evolution of host resistance and tolerance

28 October 2023

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**
  - 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)

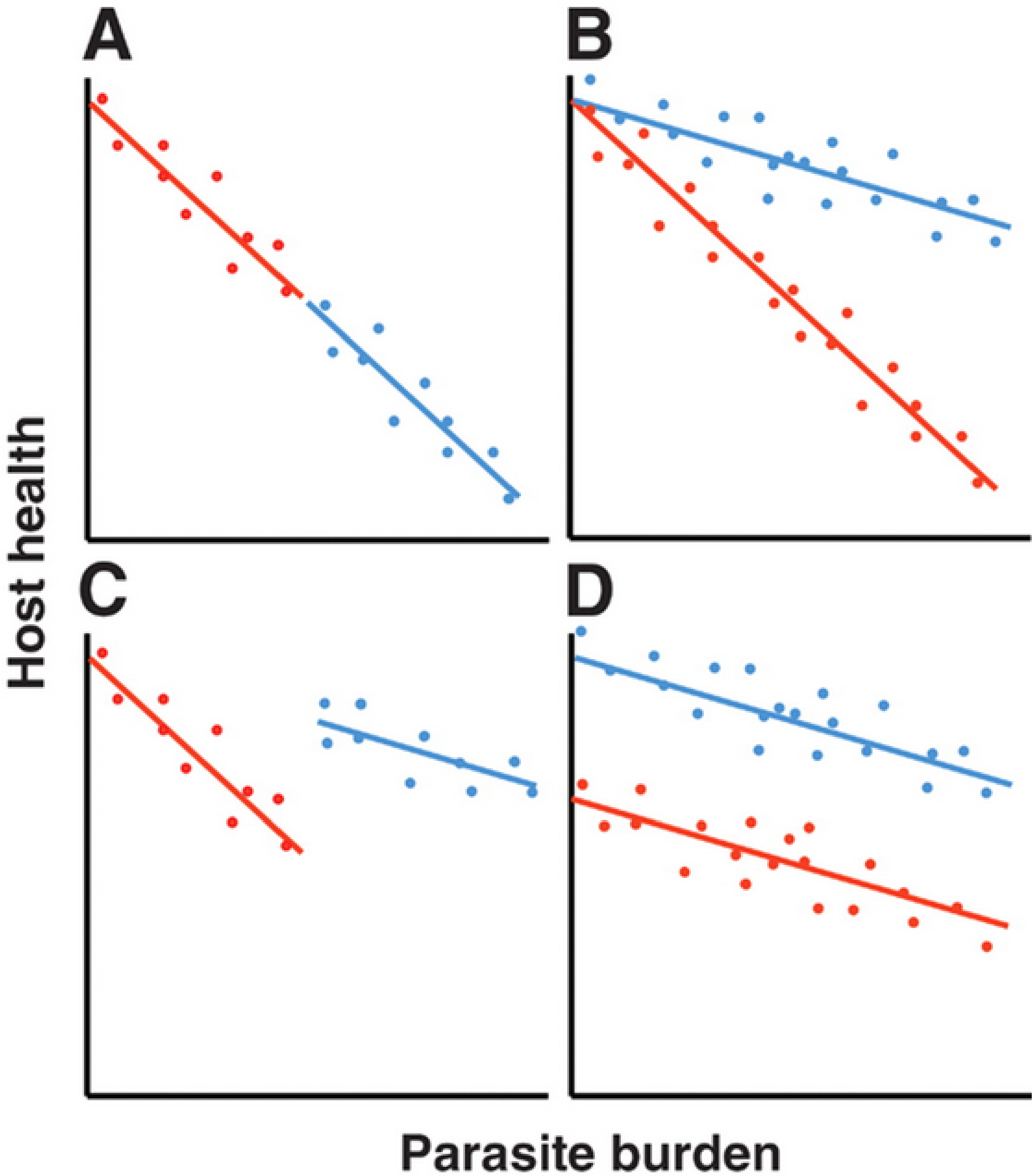
Stahl et al. (1999); Roy and Kirchner (2000)

- 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)


