Research Square

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Genetic architecture of SARS-CoV-2 -triggered cytokine responses in humans

Nick Keur
Radboud University Medical Center
Nicholas A Sumpter
Radboud University Medical Center
Hadewych ter Hofstede
Radboud University Medical Center
Helga Dijkstra
Radboud University Medical Center
Heidi Lemmers
Radboud University Medical Center
Manon Reesink
Radboud University Medical Center
Collins Boahen
Radboud University Medical Center
Martin Jaeger
Radboud University Medical Center
Leo A B Joosten
Radboud University Medical Center
Mihai G Netea
Radboud University Medical Center
Vinod Kumar
v.kumar@radboudumc.nl

Radboud University Medical Center

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Abstract

Background

Host genetic variation shapes immune responses to different pathogens including viruses, but many regulatory effects are context-dependent and remain undetected in baseline analyses. Excessive induction of inflammation is an important mechanism in the pathogenesis of viral infections such as those induced by SARS-CoV-2 viruses. Understanding the regulation of proinflammatory cytokine responses in viral diseases is crucial for designing novel immunotherapies.

Methods

We performed cytokine quantitative trait locus (cQTL) mapping in peripheral blood mononuclear cells (PBMCs) in a cohort of 126 healthy individuals following 24 hours *ex vivo* stimulation with SARS-CoV-2 and additional viral, bacterial, and fungal stimuli. Production capacity of IL-6, IL-1β, IL-1Ra, and IFN-α was quantified and integrated with correlation analyses, hierarchical clustering, functional genomic annotation, and intersection with large COVID-19 genome-wide association studies.

Results

We identified a genome-wide significant IL-6 cQTL for SARS-CoV-2 at the TLR1/6/10 locus, with directionally consistent effects across multiple cytokines and innate immune stimuli, indicating a general role in inflammatory regulation. Most variants with cQTLs effects were cytokine-specific; however, IL-6 and IL-1β shared regulatory variants that clustered by viral stimulus. A suggestive shared locus upstream of the transcription factor *AFF3* showed coordinated effects on IL-6 and IL-1β production and overlapped immune-cell regulatory elements and autoimmune disease–associated variation. Overlap with COVID-19 GWAS loci was limited, with only one locus showing suggestive colocalization.

Conclusions

Viral stimulation reveals context-dependent genetic regulation of cytokine responses, identifying immune regulatory loci with potential relevance beyond COVID-19. Functional genomics under defined immune challenges complement disease-focused genetic studies by providing functional context for interpreting mechanisms underlying human immune variation.

Introduction

Clinical manifestations of SARS-CoV-2 infection vary widely, ranging from asymptomatic infection to severe respiratory failure accompanied by systemic inflammation. Host genetic variation has emerged as an important determinant of this heterogeneity, with large genome-wide association studies (GWAS),

such as the COVID-19 Host Genetics Initiative (HGI), identifying multiple loci associated with susceptibility and severity of the disease [1]. However, for most of these loci, the molecular mechanisms linking genetic variation to immune dysfunction remain poorly understood.

A major challenge in interpreting GWAS findings is that the majority of associated variants reside in non-coding regions and likely act through regulatory mechanisms that are highly context dependent. In immune cells, many genetic regulatory effects become detectable only after cellular activation and may depend critically on the nature and duration of the triggering stimulus [2, 3]. Therefore, baseline expression studies often fail to capture regulatory variation that becomes relevant during active infection.

Pathogen-stimulated functional genomics offers a powerful strategy to reveal these context-dependent genetic effects. Previous studies have demonstrated that cytokine production is strongly heritable and frequently governed by stimulus-specific regulatory architecture [4, 5]. Such regulatory programs often converge on core innate immune pathways, including Toll-like receptor (TLR) signaling and NF-κB–mediated inflammatory responses. Importantly, these regulatory mechanisms may influence not only infectious disease outcomes but also the development of inflammatory and autoimmune diseases, in which viral triggers are frequently involved [3, 6].

Despite the central role of inflammatory cytokines in COVID-19 pathogenesis, the genetic determinants of cytokine responses following SARS-CoV-2 stimulation remain incompletely characterized. In particular, it is unclear to what extent virus-induced cytokine QTLs represent SARS-CoV-2-specific effects or broader regulatory mechanisms that govern innate immune responses.

In this study, we systematically investigated the genetic architecture of cytokine responses following pathogen stimulations in a cohort of healthy individuals. By quantifying production of IL-6, IL-1β, IL-1Ra, and IFN-α after in vitro stimulation with SARS-CoV-2 and additional microbial ligands, we mapped cytokine quantitative trait loci (cQTLs) and characterized their stimulus specificity. Integration with functional genomic annotations and large COVID-19 GWAS datasets allowed us to identify regulatory loci shaping inflammatory responses and to assess their relevance for infectious and immune-mediated diseases.

