Genetische Aspekte der Langlebigkeit

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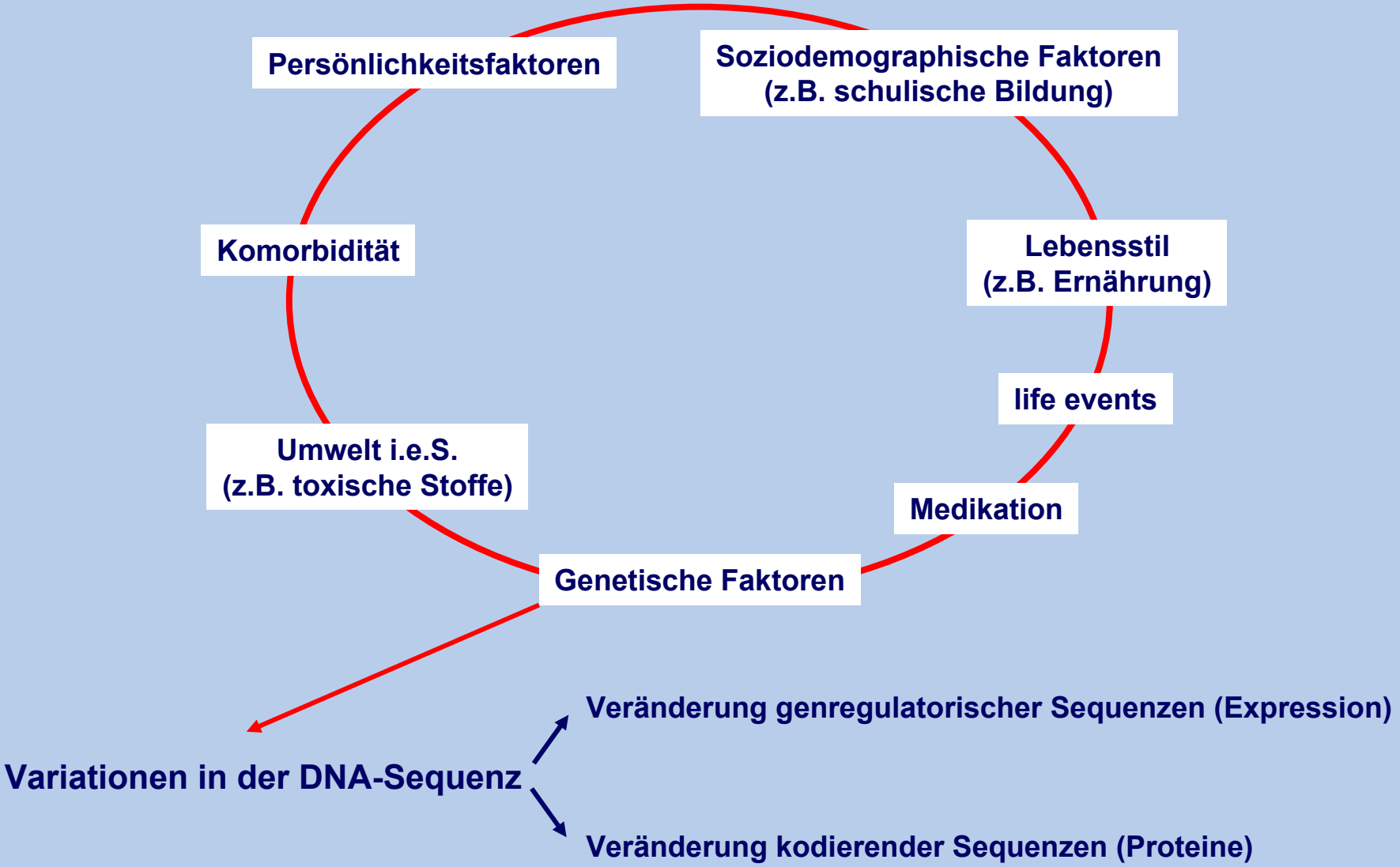
Multifaktorielles Entstehungsmodell



