Nottingham University Hospitals NHS
NHS Trust

Pseudohypoaldosteronism

Drew Maxted

@docdrewm

Nottingham Children's Hospital

EMEESY

We are here for you

Outline

- Case presentation
- Some pathophysiology
- Genetic case series
- Treatment options

Case 1

- 1 month old baby boy, presents to local DGH clinic with:
    - Failure to thrive
    - Difficulty with feeding – unsettled after feeds
    - Vomiting
    - Constipation
    - Sleepier than usual
- Admitted from clinic for bloods and feeding observation

Case 1

- Background:
  - 38^{+5}
  - Normal pregnancy and delivery
  - Few days of observation for feeding on PNW
  - BW 3.04kg, CW 3.12kg at 1 month
  - Mother Hep B positive
  - No other significant family history
  - Lithuanian – older sister often translated

Case 1

- Became mottled/starey when having bloods
  - 10ml/kg bolus and full septic screen done (IV antibiotics started)
- Initial bloods show Na 96 and K 6.8
- Started on IV fluids

- Repeat sodium in the morning 101, potassium 7, creat 23

- Had ?vacant episode – no clear fitting, felt cool
  - Further 10ml/kg bolus given

- Transferred to Nottingham

Case 1

- On arrival; cool, mottled – had :
    - 2 x 10ml/kg fluid boluses of 0.9% saline
    - 1 x 20ml/kg fluid bolus of 0.9% saline and 5% dextrose
    - 1 x 10ml/kg fluid bolus of 0.45% saline and 5% dextrose

- Na 112, K 4, Bicarb 20 and Chloride 86

- Improved perfusion over next 2 hours

- Started on IV fluids – 0.9%NaCl and 5%dextrose

- Slow improvement in sodium

Case 1

- Investigations:
  - Infection screen NAD
  - Ammonia normal
  - TFTs normal
  - Cortisol 936
  - Renin >5000
  - Aldosterone 15030
  - Normal renal u/s

