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- (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)

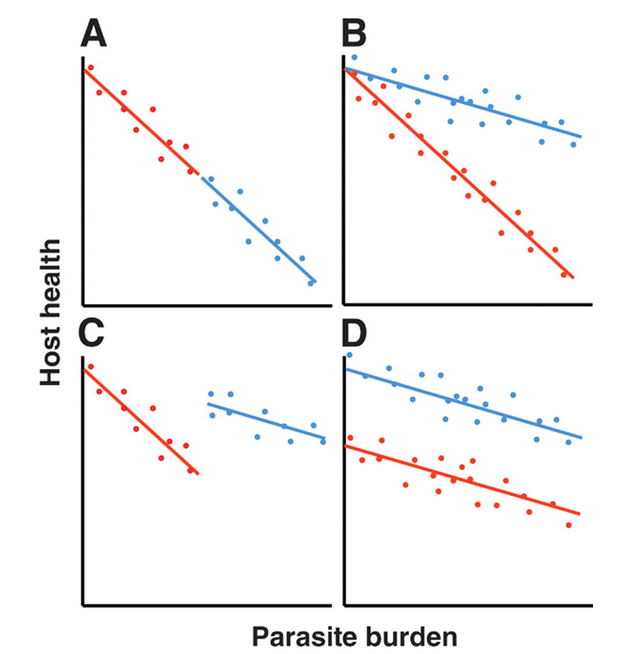
Stahl et al. (1999); Roy and Kirchner (2000)

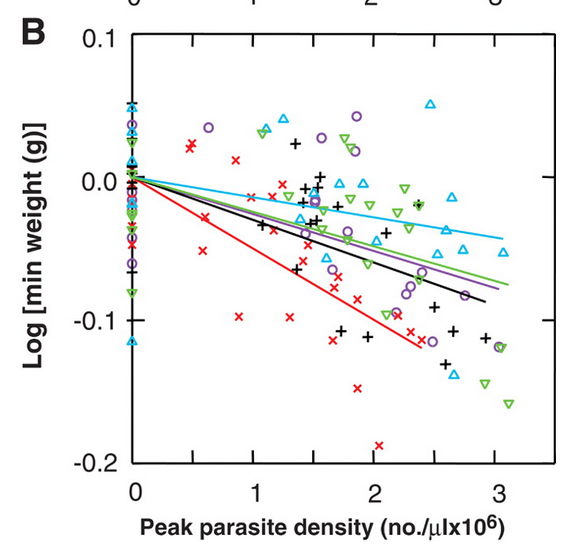
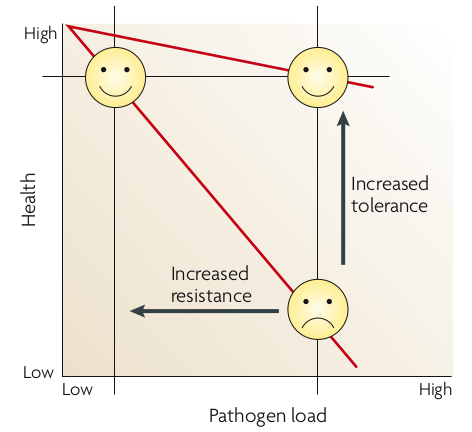
* resistance lowers prevalence - selects against itself; expect *polymorphism*
* tolerance increases prevalence - selects for itself (*apparent competition* with non-tolerant genotypes); expect *fixation*. (Is tolerance evolution-proof? (Schneider and Ayres 2008))

