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REVIEW

Severe COVID-19 represents an undiagnosed primary immunodeficiency in a high proportion of infected individuals

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Abstract

Since the emergence of the COVID-19 pandemic in early 2020, a key challenge has been to define risk factors, other than age and pre-existing comorbidities, that predispose some people to severe disease, while many other SARS-CoV-2-infected individuals experience mild, if any, consequences. One explanation for intra-individual differences in susceptibility to severe COVID-19 may be that a growing percentage of otherwise healthy people have a pre-existing asymptomatic primary immunodeficiency (PID) that is unmasked by SARS-CoV-2 infection. Germline genetic defects have been identified in individuals with life-threatening COVID-19 that compromise local type I interferon (IFN)-mediated innate immune responses to SARS-CoV-2. Remarkably, these variants – which impact responses initiated through TLR3 and TLR7, as well as the response to type I IFN cytokines – may account for between 3% and 5% of severe COVID-19 in people under 70 years of age. Similarly, autoantibodies against type I IFN cytokines (IFN-α, IFN-ω) have been detected in patients' serum prior to infection with SARS-CoV-2 and were found to cause *c.* 20% of severe COVID-19 in the above 70s and 20% of total COVID-19 deaths. These autoantibodies, which are more common in the elderly, neutralise type I IFNs, thereby impeding innate antiviral immunity and phenocopying an inborn error of immunity. The discovery of PIDs underlying a significant percentage of severe COVID-19 may go some way to explain disease susceptibility, may allow for the application of targeted therapies such as plasma exchange, IFN-α or IFN-β, and may facilitate better management of social distancing, vaccination and early post-exposure prophylaxis.

Keywords: COVID-19, inborn errors of immunity, interferon autoantibodies, primary immunodeficiency

INTRODUCTION

The novel coronavirus SARS-CoV-2 is the cause of COVID-19, a disease which swept the world in 2020, and has resulted in more than 250 million infections and 5 million deaths to date. The pathogenesis of severe COVID-19 may relate both to viral load and persistence, and to the effects of an excessive inflammatory response.[1] It is not surprising therefore that there is a role for antiviral therapies such as remdesivir and molnupiravir,[2] and passive immunity afforded by convalescent plasma[3–5] and monoclonal antibodies to SARS-CoV-2,[6] as well as for anti-inflammatories such as dexamethasone[7] and IL-6 blockade via tocilizumab,[8] in managing severe COVID-19.

A majority of SARS-CoV-2-infected people do not suffer severe disease. Despite this, several risk factors have been identified that predict severe and even fatal COVID-19, including male gender, advanced age, pre-existing heart disease, hypertension, diabetes, malignancy and obesity.[9] However, these factors constitute only a small part of the risk, given that many elderly people have also been reported to have minimal or asymptomatic disease, whereas some young, seemingly healthy individuals can suffer significant morbidity or mortality. The inference here is that – in contrast with the last great pandemic caused by human immunodeficiency virus (HIV) – humans do not exhibit a species-level vulnerability to SARS-CoV-2, but rather some individuals manifest a risk which is far greater than the average human.

To understand what might underlie this excess risk in some people, studies have assessed the role of common genetic variation in mediating risk, using technologies such as genome wide association studies (GWAS).[10,11] These studies have defined a number of susceptibility loci for severe COVID-19; however, the associated relative risk of these loci is generally far too small (e.g. twofold[10,12]) to uniquely explain more than a small portion of the undefined risk. Far more revealing are studies that have searched for rare or even 'private' genetic variation using genomic sequencing technologies. This process has been led by the COVID Human Genetic Effort (CHGE, www.covidhge.com) and has identified a range of variants in immune genes that carry an extremely high relative risk of severe disease (e.g. 50-fold). These single gene pathogenic variants explain most if not all of the individual risk in ~ 3–5% of patients and have effectively unmasked a previously undiagnosed primary immunodeficiency (PID) in these individuals.[13–17] Additionally, the CHGE and others have discovered that a further *c.* 10% of cases of severe COVID-19[13] (*c.* 20% in the elderly[16]) results from another type of previously asymptomatic PID associated with anti-cytokine autoantibodies, which may explain 20% of all COVID-19 deaths.[16]

