

**Cancer Genetics: Inherited
cancer syndromes
associated with Tumor
Suppressor Gene Mutations**

Dr Anne Lampe

Aims of the lecture

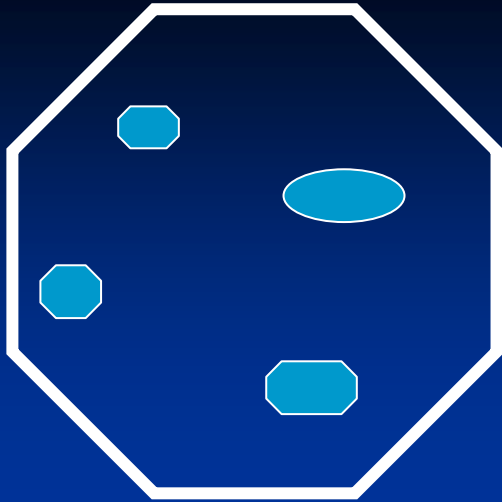
- Review 2-hit hypothesis for tumour development
- Present characteristic features of 3 inherited cancer syndromes
 - Neurofibromatosis
 - Familial Adenomatous Polyposis
 - Von Hippel Lindau Disease
- Discuss “screening” for early cancers

Cancer

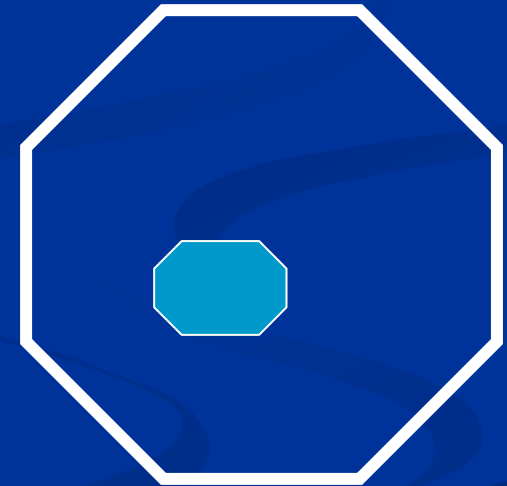
- Is common
- Involves genetic change
- Is rarely inherited

Retinoblastoma

- Commonest childhood eye tumour
- 1 in 15,000 children
- 3rd most common childhood malignancy
- Average age of onset 18 months
- 60% present with leukocoria
- Treat with radiotherapy/laser/cryotherapy or enucleation