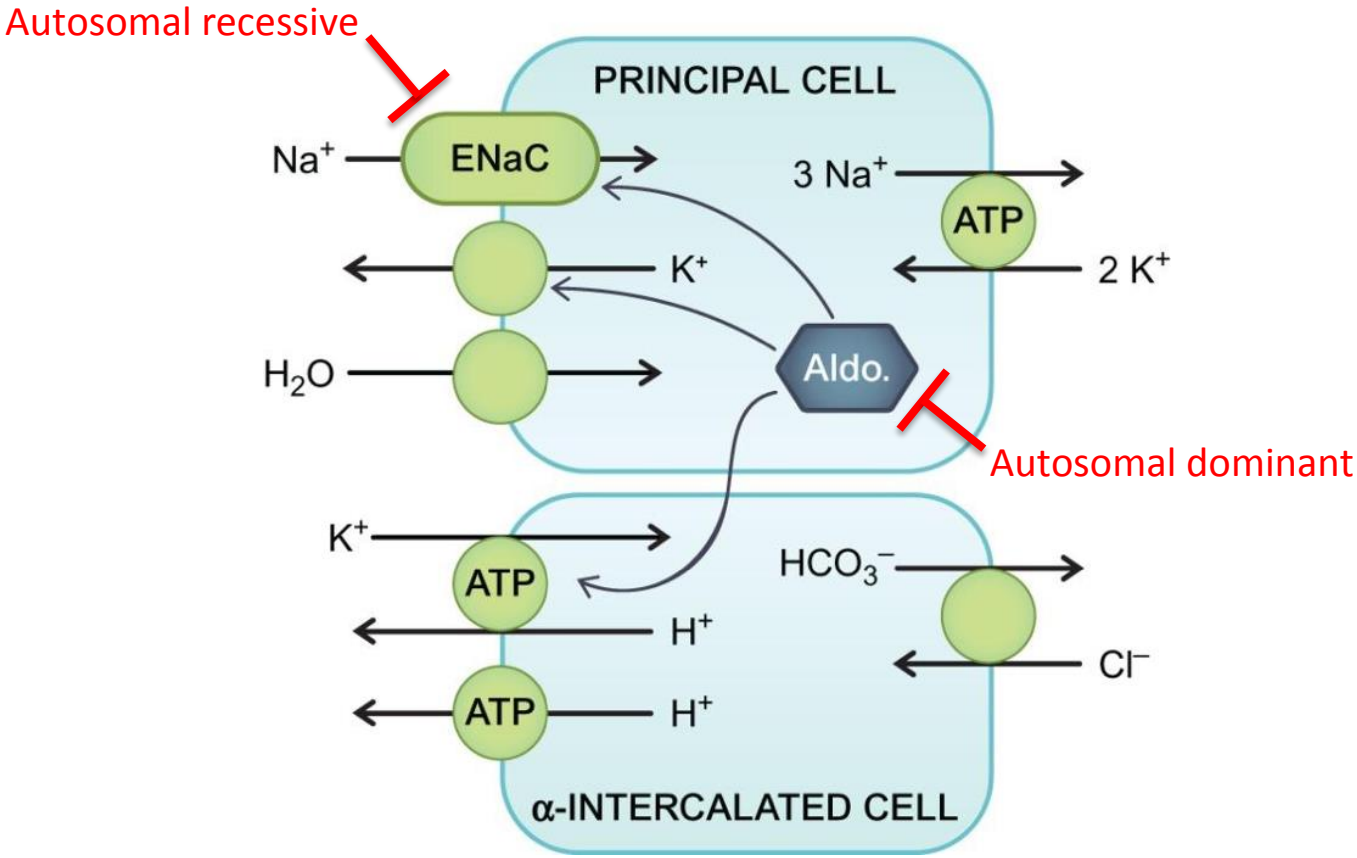
Case 1

- Investigations:
  - 17-OHP normal
  - ACTH normal
  - Urine steroid profile: “In keeping with PHA type 1”
    - High corticosterone metabolites
    - High aldosterone metabolites such as tetrahydroaldosterone
  - Genetic testing sent

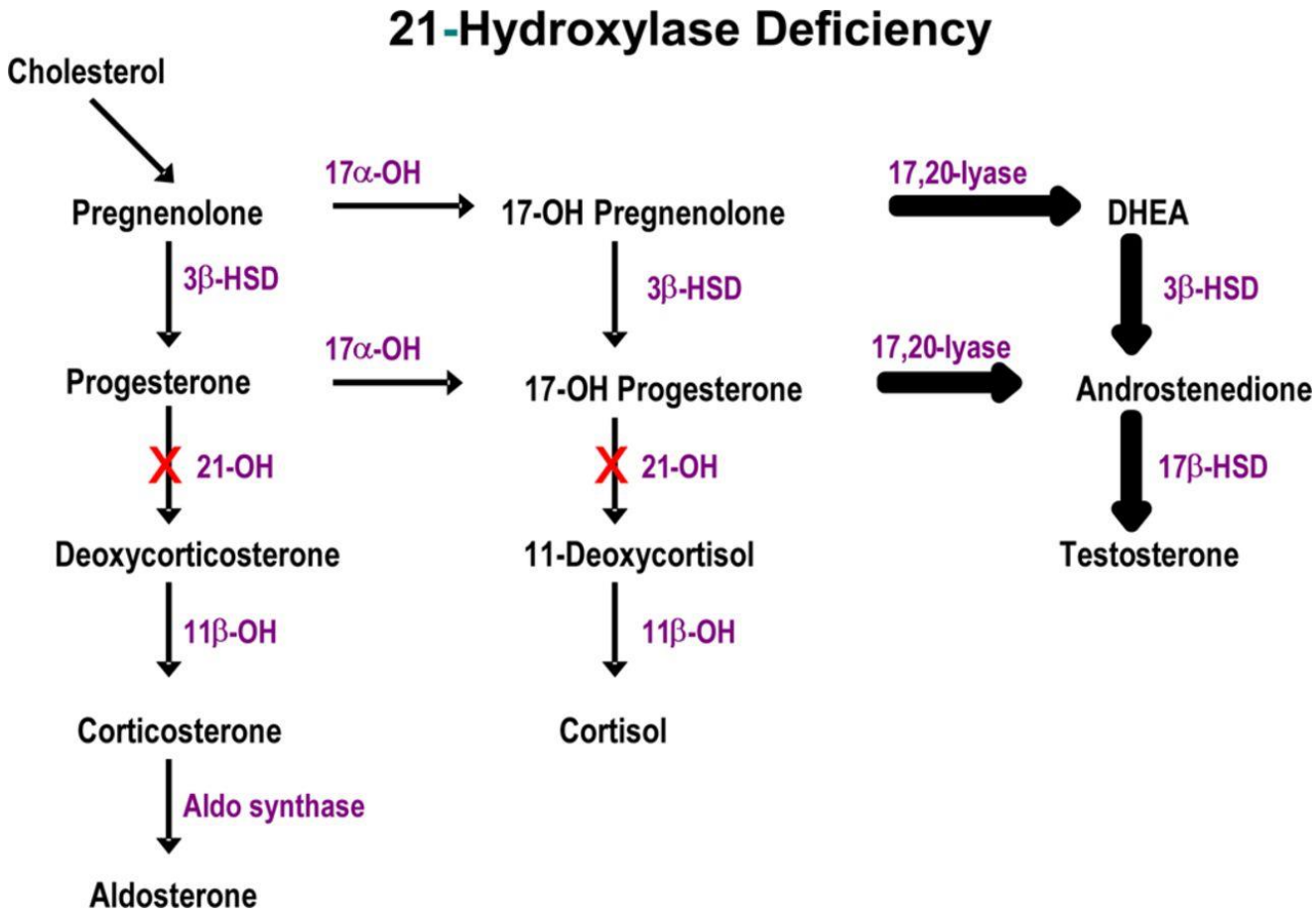
Differential

Condition	Serum Na^+	Serum K^+	Serum aldosterone	Plasma renin	Serum cortisol	Serum 17OH progesterone	Urine Na^+
Systemic PHA type I	Low	High	High	High	Normal	Normal	High
Salt wasting congenital adrenal hyperplasia	Low	High	Low	High	Low	High	High
Renal PHA type I [6]	Low	High	High	High	Normal	Normal	High
Secondary PHA [7–9]	Low	High	High	High	Normal	Normal	High
Renal tubular acidosis type IV [10]	Low	High	Low	Low	Normal	Normal	Normal

