Genetics of common disorders with complex inheritance

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Knowledge / Experience / Care

Universiteit Antwerpen / UZA

Program

Day 6: Genetics of common disorders with complex inheritance
Thompson&Thompson chapter 8

9.30-10h	Elementary concepts of multifactorial diseases *Bettina Blaumeiser*
10-10.45h	Concepts in complex genetics: from Fisher to GWAS *Guy Van Camp*
10.45-11.30h	Beyond GWAS *Erik Fransen*
11.30-12h	Osteoporosis as paradigm for studies into complex diseases *Wim Van Hul*
12-13h	**lunch break**
13-14h	Of mice and human genetics *Frank Kooy*
14-17h	Data mining *Geert Vandeweyer, Wim Wuyts*

Location
Z.421, Z.422, Z.423 (for the part 'Data mining')

Influenza	Diabetes	**Cystic fibrosis**
Varicella	Cancer	**Huntington**
Infections	Cardiac disease	**Steinert**

Environment **Genes**

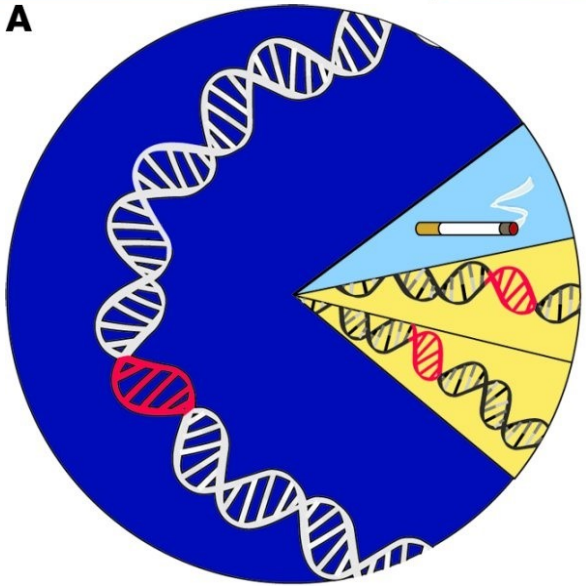
Frequency of genetically determined diseases

Type genetic disease	frequency/1000 individuals
• multifactorial diseases	70 - 90
• congenital malformations	20 - 50
• chromosome abberrations	6 - 9
• monogenic	4.5 - 15
- autosomal dominant	3 - 9.5
- autosomal recessive	2 - 2.5
- X-linked	0.5 - 2

Multifactorial inheritance

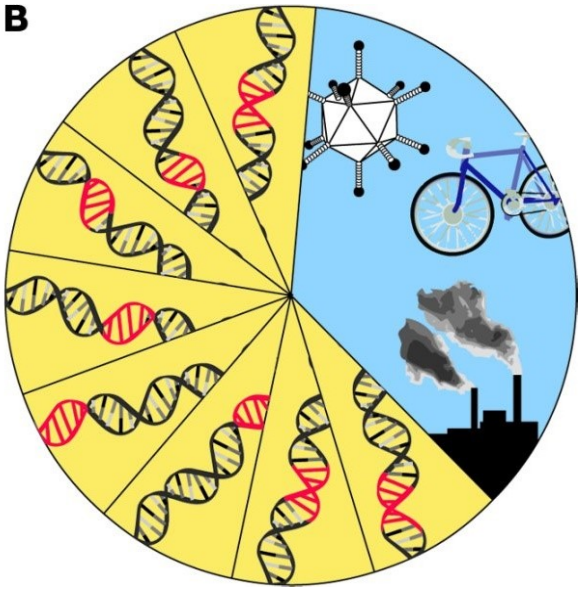
A. Monogenic disease: rare

- cf. CF: incidence 1/2500, most frequent AR disease
- genes largely known



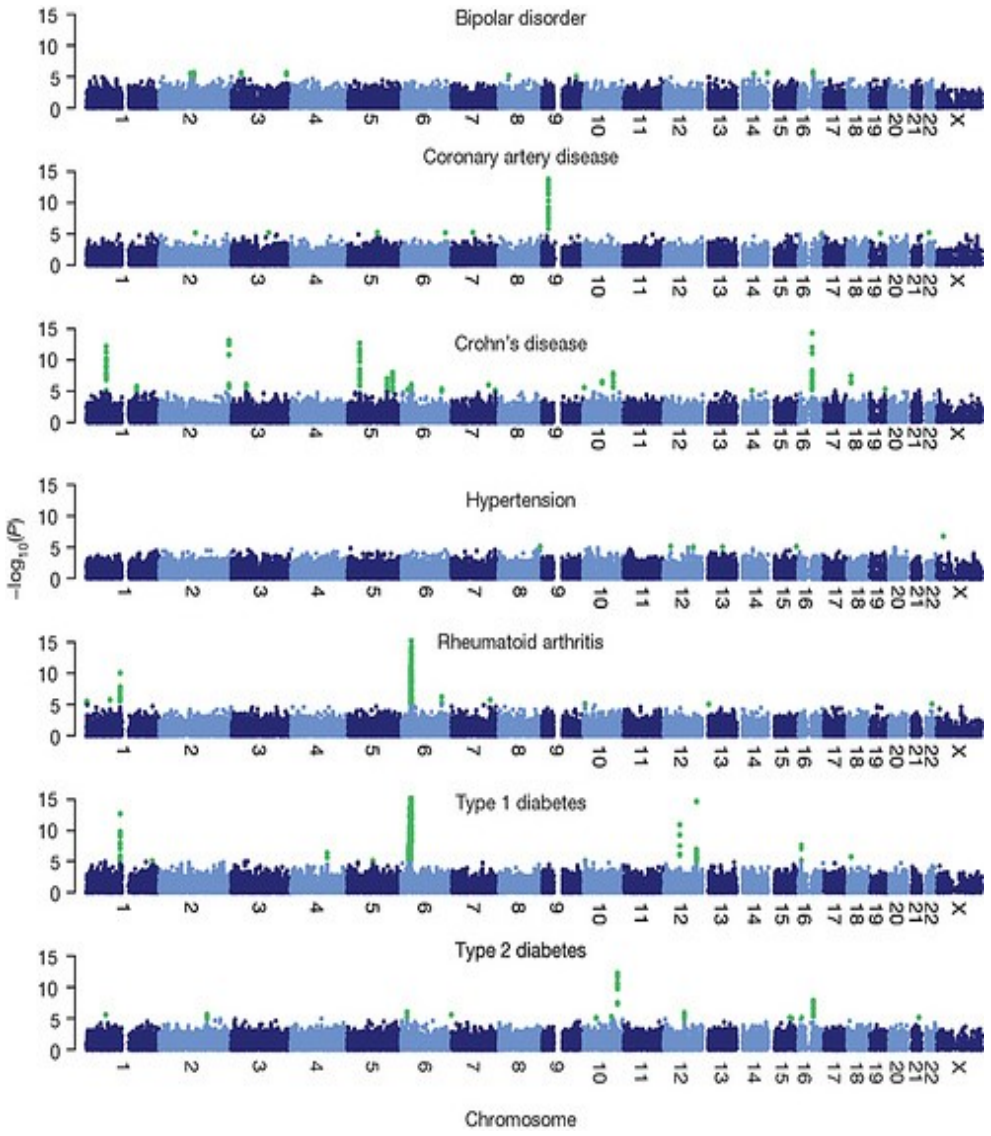
B. Multifactorial disease: frequent

- More complex study design
- 2007 WTCCC study



Genome-wide scan for associations of SNPs with each of the seven diseases.

Chromosomes are shown in alternating shades of blue, significant SNPs (p-values<1 x 10-5) are highlighted in green.



Nature **447**, 661-678 (7 June 2007)
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls
The Wellcome Trust Case Control Consortium

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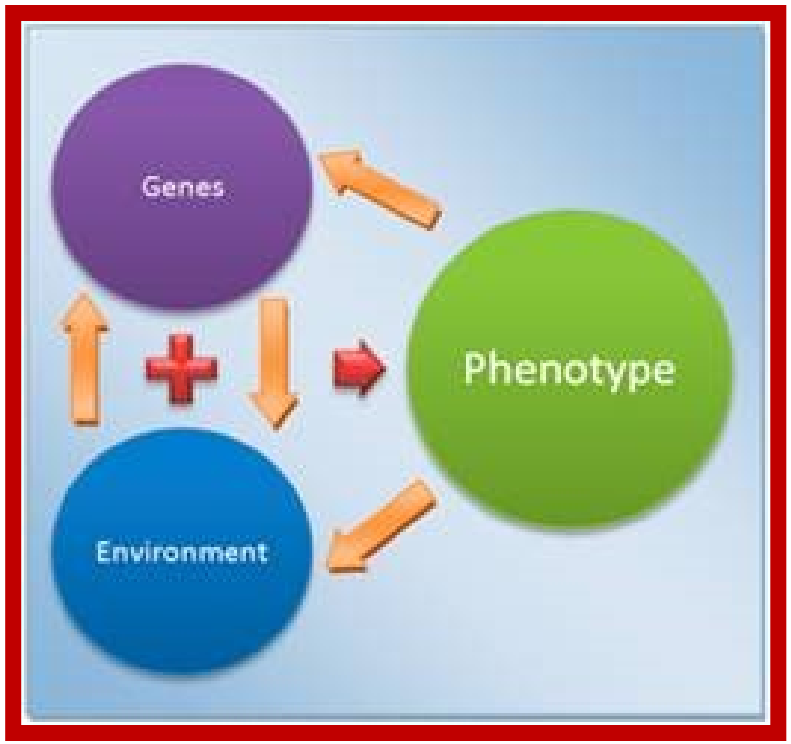
Multifactorial or complex disease



