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ADRENAL GLAND

The genetics of adrenocortical carcinoma revealed

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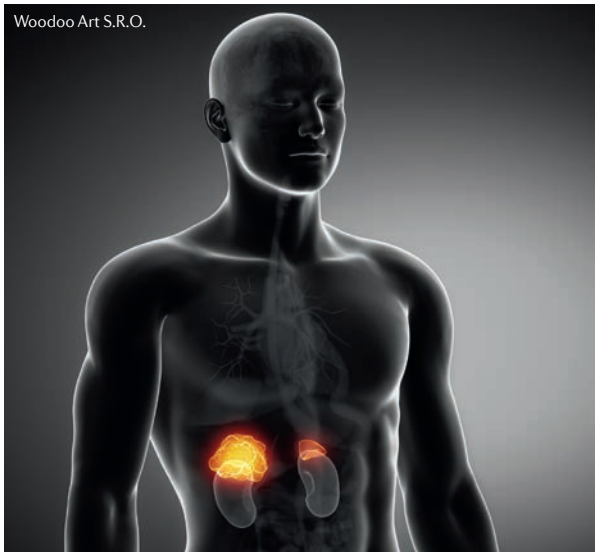
Current understanding of the pathogenesis of adrenocortical carcinoma (ACC) is incomplete, and treatment options are limited. A new international collaboration, co-chaired by Roel Verhaak, Gary Hammer and Tom Giordano as part of The Cancer Genome Atlas (TCGA), has identified several new genetic characteristics of ACC, which could aid the development of novel therapies.

"Prior work on ACC genomics had been performed in small cohorts, most often using one platform at a time," explains Hammer. "This iteration was a unique opportunity to apply a multitude of omic technologies across a large set of ACCs, enabling joint bioinformatic analysis of the data … and deep coverage of the genome across various platforms." The team collected samples from 91 ACCs from countries across four continents, which were comprehensively analysed. "TCGA has a standardized genomic platform that includes next-generation sequencing for DNA exomes and RNA, methylation profiling, copy number analysis using high density single nucleotide polymorphism arrays and proteomics using reverse phrase protein array," explains Giordano.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These analyses enabled the researchers to identify several new genes associated with ACC — *PRKAR1A*, *RPL22*, *TERF2*, *CCNE1* and *NF1*. Intriguingly, the loss-of-function mutation in *PRKAR1A* is known to be associated with benign adrenocortical cancers, which suggests that there could be pathophysiological links between benign and malignant adrenocortical tumours. Amplification of *TERF2* and telomerase was found in several samples, which suggests that telomere maintenance could be involved in the development of ACCs. The researchers found that 16% of the samples had a homozygous deletion of *ZNRF3* (a gene involved in the Wnt signalling pathway), with an overall 19.3% having some kind of alteration in this gene.

A subset of ACCs in the study were found to have profound genomic instability, including genomic loss and whole-genome doubling. While whole-genome doubling is common across a range of cancers, an association with patient outcomes has only been demonstrated in ovarian cancer. Verhaak, Hammer, Giordano and co-workers have now shown that whole-genome doubling is associated with an aggressive clinical course in ACC, which suggests that it could be a marker of ACC progression. However, Hammer cautions that much is still unknown about why whole-genome doubling occurred in this particular subset of ACCs, the mechanisms underlying the process and the implications for cancer initiation, maintenance and progression.

The researchers also generated a robust molecular classification system for ACCs. They began by using unsupervised clustering to identify four mRNA expression groups, six microRNA expression groups, three DNA-methylation groups, three copy-number groups and three protein expression groups. These subsets (excluding the protein expression groups) were integrated using a cluster of cluster (CoC) analysis. This analysis identified three distinct CoC subtypes with different clinical outcomes; disease progression rates were 7%, 56% and 98% for CoC I, CoC II and CoC III, respectively. To simplify the required molecular profiling for use in the clinic, the team derived a methylation signature consisting of 68 probes that could classify the cohort into the three CoC subtypes with 92.4% accuracy. The prognostic power of this signature was validated in an independent cohort.

"This project is a resource that we consider a hypothesis generator," says Hammer. "We now need to go back to the bench and understand how these genes and pathways contribute to the pathogenesis of ACC." The researchers hope that their findings will lead to improved prognostication and novel therapeutics. "We are actively considering pathways for clinical translation, including DNA methylation," adds Giordano.

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