Following infection with SARS-CoV-2, individuals with Down syndrome (DS) present with higher rates of COVID-19-related complications, including acute respiratory distress syndrome (ARDS). Both children and adults with DS have been shown to require longer periods of hospitalization and mechanical ventilation in response to SARS-CoV-2 infection, and among patients who were hospitalized with COVID-19, 83.3% of patients with DS progressed to sepsis compared with 46.7% of patients without DS. Moreover, following hospitalization with COVID-19, 25% of patients with DS died compared with only 6.7% of patients who did not have DS. These and other datasets show that individuals with DS are more vulnerable to the downstream effects of SARS-CoV-2 infection. Below, we highlight the importance of understanding the impact of DS genetics on the immune pathways associated with this poor prognosis.

Factors influencing COVID-19 severity

DS is caused by partial or complete trisomy of human chromosome 21 (HSA21), which predisposes affected individuals to the development of a heterogeneous range of comorbidities. Several components of the immune system are affected as HSA21 contains a number of genes with key roles in innate and adaptive immunity, including genes encoding four of the six interferon receptor (IFNR) subunits, namely: IFNAR1, IFNAR2, IFNGR2 and IL-10 receptor 2 (IL-10R2), which also serves as the type III interferon receptor. This leads to higher levels of expression of these IFNRs in individuals with DS, which is also accompanied by higher plasma concentrations of type I interferons. Consequently, immune cells from individuals with DS are three to seven times more responsive to interferon-mediated signalling. Heightened engagement of interferons with their receptors triggers innate immune antiviral pathways that should lead to efficient control of viral infections. However, individuals with DS who become infected with SARS-CoV-2 show a more aggressive course of disease, suggesting that other immune pathways are impacted by the dysregulation of interferons prior to infection, probably leading to the immune dysfunction and comorbidities observed in these subjects.

The engagement of IFNAR1 and IFNAR2 with their ligands leads to the activation of JAK–STAT signalling pathways and the formation of interferon-regulatory factor (IRF) complexes, which translocate to the nucleus to initiate gene transcription. Total and phosphorylated STAT1 levels are constitutively higher in both unstimulated and interferon-stimulated monocytes from individuals with DS. Consequently, monocytes from individuals with DS express higher levels of interferon-stimulated genes (ISGs) than monocytes from healthy controls. Such chronic immune activation has been observed in chronic viral infections, such as HIV, and can result in an overall state of immune dysfunction. The constitutive upregulation of IFNRs and the consequent increase in their downstream signalling can result in an interferonopathy, which may impair immune responses to infections, possibly owing to the upregulation of several co-inhibitory receptors, such as PD1, TIM3 and LAG3, on T cells. These receptors dampen adaptive immune responses and lead to immune senescence and exhaustion. Pro-inflammatory cytokines and chemokines that act downstream of interferon-induced signalling, such as IL-6, IL-22, CCL2, TNF and VEGFA, are also upregulated in the plasma of individuals with DS. This immune dysregulation is also associated with increased frequencies of natural killer cells and terminally differentiated CD8+ T cells, and with decreased frequencies of B cells. Such chronic immune dysregulation can also lead to higher rates of autoimmune disorders and/or immunosuppression, contributing to the comorbidities observed in DS.

Finally, individuals with DS may be more susceptible to infection with SARS-CoV-2 owing to altered expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), which are the host proteins that facilitate virus entry. Heightened engagement of the interferon pathway leads to elevated expression of ACE2 in lung epithelial cells, and as
TMPRSS2 is encoded on chromosome 21 (REF\(^3\)), individuals with DS show triplication of TMPRSS2 expression. These changes in the SARS-CoV-2 entry machinery may support productive infection in individuals with DS.

**Therapies and vaccination**

While antibody responses to vaccination are generally induced in individuals with DS\(^1\), some studies have shown that individuals with DS show lower antibody titres and avidity compared with individuals without DS. These events were associated with B cell intrinsic defects, such as decreased total memory and class-switched memory B cells, with defective T cell help, or with defects in both the B cell and T cell responses\(^8\). A transcriptomics-based pre-vaccination predictor of responses to the Hepatitis B vaccine has shown that higher levels of inflammation and increased frequencies of pro-inflammatory innate immune cells correlated with weaker responses to vaccination\(^7\). Therefore, the increased baseline levels of inflammation seen in individuals with DS might contribute to poorer longevity of the responses to COVID-19 vaccines. Several studies evaluating vaccine responses and longevity in children and adults with DS are ongoing worldwide, including studies by the trisomy 21 research society (T21RS) taskforce. In this context, administration of baricitinib could provide a promising intervention, as pre-treatment with this JAK1/JAK2 inhibitor could decrease baseline inflammation in individuals with DS, restoring functional immune homeostasis and the ability to mount a durable antibody response to vaccines.