Different causes:

genes

environment

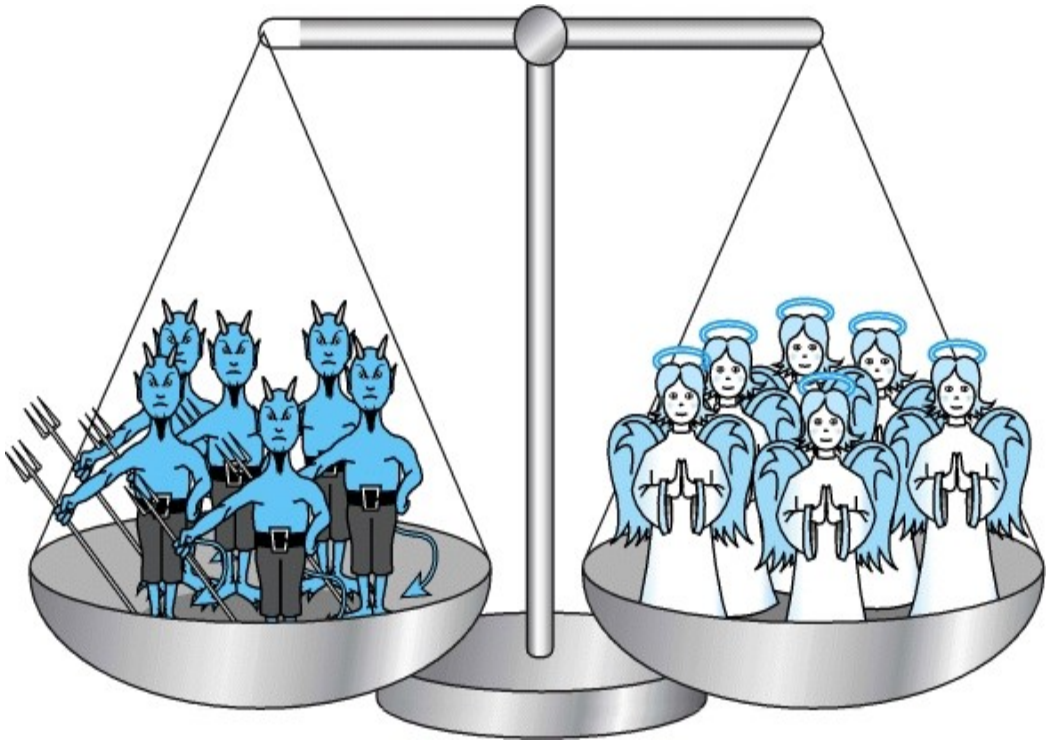
infection

stress

nutrition

cf. polygenic: multiple genes involved in development of disease

Health or illness and complex diseases



- Balance of risk and protective factors from genes and environment
- Interaction

Qualitative & Quantitative traits

Qualitative or discrete trait

disease present or absent

Quantitative trait

measurable physiological or biochemical quantities

Genetic analysis of qualitative traits

1. Familial aggregation of disease

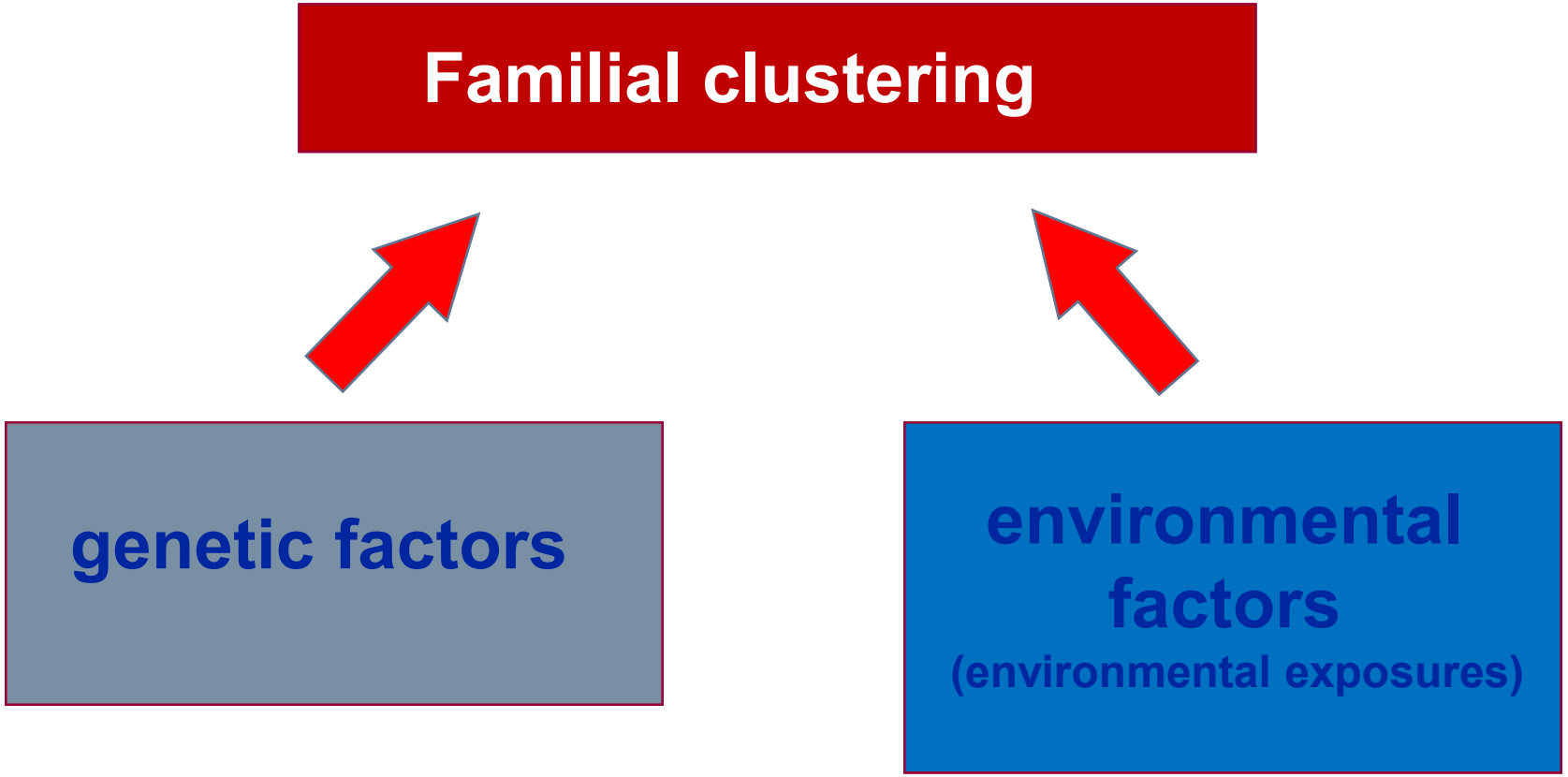
→ clustering of affected individuals in families

characteristic for complex disease

familial aggregation ≠ complex disease

cf. - chance (common trait)

- environment
- diet
- socioeconomic status
- behavior


Familial clustering
genetic factors
environmental factors
(environmental exposures)

Genetic analysis of qualitative traits

1. Familial aggregation of disease
2. Concordance & discordance
    - lack of penetrance
    - phenocopy

Genetic analysis of qualitative traits

1. Familial aggregation of disease
2. Concordance & discordance
3. Measuring familial aggregation

a. relative risk ratio λ_r

$$\frac{\text{prevalence of disease in relatives of affected person}}{\text{prevalence of disease in general population}} = \lambda_r$$

if $\lambda_r=1$ => relative risk = population risk

Risk ratios λ_r for selected complex diseases (siblings of probands)

Disease	λ_s
• Schizophrenia	12
• Autism	150
• Bipolar disorder	7
• DM type I	35
• Crohn‘s disease	25
• Multiple sclerosis	24

Genetic analysis of qualitative traits

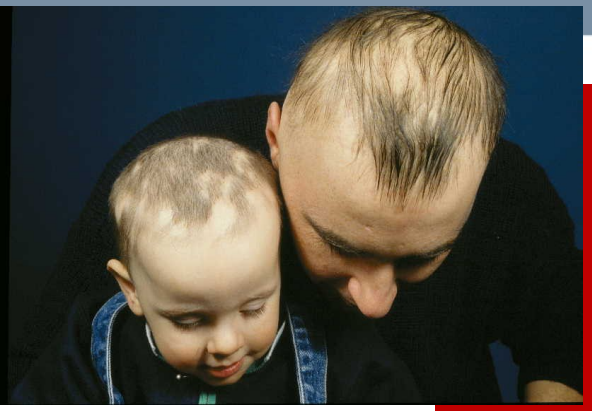
1. Familial aggregation of disease
2. Concordance & discordance
3. Measuring familial aggregation

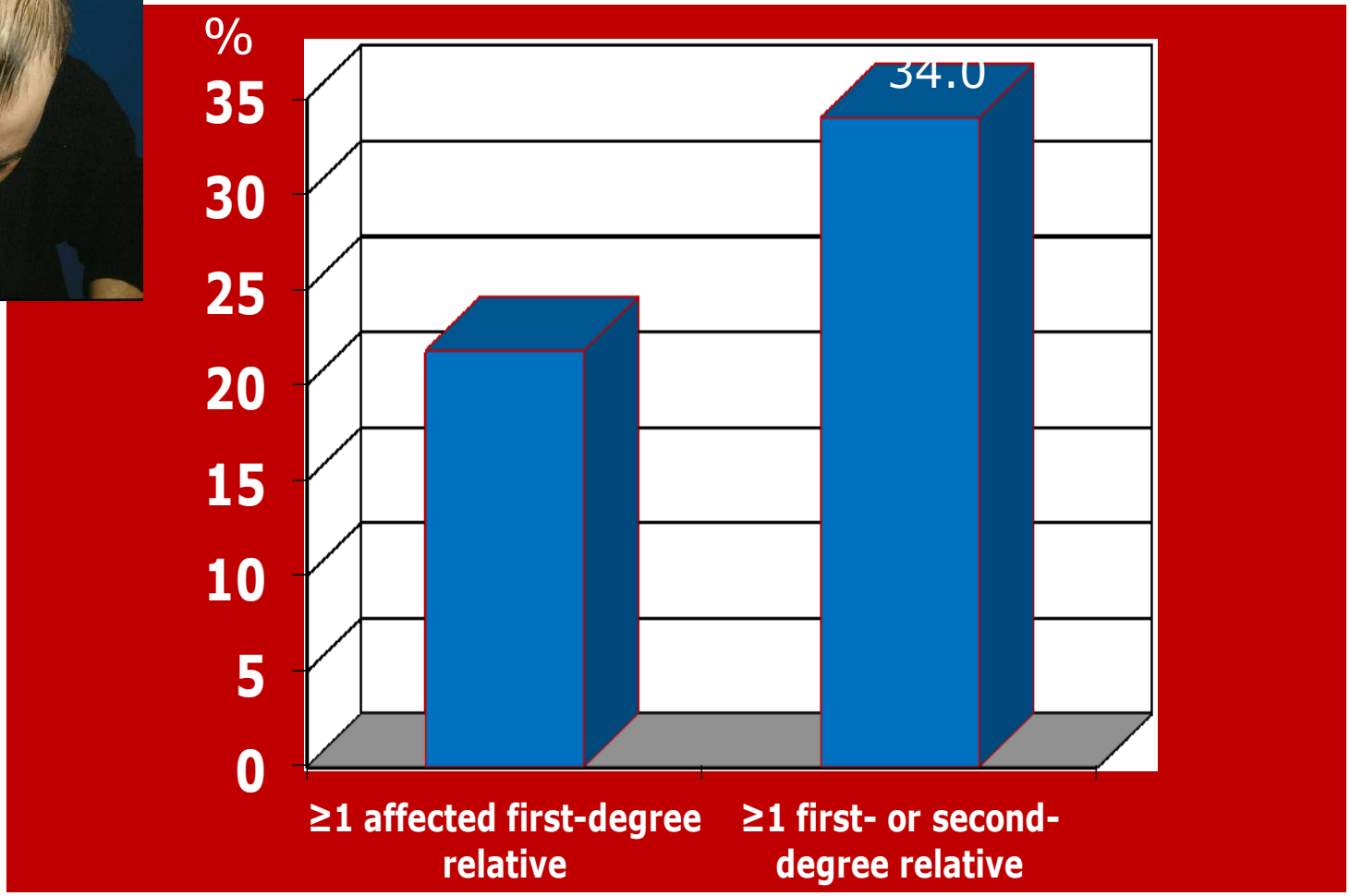
b. Case-control studies

compare cases with controls with respect to family history

Cave: - ascertainment bias
- recall bias

Familiality of alopecia areata (AA)





