Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infection, Genetics and Evolution 85 (2020) 104512

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

Chemokine receptor gene polymorphisms and COVID-19: Could knowledge gained from HIV/AIDS be important?

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ARTICLE INFO

Keywords:
CCR5
COVID-19
HIV/AIDS
Host genetics

ABSTRACT

Emerging results indicate that an uncontrolled host immune response, leading to a life-threatening condition called cytokine release syndrome (also termed "cytokine storm"), is the major driver of pathology in severe COVID-19. In this pandemic, considerable effort is being focused on identifying host genomic factors that increase susceptibility or resistance to the complications of COVID-19 and translating these findings to improved patient care. In this regard, the chemokine receptor-ligand nexus has been reported as potentially important in severe COVID-19 disease pathogenesis and its treatment. Valuable genomic insights into the chemokine receptor-ligand nexus have been gained from HIV infection and disease progression studies. Applying that knowledge, together with newly discovered potential host genomic factors associated with COVID-19, may lead to a more comprehensive understanding of the pathogenesis and treatment outcomes in COVID-19 patients.

1. Introduction

The interactions between chemokine receptors and their ligands may affect susceptibility to a variety of infectious diseases as well as their clinical manifestations. In general, the chemokine receptor-ligand interactions mediate both the traffic of inflammatory cells and pathogen-associated immune responses. The role of the immune system in producing an uncontrolled and generalized inflammatory response (termed "cytokine storm") in COVID-19 disease, caused by SARS-CoV-2 virus, is becoming increasingly clear (Qin et al., 2020; Mehta et al., 2020; Coperchini et al., 2020). Although much is yet to be understood, based on current knowledge, the "cytokine storm" may manifest as one of the most dangerous and potentially life-threatening COVID-19-related events called acute respiratory distress syndrome (ARDS) (Qin et al., 2020; Mehta et al., 2020). Therefore, the immune response to SARS-CoV-2 infection and the role of the chemokine receptor-ligand system is being characterized with the final goal of identifying targeted therapeutic strategies (Sorbera et al., 2020; Ray et al., 2020; Chua et al., 2020). Here is a brief description of the studies showing that the chemokine receptor-ligand system is potentially important in severe COVID-19 disease pathogenesis and its treatment. In addition, presenting significant genomic characteristics of this system that we have learned from HIV infection and disease progression studies may be useful for future COVID-19 studies.

2. Role of chemokine receptor in COVID-19

2.1. Chemokine receptor-ligand interactions and COVID-19 severity

A study by Ray et al. (Ray et al., 2020) used a computational framework to test the hypothesis that SARS-CoV-2 infection drives changes in immune cell-derived factors that then interact with receptors expressed by the sensory neuronal innervation of the lung to further promote important aspects of disease severity, including ARDS. To test this hypothesis, the authors used published data from patients, existing RNA sequencing datasets from human thoracic dorsal root ganglion (hDRG) neurons and other sources, and a genome-wide ligand-receptor pair database curated for pharmacological interactions relevant for neuro-immune interactions. Their findings revealed a landscape of ligand-receptor interactions in the lung caused by SARS-CoV-2 viral infection and point to potential interventions to reduce the burden of neurogenic inflammation in COVID-19 pulmonary disease. In particular, genes upregulated in the COVID-19 patient samples include a multitude of genes that recapitulate clinical characteristics, such as increased cytokine signaling causing a "cytokine storm", hypoxia, and inflammasome and sepsis-related genes. Many receptors for cytokines/

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https://doi.org/10.1016/j.meegid.2020.104512
Received 9 July 2020; Received in revised form 20 August 2020; Accepted 21 August 2020
Available online 26 August 2020

chemokines, identified as upregulated in COVID-19 patients, including C−C chemokine receptor (CCR) 1 (*CCR1*), *CCR2*, and *CCR5* were also expressed in hDRG, suggesting a potential direct connection between those cytokines/chemokines and sensory neuron activation in the lung. Based on these findings, the authors claim, "our work highlights opportunities for clinical trials with existing or under development rheumatoid arthritis and other (e.g. C-C chemokine ligand 2 [CCL2], CCR5) drugs to treat high risk or severe COVID-19 cases."