This review will introduce the concepts of rare defects in immune genes leading to an infectious predisposition and specifically COVID-19, which are most correctly referred to as 'inborn errors of immunity' (IEI), and the phenocopies of those diseases caused by anti-cytokine autoantibodies. For ease of understanding, we will use the acronym IEI to refer to genetic entities, whereas when discussing the combination of the two groups, we will preference the term PID.[18]

INBORN ERRORS OF IMMUNITY

Inborn errors of immunity are rare germline defects in single genes that predispose an individual to a severe – and often fatal – immune disease, such as recurrent or opportunistic infection, autoimmunity, autoinflammation, allergy or even malignancy. There are currently more than 450 different IEI,[19,20] which vary widely in their presentations. Among those IEI which predispose to infection, many of the better known entities involve a broad vulnerability to different organisms. These include defects of adaptive immunity through disrupted development of B cells or T cells in X-linked agammaglobulinaemia (XLA) or severe combined immunodeficiency (SCID), respectively, or loss of innate immune cell function, as occurs in neutrophils in chronic granulomatous disease (CGD).[19,20] There are also many IEI where rather than complete loss of an entire cell function, there is dysfunction of a molecular pathway which may have evolved to mediate host defence against a subgroup of organisms. In these instances, there may be a narrow predisposition to one or a few infectious agents. Examples of the latter include genetic defects in the complement pathway that predispose to recurrent Neisseria disease,[21] defects of the IFNγ/IL-12 pathways that predispose to invasive infection with low pathogenicity non-tuberculous mycobacteria

(NTM)[19,20] or defects in IL-17-mediated immunity resulting in chronic mucocutaneous fungal infections.[22,23] It has even been suggested that many or most humans may harbour a susceptibility to one or more of the vast array of microbes to which we may be exposed.[24]

Inborn errors of immunity that predispose specifically to severe viral infection – including RNA viruses such as SARS-CoV-2 – are also well described. Defects have been identified in genes that either encode for pattern recognition receptors that bind viral RNA within cytoplasmic endosomes (e.g. *TLR3* which binds double-stranded RNA, dsRNA) or are important for molecular pathways that generate an innate antiviral state in surrounding tissues following infection (e.g. *IRF3*, *IRF7*, *IFNAR1*, *IFNAR2*, *STAT2*, *IFIH1*). Mechanistically, binding of intracellular dsRNAs to Toll-like receptor 3 (TLR3) elicits a cascade leading to the production and release of type I IFNs, which in turn act on other local cells to activate antiviral IFN-stimulated genes (ISGs; Figure 1). Defects in the TLR3/type I IFN/ISG pathway have previously been associated with severe viral infections, including herpes simplex encephalitis,[25] influenza pneumonitis,[26,27] respiratory syncytial viruses and rhinoviruses,[28] and even with attenuated live vaccine-strain viruses such as measles/mumps/rubella or yellow fever.[29] Prior to the COVID-19 pandemic, 13 genes in the TLR3/type I IFN pathway had been associated with a single gene predisposition to viral infection.[25–27,29–36] Based on the observations that (1) the innate response to SARS-CoV-2 involved the release of type I IFN cytokines from infected lung epithelia, monocytes and dendritic cells,[37] (2) SARS-CoV-2 genome encodes a viral antagonist of human type 1 IFN[38] and (3) SARS-CoV-2 produces dsRNA species early during infection,[39] there were early suspicions that this pathway might be compromised in individuals with severe COVID-19.[40]