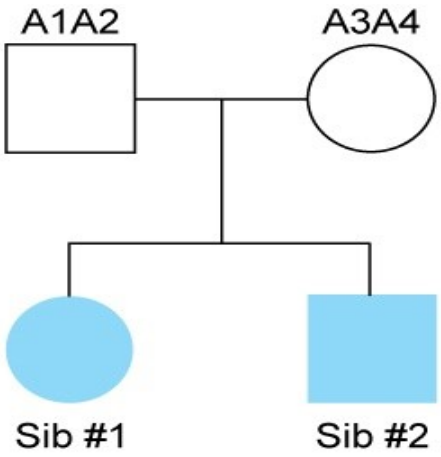
General population: 1-2%

Determining the relative contributions of genes and environment to complex disease

1. Concordance and allele sharing among relatives

dissect the contribution of genetic from environmental influences by comparing disease concordance in relatives

- monozygotic twins
- first degree relatives



Number of alleles shared in sibs:
¼ (2 alleles) + ½ (1 allele) +
¼ (0 alleles) = 1 allele

Genotype of sib #1

Genotype of sib #2	A1A3	A1A4	A2A3	A2A4
A1A3	2	1	1	0
A1A4	1	2	0	1
A2A3	1	0	2	1
A2A4	0	1	1	2

Relationship	**alleles shared**
MZ twins	1
I degree	½
II degree	¼
III degree	⅛

Determining the relative contributions of genes and environment to complex disease

1. Concordance and allele sharing among relatives
2. Unrelated family member controls

Determining the relative contributions of genes and environment to complex disease

1. Concordance and allele sharing among relatives
2. Unrelated family member controls
3. Twin studies

Twin studies

monozygotic twins (MZ):

- genetic identical, except somatic mutations and epigenetic changes

dizygotic twins (DZ):

- first degree relatives

concordant: both relatives display feature/disease

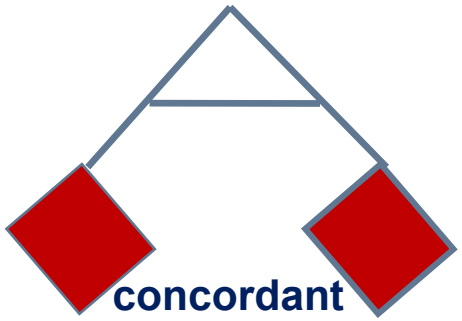
discordant: feature/disease only displayed by one relative

degree of concordance: 0 – 1

=> degree of concordance larger among MZ twins (C_{MZ}) than DZ (C_{DZ}) if genetic factors are concerned

Twin studies

monozygotic twins



dizygotic twins

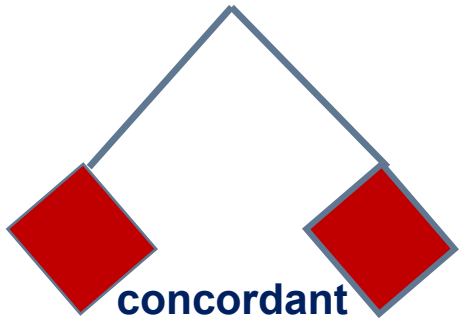


Fig. 12-5. Monozygotic twins, showing a striking similarity in physical appearance. Both twins developed myopia as teenagers.

Concordance rates in MZ and DZ twins

Disorder	C_{MZ} (%)	C_{DZ} (%)
• Nontraumatic epilepsy	70	6
• Multiple sclerosis	17.8	2
• DM type I	40	4.8
• Schizophrenia	46	15
• Bipolar disease	62	8
• Osteoarthritis	32	16
• Rheumatoid arthritis	12.3	3.5
• Psoriasis	72	15
• CL/CP	30	2
• SLE	22	0

Limitations of twin studies

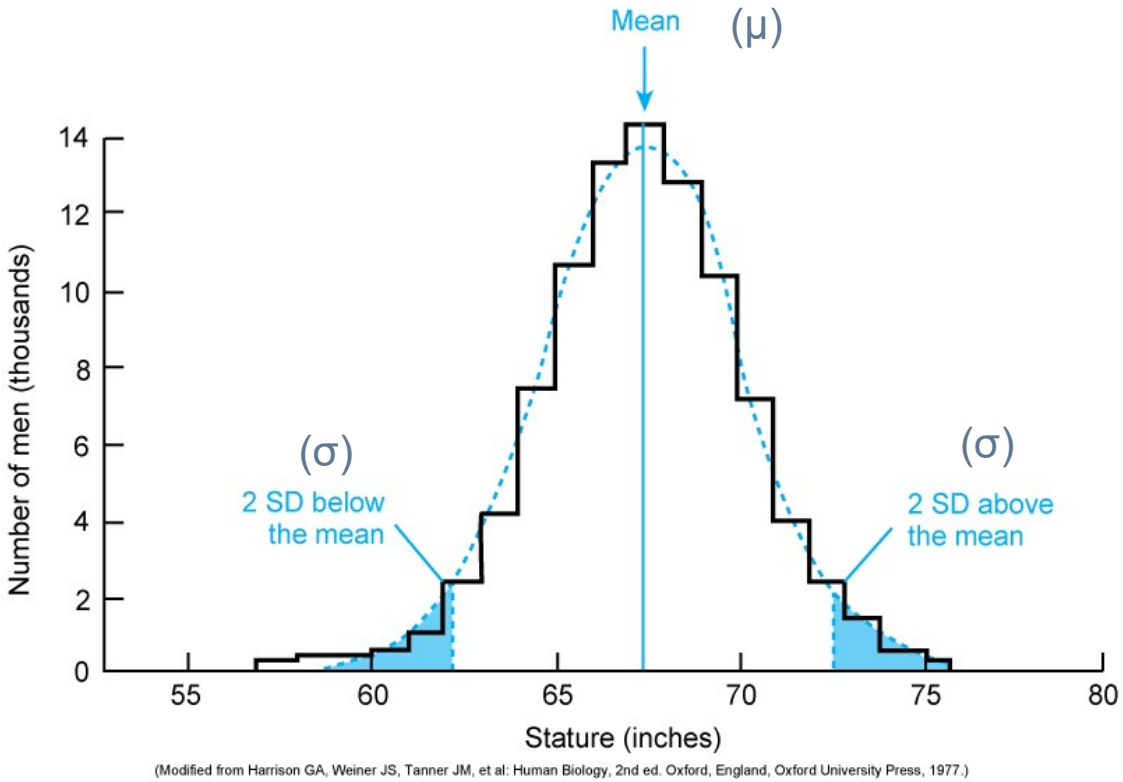
1. **Genetic differences:** - somatic rearrangements
   - random X inactivation
   - epigenetic changes
2. **Environmental differences:** - different adulthood environment
   - intrauterine disparity
3. **Difference between different twin pairs**
   - observed concordance is an average that applies to neither pair of twins
   - non-genetic phenocopies
4. **Ascertainment bias:** - volunteer-based ascertainment
   - population-based ascertainment

Genetic analysis of quantitative traits

1. The normal distribution

variance (σ^2) of a measured quantity in the population:

total phenotypic variance



(Modified from Harrison GA, Weiner JS, Tanner JM, et al: Human Biology, 2nd ed. Oxford, England, Oxford University Press, 1977.)

Fig. 8-2. Distribution of stature in a sample of 91,163 young English males in 1939 (black line). The blue line is a normal (gaussian) curve with the same mean and standard deviation (SD) as the observed data. The shaded areas indicate persons of unusually tall or short stature (>2 SD above or below the mean).

Genetic analysis of quantitative traits

1. The normal distribution
2. **The normal range**

    e.g. hypertension, hypercholesterolemia, obesity: values outside the normal range

when a quantitative trait is normally distributed in a population only 5% of the population will have measurements more than 2 SD above or below the population mean

Genetic analysis of quantitative traits

1. Familial aggregation of quantitative traits

measurement of correlation of particular physiological quantities among relatives

coefficient of correlation (r): statistical measure applied to a pair of measurements

positive correlation (r = 1)

negative correlation (r = -1)

no correlation (r = 0)

Assumption: degree of similarity ~ to the number of alleles shared at relevant loci

=> the more closely individuals are related, the more alleles they share, the stronger the correlation of values will be

