evolution of host resistance and tolerance

7 March 2022

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)

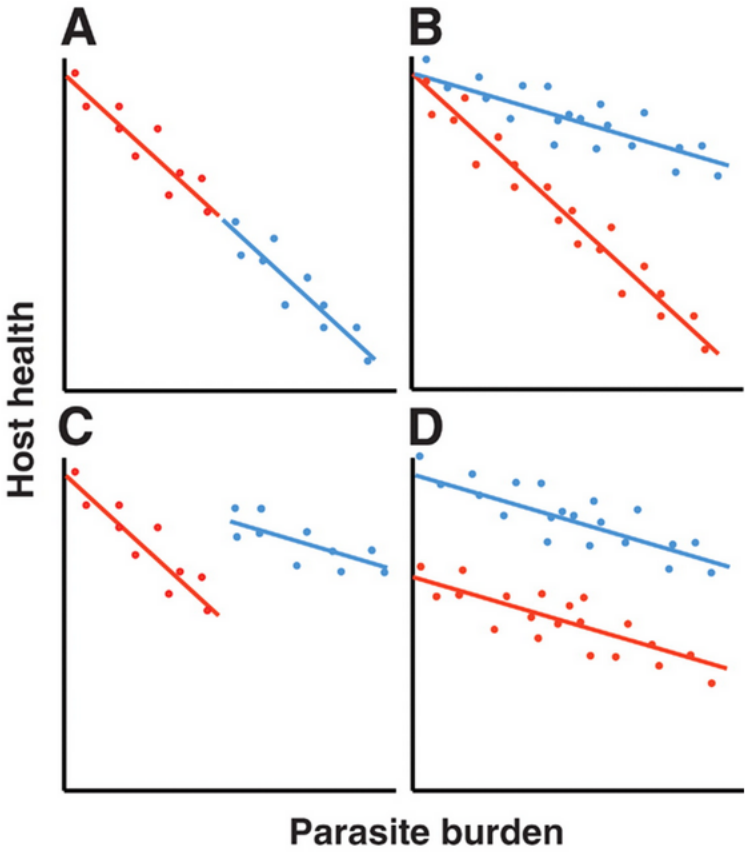
Stahl et al. (1999); Roy and Kirchner (2000)

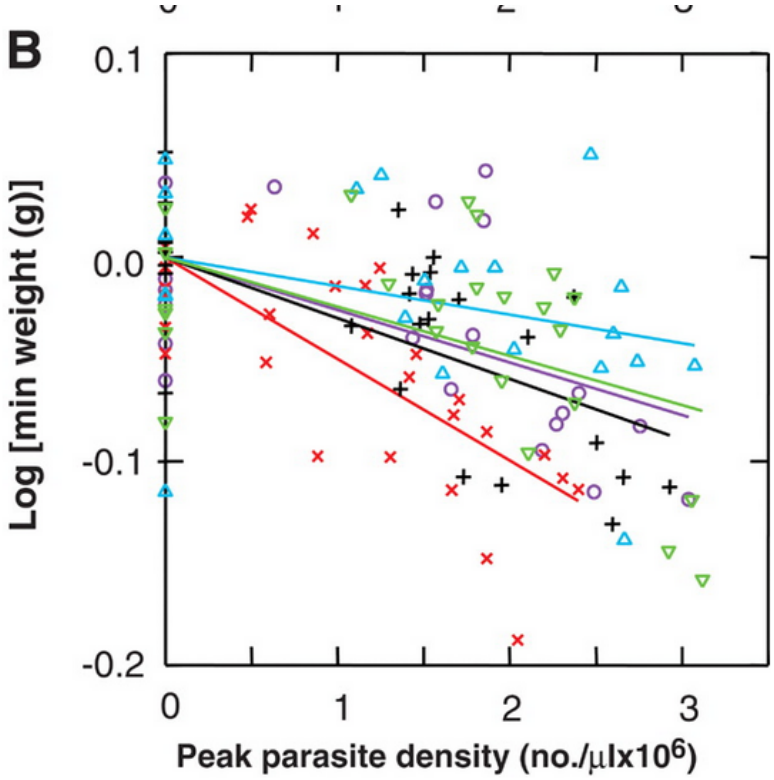
- resistance lowers prevalence - selects against itself; expect *polymorphism*
- tolerance increases prevalence - selects for itself (*apparent competition* with non-tolerant genotypes); expect *fixation*. (Is tolerance evolution-proof? (Schneider and Ayres 2008))

