Aquaporin 3 modulates the risk of death conferred by dehydration in COVID-19

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Abstract

Severe COVID-19 has been associated with dehydration. Recently, a genetic variant near the aquaporin 3 (AQP3) water channel was associated with severe COVID-19 (rs60840586:G, Odds Ratio: 1.07, P=2.5*10-9). We show that dehydration is associated COVID-19 mortality (OR = 2.06 [95% CI = 1.62-2.65], P = 9.13*10-9), and is modulated by interaction with rs60840586:G genotype (OR = 1.95 [95% CI = 1.22-3.28], P = 0.0075).

Full Text

Severe corona virus infectious disease 2019 (COVID-19) has been associated with dehydration [1], and early dehydration has been proposed as a mechanism of more severe disease [2]. Recently the COVID-19 Host Genetics Initiative [3,4] (https://www.covid19hg.org) identified genetic variation near the gene *AQP3*, encoding the aquaporin 3 water channel, to be associated with severe COVID-19. *AQP3* is widely expressed and is important for water regulation in the airway [6] and immune cells [7] which may be of importance in severe COVID-19. It is further expressed in the kidney where it facilitates water reabsorption to regulate total-body water balance [8]. Interestingly, rs60840586:G is known to increase gene expression of *AQP3* in several organs including the lung (NES = 0.33, P = $4.1 * 10^{-20}$), skin (NES = 0.23, P = $2.1 * 10^{-12}$) and whole blood (NES = 0.08, P = 0.004) in GTEx (http://gtexportal.org). However, it may be less impactful in the kidney (NES = -0.02, P = 0.9) with the caveat that only the kidney cortex was investigated and not medulla, which is arguably more important for water balance. Delineating the role of AQP3 is therefore important not only in the prognosis or diagnosis of severe COVID-19, but also in its management, since proper water homeostasis management is one of the chief concerns in patients admitted to critical care. Thus, we hypothesized that this novel association near AQP3 may influence hydration status measured by plasma osmolality or the cellular ability to compensate for dehydration, which in turn, may influence severity of COVID-19.

We therefore investigated the interaction between the allelic dose of the lead SNP at the locus, rs60840586:G, and estimated maximal plasma osmolality (eOSM = [$2Na^+ + 2K^+$ + Urea + Glucose]) as a risk factor for death in hospitalized patients in the Biobanque Québécoise de la COVID-19 (BQC19). A total of 3768 patients presenting with symptoms consistent with COVID-19 from 10 hospitals in Québec, Canada, were recruited into the BQC19 beginning January 12, 2020. The analysis is based on 1,073 hospitalized patients with data on plasma osmolality and rs60840586 genotype. Estimated osmolality was calculated as:

$eOSM = 2 * Na^+ + 2 * K^+ + Glucose + Urea$

For logistic regression eOSM was normalized to have a mean of zero and a standard deviation of one. Individuals with missing values were omitted from the analysis leaving 576 patients with all covariates. The main outcome was in-hospital death, which occurred in 73 (12.7%) cases. Analyses were conducted using R version 4.0.5.

The allelic dose of *AQP3* SNP rs60840586:G was calculated as: GTAAC:GTAAC = 0, GTAAC:G = 1, G:G = 2, and was not associated with maximal osmolality using linear regression without (P = 0.12, Figure 1A), or after adjustment for sex and age, hospital and the top ten principal components (beta = 1.02 [95% CI = 0.97-1.07], P = 0.37). Maximal osmolality was, as we have previously reported [9], associated with a marked increase in mortality in COVID-19 after adjustment for covariates (OR = 2.06 [95% CI = 1.62-2.65], $P = 9.13*10^{-9}$). Interestingly, adding an interaction term (rs60840586:G * eOSM) to the multivariable analysis revealed that individuals carrying the deletion with higher eOSM had a higher odds of death (OR = 1.95 [95% CI = 1.22-3.28], P = 0.0075, Figure 1B). We performed sensitivity analysis of the effect of any deletion compared to homozygous wild-type (GTAAC:GTAAC = 0, GTAAC:G = 1, G:G = 1), which showed consistent results with the main analysis (OR = 1.75 [95% CI = 1.02-3.1], P = 0.047). A further sensitivity analysis of heterozygosity showed no significant effect (GTAAC:GTAAC = 0, GTAAC:G = 1, G:G = 0) (OR = 1.25 [95% CI = 0.73-2.22], P = 0.43).

In conclusion, we have identified the interaction of a genetic risk factor near *AQP3* with dehydration for in-hospital death of COVID-19. While rs60840586 genotype does not seem to directly influence total body water balance, it is associated with worse outcome in those who become dehydrated over the course of their illness. Given that rs60840586 is likely associated with *AQP3* expression, this opens the possibility of novel treatment approach targeting aquaporin or water reabsorption in the management of COVID-19 critical illness.

