

Letter to the Editor

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COVID-19 related mortality and religious denomination vs. genetics

<https://doi.org/10.1515/cclm-2022-0393>

Received April 21, 2022; accepted April 22, 2022;

published online May 2, 2022

Keywords: ACE polymorphism; COVID-19; religion.

To the Editor,

In a recent paper [1], social interactions, as shaped by religious denomination, have been related to COVID-19 incidence and associated mortality in Western Germany. The number of infections and deaths during the early pandemic phase (spring 2020) was found to be higher in predominantly Catholic countries with stronger family and social ties. The relationship was confirmed at the county level and the individual level. Catholics, relative to non-Catholics, had tighter and more frequent interactions with their family and friends. The intensity of social interaction was able to partially explain the relationship between COVID-19 incidence and the share of Catholics at the country level. To test this hypothesis, we carefully analyzed this statement and compared the relationship between the COVID-19 religious denomination with several genetic confounders.

Because religious geography is explained in part by historical political facts, which are associated with genographics, the pronounced geographical variation in prevalence and mortality during the COVID-19 pandemic has also been linked to genetic variability [2–6]. As a result, the question arises if the relationship between religion and COVID-19 is independent from an underlying genetic variation of the host. We previously showed that the variability in genotype distribution of a number of immune-related human polymorphisms [2–6] also partly

explains the variable geographical prevalence of the COVID-19 infection.

Mortality data (per 1,000,000 inhabitants) of the COVID-19 infection from several European countries were included in the study: Austria, Belgium, Cyprus, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Latvia, Lithuania, Luxemburg, Moldova, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom were included in the analysis. Data reported on April 30, 2020 by Johns Hopkins were analyzed [7].

Concurrently, data on the geographical variation of some immune system-related human plasma protein polymorphisms were collected from the literature, including the deletion/insertion (D/I) polymorphism of the angiotensin-converting enzyme 1 (*ACE1*) gene, human homeostatic iron regulator protein (HFE), complement factor C3, haptoglobin, and vitamin D binding protein [2, 6].

In a first analysis, the various COVID-19 mortality data of the 11 Dutch provinces were plotted against COVID-19 mortality [8]. Using regression analysis, a striking relationship between COVID-19 mortality and the percentage of Catholics in the population was found: y (COVID-19 mortality per 100.000 inhabitants) = 0.891 (% Catholics) + 3.120 ; $r^2 = 0.907$. This relationship was confirmed in a multiple regression model, including the S-116 haplotype.

However, when investigating the European COVID-19 prevalence in a multiple regression analysis model (including the religious denomination [9]), the prevalence of COVID-19 significantly correlated with *ACE1* polymorphism. The log-transformed mortality of COVID-19 in Europe (on April 30, 2020) negatively correlated with the *ACE* D allele frequency: $\log(\text{COVID-19 mortality; no. of cases}/10^6 \text{ inhabitants}) = 5.567 - 0.05$ (D-allele frequency, %) + 0.0156 (% Catholics), $r^2 = 0.623$; $p = 0.0001$. In this equation, the p value for the D-allele frequency was 0.02 (vs. only 0.668 for the religious denomination).

Although the local data in the Netherlands seem to support the thesis that religious denomination can be

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related to COVID-19 associated mortality as in neighbouring Western Germany, this observation could not be expanded to a larger European context. The 1555 Peace of Augsburg dramatically changed the scenery for the coexistence of Lutheranism and Catholicism in the Holy Roman Empire along the principle of “Cuius regio, eius religio” (The ruler dictates the religion of those ruled). The rule initially did not hold for Calvinism but the 1648 Peace of Westphalia prohibited converting rulers to force-convert their subjects and by determining the official religion of imperial territories to the status of 1624 as a normative year. Thus the regional distribution between Catholicism, Lutheranism and Calvinism remained essentially stable over time. Our data are pleading for a role of genetics rather than of religious denomination in COVID-19 associated mortality.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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