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GENETIC STUDY OF HEPATOCYTE NUCLEAR FACTOR-1 ALPHA (HNF-1A) MUTATIONS IN DIABETES MELLITUS PATIENTS

Studi Genetik Mutasi Hepatocyte Nuclear Factor-1 Alpha (Hnf-1α) pada Pasien Diabetes Mellitus

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ABSTRAK

Maturity-Onset Diabetes of the Young *(MODY) merupakan bentuk diabetes monogenik yang sering salah diklasifikasikan sebagai diabetes tipe 1 atau tipe 2, seringkali mengakibatkan penanganan klinis yang kurang optimal. Salah satu penyebab paling umum dari MODY adalah mutasi pada gen HNF1A, yang berperan penting dalam mengatur ekspresi gen di dalam sel beta pankreas. Penelitian ini bertujuan untuk mengidentifikasi mutasi potensial pada gen HNF1A pada pasien yang dicurigai menderita MODY secara klinis menggunakan* Sanger sequencing*. DNA diisolasi dari dua pasien yang dicurigai menderita MODY sebagai studi molekuler awal untuk mengeksplorasi mutasi potensial pada gen HNF1A, diikuti dengan amplifikasi sepuluh ekson HNF1A menggunakan PCR konvensional. Produk PCR dievaluasi dengan elektroforesis gel agarosa untuk memastikan amplifikasi yang berhasil sebelum dilakukan* Sanger sequencing*. Data urutan yang dihasilkan kemudian dianalisis menggunakan perangkat lunak BioEdit dan ClustalW untuk mendeteksi variasi nukleotida dengan membandingkannya dengan urutan referensi HNF1A (NM_001306179.2). Ditemukan enam mutasi titik pada gen HNF1A yang tersebar di ekson 7, 9, dan 10, terdiri atas satu mutasi silent (p.Leu459Leu), empat mutasi missense (p.Gln460His, p.Ser486Asn, p.Ser581Gly, dan p.Val705Leu), serta satu mutasi nonsense (p.Trp785*) yang menyebabkan terminasi translasi dini. Mutasi yang ditemukan berpotensi memengaruhi struktur dan fungsi protein HNF1A, termasuk domain transaktivasi yang penting dalam regulasi ekspresi gen target. Penelitian ini menunjukkan bahwa deteksi mutasi genetik, khususnya pada HNF1A, penting dalam mendiagnosis MODY secara akurat dan dapat menjadi dasar pemilihan terapi yang lebih tepat, seperti penggunaan sulfonilurea sebagai alternatif insulin.*

Kata kunci: *diabetes monogenik, HNF1A, MODY, mutasi gen,* Sanger sequencing

ABSTRACT

Maturity-Onset Diabetes of the Young (MODY) is a monogenic form of diabetes that is frequently misclassified as type 1 or type 2 diabetes, often resulting in suboptimal clinical management. One of the most prevalent causes of MODY is mutations in the *HNF1A* gene, which plays a critical role in regulating gene expression within pancreatic beta cells. This study aims to identify potential mutations in the HNF1A gene among clinically suspected MODY patients using Sanger sequencing. DNA was isolated from two MODY-suspected patients as a preliminary molecular study to explore potential mutations in the HNF1A gene, followed by amplification of ten HNF1A exons using conventional PCR. Analysis PCR products by agarose and Sanger sequencing. The resulting sequence

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data were then analyzed using BioEdit and ClustalW software to detect nucleotide variations by comparison with the HNF1A reference sequence (NM_001306179.2). Six-point mutations were identified in the HNF1A gene, distributed across exons 7, 9, and 10, consisting of one silent mutation (p.Leu459Leu), four missense mutations (p.Gln460His, p.Ser486Asn, p.Ser581Gly, and p.Val705Leu), and one nonsense mutation (p.Trp785*) causing premature translation termination. The identified mutations had the potential to affect the structure and function of the HNF1A protein, including the transcription activation domain, which was crucial in regulating the expression of target genes. This study demonstrated that the detection of genetic mutations, especially in HNF1A, was important in accurately diagnosing MODY as well as determining appropriate therapy approaches, such as the use of sulfonylureas as an alternative to insulin.