Pathophysiology



Differential



Pathophysiology

- PHA type 1:
  - Present in infancy with hyponatraemia, hyperkalaemia and metabolic acidosis
  - AD = transient (childhood) illness
  - Good long term prognosis not linked with seriousness of initial presentation
    - Can present with significant FTT and hypovolaemia
  - Often can wean off sodium

Pathophysiology

- PHA type 1:
  - AR = systemic illness
  - Can mimic CF (as ENaC affected) – have elevated sodium chloride on sweat test
  - Often have very high sodium/bicarb requirement long term
  - Need potassium restriction and potassium binding resins
  - Can have periods of quick decompensation

EMEESY

Children's Kidney Network
for the East Midlands, East of England and South Yorkshire

NHS England

PSEUDOHYPOALDOSTERONISM

A REVIEW OF GENOTYPE-PHENOTYPE PRESENTATIONS IN PATIENTS WITH PSEUDOHYPOALDOSTERONISM TYPE-1 FOLLOWING THE IDENTIFICATION OF NOVEL MUTATIONS

Arpan Doshi, Jaya Sujatha Gopal-Kothandapani, Kath Smith, Martin Christian, Talat Mushtaq, Indraneel Banerjee, Raja Padidela, Renuka Ramakrishnan, Catherine Owen, Timothy Cheetham, Paul Dimitri

Background

	PHA1a - Renal form	PHA1b - Systemic form
Inheritance	Autosomal dominant	Autosomal recessive
Genes affected	NR3C2	SCNN1A/SCNN1B/SCNN1G
Organs affected	Kidneys	Multiple target organ disease- kidneys, distal colon, sweat glands, lungs, salivary glands
Clinical manifestations	Hyponatraemia, Hyperkalaemia, metabolic acidosis,	Hyponatraemia, Hyperkalaemia, metabolic acidosis
Long term outcome	Renal maturation with age leads to decrease in phenotype (decrease symptom presentation)	Does not improve with age – lifelong condition requiring sodium supplements throughout life

Aims & Objectives

- **Aim**:
  - To study the clinical presentation and management in relation to the underlying genetic abnormality of patients with PHA1 i.e **a genotype – phenotype correlation** following the identification of a number of novel mutations from our survey.

Methodology

- A Questionnaire-based, cross-sectional survey, of all the paediatric consultants in the United Kingdom was undertaken through the British Society of Paediatric Endocrinology and Diabetes (BSPED) in Jaunary 2015.
- The questionnaire collected information on:
  - Number of PHA1 patients
  - Demographics (including ethnicity)
  - Clinical features of PHA1 (vomiting, weight loss, dehydration, drowsiness, seizures)
  - Investigations – Biochemistriy , imaging, genetic analysis
  - Management at presentation & ongoing
  - Duration, clinical course & other complications

Results

- Total patients reported -17
- Tertiary paediatric endocrine centres involved (UK) - 5
- Genetically confirmed PHA1 - 12 patients (M:F – 9:3)
- Autosomal Dominant Renal type PHA1a:
  - 4 patients (1 novel mutation, NR3C2 gene)
- Autosomal Recessive Systemic type PHA1b:
  - 8 patients (2 novel mutations, SCNN1A gene; 1 novel mutation, SCNN1B gene)