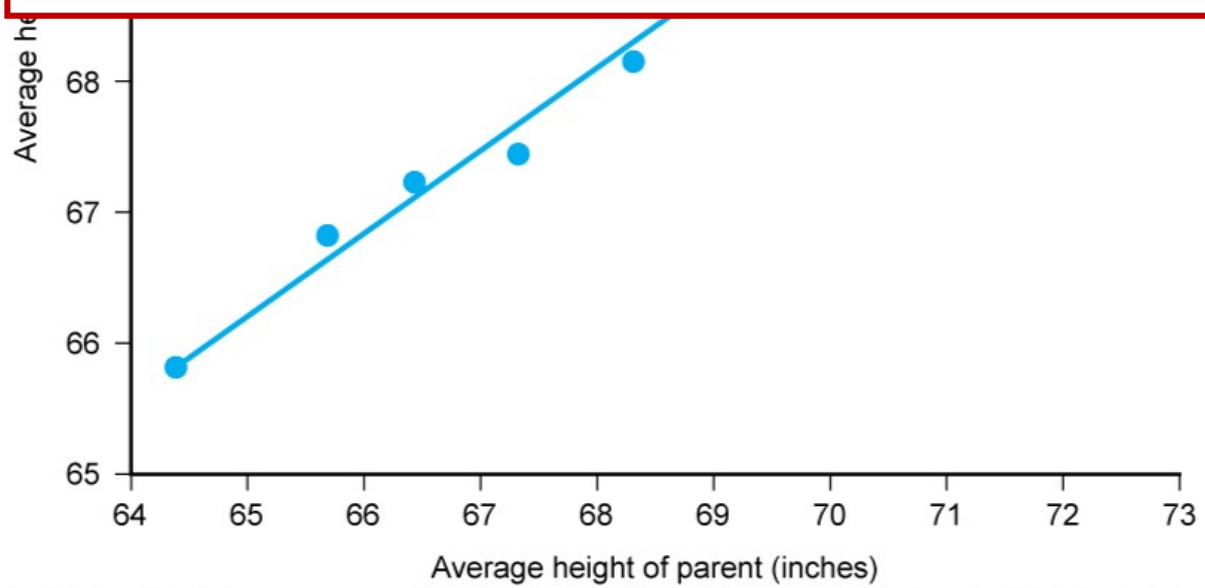


Fig. 8-3. Correlation between average parental height and height of children. The average height of parents within intervals of 1 inch (64 to 65 inches, 65 to 66 inches, and so on) is plotted along the abscissa; the average height within a 1-inch interval of their children is plotted on the ordinate. The straight line is a "best fit" through the data points. (The astute observer will note that the slope of the line is not 45 degrees. This reflects the fact that children of tall parents, although still taller than average, tend to be shorter than their parents, whereas the children of short parents, although still shorter than average, tend to be taller than their parents. This phenomenon, known as regression to the mean, was observed more than 100 years ago by Galton.)

Genetic analysis of quantitative traits

1. Heritability

H^2 = fraction of the total phenotypic variance of a quantitative trait that is caused by genes

$H^2 = 0$ no genetic contribution to the total phenotypic variance
$H^2 = 1$ genes are totally responsible for the total phenotypic variance

Estimating heritability from twin studies

$$H^2 = 2 \times r_{MZ} - r_{DZ})$$

difference in variance between MZ and DZ twins as degree for the importance of genes

Feature	H^2
Height	0.8
BMI	0.7-0.8
AD disorder	1

Practical difficulties in measuring and interpreting H^2

1. Relatives share more than their genes

2. Even when the heritability of a trait is high it does not reveal the underlying mechanism of inheritance of the trait

3. Heritability is no intrinsic quality of a particular quantitative trait and cannot be considered in isolation from the population group and living conditions in which the estimate is being made

Limitations of studies of familial aggregation, disease concordance and heritability

- no specification of loci and alleles involved, number of loci or how a particular genotype and set of environmental influences interact to cause a disease

  => show only genetic contribution

- need of theoretical models to explain the underlying mechanisms of complex disease: genetic epidemiology

Characteristics of inheritance of complex diseases

- Genes contribute to complex diseases but they are not single-gene disorders and have no simple Mendelian pattern of inheritance
- Complex diseases demonstrate familial aggregation because relatives of an affected individual are more likely to have disease-predisposing alleles in common with the affected person than unrelated individuals
- Pairs of relatives who share disease-predisposing genotypes at relevant loci may still be discordant for phenotype (=lack of penetrance) because of crucial role of nongenetic factors in aetiology of disease, cf. discordant MZ twins
- The closer the relationship between family members the more common the disease becomes and vice versa

Characteristics of inheritance of complex diseases

Recurrence risk is higher if proband's disease expression is more serious

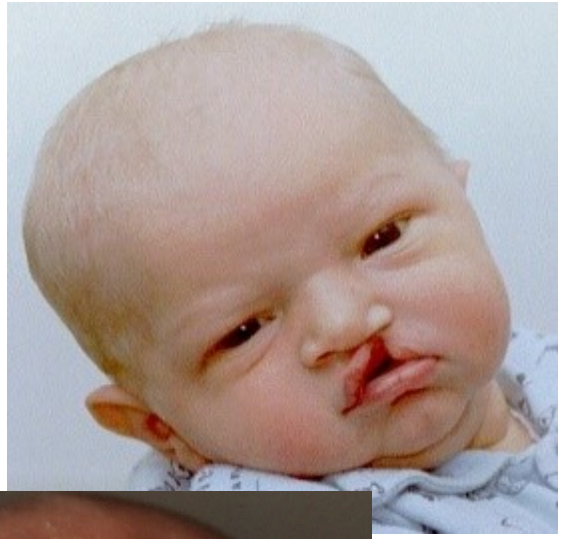
Recurrence risks for isolated CL and isolated CL/P

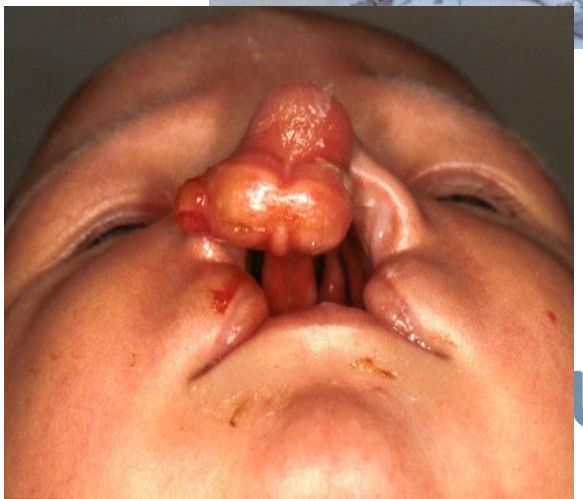
Relationship to index case	Recurrence risk (%)
Sibling unilateral CL	2–3
Sibling unilateral CL/P	4
Sibling bilateral CL/P	
Two affected siblings	10
Affected sibling and parent	10*
Affected parent	4

* Consider dominant risks with reduced penetrance.

Recurrence risk for isolated CP

Relationship to index case	Recurrence risk (%)
Sibling	2–3
Affected parent	4



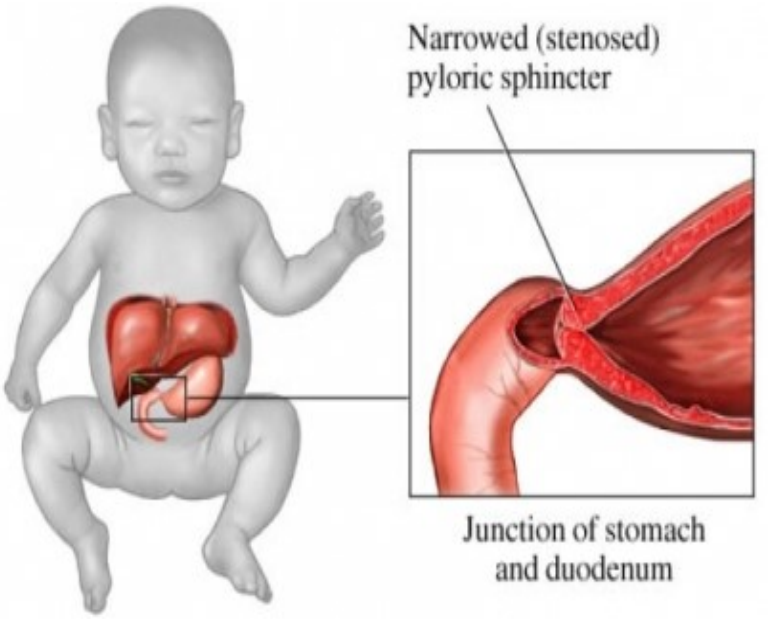


Characteristics of inheritance of complex diseases

Recurrence risk is higher if the proband belongs to the least affected sex (=Carter effect)

e.g. pyloric stenosis is more frequent among males => recurrence risk for brother of affected male lower than for brother of affected female

- susceptibility threshold higher for females
- more risk factors needed until they develop disease



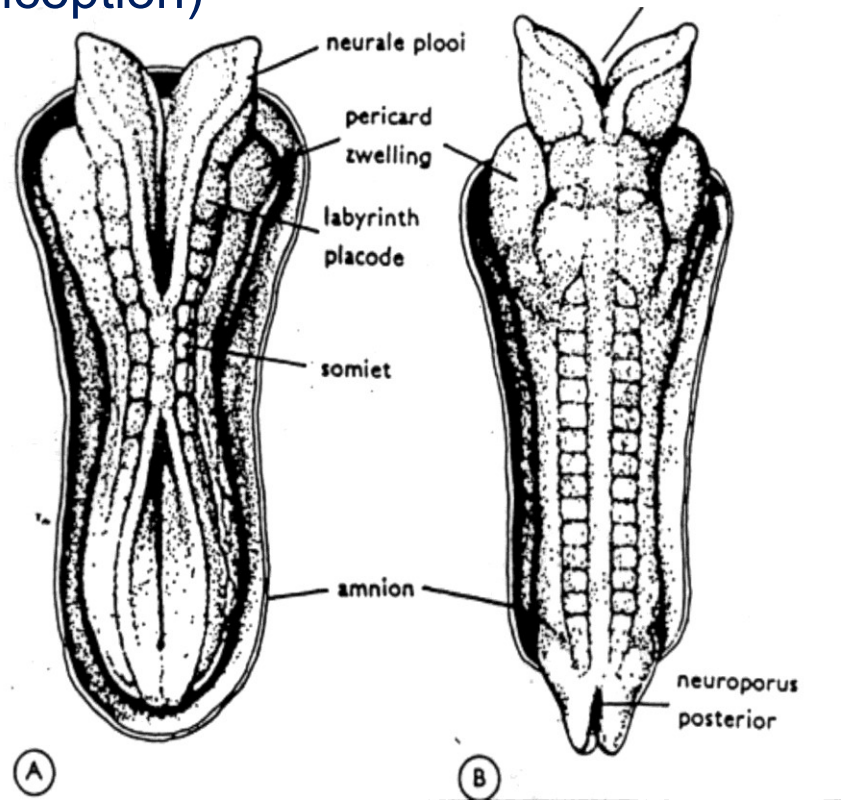
recurrence risks	male index	female index
	risk (%)	risk (%)
brother	3.8	9.2
sister	2.7	3.8
son	5.5	18.9
daughter	2.4	7.0

