Genes & Disease

George Vassiliou

T82

Genes play a role in (nearly) all human diseases!

Increasing role of genes

Lead poisoning

Chickenpox

Diabetes

Schizophrenia

Cystic fibrosis

Myxomatosis!!!!!!

Talk outline

1. How can genes cause disease?
2. Mutations and Polymorphisms
3. Types of genetic inheritance
4. Monogenic Disorders
5. Polygenic disorders
6. Chromosomal disorders
7. Cancer

How can genes cause disease?

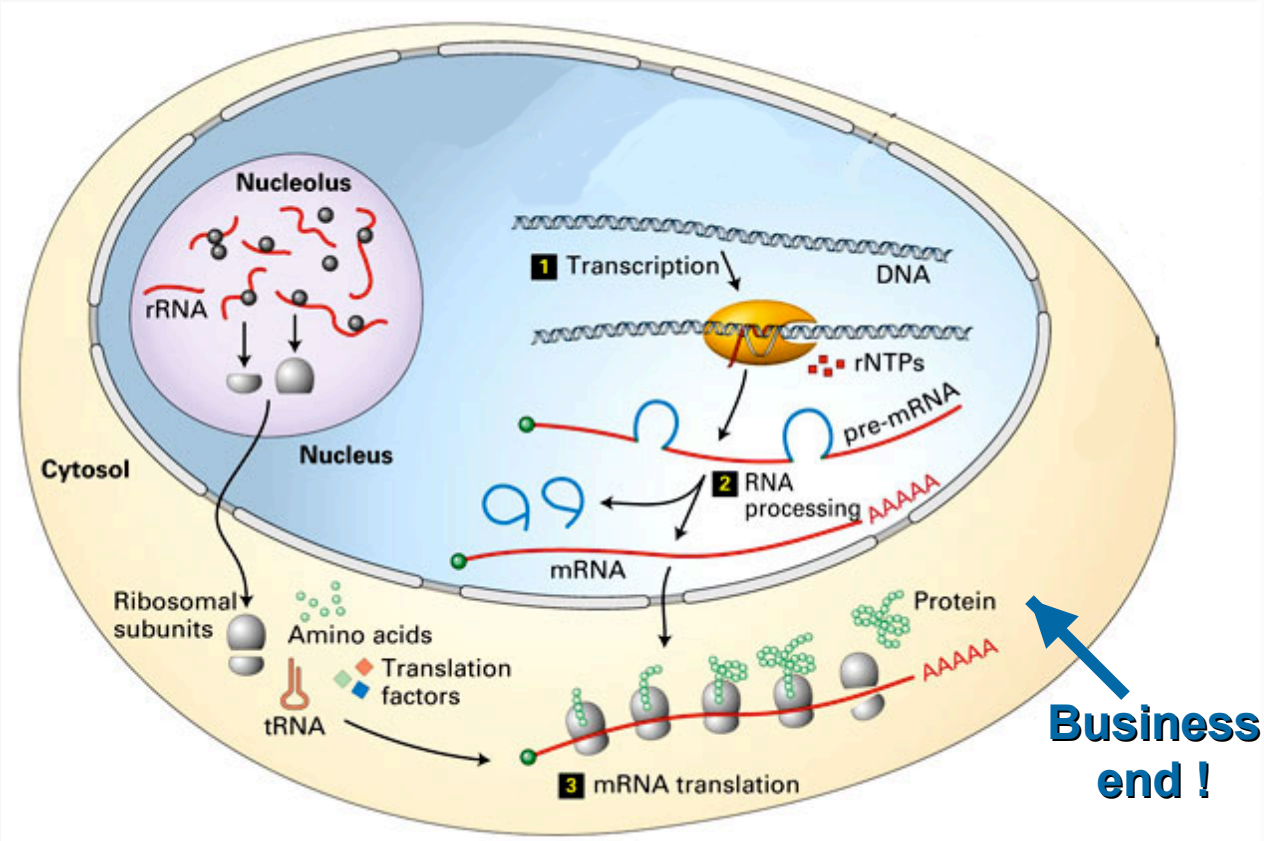
DNA

↓

RNA

↓

Protein



Changes in gene DNA and disease

1. Mutations

Rare variants in DNA code or copy number

Inherited or acquired during life

~ Defective forms of a gene (e.g. Cystic fibrosis mutation)

2. Polymorphisms

Common variants in DNA code or copy number

Always inherited

~ Normal versions of a gene (e.g. blue vs brown eyes)

Mutations and polymorphisms

```
DNA:      ACT CAT ATT TCA ATT TCA TCA ACT GAA GAA CCT TAA
PROTEIN:   T   H   I   S   I   S   S   T   E   E   P   *
```

Silent

```
DNA:      ACT CAT ATT TCA ATT TCA TCA ACT GAG GAA CCT TAA
PROTEIN:   T   H   I   S   I   S   S   T   E   E   P   *
```

Missense

```
DNA:      ACT CAT ATT TCA ATT TCA TCA ACT GAA GAA CTT TAA
PROTEIN:   T   H   I   S   I   S   S   T   E   E   L   *
```

