

# Neuroendocrine tumours in children

*Kate Davies*

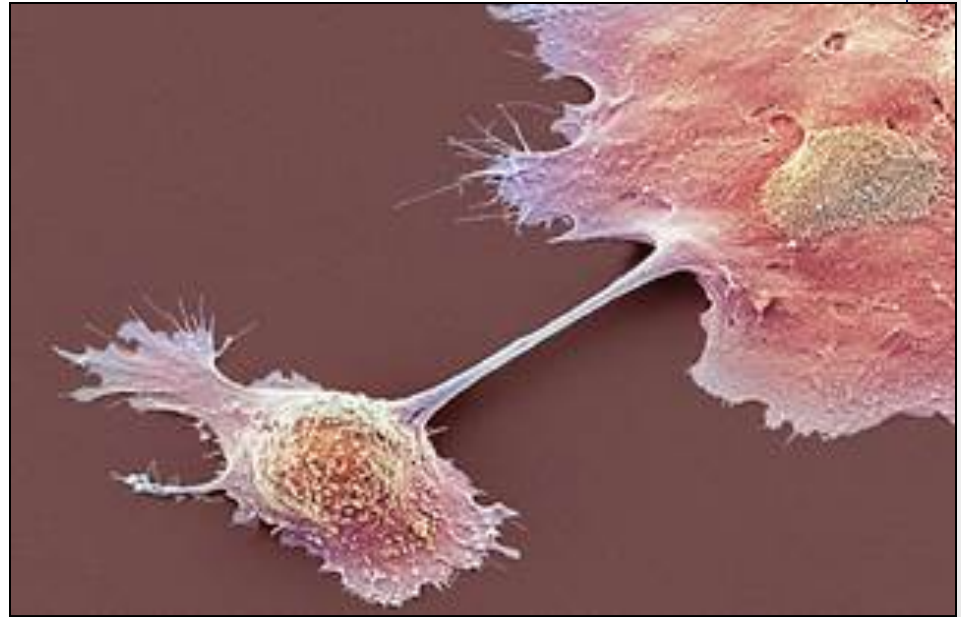
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London South Bank University &*

*Research Nurse in Paediatric Endocrinology  
Centre for Endocrinology, William Harvey Research Institute  
Barts and The London School of Medicine and Dentistry*



# Introduction

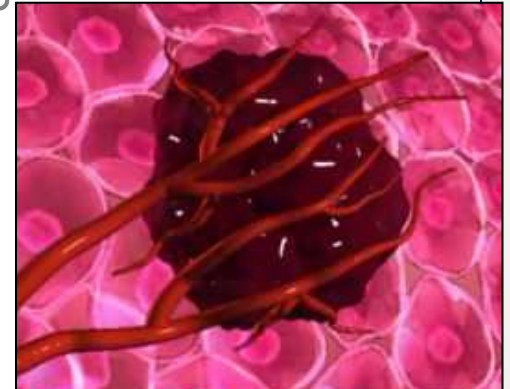
- NETs in children
- Screening
- Family trees
- MEN1
- MEN2a
- MEN2b
  - FMTC
  - Pheochromocytomas and Paragangliomas
- VHL
- Case study





# Neuroendocrine tumours in children

- Relatively rare amongst children
- Majority occur sporadically and are non-hereditary
- Despite this, carcinoid tumours may also be associated with hereditary syndromes
- Most endocrine tumours in children
  - Clinically benign
  - Low grade malignancies
- NETS
  - Known for late diagnoses
    - Liver or bone metastases
    - Multi year history of symptoms before malignancy identified
  - Few reports in children
    - At least 10% of children have metastatic disease at presentation

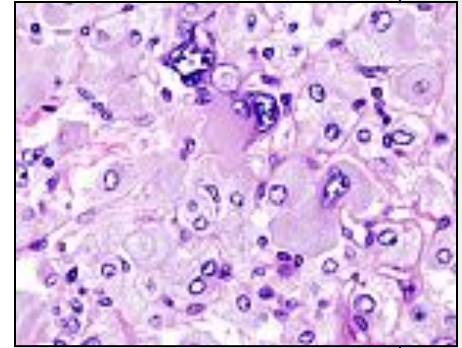


# Distribution of NETS in children and young adults <30 years

Tumour type	Percentage of NET in this age group
Bronchial NET	28
Medullary carcinoma of the breast	18
Appendiceal NET	18
Colon and rectal NET	9
Jejunal and ileal NET	5
Small cell carcinoma (ovary)	5
Unknown primary NET	5
Pancreatic and gastric NET *	4
Medullary carcinoma thyroid *	4
Small cell carcinoma (cervix)	4

# Other NETs

- Phaeochromocytoma
  - MEN 2A
  - MEN 2B
  - VHL disease
  - NF1
  - Peak incidence between 9 -12 years of age
    - Nearly 10% occur in children
    - 10% of these are malignant
- Paranganglioma
  - Extra adrenal in origin
  - Parasympathetic nervous system



# Screening

- MEN 1 & 2 and VHL
  - Autosomal dominant
    - Only one mutation in one pair of genes is needed to cause the condition
    - 50% chance of having a boy or a girl with the same condition
  - Most commonly present in early adulthood and onwards
  - Can now target individuals at risk
  - Genetic screening allows the children from affected families who have NOT inherited the mutation
    - Reassured
    - Avoid regular clinical monitoring
    - Issues re: Informed consent, counselling and confidentiality



TYPE	SYSTEM	CLINICAL / BIOCHEMICAL	RADIOLOGY	AGE TO START	FREQUENCY
MEN-1	Parathyroid	Serum calcium (parathyroid hormone)		10-15 yrs	Annual
	Pancreas	Pancreatic polypeptide, Gastrin	US pancreas	10-15 yrs	Annual
			MRI pancreas	10-15 yrs	3 yearly
	Pituitary	Prolactin, IGF-1		10-15 yrs	Annual
			MRI pituitary	10-15 yrs	5 yearly
MEN-2	Thyroid	(mutation known) Prophylactic thyroidectomy		5 yrs	
		(mutation not yet known) Pentagastrin test for calcitonin		5 yrs	Annual
	Adrenal (phaeochromocytoma)	Blood pressure 24-hour urine collections (x3) – catecholamines (plus corresponding serum metanephrines)	US adrenals	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly
	Parathyroid	Serum calcium		10 yrs	Annual
VHL	Eyes	Fundoscopy	Fluorescein angiography	5 yrs	Annual
	CNS	Full examination		10 yrs	Annual
			MRI brain & spinal cord	10 yrs	3 yearly
	Renal	Abdominal examination	US kidneys	5 yrs	Annual
			MRI kidneys	5 yrs	3 yearly
FPS	Adrenal (phaeochromocytoma)	Blood pressure 24-hour urine collections (x3) – catecholamines (plus corresponding serum metanephrines)	US adrenal	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly
	Cervical chain/ carotid bodies	Examination	US head and neck	10-15 yrs	Annual
	Adrenal	Blood pressure 24-hour urine collections (x3) – catecholamines (plus corresponding serum metanephrines)	US adrenals	8-10 yrs	Annual
	Parasympathetic chain		MRI chest/abdo/pelvis	8-10 yrs	Annual

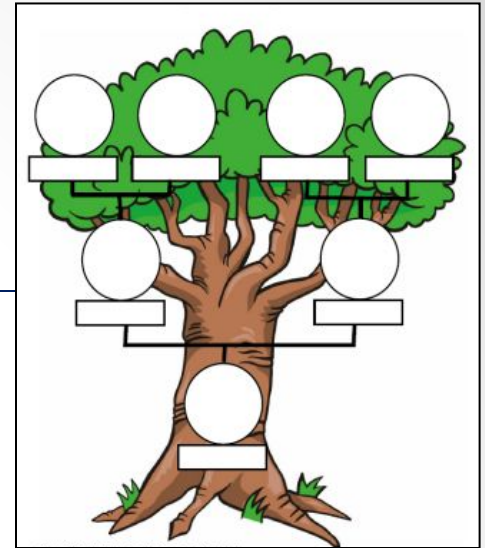


# Family trees

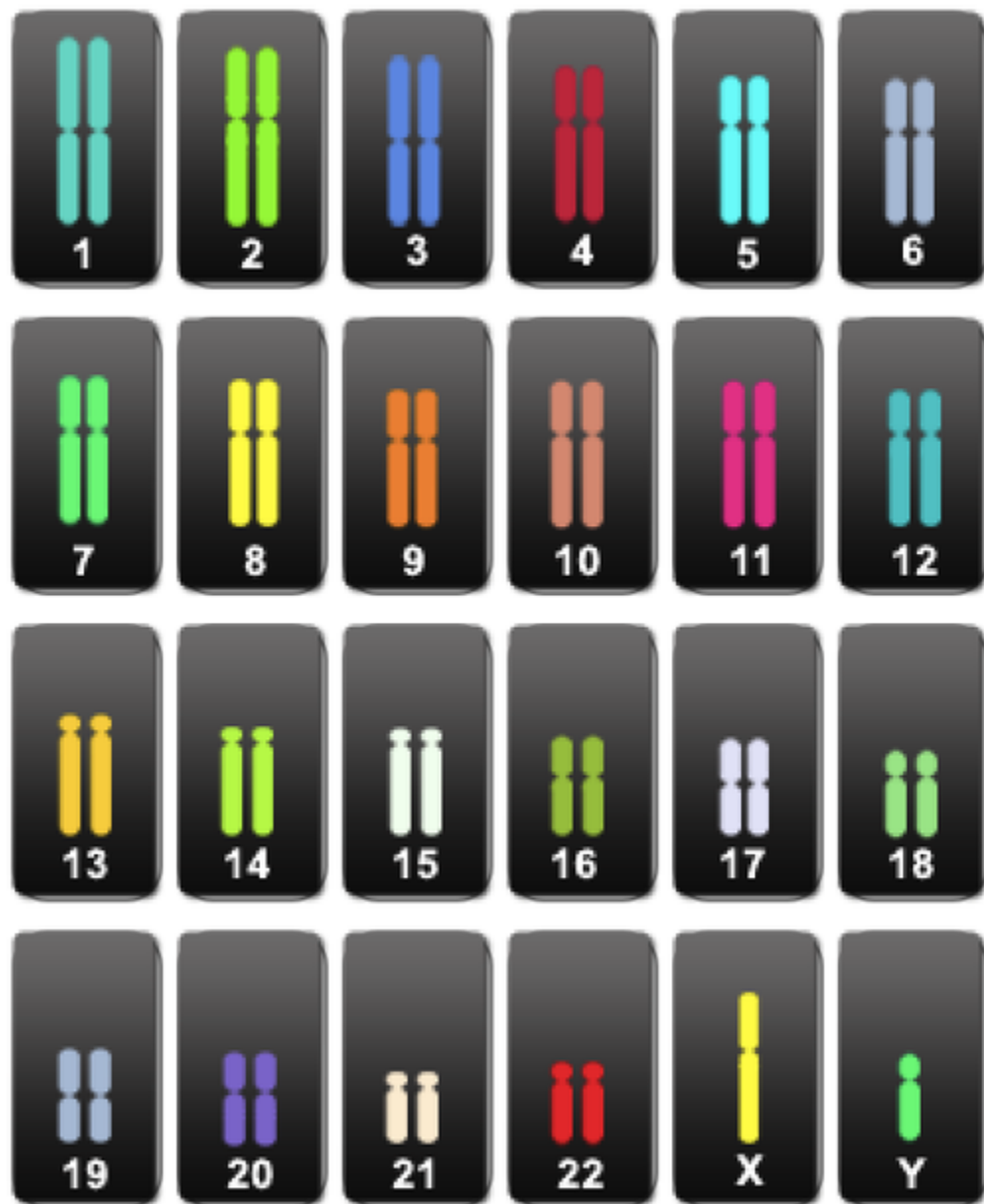
- Biological relationships between family members
- Any medical conditions
  - Reveal patterns of inheritance
  - Assesses likelihood of genetic diseases in relatives
  - Individuals can then be offered targeted surveillance