## 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)

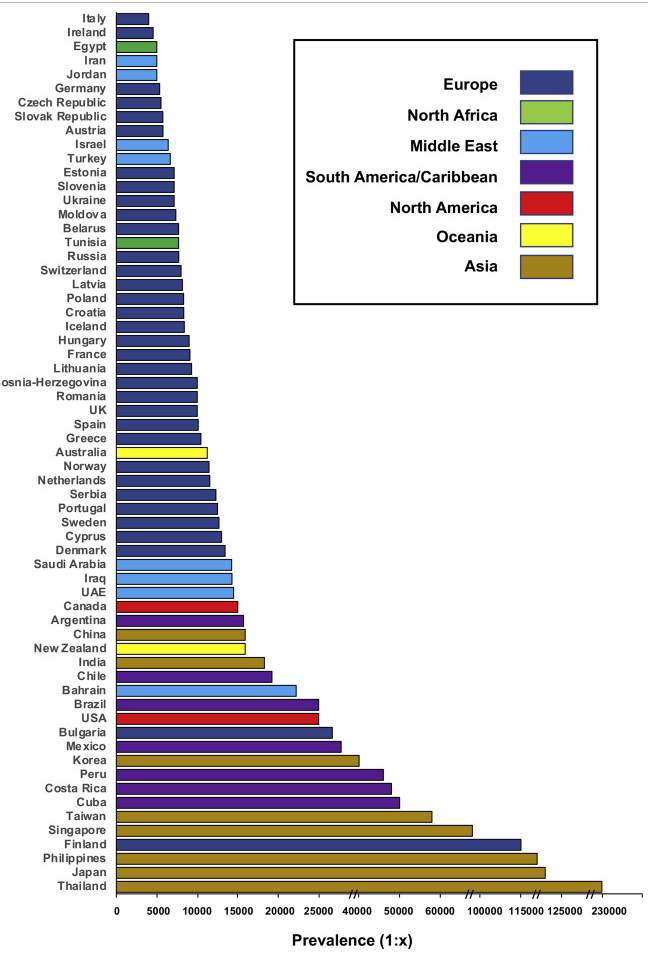
## Tay-Sachs disease

* Lethal abnormality in hexosaminidase A (lipid metabolism); early (infant/toddler) death
* Mendelian, recessive lethal ()
* allele frequency 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 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 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

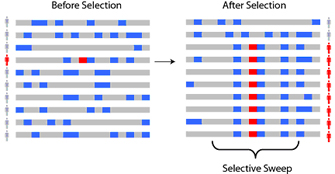
* overdominance  
  (heterozygote advantage)
* selection for *falciparum* malaria resistance
* geographic patterns;  
  consistency with malaria distribution
* mechanistic basis for protection
* evidence for positive selection (age??)

## Balanced polymorphisms

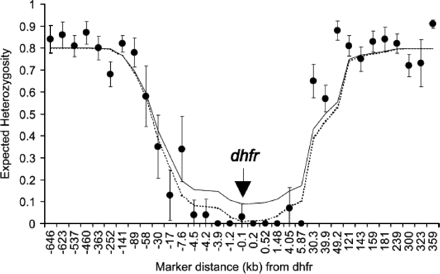
* Sickle-cell (and all cases of overdominance) depends on genetic makeup of the *population*
* chance of mating with a carrier is higher when allele is more common
* easier to do the math at the level of alleles