PRE-EXISTING IEI AND COVID-19

At the commencement of the pandemic, there was concern that many individuals with an existing IEI would be at risk of severe disease. However, and perhaps surprisingly, when taken as an entire group, cohorts of PID patients may have a rate of severe COVID-19 not greatly different from the general population.[41] This includes patients with combined immunodeficiencies who might have been expected to have difficulties controlling SARS-CoV-2 infection.[42] Where patients have had a severe or even fatal outcome, they have usually had the same comorbidities – lung disease, heart disease, obesity, co-infection – that were found to predispose to severe COVID-19 in the general population.[42] This includes patients with complex syndromes that include a degree of immunodeficiency, such as Down syndrome (DS) where children are at risk of more severe presentations, but with relatively low mortality in line with other paediatric patients,[43] and with adult DS patients appearing to demonstrate increased mortality.[44] This subject of pre-existing IEI and COVID-19 is well summarised in a recent review[45] which collated details of over 600 reported cases of COVID-19 in IEI and found that the overall impact of disease was proportional to the general population, but that the age distribution was younger, and the rate of admission to ICU notably higher.[45] There was also little difference between subtypes of IEI, including antibody deficiency, combined immunodeficiency, phagocyte defects or innate immune defects, and severity of disease following SARS-CoV-2 infection, with the single exception of the disease autoimmune polyendocrinopathy, candidiasis and ectodermal dysplasia (APECED) also known as autoimmune polyglandular syndrome type I (APS-1),[46] which we will discuss in detail later.

Caveats to these data about the outcomes of the general cohort of IEI include that any infection with SARS-CoV-2 in IEI patients may be less likely than in the general population, due to more diligent social distancing.[47] Also, the case fatality rate (CFR) has not been uniform across regions or countries ranging from 0% in Israel[41] to 20% in Mexico[48] and 42% in Iran,[49] potentially reflecting differences in the composition of cases or the standard of healthcare provision. A large Italian cohort derived from 21 centres may best represent the outcomes in a developed-world healthcare setting, with the CFR in IEIs being 3.81%, comparing very reasonably to a CFR of 3.28% in the general Italian population.[47]

PREVIOUSLY UNDIAGNOSED INBORN ERRORS OF TYPE I INTERFERON IMMUNITY IN COVID-19

To investigate the presence of rare variation underlying severe COVID-19, the CHGE (www.covidhge.com) was formed, comprising clinical teams from around the world. The group