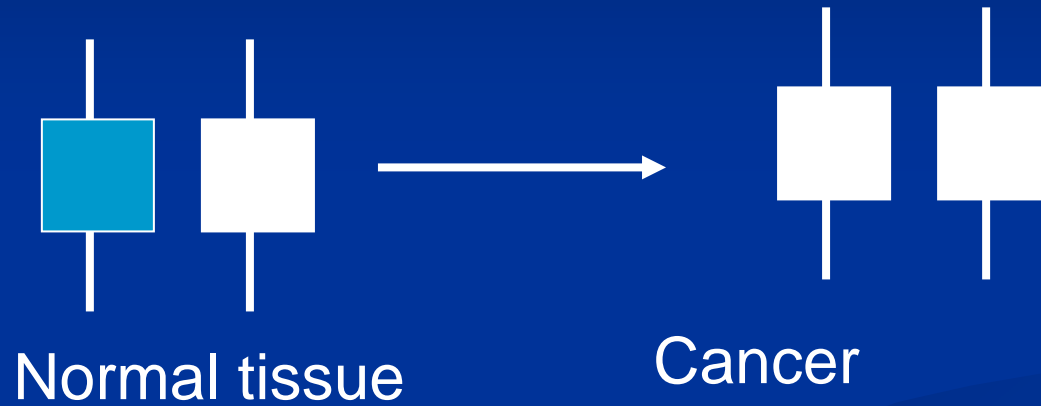
Germline RB1
mutation carrier



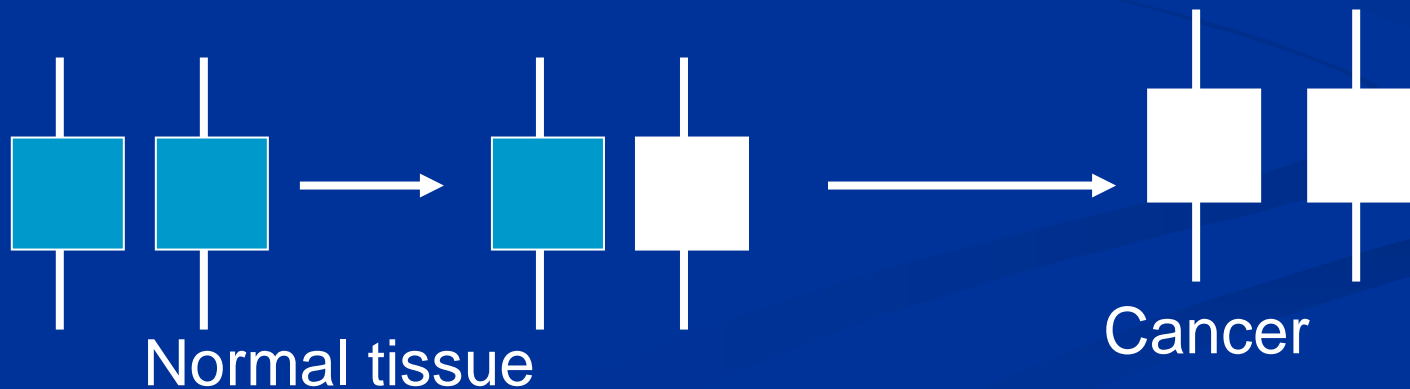
No germline
mutation

Knudson's 2-hit hypothesis

Mutation carrier



Sporadic Cancer



Tumour Suppressor Genes

- Control cell growth and differentiation
- Function as “cellular recessives”

Retinoblastoma

- Predisposition to develop Retinoblastoma (“first hit” germline mutation) inherited in autosomal dominant fashion
- 10% of RB is familial
- If no FHx and bilateral RB 90% chance of RB1 germline mutation
- If no FHx and unilateral multifocal RB 15-90% chance of RB1 germline mutation
- If no FHx and unilateral unifocal RB 15% chance of germline mutation

Neurofibromatosis type1 (NF1)

- Affects 1 in 2,500
- Multisystem disorder
- Dominant
- Fully penetrant
- Highly variable expressivity
 - Great variability between affected individuals in the same family

NF1

- The NF1 gene on chromosome 17 encodes the protein Neurofibromin .
- 59 exons (350kb genomic DNA)
- 50% cases NF1 new mutations

NF1

- Neurofibromin suppresses Ras, a potent activator of cell growth and proliferation.

NF1- Clinical Features

- Neurofibromas
 - Discrete cutaneous neurofibroma of dermis or epidermis
 - Discrete subcutaneous neurofibromas that lie deeper in the skin
 - Deep nodular neurofibromas
 - Diffuse plexiform neurofibromas

NF1- Clinical Features

- Other skin manifestations
 - Axillary freckling

NF1- Clinical Features

- Ophthalmological findings
 - Lisch Nodules
 - 90%

NF1- Clinical Features

- Ophthalmological findings
 - Optic Glioma
 - 15%
 - Usually asymptomatic
 - Presents with deteriorating vision

NF1- Clinical Features

- Skeletal problems
 - Scoliosis
 - 10%
 - Usually mild
 - Very small number with severe presentation
 - Pseudarthrosis
 - 1%
 - Usually of long bones
 - Pathological fractures

