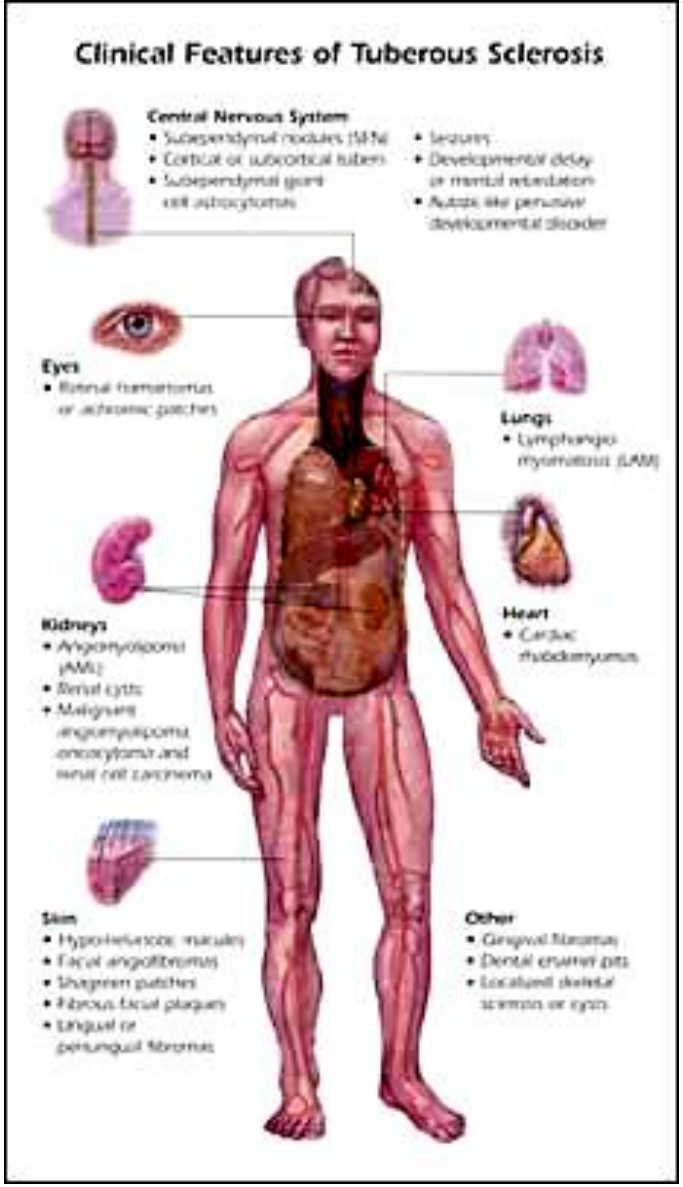
The Genetics of TSC, accessing genetic services and support

Professor Martin Delatycki

Director, Clinical Genetics

Tuberous Sclerosis

- 1:5000 of those < 5 years
- 1:25 000 of all ages



Austin Health

Major Features

- Facial angiomas of forehead plaques
- Nontraumatic ungual or periungual fibroma
- >3 hypomelanotic macules
- Shagreen patch
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features

- Multiple pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter migration lines
- Gingival fibromas
- Nonrenal hamartomas
- Retinal achromic patch
- “Confetti” skin lesions
- Multiple renal cysts

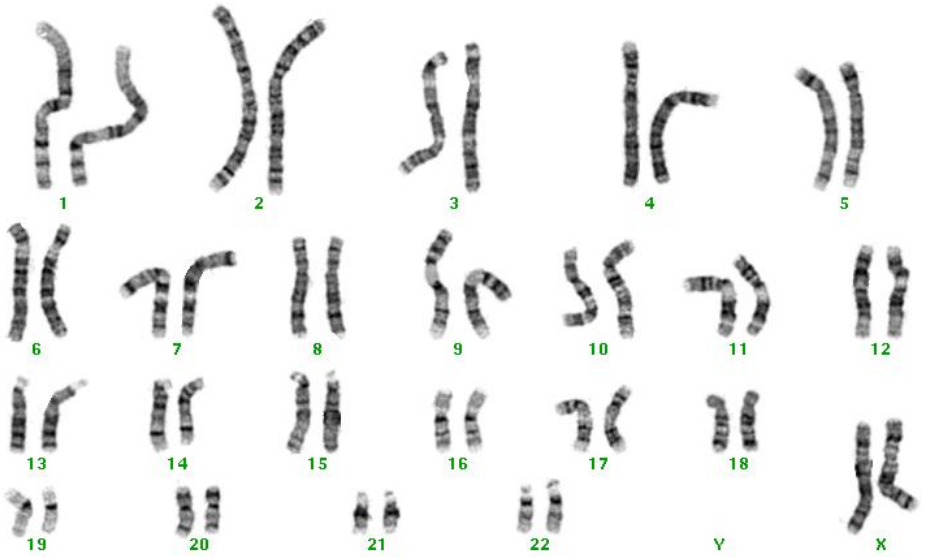
Diagnostic Criteria

- Definite TS
  - 2 major OR 1 major + 2 minor
- Probable TS
  - 1 major + 1 minor
- Possible TS
  - 1 major OR 2 minor

A Brief Lesson in Genetics

- Genes are inheritance particles
- ≈25,000 pairs
- Lie on 23 pairs of chromosomes
- X and Y- sex chromosomes
- Males- XY
- Females- XX

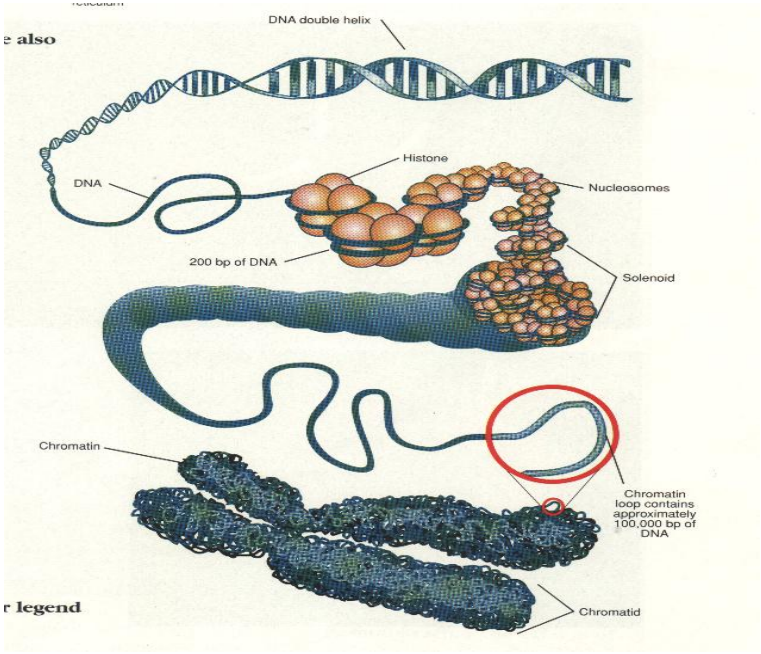
Human Chromosomes



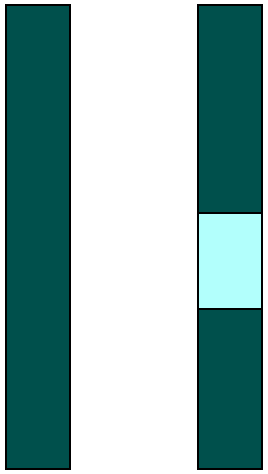
Genes

- Made up of DNA
- A, C, G, T
- 3 make up the code for an amino acid
- ACG GAA TCT ……
- Amino acids joined to make proteins
- Genes encode proteins
- Human genome (entire set of instructions) contains 3 billion bp of DNA

