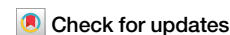


<https://doi.org/10.1038/s42003-024-05805-6>

Clonal chromosomal mosaicism and loss of chromosome Y in elderly men increase vulnerability for SARS-CoV-2



Luis A. Pérez-Jurado ^{1,2,3,279} ✉, Alejandro Cáceres ^{4,5,279}, Laura Balagué-Dobón ^{4,5}, Tonu Esko ^{6,7}, Miguel López de Heredia ³, Inés Quintela ^{3,8}, Raquel Cruz ^{3,8,9,10}, Pablo Lapunzina ^{3,11,12}, Ángel Carracedo ^{3,8,9,10,13}, SCOURGE Cohort Group* & Juan R. González ^{4,5,14} ✉

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) had an estimated overall case fatality ratio of 1.38% (pre-vaccination), being 53% higher in males and increasing exponentially with age. Among 9578 individuals diagnosed with COVID-19 in the SCOURGE study, we found 133 cases (1.42%) with detectable clonal mosaicism for chromosome alterations (mCA) and 226 males (5.08%) with acquired loss of chromosome Y (LOY). Individuals with clonal mosaic events (mCA and/or LOY) showed a 54% increase in the risk of COVID-19 lethality. LOY is associated with transcriptomic biomarkers of immune dysfunction, pro-coagulation activity and cardiovascular risk. Interferon-induced genes involved in the initial immune response to SARS-CoV-2 are also down-regulated in LOY. Thus, mCA and LOY underlie at least part of the sex-biased severity and mortality of COVID-19 in aging patients. Given its potential therapeutic and prognostic relevance, evaluation of clonal mosaicism should be implemented as biomarker of COVID-19 severity in elderly people.

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represented a major health threat to the entire world¹. During three years, there have been almost 700 million confirmed cases of COVID-19 worldwide, with more than 7 million deaths reported. A best estimate of the overall case fatality ratio after adjusting for demography and under-ascertainment in the initial outbreak in China was 1.38% (95% confidence interval 1.23–1.53), being significantly higher in aging people (6.4% in ≥ 60 and 13.4% in ≥ 80 age groups) and in males². World-wide data of the age-stratified case fatality ratio and infection fatality ratio show a similar pattern with a remarkable sex-bias increasing with advanced age, with 60% overall deaths reported in men (estimated hazard ratio of 1.59, 95% confidence interval 1.53–1.65)³. Interestingly, sex-dependent differences in disease outcomes were also found during the past SARS-CoV and MERS-CoV epidemics^{4,5} and also in mice infected with the virus⁶.

Understanding the underlying basis of this different sex and age vulnerability is crucial because aging men and women are likely to have fundamentally different reactions to the SARS-CoV-2 virus infection, treatments, and vaccines. Male patients with COVID-19 have higher plasma levels of innate immune cytokines (IL-8 and IL-18) and stronger induction of non-classical monocytes, while females had more robust T cell activation

during infection. Proposed causes include different case definition of disease, different environmental and social factors (such as lifestyle, smoking history or work-environment) and sex-specific immune-defense factors. The X chromosome harbors multiple genes important for immunity and there are many X-linked immunodeficiencies, so males have greater susceptibility to infections starting at birth⁶. More specifically, SARS viruses use the angiotensin converting enzyme (ACE2), encoded by an X-linked gene, as a receptor to enter and infect ACE-2 expressing cells¹. Sex variation in the expression of this gene with paradoxically higher expression and higher circulating levels in men than in women has also been proposed as a candidate mechanism⁷. However, ascertainment bias and environmental factors are unlikely to prevail in different populations while the gender-specific immune factors or ACE2 variation would not fully explain the increased risk and sex-divergence with aging. The analysis of previously untreated patients with moderate COVID-19 disease revealed that male patients have higher levels of innate immune cytokines and more robust induction of non-classical monocytes, while female patients have more robust T-cell activation, which is sustained in old age⁸. A B-cell autoimmune disorder present in about 10% of individuals with life-threatening COVID-19 pneumonia has been reported, 5 times more common in males than females, characterized by detection of neutralizing immunoglobulin G autoantibodies against

A full list of affiliations appears at the end of the paper. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: luis.perez@upf.edu; juanr.gonzalez@isglobal.org

interferon type 1⁹. Finally, a meta-analysis of genome-wide association studies searching for host-specific genetic factors has revealed 13 loci significantly associated with SARS-Cov2 infection or severe manifestations of COVID-19, but do not fully explain the gender differences¹⁰.

