Polymerase chain reaction and Sanger sequencing were performed. All the different genes are responsible for various MODY subtypes. Heterozygous mutations in the hepatocyte nuclear factor 1 alpha (HNF1A) gene are responsible for the MODY3 subtype, which is a common subtype of MODY in different studied populations. To date, more than 450 different variants of this gene have been reported as disease causing for MODY3. This study was carried out to evaluate HNF1A mutations in Iranian diabetic families fulfilling MODY criteria.

Materials and Methods: Polymerase chain reaction and Sanger sequencing were performed. All the ten exons of the HNF1A gene were sequenced in ten families, followed by cosegregation analysis and in silico evaluation. Computational protein modeling was accomplished for the identified mutation.

Results: MODY3 was confirmed in two large families by detecting a mutation (p.G253E) in coding regions of HNF1A. Compound heterozygous state for two common variants in HNF1A (p.I27L and p.S487N) was detected in affected members of 5 families, and in one family, a rare benign variant in the coding sequence for Kozak sequence was detected. Two new nonpathogenic variants were found in noncoding regions of HNF1A. Conclusion: It seems that HNF1A mutations are a common cause of MODY in Iranian diabetic patients. Identified common variants in heterozygous state can cause diabetes Type II in earlier ages. The role of rare variant rs3455720 is unknown, and more investigation is needed to uncover the function of this variant.

Keywords: Gene, hepatocyte nuclear factor 1 alpha, Iran, maturity-onset diabetes of the young 3, mutation

Introduction

Maturity-onset diabetes of the young (MODY) is a clinically and genetically heterogeneous group of diabetes characterized by noninsulin-dependent, autosomal-dominant disorders with strong familial history, early age of onset, and pancreatic beta-cell dysfunction. MODY is the most common type of monogenic diabetes and accounts for 1%-2% of all diabetes. Disease onset occurs usually under the age of 25, and strong family history is observable in the pedigrees. Heterozygous mutations in at least 14 different genes can cause 14 different MODY subtypes. The frequent misdiagnosis of MODY cases with common types of diabetes often leads to improper treatment of the disease and unfavorable outcomes. Therefore, molecular diagnosis of MODY is necessary to distinguish it from other types of diabetes and to diagnose the related MODY subtypes which would help in providing the best management of the disease.

In MODY patients, insulin is produced by beta-cells, but failure in insulin secretion leads to hyperglycemia. Although at the final stages of some subtypes of MODY insulin, outcomes, therefore, molecular diagnosis of MODY is necessary to distinguish it from other types of diabetes and to diagnose the related MODY subtypes which would help in providing the best management of the disease.

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The frequency of MODY3 and MODY1 are highly sensitive to oral sulfonylureas tablets.\textsuperscript{[8,9]} Mutations in HNF4A (MODY1), GCK (MODY2), hepatocyte nuclear factor 1 alpha (HNF1A) (MODY3), and HNF1B (MODY5) genes have been reported as the most common causes of MODY. HNF1A mutations are the most common causes of MODY in many different studied populations.\textsuperscript{[9]} HNF1A or TCF1 (MIM; 124210) on human chromosome 12 (12q24.31), containing 10 exons, is expressed predominantly in the liver and kidney and encodes a peptide containing 631 amino acids, known as HNF1A.\textsuperscript{[10]} Three functional domains have been identified in HNF1A protein: dimerization domain, DNA-binding domain (DBD), and transactivation domain. HNF1A interacts with other Transcription Factors such as HNF1B and HNF4A via dimerization domains to regulate the related genes expression.\textsuperscript{[10]} For the first time, Yamagata et al. reported mutations in the HNF1A gene in MODY patients.\textsuperscript{[11]} To date, more than 450 various mutations including missense, frameshift, insertions/deletions, and complete or partial deletion of exons have been reported in the HNF1A gene.\textsuperscript{[12]} Heterozygous mutations of HNF1A lead to MODY3 (MIM; 600496). Without suitable medical interventions, it can lead to macro- or micro-vascular heart, kidney, and eye complications.\textsuperscript{[13,14]} Usually, age of MODY onset is under 25; therefore, the course of the disease is longer than type 2 diabetes. Untreated MODY3 patients finally will experience awesome consequences of diabetes, even ketoacidic attacks.\textsuperscript{[15]} The frequency of MODY3 and HNF1A-related mutations are not estimated in Iran. In the present research, based on MODY criteria, the authors evaluated the prevalence of HNF1A mutations among Isfahan province diabetic patients.

