

# *evolution of host resistance and tolerance*

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## *Definitions/questions*

- **resistance**: host's ability to resist or minimize infection
- **tolerance**: host's ability to support parasite infection without losing fitness
- **competence**: host's ability to support *and transmit* parasites (especially vector-borne)
- encounter and compatibility filters: avoiding parasites vs killing vs tolerating them

## *Mechanisms*

- active defense (*plastic* or *facultative* defenses): **recognition systems** and **effectors**
  - recognition systems are the *qualitative* component of host defense: does the host recognize that the parasite (specifically, a parasite **antigen**) is present? These will typically evolve by Red Queen dynamics (i.e., via an inverse matching allele model). In vertebrates: **antibodies**
  - must be **specific** (self/non-self recognition), trigger proportionate response
  - coded by the **major histocompatibility complex** (self/non-self recognition), **somatic recombination**, deletion of host-specific antigens (Borghans, Beltman, and De Boer 2004; Acevedo-Whitehouse and Cunningham 2006; Rauch, Kalbe, and Reusch 2006; Spurgin and Richardson 2010)
  - *effectors*: what does the host do once the parasite is detected?
- passive/always-on defense (*constitutive* defenses)
  - changing cell surface receptors (e.g. CCR5-Δ32 (HIV, Hummel et al. (2005)); matching-allele model
- parasite countermeasures (immune evasion [trypanosomes], immune suppression [measles, anthrax, ...]) (Schmid-Hempel 2009)

## *Costs and tradeoffs*

What are the **costs** of resistance and tolerance? (= Why aren't all hosts tolerant/resistant to all parasites?)

(Klemme, Hyvärinen, and Karvonen 2020)

- cost of maintaining recognition mechanisms

- cost of choosing different habitats
- tradeoffs (RQ-related or ?)

*Population-level evolution (eco-evolution)*

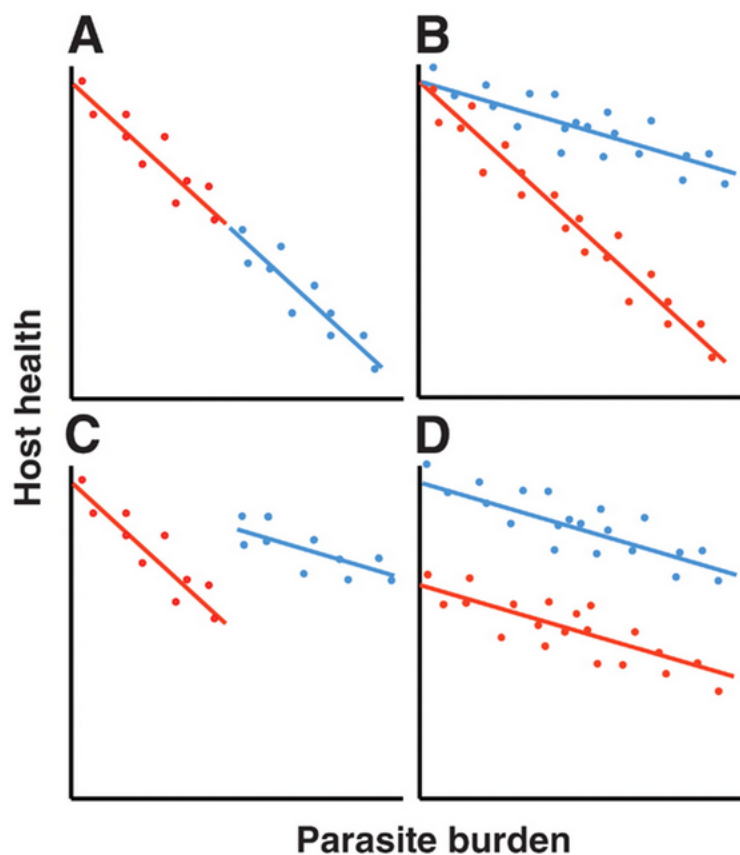
Stahl et al. (1999); Roy and Kirchner (2000)