A study by Chua et al. (Chua et al., 2020) investigated the immune response and mechanisms associated with severe COVID-19 by performing single-cell RNA sequencing on nasopharyngeal and bronchial samples from 19 clinically well-characterized patients with moderate or critical disease. The chemokine and chemokine receptor expression of the different cell populations increased markedly in the critical compared to the moderate cases, suggesting an augmented recruitment of immune cells to the sites of inflammation. In particular, inflammatory macrophages showed high expression of the chemokine encoding genes *CCL2* (encoding MCP1), *CCL3* (encoding MIP1α), *CCL20*, C-X-C chemokine ligand 1 (*CXCL1*), *CXCL3*, and *CXCL10*, and pro-inflammatory cytokines. The authors state, "The transcriptional differences in critical cases compared to moderate cases likely contribute to clinical observations of heightened inflammatory tissue damage, lung injury and respiratory failure. Our data suggest that pharmacologic inhibition of the CCR1 and/or CCR5 pathways might suppress immune hyperactivation in critical COVID-19."

2.2. A chromosome 3 gene cluster and respiratory failure in COVID-19 patients

A study by Ellinghaus et al. (Ellinghaus et al., 2020) has tested for association between > 8 million single nucleotide polymorphisms (SNPs) and the development of respiratory failure in COVID-19 patients (835 from Italy, 775 from Spain). The authors found the rs11385942 insertion-deletion GA/A SNP at chromosome 3p21.31 (association boundary chr3:45800446–46,135,604, Hg38) to be associated with COVID-19-induced respiratory failure, with genome-wide significance ($P < 5 \times 10^{-8}$) in the meta-analysis. The locus showed nominally significant association in both the Italian and Spanish sub-analyses. Furthermore, an age- and sex-corrected analysis corroborated these observations. The association signal at chromosome 3p21.31 comprised six genes including *CCR9* and the C-X-C chemokine receptor 6 (*CXCR6*). The authors claim, "The preliminary results from the COVID-19 Host Genetics Consortium include suggestive associations within the same locus at chromosome 3p21.31, which lend considerable support to our findings….As such, it seems reasonable to conclude that the chromosome 3p21.31 locus is involved in COVID-19 susceptibility per se, with a possible enrichment in patients with severe disease. This latter interpretation is supported by the significantly higher frequency of the risk allele GA among patients who received mechanical ventilation than among those who received supplemental oxygen only as well as by the finding of younger age among patients who were homozygous for the risk allele than among patients who were heterozygous or homozygous for the nonrisk allele."

The authors acknowledge that extensive genotype-phenotype elaboration of current findings could not be conducted and, therefore, a causative gene cannot be reliably implicated by the present data. Among the six genes included in the association signal, CXCR6 regulates the specific location of lung-resident memory CD8 T cells throughout the sustained immune response to airway pathogens, including influenza viruses. Flanking genes (e.g., *CCR1* and *CCR2*) also have relevant functions, and further studies will be needed to delineate the functional consequences of detected associations (Ellinghaus et al., 2020).

2.3. CCR5 as a therapeutic target for COVID-19

A study by Patterson et al (Patterson et al., 2020) has reported profound elevation of plasma IL-6 and CCL5 (also known as RANTES), a ligand for CCR5, decreased $CD8^+$ T cell levels, and SARS-CoV-2 plasma viremia in 10 terminally-ill, critical COVID-19 patients. Following treatment with the CCR5-blocking antibody leronlimab, the authors observed complete CCR5 receptor occupancy on macrophage and T cells, rapid reduction of plasma IL-6, restoration of the CD4/CD8 ratio, and a significant decrease in SARS-CoV-2 plasma viremia. Consistent with reduction of plasma IL-6, single-cell transcriptomics showed that there were declines in myeloid cell clusters expressing IL-6 and interferon-related genes. The authors state, "These results demonstrate a novel approach to resolving unchecked inflammation, restoring immunologic deficiencies, and reducing SARS-CoV-2 plasma viral load via disruption of the CCL5-CCR5 axis, and support randomized clinical trials to assess clinical efficacy of leronlimab-mediated inhibition of CCR5 for COVID-19."

According to the authors, leronlimab does not downregulate CCR5 surface expression or deplete CCR5-expressing cells, but does prevent CCL5-induced calcium mobilization in $CCR5^+$ cells. This ability to specifically prevent CCL5-induced activation and chemotaxis of inflammatory $CCR5^+$ macrophages and T cells suggests how leronlimab-mediated CCR5 blockade may be effective in resolving the hyperinflammatory state in COVID-19 and restoring more effective anti-viral immunity (Patterson et al., 2020).

