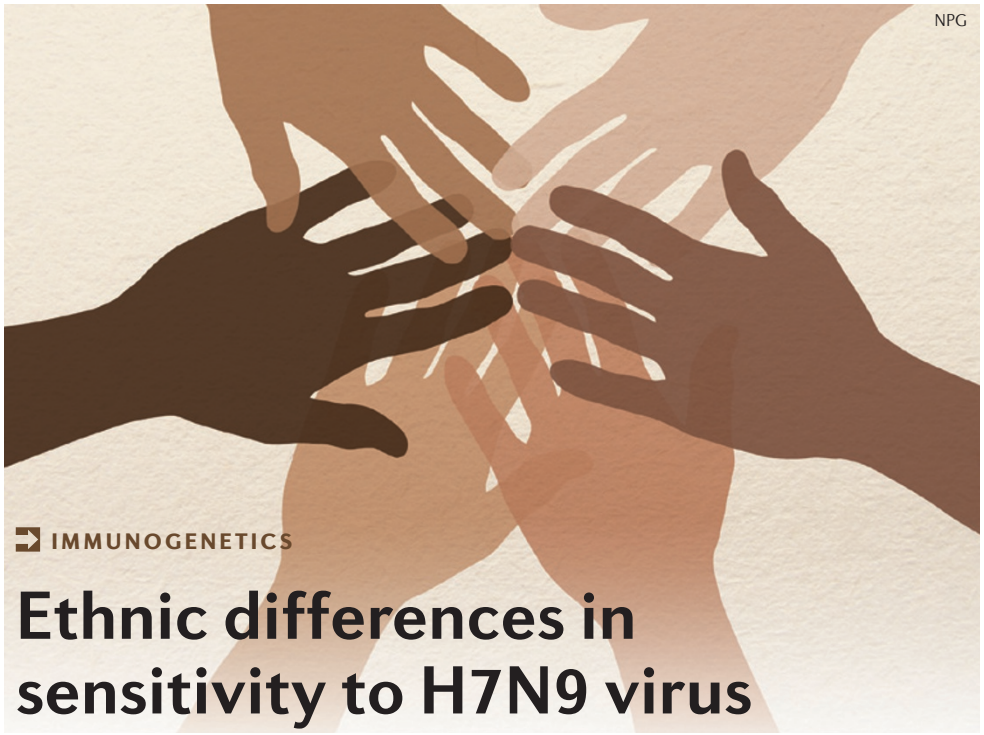

IMMUNOGENETICS

Ethnic differences in sensitivity to H7N9 virus

> HLA types that present conserved immunogenic H7N9 peptides vary substantially across ethnicities

In the absence of protective neutralizing antibodies, pre-existing memory cytotoxic T lymphocytes (CTLs) specific for influenza A virus-infected cells could potentially increase protection against H7N9 avian influenza A virus. Thus, the severity of a possible H7N9 influenza A virus pandemic might be limited by a CTL-directed vaccine. Now, Kedzierska, Doherty and colleagues have identified conserved immunogenic H7N9 virus peptides that can elicit strong CTL responses against any human influenza A virus, including H7N9. However, the prevalence of the MHC class I molecules that can present these peptides differs among human populations, as does the CTL response.

The authors identified immunogenic peptides in the nucleoprotein and matrix-1 proteins that are conserved across influenza A viruses and those that are unique to H7N9. Next, they determined human CTL immunity towards H7N9 by characterizing the recall potential of pre-existing influenza A-specific memory CTLs to the conserved immunogenic H7N9 peptides. Six conserved H7N9 peptides induced a strong memory CTL response in peripheral blood mononuclear cells (PBMCs) from 42 healthy humans of different ethnic backgrounds. Importantly, the authors identified specific HLA alleles — HLA-A*0201, HLA-A*0301, HLA-B*5701, HLA-B*1801 and HLA-B*0801 — that were associated with a strong immune response against all influenza A virus peptides examined. However, they also found that the frequency of the HLA types that present conserved immunogenic H7N9 peptides vary substantially across ethnicities (they are expressed by 16% of indigenous Alaskans and indigenous Australians, and by 57% of Caucasians).

Australian aboriginals and Alaskan natives frequently express specific HLA alleles — HLA-A*0101, HLA-A*6801, HLA-B*1501 and HLA-A*2402 — that encode MHC class I molecules that can only present unique H7N9 peptides. These alleles were associated with poor CTL responses to conserved H7N9 peptides. Interestingly, indigenous Australian and Alaskan populations also experienced higher infection rates and morbidity during the pandemic H1N1 outbreak, which could partly be due to a lack of the MHC class I molecules that present the conserved influenza A virus peptides.

Taken together, the data indicate that humans who express MHC class I molecules that can present conserved influenza A virus peptides have pre-existing CTL memory and, consequently, increased resistance to new strains of influenza A virus. By contrast, Australian aboriginals and Alaskan natives probably have little CTL immunity to viruses such as H7N9. These findings could be important for H7N9 virus vaccine delivery and development.

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ORIGINAL RESEARCH PAPER Quiñones-Parra, S. *et al.* Preexisting $CD8^+$ T-cell immunity to the H7N9 influenza A virus varies across ethnicities. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1322229111 (2014)