Tolerance vs. Resistance of infectious diseases

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Introduction

Definitions:

- Tolerance: the ability to limit the disease severity induced by a given parasite burden

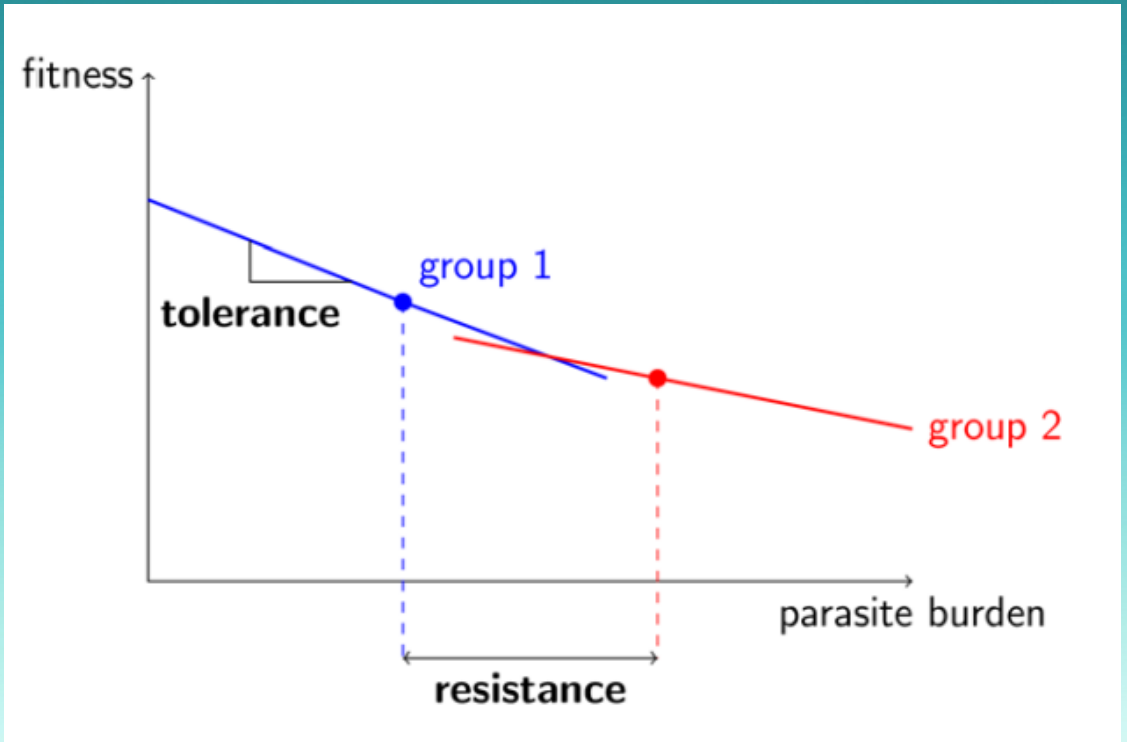
- Resistance: the ability to limit parasite burden

Source: Råberg et al., 2007

Introduction

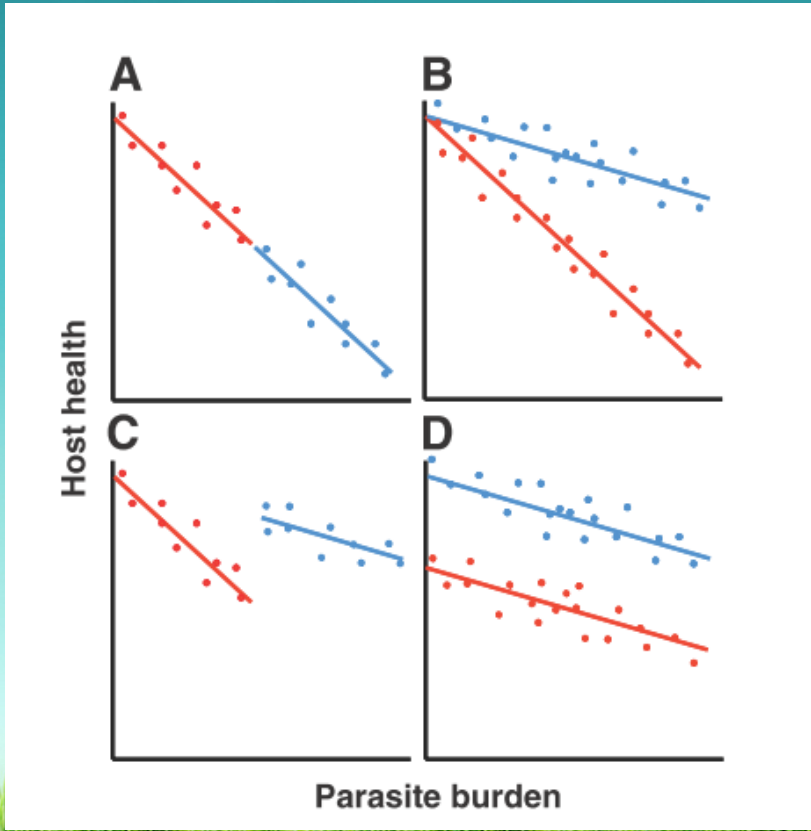
- Tolerance and resistance are different strategies to face disease.
- Is there a trade-off between resistance and tolerance?
- Tolerance benefits both the host and the parasite. Resistance doesn‘t benefit the parasite but benefits the host.