Methods

Data collection

A total of 134 healthy participants were included as part of the Human Functional Genomics Project in October 2020 [7]. For all participants, peripheral blood mononuclear cells (PBMCs) were isolated from EDTA blood tubes described earlier [8].

Stimulation assays and cytokine measurement

PBMCs were stimulated for 24h with a total of 7 stimuli: RPMI (control), SARS-CoV-2, Influenza, LPS, *Candida albicans*, *Borrelia burgdorferi*, and Imiquimod. and SARS-CoV-2 Wuhan were used at a working concentration of 11.9 x 10^3 per mL. Influenza virus strain pH1N1 A/Netherlands/602/09 was used as described previously [4]. LPS (*E. coli* serotype 055:B5), a TLR4 ligand, was purchased from Sigma-Aldrich (St. Louis) and an extra purification step was performed as described previously [9]. Heat-killed *C. albicans* blastoconidia (strain ATCC MYA-3573, UC 820) in a concentration of 10^6 CFU/mL were used throughout this study. *B. burgdorferi*, ATCC strain 35210, was cultured at 33°C in Barbour-Stoenner-Kelley (BSK)-H medium (Sigma-Aldrich) supplemented with 6% rabbit serum. Spirochetes were grown to late-logarithmic phase and examined for motility by dark-field microscopy. Organisms were counted using a Petroff-Hauser counting chamber. Bacteria were harvested by centrifugation of the culture at 3000 g for 30 min, washed twice with sterile PBS (pH 7.4), and diluted in the specified medium to the required concentrations of 1 × 10^6 spirochetes per mL. Following stimulation, a total of 5 cytokines were measured using ELISA: IL-6, IL-1β, TNF, IFN-a, and IL-1Ra.

Genotyping and imputation

Genotypes were determined as part of a larger group of 487 individuals. Genotyping was performed in a total of 6 batches using either the Infinium Human CoreExome-24 array, the Illumina Global Screening Array v1, or the Illumina Global Screening Array v3. Quality control was performed within each batch as follows: we first excluded individuals with a mismatch between the genetic sex and reported gender, we then excluded indels and non-autosomal SNPs, we removed any duplicated SNPs or multi-allelic locations, then we excluded SNPs without rs identifiers. Following this, we merged all the genotype batches and performed the following quality control: excluded SNPs with a minor allele count of 0 (non-varying SNPs), excluded SNPs with more than 10% missing data, excluded SNPs that deviated from Hardy-Weinberg equilibrium ($P < 1e-6$), excluded 2 samples with more than 5% missing data, excluded 3 samples that were outliers for heterozygosity, excluded 3 duplicate samples that were mismatched between batches, and finally excluded 8 samples with non-European ancestry. Imputation was performed using the TOPMed imputation server [10]. Following imputation, quality control was again performed as follows: excluded SNPs with a minor allele frequency of less than 1%, excluded SNPs without rs identifiers, excluded non-biallelic SNPs, and excluded a further 3 samples that were genetic outliers. Following all steps, we retained a total of 8,275,748 SNPs in 460 individuals, including 126 of the 134 participants with cytokine data in 2020.

Cytokine QTL mapping

Cytokine data was first transformed using a rank-based inverse normal transformation. Cytokine QTL mapping was performed using an additive linear regression model implemented in the MatrixEQTL R package with the imputed genotype dosages and adjusted for sex, age, lymphocyte:monocyte ratio, neutrophil %, and stimulation batch. Cytokine-stimulus pairs with more than 25% missing data or more

than 25% of samples at the lower limit of detection were excluded, as were any pairs that did not show normal distributions after transformation. Genome-wide significance was defined as $p < 5 * 10^{-8}$ while the suggestive was defined as $p < 1 * 10^{-5}$.

LD-clumping and identification of independent loci

To identify independent associated loci, we performed LD clumping using PLINK (v1.9). For each cytokine, variants were clumped using a 500 kb window, LD threshold of $r^2 < 0.2$, and minimal statistical significance of $P < 1x10^{-5}$ (--clump_kb = 500, --clump_r2 = 0.2, --clump-p1 = 1e-5). For each clumped locus, we retained the most significant variant within the defined window as the lead variant.

Variant to gene mapping and functional characterization

Prioritized loci were annotated by mapping the lead genetic variants to nearby genes based on genomic proximity and by integrating publicly available functional genomic resources. In order to capture the broader associated signal of these loci, we expanded the lead genetic variants by including variants in high linkage disequilibrium (r2 > 0.9). We systematically annotated prioritized loci with regulatory targets by querying multi-tissue functional genomic databases, including eQTL and pQTL resources from eQTLgen, GTEx, eQTL Catalogue and other publicly available data sets. Variant and genes to trait associations were further evaluated using the Open Targets Genetics Platform. To further evaluate the regulatory context of our variants we used data from ENCODE and RegulomeDB, integrating histone modifications, chromatin accessibility and transcription factors (TF) binding profiles to evaluate whether genetic variants overlapped regulatory elements such as enhancers or promoters. Lastly, disease relevance was explored by integration of loci with signal reported in GWAS catalogue and other large GWAS resources.