A
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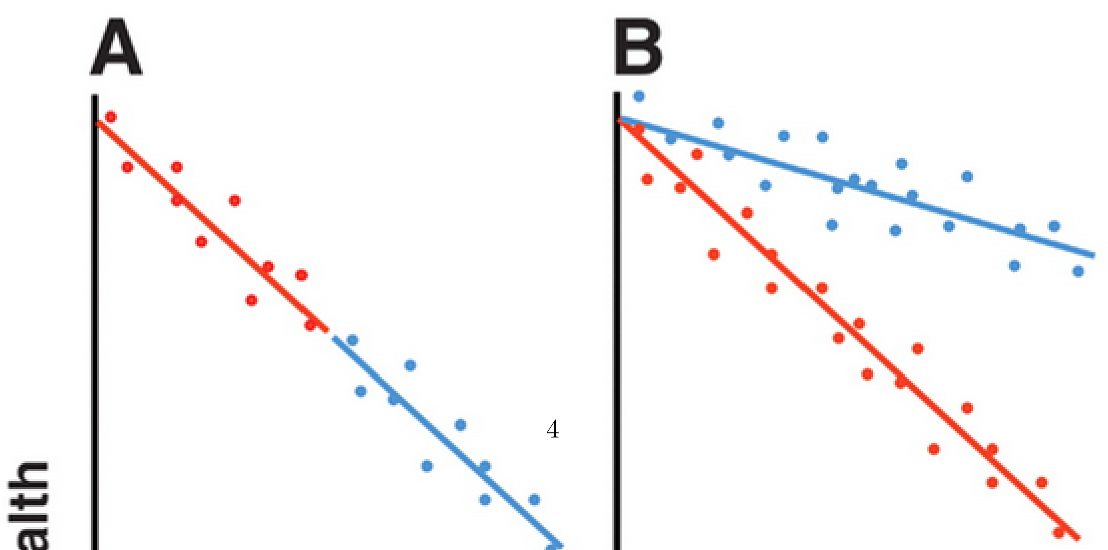
Host health
Parasite burden


A
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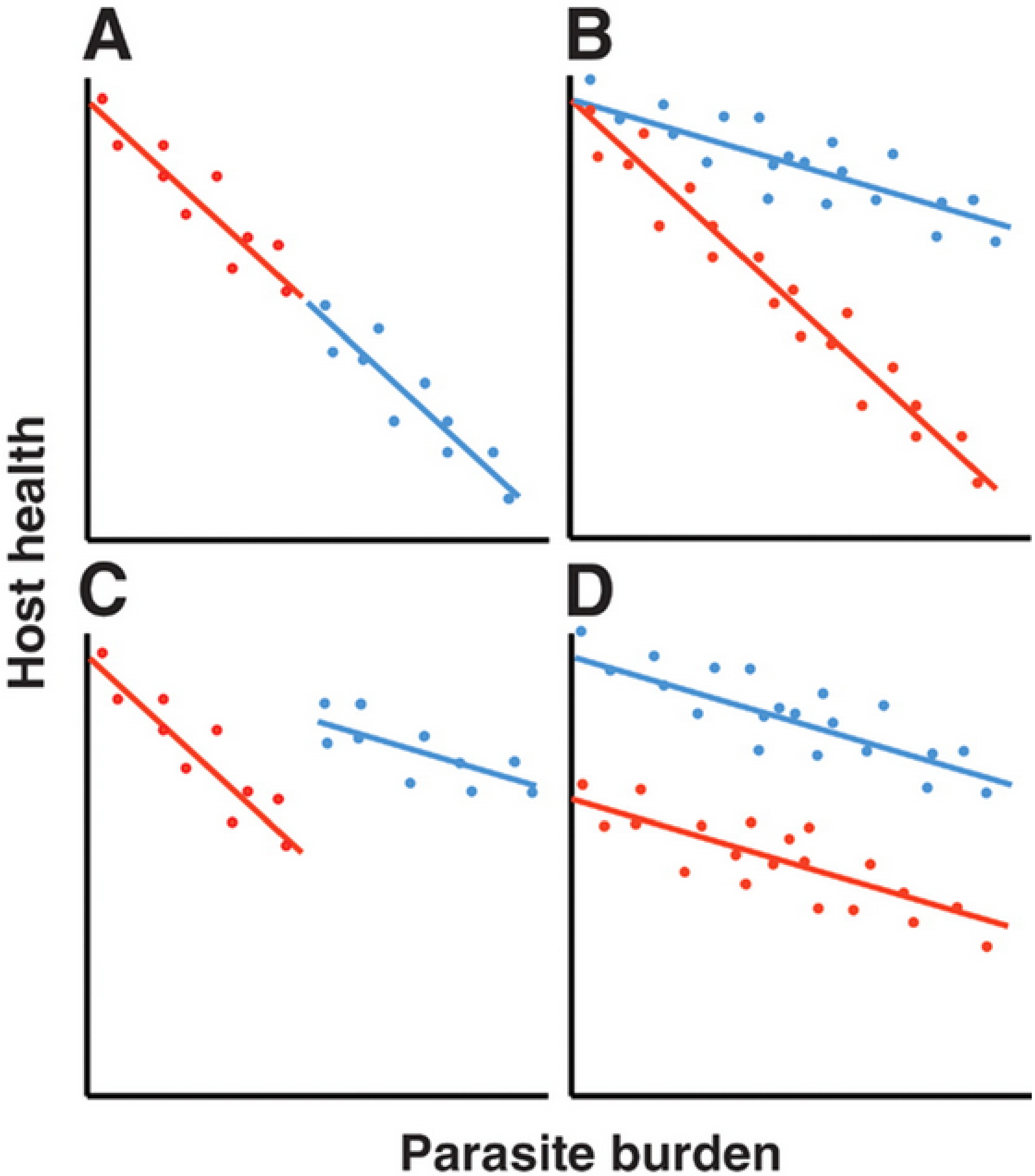


