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Pan-ancestry exome-wide association analyses of COVID-19 outcomes in 586,157 individuals

Jack A. Kosmicki,1,27 Julie E. Horowitz,1,27 Nilanjana Banerjee,1 Rouel Lanche,1 Anthony Marcketta,1 Evan Maxwell,1 Xiaodong Bai,1 Dylan Sun,1 Joshua D. Backman,1 Deepika Sharma,1 Fabricio S.P. Kury,1 Hyun M. Kang,1 Colm O’Dushlaine,1 Ashish Yadav,1 Adam J. Mansfield,1 Alexander H. Li,1 Kyoko Watanabe,1 Lauren Gurski,1 Shane E. McCarthy,1 Adam E. Locke,1 Shareef Khalid,1 Sean O’Keeffe,1 Joelle Mbatchou,1 Olympe Chazara,2 Yunfeng Huang,3 Erika Kvikstad,3 Amanda O’Neill,2 Paul Nioi,3 Meg M. Parker,4 Slavie Petrovski,2 Heiko Runz,3 Joseph D. Sutzastkowski,5 Quanli Wang,2 Emily Wong,6 Aldo Cordova-Palomera,6 Erin N. Smith,6 Sandor Szalma,6 Xiwen Zheng,7 Sahar Esmaeeli,7 Justin W. Davis,7 Yi-Pin Lai,8 Xing Chen,8 Anne E. Justice,9 Joseph B. Leader,9 Tooraj Mirshahi,9 David J. Carey,9 Anurag Verma,10 Giorgio Sirugo,10 Marylyn D. Ritchie,10 Daniel J. Rader,10 Gundula Povysil,11 David B. Goldstein,11,12 Krzysztof Kiryluk,11,13 Erola Pairo-Castinea,14,15 Konrad Rawlik,14 Dorota Pasko,16 Susan Walker,16 Alison Meynert,15 Athanasios Kousathanas,16 Loukas Moutsianas,16 Albert Tenesa,14,15,17 Mark Caulfield,16,18 Richard Scott,16,19 James F. Wilson,15,17 J. Kenneth Baillie,14,15,20 Guillaume Butler-Laporte,21,22 Tomoko Nakaniashi,21,23,24 Mark Lathrop,25,25 J. Brent Richards,21,22,23,26 Regeneron Genetics Center, UKB Exome Sequencing Consortium, Marcus Jones,1 Suganthi Balasubramanian,1 William Salerno,1 Alan R. Shuldiner,1 Jonathan Marchini,1 John D. Overton,1 Lukas Habegeeber,1 Michael N. Cantor,1 Jeffrey G. Reid,1 Aris Baras,1,28 Goncalo R. Abecasis,1,28,* and Manuel A.R. Ferreira1,28,*

Summary

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), a respiratory illness that can result in hospitalization or death. We used exome sequence data to investigate associations between rare genetic variants and seven COVID-19 outcomes in 586,157 individuals, including 20,952 with COVID-19. After accounting for multiple testing, we did not identify any clear associations with rare variants either exome wide or when specifically focusing on (1) 13 interferon pathway genes in which rare deleterious variants have been reported in individuals with severe COVID-19, (2) 281 genes located in susceptibility loci identified by the COVID-19 Host Genetics Initiative, or (3) 32 additional genes of immunologic relevance and/or therapeutic potential. Our analyses indicate there are no significant associations with rare protein-coding variants with detectable effect sizes at our current sample sizes. Analyses will be updated as additional data become available, and results are publicly available through the Regeneron Genetics Center COVID-19 Results Browser.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)3 causes coronavirus disease 2019 (COVID-19).2 COVID-19 ranges in clinical presentation from asymptomatic infection to flu-like illness with respiratory failure, hyperactive immune responses, and death.4–5 Known risk factors for severe disease include male sex, older age, ancestry, obesity, and underlying cardiovascular, renal, and respiratory diseases,6–9 among others. Since the start

