Differential expression of COVID-19-related genes in European Americans and African Americans

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ABSTRACT

The COVID-19 pandemic affects African American populations disproportionately. There are likely a multitude of factors that account for this discrepancy. Here, we re-mine The Cancer Genome Atlas (TCGA) public RNA-Seq data to catalog whether levels of expression of genes implicated in COVID-19 vary in African Americans as compared to European Americans. Multiple COVID-19-related genes, functioning in SARS-CoV-2 uptake, endosomal trafficking, autophagy, and cytokine signaling, are differentially expressed across the two populations. Most notably, F8A2 and F8A3, which may mediate early endosome movement, are more highly expressed by up to 24-fold in African Americans. Such differences can establish prognostic signatures and have implications for precision treatment of diseases such as COVID-19.

Introduction

As of June 1, 2020, the COVID-19 pandemic has infected over 6.3 million people and killed over 370,000 worldwide (https://coronavirus.jhu.edu/map.html). Its causative agent, the novel SARS-CoV-2, is an enveloped single stranded RNA virus that infects tissues including lung alveoli[1,2], renal tubules[3,4], the central nervous system[5], illeum, colon and tonsils[6–8], and myocardium[9,10].

The complex combinations of symptoms caused by SARS-CoV-2 include fever, cough, fatigue, dyspnea, diarrhea, stroke, acute respiratory failure, renal failure, cardiac failure, potentially leading to death[9,11–14]. The symptoms are induced by direct cellular infection and proinflammatory repercussions from infection in other regions of the body[13–15]. A body of evidence indicates potential long-term health implications following SARS-CoV-2 infection[16,17]. The attributes of the human host that impact COVID-19 morbidity and mortality are not well understood[6,13,14,18–23].

Environmental/physiological risk factors for COVID-19 include age, obesity, and comorbidities such as diabetes, hypertension and heart disease[24]. Heritable factors in the human host influence COVID-19 symptoms[25]. However, to date, only a few of the genetic determinants of COVID-19 severity have been even partially elucidated. Genetic variants of Angiotensin-Converting Enzyme2 (ACE2), the major human host receptor for the SARS-CoV-2 spike protein, may be linked to increased infection by COVID-19[26–29]. Human Leukocyte Antigen (HLA) gene alleles have been associated with susceptibility to diabetes and SARS-CoV-2[30]. The genetic propensity in southern European populations for mutations in the pyrin-encoding Mediterranean Fever gene (MEFV) may elevate levels of pro-inflammatory molecules, leading to a cytokine storm[31] and greater severity of COVID-19[32–35]. Identifying those individuals most at-risk for severe COVID-19 infection, and determining the molecular and physiological basis for this risk, would enable more informed public health decisions and interventions.

COVID-19 cases and deaths are disproportionately higher among African Americans; this is often attributed to a complex combination of socio-economic factors[15,36,37]. However, a number of studies have shown differences in genes expression among races[38–41]. Gene expression reflects the interaction between environmental/physiological and genetic influences. This study specifically investigates whether the expression of genes that are implicated in the severity of COVID-19 infection varies with race.

Here, we re-mine existing RNA-Seq data and reveal significant differences in expression of multiple genes related to COVID-19 infection between European Americans and African Americans. These factors could help predict risk factors and identify potential, more personalized, treatments for COVID-19.

Results

We evaluated differential expression by re-mining an aggregated dataset of 7,142 RNA-Seq samples[42] modified from the normalized and batch-corrected data from the GTEx and TCGA projects[43]. The GTEx project provides data representing normal conditions from diverse organs. The well-curated TCGA project is the largest project available with easily accessible

Project	Disease	#AA	#EA	#Upregulated	#Downregulated
TCGA	Breast invasive carcinoma (BRCA)	142	674	83	164
TCGA	Colon adenocarcinoma (COAD)	54	188	30	21
TCGA	Kidney renal clear cell carcinoma (KIRC)	46	410	68	94
TCGA	Kidney renal papillary cell carcinoma (KIRP)	49	166	19	13
TCGA	Lung adenocarcinoma (LUAD)	48	368	16	5
TCGA	Lung squamous cell carcinoma (LUSC)	28	337	2	0
TCGA	Thyroid carcinoma (THCA)	25	292	3	3
TCGA	Uterine Corpus Endometrial Carcinoma (UCEC)	54	70	28	5

Table 1. Number of DE genes in African Americans compared to European Americans in eight cancer types. Criteria for DE, >2-fold difference in expression, Mann-–Whitney U test is significant with BH-corrected p-value < 0.05.

metadata on the races of the individuals who contributed samples representing diverse diseased organs. These large data provide a unique opportunity to evaluate differences in gene expression across populations in multiple organs in diseased and normal states.

Re-mining existing RNA-Seq data and metadata has several caveats. Because race assignments are self-reported, many of the individuals sampled will be from admixed populations[41,44]. We are terming those self-reporting as "black or African American" as "African Americans" and "white" as "European Americans". The ancestry of the preponderance of African Americans is Western Africa[44], thus our results for African Americans would mostly reflect more specifically Western Africans. Those self-reporting as whites are presumed to be predominantly European Americans.

