Title: A genetic predisposition for Cytokine Storm in life-threatening COVID-19 infection

Authors: Yin-Ling Woo¹, Adeeba Kamarulzaman¹, Yolanda Augustin², Henry Staines², Frederick Altice³, Michael Barrett⁴, Sanjeev Krishna²

Institutions

1. Faculty of Medicine, University of Malaya, Malaysia
2. Institute of Infection & Immunity, St George's University of London, United Kingdom
3. Department of Infectious Diseases, Yale School of Medicine, New Haven, United States
4. Institute of Infection, Immunity and Inflammation, University Place, Glasgow G12 8TA

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Corresponding author: Professor Sanjeev Krishna

Email: sgjf100@sgul.ac.uk

Globally, COVID-19 is currently estimated to have a case fatality rate of 1-10% with countries throughout the world reporting very different case fatality ratios. Uncertainties in estimates of mortality partly relate to the unknown size of denominator, the numbers of people tested, local demographics and healthcare systems (<https://coronavirus.jhu.edu/data/mortality>).

The natural history of COVID-19 infection is broadly divided into four stages. After infection, there may be a pre- or asymptomatic phase that lasts a few days (Stage 1). When symptoms of fever, cough and systemic malaise manifest themselves, viral loads are highest, and even higher in severely affected patients compared with those who have milder symptoms. The disease progresses from upper to lower respiratory tract to become a viral pneumonia (Stage 2 after a median of 5 days). Detectable upper respiratory viral load decreases over a period of around 7-10 days and antibody responses are generated¹. Most patients do not progress but improve gradually, presumably after an adequate adaptive immune response. After 1-2 weeks a small proportion of patients develop features of a cytokine release syndrome (CRS)/cytokine storm (CS) with elevated pro-inflammatory cytokines and other host markers of inflammation (e.g. increased CRP, hyperferritinaemia, D-dimers, lactate dehydrogenase), lymphopenia and progressive respiratory failure (Stage 3) that can rapidly progress into acute respiratory distress syndrome (ARDS) and multi-organ involvement (Stage 4). ARDS is a feature in 60–70% of patients admitted to Intensive Care Units together with shock (30%), myocardial dysfunction (20–30%) and acute kidney injury (10–30%)^{2,3,4,5,6,7}. In the critically ill, the need for mechanical ventilation ranges from 42-100%^{4,5,7,8,9}. The median time from symptoms to clinical recovery is 6–8 weeks and to death is 2-8 weeks^{10,11}.

In COVID-19, severe disease and mortality is associated with older age, male sex, comorbidities (including chronic lung disease, cardiovascular disease, hypertension, diabetes, obesity and cancer), higher severity illness scores¹² and ethnicity¹³. Many of these risk factors probably predispose to fatal outcomes due to reduced cardiorespiratory reserve. Chronic inflammatory processes underlying these risks may also contribute. Furthermore, in a substantial but unpredictable number of patients, there are no clear identifiable risk factors. Younger, previously fit patients are not spared from progressing inexorably through to the late stages and dying from severe COVID-19. Although children were initially thought to be relatively protected from developing severe COVID-19, there is now emerging evidence of a novel severe Kawasaki-like disease in children^{14,15}. Kawasaki disease (KD) is a paediatric inflammatory disease associated with vasculitis affecting predominantly the coronary arteries, thought to be triggered by an infectious agent or toxin that results in an acute inflammatory response¹⁶. Could there therefore be a genetic predilection for life-threatening COVID-19?

SARS-CoV-2 shares the angiotensin-converting enzyme 2 (ACE2) as a receptor similar to SARS-CoV-1. ACE2 is a membrane-bound receptor richly expressed in the lungs, heart, kidney and gastrointestinal tract. SARS-CoV-2 may have a higher affinity for ACE2 than SARS-CoV-1 causing more severe lung sequelae in COVID-19 compared to SARS. Earlier studies in macaques with Sars-CoV-1 demonstrated the importance of anti-spike protein antibody responses that trigger a large inflammatory response in the lungs of infected animals by stimulating pro-inflammatory response

pathways at the expense of anti-inflammatory responses¹⁷. These findings consolidate the respective roles of innate and acquired defence pathways in SARS. During Stage 1-2 of COVID-19 infection, a specific adaptive immune response is triggered to eliminate the virus and to prevent disease progression to more severe clinical stages^{18,19}. Effective adaptive immune responses are likely to be influenced by genetic factors. If the response is maladaptive then progression to Stages 3-4, leads to destruction of tissues that express ACE2.