Nonsense

```
DNA:      ACT CAT ATT TCA ATT TCA TAA ACT TAA GAA CCT TAA
PROTEIN:   T   H   I   S   I   S   S   T   *
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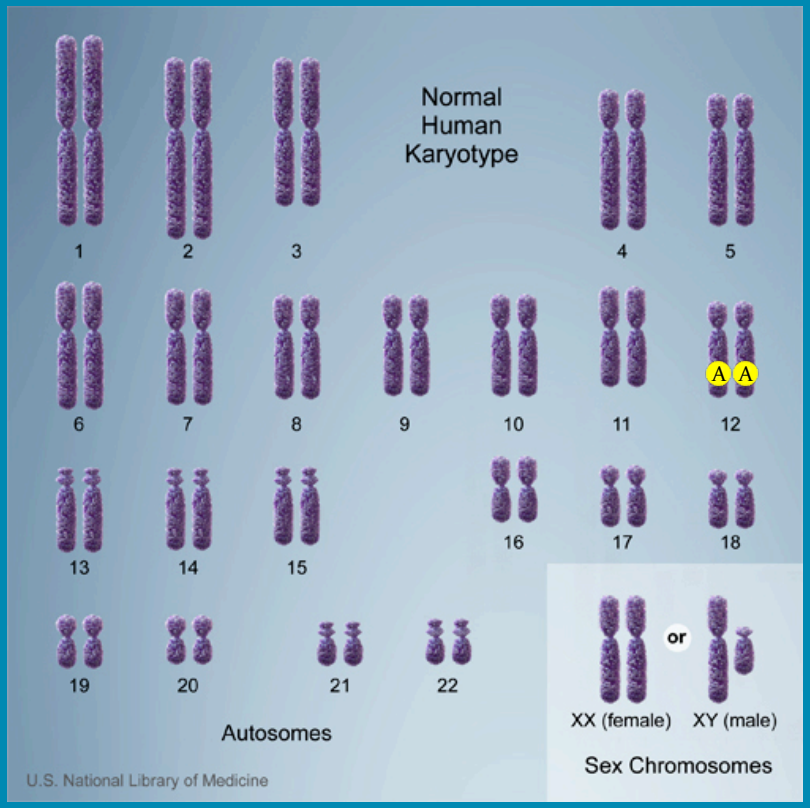
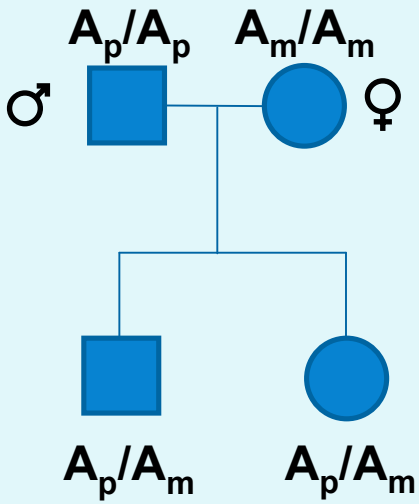
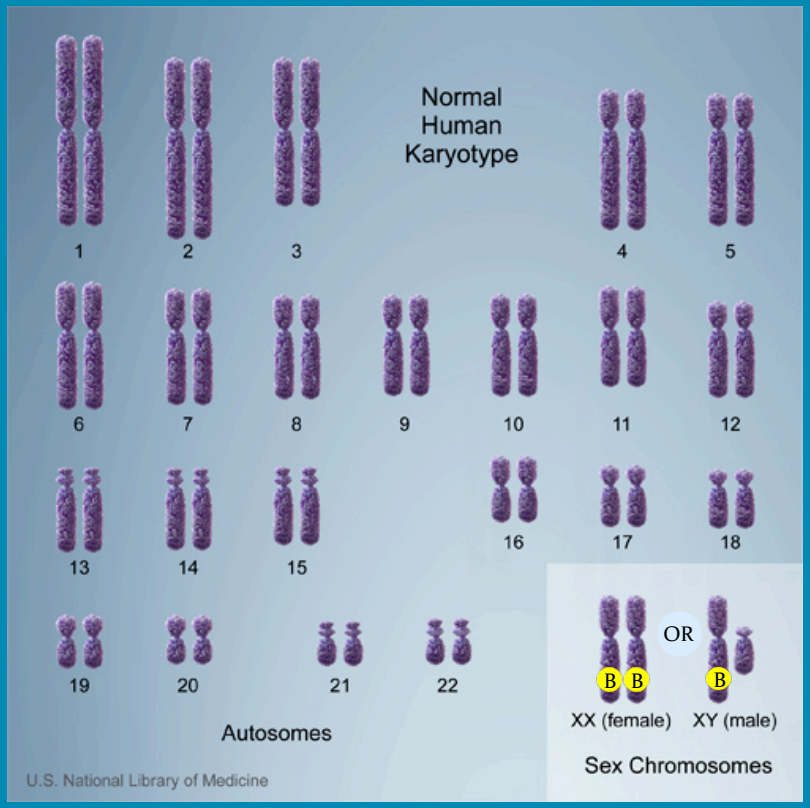
Chromosomes, genes & inheritance



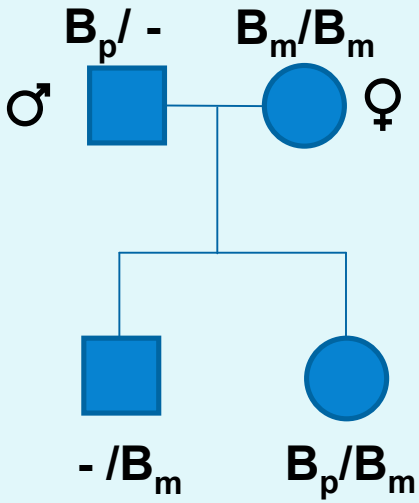
Autosomal Inheritance



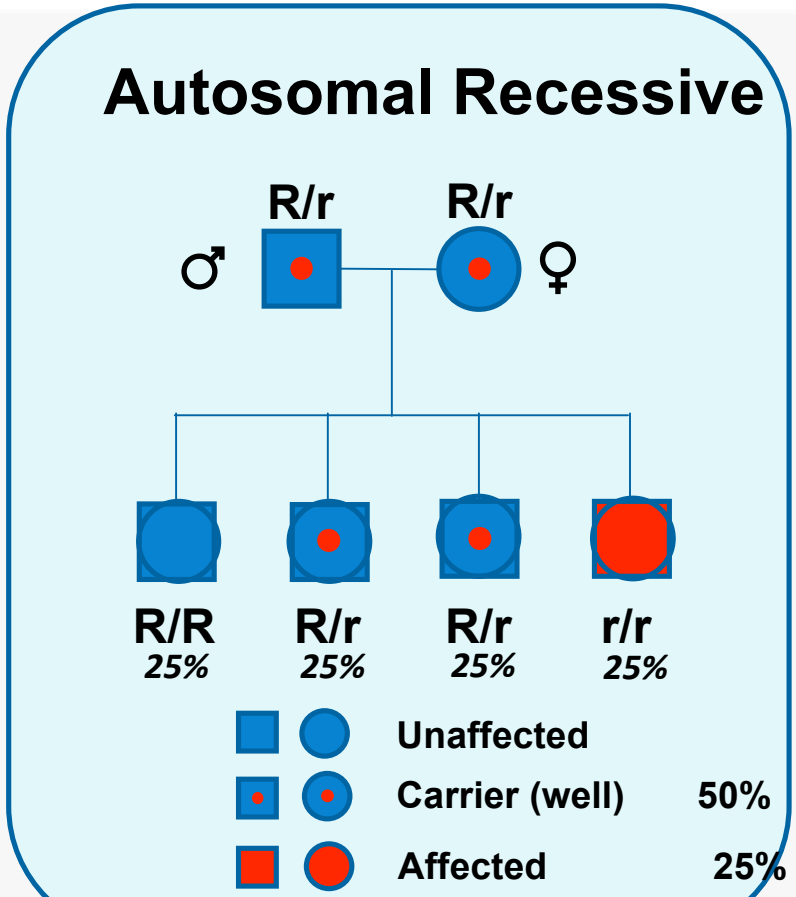
Chromosomes, genes & inheritance

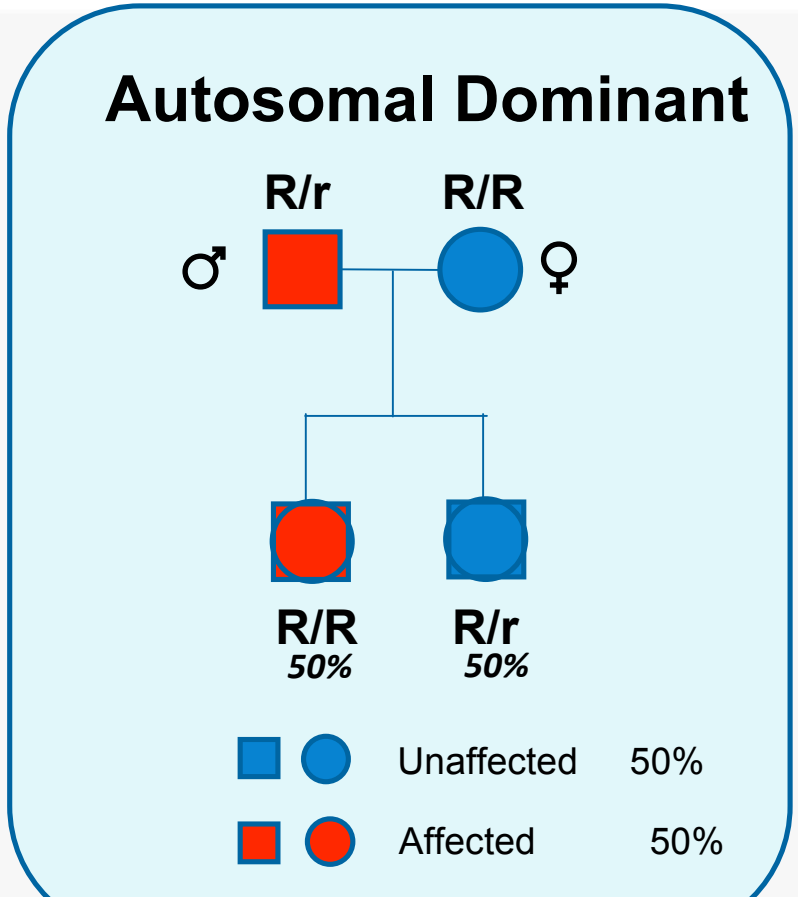


X-linked Inheritance

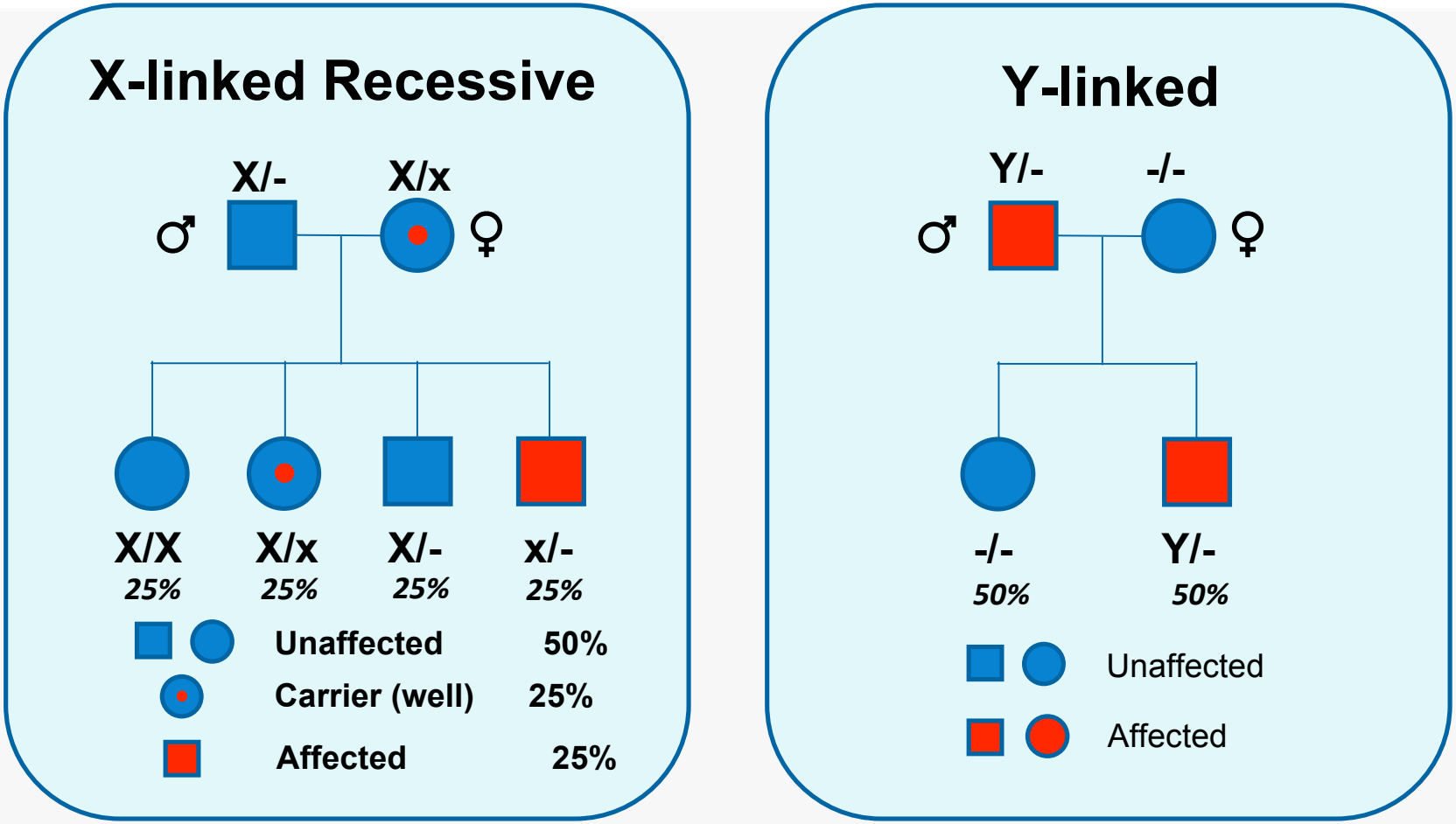


Dominant and recessive diseases





Sex-linked diseases

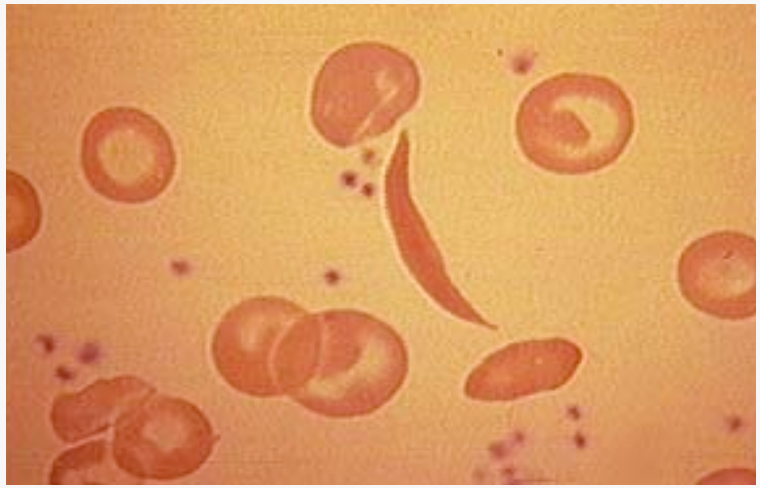


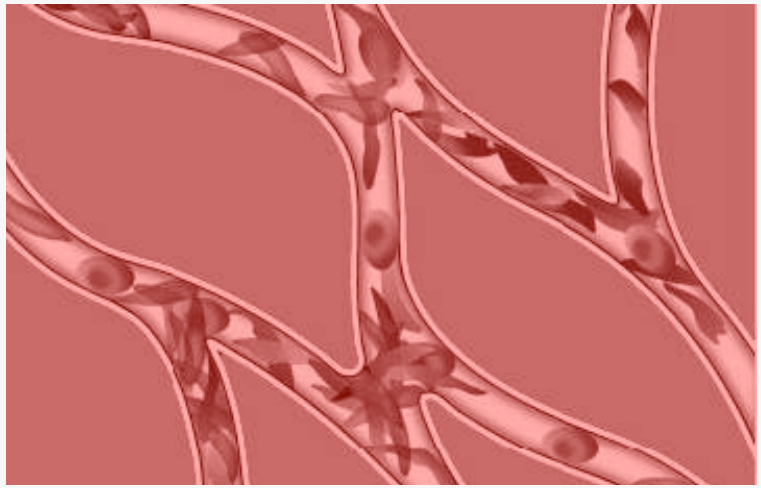
Single gene diseases (monogenic)

Mutations – Who gets it?

Disease	Gene (protein)	Tissue(s)	Inheritanc
Thalassaemia	Haemoglobin	Red Blood Cells	AR
Tay Sachs	Hexosaminidase A	Brain	AR
Cardiomyopathy	e.g. MYH7	Heart	AD
Huntington's disease	Huntingtin	Brain	AD
Muscular Dystrophy	Dystrophin	Muscle	XLR