3. Role of CCR5 in HIV/AIDS and other diseases

CCR5 is the main HIV-1 co-receptor involved in virus entry and cell-to-cell spread during acute and chronic infections: such CCR5-using and T cell-tropic viruses are adapted to and replicate in $CD4^+$ memory T cells (Joseph and Swanstrom, 2018). Polymorphisms in *CCR5* regulate CCR5 expression, which in turn influences HIV infection acquisition and subsequent disease progression. Among these polymorphisms, a 32 base pair deletion in the *CCR5* open reading frame (ORF) (*CCR5* Δ32, rs333) (McLaren and Carrington, 2015; Naranbhai and Carrington, 2017; Tough and McLaren, 2019) and a SNP in the promoter (−2459G/A, rs1799987) (Martin et al., 1998; McDermott et al., 1998) are the most well-characterized ones. *CCR5* Δ32 provides partial to full protection against HIV infection, and therefore serves as a basis for gene deletion studies attempting to achieve a permanent HIV cure (Allen et al., 2018; Xu, 2020). Recent studies have discovered that certain SNPs in the *CCR* region, not within *CCR5*, also affect CCR5 expression, HIV infection, and disease progression (McLaren et al., 2015; Kulkarni et al., 2019).

3.1. CCR5 in other diseases

Beyond HIV, researchers have been investigating the involvement of CCR5 and the effects of *CCR5* Δ32 on autoimmune and inflammatory diseases, cancers, and other viral diseases (Jiao et al., 2019; Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a). Data suggest that there are varied impacts of CCR5 regulation and *CCR5* Δ32 on human infections caused by the following non-HIV viruses: West Nile virus, Tick-borne encephalitis virus, Influenza virus, Human papillomavirus, Hepatitis B virus, Hepatitis C virus, Poliovirus, Dengue virus, Human cytomegalovirus, Crimean-Congo hemorrhagic fever virus, Enterovirus, Japanese encephalitis virus, and Hantavirus (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a). The role of CCR5 in bacterial, parasitic, and fungal diseases has not been much studied (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020b).

3.2. CCR5 Δ32 and SARS-CoV-2 infection and death

In a study by Panda et al. (Panda et al., 2020) data of COVID-19

disease and mortality rate per million of inhabitants were obtained from the website (https://www.worldometers.info/coronavirus/, accessed on 29th June 2020). The prevalence of *CCR5* Δ32 allele in healthy controls from 107 countries was obtained from an earlier publication (Solloch et al., 2017) and PubMed search. Spearman Rank Correlation tests ($\alpha = 0.0001$) were performed, and a significant positive correlation was observed between COVID-19 infection rate/million (Spearman $r = 0.4628$, $P < 0.0001$, $n = 107$) and mortality rate/million (Spearman $r = 0.5517$, $P < 0.0001$, $n = 107$) with the frequency of the Δ32 allele. In addition, a positive correlation was noticed between COVID-19 mortality rate and the Δ32 allele frequency in an African population (Spearman $r = 0.6210$, $P = 0.0045$). The authors state, "These data and findings are indicative of an association of *CCR5* Δ32 with susceptibility to SARS-CoV-2 infection and mortality. However, the mechanism of *CCR5* Δ32 allele offering predisposition to SARS-CoV-2 infection susceptibility and death of the patient is not known."

Chemokine receptors and their ligands, including CCR5 and CCL5, have been found to play important role in inflammatory response, which most commonly involve the recruitment of leukocytes to eliminate infectious agents. Differential expression of chemokine receptor and ligand may contribute to variations in inflammatory pattern, which in turn may have distinct effects on the course or establishment of infections. As CCR5 is a primary entry receptor for HIV, it is appreciable that expression variations of CCR5 due to *CCR5* polymorphisms may influence the acquisition of HIV infection as well as the disease progression. However, the impacts of *CCR5* polymorphisms on the replication and infection of non-HIV viruses and other pathogens are complex and may not be generalized (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a; Ellwanger et al., 2020b). These impacts could be disease-specific and/or population-specific.

