UNIVERSITY^{OF} BIRMINGHAM University of Birmingham Research at Birmingham

Diagnosis and management of adrenal insufficiency

Bancos, Irina; Hahner, Stefanie; Tomlinson, Jeremy; Arlt, Wiebke

DOI: 10.1016/S2213-8587(14)70142-1

License: Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version Peer reviewed version

Citation for published version (Harvard):

Bancos, I, Hahner, S, Tomlinson, J & Arlt, W 2015, 'Diagnosis and management of adrenal insufficiency', *The Lancet Diabetes and Endocrinology*, vol. 3, no. 3, pp. 216-26. https://doi.org/10.1016/S2213-8587(14)70142-1

Link to publication on Research at Birmingham portal

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)

•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

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

Disorder	Mutated gene	Comments/additional features
	(Chromosomal location)	
Congenital adrenal hyperplasia due to 21- hydroxylase deficiency (210HD) (OMIM #201910)	<i>CYP21A2</i> (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 (110HD) (OMIM #610613)	<i>CYP11B1</i> (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)	<i>CYP17A1</i> (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)	<i>STAR</i> (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)	<i>CYP11A1</i> (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 <i>NR0B1</i> , the Duchenne muscular dystrophy gene dystrophin and the glycerol kinase gene <i>GK</i> (Xp21)	 Duchenne muscular dystrophy glycerol kinase deficiency psychomotor retardation

NR5A1 encoding	• 46,XY DSD		
steroidogenic factor 1 (SF-1)	• variable with milder mutations: premature ovarian failure and		
(9q33.3)	spermatogenic failure		
Inactivating mutations in the	Intrauterine growth retardation		
tumour suppressor gene	• 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		
(11p15.4)	formation in childhood		
mitochondrial DNA deletions	• External ophthalmoplegia, retinal degeneration, cardiac conduction		
	defects, other endocrinopathies		
ABCD1 encoding for a	• 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		
(Xq28)	same genotype, with variable penetrance		
	• Triad of Primary adrenal insufficiency (ACTH resistance), alacrimia,		
U	and achalasia (= Triple A); additional phenotypic features include		
*	neurological impairment, deafness, mental retardation, hyperkeratosis		
	hyperketatosis		
ticoid deficiency (FGD)			
MC2R encoding the ACTH rec	• Usually neonatal presentation with severe adrenal		
(melanocortin 2 receptor)	insufficiency, hypoglycaemia, infections,		
(18p11.21)	hyperpigmentation		
MRAP encoding the MC2R-an	• Normal aldosterone, normal renin		
protein responsible for transloc	cation of • Tall stature in FGD type 1 patients		
the ACTH receptor to the mem	ibrane		
(21q22)			
STAR (8q 11.2-q13.2); see abo	ve for		
description of StAR deficiency			
	steroidogenic factor 1 (SF-1) (9q33.3) Inactivating mutations in the tumour suppressor gene <i>CDKN1C</i> encoding cyclin- dependent kinase inhibitor 1C (11p15.4) mitochondrial DNA deletions <i>ABCD1</i> encoding for a peroxisomal membrane transporter protein (Xq28) Triple A gene (<i>AAAS</i>) encoding the WD-repeat protein ALADIN (12q13.13) ticoid deficiency (FGD) <i>MC2R</i> encoding the ACTH rec (melanocortin 2 receptor) (18p11.21) <i>MRAP</i> encoding the MC2R-an protein responsible for transloo the ACTH receptor to the men (21q22) <i>STAR</i> (8q 11.2-q13.2); see abo		

FGD type 4 [8] (OMIM #614736)	<i>NNT</i> 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	<i>MCM4</i> (8q11.21)	 growth failure increased chromosomal breakage
DNA repair defect [9] (OMIM #609981)		• natural killer cell deficiency

Suppl. Table 2: Monogenic causes of secondary adrenal insufficiency

#312000)

CPHD type	Gene	Pituitary hormone	ACTH deficiency	Other clinical and imaging features
CI IID type	(location)	deficiencies	ACTITUEIICIEIICy	Other childer and magning reatures
CPHD 2[10] (OMIM #262600)	<i>PROP1</i> (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)	<i>LHX3</i> (9q34.3)	GH, TSH, prolactin, LH, FSH, ACTH	+/-	 Hypoplastic anterior pituitary +/- Rigid cervical spine sensorineural deafness Mental retardation +/-
CPHD4 [12] (OMIM #262700)	<i>LHX4</i> (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)	<i>OTX2</i> (14q22.3)	GH, TSH, ACTH, FSH, LH	+	Hypoplastic anterior pituitary
Other monogenic c	auses of cong	genital ACTH deficiency		
Holoprosencephaly [14] (OMIM #610829)	<i>GLI2</i> (2q14.2)	Panhypopituitarism	+	Hypoplastic anterior pituitaryMidface hypoplasia
X-linked panhypopituitarism [15] (OMIM #312000)	<i>SOX3</i> (Xq27.1)	Panhypopituitiarism	+	Hypoplastic anterior pituitary

Syndromic microphthalmia 3[16] (OMIM #206900)	<i>SOX2</i> (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)	<i>TBX19</i> (1q24.2 9)	ACTH deficiency only	+	
Pro- opiomelanocortin deficiency syndrome [17] (OMIM #609734)	<i>POMC</i> (2q23.3)	ACTH deficiency only	+	Early onset obesityRed hair pigmentation
Prader-Willi syndrome [18] (OMIM #176270)	Contiguous deletion including <i>SNRPN</i> and <i>NDN</i> (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.
- 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.

- Ragge, N.K., et al., SOX2 anophthalmia syndrome. Am J Med Genet A, 2005. 135(1): p. 1-7; discussion 8.
- 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.