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Autoimmune Addison's disease is the predominant cause of primary adrenal failure, and is highly heritable. The genetic background has remained poorly understood due to the low prevalence and complex inheritance of the disease. We performed a genome-wide association study, which identified nine independent risk loci ($P < 5 \times 10^{-8}$). In addition to novel and previous risk loci involved in lymphocyte functionality, we further associated autoimmune Addison's disease with two independent protein-coding alterations in the gene *Autoimmune Regulator* (*AIRE*). The most striking is the amino-acid substitution p.R471C (rs74203920, OR = 3.4 (2.7–4.3), P = 9.0×10^{-25}), which introduces an additional cysteine residue in the zinc-finger motif of the PHD2 domain of AIRE. This unbiased elucidation of the genetic contribution to development of autoimmune Addison's disease points to the importance of central immunological tolerance, and explains 35–41 percent of heritability.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Insights From Targeted Genetic Analysis of 364 Adrenocortical Carcinomas

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy affecting individuals across a broad age spectrum. Disease rarity, scarcity of pre-clinical models, lack of effective targeted therapy and limited clinical trials have contributed to poor prognosis for patients with ACC. Identifying targetable genetic drivers and pathways to guide precision medicine approaches is therefore critical to improve outcomes. The purpose of this study was to analyze the genomic profile of a large cohort of ACC to identify potential therapeutic targets. FoundationOne (Foundation Medicine Inc.; FMI, Cambridge, MA) is a next-generation sequencing-based platform for somatic genetic testing in solid tumors. The FoundationOne genomic data and limited demographic data through 2018 for 364 unique ACC specimens were analyzed. The cohort of 364 tumors were from 222 females and 141 males (1 gender unknown). The mean age (SD) was 48.6 (13.6) for females and 50.6 (12.20) for males with overall median age of 52 years. A total of 3117 genomic alterations were identified impacting 457 genes. The median number of genomic alterations per tumor was 7 (range 1–56), with single nucleotide variants and indels being the most common alterations (median=4), followed by copy number alterations (median=1) and rearrangements (median=0). The most frequently altered genes were *TP53* (38%), *CTNNB1* (28%), *ZNRF3* (17%), *CDKN2A* (13%), *ATRX* (11%), *TERT* promoter (10%). Several novel recurrent alterations were identified including *IL7R* (6%), *LRP1B* (8%), *FRS2* (4%), *PTCH1* (4%) and *KRAS* (3%). Pathway enrichment analysis confirmed that tumor suppressor genes (51%) and Wnt signaling pathways (51%) are the most commonly dysregulated in ACC tumors. Epigenetic alterations, including histone modification (38%), SWI/SNF (21%) and DNA methylation (8%), affected upwards of one third of ACC tumors. Mutation signature analysis identified tumors with signatures 6, 15 and 26 associated with defective DNA mismatch repair (MMR), which was not reported previously. In addition, fifty ACCs (13.7%) exhibited 60 genomic alterations in MMR genes, *MLH1, MSH2, MSH6* and *PMS2*, which included 49 SNVs/indels, 10 CNAs and one truncating rearrangement. In addition to MMR gene alterations, potentially actionable (www.oncokb.org) genomic alterations were found in 46 genes in 213 (58.5%) ACCs. In summary, this study represents the largest to date genomic analysis of ACC that showed that over 50% of ACC tumors had potentially actionable genomic alterations. Approximately 13% of tumors had an alteration in MMR pathway, suggesting that immunotherapy is a relevant therapeutic modality in a significant subset of patients with ACC.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Novel Germline SUCLG2 Mutations in Patients With Pheochromocytoma and Paraganglioma

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors derived from neural crest cells