Keywords: gene mutation, HNF1A, MODY, monogenic diabetes, Sanger sequencing

INTRODUCTION

Diabetes Mellitus (DM) is a disorder of the endocrine system characterized by chronic hyperglycemia. According to data from the International Diabetes Federation, 537 million adults were living with diabetes in 2021. This number is expected to increase to 643 million in 2030 and 783 million in 2045 [1], [2], [3], [4].

Maturity-onset Diabetes of the Young (MODY) is a monogenic form of diabetes that is often confused with type 1 and type 2 diabetes mellitus. The pathophysiology of MODY involves genetic mutations in nuclear transcription factors and glucokinase, resulting in pancreatic beta-cell dysfunction. In patients with MODY, insulin is produced by beta cells, but failure in insulin secretion causes hyperglycemia. MODY is estimated to account for 1-5% of all diabetes cases, and due to its diverse clinical presentation, it is often misdiagnosed as T1DM or T2DM [5].

Misclassification of MODY often results in inappropriate clinical management. Therefore, molecular diagnosis of MODY is necessary to distinguish it from other types of diabetes [6], [7], [8]. Several biomarkers play a crucial role in distinguishing MODY subtypes from type 1 and type 2 diabetes. Biomarkers such as preserved C-peptide levels, diabetes-related autoantibodies, and high-sensitivity C-reactive protein (hs-CRP) may support clinical suspicion of MODY. However, genetic testing remains the gold standard for confirming the diagnosis and guiding accurate prognosis and management [9]. Molecular diagnostic testing can identify genetic mutations causing MODY, improve diagnostic accuracy, and support precision medicine, that is, to help determine the appropriate method of blood glucose monitoring and to prevent unnecessary insulin use [10], [11].

Several subtypes of MODY can be clearly identified using molecular genetic testing. Hepatocyte Nuclear Factor 1 homeobox A (HNF1A) MODY3 is the most common form of MODY, caused by a mutation in the HNF1A gene on chromosome 12 (12q24.31), found primarily in the liver and kidneys, and encoding a protein containing 631 amino acids. HNF1A has three domains: a dimerization domain, a DNA-binding domain (DBD), and a transactivation domain. HNF1A interacts with other transcription factors such as HNF1B and HNF4A through the dimerization domain to regulate gene expression. To date, more than 450 different mutations, including missense, frameshift, insertion, and complete or partial exon deletions, have been reported in the HNF1A gene [8],[13],[12]. The National Center for Biotechnology Information (NCBI) notes that the HNF1A reference genome has 10 exons organized into two different transcript variants (variant 1 and 2), which serve as the reference sequence for genetic analysis. Recent large-scale studies have demonstrated that HNF1A variants are distributed across multiple exons, with mutations most frequently identified in exons 2 and 4, while variants located in exons 8–10 are associated with later disease onset in MODY3 patients, underscoring the

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clinical relevance of exon-specific mutation patterns [13]. Missense mutations such as g.1566G>A (c.758G>A; p.G253E) have been reported in Iran, identified using Sanger sequencing [8], further emphasizing the critical role of genetic testing in ensuring accurate diagnosis and optimal sulfonylurea-based therapy. However, data on HNF1A variants in Indonesian patients with suspected MODY remain scarce or unreported.

Mutations in the HNF1A gene cause a progressive decrease in insulin secretion, eventually requiring patients to undergo insulin replacement therapy and leading to vascular complications, heart damage, kidney complications, and eye complications. Untreated MODY3 patients who do not receive proper medical treatment will eventually experience the devastating effects of diabetes, including ketoacidosis. Based on this background, the authors were interested in conducting a genetic study to detect base changes in DNA by analyzing sequencing results against reference database sequences, to support specific and accurate DM diagnosis and enable appropriate treatment for patients [7], [14].

Therefore, this study aims to conduct a genetic analysis of sequence variants in the HNF1A gene as an early diagnostic approach for diabetes mellitus patients clinically suspected of having Maturity-Onset Diabetes of the Young (MODY). This study is particularly important for identifying population-specific HNF1A variants in local MODY-suspected patients, for whom genetic data remain limited. The findings are expected to provide preliminary molecular data that may support future genetic screening strategies and contribute to a better understanding of the HNF1A mutation profile in the local population.