Some examples of multifactorial traits

1. Neural tube defects (NTD)
2. Alopecia areata (AA)

1.Neural tube defects (NTD)

Defects in closure of NT (day 22-28 after conception)



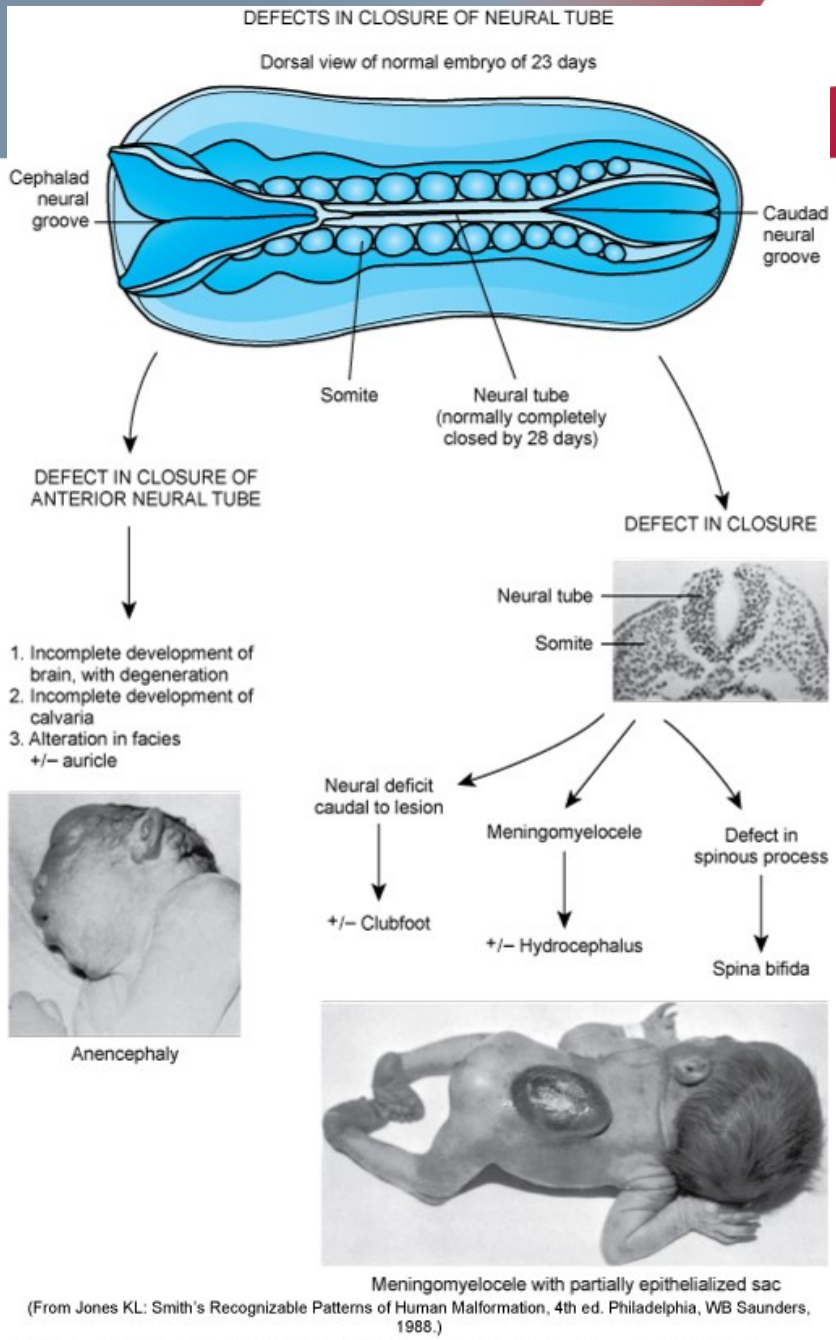
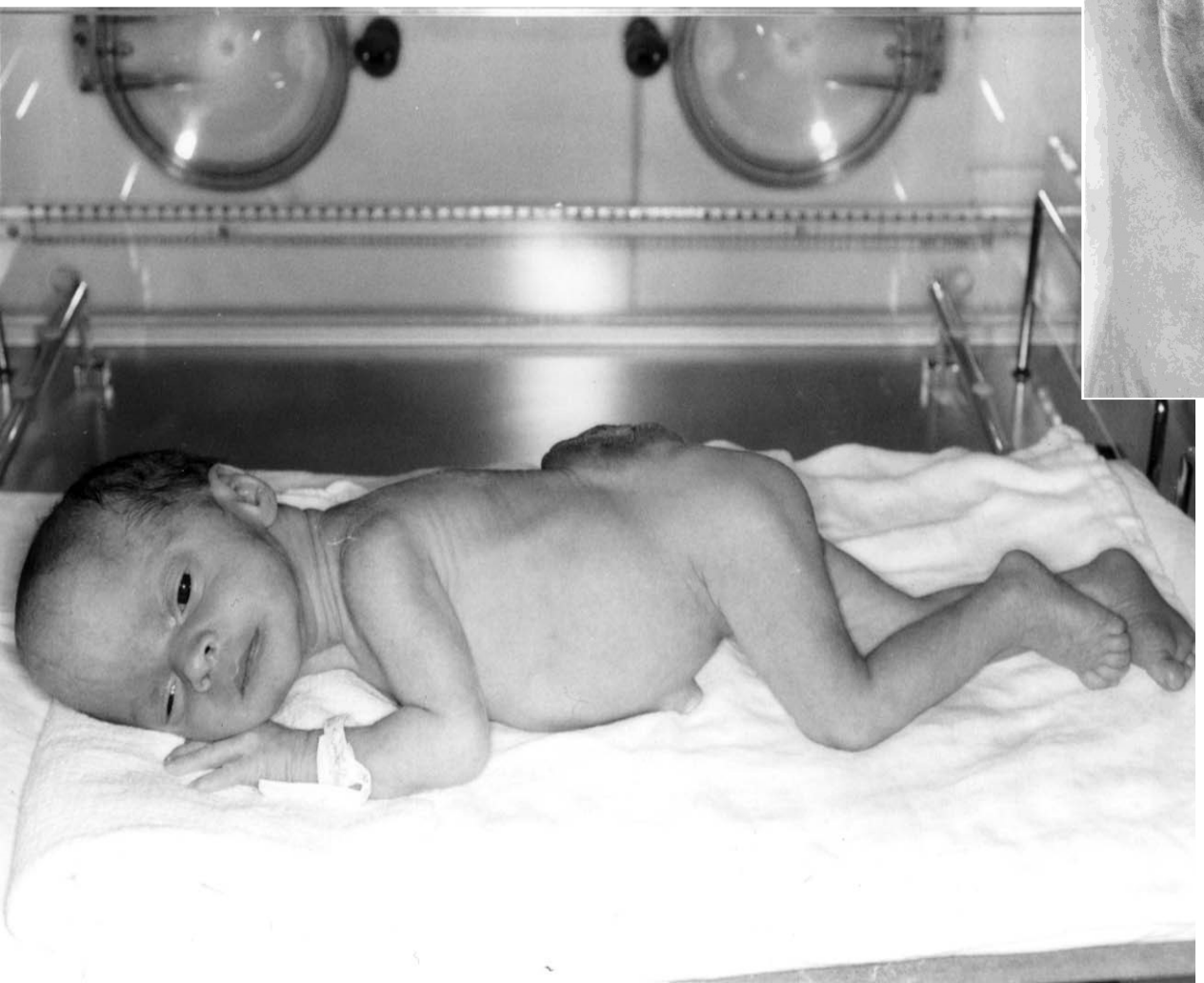
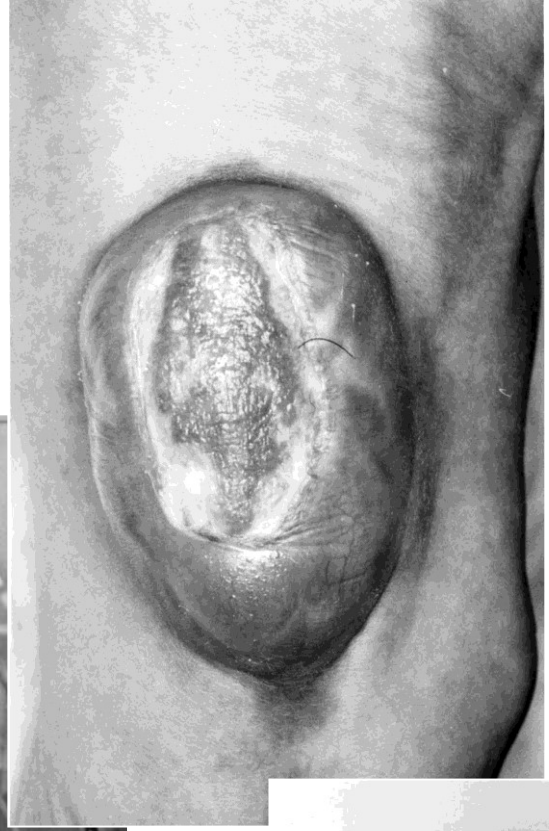
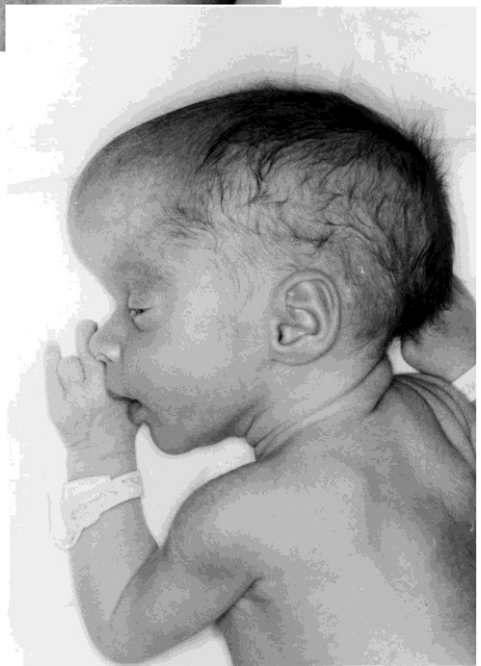


Fig. 8-8. The origin of the neural tube defects anencephaly and spina bifida.