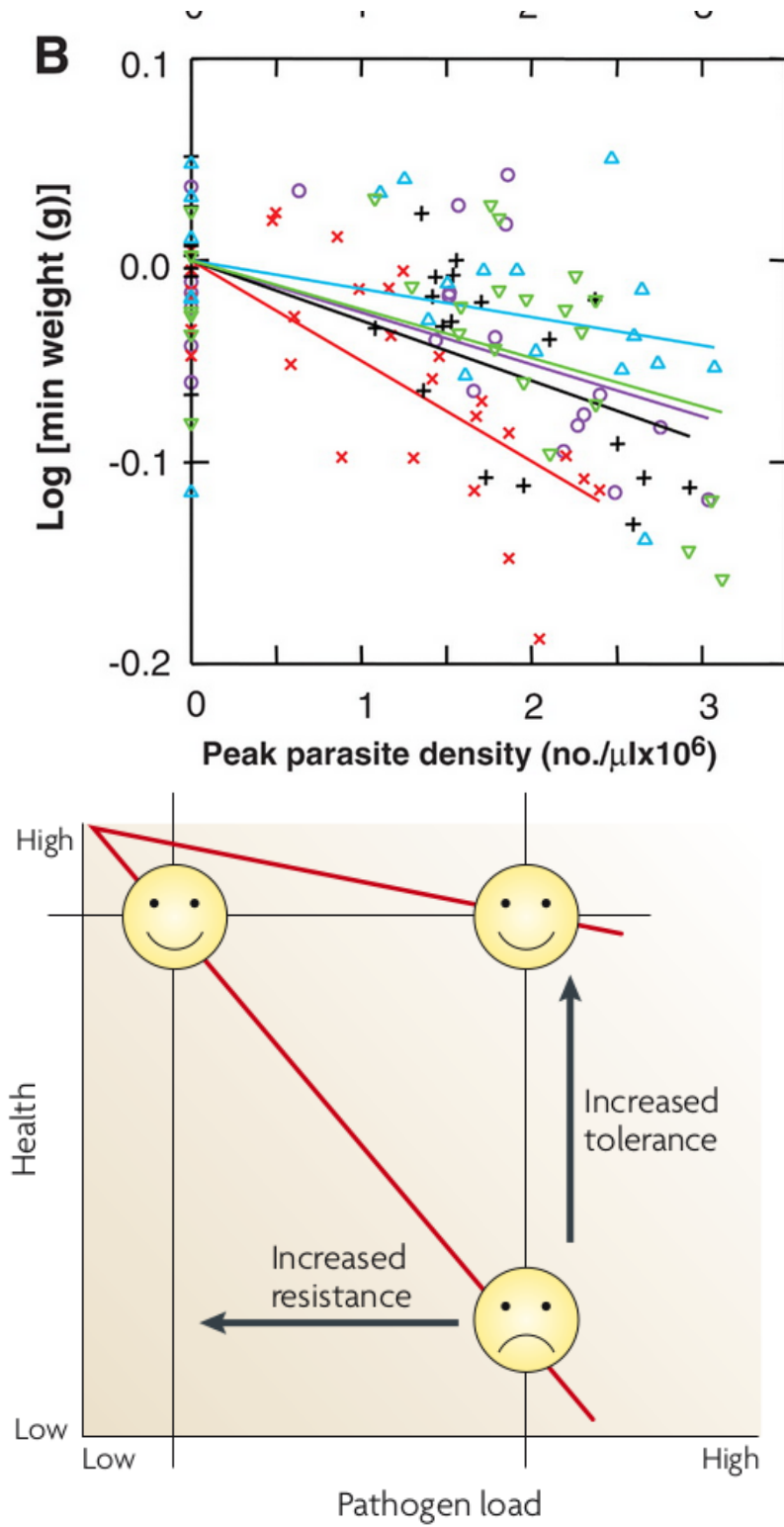
- resistance lowers prevalence - selects against itself; expect *polymorphism*
- tolerance increases prevalence - selects for itself (*apparent competition* with non-tolerant genotypes); expect *fixation*. (Is tolerance evolution-proof? (Schneider and Ayres 2008))

*Measuring quantitative resistance/tolerance*

- tolerance: loss of fitness **per unit parasite load**
- resistance: level of parasite load

(Raberg, Sim, and Read 2007; Råberg, Graham, and Read 2009)





*Disentangling the history/origin of deleterious recessive Mendelian alleles*

- Genetic *polymorphisms* are interesting; why haven't they been eliminated or fixed?