Colocalization

To determine shared genetic signals between our cQTL data and COVID-19 GWAS we performed colocalization using the coloc framework implemented in the coloc R package (v6.0.0). Summary statistics for the COVID-19 Host Genetics Initiative (Release 7) were processed and formatted as recommended. We selected and harmonized all common variants in a ± 250kb window around each lead variant to ensure consistent allelic directions, genetic variants with inconsistent allele mappings were removed.

Statistical analysis and visualization

Statistical analyses and data processing were performed using R (v4.1). Pairwise correlations across cytokines were assessed using the spearman correlation coefficients. Moreover, visualization such as the heatmaps are generated using ComplexHeatmap (v2.2), Manhattan plot using topr (v2.0.2) and

genomic regional association plots were generated using locuszoomr (v0.3.1) and locuscomparer (v1.0). Other custom visualizations are generated using ggplot2 (4.0).

Results

Cytokine responses show stimulus- and cytokine-specific correlation

We quantified the secreted concentrations of IL-6, IL-1β, IL-1Ra and IFN-α in healthy individuals (n = 126) following a 24-hour stimulation with SARS-CoV-2 and additional viral, bacterial and fungal stimuli (influenza virus, Imiquimod, LPS, *Candida albicans* and *Borrelia burgdorferi*). To evaluate the extent of overlap across cytokine-stimuli response pairs, we calculated pairwise spearman correlations and performed hierarchical clustering on the significant pairs ($p < 0.05$). The analysis revealed distinct patterns associated by cytokine-stimuli pairs (Figure S1). For IL-1Ra, we observed clusters grouped by cytokine responses rather than by stimulus, suggesting a largely stimulus-independent regulatory architecture. In contrast, IL-1β and IL-6 responses clustered by stimulus, with particularly strong correlations observed following viral stimuli (SARS-CoV-2, influenza virus). Furthermore, while for SARS-CoV-2 stimulation IL-6 and IL-1β were highly correlated ($r = 0.8$), IFN-α responses, showed little to no correlation with these pro-inflammatory cytokines. Because IFN-α was only quantified following SARS-CoV-2 stimulation, it formed a distinct cluster, consistent with activation of a specialized antiviral interferon program. These findings suggest that IL-6 and IL-1β share stimulus-dependent regulatory mechanisms, whereas IL-1Ra is governed by more cytokine-intrinsic control.

TLR1/6/10 variation modulates IL-6 responses to SARS-CoV-2 stimulation

To investigate the effect of host genetic variation in cytokine responses, we performed cytokine-quantitative trait locus (cQTL) mapping across all cytokine-stimulus pairs, adjusting for age, sex, stimulation batch and immune cell composition. We focused primarily on the SARS-CoV-2 stimulation as a viral model to investigate context-dependent regulation. This analysis identified a single genome-wide significant association ($p < 5 \times 10^{-8}$), observed for IL-6 production following SARS-CoV-2 stimulation (Fig. 1A). The lead variant, rs5743604 ($p = 1.6 \times 10^{-9}$), is located within a linkage disequilibrium (LD) block spanning the TLR1, TLR6, and TLR10 genes (Fig. 1B). The regional association analysis confirmed rs5743604 as the lead signal within this locus.

This locus has been repeatedly identified for other cytokine-stimulus pairs, though to our knowledge this is the first time it has been shown for a viral stimulus (ref). To determine whether this locus displayed broader regulatory effects, we examined associations across other cytokine-stimulus pairs using a nominal significance threshold ($p < 0.05$). The rs5743604 locus showed consistent directional effects on IL-6, IL-1Ra, and IL-1β responses following influenza virus and Imiquimod stimulation (Fig. 1C). Genotype-stratified cytokine levels further demonstrated coherent effects across stimuli (Fig. 1D),

suggesting that this locus functions as a general regulator of innate cytokine responses rather than being SARS-CoV2-specific.

Identification of suggestive cQTLs reveals limited cross-cytokine sharing and highlights shared regulation of IL-6 and IL-1β

Beyond the genome-wide significant signal, we identified multiple suggestive cQTLs ($p < 1 \times 10^{-5}$) under SARS-CoV-2 stimulation: 24 for IFN-α, 18 for IL-1β, 22 for IL-1Ra, and 18 for IL-6 (Figures S2-S5). Most loci were specific to a single cytokine, consistent with predominantly cytokine-specific genetic regulation.

To explore shared genetic signals in more detail, we performed LD-based clumping to define independent loci and visualized their effects across all cytokine-stimulus pairs using a signed heatmap (Fig. 2A). This analysis revealed two prominent patterns. First, shared genetic effects were most frequently observed for IL-1β and IL-6. Second, these shared effects were strongest across viral stimuli, particularly SARS-CoV-2 and influenza virus, consistent with the stimulus-dependent clustering observed in the correlation analysis.

