OBSERVATIONS

Double Heterozygous Germline HNF1A Mutations in a Patient With Liver Adenomatosis

The *HNF1A* gene is inactivated by mutations in 35% of hepatocellular adenomas (HCAs) (1,2), rare benign liver tumors. In 90% of these HCAs, mutations are biallelic and somatic. In rare cases, one mutation has a germline origin and the second mutation is somatic, thus meeting the genetic criteria of maturity-onset diabetes of the young type 3 (MODY3).

Liver adenomatosis (LA) with more than 30 nodules was diagnosed in a 27-year-old patient during the second trimester of a first pregnancy. She has taken oral contraceptives for 10 years and had a slightly abnormal glucose tolerance test at age 18. Gestational diabetes was diagnosed at the 6th month, but she refused insulin therapy and had induced labor at 8 months. Glycemia came back to normal 6 days after delivery and always has been since.

Three months after delivery, a liver biopsy of the largest nodule (60 mm) showed a proliferation of benign hepatocytes with glycogenic nuclei and steatosis (80%). Immunohistochemistry showed in tumor hepatocytes an absence of liver-fatty acid binding protein (LFABP), a target of HNF1A, which is a hallmark of HNF1A-inactivated HCA (H-HCA) (2). Magnetic resonance imaging suggested typical hepatocellular adenomatosis inactivated for HNF1A (3); the patient is currently monitored by ultrasound.

Sequencing of the *HNF1A* gene revealed a heterozygous nonsense p.Q444× (c.1330C>T) and a heterozygous missense p.R583Q (c.1748G>A) mutations in the proband. Both mutations were also identified in her obese brother who developed diabetes at age 22. Q444× was inherited from the mother and grandmother, both diabetic, whereas R583Q was inherited from the nondiabetic father. None of the relatives had liver nodules on liver ultrasound examination.

To our knowledge this is the first report of two heterozygous germline *HNF1A* mutations in a MODY3 patient, with the transmission of a new nonsense mutation, Q444×. This mutation is predicted to inactivate HNF1A function because usually all nonsense *HNF1A* mutations lead to RNA degradation by nonsense mediated decay (1,4). In contrast, R583Q was previously described in MODY3 families but never identified in H-HCA. In a recent study, we showed that MODY3 individuals with mutations leading to a severe impaired HNF1A function could be more at risk for H-HCA than the others (4). In the current study, the nontumor liver tissue expressed LFABP, demonstrating a residual basal HNF1A activity; it was null in tumor hepatocytes, suggesting that an additional somatic mutation may have occurred to completely inactivate HNF1A.

These data also confirm that MODY3 individuals may develop LA. In previous studies, we observed an incomplete penetrance of the LA phenotype and demonstrated the importance of a systematic screening of LA in MODY3 families (5). Additionally, LA was more frequently discovered in very young females (5), suggesting that female sex and/or oral contraceptives played a role in LA development in MODY3 patients.

In conclusion, this study showed that two germline *HNF1A* mutations could coexist in the same patient, which could increase the risk of LA. In clinical practice, MODY3 should be searched for in all patients presenting adenomatosis with H-HCA features and their relatives. However, the entire coding sequence should be screened to detect double heterozygous events.

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References

1. Bluteau O, Jeannot E, Bioulac-Sage P, et al. Bi-allelic inactivation of TCF1 in hepatic adenomas. Nat Genet 2002;32:312–315
2. Zucman-Rossi J, Jeannot E, Nhieu JT, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 2006;43:515–524
3. Laumonier H, Bioulac-Sage P, Laurent C, Zucman-Rossi J, Balabaud C, Trillaud H. Hepatocellular adenomas: magnetic resonance imaging features as a function of molecular pathological classification. Hepatology 2008;48:808–818
4. Jeannot E, Mellottee L, Bioulac-Sage P, et al.; Groupe d'étude Génétique des Tumeurs Hépatiques (INSERM Network). Spectrum of HNF1A somatic mutations in hepatocellular adenoma differs from that in patients with MODY3 and suggests genotoxic damage. Diabetes 2010;59:1836–1844
5. Reznik Y, Dao T, Coutant R, et al. Hepatocyte nuclear factor-1 alpha gene inactivation: cosegregation between liver adenomatosis and diabetes phenotypes in two maturity-onset diabetes of the young (MODY)3 families. J Clin Endocrinol Metab 2004;89:1476–1480