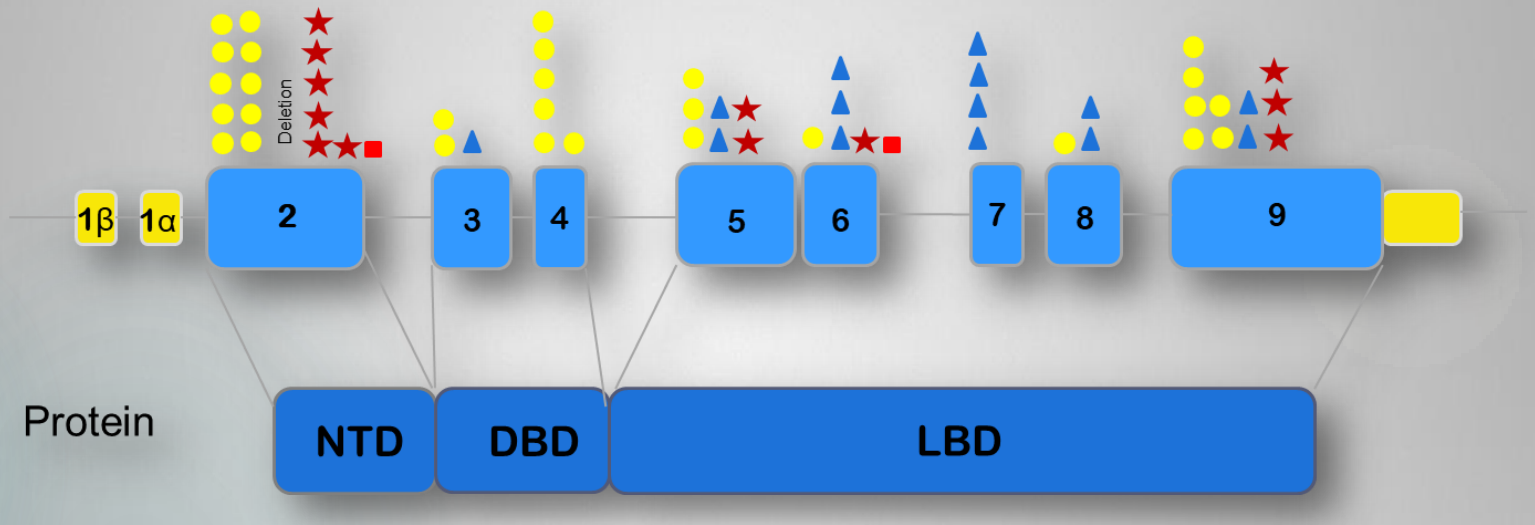
Largest case series on genetically confirmed PHA1

	PHA1a- Renal type (Autosomal Dominant)				PHA1b- Sytemic type (Autosomal recessive)							
	NR3C2				SCNN1A						SCNN1B	
Patient	2A	7A	10A	12A	1B	3B	4b	6B	8B	9B	5B	11B
Gender	Male	Female	Male	Male	Male	Male	Female	Male	Male	Male	Female	Male
Birth	Term	Term	Term	Term	Term	Term	Term	Term	Term	36+3 wks	31+4 wks	Term
Ethnicity	White Caucasian	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani	White Caucasian	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani	Asian-Pakistani
Consanguinity	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Day at presentation	10d	11d	20d	14d	10d	1d	1d	17d	9d	7d	1d	8d
Clinical features	Weight loss, drowsiness, dehydration	Weight loss, drowsiness, urinary tract infection	Weight loss, vomiting, failute to thrive	Vomiting, dehydration	Weight loss, drowsiness	Vomiting, dehydration, shock	Vomiting, feeding difficulty, respiratory distress	Weight loss, lethargy	Weight loss, drowsiness, vomiting	Drowsiness	Feeding difficulty, respiratory distress	Weight loss, purulent eye discharge, rash
Sodium (mmol/l)	128	124	123	121	126	110	120	125	129	124	128	113
Potassium (mmol/l)	7.1	6	7.8	6.2	10	8	6	7.6	7.6	10	7.8	11
Aldosterone (pmol/l)	>19,000	64000	32000	38200	16580	2000	_	3885	21800	19780	1795	16650
Affected family member	Mother	Father	-	Mother	_	Sister	_	_	Brother	Brother	_	_
Complications	None	None	Gastrostomy at 9 months	None	Recurrent tonsillitis	Died on day 30 from septicaemia	Recurrent chest infections	Died from cardiac arrest secondary to electrolyte disturbance	Cardiac arrest, bowel perforation secondary to ischaemia	Recurrent chest infections, speech delay	Recurrent episodes of electrolyte disturbances	Recurrent chest infections, dry skin

NR3C2 gene

- Broad phenotypic variability - ?increasing mineralocorticoid receptor protein expression with increasing age.
- Non-functional or abnormally functioning mineralocorticoid receptor (MR) protein
- Intra-familial phenotypic variability observed in 2 patients (patient 2a & 7a)
- Variation in the length of sodium supplementation required (4weeks to 2 years)
- Patient 7a: Novel heterozygous missense mutation in exon 7 (c.2555t>C, p.MS52T)