Also, we were limited to comparison of differences between gene expression in African American and European American populations, because even in these large studies, the sample numbers for the other three major population groups (Asian, Native American, and Pacific Islanders)[45] were too low for robust statistical assessment. Even between these two populations, not all conditions (cancers or organs) had sufficient samplings of African Americans and European Americans for robust statistical assessment (Table 1; Supplementary Table S1).

We analyzed the data and metadata with MetaOmGraph (MOG), software that supports interactive exploratory analysis of large, aggregated data[42]. Exploratory data analysis uses statistical and graphical methods to gain insight into data by revealing complex associations, patterns or anomalies within that data at different resolutions[46].

Differentially expressed (DE) genes among samples from European Americans and African Americans were identified in a tumor-specific or organ-specific manner using MOG (Mann-Whitney U test). Of the tumor types in the TCGA data, BRCA, COAD, KIRC, KIRP, LUAD, LUSC, THCA, and UCEC had sufficient numbers of samples for DE analysis (Table 1). GTEx normal organs that had sufficient sample size were: Breast, Colon, Esophagus, and Thyroid (Table 1). We define a gene as DE between two groups if it meets each of the following criteria:

1. Estimated fold-change in expression of 2-fold or more (log fold change, $|logFC| \geqslant 1$ where $logFC$ is calculated as in limma[47].)

2. Mann-–Whitney U test is significant between the two groups (BH corrected p-value < 0.05)

Supplementary Tables S2-S25 contains the full list of DE genes between African American and European American populations for each condition.

The numbers of DE genes vary depending on the condition the samples were obtained from. Several genes follow a similar DE pattern in diseased as in normal organs, however, in each case, the fold-change difference of expression among the DE genes was larger in the cancers than in the corresponding normal organs (Table 1). Supplementary Table S29 provides the overrepresented Gene Ontology (GO) terms among DE genes for each disease or normal organ.

We performed the two-sample Kolmogorov–Smirnov test (KS test) to assess whether there is a significant difference in distribution of gene expression between African Americans and European Americans. To test whether a distribution shows bi or multi-modality, we performed the Hartigans' dip test. Bi- or multi-modal distributions indicate there may be hidden or unknown covariates affecting the gene expression. Within a race, this could imply presence of sub-population structure.

Not only are genes differentially expressed between the two populations, but in many cases the shape of expression is different. One population or both, might be bimodal, for example, GSTM1 expression in BRACA has a bimdodal distribution in European Americans but not African Americans (Figure 5). The overall distribution in expression values also might differ between the populations, for an obvious example, GSTM1 expression in KIRC (Figure 5).

We focus on the differential expression of genes implicated in response to SARS-CoV-2 infection, drawing from *in silico* studies[48] and experimental analyses especially human responses to infection by SARS-CoV-2 and other coronaviruses[49–52].

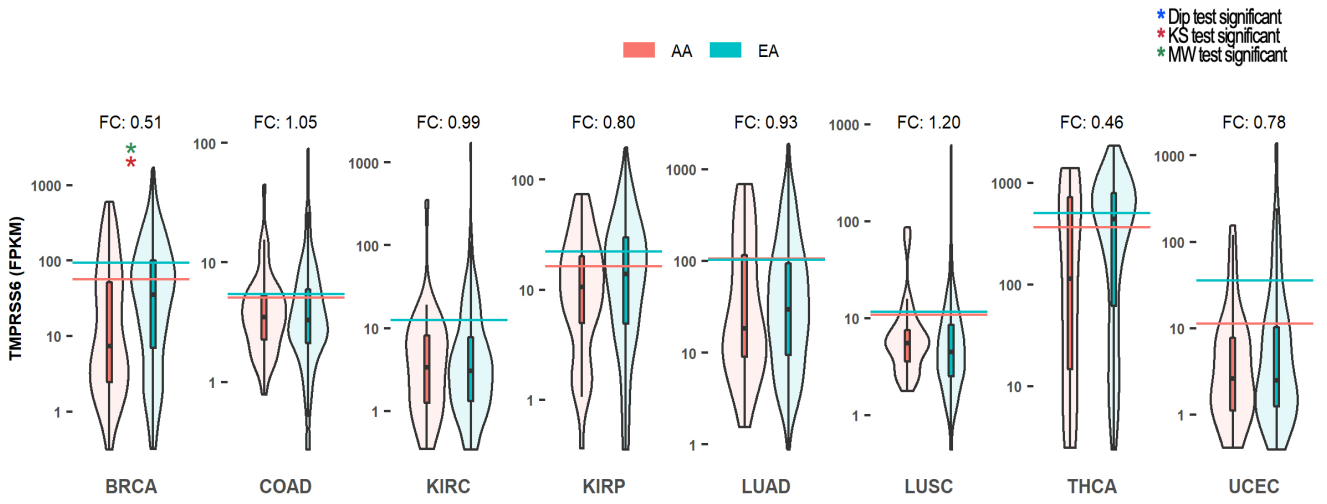

Figure 1. Expression of the **TMPRSS6** protease gene in African Americans and European Americans across eight cancer conditions. Violin plots summarizing the expression over each tumor sample in the two populations. AA, African American; EA, European American. Horizontal lines represent mean log expression. ∗, Hartigans' dip test significant (p-value < 0.05); ∗, KS test significant (p-value < 0.05); ∗, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

These genes are integral to central cellular processes that affect pathogenesis by SARS-CoV-2 including viral entry, endosomal development, autophagy, immunity and inflammation[6,51,53]. Molecular functions of these genes include receptor kinases, proteases, cytokines and other signal transduction molecules, and antioxidants. Multiple such genes are among those differentially expressed in African American and European American populations. We describe 11 such genes in more detail.

