American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

HNF1α Associated Novel Missense Mutation Associated with MODY-3 and Type 2 Diabetes in an Indian Family

Kanjaksha Ghosh, Kinanka Ghosh* and Bipin Kulkarni

National Institute of Immunohematology, Mumbai, India.

***Corresponding author:** Kinanka Ghosh, National Institute of Immunohematology, Mumbai, India.

To Cite This Article: *Kanjaksha Ghosh, Kinanka Ghosh* and Bipin Kulkarni. HNF1α Associated Novel Missense Mutation Associated with MODY-3 and Type 2 Diabetes in an Indian Family. Am J Biomed Sci & Res. 2023 19(2) AJBSR.MS.ID.002574,* DOI: 10.34297/AJBSR.2023.19.002574

Received: April 12, 2023; **Published:** July 03, 2023

Abstract

Commonest cause of Maturity onset Diabetes Mellitus of the Young (MODY) in European ancestry is the inheritance of mutation in HNF1α gene. Though MODY is not uncommon in India but extensive genetic studies in this condition is lacking. We report here a novel base change in the aforementioned gene leading to MODY as well as NIDDM in the members of the same family.

Keywords: MODY-3, HNF1α Mutation, India, diabetes, NIDDM

Introduction

Maturity onset diabetes of the young (MODY) is a dominantly inherited insulin nondependent diabetes mellitus affecting persons of less than 35 years of age. These patients generally do not need insulin for their management and are not prone to ketoacidosis. Normally they constitute less than 1 % of NIDDM (Noninsulin dependent diabetes mellitus) in European countries but is seen more often in Asian subcontinent. Fourteen different genes have been implicated in the inheritance of the disease known as MODY.

Commonest cause of MODY in European ancestry is the inheritance of mutation in HNF1α gene. Though MODY is not uncommon in India but extensive genetic studies in this condition is lacking. We report here a novel base change in the aforementioned gene leading to MODY as well as NIDDM in the members of the same family.

Case Presentation

The patient who is now 30 years old developed at the age of 28 years dryness of mouth, difficulty in vision, indigestion, and sticky sweating. One of the days he felt dizzy with black out and was admitted in emergency room and was found to have high blood sugar of (10 hour without food) of 311mg/dl (17.5mmol/l). He was acutely managed with soluble human Insulin and subsequently investigated in detail for Diabetes mellitus. His plasma insulin level was 25.2mIU/l, (Blood glucose 17 mmol/l), C-peptide levels 2.35ng/ml, HbA1c of 9.5 %, Calculated HOMA IR -19.35, HOMA-A2:5.59, Auto antibodies to GAD and PS2 negative. These investigations were repeated after 4 years with essentially similar results.

Imaging studies which included ultrasound and MRI of abdomen was normal and no calcification in Pancreas was noted. Serum CPK MB, Liver and renal Function tests, serum amylase all was normal. The patient responded extremely well on metformin and 1.25 mg Glipizide daily and was on similar regimen for last 2 years. Presently his fasting blood glucose is between 5.5-6.5 mmol/l and HbA1C between 6.5 and 7%. He did not have any documented hypoglycaemic attacks during the period. There was no significant past history except of falciparum malaria 8 years back and an operation for semilunar cartilage repair of the right knee joint 10 year back when all investigations prior to operation was normal. For almost 6 months prior to detection of diabetes he had intense mental pressure on account of studies and in his quest for getting a job in a foreign land.

The patient had a three-generation history of NIDDM affecting his father (at 62 years of age) father's sister (at 69 years, deceased 77years), Fathers paternal uncle (diagnosed 71 years, deceased 79 years). Some of the other members of the family had cataract operation or cancer or complete heart block. Fasting and postprandial blood sugars available for them in those times (beyond 55 years of

age) were all normal. None of them developed any known diabetes related complication.

Index cases underwent whole exome analysis for MODY and related genes using Illumina Hiseq 2500 analyser. (At 110 X). A missense pathogenic base change in HNF1α gene (Glu71Lys) was recorded. The same heterozygous change was confirmed by Sanger sequencing (Figure 1) and the same change was seen in his father who was a diabetic and in his elder brother (34 years) who has not yet developed any diabetes. Index case's paternal uncle (63 years) is a non-diabetic and does not have the mutation in the said gene.