METHODS

This study was designed as a descriptive molecular case series and preliminary study involving two patients clinically suspected of MODY was conducted at the Molecular Biology Laboratory of the Department of Medical Laboratory Technology, Bandung Health Polytechnic, Ministry of Health, Indonesia, while the sequencing process was performed at Macrogen, China, during March–May 2025. Ethical approval was obtained from the Health Research Ethics Committee with certificate number 137/KEPK/EC/11/2025.

The samples consisted of two diabetes mellitus (DM) patients suspected of having MODY, coded A and B, comprising a 17-year-old female and a 45-year-old male. These samples were selected using purposive sampling based on inclusion criteria of clinically confirmed DM patients aged 10–45 years with a family history of diabetes in at least two generations, reflecting an early age of onset and an autosomal dominant inheritance pattern characteristic of MODY, while the exclusion criteria included DM patients with obesity and DM patients presenting with ketoacidosis. to minimize the likelihood of T2DM and T1DM. Written informed consent was obtained from all subjects or their legal guardians, including consent for participation and for the use of clinical data and genetic sequence information for research purposes.

The main variable analyzed in this study was the presence of HNF1A gene mutations. Whole blood specimens were collected from both patients and were processed for DNA isolation using the Promega Wizard® Genomic DNA Purification Kit, which involved four sequential steps: erythrocyte lysis, leukocyte and nuclear lysis, protein precipitation, and DNA precipitation using isopropanol. The purified genomic DNA was subsequently amplified using conventional PCR with ten primer pairs targeting all exons of the HNF1A gene.

The PCR cycle was performed with enzyme activation at 95 °C for 2 minutes, followed by 35 cycles consisting of denaturation at 95 °C for 15 seconds, annealing at exon-specific optimized temperatures for 1 minute, and extension at 60 °C for 1 minute, which was selected based on preliminary PCR optimization experiments to ensure specific and efficient amplification, and was completed with a final cooling step at 35 °C

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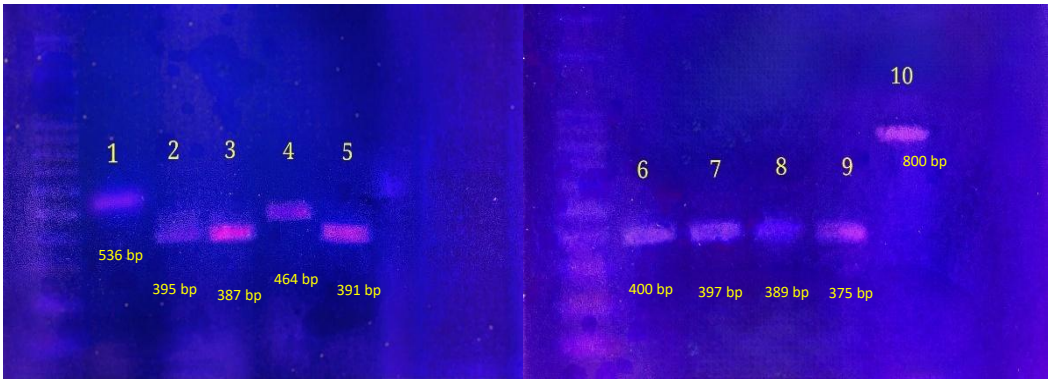
for 30 seconds. The resulting amplicons were visualized using agarose gel electrophoresis, subsequently prepared with diluted forward and reverse primers before being submitted to PT. Genetika Science Indonesia, which coordinated the Sanger sequencing analysis performed at Macrogen (China).

The sequencing results were analyzed using descriptive sequence analysis to identify sequence variants in the HNF1A gene, without statistical testing due to the descriptive molecular design of the study. Sequence alignment and variant identification were performed using BioEdit and ClustalW software, with comparison to the HNF1A reference sequence (NM_001306179.2). All obtained data were recorded, processed, and presented in narrative form, supported by tables and representative electropherogram curves.