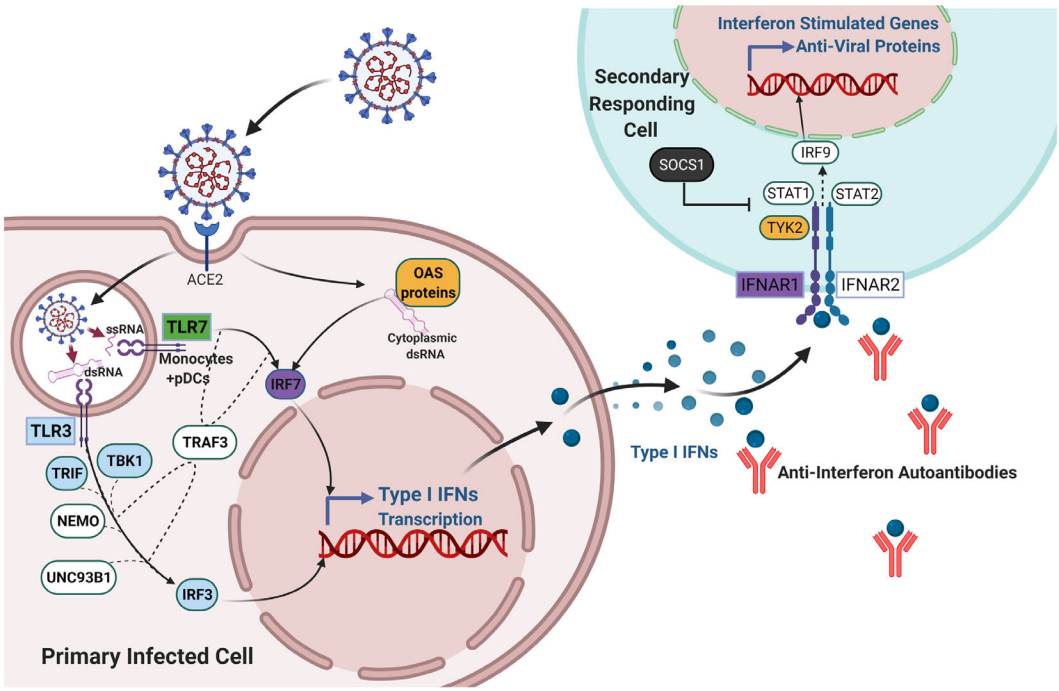

Figure 1. Genes and autoantibodies impacting type I interferon immunity, associated with severe COVID-19. Loss of function primary immunodeficiency (PID) gene defects in patients with severe COVID-19, inherited in a pattern that was known to be associated with risk of viral disease prior to the pandemic,[14] are marked in purple if they are autosomal recessive and blue if they are autosomal dominant. Those genes presented in white have not yet been identified in the group of severe COVID-19 patients in a pre-pandemic inheritance pattern.[14] TLR7 highlighted in green is a novel PID gene identified in the context of COVID-19.[15,53–55] Genes/proteins highlighted in gold were identified as associated with severe COVID-19 from GWAS studies, but with a low relative risk would not yet be considered to be PIDs in this context.[10] The interaction of SARS-CoV-2 viral RNA species with TLR3, TLR7 or OAS proteins leads to the transcription and secretion of type I interferon cytokines which act through the IFN receptor on other cells to induce an antiviral state. This signal is blocked by anti-interferon autoantibodies impeding the antiviral response and resulting in failure of virus control.[13,16,46,59,67,69,75,103] In contrast, the signal through IFNAR may be amplified in individuals with heterozygous deficiency of the regulatory protein SOCS1,[87] leading to excessive type I IFN signalling, and this has been reported in the post-COVID-19 inflammatory syndrome (MIS-C).[85]

recruited 987 patients with proven life-threatening COVID-19, two-thirds of whom were under 65 years of age, along with 663 asymptomatic or pauci-symptomatic individuals with proven COVID-19, and 1227 uninfected healthy controls.[13,14] In the first study, Zhang *et al.*[14] performed whole exome or whole genome sequencing (WGS) on severe COVID-19 patients and mild or asymptomatic SARS-CoV-2-infected individuals, with targeted analysis of the 13 known disease-associated TLR3/type I IFN genes (*TLR3*, *IRF3*, *IRF7*, *IRF9*, *TBK1*, *TICAM1 (TRIF)*, *UNC93B1*, *IFNAR1*, *IFNAR2, TRAF3, STAT1, STAT2 and IKBKG/NEMO*; Figure 1). The group of patients who were severely affected was found to have a higher number of rare genetic variants (minor allele frequency < 0.001, or less than 1:1000 alleles in the healthy population), predicted to be loss of function (pLOF; Figure 1), than did minimally affected COVID-19 patients [odds ratio (OR) = 8.28; 95% confidence interval (CI) = 1.04–65.64].[14] This included two patients with biallelic LOF mutations in each of *IRF7* and *IFNAR1*,[14] which would be expected to predispose to severe viral infection with complete or near-complete penetrance,[27,29] and eleven individuals carrying heterozygous LOF variants in *TLR3, TICAM1, TBK1* and *IRF3*, which have been associated with heterozygous predisposition to infection with other viruses prior to the pandemic.[26,32,33] In fact, there was only a single heterozygous pLOF variant found in a single patient in the asymptomatic/mild group.[14] The team then went through a complex process of validating each variant, by creating cell lines transfected with plasmids containing each of 118 different variants identified from WGS, and using an array of molecular assays to assess pathway

function. They demonstrated 24 true LOF genetic variants in eight genes – *TLR3*, *IRF3*, *IRF7*, *TBK1*, *TICAM1*, *UNC93B1*, *IFNAR1* and *IFNAR2* – in 23 individuals with life-threatening COVID-19, showing decreased function through the TLR3/IFN/ISG pathway, and increased *in vitro* growth of SARS-CoV-2.[14] Overall, these rare LOF variants were calculated to account for predisposition to severe COVID-19 in 3.5% of the entire cohort SARS-CoV-2-infected individuals.[14]

