# Hepatocellular Adenomas

## Morphology and Genomics

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**KEYWORDS**

- Hepatocellular adenomas • Genomics • Genoptye/phenotype
- Hepatocellular adenoma classification • Malignant transformation

**KEY POINTS**

- Hepatocellular adenoma (HCA) is a global entity encompassing several subtypes identified by specific mutations.
- Immunomarkers, liver-type fatty acid binding protein (LFABP) and C-reactive protein (CRP), allow the identification of the 2 major subtypes, hepatocyte nuclear factor (HNF) 1α-inactivated HCA (H-HCA) and inflammatory HCA (IHCA).
- Glutamine synthetase (GS) is a surrogate marker to identify β-catenin–activated HCA (β-HCA): homogeneous and diffuse for exon 3 mutation (outside S45) and heterogeneous and diffuse for exon 3 S45, both linked to potential malignancy.
- IHCA can be β-catenin mutated.
- β-Catenin mutation alone is not sufficient to induce malignancy. A second hit is necessary, such as telomerase reverse transcriptase promoter mutation.
- HCA classification using immunomarkers may require expertise, particularly on liver biopsy, and, if necessary, molecular confirmation.

HCAs are rare benign monoclonal liver tumors, described for the first time by Edmondson in 1953.[1] HCAs have since been linked to the use of oral contraceptives by Baum and colleagues in 1973.[2] The understanding of HCA was completely renewed when the 2 first underlying gene mutations were discovered in 2002, soon followed by others. These mutations are the basis of the genotype/phenotype classification of HCA discussed in this article.

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## HEPATOCELLULAR ADENOMAS: GENOMICS—THE GENOTYPE CLASSIFICATION

The first mutations responsible for the development of HCA were described in 2002, in Taiwan and in France. The first one is an activating mutation of *CTNNB1* gene coding for β-catenin[3] and the second corresponds to a biallelic inactivating mutation of *HNF1A*.[4] Consequently, HCAs are classified today into 3 main categories[5]: (1) *HNF1A*-mutated HCA [H-HCA] (35%–40%); (2) IHCA (40%–50%), with multiple mutated genes identified, mainly *IL6*[6]; and (3) β-catenin–mutated HCA (β-HCA) (15%–20%). An additional important leap forward was made recently, in 2014 and 2016, when β-HCA was subdivided into several subgroups according to the degree of activation of β-catenin.[7,8] β-Catenin mutation is also found in 10% of IHCA (β-IHCA). So far, fewer than 10% of HCAs remain unclassified HCAs (UHCAs).

HCAs, mainly β-HCA (discussed later), have a malignant potential and can evolve into hepatocellular carcinoma (HCC). The transformation depends on the occurrence of additional mutations. Telomerase reverse transcriptase (TERT) promoter mutations have been identified as responsible for this complication in half of the β-HCAs (mainly those showing mutations in exon 3).[9] In HCC derived from HCA, the observed number of genetic alterations is much lower than in classic HCC.[7]

The different mutated genes in HCA identified to date, in 2016, are presented in **Box 1**.[5–8,10–19]

Despite the great achievements, the underlying mutated genes are still unidentified in 15% of IHCA, and 10% of HCAs are still unsolved (UHCAs). In 2016, microarray analysis revealed an additional subgroup of HCAs previously unclassified, associated with dysregulation of the prostaglandin pathway, therefore named prostaglandin HCAs.[20] The genetic alterations, however, have not yet been identified. In multiple HCAs, different subtypes are occasionally observed and remain puzzling.[21] An intriguing and important question is why, within the large number of women taking oral contraceptives, only a few develop HCA. This is also observed in patients with genetic diseases associated with HCA development, such as maturity-onset diabetes of the young type 3 (MODY3) or glycogen storage disease (GSD).[12,18] This suggests that different genetic and environmental factors predispose to the development of HCAs, which are, therefore, often multiple.[5] In less than 20 years, molecular biology has made tremendous progress to understand HCA. At present, in practice, hematoxylin-eosin stain (H&E) combined with immunohistochemistry (IHC) allows classification and has largely replaced the need for molecular biology. When there is doubt about interpretation, this molecular analysis can be performed on frozen but also fixed tissue.

## HEPATOCELLULAR ADENOMAS: MORPHOLOGY—THE GENOTYPE/PHENOTYPE CLASSIFICATION

The genotype/phenotype classification has been a great step forward in recognizing the different HCA subtypes. Several reviews on the subject have been published in the literature.[22–32]

### *Technical Considerations*

A correct interpretation of the histologic and immuno-histochemical data can only be performed if the sampling and the techniques are adequate. Advice (through slides or virtual slides) are more and more common. Interpretation is facilitated when the techniques are of good quality and requires the comparison with the nontumoral liver. The size of the biopsy is still a major problem. The main considerations are presented in **Box 2** and **Table 1**.