## *Including children*

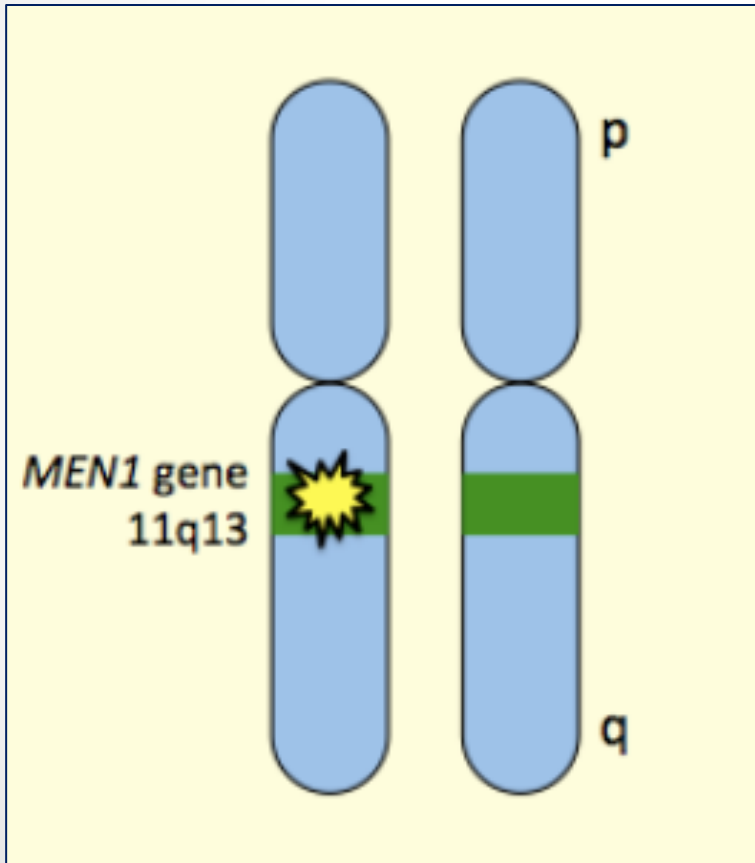
- Builds rapport with patients
  - Develop trust, to ask questions
  - Correct any misconceptions about symptoms







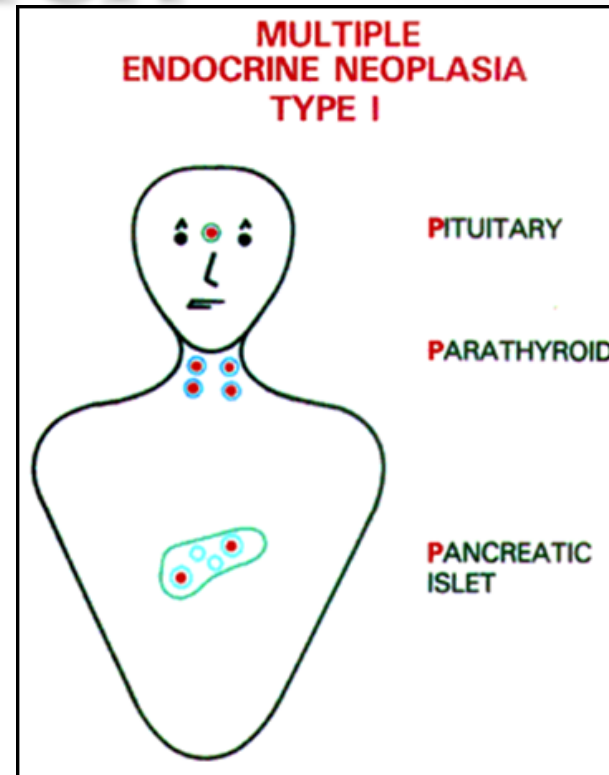
# MEN 1



- Parathyroid tumours
  - 90% of MEN1 patients
- Pituitary tumours
  - 30% of MEN1 patients
- Pancreatic Islet cell tumours
  - 75% of MEN1 patients
- Carcinoid tumours
  - Chest / stomach
  - Lipomas
  - Thyroid
  - Adreno-cortical tumours

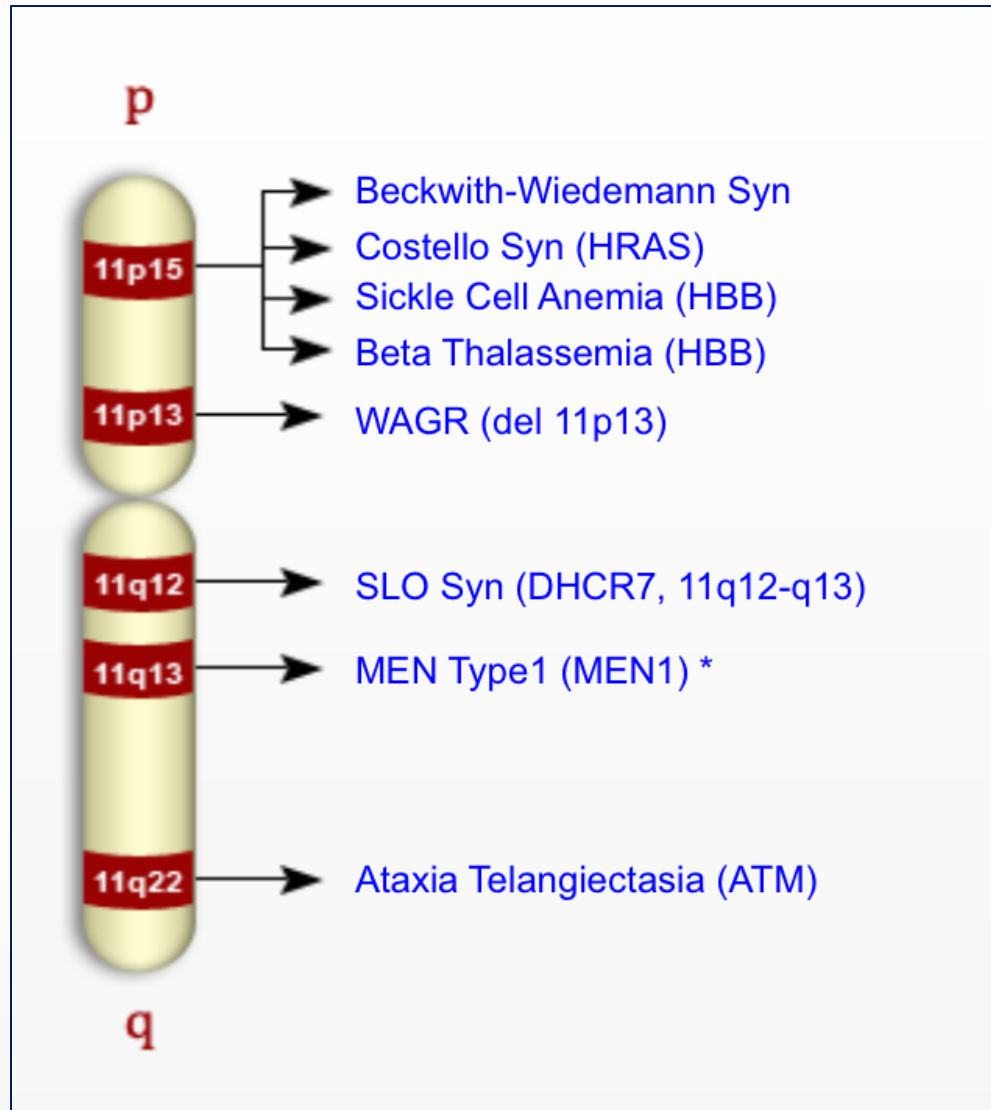
# MEN 1 screening in children

- Children of an identified MEN1 patient
  - Screened genetically initially
  - Screened clinically from age 10
    - Annual measurements
      - Calcium, PTH
      - Pancreatic polypeptide and gastrin
        - Imaging
      - Prolactin, IGF-1
        - Imaging

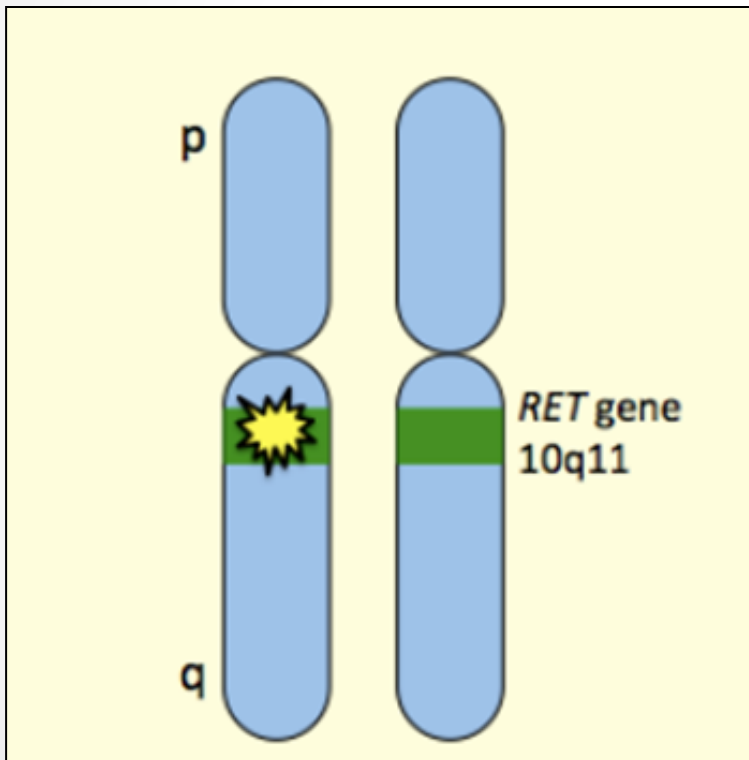


TYPE	SYSTEM	CLINICAL / BIOCHEMICAL	RADIOLOGY	AGE TO START	FREQUENCY
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			MRI pancreas	10-15 yrs	3 yearly
	Pituitary	Prolactin, IGF-1		10-15 yrs	Annual
			MRI pituitary	10-15 yrs	5 yearly

# Chromosome 11



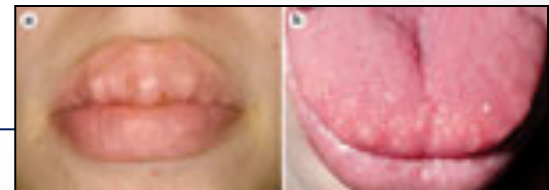
# MEN 2a



- Thyroid gland
  - MTC
  - Child with a known MEN2a gene change
    - Total thyroidectomy before age of 5yrs
  - Newly diagnosed adults
    - Screen children asap
- Parathyroid glands
- Adrenal glands
  - Pheochromocytomas
    - 24hr urine collections