Mosaic chromosomal alterations (mCA) detectable in blood, including deletions, gains or copy neutral changes, are age-related somatic alterations that indicate clonal hematopoiesis when detectable and have been associated with increased risk for cancer, cardiovascular disease and overall mortality¹¹⁻¹⁵. Expanded mCAs have also been recently associated with increased risk for incident infections, including COVID-19 hospitalization¹⁶. Multiple germline genetic alleles involved in susceptibility to clonally expanded mCA have been identified, with enrichment at regulatory sites for the immune system¹⁶. In men, mosaic X chromosome monosomy (XCM), acquired by somatic loss of the Y chromosome (LOY), is the most common copy number alteration in male leukocytes, estimated to occur in <2% men under 60 years of age, but exponentially increasing with aging to 15–40% in 70–85 year-old males and >50% at 93 years of age¹⁷. LOY has also been associated with a wide spectrum of human diseases including cancer, Alzheimer’s disease, cardiovascular disease, and reduced overall life expectancy in men¹⁸⁻²¹. Genetic variation in multiple loci is involved in the inherited susceptibility to LOY, which can also be driven by smoking and other environmental exposures¹⁷. Extreme down-regulation of chromosome Y gene expression mainly driven by genes with X-chromosome homologs that escape X-inactivation seems to be the functional mediator of the reported association between LOY and disease^{22,23}.

In women, developmental (causing Turner syndrome) or late onset XCM detectable in leukocytes, usually with loss of the inactive X-chromosome, is found with lower frequency than in men but also increasing with age (0.05% in 50-year old; 0.25% in 75-year old)²⁴. Females with XCM have an increased risk for autoimmune disease, recurrent viral infections and earlier cardiovascular mortality²⁵, which is associated with excessive production of pro-inflammatory cytokines (IL-6), decrease in anti-inflammatory cytokines (IL-10, TGF-β) and a lower CD4:CD8 ratio²⁶.

We have tested here the hypothesis that mCA and XCM/LOY could be underlying factors for the increased severity and mortality of COVID-19 in the elderly and mainly in men. Overall, we have associated clonal mosaicism with a 50% increase in the risk of COVID-19 lethality. We have also correlated LOY in aging males with multiple parameters of cardiovascular dysfunction, and defined the transcriptomic deregulation that underlies disease risks, including signatures of immune system dysfunction and increased coagulation activity. We have finally studied how some of the genes deregulated by LOY are involved in the response to SARS-CoV-2 infection.

Results

Higher Covid-19 severity and mortality in males, a sex-bias that increases with aging

Accumulated data on the age-stratified case fatality ratio and infection fatality ratio in a large sample from Spain, show a pattern with a remarkable sex-bias increase with advancing age (Fig. 1). Available reports, mostly based on hospital records, show the same tendency in other countries. COVID-19 lethality, mCA prevalence and LOY prevalence in men, as previously