Declarations

Ethics approval and consent to participate

The Biobanque Québécoise de la COVID-19 (BQC19) received ethical approval under the REB of the the Centre Hospitalier de l'Universite de Montréal (MP-02-2020-8929) and Jewish General Hospital (2020-2137). The Declaration of Helsinki and its subsequent revisions were followed.

Availability of data and material

Data is available through the Biobanque Québécoise de la COVID-19 (BQC19) after securing ethical permission and appropriate data access agreements (https://www.quebeccovidbiobank.ca).

Conflicts of interest

JBR served as an advisor to GlaxoSmithKline, Deerfield Capital, and is the founder and CEO of 5 Prime Sciences. The other authors declare that they have no conflicts of interest.

Author contributions

All authors participated in project design and planning. All authors participated in data analysis and interpretation. MH performed statistical analysis and wrote the first draft. All authors revised the paper and approved the final version for publication.

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Figures

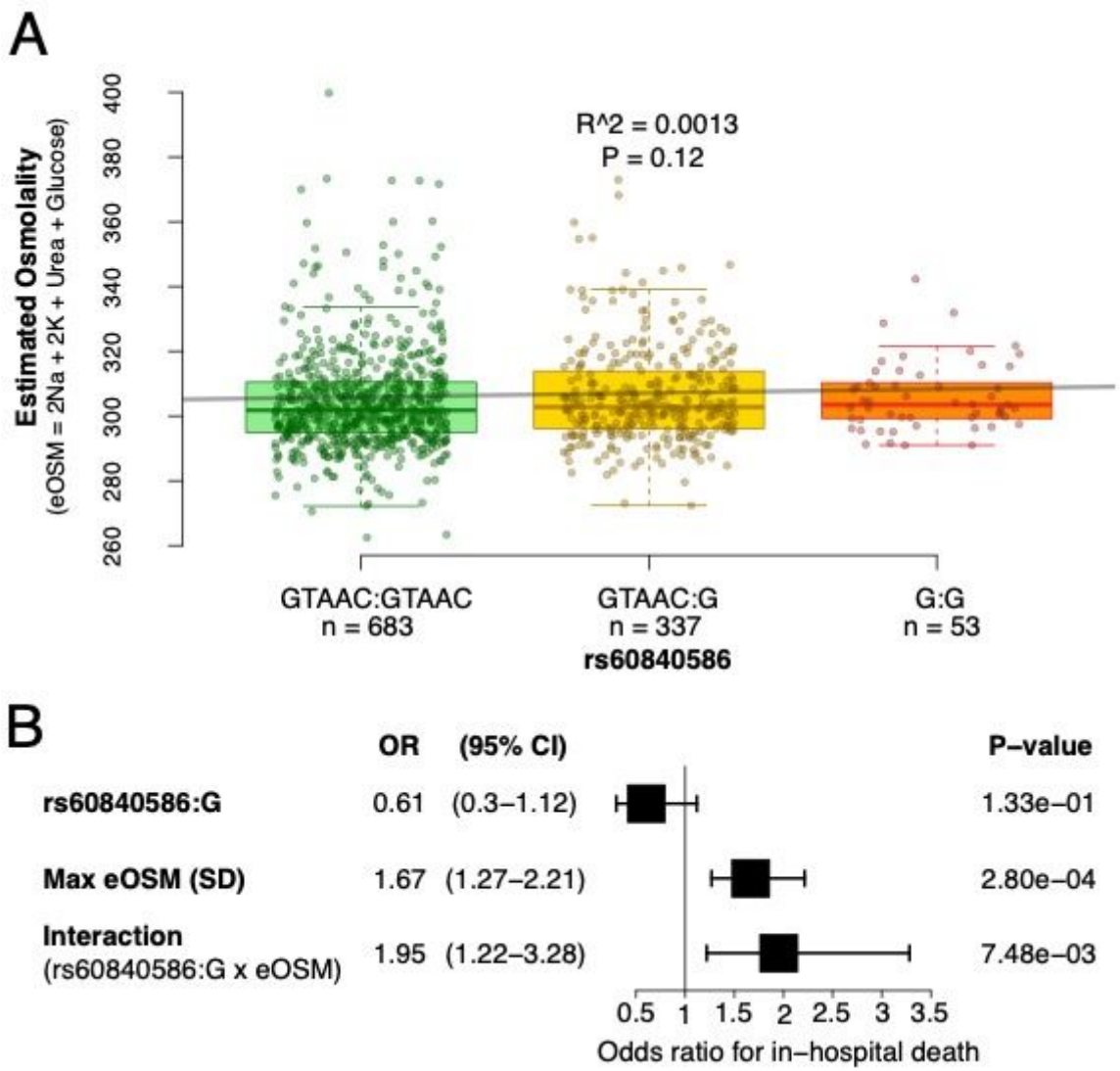

Figure 1

A: Maximal estimated plasma osmolality (eOSM = $2Na^+ + 2K^+$ + Urea + Glucose) did not associate with rs60840586, a genetic variant near aquaporin 3 (AQP3) that is associated with severe COVID-19 in 1073 hospitalized COVID-19 patients in Biobanque Québécoise de la COVID-19 (BQC19). The line represents a linear regression with the R^2 and P-values shown in the figure.