4. Genetic variation, CCR5, and HIV/AIDS outcomes

4.1. *CCR5 Δ32 and promoter SNP −2459G/A*

A variety of studies conducted in the 1990s examined the associations between *CCR5* polymorphisms Δ32 and −2459G/A (also known as 59029G/A and 303G/A) and HIV-1 infection and disease progression. In those studies, the Δ32 allele, compared with the wild-type (wt) allele, was associated with protection against HIV infection and/or delayed disease progression (Martin et al., 1998; Dean et al., 1996; Zimmerman et al., 1997). The −2459G allele, compared with the −2459A allele, was associated with delayed HIV disease progression (Martin et al., 1998; McDermott et al., 1998). In a number of studies, the Δ32 and −2459G alleles were associated with significantly reduced in vitro promoter activity, CCR5 expression, and HIV propagation, compared with the ORF wt and −2459A alleles, respectively (McDermott et al., 1998; Hladik et al., 2005; Kawamura et al., 2003; Mummidi et al., 2000; Salkowitz et al., 2003; Shieh et al., 2000). Recent studies have provided insight into the molecular mechanisms regarding the association between *CCR5* promoter polymorphisms and transcriptional regulation of the promoter, and how this association correlates with CCR5 cell surface expression as well as HIV disease phenotype (Jiang et al., 2011; Gornalusse et al., 2015; Joshi et al., 2017).

The *CCR5* Δ32 allele is found predominantly in European populations, with rare occurrences in Asians and native populations from Africa, the Americas, and Oceania (Solloch et al., 2017) (see Table 1). On the other hand, allele frequency of *CCR5* −2459A ranges from 32% to 66% in most populations (see Table 1). In Papua New Guinea, an Oceania country, this allele frequency was much higher, 85% in one study (Clark and Dean, 2004) and 98% in another (Mehlotra et al., 2015).

The *CCR5* haplotype nomenclature system consists of a total of nine polymorphisms, which include *CCR5* ORF wt/Δ32 and −2459G/A. *CCR5* haplotypes are organized into nine evolutionarily distinct human haplogroups (HH) designated HHA, −B, −C, −D, −E, -F*1, -F*2, −G*1, and -G*2 (Mummidi et al., 2000; Gonzalez et al., 1999). Haplotypes HHA to HHD carry the −2459G allele, whereas HHE to HHG*2 carry the −2459A allele (Mummidi et al., 2000; Gonzalez et al., 1999). Only HHG*2 carries the Δ32 allele. HHE, HHF*1, and HHG*1 are grouped together as Haplotype-P1 (Hap−P1) (Martin et al., 1998; Gonzalez et al., 1999). In the same way that the ORF wt/Δ32 and −2459G/A alleles show differences in phenotypic effects in vitro as well as in HIV/AIDS cohorts, different *CCR5* haplotypes influence HIV infection and disease outcomes differently (Gonzalez et al., 1999; Mehlotra, 2019).

4.2. *Identification and functional characterization of a new SNP rs1015164G/A*

A recent study by McLaren et al. (McLaren et al., 2015) tested for association between ~8 million common variants and HIV set-point viral load (spVL) in 6315 individuals of European ancestry. In this analysis, they found that the top chromosome 3 SNP was rs1015164G/A ($P = 1.5 \times 10^{-19}$). The SNP rs1015164 lies near an antisense transcribed sequence *RP11-24F11.2* that overlaps *CCR5* and is only weakly correlated to *CCR5* Δ32 ($D' = 0.89$, $r^2 = 0.03$). Fine mapping of the 1.5 Mb *CCR* region (chr3:45.5–47, Hg19) association signals in the subset of 5559 individuals, for whom the *CCR5* Δ32 genotype data was available and *CCR5* Hap-P1 (carrying −2459A) carriage could be determined, showed that another SNP rs4317138T/C was the top SNP associated with spVL ($P = 7.7 \times 10^{-22}$). Interestingly, this SNP highly correlated to the top SNP identified in the analysis of the full sample, rs1015164G/A ($D' = 1$, $r^2 = 0.97$). Using conditional association analysis, rs1015164G/A remained associated with spVL when conditioning on both *CCR5* Δ32 and Hap-P1 (conditional $P = 5.2 \times 10^{-4}$).