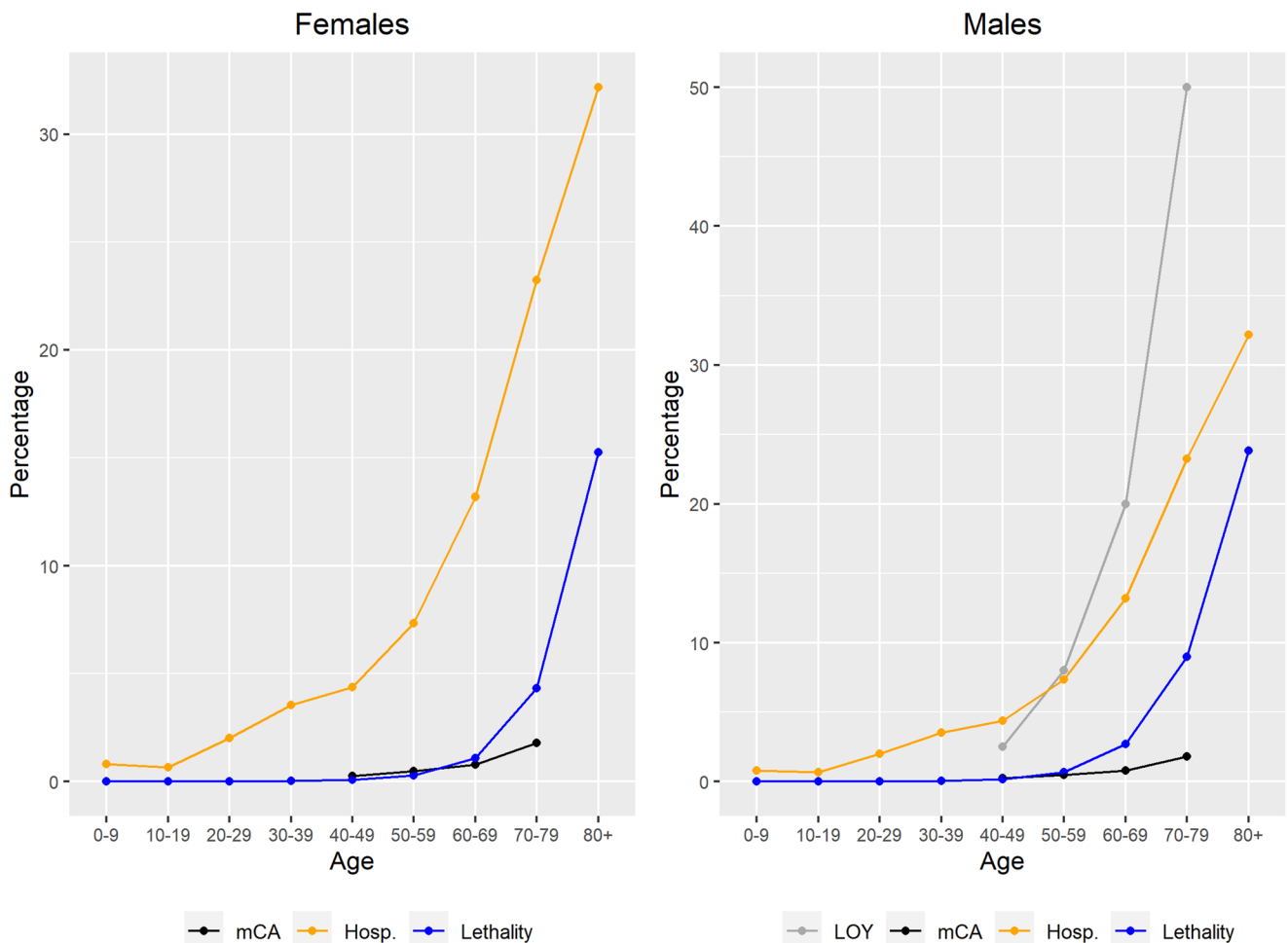


Fig. 1 | COVID-19 lethality and mCA and LOY prevalence as functions of age. Increasing sex-specific hospitalization (orange) and mortality (blue) rates for COVID-19 in Spain in the different age intervals (updated July 2022). Estimated

prevalence by age in the general population of detectable mCA (black) or LOY in men (grey) in blood is also shown^{15,14}.

Table 1 | Number, proportion and mean age of patients in the different clinical categories of COVID-19 severity in the SCOURGE study, with and without detectable mCAs or LOY (males)

