Diagnosis and management of adrenal insufficiency

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Supplemental Table 1: Inherited steroidogenic disorders as causes of primary adrenal insufficiency

Disorder	**Mutated gene** (Chromosomal location)	**Comments/additional features**
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD) (OMIM #201910)	*CYP21A2* (6p21.3)	• Cause of disease in 90-95% of all CAH • 1:12,000-15,000 births • 46,XX DSD, precocious pseudopuberty • spectrum of disease with regard to severity of glucocorticoid deficiency and presence and severity of mineralocorticoid deficiency dependent on significance of mutation • milder mutation defines phenotype
Congenital adrenal hyperplasia due to 11β-hydroxylase deficiency (11OHD) (OMIM #610613)	*CYP11B1* (8q21-22)	• Cause of disease in 2-5% of CAH patients • 1:100,000-1:200,000 births • 46,XX DSD, precocious pseudopuberty in both sexes • arterial hypertension due to accumulation of 11-deoxycorticosterone
Congenital adrenal hyperplasia due to P450 oxidoreductase deficiency[1, 2] (PORD) (OMIM #613571)	*POR* (7q11.23)	• Cause of disease in <1% of CAH patients • Biochemically presents with combined 21-hydroxylase and 17-hydroxylase deficiency • POR acts as electron donor to all microsomal human cytochrome P450 (CYP type II enzymes), including multiple enzymes involved in steroid and sterol synthesis, retinoic acid metabolism, drug and xenobiotic metabolism • Can present with skeletal malformations resembling the Antley-Bixler syndrome phenotype (OMIM #207410) • Circulating androgen concentrations are low in both sexes, but neonatal presentation is both with 46,XX DSD and 46,XY DSD
Congenital adrenal hyperplasia due to 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD2) deficiency	*HSD3B2* (1p12)	• Cause of disease in <1% of CAH patients • Spectrum of disease severity: salt wasting form, non-salt wasting form, possible 46XY DSD, occasional presentation as isolated pubarche, late onset form presenting with hirsutism and menstrual irregularities

(OMIM #613890)		
Congenital adrenal hyperplasia due to17α-hydroxylase deficiency (17OHD) (OMIM #202110)	*CYP17A1* (10q24.32)	• Cause of disease in <1% of CAH patients • Loss of 17-hydroxylase results in glucocorticoid deficiency and accumulation of mineralocorticoids in hypokalaemic hypertension • Glucocorticoid deficiency not always clinically manifest as accumulating corticosterone activates the glucocorticoid receptor • Disruption of CYP17A1 17,20 lyase activity results in lack of sex steroids and consequently 46,XY DSD in affected boys and lack of puberty in both sexes
Congenital lipoid adrenal hyperplasia (CLAH) due to StAR deficiency (OMIM #201710)	*STAR* (8p11.23)	• Disruption of the activity of the steroidogenic acute regulatory protein (StAR) responsible for rapid cholesterol transport into the mitochondrion • Enlarged adrenals due to accumulation of lipid droplets in the cytosol • 46,XY DSD
CYP11A1 deficiency (also P450 cytochrome side cleavage (P450scc) deficiency) (OMIM #613743)	*CYP11A1* (15q24.1)	• No adrenal hyperplasia • 46,XY DSD
Congenital adrenal hypoplasia, X-linked with hypogonadotrophic hypogonadism (OMIM #300200)	*NR0B1 (=DAX1)* (Xp21.2)	• Developmental lack of adrenocortical zonation results in adrenal failure • Hypogonadotrophic hypogonadism in males
Congenital adrenal hypoplasia, Chromosome Xp21 deletion syndrome (OMIM #300679)	Contiguous deletion of *NR0B1*, the Duchenne muscular dystrophy gene dystrophin and the glycerol kinase gene *GK* (Xp21)	• Duchenne muscular dystrophy • glycerol kinase deficiency • psychomotor retardation

