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Case Report

# Diabetes Mellitus With Renal and Müllerian Anomalies

Khushboo Agarwal, MBBS, MD [1], Aaron Chapla, MSC, PhD [1], Anuradha Chandramohan, MBBS, MD [2], Chandra J. Singh, MS, MCh, DNB [3], Nihal Thomas, MBBS, MD, DNB, PhD [1], Felix K. Jebasingh, MBBS, MD, DM, DNB [1,*]

[1] Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India
[2] Department of Radiodiagnosis, Christian Medical College, Vellore, Tamil Nadu, India
[3] Department of Urology, Christian Medical College, Vellore, Tamil Nadu, India

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ABSTRACT

*Objective:* Maturity-onset diabetes of the young (MODY) type 5 is caused by an autosomal dominant mutation in the *HNF1B* gene. Our objective was to report a case of a young girl with bicornuate uterus and recurrent renal stones with diabetes mellitus (DM) without a family history that was diagnosed to be MODY 5.
*Case Report:* A 12-year-old girl presented with recurrent renal stones that were managed with lithotripsy and double-J stenting at various time points. At the age of 14 years, she was found to have a bicornuate uterus with an absent cervix and vagina. She was diagnosed with DM at the age of 16 years without a preceding history of osmotic symptoms or steatorrhea. Although there was no family history of young-onset diabetes, given her long-standing history of müllerian abnormalities, renal cysts, and pancreatic hypotrophy, she was evaluated for MODY. Using the next-generation sequencing, she was found to be positive for a reported *HNF1B* gene pathogenic mutation c.494G>A (p.Arg165His), confirming a diagnosis of MODY 5.
*Discussion:* There is a significant overlap in clinical criteria for type 2 DM and MODY in the Asian Indian population. The *HNF1B* gene mutation is difficult to diagnose as none of the clinical manifestations are pathognomonic and many lack a family history of DM. Diagnostic algorithms with specific clinical and biochemical criteria along with pancreatic imaging can help in case detection and direct toward particular genetic mutation analysis.
*Conclusion:* We suggest that genetic testing be offered to patients with otherwise unexplained DM and such genitourinary anomalies.


## Introduction

Maturity-onset diabetes of the young (MODY) is a set of monogenic autosomal dominant form of diabetes mellitus (DM) that occurs due to β-cell dysfunction, responsible for approximately 2% of all patients with DM.[1] Typically, the mean age of presentation is close to 25 years, although up to 80% of cases may be misdiagnosed from an etiologic perspective.[2] Clues to the diagnosis include a lack of typical characteristics of type 1 diabetes (no pancreatic autoantibodies, low or no insulin requirement for 5 years after diagnosis, and an absence of ketoacidosis) or type 2 diabetes (lack of obesity, hypertension, dyslipidemia, and signs of insulin resistance) in the presence of a strong family history.[1] At least 14 genes have been reported to be involved in the etiology of MODY; of these genes, mutations of the *HNF1A*, glucokinase, and *HNF4A* are the most frequently involved.[3]

Renal cysts and diabetes syndrome or MODY 5 is a form of monogenic diabetes caused by a mutation in the transcription factor hepatocyte nuclear factor-1 beta (HNF1β) gene.[4] It is pivotal in the development of the kidney, genital tract, pancreas, and liver.

## Case Report

We report the case of a 12-year-old girl who presented primarily with renal anomalies and müllerian agenesis but also had associated DM. She had a history of recurrent renal stones and a baseline creatinine level of 2.5 mg/dL. Ultrasonography and noncontrast computed tomography of the abdomen performed at that time

*Abbreviations:* DM, diabetes mellitus; HNF1β, hepatocyte nuclear factor-1 beta; MODY, maturity-onset diabetes of the young.

* Address correspondence to Dr Felix K. Jebasingh, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India.
*E-mail address:* felixjebasingh@msn.com (F.K. Jebasingh).

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revealed shrunken kidneys, right renal calculi, and right hydroureteronephrosis. Therefore, ureteroscopy with double-J stenting and laser lithotripsy were performed for the same. Thereafter, she was on medical management for chronic kidney disease. Subsequently, renal calculi were also detected on the left side on multiple occasions, and lithotripsy was performed for the same. At the age of 14 years, she began having cyclical lower abdominal pain lasting 10 to 12 days in a month, which was severe enough to impair her daily activities. She had not yet attained menarche, and her examination revealed Tanner stage 4 in both breasts and pubic hair. Magnetic resonance imaging of the abdomen and pelvis revealed cavitated rudimentary horns or uterine buds along both the pelvic side walls with absent cervix and vagina (Fig. 1). Laparoscopic removal of the uterine buds was performed, and the ovaries were spared. Magnetic resonance imaging scan also showed a normal head and uncinate process of the pancreas (Fig. 2). However, the body and tail of the pancreas were absent, and these were seen as skeletonized retropancreatic splenic vessels (Fig. 3).

