



遺傳病之科學基礎及 診治

盧輝文醫生

衛生署醫學遺傳科高級醫生

孟德爾定律

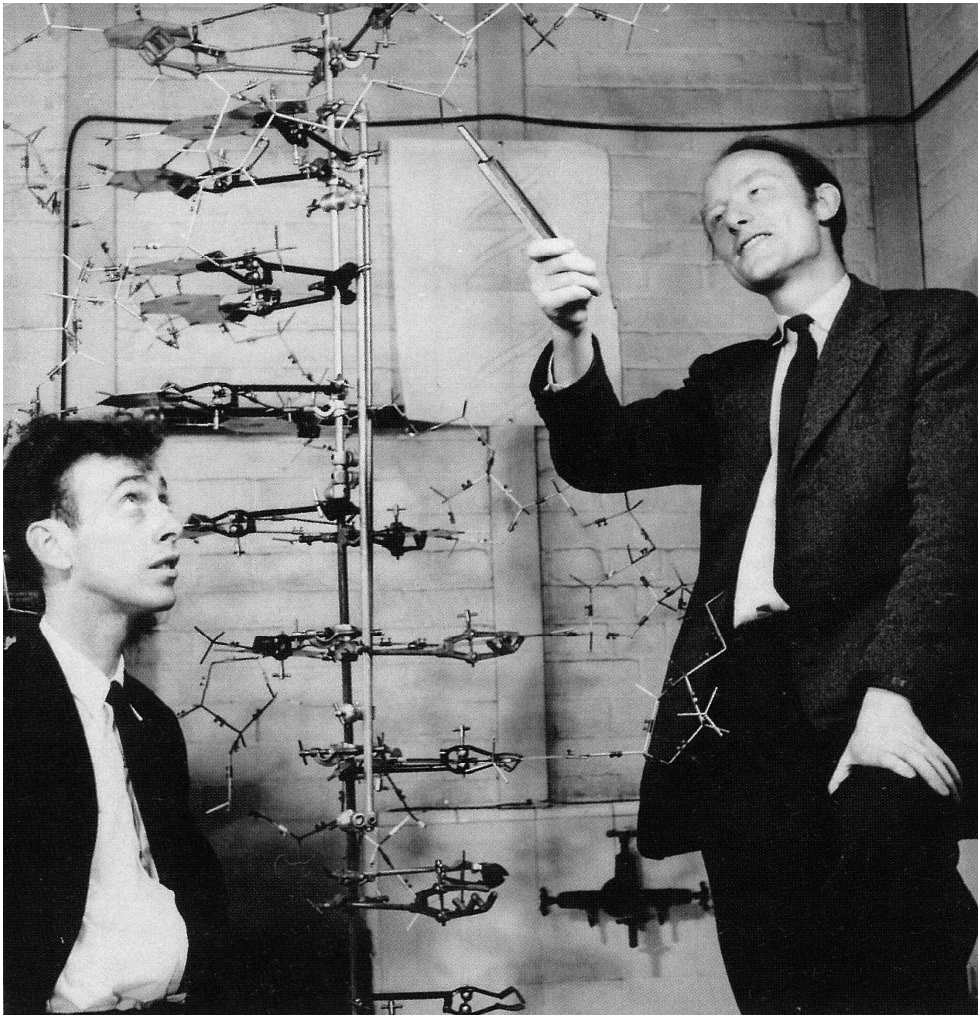
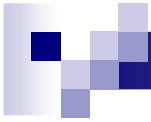
1. 分離律
2. 獨立分配律



Gregor Johann Mendel

約翰·孟德爾

1822 - 1884

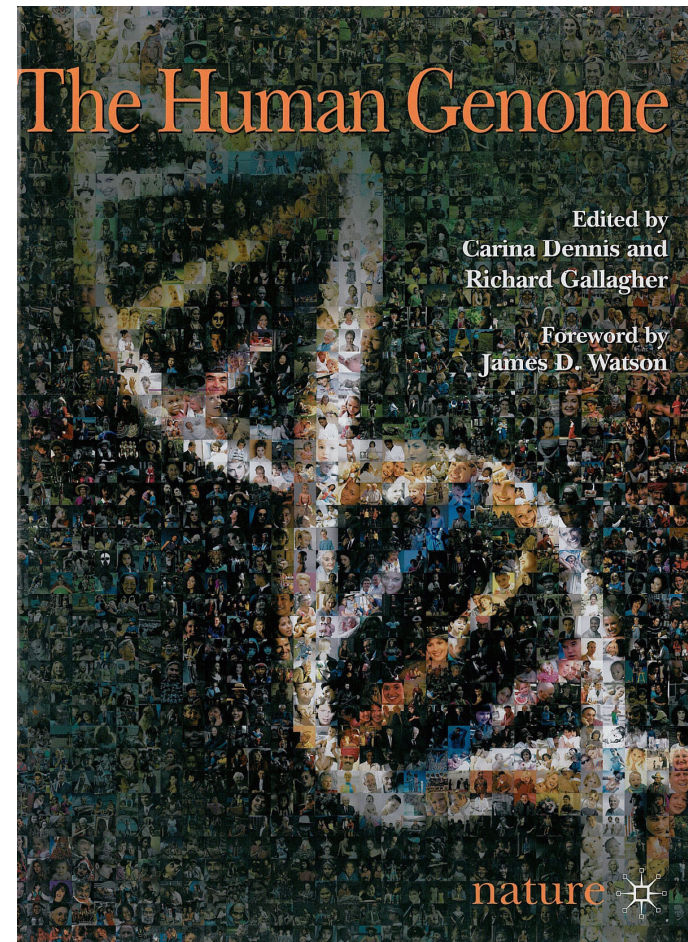


James Watson & Francis Crick
1953



Genome (基因組)

