Host genetics of pediatric SARS-CoV-2 COVID-19 and multisystem inflammatory syndrome in children

Grant S. Schulert[a,b], *Sydney A. Blum*[a] *and Randy Q. Cron*[c]

Purpose of review
This review is meant to describe the genetic associations with pediatric severe COVID-19 pneumonia and the postinfectious complication of the multisystem inflammatory syndrome in children (MIS-C). Multiple genetic approaches have been carried out, primarily in adults with extrapolation to children, including genome-wide association studies (GWAS), whole exome and whole genome sequencing (WES/WGS), and target gene analyses.

Recent findings
Data from adults with severe COVID-19 have identified genomic regions (human leukocyte antigen locus and 3p21.31) as potential risk factors. Genes related to viral entry into cells (ABO blood group locus, *ACE2, TMPRS22*) have been linked to severe COVID-19 patients by GWAS and target gene approaches. Type I interferon (e.g. *IFNAR2*) and antiviral gene (e.g. *TLR7*) associations have been identified by several genetic approaches in severe COVID-19. WES has noted associations with several immune regulatory genes (e.g. *SOCS1*). Target gene approaches have identified mutations in perforin-mediated cytolytic pathway genes in children and adults with severe COVID-19 and children with MIS-C.

Summary
Several genetic associations have been identified in individuals with severe COVID-19 and MIS-C via various genetic approaches. Broadly speaking, COVID-19 genetic associations include genes involved with antiviral functions, viral cell entry, immune regulation, chemotaxis of white blood cells, and lymphocyte cytolytic function.

Keywords
COVID-19, cytokine storm syndrome, genetics, multisystem inflammatory syndrome in children, SARS-CoV-2

INTRODUCTION

As of August 2021, the pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus has infected over 198 million individuals worldwide resulting in over 4.2 million deaths yielding a mortality rate of about 2%. Much of the mortality associated with severe infection (COVID-19 pneumonia) is believed to result from proinflammatory hypercytokinemia, including elevated levels of interleukin-6 (IL-6), IL-1, and others [1]. Perhaps, the best evidence for the detrimental role of the immune response in COVID-19 is the benefit afforded by immunosuppressive glucocorticoids, Janus kinase inhibitors, and IL-6 inhibitors. Glucocorticoids specifically, when given during hypoxic phases of the disease, have been demonstrated in randomized, blinded, placebo-controlled trials to improve mortality [2]. Why some infected individuals are asymptomatic, some experience a flu-like illness, and others develop severe and sometimes fatal pneumonia and acute respiratory distress syndrome, however, remains a conundrum.

There have been many identified clinical risk factors for severe COVID-19, including old age, obesity, diabetes, hypertension, and several other chronic conditions. But why some individuals, including younger adults and children, develop severe COVID-19 pneumonia remains unclear. Some have posited initial viral load of infection,

[a]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, [b]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio and [c]Division of Rheumatology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to Dr Randy Q. Cron, Children's of Alabama, Pediatric Rheumatology, 1600 7th Ave. S, CPPN, suite G10, Birmingham, AL 35233-1711, USA. Tel: +1 205 638 9438;
e-mail: randycron@uabmc.edu

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KEY POINTS

- Not all children experience the same disease course when infected with SARS-CoV-2 suggesting inherent genetic risk factors may predispose to disease severity.
- The genetic risk factors associated with COVID-19 are poorly understood, and much of what is known about host genetic risk factors for severe COVID-19 in children has been extrapolated from studies in adults.
- Genome-wide association studies in adults with severe COVID-19 have identified genes associated with antiviral functions, viral cell entry, and white blood cell chemotaxis.
- Whole-exome and whole-genome sequencing approaches have identified loss of function mutations in genes relevant to antiviral responses, including type I interferon genes and *TLR7*.
- Missense mutations and spice site variants in cytokine storm syndrome-associated genes (e.g. *PRF1*, *XIAP*) have been reported in children and adults with severe COVID-19 and children with MIS-C.