Congenital adrenal hypoplasia SF-1 linked (OMIM #612965)	*NR5A1* encoding steroidogenic factor 1 (SF-1) (9q33.3)	• 46,XY DSD • variable with milder mutations: premature ovarian failure and spermatogenic failure
Congenital adrenal hypoplasia: IMAGe syndrome (OMIM #614732) [3, 4]	Inactivating mutations in the tumour suppressor gene *CDKN1C* encoding cyclin-dependent kinase inhibitor 1C (11p15.4)	• Intrauterine growth retardation • metaphyseal dysplasia, • genital abnormalities (cryptorchidism, small penis, hypospadias) • NB: gain-of-function mutationsconti in CDKN1C are the cause of Beckwith-Wiedemann syndrome associated with increased tumour formation in childhood
Kearns-Sayre syndrome (OMIM #530000)	mitochondrial DNA deletions	• External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrinopathies
X-linked adrenoleukodystrophy (ALD) or adrenomyeloneuropathy (AMN) (OMIM #300100)	*ABCD1* encoding for a peroxisomal membrane transporter protein (Xq28)	• 1:20,000 males • Demyelination of CNS (ALD), spinal cord (AMN), peripheral nerves • ALD and AMN phenotypes can be observed within a family with the same genotype, with variable penetrance
Triple A syndrome – Allgrove's syndrome (OMIM #231550))	Triple A gene (*AAAS*) encoding the WD-repeat protein ALADIN (12q13.13)	• Triad of Primary adrenal insufficiency (ACTH resistance), alacrimia, and achalasia (= Triple A); additional phenotypic features include neurological impairment, deafness, mental retardation, hyperkeratosis
Variants of Familial glucocorticoid deficiency (FGD)		
FGD type 1 [5] (OMIM #202200)	*MC2R* encoding the ACTH receptor (melanocortin 2 receptor) (18p11.21)	• Usually neonatal presentation with severe adrenal insufficiency, hypoglycaemia, infections, hyperpigmentation • Normal aldosterone, normal renin • Tall stature in FGD type 1 patients
FGD type 2 [6] (OMIM #607398)	*MRAP* encoding the MC2R-ancessory protein responsible for translocation of the ACTH receptor to the membrane (21q22)	
FGD type 3 [7] (OMIM #609197)	*STAR* (8q 11.2-q13.2); see above for description of StAR deficiency (CLAH)	

FGD type 4 [8] (OMIM #614736)	*NNT* encoding nicotinamide nucleotide transhydrogenase involved in regulation of mitochondrial redox balance through detoxification of reactive oxygen species (5p12)	
Natural killer cell and glucocorticoid deficiency with DNA repair defect [9] (OMIM #609981)	*MCM4* (8q11.21)	• growth failure • increased chromosomal breakage • natural killer cell deficiency

Suppl. Table 2: Monogenic causes of secondary adrenal insufficiency

Variants of Combined Pituitary Hormone Deficiency (CPHD)				
CPHD type	*Gene (location)*	Pituitary hormone deficiencies	**ACTH deficiency**	**Other clinical and imaging features**
CPHD 2[10] (OMIM #262600)	*PROP1* (5q35.3)	Sequential loss of pituitary hormones: GH, LH, FSH, TSH, prolactin, ACTH	+	• Hypoplastic anterior pituitary • ACTH deficiency characteristically manifests later in life (during third decade)
CPHD 3[11] (OMIM #221750)	*LHX3* (9q34.3)	GH, TSH, prolactin, LH, FSH, ACTH	+/-	• Hypoplastic anterior pituitary +/- • Rigid cervical spine • sensorineural deafness • Mental retardation +/-
CPHD4 [12] (OMIM #262700)	*LHX4* (1q25.2)	GH, TSH, ACTH, prolactin, FSH, LH	+	• Hypoplastic anterior pituitary • Ectopic posterior pituitary • Chiari malformation +/-
CPHD5 [23] (OMIM #182230)	*HESX1* (3p14.2)	Variable deficiency of GH, LH, FSH, TSH; ACTH deficiency in 60%; +/- Diabetes insipidus	+/-	• Septooptic dysplasia, visual impairment • agenesis of midline structures • developmental delay
CPHD6[13] (OMIM #613986)	*OTX2* (14q22.3)	GH, TSH, ACTH, FSH, LH	+	• Hypoplastic anterior pituitary
Other monogenic causes of congenital ACTH deficiency				
Holoprosencephaly [14] (OMIM #610829)	*GLI2* (2q14.2)	Panhypopituitarism	+	• Hypoplastic anterior pituitary • Midface hypoplasia
X-linked panhypopituitarism [15] (OMIM #312000)	*SOX3* (Xq27.1)	Panhypopituitiarism	+	• Hypoplastic anterior pituitary

