

SHORT REPORT

A genetic variant associated with aquaporin 3 expression is correlated to in-hospital death in COVID-19 patients with extracellular hyperosmolality

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Abstract

Hyperosmolality is increasingly recognized as a factor contributing to severe COVID-19. Recently, a genetic variant near the aquaporin 3 (AQP3) water channel was associated with severe COVID-19 [rs60840586:G; odds ratio (OR): 1.07, $P = 2.5 \times 10^{-9}$]. The variant is known to increase gene expression of AQP3 in several organs, including the lung [normalized expression scores (NES) = 0.33, $P = 4.1 \times 10^{-20}$] in GTEx. In this study, we investigated 576 patients in the Biobanque Quebecoise de la COVID-19 (BQC-19) with both genetic and clinical data available. We estimated plasma osmolality using the formula: $eOSM = 2 \times [Na^+] + 2 \times [K^+] + [Urea] + [Glucose]$. Using a logistic regression of mortality against eOSM, genotype at rs60840586, sex, age, and the first 10 genetic principal components, we confirm that hyperosmolality is associated with COVID-19 mortality (OR = 2.06 [95% CI = 1.62–2.65], $P = 9.13 \times 10^{-9}$). Interestingly, we found that the risk of death linked to hyperosmolality is influenced by the AQP3 variant rs60840586:G genotype (OR = 1.95 [95% CI = 1.22–3.28], $P = 0.0075$). However, the rs60840586 genotype did not independently affect mortality in this cohort. These findings suggest that the body's ability to regulate and accommodate hyperosmolality may be disrupted by overexpression of AQP3, potentially worsening outcomes in COVID-19. Given the role of AQP3 in water transport and homeostasis, further defining the functionality of its variants may provide key insights into COVID-19 severity and guide clinical management strategies, particularly in critically ill patients with hyperosmolality.

NEW & NOTEWORTHY A genetic variant near water channel AQP3, linked to severe COVID-19, amplifies the risk of death in patients with elevated plasma osmolality. In patients hospitalized with COVID-19, we show that although the variant does not affect systemic osmolality directly, it interacts with hyperosmolality to increase mortality risk. These findings highlight a potential mechanism where AQP3 overexpression disrupts cellular water handling during critical illness, offering new insight into the role of water balance in COVID-19 pathophysiology.

COVID-19; personalized medicine; risk factors; water balance

INTRODUCTION

Severe corona virus disease 2019 (COVID-19) has been associated with dehydration, with early dehydration proposed as a mechanism contributing to more severe disease (1). Recent

genome-wide association studies (GWAS) have identified a genetic variant near the water channel aquaporin 3 (AQP3) associated with an increased risk of severe COVID-19 requiring hospitalization or treatment in an intensive care unit (rs60840586:G; odds ratio: 1.07, $P = 2.5 \times 10^{-9}$) (2). This variant is a deletion