A shared IL-6 and IL-1β locus upstream of AFF3 shows context-dependent regulatory effects

Among the shared loci, rs10167279 emerged as a notable independent variant with suggestive associations for both IL-6 and IL-1β following SARS-CoV-2 stimulation ($p < 1 \times 10^{-5}$; Fig. 2B, C). Genotype-stratified analyses consistently demonstrated directional effects of rs10167279 on both IL-6 and IL-1β production across viral stimuli (Fig. 2F). This variant is located within a dense LD block ($r2 > 0.92$, CEU) approximately 40–45 kb upstream of AFF3, a transcription factor with established roles in immune regulation and autoimmune disease susceptibility.

Using rs10167279 and its high-LD proxies ($r^2 > 0.9$) we observed consistent regulatory effects on AFF3 across molecular QTLs. At baseline, rs10167279 acted as a strong whole-blood eQTL (eQTLgen; $p = 1.71 \times 10^{-88}$), while in stimulated settings it displayed context-dependent eQTL effects in multiple immune cell types (IFN-β–stimulated monocytes and TCR-activated $CD4^+$ T cells). Additionally, the same LD-block lies within a regulatory domain with strong DNase accessibility in primary CD14 + monocytes, as well as enhancer-gene connections to AFF3 derived from ENCODE-scE2G models (Fig. 2E). These convergent signals suggest that this LD-block modulates AFF3 regulation across different immune contexts (Fig. 2G).

Interestingly, rs10167279 also resides within the fine-mapped credible set for autoimmune disease signal in the FinnGen cohort (Fig. 2D). Colocalization analysis further supported a shared genetic signal between the FINNGEN signal and both IL-6 (H4 = 0.64) and IL-1b (H4 = 0.5). Together, these findings

support a model in which virus-induced regulatory variation at this locus modulates AFF3 expression, thereby coordinately influencing IL-6 and IL-1β responses.

Limited overlap between SARS-CoV-2 cQTLs and COVID-19 GWAS highlights broader relevance of virus-induced immune regulation

Next, we extracted all independent COVID-19 HGI GWAS risk loci (HGI, EUR, release 7) and intersected these with our SARS-CoV-2-induced cQTLs. This analysis identified a single overlapping region on chromosome 21 associated with IL-1Ra production and COVID-19 susceptibility (Fig. 3A, B). The HGI lead variant (rs12627323) is located within a regulatory region encompassing *LINC00649* and *ATP5PO*. Colocalization analysis provided suggestive evidence for a shared genetic signal between IL-1Ra response and COVID-19 severity at this locus (posterior probability for a shared causal variant, PP.H4 = 0.38; Fig. 3C), although this did not reach strong statistical support. Functional annotation revealed multiple eQTLs and immune-cell–specific regulatory features in this region, suggesting broader immunoregulatory relevance.

Notably, the limited overlap between SARS-CoV-2 cQTLs and COVID-19 GWAS signals indicates that many virus-induced regulatory variants captured in this study are not disease-specific risk loci but instead reflect fundamental mechanisms of immune regulation that may be relevant human pathology.

Discussion

This study demonstrates that viral stimulation reveals context-dependent genetic regulation of inflammatory cytokine responses in human innate immunity. By integrating cQTL mapping with functional genomic annotation and COVID-19 GWAS data, we identify regulatory variants modulating innate immune responses and link pathogen-induced immune programs to broader inflammatory and autoimmune disease biology.

A central finding of this study is the identification of a genome-wide significant IL-6 cQTL within the TLR1/6/10 locus following SARS-CoV-2 stimulation. This locus represents a well-established regulatory hotspot for innate immune signaling and has been repeatedly implicated in variation on cytokine responses to various pathogens [4, 11, 12]. Toll-like receptors (TLRs) are key pathogen recognition receptors that initiate inflammatory signaling upon pathogen detection. Both in vitro and in vivo studies have shown that TLR1, TLR2 and TLR6 can recognize structural components of SARS-CoV-2 [13–15]. Experimental and genetic evidence suggest that TLR1 and TLR6 form functional heterodimers with TLR2, promoting NF-κB–dependent production of pro-inflammatory cytokines such as IL-6 and IL-1β, whereas TLR10 acts as a negative regulator within the TLR family and promotes anti-inflammatory responses, including IL-1Ra production [16]. Because these receptors reside within a single linkage disequilibrium (LD) block, regulatory variants within this locus likely affect the balance between pro- and anti-inflammatory signaling rather than acting on a single gene in isolation.

Importantly, the lead variant at this locus, rs5743604, showed consistent directional effects across multiple cytokine-stimulus pairs, extending the SARS-CoV-2 stimulation to other viral and innate immune challenges. This observation suggests that the TLR1/6/10 locus acts as a general regulator of innate immune responsiveness, rather than a pathogen-specific determinant of SARS-CoV-2 responses. Such pleiotropic regulation is consistent with previous studies demonstrating that genetic variation within innate immune signaling pathways can broadly influence inflammatory capacity. These regulatory variants may therefore contribute to inter-individual differences in immune responsiveness across multiple infectious contexts.

