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MODERN PATHOLOGY

Molecular profiles of adrenocortical carcinomas

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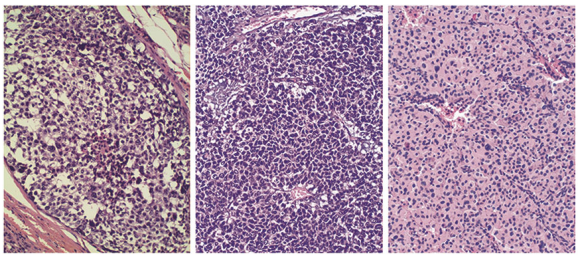
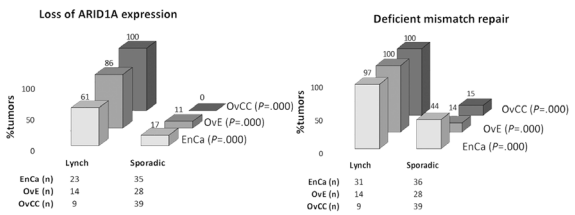


Adrenocortical carcinoma is a rare malignancy with a dismal prognosis. Vatrano and colleagues performed targeted next-generation sequencing and analyzed copy number variation for the most frequently altered genes in 62 adult cases to identify any correlation with clinical and pathological characteristics of the tumors. They detected 433 somatic deleterious genetic alterations in 57 cases. *TERT*, *CDK4*, *ZNRF3*, and *RB1* were altered in more than 30% of cases. Among histological variants, genotypes were significantly different. The lowest mutation burden was found in the oncocytic type; the highest was found in the conventional and myxoid types. Alteration in the p53/Rb1pathway was the strongest adverse molecular signature and was associated with high Ki-67 index, high tumor stage, aggressive disease status, and shorter disease-free survival. The investigators also analyzed 10 matched primary and metastatic/recurrent samples to determine genetic heterogeneity during tumor progression. None of these cases showed a stable genotype, emphasizing the clinical problem of biomarker testing in patients with advanced adrenocortical carcinoma.

Molecular changes preceding endometrial and ovarian cancer

doi:10.1038/s41379-018-0044-4

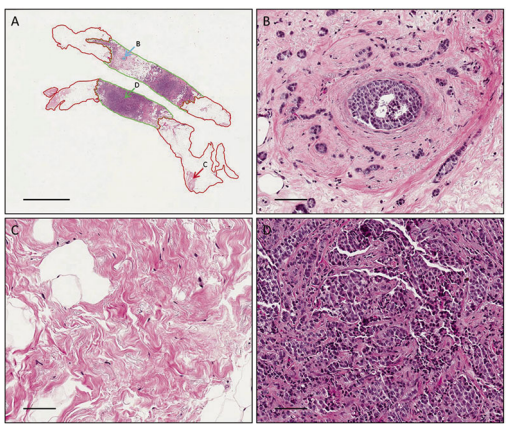


Up to 54% and 24% of female patients with Lynch syndrome develop endometrial and ovarian cancer, respectively, which necessitates lifelong surveillance against gynecological cancer. Niskakoski et al. profiled 213 biopsy specimens from Lynch syndrome mutation carriers, along with 197 corresponding tissues from sporadic cases, for genetic and epigenetic changes. First, they identified early tumorigenic changes, including ARID1A loss, that appeared in endometrial hyperplasia (Lynch syndrome and sporadic), whereas defective mismatch repair (Lynch syndrome) and tumor suppressor gene promoter hypermethylation (Lynch syndrome and sporadic) were detectable even in histologically normal endometrium. Second, in Lynch syndrome and sporadic cases, they used molecular alterations to classify endometrial samples into three groups of increasing abnormality. Third, they found quantitative differences between Lynch syndrome and sporadic cases; notably, loss of ARID1A protein and deficient mismatch repair were characteristic of Lynch syndrome–associated endometrial and ovarian carcinomas. These results define the molecular trajectories of endometrial and ovarian cancer and can potentially guide patient management.

LABORATORY INVESTIGATION

Macrodissection and detection of breast cancer markers

doi:10.1038/s41374-018-0064-1



Immunohistochemistry (IHC) is the method currently used to measure HER2, ER, PR, and Ki-67 protein expression in breast cancer, and ERBB2 status is assessed via fluorescence in situ hybridization (FISH). Seeking alternative methods, Gupta et al. used the RT-qPCR GeneXpert system to measure messenger RNA (mRNA) expression levels of ERBB2, ESR1, PGR, and MKi67 in formalin-fixed, paraffin-embedded core needle biopsies, some of which were macrodissected. Two cohorts were employed: 60 infiltrating ductal carcinoma

(IDCA) cases and 20 IDCA cases with ductal carcinoma in situ. The authors found excellent agreement of mRNA transcript levels between macrodissected and non-macrodissected samples for all mRNAs in both cohorts. In addition, they noted a significant concordance between RT-qPCR and IHC/FISH for HER2, ER, and PR positivity, independent of specimen dissection. The simplicity of the assay workflow developed in this study may be valuable in settings where access to pathology expertise and high-quality IHC/FISH is challenging.

