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Genomic analyses to identify molecular subtypes of pancreatic cancer

Pancreatic cancer is a particularly difficult disease to treat and has a dismal five-year survival rate of less than five percent. The authors published a study using a variety of genomic analyses to identify four subtypes of pancreatic cancer and elucidate the molecular pathology of these tumors in hopes that doing so will lead to improved prognostic markers and therapeutic options. For the study, the authors used whole genome and deep whole exome DNA sequencing in 456 pancreatic ductal adenocarcinomas to identify 32 recurrently mutated genes representing 10 biological pathways. These pathways include activating *KRAS* mutations, disruption of G1/S checkpoint machinery (*TP53, CDKN2A*, and *TP53BP2*), disruption of TGF-β signaling (*SMAD4, SMAD3, TGFBR1, TFGBR2, ACVR1B,* and *ACVR2A*), and disruption of histone modifications (*KDM6A, SETD2, MLL2,* and *MLL3*), in addition to a smaller proportion of mutations in the *SWI/SNF* complex, BRCA pathway, WNT signaling, and RNA processing genes. Overall, DNA deamination, ectopic APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) activity, BRCA deficiency, and mismatch repair were the main mutational mechanisms in pancreatic cancer. No recurrent fusion events were detected, and chromothripsis and other related genomic catastrophes were uncommon. The study also investigated the transcriptional networks by performing RNA next-generation sequencing (RNA-seq) on 96 pancreatic cancer specimens with high epithelial content followed by mRNA expression arrays on an additional 232 pancreatic cancer specimens to replicate the RNA-seq analysis. The results of these analyses revealed four subtypes: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). The squamous tumors included gene networks involved in inflammation, hypoxia response, metabolic reprogramming, and TGF-β signaling and were associated with mutations in *TP53* and *KDM6A*. This subtype was associated with poor prognosis. The pancreatic progenitor subtype contained networks of transcription factors pivotal for pancreatic endoderm cell-fate determination and involved genes that played a part in early pancreatic development and were enriched for *TGFBR2* inactivating mutations. The ADEX subtype contained transcriptional networks important in later stages of pancreatic development and differentiation; the networks included upregulated genes involved in *KRAS* activation and exocrine and endocrine differentiation. Finally, the immunogenic subtype shared many features with the pancreatic progenitor subclass but was also associated with evidence of a significant immune infiltrate. In particular, the acquired tumor immune suppression pathways CTLA4 and PD1 were upregulated in this subclass, which may indicate potential response to novel immune modulator-based therapies. This study provided insight into the molecular pathology of pancreatic cancer and may encourage clinical trials based on these molecular subtypes, with the ultimate goal of achieving better outcomes for patients with pancreatic cancer.

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Utility of noninvasive prenatal screening to detect abnormalities genome wide

Noninvasive prenatal testing has made a large impact on prenatal screening for chromosome abnormalities in high-risk pregnancies. Several noninvasive prenatal testing (NIPT) screening assays report fetal trisomies for chromosomes 13, 18, and 21; sex chromosome aneuploidies; and selected microdeletions, such as 22q11.2 (DiGeorge syndrome) and 15q11-13 (Prader Willi/Angelman syndrome). The authors presented the results of a retrospective clinical validation study to assess the utility of using a NIPT screening test to detect genome-wide abnormalities. This study included more than 1,000 women who underwent NIPT as well as prenatal diagnostic testing because of a high risk for fetal aneuploidies due to advanced maternal age, history of aneuploidy, positive serum screen, or abnormal ultrasound findings. The goal of the study was to compare a genome-wide analysis to detect any chromosome aneuploidies as well as genome-wide gains or losses of 7 Mb and larger and specific microdeletions smaller than 7 Mb to standard-of-care diagnostic methods, including chorionic villus sampling or amniocentesis followed by G-banded chromosome or microarray analysis. The NIPT assay interrogates circulating cell-free fetal DNA from the maternal blood; the fetal DNA is thought to be largely derived from placental trophoblasts. The NIPT assay relied on next-generation sequencing (NGS) of DNA derived from maternal plasma and counting methods to assess copy gains and losses in the fetus. The study included a comparison of assay results for approximately 1,200 samples. For trisomies 21, 18, and 13, all aneuploidies identified by diagnostic procedures (n=113) were also detected using the NIPT screen. For sex chromosome abnormalities, after accounting for placental or maternal mosaicism, it was determined that there was one false-positive result in the 27 sex chromosome aneuploidies detected. For the copy number variant (CNV) analysis, there was one false-positive result in the 43 CNVs, including eight whole chromosome trisomies other than chromosomes 13, 21, and 18, or sex chromosomes, and 35 subchromosomal CNVs. It was not clear which of the 35 subchromosomal CNVs would have been detected by the current NIPT screening tests and which were unique to a whole genome approach. The authors estimated an overall positive predictive value to be between 68 and 83 percent assuming an overall incidence rate of one in 200 to one in 400. The study shows promising evidence that this method can be expanded to encompass genome-wide gains and losses. However, alone, it is not sufficient to assess the accuracy and positive predictive value of detecting events above and beyond current NIPT screening tests that target only trisomies 21, 18, and 13; sex chromosome abnormalities; and select microdeletions. The study may, however, encourage larger studies to assess the efficacy of NIPT screening to detect rare events.

Lefkowitz RB, Tynan JA, Liu T, et al. Clinical validation of a non-invasive prenatal test for genome-wide detection of fetal copy number variants [published online ahead of print February 17, 2016]. *Am J Obstet Gynecol.* doi:10.1016/j.ajog2016.02.030.

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