# MEN 2b

- Thyroid gland tumours
- Pheochromocytomas
- Benign lumps on the lips, in the mouth and throughout the gut
  - Children
    - More likely to have feeding problems, bowel problems
  - Present with FTT





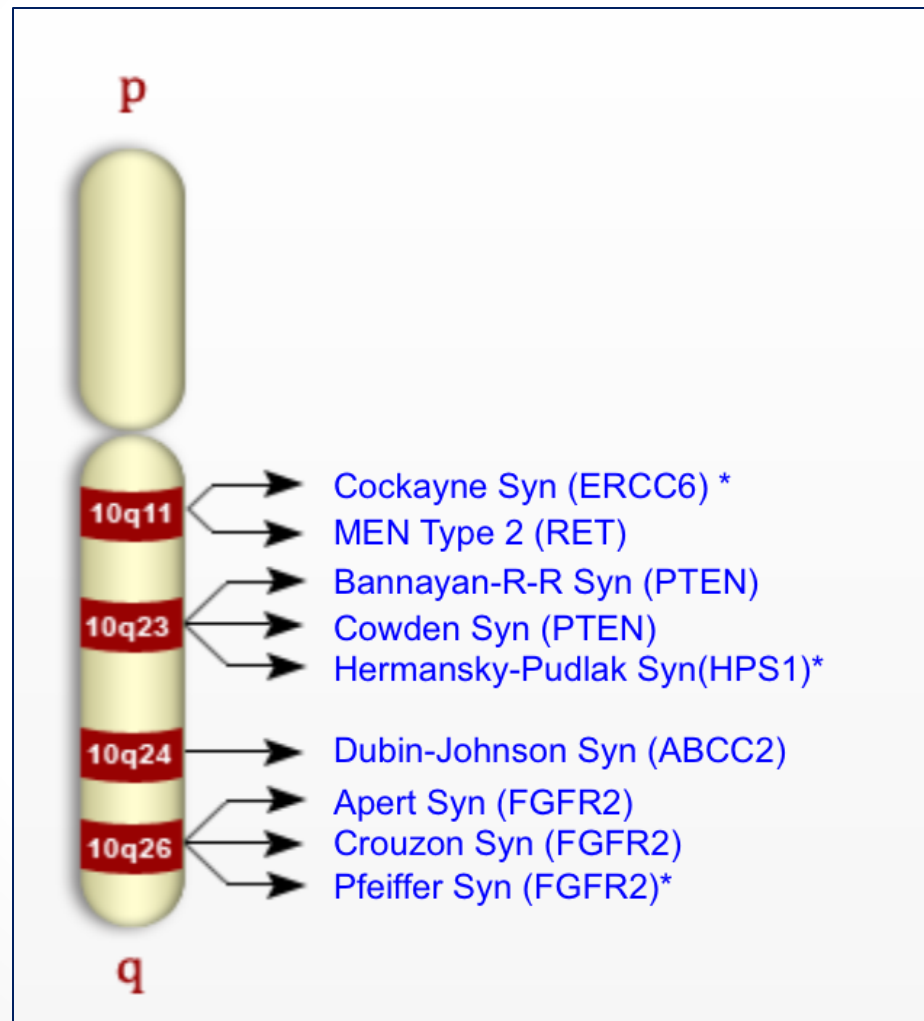
# MEN 2 screening

- Screened genetically
  - MTC assoc with MEN2b
    - Can occur in first year of life
  - MEN2b – age 1yr
  - MEN2a – age 5yrs
- Clinical screening
  - Thyroid
  - Adrenal



<b>MEN-2</b>	Thyroid	<i>(mutation known)</i> Prophylactic thyroidectomy		5 yrs	
		<i>(mutation not yet known)</i> Pentagastrin test for calcitonin		5 yrs	Annual
	Adrenal <i>(phaeochromocytoma)</i>	Blood pressure 24-hour urine collections (x3) – catecholamines <i>(plus corresponding serum metanephrines)</i>	US adrenals	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly

# Chromosome 10



# Patient support

- AMEND
  - UK Patient support group
  - [www.amend.org.uk](http://www.amend.org.uk)

The screenshot displays the AMEND website interface. At the top, a yellow header bar contains the 'Text Size' control. Below this, the AMEND logo (a sun icon) is followed by the text 'Association for Multiple Endocrine Neoplasia Disorders'. A navigation menu includes links for 'Guide to the disorders', 'About us', 'How we help', 'Resources', 'Get involved', 'Professionals', 'Research', 'News', and 'Home'. The main content area is titled 'Introduction to MEN and associated tumours' and includes a sub-header 'Introduction to MEN'. It features a date stamp: 'Last Updated on Monday, 14 July 2014 12:18' and 'Written by Jo Grey'. A sidebar on the right contains buttons for 'Sign up now' and 'Make a donation', a search bar labeled 'AMEND search', and social media links for Facebook, Twitter, and YouTube. The main text area includes a diagram of a human head and neck with labels for 'pituitary' and 'thyroid and parathyroids', and a section titled 'What is MEN?' which explains the condition and its inheritance.

**AMEND** Association for Multiple Endocrine Neoplasia Disorders

• Guide to the disorders • About us • How we help • Resources • Get involved • Professionals • Research • News • Home

Guide to the disorders > Introduction to MEN

## Introduction to MEN and associated tumours

Last Updated on Monday, 14 July 2014 12:18  
Written by Jo Grey  
Tuesday, 09 November 2010 10:37

### What is MEN?

MEN stands for Multiple Endocrine Neoplasia, of which there are three distinct types – MEN1, MEN2 and MEN3. MEN2 was formerly called MEN2a and MEN3 was formerly called MEN2b, and indeed there are similarities between the two.

Multiple Endocrine Neoplasia syndromes are inherited disorders – This means that they can be passed down in families, with each child of an affected parent having a 1 in 2 or 50% risk of inheritance.

MEN disorders cause more than one gland of the body's endocrine (gland) system to develop growths (tumours). The affected glands then produce abnormally increased

pituitary

thyroid and parathyroids

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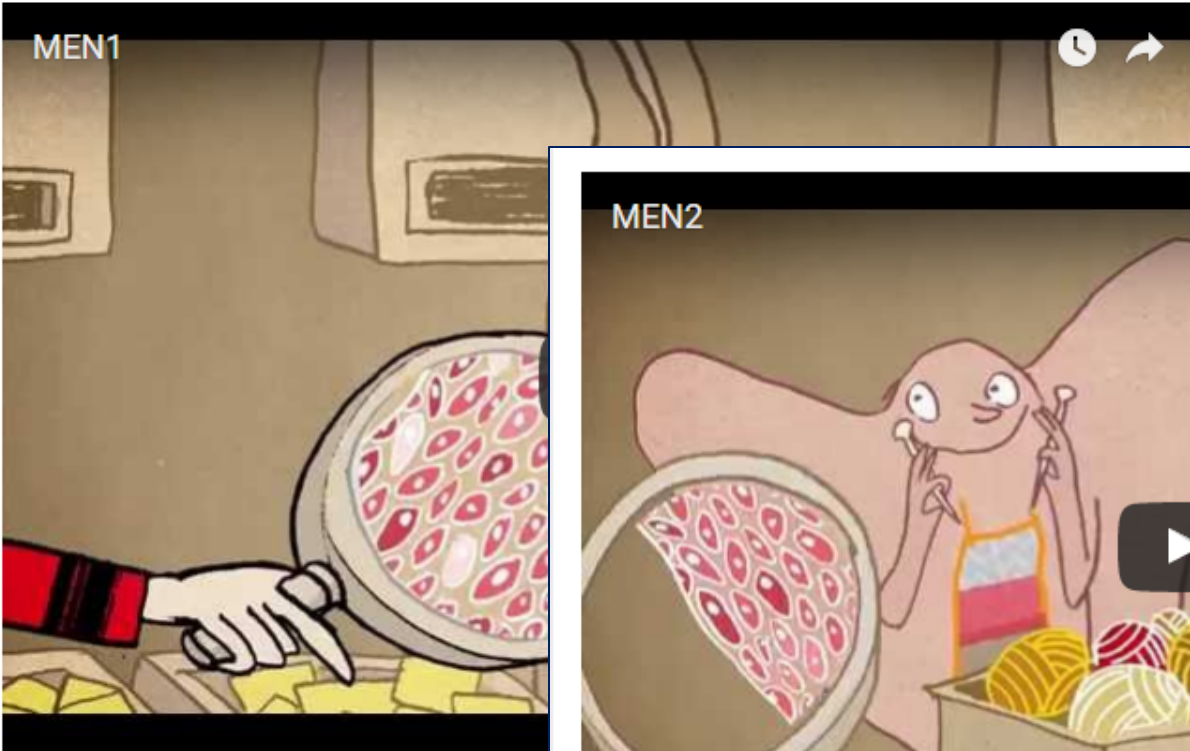
f t YouTube

This site complies with the HONcode standard for trustworthy

# Children's area

Daniel has MEN1 and Lisa has MEN2. With the help of their pet cats and animated friends, they explain their conditions simply.

