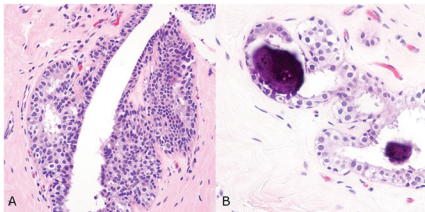# INSIDE THE USCAP JOURNALS

MODERN PATHOLOGY

### Prostatic and pilar metaplasia in mastectomy specimens from transgender individuals

Kim et al. describe novel findings in mastectomy specimens from adolescents and young adults undergoing gender-affirming surgery. In 18 of 22 transmasculine patients (95% receiving testosterone cypionate), the group identified prostatic metaplasia, characterized by glandular proliferation along the basal layer of epithelium in breast ducts and, in one case, lobules. Immunohistochemistry showed that prostatic metaplasia was positive for prostate-specific antigen in 16 of 20 cases and positive for NKX3.1 in 15 of 20 cases. In 4 of 22 patients, pilar metaplasia was identified, consisting of intraductal hair shafts associated focally with matrical differentiation. Neither finding was identified in control cases from reduction mammoplasty specimens. The cause of these alterations is unknown and may be multifactorial (e.g., androgen therapy, breast binding practices, exogenous progesterone for menses suppression). Identification of these previously underappreciated findings in the breast is important, both to distinguish them from other breast epithelial proliferations and to improve understanding of their natural history to advance care in this field.

### Characteristics of low-grade oncocytic renal tumors (LOT)
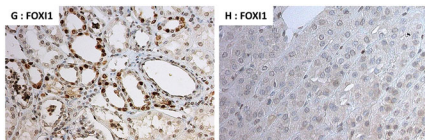
To distinguish low-grade oncocytic renal tumor (LOT) that shared CD117 negativity and diffuse CK7 positivity from the spectrum of other eosinophilic renal cell tumors, Morini et al. performed clinicopathological, immunohistochemical, and genetic characterization of ten cases. All cases showed favorable clinical behavior and local and sporadic presentation. Using next-generation sequencing, the authors identified somatic genetic variations in mTOR pathway-related genes in 80% of cases involving either MTOR (seven cases) or TSC1 (one case). Activation of the mTOR pathway was also demonstrated by overexpression of phosphorylated and activated forms of 4EBP1 and S6K in 9 of 10 LOT. To further distinguish LOT from renal oncocytoma and the eosinophilic variant of chromophobe renal cell carcinoma (CHRCC)—the two main differential diagnoses—the group also explored FOXI1 expression, which is, along with CD117, another lineage-specific marker of intercalated cells of the distal nephron and a hallmark of renal oncocytoma and CHRCC. Concordant with the negativity of CD117 in LOT, they found negative expression of FOXI1 in all LOT. Their data highlight the major role of the mTOR pathway in tumorigenesis of LOT and support consideration of LOT as a distinct entity with a favorable clinical outcome. Distinguishing LOT from eosinophilic CHRCC may bring them closer to other FOXI1-negative eosinophilic CHRCC in the presence of MTOR/TSC mutations and allow targeted therapy.

LABORATORY INVESTIGATION

Utilizing AI to distinguish fibroadenoma and phyllodes tumor
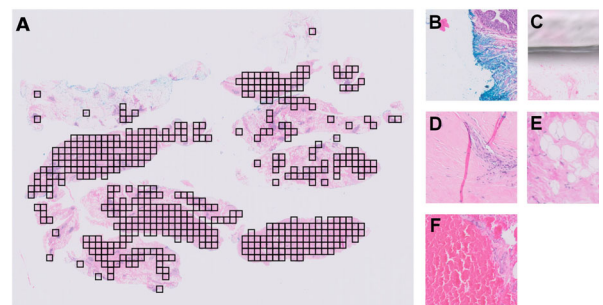
Accurate diagnosis of diseases whose pathological features can overlap is crucial, especially when their clinical management approaches differ. Focusing on breast fibroepithelial lesions (FEL), which encompass benign fibroadenomas (FAs) and phyllodes tumors (PTs), Cheng et al. performed whole-slide analysis to investigate the potential role of artificial intelligence (AI) in FEL diagnosis. Their model—a two-stage convolutional neural network and a recurrent neural network for whole-slide classification—showed an overall slide-level accuracy of 87.5%. The model compares favorably with one described

by Zheng et al. The group notes that AI was able to attain diagnostic discrimination between FA and PT on core biopsies, which could lead to a reduction in the need for surgical management of cases where there is uncertainty with traditional pathologic assessment.