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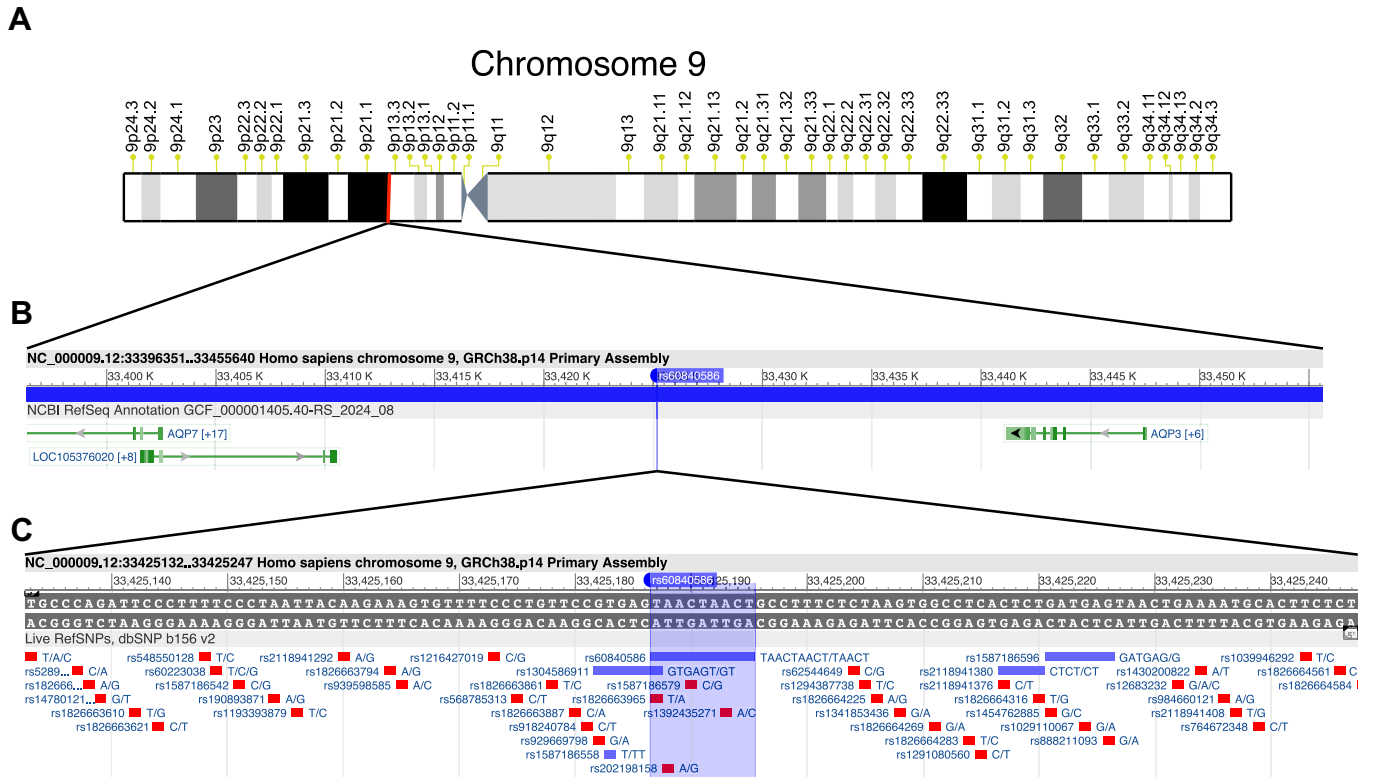


Figure 1. A: genomic location of the lead variant (rs60840586) from the COVID-19 Host Genetics Initiative GWAS. B: the variant is flanked by aquaporin 3, a plasma membrane water channel, the predicted gene *LOC105376020*, and the intracellular water channel aquaporin 7. C: the variant is a deletion GAACT to G in the downstream region of *AQP3* on the short arm of chromosome 9 in position 33425187–33425195 (GRCh38.p14). *AQP3*, aquaporin 3; GWAS, genome-wide association studies.

Guanine – Adenine – Adenine – Thymine – Cytosine (GAACT) to Guanine (G) in the downstream region of *AQP3* on chromosome 9 in position 33425187–33425195 (GRCh38.p14, Fig. 1, A–C).

AQP3 is widely expressed and plays a critical role in water regulation in the airway (3) and immune cells (4), which may be relevant to severe COVID-19 pathophysiology. In addition, *AQP3* facilitates water reabsorption in the kidney, regulating total-body water balance in both homeostasis (5) and disease (6).

Genome-wide association studies (GWAS) offer robust evidence that the system in question plays a causal role in disease development (7). This is particularly compelling when the gene has a known physiological function relevant to known clinical risk factors, in this case, dehydration and hyperosmolality in severe COVID-19 (1). Notably, the genetic variant rs60840586:G is associated with an increase gene expression of *AQP3* in multiple tissues, including the lung [normalized expression score (NES) = 0.33, $P = 4.1 \times 10^{-20}$], skin (NES = 0.23, $P = 2.1 \times 10^{-12}$), and whole blood (NES = 0.08, $P = 0.004$) in GTEx (<http://gtexportal.org>) (8), but appears to have minimal impact on kidney expression (NES = -0.02, $P = 0.9$; Fig. 2).

Delineating the role of *AQP3* is important to further understand both COVID-19 and clinical management, considering the importance of water homeostasis in patients admitted to intensive care. Thus, we hypothesized that this novel association near *AQP3* may influence plasma osmolality or the cellular ability to compensate for hyperosmolality, which in turn, may influence the severity of COVID-19.

METHODS

In the present investigation, there are two main analyses. First, we investigate the association between the allelic dose of the lead single nucleotide polymorphism (SNP) at the locus, rs60840586:G, and estimated plasma osmolality, to determine whether the variant affects whole body water balance. Second, we investigate the interaction between the variant and estimated plasma osmolality during hospitalization for COVID-19, as a risk factor for death in hospitalized patients.