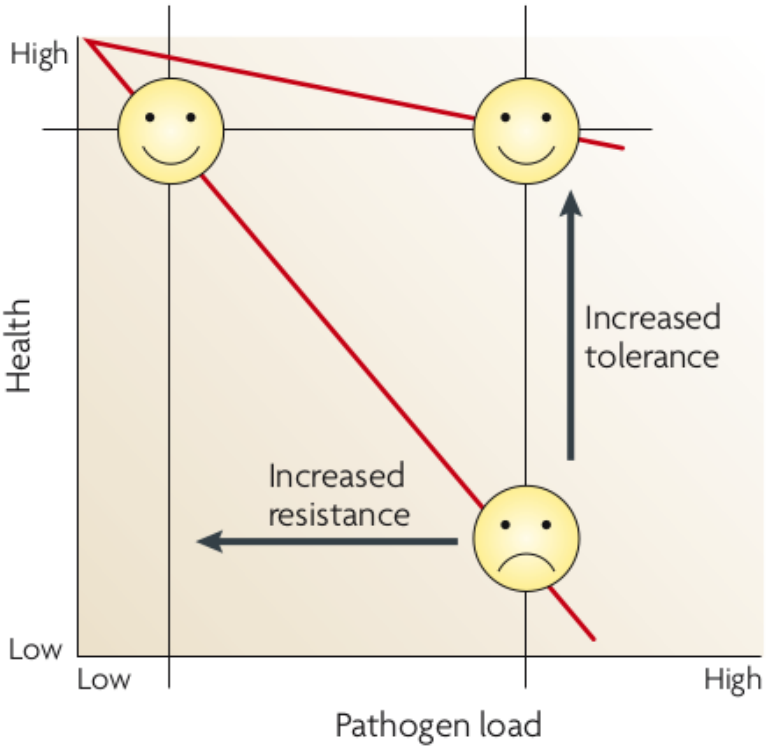
Measuring quantitative resistance/tolerance

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

(Raberg, Sim, and Read 2007, @raberg_decomposing_2009)




B
0.1
0.0
-0.1
-0.2
Log [min weight (g)]
0
1
2
3
Peak parasite density (no./μlx10^6)


High
Health
Low
Low
High
Pathogen load
Increased tolerance
Increased resistance

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)