Interaktionsebenen

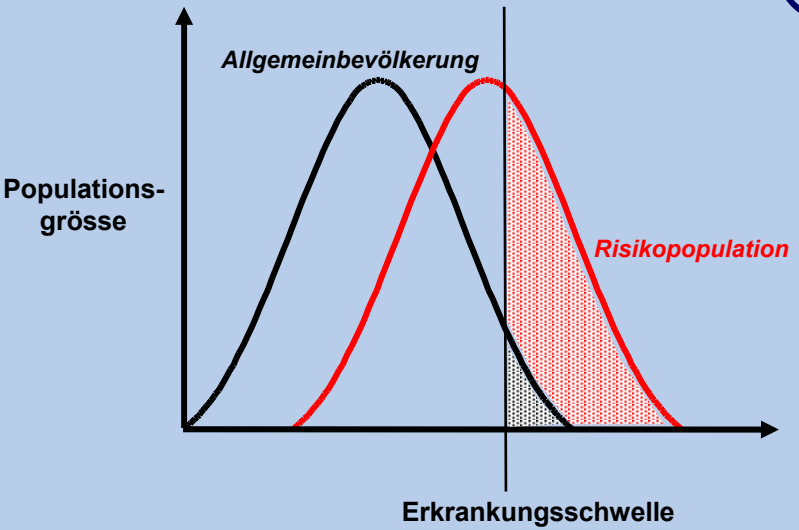
Umwelt

Gen-Unwelt-Interaktion

Gene

Monogene traits | **Oligogene traits** | **Polygene traits**

Allelische Heterogenität

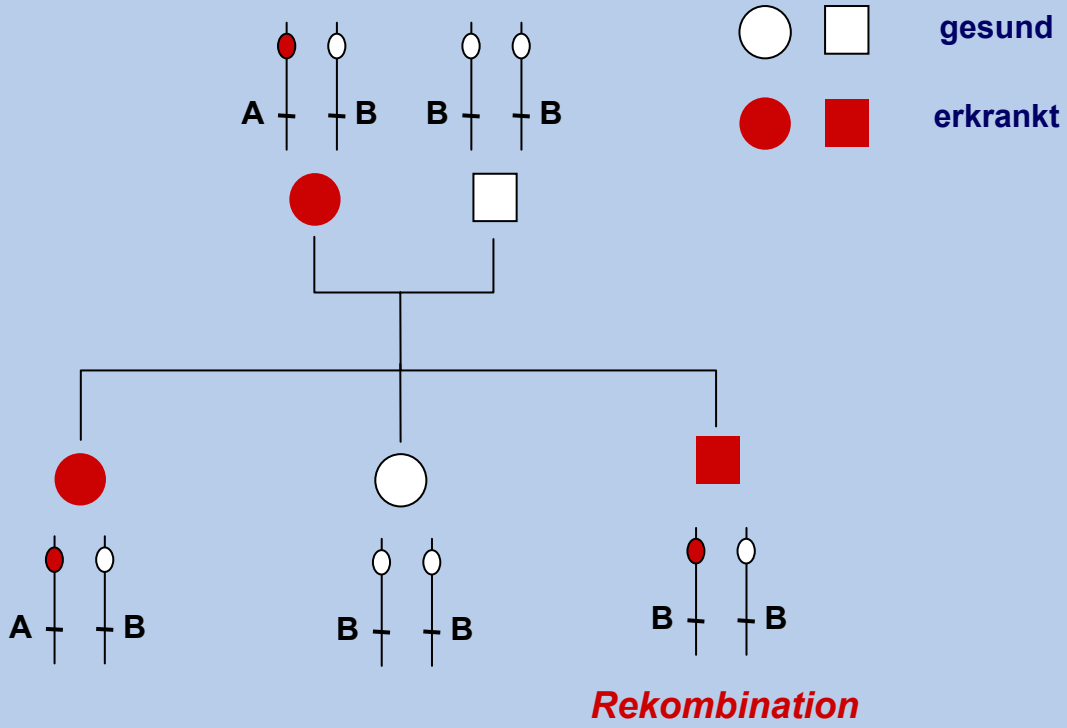


Gen-Gen-Interaktion

- *additiv*
- *sub-additiv*
- *synergistisch*
- *epistatisch*

Kopplungsuntersuchungen

Kopplung: genetischer Marker und Phänotyp (Erkrankung) werden in Familien überzufällig häufig gemeinsam vererbt => *Marker und Krankheitsgenort benachbart auf gleichem Chromosom*