## 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 ~ 2-3 mya (Groot et al. 2002)



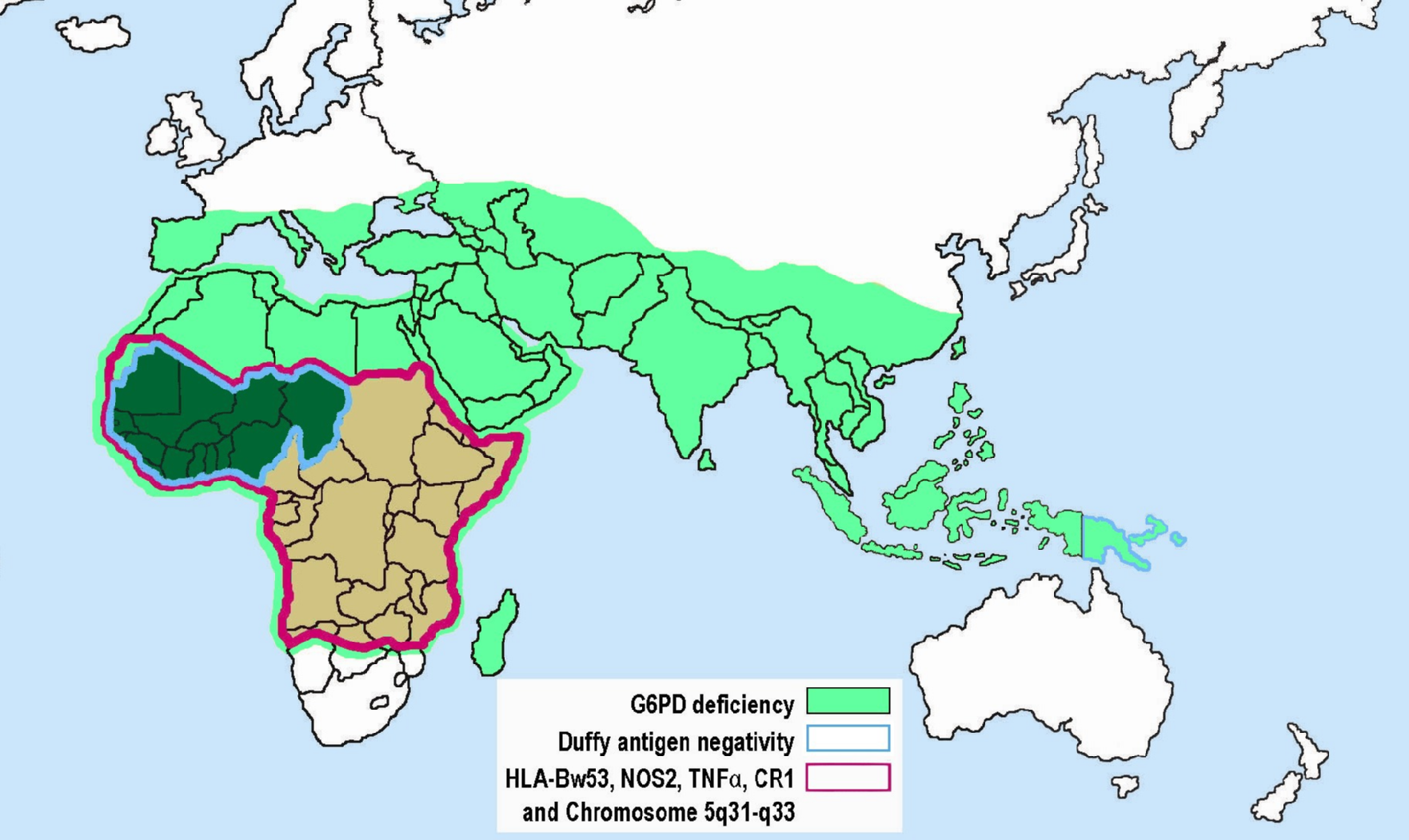
## Selective sweep: chromosome pattern



(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)



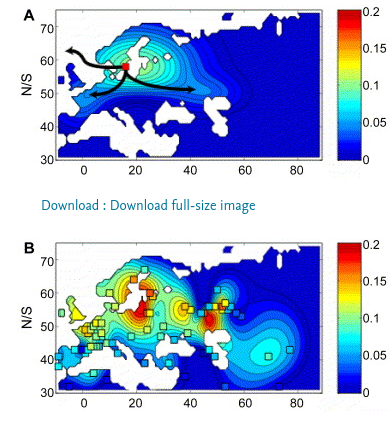
[Wikipedia](https://en.wikipedia.org/wiki/Genetic_resistance_to_malaria)

## 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: )
* 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

From Galvani and Novembre (2005):



* where does CCR5- 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 were neutral, population genetics theory predicts it would have to be much older given its frequency.”
* high dispersal, sustained strong selection (); 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 × 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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