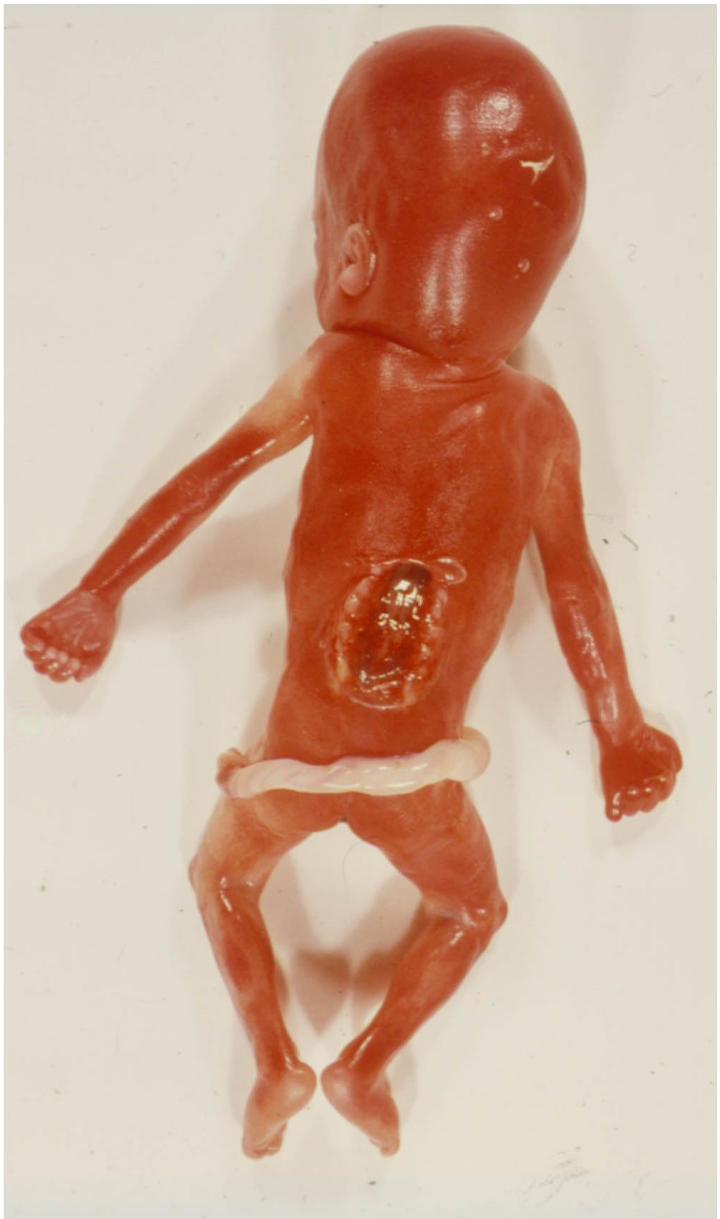
Spina bifida + encephalocele



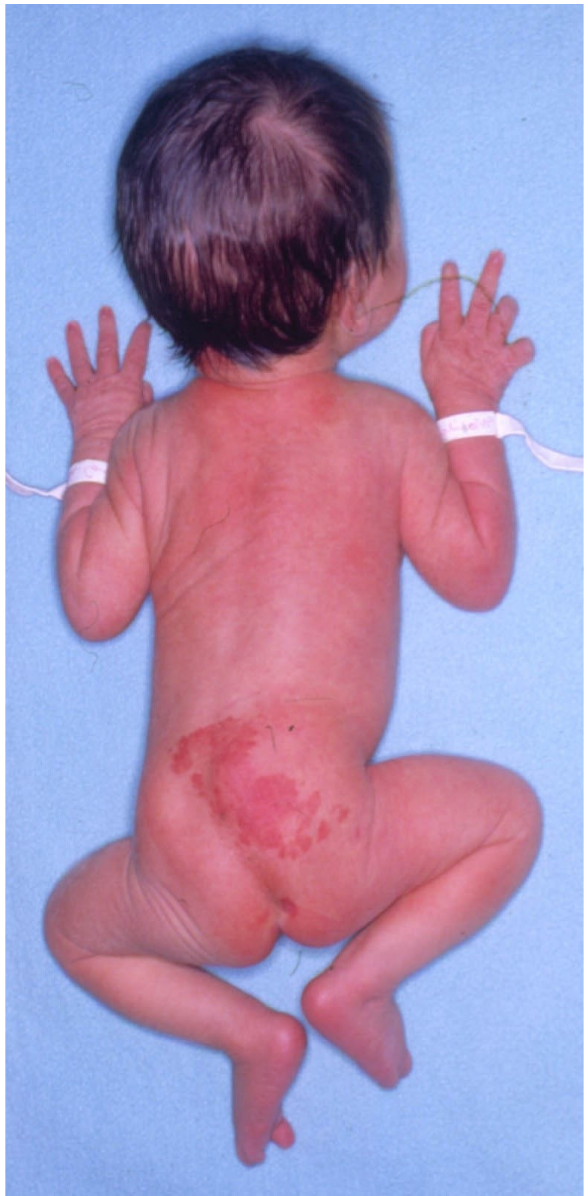




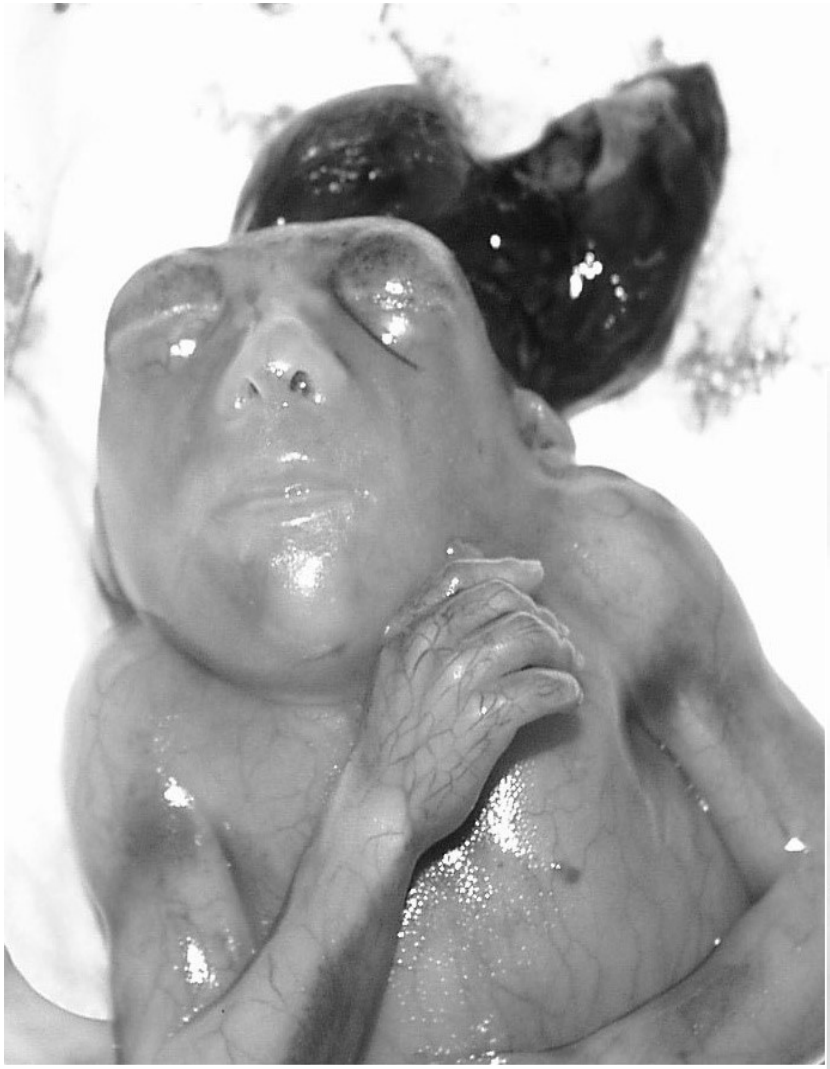
spina bifida aperta



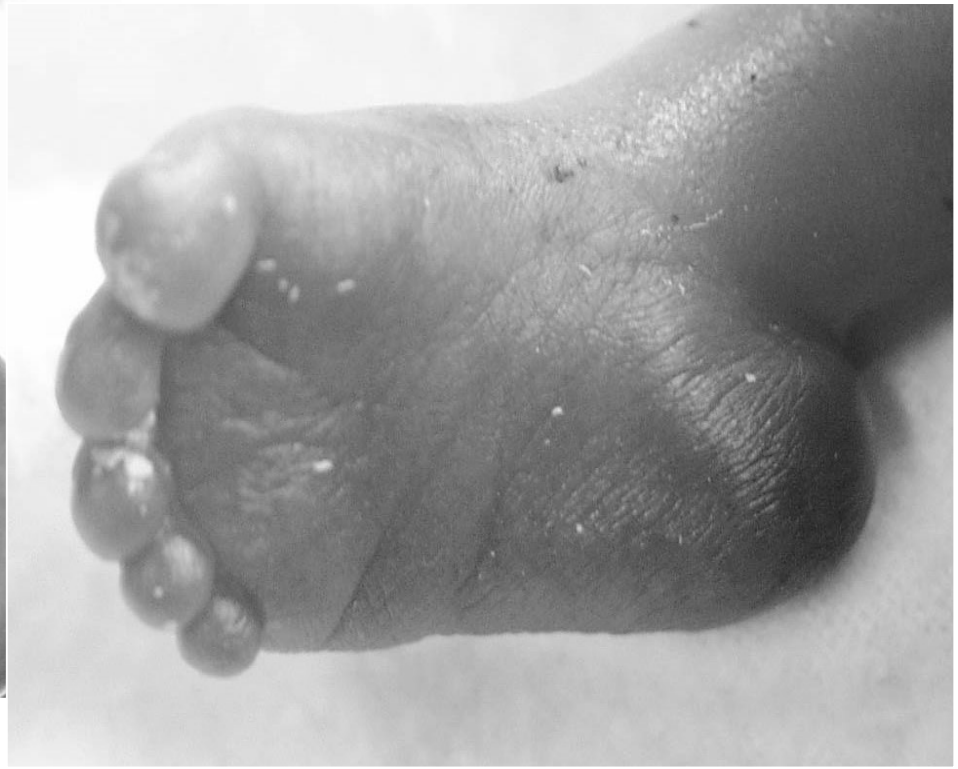
spina bifida occulta



anencephaly



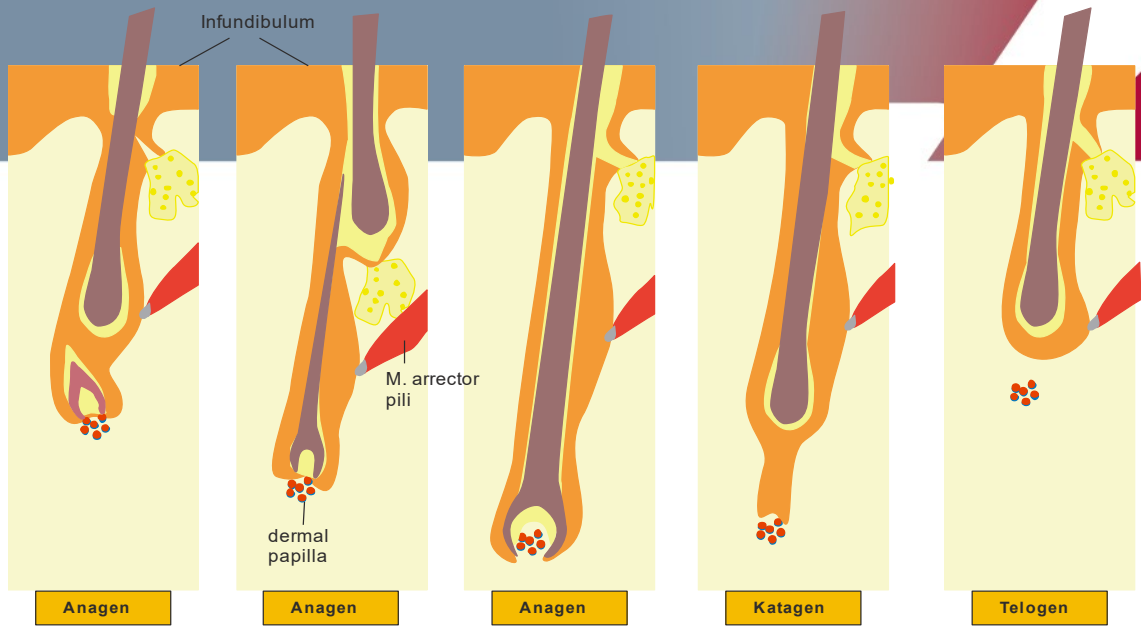
pes equinovarus



Recurrence risk NTD

• population risk	0,1%
• 1 parent	2-4%
• 1 sib	1-3%
• 2 sibs	5-10%
• 2nd degree	0,5-1%
• 3d degree	0,5%

2. Alopecia areata (AA)