**Materials and Methods**

**Subjects**

In the present research, 6500 patient files of diabetic patients (from Sedighe Tahereh Endocrine and Metabolism Research Center, Isfahan, Iran and Dr. Mahin Hashemipour Endocrinology Clinic, Isfahan, Iran) were checked to find MODY patients. 250 patients were selected for genetic counseling. After taking informed consent, sampling was done for selected individuals. Based on MODY criteria, 50 patients were examined for clinical and laboratory features of MODY (hyperglycemia, age of onset under 30, strong history of diabetes [at least observed in three generations], detectable values of C-peptide [≥10 ng/ml], negativity for gamma glutamic acid decarboxylase (GAD 65) autoantibodies, responsively to sulfonylureas drugs [gliclazide and glibenclamide], and no history for ketoacidosis attacks, regardless to diagnosis as type 1 or type 2 of diabetes). Finally, 10 patients fulfilling MODY criteria were selected for genetic testing of HNF1A. Familial history of each patient was obtained, and pedigrees were drawn by a geneticist. After taking informed consent, blood sampling was done for affected and normal available members of the families. Blood samples were obtained from each individual; samples were kept in ethylenediaminetetraacetic acid containing vials.

**DNA extraction and Sanger sequencing**

Genomic DNA extraction from peripheral blood lymphocytes was carried out using Prime Prep Genomic DNA Extraction kit from blood (GeNet Bio, Korea). Qualitative and quantitative control of genomic DNA was performed by 1.2% agarose gel and Nanospec cube biophotometer (Nanolytik®, Dusseldorf, Germany), respectively. Primers for all 10 exons of the HNF1A gene were designed using primer3 v. 0.4.0 (http://bioinfo.ut.ee/ primer3-0.4.0/) online web-based software, encompassing at least 60 base pair nucleotides flanking exons, and they were checked by the NCBI primer blast for affinity and specificity. Primer sequences are presented in Table 1. Under standard conditions, polymerase chain reaction (PCR) was applied in all the exons amplification (V: 2 µl Genomic DNA, 2X Master Mix [Ampliqon®, Denmark]). An automated Genetic Analyzer ABI 3130XL (Applied Biosystems, Foster City, California, USA) was recruited for bidirectional sequencing of PCR products using Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, California, USA). For coding variant calling, sequences were compared to reference sequences NM_000545 and NP_000536.5. In silico analysis was performed using MutationTaster2.0, SIFT, PolyPhen-2, PON-P2, PROVEAN, PANTHER, and FATHMM. According to the ACMG guidelines, variant interpretation was done, and variant nomenclature was based on HGVD rules.

**Results**

**Clinical findings**

The first proband carrying mutation was a 35-year-old woman diagnosed with gestational diabetes at age 23, with elevated levels of oral glucose tolerance test (OGTT) and glycosuria. She received insulin during the gestational period. After delivery, treatment with insulin was stopped, and metformin was prescribed but no proper blood glucose level control was achieved even with high doses of metformin. Elevated levels of HbA1c showed that metformin could not be the drug of choice for her. Serum was negative for Anti-GAD 65 autoantibodies, and C-Peptide levels were detectable, and there was no evidence of insulin resistance. Body mass index (BMI) was 23.2 kg/m². Her 70-year-old mother had been diagnosed with diabetes Type II at age 32 and she had received oral hypoglycemic drugs such as metformin and glibenclamide for many years; but now, the mother’s blood sugar levels are controllable by administration of a low to moderate doses of insulin. After confirmation of MODY for the
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proband, metformin was changed to glibenclamide (a sulfonylureas), and proper glycemic control was achieved. Family history chasing showed the history of diabetes in three generations, and multiple affected members were found, indicative of autosomal dominant (vertical) transmission mode of inheritance [Figure 1].

In the second case, the proband was a 12-year-old girl. Having a positive family history of diabetes in the paternal family, she was referred to an endocrine specialist. She experienced mild progressive hyperglycemia since age 10. Fasting blood sugar levels such as OGTT were increased slightly. Serum was negative for anti-GAD 65 autoantibodies, and measurable amounts of C-peptide were detected. Her BMI was normal (24.7 kg/m²), and glycosuria was absent. There was no history of insulin resistance in the family. She was responsive to low doses of metformin. Her affected father had experienced diabetes, and subsequently, hypoglycemia caused by gliclazide (sulfonylureas) was prescribed at age 20. The pedigree information showed autosomal dominant inheritance of diabetes in the family, and multiple affected members were observed in the family pedigree [Figure 2].

In the remained families in this research, the mean age of diabetes onset was between 5 and 25 years, BMI was between 22 and 26, history of diabetes was positive in only one parental family, and there was no history of diabetic ketoacidosis attacks.

DNA sequencing results

Sanger sequencing results revealed the missense mutation g.1566G>A (c.758G>A; p.G253E) [Figure 3] in two unrelated probands, both of whom were heterozygous for the mutation. Cosegregation analysis was performed for both families and revealed the same mutation in affected members, and no mutation was detected in the normal members of both families.