Haemophilia A	Factor VIII	Clotting System	XLR
Sickle Cell Anaemia	Haemoglobin	Red Blood Cells (Blood/Brain/Bones/Splee n/Eyes/Heart/Lungs/Liver)	AR
Cystic Fibrosis	CFTR	Lungs/Liver/Pancreas	AR
Neurofibromatosis 1	NF1	Nerves/Brain/Skin/Eyes/ Adrenals/Skeleton/Blood	AD

Sickle Cell Disease





Autosomal Recessive

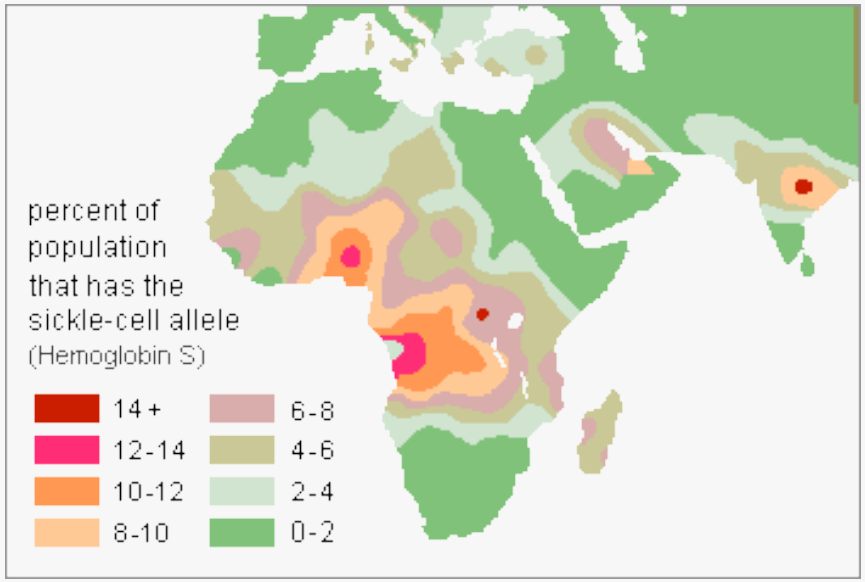
Missense point mutation in the β-globin gene(Haemoglobin).

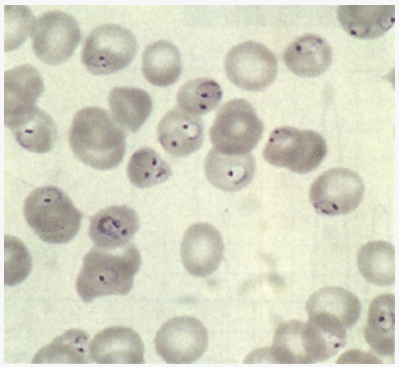
Abnormal Haemoglobin (HbS) precipitates and deforms red blood cells.

Chronic anaemia due to destruction of red cells and intermittent “crises” caused by obstruction of small blood vessels

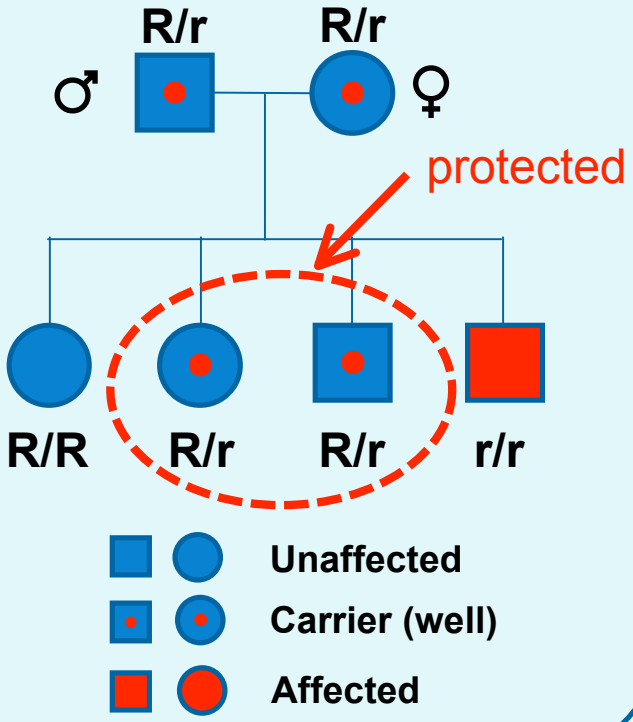
Affects most organs

Sickle Cell Disease & Malaria



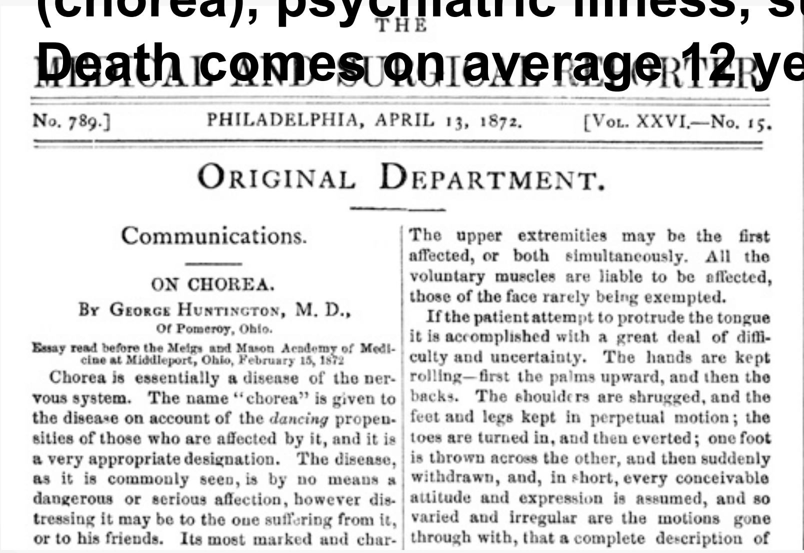


Autosomal Recessive



Huntington's Disease (Chorea)

Autosomal Dominant Neurodegenerative disorder
Deposition of abnormal protein in neurons
Symptoms usually begin between ages of 30-50 years