The patients in the analysis are from the Biobanque Québécoise de la COVID-19 (BQC19) (9). A total of 3,768 patients presenting with symptoms consistent with COVID-19 from 10 hospitals in Québec, Canada, were recruited into the BQC19 after providing written informed consent from January 12, 2020, to December 12, 2021. All patients who came to one of the participating hospitals with suspected COVID-19 and with a positive PCR test for SARS-CoV-2 were eligible for inclusion in the cohort. In the present study, we used 576 hospitalized patients of European heritage with data on plasma osmolality, the rs60840586 genotype, as well as all covariates.

The allelic dose of *AQP3* SNP rs60840586:G was calculated as follows: GTAAC:GTAAC = 0, GTAAC:G = 1, G:G = 2. In lieu of measured osmolality, we estimated plasma osmolality using the formula: $eOSM = [2Na^+ + 2K^+ + Urea + Glucose]$, as done previously (1, 10, 11). The effect of allele dose on eOSM was calculated using linear regression. For logistic regression,

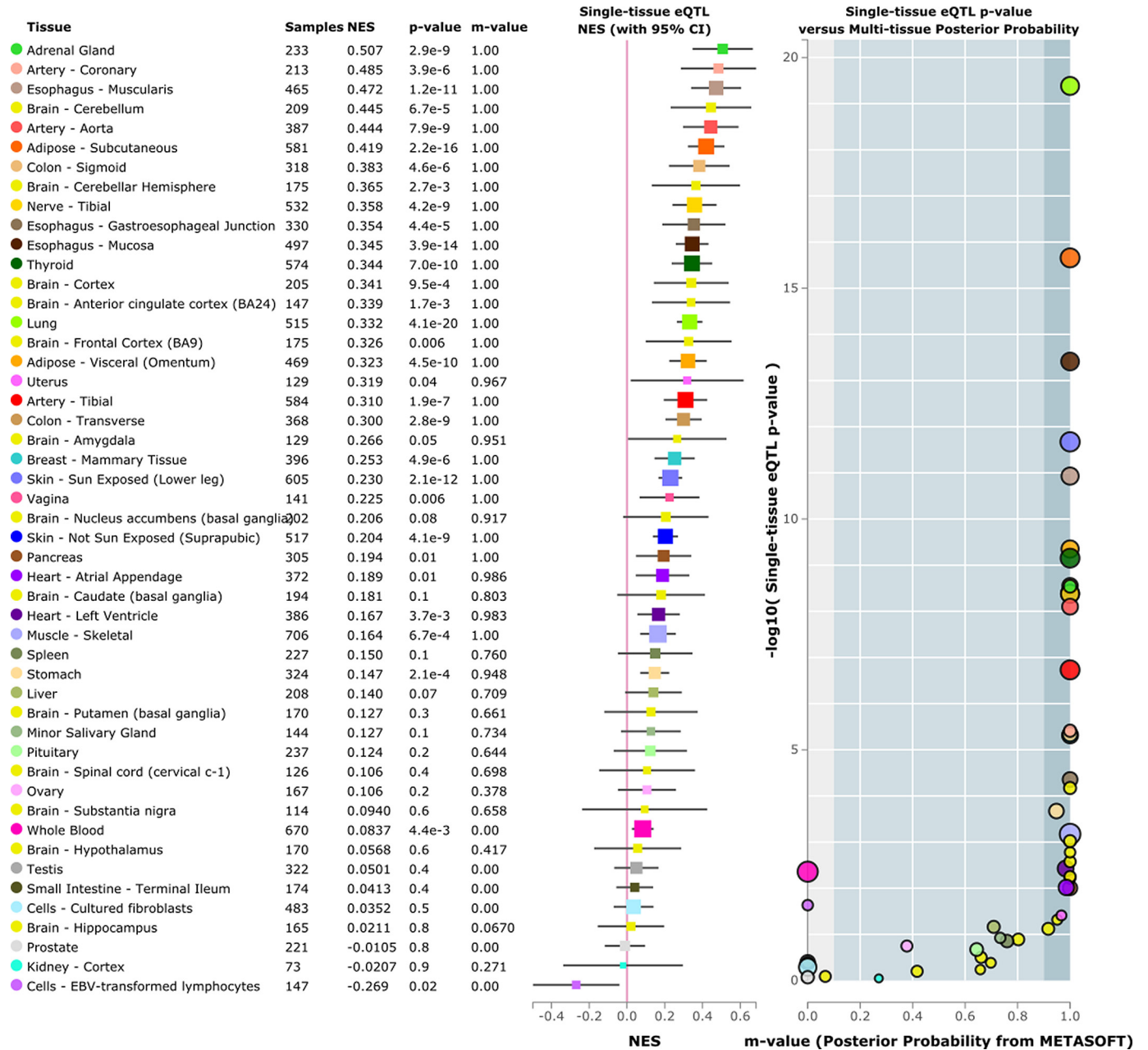