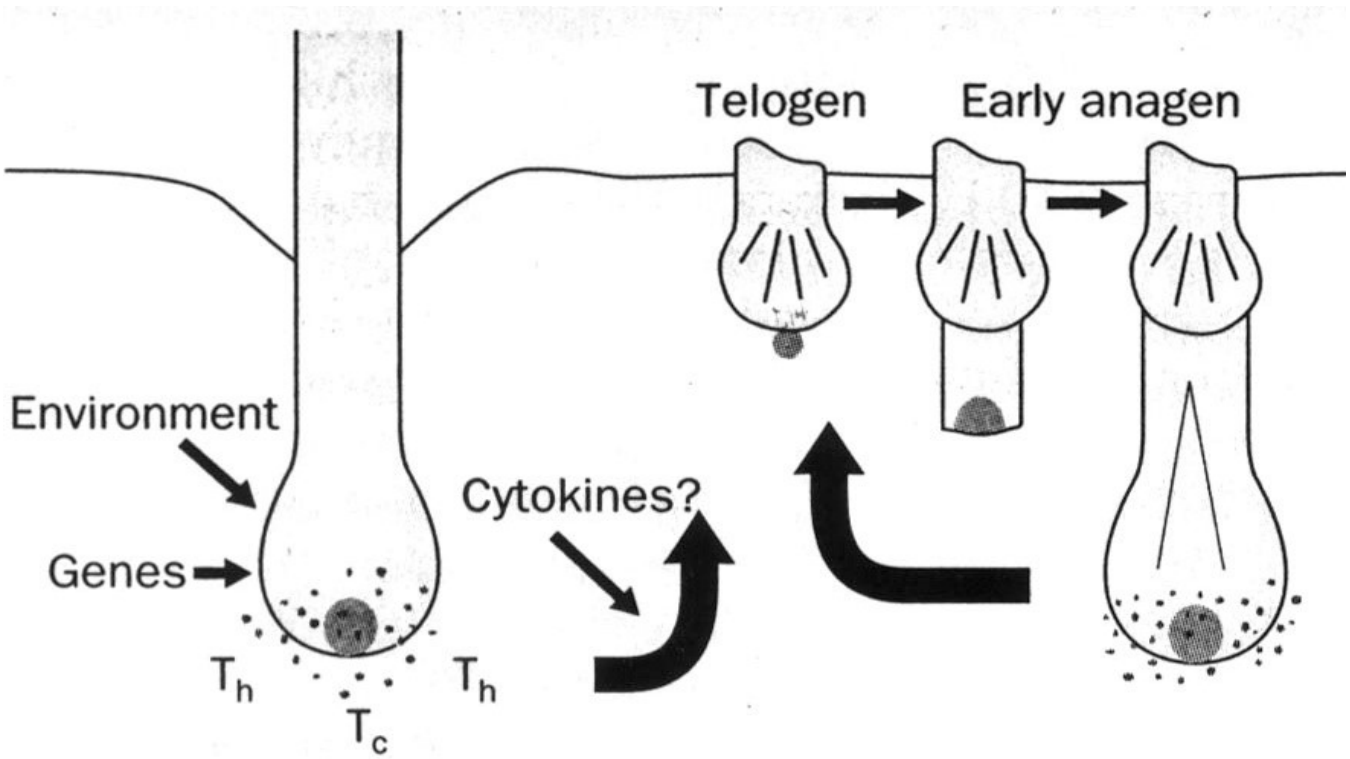


Non-scarring reversible circumscribed hair loss with sudden onset and recurrent course

Population risk : 1-2%

AA in families: familial clustering has been reported for all investigated populations (e.g. US- Americans, West-Europeans, Indians, Chinese)

Pathogenesis



immune privilege of the hairfollikel dissapears

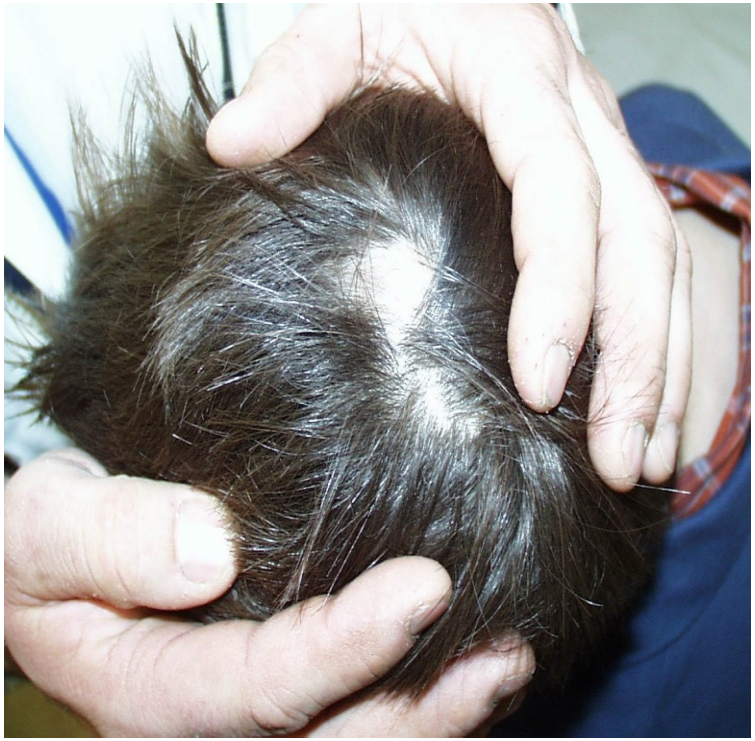
⇒recognition of antigenes of the hairbulbus