There is growing evidence that Interleukin-6 (IL-6) is a central mediator of CRS. In addition to general markers of hyperinflammation (above), circulating IL-6 levels are increased in severely ill patients. Elevated IL-6 levels are also thought to play an important role in the acute inflammatory response of KD¹⁶. Most tellingly, there is accruing evidence for beneficial effects of administering anti IL-6 antibody (Tocilizumab) in these patients^{20,21,22,23}. Tocilizumab binds membrane bound as well as soluble IL-6 receptors, blocking IL-6 from exerting its pro-inflammatory effects. Tocilizumab is licensed for the treatment of rheumatoid arthritis and CRS related to CAR-T cell therapy.

Compassionate use of tocilizumab in a select group of severe COVID-19 patients displaying features of CRS has led to clinical improvement in patients who otherwise were likely to deteriorate [unpublished data and communications USA (Yale), Italy (Naples), Malaysia (Kuala Lumpur) and UK (London)]. Phase 2 trials are now in progress (ClinicalTrials.gov Identifier: NCT04331808 ; NCT04317092).

While considering possible risk factors for CRS, we observed that countries with the highest number of COVID-19 deaths per 100,000 population are in southern Europe (Spain, Italy, and France) or the Middle East (Iran). In the United States and United Kingdom, the highest numbers of deaths are in New York and London, respectively, cities that have high numbers of migrants. These observed ethnic and population mortality rates along with the understanding of the natural history of COVID-19 have led us to hypothesize that carriers of certain mutations, for example in the *Mediterranean Fever* gene (*MEFV*), the cause of Familial Mediterranean Fever (FMF), could predispose the individual to the more severe forms of COVID-19.

FMF is a hereditary fever syndrome that was first described in Mediterranean populations. It is an autosomal recessive disorder characterized by short, recurrent bouts of fever with raised inflammatory markers, polyserositis and dermal manifestations that typically last 12–72 h. Elevated levels of serum TNF alpha, IL-1 and IL-6 are seen in FMF patients during acute attacks²⁴. FMF is the most common inherited monogenic autoinflammatory disease mainly affecting ethnic groups of Mediterranean, Arab, Jewish, Turkish, Armenian North Africans and those of Arabic descent. Mutations in *MEFV* and different phenotypes of FMF have been reported among Jewish²⁵, Japanese²⁶, Spanish²⁷ and Iranian^{28,29} populations.

MEFV encodes a protein named pyrin (also called marenostrin or TRIM20) and mutations are gain-of-function, producing clinically heterogeneous phenotypes that reflect the complexity and multiplicity of pyrin functions. Pyrin is involved in innate immune responses such as inflammasome assemblage. The inflammasome senses intracellular danger signals, activates mediators of inflammation, and resolves inflammation by the autophagy of regulators of innate immunity³⁰. Based on these

functions, FMF-associated versions of pyrin confer a heightened sensitivity to a variety of intracellular danger signals and postpone the resolution of innate immune responses. Hence, we hypothesise that carriers with mutations in *MEFV* may be predisposed to the development of CRS with SARS-CoV-2 infection.

Figure 1

Figure 1: Cytokine storm and COVID-19

Several conditions that respond to targeted anti-inflammatory therapies (Table 1) are listed on the left-hand side: G6PD; Glucose-6-phosphate dehydrogenase deficiency: FMF; Familial Mediterranean Fever: TRAPS; Tumor necrosis factor receptor-associated periodic syndrome: CAPS; Cryopyrin-associated periodic syndromes: NLRP12AD; NLRP12-associated autoinflammatory disorder: RA; Rheumatoid Arthritis. The risk of developing cytokine release syndrome may be modulated by genetic factors that may also influence adaptive immune response to COVID-19. CRP; C-reactive protein: MMP8/MMP9; matrix metalloproteinase-8 /9.

There are currently more than 300 sequence variants reported for *MEFV* (<https://infevers.umai-montpellier.fr/web/search.php?n=1>), most of which are clustered in exon 10 of the gene, with various degrees of penetrance. The six most prevalent mutations (M694V, V726A, M680I, M694I, V694I, E148Q) represent some 80% of all cases. Some mutations are likely to be polymorphisms and not disease-causing mutations.

A retrospective review of 1687 children with FMF examined the correlation between phenotype-genotype and comorbidities.³¹ Within this cohort, 7% of patients had at least one concomitant disease and 72% carried at least one M694V mutation. Homozygous carriers for the M694V mutation appeared to have a significantly earlier age of disease onset and more severe disease clinical course ($p < 0.001$).

