

## Immunohistochemistry Division

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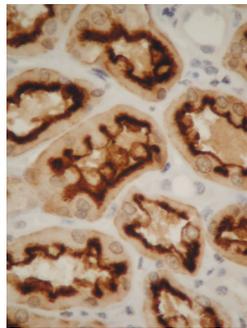
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## Focus on Immunohistochemistry - June 2001

### Villin

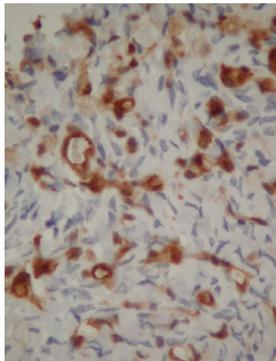
Villin is a gastrointestinal-related cytoskeletal protein that is associated with microfilament bundles of brush border microvilli. In normal tissues, villin expression is generally restricted to cells that possess a brush border, including GI tract epithelium, pancreatic and biliary epithelium, and certain types of epithelium within the kidney (particularly proximal tubules). Because of the restricted distribution of this protein, the use of anti-villin antibodies has been investigated by a number of authors for a variety of diagnostic applications. Indeed, we have found villin to be a very useful marker for a number of situations, and villin is one of our most frequently performed immunostains. A brief overview of potential applications for villin is provided below.



Renal proximal tubules

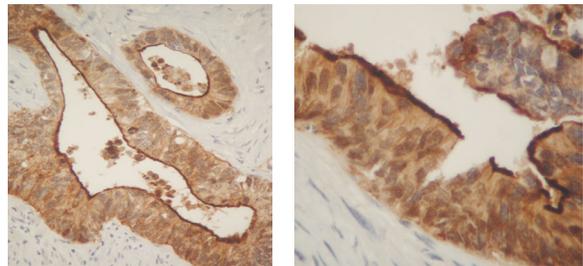
### Carcinoma of Unknown Origin

Villin can be an extremely useful reagent when trying to determine the most likely primary site of origin of metastatic carcinomas. As one might expect from the normal distribution of this protein, the expression of villin is very common in gastrointestinal, pancreatic,



Villin on metastatic gastric ca to ovary (Krukenberg tumor)

gallbladder, and bile duct carcinomas, where it is expressed in a very high percentage of those tumors (particularly when they show morphologic evidence of glandular differentiation). Often, one can appreciate localization of villin immunoreactivity to the apical surfaces of cells, reflecting its association with brush border microvilli. In other cases, villin may highlight small luminal structures that are not apparent on standard H&E examination, providing supportive evidence for the interpretation of a poorly differentiated tumor as an adenocarcinoma. Therefore, the absence of expression of villin in a gland-forming tumor argues against an origin from the GI tract, pancreas, gallbladder, or bile ducts.



Villin on colonic adenocarcinoma, demonstrating typical "brush border" pattern

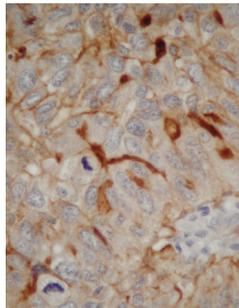
Because of its frequent occurrence, breast carcinoma often enters into the differential diagnosis of female patients with metastatic carcinoma of unknown primary. Villin can be extremely useful in this situation, since identification of significant villin immunoreactivity in a metastatic carcinoma renders breast primary origin extremely unlikely. In the numerous breast carcinomas that we have studied at ProPath, only one has shown

expression of villin. This tumor occurred in a male patient, and showed only weak and focal expression. Other tumors that are generally negative for villin may include ovarian serous carcinoma, transitional cell carcinoma of urothelial origin (although I have seen focal villin expression in the nested variant of transitional cell carcinoma), and prostate carcinoma. Mesothelioma is also villin negative, so on some occasions this antibody is useful as part of a panel to distinguish mesothelioma from adenocarcinoma.

There are also several non-GI carcinomas that may express villin, including a proportion of lung carcinomas, endometrioid adenocarcinoma, mucinous carcinoma of the ovary, and renal cell carcinomas. I have also observed expression of this marker in some cases of endocervical adenocarcinoma and in a case of acinar cell carcinoma of the pancreas.

### Diagnosis of Hepatoma

Since villin highlights bile canalicular structures, it may also prove to be useful in highlighting a canalicular pattern of reactivity in a proportion of hepatomas. Polyclonal CEA was the first reagent that was used for this purpose, and we have also found CD10 (CALLA) to be very useful for highlighting this pattern in hepatomas. From our experience, there does not seem to be any consistent correlation between the expression of polyclonal CEA, villin, and CD10 (CALLA) in cases of hepatoma, so if hepatoma is a serious consideration, we generally employ all three of these markers to assist in difficult cases.

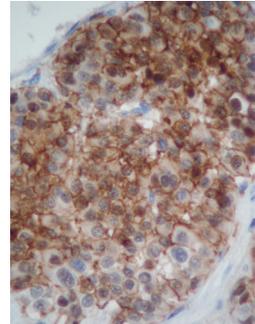


Villin on hepatoma highlighting canaliculi

### Villin in Neuroendocrine Tumors

Villin also has utility in studying neuroendocrine tumors. It is well known that carcinoid tumor and islet cell tumor of the pancreas can have identical morphologic appearances, and often it is impossible to distinguish between these two possibilities on morphology alone. Villin is particularly useful in this regard, since expression of villin has been reported in 85% of

gastrointestinal carcinoid tumors, but rarely if ever in islet cell tumors of the pancreas. The expression of villin in carcinoid tumors is usually membranous in character. In addition, there is some evidence to suggest that expression of villin is more common in small cell carcinomas arising from the stomach and lower GI tract than in small cell carcinomas arising in other organs, such as lung, esophagus, bladder, or prostate. The numbers of reported cases are relatively small however, so acceptance of these findings should await further study of larger numbers of cases. Roughly 40% of lung carcinoid tumors are reported to be villin positive. We have also observed villin immunoreactivity on occasion in cases of other neuroendocrine tumors, including medullary carcinoma of the thyroid and in a minority of Merkel cell tumors.



Villin on carcinoid tumor of small bowel, showing typical membranous staining. This finding renders islet cell tumor unlikely.

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