NR3C2 gene

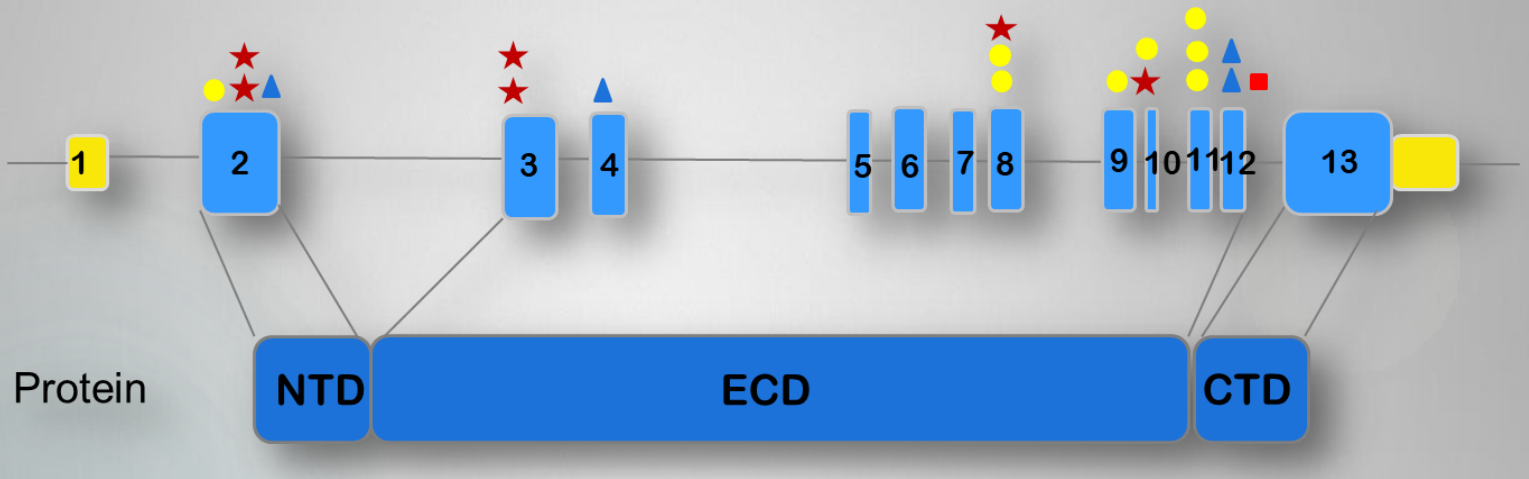


Schematic representation of the *NR3C2* gene (NM_000901.4). Large blue boxes represent the nine exons, smaller yellow boxes represent untranscribed regions. The heterozygous mutations detected in this patient series are shown in approximate positions. Missense mutations are represented as ▲, nonsense mutations as ●, frameshift mutations as ★ and intronic mutations as ■ .
The protein has three domains, the N-terminal Domain (NTD), the DNA Binding Domain (DBD) and the Ligand Binding Domain (LBD).

SCNN1 gene

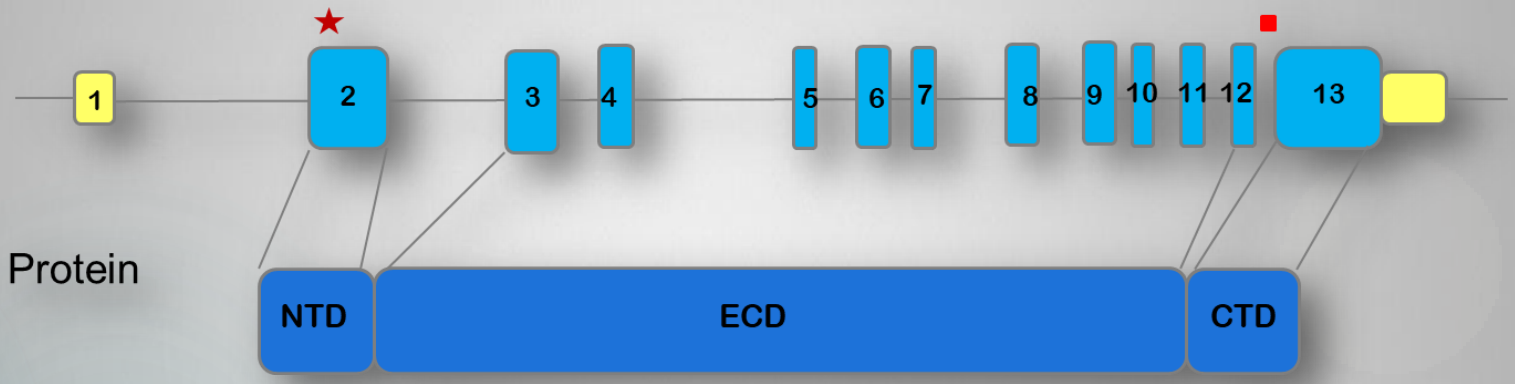
- Inactivating mutations in 3 subunit genes of epithelial Sodium channels (ENaC) – *SCNN1A, SCNN1B, SCNN1G*
- 3 novel mutations in 8 patients
  - homozygous missense mutation, exon 12, *SCNN1A* gene (c.1640T>C, p. V547A) in patients 3b & 4b
  - homozygous 3-bp inframe deletion, exon 11,*SCNN1A* gene (c.1582_1584delTTC, p.Phe528del) in patient 6b
  - 17-bp frame shift deletion, exon 2, *SCNN1B* gene in patient 12b
- PHA1b patients present earlier than PHA1a
- Complications more frequent in PHA1b

SCNN1A gene



Schematic representation of the *SCNN1A* gene (NM_001159575.1). Blue boxes represent the thirteen exons, yellow boxes represent untranscribed regions. The homozygous mutations detected in this patient series are shown in approximate positions. Missense mutations are represented as ▲, nonsense mutations as ●, frameshift mutations as ★ and intronic mutations as ■.
The protein has three domains, the N-terminal Domain (NTD), the Extracellular Domain (ECD) and the C-terminal Domain (CTD).