Introduction



(Source: Regoes et al., 2014)

Tolerance vs. Resistance



- Tolerance difference; no resistance difference

- No tolerance and no resistance difference

- Tolerance and resistance difference

- No tolerance difference; resistance difference

Source: Råberg et al., 2007

Disentangling Genetic Variation for Resistance and Tolerance to Infectious Diseases in Animals

Råberg et al., 2007

Objective

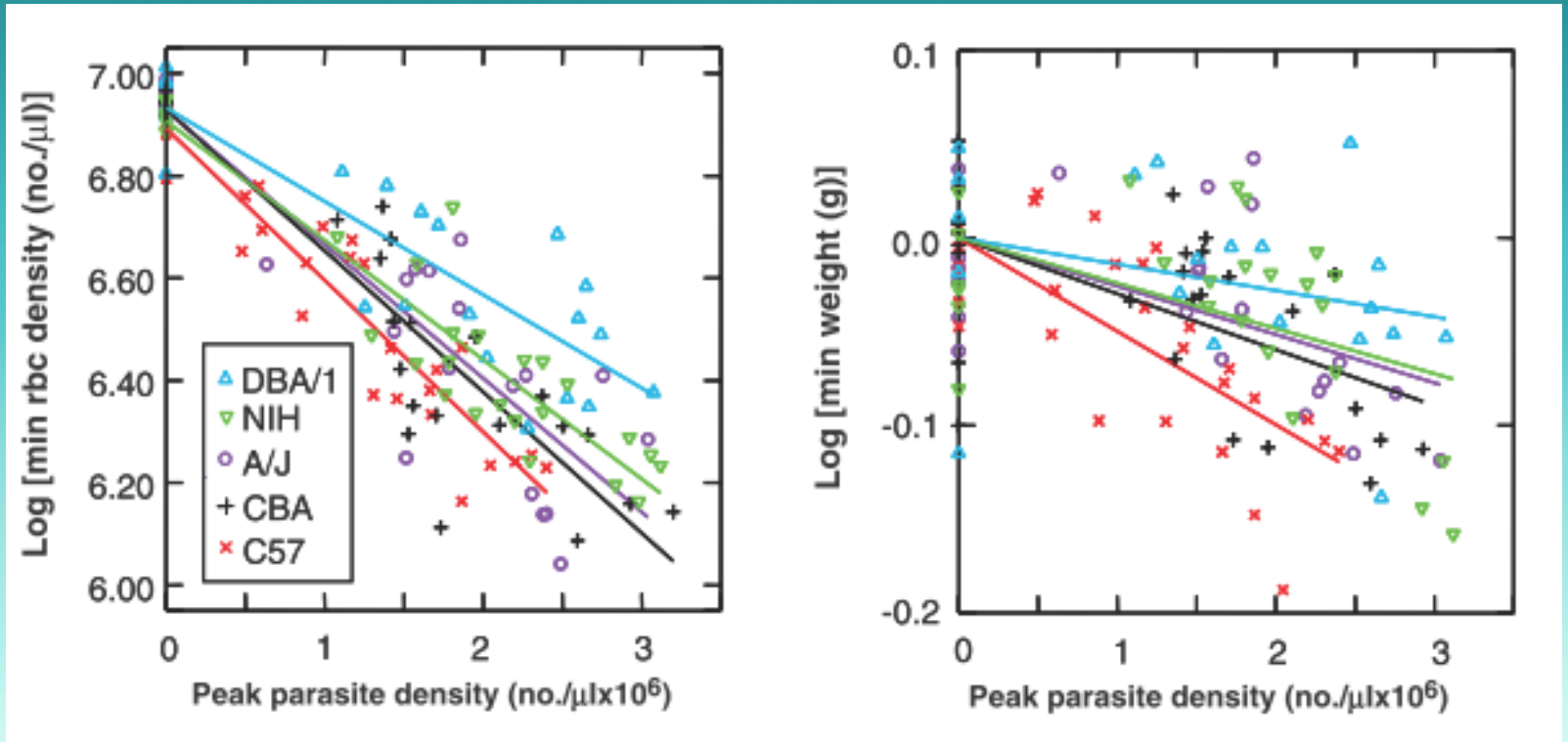
- Is there a genetic variance for tolarance in rodent malaria?