NF1- Clinical Features

- CNS
 - Learning disability
 - Usually mild
 - 30-50%
 - Large head

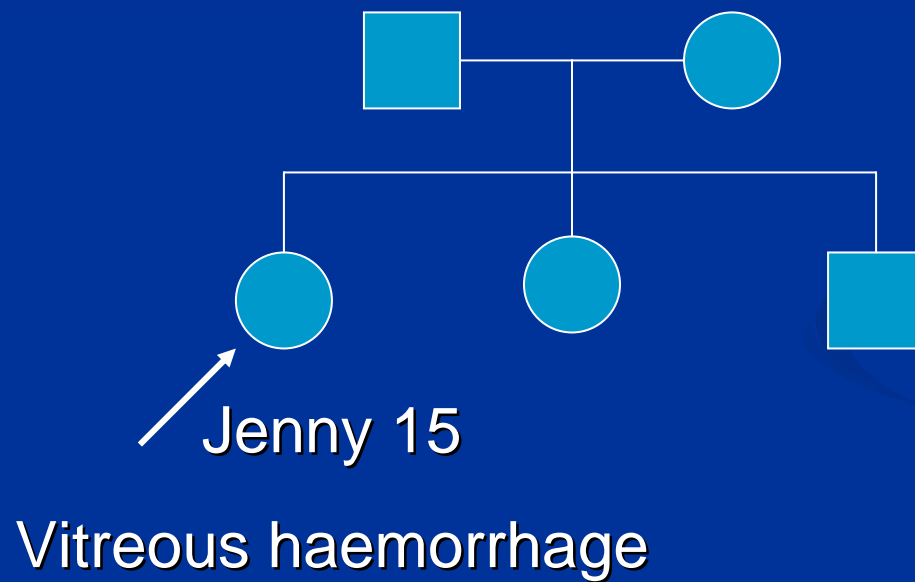
NF1- Cancer predisposition

- Malignant tumour of the peripheral nerve sheath
 - Life time risk of 13%
 - Usually from pre-existing plexiform neurofibroma
- Astrocytoma 2%
- Pheochromocytoma 0.7%
- Rhabdomyosarcoma 1.4%

Genetic counselling issues

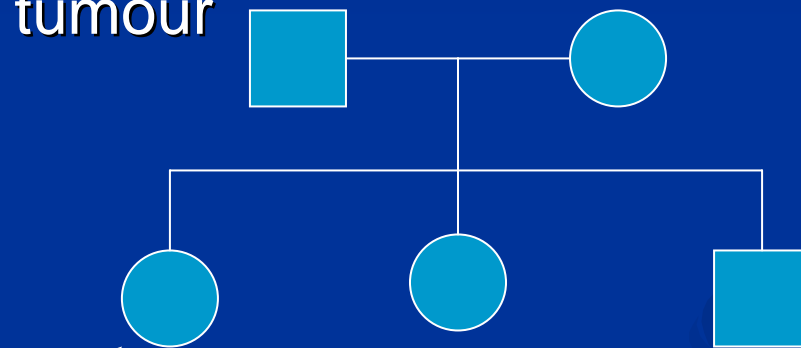
- Variability in phenotype makes reproductive decision making difficult
- Value of screening - differences between different healthcare systems
- Mutation analysis of limited value