TMPRSS proteases

Transmembrane protease serines (TMPRSSs) are low-density lipoprotein receptors in the chymotrypsin serine protease family. TMPRSS2 and most recently, TMPRSS4, have been shown to hydrolyze the spike protein of SARS-CoV and SARS-CoV-2, priming the virus for infection; they are considered a potential therapeutic target to mitigate infection[54–57]. TMPRSS6 also has been suggested as a potential candidate for also cleaving the SARS-CoV-2 spike protein[58]. In THCA, TMPRSS6 is about 2-fold more highly expressed in European Americans than in African Americans (Figure 1).

Cytokines and the storm

Many COVID-19 deaths have been attributed to a cyclic over-excitement of the innate immune system, often termed a cytokine storm, which results in the massive production of cytokines and the body attacking itself more generally, rather than specifically destroying the pathogen-containing cells[14]. Thus, people with comorbidities, the elderly, and immunosuppressed individuals, may be at a greater risk for COVID-19 morbidity and mortality because they may not respond to infection with sufficient immune response[50] and/or because they may be more likely to develop a cytokine storm[14]. We investigated differences in expression of genes of the innate immune response between African American and European American populations.

Several genes of the innate immune system are upregulated in response to SARS-CoV-2 but not in response to influenza[49]. These genes are: interleukins 6 and 7 (IL6, IL7), chemokine (C-X-C motif) ligands 9-11 (CXCL9, CXCL10, CXCL11), and Interferon Gamma (IFNG).

IL6 and IL7 are central to B and T cell development. Expression of IL6 and IL7 is similar between African American and European American populations. However, expression of IL6ST, a component of the cytokine receptor complex that acts as signal transducer for IL6 and IL7, is 2-fold lower in African Americans than European Americans in BRCA (Figure 2).

Circulating chemokines CXCL9 and CXCL10 initiate human defenses, and potentially instigate autoimmune and inflammatory diseases, by activating G protein-coupled receptor CXCR3[59–61]. CXCL9 or CXCL10 are differentially expressed in African Americans as compared to European Americans in several cancers. CXCL9 expression is 2-fold greater in KIRP and over two-fold lower in COAD and KIRC; CXCL10 expression is 1.5-fold higher in BRCA, and over 2-fold lower in COAD, KIRC and TCHA (Figure 3).

CCL3L3 is a member of the functionally-diverse C-C motif chemokine family. It encodes CCL3, which acts as ligand for CCR1, CCR3 and CCR5 recruits and activates granulocytes; it also inhibits HIV-1-infection[62]. CCL3L3 is upregulated in younger and impoverished white males[63].

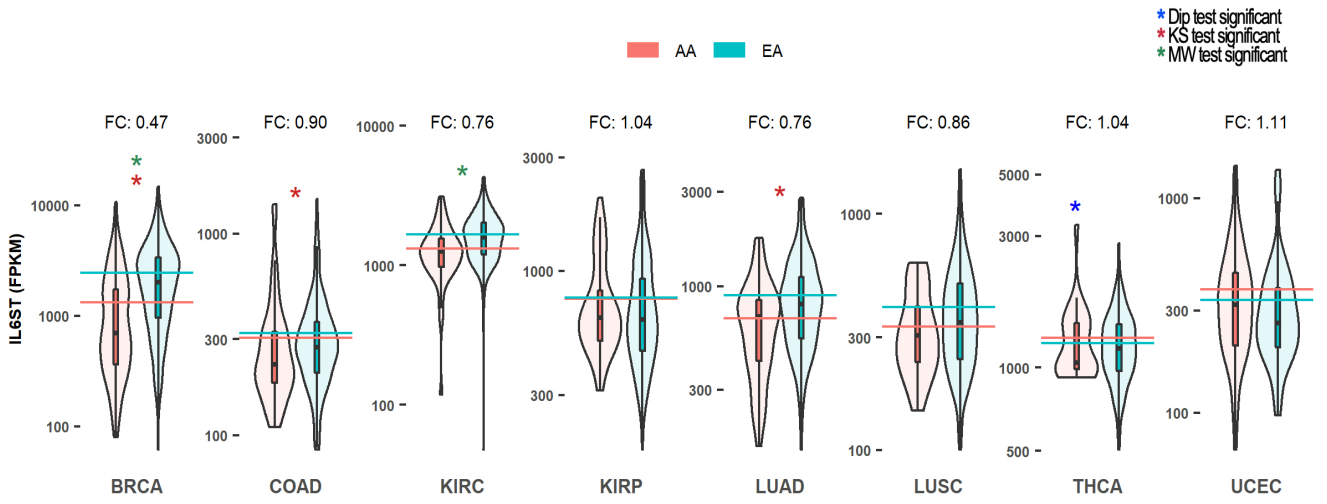

Figure 2. Expression of the **IL6ST** interleukin signal transducer gene in African Americans and European Americans across eight cancer conditions. Violin plots summarizing the expression over each tumor sample in the two populations. AA, African American; EA, European American. Horizontal lines represent mean log expression. ⁎, Hartigans' dip test significant (p-value < 0.05); ⁎, KS test significant (p-value < 0.05); ⁎, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