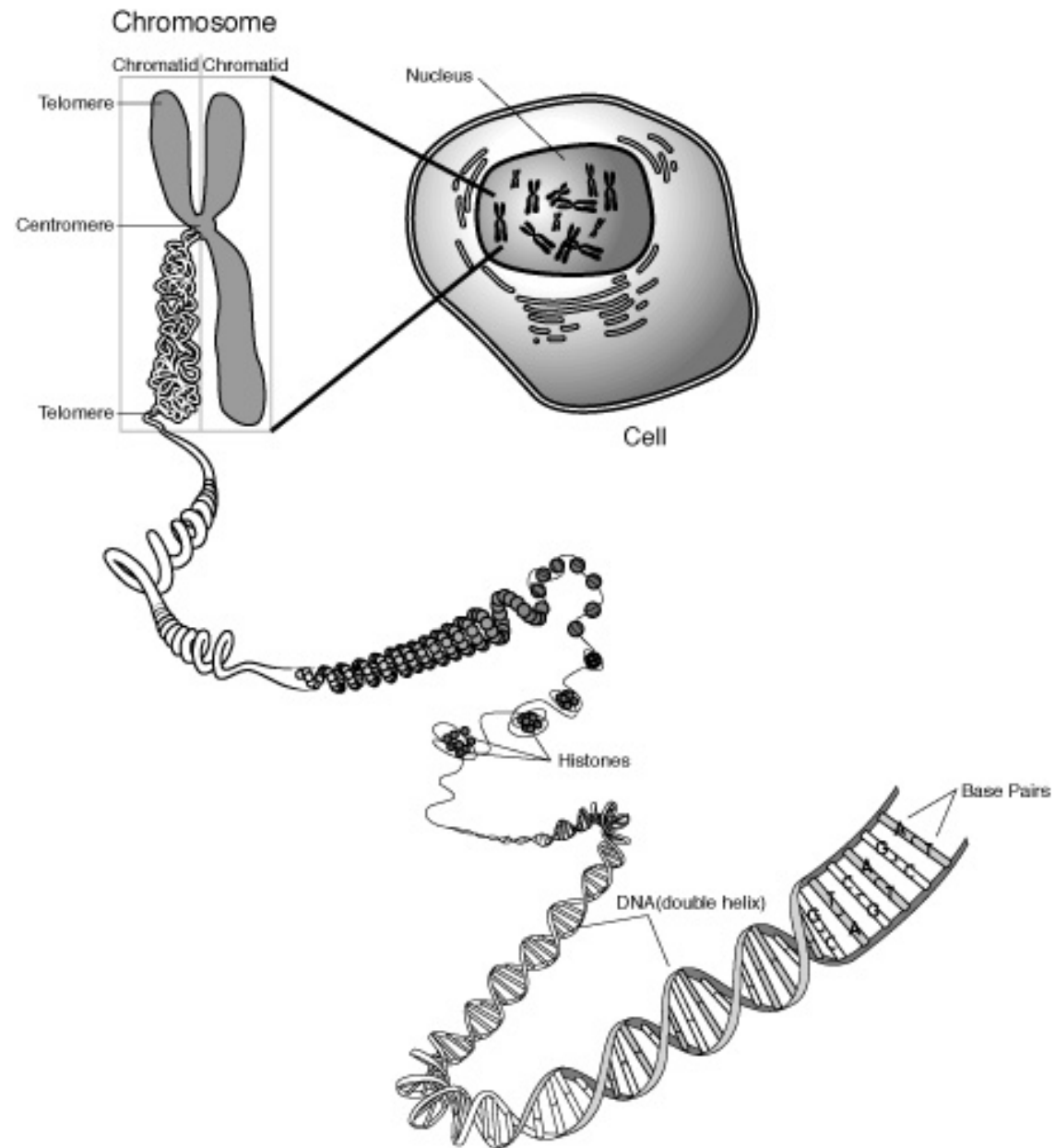
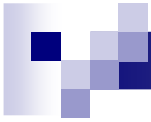
- Human Genome Project (人類基因組計劃)
 - 1990 – 2003
- Sped up gene discovery
 - estimated ~30,000 genes
- Variations: ~0.1% between any two individuals





Types of genetic disorders

- Chromosomal disorders (染色體異常)
- Monogenic disorders (單基因遺傳病)
- Multifactorial disorders (多種因素形成之疾病)





Chromosomes (染色體)

- Human beings have 46 chromosomes
 - 22 pairs autosomes (常染色體)
 - 1 pair sex chromosomes (性染色體)
 - Male - XY
 - Female - XX

染色體分析



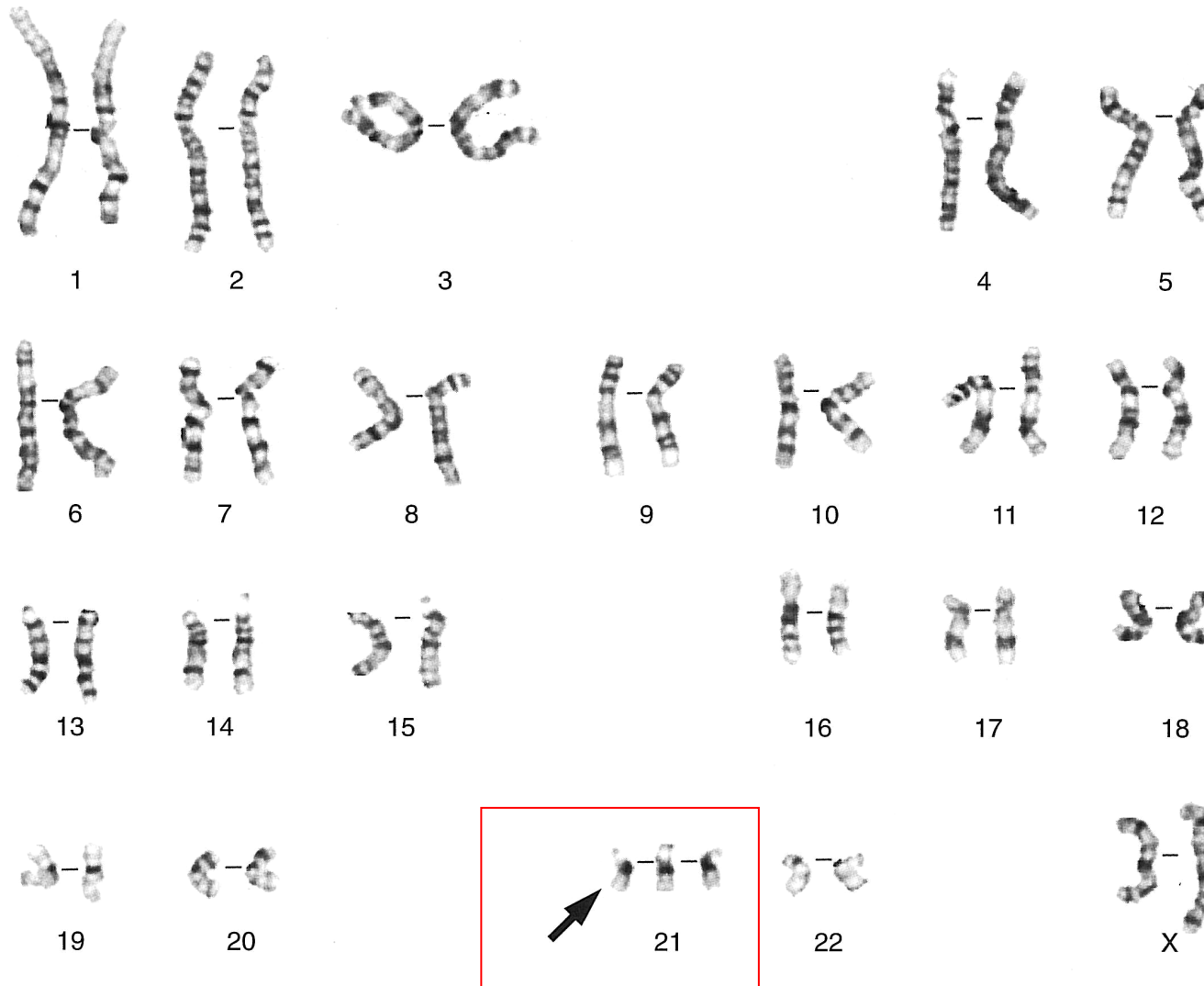


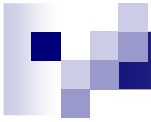
染色體異常

- **Aneuploidy (數目異常)**
 - E.g. Down syndrome (唐氏綜合症), Turner syndrome (特納氏綜合症)
- **Structural abnormalities (結構異常)**
 - Deletion, duplication, inversion, translocation (易位)

