Molecular pathology selected abstracts

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Detecting homologous recombination deficiency and olaparib response in ovarian carcinoma

October 2023—Ovarian cancer is the eighth most common cancer in women. There are several histological types of ovarian neoplasms, and all rank among the deadliest gynecological cancers. However, those with homologous recombination deficiency (HRD) may benefit from a recently discovered category of drugs, called poly ADP-ribose polymerase inhibitors (PARPi). The homologous recombination repair pathway, which is responsible for repairing double-strand DNA damage, involves several genes, including *BRCA1, BRCA2*, and *ATM*. People with germline or somatic deleterious alterations of these genes are at higher risk of certain malignancies, such as ovarian, breast, prostate, and pancreatic cancers. PARPi prevents base excision repair, leading to an accumulation of DNA with single-strand breaks, collapse of the replication fork, and, consequently, double-strand breaks. Cells with HRD cannot repair this synthetic double-strand break and will die. Although several clinical studies have shown the efficacy of PARPi, there is need for a laboratory assay that can detect HRD in high-grade serous ovarian carcinoma, as current approaches have shortcomings relative to technical characteristics and cost. Therefore, the authors developed a test to assess HRD status. As part of that process, they evaluated an HRD scoring method, based on a previous study by Telli, et al. (*Clin Cancer Res*. 2016;22:3164–3773), that incorporates a number of genomic scars associated with HRD. These scars include whole genome doubling (WGD), which is the duplication of a complete set of chromosomes; large-scale state transition (LST), which is the chromosomal breakage that results in partial gains or losses of 10 Mb or greater; telomeric allelic imbalance (TAI), which is defined as the number of regions with allelic imbalance involving the subtelomeric region; and regions of loss of heterozygosity (LOH). Examining these markers on The Cancer Genome Atlas publicly available database, the authors observed that as the number of WGD events increased, so did the number of LST and TAI, while the number of LOH decreased. They hypothesized that the numbers of LOH and TAI events in the HRD score from the study by Telli, et al., act as surrogate markers to normalize the ploidy or the number of WGD events but do not, in themselves, add value to a normalized LST (nLST) score. Therefore, the authors normalized LST by the number of WGD events, which further confirmed two separate clusters with high *BRCA* mutation status detection rates. This method was evaluated on 469 clinical samples from the European Network of Gynecological Oncology Trial (ENGOT). The results for the ENGOT samples showed tight correlation with the results from the commercially available Myriad MyChoice assay for evaluating *BRCA* mutation status and genomic instability score. Combining nLST and OncoScan (Thermo Fisher Scientific) correctly classified patients with *BRCA* mutations as HRD positive (high positive, 20 or more) with good progression-free survival (PFS) on PARPi maintenance. In *BRCA* wild-type patients, those with a negative nLST score (less than 15) had shorter PFS and those with 15≤nLST<20 (mid-positive) had good one-year PFS, when compared with the high-positive group, but lower long-term PFS. The authors concluded that the nLST score can identify patients with HRD and those who may benefit from PARPi.

Christinat Y, Ho L, Clément S, et al. Normalized LST is an efficient biomarker for homologous recombination deficiency and olaparib response in ovarian carcinoma. *JCO Precis Oncol*. 2023. doi: 10.1200/PO.22.00555

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Genetic architecture of binge eating disorder

Binge eating disorder is a psychological condition with episodes of overeating, often to the point of discomfort, followed by feelings of guilt and body-image disturbance. However, binge eaters do not pursue compensatory purging activities, as seen in bulimia nervosa. Binge eating disorder (BED) is associated with obesity, metabolic dysfunction, multiple psychiatric disorders, and low overall well-being. Because BED was not added to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), a widely used diagnostic classification system, until 2014, the underlying biology of BED is not well known. The authors explored a computational approach to defining the genetics underlying BED. Via a search of Veterans Health Administration databases, they identified approximately 800 people diagnosed with BED, of whom only 500 were genotyped. To improve the power of their study, the authors designed a machine-learning algorithm to compare a group of patients with reliable diagnoses of BED to a control group and thus create a BED score. This algorithm was further used to classify people who have a high probability of BED but do not have the diagnosis in their charts. The authors used a genomewide association study (GWAS) to identify the genetic alterations associated with BED in people of European and African ancestry, and they validated their findings in three cohorts: the Adolescent Brain and Cognitive Development Study (ABCD study), Philadelphia Neurodevelopmental Cohort (PNC), and UK Biobank (UKBB). The authors discovered three loci, near the *HFE, MCHR2*, and *LRP11* genes, implicated in BED with genomewide significance in those of European ancestry. This association was not observed in people of African ancestry. They also demonstrated a significant genetic correlation between BED and other psychiatric conditions, such as depression, bipolar disorder, and attention deficit hyperactivity disorder, as well as with lobar intracerebral hemorrhage and cannabis use. Interestingly, one of the significant alleles identified in the study is a pathogenic missense variant in the *HFE* gene (p.C282Y) associated with hemochromatosis. Using different analytical methods, iron dysregulation in the form of iron overload was genetically correlated with BED, even after excluding loci near the HFE gene. In addition to the three genes that were discovered in the initial GWAS and replicated in other cohorts, *APOE* was implicated in BED with genomewide significance in the validation cohort. This genetic correlation can explain the poor lipid profiles of obese patients with BED compared with obese patients without BED. One loci, near *MCHR2*, was detected in the primary GWAS and further replicated in validation cohorts. *MCHR2* plays an important role in glucose metabolism and regulates eating behavior. The authors concluded that their findings provide insight into the genetics underlying BED and suggest directions for future translational research.

Burstein D, Griffen TC, Therrien K, et al. Genome-wide analysis of a model-derived binge eating disorder phenotype identifies risk loci and implicates iron metabolism. *Nat Genet*. 2023. doi:10.1038/s41588-023-01464-1

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