Genes, DNA and Chromosomes



Autosomal Dominant

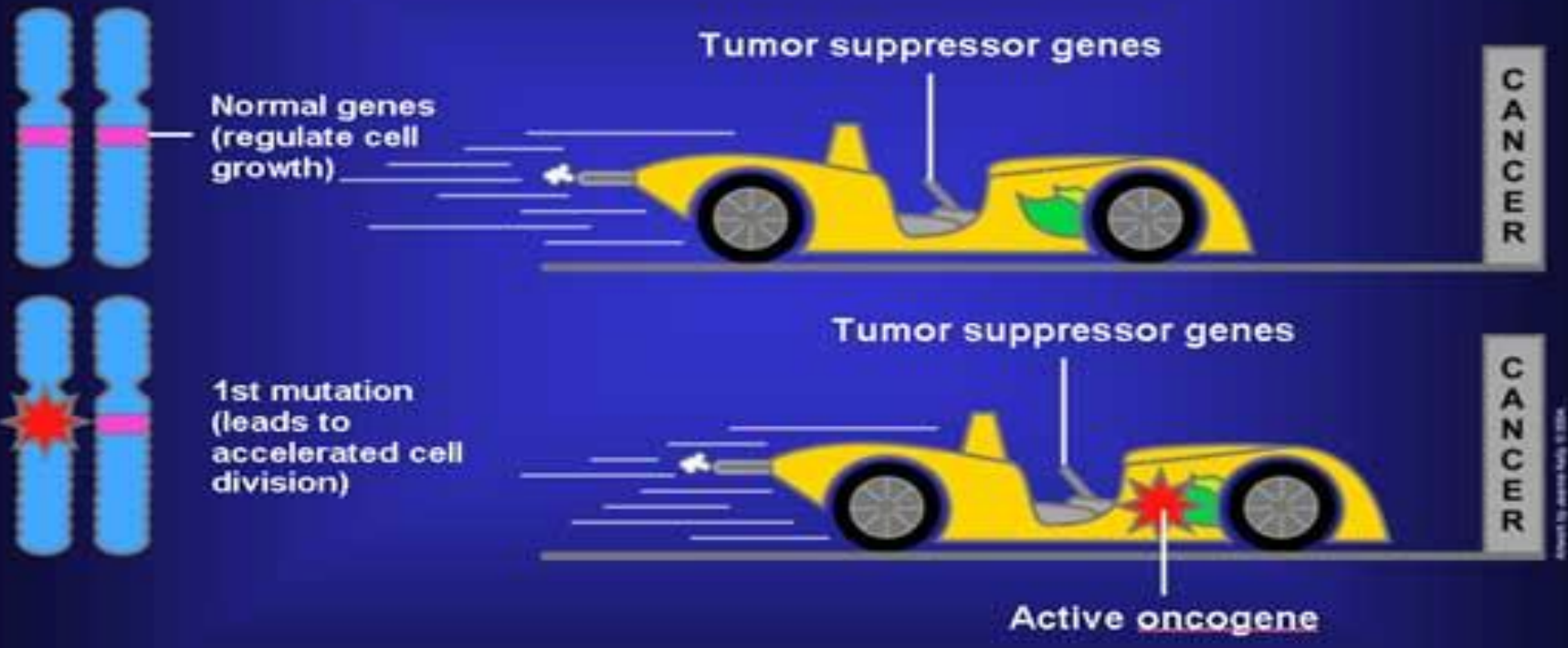


50:50 risk that offspring will inherit the faulty gene

Genetics of tuberous sclerosis

- Autosomal dominant
- 2/3 sporadic, 1/3 inherited
- 2 genes
- TSC1- 9q34
- TSC2- 16p13.3
- Tumour suppressor genes

Tumor Suppressor Genes



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Testing

Gene	% of Probands with Definite TSC and an Identifiable Mutation in This Gene	Mutation Detection Frequency by Gene, Family History, and Test Method	
		Familial Cases	Simplex Cases
TSC1	~31%	~30%	~15%
TSC2	~69%	51%	~60%-70%

Genetics

- Mutations tend to cluster but the majority are family specific
- ~US$2000
- Mutation found in about 85%

Genetic Counselling

- Parent with TS
- 50% risk to offspring
- If affected ~50% chance intellectual disability therefore ~25% risk intellectual disability
- 75% risk epilepsy