- Is there a trade-off between resistance and tolarance in rodent malaria?

Introduction

- Study subjects: mice and Plasmodium chabaudi (used as a model of human malaria)
- Malaria symptoms in mice: anemia and weight loss
- Tolerance measures in mice: minimum weight & minimum red blood cells
- Resistance measures in mice: peak parasite density

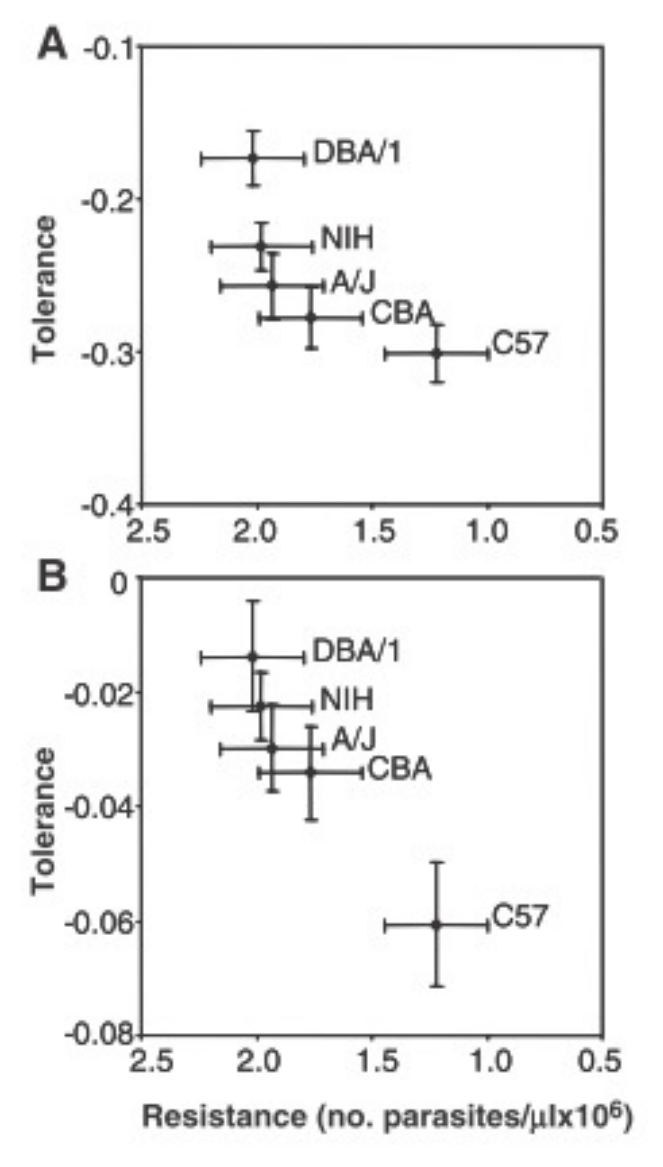
Results



Source: Råberg et al., 2007

Results

A: Tolarance (change in rbc minimun
B: Tolarence(change in minimum weight)



Quelle: (Råberg et al., 2007)

Discussion

- Genetic variation in tolerance
- Trade-off between resistance and tolerance

- Further questions:

  - Is tolarance „Evolution proof“?
  - Does tolerance reduce the constant battle of coevolution?