More recently, findings from another group queried the relationship between genetic defects in the TLR3/type I IFN pathway and severe COVID-19 at a population statistical level[50] Thus, there remains an open debate as to what proportion of severe COVID-19 results from defects in this pathway.[17,51] The two studies were very different in their aims and the constitution of the cohorts. For instance, the second study by Povysil *et al*.[50] not including mild or asymptomatic COVID-19-positive controls, while the composition of the CHGE including specialists in the field of inborn errors, might have resulted in an unintentional bias towards the inclusion of cases with features of possible single gene inheritance (e.g. familial occurrence or consanguinity).[14] However, irrespective of the size of the effect, there can be little doubt that patients exist with undiagnosed genetic defects in TLR3/type I IFN pathway, and these patients are already benefitting from being identified.[52]

Additionally, the CHGE and others have now also reported LOF variants in another IFN-related gene – *TLR7* – associated with severe COVID-19.[15,53,54] Similar to *TLR3*, *TLR7* encodes an endosomal receptor for RNAs, but is targeted by the native single-stranded RNA (ssRNA) and has a different cellular distribution to TLR3, being expressed by B cells and certain myeloid-lineage cells, including plasmacytoid dendritic cells, which produce copious amounts of type I IFNs[37] (Figure 1). Defects in this X-linked gene, which had not been identified as causing a PID before the pandemic, have been estimated to cause an additional 1–2% of severe cases in men, but with incomplete penetrance.[15,53–55]

AUTOANTIBODY-MEDIATED PHENOCOPIES OF INBORN ERRORS OF IMMUNITY

For many years, it has been recognised that groups of HIV-negative patients may present in adult life with what might otherwise be considered as AIDS-defining opportunistic infections. An example is a group of predominately female patients living in or descending from parts of South-East Asia, presenting with invasive NTM infection, or less commonly other exotic infections including Histoplasmosis and Cryptococcosis.[56] These individuals do not possess genetic defects in the IFNγ pathway, but rather produce autoantibodies against IFNγ or IL-12 itself, thereby interrupting this pathway and the signals that innate and adaptive immune cells provide to monocytes that allow them to clear infection.[56,57] Other examples of anti-cytokine antibodies predisposing to infection include the following: anti-IL-6 causing recurrent staphylococcal infection,[58] a single report of anti-type I IFN autoantibody-associated chickenpox[59] and a range of anti-cytokine antibodies to IL-12, IL-17, IL-1 and type I interferons in patients with thymic neoplasia.[60]

One of the most informative but rare examples of infectious diseases associated with anti-cytokine autoantibodies comes from the IEI due to inactivating mutations in *AIRE* resulting in APECED, which – consistent with the role of AIRE in self-tolerance – is associated with a powerful predisposition to autoimmunity.[61] Mucosal candidiasis in these patients is attributed to neutralising autoantibodies that block the function of IL-17 and IL-22.[62,63] Strikingly, it has been well established that autoantibodies against type I IFNs were almost ubiquitous in this disease,[64] and recently, these antibodies have been associated with susceptibility to severe herpesvirus infections.[65] Thus, when APECED patients began to be identified with severe COVID-19,[13,66] including 86% of infected patients requiring hospitalisation in one study,[46] one inference was that predisposition to life-threatening SARS-CoV-2 infection might be autoantibody mediated and that the candidate pathogenic autoantibodies might target type I IFNs.

AUTOANTIBODIES TO TYPE I INTERFERONS IN COVID-19

The same groups of relatively younger COVID-19 patients who underwent WGS by the CHGE were subsequently assessed for the presence of autoantibodies to type I IFNs (IFN-α, IFN-β and IFN-ω).[13] A total of 101/987 (10.2%) of severe COVID-19 patients were found to have