B: rs60840586 was not associated with mortality amongst 576 hospitalized COVID-19 subjects in Biobanque Québécoise de la COVID-19 (BQC19). However, maximal estimated plasma osmolality (eOSM = $2Na^+ + 2K^+$ + Urea + Glucose) analyzed as a continuous variable was a strong predictor of death. Interestingly, rs60840586 displayed an interaction effect with maximal eOSM, where the deletion at rs60840586 was associated with increased risk of death in subjects with higher eOSM. The Forest plot is based on a multivariable logistic regression of the risk of death by rs60840586 and maximal eOSM adjusted for sex, age, hospital, and the top ten prinicipal components with an interaction term rs60840586*eOSM.

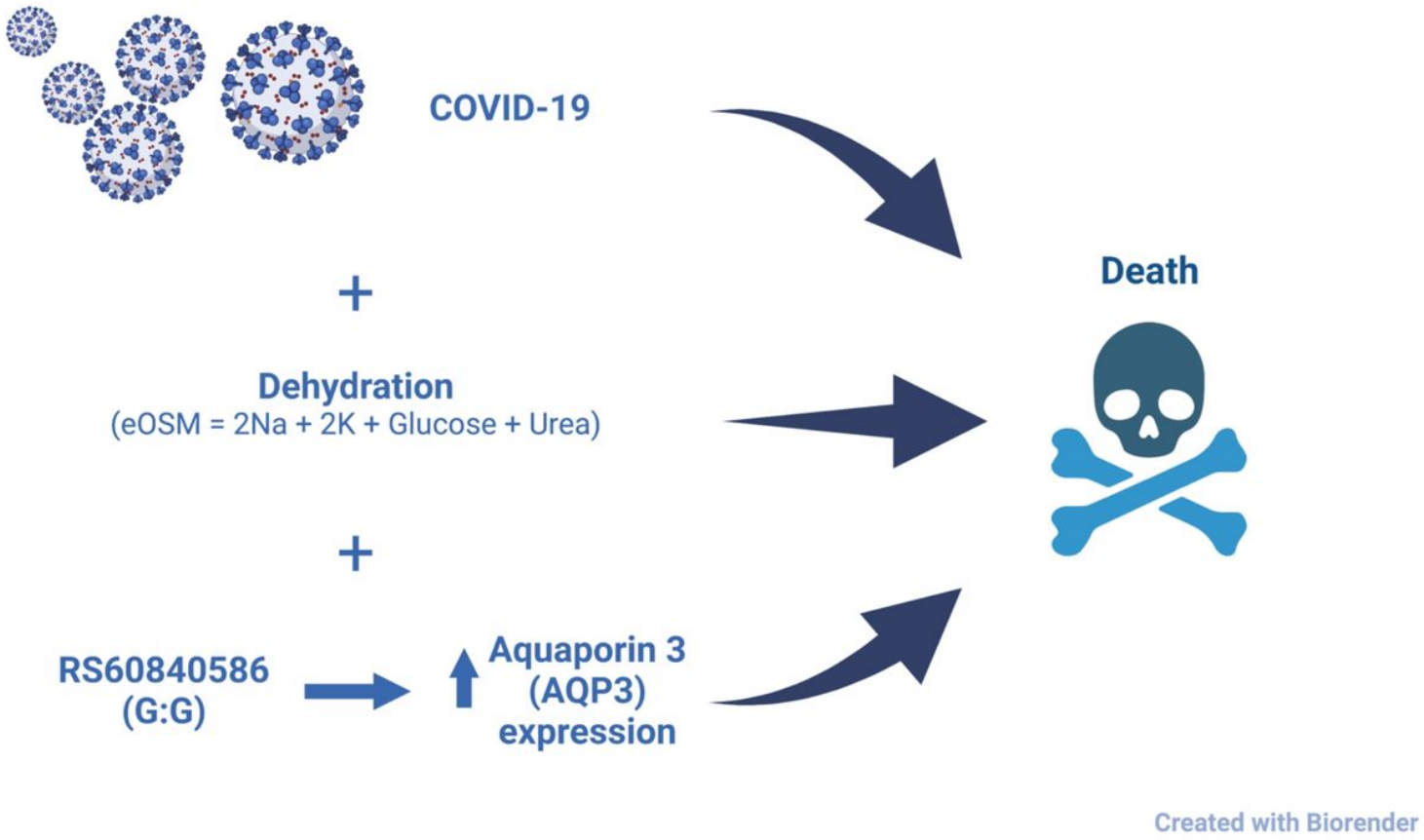

Figure 2

The present study shows that patients with COVID-19 who are dehydrated as measured using estimated osmolality (eOSM = = $2Na^+ + 2K^+$ + Urea + Glucose) have an increased risk of dying. Interestingly, we find that a deletion in the aquaporin 3 (AQP3) promoter region (rs60840586) modulates this risk and further increases the risk of death in dehydrated patients.