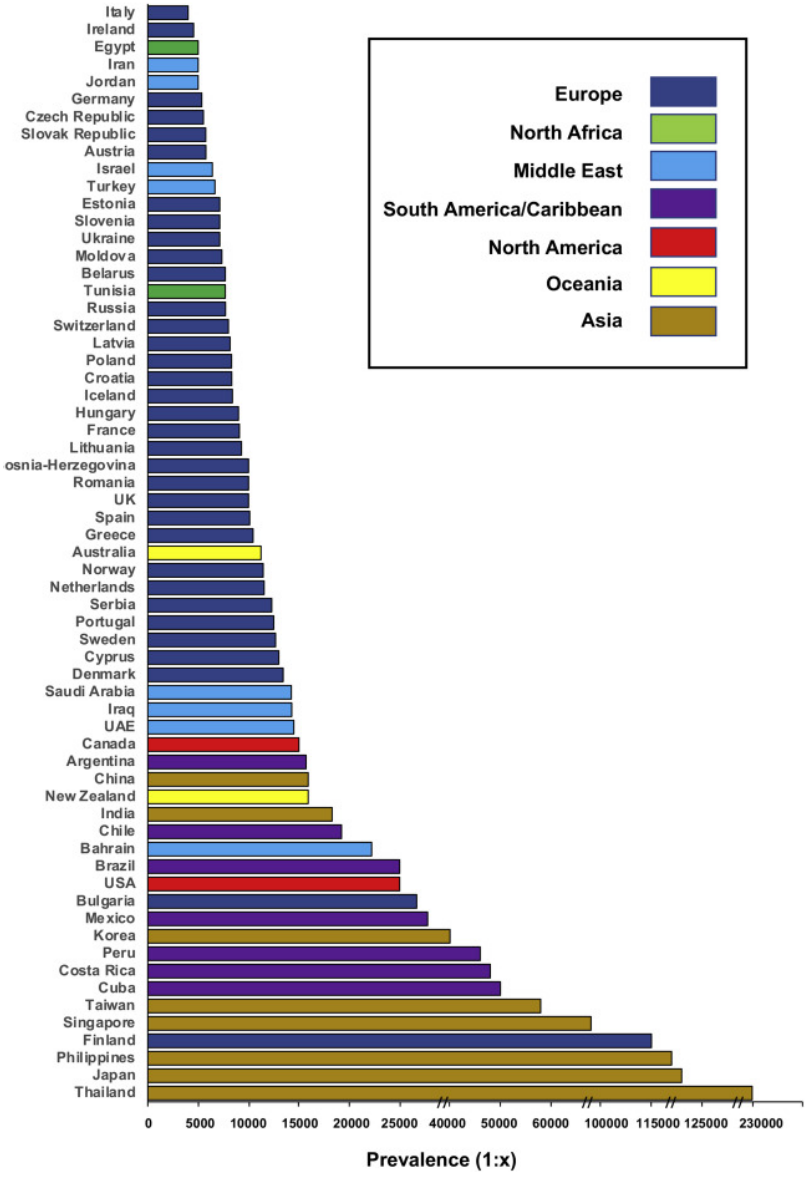
Tay-Sachs disease

- 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

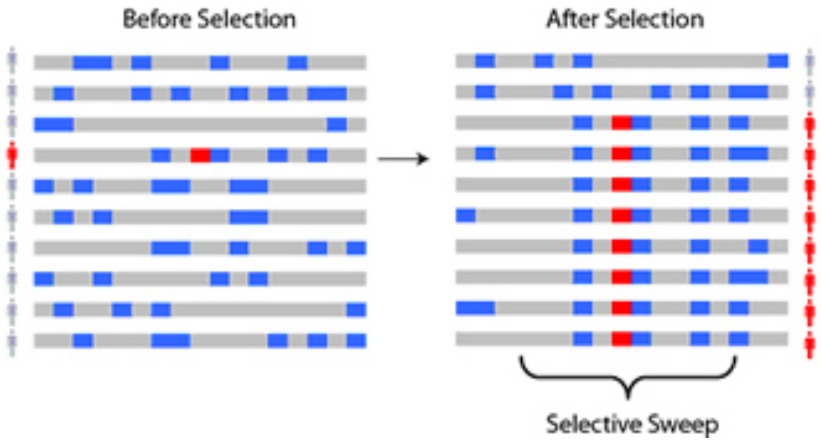
- overdominance
  (heterozygote advantage)
- selection for *falciparum* malaria resistance
- geographic patterns;
  consistency with malaria distribution
- mechanistic basis for protection
- evidence for positive selection (age??)

