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Increased Liver Enzyme Levels and HNF-1 β Gene Mutation

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A31-year-old woman with diabetes mellitus presented with a history of abnormal liver function tests. Her physical examination was unremarkable. Her alkaline phosphatase level was 320 U/L, aspartate aminotransferase level was 129 U/L, and alanine aminotransferase level was 168 U/L. Imaging and histopathology of the liver was repeatedly normal. Magnetic resonance imaging of the abdomen, however, revealed renal cysts (Figure A) and pancreatic atrophy (Figure B). Pelvic ultrasound revealed ovarian cysts. This clinical scenario prompted a TCF2 (*MODY5*) gene sequencing test by polymerase chain reaction, which revealed a missense mutation at codon 827. This mutation was diagnostic of *MODY5*, in which the patient inherited the mutation as an autosomal dominant.

Discussion

Maturity-onset diabetes of the young (*MODY*) is an autosomal-dominant form of diabetes mellitus, caused by a primary defect of β -cell functioning in the pancreas. There are 6 different gene mutations associated with 6 *MODY* subtypes. Heterozygous mutations in the HNF-1 β gene located on chromosome 17q21.3, encoding for the transcription factor HNF-1 β , results in maturity-onset diabetes of the young, type 5 (*MODY 5*).¹ Transcription factor HNF-1 β is expressed in β cells and mutation of this gene leads to β -cell dysfunction, resulting in diabetes mellitus. HNF-1 β also is widely distributed in kidneys, liver, müllerian ducts, and plays a key role in organogenesis. HNF-1 β is responsible for regulating the expression of liver enzymes and mutations in this gene may result in abnormal biochemical liver function tests. The syndrome of *MODY5* encompasses a spectrum of clinical features.² Rarely reported, the most consistent clinical features associated with a HNF-1 β gene mutation are structural and functional renal abnormalities. Other phenotypic manifestations include early onset diabetes mellitus, internal genital tract malformations, and pancreatic hypoplasia. Biochemical liver function test abnormalities have been reported; however, there does not appear to be an association with specific morphologic abnormalities or disease. To date, only 5 cases of HNF-1 β mutations with increased liver enzyme levels have been reported. Abnormal liver enzymes in the setting of diabetes, pancreatic atrophy, and renal and genital tract malformations should raise the suspicion for the diagnostic possibility of *MODY5*. Family members should be offered genetic screening to diagnose *MODY5* and initiate prompt treatment of diabetes mellitus as well as to screen for renal and pancreatic complications that are known to occur to prevent or minimize serious complications.

References

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Figure 1.