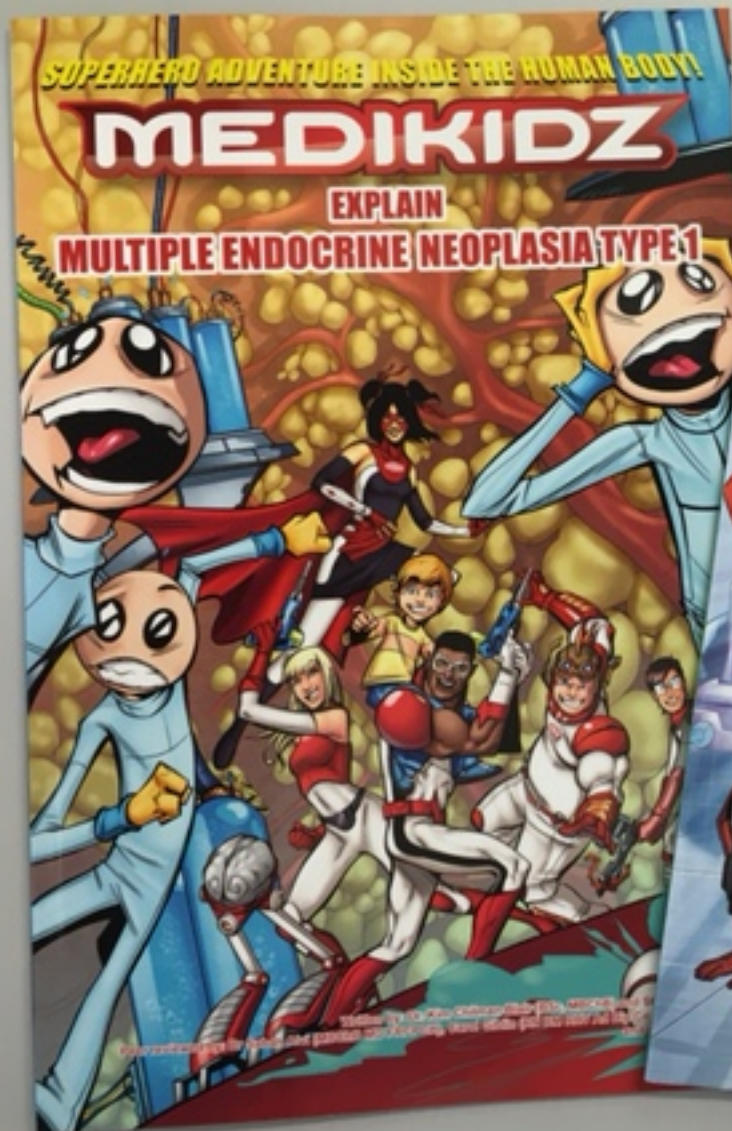
MEN1



MEN2



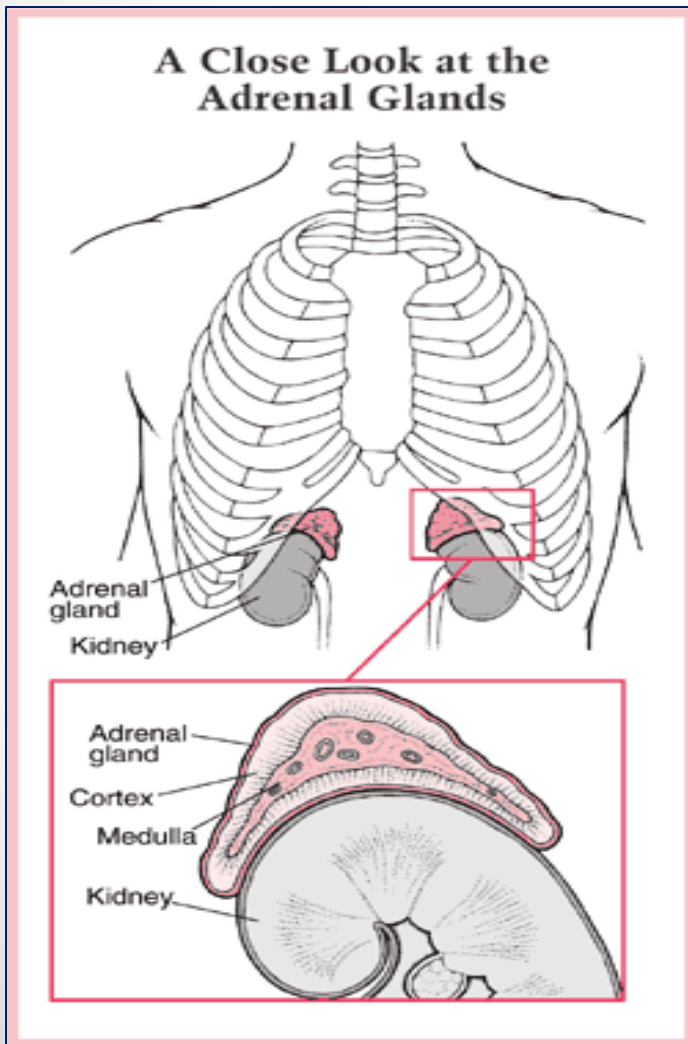




# Phaeochromocytomas



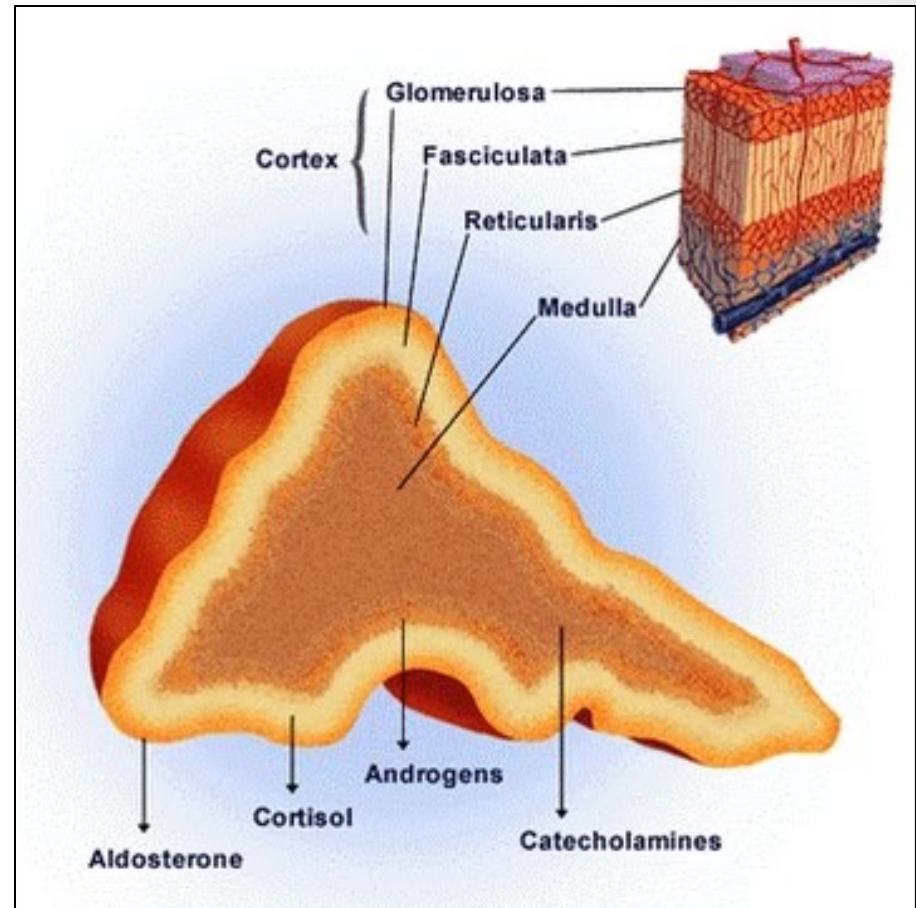
# Adrenal Gland A & P



- Adrenal cortex
  - Outer portion
- Adrenal medulla
  - Inner portion

# Adrenal Cortex

- **Mineralocorticoids**
  - **ALDOSTERONE**
    - Helps regulate BP by controlling how much salt is retained in the body
- **Glucocorticoids**
  - **CORTISOL**
    - The body's natural steroid, 3 main functions:
      - Helps control the blood sugar level
      - Helps the body deal with stress
      - Helps to control BP and blood circulation
- **Sex Steroids / Androgens**
  - DHEA
  - DHEA-S
  - Androstenedione
    - Secondary sexual characteristics

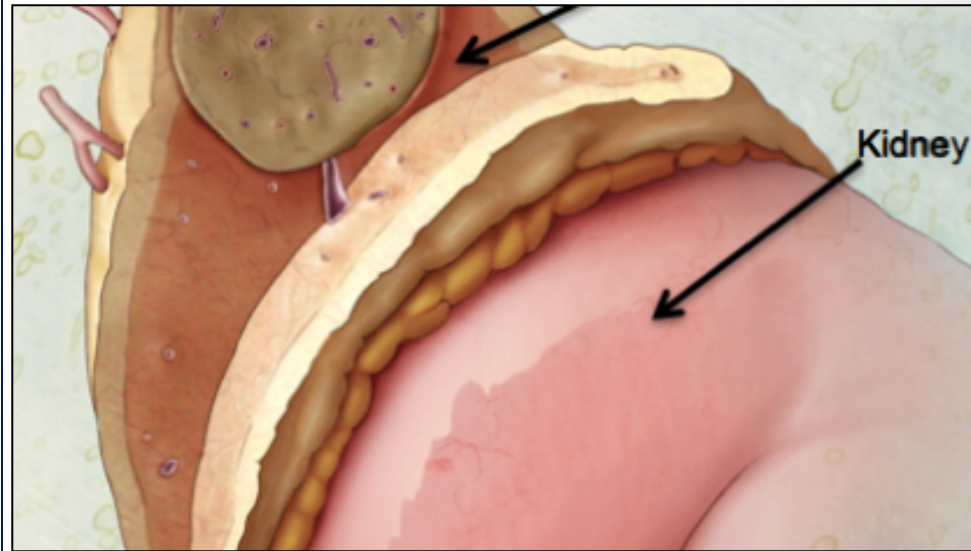


# Adrenal Medulla

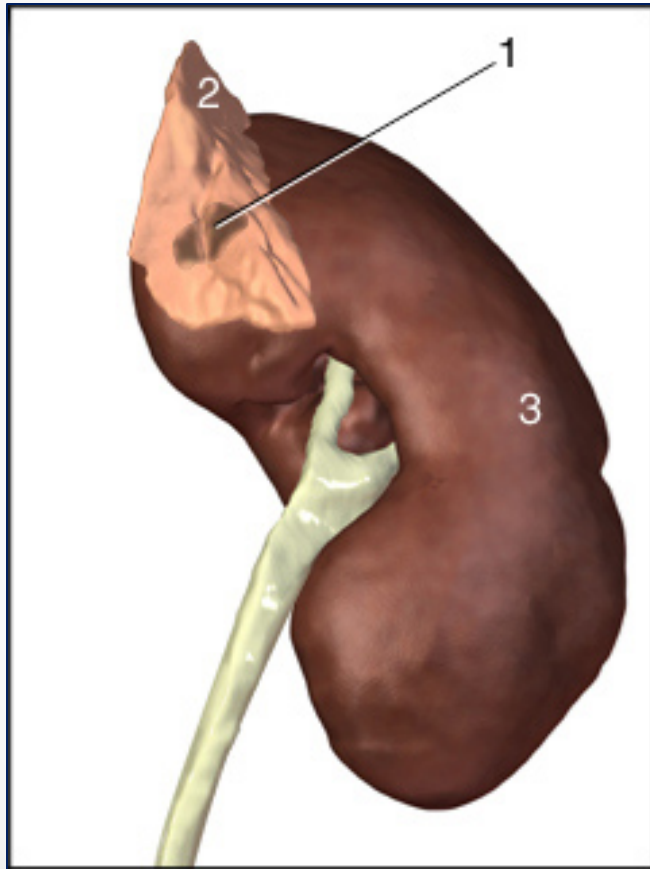
- Catecholamines
  - Adrenaline
    - Released in response to signals from the sympathetic nervous system
    - Increases
      - Blood sugar
      - Muscle glycogen breakdown
      - Blood flow to muscle
      - Respiration
  - Noradrenaline
    - Similar effects to adrenaline, as well as maintains BP
  - Dopamine
    - Precursor to adrenaline and noradrenaline
      - Neurotransmitter

# Phaeochromocytoma

- Neuroendocrine tumour
- Usually benign, can be malignant
- Excretes excess catecholamines
- Uncommon cause of  $\uparrow$  BP  $\therefore$  can easily be missed
- We have occasional bursts of cats when we are upset or stressed
  - Those with phaeos have it all the time



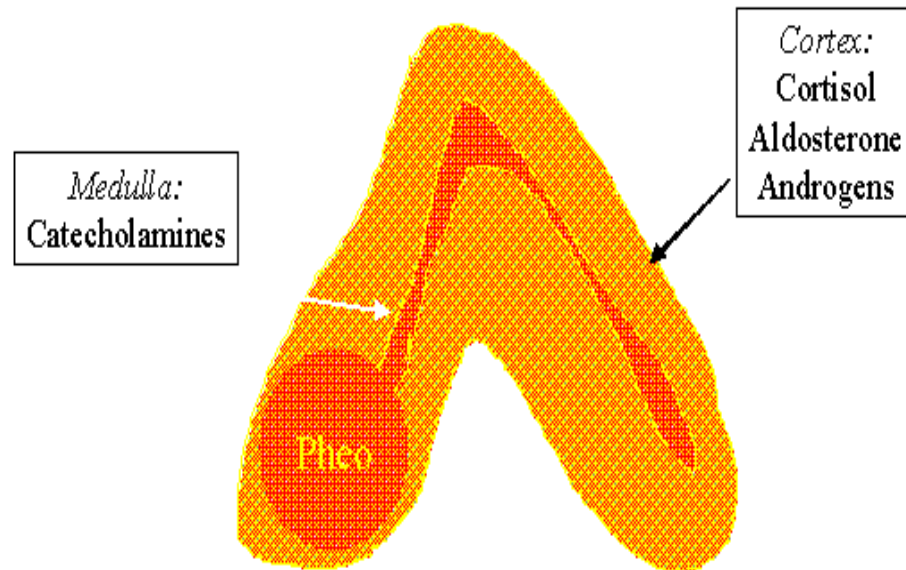
# Phaeochromocytoma



- Only present in 10% of VHLs
- French study in the 90s
  - Phaeos were the first manifestation of VHL disease in 51% of pts
  - Only manifestation for up to age 21 yrs, or even indefinitely
- Easy to miss the diagnosis
- *Usually* arise in the adrenals, may also originate in paraganglia outside the adrenals