Syndromic microphthalmia 3[16] (OMIM #206900)	*SOX2* (3q26.33)	Panhypopituitarism	+	• Hypoplastic anterior pituitary • Anophthalmia or microphthalmia • Brain anomalies, seizures, neurocognitive delay • Oesophageal atresia
Isolated ACTH deficiency due to mutations in TBX19 [99] (OMIM #201400)	*TBX19* (1q24.2 9)	ACTH deficiency only	+	
Pro-opiomelanocortin deficiency syndrome [17] (OMIM #609734)	*POMC* (2q23.3)	ACTH deficiency only	+	• Early onset obesity • Red hair pigmentation
Prader-Willi syndrome [18] (OMIM #176270)	Contiguous deletion including *SNRPN* and *NDN* (15q11-q13)	LH, FSH and ACTH deficiency	+/-	• Obesity • Mental retardation • Penetrance and severity of adrenal insufficiency variable

References

1. Fluck, C.E., et al., *Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome.* Nat Genet, 2004. **36**(3): p. 228-30.
2. Arlt, W., et al., *Congenital adrenal hyperplasia caused by mutant P450 oxidoreductase and human androgen synthesis: analytical study.* Lancet, 2004. **363**(9427): p. 2128-35.
3. Vilain, E., et al., *IMAGe, a new clinical association of intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies.* J Clin Endocrinol Metab, 1999. **84**(12): p. 4335-40.
4. Balasubramanian, M., A. Sprigg, and D.S. Johnson, *IMAGe syndrome: Case report with a previously unreported feature and review of published literature.* Am J Med Genet A, 2010. **152A**(12): p. 3138-42.
5. Tsigos, C., et al., *Hereditary isolated glucocorticoid deficiency is associated with abnormalities of the adrenocorticotropin receptor gene.* J Clin Invest, 1993. **92**(5): p. 2458-61.
6. Metherell, L.A., et al., *Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2.* Nat Genet, 2005. **37**(2): p. 166-70.
7. Genin, E., et al., *Linkage of one gene for familial glucocorticoid deficiency type 2 (FGD2) to chromosome 8q and further evidence of heterogeneity.* Hum Genet, 2002. **111**(4-5): p. 428-34.
8. Meimaridou, E., et al., *Mutations in NNT encoding nicotinamide nucleotide transhydrogenase cause familial glucocorticoid deficiency.* Nat Genet, 2012. **44**(7): p. 740-2.
9. Hughes, C.R., et al., *MCM4 mutation causes adrenal failure, short stature, and natural killer cell deficiency in humans.* J Clin Invest, 2012. **122**(3): p. 814-20.
10. Turton, J.P., et al., *Mutations within the transcription factor PROP1 are rare in a cohort of patients with sporadic combined pituitary hormone deficiency (CPHD).* Clin Endocrinol (Oxf), 2005. **63**(1): p. 10-8.
11. Rajab, A., et al., *Novel mutations in LHX3 are associated with hypopituitarism and sensorineural hearing loss.* Hum Mol Genet, 2008. **17**(14): p. 2150-9.
12. Pfaeffle, R.W., et al., *Three novel missense mutations within the LHX4 gene are associated with variable pituitary hormone deficiencies.* J Clin Endocrinol Metab, 2008. **93**(3): p. 1062-71.
13. Diaczok, D., et al., *A novel dominant negative mutation of OTX2 associated with combined pituitary hormone deficiency.* J Clin Endocrinol Metab, 2008. **93**(11): p. 4351-9.
14. Roessler, E., et al., *Loss-of-function mutations in the human GLI2 gene are associated with pituitary anomalies and holoprosencephaly-like features.* Proc Natl Acad Sci U S A, 2003. **100**(23): p. 13424-9.
15. Hol, F.A., et al., *Identification and characterization of an Xq26-q27 duplication in a family with spina bifida and panhypopituitarism suggests the involvement of two distinct genes.* Genomics, 2000. **69**(2): p. 174-81.

16. Ragge, N.K., et al., *SOX2 anophthalmia syndrome.* Am J Med Genet A, 2005. **135**(1): p. 1-7; discussion 8.
17. Mendiratta, M.S., et al., *Early onset obesity and adrenal insufficiency associated with a homozygous POMC mutation.* Int J Pediatr Endocrinol, 2011. **2011**(1): p. 5.
18. Grugni, G., et al., *Central adrenal insufficiency in young adults with Prader-Willi syndrome.* Clin Endocrinol (Oxf), 2013. **79**(3): p. 371-8.