RESULT

Agarose Gel Electrophoresis Visualization Results

In this study, agarose gel electrophoresis was used to confirm the presence and expected sizes of HNF1A gene DNA fragments before sequencing. Clear single DNA bands were observed in each sample at the expected fragment sizes (approximately 375–536 bp and 800 bp) based on comparison with the DNA ladder, indicating successful, specific, and efficient PCR amplification, as shown in Figure 1.



(a) (b)

Figure 1. Agarose gel electrophoresis of PCR products for HNF1A exons

Sequencing Results Analysis

The DNA template that had been analyzed through electrophoresis was then packaged along with each specific primer for 10 exons of the HNF1A gene, which had been diluted to a concentration of 10 µM in a volume of 10 µL. All samples were then sent to PT. Genetika Science Indonesia for sequencing analysis to detect possible mutations. Mutations were analyzed using the Sanger sequencing method. The sequencing results were obtained in the form of .ab1 files, which were then analyzed using BioEdit software to obtain FASTA format and view the resulting chromatogram graphs. The chromatograms for samples A and B showed good signals and could be analyzed.

Figure 2 shows a representative chromatogram for exon 7 of sample A, demonstrating sharp, non-overlapping peaks and a regular signal pattern, indicating high-quality Sanger sequencing suitable for mutation analysis. Further analysis was performed using ClustalW software to compare the nucleotide sequences of the samples with reference sequences from NCBI (to identify possible mutations).

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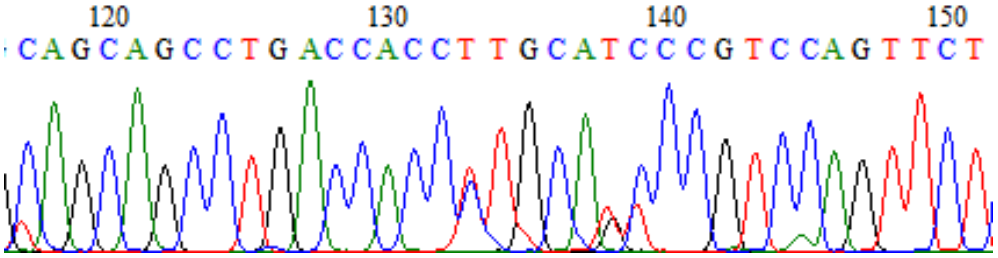

Figure 2. Representative Sanger Sequencing Chromatogram of HNF1A exon 7 (sample A)

Table 1. Results of nucleotide base mapping of sample A

No.	Exon	Reference Nucleotide (NM_001306179.2)	Sample Nucleotides (Sample A)	Base Point	Type of Mutation
1.	7	C	T	1375	Substitution (Transition) base changes
2.	7	G	T	1380	Substitution (Transversion) base changes
3.	7	G	A	1460	Substitution (Transition) base changes
4.	9	A	G	1741	Substitution (Transition) base changes
5.	10	G	T	2114	Substitution (Transversion) base changes

Based on the results of DNA sequencing analysis of the target gene compared to the reference sequence NM_001306179.2, five mutations were identified in sample A. Several sequence variants were identified across exons 7, 9, and 10 of the HNF1A gene, with exon 7 harboring the highest number of substitutions. The predominance of substitution variants, particularly transition mutations, is consistent with commonly reported mutational patterns in HNF1A. Variants detected in exons 7–10 are located within or adjacent to the transactivation domain, which has been reported to play a critical role in transcriptional regulation and has been associated with MODY3 phenotypes in previous studies. Detailed nucleotide positions and substitution types are summarized in Table 1.

Table 2. Results of Mapping Changes in the DNA and Protein Levels of Sample A

No.	**Exon**	Changes at the DNA Level	Codon	Changes at the Protein Level	Types of Mutation	Description
1.	7	c.1375C>T	CTG>TTG	p.Leu459Leu	Silent	No amino acid change
2.	7	c.1380G>T	CAG>CAT	p.Gln460His	Missense	Amino acid change occurs
3.	7	c.1460G>A	AGC>AAC	p.Ser486Asn	Missense	Amino acid change occurs
4.	9	c.1741A>G	AGC>GGC	p.Ser581Gly	Missense	Amino acid change occurs
5.	10	c.2114G>T	GTG>TTG	p.Val705Leu	Missense	Amino acid change occurs

Analysis of HNF1A gene sequencing in sample A identified five protein-level variants distributed across exons 7, 9, and 10, as summarized in Table 2. These variants consisted of one synonymous (silent) change and four missense mutations, indicating the presence of variants resulting in amino acid substitutions predominantly within the downstream exons of the gene. All identified variants were located within regions encoding the transactivation domain of the HNF1A protein, which plays an important role

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in transcriptional regulation. However, the functional consequences of these specific variants were not evaluated in this study.

