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Case Report

# MODY5 and Serous Ovarian Carcinoma in 17q12 Recurrent Deletion Syndrome

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ABSTRACT

*Background/Objective:* Maturity-onset diabetes of the young type 5 (MODY5) is caused by a hepatocyte nuclear factor 1β (HNF1β) gene mutation on chromosome 17q12. HNF1β mutations have also been found in ovarian clear cell carcinoma, whereas ovarian non–clear cell carcinoma expresses this mutation rarely. 17q12 recurrent deletion syndrome features include MODY5, urogenital anomalies, and psychiatric and neurodevelopmental disorders. This is a report of a patient with 17q12 recurrent deletion syndrome with MODY5, uterine abnormalities, and low-grade serous ovarian cancer.
*Case Report:* A 25-year-old woman with recently diagnosed stage IIIC low-grade serous ovarian carcinoma was evaluated at the endocrinology clinic for diabetes, which was diagnosed at the age of 12 years. C-peptide level was detectable and T1DM antibodies were negative. The mother had diabetes, partially septated uterus, and solitary kidney. Abdominal computed tomography showed pancreatic atrophy, ascites, omental and peritoneal nodularity, and calcifications. Laparoscopy revealed bicornuate uterus, 2 cervices, and vaginal septum. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, lymph node dissection, and omentectomy. Chromosomal microarray analysis revealed a pathogenic ~1.8 Mb loss of 17q12, denoted arr[hg19] 17q12(34477479_36283807)x1.
*Discussion:* 17q12deletion has been described as a susceptibility locus in some ovarian cancers. However, to our knowledge, predisposition to ovarian cancer as a feature of 17q12 recurrent deletion syndrome or MODY5 was not reported previously.
*Conclusion:* The disease association reported suggests that medical providers should periodically evaluate for ovarian cancer, gut, and urogenital abnormalities in individuals with MODY5. Likewise, individuals with diabetes plus urogenital tract abnormalities or 17q12deletion in an ovarian tumor should undergo genetic testing for MODY5.


## Introduction

Maturity-onset diabetes of the young type 5 (MODY5) is caused by a mutation in the hepatocyte nuclear factor 1 homeobox β (HNF1β) gene on chromosome 17q12. The most common mutation is a whole gene deletion associated with 17q12 recurrent deletion syndrome.[1] This syndrome presents with a variable number of clinical manifestations, including congenital abnormalities of the kidney and urogenital tract (CAKUT), nonketotic hyperglycemia (MODY5), and ocular problems, including strabismus, liver transaminitis, hypomagnesemia, hyperuricemia, and neurodevelopmental and psychiatric disorders.[2] HNF1β mutations have also been found in ovarian clear cell carcinoma (CCC), whereas ovarian non-CCC expresses this mutation rarely.[3] This is a report of a patient with 17q12 recurrent deletion syndrome with MODY5, uterine abnormalities, and low-grade serous ovarian carcinoma.

*Abbreviations:* CAKUT, congenital abnormalities of the kidney and urogenital tract; CCC, clear cell carcinoma; MODY, maturity-onset diabetes of the young.