In five families, compound heterozygosis state was disclosed for two common variants (p.I27L and p.S487N) [Figure 4]. In one of the families, a rare variant rs561269721 [Figure 5] was detected in affected members.

Table 1: Primer sequences for amplification of the exons of hepatocyte nuclear factor 1 alpha

| Exon | Forward primer (5’→3’) | Reverse primer (5’→3’) | PCR product length (bp) | Annealing temp (°C) |
|------|------------------------|------------------------|-------------------------|-------------------|
| 1    | TGCAGGAGTGGTTGTTGTC    | GAAGGTCTAGGGGGACTCAAC  | 536                     | 58                |
| 2    | CCTCAAGGTTGCAAGAGGTC   | TGTGTAATGGGGATGGTGA    | 395                     | 57                |
| 3    | GCCATGCGAAATGAAAAGA    | GGAAGCTGCAAGCGCTTAA    | 387                     | 55                |
| 4    | GGCCAGAGCTCAGCTCTCAG   | AAGGAGTGGCATGAATGGAA   | 464                     | 55                |
| 5    | GCCTAAGGCACTGACTGAGG   | CAGCTGCTGACCTGAGAGG    | 391                     | 58                |
| 6    | CCAACTCTCTTCTTCTTGG    | AATGAATGAGATGTCCCAAGT  | 400                     | 61                |
| 7    | CTCTGGGAGAGAGAGGTTG    | GTCCCCAGAGACATCATGAGA  | 397                     | 63                |
| 8    | TTTTGAATAACAGGCTTGA    | CTGGGAGAGGCCATGTTCTG   | 389                     | 59                |
| 9    | ACCAAGCTGAGAAGCTCCAG   | CTTCCACAGCACGGCCTA     | 375                     | 61                |
| 10   | TGATTACCCCTAGGGACAGG   | CCTGCCCCCTTGTTAGCTT    | 640                     | 62                |

PCR: Polymerase chain reaction

In silico analysis

Sanger sequences results were analyzed using Mutation taster 2.0, Polyphen-2, FATHMM, SIFT, PON-P2, PROVIAN, and PANTHER software tools to predict the effects of the identified variants [Tables 2 and 3]. Protein modeling was accomplished using swissmodel.expasy.org online program, based on 1IC8 PDB structure of HNF1A [Figure 7a and b].

Discussion

So far, up to 450 different mutations in HNF1A gene have been reported to cause MODY3.[12] For the first time, here, we report a mutation c.758G>A (p.G253E) in exon 4 of HNF1A in two unrelated kindreds from Iran. The mutation was first reported by Colclough et al. (2014, unpublished data).[1]

We also looked at the molecular mechanisms through which the current mutation causes diabetes. G253 is within the DBD of the HNF1A protein. It is a small neutral amino acid which apparently plays important roles in establishing intermolecular hydrogen bounds in the protein.[16] Indeed, G253 is situated in the POU domain of the protein, a highly conserved domain having homology with Pit-1 and Oct-1 POU domains. The side chain of glycine is a sole hydrogen atom, whereas glutamic acid has a double negative charge with a big side chain. G253>E substitution
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Figure 2: Pedigree of the second family with p.G253E mutation

Figure 3: Heterozygous mutation c.758G > A (p.G253 > E) in the hepatocyte nuclear factor 1 alpha gene

Figure 4: Common variant p.I27L (above) in exon 4 and common variant S487N (down) in exon 7 of hepatocyte nuclear factor 1 alpha

can lead to considerable changes in this substantial region of the protein. Based on Chi et al.'s work on the effects of some mutations in the crystallized structure of the HNF1A protein, missense mutations in the DBD of HNF1A reduce
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Table 2: In silico analysis of variant pathogenicity

| Variant/genomic location | Exon | Amino acid alteration | Software | Mutation Taster 2.0 | Polyphen-2 | FATHMM | SIFT | Pon-p2 | PANTHER |
|--------------------------|------|-----------------------|----------|---------------------|------------|--------|------|--------|----------|
| g.223                    | 5'UTR| No                    | Prediction Score | Disease-Causing | -          | -      | -    | -      | -        |
| g.305A>Cc. 79A>C         | 1    | p.I27L                | Prediction Score | polymorphism    | Probably Damaging | 1.00  | 1    | 0.331  | 0.352    |
| g.15666G>Ac. 758 G>A     | 4    | p.G253E               | Prediction Score | Disease-Causing | Probably Damaging | 1.00  | −3.73 | 0.00   | 0.961    |
| g.19082 G>Ac. 1460 G>A   | 7    | p.S487N               | Prediction Score | benign            | Damaging     | 1.00  | −4.39 | 0.14   | 0.961    |