		Asymptomatic (0)	Mild (1)	Moderate (2)	Severe (3)	Critical (4)	Subtotal	No data	Dead ^a	Alive ^a	Subtotal	Total
Cohort (no mCA)	cases	607	2727	2141	2449	1157	9081	494	810	8054	8864	9578
	(%)	(6.7)	(30.0)	(23.6)	(27.0)	(12.7)			(9.1)	(90.9)		
	age	53.3	51.3	66.9	70.6	65.4			79.9	60.5		
mCAs	cases	4	18	34	46	17	119	14	29	90	119	133
	(%)	(3.4)	(15.1)	(28.6)	(38.7)	(14.3)			(24.4)	(75.6)		
	age	80.9	65.6	78.2	79.5	71.4			81.1	74.1		
	males	2	7	18	18	15	61	8	18	42	60	69
	(%)	(3.3)	(11.5)	(29.5)	(29.5)	(24.6)			(30.0)	(70.0)		
	age	80.5	73.9	76.7	78.1	70.5			80.7	72.1		75.4
	females	2	10	16	27	2	58	6	11	48	59	64
	(%)	(3.4)	(17.2)	(27.6)	(46.6)	(3.4)			(18.6)	(81.4)		
age	81	60.1	79.7	79.8	72.5			80.6	75.4		76.5	
Males (no LOY)	cases	163	743	1068	1241	792	4007	323	398	3494	3892	4218
	(%)	(4.1)	(18.5)	(26.7)	(31.0)	(19.8)			(10.2)	(89.8)		
	age	53.2	51.9	64.8	69.1	64.0			77.2	61.5		
Males LOY	cases	4	13	47	97	47	208	18	65	143	208	226
	(%)	(1.9)	(6.3)	(22.6)	(46.6)	(22.6)			(31.3)	(68.8)		
	age	81.2	78.5	81.0	83.5	79.3			84.1	81.5		

^a>90 days after COVID-19.

reported in multiple reports including the UK biobank dataset, appear to increase exponentially with age (Fig. 1)^{18–21}.

COVID-19 severity variables and their association with age

We first studied the SCOURGE clinical data. Phenotype data was available from all 9578 individuals (5134 females and 4444 males) diagnosed with COVID-19 and recruited to the SCOURGE study (Table 1). According to disease severity, there were 607 cases asymptomatic (6.8% A), 2727 individuals with mild symptoms (30% L), 2141 patients with moderate disease (23.6% M), 2449 with severe manifestations (27% G), 1157 critical (12.7% C). We visually inspected the contrasts defined together with the level of severity and the age of the patients. Mean age was 62.58 years, 64.34 for males and 61.06 for females, with an age difference between sexes that was statistically significant ($P = 4.1 \times 10^{-19}$). All clinical categories and variables correlated with age except for “critical” and “history of pulmonary thromboembolism”.

Association between mCA and COVID-19 severity

The algorithm followed by manual curation finally detected 133 individuals (1.42%), 61 males and 72 females, carrying mCAs in blood affecting the autosomes and/or the X chromosome (Table 1, Supplementary Data 1, Fig. 2a & 2b and Figure S1). Globally, 95 individuals had a single mCA while 38 of them had more than one event, for a total of 213 mCAs. There were 88 deletions, 5 whole chromosome monosomies, 20 segmental gains and 21 whole chromosome trisomies, along with 78 copy-neutral changes (somatic segmental uniparental disomies), and a few complex rearrangements. Mean age for individuals with mCAs was 75.04 ± 12.7 . We then performed association analyses across the different outcome variables related to COVID-19 severity and the presence of mosaicism. We first confirmed the strong association between mosaicism and age (year) ($OR = 1.051$, $P = 1.05 \times 10^{-16}$), as previously reported. We then observed a significant association between the presence of mCA and COVID-19 lethality (1-survival, $OR = 1.75$, $P = 0.015$), after adjusting for sex and age (Fig. 3). The contribution of mCAs to COVID 19 lethality was stronger and more significant in males only ($OR = 2.16$; 95%CI: 1.19–3.93). Although in the same direction, the split sample size was not enough to achieve statistical significance for an association in females ($OR = 1.32$; 95%CI: 0.66–2.67).

Association between LOY and COVID-19 severity

Among all male cases, we detected 226 individuals with LOY (mean age 82.0 ± 7.9), a 5.08% prevalence of LOY in this cohort (Table 1, Supplementary Data 2), which is within the reported range in previous publications^{17–20}, albeit significantly below the prevalence reported by others in the UK biobank using the same threshold²¹. The reasons for this discrepancy are unclear, but our calling method of LOY has demonstrated robustness in comparison with others, using both simulations and real data²⁷. According to the estimated proportion of cells with XCM or LOY, 162 individuals had mild LOY (<25% cells with LOY), 43 moderate LOY (25–65% cells with LOY) and 21 had extreme LOY (>65% cells with LOY) (Fig. 2c). We also identified three women with detectable chromosome Y in a proportion of cells, then likely corresponding to X0/XY mosaicism and a possible diagnosis of Turner syndrome, as well as three individuals with non-mosaic XYY (Fig. 2c). We observed 6 men with both LOY and mCA, 220 with LOY and no mCA, and 55 with mCA and no LOY, which resulted in no significant correlation between the presence of LOY and mCA.

