oral hypoglycemic drugs and insulin.

In the current study, the result of Exon 5 DNA sequencing reveals normal exon with no variation detected, Similar to **Trhanint et al. (2021)** identified twenty suspected MODY patients, with a slight male predominance (60%). The subjects were an average of 19 years old (range: 5-31 years old) and were screened for HNF1A and GCK mutations using Sanger sequencing and MLPA methods in Morocco did not detect any variations in Exon 5. Also, **Dalalli et al. (2019)** Exon 5 was not identified to have a mutation in the study's targeted sequencing of 27 genes known to produce monogenic diabetes in 11 phenotypically suspected Tunisian groups under 40 years of age.

In **Wang et al. (2019)** a total of 74 patients, aged below 45, from 59 families, who have a high clinical suspicion of having MODY3 or MODY1, were studied between January 2014 and December 2016 and analyzed by Sanger sequencing as cohort study in China. They did not find any exon 5 variant. The results of the previous three studies are consistent with that of the current study due to the same age group and same genetic detection method.

In contrast, **Ghosal et al. (2012)** assessed 114 non-diabetic control participants and 98 subjects who met the MODY criteria by the conventional PCR SSCP method for mutational analysis. All of the participants in the study were under 25 years of age old and had a thorough family history that covered at least two generations. The healthy subjects served as controls. Three novel variants were found in exon 5 as a result of the sequencing analysis in the Eastern Indian population. It has been observed that in the Eastern Indian population, which may be referred to as a mutational hot zone of exon 5 due to geographic and ethnic factors, the age at which the disease developed in people who had these polymorphisms in exon 5 was between 20 to 22 years.

According to **Yorifuji et al. (2018),** exon 5 mutation was found in two suspected MODY cases in 263 Japanese individuals under 30 years of age old with early-onset, non-obese, MODY-like diabetes mellitus were discovered in Japan, and this result does not correspond with this current study due to geographic and ethnic factors.

Conclusion

For a better outcome and greater understanding of the clinical characteristics and genotype among the Egyptian pediatric diabetic population with a possible MODY3 mutations, we came to the view that all of HNF1A gene with its ten (10) exons forming Exons should be in tandem screened especially for this new area of research in pediatric diabetes mellitus if negative

other gene of MODY like HNF4A, GCK and HNF1B.

References

- **Al-Kandari H, Al-Abdulrazzaq D, Davidsson L, Nizam R, Jacob S, Melhem M, et al. (2021).** Identification of Maturity-Onset-Diabetes of the Young (MODY) mutations in a country where diabetes is endemic. Sci Rep, 11(1):1-11.
- **Behl R, Malhotra N, Joshi V, Poojary S, Middha S, Gupta S, et al. (2022).** Meta-analysis of HNF1A-MODY3 variants among human population. J Diabetes Metab Disord,1–10.
- **Beysel S, Eyerci N, Pinarli FA, Kizilgul M, Ozcelik O, Caliskan M, et al. (2019).** HNF1A gene p. I27L is associated with early-onset, maturity-onset diabetes of the young-like diabetes in Turkey. BMC Endocr Disord, 19(1):1–7.
- **Bhat JA, Masoodi SR, Bhat MH. (2022).** Prevalence and clinical profile of maturity onset diabetes of the young among people with diabetes attending a tertiary care institute in North India. Indian J Endocrinol Metab, 26(Suppl 1): S25.
- **Boutin P, Vasseur F, Samson C, Wahl C, Froguel P. (2001).** Routine mutation screening of HNF-1α and GCK genes in MODY diagnosis: How effective are the techniques of DHPLC and direct sequencing used in combination? Diabetologia, 44(6):775-8.
- **Chandran S, Rajadurai VS, Hoi WH, Flanagan SE, Hussain K, Yap F. (2020).** A novel HNF4A mutation causing three phenotypic forms of glucose dysregulation in a family. Front Pediatr, 8:320.
- **Corrales PJP, Garrido MPL, Rodríguez SA, Rubio LL, Jiménez LML, Oliveira CL, et al. (2010).** Clinical differences between patients with MODY-3, MODY-2 and type 2 diabetes mellitus with I27L polymorphism in the HNF1α gene. Endocrinología y nutrición, 57(1):4-8.
- **Dallali H, Pezzilli S, Hechmi M, Sallem OK, Elouej S, Jmel H, et al. (2019).** Genetic characterization of suspected MODY patients in Tunisia by targeted next-generation sequencing. Acta Diabetologica, 56:515-23.
- **Ghosal C, Sen A, Chowdhury S, Pandit K, Banerjee S, Paine SK, et al. (2012).** Novel variants in the hepatocyte nuclear factor-1-alpha gene in MODY and early onset NIDDM: Evidence for a mutational hotspot in exon 5. Open J Prev Med, 2(01):116–22.
- **Haliloglu B, Hysenaj G, Atay Z, Guran T, Abalı S, Turan S, et al. (2016).** GCK gene mutations are a common cause of childhood-onset MODY (maturity-onset diabetes of the young) in Turkey. Clinical endocrinology, 85(3):393-9.
- **Hoffman LS, Fox TJ, Anastasopoulou C, Jialal I. (2021).** Maturity Onset Diabetes in the Young. In: StatPearls [Internet]. StatPearls Publishing.
- **Jang KM. (2020).** Maturity-onset diabetes of the young: update and perspectives on diagnosis and treatment. Yeungnam Univ J Med,37(1):13–21.
- **Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, et al. (2017).** Targeted next-generation sequencing reveals MODY in up to 6.5% of

antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. Diabetologia, 60:625-35.

- **Katashima R, Matsumoto M, Watanabe Y, Moritani M, Yokota I. (2021).** Identification of Novel GCK and HNF4α Gene Variants in Japanese Pediatric Patients with Onset of Diabetes before 17 Years of Age. Journal of Diabetes Research, 2021.
- **Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, Aschner P, Craig ME. (2018).** ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatric diabetes, 19(Suppl 27):7.
- **McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, et al. (2011).** Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabetic Medicine, 28(9):1028-33.
- **Oliveira SC, Neves JS, Pérez A, Carvalho D. (2020).** Maturity-onset diabetes of the young: from a molecular basis perspective toward the clinical phenotype and proper management. Endocrinol Diabetes y Nutr, 67(2):137–47.
- **Pavić T, Juszczak A, Pape Medvidović E, Burrows C, Šekerija M, Bennett AJ, et al. (2018).** Maturity onset diabetes of the young due to HNF1A variants in Croatia. Biochem medica, 28(2):285–95.
- **Pruhova S, Dusatkova P, Neumann D, Hollay E, Cinek O, Lebl J, et al. (2013).** Two cases of diabetic ketoacidosis in HNF1A-MODY linked to severe dehydration: is it time to change the diagnostic criteria for MODY? Diabetes Care, 36(9):2573-4.
- **Sanger F, Nicklen S, Coulson AR. (1977).** DNA sequencing with chain-terminating inhibitors. Proceedings of the national academy of sciences, 74(12):5463-7.
- **Sanyoura M, Philipson LH, Naylor R. (2018).** Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep, 18(8):1–13.
- **Trhanint S, Bouguenouch L, Abourazzak S, El Ouahabi H, Latrech H, Benyakhlef S, et al. (2022).** Molecular and clinical assessment of maturity-onset diabetes of the young revealed low mutational rate in Moroccan families. International Journal of Pediatrics and Adolescent Medicine, 9(2):98-103.
- Wang X, Wang T, Yu M, Zhang H, Ping F, Zhang Q, et al. (2019). Screening of HNF1A and HNF4A mutation and clinical phenotype analysis in a large cohort of Chinese patients with maturity-onset diabetes of the young. Acta diabetologica, 56:281-8.
- **Yorifuji T, Higuchi S, Kawakita R, Hosokawa Y, Aoyama T, Murakami A, et al. (2018).** Genetic basis of early-onset, maturity-onset diabetes of the young-like diabetes in Japan and features of patients without mutations in the major MODY genes: dominance of maternal inheritance. Pediatric Diabetes, 19(7):1164-72.
- **Zubkova NA, Gioeva OA, Tikhonovich YV, Petrov VM, Vasilyev EV, Timofeev AV, et al. (2010).** Clinical and molecular

genetic characteristics of MODY1—3 cases in the Russian Federation as shown by NGS. Problems of Endocrinology, 63(6):369-78.