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## Case Report

The patient was a 25-year-old woman who was recently diagnosed with ovarian cancer. She was evaluated at the endocrinology clinic for diabetes. The patient was diagnosed with type 2 diabetes at the age of 12 years, when she presented with moderate hyperglycemia. GAD65, islet cell, and insulin auto-antibodies were negative, and C-peptide was detectable (Table). She was treated with metformin, glargine, and lispro. Her diabetes was not optimally controlled during adolescent and young adult years; however, her chart notes record no history of diabetic ketoacidosis despite occasionally missing basal insulin. Her medical history is also notable for short stature, strabismus, depression, and anxiety. The patient has had chronic transaminitis since early teens with nondiagnostic serologic evaluation and 2 nondiagnostic liver biopsies. On imaging, mild focal lobular inflammation was seen. She was found to be a heterozygote for the hemochromatosis gene HFE C282Y. Her ferritin level was normal. She has a history of acute respiratory distress syndrome of unclear etiology. Family history was significant for hemochromatosis, diabetes, solitary kidney, and a partially septated uterus with recurrent miscarriages in her mother (Fig. 1). At the age of 25 years, the patient presented with abdominal pain. Computed tomography of the abdomen pelvis with contrast showed distal pancreatic atrophy (Fig. 2 *A* and *B*), ascites, omental and peritoneal nodularity, and calcifications. Except for an elevated CA-125, tumor markers were normal. Exam under anesthesia and laparoscopy revealed a bicornuate uterus, 2 cervices, and vaginal septum. She underwent total abdominal hysterectomy with bilateral salpingo-oopherectomy, lymph node dissection, and omentectomy. Pathology confirmed stage IIIC low-grade serous ovarian carcinoma that was strongly positive for estrogen receptors and weakly positive for progesterone receptors. She denies tobacco, alcohol, or illicit/recreational drug use. Her examination was otherwise notable for short stature, with a height of 147 cm. The body mass index was 27 kg/m$^2$. Chromosomal microarray analysis revealed a pathogenic ~1.8 Mb loss of 17q12, denoted arr[hg19] 17q12(34477479_36283807)x1.

### Highlights

- A mutation in HNF1β gene on chromosome 17q12 is responsible for MODY5
- MODY5 may be overlooked in diabetes with features of 17q12 recurrent deletion syndrome
- Perform genetic evaluation of MODY5 in diabetes plus liver, pancreas, and urogenital abnormalities
- Perform genetic evaluation of MODY5 in diabetes and 17q12 deletion in an ovarian tumor
- Periodically test women with MODY5 for ovarian cancer, urogenital and gut abnormalities

### Clinical Relevance

Endocrinologists, gynecologists, oncologists, and primary care physicians should suspect maturity-onset diabetes of the young type 5 (MODY5) in patients with diabetes and other features of the 17q12 recurrent deletion syndrome and vice versa. When such suspicion is established, genetic testing is warranted as such a diagnosis may have a significant impact on management of patients with this syndrome.

## Discussion

Mutations of the HNF1β gene cause monogenic diabetes known as MODY5, which represents only 2% to 6% of MODY5 cases.[1] HNF1β is a transcription factor that is required for the development of the kidney, genitourinary tract, liver, lungs, gastrointestinal tract, and pancreas. Most HNF1β mutation carriers present with CAKUT, and hypoplastic glomerulonephritic kidney disease. Thus, CAKUT is the earliest presentation of MODY5 in children, and up to 20% of patients with CAKUT have a gene mutation in HNF1β. Highly variable phenotypes and clinical manifestations are variable even within families.[1,2]

17q12 recurrent deletion syndrome presents with a variable combination of urogenital anomalies, young-onset non–ketosis prone diabetes (MODY5), and neurodevelopmental/psychiatric disorders.[2,3] This microdeletion syndrome has a prevalence of 1 per 14 000 to 1 per 50 000.[4] Inheritance can be autosomal dominant from an affected parent in 30% of cases; however, de novo mutations are seen in about 70% of cases.[1,2,4] Although >50 mutations in the HNF1β gene causing MODY5 have been described, the most frequent mutation, occurring in ~50% of patients, is a whole gene deletion.

MODY5 due to 17q12 recurrent deletion syndrome should be considered in individuals with diabetes and nondiabetic kidney disease, genitourinary tract, and gut malformations, particularly uterine abnormalities, pancreatic hypoplasia, and hepatic dysfunction. Because of pancreatic hypoplasia and hepatic insulin