Beyond this genome-wide significant signal, our analysis of suggestive cQTLs revealed that most loci were cytokine-specific, with relatively limited genetic sharing across different cytokines. However, a notable exception was observed for IL-6 and IL-1β, which frequently shared regulatory variants and displayed highly correlated responses across stimuli. These cytokines are both strongly regulated by NF-κB signaling and predominantly produced by activated monocytes and macrophages. The consistent coregulation observed here suggests the existence of shared genetic control of inflammatory cytokine programs. Such coordinated regulation reflects variation in upstream signaling pathways that govern activation of inflammatory transcriptional networks.

Among the shared loci, a suggestive signal upstream of the transcription factor AFF3 emerged as a particularly interesting candidate. The lead variant at this locus showed coordinated effects on IL-6 and IL-1β production following viral stimulation and lies within a dense LD block approximately 40–45 kb upstream of *AFF3* gene. *AFF3* encodes a transcription elongation factor involved in regulation of immune gene expression and has been implicated in multiple autoimmune diseases, including rheumatoid arthritis and Type 1 diabetes [17, 18]. Functional annotation of this locus revealed strong evidence for regulatory activity, including chromatin accessibility in primary monocytes and predicted enhancer–gene interactions linking the variant region to AFF3. Moreover, multiple expression QTL datasets indicate that variants within this LD block regulate AFF3 expression across different immune cell types.

Interestingly, the same region overlaps with a fine-mapped autoimmune susceptibility locus in the FinnGen dataset, and colocalization analysis suggested moderate evidence for a shared genetic signal between autoimmune disease risk and cytokine regulation at this locus. Moreover, an independent multi-tissue TWAS of COVID-19 hospitalization risk (B2) identified AFF3 GReX associations, linking AFF3 to COVID-19 susceptibility [19]. This convergence of cQTL, eQTL, chromatin accessibility, and autoimmune disease associations at this locus highlights how viral immune triggers can reveal regulatory mechanisms that are relevant beyond acute infection.

Integration of our cQTL results with COVID-19 HGI GWAS loci revealed limited overlap between virus-induced cytokine regulatory variants and genetic risk loci for COVID-19 susceptibility or severity. Only a single region on chromosome 21, encompassing ATP5PO and LINC00649, showed suggestive colocalization (PP.H4 = 0.38) between IL-1Ra modulation and COVID-19 GWAS signals. This observation is consistent with other studies, in which a modest overlap was reported between cytokine/immune

QTLs and COVID-19 GWAS signals. [20, 21]. Although the evidence for a shared causal variant was modest, functional annotation of this locus revealed multiple regulatory features in immune cells, indicating potential biological relevance. Nevertheless, the overall limited overlap between SARS-CoV-2 cQTLs and COVID-19 GWAS signals suggests that many variants controlling cytokine production represent general regulators of immune responsiveness rather than primary determinants of disease susceptibility.

This distinction highlights an important conceptual point. Genetic variants that modulate cytokine production capacity may influence disease progression, severity, or treatment response without necessarily conferring large effects on disease risk itself. Such variants may shape the magnitude and quality of inflammatory responses once infection has occurred. In this context, functional immune phenotypes such as cytokine production provide complementary insight into disease-focused genetic studies by capturing regulatory mechanisms that influence immune system behavior under defined environmental conditions.

Several limitations of this study should be acknowledged. First, the moderate cohort size limits statistical power to detect cQTLs with smaller effect sizes and likely underestimates the full extent of shared genetic regulation across cytokines and stimuli. Second, our analyses focused exclusively on autosomal variation and therefore did not capture potential contributions of sex-linked immune regulatory variants, which may be relevant given the richness of immune-related genes on the X-chromosome and the known sex differences in antiviral immunity and autoimmune disease risk. Third, cytokine quantification in bulk PBMC cultures limits cell-type resolution. Future work using single-cell cQTL mapping will be important for uncovering cell-type specific effects and refine these findings.

In summary, our study demonstrates that SARS-CoV-2 stimulation reveals a complex and largely context-dependent genetic architecture governing cytokine responses in human innate immunity. By focusing on functional immune phenotypes rather than disease endpoints alone, we identify regulatory loci that shapes innate immune responses and link pathogen-triggered immune programs to broader inflammatory and autoimmune disease biology. These findings underscore the value of stimulation-based functional genomics for interpreting immune–associated genetic variation and provide a framework for understanding how inherited differences in immune regulation influence human responses to infection.

Declarations

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Radboud University Nijmegen (approval number: 42561.091.12)

Consent to participate

Written informed consent was obtained from all participants prior to inclusion in the study.