Ophthalmological referral



Peter aged 42

Radiotherapy for brain
tumour

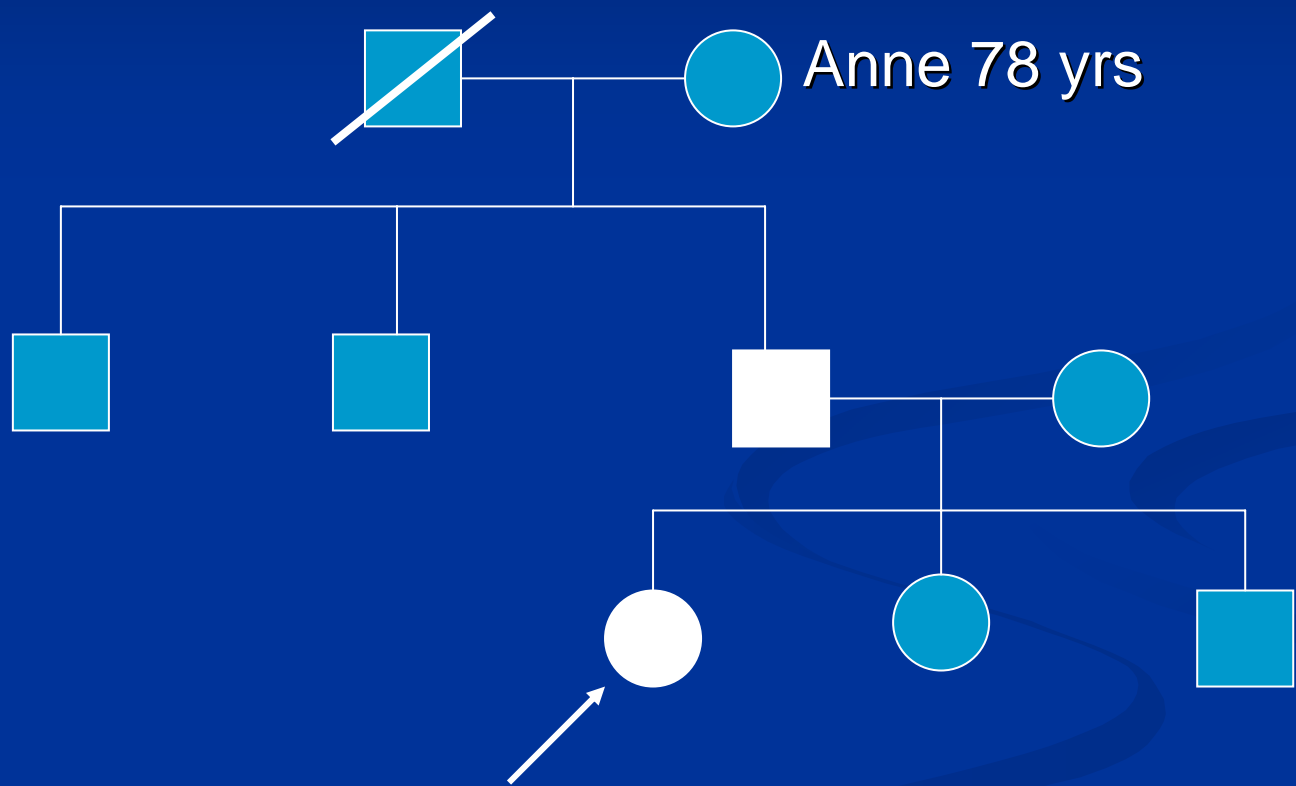


↗ Jenny 15

Vitreous haemorrhage

Could Jenny and Peter have the same disorder?

- vHL Mutation analysis performed
- Whole gene deletion of vHL identified in Jenny and Peter
- Testing offered to rest of family