but there are likely host genetic factors that contribute to disease severity in COVID-19. Fortunately, children seem to be largely spared of severe acute disease, and many infected children are asymptomatic. However, a small subset of children develops a postinfectious SARS-CoV-2-related multisystem inflammatory syndrome in children (MIS-C) [3]. MIS-C in younger children resembles Kawasaki disease and toxic shock syndrome, whereas in older children MIS-C can present as shock with features of a cytokine storm syndrome (CSS) [4] or macrophage activation syndrome (MAS) [5▪,6▪,7▪]. Unlike most children with severe primary COVID-19, children with MIS-C do not tend to have preexisting medical conditions [8], but do respond to glucocorticoids [9]. Again, the reason for why only some SARS-CoV-2 infected children develop MIS-C but most do not suggest a key role for host genetic susceptibility [10].

Host genetic factors that contribute to severe COVID-19 have been explored largely in adults by genome-wide association studies (GWAS) and whole exome (WES)/genome (WGS) sequencing. Because there is little data on host genetics in children with COVID-19, much is extrapolated from genetic findings in adults. There is even less data on host genetic risk factors for the development of MIS-C, but it shares some features with CSS, such as elevated markers of interferon-gamma (IFNγ), like CXCL9 [11]. IFNγ is classically elevated in hemophagocytic lymphohistiocytosis (HLH) [12], a familial form of CSS, and therefore MIS-C may share genetic contributions that predispose to related CSS. In this review, we will focus on host genetic risk factors for the development of severe primary COVID-19 in children, as well as post-COVID MIS-C.

GENOME-WIDE ASSOCIATION STUDIES OF SEVERE COVID-19

The first rigorous insights into the host genetics of severe COVID-19 infection were provided by large GWAS. GWAS is ideal for identifying relatively high-frequency (>5% minor allele frequency) variants linked to specific single-nucleotide polymorphisms (SNPs), and whereas the overall relative risk of these SNPs is generally small, they can highlight specific genes that may have key pathogenic roles in disease [13]. Of note, the GWAS for COVID-19 have examined almost exclusively adult patients, and whereas findings likely have broad applicability to disease pathogenesis they do not address the etiology of rare, severe outcomes in children. The most consistently identified region amongst the several GWAS of severe COVID-19 is in chromosome 3p21.31 spanning numerous genes including *SLC6A20, LZTFL1, CCR2, CCR3, CCR9, FYCO1*, and *CXCR6* (Table 1). This was first identified in a GWAS of 1980 Italian and Spanish patients with severe COVID and respiratory failure, with the risk haplotype conferring a 1.77 odds ratio (OR) for disease [14▪▪]. A second large GWAS utilizing research participants via 23andMe and patient-reported severe disease also identified this genomic region, with the protective haplotype conferring 0.59 OR for severe respiratory disease [15]. This was most pronounced in the European population with an increased frequency of the risk haplotype. This association was also detected in two additional studies that performed transcriptome-wide association studies to link results to tissue-specific gene expression data and found multiple genes within this cluster with significant differences in predicted expression [16,17]. Interestingly, it has recently been proposed that this genomic region is part of a 50 kilobase region of DNA inherited from Neanderthals [18].

Several additional genomic regions conferring risk for severe COVID-19 have been identified through GWAS and other approaches. The initial GWAS study also identified a locus in the ABO blood group (Table 1), and particularly that the risk for severe COVID was higher with blood group A versus other blood groups (1.45 OR), whereas blood group O was protective (0.65 OR) [14▪▪]. This association has also been observed in other GWAS [15,17] but not all [16]. Several other putative genome-wide associations have been identified in individual studies with various approaches, including antiviral effectors *OAS1, OAS2, OAS3; TYK2; IL10RB*; and