Figure 2. The effect of the variant rs60840586 on gene expression in tissues is available in GTEx (<http://gtexportal.org>) and is expressed as normalized expression scores (NES) with 95% confidence intervals. Of the tissues likely to be important in severe COVID-19 and hyperosmolality, the variant has a significant effect on lungs and in whole blood, but not in kidney cortex. eQTL, gene expression quantitative trait locus.

eOSM was normalized to have a mean value of zero and a standard deviation of one. The regression analyses were adjusted for sex, age, and treating hospital. In addition, we adjusted for population stratification using the top 10 genetic principal components that explained the greatest proportion of genetic variation. Individuals with missing values were omitted from the analysis. Analyses were conducted using R version 4.0.5.

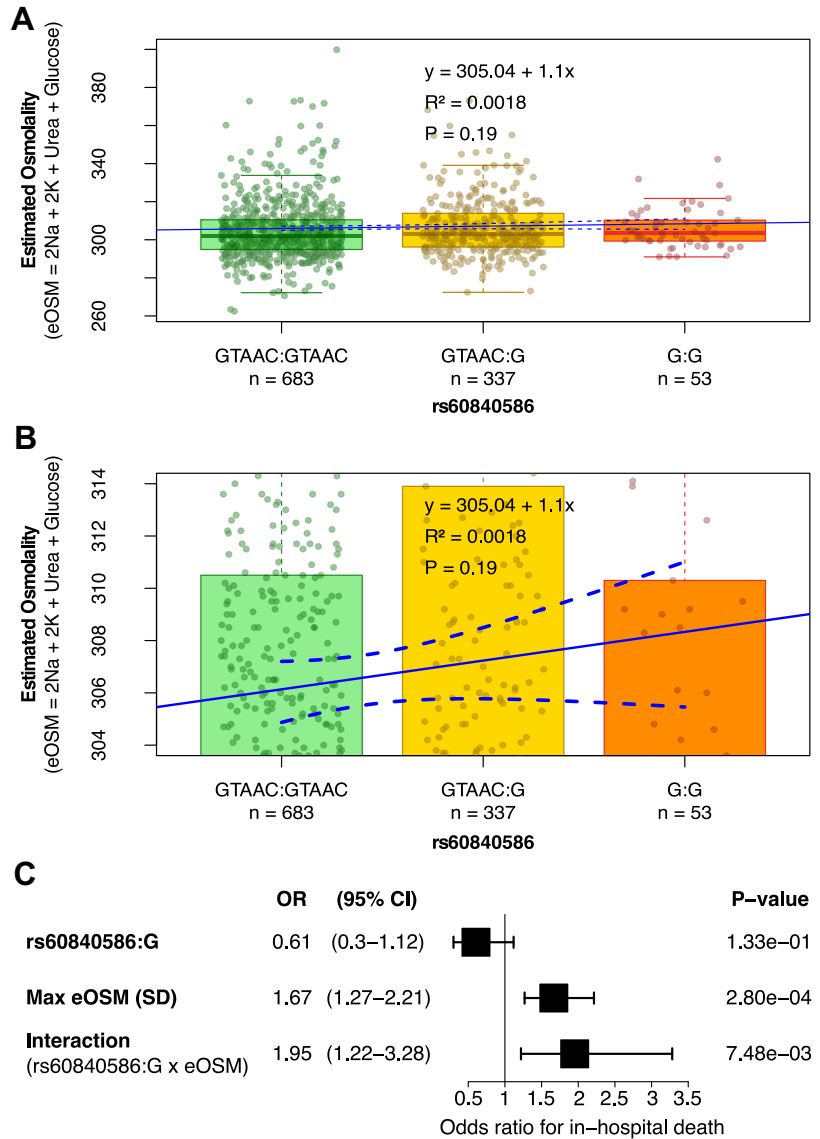
RESULTS

The allelic dose of AQP3 SNP rs60840586:G was not associated with maximal osmolality using linear regression

without ($P = 0.12$; Fig. 3, A and B), or after adjustment for sex, age, hospital, and the top 10 genetic principal components ($\beta = 1.02$ [95% CI = 0.97–1.07], $P = 0.37$).

