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

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Aims of the lecture

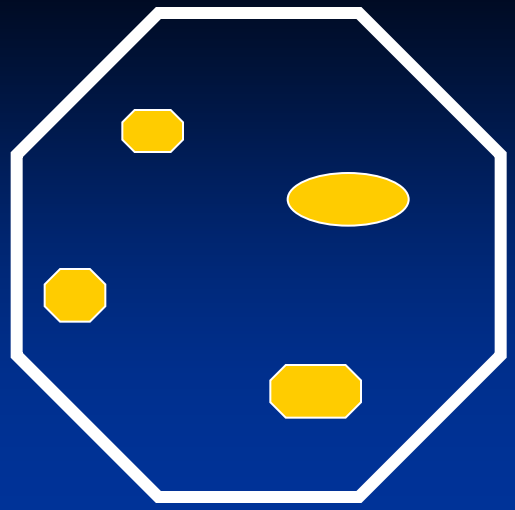
- Review 2-hit hypothesis for tumour development
- Present characteristic features of 3 inherited cancer syndromes
  - Neurofibromatosis type 1
  - Familial Adenomatous Polyposis
  - Von Hippel Lindau Disease
- Discuss “screening” for early cancers

Cancer

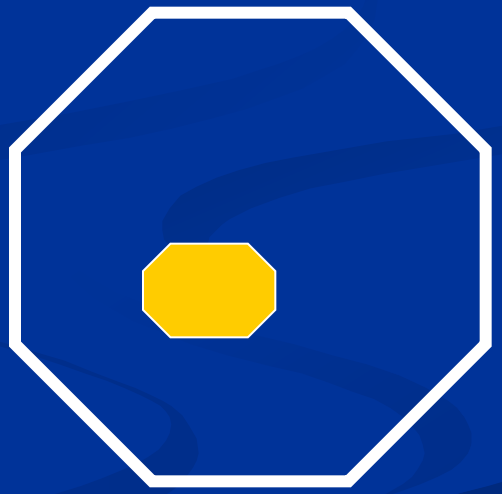
- Is common
- Involves genetic change
- Is rarely inherited