Table 1. Genes implicated in COVID-19 and MIS-C development or severity

Gene/region	Method of identification	Function	References (PMID#)	Notes
Genomic regions				
3p21.31	GWAS	Multiple genes including *SLC6A20*, *LZTFL1*, *CCR2*, *CCR3*, *CCR9*, *FYCO1*, and *CXCR6*	32558485; 34315903; 33888907, 33307546	
HLA locus	Target gene		33343579, 32717807	Not replicated by GWAS
Viral entry				
ABO	GWAS	ABO blood group	32558485, 34315903, 33888907	Not replicated in 33307546
ACE2	GWAS and target gene	Angiotensin-converting enzyme, receptor for SARS-CoV-2	33837377, 32681121, 33704002	Conflicting findings
TMPRSS2	Target gene	Transmembrane serine protease, used for SARS-CoV-2 entry	33921689, 34075330	Not replicated by GWAS
Type I interferon and antiviral				
OAS1-3	GWAS	Degrades viral RNA and inhibits replication	34315903	
IFNAR1	WES/WGS	Interferon alpha and beta receptor subunit 1	32972995	Not replicated in 34043590
IFNAR2	GWAS	Interferon alpha and beta receptor subunit 2	34315903, 33307546, 33837377	
TLR7	WES	Pattern recognition receptor binding viral RNA	34115965, 32706371	
IRF7	WES	Transcriptional activation of interferon-induced genes	32972995	
Immune dysregulation				
SOCS1	WES	Negative regulator of cytokine production	32853638	MIS-C
XIAP	WES	Regulates apoptosis and modulates inflammation	34224783	MIS-C
CYBB	WES	Component of phagocyte NADPH oxidase	34224783	MIS-C
TBK1	WES	Mediates NFκB activation, activates interferon responses	34210994	Fatal pediatric COVID-19
Known cytokine storm genes				
UNC13D	Target genes	Involved in cytolytic vesicle maturation and binding	33867526	
AP3B1	Target genes	Involved in vesicle biogenesis	33867526	
PRF1	Target gene	Released by cytolytic cells to form pores in target cells	33256384	
LYST	Target gene	Regulates cytolytic vesicle size and trafficking	34132389	
STX11	Target genes	Regulates targeting and membrane fusion of cytolytic vesicles	33442938	MIS-C

GWAS, genome wide association study; HLA, human leukocyte antigen; MIS-C, multisystem inflammatory syndrome in children; NADPH, nicotinamide adenine dinucleotide phosphate; PMID, PUBMED identifier; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WES, whole exome sequencing; WGS, whole genome sequencing.

ACE2 [16,17,19] (Table 1). Interestingly, these studies have not identified a significant association in the human leukocyte antigen (HLA) locus, although two targeted analyses of HLA types have reported significant associations with SARS-CoV-2 infection [20,21]. Finally, several studies that also considered gene expression data highlighted low-expression risk alleles of *IFNAR2* as conferring risk for severe COVID-19 (see below) [16,17,19] (Table 1).

Finally, there is some evidence that genetic polymorphisms may impact the risk for infection by SARS-CoV-2 through viral entry including *ACE2*

and *TMPRSS2* [22,23]. Several studies have utilized a target gene approach to identify functional variants of these proteins associated with COVID-19 disease and severity. For example, two independent studies found that the p.Val160Met variant of *TMPRSS2* was associated with decreased disease severity [23,24] (Table 1). Other studies have found more frequent *ACE2* allelic variability in uninfected versus SARS-CoV-2 infected individuals in Italy [25], and specific SNPs enriched in health-care works highly exposed but never infected with SARS-CoV-2 [26] (Table 1). However, such target gene associations must be interpreted with caution, as large GWAS above have largely not found associations with these loci to have genome-wide significance [14▪▪,16,19].