CCL3L3 is significantly upregulated in African Americans by 2-to 3-fold in BRACA, COAD, and KIRP (Figure 4) but not in corresponding normal organs (Supplementary Table S16-S25).

Carcinoembryonic Antigen-related Cell Adhesion Molecules CEACAM5 and CEACAM6 are members of the C-Type Lectin Domain Family. This gene family encodes a diverse group of calcium (Ca2+)-dependent carbohydrate binding proteins, several of which, including CEACAM5 and CEACAM6 have been implicated as having specific cell adhesion, pathogen-binding and immunomodulatory functions[64]. CEACAM5, a driver of breast cancer[65] and modulator of inflammation in Crohns Disease[66], and CEACAM6, an inhibitor of breast cancer when coexpressed with CEACAM8[67], are both downregulated 2 to 3-fold in BRACA in African Americans. (Supplementary Table 2).

Reactive Oxygen Species

Reactive Oxygen Species (ROS) generated in the mitochondria promote the expression of proinflammatory cytokines and chemokines, thus playing a key role in modulating innate immune responses against RNA viruses[68–72]. Mitochondrially-targeted glutathione S-transferase, GSTM1, is a key enzyme in the metabolism of ROS, as well as of many xenobiotics including pharmaceuticals[71]. GSTM1 is induced by nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that integrates cellular stress signals[56,73–75]. Low expression of GSTM1 can lead to increased mitochondrial ROS, which may ultimately result in a cytokine storm that triggers inflammation and/or autoimmune disease. Conversely, if GSTM1 is too highly expressed, pharmaceuticals may be metabolized and thus rendered inactive, and ROS may be metabolized too rapidly to maintain a sufficient signaling role in the immune system.

Allele frequencies of GSTM1 vary among Asian, African and European populations[76]; the biological significance of these alleles is being investigated[77,78]. The median level of expression of GSTM1 differs between African Americans and European Americans; estimated change in GSTM1 expression is 2- to 6-fold higher in African Americans in eight of the cancers we evaluated and is significantly upregulated in BRCA and KIRC (Figure 5). GSTM1 expression is 2-fold different in normal esophagus and thyroid gland (Supplementary Table S18, S24).

F8As, endocytosis, and autophagy

SARS-Cov-2 and other coronaviruses mainly enter host cells via binding to the ACE2 receptor followed by endocytosis[20,29,51]. The nascent early endosomes are moved along the microtubule cytoskeleton, fusing with other vesicles; varied molecules can be incorporated into the membrane or the interior[51,79–81]. This regulated development enables diverse fates. In the context of SARS-CoV-2, endosomes might release viral RNA or particles; might merge with lysosomes that digest their viral cargo; or might fuse with autophagosomes (autophagy) and subsequently with lysosomes that digest the cargo[51,79–81]. SARS-CoV-2 might reprogram cellular metabolism, suppressing or otherwise altering autophagy and promoting viral replication,[82]. The cell might modify autophagy machinery to decorate the invaders with ubiquitin for eventual destruction, activate the immune system