*hypotheses*

- genetic drift (null)
  - historic size of populations? (historical records, population genetics [*coalescents*])
  - strength of selection/maintenance in large populations?
- heterozygote advantage
- frequency-dependent selection (RQ vs. arms race)

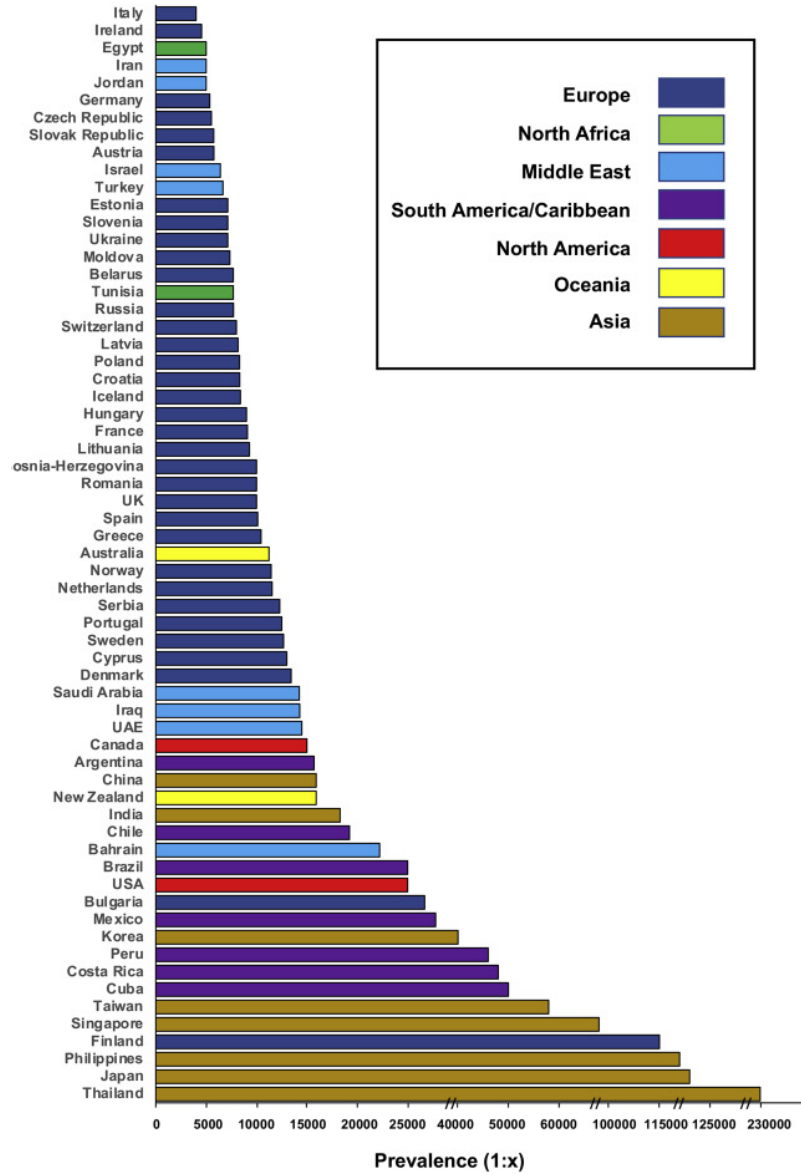
*Tay-Sachs disease*

- Lethal abnormality in hexosaminidase A (lipid metabolism); early (infant/toddler) death
- Mendelian, recessive lethal ( $s = 1$ )
- allele frequency  $\approx 1/300$  in US population,  $1/30$  in Ashkenazi (E. European) Jews: also high in French Canadians, Cajuns, Pennsylvania Dutch ...
- Population-genetic evidence suggests drift
- (Terrible!) speculation about **overdominance** or **heterozygote advantage**: Tb resistance, intelligence: ???  
(Spyropoulos 1988; Frost 2012; Frisch et al. 2004)

*phenylketonuria (PKU)*

- metabolic disorder (phenylalanine)
- many different mutations
- homozygous PKU historically lethal (**selection coefficient** = 1)
- PKU alleles are old

*PKU incidence (Hillert et al. 2020)*



*PKU genetics*

why not drift? (Krawczak and Zschocke 2003)

- many different mutations
- present across many populations
- populations without history of being small
  - e.g. Irish gene pool from  $\approx 2500$  BC
  - population size was 100K-200K
  - current expected frequency 0.6% is twice as high as expected

*PKU genetics: conclusion*

- calculation from genetic models
- heterozygote advantage probably  $\approx 1.5\%$
- hard to measure directly!
- probably due to higher phenylalanine levels in heterozygotes
- phenotypic effects?
  - higher birth weight
  - mycotoxin resistance?
  - starvation resistance?