TRISOMY 21 KARYOTYPE - DOWN SYNDROME

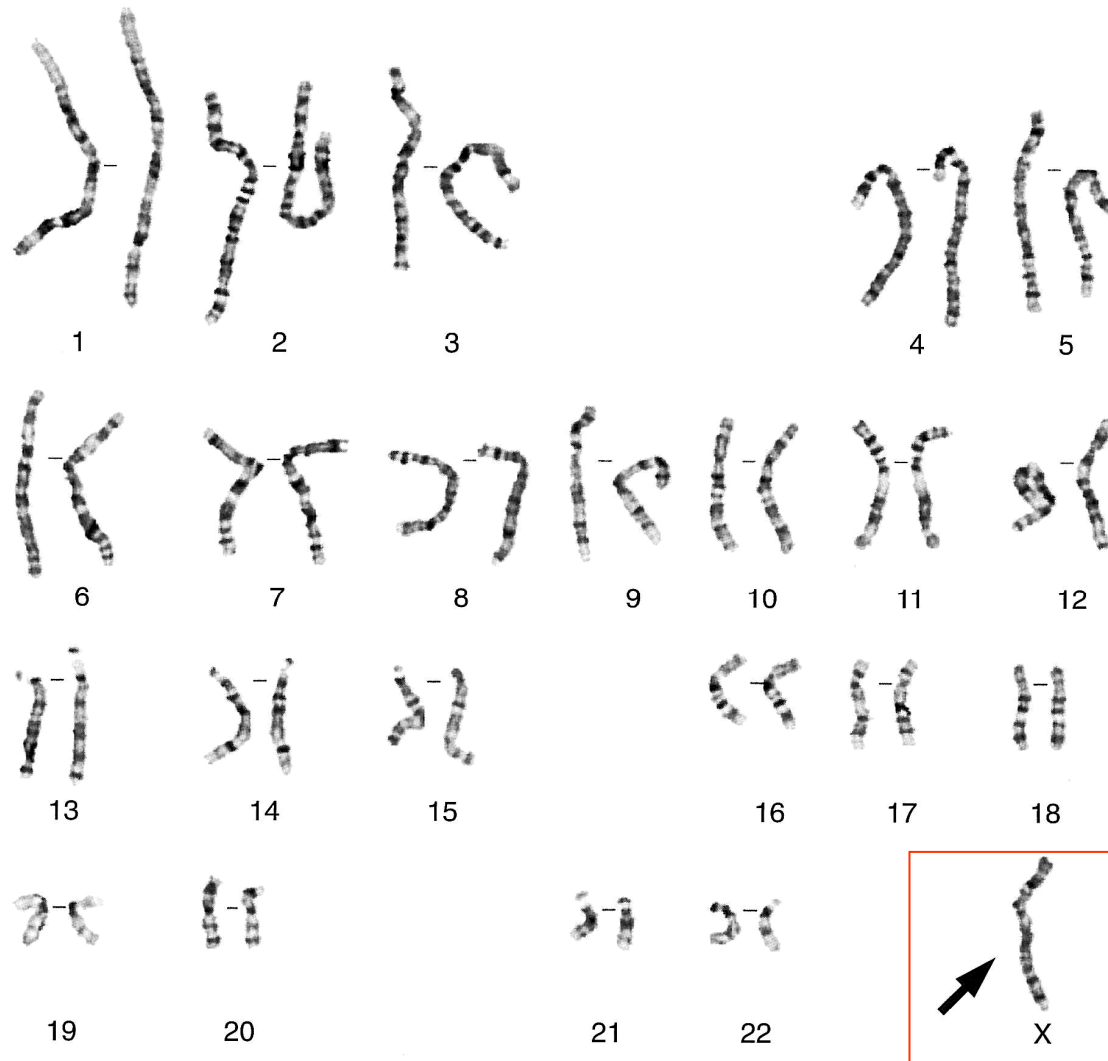
47,XX,+21



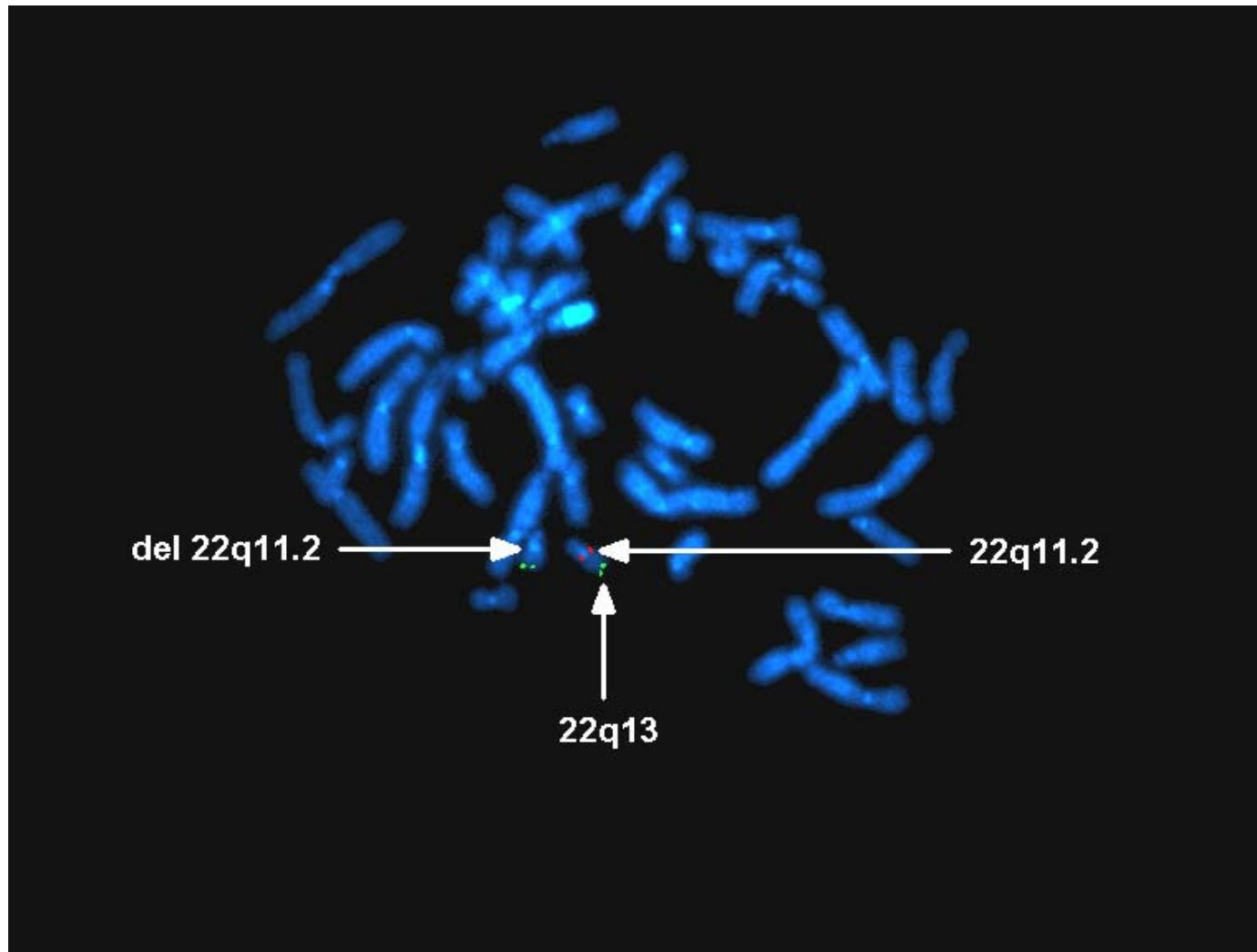


TURNER SYNDROME KARYOTYPE

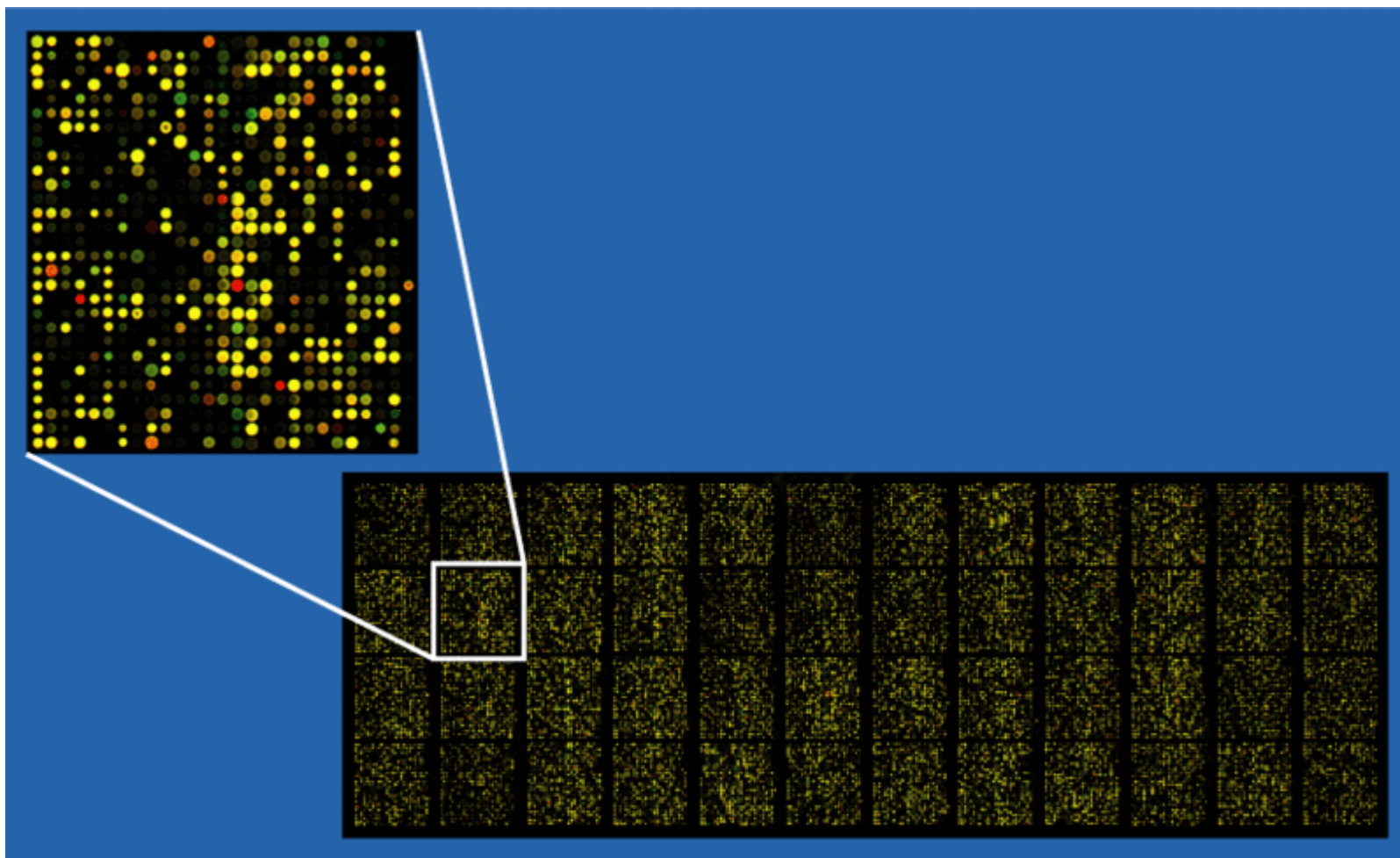
45,X



螢光雜交技術 (FISH)



DNA 芯片 (Microarray)





單基因遺傳病

■ Mendelian inheritance

- Autosomal dominant (常染色體顯性遺傳)
