TAG 2007 335

6th Genodermatoses in Mediterranean working session
1st TAG meeting

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Prevention of genetic disorders

Medical genetics

Genetic factors contribute significantly in the etiology of human disease

Contribution of molecular genetics in the identification of genes involved in human disease

Genetic and congenital disorders

Birth prevalence: 25-60 per 1000

2-3% of newborns have at least 1 major congenital abnormality

~ 10% by the age of 10

Account for :

>30% of admissions in Pediatric hospitals

> 40-50% of deaths in childhood

Mc Candless et al, Am J Hum Genet ,2004

Congenital malformations in adults

> 1% of malignancies are of genetic origin

> 10% of known cancers (breast,intestine,ovaries) have a genetic contribution

By the age of 25

~ 5% of the population has an abnormality of genetic background

During a lifetime

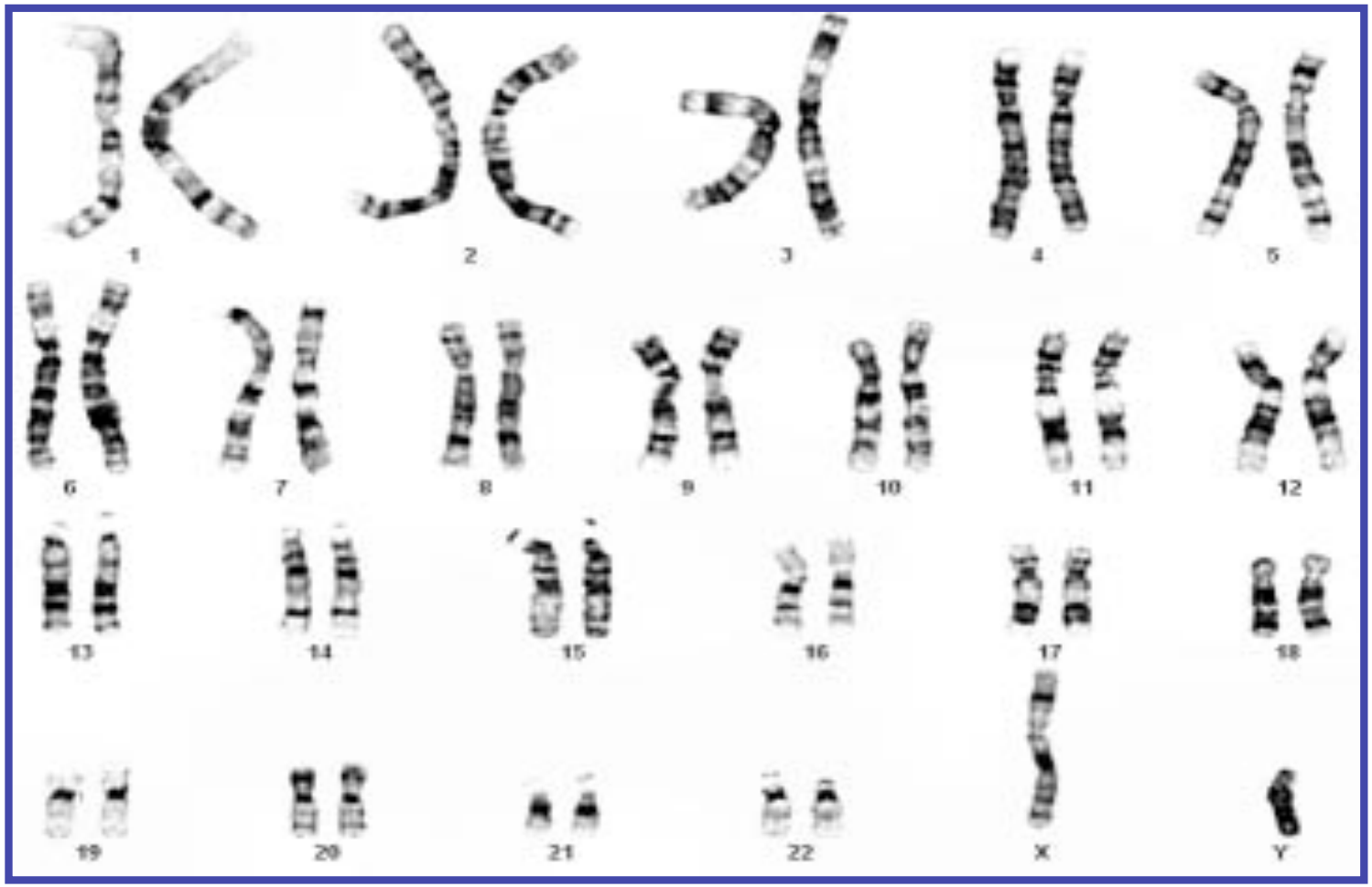
> 30-40% of the population will develop a genetic or multifactorial disorder

Incidence of Genetic Disorders in the General Polulation (per 1000 births)