In-hospital death occurred in 73 (12.7%) cases. The highest osmolality during hospitalization was, as previously reported (1), associated with a marked increase in mortality in COVID-19 after adjustment for covariates (OR = 2.06 [95% CI = 1.62–2.65], $P = 9.13 \times 10^{-9}$). Interestingly, adding an interaction term (rs60840586:G \times eOSM) to the multivariable analysis revealed that individuals carrying the deletion with a higher eOSM had a higher odd of death (OR = 1.95 [95% CI = 1.22–3.28], $P = 0.0075$; Fig. 3B). We performed sensitivity analysis of the effect of any deletion compared with

Figure 3. A: maximal estimated plasma osmolality during hospitalization ($eOSM = 2Na^+ + 2K^+ + Urea + Glucose$) did not associate with rs60840586, a genetic variant near aquaporin 3 (AQP3) that is associated with severe COVID-19 in 1,073 patients hospitalized with COVID-19 in Biobanque Québécoise de la COVID-19 (BQC19). The line represents a linear regression with the linear formula, and regression R^2 and P values are shown in the figure. B: detailed view of A showing the regression model in greater detail. The line represents a linear regression with the linear formula, and regression R^2 and P values are shown in the figure. C: rs60840586 was not associated with mortality among 576 subjects hospitalized with COVID-19 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 an increased risk of death in subjects with a 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 10 principal components with an interaction term $rs60840586 \times eOSM$. CI, confidence interval; OR, odds ratio.



homozygous wild-type (GTAAC:GTAAC = 0, GTAAC:G = 1, and 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], $P = 0.43$). These findings suggest that both osmolality and specific genetic variants contribute to COVID-19 mortality risk, with the AQP3 SNP amplifying the adverse effects of elevated osmolality.

DISCUSSION

The main finding of this study is that the genetic variant rs60840586:G is associated with a higher risk of death in patients with hyperosmolality in COVID-19. Although not shown in the present study, the likely mechanism is through altering gene expression in the lung and/or immune cells. Cellular water balance is important in ARDS, contributing to both cellular swelling and alveolar fluid accumulation (12). Indeed, several aquaporins have previously been implicated

in the pathogenesis and resolution of acute respiratory distress syndrome (ARDS) (3). Regulation of cell volume is also important for immune cell activation, proliferation, and cell death (13). Hypertonicity as such has been tied to reduced activity and increased apoptosis in neutrophils (14), and impaired water transport has been suggested to mediate inflammatory dysregulation during sepsis (15). This provides a potential mechanism by which the variant could affect the inflammatory response to SARS-CoV-2 through AQP3 gene expression in immune cells. Neutrophil activity in particular has been intimately tied to disease severity and mortality in COVID-19 (16, 17).

Hyperosmolality is a well-recognized risk factor for mortality in critically ill patients, and the findings of this study further confirm its association with an increased risk of death in COVID-19 (1). Although some research suggests that hyperosmolality may be specific to COVID-19 (18), similar associations have been observed in non-COVID cohorts as well (10, 11, 19, 20). Hyperosmolality can arise from both dehydration and sodium administration during the fluid

resuscitation efforts; critically ill patients receive large volumes of fluids—often sodium-based solutions—to restore hemodynamic stability (21). In contrast, during the deresuscitation phase, efforts are made to remove excess fluid, leading to shifts in water balance. This process can contribute to hyperosmolality, often manifested as hypervolemic hyperosmolality (20). From a cellular perspective, total body fluid volume is less critical than hyperosmolality itself, which directly affects cell volume and electrolyte balance. Our analysis did not demonstrate an effect on systemic water balance, as plasma osmolality remained unchanged. This finding aligns with the observation that the rs60840586:G variant does not influence renal expression of AQP3, as indicated by data from the GTEx database.

