Genetics of Endocrine Disease

Sunita De Sousa
Royal Adelaide Hospital

Outline

ENDOCRINE TUMOUR SYNDROMES

MONOGENIC DIABETES

DISORDERS OF SEXUAL DEVELOPMENT

HORMONAL DISORDERS

SKELETAL DYSPLASIAS

I. Endocrine tumour syndromes

- Classical MEN syndromes
  - MEN1
    - Parathyroid (95%), pancreas (NETs, 30-60%), pituitary (40%) tumours
    - + adrenal (30%), meningioma (8%), skin lesions e.g. angiofibromas (80%)
  - MEN2 (*RET*)
    - 2A (95%): medullary thyroid cancer (>95%), phaeo (50%) + parathyroid (30%) +/- cutaneous lichen amyloidosis (<30%), Hirschprung's (7%)
    - 2B (5%): MTC (100%), phaeo (50%) + Marfanoid body habitus, mucosal neuromas, 75% sporadic (cf 10% in MEN2A)
    - 'Codon-directed management' with eventual thyroidectomy in most
  - MEN4 (*CDKN1B*)
    - MEN1 mimic, ?less NETs, ?less aggressive pituitary adenomas
    - Discovered 2006, <50 cases

I. Endocrine tumour syndromes

- ‘Single’ tumour syndromes
  - Phaeochromocytoma/paraganglioma syndromes (△ in 30% all comers)
    - Pseudohypoxia genes e.g. *SDHx*, *VHL*, *FH*, *EPAS1*/*HIF2A*
    - Tyrosine kinase receptor genes e.g. *RET*, *NF1*, *MAX*, *TMEM127*
  - Familial pituitary tumour syndromes (△ in 5% all comers → 20% if ≤40yo / additional endocrine tumour Hx)
    - *AIP*, *MEN1*
    - *CDKN1B*, *PRKAR1A*, *SDHx*
  - Familial hyperparathyroidism (△ in 5% → 25% if ≤45yo / multiglandular)
    - *MEN1*, *CDKN1B*, *RET*, *CDC73*
    - *GCM2* (isolated PHPT, first described 2016)
    - Vs familial hypocalciuric hypercalcaemia (*CASR*, *AP2S1*, *GNA11*) – previous Ca++, relatives’ Ca++, CCCR

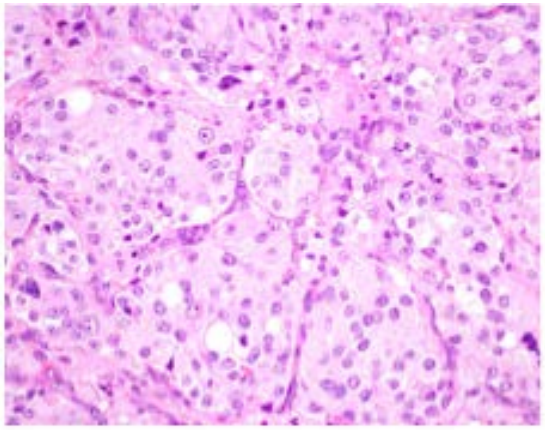
I. Endocrine tumour syndromes

- Non-endocrine overlap
  - Neurofibromatosis type 1
    - Phaeo in 1-3%
  - Von Hippel Lindau
    - Phaeo in 20 % (often Asx)
    - pNET in 10% (usually non-secretory)

I. Endocrine tumour syndromes

- Autosomal dominant
- Tumour suppressor genes
  - LoF △ spread across genes
  - Knudson's 2-hit model → variable expressivity, reduced penetrance
  - Exception: *RET* proto-oncogene
- Tumour IHC complementary
  - Loss of parafibromin in *CDC73*-associated PHPT
  - Loss of SDHB in any *SDHx*-associated tumours
- Usually adult-onset, but surveillance from childhood (eg 5-10yo in MEN1)
- Consider in young onset, multifocal, rare tumours +/- FHx
  - Routine in PPGL, gastrinoma, MTC
- Rationale for genetic testing (NGS panels):
  - Guide Rx of the presenting tumour
  - Screen proband for additional tumours
  - Tumour surveillance/Rx in relatives