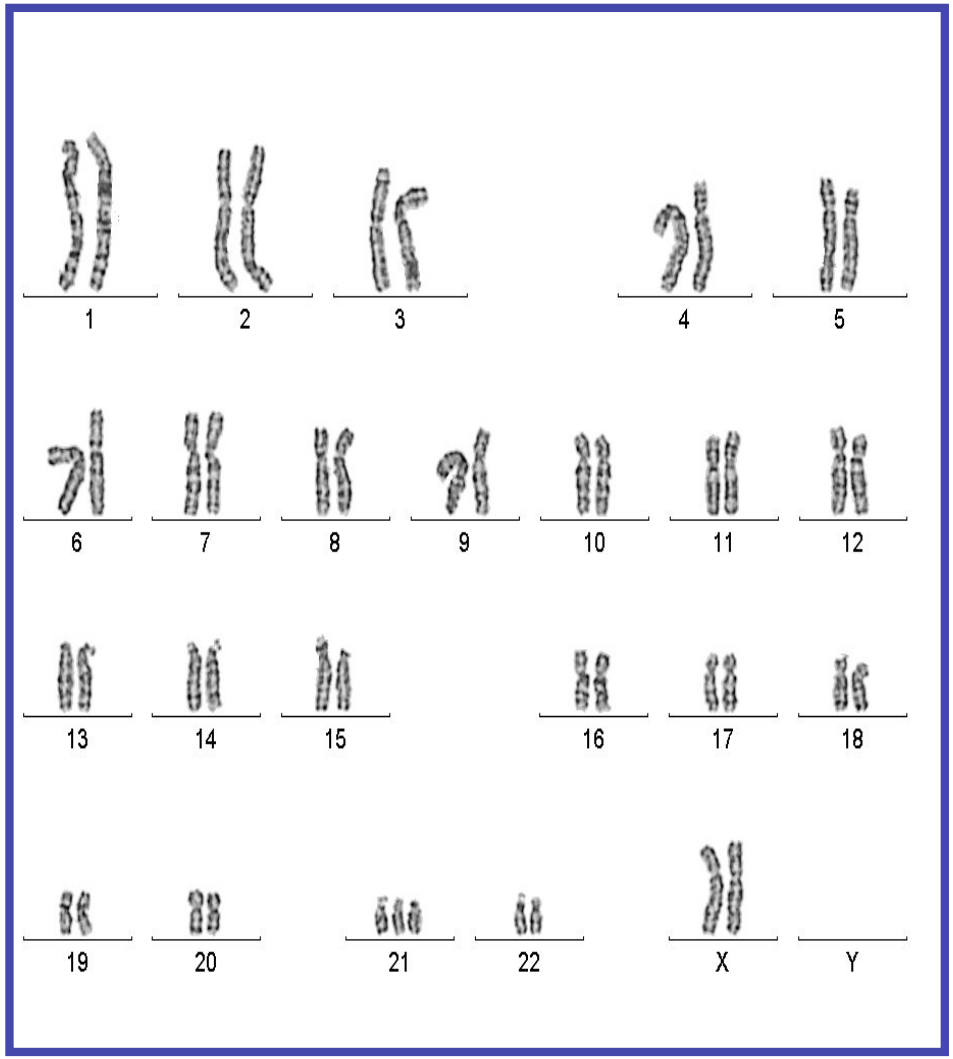
Monogenic disorders	
Dominant Recessive X-linked	3.0 - 9.5 2.0 - 2.5 0.5 - 2.0
Chromosomal abnormalities	6.0 - 9.0
Congenital anomalies*	20.0-50.0
Total	31.5-73.0

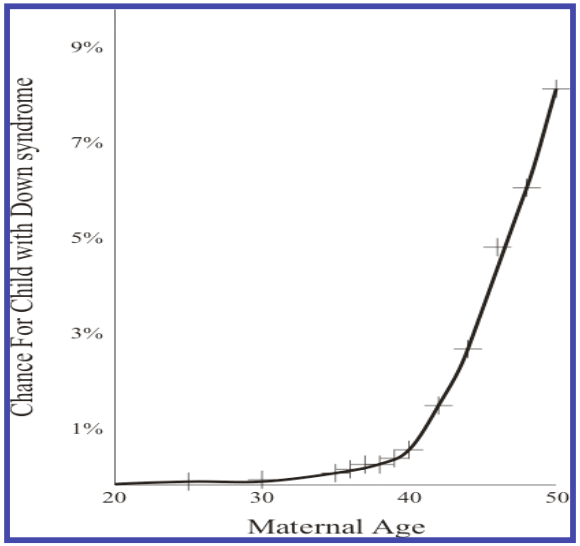
* *Most congenital anomalies follow multifactorial inheritance caused by genetic and environmental factors*