Loss of coordination, involuntary movements (chorea), psychiatric illness, suicide.
Death comes on average 12 years after onset



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ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

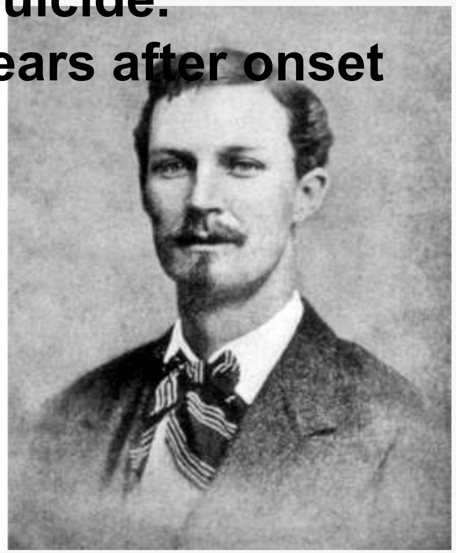
By George Huntington, M. D.,
Of Pomeroy, Ohio.

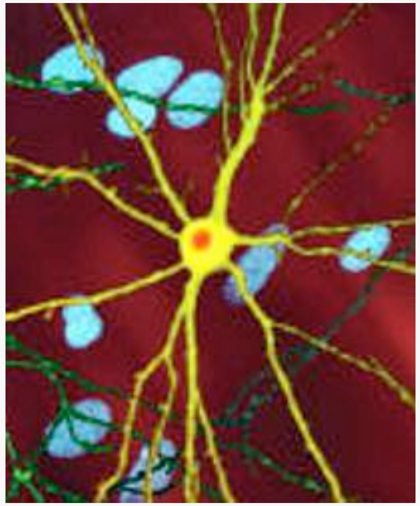
Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of



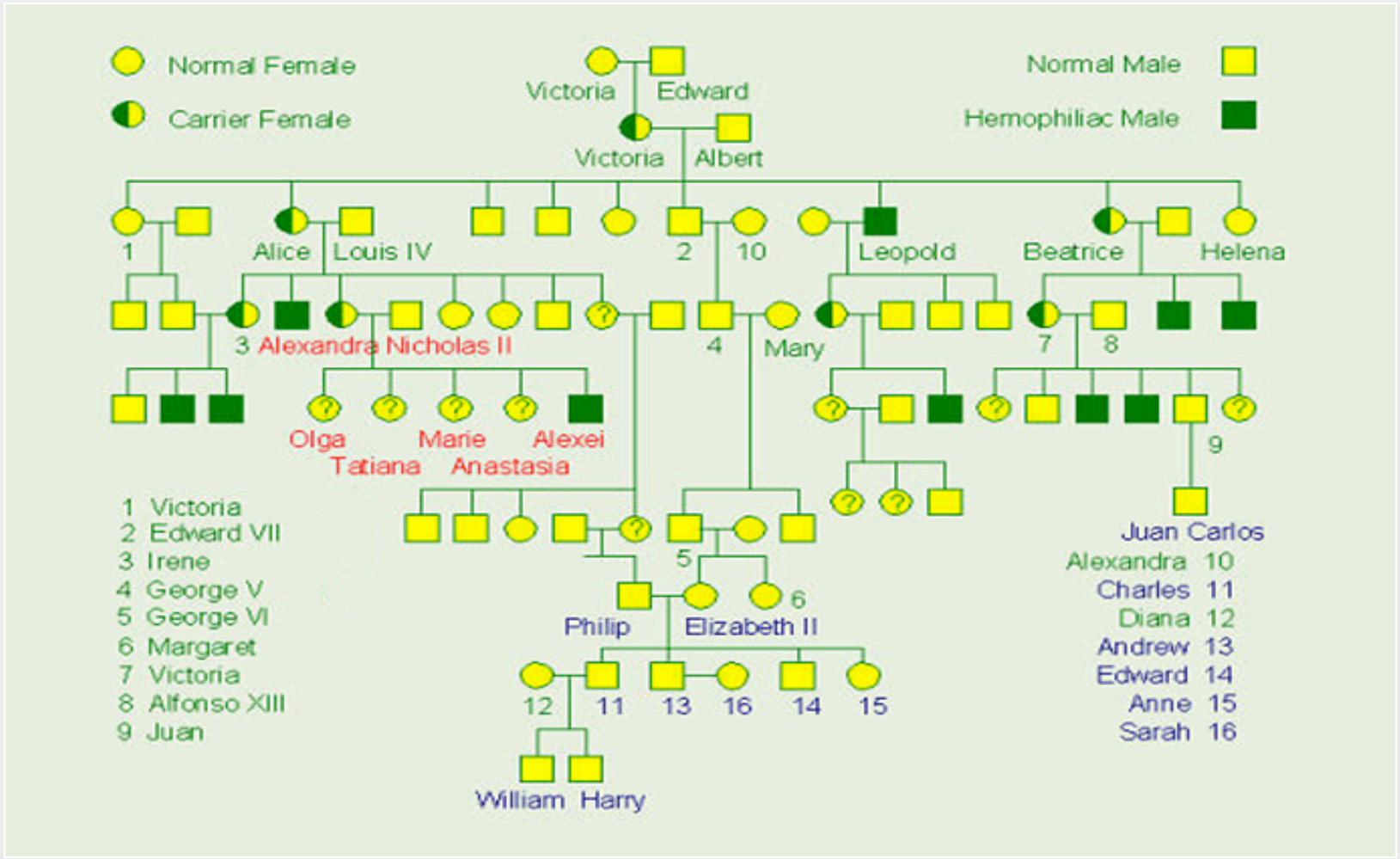


Haemophilia A

- The first bleeding disorder described
- Mutation in factor VIII gene
- X-linked recessive
- Severity varies according to amount of factor VIII
- Most patients have severe disease (<1%)
- Spontaneous bleeding
- Treated with Factor VIII replacement

- Up to 30% have no family history !!
- Spontaneous mutations arise in sperm more often than eggs (3:1)

Haemophilia A – the royal disease



Autosomal Recessive

PKU (Phenylketonuria)

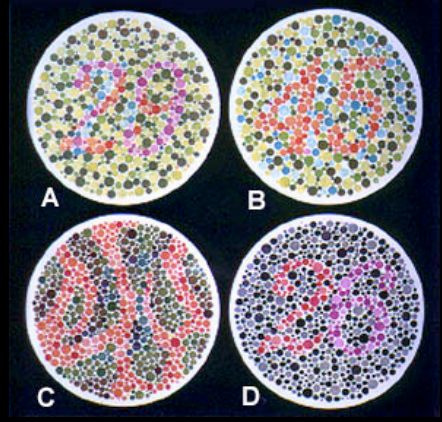
Albinism

Autosomal Dominant

Polycystic Kidney Disease

Progeria

X-linked Recessive