Table 3. Results of Nucleotide Base Mapping of Sample B

No.	Exon	Reference Nucleotide (NM_001306179.2)	Sample Nucleotides (Sample A)	Base Point	Type of Mutation
1.	7	G	T	1380	Substitution (Transversion) base changes
2.	7	G	A	1460	Substitution (Transition) base changes
3.	9	A	G	1741	Substitution (Transition) base changes
4.	10	G	T	2114	Substitution (Transversion) base changes
5.	10	T	A	2355	Substitution (Transversion) base changes

Table 4. Results of mapping changes in the DNA and protein levels of sample B

No.	Exon	Changes at the DNA Level	Codon	Changes at the Protein Level	Types of Mutation	Description
1.	7	c.1380G>T	CAG>CAT	p.Gln460His	Missense	Amino acid change occurs
2.	7	c.1460G>A	AGC>AAC	p.Ser486Asn	Missense	Amino acid change occurs
3.	9	c.1741A>G	AGC>GGC	p.Ser581Gly	Missense	Amino acid change occurs
4.	10	c.2114G>T	GTG>TTG	p.Val705Leu	Missense	Amino acid change occurs
5.	10	c.2355T>A	TTG>TAG	p.Trp785*	Nonsense	A change to a stop codon occurs

Based on DNA sequencing analysis of the target gene compared with the reference sequence NM_001306179.2, five point mutations were identified in sample B across three exons (exons 7, 9, and 10), as summarized in Table 3. The mutation pattern in sample B was largely similar to that observed in sample A, particularly at positions 1380 and 1460 in exon 7, position 1741 in exon 9, and position 2114 of exon 10. A different mutation was found at position 2355 of exon 10.

As presented in Table 4, most of the mutations found in sample A were also found in sample B, namely the missense mutations p.Gln460His, p.Ser486Asn, p.Ser581Gly, and p.Val705Leu. This indicates a similarity in the mutation profiles between the two patients, suggesting the possibility of consistent recurrent mutations between individuals and the possibility of a characteristic mutation pattern in MODY3 DM patients in the studied population.

The main difference between the two samples was the presence of a nonsense mutation at position 785 (p.Trp785*), which was detected exclusively in sample B. This variant introduces a premature stop codon by substituting tryptophan (Trp) with a termination signal (TAG), and is predicted to result in a truncated HNF1A protein, potentially affecting normal protein function.

DISSCUSION

Successful amplification of all ten HNF1A exons was confirmed by the presence of PCR amplicons with expected fragment sizes.The use of 1.5% agarose gel provided adequate resolution for the separation of HNF1A PCR amplicons within the expected size range (approximately 300–800 bp) [15]. Therefore, selecting the appropriate

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agarose gel concentration is an important factor in obtaining optimal gel resolution tailored to the size of the DNA fragments to be analyzed [16].

The electrophoresis results of the PCR products from the ten exons of the HNF1A gene showed that DNA amplification was successful in all exons, both for sample A and sample B. This was indicated by the appearance of clear DNA bands and the estimated DNA fragments for exons 1 to 10. The higher the DNA concentration, the sharper the intensity of the resulting bands [17].

In this study, BioEdit software was used as a tool in the sequencing data analysis stage, specifically to review the quality of the sequencing chromatograms from each exon to see the nucleotide sequence [18]. One of the main features utilized in this study was BioEdit's ability to open and display sequencing result files in .ab1 format, obtained from the Sanger sequencing method. DNA [19]. In addition, this software was also used to obtain files in FASTA format to be aligned with the HNF1A gene reference sequence (RefSeq: NM_001306179.2).

