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## Modern Pathology

### BAP1 immunohistochemistry in uveal melanoma

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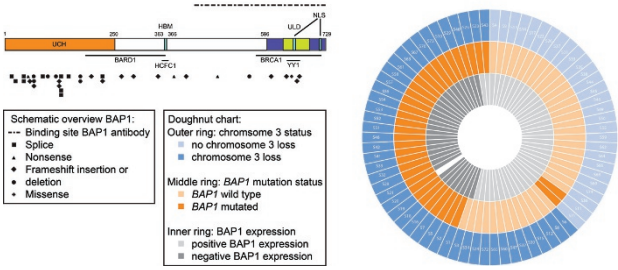


Uveal melanoma is an unusual type of melanoma in its propensity for first metastasis to liver. Loss of chromosome 3 in uveal melanoma portends a poorer outcome. BRAC1-associated protein 1 (BAP1) residing at 3p21.1 is thought to mediate the effects of chromosome 3 loss. *BAP1* loss-of-function mutations are present in melanoma and other cancers. Koopmans *et al* characterized 74 uveal melanomas via single-nucleotide polymorphism arrays, fluorescence *in situ* hybridization, deep sequencing of *BAP1*, and immunohistochemistry for BAP1. Loss of chromosome 3 (62% of cases), mutation of *BAP1* (47% of cases), and BAP1 loss of protein expression (43% of cases) showed strong positive correlation with one another, particularly the last two categories. Loss of chromosome 3 correlated with a much poorer outcome; with concurrent mutation of *BAP1*, it was even worse. Additional studies are needed to determine the best approach to characterizing BAP1.

### Mitochondrial DNA genotyping provides clonality insights

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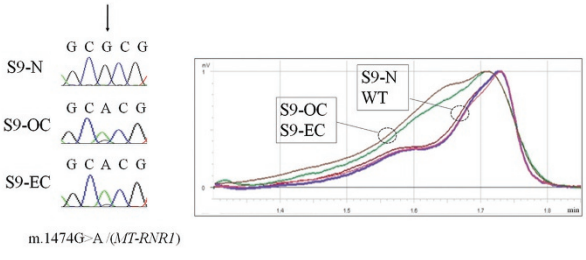


Gynecological tumors are synchronous at different sites or organs in 1–2% of cases—most frequently ovarian and endometrial sites. Determining whether these are independent primaries or cognate primary and metastatic lesions is important for staging, treatment, and prognosis. The criteria for this determination are often difficult to apply to specific cases, and the results can be ambiguous. Morphology alone is often not adequate to the task owing to overlapping features. Molecular examination of microsatellites or sequencing of oncogenes commonly mutated in gynecologic tumors can be informative, but neither will distinguish every case. Guerra found that mitochondrial DNA genotyping of a series of 12 synchronous ovarian and endometrial tumors was more informative than a combination of histology, β-catenin immunohistochemistry, *CTNNB1* sequencing, and microsatellite analysis. Although these methods provided insights in most cases, mitochondrial DNA genotyping was necessary for definitive determination in more than 40% of cases.

## Laboratory Investigation

### Uric acid–induced fat accumulation in hepatocytes

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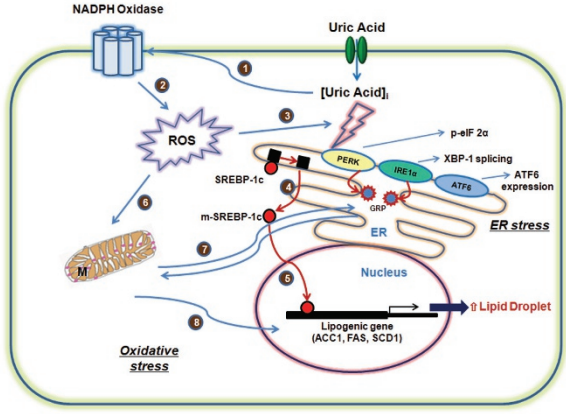


One of the most common types of chronic liver damage is nonalcoholic fatty-liver disease (NAFLD). Elevated levels of serum uric acid are known to be a strong predictor of fatty liver, but it is unclear whether uric acid drives pathogenesis as well. Endoplasmic reticulum stress is a known cause of fatty liver. Choi and colleagues demonstrated that uric acid induces endoplasmic reticulum stress through the unfolded protein response in mouse and human hepatocytes, leading to SREBP-1c cleavage and nuclear translocation. Nuclear SREBP-1 enhances expression of a variety of enzymes involved in lipogenesis, such as fatty-acid synthase. The finding that metformin, an inhibitor of SREBP-1c, as well as blockers of endoplasmic reticulum stress, effectively prevented

hepatic lipid accumulation suggests a potential treatment for NAFLD.