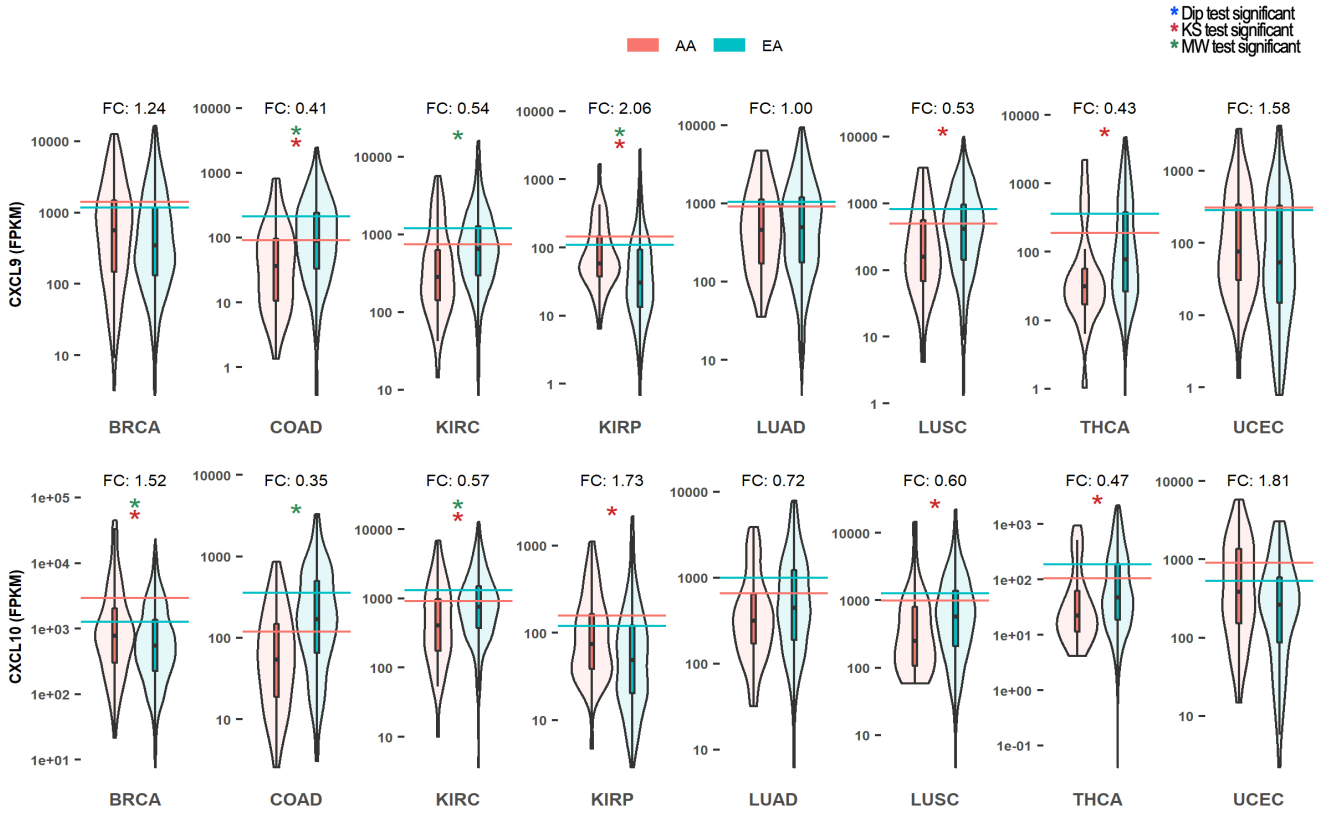

Figure 3. Expression of the **CXCL9** and **CXCL10** circulating chemokine genes in African Americans and European Americans across eight cancer conditions. Violin plots summarize the expression over each tumor sample in the two populations. AA, African American; EA, European American. Horizontal lines represent mean log expression. ⁎, Hartigans' dip test significant (p-value < 0.05); ⁎, KS test significant (p-value < 0.05); ⁎, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

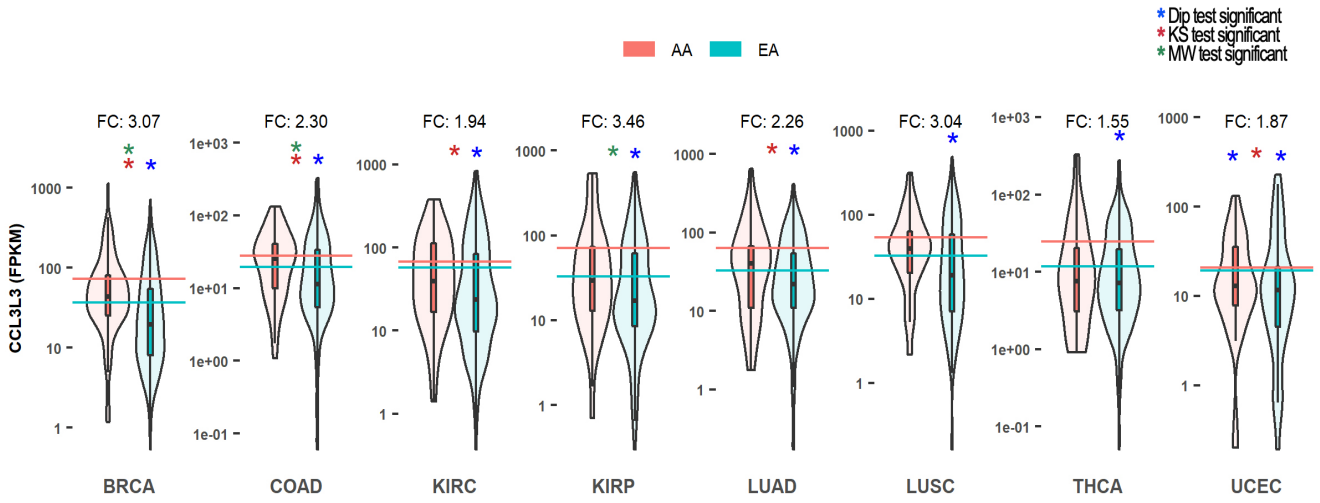

Figure 4. Expression of the **CCL3L3** chemokine gene in African Americans and European Americans across eight cancer conditions. AA, African American; EA, European American. Horizontal lines represent mean log expression. ⁎, Hartigans' dip test significant (p-value < 0.05); ⁎, KS test significant (p-value < 0.05); ⁎, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