A more recent study by Kulkarni et al. (Kulkarni et al., 2019) has further substantiated the fact that human genetic variation affects HIV infection and disease progression. It also has shown that the role of human genetic variation in HIV/AIDS is not straightforward. The major findings of the study were: rs1015164 G/A is in close genomic proximity to an antisense long noncoding RNA (lncRNA) gene, *RP11-24F11.2*, that overlaps with *CCR5* and is transcribed into CCR5AS; the CCR5AS transcript levels are influenced by the SNP – rs1015164A is associated with higher expression levels of CCR5AS; higher expression levels of CCR5AS enhance *CCR5* messenger RNA (mRNA) stability, thereby increasing *CCR5* mRNA and cell surface expression; and the rs1015164 SNP associates with HIV outcome (viral loads and $CD4^+$ T cell counts) after infection. Thus, the complex interplay among rs1015164A, CCR5AS, and CCR5 provides the functional basis for the association between rs1015164A and lack of HIV control. Furthermore, these results represent a rare determination of the functional importance of a genome-wide disease association where expression of a lncRNA affects HIV infection and disease progression.

5. Population genetics of rs1799987G/A (−2459G/A) and rs1015164G/A

The rs1799987A allele is highly prevalent all across the world (frequencies 32–66%), whereas the rs1015164A allele has frequencies of 14–37% in most populations and 2–8% in those from Africa (see Table 1). Given these frequencies, one may ask, how probable it is that both rs1799987A and rs1015164A alleles occur together by chance? Using the 1000 Genomes populations, the allele frequencies (see Table 1) and linkage disequilibrium (LD, see Table 2) values suggest that it is reasonably probable in certain populations. The LD between rs1799987 and rs1015164 SNPs suggests that they are not independent of one another in all populations. To demonstrate that the rs1799987A and rs1015164A alleles occur together, frequencies of the haplotype containing both variant alleles (A_A) were calculated using sample genotype data from the 1000 Genomes populations (Li et al., 2009). In

Table 1
Certain functional polymorphisms within and around *CCR5* in 1000 Genomes populations.[a]

Polymorphism	Alleles[c]	Location[d]	Overall frequency (range)[e]				
			African	American	East Asian	European	South Asian
rs1799987[b]	G/A	Chr 3:46370444	40% (32–49%)	57% (50–66%)	41% (35–52%)	54% (47–57%)	39% (38–41%)
rs333	wt/Δ32	Chr 3:46373453	0 (0–3%)	3% (2–4%)	0	11% (7–16%)	1% (0–3%)
rs1015164	G/A	Chr 3:46410189	5% (2–8%)	22% (19–25%)	19% (14–24%)	32% (28–37%)	28% (21–32%)
rs4317138	T/C	Chr 3:46420653	5% (2–8%)	23% (19–26%)	19% (14–26%)	33% (28–38%)	29% (23–33%)

[a] Phase 3 populations (26 populations, 2504 samples).
[b] Known as −2459G/A, 59029G/A, and 303G/A.
[c] Ancestral allele/Mutant allele; wt = wild-type, Δ32 = 32 bp deletion.
[d] GRCh38 coordinate.
[e] Mutant allele.

4 out of 5 super populations, the A_A haplotype frequencies range from 14% to 37% (see Table 2). A_A may be considered a "risk" haplotype, as it may be associated with higher CCR5 expression compared with rs1799987A or rs1015164A (Mehlotra, 2020).

6. Conclusions

Hyperimmune activation and "cytokine storm" are present in cases of severe COVID-19. In this pandemic, the goal is to identify host genomic factors that increase susceptibility or resistance to the complications of the disease, and to translate these findings in a timely manner to improved patient care (Murray et al., 2020). As various approaches are being taken to uncover biological networks underlying host-pathogen (SARS-CoV-2) interactions and common variants therein, it may be important to consider that common variants occur in some of those networks, which have been characterized to play functionally significant roles in other global epidemic diseases. In this regard, the role of certain polymorphisms within as well as outside *CCR5* in HIV/AIDS may be worth considering. CCR5 receptor and a nearby gene cluster, where many other chemokine receptor genes are located, may be potentially involved in COVID-19 treatment (Patterson et al., 2020) and may contribute to susceptibility to the complications of the disease (Ellinghaus et al., 2020; Panda et al., 2020). In other words, the 1.5 Mb *CCR* region on chromosome 3 (chr3:45.5–47, Hg19) may be playing roles in both HIV/AIDS and COVID-19. This region contains *CCR5* and several functionally significant SNPs including rs1015164 (McLaren et al., 2015; Kulkarni et al., 2019). It also includes the 335 kb region (chr3:45800446–46,135,604, Hg38 [chr3:45841938–46,177,096, Hg19]) containing the rs11385942 insertion-deletion GA/A SNP, which was found to be associated with COVID-19-induced respiratory failure (Ellinghaus et al., 2020). Therefore, further characterization of this chromosomal region in COVID-19 patients seems warranted.