She was diagnosed to have DM at the age of 16 years during a routine evaluation. There was no preceding history of osmotic symptoms. She did not report a history of steatorrhea. On examination, she had a body mass index of 21.2 kg/m$^2$ with no clinical signs of insulin resistance. She was managed with short-acting insulin administered thrice daily, in view of a reduced glomerular filtration rate. Her mother had prediabetes, and her paternal aunt was diagnosed with DM late in adulthood. Her mother was a divorcee; thus, the father was not available for screening.

Although there was no family history of young-onset diabetes, given her long-standing history of müllerian abnormalities, renal anomaly, and atrophic pancreas, she was evaluated for probable MODY. Using the next-generation sequencing technology, we identified a reported *HNF1B* gene mutation c.494G>A (p.Arg165His), resulting in an amino acid change at codon 165 from arginine to histidine (p.Arg165His). This variant has been reported in the Human Gene Mutation Database and has been classified in ClinVar as likely pathogenic.[4] Additionally, there are 2 more amino acid substitutions at this codon resulting in Arg165Pro in a patient with hyperechogenic kidneys and Arg165Cys in a patient with congenital anomalies of the kidney and urinary tract.[5,6] In addition, with more than 11 pathogenic variants (within 51 base pairs) and no benign variants, this region qualifies as an *HNF1B* hotspot. Furthermore, this variant has not been reported in gnomAD exomes/genomes, and all the available in silico tools predict a pathogenic outcome. Therefore, based on the available data suggesting a strong evidence of pathogenicity and the American College of Medical Genetics and Genomics 2015 guidelines, this variant can be classified as pathogenic. The proband's mother with prediabetes was found to be negative for the *HNF1B* mutation.

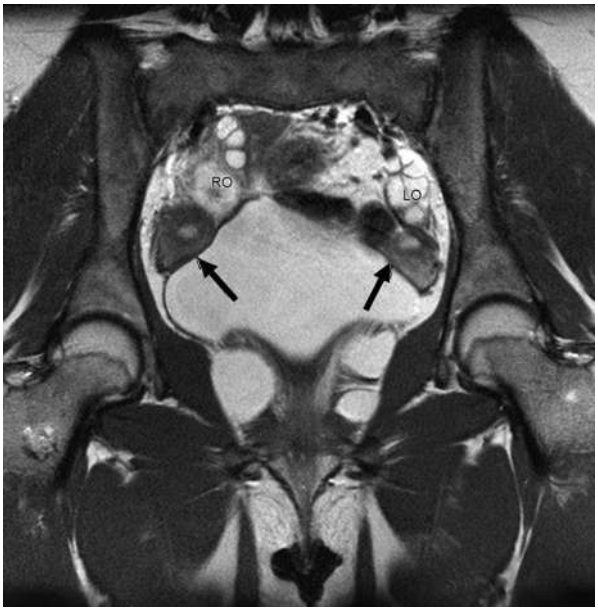


**Fig. 1.** Coronal T2-weighted magnetic resonance imaging through the pelvis showed bilateral cavitated rudimentary horns or uterine buds (arrows) and normal ovaries (marked as "RO" and "LO"). *LO* = left ovary; *RO* = right ovary.

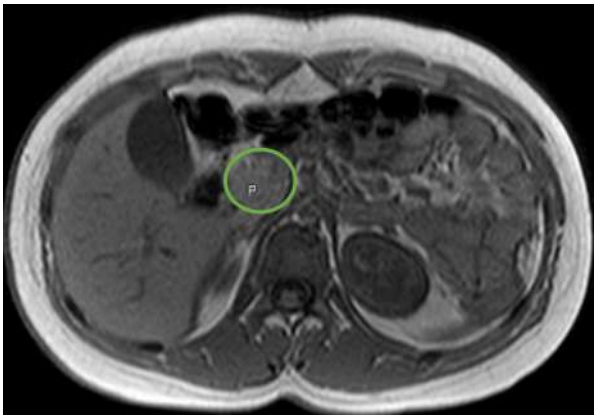


**Fig. 2.** T1-weighted axial magnetic resonance imaging through the upper abdomen showed a normal head of the pancreas (circle). *P* = pancreas.