Colour Blindness

X-linked Dominant

Vitamin D resistant rickets

Y-linked condition ?

Hairy ears !!!

All his sons would get it, but thankfully not his daughters !!

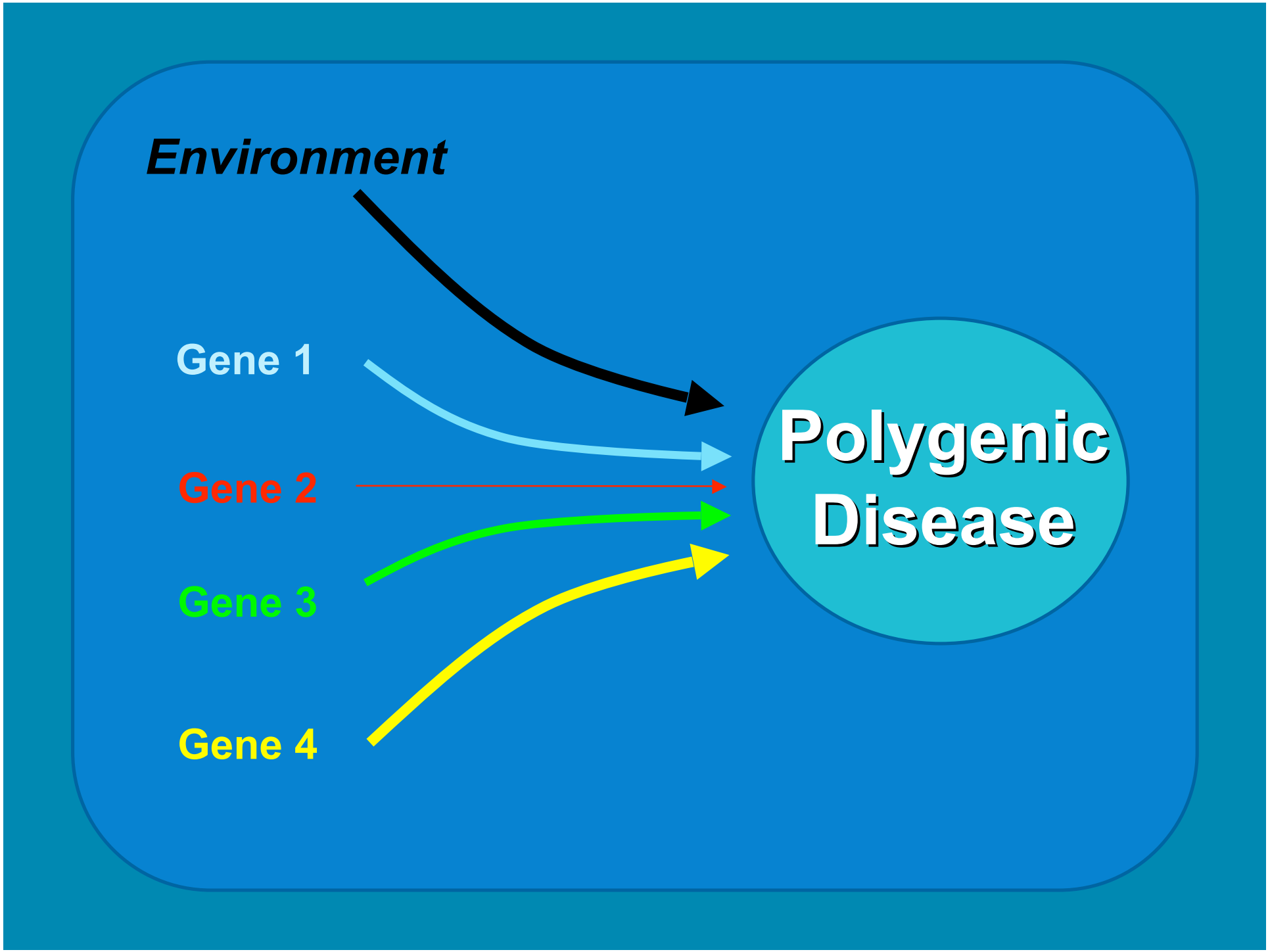
Multi-gene diseases (polygenic)

Polygenic disorders

- Common
- Multiple genes involved
- Environment plays a significant role
- Many gene variants identified that increase/decrease the risk of most common polygenic diseases
- Many remain unknown
- Each variant affects the function of the gene only slightly

Prevalence of some polygenic disorders

Disorder	Frequency (%)
Schizophrenia	1
Asthma	4
Ankylosing spondylitis	0.2
Crohn's disease	0.15
Hypertension (essential)	5
Osteoarthritis	5
Type II diabetes	5


Environment
Gene 1
Gene 2
Gene 3
Gene 4
Polygenic Disease

What % of the risk of polygenic diseases is due to inherited genes ?

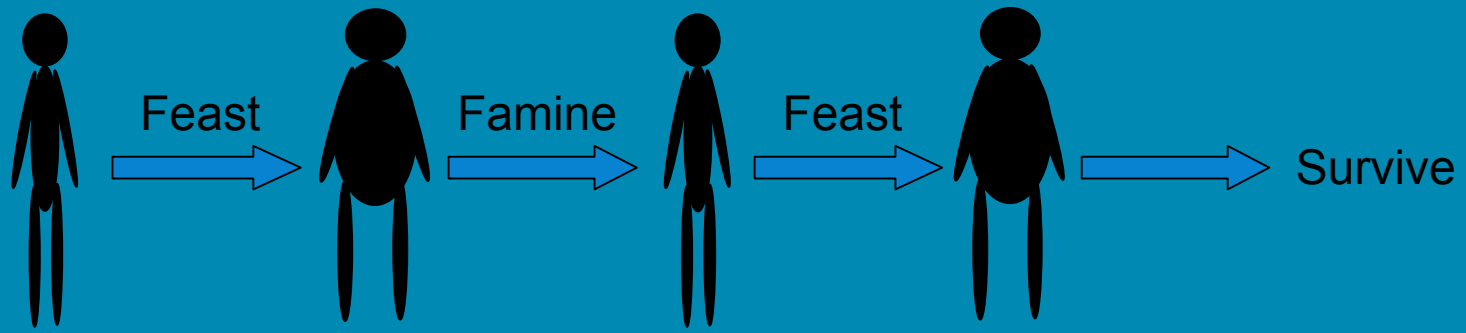
Disorder	Frequency (%)	Heritability (%)
Schizophrenia	1	85
Asthma	4	80
Ankylosing spondylitis	0.2	70
Crohn's disease	0.15	55