In addition, as the studies targeting CCR5 for COVID-19 treatment are performed, and such a treatment starts becoming increasingly available, it is imperative to include ORF wt/Δ32, −2459G/A, and rs1015164G/A polymorphisms in the treatment outcome analyses. Given the significance of Δ32, even when present as a single allele, the ORF wt/Δ32 genotype information ought to be included in such studies.

Table 2
CCR5 promoter polymorphism linkage disequilibrium and haplotype frequencies in 1000 Genomes populations.

Population	Description	rs1799987-rs1015164	
		D' (r^2)	haplotype frequency[a]
African	African Caribbean in Barbados (ACB)	1 (0.11)	8%
	African Ancestry in Southwest USA (ASW)	1 (0.08)	6%
	Gambian in Western Division, The Gambia (GWD)	0.86 (0.10)	6%
	Mende in Sierra Leone (MSL)	1 (0.05)	2%
	Yoruba in Ibadan, Nigeria (YRI)	0.75 (0.05)	4%
	Luhya in Webuye, Kenya (LWK)	–	3%
	Esan in Nigeria (ESN)	–	3%
American	Colombian in Medellin, Colombia (CLM)	1 (0.26)	21%
	Mexican Ancestry in Los Angeles, CA (MXL)	1 (0.26)	24%
	Peruvian in Lima, Peru (PEL)	0.85 (0.09)	18%
	Puerto Rican in Puerto Rico (PUR)	1 (0.27)	25%
East Asian	Chinese Dai in Xishuangbanna, China (CDX)	1 (0.33)	16%
	Han Chinese in Bejing, China (CHB)	1 (0.24)	14%
	Southern Han Chinese, China (CHS)	1 (0.39)	21%
	Japanese in Tokyo, Japan (JPT)	0.94 (0.26)	24%
	Kinh in Ho Chi Minh City, Vietnam (KHV)	0.94 (0.35)	17%
European	Utah residents with Northern and Western European Ancestry (CEU)	1 (0.42)	32%
	Finnish in Finland (FIN)	0.95 (0.33)	32%
	British in England and Scotland (GBR)	1 (0.31)	29%
	Iberian population in Spain (IBS)	1 (0.48)	37%
	Toscani in Italy (TSI)	0.96 (0.39)	27%
South Asian	Bengali in Bangladesh (BEB)	1 (0.44)	22%
	Gujarati Indian in Houston, TX (GIH)	0.94 (0.57)	30%
	Indian Telugu in the UK (ITU)	0.97 (0.64)	31%
	Punjabi in Lahore, Pakistan (PJL)	0.87 (0.49)	26%
	Sri Lankan Tamil in the UK (STU)	1 (0.60)	28%

- Data not available.
[a] haplotype rs1799987A_rs1015164A.

Also, −2459G/A and rs1015164G/A polymorphisms should be included because they regulate CCR5 expression and are prevalent worldwide, the latter in American, East Asian, European, and South Asian populations. Moreover, the potential "risk" haplotype A_A of these polymorphisms is also quite prevalent. If A_A is associated with higher CCR5 expression, it may affect CCR5-based treatment outcomes in COVID-19 patients. Knowing whether an individual receiving such an immunologic or chemotherapeutic intervention is carrying two, one, or no A_A haplotype would enable a better understanding of the response to the intervention.

It is acknowledged that direct information on the influence of *CCR5* polymorphisms on COVID-19 disease severity is very limited at the moment. Moreover, mechanistic studies providing plausible explanations on how polymorphisms in *CCR5* and other related genes would correlate with the disease severity and clinical manifestations of COVID-19, including the recruitment of immune cells/inflammatory cells to the infection sites, are needed. Nevertheless, with the discovery of potential host genomic factors associated with COVID-19 and knowledge already gained from other global infectious diseases, there is now a greater potential to improve clinical management and foster better patient outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

R.K.M. wrote the manuscript.

Declaration of Competing Interest

None.

Acknowledgements

This article is dedicated to the loving memories of the late Dave McNamara, a former colleague and a dear family friend, and Dr. Benigno Rodriguez, a well-respected colleague and a very helpful collaborator. The author is grateful to Marlin Linger, Ramalakshmi Janamanchi, and Dr. Carolyn Myers for commenting on the manuscript.

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