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



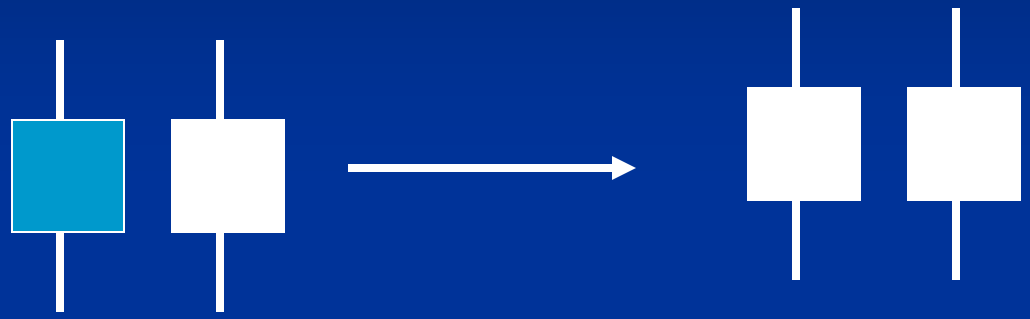
Germline RB1 mutation carrier



No germline mutation

Knudson's 2-hit hypothesis

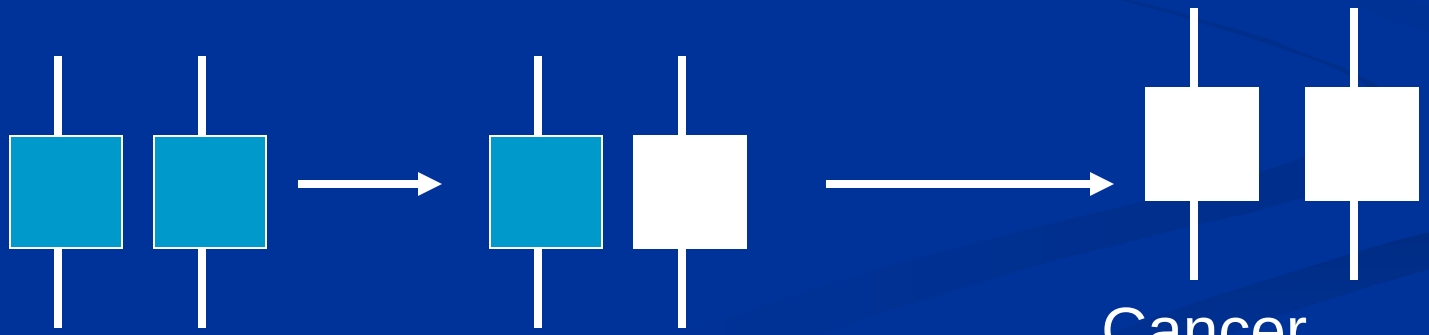
Mutation carrier



Normal tissue

Cancer

Sporadic Cancer



Normal tissue

Cancer

Tumour Suppressor Genes

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

Molecular testing & Screening

- 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
- Risk of non-ocular tumors – lifestyle advice

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
    - Can present 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%