autoantibodies against type I IFNs, versus 0/663 (0%) of those with minimal disease.[13] These autoantibodies are extremely effective at neutralising type I IFN cytokines, thereby facilitating SARS-CoV-2 infection of cell lines *in vitro*, appearing more powerful in this respect than a monoclonal antibody designed for exactly that purpose.[13] While patients with COVID-19 generally demonstrate low levels of IFN-stimulatory genes, this has been found to be particularly evident in dendritic cells isolated from individuals with critical disease who have autoantibodies against type I IFNs.[67] These patients were on average, older than the median age of the cohort,[13] while 95/101 (94%) were male.[13] More recently, the CHGE reported on these autoantibodies in a cohort of older patients, demonstrating an increasing prevalence associated with age (specifically against IFN-α and IFN-ω) and disease severity, rising to 21% of severe cases in $>$ 80 year olds, and about 20% of fatal COVID-19.[16] The increasing prevalence of autoantibodies in older patients with severe disease mirrors an increase in these autoantibodies in the healthy uninfected population, being present in[68]approximately 4% of healthy individuals aged $>$ 70 years old.[16] These findings are now being reproduced by other investigators in other cohorts.[5,67–71]

IMPLICATIONS OF RARE DEFECTS IN TYPE I INTERFERONS FOR THE TREATMENT OF SEVERE COVID-19

Moving forward, the identification of PIDs underlying severe COVID-19 has significant implications for therapy. Patients with genetic defects that cripple production of type I IFNs, but have intact functioning IFNαR1/IFNαR2 heterodimer, may benefit from cytokine supplementation with exogenous IFN-α [52] or IFN-β (may even work for patients with autoantibodies),[67] which are approved for the treatment of hepatitis B,[72] hepatitis C[73] and multiple sclerosis.[74] Patients with autoantibodies against type I IFNs may also be responsive to removal of these antibodies by plasma exchange,[75] and this will include many patients with APECED who have an exceptionally high rate of severe COVID-19 due to these autoantibodies.[46] Additionally, the presence of high titre autoantibodies in plasma of a low proportion of patients who have recovered from COVID-19 may explain why convalescent plasma is a less effective treatment for COVID-19 than might otherwise have been expected.[76]

WHERE TO LOOK FOR OTHER RARE IMMUNE DEFECTS IMPACTING COVID-19 SEVERITY

Further PIDs underlying severe COVID-19 may well also be associated with the type I IFN response, which has been found to be defective in most patients with or without autoantibodies.[67] The viral sensing genes *OAS1/2/3* and the signalling molecule *TYK2* which are integral components of the type I IFN signalling pathway[77] have been identified as susceptibility loci in GWAS.[10] Additionally, direct sequencing of two genes coding for the interferon lambda cytokine, IFNL3 and IFNL4, has been associated with severe disease.[78] Data from GWAS are now pointing towards monocyte and macrophage cell homing molecules such as chemokines and chemokine receptors, as potentially increasing susceptibility to severe disease.[79,80] However, further entities may not be identified quickly, given that prior to the pandemic, it was difficult to identify more than 50% of gene defects underlying presumed monogenic PIDs.[81] Low identification rates can reflect pathogenic variants in non-coding regions of known genes that require different sequencing technologies to identify them,[82] or variants in novel genes which, because of their rarity, do not give a statistical signal even within large populations, and where the process of proving pathogenesis through molecular modelling may take years.[83]

There are two main strategies being employed to identify additional genes where rare variation may underlie undiagnosed PIDs in COVID-19 patients. The first is the example of the CGHE, comparing the complete genomic sequence of individuals with severe disease versus those with mild or asymptomatic infection. This optimal technique has the capacity to identify variants in known disease-associated genes,[14] but also novel genes such as *TLR7*.[54]

The second strategy is to focus on sequencing candidate genetic regions identified by GWAS. This approach can be successful because, even though the low relative risk of variants associated with GWAS informs little about why a given patient suffered bad disease,[84] the signal from the GWAS may actually reflect much rarer variants

carrying a far greater risk and relevance, travelling in linkage disequilibrium with the common variant identified in the GWAS. This strategy has revealed rare variants in *CCR5* in severe COVID-19 patients,[80] although further molecular validation of this latter association is needed before it can be added to the list of COVID-19-predisposing gene defects.