Osteoarthritis	5	55
Type II diabetes (NIDDM)	6	26

Concordance rates in twins (%)

	Identical	Non-identical
Cystic Fibrosis	100	25
Die on a Monday	14	14
Hypertension	30	10
Rheumatoid Arthritis	30	5
Type I diabetes (IDDM)	36	5

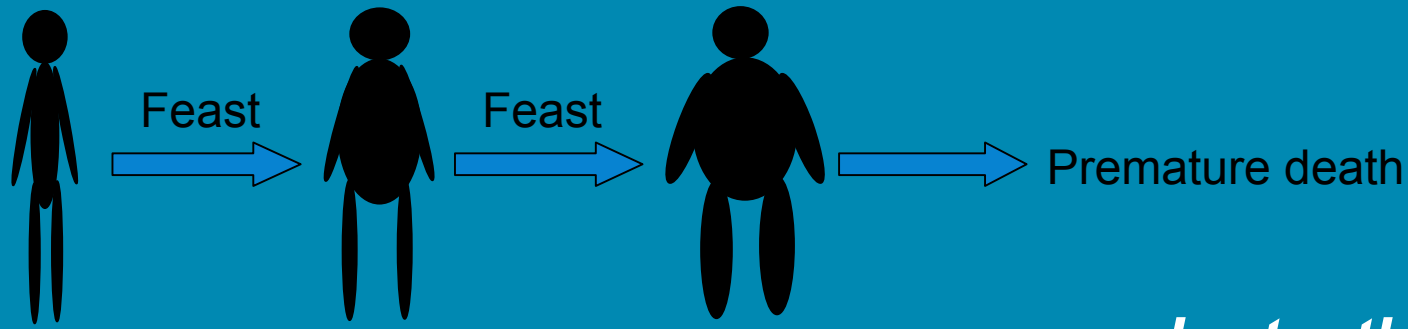
Why are diabetes & obesity so common?

Ancient times



Genes persist as they offer a survival advantage

Modern times

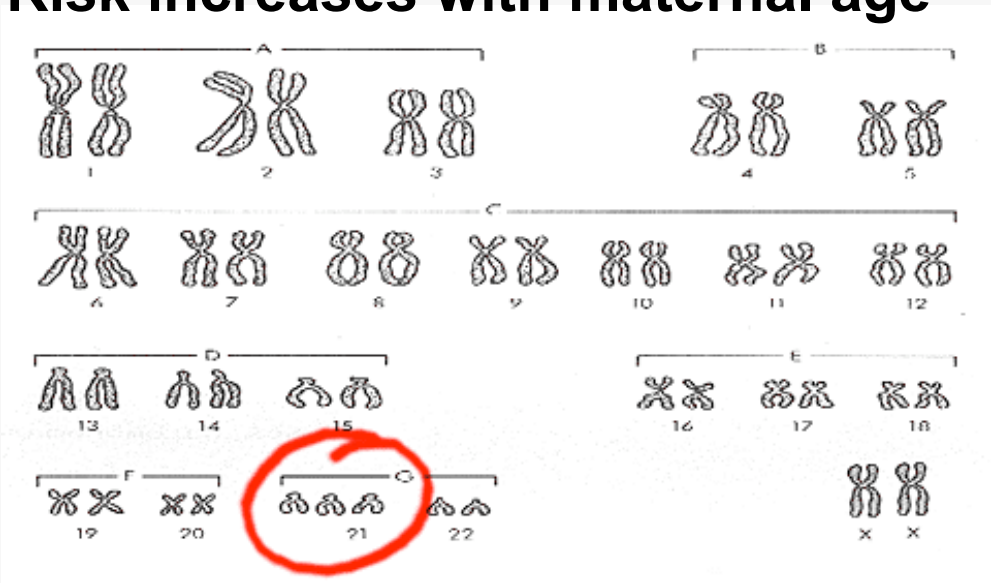


Just a theory...

Chromosomal disorders

Down Syndrome

Spontaneous mutation, 1 in 800 births
Three copies of chromosome 21 (contains approx. 350 genes)
>90% due to failure of chromatids to separate during meiotic cell division (eggs)
Risk increases with maternal age



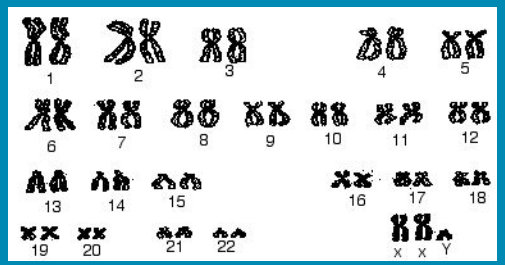
Down Syndrome - features

Symptoms are due to all cells having 3 copies of all the genes on chromosome 21. The genes themselves are normal.

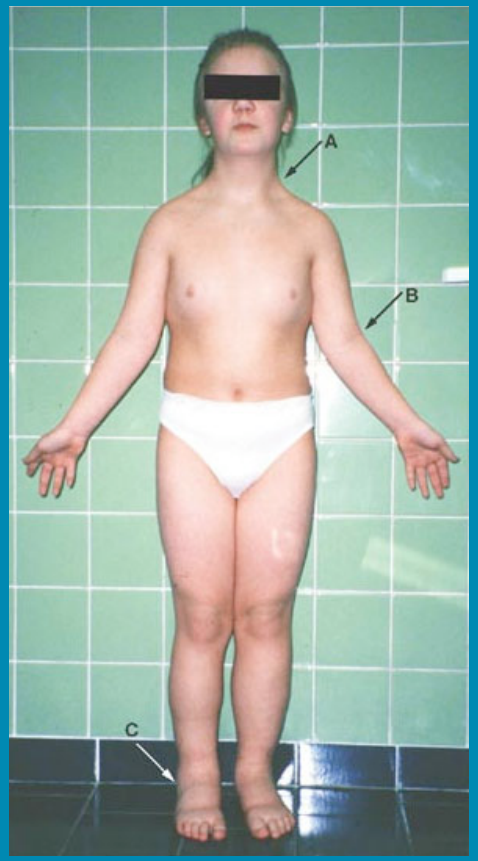
- Characteristic facial appearance
- Single deep crease across center of palm