CASE: 53 M metastatic paraganglioma



- Para-aortic primary, LN/bony mets
- Noradrenaline and dopamine secretion
- ‘Normal’ SDHB IHC but zellballen architecture
- No PHx/FHx of PPGL/related tumours
- ‘30-60% chance’ of hereditary PPGL gene △
- NGS PPGL panel at SA Pathology: *SDHB* c.649C>T, p.Arg217Cys
  - Class 4 (likely pathogenic)
  - Tumour → RNSH for repeat IHC and metabolomics
  - Explained likely cause of his PGL
    - Risks of RCC (10%), GIST (1%), pituitary adenoma (1%)
    - Beware false negative MIBG scans, watch for additional tumours, do not smoke
    - If confirmed → cascade testing parents, brother +/- nieces → 1-2yr tumour surveillance

II. Monogenic diabetes

- MODY
  - *GCK*: altered glucose setpoint, f glu 5.4-8.3, HbA1c 5.8-7.6%, 2% all GDM
  - *HNF1A*/*4A*: sulphonylurea sensitive, 2hr glu rise >5, glycosuria in *HNF1A*
  - *HNF1B*: GU anomalies, exocrine dysfunction, ↑LFTs/Cr, ↓Mg
  - Rarer forms: *CEL*, *PAX6*, *INS*, *ABCC8*, *KCNJ11* etc
- Mitochondrial diabetes (classically MIDD due to m.3243A>G)
  - Maternal transmission
  - SNHL, short, pregnancy loss, cardio/other myopathy, neurological dse, FSGS
  - Insulinopenic, risk of lactic acidosis → avoid metformin, beware statins

II. Monogenic diabetes

- Neonatal diabetes (<6mo, △ in 80%)
  - Free genetic testing via Wellcome Trust if <9mo at Dx
  - GoF *KCNJ11* (AD), *ABCC8* (AD/ AR) in 40% of NDM, sulphonylurea responsive
  - + Cardiac malformations → *GATA6*, *GATA4*
  - Other syndromic disorders eg Wolfram syndrome (*WFS1*; aka DIDMOAD)
- Congenital hyperinsulinism
  - LoF *ABCC8*, *KCNJ11* in 50% of all cases
  - LoF *HNF4A* △ → macrosomia, neonatal hyperinsulinism → MODY
  - △ type/gene dictates extent of pancreatic involvement, diazoxide response

II. Monogenic diabetes

- Considered in:
  - Slim, young person with antibody-negative DM, persistent insulin
    - +/- FHx
    - Exeter MODY calculator
  - Neonatal DM
  - Additional features: low-threshold glycosuria, *HNF1B*/mitochondrial features
- Clinical screening with sulphonylurea trial?
- Rationale for genetic testing (NGS panel):
  - *GCK* → obviates treatment/intensive lifelong follow-up
  - *HNF1A*/*4A, KCNJ11*, *ABCC8* → switch to sulphonylurea
  - Mitochondrial DM → surveillance for other features, Rx
  - Cascade testing: early Dx, tailoring of Tx, appropriate pregnancy Rx in *GCK*

CASE: 31 F

- ‘GDM’ in 3 pregnancies but young, lean & Caucasian
  - Metformin, insulin, extreme lifestyle Rx (50kg throughout pregnancy)
  - HbA1c 5.4-6.2%, never diabetic Sx/Cx
- FHx: ‘T2DM’ at 61yo in father, known *GCK* diabetes in brother
- ‘Most likely’ inherited the familial *GCK* △
- Sanger sequencing at SA Path: *GCK* c.574C>T, p.Arg192Trp
  - Revised Dx
  - Stop Tx or Cx monitoring
  - ?growth scans from 26/40 (wild-type fetus may be large → insulin Tx)
  - Glu check in husband (rare risk of neonatal DM if biallelic △)
  - Cascade testing in children (glu), father (△)