Normal karyotype

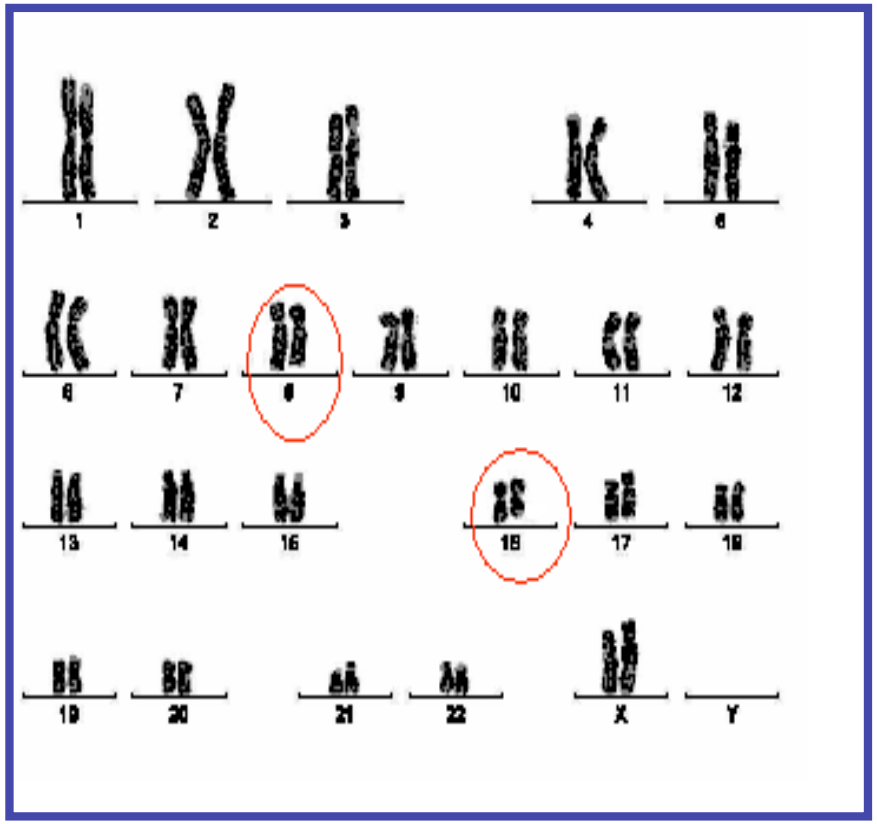


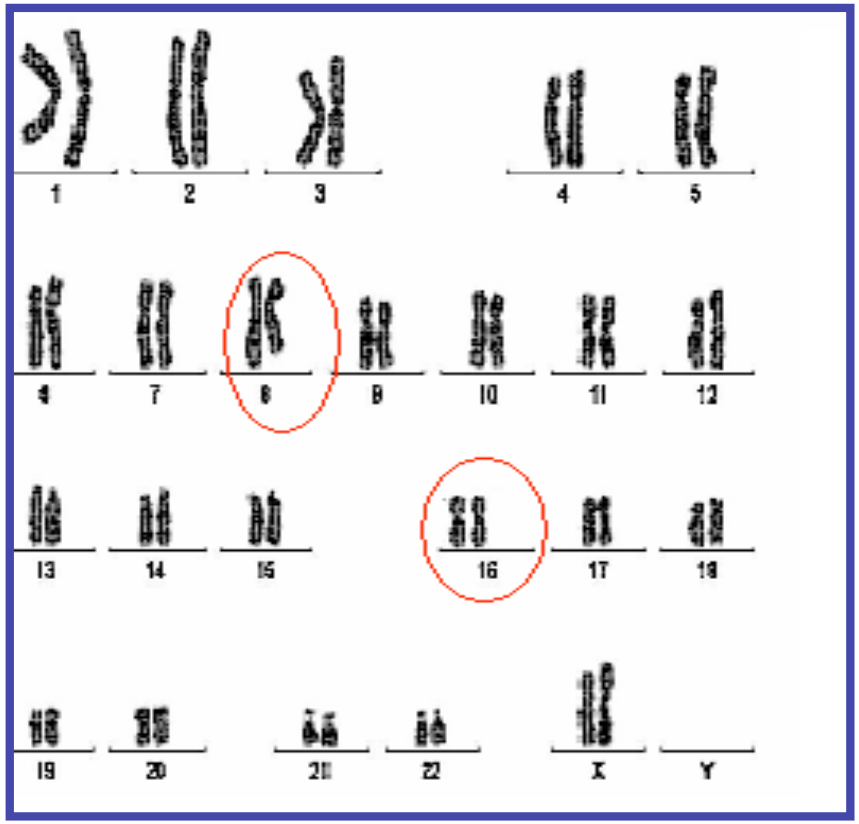
DOWN SYNDROME





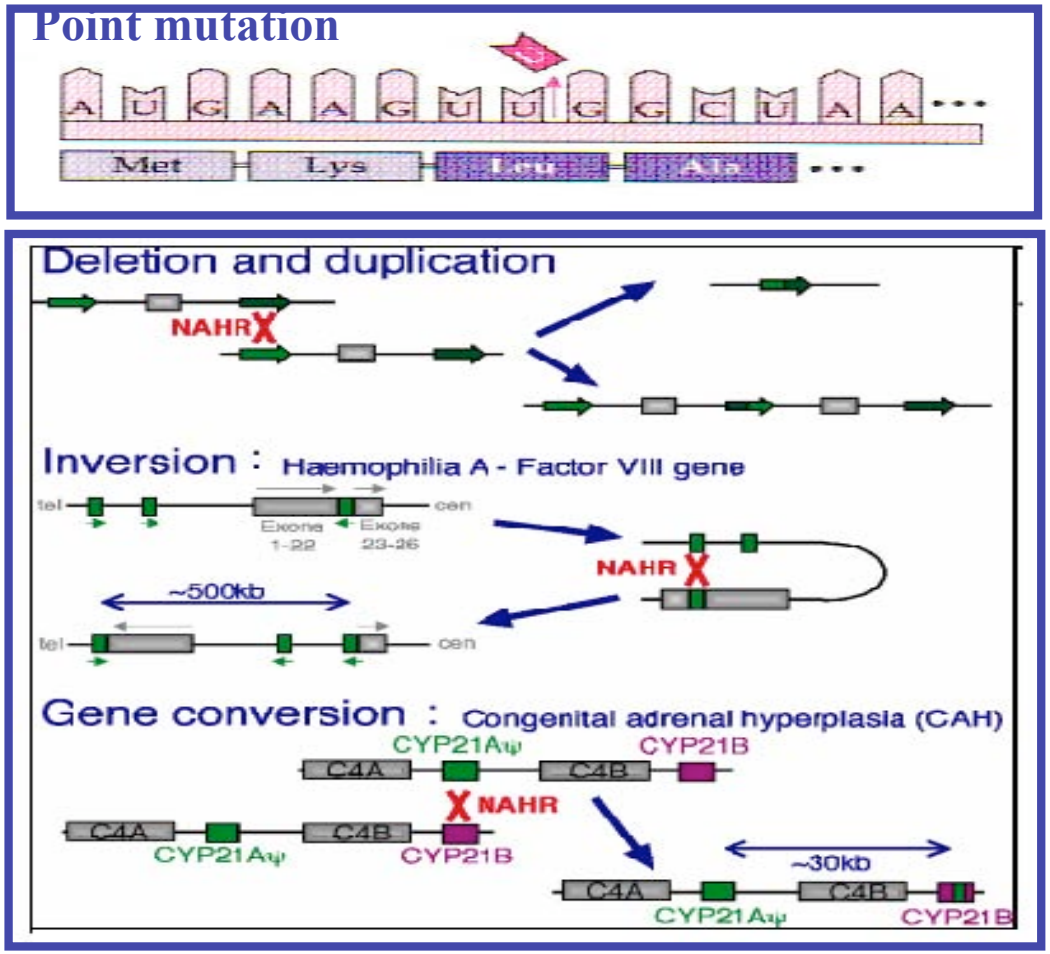
Reciprocal Translocation



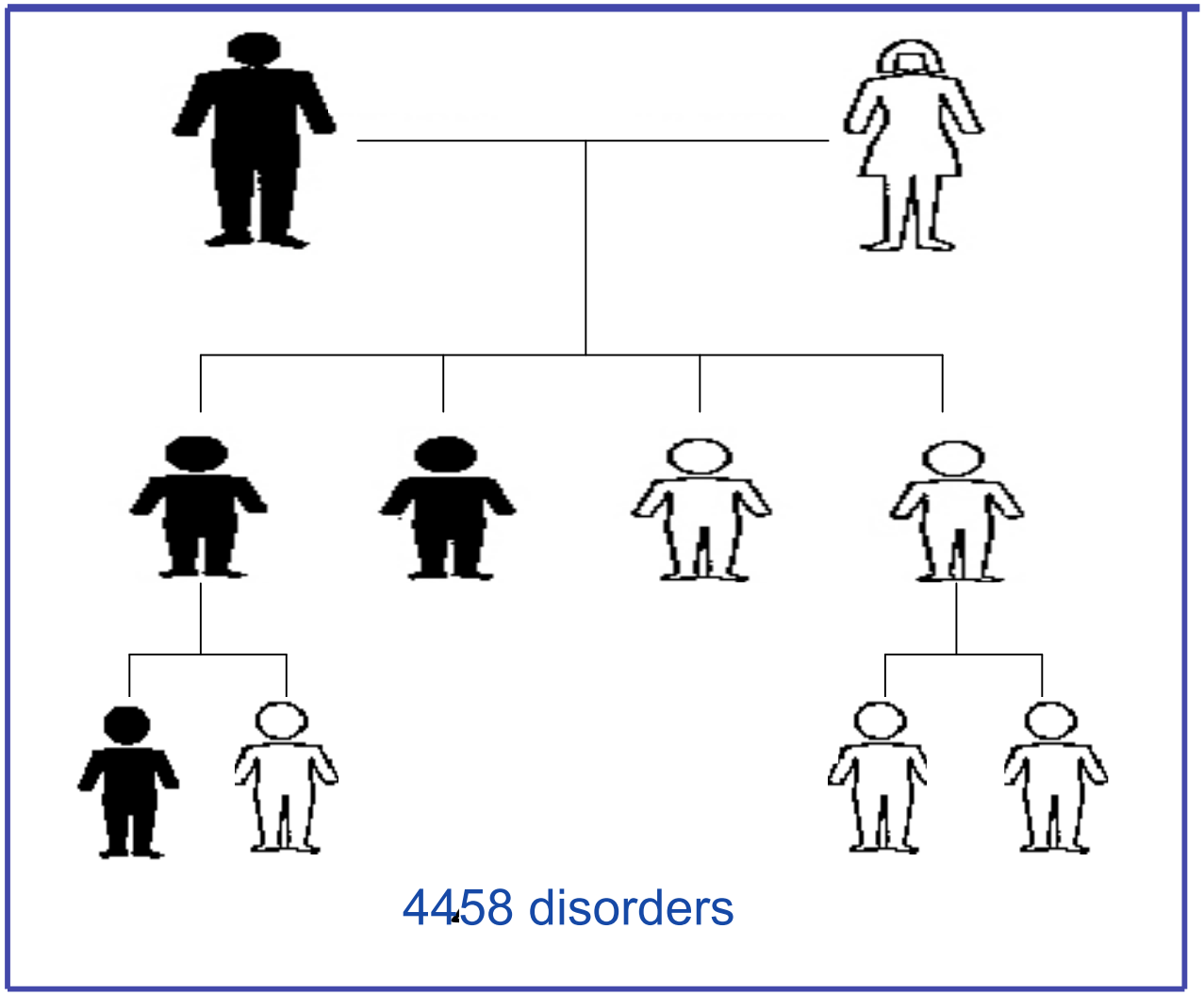


Single gene disorders

Mutations in one gene that have a serious phenotypic effect

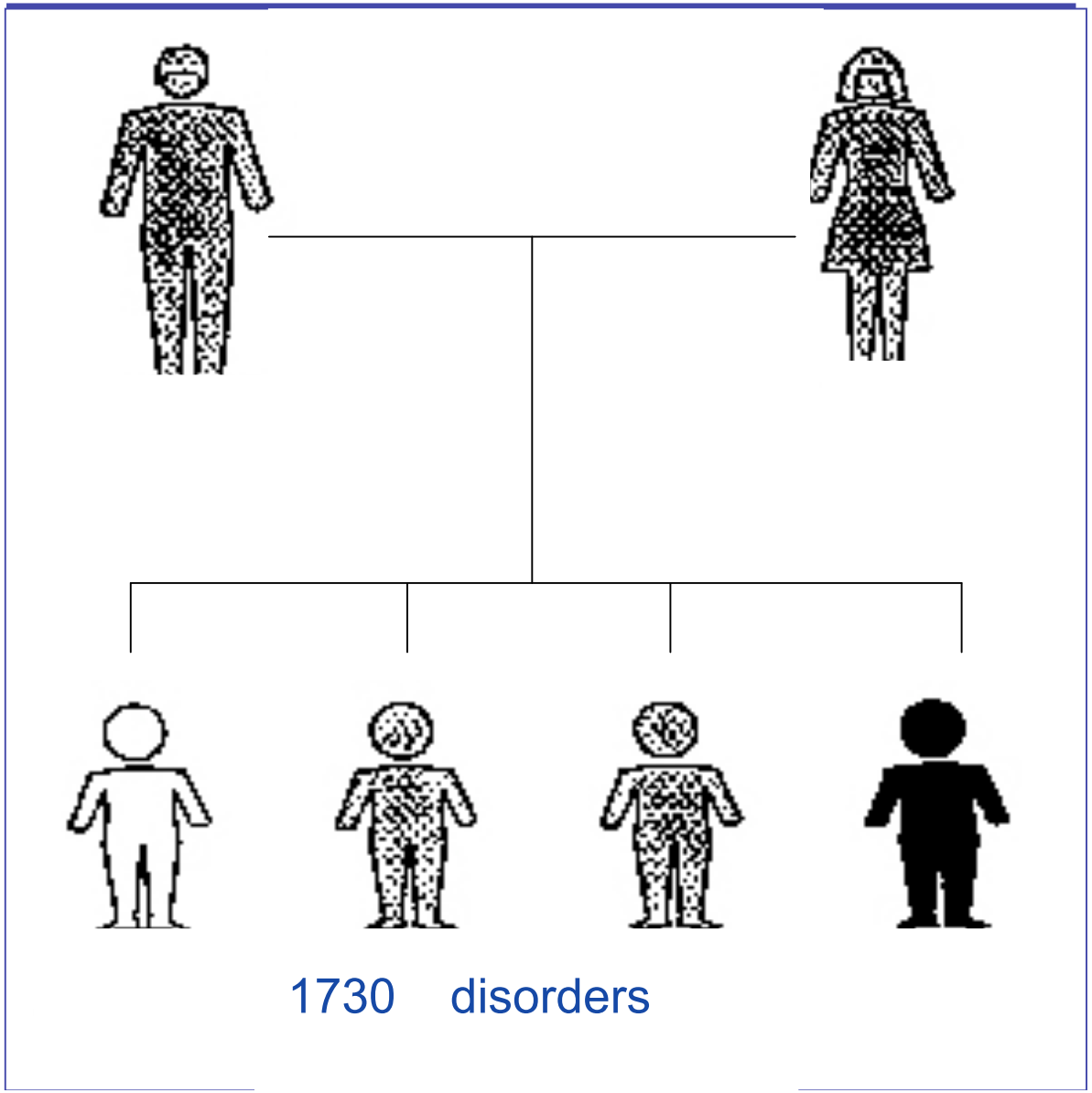


Autosomal dominant inheritance

