Abstract citation ID: bvac150.1194

Neuroendocrinology and Pituitary

RF01 | PMON167

Isolated Cushing's Disease Associated With Rare Germline SDHx Variants

Prashant Chittiboina, MD, Denise M. Kay, PhD, James L. Mills, MD, MS, Constantine A. Stratakis, MD, D(Med)Sc, Laura C. Hernãndez-Ramírez, MD, PhD, Nathan Pankratz, PhD, John Lane, PhD, and Fabio R. Faucz, PhD

Introduction: Loss-of-function (LOF) germline variants in the SDHx genes (SDHA, SDHB, SDHC, and SDHD), encoding the succinate dehydrogenase subunits, are a rare

cause for pituitary tumors in the setting of various familial tumor syndromes. Occasional case reports have highlighted SDHx mutations in isolated pituitary tumors (including one case of Cushing's disease, CD). The actual frequency of SDHx variants as genetic drivers of pituitary tumors, however, remains elusive.

Aim: We sought to determine the frequency of germline SDHx variants in a large cohort of CD patients.

Methods: Of the 245 unrelated CD patients studied (139 females, 56.7%; 230 pediatric, 93.9%), 184 underwent whole-exome sequencing (WES) of peripheral blood and 27 of them underwent additional tumor WES. Forty-three additional germline samples and 92 tumor samples underwent Sanger sequencing of specific genes. Rare variants of uncertain significance (VUS), likely pathogenic or pathogenic variants of the SDHx genes were reviewed. Immunocytochemistry was used to analyze protein expression in tumor samples.

Results: Germline heterozygous variants of SDHA (three missense and one frameshift) and SDHD (two missense) were identified in six patients (four female; mean age of 8.8 ±2.2 years at onset of CD and 11.5±2.6 years at diagnosis). The variants were inherited in all 5 cases where parental germline samples were available. We found the following SDHA variants: Case 1 carried p.A21T (absent from gnomAD), Case 2 carried p.L74Ffs*9 (absent from gnomAD), Case 3 carried p.I235T (allele frequency, MAF=0.0100% in gnomAD exomes), and Case 4 carried p.H424Q (MAF=0.0056% in gnomAD exomes). Two patients (Cases 5 and 6) carried the SDHD missense VUS c.53C>T, p.A18V (MAF= 0.0068% in gnomAD exomes). Case 6 had a maternal family history of familial isolated pituitary adenomas, but an SDHD variant of paternal origin; disease presentation was apparently sporadic in the rest of cases. Case 2 displayed somatic loss of heterozygosity (LOH) for the SDHA variant, while no LOH was found in the three other cases tested. Somatic hotspot variants were absent in all tumors tested in USP8 (5/5 cases), USP48 (4/4 cases), and BRAF (4/4 cases). All patients carried microadenomas and achieved remission after one transsphenoidal surgery. Case 4 was diagnosed with a Crooke's cell corticotropinoma and also carried germline VUS in DICER1 and TSC2. In all three tumors tested, SDHx subunit expression was reduced: SDHB reduced in Cases 2, 4, and 5; SDHA reduced in Cases 2 and 4; absent SDHD in Case 2, and absent SDHC in case 5. **Conclusion:** Altogether, SDHx variants were found in 2.4% of the cohort (2.6% of pediatric patients). Our findings suggest that germline SDHx variants are a rare but significant genotype associated with isolated sporadic Cushing's disease.

* JLM and CAS contributed equally.

Presentation: Saturday, June 11, 2022 1:24 p.m. - 1:29 p.m., Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.