**Table**
Laboratory Values[a]

| Laboratory value | Patient result | Std normal range |
|---|---|---|
| C-peptide (ng/mL) | 2.7 | 1.1-4.4 |
| Anti–GAD-65 antibodies (nmol/L) | 0.00 | ≤0.02 |
| Islet cell (ICA512) antibodies (units/mL) | <0.8 | 0.0-0.9 |
| Insulin antibodies (mcUnits/mL) | 2.7 | 0.0-4.9 |
| CA 19-9 (units/mL) | 18.6 | 1.0-35.0 |
| CA 125 before surgery (units/mL) | 240.2 | 0.0-35.0 |
| CA 125 6 months after surgery (units/mL) | 9.2 | 0.0-35.0 |
| CEA (ng/mL) | 1.5 | 0.1-5.0 |
| α-Fetoprotein (ng/mL) | <2.0 | 0.0-8.3 |
| Inhibin A (pg/mL) | 1.3 | <97.5 |
| Inhibin B (pg/mL) | 11 | <139 (premenopausal, follicular)<br><92 (premenopausal, luteal) |
| Magnesium (mg/dL) | 1.2 | 1.4-2.5 |
| AST (units/L) | 128 | 10-45 |
| ALT (units/L) | 149 | 7-4 |

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CA = cancer antigen; GAD = glutamic acid decarboxylase; Std = standard.
[a] Type 1 diabetes mellitus antibodies were obtained at the age of 12 years. Other laboratory values were obtained at the age of 25 years.

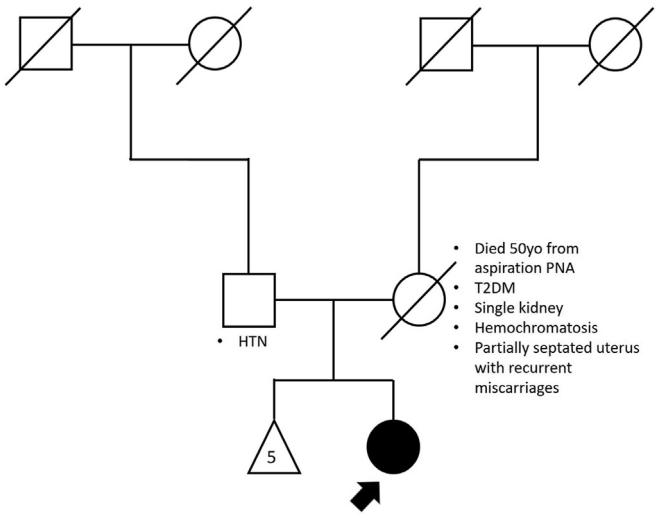


**Fig. 1.** Pedigree. *HTN* = hypertension; *PNA* = pneumonia; *T2DM* = type 2 diabetes mellitus.

resistance, patients often need insulin as treatment.[2,5] Diabetes complications, chronic kidney disease stages 3 and 4, and end-stage renal disease are common in adults with MODY5 and less common in children.[5]

The most common renal manifestation of HNF1β mutations is renal cysts. Other manifestations include poor corticomedullary differentiation, hydronephrosis, or dilated ureter. Renal function may be impaired in ~41% of the cases. Renal dysfunction is frequently associated with hypomagnesemia, hypocalciuria, and hyperuricemia.[1,3] Interestingly, in a report, a single kidney, a finding noted in our patient's mother, was found in about 20% of adults carrying HNF1β mutation. [6] Involution of multicystic dysplastic kidneys and unilateral kidney agenesis are 2 hypotheses for a single kidney in adults carrying HNF1β mutation.[1,3]

Individuals with 17q recurrent deletion syndrome may also have pancreatic involvement. Our patient's imaging showed pancreatic atrophy (Fig. 1). A literature review reports 52% of patients with this syndrome have structural abnormalities, including hypoplasia or aplasia, disruption of the main pancreatic duct, or aplasia of the great pancreatic artery. Approximately 70% of the patients may experience exocrine pancreatic insufficiency in addition to diabetes. Up to 65% of the patients may have cholestatic hepatopathy.

Structural involvement of the genital tract, including bilateral or unilateral undescended testicles or bicornuate uterus, has been documented in half of the patients with 17q12 recurrent deletion syndrome.[1] Our patient has a bicornuate uterus, and her mother was reported to have partially septated uterus leading to recurrent miscarriages.

MODY5 caused by 17q12 recurrent deletion syndrome explains many of our patient's medical problems, including bicornuate uterus, MODY5, pancreatic atrophy, short stature, chronic transaminitis, intermittent hypomagnesemia, depression, and anxiety. In addition, the less common autosomal dominant inheritance pattern of this syndrome is shown in our patient as we highly suspect a maternal inheritance given a mother's similar phenotype. What is unique to this case is the presence of low-grade serous ovarian cancer occurring at a young age, suggesting an association between 17q12 recurrent deletion syndrome and cancer.