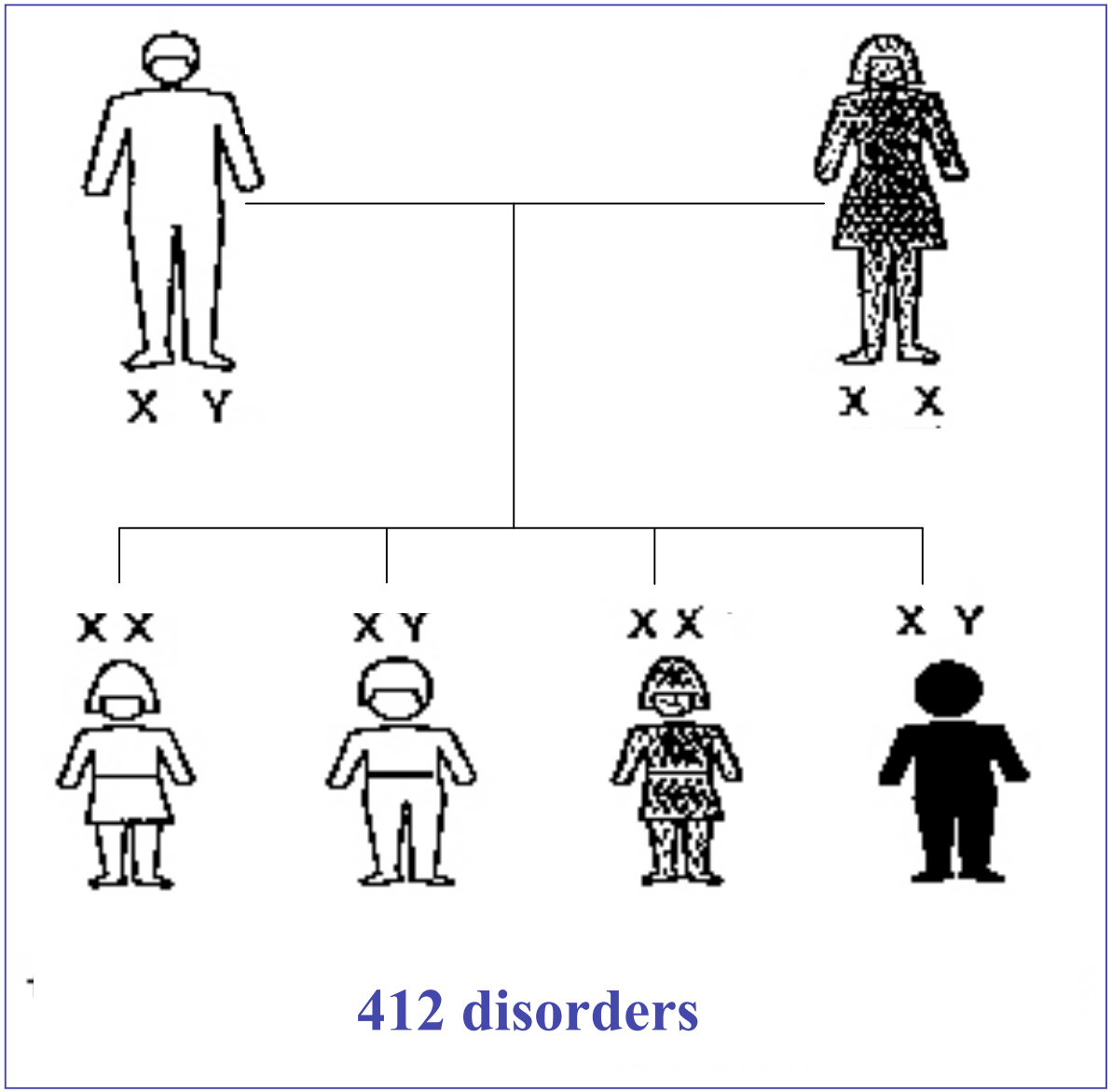


4458 disorders

Autosomal recessive inheritance



X-linked inheritance



Multifactorial disorders

- ¨ Result from the interaction of several genetic loci with environmental factors
- ¨ Risk of re occurrence in the same family is higher than in the general polulation

Risk of re occurrence of a multifactorial disease in a relative

		Risk %		
