



Editorial

Genetic mutation in hepatic adenoma: Seeing is believing

Pei-Jer Chen*

Graduate Institute of Clinical Medicine, National Taiwan University and Hospital, Taipei, Taiwan

Hepatic adenoma is one of the most common benign tumors in the liver, usually occurring in young females with continuous use of oral contraceptives [1]. Hepatic adenoma is sometimes accidentally detected during a physical examination or through medical imaging of the abdomen for other purposes. Some (about 10%) emergency cases presented with sudden and severe abdominal pain due to bleeding and the rupture of a large, superficial hepatic adenoma. Treatment for symptomatic cases requires complete surgical resection. For asymptomatic hepatic adenoma, regular follow-up and observation is sufficient, as tumors usually do not grow or even regress in rare cases. However, one major and unsettled problem regarding this wait-and-see policy has been the low, but true, risk of malignant transformation from hepatic adenoma to hepatocellular carcinoma (HCC). In addition, the histology characteristics of certain well-differentiated HCC cannot be confidently differentiated from that of hepatic adenoma. Careful pathological examination plus advanced imaging by contrast MRI may help in some cases, but physicians still look for more reliable diagnosis criteria for high-risk adenoma. Fortunately, new and promising genetic criteria are emerging from recent molecular genetic studies of hepatic adenoma.

Genetic mutations leading to hepatic adenoma formation can be approached from two directions. The first one is the candidate gene approach, which is drawn by the known genes involved in two other common liver cancers, HCC and hepatoblastoma [2,3]. One well-known example is the β -catenin gene (*CTNNB1*), which is a key molecule in the Wnt signaling pathway. When migrating into the nucleus, β -catenin can activate the transcription of a variety of genes and lead to aberrant cell proliferation. In normal hepatocytes, β -catenin is usual-

ly rapidly degraded after phosphorylation by the GSK-3 β kinase on its so-called “degradation domain”, which makes its activation transient and strictly regulated. However, because of somatic deletions or mutations in the “degradation domains”, mutant β -catenin resists degradation. The nucleus accumulation and continuous activation of mutant β -catenin may render hepatocytes to grow autonomously and even accelerate the tumor formation [2]. Mutation of β -catenin and its aberrant activation was reported to be common both in HCC and hepatoblastoma. Taking this precedent, we and others have found that about 30% of hepatic adenomas actually harbored mutations in the degradation domains of β -catenin [4]. However, other genes in the Wnt pathways, such as adenomatous polyposis coli (*APC*) or Axin family genes, did not show any mutations in the sporadic adenomas [4].

The second approach is a genome-wide search for mutated genes in the hepatic adenoma [5]. Bluteau et al. conducted a comprehensive screening for chromosomal deletions in hepatic adenomas. They succeeded in identifying a homozygous deletion locus in the chromosome 12 and finally discovered a gene within this region, the hepatocyte nuclear factor (HNF)-1 α (*TCF1*) gene, to be mutated in about 50% of their collected hepatic adenomas. Two alleles of HNF-1 α gene were inactivated either by frame-shift or by mis-sense somatic mutations [6]. This has been hailed as a major new understanding for hepatic adenoma. Interestingly, in their initial series of samples they did not find any cases with β -catenin mutations and thus suggested the mutations at HNF-1 α and β -catenin genes appeared to be mutually exclusive [7].

To address the clinical significance of the mutation of β -catenin versus that of HNF-1 α , Zucman-Rossi et al. further performed a large series of genetic-clinical association studies in France [8]. They studied 96 hepatic adenomas for mutations of HNF-1 α and β -catenin

* Tel.: +886 2 23123456x7072; fax: +886 2 23317624.
E-mail address: peijer@ha.mc.ntu.edu.tw.

genes. Forty-four cases were found with biallelic HNF-1 α mutations and 13 cases with β -catenin mutations. No tumors concomitantly harbored mutations of both genes and therefore mutation of each gene was proposed to define a unique group of hepatic adenomas. The pathologic features also supported this hypothesis. The hepatic adenomas with HNF-1 α mutations were characterized by marked steatosis and lacked inflammatory infiltrates, while hepatic adenomas with β -catenin mutation commonly presented with different features such as pseudoglandular formation. More importantly, the association with malignant HCC was found in 46% of hepatic adenomas with β -catenin mutations, but rarely with those of HNF-1 α mutations (7%) [8]. Therefore this study enabled classifying hepatic adenoma into two groups: one is the high-risk group, namely those with β -catenin mutations, and the other is the low-risk group, of those with biallelic HNF-1 α mutations [9]. The two groups of patients hence may receive different follow-up and therapeutic plans. However, this dichotomy of genetic classification has to be examined in more adenomas from other areas. Our limited experience in Taiwan did support a higher association between hepatic adenoma with β -catenin mutations and HCC. However, for HNF-1 α gene, we only identified the type of one allelic mis-sense mutation in some adenoma cases (Y.J. Wu, S.H. Yeh and P.J. Chen, unpublished information), which belongs to a group not described in the previous report [8]. It is likely that there remained some other mutated genes not yet identified. Despite these limitations, Zucman-Rossi's new genetic classification could be very useful in clinical practice and management of hepatic adenoma.