Disentangling the history/origin of deleterious recessive Mendelian alleles

- 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)

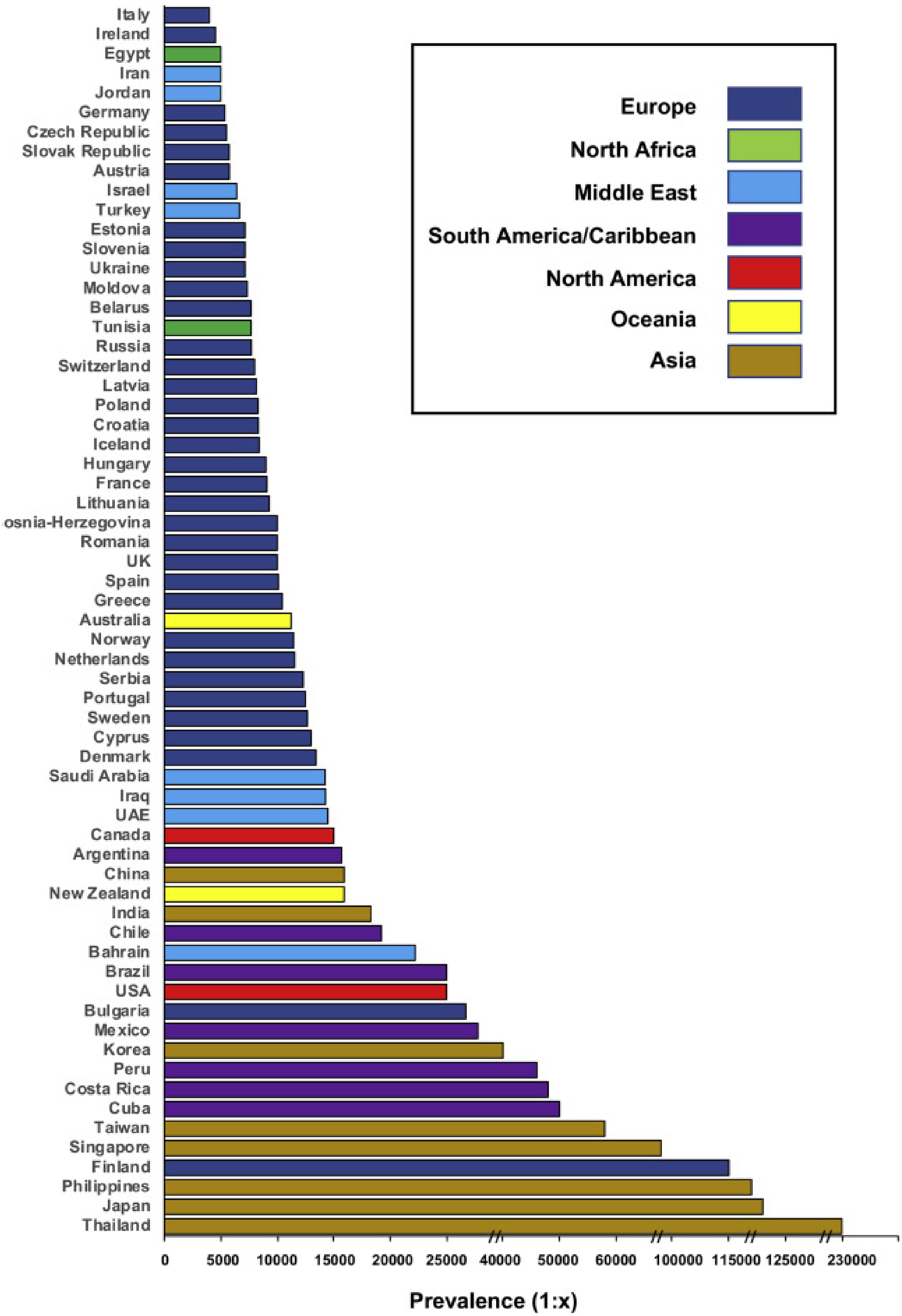
Tay-Sachs disease

- 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)

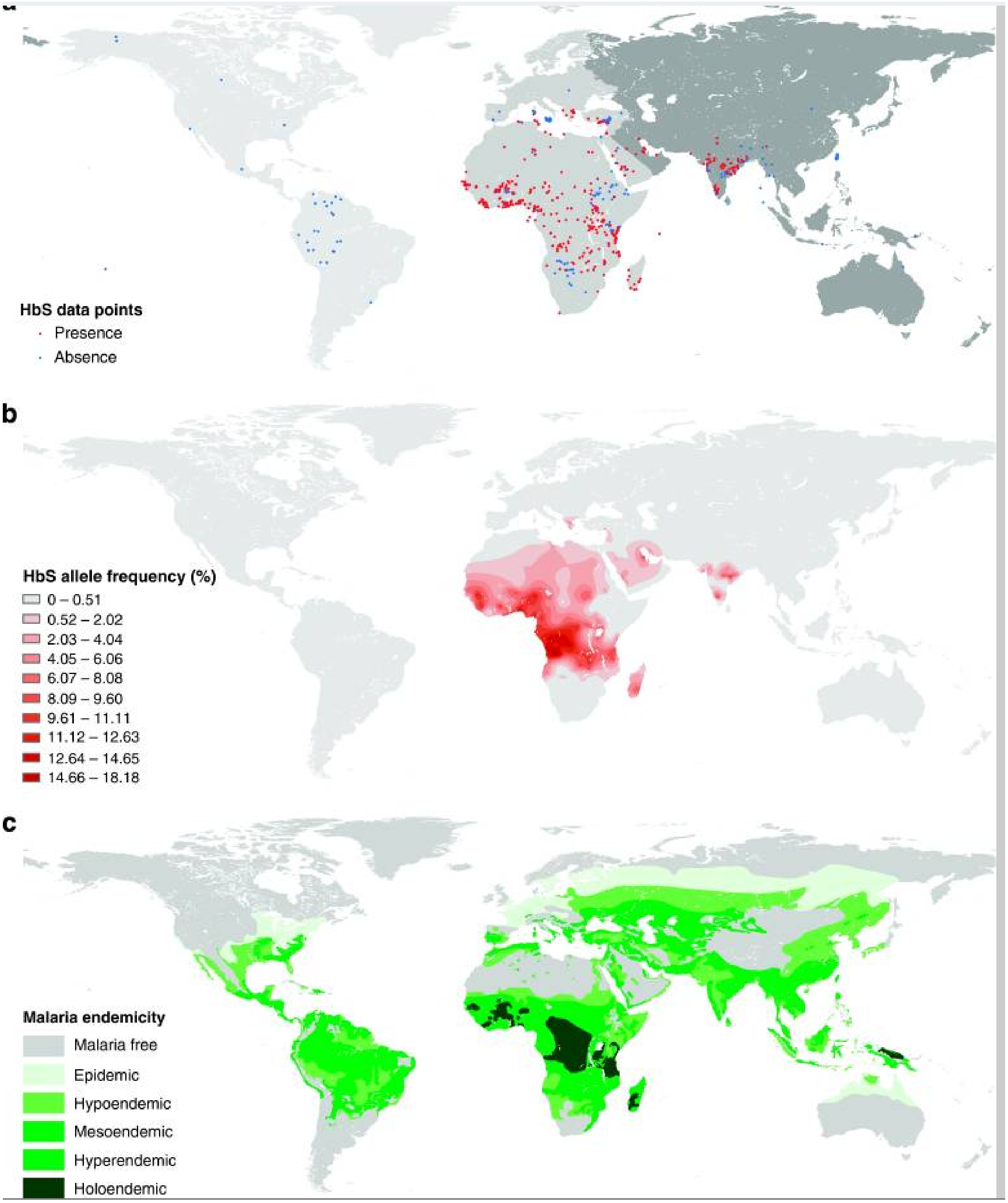
- many different mutations
- present across many populations
- populations without history of being small
  - e.g. Irish gene pool from $\approx$ 2500 BC
  - population size was 100K-200K
  - current expected frequency 0.6% is twice as high as expected