Author Contribution

N.K. and N.A.S. performed the cytokine quantitative trait locus analyses; N.K. performed functional genomic annotation, colocalization analyses, and data visualization, with analytical support from C.B. ; H.t.H., H.D., H.L., and M.R. performed the PBMC stimulation experiments, cytokine measurements, and data acquisition. M.J. and L.A.B.J. contributed to the study cohort and interpretation of the findings. M.G.N. and V.K. conceived and supervised the study and provided the necessary resources. V.K. coordinated the project. N.K. wrote the main manuscript text, with contributions from N.A.S., M.J., L.A.B.J., M.G.N., and V.K. N.K. and N.A.S. prepared the figures. All authors critically reviewed and approved the final manuscript.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

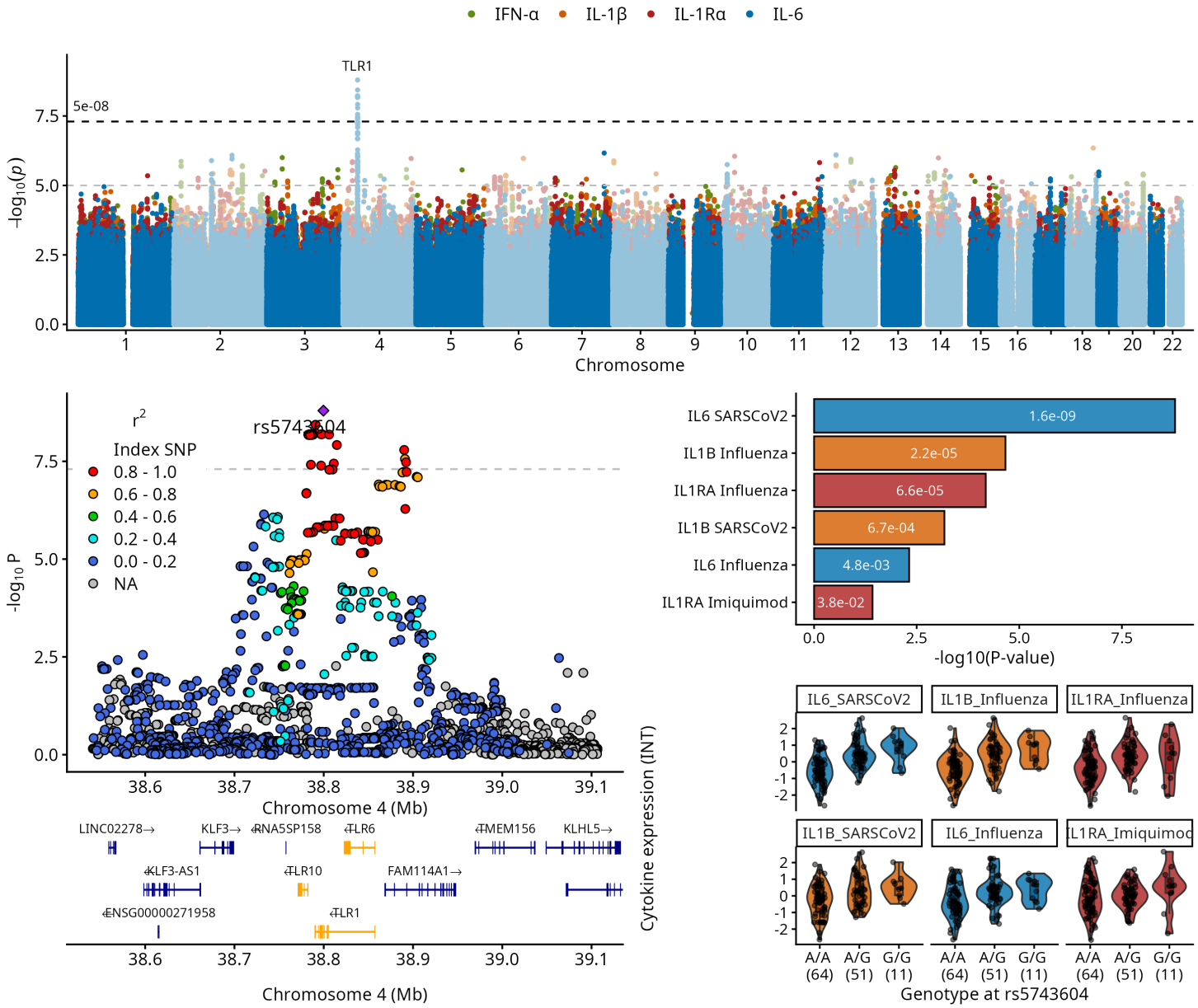

Figure 1

Genome-wide significant IL-6 cytokine-QTL at the TLR1/6/10 locus

(A) Manhattan plot showing results of the cytokine-QTL mapping following SARS-CoV-2 stimulation. Each point represents a genetic variant. The x-axis depicts the genetic location, while the y-axis shows the -log10(p) indicating the strength of the genetic association. The colours indicate the cytokine (green = IFN-a, orange = IL1β, red = IL-1Ra, blue = IL-6). **(B)** Regional association plot of the genome-wide significant TLR-1/6/10 locus with lead variant rs5743604. LD-information is extracted from EU 1000 Genome panel. **(C)** Bar plot showing nominal significance ($p < 0.05$) across other cytokine-stimuli pairs. **(D)** Violin plot shows the cytokine expression data stratified by genotype for rs5743604.