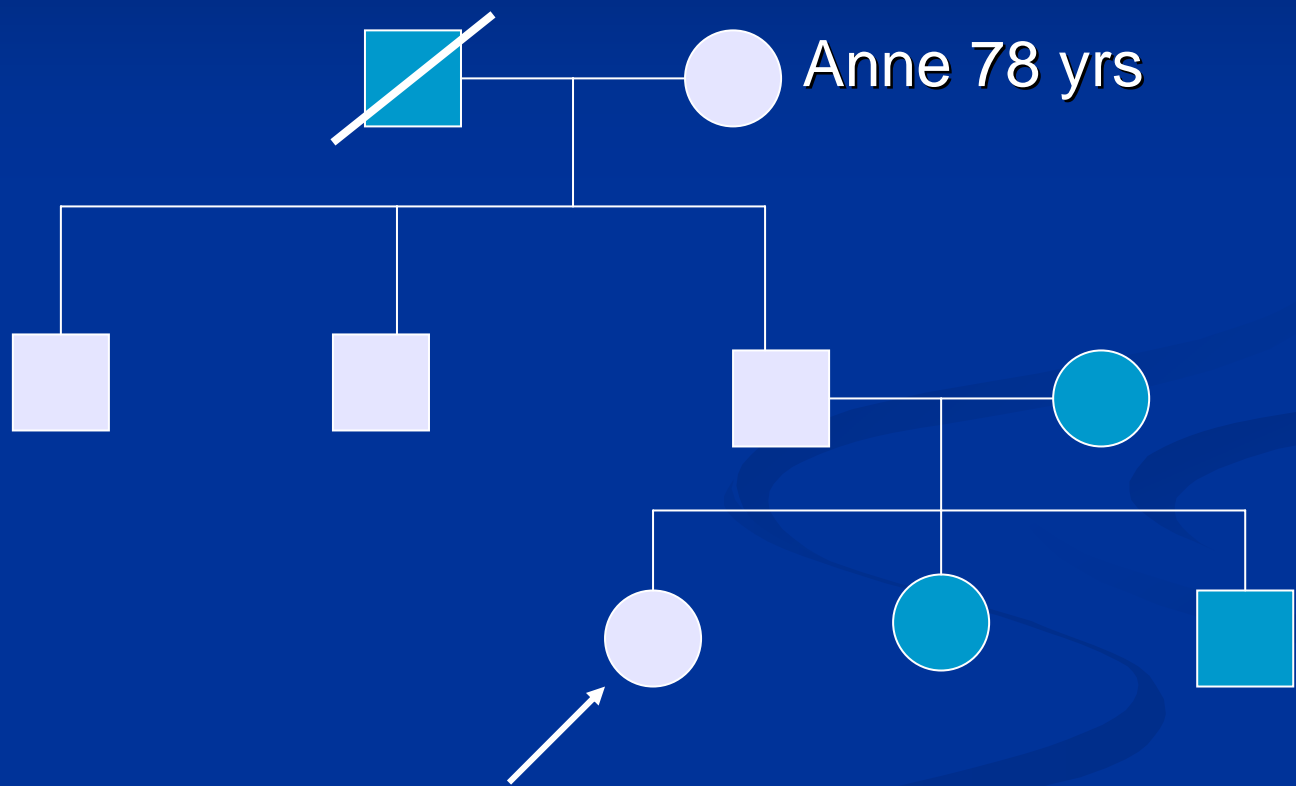


Von Hippel Lindau Disease

- Affects 1 in 35,000 individuals
- Penetrance high
- Associated with a wide variety of tumours,
 - retinal angiomas (60%)
 - haemangioblastomas
 - (cerebellar 60%, spinal 25% and brainstem 18%)
 - renal cell carcinoma (28%)
 - phaeochromocytoma (15%).

vHL Gene

- vHL protein suppresses tumour growth and downregulates angiogenic factors.
- ~ 90% individuals with clear diagnosis of vHL will have mutation identified



Screening regimen for vHL (yearly)