Disentangling Human Tolerance and Resistance Against HIV

By R. Regoes et al., 2014

- We already learned, that usually there’s a trade-off between disease tolerance and disease resistance.

- This study was the first time that a clinically relevant human infection was investigated regarding the association of resistance and tolerance

Subjects

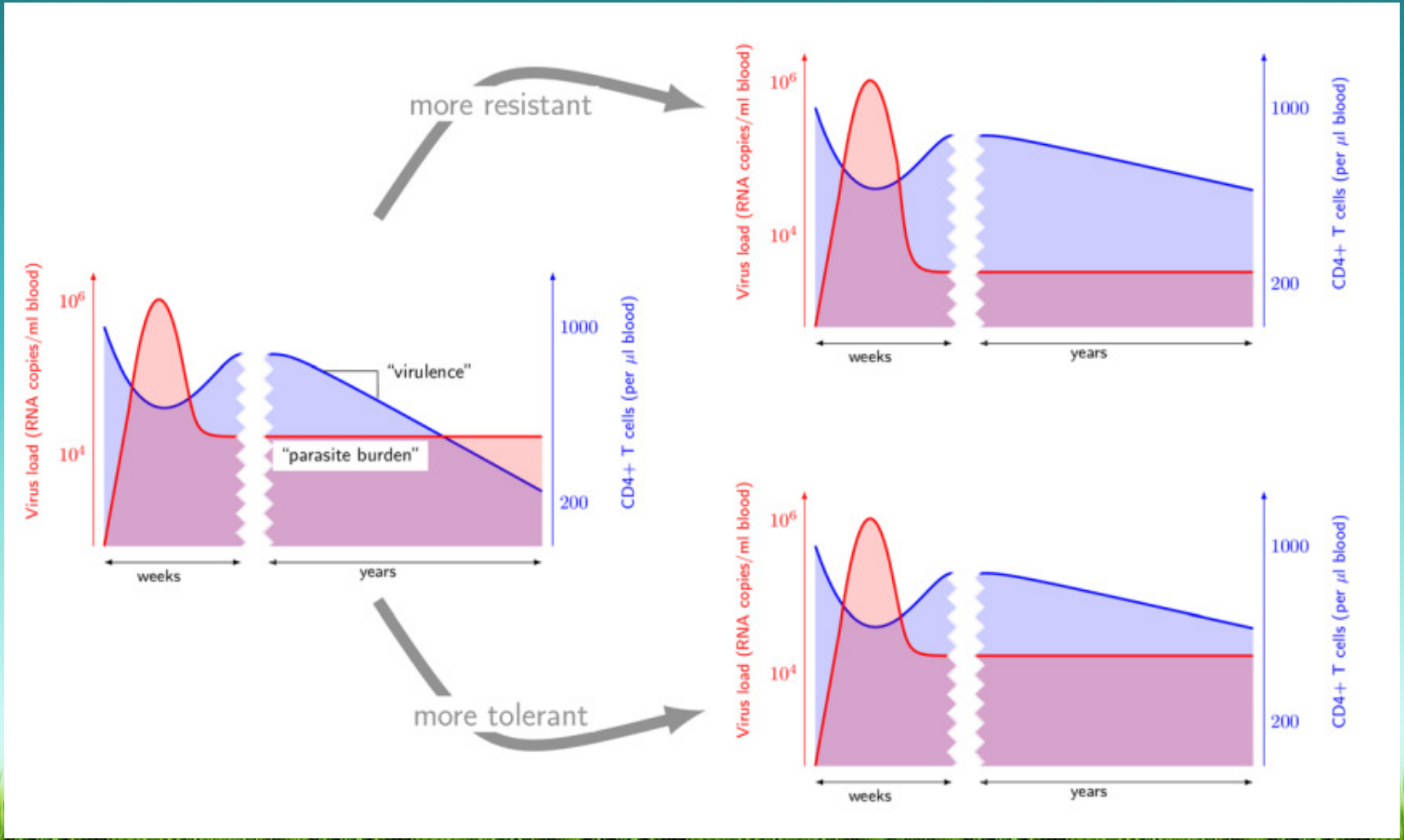
- 3036 individuals in the Swiss HIV Cohort study
  - With information about set-point viral load (spVL) and CD4+ T-cell decline