1Regeneron Genetics Center, 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA; 2Centre for Genomics Research, Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, Cambridge CB2 0AA, UK; 3Biogen, 300 Binney Street, Cambridge, MA 02142, USA; 4Alylyam Pharmaceuticals, 675 West Kendall Street, Cambridge, MA 02142, USA; 5Bristol Myers Squibb, Route 206 and Province Line Road, Princeton, NJ 08543, USA; 6Takeda California, Inc., 9925 Towne Centre Drive, San Diego, CA 92121, USA; 7Abbvie, Inc., 1 N. Waukegan Road, North Chicago, IL 60064, USA; 8Pfizer, Inc., 1 Portland Street, Cambridge, MA 02139, USA; 9Geisinger, Danville, PA 17117, USA; 10Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; 11Institute for Genomic Medicine, Columbia University Irving Medical Center, New York, NY 10032, USA; 12Department of Genetics and Development, Columbia University, New York, NY 10032, USA; 13Division of Nephrology, Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA; 14Roslin Institute, University of Edinburgh, Easter Bush, Edinburgh EH25 9RG, UK; 15MRC Human Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; 16Genomics England, London EC1M 6BQ, UK; 17Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, Teviot Place, Edinburgh EH8 9AG, UK; 18William Harvey Research Institute, Bart’s and the London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK; 19Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK; 20Intensive Care Unit, Royal Infirmary of Edinburgh, 54 Little France Drive, Edinburgh EH16 9SA, UK; 21Lady Davis Institute, Jewish General Hospital, Montréal, QC H3T 1E2, Canada; 22Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, QC H3A 0G4, Canada; 23Department of Human Genetics, McGill University, Montréal, QC H3A 0G4, Canada; 24Kyoto-McGill International Collaborative School in Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan; 25Canadian Centre for Computational Genomics, McGill University, Montréal, QC H3A 0G4, Canada; 26Department of Twins Research, King’s College London, London WC2R 2LS, UK
27These authors contributed equally
28Senior author
*Correspondence: manuel.ferreira@regeneron.com (M.A.R.F.), goncalo.abecasis@regeneron.com (G.R.A.)
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of the SARS-CoV-2 pandemic, host genetic analysis of common genetic variation among SARS-CoV-2 patients have identified at least 15 genome-wide significant loci that modulate COVID-19 susceptibility, including variants in/near LZTFL1, IFNAR2, and DPP9,\(^{10,12}\) thus demonstrating that our phenotypes are calibrated with those used in other studies.

To identify rare variants (RVs, minor allele frequency [MAF] < 1%) associated with COVID-19 susceptibility and severity, we received approval from institutional review boards (supplemental methods) and analyzed exome-wide sequencing data for 586,157 consented individuals from three studies (Geisinger Health System [GHS], Penn Medicine Biobank [PMBB], and UK Biobank [UKB]) across five continental ancestries (African, Admixed American, European, East Asian, and South Asian; Table S1). Of these, 20,952 had COVID-19, and among those, 4,928 (23.5%) were hospitalized and 1,304 (6.2%) had severe disease (i.e., requiring ventilation or resulting in death; Table S2). Using these data, we tested the association between RVs and seven COVID-19 outcomes: five related to disease susceptibility and two related to disease severity among individuals with COVID-19 (Table S3). In a separate paper,\(^{13}\) we used these same phenotypes to validate the association with common risk variants reported in previous COVID-19 genome-wide association studies (GWASs),\(^{10,12,14}\) thus confirming the role of these variants in modulating COVID-19 susceptibility and severity.

| Gene   | Variant* | Variant effect | Odds ratio (95% CI) | p value | N affected individuals with 0/1/2 copies of effect allele | Effect allele frequency | Heterogeneity p value |
|--------|----------|----------------|---------------------|---------|--------------------------------------------------------|------------------------|------------------------|
| ZC3HAV1 | rs769102632 | missense | 26.72 (8.37, 85.38) | 2.95E–8 | 13,950|70 | 401,218|80 | 0.00002 | 0.9517 |
| FLNB   | rs1256764500 | missense | 26.6 (8.25, 85.77) | 3.97E–8 | 18,616|70 | 500,616|80 | 0.00001 | 0.4354 |
| DISP3  | burden   | pLoF and deleterious missense with MAF < 10\(^{–3}\) | 1.88 (1.51, 2.34) | 2.26E–8 | 20,727|145|0 | 74,172|301|0 | 0.00234 | 0.9972 |
| WDR78  | rs754119466 | splice region | 49.21 (13.61, 177.85) | 2.81E–9 | 3,619|6|0 | 392,658|24|0 | 0.00004 | 1 |
| TES    | rs761377603 | missense | 38.91 (10.75, 140.9) | 2.44E–8 | 4,555|5|0 | 511,328|23|0 | 0.00003 | 0.6601 |
| MARK1  | burden   | pLoF variants with MAC = 1 | 40.19 (10.9, 148.1) | 2.86E–8 | 4,473|5|0 | 530,595|34|0 | 0.00004 | 0.4035 |
| SHC2   | rs2287960 | stop gained | 42.94 (11.17, 165.02) | 4.42E–8 | 4,237|5|0 | 483,826|17|0 | 0.00002 | 0.6742 |
| TLR7\(^{p}\) | burden | pLoF and missense variants with MAF < 10\(^{–3}\) | 4.53 (2.64, 7.77) | 4.28E–8 | 1,266|7|0 | 517,523|383|123 | 0.00062 | 0.7188 |