Anomaly	1st Degree relative	2nd Degree relative	3rd Degree relative	General population
Cleft lip	4	0.6	0.3	0.1
Spina bifida	4	1.5	0.6	0.3
Pyloric stenosis	2	1	0.4	0.3
Epilepsy	5	2.5	1.5	1
Schizophrenia	10	4	2	1
Manic depression	15	5	3.5	1

Genetic Disorders

NO DEFINITE CURE

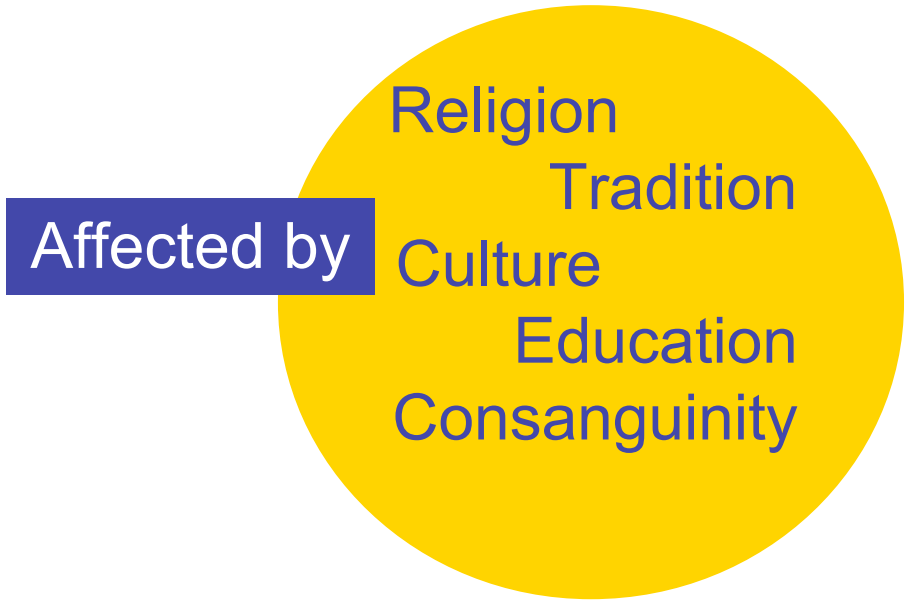
Prevention through

Education of the public
Population screening
Genetic counselling
Prenatal diagnosis