Balanced polymorphisms

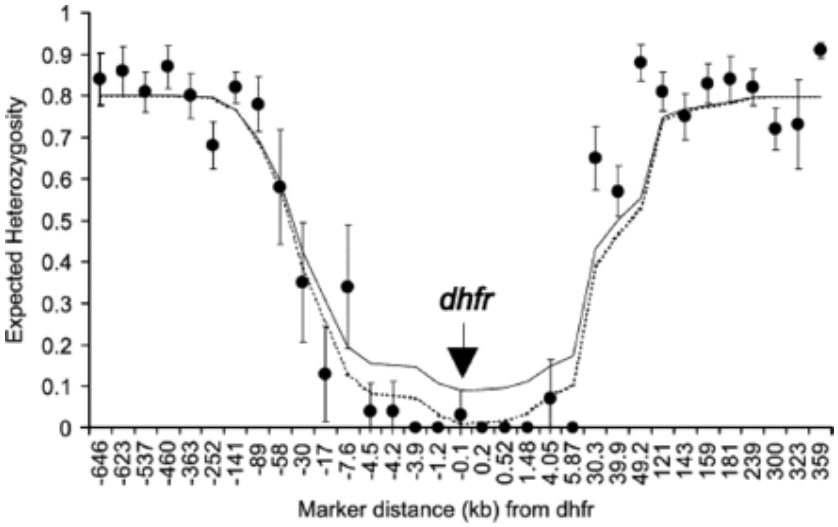
- Sickle-cell (and all cases of overdominance) depends on genetic makeup of the *population*
- chance of mating with a carrier is higher when allele is more common
- easier to do the math at the level of alleles

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



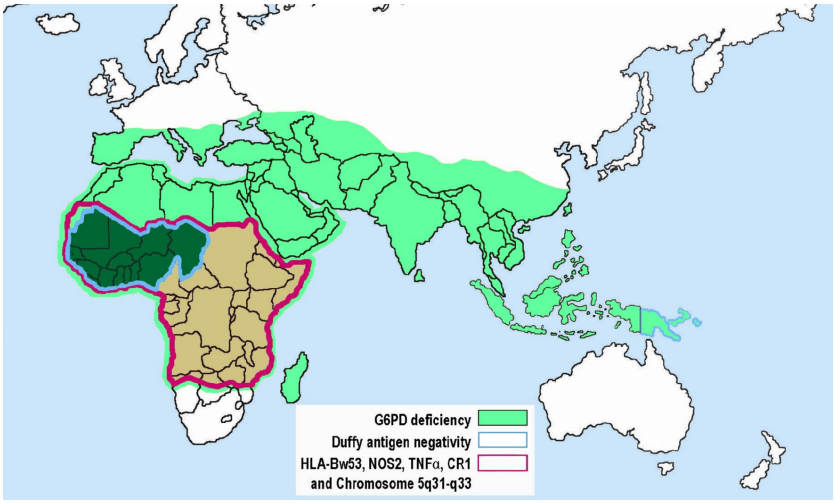
Selective sweep: chromosome pattern



(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)