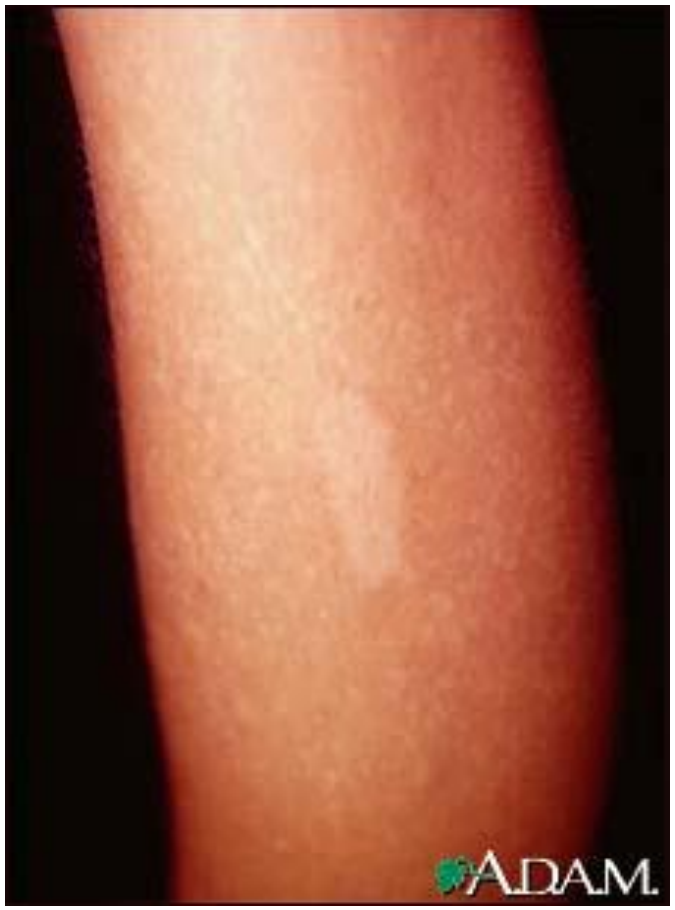
Genetic Counselling

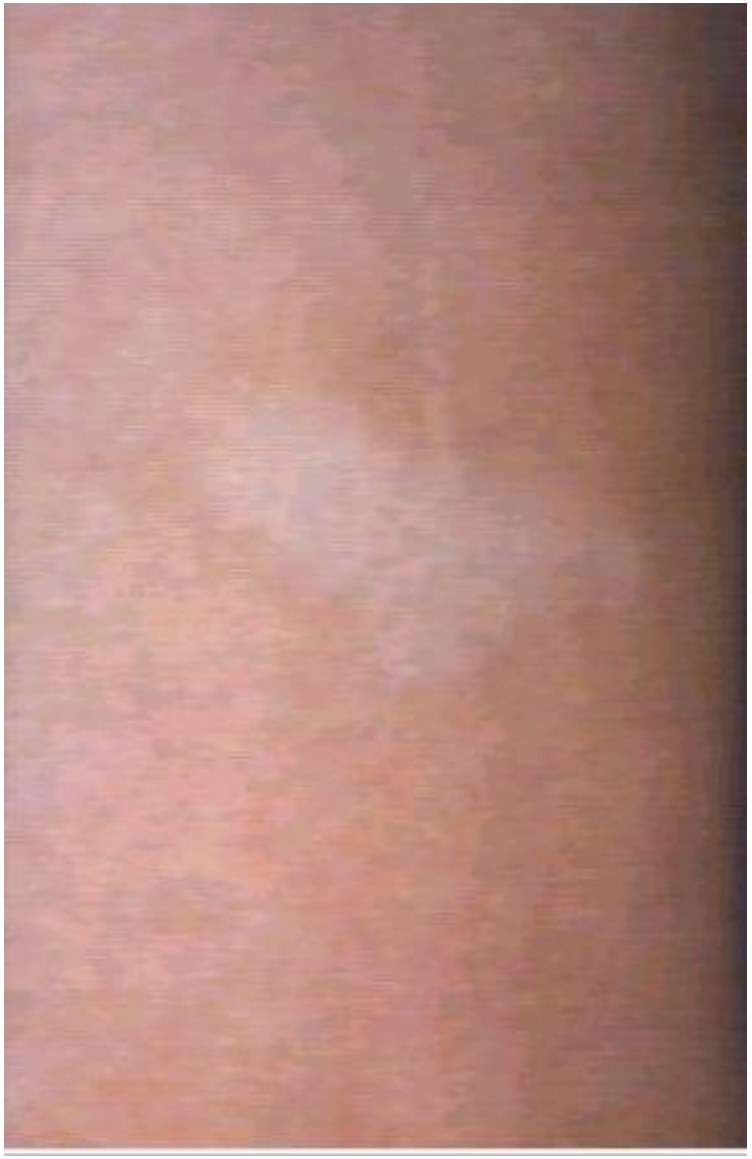
- Apparent sporadic case
- MUST assess parents
  - Skin examination including Woods lamp
  - CT ± MRI brain
  - Kidney ultrasound
  - Eye examination
- If normal, recurrence risk 2% (gonadal mosaicism)

Mosaicism

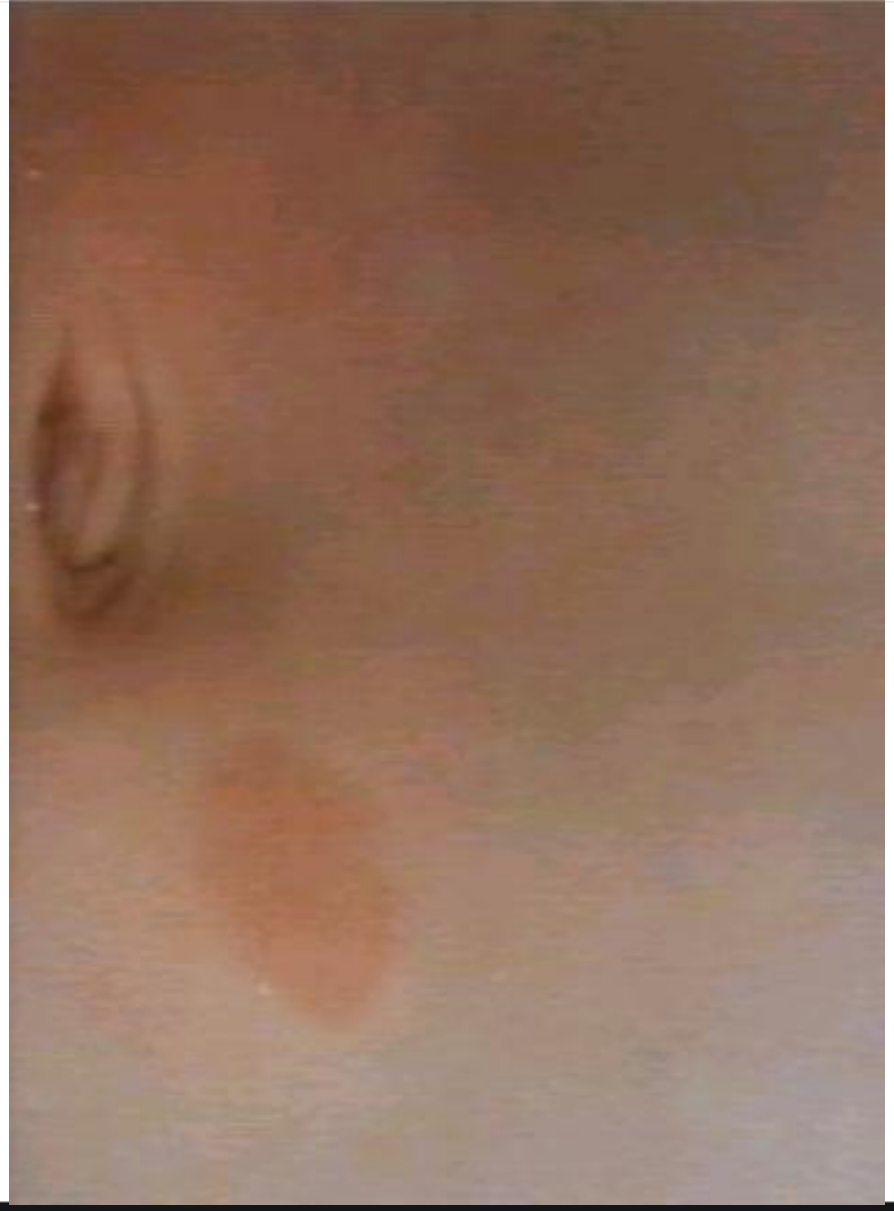
- Mutation present in some cells but not others
- Somatic mosaicism = mutation present in some cells of body but not others- one explanation for mild symptoms- affects ~1% of people with TS
- Gonadal mosaicism = mutation present in some germ cells (eggs, sperm) but not in other body cells- can result in unaffected parents having > 1 affected child- rare