AIM

Offer informed choice to couples at risk

Prevalence of genetic diseases Variable among different ethnic groups



Genetic Counselling

An educational process by which patients and at risk individuals are given information in order to understand the nature of the genetic diseases, the mode of transmission and the options available for management and family planning

Essential Components of Genetic Counselling

History and pedigree construction

Clinical Examination

Confirmatory diagnosis

- History findings
- Clinical examination findings
- Radiology findings
- Laboratory parameter results
- DNA studies results
- Others

Calculation of recurrence risk

Counseling

Available options

Follow-up

Common autosomal recessive disorders

- Thalassemias
- G-6-PD deficiency
- Cystic fibrosis
- Mediterranean fever
- SMA
- Tay- Sachs Disease

Population screening & genetic counselling

Haemoglobin disorders

The most common clinically serious single gene disorders in the world

√ Over 5% of the world's population are healthy carriers

√ Carriers detected through blood tests and/or DNA analysis

300.000 affected births each year
60.000- 70.000 β- thalassaemia
Patients depend on transfusion to control their disease

Haemoglobinopathy screen

WHO recognized that this disease offers an important model of genetic population screening and recommended development of methods for assessing the personal and public health implications

Haemoglobinopathies in Greece

Frequency of carriers in the population	**10% Hb abnormalities (8.5% α-thalassaemia)**
Number of prevention centers	**20**
Carrier testing	**>70%**
Number of sick children expected to be born each year without prevention	**160**
Pregnancies that must be tested each year prenataly	**800**
Prenatal diagnoses performed per year	**700**
Sick children born each year	**10-15**

Haemoglobinopathies in the UK

√ Over 7% of residents

√ 11% of births are in ethnic groups at risk for haemoglobin disorders (Health education authority, 1998)

A national register for surveillance of inherited disorders:
β- thalassemia in the United Kingdom

B Modell et al Bulletin of the WHO, 2001

A multidisciplinary approach for improving services in primary care: randomized controlled trial of screening for hemoglobin disorders

B Modell et al BMJ 1998; 317:788-791

AIM

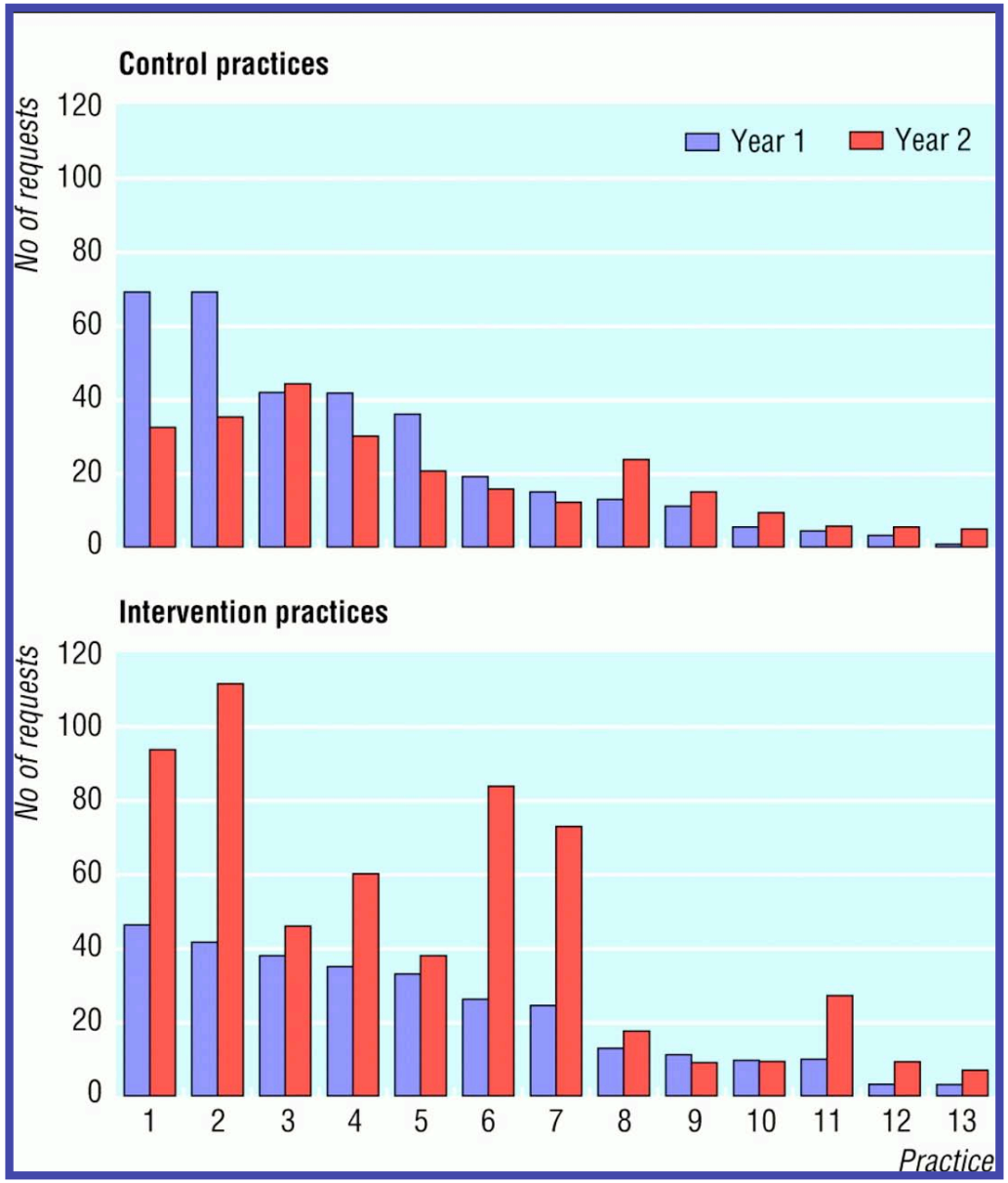
To investigate the feasibility of improving screening for hemoglobin disorders in general practice by using a nurse facilitator to work with primary care teams