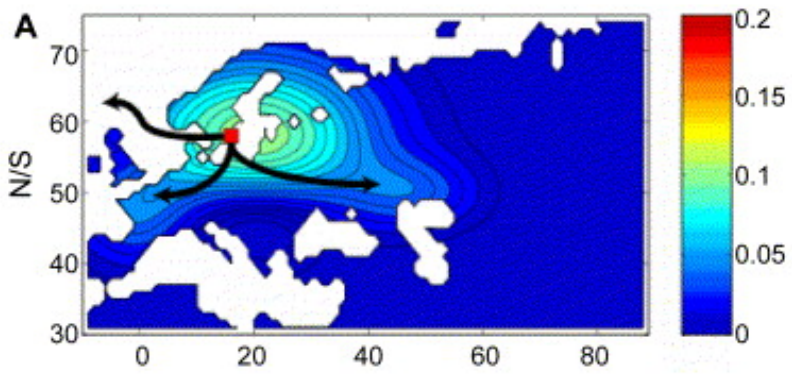


Wikipedia

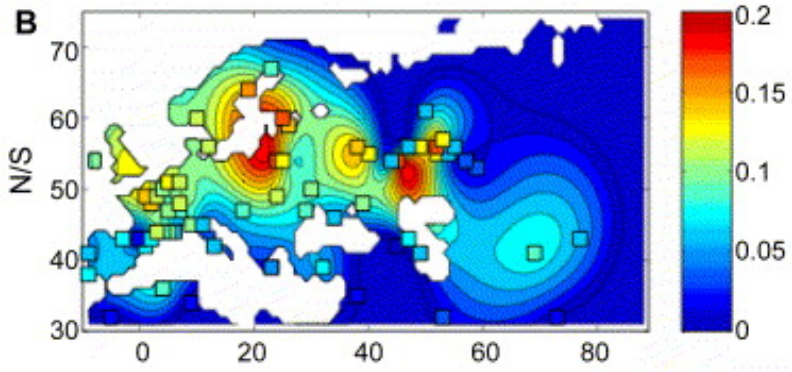
Cystic fibrosis

- 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



Download : Download full-size image



- 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 × environment interaction
- evidence
  - ancient DNA
  - phylogenetic patterns/*coalescent* methods to estimate origin times/places
  - biogeography/history of disease/environment
  - mechanism
  - population history

References

Acevedo-Whitehouse, K., and A. A Cunningham. 2006. "Is MHC Enough for Understanding Wildlife Immunogenetics?" *Trends in Ecology & Evolution* 21 (8): 433–38.

Borghans, J. A. M, J. B Beltman, and R. J De Boer. 2004. "MHC Polymorphism Under Host-Pathogen Coevolution." *Immunogenetics* 55 (11): 732–39.

Frisch, Amos, Roberto Colombo, Elena Michaelovsky, Mazal Karpati, Boleslaw Goldman, and Leah Peleg. 2004. "Origin and Spread of the 1278insTATC Mutation Causing Tay-Sachs Disease in Ashkenazi Jews: Genetic Drift as a Robust and Parsimonious Hypothesis." *Human Genetics* 114 (4): 366–76. https://doi.org/10.1007/s00439-003-1072-8.

Frost, Peter. 2012. "Tay-Sachs and French Canadians: A Case of Gene-Culture Co-Evolution?" *Advances in Anthropology* 02 (03): 132–38. https://doi.org/10.4236/aa.2012.23016.

Galvani, Alison P., and John Novembre. 2005. "The Evolutionary History of the CCR5-Δ32 HIV-Resistance Mutation." *Microbes and Infection* 7 (2): 302–9. https://doi.org/10.1016/j.micinf.2004.12.006.

Groot, Natasja G. de, Nel Otting, Gaby G. M. Doxiadis, Sunita S. Balla-Jhagjhoorsingh, Jonathan L. Heeney, Jon J. van Rood, Pascal Gagneux, and Ronald E. Bontrop. 2002. "Evidence for an Ancient Selective Sweep in the MHC Class I Gene Repertoire of Chimpanzees." *Proceedings of the National Academy of Sciences* 99 (18): 11748–53. https://doi.org/10.1073/pnas.182420799.

Hillert, Alicia, Yair Anikster, Amaya Belanger-Quintana, Alberto Burlina, Barbara K. Burton, Carla Carducci, Ana E. Chiesa, et al. 2020. "The Genetic Landscape and Epidemiology of Phenylketonuria." *The American Journal of Human Genetics* 107 (2): 234–50. https://doi.org/10.1016/j.ajhg.2020.06.006.

Hummel, S., D. Schmidt, B. Kremeyer, B. Herrmann, and M. Oppermann. 2005. "Detection of the CCR5-Δ32 HIV Resistance

Gene in Bronze Age Skeletons." *Genes & Immunity* 6 (4): 371–74. https://doi.org/10.1038/sj.gene.6364172.

Klemme, Ines, Pekka Hyvärinen, and Anssi Karvonen. 2020. "Negative Associations Between Parasite Avoidance, Resistance and Tolerance Predict Host Health in Salmonid Fish Populations." *Proceedings of the Royal Society B: Biological Sciences* 287 (1925): 20200388. https://doi.org/10.1098/rspb.2020.0388.