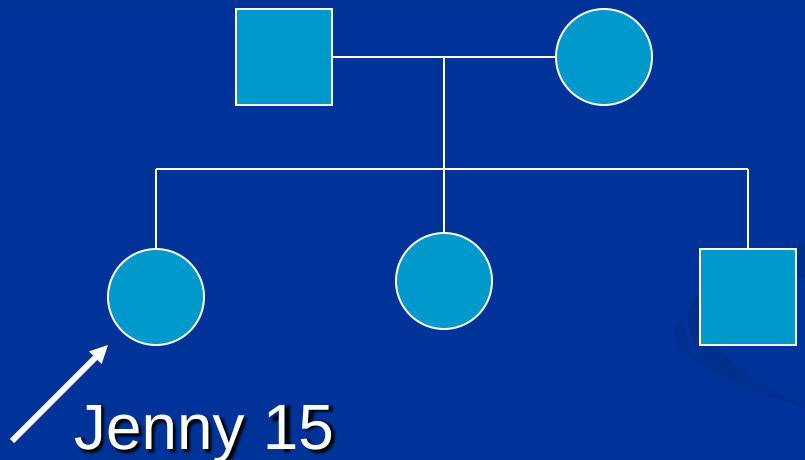
NF1

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

Genetic counselling issues

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

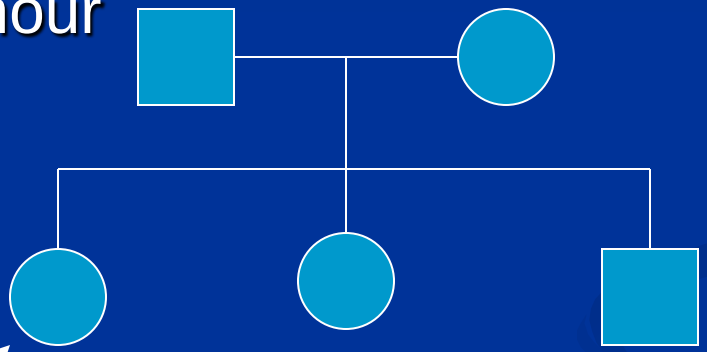
Ophthalmological referral



Vitreous haemorrhage

Peter aged 42

Radiotherapy for brain tumour