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 Esoh and Wonkam (2021)
- mechanistic basis for protection
- evidence for positive selection (age??)

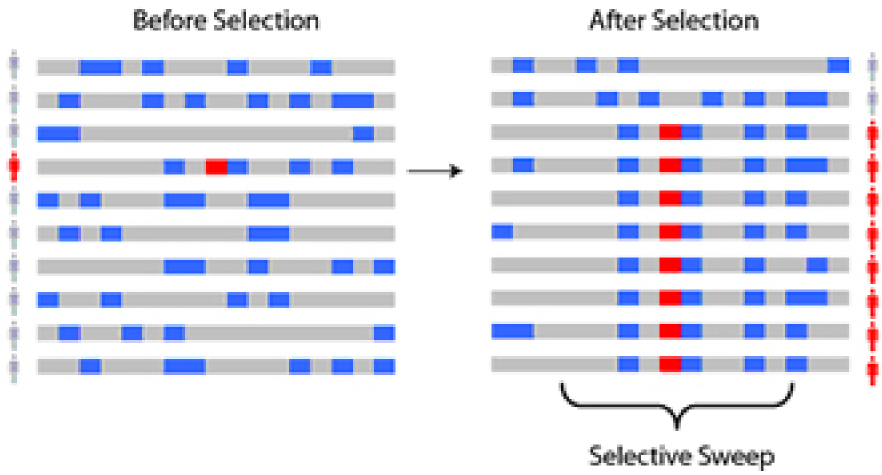


Balanced polymorphisms

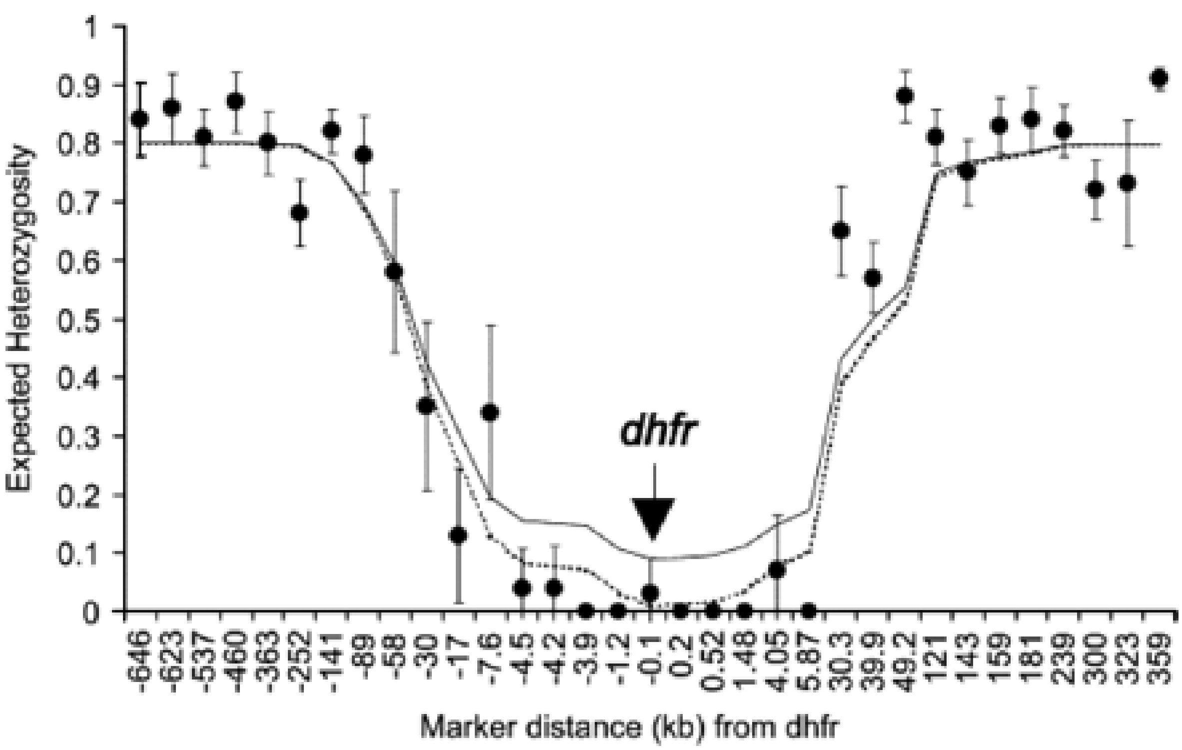
- Sickle-cell (and all cases of overdominance) depends on genetic makeup of the *population*
- chance of mating with a carrier is higher when allele is more common
- easier to do the math at the level of alleles