- The data was tested for associations of HIV tolerance and:
  - HLA genes
  - CCR5
  - Age at infection
  - Sex

To briefly let you know some concepts

- Set-point viral load
- CD4+ T-cell decline
- Human Leukocyte Antigen (HLA)

Set point viral load & CD4+ T-cell decline



Regoes et al., 2014

Human Leukocyte Antigen

- HLA are MHC molecules in humans
- MHC-like molecules are expressed at the surface of somatic cells and regulate the immune response
- They bind and display self- or foreign peptides to T-cells which can interact with them

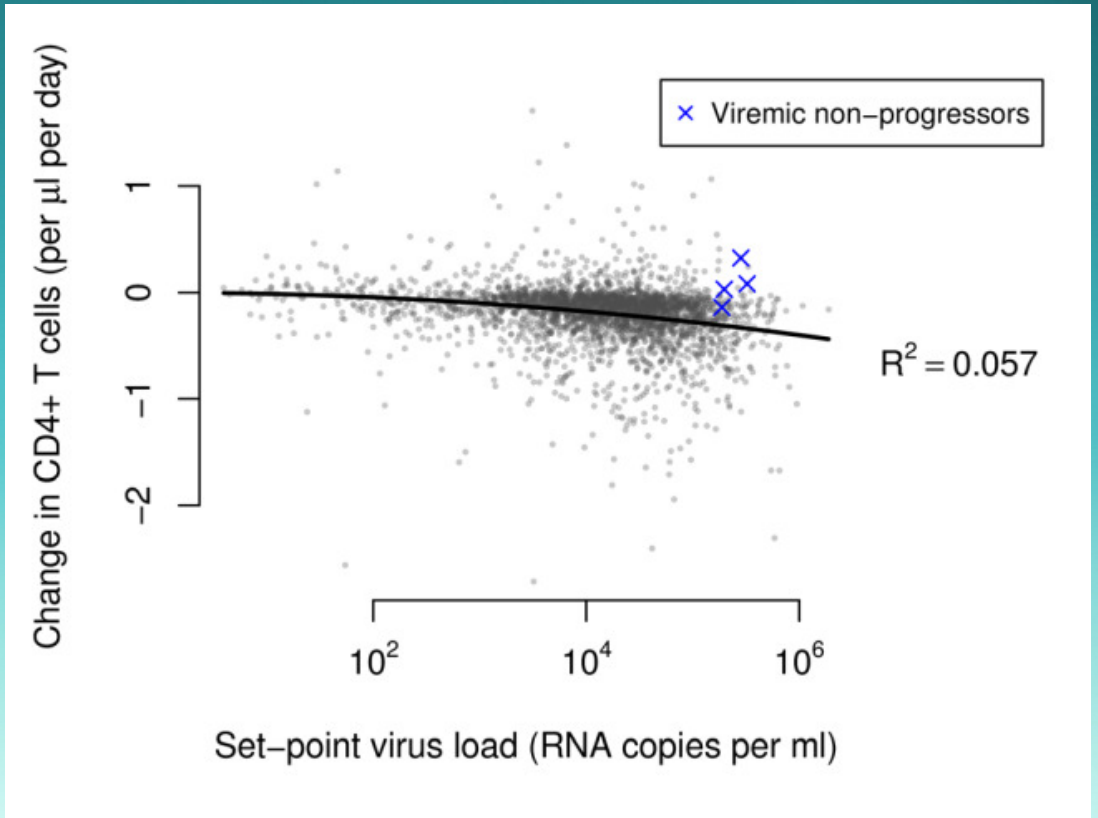
What did they do?

- They calculated the relationship between set-point viral load and CD4+ T-cell decline (= baseline -> tolerance phenotype)
- Measures were taken after primary infection and before treatment
- Then, they compared this relationship in different subgroups

Results

- Baseline relationship via.