We first confirmed a strong association between LOY in males and age ($OR = 1.11$, $P = 5.65 \times 10^{-51}$). We then fitted a series of models between LOY and the contrast C or $G > M$ or L or A , for which we had observed a strong association with age. We first observed a significant association between the contrast and LOY, primarily due to its association with age (not significant after adjusting by age, $OR = 1.25$, $P = 0.15$). We also performed association tests for all the contrasts and clinical variables adjusting only by age and we observed some significant associations. LOY was associated with reduction in survival ($OR = 0.713$, $P = 0.045$) and with clinical history of vascular disease ($OR = 0.627$, $P = 0.001$) and lung thromboembolism ($OR = 0.271$, $P = 0.042$). While associations with severity were not significant, we observed a consistent estimate of their risk given by LOY.

We then tested the association with the continuous value for mLRRY across all severity contrast and clinical variables. We found a significant association with survival for higher relative levels of chromosome Y content ($\beta = 0.86$, $P = 0.0054$).

We then performed a joint analysis for all mosaicisms, mCAs and LOY, confirming their strong association with age ($OR = 1.08$, $P = 1.95 \times 10^{-62}$) and with COVID-19 lethality ($OR = 1.53$, $P = 0.004$) after corrections, including adjustment for other clinical variables (Fig. 3). The associations of