**MAF**, minor allele frequency; **MAC**, minor allele count; **CI**, confidence interval.

*Effect allele for individual variants was rs769102632:A, rs1256764500:G, rs754119466:G, rs761377603:T, and rs2287960:T. For burden tests, individuals were considered to have 0 copies of the effect allele if they were homozygous for the reference allele for all variants included in the burden test, 1 copy of the effect allele if they were heterozygous for at least one variant, and 2 copies if they were homozygous for the alternate allele for at least one variant.

\(^{p}\)TLR7 is located on the X chromosome. Hemizygous males are included in the N of individuals with two copies of the effect allele.

**Table S1**. Of these, 20,952 had COVID-19, and among those, 4,928 (23.5%) were hospitalized and 1,304 (6.2%) had severe disease (i.e., requiring ventilation or resulting in death; Table S2). Using these data, we tested the association between RVs and seven COVID-19 outcomes: five related to disease susceptibility and two related to disease severity among individuals with COVID-19 (Table S3). In a separate paper,\(^{13}\) we used these same phenotypes to validate the association with common risk variants reported in previous COVID-19 genome-wide association studies (GWASs),\(^{10,12,14}\) thus confirming the role of these variants in modulating COVID-19 susceptibility and severity.

For each phenotype, exome-wide association analyses were performed separately in each study and ancestry via REGENIE,\(^{15}\) testing individual RVs (~7 million) and a burden of RVs in 18,886 protein-coding genes. The genomic inflation factor (\(\lambda_{GC}\)) for RVs was often <1 in individual studies, caused by a large proportion of variants having a minor allele count (MAC) of 0 in affected individuals (Table S4). In meta-analyses across studies and ancestries, we found no RV associations at a conservative p < 9.6E–10, which corresponds to a Bonferroni correction for the number of variants and traits tested. At a less conservative significance threshold of p < 5E–8, we found eight genes with RV associations (Table 1), of which, we highlight two with an established role in anti-viral responses. First, we highlight an association between higher risk of severe COVID-19
and a burden of ultra-rare (MAF < 0.001%) predicted loss-of-function (pLoF) and missense variants in the toll-like receptor 7 gene (TLR7; p = 4E−8; OR = 4.53; 95% CI = 2.64–7.77), consistent with relatively small exome-sequencing studies of males with severe COVID-19.16,17 TLR7 encodes a single-stranded viral RNA sensor that recognizes coronaviruses, including SARS-CoV-1, MERS, and most likely SARS-CoV-2,18 and that activates the type-1 interferon pathway in COVID-19.16 Second, we highlight an association between higher risk of COVID-19 and an ultra-rare missense variant in ZC3HAV1 (rs769102632:A, MAF = 0.002%; p = 3E−8; OR = 26.7; 95% CI 8.37–85.38; Figure S1), a gene that encodes a zinc finger antiviral protein19,20 that inhibits SARS-CoV-2 replication,21 potentially by upregulating type I interferon responses.22 Given the potential significance of this finding, we attempted to replicate the ZC3HAV1 rs769102632:A association in an additional 6,223 individuals with COVID-19 with exome or whole-genome sequence data generated as part of the GenOMICC (n = 4,851),11 Columbia University COVID-19 Biobank (n = 1,152), and Biobanque Quebec (n = 220)23 studies. We found no carriers for this variant in these additional COVID-19 cases (Table S5) when we expected about four given the observed allele frequency in cases in our study (three and one carriers expected in individuals of African and European ancestry, respectively). Given these findings, we conclude that it is unlikely that there is a true association between rs532051930 and COVID-19 risk. Similarly, the association with a promoter variant in EEF2 that we reported in an earlier version of these analyses24 was considerably attenuated (from p = 6E−9 to 3E−6), consistent with a false-positive association.