- Autosomal recessive (常染色體隱性遺傳)
- X-linked dominant (性連鎖顯性遺傳)
- X-linked recessive (性連鎖隱性遺傳)

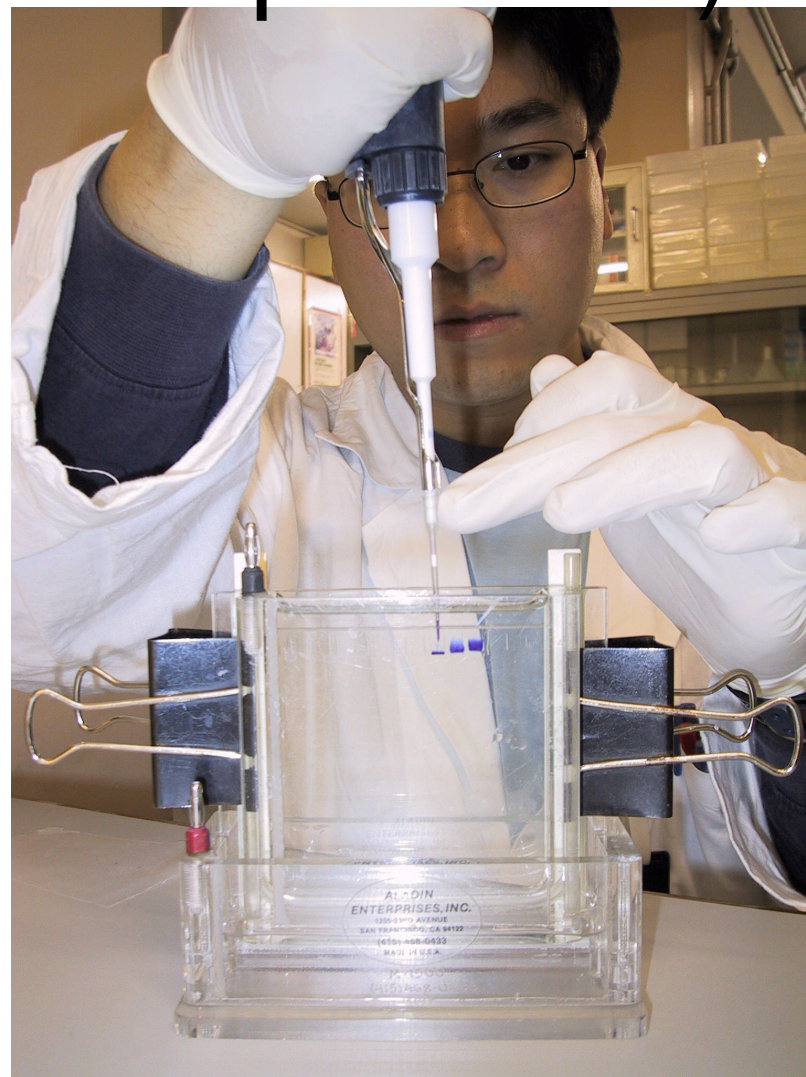
DNA (脱氧核糖核酸)

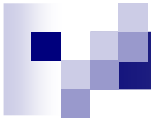


聚合酶鏈反應 (PCR)



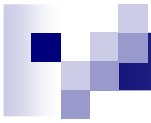
電泳 (Electrophoresis)



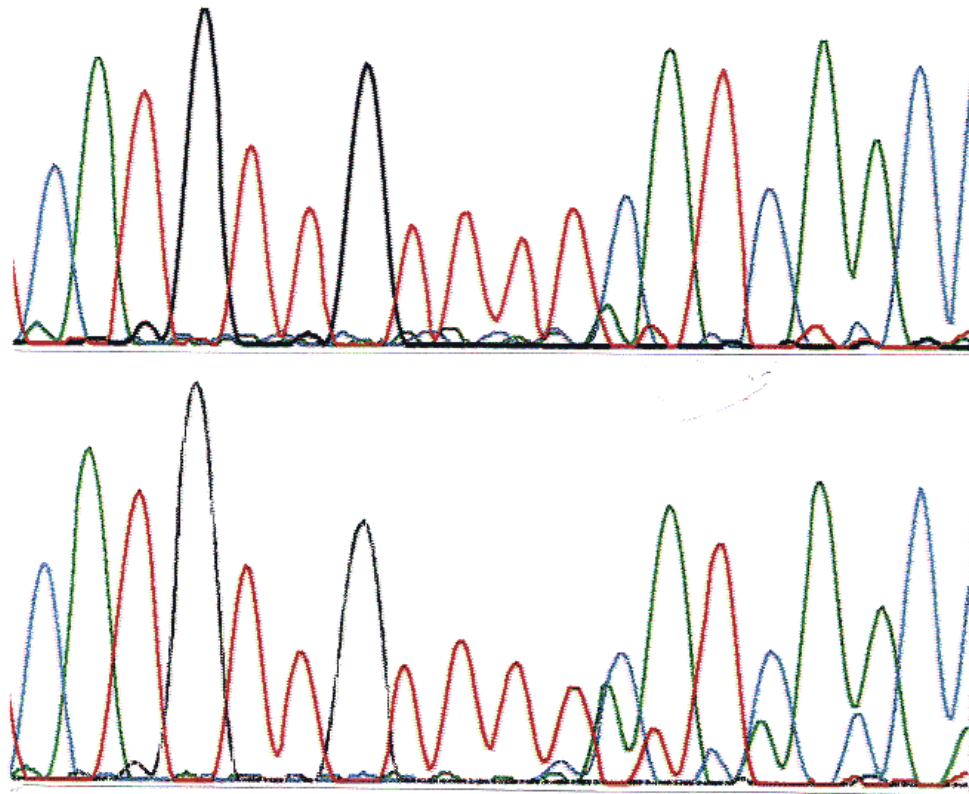


DNA 序列 (sequencing)





