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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

that are frequently linked to mutations including those in Krebs cycle enzymes, particularly succinate dehydrogenase (SDH). Succinyl-CoA ligase (SUCL) catalyzes reversible conversion of succinyl-CoA to succinate providing the substrate for SDH. While mitochondrial diseases were documented for the mutations in SUCL subunits G1 and A2, the association of GDP/GTP-specific subunit *SUCLG2* mutations with specific pathologies including cancer have not been reported. In our study, 352 patients with apparently sporadic PPGLs underwent genetic testing using a panel of 54 genes developed at the National Institutes of Health. Additionally, human pheochromocytoma (hPheo1) cells were used for gene manipulation to produce SUCLG2 knock-out (KO). Tumor tissues and hPheo1 SUCLG2 KO cells were used for further analysis focusing on mechanism of germline variants effect on mitochondrial functions. We detected eight germline *SUCLG2* mutations in 15 patients which represents 4.3% of the cohort. Germline variants together with LOH led to decreased levels of SDH subunit B resulting in aberrant respiration and accumulation of succinate, well recognized oncometabolite. Manipulation of SUCLG2 in hPheo1 cells confirmed decrease in SDHB leading to faulty assembly of mitochondrial complex II and alteration of its respiration and activity. In summary, our study identified an association between *SUCLG2* and PPGL. Larger scale sequencing and uncovering additional cases bearing *SUCLG2* variants will further clarify the relationship between SUCLG2 and SDHx, particularly SDHB, as well as their role in disease etiology.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORT

A Challenging Case of Vitamin D Toxicity Responding to Cinacalcet

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Background: Interest in the role of vitamin D in various physiological processes, the prevalence of its deficiency and importance of replacement has increased significantly over the past few decades. However, many formulations of vitamin D are not regulated and are available to the public without clear guidance on safe administration, which has contributed to the uptrend in the incidence and severity of vitamin D toxicity cases. Clinical Case A 57- year-old man with a medical history significant for amyotrophic lateral sclerosis, cervical myelopathy, and oropharyngeal dysphagia presented with weakness, constipation, polydipsia, polyuria and was found to have hypercalcemia with a total Calcium level of 15.5 mg/dL (n 8.6- 10.4), and albumin 4.2 g/dL (n 3.5–5.1). He soon developed acute hypoxic respiratory failure requiring prolonged intubation followed by tracheostomy. Evaluation of the hypercalcemia revealed an elevated 25-hydroxyvitamin D [25(OH)D] > 392 ng/mL (n 30–80), 1,25- dihydroxyvitamin D [1,25(OH)D] >600 pg/mL (n 19.9 - 79.3), PTH 8 pg/mL (n 12–88), and PTHrP 0.7 pmol/L (n< 4.2). The patient had initially stated that he was taking 5000 IU of vitamin D daily but further discussion with his wife revealed that he had been taking 2 teaspoons of a powder cholecalciferol preparation with 125 mcg (5000 IU of vitamin D) per 50 mg, which would be about 800,000 IU/day. He was treated with aggressive IV hydration, calcitonin and received 2 doses of pamidronate with an initial improvement in his Calcium level down to 10 mg/dL followed by recurrence of hypercalcemia. Work up for granulomatous disease and multiple myeloma revealed latent TB. At significantly elevated [25(OH)D] levels, toxicity is partially caused by the direct action of [25(OH)D] on the vitamin D receptor (VDR), and [25(OH)D] can also cross-react with the [1,25(OH)D] assay causing false elevation. Steroids were avoided because of his recent diagnosis of latent TB; hence he was started on Cinacalcet which was gradually increased to 60 mg twice a day with sustained Calcium normalization. Repeat labs showed improvement in [25(OH)D] to 292, and normalization of [1,25(OH)D] at 69.4. He was discharged on Cinacalcet 30 mg twice a day. Conclusion PTH-independent hypercalcemia is usually treated with hydration, anti-resorptive agents including bisphosphonates, denosumab and calcitonin, in addition to steroids in cases of increased 1 αλπηα-hydroxylase activity. Cinacalcet acts on the Calcium sensing receptor (CaSR) in parathyroid tissue, kidneys, bones and the intestine and was recently shown to improve hypercalcemia of malignancy in a report of 2 cases by Sheehan et al. Cinacalcet has helped our patient and might have a potential role for the prompt treatment of vitamin D toxicity, but more data is needed.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORT

1-25OH^{2}D Mediated Hypercalcemia Secondary to DISR From Immune Checkpoint Inhibitors

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Background: Drug induced sarcoid like reactions (DISR) have recently been described as a potential consequence of immune checkpoint inhibitor therapy. However, hypercalcemia associated with DISR has not been reported. **Clinical Case:** A 72 year old male presented with metastatic melanoma. He initiated therapy with Ipilimumab/Nivolumab (Ipi/Nivo). Three weeks after his first cycle he developed symptomatic hypercalcemia (calcium 14.4 mg/dL), and acute kidney injury (creatinine 3.45mg/dL), PTH 12 pg/mL, 25OHD 51, and PTHrp 0.5. He received IV fluids and IV bisphosphonates and calcium normalized to 9.1 mg/dL and creatinine 1.85 mg/dL. His Ipi/Nivo were stopped due to concern for neurotoxicity. He subsequently switched to Q3week Pembrolizumab (Pembro) and after 2 infusions, he again developed hypercalcemia (calcium 11.8 mg/dL). FDG PET demonstrated a complete radiographic response. Labs showed a 1,25OH^{2}D of 103 pg/mL (reference range 19.9–79.3 pg/mL), PTH of 4 pg/mL and calcium of 11.4 mg/dL. He was treated with prednisone 20 mg QD. After 9 days on prednisone, 1,25OH^{2}D was 26 pg/mL and calcium 9.4 mg/dL. He took prednisone for 3 weeks total. Repeat labs off prednisone for one week were 1,25OH^{2}D of 38 pg/mL and calcium 9.1 mg/dL. He continued on Pembro. After being off steroids for 5 weeks, he developed body aches and swelling of the hands. 1,25OH^{2}D increased to 100 pg/mL and calcium