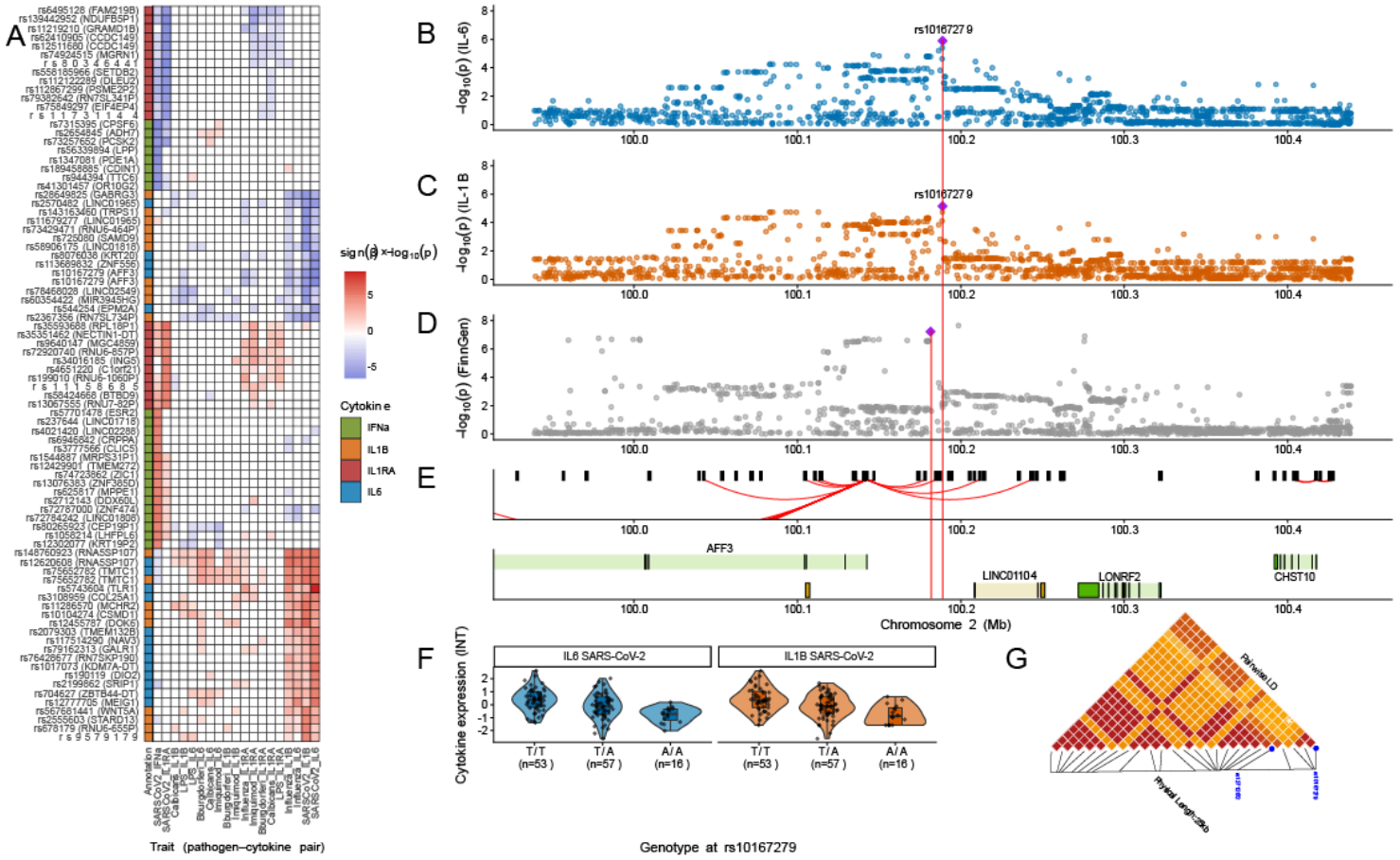

Figure 2

Overview of shared genetic signals following SARS-CoV-2 stimulation.