PSEP: Preservation time for evaluated position, NA: Not available, MY: Million years

Table 3: Effect of the variant p.G>253E on protein deduced by PROVEAN

| Software | p.I27L | p.G253E | p.S487N |
|----------|--------|---------|---------|
| PROVEAN  | Neutral| Deleterious| Neutral|
| Score    | −0.917 | −5.472  | −0.610  |

transcriptional activity of the gene.[16] They investigated the effects of some mutations on the transcriptional activity of the gene and found that the V246D and N257W (which are situated in 5 prime and 3prime sides of the current mutation) reduced the transcriptional activity of HNF1A by 70%–75%, respectively.[16] The rigidity of POU domains in the interface between POUH and POUS domains seems to be necessary for optimal transcription activity of the gene. One possible effect of the p.G>253E mutation is gain of flexibility for this region of the protein that can affect its optimal transcription activity.[16] Missense mutations in TFs at DNA-binding or protein-binding sites are disease causing.[17] Indeed, Kim et al. have worked on the effects of missense mutations within POU domains of the HNF1A protein in Korean patients. They found the p.R263L mutation (exactly ten aminoacid residues next to the p.G253) reduced the activation of downstream gene promoters, such as insulin and glucose transporter type 2 (GLUT2) promoters in NIH3T3 and MIN6N8 cells.[18] Therefore, the p.G253E is important from two points of view. First, specific side chain-backbone hydrogen bond G253:Q176 and backbone-backbone G253:Q176 will be disrupted, and new hydrogen bonds are formed between glutamic acid big sidechain with other intermolecular aminoacids in the HNF1A protein; the result is interruption of correct configuration of the protein or protein domains, and the second is the negative charge of glutamic acid that can interrupt interactions of DBD domain with DNA phosphate backbone. Therefore, these changes can lead to a reduction of optimal DNA-binding affinity of HNF1A with the promoter of downstream genes such as GLUT2, insulin, and pyruvate kinase, genes involved in glucose metabolism.[19]
The diabetes age of onset for the probands of two families carrying the same mutation was different; but, no main interfamilial differences were observed. The common phenotypic features include increased OGTT and high sensitivity to sulfonylureas. Clinical variation has been reported among MODY patients. The difference in age of onset between the two probands may be due to errors of diagnosis, or inheritance of different genes modifying the phenotype, and even environmental factors or different lifestyle.

Common variants p.I27L and p.S487N in HNF1A were reported as causing early-onset-inherited diabetes Type 2; also, these two common variants have been reported as MODY3 causing at heterozygous state. The findings of this research are in accordance of this two mentioned studies. The unknown issue is that any compound heterozygous state for these two variants can cause diabetes in early ages, or other factors such as cis and trans conditions for the two variants are important too. If the two variants in cis conditions cause diabetes, one of the possible interpretations may be haploinsufficiency; therefore, the diabetes is MODY. In trans condition, the possible interpretation may be additive effect of the two variants, and early type 2 diabetes is the resulted condition. The other possibilities such as modifier loci, environmental factors, and other modifier variants in the gene should not be ignored.

The third finding of this study was rs561269721 (g.223G>A), a rare benign mentioned variant (MAF 0.012) in the Kozak sequence, that cosegregated with the condition in one of the studied families (LOD score = 3.01/easy linkage software). The pathogenicity of this variant is in query because its global MAF is very low; the effect prediction for the variant was disease causing and the position of the variant is a critical position (-4 nucleotide) that may affect ribosomal binding activity or affinity.

Finally, two novel polymorphisms were detected in intron 8 of the gene. These two variants were predicted as nonpathogenic in in silico analyses, and they have no effect on splice sites or exon–intron junctions.

**Conclusion**

The role of HNF1A variants in development of diabetes has been somewhat known. Few studies have been performed on MODY and its subtypes in Iranian population. The etiology of MODY in our studied families was elucidated in 20% of the families, related to a missense mutation in HNF1A. Indeed, in this research, at least 70%–80% of early-onset diabetes depended on mutation or common variants in HNF1A. Whether or not, these common variants in the gene are considered as liability factors for T2DM or as MODY causing mutations, it is noteworthy.
that compound heterozygous conditions of common variants in HNF1A can cause early-onset diabetes, and check of the population for this variants is necessary for the best management of this types of diabetes. The estimations of the current study may highlight the role of HNF1A in diabetic population of Iran. Certainly, to estimate the frequency of HNF1A MODY3 causing variants in Iranian population, more investigations are warranted. The project is in progress with consideration of the remaining families for the next generation sequencing.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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