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

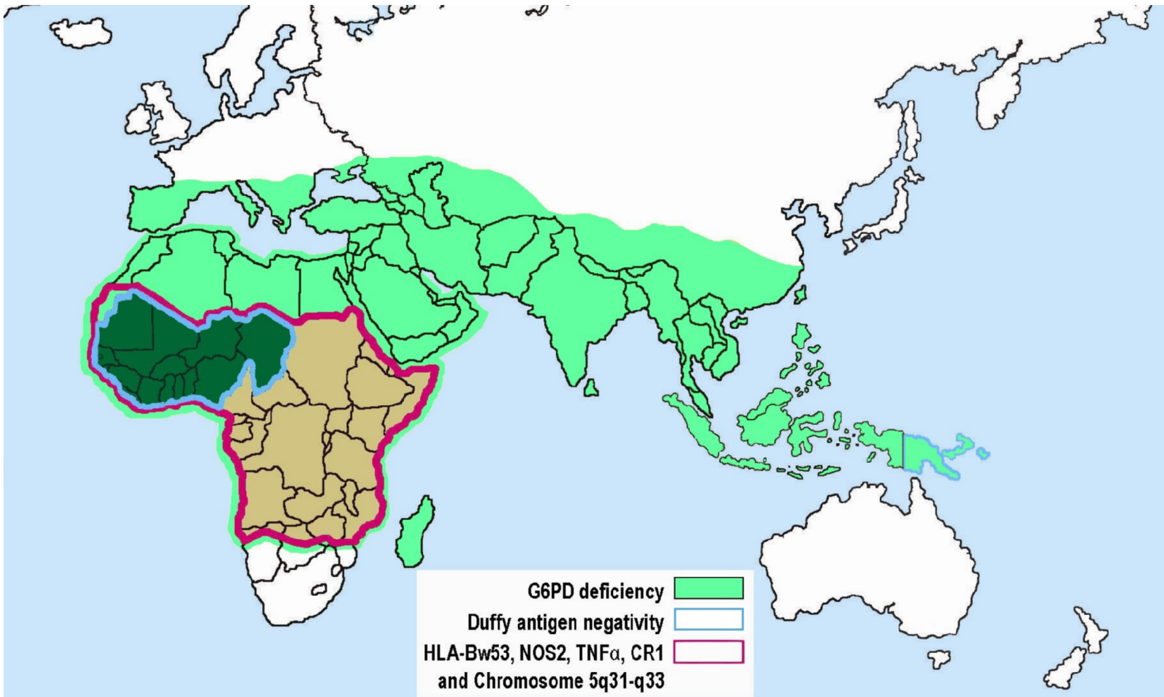


(Nair et al. 2003)

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)