III. Disorders of sexual development

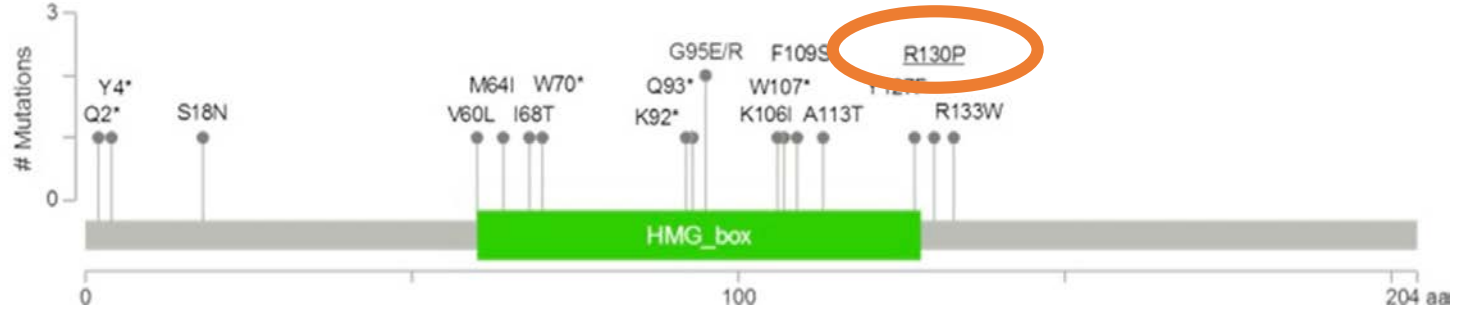
- Mismatch between chromosomal, gonadal and anatomical sex
- Chromosomal: Klinefelter's, Turner's, ovotesticular DSD (46,XX/46,XY)
- 46,XX DSD
  - 46,XX male: *SRY* translocation in 80%
- 46,XY DSD
  - 46,XY female: complete androgen insensitivity syndrome (*AR*) > complete gonadal dysgenesis (*DHH*, *SRY* etc)

III. Disorders of sexual development

- Presentation
  - Neonatal with ambiguous genitalia
  - Adolescence with pubertal delay
  - Adulthood with infertility
  - + NIPT with US discordance
- Karyotype, FISH, microarray, Sanger or NGS
  - Sinclair's lab, Murdoch Childrens Research Institute
- Rationale:
  - Gender Rx in paediatrics
  - Gonadectomy in 46,XY females
  - Rx of fertility / hormone replacement / other features
  - Patient wishes

CASE: 48 F presenting for HRT

- Primary amenorrhoea at 18yo → 46,XY karyotype → gonadectomy → bilateral gonadoblastoma and dysgerminoma
- Original Dx of complete androgen insensitivity syndrome
  - Tall, lean, female external genitalia, scarce secondary sexual hair
  - But withdrawal bleeds on COCP, no breast development
  - ?complete gonadal dysgenesis
- Repeat investigations at SA Pathology
  - 46,XY karyotype, FISH positive for SRY
  - No copy number variation by microarray (0.2 MB resolution)
  - Whole genome sequencing: *SRY* c.389G>C, p.Arg130Pro (class 4)
  - Revised Dx to complete gonadal dysgenesis



