Pitfalls in the diagnosis of an infant with 46,XX DSD with Congenital Adrenal Hyperplasia due to Cytochrome P450 Oxidoreductase deficiency: the value of simultaneous genetic analysis to the diagnosis in DSD

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Background

- Congenital adrenal hyperplasia (CAH) is the underlying diagnosis in most newborns with 46,XX disorders of sex development (DSD).
- Cytochrome P450 oxidoreductase deficiency (PORD) is a rare form of CAH caused by inactivating mutations in the POR gene1.
- POR is an electron donor to all microsomal type 2 P450 cytochromes (CYPs), including 21-hydroxylase (CYP21A2), 17alpha-hydroxylase (CYP17A1) and P450 aromatase (CYP19A1) (Fig. 1).

![Figure 1](image)

- Skeletal malformations resembling the Antley-Bixler Syndrome (ABS) phenotype are reported in most patients.
- Impairment of combined enzyme deficiencies in PORD can be readily detected by urinary steroid profiling1,2.

Case report

- Citromegaly, fused labia majora and a single opening was noted after term birth. The karyotype was 46,XX. No overt skeletal malformations were evident.
- Hormonal investigations showed a normal 17OHP but an insufficient cortisol increase after synacthen indicating glucocorticoid deficiency (Tab. 1).
- Under the clinical assumption of CAH due to CYP21A2 deficiency, the patient was started on hydrocortisone and fluocortisone replacement with salt supplementation.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>6d</th>
<th>Age 2m</th>
<th>10m</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Na (mmol/L)</td>
<td>135</td>
<td>136</td>
<td>140</td>
<td>135-145</td>
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<td>K (mmol/L)</td>
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<td>6.2</td>
<td>4.3</td>
<td>3.5-5.5</td>
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<tr>
<td>Aldosterone (pmol/L)</td>
<td>-</td>
<td>368</td>
<td>82</td>
<td>165-2930</td>
</tr>
<tr>
<td>Renin (mU/L)</td>
<td>-</td>
<td>53</td>
<td>-</td>
<td>61-236</td>
</tr>
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<td>Cortisol (nmol/L)</td>
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<td>30' 216</td>
<td>60' 243</td>
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<td>17OHP (nmol/L)</td>
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<td>3.2</td>
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<td>-</td>
<td>-</td>
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<td>A’dione (nmol/L)</td>
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<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>&lt; 1.9</td>
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</table>

- Fluidcortisone and salt replacement was discontinued after 3 months of age with normal aldosterone and electrolyte levels (Tab. 1).
- At 10 months of age, there is no evidence of craniosynostosis / overt skeletal malformations of the ABS phenotype.

![Figure 2](image)

Urinary steroid profiling

Urinary steroid profiling performed by an external service lab at 7 days of age showed high amounts of 16-alpha hydroxyprogrenolone, but steroid metabolites typically raised in common forms of CAH were not elevated, including 5-pregnenediol, a steroid marker metabolite commonly elevated in PORD (Fig. 3).

Genetic Analysis

Next generation sequencing employing a multi-gene DSD panel (Fig. 2A) revealed a homozygous mutation (p.Gly539Arg) of the POR gene (Fig. 2B).

Discussion

- This is the first 46,XX case with p.Gly539Arg in homozygosity, previously reported in four patients (46,XY) with a mild phenotype1.
- Urinary steroid profiling on day 7 failed to establish the diagnosis in our case. Data from the Birmingham PORD cohort indicate drastic changes in the PORD steroid metabolome during infancy (Fig. 3).
- This case illustrates the value of early genetic testing via non-targeted sequencing panels in the work-up of DSD.

References