POTENTIAL MONOGENIC CAUSES OF SEVERE COVID-19 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In contrast to GWAS, WES/WGS of cohorts with defined phenotypes has the potential to identify monogenic causes of severe disease. The relatively rare occurrence of life-threatening acute COVID-19 and MIS-C in healthy children indeed suggests the presence of rare, single-gene mutations [27]. Indeed, work from a large international consortium has proposed that rare inborn errors in type I IFN responses may occur in some previously healthy individuals with severe COVID-19 [28▪]. This study performed WES or WGS on 659 previously healthy patients with severe COVID-19 including children as young as 1 month of age and used a targeted analysis of 13 genes related to influenza immunity. Patients with severe COVID-19 showed enrichment in predicted loss of function (pLOF) variants at these loci compared to healthy controls, and 3.5% of severe COVID-19 patients carried variants experimentally found to cause impaired type I IFN responses. This included 4 unrelated patients with biallelic *IFNAR1* or *IRF7* mutations (Table 1), and dominantly acting variants in 7 other genes in these pathways. This work is further supported by the identification of *IFNAR2* in several GWAS discussed above (Table 1), and together with the identification of functional autoantibodies that can inhibit type I IFN responses [29] contribute to a model of COVID-19 pathogenesis where the failure of early interferon responses is central to severe disease progression. However, a recent study has questioned this association by analyzing 4 independent, international cohorts of adult patients with severe COVID-19 [30]. This work found first, very few patients with rare pLOF variants in type I IFN pathway genes, and second, no enrichment for either pLOF or any rare missense variants in cases versus controls. There are a number of methodologic differences between the approaches used, including ancestral matching, different definitions of 'severe' COVID-19 on the WHO scale, using pauci-symptomatic or asymptomatic controls versus the general population, stratifying for age, and assessing type I IFN autoantibody presence [31,32]. These conflicting results, though, do raise questions about whether the findings of Zhang *et al.* are generally applicable, and, as such, the relative contribution of type I IFN pathway mutations as a risk factor for severe COVID-19 remains unsettled.

Similar WES/WGS based studies have also examined individual children and young adult patients with unusually severe COVID-19. One case series of 2 unrelated pairs of previously healthy brothers age 21–32 with severe COVID-19 identified rare loss of function variants of the X-chromosome gene *TLR7* [33▪] (Table 1). Functionally, these patients' peripheral blood mononuclear cells showed impaired upregulation of type I IFN-related genes [33▪]. Interestingly, Solanich et al. identified a third pair of previously healthy brothers <30 affected with severe COVID-19 both possessing a missense variant in the *TLR7* coding region [34]. It has been suggested that since *TLR7* escapes X-inactivation and has higher expression levels in women, TLR7 could play a role in the greater severity of COVID-19 seen in men [33▪]. Indeed a large exome-based study also found an increased burden of rare pLOF variants in *TLR7* in patients with severe COVID-19 [35].

Finally, there are several smaller WES studies suggesting potential monogenic causes of severe pediatric COVID-19 as well as MIS-C. Prior to the COVID-19 pandemic, unique heterozygous truncation variants in a suppressor of cytokine signaling 1 (*SOCS1*) were identified in 2 unrelated boys with immune thrombocytopenia and autoimmune hemolytic anemia in the setting of acute infections [36] (Table 1). One of these patients later developed MIS-C after a documented SARS-CoV-2 infection [36]. This observation inspired a single-center prospective cohort study of 18 MIS-C patients which identified additional candidate variants in *XIAP* and *CYBB* [37▪] (Table 1). XIAP has been shown to dysregulate inflammasome activity leading to elevations in IL-1β, IL-18, and CXCL9 [38]. Interestingly, *XIAP* deficiency has also been associated with CSS, particularly in the context of epstein-barr virus infection (see below) [38]. *CYBB* encodes the p91phox subunit of the nicotinamide adenine dinucleotide phosphate oxidase necessary for phagocytic oxidative burst, impairing neutrophil cytotoxic responses. Although the full loss of p90phox activity causes chronic granulomatous

disease, this patient's variant reduced but did not eliminate the neutrophil respiratory burst [37▪]. Finally, homozygous *TBK1* and *TNFRSF13B* mutations were recently identified in a 3-year-old girl with fatal COVID-19 and a history of autoimmune disease [39]. Notably, *TBK1* is a known regulator of the type I IFN pathway, and homozygous variants were recently reported in a child with systemic autoinflammation [40] (Table 1).