Ages 5-18

Eye/retinal examination

24 hour urine collection for catecholamines

Ages 18-65

Eye/retinal examination

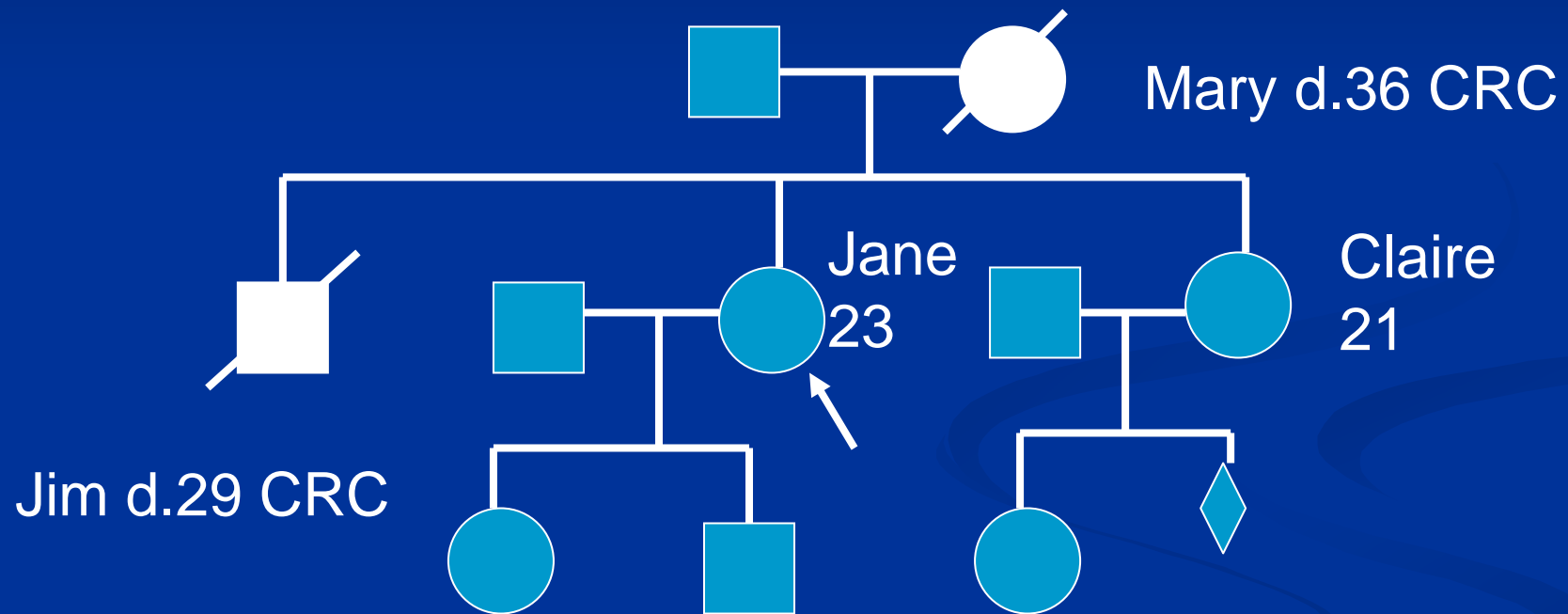
Physical examination

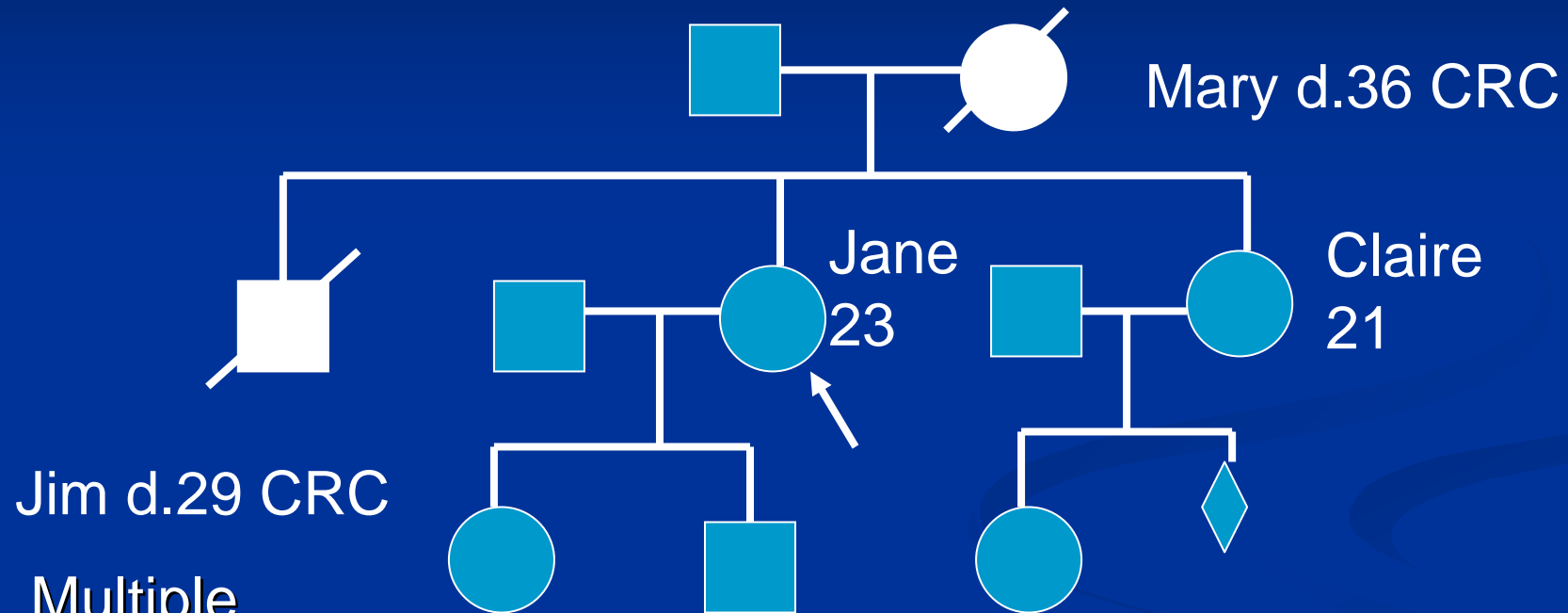
24 hour urine collection for catecholamines