The 5 main subtypes of epithelial ovarian cancer are high-grade serous carcinoma (70%-80%), endometrioid (10%), CCC (10%), mucinous carcinoma (3%), and mixed. Low-grade serous carcinoma (<5%) is less common compared with high-grade serous carcinoma and is more amenable to surgical and hormonal treatments.[7] 17q12 deletion has been described as a susceptibility locus in some ovarian cancers. HNF1β expression has been identified frequently as a biomarker in ovarian CCC but rarely in non-CCC.[8] Yet, ovarian cancer predisposition is not a reported feature of either MODY5 (HNF1β mutation) or 17q12 recurrent deletion syndrome. This is a possible association suggested by our patient who has MODY5/17q12 recurrent deletion syndrome and ovarian low-grade serous carcinoma.[8]

This case suggests that monitoring of persons with 17q12 deletion syndrome in adulthood should involve renal ultrasound every 3 to 5 years, annual monitoring of renal function, and hemoglobin A1C. At initial diagnosis, pelvic ultrasonography, liver function tests, and ophthalmologic and audiologic examinations are indicated. Siblings and other relatives who may be at risk should be evaluated as well so that they can be closely monitored for renal abnormalities, MODY5, and neuropsychiatric manifestations. If the deletion is not found in either parent, then the risk to siblings is <1%, although higher than the general population due to the possibility of germline mosaicism.[4]

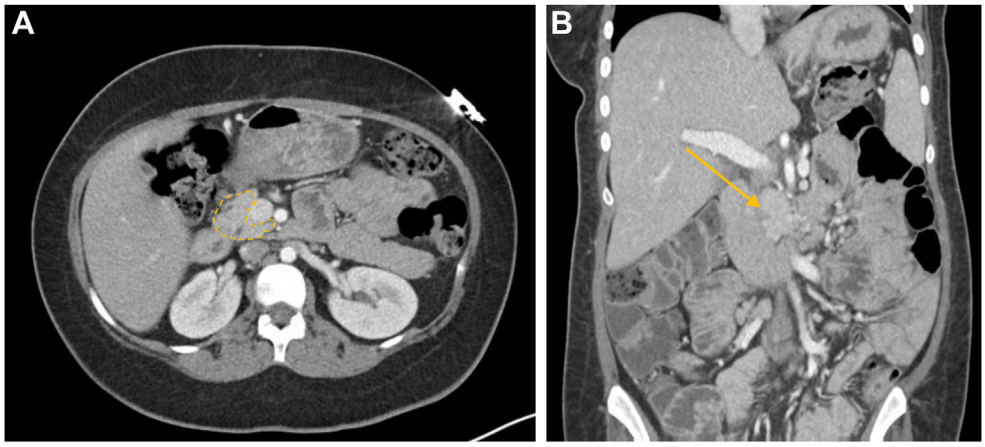


**Fig. 2.** *A*, Computed tomography of abdomen: cross-sectional view showing the atrophy of pancreatic body and tail. *B*, Computed tomography of abdomen: coronal view showing the atrophy of pancreatic body and tail.

## Conclusions

The disease association reported in this case suggests that women with MODY5 should be periodically evaluated for ovarian cancer and screened for abnormalities in the urogenital tract and gut. More research will be needed to determine optimal screening recommendations. Genetic testing for MODY5 should be pursued in patients with diabetes plus liver, pancreas, and urogenital tract abnormalities or 17q12 deletion in an ovarian tumor.

## Disclosure

The authors have no multiplicity of interest to disclose.

## Acknowledgment

Patient consent was obtained. This case was previously published as an abstract (not full case report) at the American Diabetes Association meeting 2019. Hollar L, Salam M, Thaker PH, McGillL JB. MODY5 and serous ovarian carcinoma in 17q12 recurrent deletion syndrome. Diabetes. 2019;68 (suppl 1):1716–P.

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