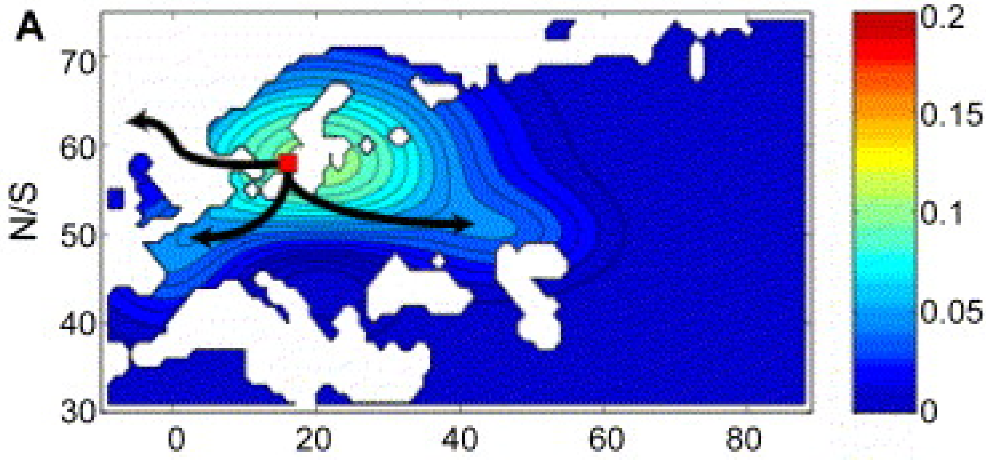
Wikipedia

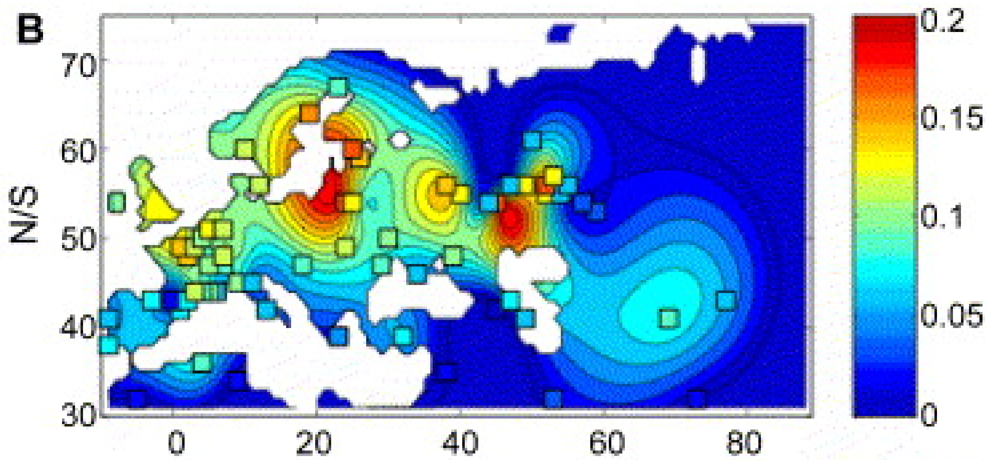
Cystic fibrosis

- Lethal lung disease: mucus build-up
  (1/4 chance of death before 30, previously much higher)
- 4% carriers in European whites (1/2500 diseased: $2pq = 0.04 \to q^2 = 0.0004$)
- 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

From Galvani and Novembre (2005):





- where does CCR5-Δ32 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 Δ32 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

more examples

Domínguez-Andrés and Netea (2019)

Pathogen or disease	Gene or gene variants	Effect association	Refs
Plasmodium falciparum	*HBB, HBC, HBA1, HBA2* *FCGR2B*	Protection (associated with hemoglobinopathies) Protection (associated with SLE[a])	[9,13,102] [69]
Plasmodium vivax	*DARC, HLA-DRB1** and *HLA-DQB1**	Protection	[11,12,103]
Bacterial sepsis	*CASP12* (T^{125}C)	Protection	[14]
Mycobacterium tuberculosis	*VDR, SLC11A1, TIRAP, HLA, CCL2, IL12A* *IFNG* (874T/A)	Protection Detrimental	[17,18,104] [40]
Lassa virus	*IL21* and *LARGE*	Protection	[20]
Trypanosoma brucei	*APOL1*	Protection (associated with SLE)	[68]
Viral infections (e.g., HSV type 2, influenza, papillomavirus)	*HLA-DQ2* and *HLA-DQ8*	Protection (associated with CD)	[105,106]
Bacterial products (*Escherichia coli* LPS and muramyl dipeptide)	*SH2B3* rs3184504*A	Protection (detrimental for CD)	[72]
Gram-negative bacterial infections and parasitic infections	*NOD2* and *TLR4/CD14*	Protection (detrimental for IBD)	[74,107,108,109]
HIV-1	CCR5Δ32	Protection	[98]