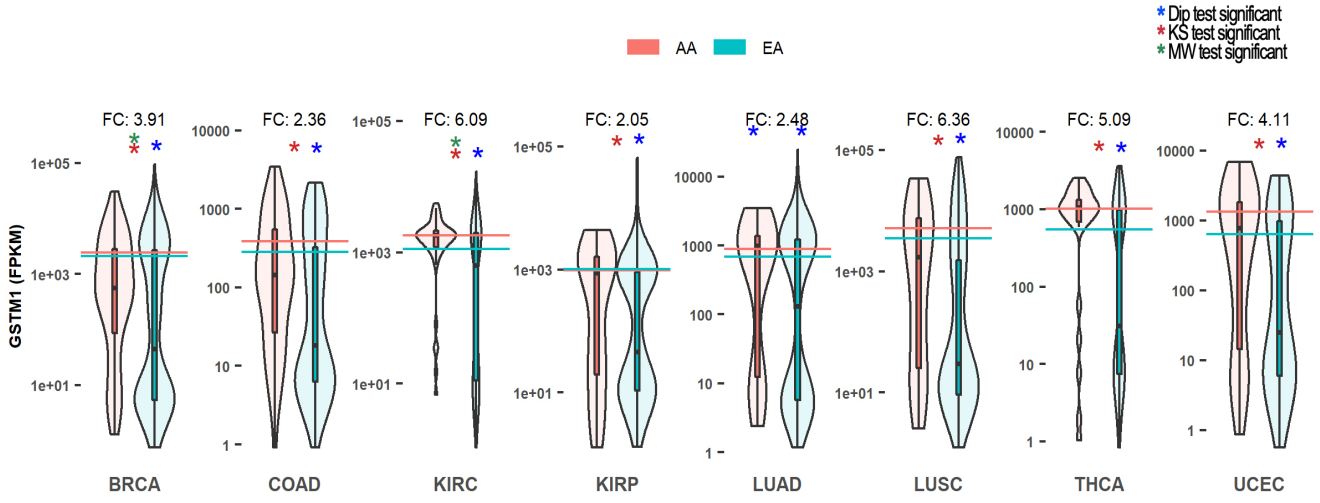

Figure 5. Expression of the mitochondrial glutathione-S-transferase gene, **GSTM1** in African Americans and European Americans across eight cancer conditions. GSTM1 is a key player in metabolism of ROS. Violin plots summarize the expression over each tumor sample in the two populations. AA, African American; EA, European American. Horizontal lines represent mean log expression. ⁎, Hartigans' dip test significant (p-value < 0.05); ⁎, KS test significant (p-value < 0.05); ⁎, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

by displaying parts of the virus, or catabolize excess pro-cytokines. The autophagy might over-induce cytokinin signaling, which could promote protective immune response or engender a destructive storm of cytokinins, inflammation and tissue damage[81].

Endosome motility and development thus plays an important but complex role in the innate immune response that can either promote or hinder the battle between SARS-CoV-2 and its human host[51,79–81].

One little-studied player in early endosome motility, and hence the endocytotic pathway and autophagy, is the seven tetratricopeptide-like repeat F8A/HAP40 (HAP40) protein[83]. HAP40 function has been researched only in the context of its critical role in early endosome maturation in Huntington's disease. In Huntington's, HAP40 forms a bridge between the huntingtin protein and the regulatory small guanosine triphosphatase, RAB5; formation of this complex reduces endosomal motility by shifting endosomal trafficking from the microtubule to the actin cytoskeleton[84].

In human genomes, three genes, F8A1, F8A2, and F8A3, encode the HAP40 protein[83]. The F8A genes are located on the X chromosome. F8A1 is within intron 22 of the coagulation factor VIII gene, which has a high frequency of mutations[85]; F8A2, and F8A3 are located further upstream.

High F8A1 expression has been reported in several disease conditions: Huntington's[86]; a SNP variant for type 1 diabetes risk[87]; cytotrophoblast-enriched placental tissues from women with severe preeclampsia[88]; and mesenchymal bone marrow cells as women age[89]. To our knowledge, F8A2 and F8A3 expression has not been described.

Although its non-disease biology has been little explored, because of its role in early endosome motility in Huntington's, HAP40 is considered a potential molecular target in therapy of autophagy-related disorders[90].

F8A1, F8A2 and F8A3 are each differentially expressed in African Americans versus European Americans. F8A1 is more highly expressed by about 2-fold in European Americans in every cancer analyzed (Figure 6) by 2-fold in normal colon (Supplementary Table S17). Conversely, F8A2 and F8A3 are more highly expressed in African Americans in all cancer types. Expression of F8A2 in African Americans is from 10-fold to 24-fold greater; expression of F8A3 in African Americans is from 2.4-fold to 6.6-fold greater. In LUSC, F8A2 and F8A3 are the only DE genes (Supplementary Table S7). Following a similar trend, F8A2 and F8A3 are more highly expressed in African Americans by 2-fold to 4-fold in normal colon, esophagus, and thyroid (Supplementary Table S17-S18). Part of the difference in levels of F8A2 and F8A3 expression is due to the distributions between populations, with low levels of expression in a subset of the European American population.