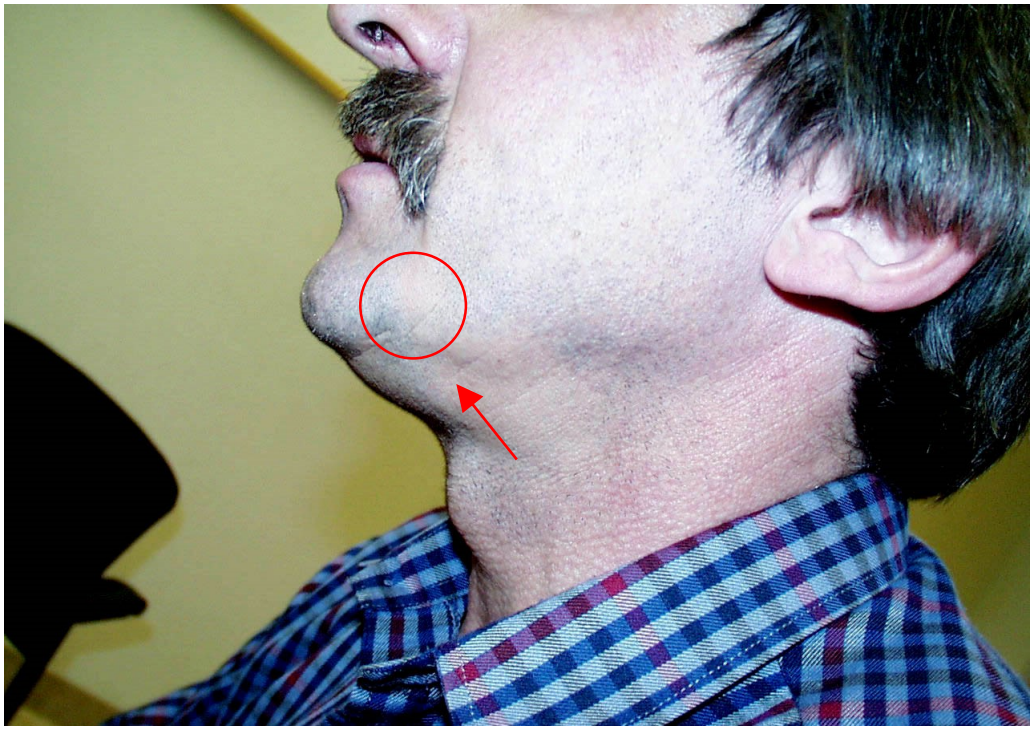
= auto-immune disease

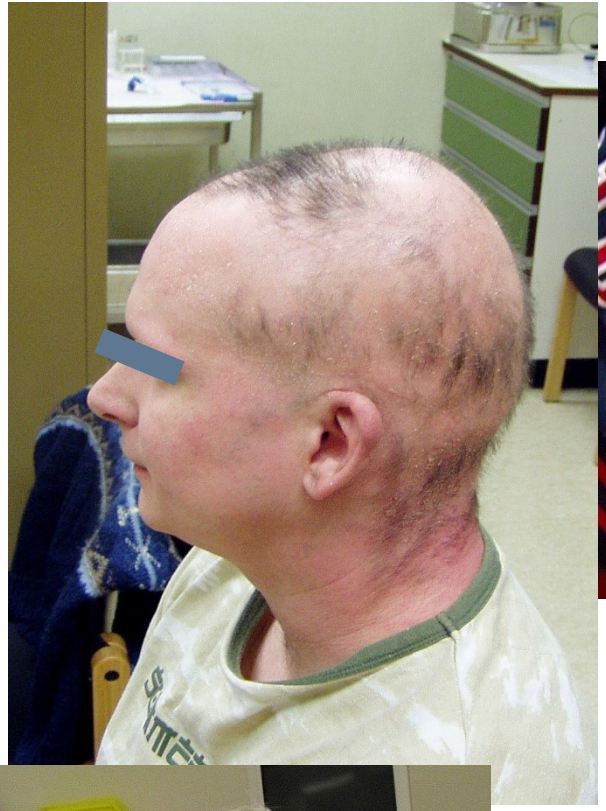
Course of the disease

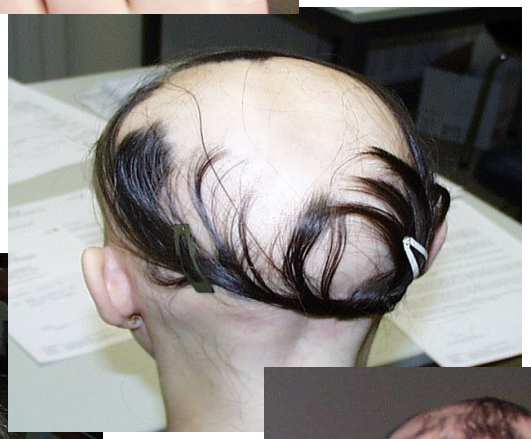
- Alopecia areata: patchy AA
- Alopecia totalis: total loss of scalp hair
- Alopecia universalis: total loss of all body hair

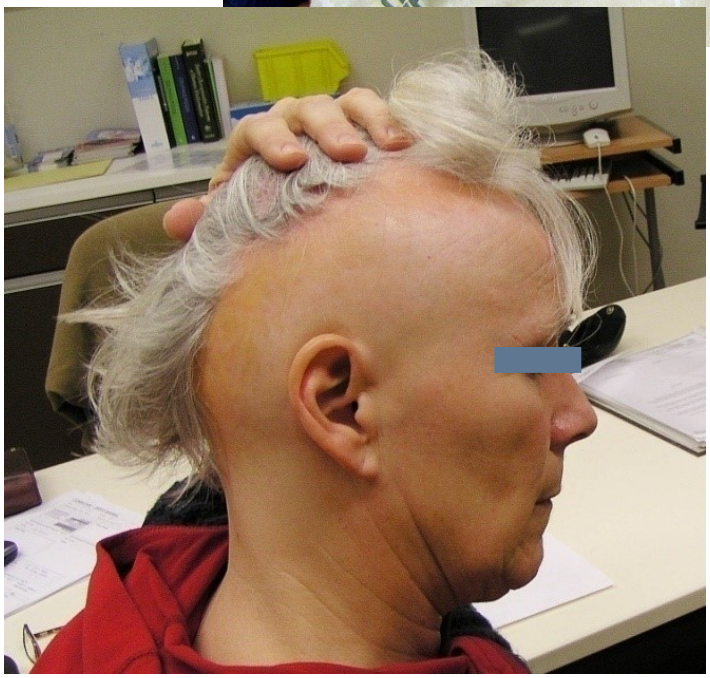
Patchy alopecia

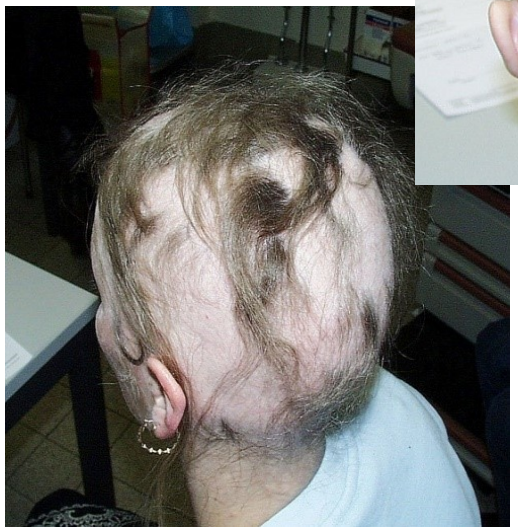


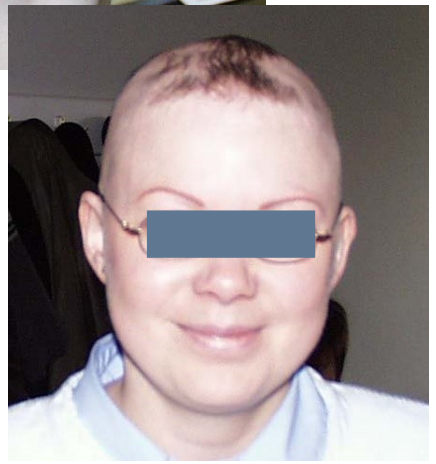




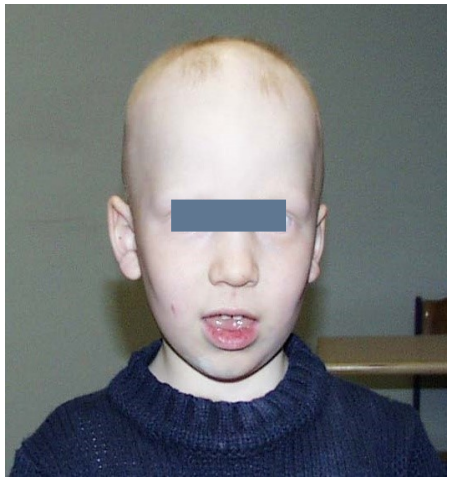


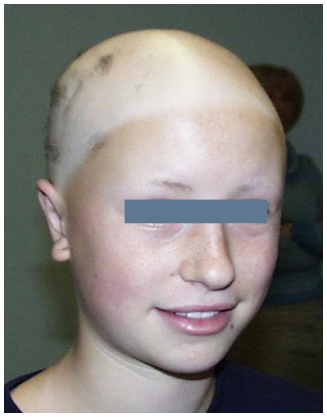


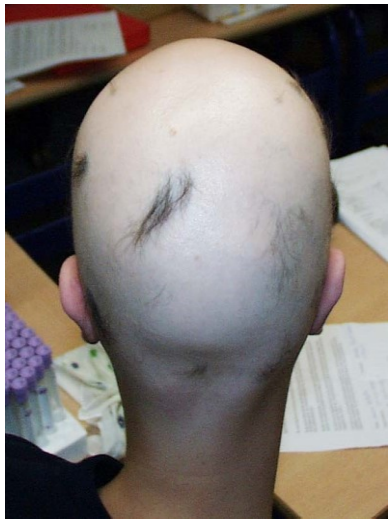


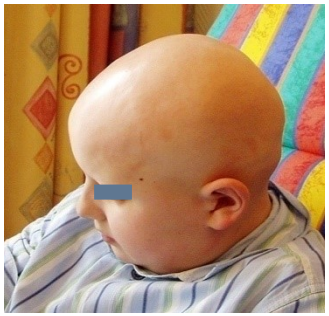


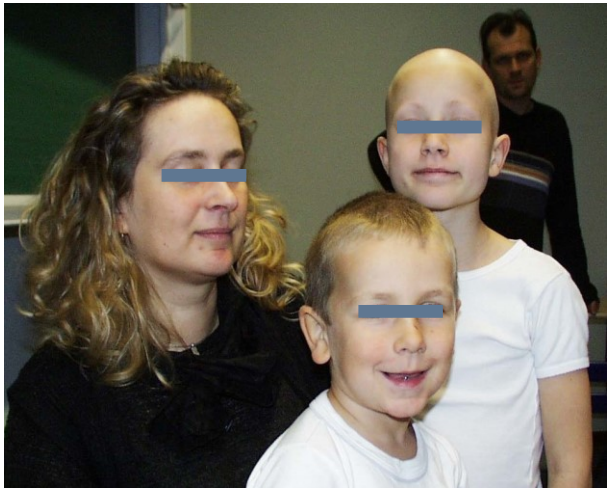
Alopecia totalis



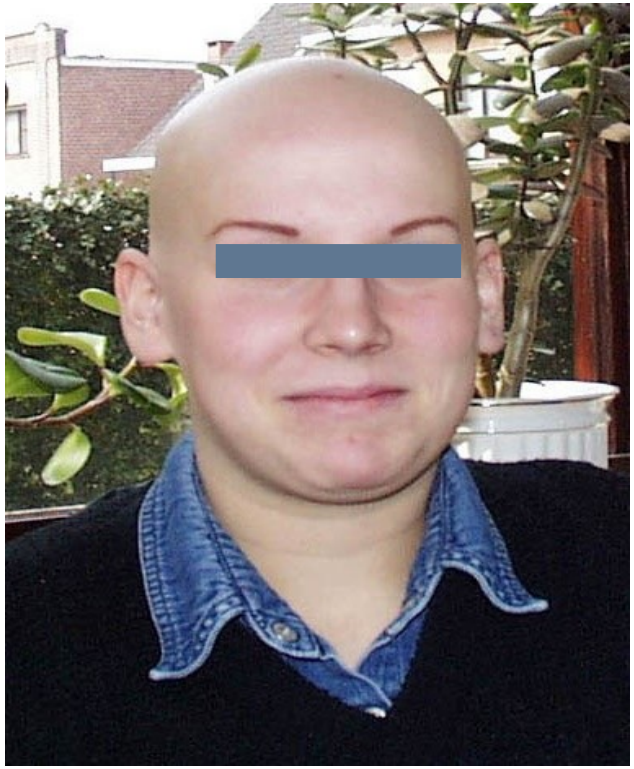








Alopecia universalis



Lifetime risks

Relation	Lifetime risk (%)
First-degree relatives	
Parents	7.8
Sibs	7.1
Children	5.7
Second-degree relatives	
Grandparents	1.6
Uncle/Aunt	1.2
Nephew/Niece	3.5

Blaumeiser et al, J Am Acad Dermatol. 2006