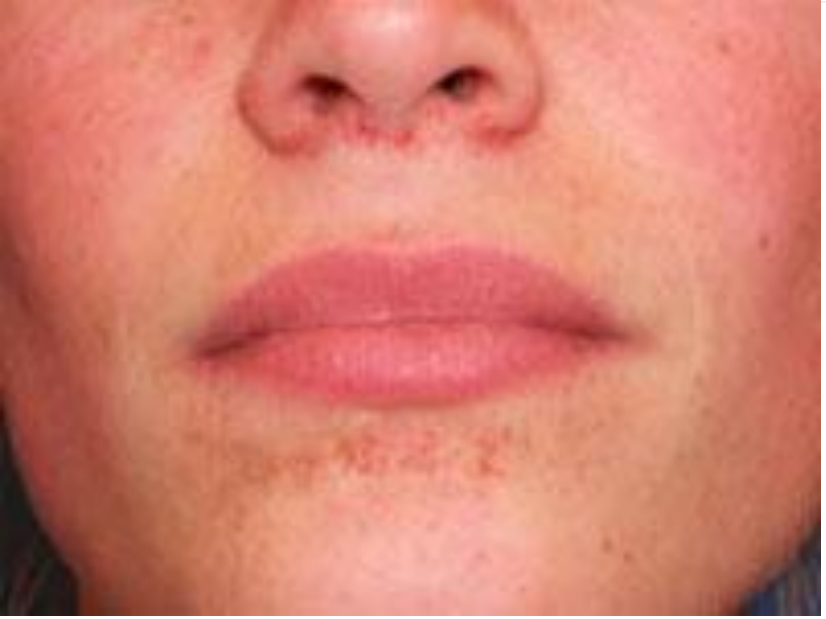
Depigmented patches

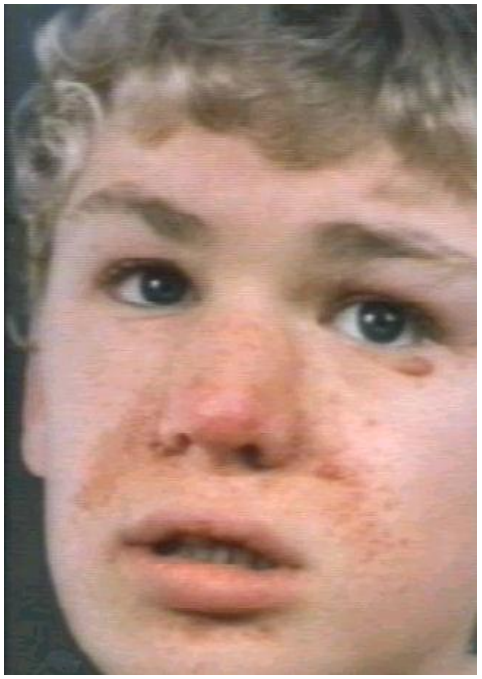


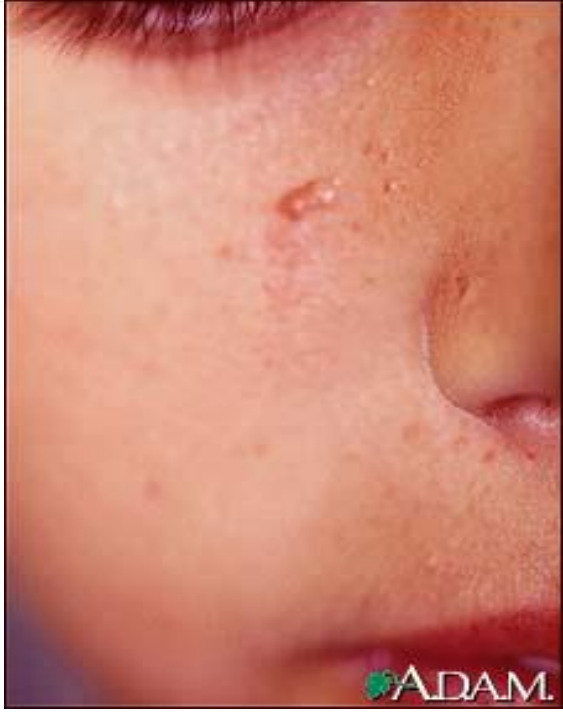


Hyperpigmented macule= café au lait

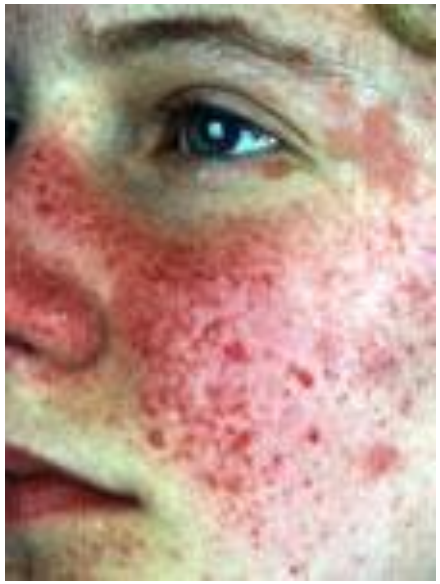




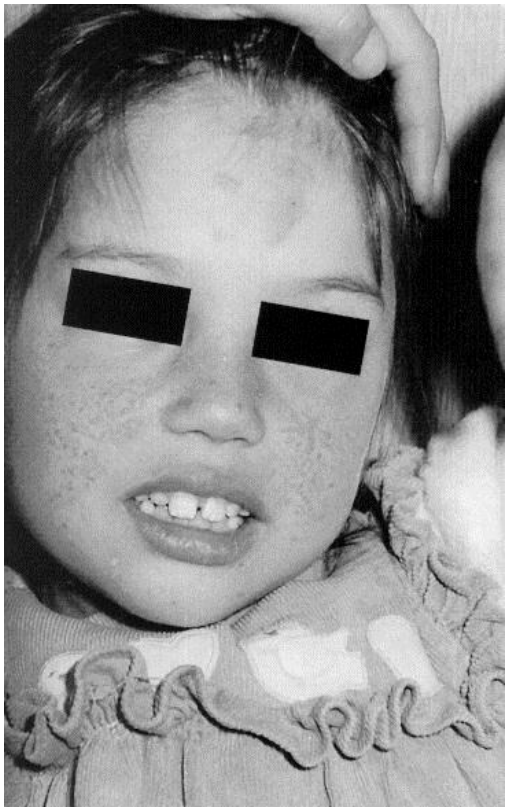


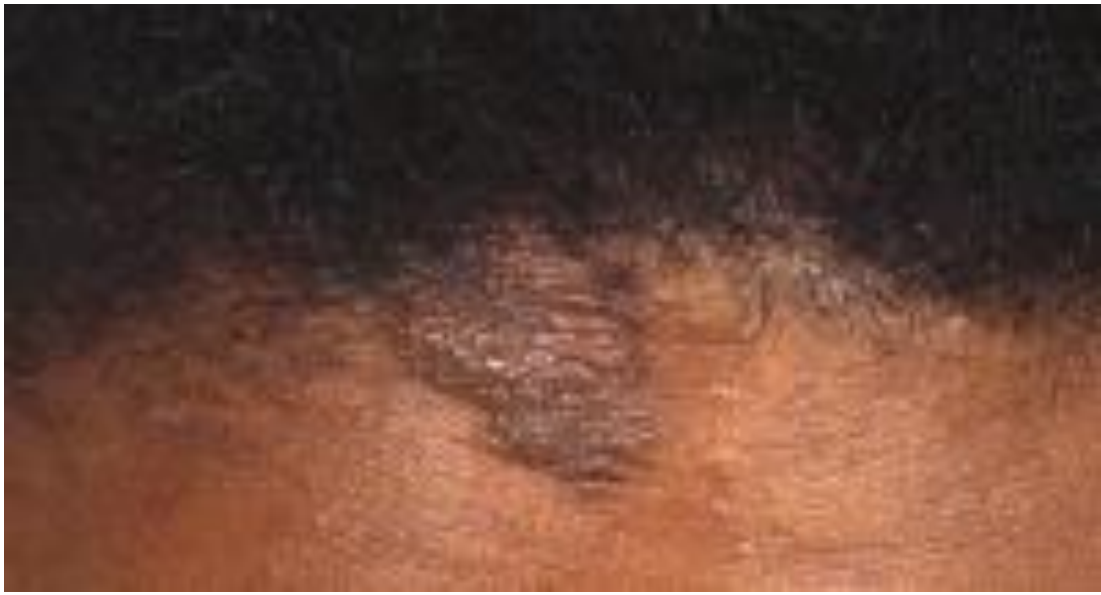


Adenoma Sebaceum

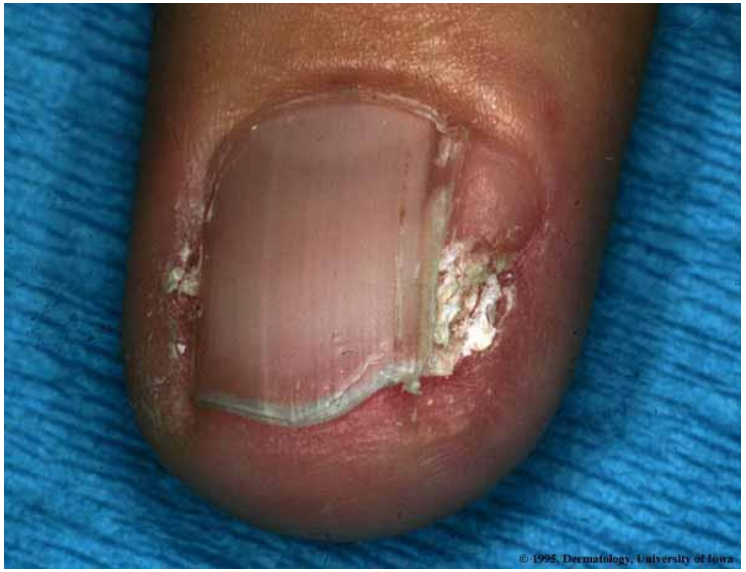


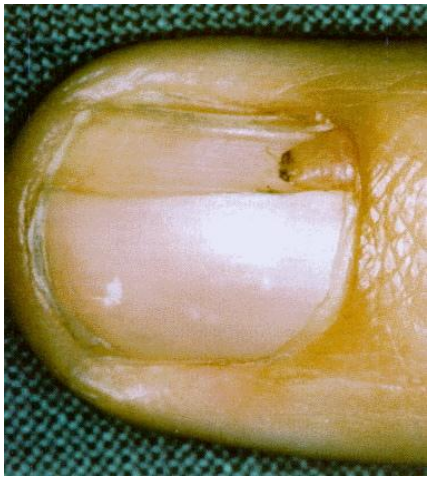
Forehead plaque

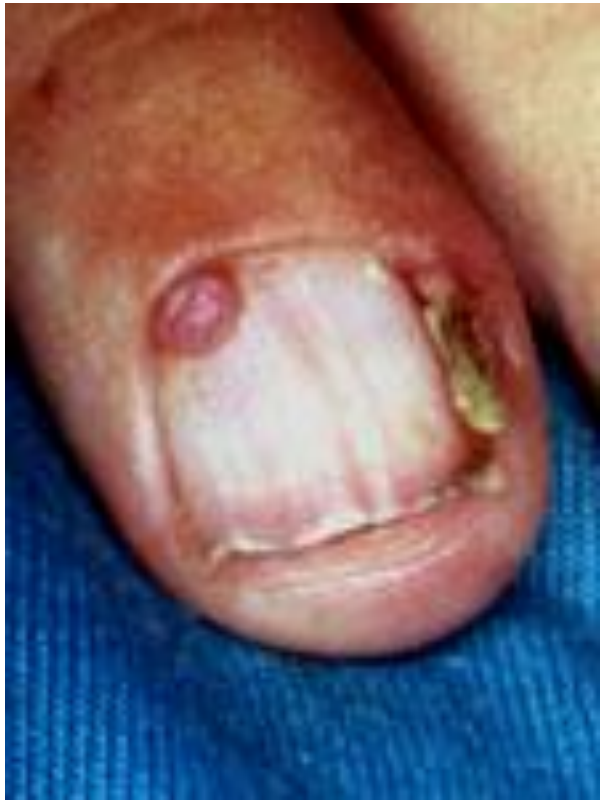




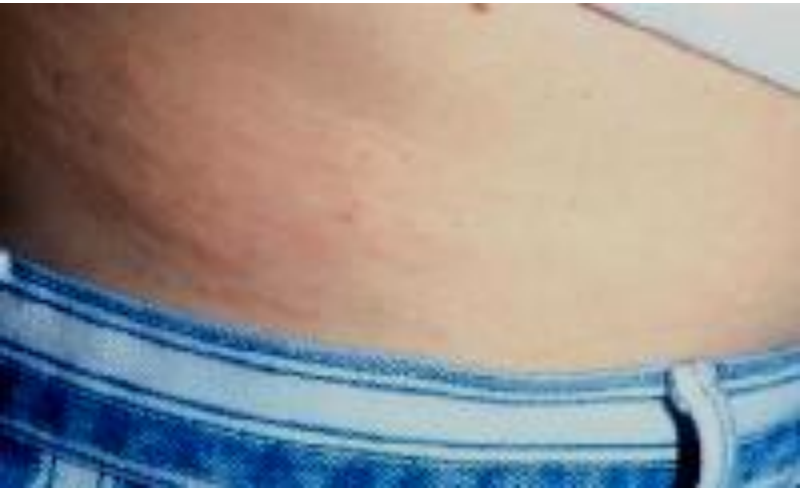
Periungual Fibroma