# Phaeochromocytoma

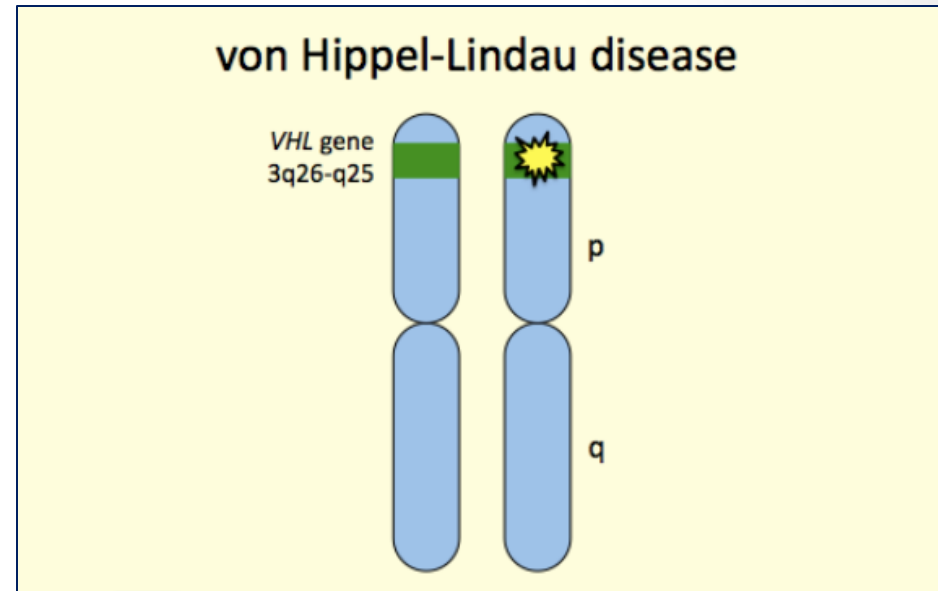
- Symptoms ?
  - ↑BP
  - Headache
  - Perspiration / episodic sweating
  - Palpitations
  - Anxiety attacks
    - May be incorrectly attributed to anxiety or depression
- Can cause life threatening conditions
  - Hypertensive crisis
  - Mets - Stroke
  - Cardiac failure - MI





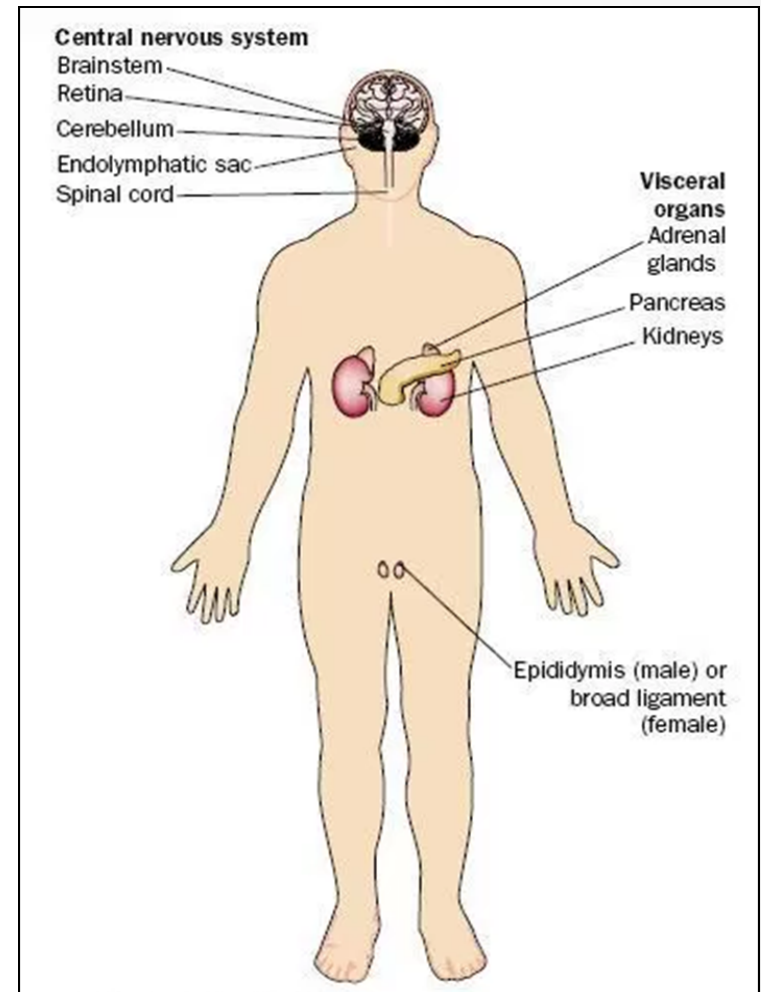
# Von Hippel-Lindau disease

- Chromosome 3
- Tumour suppressor gene
- Can identify the gene
  - Pre-symptomatic screening
- Autosomal dominant
  - Each child of an affected individual has a 1 in 2 chance (50%) to inherit the gene alteration
- Children referred
  - Fellow adult endocrine teams managing in their affected parent

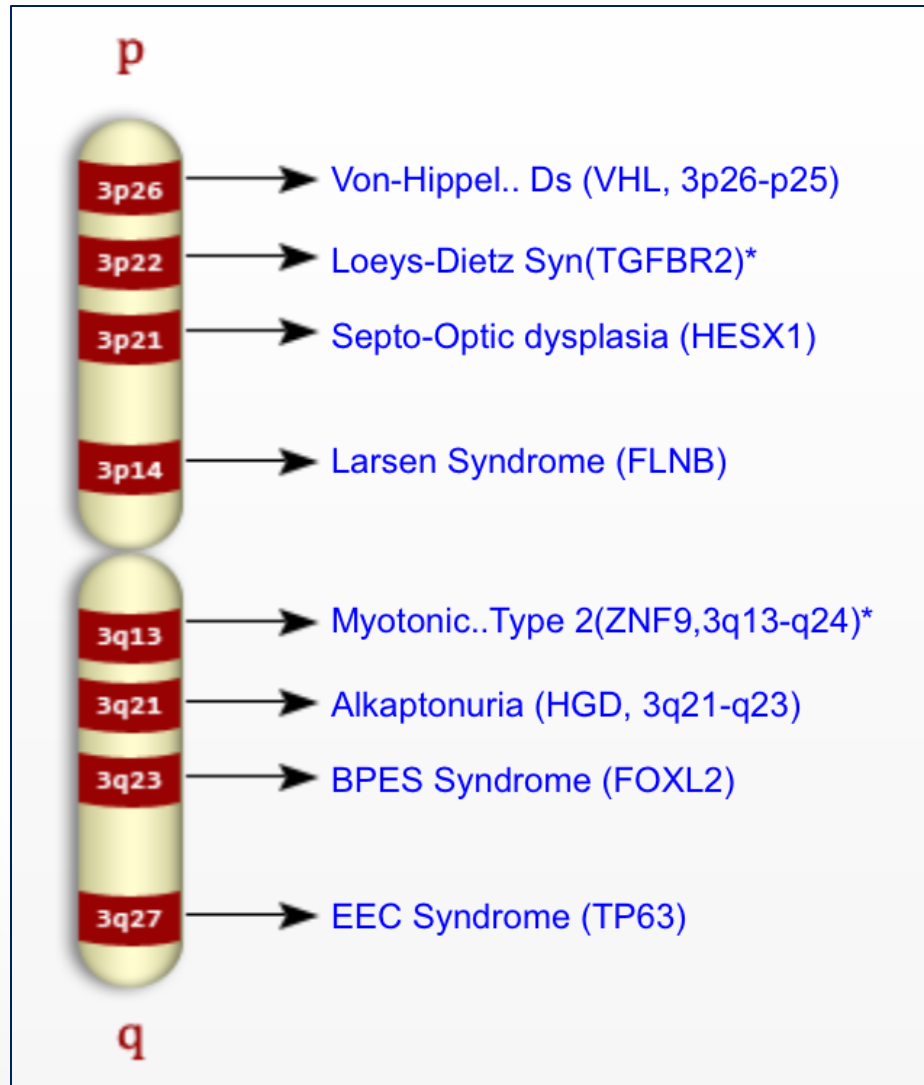


# Von Hippel Lindau disease

- Incidence
  - 1 in 40,000
  - Average age of presentation
    - 26 yrs of age
- Haemangioblastomas
  - Brain, spinal cord, retina
- Renal cysts
- Pheochromocytomas



# Chromosome 3



# Screening in VHL

## • Genetics

- Analysis of the index case is key to identifying further members of the family at risk
- Can be done from age 5yrs
  - Enable clinical screening

*Reduction in morbidity compared to their parents*

## • Ophthalmology review

- Fundoscopy screening

## • Adrenals

- Pheochromocytomas

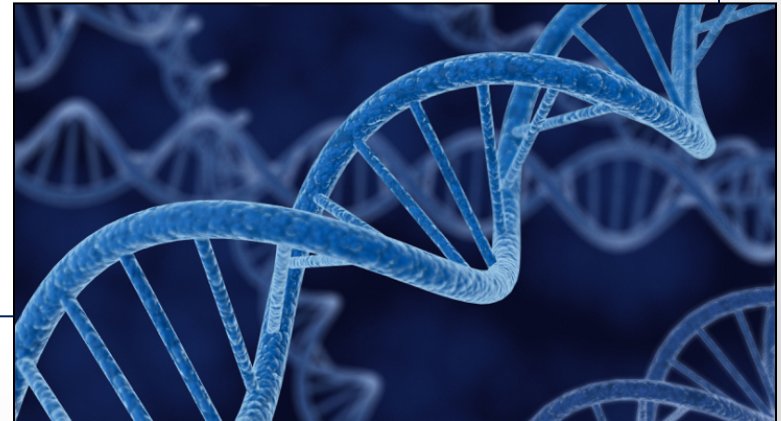
## • Renal carcinomas

- Now leading cause of death amongst VHL patients
  - Successful treatment for CNS haemangioblastomas
  - Imaging

VHL	Eyes	Fundoscopy	Fluorescein angiography	5 yrs	Annual
	CNS	Full examination		10 yrs	Annual
			MRI brain & spinal cord	10 yrs	3 yearly
	Renal	Abdominal examination	US kidneys	5 yrs	Annual
			MRI kidneys	5 yrs	3 yearly
	Adrenal (pheochromocytoma)	Blood pressure 24-hour urine collections (x3) – catecholamines (plus corresponding serum metanephrines)	US adrenal	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly

# Case study

- Male child Tom
- DOB 10.11.01
- Family history of VHL
- Positive for the familial mutation in exon 3 of the VHL gene
- Commenced screening programme
  - 2006 age 5yrs



# Family history



- **Father**

- Retinal angiomatosis
- Bilateral phaeochromocytomas 23yrs
- Cervical spine haemangioblastoma 33yrs
- Bilateral renal cell carcinomas 34 7 35yrs

- **Half-brother**

- Right phaeochromocytoma age 14yrs
  - 3 year old son

- **Paternal aunt**

- Bilateral phaeochromocytomas 7 and 21yrs
- Cerebral haemangioblastoma 16yrs
- Retinal haemangioblastoma 18yrs
- Right renal carcinoma 28yrs
- Pancreatic NET 36yrs

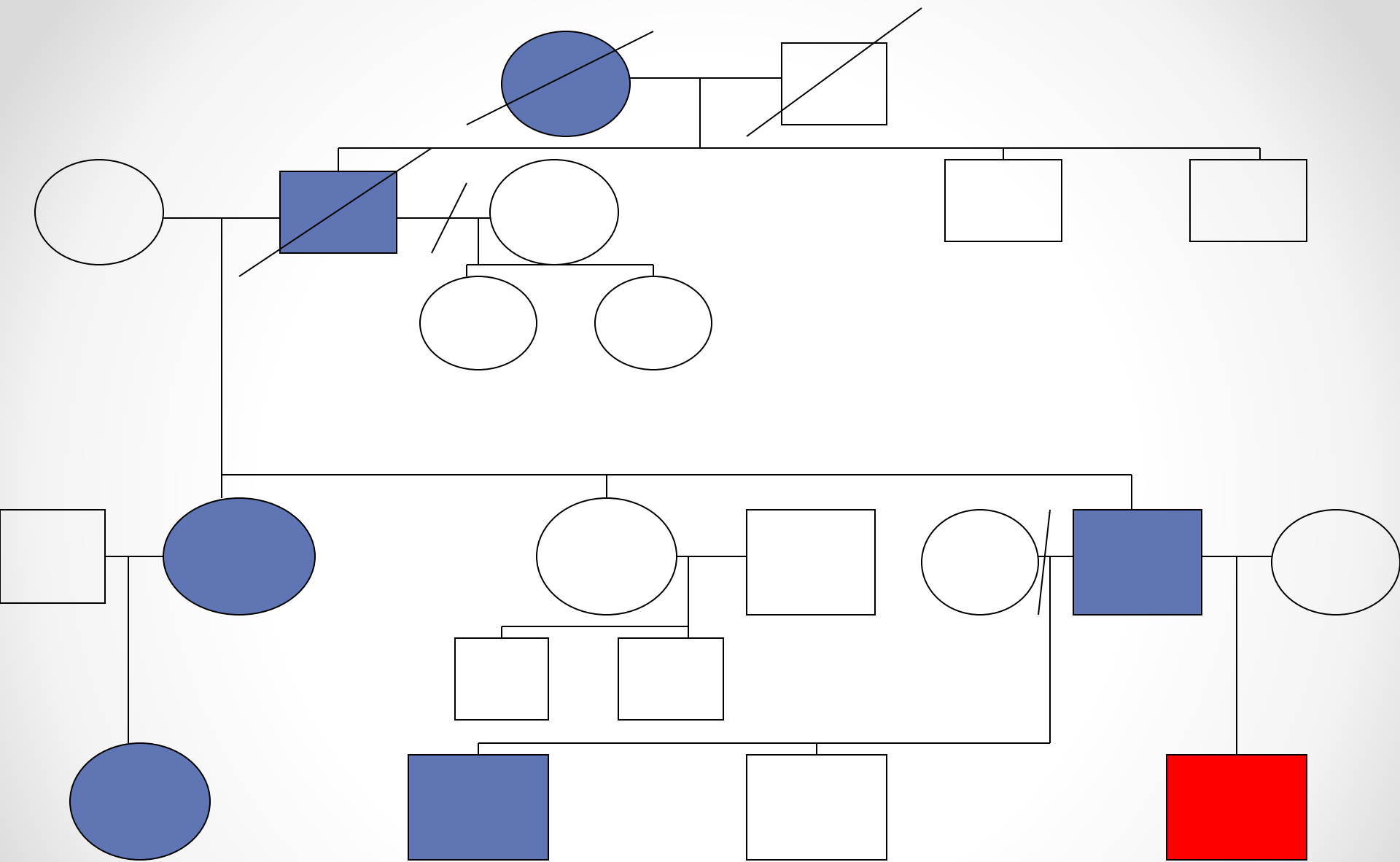
- **Cousin (female)**

- Bilateral phaeochromocytomas 12yrs and 14yrs
- Pancreatic NET 19yrs

- **Brother**

- Age 3yrs





# Clinical screening

- 2007, 2008, 2009

- All normal

- 2010

- January
- Urine catecholamine (noradrenaline) slightly elevated
  - 370nmol/day (N=below 194)
- Repeat and watch as asymptomatic
- May
  - 433nmol/day
- June
  - MRI adrenal normal
- October
  - 372nmol/day

- 2011

- February
  - 477nmol/day

- 2012

- Lesion seen on abdominal MRI
- Repeat MRI with contrast
- MIBG scan

# MRI Abdomen 12.10.12

- Review of imaging for endocrine VHL MDT 31.10.2012
- There is a 3cm MIBG positive paraganglioma in the upper retroperitoneum interposed between the aorta, IVC and portal vein. No local invasion seen. Slow increase in size since 2008.
- Small areas of soft tissue in the distal aorto-caval region but these are currently indeterminate.
- Normal kidneys, adrenals and pancreas
- Excision of paraganglioma January 2013, age 11 yrs

Slice: 0.8999999762 mm

0.001mm  
P: 7.08 (col)  
Non GE Image  
DFOV 33.2 x 27.0 cm

R  
T  
P

0.90/0.90sp

0.9mm /0.90sp

0 Sagittal

L: 30.55 (col)  
Non GE Image  
DFOV 33.2 x 27.0 cm

R

1.05/0.90sp

0.9mm /0.90sp

W = 289 L = 149

SRA

STENNING JACK

Ex:Sep 18 2012

0 Axial

S: 172.01 (col)  
Im: 88  
Non GE Image  
DFOV 33.2 x 27.0 cm

L  
R  
I

0.90/0.90sp

0.9mm /0.90sp

STENNING JACK

Ex:Sep 18 2012

Coronal

P: 7.04  
Non GE Image  
DFOV 33.2 x 27.0 cm

P

1.05/0.90sp

0.9mm /0.90sp

W = 289 L = 149

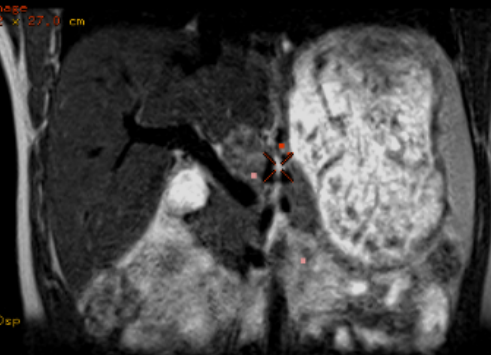
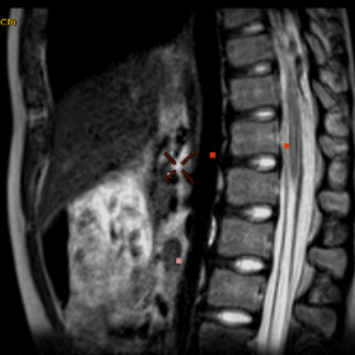
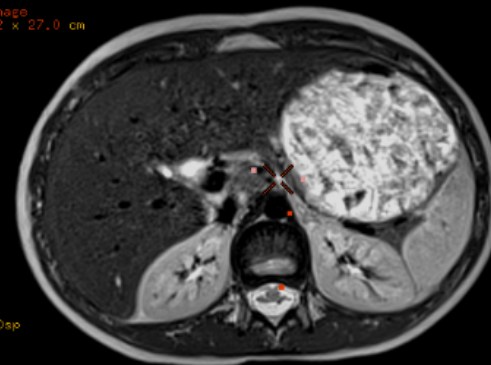
A

STENNING JACK

Ex:Sep 18 2012

C: 149.0, W: 289.0

C=149.0, W=289.0 1/5



LHA

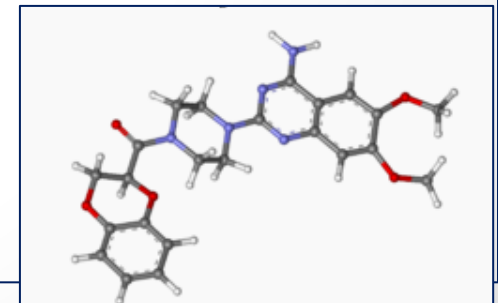
Pos: FFS  
Series: 450  
Image no: 1  
3D Saved State - AutoSave  
18/09/2012, 14:32:39

FLP

4

# Clinical management

- April 2012
  - Paraganglioma
    - Small
    - No plans for surgery
    - Intermittent symptoms and continued raised catecholamines
    - Commence Doxazocin 0.5mg once daily
      - Increase to twice a day after a week if tolerated
      - Continue until surgery planned
  - Doxazocin
    - Alpha blockade
      - Reduces BP



# MRI Abdomen 6.8.14

- New 9mm peripherally enhancing left adrenal nodule which demonstrates restricted diffusion likely to represent a small phaeochromocytoma.