Positiver Kopplungsbefund: Angabe über chromosomale Lokalisation eines Gens

Assoziationsuntersuchungen

Assoziation: **überzufällig häufiges Vorkommen eines Risikofaktors in einem Patientenkollektiv**

Risikofaktor	Erkrankungsstatus +	Erkrankungsstatus –
+	a	b
–	c	d

Odds Ratio (OR): **Auftretenswahrscheinlichkeit der Erkrankung bei Risikoträgern im Vergleich zu Nicht-Trägern**

$$OR = (a * d) / (b * c)$$

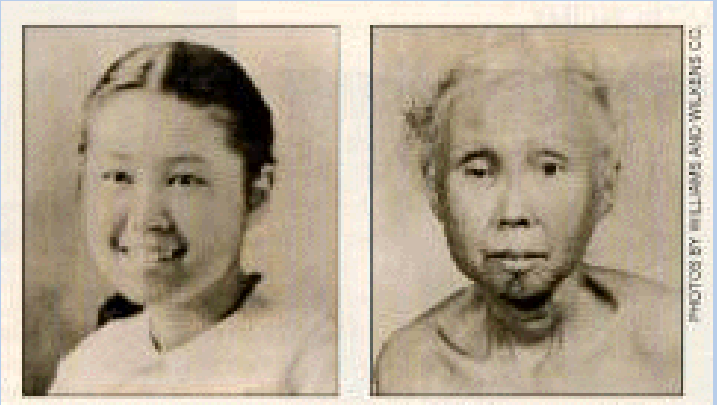
Signifikanzniveau *P*, Breite der Konfidenzintervalle

Lebensspanne-Progerien

Werner Syndrom:

Autosomal-rezessiv
Mutation im WRN Gen, chr 8
Helicase-Familie

Source: NCBI



12 J **48 J**

Hutchinson-Gilford

Extrem selten
Mutation im Lamin A/C Gen, chr 1
Nucleus

www.openknowledge.org

Hypothetical classification of longevity genes or their alternatives*.

1. Genes that cause aging (P53?).

2a. Genes that increase the risk of a specific illness early in life but do not appear to be related to aging (e.g. cystic fibrosis and CF gene).

2b. Genes that alter longevity because they increase the risk of a specific illness early in life whose features resemble, to some extent, some of the consequences of aging (e.g. Werners gene).

3. Genes that influence or cause age-related illnesses (e.g. Alzheimer's disease and Apolipoprotein Ee-4).

4. Low-fitness genes that extend maximum life-span, probably by slowing down aging (as observed in lower organism mutations, e.g. daf genes).

5. Polymorphic genetic loci that influence the rate of aging (many quantitative trait loci with varying influences on aging and age-associated diseases).

6. Genes that influence differences in life-span among species (e.g. longevity enabling genes).

**Adapted from: Miller, RA. A Position Paper on Longevity Genes. Document URL: http://sageke.sciencemag.org/cgi/content/full/sageke;2001/9/vp6*

Longevity

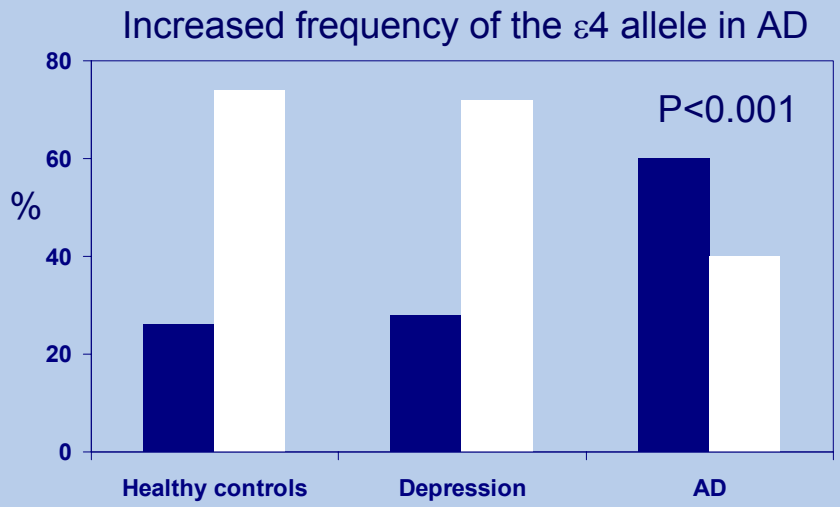
Cholesterin-Gene

Immunologisch-relevante Gene

Apolipoprotein E (Chr. 19)