The Sanger sequencing chromatograms for exons 1–10 in both samples A and B displayed clear, well-defined, and non-overlapping peaks with a consistent signal pattern. These high-quality chromatograms enabled reliable base calling and accurate alignment with the *HNF1A* reference sequence [20].

Next, analysis was performed using ClustalW as a bioinformatics tool to perform multiple sequence alignment (MSA) between the DNA sequences resulting from HNF1A gene sequencing from patient samples and the reference sequences obtained from the GenBank database. This alignment aimed to identify nucleotide variations, such as point mutations, deletions, or insertions, which could affect the structure and function of the protein encoded by the gene. This process was carried out to detect nucleotide differences in each exon. Based on the alignment results, it was found that there were several mutations with similar mutation patterns in samples A and B that occurred in exons 7, 9, and 10. Meanwhile, the nucleotide sequences in exons 1, 2, 3, 4, 5, 6, and 8 in both samples A and B were identical to the reference sequence, and no variations or base changes were found.

The results of the HNF1A gene sequence analysis of the samples studied showed six point mutations scattered across exons 7, 9, and 10. DNA molecules are double-stranded. If a mutation occurs and one base is replaced by another base, the DNA molecule will temporarily contain mismatched bases. When DNA undergoes replication, complementary base pairs will be synthesized opposite to the mismatched base pairs. As a result, one wild-type (normal) DNA molecule and one DNA molecule containing a mutation will be formed [21].

The six mutations identified consist of one silent mutation, four missense mutations, and one nonsense mutation. One mutation found in exon 7 is a silent mutation, namely the c.1375C>T nucleotide change that produces a new TTG codon from the original CTG codon, but both still encode the amino acid leucine (Leu). Therefore, this mutation does not alter the amino acid sequence at position 459 (p.Leu459Leu). Silent mutations generally do not affect protein structure or function because they do not alter the polypeptide chain [22].

Furthermore, four mutations were found that fall into the missense category, which are mutations that occur when a change in the base sequence alters a codon so that one amino acid in the protein is replaced by another amino acid. The severity of missense mutations depends on the location of the change and the nature of the replaced amino acid [21]. Two missense mutations were found in exon 7, namely the c.1380G>T;p.Gln460His mutation and the c.1460G>A;p.Ser486Asn mutation. The Ser486Asn amino acid is located in the C-terminal transactivation domain of HNF1A in a specific region involved in the recruitment of specific target genes and interaction with transcription co-activators. Previous studies have suggested that alterations in this

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domain may influence the transcriptional activity of HNF1A, indicating that the Ser486Asn variant may potentially affect gene regulatory function, although its pathogenicity has not been definitively established [23]. In exon 9, a missense mutation c.1741A>G;p.Ser581Gly was also detected. Among genes associated with monogenic diabetes, HNF1A has been consistently recognized as one of the most relevant candidates. revious reports have described the co-occurrence of several non-synonymous HNF1A variants, including Ile27Leu (rs1169288), Ser487Asn (rs2464196), Leu551Ser (rs1169304), and Ser581Gly (rs587778398), in patients with diabetes. Variants located in exons 8–10, which are present only in the longest isoform of the HNF1A gene, have been associated with a later age of MODY onset. Accordingly, missense variants such as Leu551Ser and Ser581Gly have been proposed as potential contributors to the observed clinical phenotype, although further functional and clinical studies are required to clarify their precise role [24].

A nonsense mutation was found in exon 10, namely c.2355T>A;p.Trp785*, which changes the tryptophan codon (UGG) to a stop codon (UAG). This nonsense variant introduces a premature stop codon, which is predicted to result in early termination of translation and the production of a truncated HNF1A protein at position 785. Such truncating variants may impair normal protein function, although the functional consequences of this specific variant were not evaluated in the present study [21].