(A) Signed heatmap of independent loci derived from SARS-CoV-2 stimulation. Each row represents an independent SARS-CoV-2 associated locus, while the columns represent the different pathogen-cytokine pairs. Each cell represents the signed -log10(p), indicating both the direction and strength of the genetic association. Annotation bar depicts the cytokine (green = IFN-a, orange = IL1β, red = IL-1Ra, blue = IL-6). Regional plot for the suggestive locus in **(B)**IL-6 and **(C)** IL-1β with lead variant rs10167279. **(D)** Regional plot depicting the association with Autoimmune disease in FinnGen. **(E)** Regulatory elements and arc visualizing predicted enhancer-gene (E2G) in CD14+ monocytes. **(F)** Violin plot shows the cytokine data stratified by genotype for rs10167279 for both IL-6 and IL-1β. **(G)** Heatmap depicts the pairwise linkage disequilibrium (LD) structure for the lead variants.

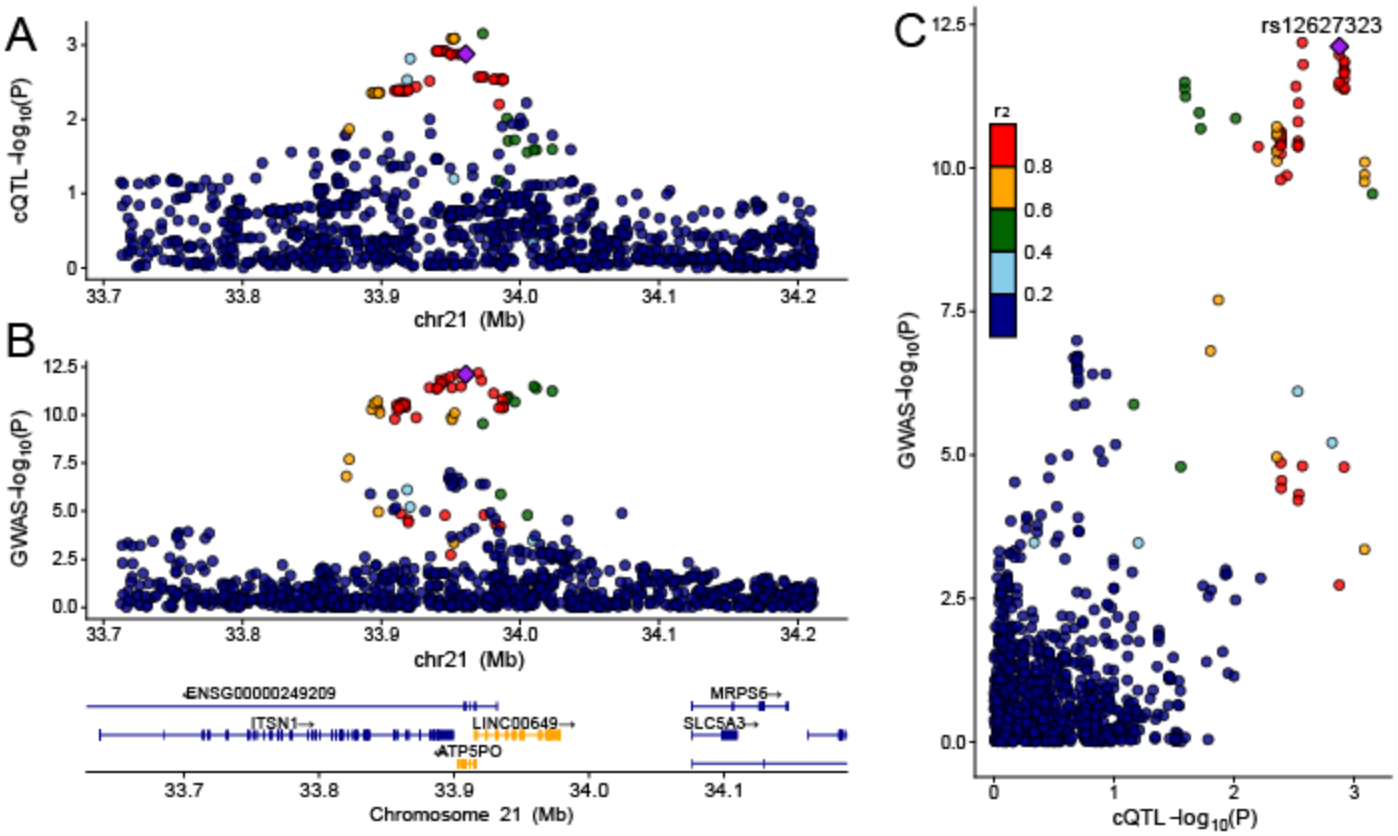

Figure 3

Shared genetic signal between IL-1Ra cytokine-QTL and COVID-19 HGI locus

Regional association plots of the overlapping shared signal between genome-wide significant COVID-19 severity associated ATP5PO and LINC00649 locus. **(A)** cQTL IL-1Ra (**B)**Human genetic initiative (HGI) Very severe respiratory confirmed covid vs. population (A2). Each point is colored with LD-information extracted from EU 1000 Genome panel. **(C)** Genetic correlation point plot for ATP5PO and LINC00649 within a 500kb region. Lead snp = rs12627323

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupFigures.pdf