Finally, as mentioned at the outset, not all of the consequences of COVID-19 relate to viral persistence, with some directly attributable to inflammation, in particular multisystem inflammatory syndrome in children (MIS-C).[85] It is possible that this entity may also have a genetic underpinning, with cases of MIS-C now reported as associated with LOF variants in the regulator gene *SOCS1*,[85] which was itself only recently identified as an IEI.[86] Interestingly, SOCS1 functions to inhibit JAK/STAT signalling,[87] including blocking TYK2-mediated signalling through the type I interferon receptor,[88] suggesting that excessive type I IFN activity may play a role in pathogenesis of MIS-C (Figure 1).

A DIFFERENT TYPE OF PANDEMIC PREDISPOSITION?

The last great pandemic to impact humanity was different from COVID-19, in that humans as a species are mostly susceptible to HIV. On the one hand, had we been unable to limit the spread of HIV, that epidemic would have exerted a huge pressure on our species, selecting exclusively for those rare individuals who by serendipity are resistant to the virus, such as those who carry the *CCR5*-Δ32 variant.[89] On the other hand, with COVID-19 as with pandemic influenza, the majority of the population do not suffer major deleterious infection, with only a small percentage being more severely impacted. For influenza, individual susceptibility is only recently beginning to be understood[26,27,90]; however, we now have an explanation for susceptibility to COVID-19 in 15–20% of individuals who suffer severe disease, with the virus seeming less likely to affect the average humans, or even humans with common variation, but rather those with rare, highly deleterious, genetic or immune variation.[13–15,55] In effect, we as a species appear to have reasonable innate resistance to the effects of SARS-CoV-2, presumably because of previously having had our genomes put under pressure by similar viruses, resulting in the evolution of a protective type I IFN response among other features of innate immunity. Exceptions to this are individuals with anti-cytokine autoantibodies, and those with deleterious rare germline variants, who in the brutal language of evolutionary biology, are being put under the pressure of 'purifying selection'.[91]

The finding of undiagnosed PIDs underlying severe COVID-19 was not arrived at in isolation, but was made possible because of an accumulated knowledge gained from decades of studying rare IEI. That work has included slowly unpicking the genetics of predisposition to a range of other infections including HSV encephalitis,[25] influenza,[26,27] candida,[92–94] EBV[95,96] and NTM.[97–100] These studies have rarely involved large cohorts, probably because, by contrast to COVID-19, for rare variants that predispose to these organisms, humans have been experiencing a purifying pressure for many generations.[101] Nonetheless, over time IEI are beginning to account for a very significant percentage of people with globally important diseases, including the recent identification of the P1104A variant in *TYK2* underlying tuberculosis in 1% of cases in people of European ancestry.[102] It is therefore unsurprising that members of the CHGE have been passionate advocates for the value of well-supported evidence deriving from humans with such genetic predispositions, even when those data come from a single individual.[83]

CONCLUSION

Rare genetic and immune variation resulting in previously undiagnosed PID has been identified as the cause of COVID-19 in *c.* 15% of individuals who suffer severe disease,[13–15] increasing to *c.* 20% in the elderly, and in fatal disease.[16] Given the slow process of proving these associations, the extent of this pathogenic variation is likely to increase with time and is already the most significant scientific contribution thus far to understanding what makes one person more susceptible to SARS-CoV-2 than another. It highlights a group of apparently healthy individuals with defective immunity, who constitute a greater priority for the generation of protection through social distancing and vaccination, as well as potentially benefitting from targeted therapies.

These findings, which have so far largely derived from the work of the CHGE but are now

being verified by other groups, may change the way we think about infectious predisposition. It seems that other than for completely novel infections such as HIV where there is a species-level vulnerability, the study of rare or novel defects constituting a high level of infectious risk in an individual or individuals who possess them, may prove to be of more benefit for identifying factors that really impact predisposition to severe infection within populations, than averaging vastly smaller predispositions across large groups. It seems that with regard to fighting infection, humans are not so much a whole, as the sum of our parts.

AUTHOR CONTRIBUTIONS

Paul Edgar Gray: Conceptualization; Writing – original draft; Writing – review & editing. **Adam W Bartlett:** Conceptualization; Writing – review & editing. **Stuart G Tangye:** Conceptualization; Writing – review & editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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