Regression analysis -> nonlinear



Regoes et al., 2014

Results: Tolerance, Sex and Age

- 2x lower viral load in females
- But, no difference in tolerance between sexes

- Age of infection was strongly associated with tolerance
- Infection at age 60 -> 1.7x faster disease progression than at 20

CCR5 and HLA

- Information about CCR5 & HLA of 850 individuals

HLA-B alleles previously associated with

low viral load („protective“)

high viral load

- No association of „protective“ HLA-B alleles with tolerance

-> Protective effect only due to lower viral load

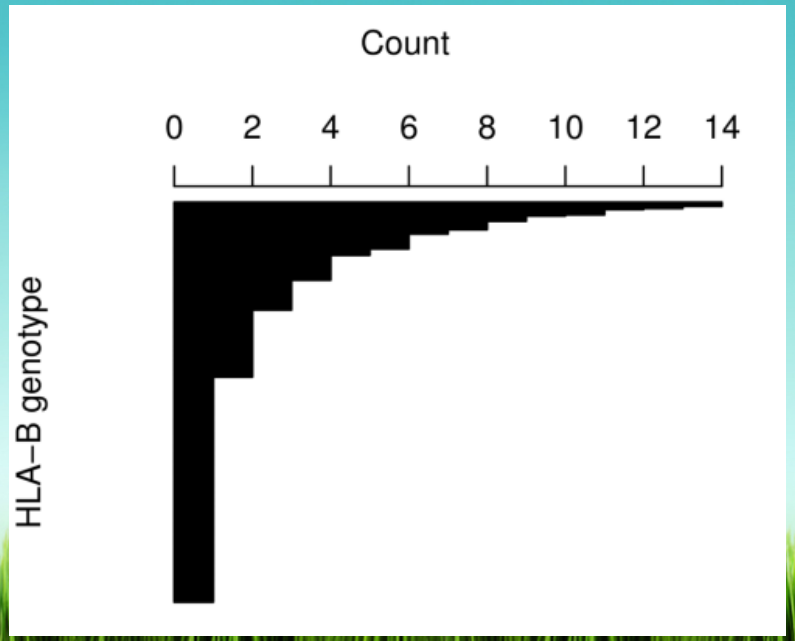
CCR5 and HLA

- CCR5 – you know it already ✓
- Homozygotes (CCR5Δ32)-> almost fully immune
- Heterozygotes -> slightly lower spVL and slower disease progression
- N(heterozygote) = 163
- No significant difference in tolerance

Variation of tolerance and HLA-B

- Could there be HLA-B genotypes that cause tolerance?
- HLA-B -> mixed-effects modeling approach
- The two alleles of each individual

