OPEN ACCESS Freely available online

ISSN: 2572-5629
Diabetes Case Reports

Case Report

HNF1A Gene Mutation (c.811del, p.Arg271Glyfs) Causing Maturity Onset of Diabetes of the Young 3: A Case Study of an Indian Patient

Neelima Chitturi*, Satish Sunkara, Sandhya Kiran Pemmasani, Anuradha Acharya

Research and Development Division, Mapmygenome India Limited, Plot No. 12/2, Royal Demeure, HUDA Techno Enclave, Sector-1, Madhapur, Hyderabad, Telangana-500081, India

ABSTRACT

Background: Maturity-Onset Diabetes of the Young (MODY), a rare class of diabetes that develops in early adulthood, is thought to have a prevalence of less than 5%. The best practice for the management of the MODY is to identify its type, through genetic testing. This paper presents a case study to identify the genetic etiology of diabetes.

Case history: The presented case was diagnosed with diabetes at the age of 17 with a strong family history of diabetes. The individual was on insulin (12 units) with high random blood sugar levels (200 mg/dL to 300 mg/dL) and HbA1c (9.2%). Whole exome sequencing has shown the presence of a known likely pathogenic variant in the *HNF1A* gene (chr12: 121432062, c.811del, p.Arg271Glyfs), known to cause MODY3. Other unaffected family members were screened for the variant using Sanger sequencing, but the results were negative. The association of this variant with the disease is reported for the first time in the Indian population.

Conclusion: Blood sugar levels can be brought under control with the right medical care, such as sulphonylurea therapy, and eventually, painful insulin medication can be stopped. For a precise diagnosis and prognosis of diabetes, it's crucial to identify the genetic cause of the disease. This case demonstrates the critical role of genetic testing in proper treatment and management of diabetes.

Keywords: Case report; Diabetes; Genetics; *HNF1A*; MODY3; Sequencing

INTRODUCTION

Diabetes is of several types and Maturity-Onset Diabetes of the Young (MODY) is one among them. Its characteristics include hyperglycemia and persistent microvascular long-term consequences such as retinopathy, nephropathy, and neuropathy [1]. It is a relatively rare type of diabetes with an autosomal dominant mode of inheritance that typically manifests in adolescence or early adulthood, before the age of 25. It is estimated to have a prevalence of about 2% globally and 7.7% in India, which ranks second with highest number of diabetic patients after China [2-4]. There are several types of *MODY*, each caused due to mutations in different genes: *MODY1* (HNF4A), *MODY2* (GCK), *MODY3* (HNF1A), *MODY4* (PDX1), *MODY5* (HNF1B), *MODY6* (NEUROD1), *MODY7* (KLF11), *MODY8* (CEL), *MODY9* (PAX4), *MODY10* (INS), *MODY11* (BLK), *MODY13* (KCNJ11) and *MODY14* (APPL1) [5, 6]. Thus, it is referred as a monogenic disorder. While many biochemical tests are used to determine the type of diabetes, whole exome sequencing helps to determine the type of diabetes, and to further plan the treatment strategy.

This study goes into great detail about the MODY3-causing mutation in the *HNF1A* gene. The *HNF1A* gene, which is located on chromosome 12, encodes a homodimeric protein that functions as a transcription factor for a number of genes unique to the pancreas and liver. It has a major role in the development of the liver and pancreas, glucose import and homeostasis, insulin production, and renal glucose absorption [6, 7]. Researchers found up to 350 distinct mutations in the gene's promoter region and exons in diabetic patients, and a few have also been found in Indians [1, 8 - 11]. The objective of this study is to demonstrate the importance of identifying underlying genetics of diabetes through whole exome sequencing.

CASE PRESENTATION

Clinical History

The patient was diagnosed with diabetes at the age of 17 years and was on insulin (12 units). The random blood sugar levels were 200 mg/dL to 300 mg/dL and HbA1c was 9.2%. The patient was recommended for MODY testing after ruling out the possibilities of type 1 and type 2 diabetes. The parents of the proband are healthy and non-diabetic. Their random blood sugar levels and HbA1c

Correspondence to: Neelima Chitturi, Research and Development Division, Mapmygenome India Limited, Plot No. 12/2, Royal Demeure, HUDA Techno Enclave, Sector-1, Madhapur, Hyderabad, Telangana-500081, India; E-mail: drneelimachitturi@mapmygenome.in

Received: 08-May-2023, Manuscript No. DCRS-23-21256; **Editor assigned:** 10-May-2023, PreQC No DCRS-23-21256(PQ); **Reviewed:** 30-May-2023, QC No DCRS-23-21256; **Revised:** 06-Jun-2023, Manuscript No. DCRS-23-21256(R); **Published:** 13-Jun-2023, DOI: 10.35248/2572-5629.23.8.158.

Citation: Chitturi N, Sunkara S, Pemmasani SK, Acharya A (2023) *HNF1A* Gene Mutation (c.811del, p.Arg271Glyfs) Causing Maturity Onset of Diabetes of the Young 3: A Case Study of an Indian Patient. Diabetes Case Rep. 8:158.

were within normal limits. The pedigree is given in Figure 1.

All experimental and analytical procedures were performed as per standard manufacturer's protocol. An informed written consent mentioning the use of the sample for research was taken from the proband and her family members. Research was carried out in compliance with the Helsinki declaration and the procedures had been approved by internal bio-safety committee at Mapmygenome.