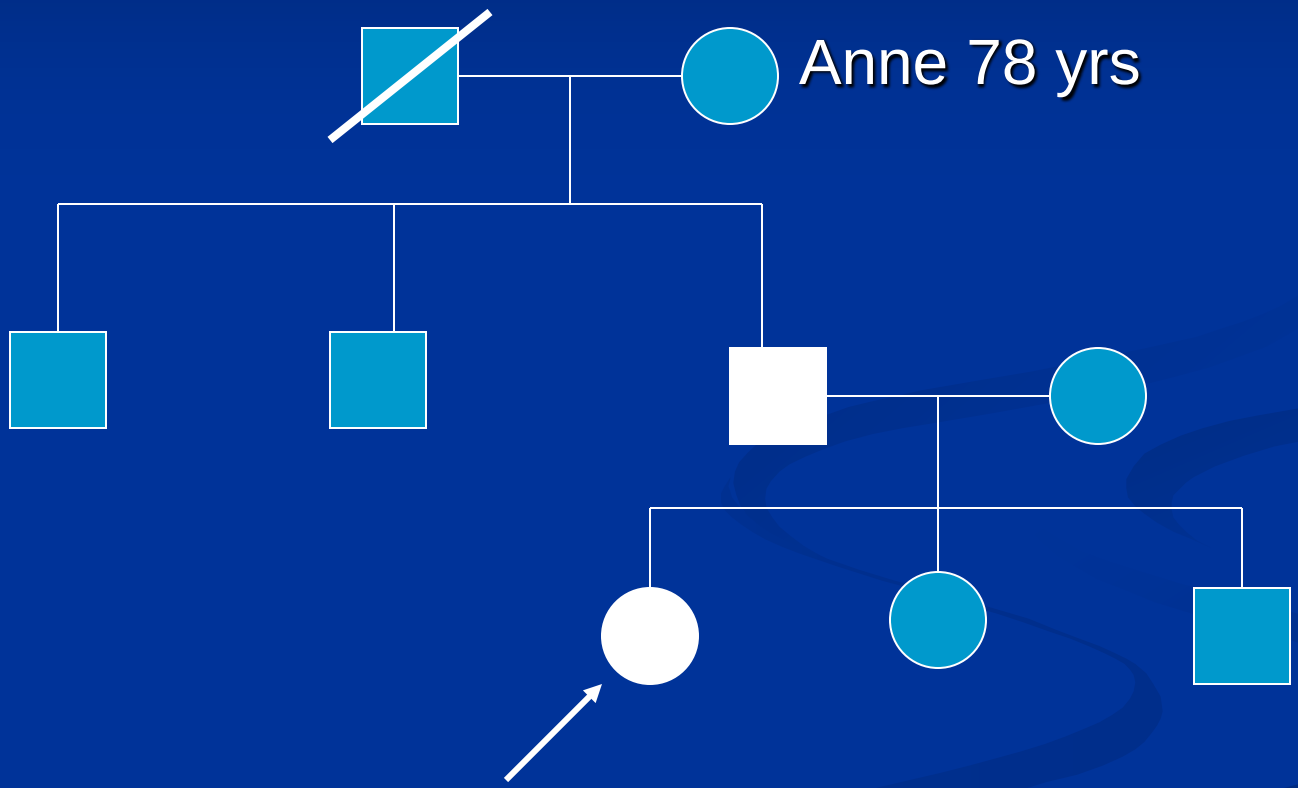


Jenny 15

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


Anne 78 yrs

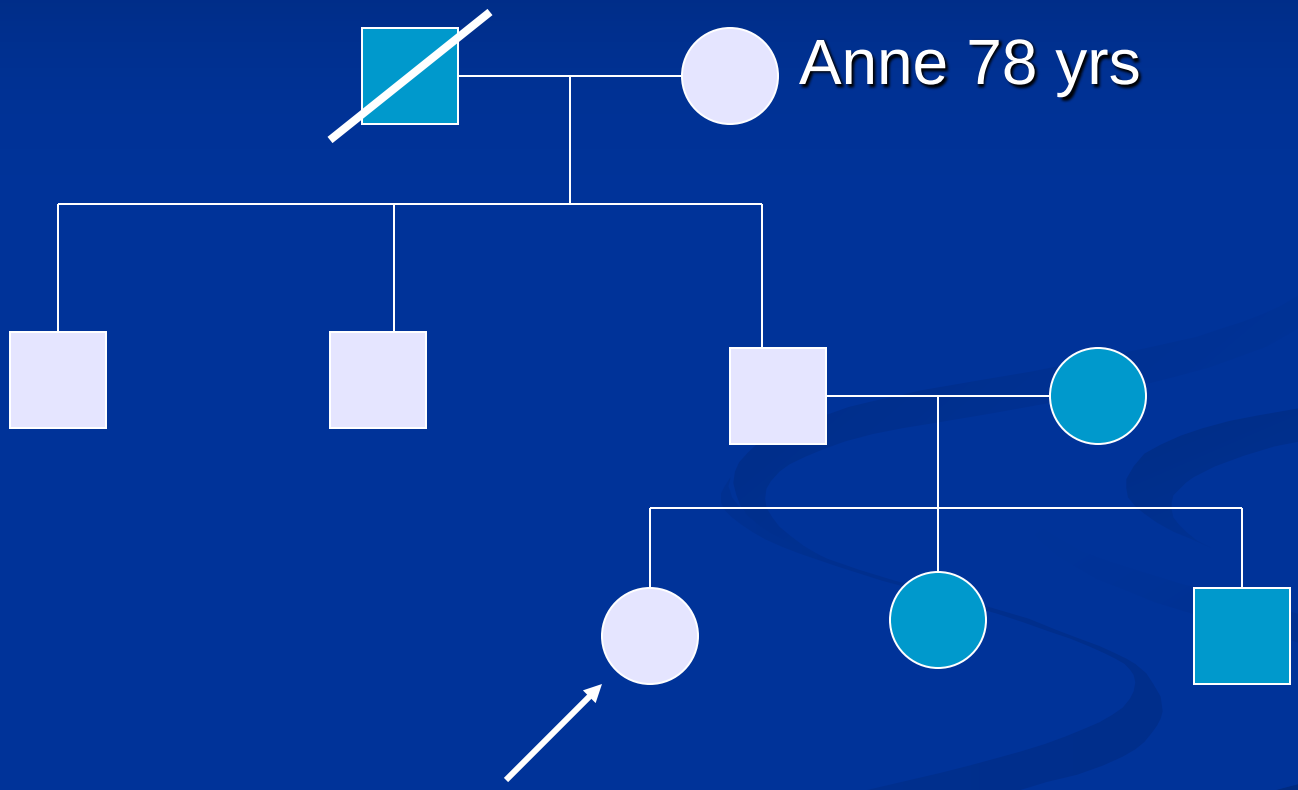
Von Hippel Lindau Disease

- 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


Anne 78 yrs

Screening regimen for vHL (yearly)