Sequence: \*h2d1\_168

Slice: 4 mm

Dist: 4.4 mm

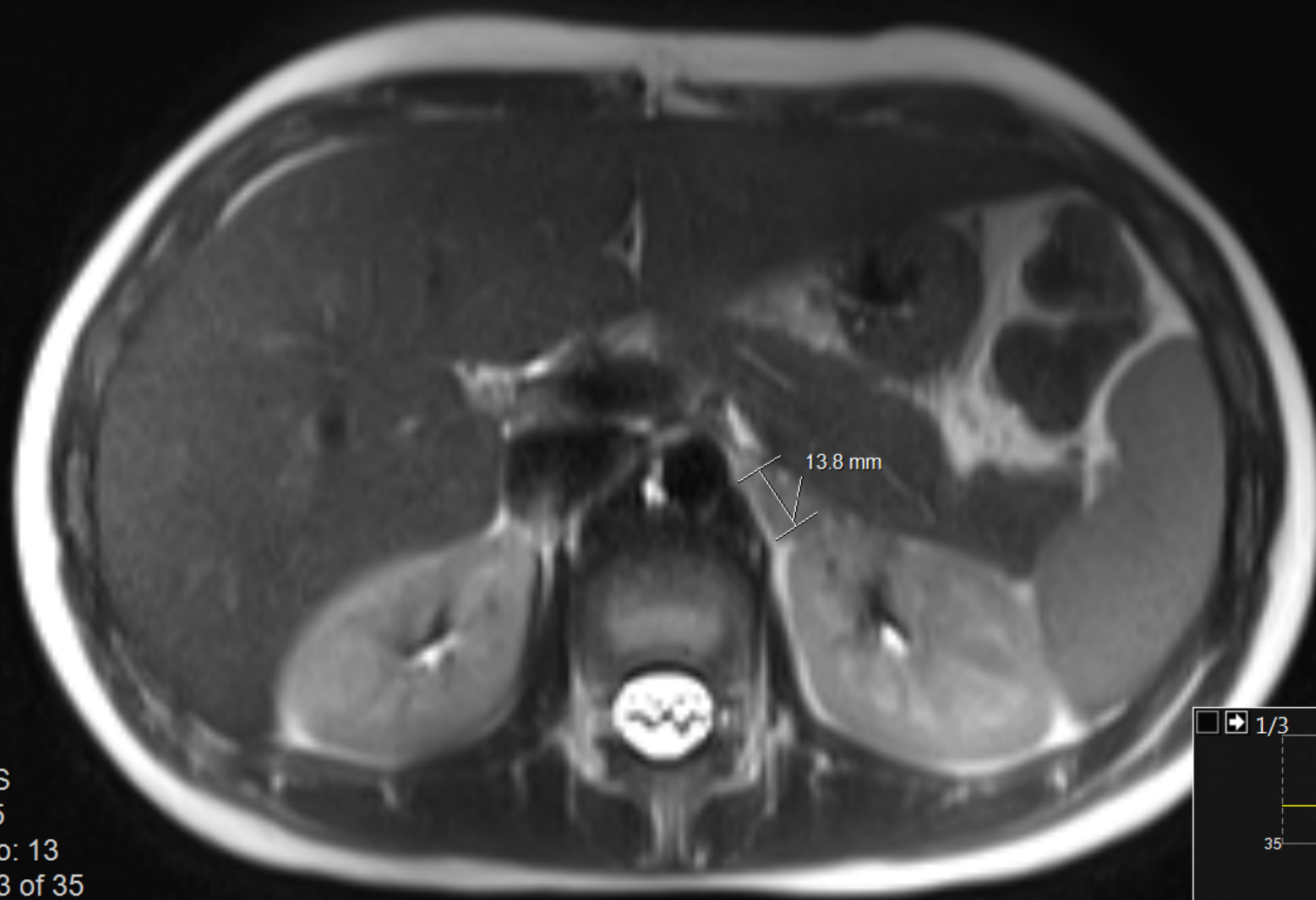
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TE: 93

AC: 1

C: 695.0, W: 1502.0

Algo1 1/5



Pos: FFS

Series: 5

Image no: 13

Image 23 of 35

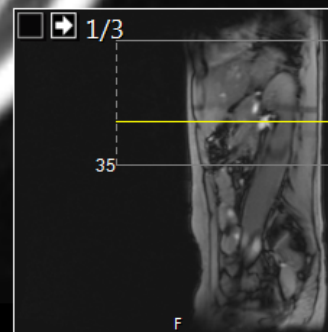
t2\_haste\_tra\_p2\_mbh\_320

06/08/2014, 11:24:08

P

L

3



# Clinical management

- 2014
  - November age 13yrs
    - Now wants to be seen without his Mum
    - ? Pheochromocytoma
    - Tom very stressed and upset
    - Psychological input offered
- 2015
  - Further imaging..

# MRI Pancreas 23.2.15

- The anterior lesion in the tail of the pancreas is still present and demonstrates an arterial blush.
- This remains suggestive of an islet cell tumour.
- No other pancreatic lesion is demonstrated.

Sequence: \*fl3d1

Slice: 2.5 mm

TR: 3.94

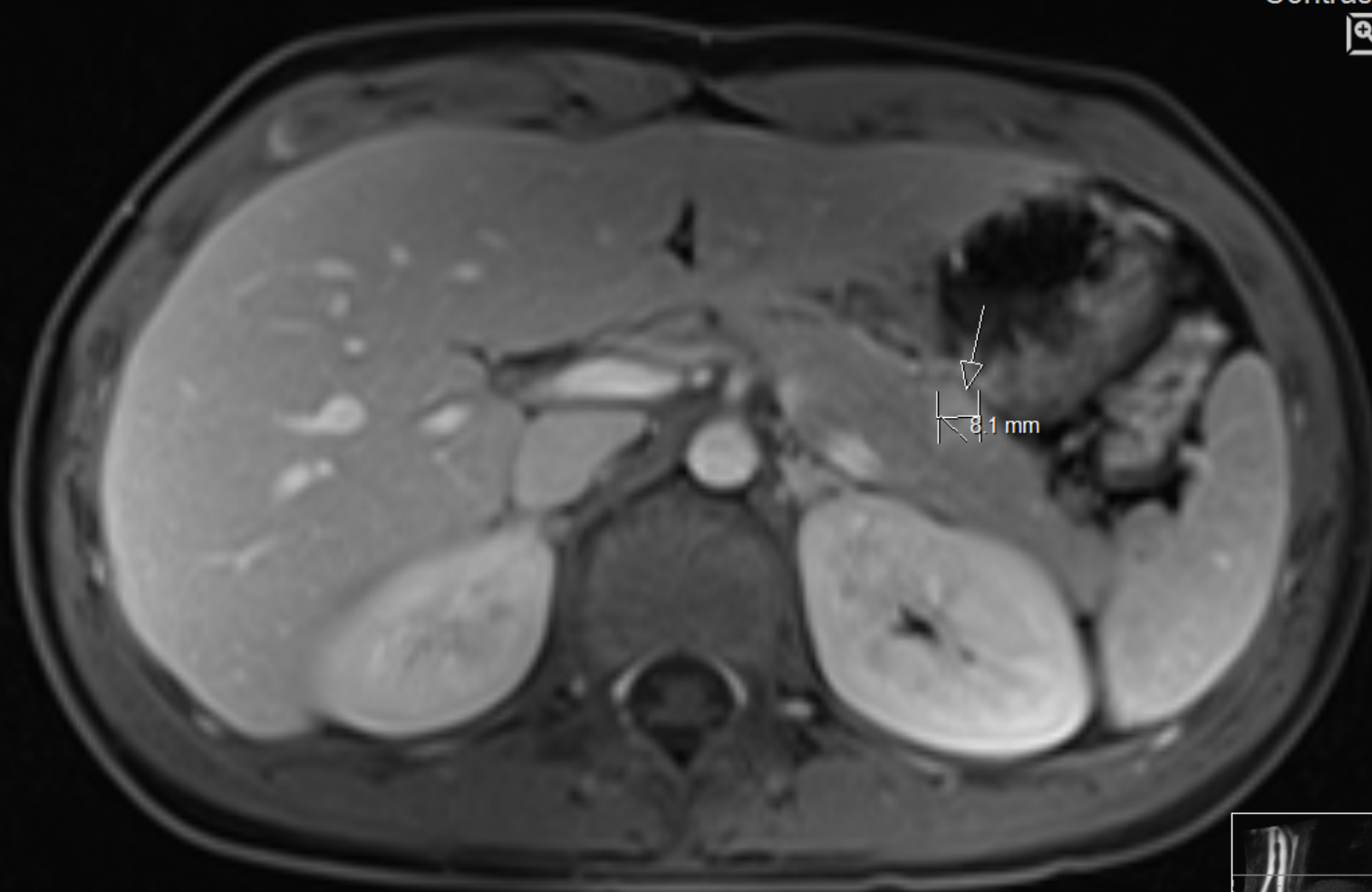
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AC: 1

C: 508.0, W: 1064.0

Algo1 1/5

Contrast: Dotarem



Pos: FFS

Series: 10

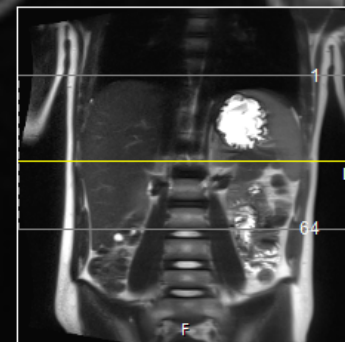
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Image 36 of 64

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23/02/2015, 12:48:04

P

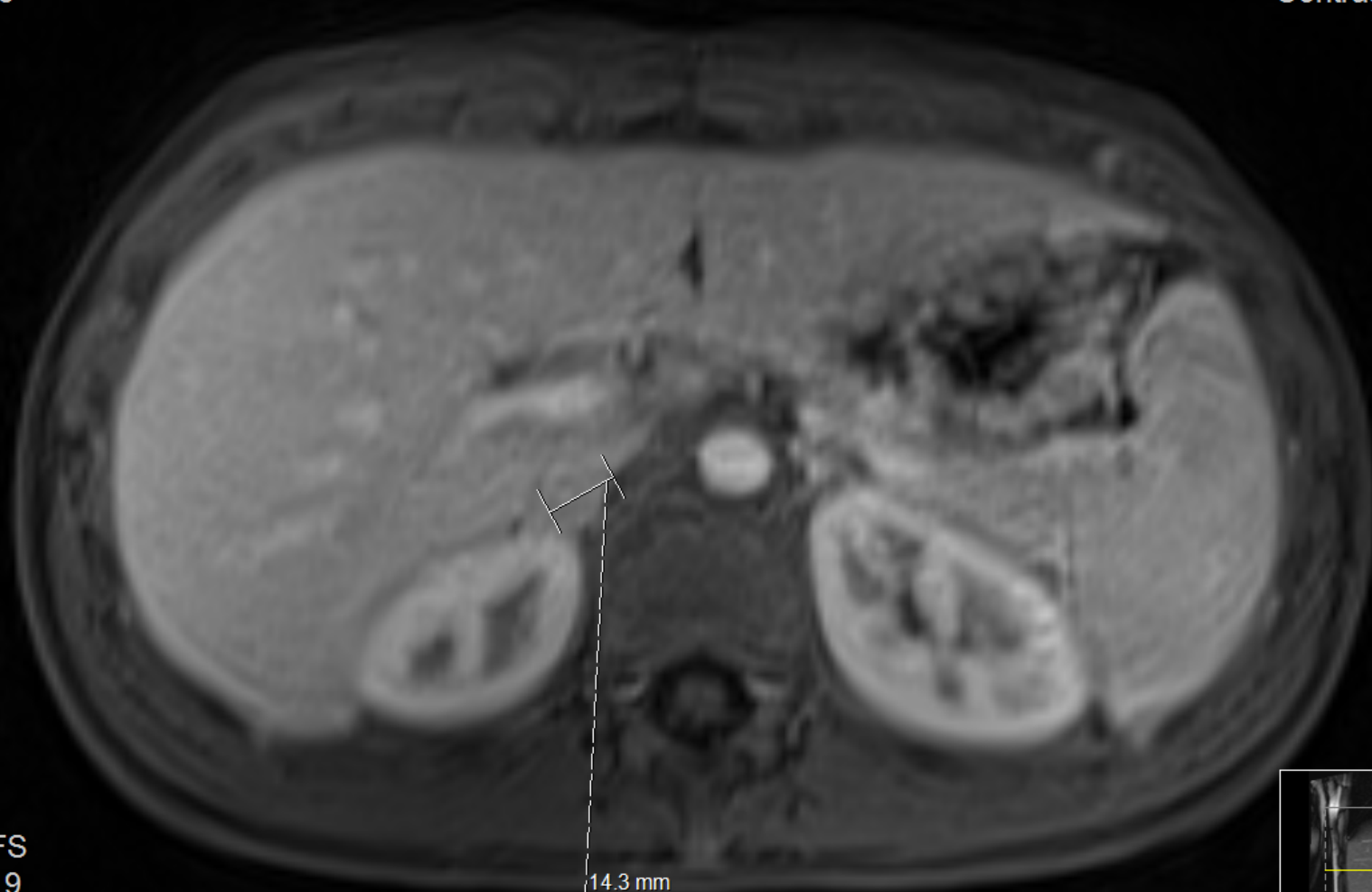


# MRI adrenals 14.7.15

- The right adrenal mass in the body of the adrenal has further increased in size now measures 13 mm.
- The left adrenal nodule in the lateral limb is stable measuring 15 mm.
- Both lesions have similar properties and the appearances are in keeping with small phaeochromocytomas