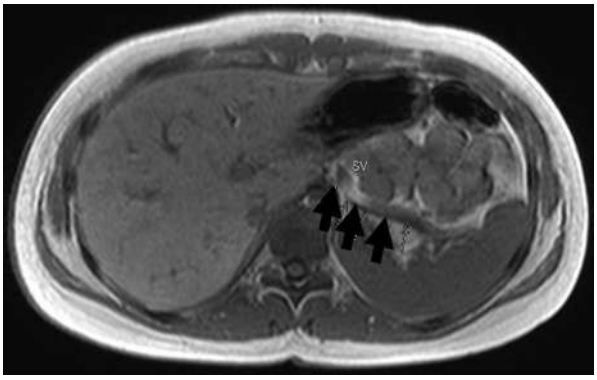


**Fig. 3.** Absent body and tail of the pancreas seen as skeletonized retropancreatic splenic vessels (arrows). *SV* = splenic vessels.

## Discussion

Until more recently, genetic studies among individuals of Asian Indian origin related to MODY have been limited to the screening of *HNF1A*, *HNF4A*, and *GCK* genes, and due to this, the mutation-positive rate has been less than 10%.[7] An extended gene panel can identify a wide spectrum of MODY mutations not previously identified. Since type 2 DM occurs a decade earlier in Asian Indians, there could be a significant overlap with MODY defined on the basis of the clinical criteria.[8] Hence, key history and biochemical features summarized in an algorithm may help with case detection.[9]

Monogenic DM generally occurs due to mutations associated with pancreatic development. Various forms of MODY have distinct characteristics such as alterations in pancreatic size (ranging from complete or partial pancreatic agenesis to diffuse pancreatic atrophy), reduced x-ray attenuation on computed tomography scan, increased pancreatic ultrasound reflectivity, pancreatic lipomatosis,

and pancreatic calcifications.[10] These findings emphasize the critical role of mutated genes in pancreatic development and differentiation. Moreover, the different findings may enable guidance in specific genetic testing. For example, pancreatic aplasia or hypoplasia is found in *EIF2AK3*, *PTF1A*, *HNF1B*, *PDX1*, or *RFX6* mutations, whereas pancreatic lipomatosis is characteristic of the *CEL* mutation.[11,12]

*HNF1*β mutations are characterized by multiorgan involvement comprising renal malformations (renal tubular leakage of magnesium and potassium, renal cysts, and progressive renal failure), pancreatic hypoplasia and/or exocrine insufficiency, liver function abnormalities, and a number of genitourinary tract malformations in both the derivatives of the müllerian and wolffian ducts.[4] None of the aforementioned clinical manifestations may be exclusively pathognomonic of HNF1β-related disease. In addition to extreme phenotypic variability among and between families, and incomplete penetrance, recognition of the condition is challenging because 50% to 60% of patients lack a family history of DM or renal involvement.[13] Therefore, individuals with HNF1β-related disease are frequently underdiagnosed and consequently are inappropriately managed regarding DM, renal replacement therapy, and genetic counseling. Subsequently, an HNF1β score has been developed as a prerequisite prescreening tool for a disease to help identify the cases. A cutoff score of 8 has a negative predictive value of 99.4%.[10]

The clinical spectrum of pancreatic morphology in HNF1β is broad, with atrophy of the pancreas being the most common finding. *HNF1*β mutation carriers have been found to have agenesis of the dorsal pancreas—the embryonic structure that gives rise to the pancreatic body, tail, and a small part of the head.[10] It has also been hypothesized that HNF1β represents a postnatal marker of progenitor cells in the pancreatic ductal tree.[14] The identified variant in HNF1β gene of our patient was first reported in a 54-year-old woman who was diagnosed with DM at the age of 20 years with a glomerulocystic kidney and subsequently developed a chromophobe renal carcinoma.[4]

## Conclusion

It is suggested that genetic testing be offered to younger female patients with uterine abnormalities and otherwise unexplained DM even in the absence of anatomical or biochemical renal anomalies on imaging.

## Author Contributions

K.A. and A.C. contributed equally to this work. K.A. and F.K.J. collected the patient data. K.A. drafted the manuscript. F.K.J., A.C., A.C.M., C.J.S., and N.T. reviewed and edited the manuscript. All authors approved the manuscript for publication.

## Disclosure

The authors have no multiplicity of interest to disclose.

## Ethics Approval

Ethics approval was not required to publish this case report.

## Consent for Publication

The case report was discussed and consent was taken from the mother who is the guardian for our patient.

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