## Somatic mutations detected via unaligned deep sequencing

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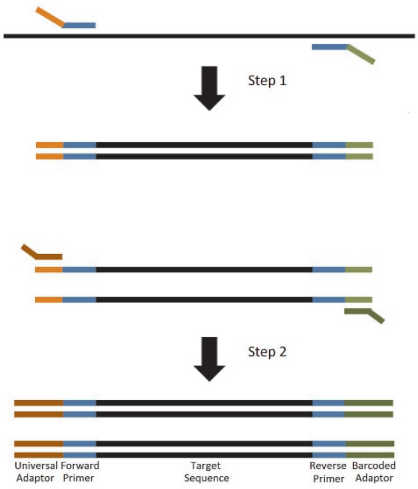
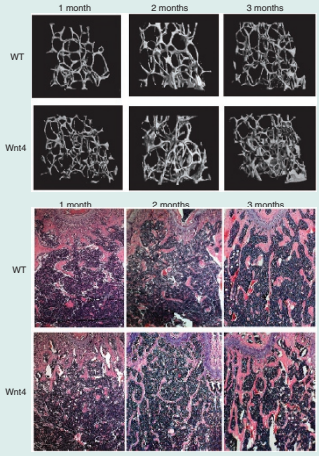



When next-generation sequencing data are produced from tumor samples, they are aligned against a reference genome and the variances are noted. Often, patient germline sequences are analyzed in an identical fashion, and comparison of the two data sets identifies somatic mutations. Depending on the number of sequencing targets, alignment of the many small amplicons produced from formalin-fixed paraffin-embedded samples against the reference genome can be computationally intensive. Sutton *et al* were able to detect single-nucleotide variations by stacking up sequences against themselves rather than first aligning them against a reference genome. Using two different algorithms, they identified the focused mutations most common in oncogenes as well as the more variable disrupting mutations common in tumor-suppressor genes. Although their method reduces computational complexity, it requires a coverage depth of at least 2,000 reads, but this is achievable in focused sequencing analyses.



# nature.com/pathology

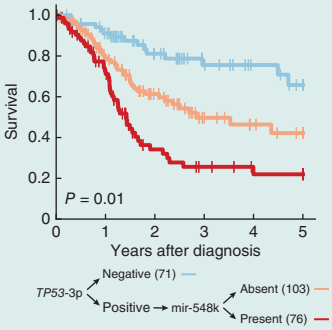
### Wnt4 signaling prevents skeletal aging




Loss of bone mass with age and osteoporosis are common worldwide. The chronic inflammation associated with aging is one mediator of bone loss. In a study reported in *Nature Medicine*, Yu *et al* determined that Wnt4 signaling protected against bone loss and chronic inflammation induced by natural aging, ovariectomy, or tumor necrosis factor in a transgenic mouse model. Wnt4 inhibited NF-κB activation mediated by transforming growth factor-β-activated kinase-1 in both macrophages and osteoclast precursors. Of interest, this was a noncanonical effect of Wnt4 and thus was independent of signaling through β-catenin. Because Wnt4 plays roles in promoting bone growth both during development and later in life, as well as in preventing resorption, it could be of therapeutic interest. However, it might be necessary to separate the canonical and noncanonical roles of Wnt4 to reduce untoward effects.

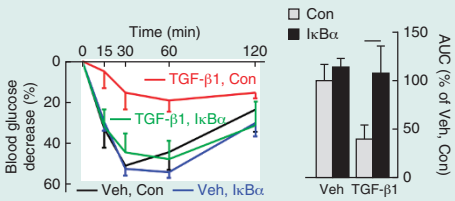
*Nature Medicine*, published online 10 August 2014; doi:10.1038/nm.3586

### Genomics links *TP53* mutation to 3p loss in head and neck cancer




Head and neck squamous cell carcinoma is aggressive, with a decided propensity for both local and distant recurrence. *TP53* mutations are common in this disease, as is human papilloma virus (HPV) infection, which also abrogates p53 signaling. In a study recently reported in *Nature Genetics*, Gross and colleagues found that loss of the short arm of chromosome 3 combined with *TP53* mutation results in much shorter survival compared with *TP53* mutation alone (1.9 years vs. >5 years). This potentiation of *TP53* mutations appears to be specific for the 3p region and has been validated in independent head and neck squamous cell and pan-cancer cohorts. 3p loss is also common in HPV-associated head and neck cancers and confers inferior survival there as well. The addition of mir-548k expression in TP53-3p cases further reduces survival. The authors use these findings to propose a new molecular classification of this disease.

*Nature Genetics* 2014;46:939–943; doi:10.1038/ng.3051




### The hypothalamus in diabetes

The hypothalamus can regulate glucose homeostasis. Although much of the research in diabetes has been focused on islet cell function in the pancreas and autoimmunity or the metabolic syndrome, Yan *et al*, in *Nature Medicine*, suggest a hypothalamic etiology of diabetes. Hypothalamic secretion of transforming growth factor-β (TGF-β) increases with both age and obesity, factors that also predispose for type 2 diabetes. Using both genetic and pharmacologic approaches, the authors found an association between excess central TGF-β secretion and hyperglycemia. This TGF-β was produced by astrocytes, and the prodiabetic effects were mediated by proopiomelanocortin neurons. The excess TGF-β induced an RNA stress response in the thalamus. Specifically, TGF-β accelerated the decay of IκBα, an inhibitor of the proinflammatory nuclear factor-κB (NFκB), with the net result of NFκB activation. Although more study is needed, this links obesity, aging, and hypothalamic inflammation and suggests a specific central nervous system role in type 2 diabetes.

*Nature Medicine*, published online 3 August 2014; doi:10.1038/nm.3616