Next, we addressed the possibility that associations with protein-coding RVs might help pinpoint target genes of common risk variants identified in GWASs of COVID-19. To this end, we focused on 281 genes located within 500 common risk variants identified in GWASs of COVID-19.24,25 Given a previous report that deletions between common variants and COVID-19 associations surpassed the Bonferroni significance threshold with deleterious missense variants (M3 burden test). No associations were found with pLoF variants alone (M1 burden test) or pLoF together with deleterious missense variants (M3 burden test). No associations surpassed the Bonferroni significance threshold of 3.5E−6, which accounts for the 14,050 gene burden tests performed (281 genes × two burden tests × five allele frequency cut-offs × five susceptibility phenotypes; Table S6). As such, at current sample sizes, RV associations do not point to potential effector genes underlying associations between common variants and COVID-19.

We then examined the association with 13 genes in the interferon pathway,25 given a previous report that deleterious RVs in these genes may be implicated in severe clinical outcomes.25 Specifically, we examined whether there was any evidence for association between the COVID-19 hospitalization phenotype (4,928 affected individuals versus 558,763 control individuals) and the burden of rare (MAF < 0.1%, as reported by Zhang et al.25) pLoF variants (M1 burden test) or pLoF plus deleterious missense variants (M3 burden test) in these 13 genes. There were no significant associations with any gene, either individually or on aggregate (all burden tests with p > 0.05; Table 2). Further, these results were unchanged when testing severe cases of COVID-19 (n = 1,304) or when restricting the burden tests to include variants with an MAF < 1% or singleton variants (Table S7). Therefore, in alignment with a similar report,23 we also found no evidence for an association between RVs in these 13 interferon-signaling genes.

Lastly, we performed the same analysis for an additional 32 genes that are involved in the etiology of SARS-CoV-2 infection (ACE2, TMPRSS2), encode therapeutic targets for COVID-19 obtained through the ClinicalTrials database (see web resources) (e.g., IL6R, JAK1), or have been implicated in other immune or infectious diseases through GWASs (e.g., IL33). After correcting for 1,600 burden tests performed (32 genes × five traits × five allele frequency thresholds × two burden tests; Bonferroni significance threshold p < 3.1E−5), there were no significant associations with deleterious RVs for this group of therapeutic target genes for COVID-19 (Table S8).

There are caveats to be considered when interpreting results from this study. First, the five continental ancestry groups considered in our analysis included a small number of individuals with admixed ancestry (specifically, those with two continental ancestries with a likelihood > 0.3; see supplemental methods). For example, individuals with admixed African and European ancestry were included in our analysis of African ancestry. This was done to maximize the number and ancestral diversity of the samples included in our analysis and was adequately controlled for in the association analyses carried out with the whole-genome regression approach implemented in REGENIE (test statistics were not inflated). Second, the burden tests we performed were not designed to identify associations with genes that harbor both risk-increasing and risk-lowering rare variants and are expected to provide limited power in these instances. Other approaches have been developed for these situations, such as SKAT26/SKAT-O.27 However, we have not tested the robustness of these alternative burden tests in the context of multi-ancestry meta-analyses, so we opted against applying them in this study. Third, we used a stringent Bonferroni correction to define significance thresholds that account for multiple testing, which are most likely conservative, given the high correlation between traits and burden tests performed.