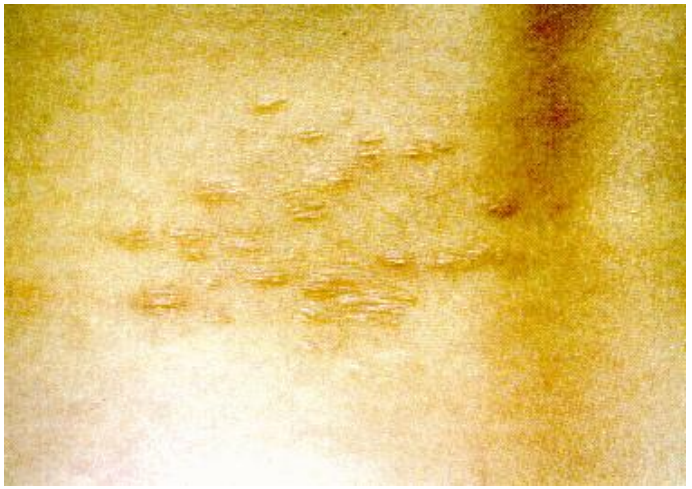


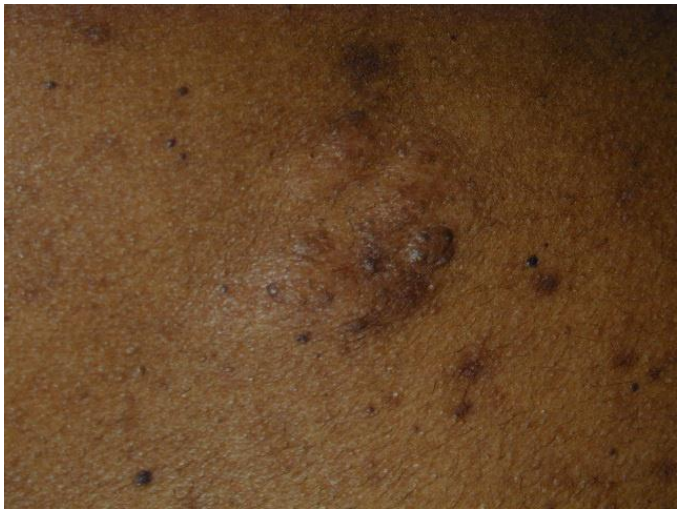




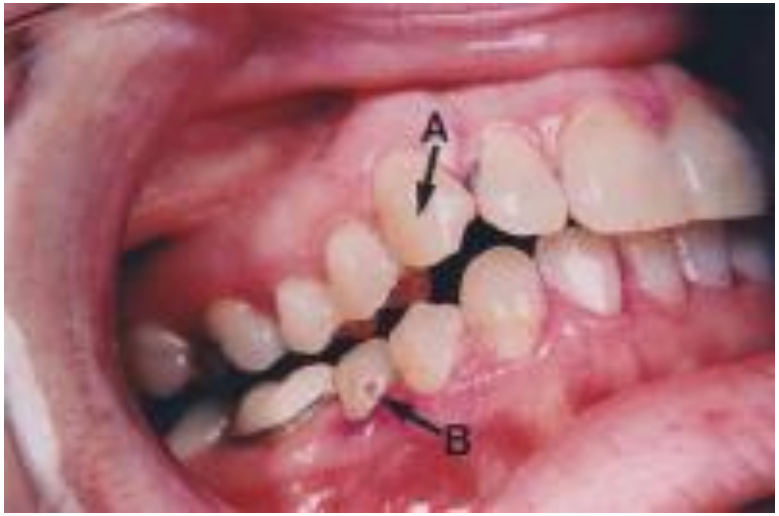
Shagreen Patch

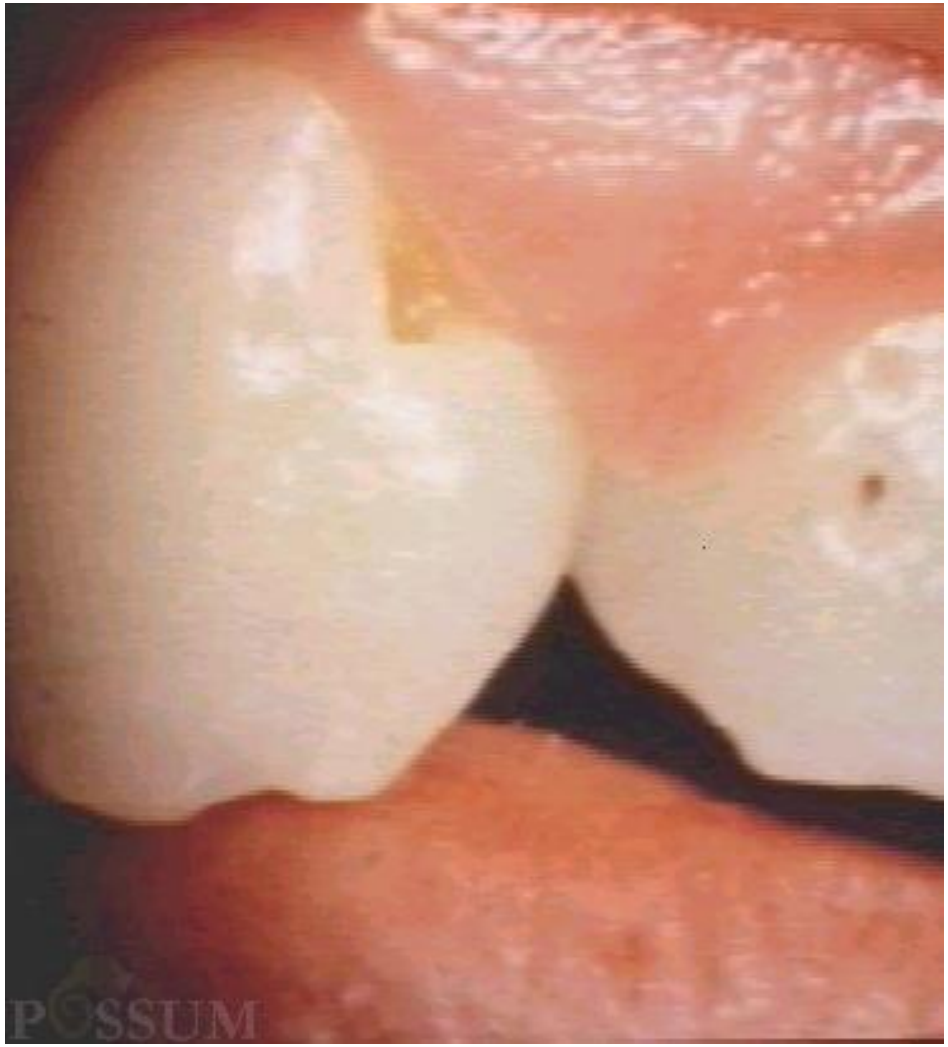






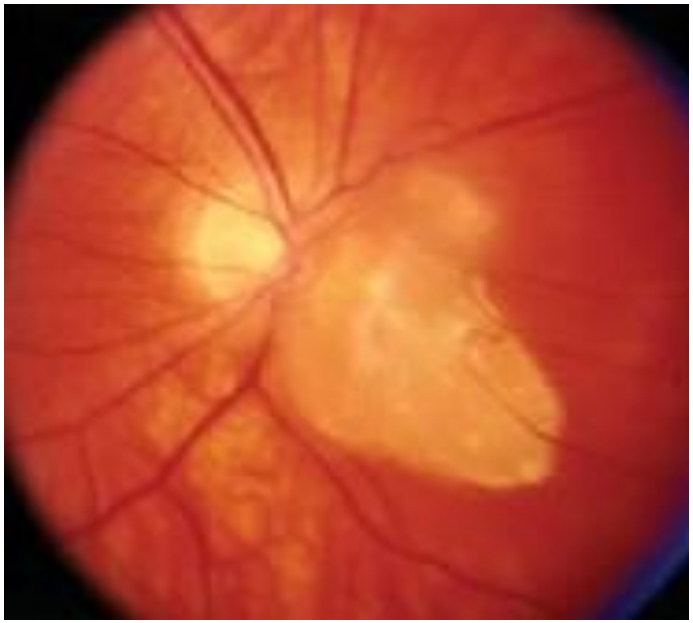
Enamel pits



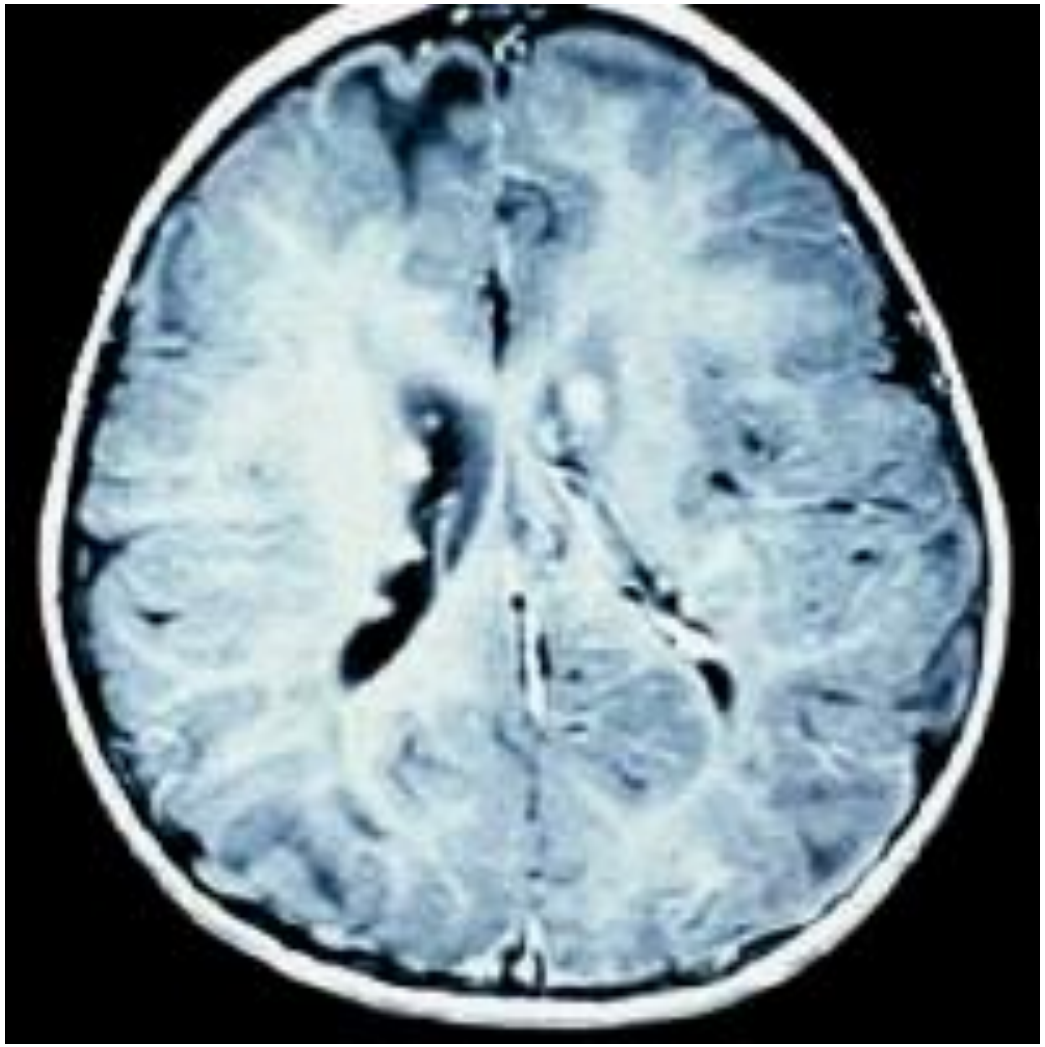


Eyes

- Retinal phakoma- rarely affect vision
- Retinal Hamartoma = “mulberry” lesions

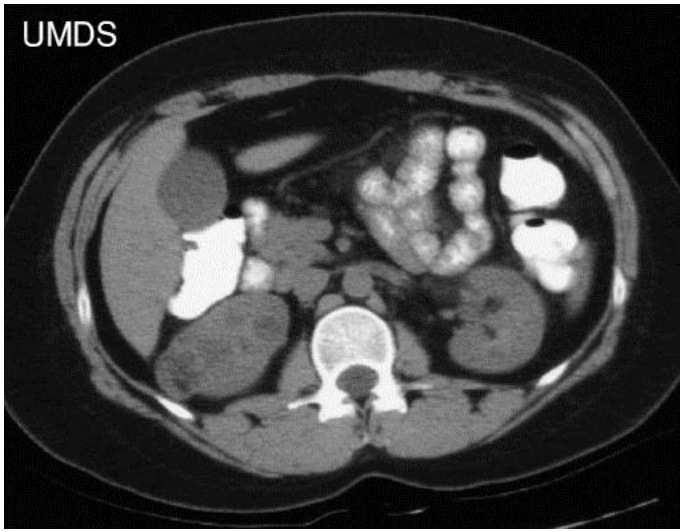


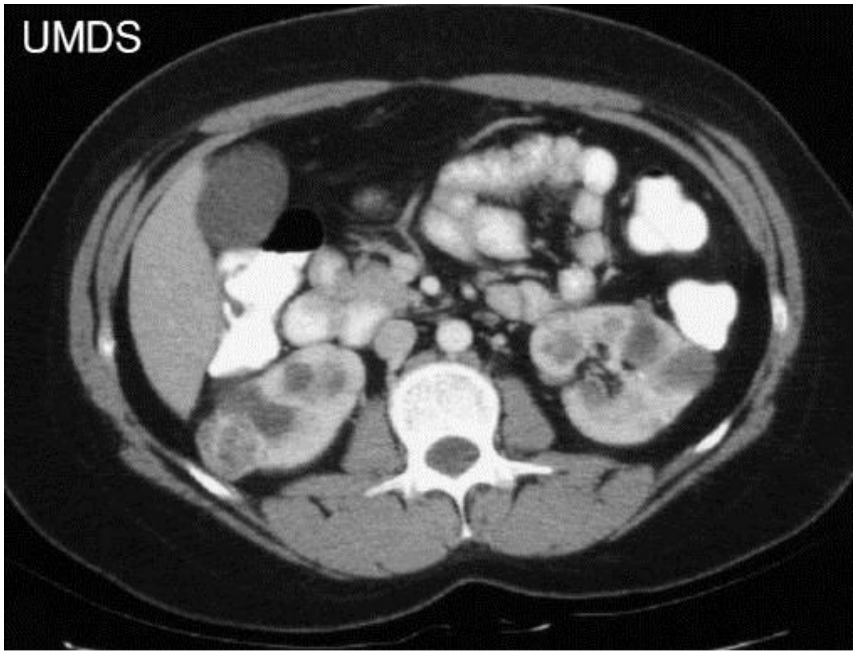
MRI showing a tuber and subependymal nodules



Multiple simple cortical cysts in both kidneys