The majority of hepatic adenoma occurs in the sporadic cases who have single tumor. However, in some unusual cases, patients suffered from hepatic adenomatosis with tumor number exceeding 10 or multiple adenoma [10]. Nevertheless, their mutation spectrum (in β -catenin or HNF-1 α gene) did not differ from those with single hepatic adenoma [8]. A careful genetic study for individual tumor is still warranted. Other even rare hepatic adenomas occur in cases with other known hereditary diseases, such as familial polyposis coli, glycogen storage diseases, or maturity-onset diabetes of the young type 3 (MODY3) [8]. In a few cases with familial polyposis coli developed hepatic adenomas were found to contain a germ-line mutation in the *APC* gene. It was reasonable to propose a hypothesis that the resulting hepatic adenoma is likely attributable by inactivation of the second *APC* allele. In fact, there were two such cases documented in the literature with the second *APC* mutations identified in their hepatic adenoma [11,12]. However, in the third case of hepatic adenoma derived from the genetic background of *APC* germ-line mutation, Jeannot et al. found biallelic HNF-1 α mutation but not the assumed mutation of the second *APC* allele [13]. In associating with Axin and GSK-3 β , *APC* functions as a component

of the cytoplasmic destruction complex of β -catenin, which keeps the β -catenin level in check through the mechanism of phosphorylation dependent proteolytic degradation. A biallelic mutation of *APC* gene will disable the function of such destruction complex and render the accumulation of β -catenin and its constitutive transcriptional activation [2]. The adenomas with biallelic *APC* mutations thus belong to the high-risk group. However, the third case reported by Jeannot et al. just contained the biallelic mutations of HNF-1 α and could be in the low-risk group. This case report thus declared an important message for hepatic adenomas: the genetic study of both β -catenin and HNF-1 α has to be carried out for evaluating the clinical outcome, even in the cases with clear hereditary predispositions. In other words, the mutations in the hepatic adenomas cannot be assumed related to the germ-line gene defects, as the case well illustrated in this report [13].

In conclusion, to more accurately evaluate the risk of malignancy associated with hepatic adenoma, the genetic classification based upon the mutation pattern of β -catenin or HNF-1 α should be pursued. This is recommended in all cases of hepatic adenoma, irrespective of the tumor number or hereditary features. The successful incorporation of genetic research of hepatic adenoma into clinical practice has been a rewarding example in molecular hepatology.

References

- [1] Edmondson HA, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med* 1976;294:470-472.
- [2] Buendia MA. Genetic alterations in hepatoblastoma and hepatocellular carcinoma: common and distinctive aspects. *Med Pediatr Oncol* 2002;39:530-535.
- [3] Laurent-Puig P, Zucman-Rossi J. Genetics of hepatocellular tumors. *Oncogene* 2006;25:3778-3786.
- [4] Chen YW, Jeng YM, Yeh SH, Chen PJ. P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia. *Hepatology* 2002;36:927-935.
- [5] Chen YJ, Chen PJ, Lee MC, Yeh SH, Hsu MT, Lin CH. Chromosomal analysis of hepatic adenoma and focal nodular hyperplasia by comparative genomic hybridization. *Genes Chromosomes Cancer* 2002;35:138-143.
- [6] Bluteau O, Jeannot E, Bioulac-Sage P, Marques JM, Blanc JF, Bui H, et al. Bi-allelic inactivation of TCF1 in hepatic adenomas. *Nat Genet* 2002;32:312-315.
- [7] Bioulac-Sage P, Laurent-Puig P, Balabaud C, Zucman-Rossi J. Genetic alterations in hepatocellular adenomas. *Hepatology* 2003;37:480.
- [8] Zucman-Rossi J, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, Rebouissou S, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology* 2006;43:515-524.
- [9] Monga SP. Hepatic adenomas: presumed innocent until proven to be beta-catenin mutated. *Hepatology* 2006;43:401-404.
- [10] Flejou JF, Barge J, Menu Y, Degott C, Bismuth H, Potet F, et al. Liver adenomatosis. An entity distinct from liver adenoma?. *Gastroenterology* 1985;89:1132-1138.

- [11] Su LK, Abdalla EK, Law CH, Kohlmann W, Rashid A, Vauthey JN. Biallelic inactivation of the APC gene is associated with hepatocellular carcinoma in familial adenomatous polyposis coli. *Cancer* 2001;92:332–339.
- [12] Blaker H, Sutter C, Kadmon M, Otto HF, Von Knebel-Doeberitz M, Gebert J, et al. Analysis of somatic APC mutations in rare extracolonic tumors of patients with familial adenomatous polyposis coli. *Genes Chromosomes Cancer* 2004;41:93–98.
- [13] Jeannot E, Wendum D, Paye F, Mourra N, de Toma C, Fléjou JF, et al. Hepatocellular adenoma displaying a HNF1 α inactivation in a patient with familial adenomatous polyposis coli. *J Hepatol* 2006;45. doi:[10.1016/j.jhep.2006.06.020](https://doi.org/10.1016/j.jhep.2006.06.020).