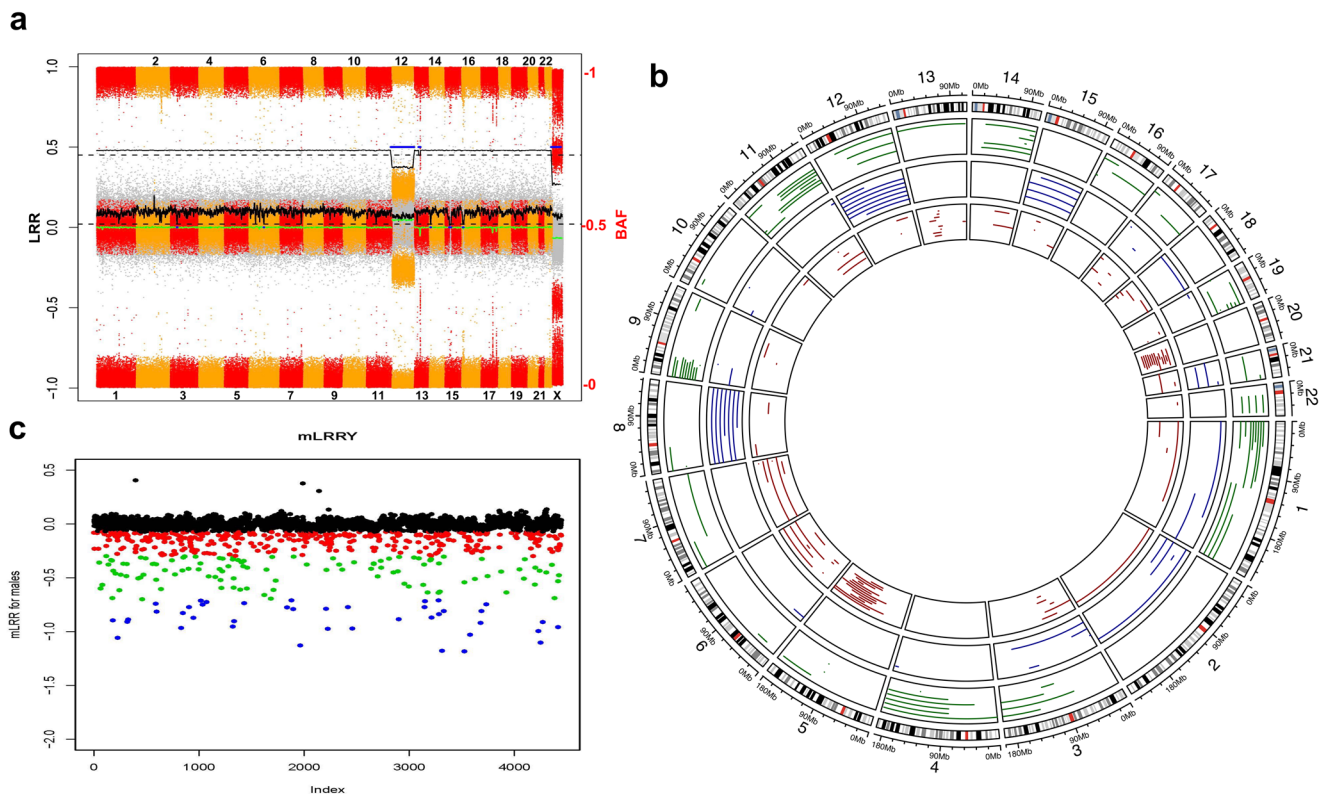


Fig. 2 | mCA and LOY detection in the SCOURGE study. **a** Plot representing the whole-genome molecular karyotype obtained by SNParray of blood DNA from an individual with several mCAs. Dots in grey are LRR values (average per window shown by a green lane), while colored dots are BAF values of homozygous and heterozygous SNPs from odd (red) and even number (orange) chromosomes, respectively. Abnormal BAF and average LRR values in three regions (blue lanes interrupting the black lane in the upper part) correspond to mosaicism for trisomy 12, a small interstitial deletion in 13q and X-chromosome monosomy. The blue lanes interrupting the green lane at LRR = 0 correspond to small regions of homozygosity.

b Circus plots showing all detected mCAs in the SCOURGE dataset. In red deletions, in blue gains and in green copy neutral events. **c** Analysis of LOY in male individuals in the SCOURGE study based on mean LRR from chromosome Y (mLRRY: relative amount of DNA from the Y chromosome with respect to autosomes). Blue dots correspond to males with mosaic LOY in more than 65% of cells (XCM > 65%), green dots to males with LOY/XCM between 25%–65%, and red dots to males with LOY/XCM in less than 25% of cells. The three individuals with top mLRRY values have apparently non-mosaic gains of chromosome Y (47,XYY).

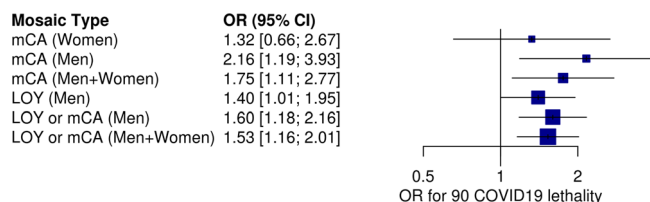


Fig. 3 | Associations of detectable mCAs and LOY with COVID-19-related mortality. Mortality was reported at most 90 days after infection. The analyses are stratified or adjusted by sex, as indicated. All analyses are adjusted for age and 10 principal components of ancestry. Individuals with prevalent hematologic cancer were excluded from the analysis. Error bars correspond to the 95% CI for the OR estimates.

all type mosaicism with severity contrasts were not significant but consistent across all contrasts.

Germline aneuploidies and COVID-19

In addition to 6 individuals with XCM and likely Turner syndrome, 3 cases with 45,X0/46,XY mosaicism mentioned above, 2 more cases with 45,X0/46,XX mosaicism and one with likely 45,X0/46,XY/46,XX mosaicism, the algorithm also detected a total of 25 individuals with germline (non-mosaic) aneuploidies. We detected 7 cases with Down syndrome (trisomy 21) and 18 with gonosomal aneuploidies, including 9 with Klinefelter syndrome (47,XXY), 6 with triple X syndrome (47,XXX) and 3 with XYY syndrome (47,XYY) (Supplementary Data 3). We found an association of aneuploidies with the presence of mCAs ($OR = 9.90, P = 0.0047$).

We then performed association tests of phenotypic features with all the aneuploidies, removing individuals with mCAs. We did not find any significant association between COVID-19 severity parameters and any type of aneuploidy given this small sample size, although previous history of cardiopathy was significantly associated, as expected ($OR = 4.02, P = 0.004$).