FMF is treated with colchicine to reduce the severity and duration of fever episodes, and to prevent the complication of amyloidosis. Interestingly, colchicine is also being used in a phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of colchicine in adult patients diagnosed with COVID-19 infection (<https://clinicaltrials.gov/ct2/show/NCT04322682>). More significantly, tocilizumab has also been given to FMF patients resistant to colchicine therapy, often with complications of amyloidosis, with benefits described in case reports and small retrospective series^{32,33,34,35}.

Pathway	Therapy
IL-6 Inhibition	Tocilizumab, Sariluma, Situximab
IL-1 Inhibition	Anakinra
JAK/STAT Pathway Inhibition	Ruxolitinib, Itactinib
GM-CSF Inhibition	Lenzilumab
TNF- α Inhibition	Infliximab, Etanercept, Adalimumab
Inflammasome Inhibition	Colchicine

Table 1: Potential therapeutic targets in Cytokine Release Syndrome

To reduce risks of patients progressing to Phase 3 and 4 of disease, it is important to understand what factors predict clinical progression. The hypothesis that *MEFV* mutations predispose to IL-6-driven CRS in severe COVID-19 and FMF has several implications. These include the search for a genetic predictive biomarker or genetic signature for clinical severity in COVID-19 infection, the development of a diagnostic panel for disease severity (elevation of IL-6, or its encoding pathways), interventions with broader range of therapies targeting IL-6 pathways (such as tocilizumab and colchicine) and the identification of key cellular subtypes that are predicted to circulate and migrate to affected tissues and organs in patients who succumb to severe infection. It is equally important to study associations between specific Human Leukocyte Antigen (HLA) loci and the development of immunity to SARS-CoV-2. In the case of asymptomatic carriers it is important to identify the alleles, either class I or II, that may confer protective immunity. Epidemiological studies that allow for confounders may also establish if there is a contribution to higher mortality rates in south European populations by *MEFV* mutations or related genes.

G6PD deficiency is one of the commonest enzymopathies and is caused by X-linked gene polymorphisms that reduce the ability of cells to deal with oxidant stresses³⁶. G6PD is responsible for the production of NADPH and is the rate-limiting enzyme in the pentose phosphate pathway. NADPH production involves the balance of reduced glutathione (GSH)/oxidized glutathione (GSSG) in both the mitochondria and cytosol.

Glutathione metabolism plays a major role in physiological anti-oxidant defense and decreased levels of G6PD result in increased levels of oxidative stress.

G6PD deficiency has a global distribution and affects 400 million people, particularly African-American blacks, blacks from sub-Saharan Africa or Brazil, Sardinia, Greece, South China, India, Thailand and Kurdish Jews (populations from geographical areas where malaria was once endemic). The prevalence of G6PD deficiency amongst African Americans is around 12%^{37,38}. The Kurdish Jewish population display the highest prevalence of 60-70%³⁸. These high frequencies are suggested to have arisen because G6PD deficiency may confer an evolutionary advantage against malaria infections.

Whilst the clinical susceptibility to haemolysis provoked by oxidant stresses is well described in G6PD deficiency, this manifestation emerges in the severe class I-III deficiencies (WHO). The G6PD Mediterranean variant (563C>T) is a class II variant associated with severe haemolysis and is the most common abnormal variant in individuals from the Mediterranean region and the Middle East³⁹. The G6PD A⁻ variant (202G>A/376A>G) is a class III variant associated with mild to moderate hemolysis and is most commonly associated with African ancestry⁴⁰.

Several observations link G6PD deficiency with the potential of developing more severe COVID-19 infections^{40,41,42}. First is the hitherto unexplained predominance of severe disease in males. Second, animal models have shown that G6PD deficiency augments cytokine responses following hyperinflammation caused by acute endotoxemia⁴³. Lipopolysaccharide (10–35 mg/kg body weight intraperitoneally) resulted in increased interleukin-1 β , interleukin-6, and interleukin-10 levels in serum and peritoneal lavage in G6PD-deficient mice compared with wild type mice. Third, G6PD deficiency rendered cells more susceptible to a common alpha coronavirus (229E) infection through impairment of oxidative stress response. Finally, G6PD deficiency decreases the production of anti-inflammatory cytokines (IL-10, for example) and increases pro-inflammatory cytokines (such as IL-6) in patients after severe trauma. These pathophysiological effects are associated with increased frequency of sepsis and longer hospital stays.

FMF and G6PD deficiency are 2 common gene polymorphisms that predispose to hyperinflammatory states. Taken together with acquired causes of inflammation such as obesity, they may predispose to increased susceptibility to infection with SARS-CoV-2 and risk of severe disease and fatality. Mendelian randomization studies may help to define the role of these genetic variants in severe COVID-19.

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