Medical Genetics

•LECTURE 5

Atypical Patterns of Inheritance
Genetic counseling (Exercise)

- Foundation Block
- Genetics
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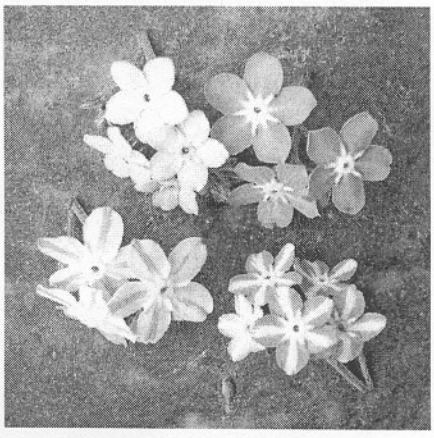
Inheritance of Codominant alleles

Codominance: **two allelic traits that are both expressed in the heterozygous state.**
Example: Blood group AB: the A and B blood groups are *codominant.*



Codominance

(Dominance / Recessive / Multiple Alleles)

ABO genotypes and phenotypes

Genotype	Phenotype	red cell antigens	serum antibodies
AA	A	A	anti-B
AO	A	A	anti-B
BB	B	B	anti-A
BO	B	B	anti-A
AB	AB	A and B	neither
OO	O	neither	anti-A and anti-B

Incomplete dominance (Intermediary inheritance)

Parental Pure Line Cross (P1): RR  x rr 

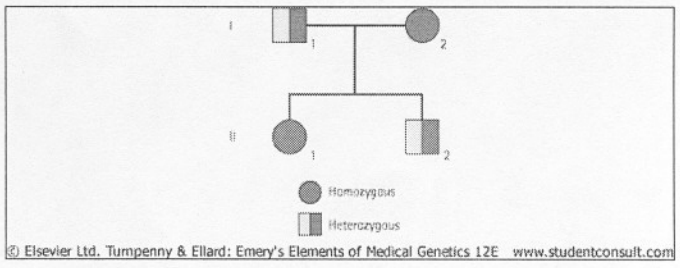
F1 generation: all Rr heterozygotes 

F1 cross: Rr  x Rr 

Gametes:

	R	r
R	 RR	 Rr
R	 Rr	 rr

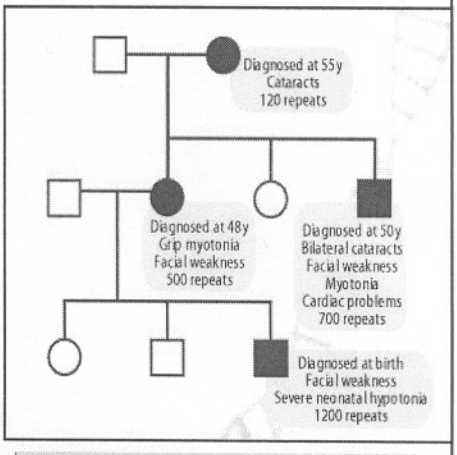
Pedigree: Pseudodominant inheritance

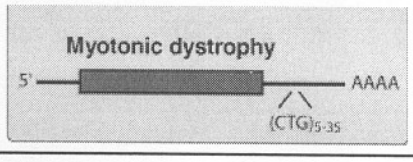


- A woman homozygous for an autosomal recessive disorder whose husband is heterozygous for the same disorder.
- Their children have a 1 in 2 (50%) chance of being affected i.e. homozygous) i.e. pseudodominant

Anticipation

- It is now known that some genetically inherited diseases have more severe symptoms each succeeding generation due to segments of the defective genes being doubled in their transmission to children (as illustrated). These are referred to as Anticipation
- Examples of diseases showing anticipation:
  - Huntington disease
  - Myotonic dystrophy

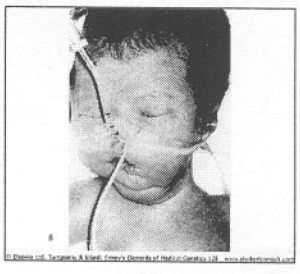




Myotonic Dystrophy

- Autosomal dominant disease
- Relatively common
- The affected gene is on chromosome 19
- The mutation is triplet repeat (CTG) expansion in the 3` untranslated region of the myotonic dystrophy gene
- Clinical manifestations:
  - –Myotonia (Muscular loss & weakness)
  - –Cataracts
  - –Testicular atrophy
  - –Heart disease: arrhythmia
  - –Dementia
  - –Baldness

Myotonic Dystrophy, CONTD.



Newborn baby with severe hypotonia requiring ventilation as a result of having inherited myotonic dystrophy from his mother

The Hardy-Weinberg law

to calculate **genotype frequencies from allele frequences**.
Let

p is the frequency of allele A1 $0 =< p =< 1$

q is the frequency of allele A2 $0 =< q =< 1$ and $p + q = 1$

if they procreate : $(p + q)^2 = p^2 + 2pq + q^2 = 1$
where:
p^2 = frequency of the A1 A1 genotype <-- HOMOZYGOTE
2pq = frequency of the A1 A2 genotype <- HETEROZYGOTE
q^2 = frequency of the A2 A2 genotyp <-- HOMOZYGOTE

these frequencies remain constant in successive generations.

autosomal recessive inheritance

--> frequency of the genotypes: :	AA = p^2	and the phenotypes [ ]:	[A] = $p^2 + 2pq$
	Aa = 2pq		[a] = q^2
	aa = q^2		

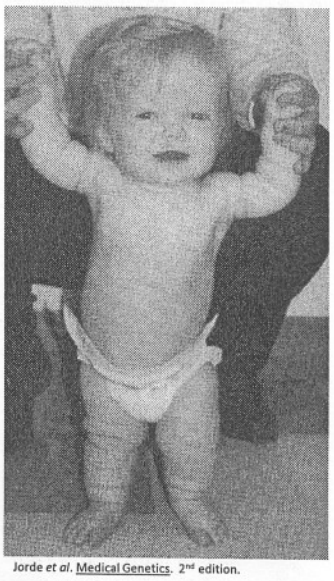
Genetic Counselling

An educational process that seeks to assist affected and/or at risk individuals to understand the nature of the genetic disorder, its transmission and the options open to them in management and family planning

Kelly 1986

Achondroplasia

- AD; 1/15,000
- Defect in *FGFR3;* 4p16
- Most common non-lethal Sk. Dys.
- 80% new mutations
- Macrocephaly with midface hypoplasia
- Rhizomelic limb shortening
- Normal intelligence, usually



Jorde *et al.* Medical Genetics. 2nd edition.

Genetic Possibilities of Achondroplasia

- Occurs in every 1/15,000 to 1/40,000 births.
- 80% of cases from a spontaneous *de novo* mutation (in spermatogenesis of father)
- 20% inherited from one or two affected parents

	A	a
a	Aa	aa
a	Aa	aa

Affected parent and non-affected parent
50% chance of having affected child

	A	a
A	AA	Aa
a	Aa	aa

Both parents affected
75% chance of having affected child

Atypical presentation for Autosomal Dominant defects

pleiotropy, reduced penetrance and variable expressivity

of a mutant allele need to be taken into account when providing genetic counseling to individuals at risk for autosomal dominantly inherited disorders.
Myotonic Dystrophy, CONTD.