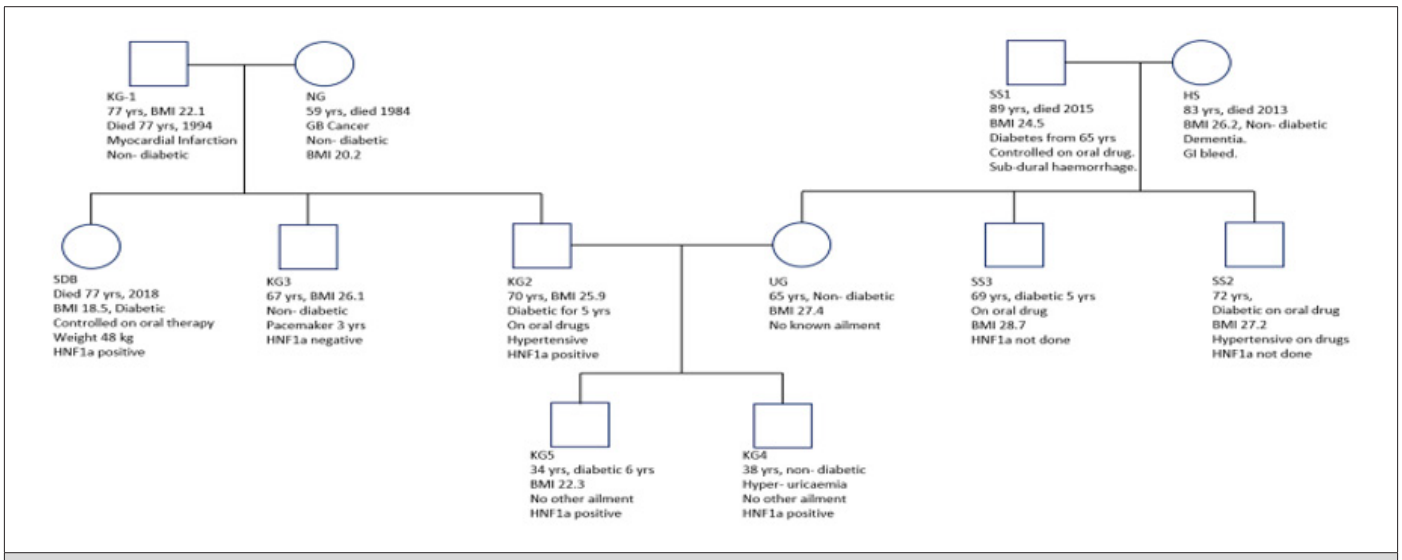

Figure 1:

There are a few large studies from Caucasian population on the nature of mutation in MODY cases [1-3] where HNF1α mution was found to be the most common (40-70 %) followed by that of glucokinase gene. In India three mutation studies on MODY showed quite different pattern of gene involvement in the disease [4-6]. In these three studies i.e., two from south and one from north India showed only 2-8% Indian MODY patients have HNF1α mutation and glucokinase mutation is also distinctly rare. Only one case report could be found [7] with this mutation from Indian patient in the literature.

One of the important findings in the present study was presence of NIDDM and MODY 3 in the same family with same mutation. It has been documented that position of mutation in HNF1α gene determines the age at which diabetes is detected [8]. Mutation in exome 8-10 cause at least 8 years early appearance of diabetes compared to mutations in preceding exons.

Our mutation is novel (Glu71Lys) and is situated in the dimerisation (Dim) domain of HNF1α gene. Here an acidic dicarboxylic amino acid (Glutamic acid) is replaced by highly basic diamino amino acid Lysine. This is an important change which can affect dimerisation rate and potential malfunction of the protein. This change has not been detected in a large number of similar populations tested elsewhere [4,5] in this country, hence it is unlikely to be a wild polymorphic variant in our population.

One of the important information from all these studies across the world on MODY genetic variants show that we have only been able to detect the genetic defect in a very small proportion of clinically defined MODY and the heterogeneity of this condition has also been highlighted in one of the studies conducted here [6].

It is important to know the type of mutation in MODY genes to understand its natural history, complications, epistatic effects with other genes and best management options. For example, HNF1α mutation patients responds very well to sulphonyl ureas and they are quite sensitive to the effect of this drug. Fasting hyperglycaemia along with mildly raised pancreatic lipase levels as seen in our index case along with good response to sulphonylurea therapy as seen could be important indicator of presence of this mutation. Our patient is well controlled with only 2.5mg of Glipizide twice daily along with 1.5gms of metformin. Management strategies of MODY depending on genetic defects has been well reviewed elsewhere [9].

In addition, the present case also shows that MODY and NIDDM may coexist in the same family with having same mutation. Why some patients develop diabetic features early and some late is an area for future exploration. Probably interaction with other genes and environment leads to this variation.

Hence in this era of whole genome/exome sequencing different strategies need to be taken to unravel genetic changes in so called MODY X [10] and it may be possible that quite a few of MODY may be linked to non-coding areas of human genome. Syndromic MODY may have a different story to tell all together (Figure 2).