MRI of abdomen

MRI of brain and spine (2-3 yearly)

Family history of colorectal cancer





Jim d.29 CRC

Multiple
polyps

Colorectal
cancer with
hepatic
metastases

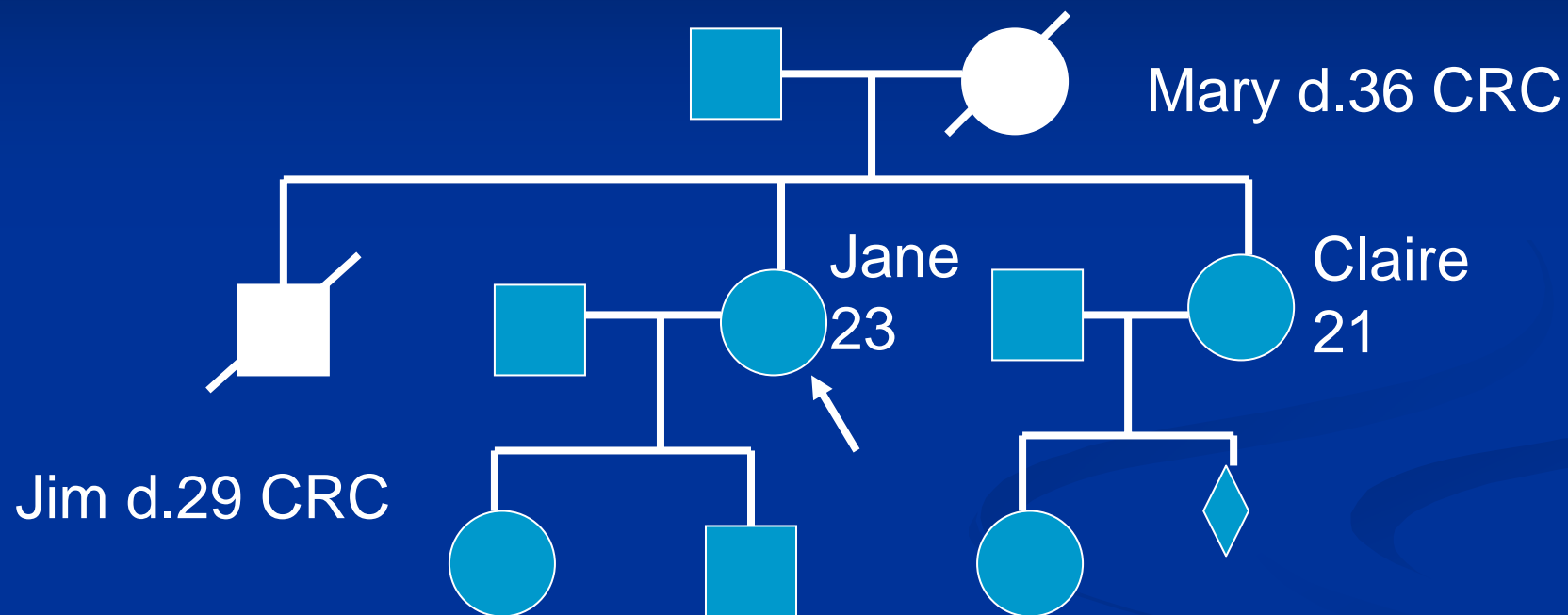
Familial Adenomatous Polyposis

- 1 in 10,000
- polyps develop during second decade
- colonic malignancies third decade
- Associated features
 - CHRPE
 - Desmoid tumours
 - Osteomas

APC mutations

- Majority truncating mutations
- Amino terminal - codon 157- attenuated FAP

Case 2



What are the counseling issues for Jane?

Issues for Jane

- What is her risk of being affected?
- How can you clarify her status?
- What screening should be offered?
- Can prenatal diagnosis be offered?