Correlation of LOY with cellular and biochemical phenotypes in EGCUT individuals

We analyzed SNP microarray data with MADloy of a selected sample of 530 apparently healthy adult men from the Estonian Genome Center of the University of Tartu cohort (EGCUT) and classified them as having ($n = 28$) or not having LOY ($n = 502$). We then correlated genotype classification with several clinical parameters. Individuals with LOY had significantly age-adjusted decrease in red cell counts, decrease in mean corpuscular hemoglobin concentration and higher red cell distribution width, low basophil counts and borderline low lymphocyte proportions. Biochemical parameters revealed low albumin levels, low triglycerides and elevated homocysteine and urea levels (Table S1).

Blood transcriptome in individuals with LOY reveals immune defects and cardiovascular risk

We also compared blood transcriptome from 11 men with LOY (median age: 69, range: 58–84) and 32 age-paired men without LOY (median age: 68, range: 60–87) as controls. Multiple genes differentially expressed between groups were found, including autosomal and gonosomal genes (Tables S2, S3 and Figures S2, S3), providing insight into the mechanisms of disease

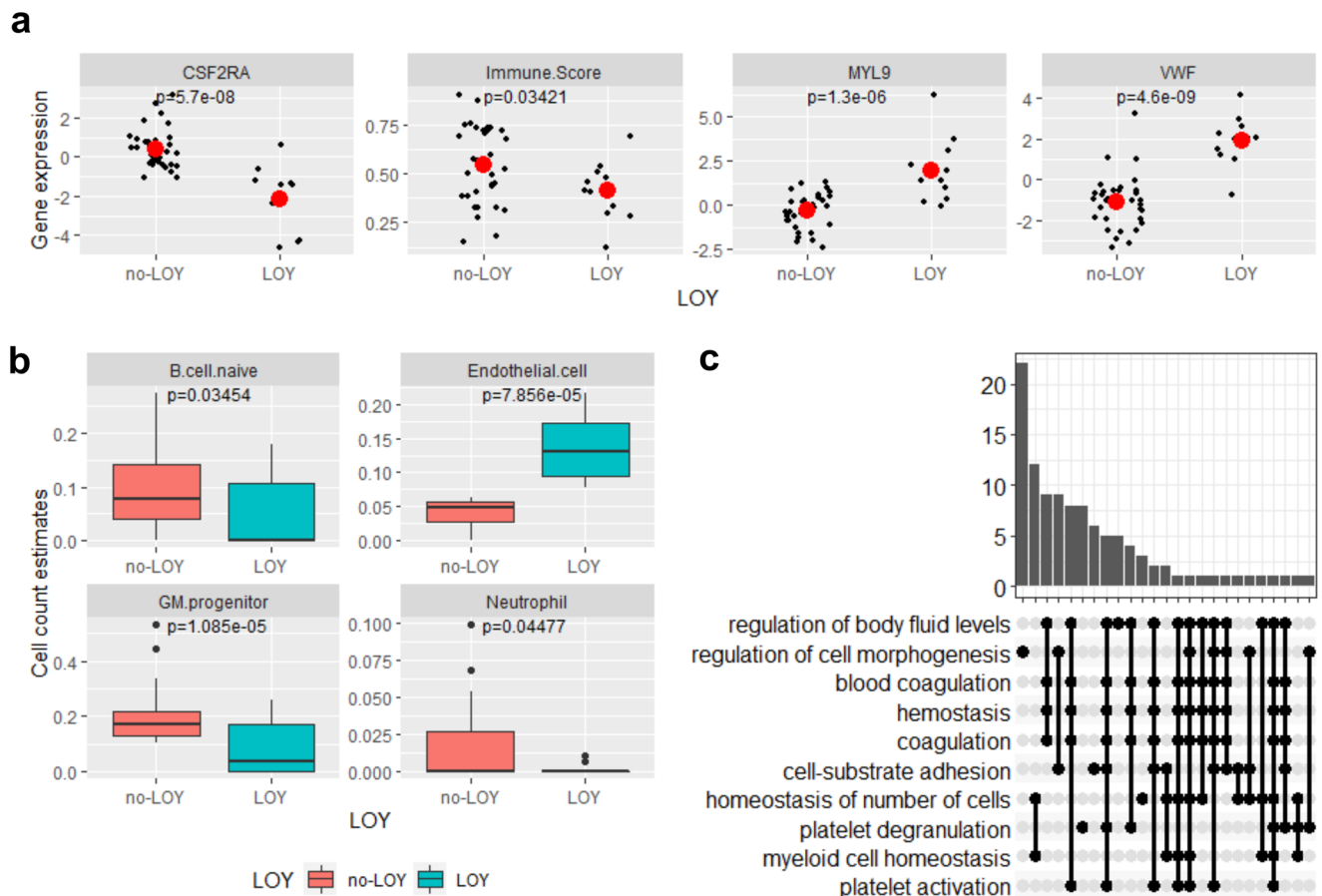


Fig. 4 | Transcriptomic signatures of LOY. **a** Decreased expression of *CSF2RA* mRNA and increased expression of *MYL9* and *VWF* in individuals with LOY compared with controls with no LOY (mean gene expression in red dot). **b** Different predicted cell counts underlying the transcriptomic differences between cases with

LOY and control individuals (no-LOY). **c** Gene Ontology (GO) enrichment of top differentially expressed genes. Boxplots show the interquartile range, while error bars represent the spread of data around the median.

susceptibility caused by LOY with implications for COVID-19. *CSF2RA*, located on the X-Y chromosome pseudoautosomal 1 (PAR1) region, is one of the most significantly down-regulated genes in LOY (Fig. 4a), along with other multiple Y chromosome genes with homologs on the X chromosome that escape X inactivation and with known function in immunity (Supplementary Data 4 and 5).

Top autosomal genes overexpressed in LOY, such as *VWF* and *MYL9* (Fig. 4a), are associated with cardiovascular risk. *VWF* codes for the von Willebrand factor (vWF), a pro-coagulant protein that promotes platelet adhesion and smooth muscle cell proliferation, while *MYL9* encodes Myosin Light Chain 9, regulatory, important in inflammatory immune responses.