The rs60840586:G variant was previously identified as a genetic determinant of severe COVID-19 linked to an increased risk of hospitalization (2). Based on this, we hypothesized that the variant would also be associated with increased mortality. However, our analysis did not reveal any direct effect of rs60840586:G on mortality. This is likely due to the smaller sample size available for assessing hyperosmolality, compared with the much larger Host Genetics Initiative data freeze 7 meta-analysis, which included an effective sample size of over 190,000 individuals.

Genetic and environmental interactions have been extensively studied, though reproducible findings remain limited, and the effects observed are generally small (22, 23). Given this background, there is a possibility of a false-positive result, as has been a concern in this field. However, in the context of acute disease, clinical disturbances may create a stronger environmental signal compared with those typically examined in the general population, making this interaction more detectable. Nonetheless, independent validation—at both epidemiological and mechanistic levels—will be crucial for future studies.

This is the first study to examine the role of hyperosmolality in the interaction between the AQP3 variant rs60840586 and COVID-19 severity. One of its key strengths is the inclusion of a large cohort of prospectively enrolled patients across multiple hospitals. However, this study also has several limitations. Osmolality was not a predefined analysis, meaning the findings rely on using estimated osmolality rather than direct measurements. The formula used for estimation is widely accepted and shows a strong correlation with measured osmolality across a broad range of osmolalities. However, the method generally underestimates osmolality by 5–10 mosmol/kgH₂O, with the exact degree of error varying based on the population and presence of substances that influence plasma water content, such as proteins and lipids. In addition, the analysis depends on clinically indicated blood samples as determined by the treating physician, which resulted in incomplete data for many patients. Notably, most missing data came from nonhospitalized patients, whereas all necessary analytes were routinely measured upon hospital admission at most participating hospitals. As a result, the patients included are highly representative of the severity criteria used in the original GWAS, but the findings may not be generalized to less severe COVID-19 cases or patients with other underlying conditions. Another limitation is the reliance on GTEx data to infer the effect of the variant on AQP3 gene expression. GTEx only includes data from the kidney cortex, whereas the kidney medulla plays a more significant role in water balance

regulation. This means that potential tissue- or region-specific regulatory mechanisms relevant to hyperosmolality may have been overlooked. On the contrary, our findings indicate that the variant does not significantly associate itself with plasma osmolality, suggesting it is unlikely to directly impact whole body water balance.

This study provides the first evidence that the genetic variant rs60840586:G, located near AQP3, and previously identified as a risk factor for COVID-19-related hospitalization, does not influence whole body water balance. However, we uncovered a significant interaction between this variant and hyperosmolality, which increases the risk of in-hospital mortality in patients with COVID-19. Given the likely association of rs60840586:G with AQP3 expression, these findings suggest a potential therapeutic avenue targeting aquaporins or water reabsorption in the management of severe COVID-19.

ETHICAL APPROVALS

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

DATA AVAILABILITY

Data is available through the Biobanque Québécoise de la COVID-19 (BQC19) after securing ethical permission and appropriate data access agreements (<https://www.quebecovidbiobank.ca>). The data on tissue expression effects presented in Fig. 1 were obtained from the GTEx Portal on 04/18/22.

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DISCLAIMERS

Funding bodies had no role in the design of the study, data collection, interpretation, or in writing of the manuscript.

DISCLOSURES

J.B.R. served as an advisor to GlaxoSmithKline, Deerfield Capital, and is the founder and CEO of 5 Prime Sciences. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

M.M.-H., R.F., M.L., H.Z., and J.B.R. conceived and designed research; M.M.-H. performed experiments; M.M.-H., Y.C., and H.Z. analyzed data; M.M.-H., A.M.M., G. B.-L., S.Y., T.L., D.R.M., T.N., V.F., Y.F., R.F., M.L., H.Z., and J.B.R. interpreted results of experiments; M.M.-H. prepared figures; M.M.-H. drafted manuscript; M.M.-H., A.M.M., G. B.-L., S.Y., T.L., D.R.M., T.N., Y.C., V.F., Y.F., R.F., M.L., H.Z., and J.B.R. edited and revised manuscript; M.M.-H., A.M.M., G. B.-L., S.Y., T.L., D.R.M., T.N., Y.C., V.F., Y.F., R.F., M.L., H.Z., and J.B.R. approved final version of manuscript.

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