Ages 5-18

Eye/retinal examination

24 hour urine collection for catecholamines

Ages 18-65

Eye/retinal examination

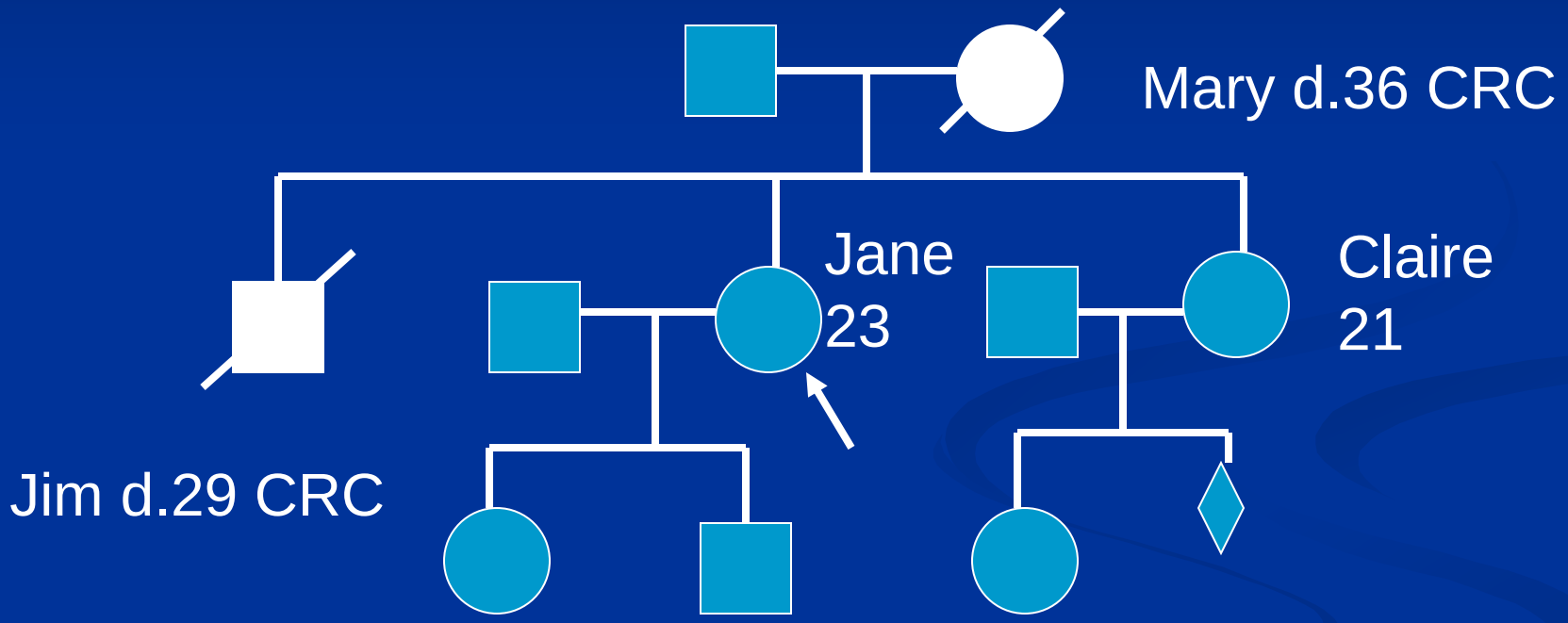
Physical examination

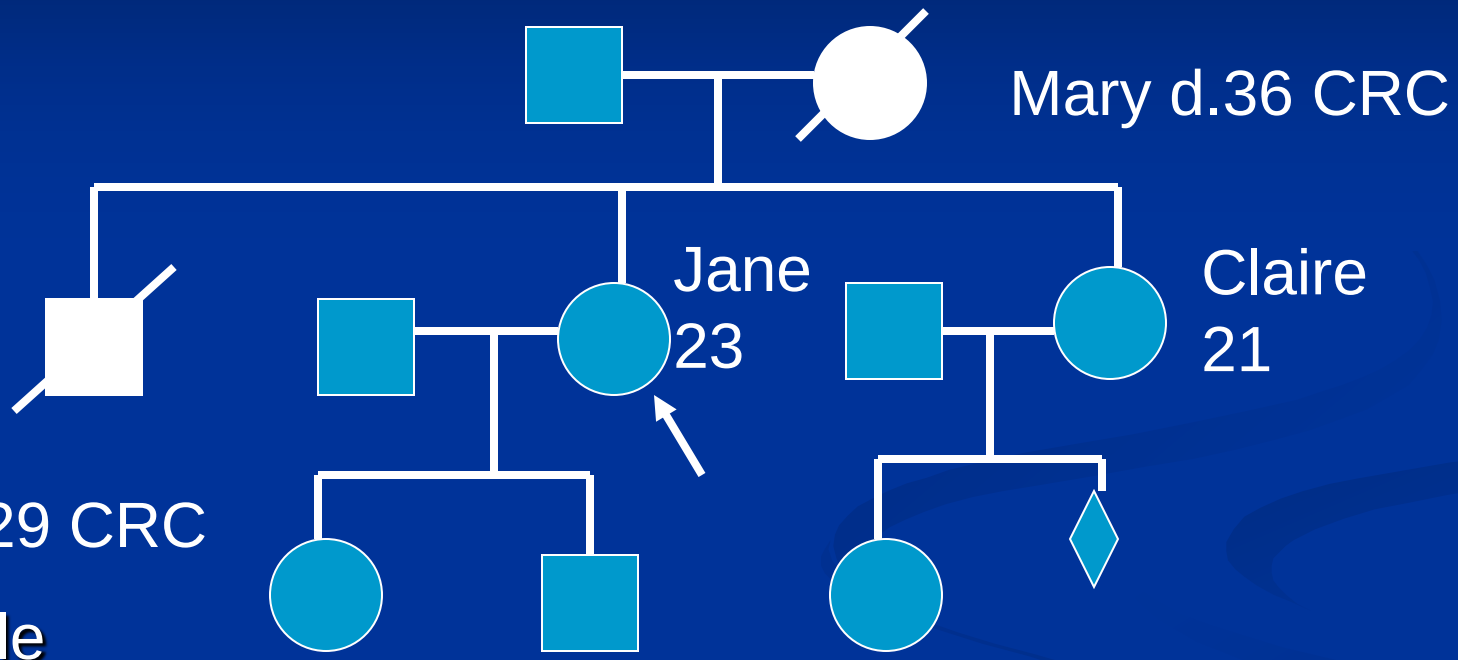
24 hour urine collection for catecholamines

