# Fibrolamellar Carcinoma
## What Is New and Why It Matters

Rondell P. Graham, MBBS[a,b,*]

**KEYWORDS**

• Fibrolamellar carcinoma • PRKACA • Protein kinase A • Hepatocellular carcinoma • Pale bodies • Fibrolamellar hepatocellular carcinoma • Carney complex • Central scar

**Key points**

- Fibrolamellar carcinoma is a unique primary liver carcinoma with a distinct predilection for young individuals, a characteristic morphology, immunophenotype and recurrent genomic abnormalities typically involving *PRKACA*.
- The diagnosis is made by recognition of the compatible morphology with the appropriate immunphenotype or detection of the key genomic event.
- Fibrolamellar carcinoma should be considered a different entity from conventional hepatocellular carcinoma on clinical, histologic, and biologic grounds. Fibrolamellar carcinoma also merits its own staging system.

## ABSTRACT

Fibrolamellar carcinoma is distinctive at clinical and histologic levels. A novel *DNAJB1-PRKACA* fusion gene characterizes almost all cases, distinguishes it from other hepatocellular neoplasms, and drives the pathogenesis of this unique tumor. A subset of cases of fibrolamellar carcinoma is associated with alternate mechanisms of protein kinase A activation. This review article discusses common and unusual histologic features of fibrolamellar carcinoma, its differential diagnoses, and how to make the diagnosis while avoiding key pitfalls. The impact of the discovery of the fusion gene on the understanding of the tumor and the prognosis of fibrolamellar carcinoma are also discussed.

## OVERVIEW

Fibrolamellar carcinoma (FLC) is a unique primary liver carcinoma. The recent discovery of the *DNAJB1-PRKACA* fusion gene in FLC[1] reenergized the study of this distinctive neoplasm, leading to important contributions that have deepened understanding of FLC, posed some new questions about the tumor's biology, and challenged some prior perceptions. This review summarizes the recent literature on the frequency and origins of FLC, its clinical presentation, the characteristic gross and microscopic findings, the molecular pathology, and prognosis.

### *Key Points*
### Epidemiology of Fibrolamellar Carcinoma

1. FLC is rare.
2. Available data indicate a frequency of approximately 1% to 5% of primary liver carcinomas with hepatocellular differentiation.
3. The etiology of FLC is unknown.
4. The earliest reported FLC is from 1915.
5. It has been reported that there is a slight predilection for FLC to affect patients of European descent.
6. FLC has a global distribution. It has been reported from every continent.

Disclosure Statement: No conflicts of interest to disclose.

[a] Division of Anatomic Pathology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA; [b] Division of Laboratory Genetics and Genomics, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA

* Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.

*E-mail address:* Graham.rondell@mayo.edu

Surgical Pathology ■ (2018) ■–■

https://doi.org/10.1016/j.path.2018.02.006

## Key Points
### Clinical Features of Fibrolamellar Carcinoma

1. FLC affects young patients.
2. In the largest published series to date, there was a single case (1 of 95 with available data) in a patient over 50 years of age and 3 patients (3%) over 40 years of age at first diagnosis.
3. FLCs frequently present with late recurrences; 5-year recurrence-free survival is approximately 10% to 20%.
4. Patients with FLC typically do not have underlying chronic liver disease
5. The diagnosis of FLC on a background of cirrhosis should be met with skepticism and thoughtful review.
6. The most common presentation of FLC is as an abdominal mass. Features of the mass effect include hepatomegaly, abdominal pain, and biliary obstruction (either from intraluminal growth or from extrinsic compression of the biliary tree).
7. Vena caval obstruction has also been reported, but this is less common.
8. FLC may uncommonly present with paraneoplastic manifestations. for example, gynecomastia, increased serum neurotensin, and increased serum transcobalamin I (haptocorrin).
9. FLC often presents with regional lymph node metastases and shows a propensity to spread along the peritoneum. Ovarian metastases have been reported.
10. FLC is not associated with serum $\alpha$-fetoprotein (AFP) elevation.
11. FLC may show a central scar on imaging. This is nonspecific.

## Key Points
### Protein Kinase A drives Fibrolamellar Carcinoma

1. *DNAJB1-PRKACA* drives FLC tumorigenesis in greater than 95% of cases.
2. A rare subset of FLC is characterized by loss of function of PRKAR1A (instead of the fusion gene). Most of these patients have the Carney complex.
3. *PRKAR1A* is the gene mutated in most cases of the Carney complex.
4. FLC is likely to be a part of the Carney complex; a notion shared by J. Aidan Carney, MD (personal communication 2017), who continues to follow families with the complex.
5. A single case of histologically typical FLC showing *PRKACA* amplification and without the *DNAJB1-PRKACA* fusion gene has been identified.
6. The discovery of the fusion gene has, therefore, also catalyzed the discovery of 2 alternate genomic events that underlie a subset of FLC.
7. Gynecomastia, increased serum neurotensin, and serum transcobalamin I in FLC have now been linked to increased PRKACA and protein kinase A activity; for example, protein kinase A increases CYP19A1, a metabolic enzyme responsible for the production of aromatase. This leads to the increased synthesis of estrogen from androgen in adipose tissue and gynecomastia.