C A T / G T T / G T T / T T C / A T C / A A C C
190



Molecular testing in Genetic Laboratory, CGS

Diseases	Genes
Fragile X-A syndrome	<i>FMR1</i>
Fragile X-E syndrome	<i>FMR2</i>
Huntington disease	<i>HTT</i>
Kennedy disease	<i>Androgen receptor</i>
Friedreich ataxia	<i>X25</i>
Myotonic dystrophy	<i>DMPK</i>
Pseudoachondroplasia	<i>COMP</i>
Spinocerebellar ataxia	<i>SCA1</i> <i>SCA2</i> <i>SCA3</i> <i>SCA6</i> <i>SCA7</i> <i>SCA8</i> <i>SCA12</i>
Dentatorubral-pallidolusian atrophy	<i>DRPLA</i>
Duchenne Muscular Dystrophy	<i>DMD</i>
Charcot-Marrie-Tooth disease	<i>PMP22</i> <i>MPZ</i> <i>GJB1</i>
Pelizaeus Merzbacher disease	<i>PLP</i>
Prader-Willi syndrome	Chromosome 15q11-q13
Angelman syndrome	Chromosome 15q11-q13
Spinal muscular atrophy	<i>SMN</i>
α -Thalassaemia	<i>HBA</i>
β -Thalassaemia	<i>HBB</i>
Achondroplasia / Hypochondroplasia/ Thanatophoric dysplasia	<i>FGFR3</i>
Craniosynostosis, syndromic	<i>FGFR2</i>
Marfan syndrome	<i>FBN1</i>
Waardenburg syndrome type 1	<i>PAX3</i>
Deafness, non-syndromic	<i>GJB2</i> , <i>GJB6</i> , mtDNA A1555G
MELAS	mtDNA A3243G
MERRF	mtDNA A8344G
NARP	mtDNA T8993G

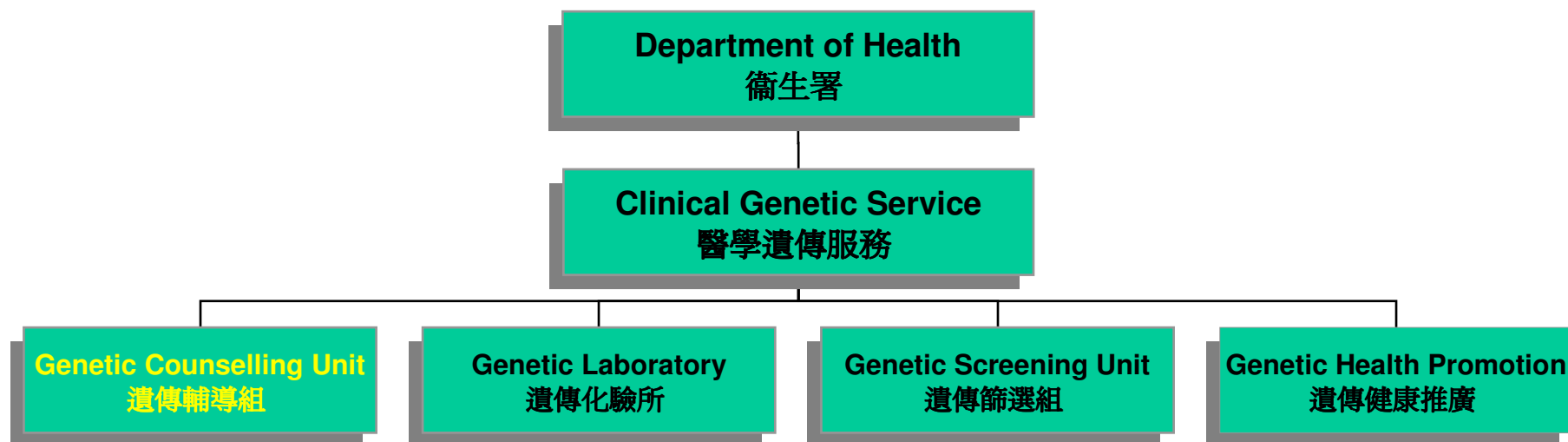
Diseases	Genes
Sex determination	<i>SRY</i>
X-inactivation	<i>Androgen receptor</i>
Polycystic kidney disease	<i>PKD1</i> (linkage) <i>PKD2</i> (linkage) <i>ARPKD</i> (linkage)
Leri-Weill syndrome	<i>SHOX</i>
Glutaric Aciduria type 1	<i>GCDH</i>
Haemophilia A	<i>Factor VIII</i>
Incontinentia pigmenti	<i>NEMO</i>
Alport syndrome	<i>COL4A5</i> (linkage)
Neurofibromatosis type 1	<i>NF1</i>
Pyruvate dehydrogenase deficiency	<i>PDH1</i>
Rett syndrome	<i>MECP2</i>
Gaucher disease	<i>GCB</i>
Noonan syndrome	<i>PTPN11</i>
Blepharophimosis-Ptois-Epicanthus Inversus syndrome	<i>FOXL2</i>
Sotos syndrome	<i>NSD1</i>
Triple A syndrome	<i>AAAS</i>
Fabry's disease	<i>GLE</i>
Subtelomeric chromosomal deletion/duplication	
Saethre-Chotzen syndrome	<i>Twist</i>
Trisomies 13, 18, 21	
Greig syndrome	<i>GLI3</i>
Congenital Central Hypoventilation	<i>PHOX2B</i>
Conradi-Hunermann syndrome	<i>EBP</i>
Schwartz-Jampel syndrome	<i>LIFR</i>
Spondylocostal dysplasia	<i>DLL3</i>
Metaphyseal dysplasia, McKusick type	<i>RMRP</i>
Pseudohypoparathyroidism	<i>GNAS1</i>
Diastrophic dysplasia	<i>DTDST</i>
Senior-Loken syndrome	<i>IQCB1</i>
Larsen syndrome	<i>FLNB</i>



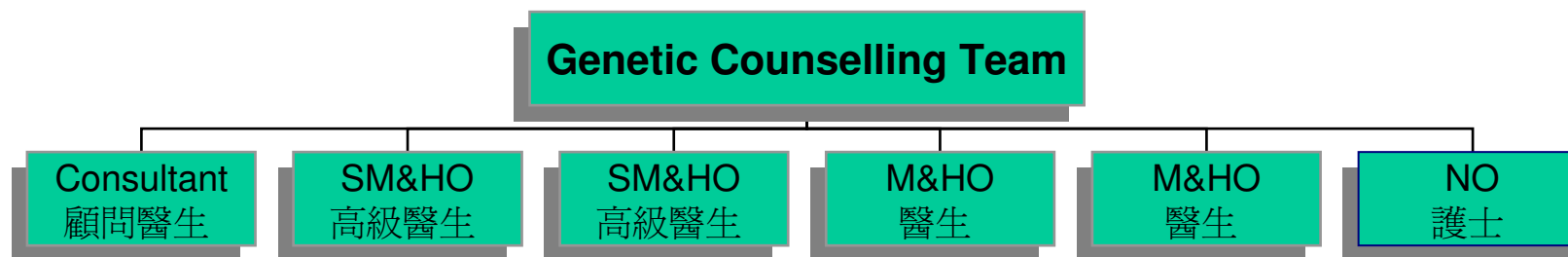
Management

- Few chromosomal or single gene disorders have curative treatment
 - Gene therapy (基因治療)
 - Transplantation (移植)
 - Stem cell (幹細胞)
- Prevention
 - Genetic counselling (遺傳輔導)
 - Prenatal diagnosis (產前診斷)