Heterogeneous, solid 2.5 cm mass in right lower pole, which contains areas of fat density





Genetic Counselling

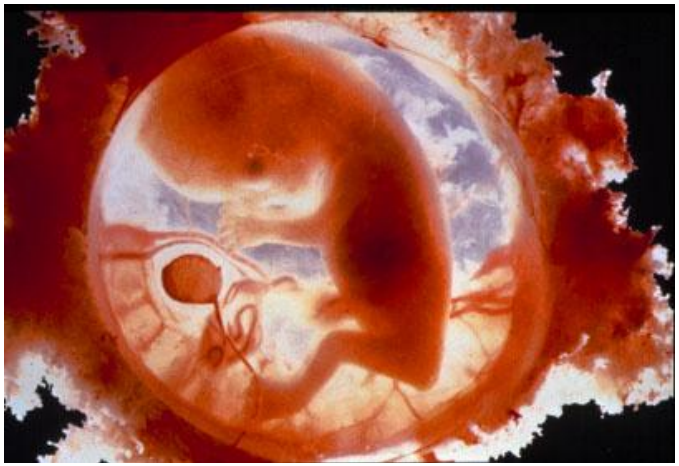
- Genetic testing generally only done when there is a request for prenatal or preimplantation diagnosis

- Rarely needed to make the diagnosis

Reproductive options

- No children
- Take chance
- CVS
- PGD
- Donor sperm, egg, embryo
- Adoption

Chorion Villous Sampling CVS

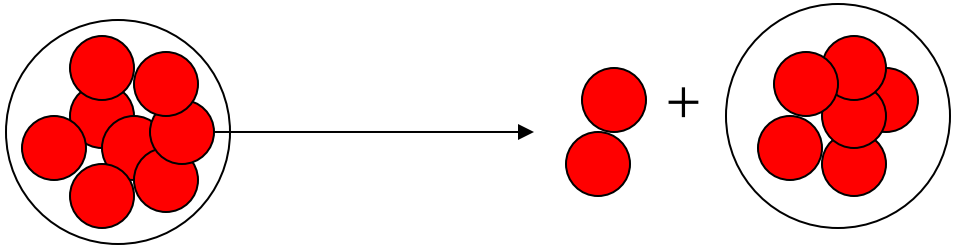


- 11-15 weeks
- Diagnosis
  - Chromosome abnorm.
  - DNA Studies