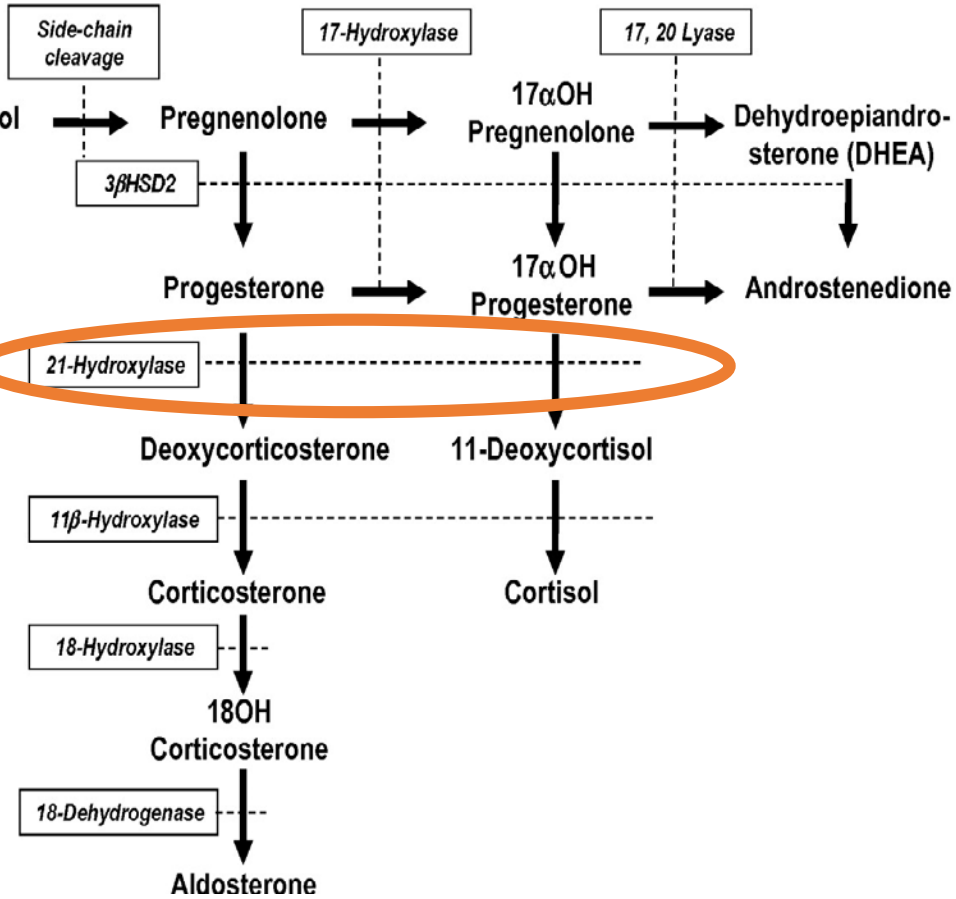
IV. Hormonal disorders

- Idiopathic hypogonadotrophic hypogonadism
  - >25 genes: *ANOS1* (*KAL1*), *FGFR1*, *GNRHR* → NGS panel
  - +/- anosmia (60%, = Kallmann's)
  - +/- congenital malformations esp renal (*ANOS1*), SNHL (*SOX10*, *CHD7*)
  - May need IVF anyway → PGD
- Fragile X syndrome (*FMR1*)
  - >200 CGG → fragile X syndrome
  - 55-200 → premutation carrier →
    - Fragile X tremor-ataxia syndrome (FXTAS) in >50% M, 10-20% F
    - Premature ovarian failure 20% F → may still conceive, discuss offspring risks

IV. Hormonal disorders

- Congenital adrenal hyperplasia (95% *CYP21A2*)
  - Autosomal recessive
  - Salt-wasting → simple virilising → non-classical subtypes, depends on △
  - Specialist input to conceive → discuss risk to offspring (carrier freq 1/60)
- Thyroid hormone resistance (usually *THRB*)
  - ↑ fT4, ↑ fT3, normal/↑ TSH, goitre, ↑HR, hyperactivity +/- hypothyroidism
  - DDx = TSHoma (prevalence 3/m, cf 1/40,000 for RTH)
  - Clinical tests: AD FHx, pit panel & MRI, a subunit, SHBG, dynamic tests
  - Sanger sequencing of *THRB*, hot spot mutations within ligand binding domain

CASE: 36 M with CAH

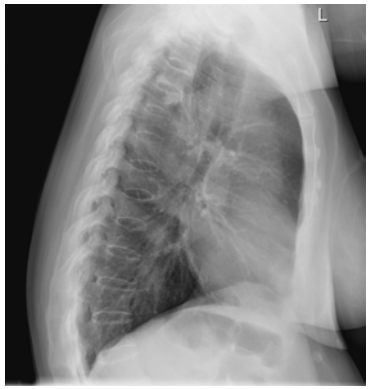


- Clinical Dx of salt-wasting CAH
  - Prednisolone and fludrocortisone, male phenotype, ↑17OH prog
  - Oligospermia, ↓LH, FSH, testo
  - Wife well, concerned re risk to offspring
- *CYP21A2* gene studies at Mater
  - Two △ in husband:
    - c.290-13C>G
    - Hybrid CYP21A2/CYP21A1P
  - No △ in wife
  - Very low residual chance of CAH (1/6000)
  - Cascade testing in husband's relatives