Baricitinib could also be a useful therapy for treating COVID-19 in individuals with DS as it blocks signalling downstream of IFNRs, which as discussed above, contributes to the hyperinflammation seen in these individuals. This drug has already received emergency use authorization for patients who are hospitalized with COVID-19 who require supplemental oxygen\(^6\), but studies on its efficacy in individuals with DS are still lacking.

**Long COVID?**

Although the mechanisms of long COVID-19 development are incompletely understood, many of the factors that are reported to increase the risk of long COVID (such as an increased hospitalization time, a higher number of comorbidities, increased symptoms during the first week of illness and the presence of autoantibodies) are commonly seen in those with DS. As such, the development of long COVID is being evaluated in individuals with DS. However, accurately diagnosing long COVID in individuals with DS can be challenging for several reasons. For instance, there are difficulties in objectively evaluating long COVID symptoms (for example, brain ‘fog’ and fatigue) in individuals with DS, there may be a lack of complaints or even the lack of perception of those complaints by the caregivers. As such, there are still no reports in the literature on long COVID and DS, but the fact that individuals with DS present most of the factors that predispose to long COVID development suggests this is an important area for future study.

**Conclusion**

Genetic, molecular and cellular factors prevalent in individuals with DS may underlie their worse prognosis following SARS-CoV-2 infection. The dysregulation of interferon pathways due to the trisomy of chromosome 21, along with the triplication of the TMPRSS2 gene, possibly boosting viral entry, may lead to T cell dysfunction and a lack of proper B cell responses. These dysfunctional immune responses — coupled with an increased rate of comorbidities such as cardiovascular disease, diabetes, obesity and secondary infections, which are all known to be associated with poorer COVID-19 outcomes — result in an even poorer prognosis in individuals with DS, including longer hospitalization and higher mortality rates. The interferon pathway has been targeted in other chronic viral infections and in SARS-CoV-2 with limited success, possibly owing to the timing of these interventions, as these pathways are required to fight viral infections. However, the targeting of this pathway in individuals infected with SARS-CoV-2 with DS could result in the restoration of immune homeostasis and in a less inflammatory immune environment leading to beneficial outcomes. It will be interesting to explore whether such interventions could help us to care for individuals with DS who become infected with SARS-CoV-2.

1. Malie, L. et al. Individuals with Down syndrome hospitalized with COVID-19 have more severe disease. *Genet. Med.* 23, 576–580 (2021).
2. Kong, X. F. et al. Three copies of four interferon receptor genes underlie a mild type I interferonopathy in Down syndrome. *J. Clin. Immunol.* 40, 807–819 (2020).
3. Sumida, T. S. et al. Type I interferon transcriptional network regulates expression of coinnhibitory receptors in human T cells. *Nat. Immunol.* 23, 632–642 (2022).
4. Ferrari, M. et al. Autoimmunity and genetic syndromes: a focus on Down syndrome. *Genes (Basel)* 12, 268 (2021).
5. Ziegler, C. G. K. et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 181, 1016–1035 (2020).
6. De Toma, I. et al. Network analysis of Down syndrome and SARS-CoV-2 identifies risk and protective factors for COVID-19. *Sci. Rep.* 11, 1930 (2021).
7. Valentin, D. et al. Safety and long-term immunogenicity of BNT162b2 vaccine in individuals with Down syndrome. *J. Clin. Med.* 11, 694 (2022).
8. Joshi, A. et al. Immune evaluation and vaccine responses in Down syndrome: evidence of immunodeficiency? *Vaccine* 29, 5404–5406 (2011).
9. Fourati, S. et al. Pre-vaccination inflammation and B-cell signalling predict age-related hypersresponse to hepatitis B vaccination. *Nat. Commun.* 7, 10356 (2016).
10. RECOVERY Collaborative Group, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. Preprint at medRxiv https://doi.org/10.1101/2022.03.02.22271625 (2022).