*Sickle-cell*

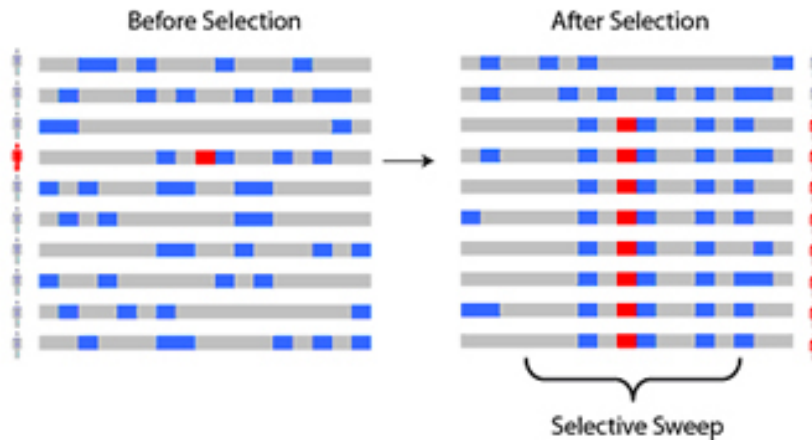
- overdominance  
(heterozygote advantage)
- selection for *falciparum* malaria resistance
- geographic patterns;  
consistency with malaria distribution
- mechanistic basis for protection
- evidence for positive selection (age??)

*Balanced polymorphisms*

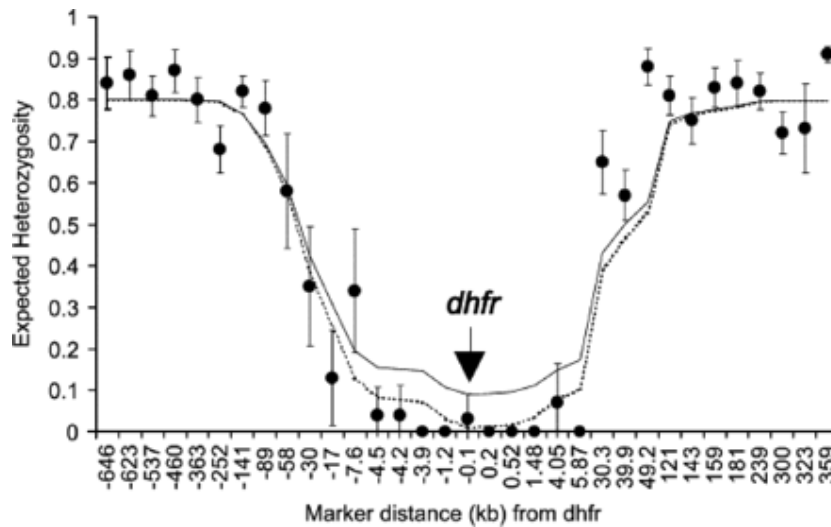
- Sickle-cell (and all cases of overdominance) depends on genetic makeup of the *population*
- chance of mating with a carrier is higher when allele is more common
- easier to do the math at the level of alleles

*Selective sweeps*

- strong selection on an allele
- individuals carrying that allele have high fitness
- lower (gene-specific) **effective population size**
- neighbouring loci carried along as **haplotypes: hitchhiking**
- haplotypes gradually erode (narrow) by recombination
- e.g. MHC class I variability in chimpanzees decreased  $\sim 2-3$  mya (Groot et al. 2002)



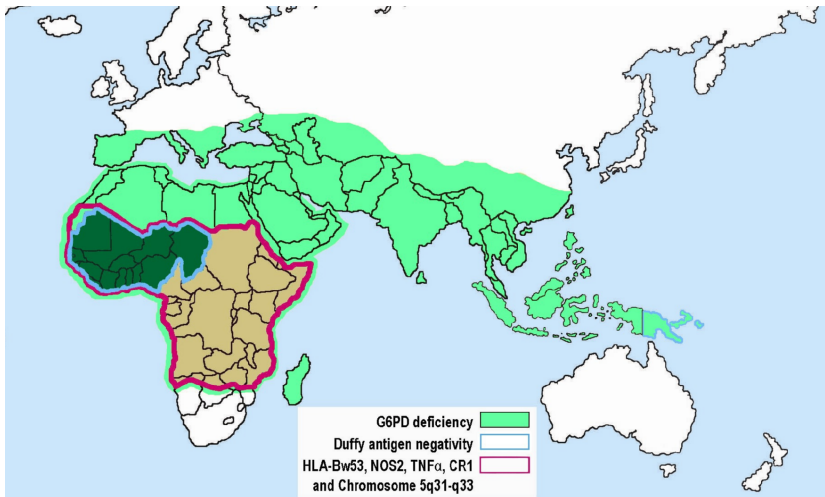
*Selective sweep: chromosome pattern*



(Nair et al. 2003)