Machine learning algorithm for muscle biopsy diagnosis

https://doi.org/10.1038/s41374-021-00647-w
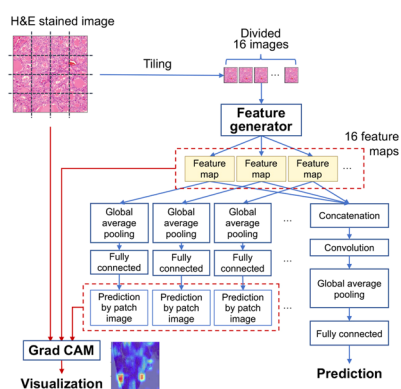
Histopathologic evaluation of muscle biopsy samples for classification and diagnosis of muscle diseases is inhibited by the limited number of experienced specialists and insufficient availability of training datasets for machine learning. Kabeya et al. developed an algorithm based on deep convolutional neural networks (CNNs) using a curated bank of specimens for training. Their algorithm differentiated idiopathic inflammatory myopathies from hereditary muscle diseases with an area under the curve of 0.996 and achieved superior diagnostic sensitivity and specificity when compared with physicians involved in the study. For example, the CNNs may have recognized rimmed vacuoles and nemaline bodies, which are important in distinguishing hereditary disease and are usually identified by physicians/pathologists only at high magnification. Also, this study used H&E stains rather than the special stains usually employed by physicians. The group propose that the findings support the use of an AI-assisted system for diagnosing neuromuscular disorders.

nature.com/pathology

Population study of plasma proteome to explore pathogenesis of disease

Ferkingstad et al. explored the plasma proteome as a bridge between the genome and disease using a genome-wide association study (GWAS) of plasma protein levels with 4907 aptamers in 35,559 Icelanders. Nineteen percent of the 18,084 associations of proteins in plasma (protein quantitative trait loci; pQTL) were with rare variants. A total of 257,490 associations were identified between plasma protein levels with 373 diseases and other traits and 938 genes encoding potential drug targets with variants that could influence levels of possible biomarkers. The group demonstrated that by colocalizing plasma pQTL to the pQTL in individual tissues, the pQTL reflected the transcriptome from the various tissues. The plasma data could thus be used to study diseases originating in specific tissues. Therefore, from a combination of proteomics, transcriptomics, and genomics in large-scale population data, a valuable resource was generated that can be used to better understand the pathogenesis of disease and assist with drug discovery and development.

Nature Genetics 2021;53:1712–1721; https://doi.org/10.1038/s41588-021-00978-w
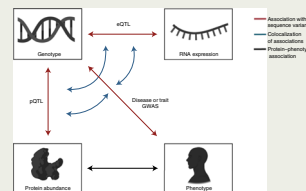
Targeting SWI/SNF ATPases in cancer therapeutics

Xiao et al. explored the SWI/SNF complex as a transcriptional dependency in AR/FOXA1-driven prostate cancer. They demonstrated that the AU-15330 compound is a novel, highly specific, and VHL-dependent PRO-TAC degrader of multiple SWI/SNF ATPase components, with preferential cytotoxicity in malignant cells. SWI/SNF ATPase degradation disrupts physical chromatin accessibility at the core-enhancer circuitry to disable oncogenic transcriptional programs. It also disrupts enhancer–promoter loops to temper super-physiologic expression of driver oncogenes such as AR, FOXA1, ERG, and MYC. The group explored mechanisms of action and found that physical chromatin accessibility could be modulated at noncoding regulatory elements and that doing so might be a novel therapeutic strategy in cancer therapeutics. They concluded that SWI/SNF ATPase inhibitors and degraders should be advanced into the clinic for safety and efficacy clinical trials.

Nature, published online 22 December 2021; https://doi.org/10.1038/s41586-021-04246-z

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