Because the literature contains little on HAP40[91] and nothing to our knowledge describing the relationships among F8A1, F8A2, and F8A3 genes, we investigated the sequences, sequence variants, and the expression patterns of these genes further. The sequences of the HAP40 proteins of F8A1, F8A2, and F8A3 are identical to each other in human reference genome GRCh38.p13 (https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.39).

Allele variants of HAP40 proteins encoded by F8A1, F8A2, and F8A3 were mined from The Genome Aggregation Database (gnomAD)[92], a database, which contains sequences of over 140,000 exomes and genomes from individuals of diverse populations. This search identified a very rare variant (<1/1000) of F8A1 found only in European (non-Finnish) populations that encodes a missense mutation (https://gnomad.broadinstitute.org/gene/ENSG00000197932?dataset=gnomad_r2_1); no variants were identified in the HAP40s encoded by F8A2 or F8A3. No structural variants were identified for F8A1 and F8A3. F8A1 and F8A3 do not have duplications; F8A2 has a rare duplication of 54 aa.

We analyzed coexpression of the three F8A genes in the context of the other 18,212 genes represented in the full TCGA-GTEx dataset, using the "Pearson correlation" function in MOG. Although the F8A genes are proximately located on the X chromosome, the genes are *not* highly coexpressed with each other ($|\text{Pearson Corr.}| < 0.46$). Furthermore, no F8A gene is coexpressed with *any* other of the 18,212 genes represented in the dataset ($|\text{Pearson Corr.}| < 0.46$) (Supplementary Table S30). Of all genes, the expression of F8A1 is most *negatively* (anti-) correlated with those of F8A2 and F8A3, with Pearson Correlations of -0.45 and -0.24, respectively (Supplementary Table S30).

Discussion

Genetics of human populations contribute to the propensity and severity of diseases[37,39,41,41,45,93–98]. Sometimes the contribution is straightforward; a single allele variation found in Ashkenazi Jews, causes the vast majority of Tay-Sachs disease[99]. Sometimes it is more complex; for example, hypertension, which more prevalent in African American than European American populations[93] in part due to detrimental APOL1 mutations that are more frequent in West African populations[95].

Ethnic bias and more practical factors (such as subject availability) often cause insufficient numbers of subjects from many populations to be represented in studies; this lack of representation prevents the development of precise prognosis or therapy based on genetics[39,100].

Despite the paucity of studies focused on Western African populations, the propensity and severity of several other diseases among this population have been attributed to genetics[41,95,101]. Here, by revealing differential expression of genes that may be key players in COVID-19 between African Americans and European Americans, we emphasize the importance of integrating gene expression into the mix of factors considered in studying this pandemic.