SCNN1B gene



Schematic representation of the *SCNN1B* gene (NM_000336.2). Blue boxes represent the thirteen exons, yellow boxes represent untranscribed regions. The homozygous mutations detected in this patient series are shown in approximate positions. Missense mutations are represented as ▲, nonsense mutations as ●, frameshift mutations as ★ and intronic mutations as ■.
The protein has three domains, the N-terminal Domain (NTD), the Extracellular Domain (ECD) and the C-terminal Domain (CTD).

Conclusions

- Our pilot survey on PHA1 provide extended genotype-phenotype spectrum of both the systemic and renal types of PHA1
- Limited genotypic and descriptive phenotypic data available in the current literature
- Our study adds substantial information to the existing literature on PHA1
- Using our cohort and review of literature, there appears to be **no obvious genotype –phenotype correlation for both PHA1a and 1b**
- This may be due to the rarity of the detailed information available for PHA1 at present

Recommendations

- **Establish a national database incorporating detailed genotypic and phenotypic data for such rare life-threatening conditions -** The national rare renal registry, RaDaR or the European rare kidney disease reference network (ERKNet)

- **This may enable identification of genetic subgroups that would have the potential to develop personalised patient care.**

Acknowledgements

- **Patients and families who took part in this survey**

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[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

[2] York Teaching Hospital, York, UK

[3]Department of Genetics, Sheffield Children's Hospital, Sheffield, UK

[4]Department of Paediatric Nephrology, Nottingham University Hospitals NHS Trust, Nottingham, UK

[5]Department of Paediatric Endocrinology, Leeds General Infirmary, Leeds, UK
[6]Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, UK
[7]Department of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK
[8]Department of Paediatric Endocrinology, The New Castle Upon Tyne Hospitals and NHS Trust, UK
[9]Department of Paediatric Endocrinology, Sheffield Children's Hospital, Sheffield, UK