衛生署醫學遺傳服務



遺傳輔導組





遺傳輔導組

- The only service in HK and in China that provides comprehensive genetic services on a territory-wide basis, playing a primary role in genetic diagnosis, counselling and prevention.
- By referral (轉介) from other medical professionals



Clinic Locations

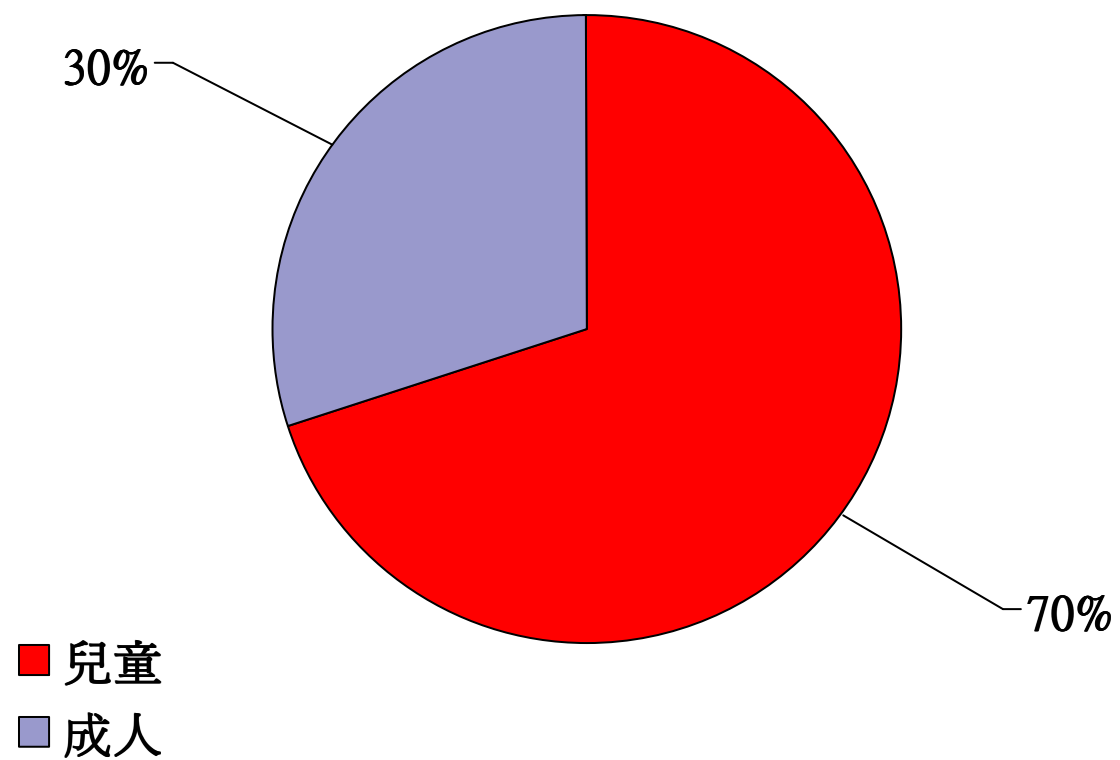
- 1/F Cheung Sha Wan Jockey Club Clinic
- Satellite clinics
 - Queen Elizabeth Hospital, KLN
 - 4/F Ambulatory Care Centre
 - L-blk



Clinic Set-up

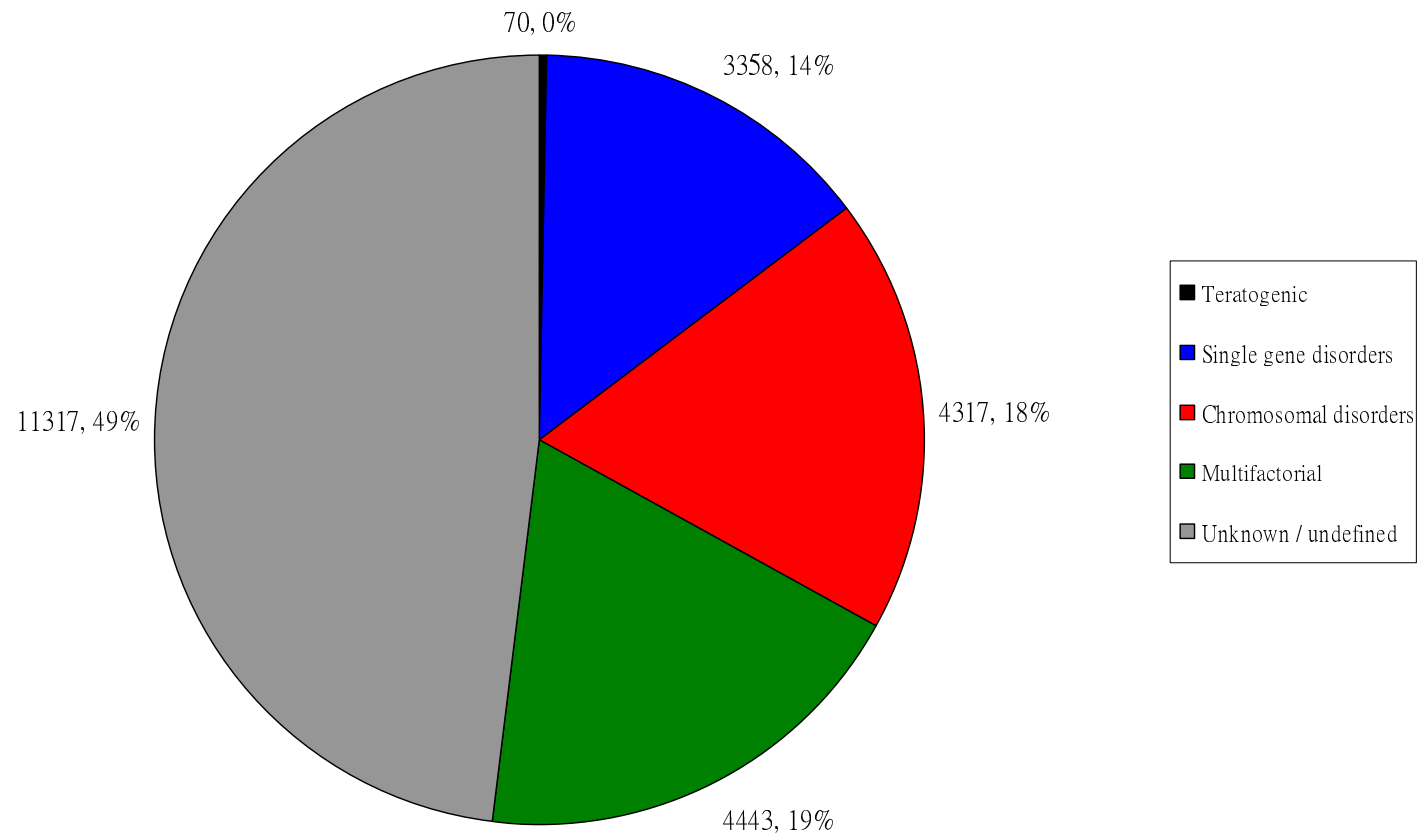
- 20-22 clinic sessions / m
 - ~1,200 new cases / yr
 - ~2,300 follow-up cases / yr
- 1981-2006
 - 23,505 families attended