CYTOKINE STORM SYNDROME GENES IN COVID-19 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Both severe COVID-19 and MIS-C have been classified under the hyperinflammatory CSS umbrella [1]. CSS are characterized by an overly exuberant immune response to a number of triggers, including many viral pathogens [4]. When CSS occurs, the host often develops multiorgan system failure, including liver dysfunction, cytopenias, and coagulopathies [41]. Although there are multiple pathways leading to CSS [42], the best studied, and perhaps the most common, involves defects in perforin-mediated cytolytic activity of natural killer (NK) cell and cytotoxic CD8 T lymphocytes [12]. There are multiple proteins involved in the delivery of perforin to the target cell (antigen-presenting cell) to trigger apoptotic cell death (Fig. 1). The genes involved in this process are largely known, and bi-allelic defects in perforin-mediated cytolysis result in frequently fatal HLH in infancy [43]. Although familial HLH is rare, secondary forms of HLH or CSS are often associated with heterozygous defects in perforin pathway genes [44]. Indeed, some of these gene defects act as hypomorphs or complete or partial dominant-negatives disrupting lymphocyte-mediated cytolysis [45–49]. Disrupted cytolysis of the target cell results in prolonged engagement of the lytic lymphocyte and the target cell resulting in increased pro-inflammatory cytokines (e.g. IFNγ) believed to contribute to the multiorgan failure seen in CSS [49–51]. This has been reported for other pandemic viruses, such as H1N1 influenza, where fatal cases are associated with heterozygous defects in perforin pathway genes (*PRF1*, *LYST*) (Fig. 1) [45].

Like H1N1 influenza, SARS-CoV-2 triggers a range of host immune responses. Similarly, severe cases of COVID-19 were found to be enriched for

