<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mutated gene</th>
<th>Comments/additional features</th>
</tr>
</thead>
</table>
| 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 |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Enzyme Deficiency</th>
<th>Causes</th>
</tr>
</thead>
</table>
| Congenital adrenal hyperplasia due to 17α-hydroxylase deficiency (17OHD) (OMIM #202110) | CYP17A1 | 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 | 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 | CYP11A1 (15q24.1) | • No adrenal hyperplasia  
• 46,XY DSD |
| Congenital adrenal hypoplasia, X-linked with hypogonadotrophic hypogonadism (OMIM #300200) | NR0B1 (=DAX1) | NR0B1 (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** |
<table>
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<tr>
<th>Condition</th>
<th>Gene/Protein Description</th>
<th>Comments</th>
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</thead>
</table>
| 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 mutations 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) | *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 |
<p>| FGD type 2 [6] (OMIM #607398)                  | <em>MRAP</em> encoding the MC2R-ancessory protein responsible for translocation of the ACTH receptor to the membrane (21q22) |                                                                                                                                    |
| FGD type 3 [7] (OMIM #609197)                  | <em>STAR</em> (8q 11.2-q13.2); see above for description of StAR deficiency (CLAH)             |                                                                                                                                    |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Phenotypes</th>
</tr>
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<tbody>
<tr>
<td>FGD type 4 [8] (OMIM #614736)</td>
<td><em>NNT</em></td>
<td>encoding nicotinamide nucleotide transhydrogenase involved in regulation of mitochondrial redox balance through detoxification of reactive oxygen species (5p12)</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Variants of Combined Pituitary Hormone Deficiency (CPHD)</th>
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</thead>
<tbody>
<tr>
<td><strong>CPHD type</strong></td>
<td><strong>Gene (location)</strong></td>
</tr>
</tbody>
</table>
| CPHD 2[10] (OMIM #262600) | PROPI (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 |
<p>| X-linked panhypopituitarism [15] (OMIM #312000) | SOX3 (Xq27.1) | Panhypopituitarism | + | • Hypoplastic anterior pituitary |</p>
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Phenotypes</th>
<th>+/−</th>
<th>Other Features</th>
</tr>
</thead>
</table>
| 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 (1q24.29) | ACTH deficiency only                             | +                   |                                                                                     |
| Pro-opiomelanocortin deficiency syndrome [17] (OMIM #609734) | POMC (2q23.3) | ACTH deficiency only                             | +                   | • Early onset obesity  
• Red hair pigmentation |
References


