Variation that protected against Black Death helps against respiratory diseases, but increases autoimmune disease risks

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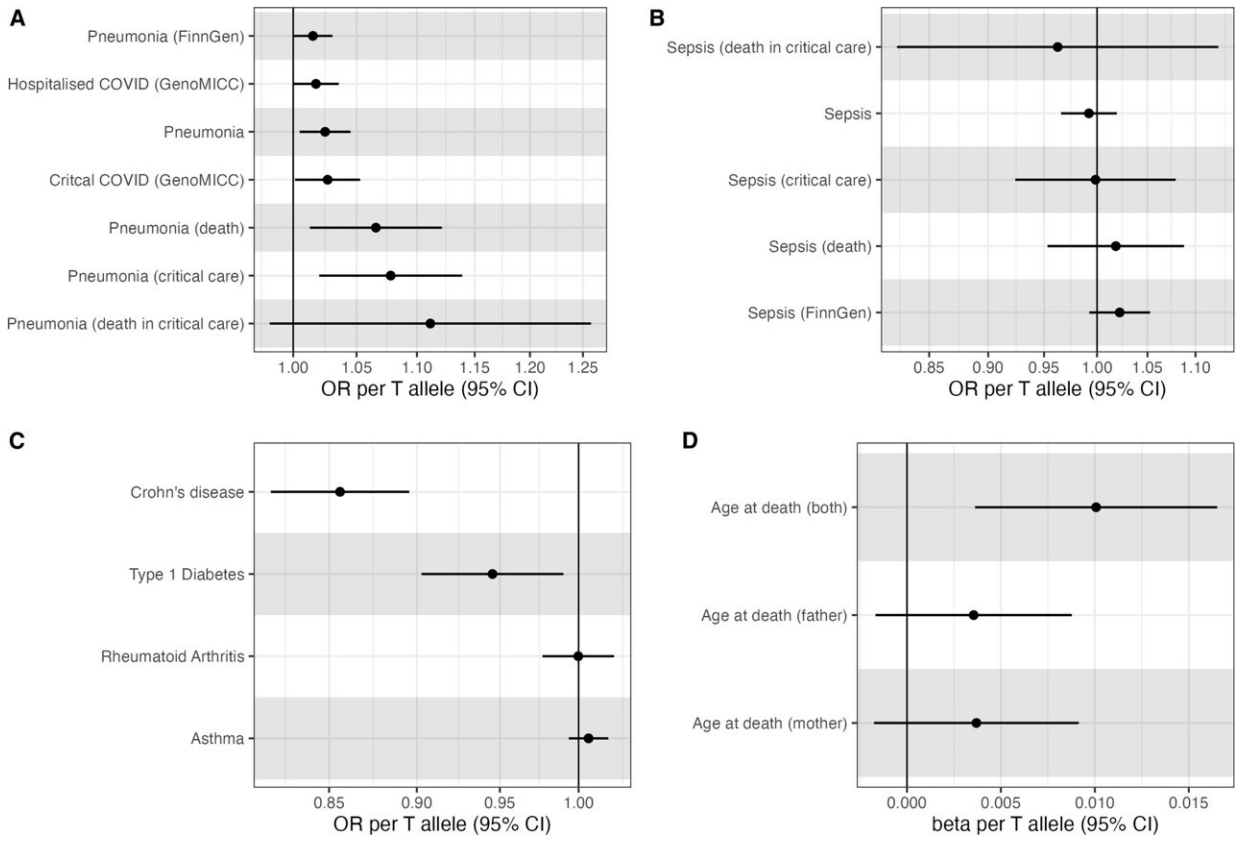

Associations between rs2549794 and outcomes in each GWAS dataset. Odds ratio for each outcome presented, with 95% confidence intervals, except for parental longevity, where the beta is presented with a 95% confidence interval. Outcomes: (A) respiratory infection, (B) sepsis, (C) autoimmune disease, (D) parental longevity. Credit: *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.02.008

The same genetics that helped some of our ancestors fight the plague is still likely to be at work in our bodies today, potentially providing some of the population with extra protection against respiratory diseases such as COVID-19, according to research led by scientists at University of Bristol. However, there is a trade-off, where this same variation is also linked to increased autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease.

Previous studies have revealed that survivors of the Black Death, the devastating bubonic plague pandemic in the Middle Ages were more likely to carry certain variants ("alleles") in a gene called ERAP2 than those who didn't survive.

In new research published in *The American Journal of Human Genetics* today, Dr. Fergus Hamilton and co-authors from the University's MRC Integrative Epidemiology Unit (MRC IEU), in collaboration with colleagues at the universities of Edinburgh, Oxford, Cardiff and Imperial College London, reveal that the same variants are present in humans today and providing similar protection against not only bubonic plagues but also other infections including pneumonia and COVID-19.

However, this is a situation of balance, and the same genetic makeup is likely to be linked with increases in various autoimmune diseases.

"This gene essentially chops up proteins for the immune system," explained lead author Dr. Hamilton, Wellcome GW4 Clinical Doctoral Fellow at the MRC IEU and North Bristol NHS Trust. "Although we don't know the exact mechanism influencing disease risk, carriers of alleles that provide more protection against respiratory disease seem to have an increased risk of autoimmune disease. It is potentially a great

example of a phenomenon termed 'balancing selection'—where the same allele has different effect on different diseases."

Dr. Hamilton and colleagues looked at infection, autoimmune disease, and parental longevity across participants in three large contemporary genetic studies (UK Biobank, FinnGen, and GenOMICC). They used an analytical technique known as Mendelian Randomization to find associations between variation in the ERAP2 gene and risk of autoimmune disease and infection.

Their findings point to antagonistic effects across these two groups of diseases driven by pressures likely to be more or less present in different human eras.

Nicholas Timpson, Professor of Genetic Epidemiology at the MRC IEU and co-author, added, "This is a theoretical story of balance—relating to historical and contemporary disease profiles—which reflects our past and is rarely seen in real human examples."

Identifying links between genetics and susceptibility to disease can pave the way for potential treatments. However, it also highlights potential challenges; therapeutics to target ERAP2 are currently being developed to target Crohn's disease and cancer so it is important to consider potential effects on the risk of infection from these agents.

More information: Fergus Hamilton et al, Variation in ERAP2 has opposing effects on severe respiratory infection and autoimmune disease, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.02.008

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