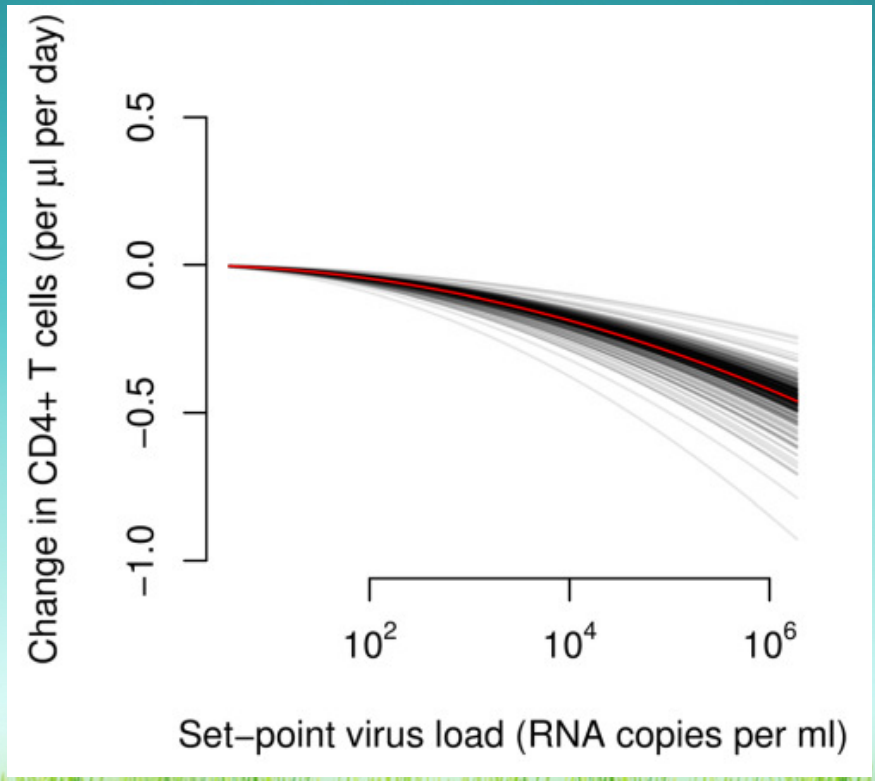
-> genotype -> 375 unique genotypes



Regoes et al., 2014

Variation of tolerance and HLA-B

- Relative standard deviation: 0.34 (relatively broad distribution)
- 1.7 fold difference in disease progression of two radom HLA-B genotype groups

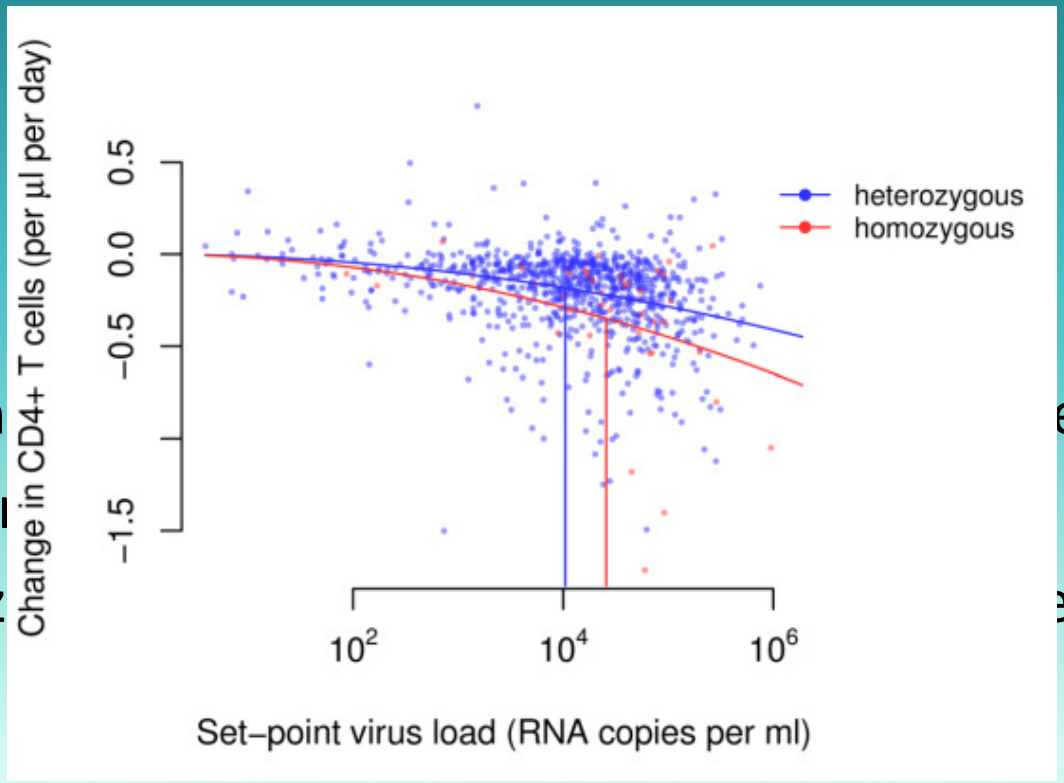


Regoes et al., 2014

HLA-B homozygosity

- 39 homozygotes, 14
- Regression analysis

- Homozygotes have h es
- Decline is even faste
- Same spVL -> homoz etero



Regoes et al., 2014

Discussion

- No negative correlation between tolerance and resistance
- The older the individuals, the lower both resistance and tolerance

- What about the lower spVL in women?

- 5-9% of CD4+ T-cell decline could be explained by spVL

-> What do you think about this?

- Why is homozygosity so bad?

References

- Paul, E. W. (2013). The major histocompatibility complex and its proteins. In: *Fundamental Immunology, 7th edition*. Philadelphia: Lippincott Williams & Wilkins.

- Raberg, L., et al. (2007). "Disentangling genetic variation for resistance and tolerance to infectious diseases in animals." Science **318**(5851): 812-814.

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