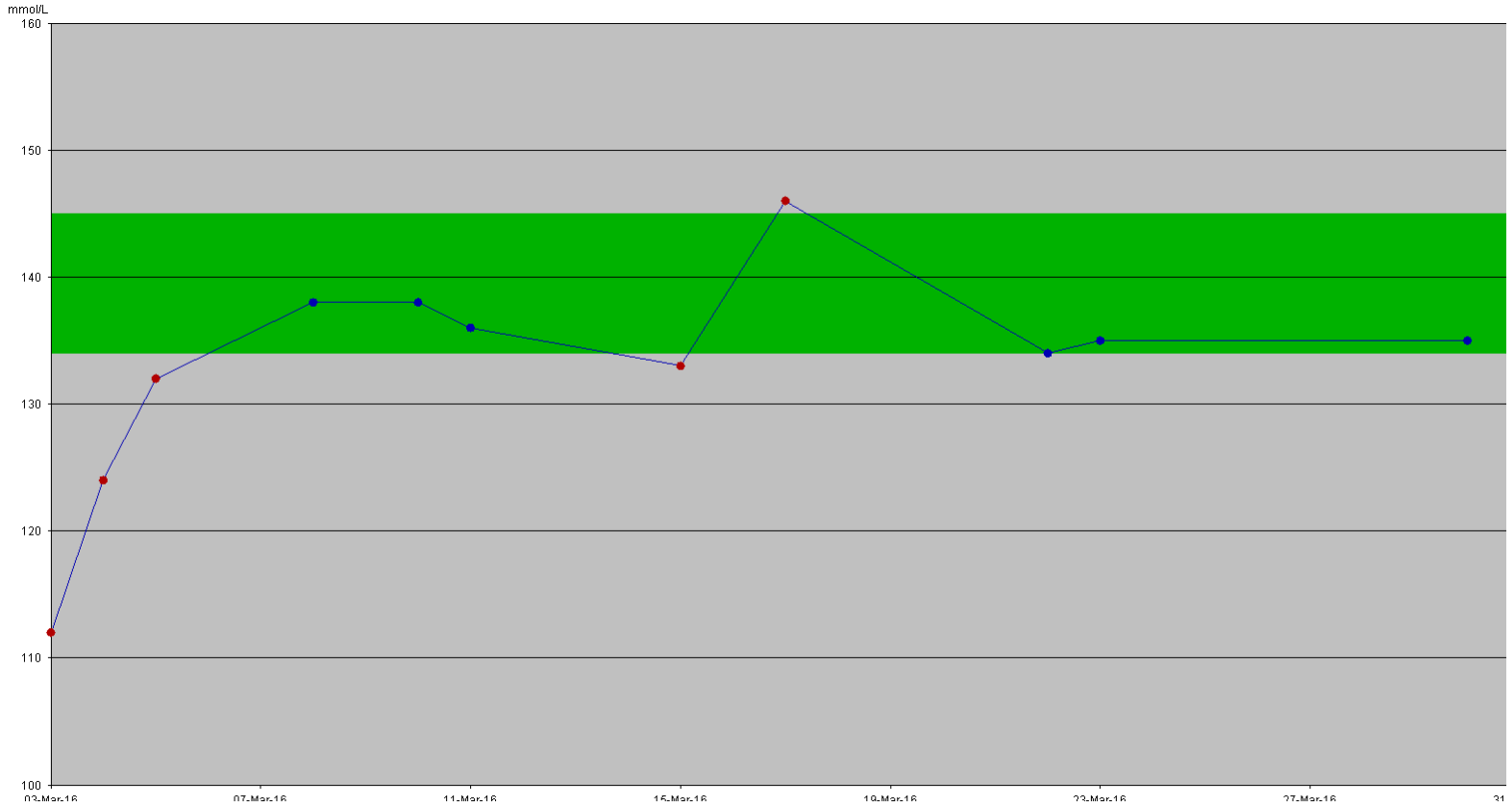
Back to case…

- Baby with FTT, hyponatraemia, hyperkalaemia, metabolic acidosis and shock
- Had multiple fluid boluses
- Investigations in keeping with PHA1 – autosomal dominant
- Mutation in NR3C2 = inframe deletion insertion: c1861_1863delinsAGAAAA
    - Novel mutation, not previously described

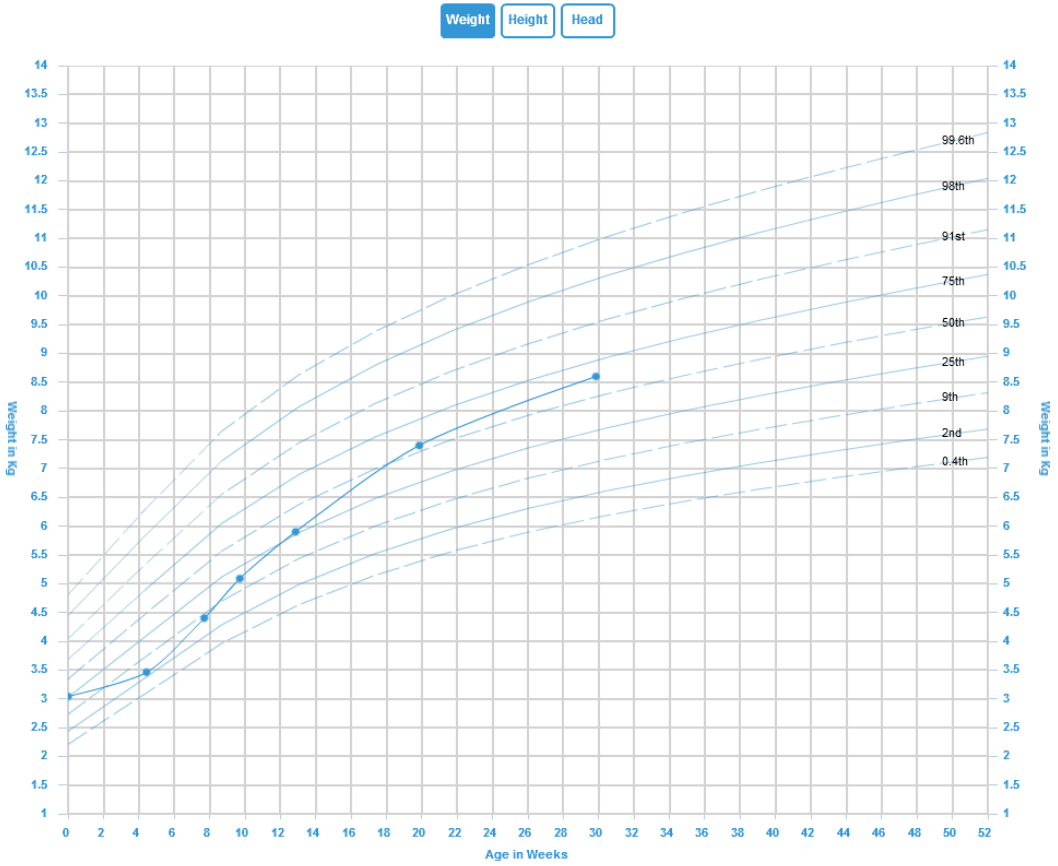
Treatment

- Initially treated with IV fluids
    - Slow sodium increase (aiming ~ 1mmol/hr max)
- Then when improved returned to normal feeds
- Sodium supplementation
- With slow improvement, pending 17-OHP and ?large penis – started steroids pending results
    - When results available admitted and stopped steroids