Krawczak, Michael, and Johannes Zschocke. 2003. "A Role for Overdominant Selection in Phenylketonuria? Evidence from Molecular Data." *Human Mutation* 21 (4): 394–97. https://doi.org/10.1002/humu.10205.

Lidén, Kerstin, Anna Linderholm, and Anders Götherström. 2006. "Pushing It Back. Dating the CCR5–32 Bp Deletion to the Mesolithic in Sweden and Its Implications for the Meso\Neo Transition." *Documenta Praehistorica* 33 (December): 29–37. https://doi.org/10.4312/dp.33.5.

Nair, Shalini, Jeff T. Williams, Alan Brockman, Lucy Paiphun, Mayfong Mayxay, Paul N. Newton, Jean-Paul Guthmann, et al. 2003. "A Selective Sweep Driven by Pyrimethamine Treatment in Southeast Asian Malaria Parasites." *Molecular Biology and Evolution* 20 (9): 1526–36. https://doi.org/10.1093/molbev/msg162.

Novembre, John, Alison P. Galvani, and Montgomery Slatkin. 2005. "The Geographic Spread of the CCR5 Δ32 HIV-Resistance Allele." *PLOS Biology* 3 (11): e339. https://doi.org/10.1371/journal.pbio.0030339.

Råberg, Lars, Andrea L Graham, and Andrew F Read. 2009. "Decomposing Health: Tolerance and Resistance to Parasites in Animals." *Philosophical Transactions of the Royal Society B: Biological Sciences* 364 (1513): 37–49. https://doi.org/10.1098/rstb.2008.0184.

Raberg, Lars, Derek Sim, and Andrew F. Read. 2007. "Disentangling Genetic Variation for Resistance and Tolerance to Infectious Diseases in Animals." *Science* 318 (5851): 812–14. https://doi.org/10.1126/science.1148526.

Rauch, G., M. Kalbe, and T. B. H Reusch. 2006. "Relative Importance of MHC and Genetic Background for Parasite Load in a field Experiment." *Evolutionary Ecology Research* 8 (2): 373–86.

Roy, B. A., and J. W. Kirchner. 2000. "Evolutionary Dynamics of Pathogen Resistance and Tolerance." *Evolution* 54 (1): 51–63. https://doi.org/10.1111/j.0014-3820.2000.tb00007.x.

Schmid-Hempel, Paul. 2009. "Immune Defence, Parasite Evasion Strategies and Their Relevance for 'Macroscopic Phenomena' Such as Virulence." *Philosophical Transactions of the Royal Society B: Biological Sciences* 364 (1513): 85–98. https://doi.org/10.1098/rstb.2008.0157.

Schneider, David S., and Janelle S. Ayres. 2008. "Two Ways to Survive Infection: What Resistance and Tolerance Can Teach Us About Treating Infectious Diseases." *Nature Reviews Immunology* 8 (11): 889–95. https://doi.org/10.1038/nri2432.

Spurgin, Lewis G., and David S. Richardson. 2010. "How Pathogens Drive Genetic Diversity: MHC, Mechanisms and Misunderstandings." *Proceedings of the Royal Society B: Biological Sciences* 277 (1684): 979–88. https://doi.org/10.1098/rspb.2009.2084.

Spyropoulos, B. 1988. "Tay-Sachs Carriers and Tuberculosis Resistance." *Nature* 331 (6158): 666. https://doi.org/10.1038/331666a0.

Stahl, Eli A., Greg Dwyer, Rodney Mauricio, Martin Kreitman, and Joy Bergelson. 1999. "Dynamics of Disease Resistance Polymorphism at the Rpm1 Locus of Arabidopsis." *Nature* 400 (6745): 667–71. https://doi.org/10.1038/23260.

Last updated: 2022-03-06 19:30:48