In summary, we explored the role of rare coding variants on COVID-19 outcomes on the basis of exome-sequence data, capturing genetic variation not assayed by array genotyping or imputation. We did not find any convincing associations with current sample sizes but will continue to expand our analyses and update results periodically at...
Table 2. Burden associations among interferon signaling genes

| Variants included in burden test | Gene | Odds ratio (95% CI) | p value | N affected individuals with RR/RA/AA genotype<sup>a</sup> | N control individuals with RR/RA/AA genotype<sup>a</sup> | AAF | Heterogeneity p value |
|---------------------------------|------|---------------------|---------|--------------------------------------------------------|--------------------------------------------------------|-----|----------------------|
| pLoF, MAF < 0.1%                |      |                     |         |                                                        |                                                        |     |                      |
| IFNAR1                          | 1.46 (0.51, 4.17) | 0.4786             | 4,775[5][0] | 549,164[374][0]                                       | 0.00034                                               | 0.9111 |                      |
| IFNAR2                          | 1.96 (0.91, 4.19) | 0.0844             | 4,920[8][0] | 558,068[695][0]                                       | 0.00062                                               | 0.0964 |                      |
| IKBKG<sup>b</sup>               | 0.51 (0.04, 6.57) | 0.6048             | 4,394[0][0] | 500,582[32][10]                                      | 0.00005                                               | 0.9584 |                      |
| IFNAR1                          | 0.91 (0.39, 2.11) | 0.8293             | 4,924[3][1] | 558,279[483][1]                                      | 0.00043                                               | 0.6339 |                      |
| IFR7                            | 1.15 (0.57, 2.31) | 0.6975             | 4,920[8][0] | 557,892[87][1]                                      | 0.00078                                               | 0.5267 |                      |
| IFR9                            | 0.36 (0.02, 6.96) | 0.5024             | 4,478[0][0] | 530,571[58][0]                                      | 0.00005                                               | 0.9996 |                      |
| STAT1                           | 0.36 (0.01, 19.89) | 0.6207             | 4,394[0][0] | 500,584[40][0]                                      | 0.00004                                               | 0.9996 |                      |
| STAT2                           | 0.36 (0.07, 1.91) | 0.2311             | 4,644[0][0] | 541,214[144][0]                                     | 0.00013                                               | 1.0000 |                      |
| TIRK1                           | 0.36 (0.04, 3.13) | 0.3553             | 4,478[0][0] | 530,539[900][0]                                     | 0.00008                                               | 0.9995 |                      |
| TICAM1                          | 0.81 (0.14, 4.73) | 0.8160             | 4,477[1][0] | 530,454[175][0]                                     | 0.00016                                               | 0.7587 |                      |
| TLR3                            | 1.56 (0.47, 5.13) | 0.4656             | 4,924[4][0] | 558,457[306][0]                                     | 0.00027                                               | 0.7039 |                      |
| TRAF3                           | 0.37 (0.0, 217.91) | 0.7576             | 4,394[0][0] | 500,597[27][0]                                      | 0.00003                                               | 1.0000 |                      |
| UNC93B1                         | 0.77 (0.28, 2.06) | 0.5974             | 4,641[3][0] | 540,929[429][0]                                     | 0.00040                                               | 0.9294 |                      |
| all autosomal genes             | 0.81 (0.56, 1.18) | 0.2709             | 4,655[23][0] | 514,810[3219][0]                                    | 0.00320                                               | 0.9492 |                      |
| pLoF and missense predicted deleterious, MAF < 0.1% |      |                     |         |                                                        |                                                        |     |                      |
| IFNAR1                          | 1.51 (0.71, 3.18) | 0.2831             | 4,918[10][0] | 557,991[72][0]                                      | 0.00069                                               | 0.8283 |                      |
| IFNAR2                          | 1.87 (0.88, 3.97) | 0.1021             | 4,920[8][0] | 558,045[718][0]                                     | 0.00064                                               | 0.0862 |                      |
| IKBKG<sup>b</sup>               | 1.48 (0.18, 12.34) | 0.7184             | 4,393[1][0] | 500,544[70][10]                                     | 0.00009                                               | 0.6366 |                      |
| IFNAR1                          | 0.9 (0.42, 1.92)  | 0.7778             | 4,923[4][1] | 558,128[634][1]                                     | 0.00057                                               | 0.7436 |                      |
| IFR7                            | 1.15 (0.67, 1.96) | 0.6102             | 4,914[14][0] | 557,238[1,525][0]                                    | 0.00137                                               | 0.3523 |                      |
| IFR9                            | 0.36 (0.02, 6.96) | 0.5024             | 4,478[0][0] | 530,571[58][0]                                      | 0.00005                                               | 0.9996 |                      |
| STAT1                           | 0.35 (0.08, 1.49) | 0.1563             | 4,762[0][0] | 547,803[231][0]                                     | 0.00021                                               | 1.0000 |                      |
| STAT2                           | 1.26 (0.73, 2.2)  | 0.4089             | 4,909[19][0] | 557,153[1,609][1]                                    | 0.00145                                               | 0.7935 |                      |
| TIRK1                           | 1.0 (0.54, 1.85)  | 0.9951             | 4,917[11][0] | 557,567[1,195][1]                                   | 0.00107                                               | 0.6983 |                      |
| TICAM1                          | 0.8 (0.14, 4.66)  | 0.8084             | 4,477[1][0] | 530,451[178][0]                                     | 0.00017                                               | 0.7558 |                      |
| TLR3                            | 0.74 (0.49, 1.11) | 0.1396             | 4,911[17][0] | 556,016[2,745][2]                                    | 0.00245                                               | 0.8319 |                      |
| TRAF3                           | 1.7 (0.44, 6.62)  | 0.4431             | 4,778[2][0] | 549,284[254][0]                                     | 0.00023                                               | 0.1923 |                      |
| UNC93B1                         | 0.92 (0.56, 1.5)  | 0.7309             | 4,913[15][0] | 557,079[1,684][0]                                    | 0.00151                                               | 0.9180 |                      |
| all autosomal genes             | 0.94 (0.76, 1.17) | 0.5835             | 4,590[88][0] | 507,793[10,233][3]                                   | 0.00990                                               | 0.5285 |                      |