Targeted sequencing using FFPE tissues

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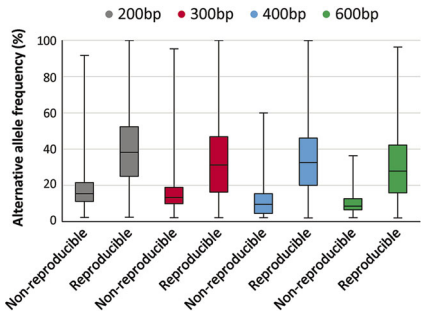
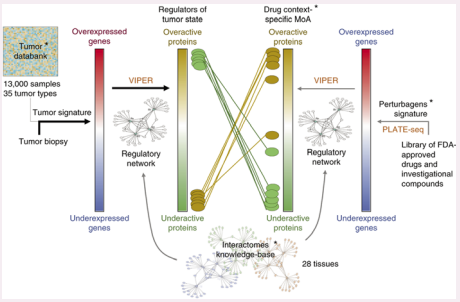


High-throughput somatic mutation screening using formalin-fixed paraffin-embedded tissues is a major challenge due to degraded DNA quality and lack of an established method. HaloPlexHS is a highly sensitive amplicon-based targeted next-generation sequencing method that incorporates molecular barcodes in the DNA library so that PCR artifacts can be separated from real variants in the original molecules. However, it is unclear to what extent variants detected using this approach should be further validated. Accordingly, the authors developed a stratified approach for mutation screening according to DNA quality. DNA samples of good quality (>400 bp) were amenable to mutation analysis with a single replicate; only variants at a depth of 15–20 alternative alleles (the number of reads that bear novel variants) required further validation. Those of suboptimal quality (≤300 bp) were better analyzed in duplicate, with reproducible variants at a depth >15 alternative alleles regarded as true genetic changes.

nature.com/pathology

Attacking master regulator proteins for precision oncology

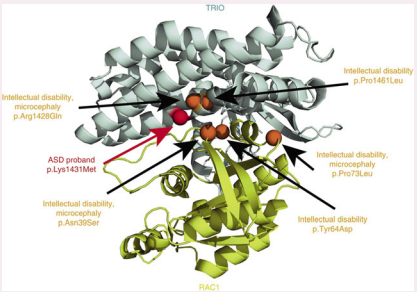
Precision oncology requires identification of a specific vulnerability in a tumor and then applying a therapy designed to exploit it. As recently described in *Nature Genetics*, Alvarez and colleagues put a twist on this approach. Rather than defining a tumor by identifying and targeting mutated oncogenic drivers, they sought to define the master regulator proteins necessary to maintain tightly regulated modules (tumor checkpoints) necessary for tumor promotion and maintenance. Using drugs to disrupt these programs extends the concept of oncogenic addiction beyond single pathways to broader regulatory networks. As proof of principle the researchers utilized bioinformatics to define master regulator proteins in gastroenteropancreatic neuroendocrine tumors, including neuroendocrine lineage progenitor state and immunoevasion regulators. They found that the HDAC class I inhibitor entinostat is a potent inhibitor of these pathways. Extension of similar analyses into other tumor types and clinical validation in patients could complement current precision-oncology efforts.



Nature Genetics 2018;50:979–989; doi:10.1038/s41588-018-0138-4

Defining damaging missense mutations in developmental disorders

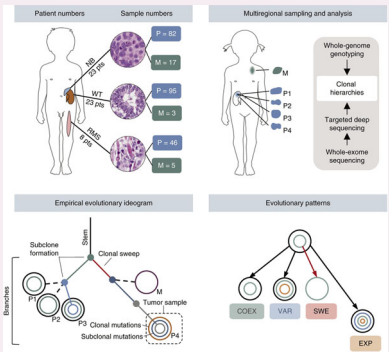
In broad-scale sequencing studies, identifying disease-associated mutations is a challenge. Family studies in inherited disorders can be helpful, but sometimes these are not available or are uninformative. Chen et al. have developed a bioinformatics and experimental approach to investigating the functional impact of human missense mutations on protein function. They tested their approach by characterizing ~2,000 de novo missense mutations in autism probands. Intriguingly, these proteins commonly disrupt proteins previously described as being involved in autism. Similar approaches could increase the efficiency of connecting mutations in patients with diseases being investigated.



Nature Genetics 2018;50:1032–1040; doi:10.1038/s41588-018-0130-z

Four types of evolution in childhood tumors

Heterogeneity in tumors is a challenge to both understanding and treating cancer. Karlsson et al. chose three childhood tumors—neuroblastoma, Wilms tumor, and rhabdomyosarcoma—to study the distribution of driver genes. They mapped tumor drivers in 250 regions from 54 tumors. They defined four distinct patterns, in descending order of frequency: (1) a few mutations confined to a single region of the tumor (VAR), (2) stable coexistence of a clone over a vast area with changes in chromosomal number (COEX); (3) emergence of a sweeping clone driver that rises to domination (SWE), and (4) emergence of a multitude of clones with *TP53* inactivation (EXP). Notably, death from disease was limited to the latter two, which were much more dynamic evolutionary patterns, rather than the first two patterns, which were more common and stable. It will be interesting to determine whether these patterns are found in other tumors and have the same prognostic implications.



Nature Genetics 2018;50:944–950; doi:10.1038/s41588-018-0131-y