Our Clients



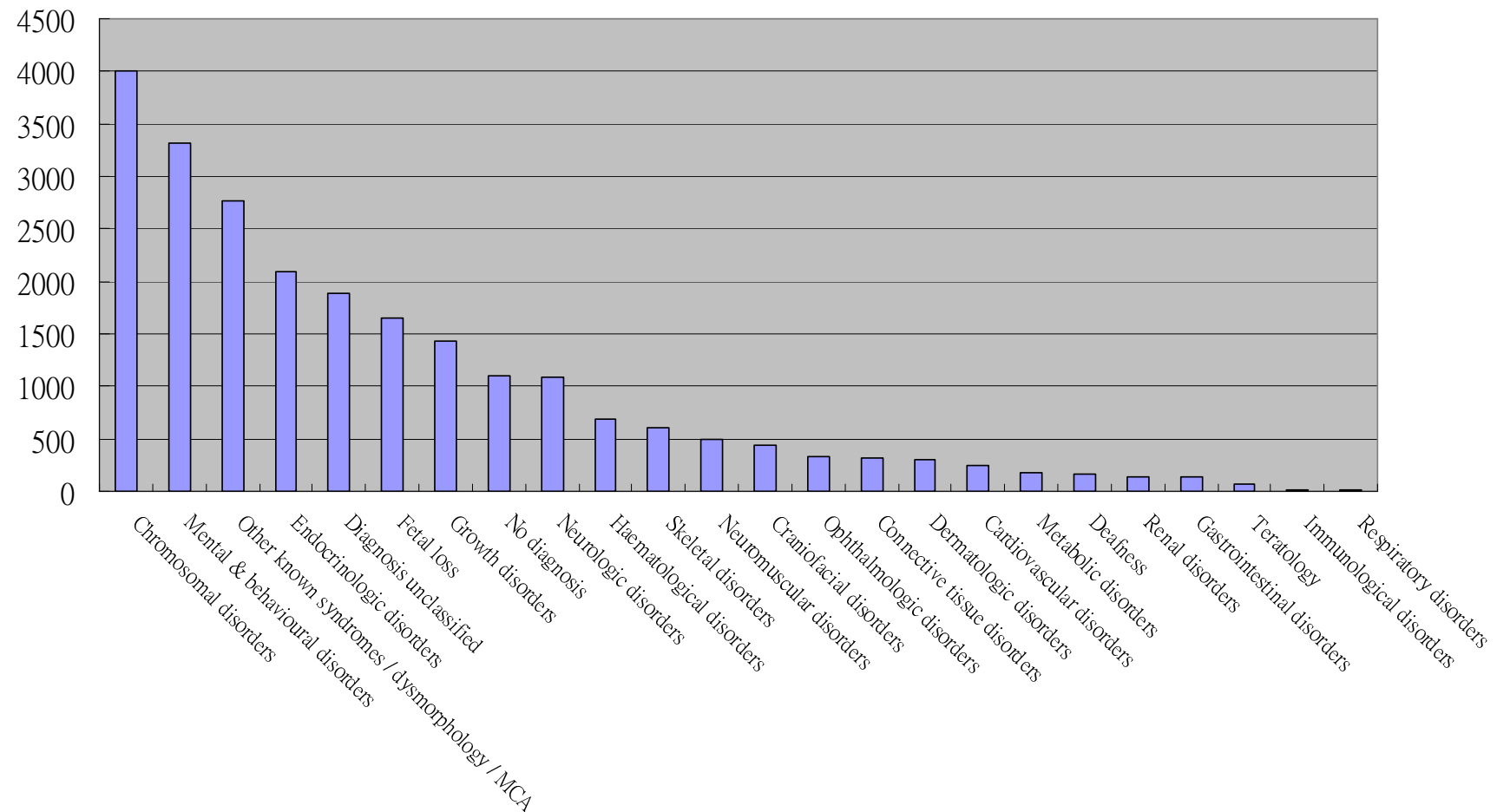
Types of Disorders (以病原分類)

Chart 1



Types of Disorders (以系統分類)

Chart 2





遺傳輔導的定義

- Peter Harper

- “Genetic counselling is the process by which patients or relatives at risk of a disorder that may be hereditary are **advised of the consequences** of the disorder, the **probability of developing or transmitting it** and of the **ways in which this may be prevented, avoided or ameliorated.**”

- Preventive medicine (預防性醫學)



遺傳輔導

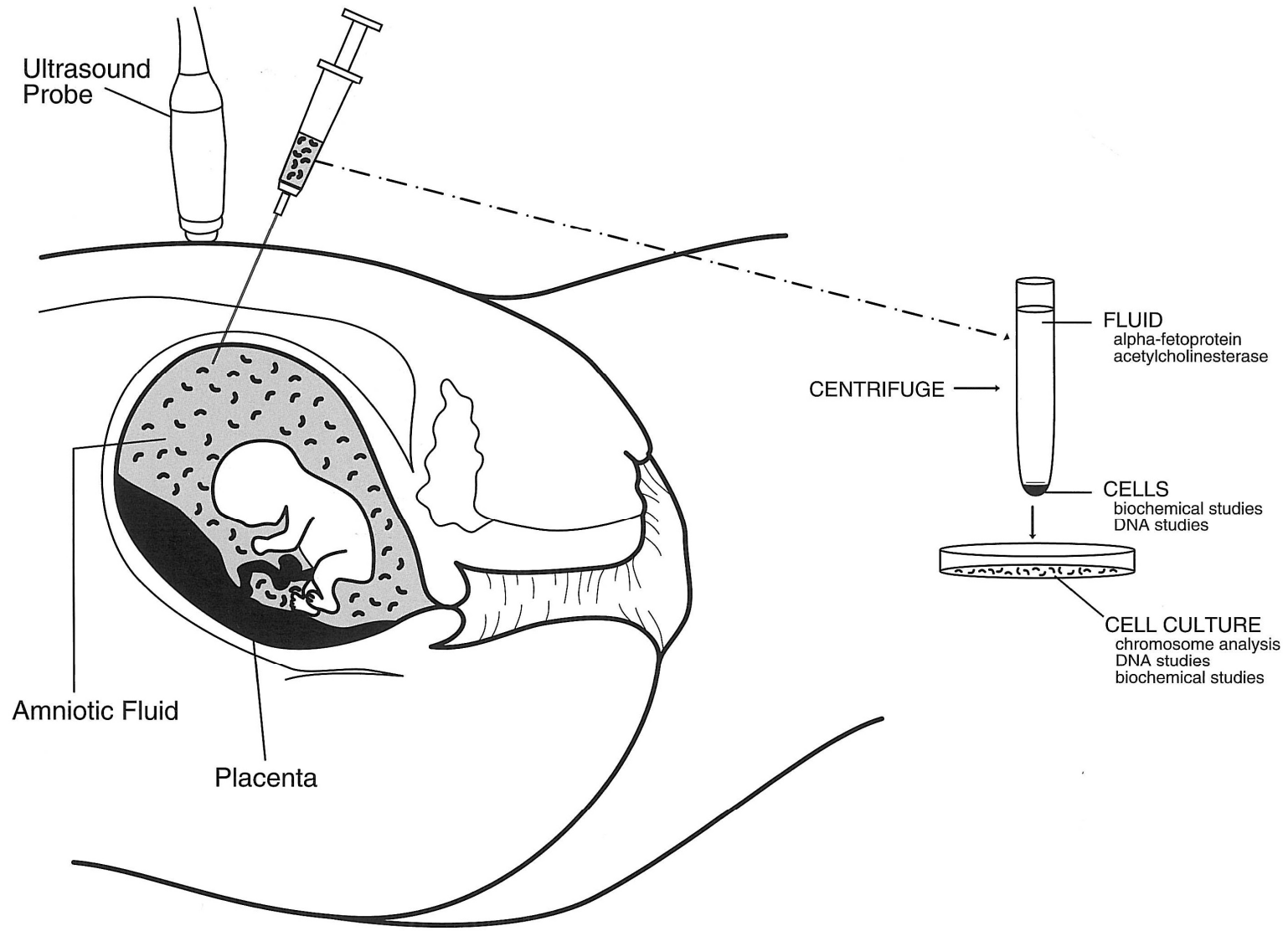
- Provide ample information for patients or family members to make fully informed decisions
 - Diagnosis, natural course
 - Hereditary or not
 - Mode of inheritance (遺傳模式)
 - Risk of recurrence (復現風險)
 - Prenatal diagnosis or PGD (產前/植入前遺傳診斷)
 - Contraception, sterilization, alternative reproductive options
 - Assess other family members at risk