Association between the phenotype COVID-19 positive hospitalized versus COVID-19 negative or unknown and 13 genes (12 autosomal) related to interferon signaling that were recently reported to contain rare (MAF < 0.1%) deleterious variants in individuals with severe COVID-19. AAF, alternative allele frequency; CI, confidence interval.

<sup>a</sup>RR, individuals who have genotype reference/reference for all variants included in burden test; RA, individuals who have genotype reference/alternate for at least one variant; AA, individuals who have genotype alternate/alternate for at least one variant.

<sup>b</sup>IKBKG is located on the X chromosome. Hemizygous males are included in the N of individuals with two copies of the effect allele.
the Regeneron Genetics Center COVID-19 Results Browser (web resources).

Data and code availability

All genotype-phenotype association results reported in this study are available for download and browsing via the RGC’s COVID-19 Results Browser (https://rgc-covid19.regeneron.com). Data access and use is limited to research purposes in accordance with the Terms of Use (https://rgc-covid19.regeneron.com/terms-of-use).

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2021.05.017.

Declaration of interests

J.A.K., J.E.H., A.D., D.S., N.B., A.Y., A.M., R.L., E.M., X.B., D.S., E.S.P.K., J.D.B., C.O’D., A.J.M., D.A.T., A.H.L., J.M., K.W., L.G., S.E.M., H.M.K., L.D., E.S., M.J., S.B., K.S.M., W.J.S., A.R.S., A.E.L., J.M., J.O., L.H., M.N.C., J.G.R., A.B., G.R.A., and M.A.F. are current employees and/or stockholders of Regeneron Genetics Center or Regeneron Pharmaceuticals. X.Z., S.E., and J.W.D. are employees of AbbVie and may hold stock in AbbVie. Financial support for this research was provided by AbbVie through the UK Exome Sequencing Consortium. AbbVie participated in the interpretation of data, review, and approval of the publication. P.N. and M.M.P. are employees and stockholders of Ayanlm Pharmaceuticals. J.B.R. has served as an advisor to GlaxoSmithKline and Deerfield are employees and stockholders of Alnylam Pharmaceuticals. Financial support for this research was provided by Alnylam through the UK Exome Sequencing Consortium. Alnylam participated in the interpretation of data, review, and approval of the publication. X.Z., S.E., and J.W.D. are employees of AbbVie and may hold stock in AbbVie. Financial support for this research was provided by AbbVie through the UK Exome Sequencing Consortium. AbbVie participated in the interpretation of data, review, and approval of the publication. P.N. and M.M.P. are employees and stockholders of Ayanlm Pharmaceuticals. J.B.R. has served as an advisor to GlaxoSmithKline and Deerfield are employees and stockholders of Alnylam Pharmaceuticals. Financial support for this research was provided by Alnylam through the UK Exome Sequencing Consortium. Alnylam participated in the interpretation of data, review, and approval of the publication.
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