2 year randomized trial in North London,UK
29% of residents and 43% of births
in ethnic groups at risk for hemoglobin disorders

From chance to choice

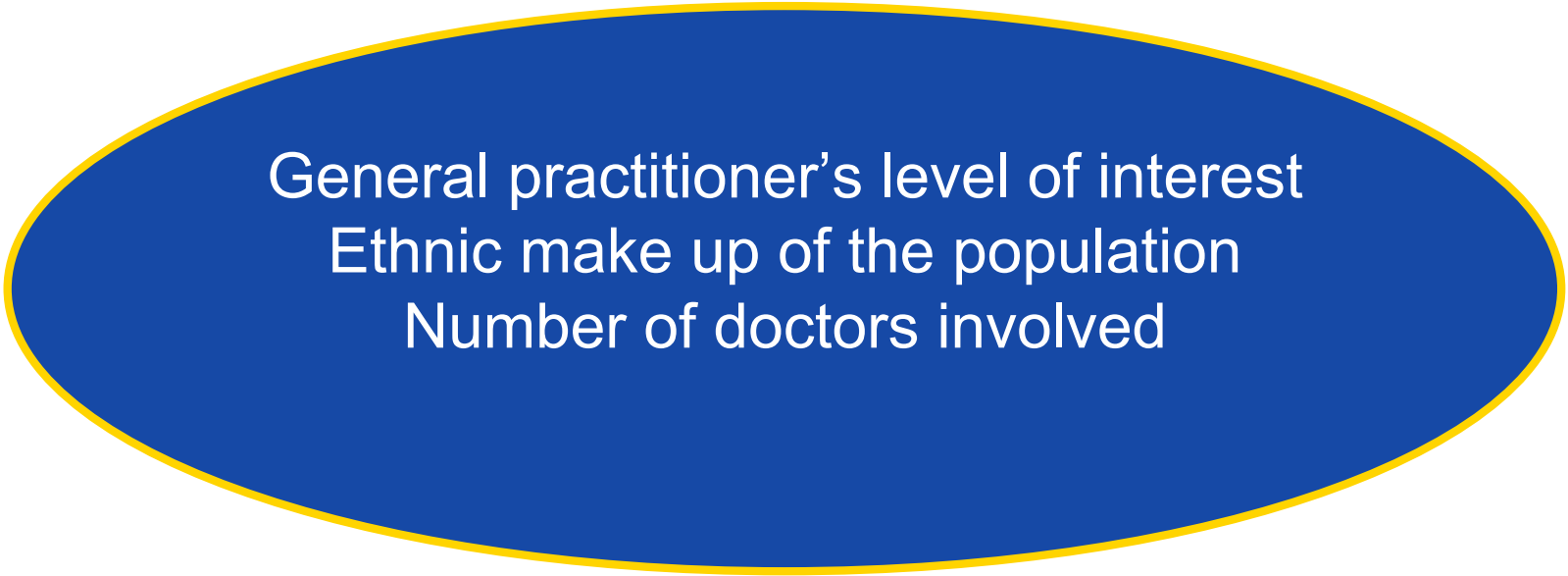
Intervention groups were offered three 30-60 minute sessions that included

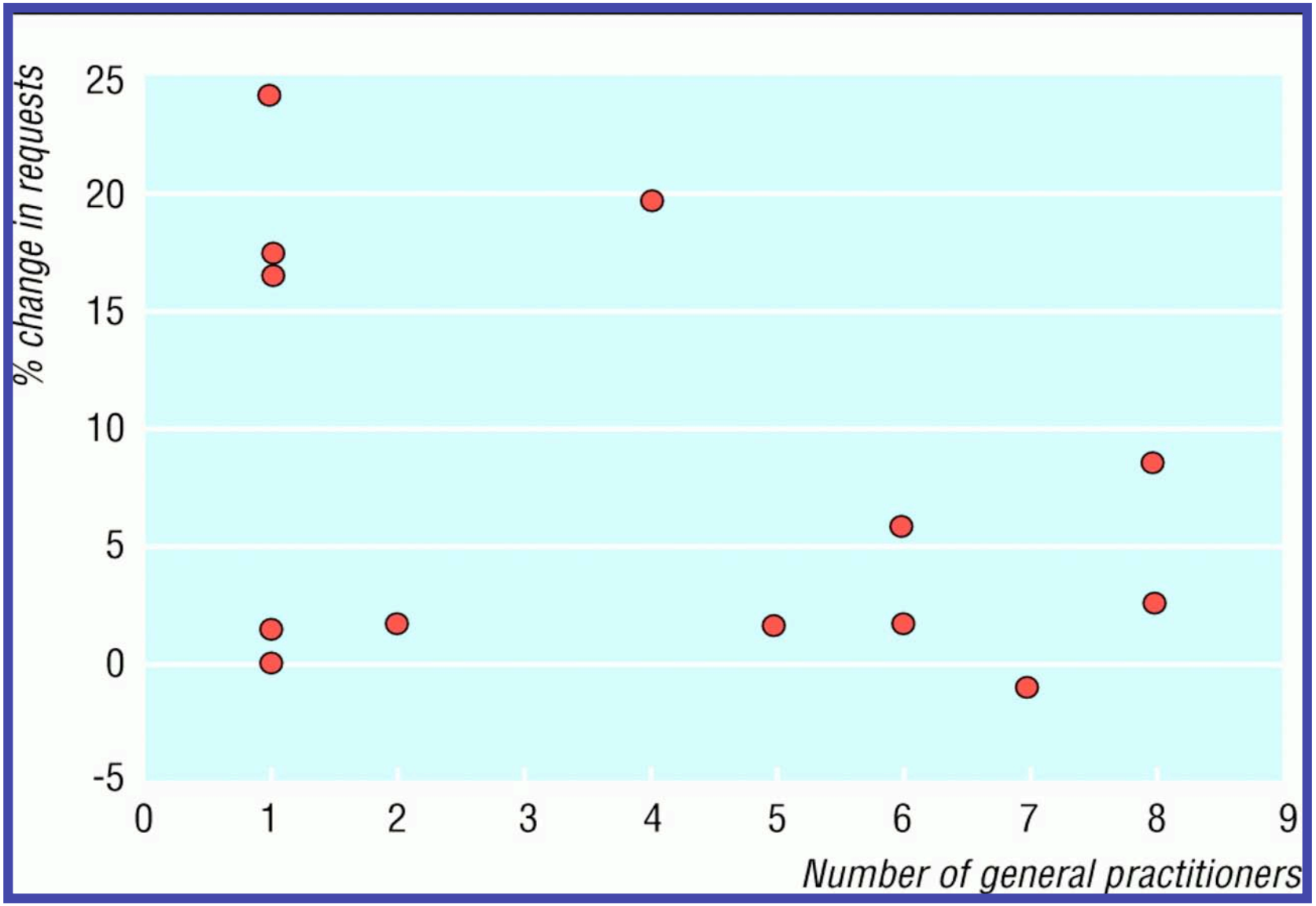
slide presentations and viewing of a video focusing on the role of the primary care team in screening for common recessively inherited diseases



