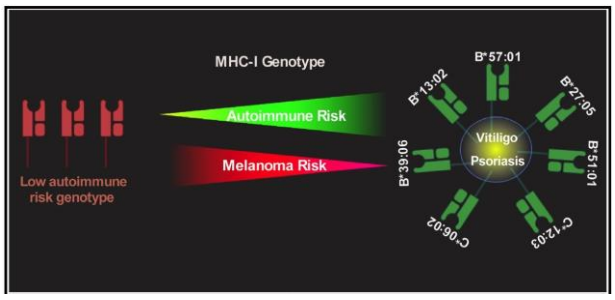
TRADE-OFF

Trade-off is a general rule in evolution. You get an advantage, but there is a price to pay.

A paper in press in Am J Hum Genet by Talwar et al[1] offers an opportunity to discuss this "rule". The paper deals with the autoimmune alleles and melanoma susceptibility. Their first Figure illustrates this concept of trade-off very well:



The trade-off is particularly evident in genes involved in the fight against pathogens, especially those that arrive unexpectedly, such as plagues. There is no time to fine-tune the response in order to minimize bad side-effects.

Here are partial summaries of some papers that emphasize this concept of trade-off:

Fumagalli et al[2]: "*Among the loci targeted by pathogen-driven selection, we found an enrichment of genes associated to autoimmune diseases, such as celiac disease, type 1 diabetes, and multiples sclerosis…*".

Kerner et al[3]: the title reads: "Genetic adaptation to pathogens and increased risk of inflammatory disorders in post-Neolithic Europe".

Hao et al[4]: "*Our study reveals the mechanisms that generate* ***beneficial*** *and deleterious indels during the process of antibody somatic hypermutation and has implications in understanding the detrimental genomic alterations in various conditions, including* ***tumorigenesis****".*

DeBoy et al[5]: The authors describe a mutation in *POT1* resulting in longer telomeres. Extended life? Maybe, but, as Science comments on this paper: "*longer telomeres comes with a price: ….increased risk for tumors*".

Zoledziewska et al[6]: Premise: animals in islands tend to undergo a reduction in size, due to the advantageous position that smaller individuals hold in the face of limited resources. In Sardinia, the authors found that a variant of the *GHR* gene "…reduces height in heterozygotes by an average of 4.2 cm". But in homozygous state it results in Laron syndrome.

The best example: the Black Death in Europe (1347-1353), in which 1/3-1/2 of the population was swept away. Klunk et al[7] analyzed DNA from people living before, during and after Black Death in London. The selection for protective variants was incredibly strong, especially for the *ERAP2* variant. Homozygous people for this variant had 40% more chance of survival! The authors conclude: "*Finally, we show that protective variants overlap with alleles that are today associated with increased susceptibility to autoimmune diseases…*".

1-https://www.cell.com/ajhg/fulltext/S0002-9297(23)00170-2

2-ttps://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1002355

3-https://www.sciencedirect.com/science/article/pii/S2666979X22002117?via%3Dihub

4-https://www.science.org/doi/10.1126/sciimmunol.ade1167?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

5-https://www.nejm.org/doi/10.1056/NEJMoa2300503?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

6-https://www.nature.com/articles/ng.3403

7- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9580435/