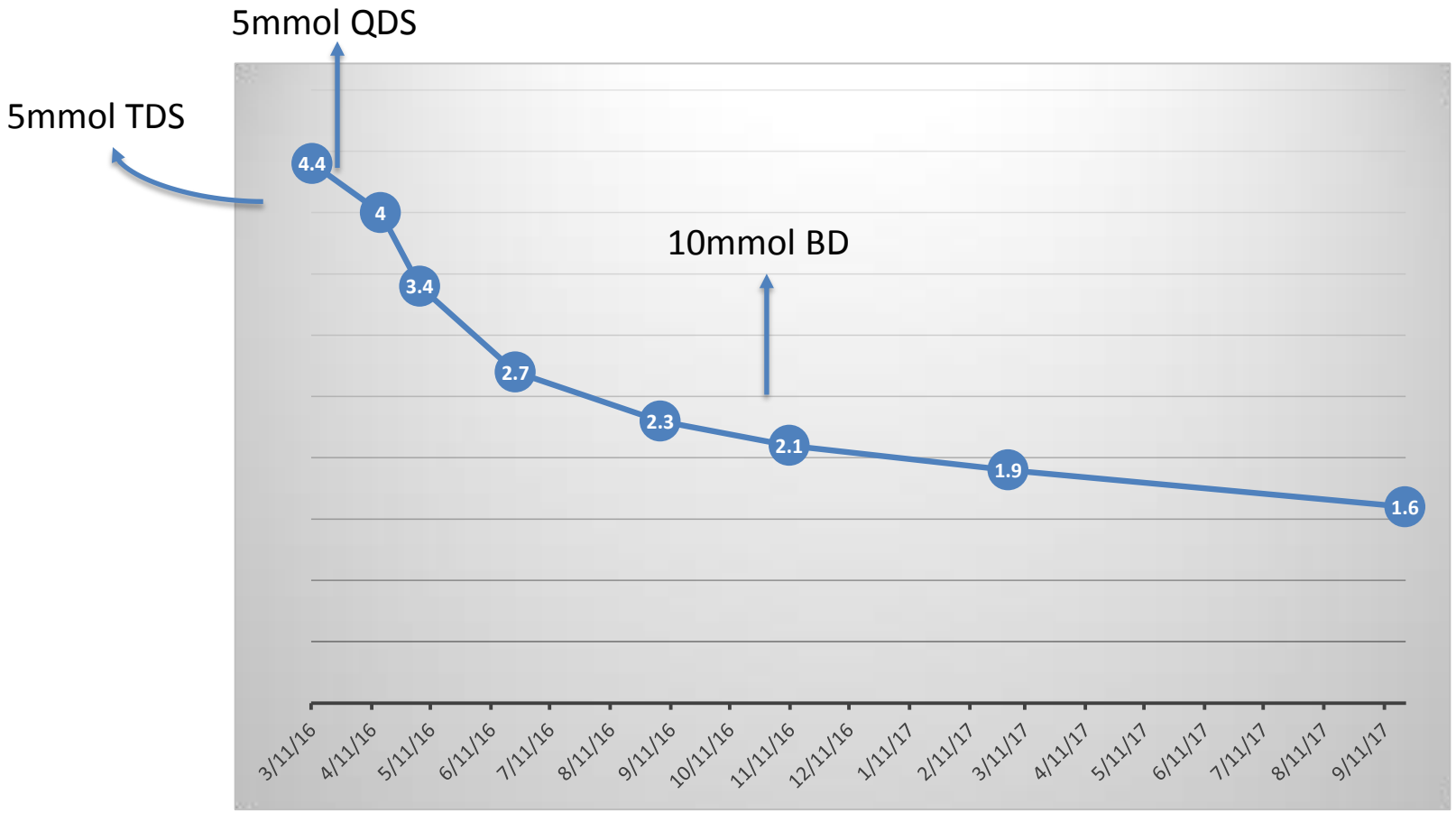
Treatment


mmol/L
160
150
140
130
120
110
100
03-Mar-16
07-Mar-16
11-Mar-16
15-Mar-16
19-Mar-16
23-Mar-16
27-Mar-16
31

Treatment


Weight
Height
Head
99.6th
98th
91st
75th
50th
25th
9th
2nd
0.4th
Weight in Kg
Age in Weeks

Treatment


5mmol QDS
5mmol TDS
10mmol BD
4.4
4
3.4
2.7
2.3
2.1
1.9
1.6
3/11/16
4/11/16
5/11/16
6/11/16
7/11/16
8/11/16
9/11/16
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6/11/17
7/11/17
8/11/17
9/11/17

Take home messages

- Pseudohypoaldosteronism presents with hyponatraemia, hyperkalaemia and metabolic acidosis
- Usually present with FTT, poor feeding, potentially shocked
- Low sodium can mean hypovolaemia if salt wasted
- Autosomal dominant better long term prognosis]
- No clear genotype-phenotype correlation exists
- Both forms can decompensate when unwell

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Thank you