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

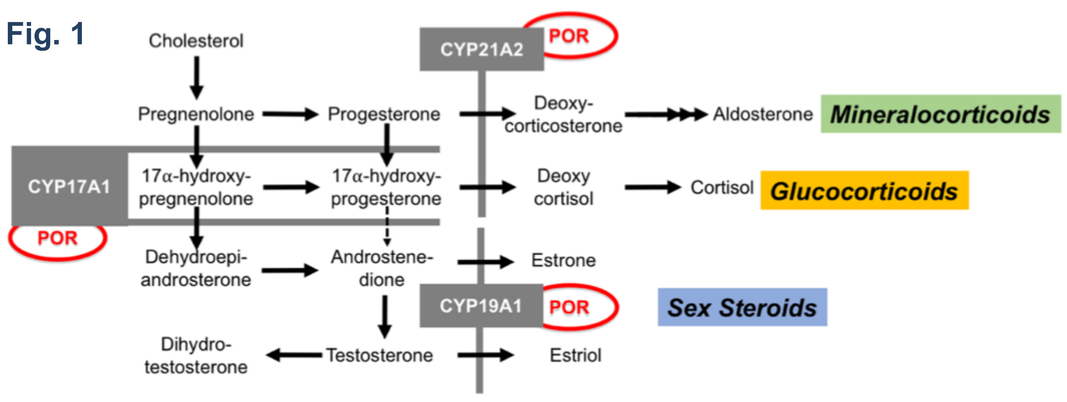
Jan Idkowiak[1,2,3], Zainaba Mohamed[1,2], Stephanie Allen[2,4], Harish Chandran[5], Liam McCarthy[5], Jeremy Kirk[1,2], Trevor Cole[2,4] and Nils Krone[1,2,6]

(1) Department of Paediatric Endocrinology, Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK; (2) Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK; (3) Institute of Metabolism and Systems Research, Medical School, Birmingham, UK; (4) West Midlands Regional Genetic Service, Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK; (5) Department of Paediatric Urology, Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK; (6) Academic Unit of Child Health, Department of Oncology & Metabolism, University of Sheffield, Sheffield, UK

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 gene[1].
- POR is a electron donor to all microsomal type 2 P450 cytochromes (CYPs), including 21-hydroxylase (CYP21A2), 17alpha-hydroxylase (CYP17A1) and P450 aromatase (CYP19A1) (**Fig. 1**).

Fig. 1



- 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 profiling[1,2].

Case report

- Clitoromegaly, 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 fludrocortisone replacement with salt supplementation.

Table 1

	Age			Reference Range
	6d	**2m**	**10m**	
Na (mmol/L)	135	138	140	*135-145*
K (mmol/L)	6.2	6.2	4.3	*3.5-5.5*
Aldosterone (pmol/L)	-	368	821	*165-2930*
Renin (mU/L)	-	53	-	*61-236*
Cortisol (nmol/L)	0' 143			
after 125 mcg IV synacthen	30' 216 60' 243			*> 550*
17OHP (nmol/L)	4.4	3.2	1.6	*<6*
DHEAS (mcmol/L)	0.11	-	-	*< 1.6*
A'dione (nmol/L)	< 0.75	0.4	< 0.3	*< 1.0*
Testosterone (nmol/L)	< 0.25	< 0.1	< 0.1	*< 1.9*

- Fludrocortisone 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.

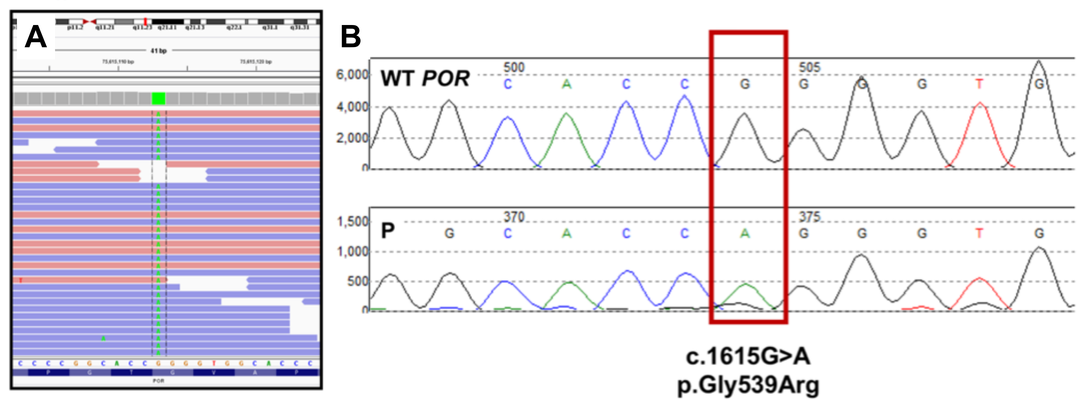
Urinary steroid profiling

Urinary steroid profiling performed by an external service lab at 7 days of age showed high amounts of **16-alpha hydroxypregnenolone**, but steroid metabolites typically raised in common forms of CAH were not elevated, including 5-pregnendiol, 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).

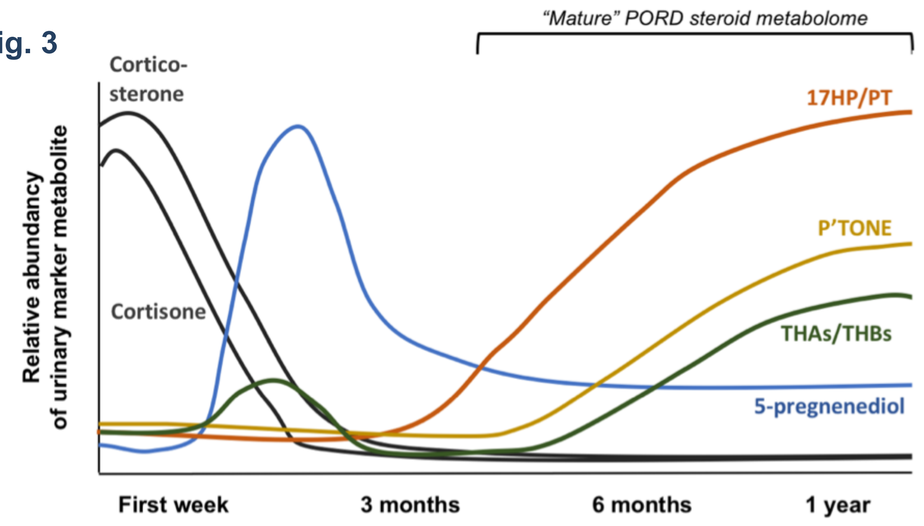
Fig. 2



Discussion

- This is the first 46,XX case with the p.Gly539Arg mutations, previously reported in 4 brothers with a mild phenotype[3].
- 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.**

Fig. 3



(Idkowiak and Shackleton, unpublished)

References

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Sex differentiation, gonads and gynaecology or sex endocrinology

Jan Idkowiak

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