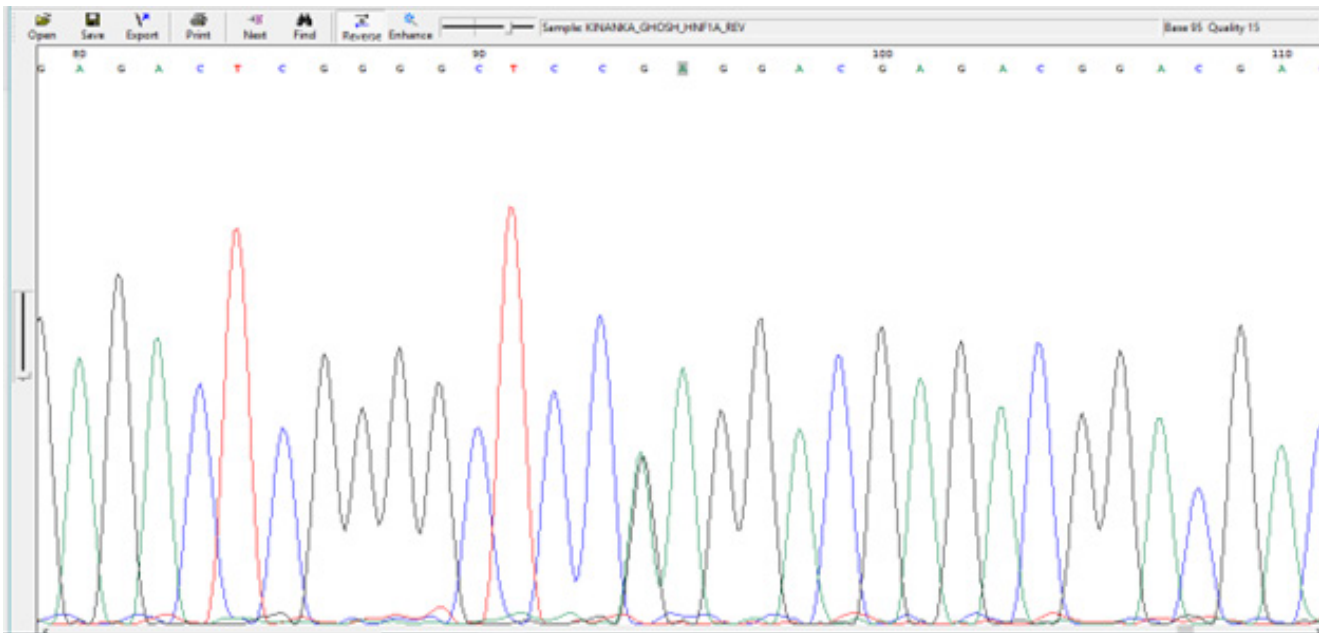

Figure 2: Index Case HeteroZygous Glu71 Lys of HNF1alpha gene.

Conclusion

In the present case we have shown a unique mutation of HNF1alpha in the index case with maturity onset diabetes of the young (MODY-3) along with other members in the same family some of them have type 2 NIDDM. Mild increase (upper limit of normal) of serum lipase was found in those with this mutation and could serve as a possible marker for this gene mutation.

Conflict of Interest

None.

Acknowledgement

None.

Role of Authors

Kanjaksha Ghosh diagnosed and worked up the patient, Kinanka Ghosh searched the literature and planned the manuscript, Bipin Kulkarni and Shrimati Shetty did the sequencing studies. All of them read the manuscript and gave valuable comments for its final shape.

Financial Assistance

None.

References

1. Bansal V, Gassenhuber J, Phillips T, Oliveira G, Harbaugh R, et al. (2017) Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. BMC Med 15: 213.
2. Anık A, Çatlı G, Abacı A, Böber E (2020) Maturity-onset diabetes of the young (MODY): an update. J Pediatr Endocrinol Metab 28: 251-263.
3. Harries LW, Ellard S, Stride A, Morgan NG, Hattersley AT (2006) Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. Hum Mol Genet 15(14): 2216-2224.
4. Mohan V, Radha V, Nguyen TT, Stawiski EW, Pahuja KB, et al. (2018) Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. BMC Med Genet 19(1): 22.
5. Chapla A, Mruthyunjaya MD, Asha HS, Varghese D, Varshney M, et al. (2015) Maturity onset diabetes of the young in India - a distinctive mutation pattern identified through targeted next-generation sequencing. Clin Endocrinol (Oxf) 82: 533-542.
6. Sahoo SK, Zaidi G, Vipin VP, Chapla A, Thomas N, et al. (2019) Heterogeneity in the aetiology of diabetes mellitus in young adults: A prospective study from north India. Indian J Med Res 149(4): 479-488.
7. Jha S, Siddiqui S, Waghdhare S, Dubey S, Krishna S, et al. (2016) Identification of a novel glucokinase mutation in an Indian woman with GCK-MODY. Lancet Diabetes Endocrinol 4(4): 302.
8. Najmi LA, Aukrust I, Flannick J, Molnes J, Burtt N, et al. (2017) Functional Investigations of HNF1A Identify Rare Variants as Risk Factors for Type 2 Diabetes in the General Population. Diabetes 66: 335-346.
9. Urakami T (2019) Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 12: 1047-1056.
10. Firdous P, Nissar K, Ali S, Ganai BA, Shabir U (2018) Genetic Testing of Maturity-Onset Diabetes of the Young Current Status and Future Perspectives. Front Endocrinol (Lausanne) 9: 253.