- multifunctional protein (lipid metabolism, acute-phase reaction)
- Amyloid metabolism, tau-phosphorylation
- three alleles (ε2, ε3, ε4)
- APOE ε4 associated with AD

Corder et al., Science, 1993



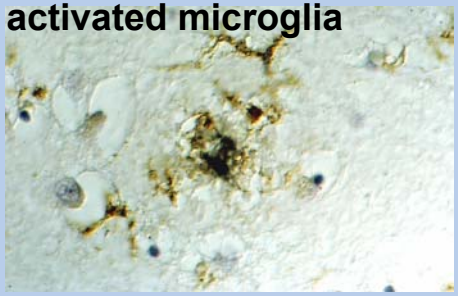
- OR in ε4 homozygotes: ~ 8
- consistent finding
- Influence on age-of-onset
- Sensitivity and specificity ~ 60%
- little or no predictive validity

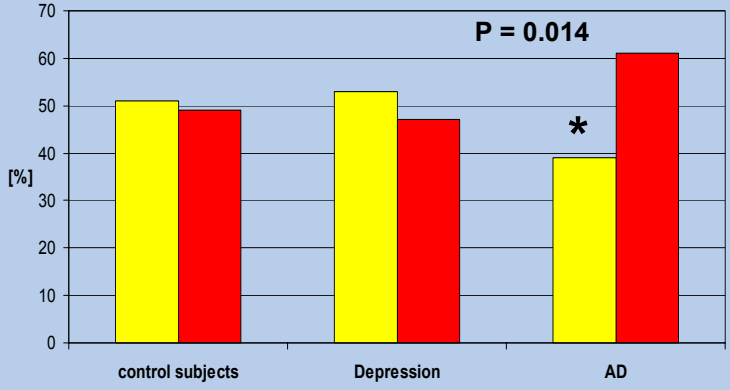
No predictive validity

Papassotiropoulos et al.
Dement Geriatr Cogn Disord, 1999

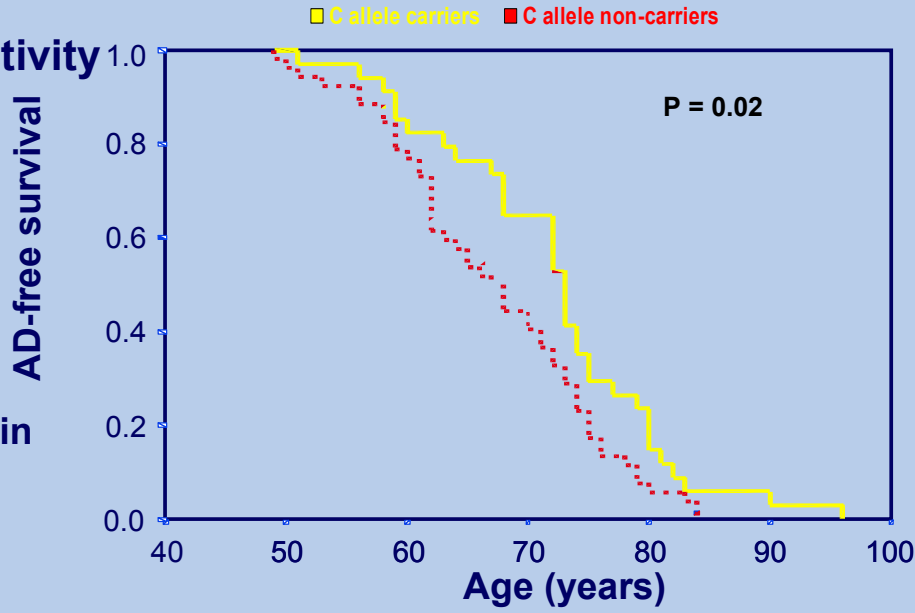
Interleukin-6 (Chr. 7)

activated microglia





- Acute-phase protein, neuroinflammation
- VNTR polymorphism in 3'-region
- C*allele associated with decreased IL-6-activity



- OR in C*allele carriers: ~ 0.5 (protective)
- influence on age-at-onset
- functional consequences (IL-6-concentration in the CSF)

Papassotiropoulos et al. Ann Neurol, 1999