## Genetic Defects Affecting Adrenal Development

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As a center of the steroidogenesis of critical mineralocorticoids, glucocorticoids, and androgens, the adrenal glands (and specifically, the adrenal cortex) play important roles in salt-retention, metabolism, and sexual differentiation. Therefore, defects in the adrenal development and maturation process can result in adverse physiological effects after birth. While the extent of the factors involved in proper development of the adrenal glands has yet to be fully understood, a reliance on a correctly functioning hypothalamic-pituitary-adrenal axis has been established. Genetic disorders that interfere with this communication, in addition to disorders affecting the glands themselves, typically result in various degrees of "adrenal hypoplasia" characterized clinically by small and hypofunctional adrenals. While the incidence of these conditions is relatively rare, occurring in around 1:12,500 live births, studies on individuals presenting with the condition have allowed for the categorization of these defects into: 1) secondary defects affecting adrenocorticotropic hormone (ACTH) synthesis and release from the pituitary, 2) adrenal resistance to ACTH, and 3) primary genetic defects within the adrenals. A number of mutations found in transcription factors active in the developing pituitary, such as TBX19 have been demonstrated to result in defective pro-opiomelanocortin (POMC) synthesis, the ACTH precursor. Furthermore, mutations in the processing machinery of POMC, such as PC-1, can result in defective ACTH signaling to the developing adrenals. Defects in the ACTH receptor (*MC2R*) and accessory proteins can result in adrenal glands unresponsive to ACTH, leading to reduced synthesis of steroid hormones required for downstream developmental events (1). Finally, while their ligands have yet to be identified, mutations in orphan steroid nuclear receptor proteins such as the X-linked DAX-1 and autosomal inherited SF-1 present within the adrenals can result in adrenal insufficiency, hypogonadism, and defects in male sexual differentiation (2).

Adrenal hypoplasia may be syndromic, as exemplified with IMAGe syndrome, a constellation of symptoms including intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies (3,4). Interestingly, a specific cluster of mutations in the proliferating cell nuclear antigen-binding domain of the *CDKN1C* gene (otherwise shown to cause Beckwith-Wiedemann, an overgrowth syndrome) is responsible for IMAGe syndrome (5).

## References

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