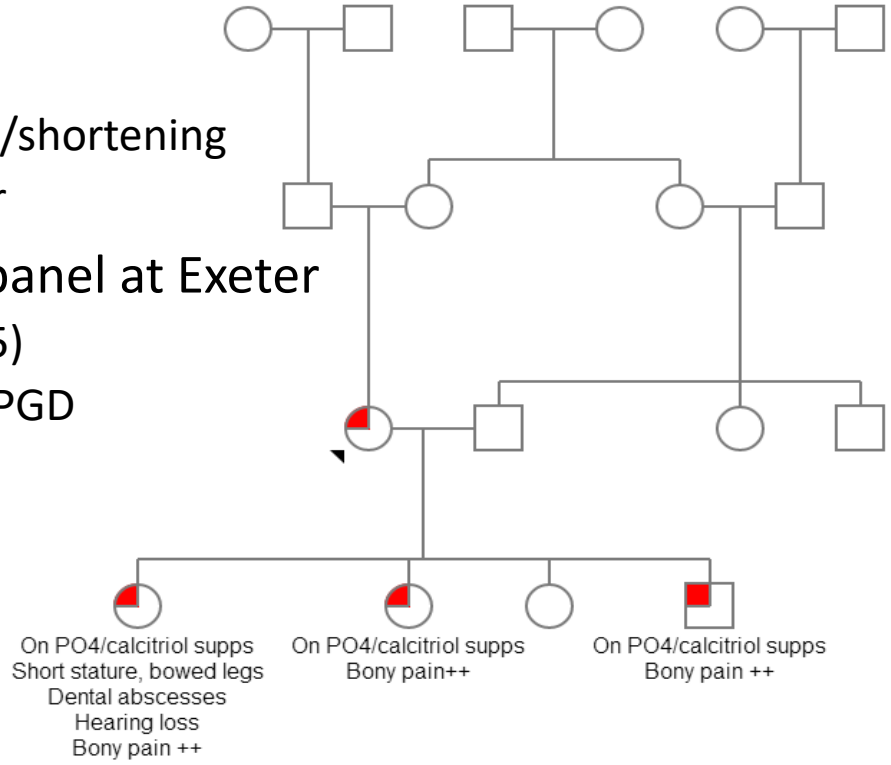
V. Skeletal dysplasias

- Paediatric domain
- Osteogenesis imperfecta:
  - Type 1/mild/classic non-deforming vs type 4/mod-severe/common variable OI
  - Osteoporosis +/- short, dentinogenesis imperfecta, blue sclerae, hearing loss
  - *COL1A1*, *COL1A2* by Sanger or NGS, MLPA if negative (deletions in 2%)
- Rare disorders
  - Hypophosphataemic rickets: *PHEX* (XLD) > *FGF23* (AD), *DMP1*/*ENPP1*/*SLC34A3* (AR)
  - Hypophosphatasia (*ALPL*): perinatal, infantile, childhood, adult onset, AR→AD
  - Familial expansile osteolysis (*TNFRSF11A*): ↑ bone turnover +/- hearing/dental loss
- May guide Tx
  - Bisphosphonates (??)
  - Denosumab
  - Asfotase alfa

CASE: 51 F



- Dx of hypophosphataemic rickets
  - Bony pain +++
  - Spontaneous dental abscesses
  - Short stature (Ht 133 cm), LL bowing/shortening
  - Renal PO4 wasting, ↑ bone turnover
- Hypophosphataemic rickets gene panel at Exeter
  - *PHEX* c.1204C>T, p.Gln402Ter (class 5)
  - Cascade testing for children ⇢ ?IVF/PGD



Genetic Testing in Endocrinology

***Sunita MC De Sousa,[1-3] Tristan SE Hardy,[3,4] Hamish S Scott,[2,3,5-7] David J Torpy[1,2]**

[1]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide; [2]School of Medicine, University of Adelaide, Adelaide; [3]Department of Genetics and Molecular Pathology, Centre for Cancer Biology, an SA Pathology and University of South Australia alliance, Adelaide; [4]Repromed, Dulwich, SA, Australia; [5]ACRF Cancer Genomics Facility, Centre for Cancer Biology, SA Pathology, Adelaide; [6]School of Biological Sciences, University of Adelaide, Adelaide; [7]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia.

*For correspondence: Dr Sunita De Sousa, Sunita.DeSousa@sa.gov.au

Abstract

The recent genomic revolution, characterised by surges in the number of available genetic tests and known genetic associations, calls for improved genetic literacy amongst medical scientists and clinicians. This has been driven by next generation sequencing, a technology allowing multiple genes to be sequenced in parallel, thereby reducing the time and financial costs associated with genetic testing in both research and clinical settings. Endocrinology is an intuitive setting in which to consider the principles of genetic testing because endocrine disorders are due to defects in circumscribed pathways, providing clues to candidate genes. This article discusses genetic testing in contemporary endocrine practice with reference to examples of endocrine genetic disorders or multisystem genetic disorders with endocrine manifestations. Monogenic disorders are prioritised as these form the bulk of endocrine genetic disorders and the associated genetic testing is readily understandable, clinically available and practice-changing. Although it remains true that genetic testing should be embarked upon only if the result will alter management, the clinical utility of genetic testing is often underestimated and there are expanding indications for genetic testing across all areas of endocrinology.

Acknowledgements