Dual Heterozygous Mutations in CYP21A2 and CYP11B1 in a Case of Nonclassic Congenital Adrenal Hyperplasia

Eric Frontera, DO, Joshua J Brown, BS,
Hagop Ghareebian, MBCHB, and Cary Mariash, MD

Background: Congenital Adrenal Hyperplasia (CAH) is classically attributed to defective 21-hydroxylase, caused by mutations in CYP21A2, impairing the production of mineralocorticoids and glucocorticoids and subsequently shifting steroidogenesis towards androgen production. This produces a classic constellation of neonatal symptoms, including genital virilization, salt-wasting, and adrenal crisis. A rare cause of CAH is a defect in 11β-hydroxylase from a mutation in CYP11B1, preventing production of cortisol and corticosterone, resulting in hypertension, hypokalemia, and androgen excess. Reports of combined mutations in CYP21A2 and CYP11B1 in the literature and the clinical manifestations of such a case are not well described. Here we present a case report wherein a pair of heterogenous mutations in CYP2A12 and CYP11B1 were detected in a new diagnosis of nonclassic Congenital Adrenal Hyperplasia, including a previously undescribed mutation in CYP11B1.

Clinical Case: The patient is a 30-year-old female who presented to her primary care clinic with teenage-onset irregular menses occurring every 2-3 months. She also reported hirsutism, but never had acne, changes in thirst or urination, or breast discharge. Primary evaluation revealed prolactin of 34.7 ng/mL, prompting a pituitary MRI which revealed a 2×3 mm lesion. At this point, referral was made to endocrinology for endocrinological. PCOS was felt to be the top differential for her hirsutism and irregular menses but further workup to rule out CAH revealed a 17-OH-Progesterone of 554 ng/dL and a Testosterone of 83 ng/dL. Subsequently, a 250 mcg cosyntropin test increased 17-OH progesterone to 837 ng/dL and resulted in a cortisol of 24.7 mCg/dL after 60 minutes. Subsequent CAH gene sequencing was performed and revealed a heterogeneous pathogenic CYP21A2 variant (c.332_339 del; p.Gly111Valfs*21) and a heterogeneous previously undescribed variant of undetermined significance in CYP11B1 (c.1123C>T; p.Leu375Phe).

Conclusion: At least 100 mutations of CYP11B1 have been found to cause CAH due to 11β-Hydroxylase deficiency. Our case adds to the growing database of described mutations in CYP11B1 and suggests that heterogenous mutations in two different genes may present phenotypically as nonclassic CAH in a potentially epistatic fashion. This enriches earlier conclusions that broader genetic analysis beyond CYP21A2 deletions is needed to identify the genotypes of those with CAH due to the complex diversity of genetic mutations, and ought to remind clinicians to consider it as a diagnosis, particularly in young women whose hyperandrogenism or menstrual irregularities cannot be explained by common endocrinological abnormalities or do not have an appropriate response to traditional treatment.

Presentation: Saturday, June 11, 2022 1:00 p.m. - 3:00 p.m.