a

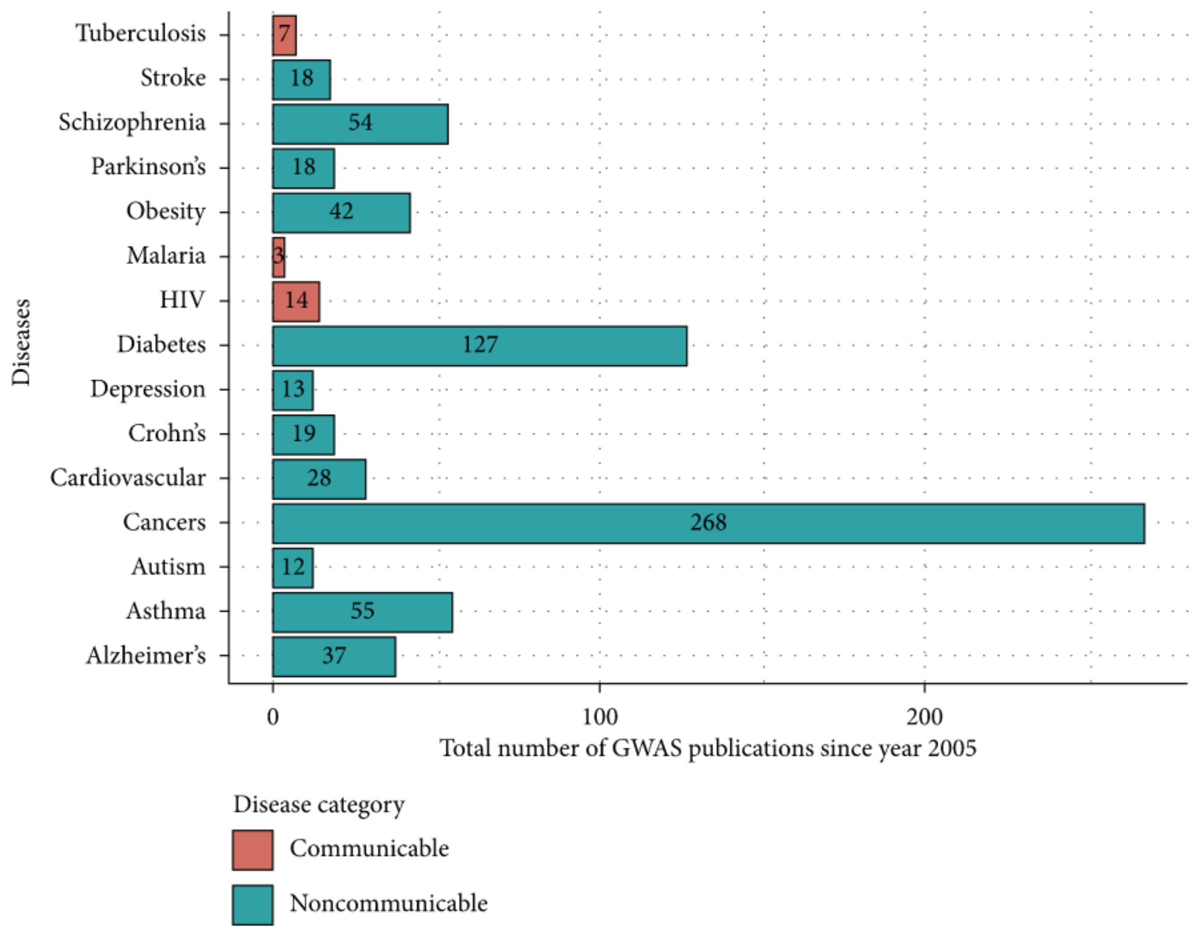
Abbreviations: CD, Crohn's disease; HSV, herpes simplex virus; IBD, inflammatory bowel

GWAS

Mboowa et al. (2018)

Figure 2

Comparison of selected communicable and noncommunicable disease GWASs since 2005.



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