Sequence: \*fl3d1  
Slice: 2.5 mm  
TR: 4.09  
TE: 1.45  
AC: 1

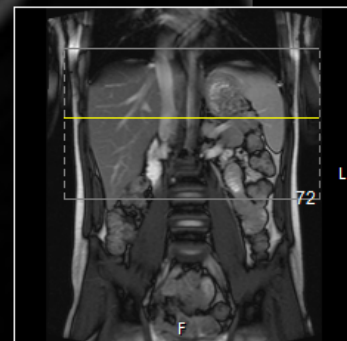
C: 540.0, W: 1088.0  
Algo1 1/5  
Sync group: 5  
Contrast: DOTAREM  
Z R L



L  
9

Pos: FFS  
Series: 9  
Image no: 34  
Image 34 of 72  
t1\_vibe\_fs\_tra\_p2\_bh\_post  
14/07/2015, 12:03:22

P



L  
72



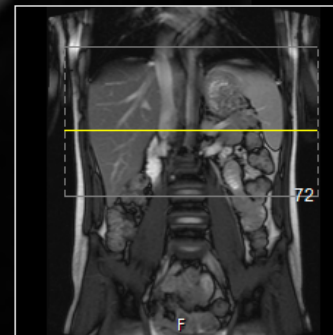
Sequence: \*fl3d1  
Slice: 2.5 mm  
TR: 4.09  
TE: 1.45  
AC: 1

C: 527.0, W: 1074.0  
Algo1 1/5  
Sync group: 5  
Contrast: DOTAREM  
∞ ↖ Z ↘



Pos: FFS  
Series: 9  
Image no: 41  
Image 41 of 72  
t1\_vibe\_fs\_tra\_p2\_bh\_post  
14/07/2015, 12:03:22

9

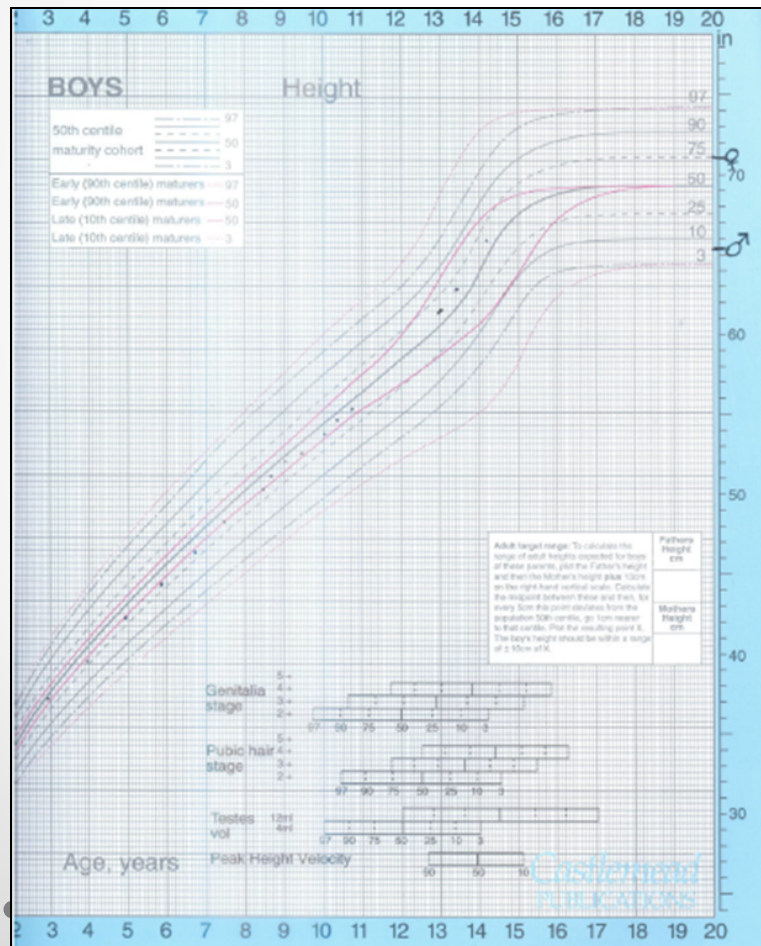


# Continued management

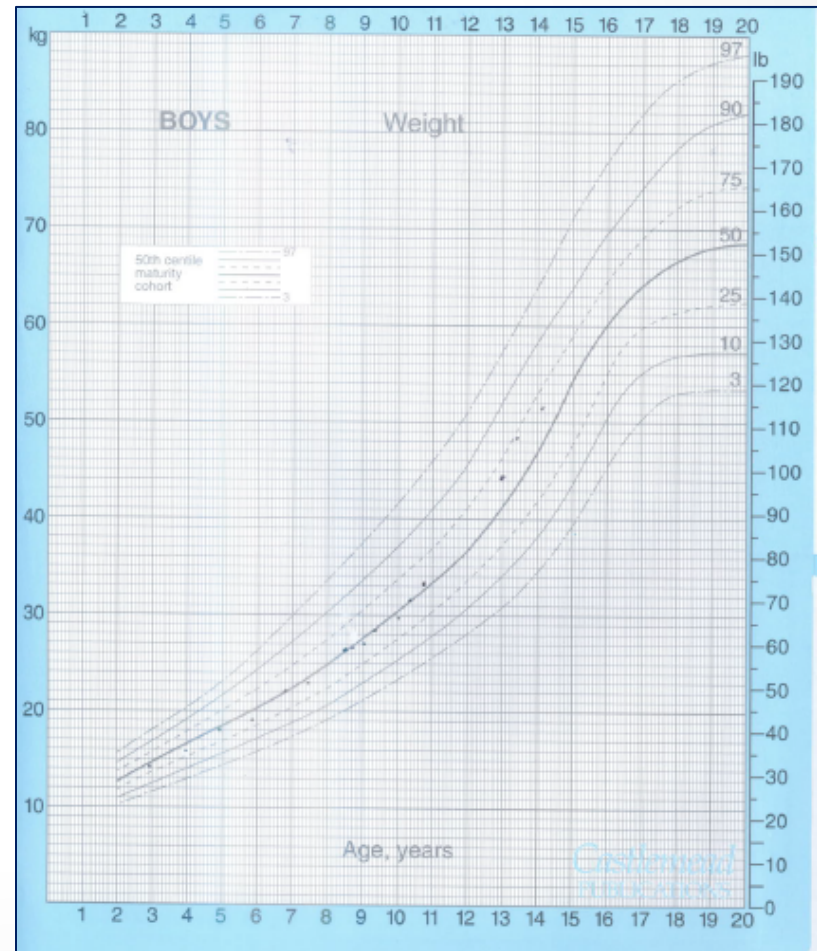
- 2015
  - July
  - Bilateral phaeochromocytomas
  - Now proceed to surgery
  - December had surgery
- 2016
  - April – surgical follow up
  - As you know he underwent a right laparoscopic adrenalectomy for a pheochromocytoma within the Von Hippel Lindau syndrome in December last year, from which he made a rapid and uncomplicated post-operative recovery.
  - On examination today, all incisions have healed well.
  - We knew pre-operatively that he had bilateral phaeochromocytomas however the right was the largest and we hoped to proceed with a staged adrenalectomy to preserve adrenal function for as long as possible.
  - Unfortunately, post-operative urinary nor-metadrenaline has not decreased substantially although his mother tells me he remains normotensive and asymptomatic.
  - I discussed the findings with him and his mother today and I have suggested that he seeks an early appointment with the paediatric endocrine team to discuss the potential for going back on to doxazosin. He particularly would like to avoid further surgery for at least a year. He is of course in his GSCE year currently.

# Auxology

Height



Weight



# Potential further management

- Bilateral
- Hydro

## Instructions for Hospital Doctor

Dear Doctor,  
If this patient is brought to hospital as an emergency the following management is advised:

- 1) Insert an IV cannula
  - 2) Take blood for U&Es, glucose, and perform any other appropriate tests (e.g. urine culture)
  - 3) Check capillary blood glucose level
  - 4) Give 100 mg hydrocortisone intravenously as bolus (unnecessary if patient has already been given IM hydrocortisone)
  - 5) Commence IV infusion of 0.45% sodium chloride and 5% glucose at maintenance rate (extra if patient is dehydrated). Add potassium depending on electrolyte
  - 6) Commence hydrocortisone infusion (50 mg hydrocortisone in 50ml 0.9% sodium chloride via syringe pump)
  - 7) Monitor for at least twelve hours before discharge
- IMPORTANT!** If blood glucose is < 2.5 mmol/l, give bolus of 2 ml/kg of 10% glucose
- If patient is drowsy, hypotensive and peripherally shut down with poor capillary return give 20ml/kg of 0.9% sodium chloride stat.

If in any doubt about this patient's management, please contact the urgent advice numbers

3. Draw up 2mls of

4. Mix the crushed

5. Then draw up 1ml

6. Give by mouth as

For f  
Great

1. Efc

Dose:

2. Plea  
already

Follow  
require

All oth

If requ

PTO f

## My Cortisol



London Ambulance Service NHS Trust

### Patient Specific Protocol

PSP Paediatric Steroid Dependent Crisis

This protocol has been specifically prepared for **STEROID DEPENDENT CRISIS** patients and details the

●●●● O2-UK

22:02

100%

Great Ormond Street  
Hospital for Children  
NHS Foundation Trust



**EMERGENCY**

CARD IS ON  
EMERGENCY THERAPY

Affix  
photo  
here



call via switchboard a

emergency - up to 1/3 tube if no

oxygen therapy as

Great Ormond Street **NHS**  
Hospital for Children

NHS Trust

Great Ormond Street  
London WC1N 3JH

Tel: 020 7405 9200

Gastroenterology, Endocrinology, Metabolic & Adolescent Medicine (GEMA)  
Direct Line: 0207-813-8214

Date:  
Reference:

Dr  
Paediatric Consultant

Dear Dr

RE:

..... is a .... year old ..... under the care of ..... at Great Ormond Street Hospital. He is a boy/girl with ....., he/she was referred with ..... and we have since found he also has cortisol deficiency.

He/She has been commenced on Hydrocortisone at a dose of 2.5mg mane, 2.5mg at lunchtime, and 2.5mg nocte. ....'s mum has had education in his/her management during times of illness and has been trained in giving IM hydrocortisone should the need arise.

I would be extremely grateful if you could arrange for ..... to have fast track access at the ..... should he/she require emergency IM hydrocortisone. Please let us know on the number below.

Please do not hesitate to contact me should you require more information on 0207 813 8214.

Many thanks,

Yours sincerely

.....  
Clinical Nurse Specialist

Hospital for Children NHS Trust  
London Hospitals NHS Trust



# Conclusion

- Management of children with NETs very complex
- Importance of screening emphasised
  - Genetics and clinical
    - Inform families
    - Reduce need for screening
    - Reduction in morbidity compared to their parents
  - Can screen from age 5yrs
    - MEN2b genetics from age 1yr
- Potentials for further management
  - Nursery / School
    - Hydrocortisone management

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