  - Biochemical studies
- 1:100 miscarriage
- Affected- option of pregnancy termination

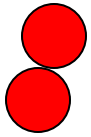
Preimplantation Genetic Diagnosis- PGD

- In the context of IVF
- Testing by removal of cells from an embryo
- Chromosomal abnormalities
- Selected single gene disorders
- Most common reason an objection to pregnancy termination
- No apparent increase in birth defects

PGD

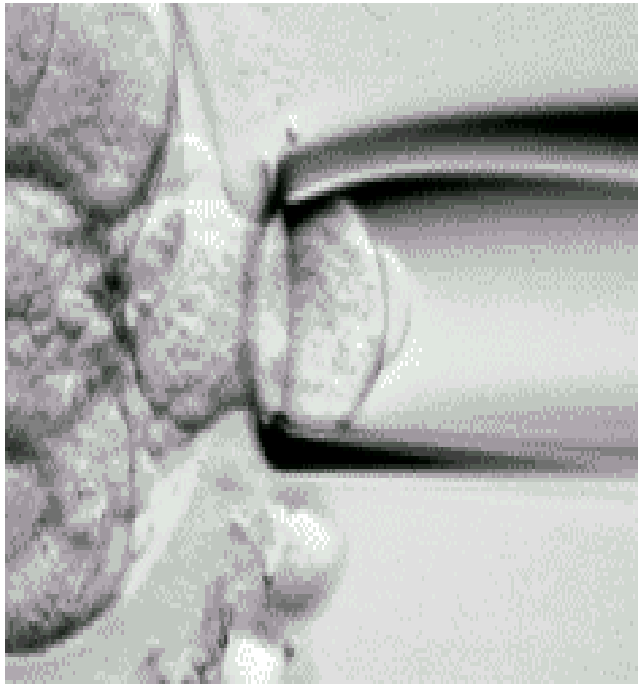


PGD



- DNA extracted and mutation detection testing done

Method of embryo biopsy



A hole is made in the outer shell of the embryo and 1 or 2 cells are removed.

The cell can then be fixed to a slide, or placed in solution to allow genetic analysis.

PGD for single gene disorders

- ~ 97% diagnostic accuracy
- ~20% pregnancy rate per cycle
- Cystic fibrosis most common indication
- Counselling by both Genetics and IVF team

Clinical Genetics in Australia

- Units in all states
- Some serve the whole state- Queensland, WA, SA, Tasmania
- Some have multiple units- Victoria, NSW
- Outreach clinics to major regional centres
- http://www.genetics.edu.au/