Fetal ultrasound



PRENATAL DIAGNOSIS BY AMNIOCENTESIS





Prevalence of Genetic Disorders

- Chromosomal disorders (染色體異常) 3.8 / 1,000
- Monogenic disorders (單基因遺傳病) 20 / 1,000
- Multifactorial disorders (多種因素形成之疾病) 650 / 1,000



多種因素形成之疾病

Genetic
mutations/variation

+ Environmental factors

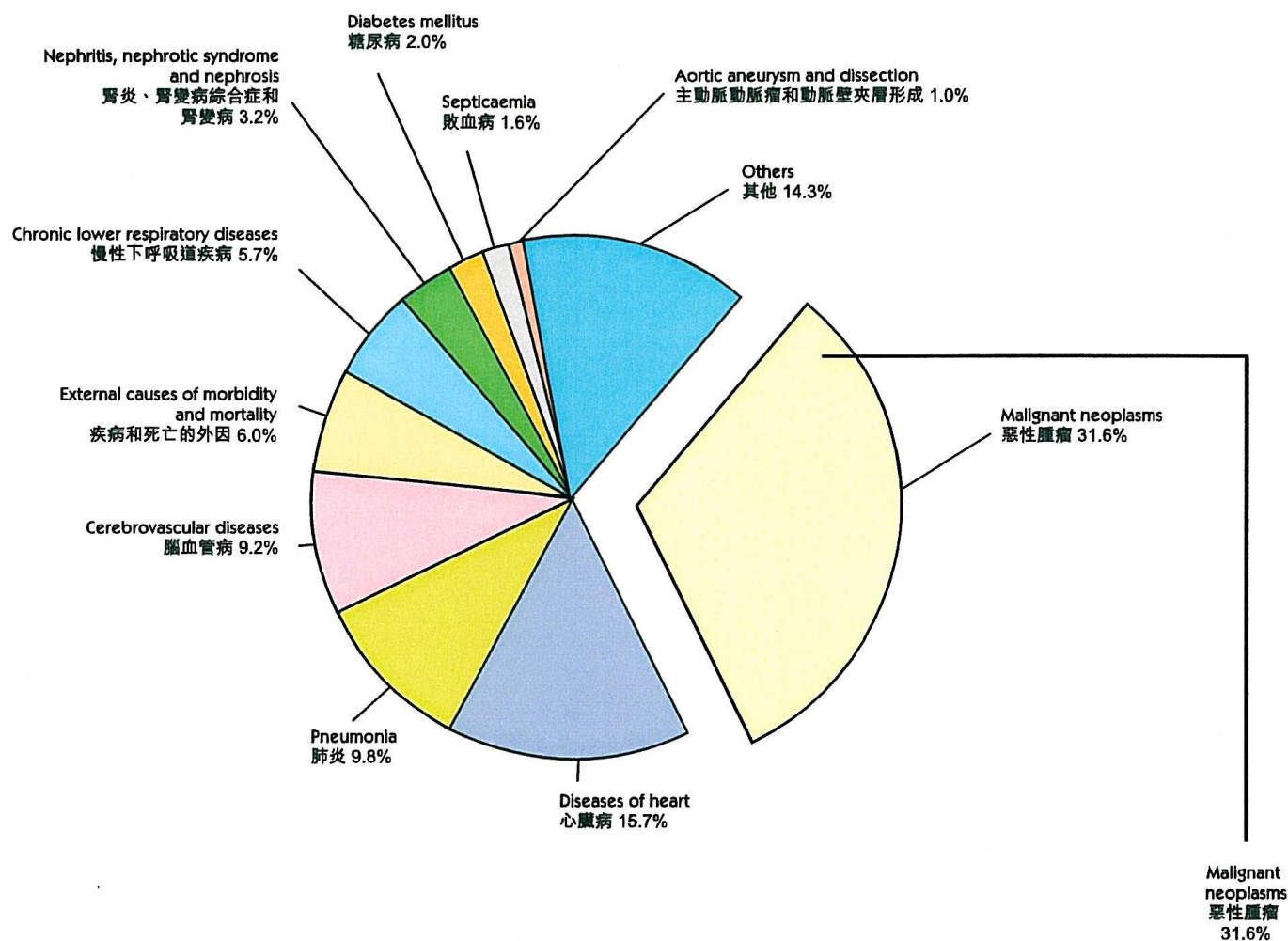
Disease



Genomics

- The study of all the genes in a person, as well as interactions of those genes with each other and with that person's environment.
- Plays a part in nine of the ten leading causes of death in the US.

10 leading causes of death (HK, 2004)



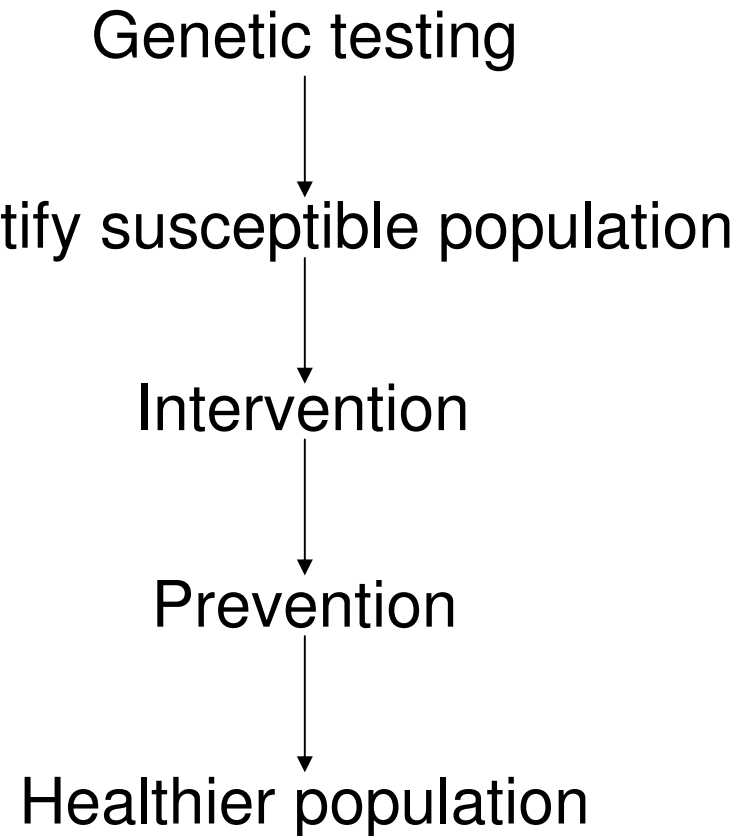


Genetic susceptibility (易感性)

- All human beings are 99.9% identical in genetic makeup, but differences in the remaining 0.1% may hold important clues about the causes of disease.



Public Health Genetics



Acknowledgment

- Dr. S. Lam, Consultant Clinical Geneticist
- Genetic Counselling Team
- Genetic Laboratory