Modell, M. et al. BMJ 1998;317:788-791

Factors affecting change in screening





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Utilization and uptake of prenatal diagnosis

Uptake varies by ethnic group

- Cypriots > 90%
- Pakistanis 20%

Time of counselling

National Diagnosis Register

- Powerful instrument for national surveillance of an inherited disorder
- Cost of running a register is much less than treating an affected patient
- Registers of inherited disorders should be incorporated into health services

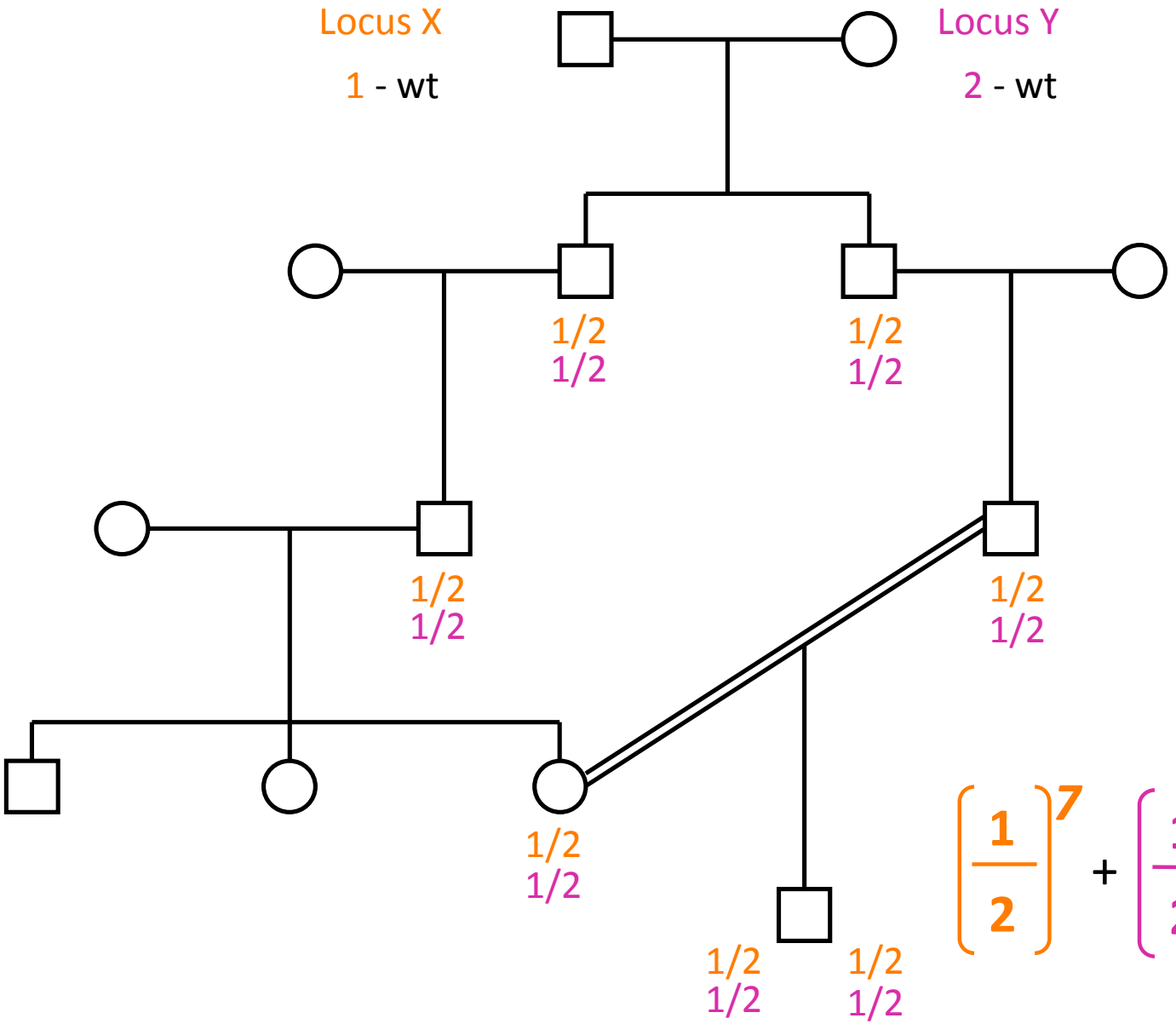
Preventive Measures for Genetic Disorders

- Genetic screening and testing programs for the most common genetic disorders
- Premarital and preconceptual testing and councelling
- Newborn screening for frequent and treatable metabolic disorders
- Consanguinity

Increase of genetic disorders, congenital anomalies and infant mortality in children born from a consanguinous marriage

Degree of Relationship	Proportion of genes shared	Chance of homozygocity	Increase of risk %
Sibs	1/2	1/4	30
First cousins	1/8	1/16	3
Second cousins	1/32	1/64	1-2

Harper PS " Practical Genetic Counselling" 2004



$$\left(\frac{1}{2}\right)^7 + \left(\frac{1}{2}\right)^7 = \frac{1}{64} \approx 1{,}5\%$$

Relative risk due to consanguinity

Prevention of Genetic Disorders

· Genomics and advances in Genetic technology have given Medical Genetics a prominent role in the diagnosis of Genetic Disease

· Sequencing the human genome will greatly increase the possibilities for genetic screening, preventing and treating genetic disorders.

· Community genetics at a primary health care level can be of great benefit

· Allocation of funding for research and genetic testing