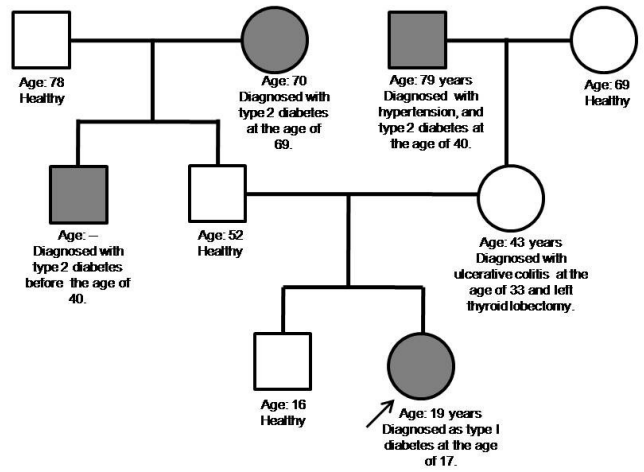

Figure 1: Pedigree of the proband.

Extraction of DNA from blood

Genomic DNA was extracted from the blood samples using Nucleospin DNA isolation kit from Takara Bio and quantified spectrophotometrically using QubitTM from Thermo Fisher Scientific.

Whole exome sequencing and analysis

Exome libraries were prepared using Twist Comprehensive Exome Panel, from Twist Bioscience. Sequencing was performed on a NovaSeq 6000 Illumina sequencer and paired-end reads of length 150 bases were generated. Quality of raw data was verified using fastqc tool version V0.1.1 and adapters were removed using Trimommatic software version 0.39. The trimmed paired end reads were aligned to reference human genome (hg19 version) using BWA version 0.7.17. Haplotype Caller package, of GATK version 4.2.0.0, was used to call variants as per Broad Institute's Best Practices protocol. Variants were annotated using VEP release 104 (against the Ensembl release 75 human gene model) and data from other resources such as dbsnp, dbnsfp, snpeff, ClinVar, HGMD, OMIM and HPO. The variants were filtered using criteria: a) variants of genes associated with diabetes in general and MODY in particular b) exclude synonymous, 5' and 3'variants c) variants with gnomAD & 1000Genomes frequency less than 5%. Variant classification was done as per American College of Medical Genetics and Genomics (ACMG) guidelines [12].

Targeted validation by Sanger sequencing

The presence or absence of variant was confirmed in samples of mother and brother using bidirectional Sanger sequencing. Father was not available and so his sample could not be tested for the identified variant.

RESULTS AND DISCUSSION

Whole exome sequencing of the proband revealed a heterozygous frame-shift deletion in exon 4 of *HNF1A* gene (NM_001306179.2:c.811del, non-functional gene product and leads to nonsense mediated decay, which is an established disease mechanism (ACMG: PVS1).

This particular variation is not seen in her mother and her sibling (Figure 2) and is likely a spontaneous mutation in the proband (ACMG: PM6). The variant is not found in gnomAD population database (ACMG: PM2). Variants in other genes that are known to cause diabetes were also considered for analysis, and no other significant variants were found (ACMG: PP4). The variant was classified by ClinVar as Likely Pathogenic (ACMG: PP5) based on unpublished results [13]. Based on above ACMG criteria, we recommend this particular variant to be re-classified as 'Pathogenic' for MODY3.

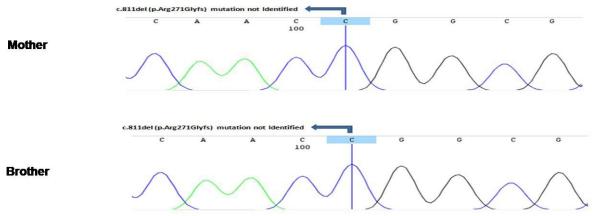

Figure 2: Sanger sequencing confirmation of the variant in the mother and brother of the proband.

Various types of mutations in HNF1A gene have been identified in diabetic patients [8-11]. The most common mutations are c.872dupC in exon 4 (present in 234 affected families) and c.391C>T in exon 2 (present in 29 affected families) [14]. But the variant reported in this case study has not been reported in the Indian population to the best of our knowledge. Mutations in the HNF1A gene can alter the normal functioning of the pancreas, impairing insulin synthesis and leading to high blood sugar levels. Affected people have hyperglycemia and a higher chance of developing other issues, such as diabetic nephropathy and cardiovascular problems. Patients with *HNF1A* mutations have been observed to respond particularly well to sulfonylurea, according to research. Its use can postpone the requirement for insulin therapy and, over time, lessen microvascular problems [15]. Though the current study could identify the genetic cause of diabetes it is limited in terms of lack of follow-up on the patient's response to sulfonylurea therapy.

CONCLUSION

According to 2019 predictions, 77 million Indians have diabetes, and by 2045, that number is projected to rise to 134 million. Finding the genetic basis of diabetes is crucial for effective treatment and a better prognosis. Correct therapy at the earliest phases of the illness will result in fewer health issues and better management. The case study presented here strongly supports the need for genetic testing for diabetic therapy.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Material preparation and wet lab analysis was performed by (Satish Sunkara), pipeline development by (Sandhyakiran Pemmasani), in silico analysis and variant identification by (Neelima Chitturi), the first draft of the manuscript was written by (Neelima Chitturi) and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

COMPLIANCE WITH ETHICAL STANDARDS AND ETHICAL APPROVAL

An informed written consent mentioning the use of the sample for research was taken from the participants. Research was carried out in compliance with the Helsinki declaration and the procedures have been approved by internal bio-safety committee at Mapmygenome.

FUNDING

This study was not funded by any agency.

CONSENT TO PARTICIPATE AND/OR CONSENT TO PUBLISH

Informed written consent was obtained from all individual participants included in the study. The authors affirm that human research participants provided informed consent for publication of the image in Figure 2.

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