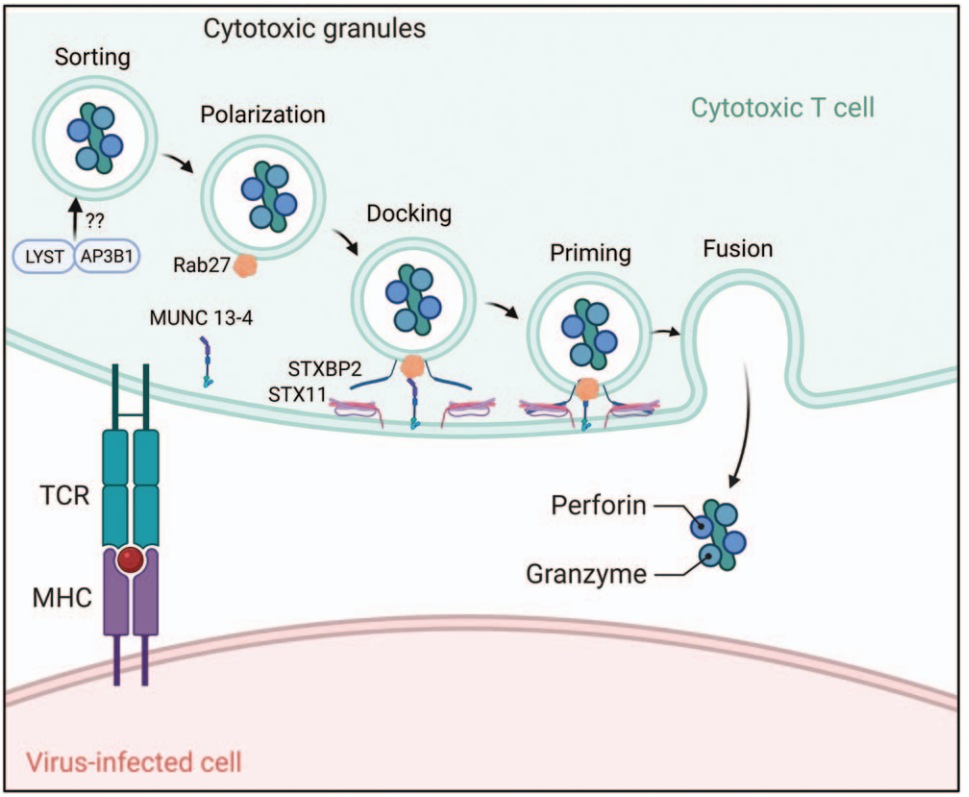

FIGURE 1. Genes involved in the perforin-mediated cytolytic pathway of cytotoxic CD8 T lymphocytes and natural killer cells. Mutations in perforin or genes involved in delivering and releasing perforin containing cytotoxic granules to the immunologic synapse (e.g. *STX11*) may contribute to a CSS-like hyperinflammatory state in children with severe COVID-19 and MIS-C. CSS, cytokine storm syndrome; MIS-C, multisystem inflammatory syndrome in children.

heterozygous missense and splice-site variants in familial HLH genes (*UNC13D*, *AP3B1*) (Fig. 1 and Table 1) among those with higher serum cytokine levels [52▪]. In another small cohort of severe COVID-19 patients, excluding the elderly and those with preexisting conditions, 2 of 22 adults were noted to have the familial HLH-associated missense mutation, *PRF1* p.A91V (Fig. 1) [53▪], similar to 2 of 14 with fatal H1N1 influenza [45]. In terms of children or infants, one 6-week old with COVID-19 was identified as having familial HLH (homozygous nonsense *LYST* mutation, p.Gly1675) (Fig. 1) (Table 1) triggered by SARS-CoV-2 [54]. Likewise, a toddler with COVID-19 was noted to have familial HLH (homozygous frameshift mutation in *STX11*, p.Gln230Alafs∗125) (Fig. 1) (Table 1), and months later developed MIS-C, both episodes responsive to IL-1 blockade [55]. Intriguingly, familial HLH genes are significantly enriched when exploring the SARS-CoV-2 host protein interactome [56▪▪]. Thus, like other infectious CSS, mutations in known familial HLH genes (Fig. 1) may serve as risk factors for both children and adults with COVID-19, and possibly for children with MIS-C as well.

A knowledge of the genetics contributing to pediatric COVID-19 and MIS-C may benefit clinicians in terms of choosing therapeutics. Those children with evidence of HLH-associated gene mutations may derive the most benefit from therapies targeting excessive inflammation used in other CSS, including glucocorticoids, cytokine blockers (e.g. IL-1, IL-6), and lymphocyte targeted treatments (e.g. calcineurin inhibitors) [1]. In contrast, SARS-CoV-2-infected children with genetic defects in innate immune responses, including type I IFN, may benefit from treatment with recombinant interferon [57] to help control viral replication in advance of a potential CSS. Genetics may thus tailor therapy for children with COVID-19 and MIS-C, but patient selection and timing of treatment will be critical.

CONCLUSION

Only a small subset of SARS-CoV-2 infected children and young adults develop severe COVID-19, suggesting a susceptibility to cellular infection and/or inability to control the virus. Similarly, small numbers of SARS-CoV-2 infected children develop a post-infectious life-threatening hyperinflammatory episode, MIS-C, with CSS features. For COVID-19 pneumonia, genes identified in younger adults and children converge on an inadequate antiviral, particularly type I interferon, response. In contrast, studies of children with MIS-C identified mutations in CSS genes. The potential to identify children at risk for severe complications of SARS-CoV-2 infection has implications for targeted therapy directed toward diminished or excessive inflammatory responses.

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Conflicts of interest

R.Q.C. has served as a consultant to Sobi, Novartis, Pfizer, and Sironax. R.Q.C. has received grant support from Sobi for investigator-initiated clinical trials. G.S.S. has received consulting fees from Novartis and Sobi.

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- ▪ of special interest
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