- Excessive space between first and second toe
- Flexible joints
- Low muscle tone
- Mild to moderate learning difficulties

- Increased incidence of Alzheimer's disease (? dosage effect of APP)
- Increased risk of leukaemia
- Decreased risk of other cancers

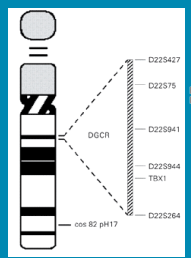
Klinefelter's syndrome (XXY)

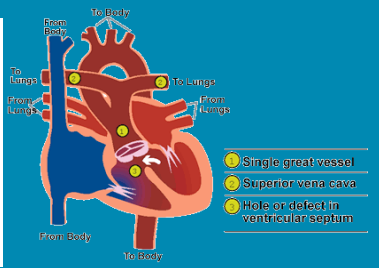


Turner's syndrome (XO)



Di George syndrome (del 22q)





Cancer

How and why does cancer develop?

- Gene mutations are responsible for cancer
- Cancers develop due to many mutations in a single cell
- Most cancer gene mutations are acquired during life

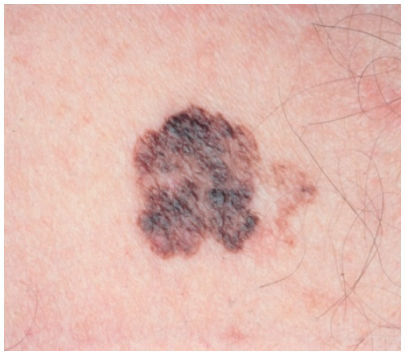
-Environmental risk factors accelerate acquisition of mutations

- Some inherited mutations increase the risk of cancer
- Some people inherit combinations of gene variants that increase the risk of cancer
- Some people develop cancer in the absence of evident inherited or environmental risks...

Heritable cancer risk

Little heritable risk (in most cases)