MRI of abdomen

MRI of brain and spine (2-3 yearly)

Family history of colorectal cancer





Multiple polyps

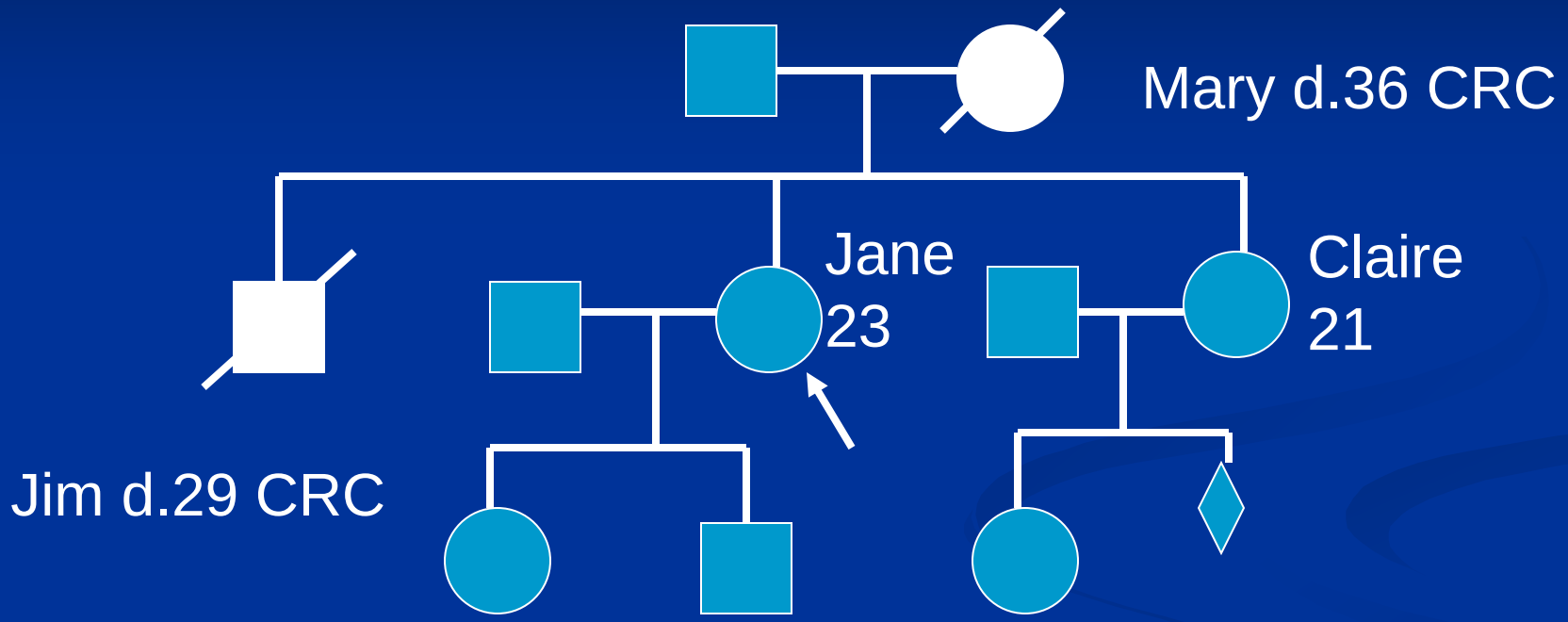
Colorectal cancer with hepatic metastases

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



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?

Summary

- Cancer involves genetic change but is rarely inherited
- Knudson's two-hit hypothesis can explain tumour development
- Tumour suppressor genes follow the two-hit hypothesis
- Screening protocols exist for patients with inherited cancer syndromes