MODY3 is caused by mutations in the HNF1A gene, which produces a protein expressed in the liver, kidneys, intestines, and pancreatic beta cells. The HNF1A protein functions in regulating insulin gene expression and plays a role in controlling the expression of glucose transport genes, such as GLUT2 [25]. One of the compensatory mechanisms regulated by HNF1A is the increase in transcription and expression of the Sodium-Glucose Cotransporter 2 (SGLT2) gene. This mechanism helps maintain relatively normal blood glucose levels (euglycemia) for a certain period of time, especially in the early stages of metabolic disorders. However, in individuals with mutations in HNF1A, SGLT2 expression is drastically reduced, which impacts the ability to reabsorb glucose in the proximal tubules of the kidneys. This causes a decrease in the efficiency of glucose recovery filtered by the kidneys, and ultimately contributes to an increase in blood glucose levels [26]. The mutations found in this study, such as silent, missense, and nonsense mutations, have the potential to cause disturbances in the structure and function of HNF1A. These mutations can inhibit the amino-terminal domain, which plays a role in dimerization and DNA binding, and can inhibit the transactivation domain, thereby disrupting the transcription of various target genes, including genes that are important in glucose uptake by cells, hepatic glucose metabolism, and insulin secretion by pancreatic β cells [27].

Thus, the mutations found in exons 7, 9, and 10 in this study not only alter the structure of the HNF1A protein but may also affect its function in regulating glucose metabolism. Disruption of the HNF1A gene function can cause disruption of the expression of important genes that play a role in the process of glucose uptake by cells and insulin production. As a result, there is a decrease in insulin secretion and the body's response to glucose becomes suboptimal. This condition may explain the onset of diabetes symptoms in patients suspected of having MODY.

One of the most important and characteristic features of MODY3 patients is their sensitivity to sulfonylurea drugs, which are the first-line therapy for MODY3 cases. This has significant clinical implications, especially for patients who were previously misdiagnosed with type 1 diabetes (T1DM), as they can discontinue insulin therapy and switch to sulfonylurea treatment, even after undergoing long-term insulin therapy. Children who previously used oral hypoglycemic agents or low-dose insulin can also discontinue insulin therapy and switch directly to low-dose sulfonylurea. The dose can be titrated gradually to achieve optimal glycemic control. Meanwhile, for patients

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undergoing full-dose insulin therapy (replacement dose), it is recommended to reduce basal insulin by at least 50% and discontinue bolus insulin when starting sulfonylurea therapy [26].

This study employed a comprehensive analytical workflow, including DNA isolation, exon-wide PCR amplification of the HNF1A gene, verification of PCR products by agarose gel electrophoresis, and sequence analysis using BioEdit and ClustalW. This approach enabled the identification of six mutations in exons 7, 9, and 10, while also providing preliminary data on the HNF1A mutation profile in the studied population. However, this study has limitations, including a limited number of samples that do not fully represent the genetic diversity of the population, the absence of in vitro or in silico functional tests to assess the biological impact of the detected mutations, and the lack of comprehensive clinical data and family history, which limits the interpretation of the genotype-phenotype relationship. Nevertheless, these findings have important implications for clinical practice and research, namely reinforcing the role of HNF1A mutations in the pathogenesis of MODY3, confirming the importance of genetic testing in the differential diagnosis of diabetic children, and supporting the potential implementation of targeted genetic screening in local populations. Furthermore, this study emphasizes the clinical relevance of early detection of MODY3, as patients with HNF1A mutations generally respond well to sulfonylurea therapy, allowing for more precise and effective treatment strategies.

CONCLUSION

In conclusion, this preliminary study identified sequence variants in the HNF1A gene across multiple exons in two patients clinically suspected of MODY. Six substitution mutations were found, namely three transversion substitution mutations c.1380G>T, c.2114G>T, c.2355T>A, and three transition mutations c.1375C>T, c.1460G>A, c.1741A>G. The mutations found were characterized as silent, missense, and nonsense mutations. One silent mutation was found in exon 7 (p.Leu459Leu). Four missense mutations were found, namely in exon 7 (p.Gln460His and p.Ser486Asn), exon 9 (p.Ser581Gly), and exon 10 (p.Val705Leu). One nonsense mutation was found in exon 10 (p.Trp785*). These findings provide preliminary data on the HNF1A mutation profile in local MODY-suspected patients. Future research with larger sample sizes and more comprehensive clinical and family data would be valuable to clarify the potential impact of these variants on HNF1A protein function, support genotype-phenotype interpretation, and enhance diagnostic accuracy.

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