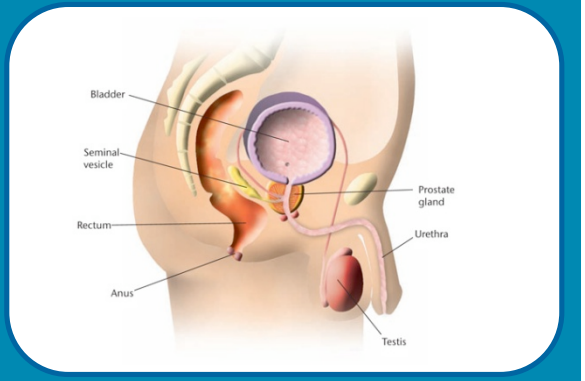
Lung Cancer



Melanoma

Increased cancer risk

BRCA1 mutations



Prostate Cancer

Very high cancer risk

Neurofibromatosis 1

Adenomatous Polyposis Col

The golfing chimp theory of Cancer !!!

1.Chimp is a very poor golfer

2.Everybody has their own chimp

3.Hole = mutation

4.18-hole golf course

5.If you inherit a high cancer risk, the chimp starts at later hole (e.g. No 9)

6.If you smoke, drink, suntan etc the monkey takes shots more often

7.On average the chimp finishes the course after 90 years (5 years per hole) – but can be shorter or longer

Genes & disease - Summary

- Our genes make us what we are
- Changes in our genes can cause disease
- Our environment and behaviour modify the effects of genes
- Some diseases are cause by single gene changes
- Several common diseases are due to many genes + the effects of the environment
- Most genes changes that lead to cancer happen during life, some are inherited

- *Monkeys do not cause cancer !!*