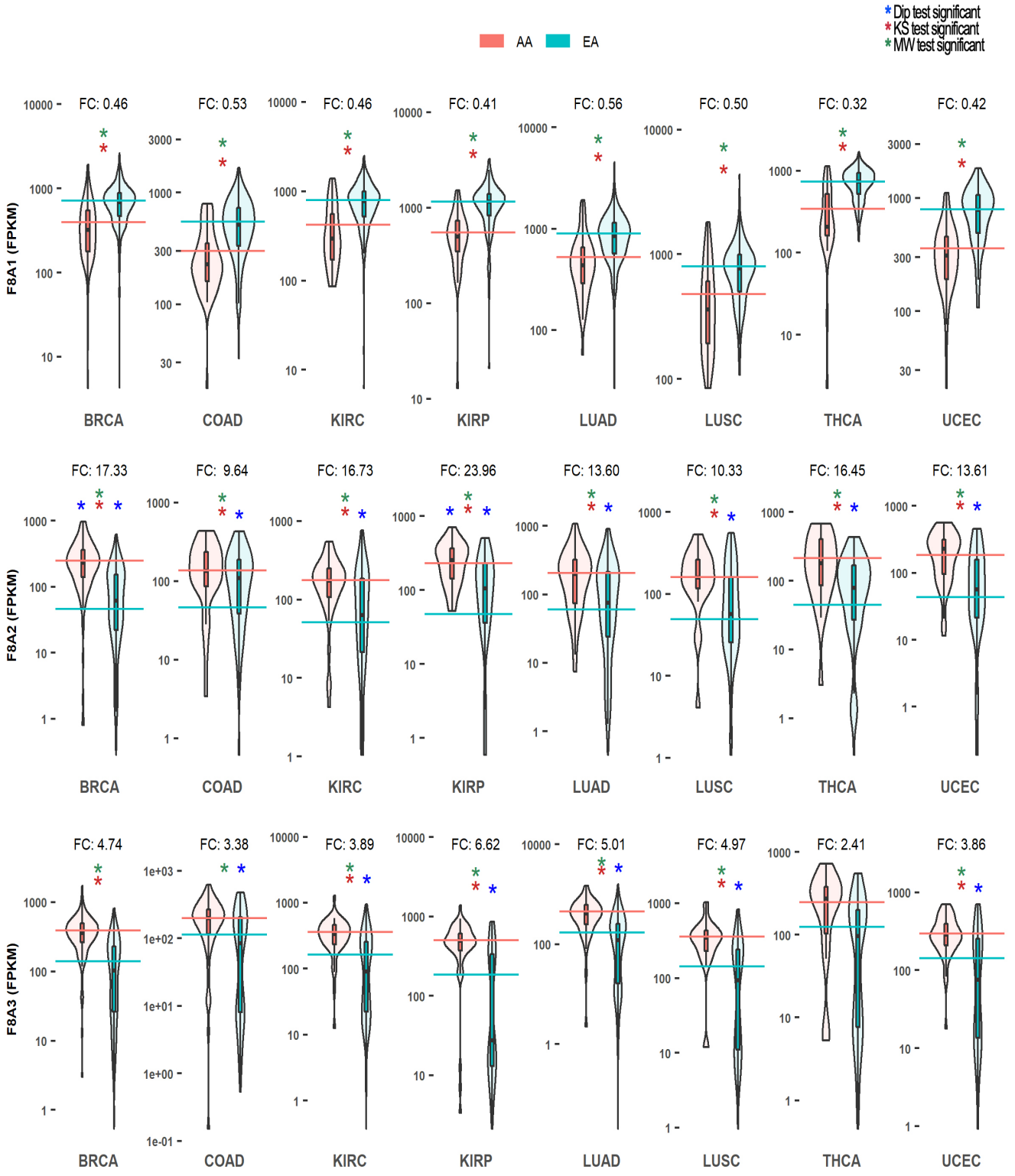

Figure 6. Expression of the HAP40 putative early endosome trafficking genes: **F8A1, F8A2 and F8A3** in African Americans and European Americans across eight cancer conditions. Although the function of HAP40 has not been investigated in normal individuals, this protein is a key component of Huntington's Disease; in Huntington's, HAP40 shifts endosomal trafficking from the microtubules to actin[84]. Violin plots summarize the expression over each tumor sample in the two populations. AA, African American; EA, European American. Horizontal lines represent mean log expression. ⁎, Hartigans' dip test significant (p-value < 0.05); ⁎, KS test significant (p-value < 0.05); ⁎, Mann-–Whitney U test significant (BH corrected p-value < 0.05).

Our study indicates that in diseased and normal conditions many genes that are differentially expressed between African Americans and European Americans are involved in infection, inflammation, or immunity. One contributing explanation for the differential expression of disease-related genes is that the selection pressure due to disease is very strong on both (ancestral) regions, but these regions have very different complements of pathogens. Humans living in Europe and those living in Western Africa would have had to evolve the ability to resist the prevalent local pathogens.

Among the vast body of human RNA-Seq data being deposited, fields for age and gender are typically represented and available in the metadata. However, except in specialized studies, metadata on the race and ethnic heritage of the sampled individuals are often not included, or are very difficult to access. The same can be true of fields such as obesity, alcohol intake, or smoking history. Well-constructed metadata is key to the usefulness of data. Without routine inclusion of diverse metadata for human 'omics samples, data re-mining is hampered, and important information is lost.

Conclusion

Here, we show that the levels of expression of multiple genes implicated in COVID-19 are significantly different in African American and European American populations. The differential expression is evident despite the fact that race is self-reported in and metadata, and many Americans are racially admixed[41].

This study does not distinguish the causes of the differences in expression, which are due to a combination of genetic and environmental factors. Inclusion of information on ethnicity, race, and other metadata for each individual sampled, and ensuring adequate representation of populations, will empower future large-scale data-driven approaches to dissect the relationships between genomics, expression data and metadata.

By highlighting the wide-ranging differences in expression of several disease-related genes across populations, we emphasize the importance of harvesting this information for medicine. Such population-informed research will establish prognostic signatures with vast implications for precision treatment of diseases such as COVID-19.

Methods

The MOG tool was used to interactively explore, visualise and perform differential expression and correlation analysis of genes. We downloaded the precompiled MOG project http://metnetweb.gdcb.iastate.edu/MetNet_MetaOmGraph.htm[42], created using the data processed by Wang et. al., in which expression values have been normalized and batch corrected to enable comparison across samples[43]. This *MOG_HumanCancerRNASeqProject* contains expression values for 18,212 genes, 30 fields of metadata detailing each gene, across 7,142 samples representing 14 different cancer types and associated non-tumor organs (TCGA and GTEX samples) integrated with 23 fields of metadata describing each study and sample.

Since the data was normalized and batch corrected, we used Mann-Whitney U test, a non-parametric test, to identify differentially expressed genes between two groups. An R script was written to perform KS and dip tests, and create the violin plots and executed via MOG interactively.

Pearson correlation values were computed, after data was log_2 transformed within MOG, in MOG's statistical analysis module.

Information on how to reproduce the results are available at https://github.com/urmi-21/COVID-DEA.

Data availability

We subscribe to FAIR data and software practices[102]. MOG is free and open source software published under the MIT License. MOG software, user guide, and the *MOG_HumanCancerRNASeqProject* project datasets and metadata described in this article are freely downloadable from http://metnetweb.gdcb.iastate.edu/MetNet_MetaOmGraph.htm. MOG's source code is available at https://github.com/urmi-21/MetaOmGraph/. Additional files are available at https://github.com/urmi-21/COVID-DEA.

Supplementary data

Supplementary data are available at medRxiv.

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