#### *Other malaria-protective variation*

- hemoglobin variants:
  - blood groups, Rh-negativity (older than malaria)
  - thalassemia
- enzyme variants:
  - GP6D deficiency/favism
    - \* Mediterranean populations
    - \* X-linked
    - \* arose 5-10K years ago: agriculture?
- Duffy antigens (protection against *vivax* malaria)



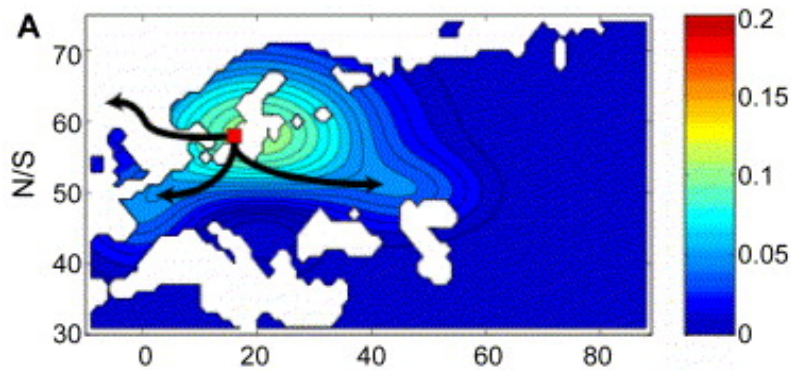
Wikipedia

### *Cystic fibrosis*

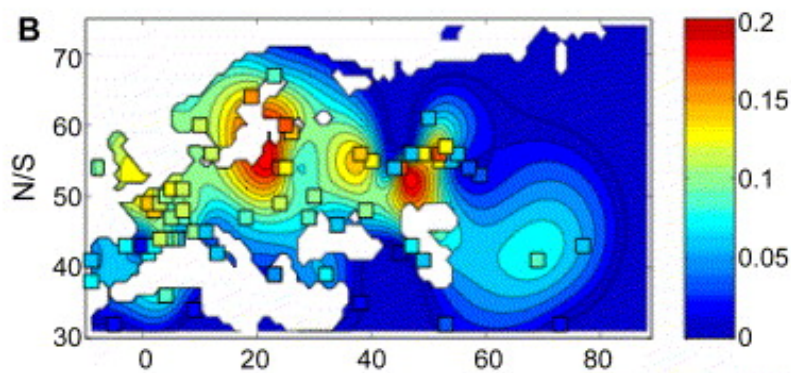
- Lethal lung disease: mucus build-up  
(1/4 chance of death before 30, previously much higher)
- 4% carriers in European whites (1/2500 diseased:  $2pq = 0.04 \rightarrow q^2 = 0.0004$ )
- Mutated cftr gene, changes chloride metabolism;  
age approx. 50 KYA
- Protection from cholera? (First European cholera epidemic 1817)  
Dehydrating intestinal diseases? Typhoid?
- **Pleiotropy** (multiple effects from one gene)



## HIV



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- where does CCR5- $\Delta$ 32 come from?
- homozygous individuals are healthy ...
- at least 5000 years old; Hummel et al. (2005); Novembre, Galvani, and Slatkin (2005); Galvani and Novembre (2005); Lidén, Linderholm, and Götherström (2006)
  - “If  $\Delta$ 32 were neutral, population genetics theory predicts it would have to be much older given its frequency.”
- high dispersal, sustained strong selection ( $s > 0.1$ ); what selective agent? plague? smallpox?

*Summary: variation in Mendelian traits*

- (relatively) simple inheritance
  - recessive/dominant, autosomal/X/Y-linked
- mechanisms
  - drift

- heterozygote advantage
- balancing selection/tradeoffs; gene  $\times$  environment interaction
- evidence
  - ancient DNA
  - phylogenetic patterns/*coalescent* methods to estimate origin times/places
  - biogeography/history of disease/environment
  - mechanism
  - population history

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