Since changes in gene expression may reflect differences in cell-type composition and functionality, we estimated the average cell-type functional composition of samples from individuals with LOY compared to those without LOY using bulk transcriptome data (Table S4). The results were consistent with LOY individuals having significantly decreased GM-progenitors and B cell naïve cells, along with increased counts of endothelial cells (Fig. 4b). Enrichment gene set analysis using differentially expressed genes revealed a few categories significantly over-enriched, most notably the coagulation and cellular detoxification, the leukocyte migration and neutrophil activation (Fig. 4c, Tables S5 and S6). Overall, gene expression in LOY individuals leads to a down-regulated immune score.

Blood transcriptome in individuals with mCAs

For transcriptome analysis, we selected individuals only with copy-neutral mCAs to minimize the variability secondary to the individual

rearrangements. We then compared blood transcriptome from the 9 individuals with mCA and 90 age-paired individuals without mCA as controls. A total of 83 genes differentially expressed between groups were found, but enrichment analysis did not reveal any significantly deregulated pathway (Supplementary Data 6).

Down-regulated genes in LOY involved in response to SARS-CoV-2 infection

We tested whether the genes that participate in the primary response to SARS-CoV-2 infection were significantly deregulated in blood cells of individuals with LOY. We obtained 249 deregulated genes with SARS-CoV-2 infection in primary human lung epithelium (NHBE) and 130 for transformed lung alveolar (A549) (339 unique genes for the two cell lines). This gene set is highly over-represented in several pathways including defense response to virus, IL-17, type I interferon and NF-Kappa B signaling (Table S7). From the deregulated genes in cells infected with SARS-CoV-2, 13 were also deregulated in individuals with LOY (Fig. 5a and Table S8) indicating a strong significant over-representation (OR of enrichment = 7.23, $p = 1.5 \times 10^{-7}$). Most of these genes are interferon response genes (*IFIT3*, *IFI44L*, *ITFT1*, *IFI6*), which are down-regulated in individuals with LOY (Fig. 5b–d).

Discussion

We have shown in the SCOURGE study that clonal detectable mCAs, including XCM, are relatively common in blood of aging individuals, as previously reported¹⁴, with much higher frequency in males due to somatic LOY¹⁸. In addition to a risk factor for cancer, cardiovascular complications,

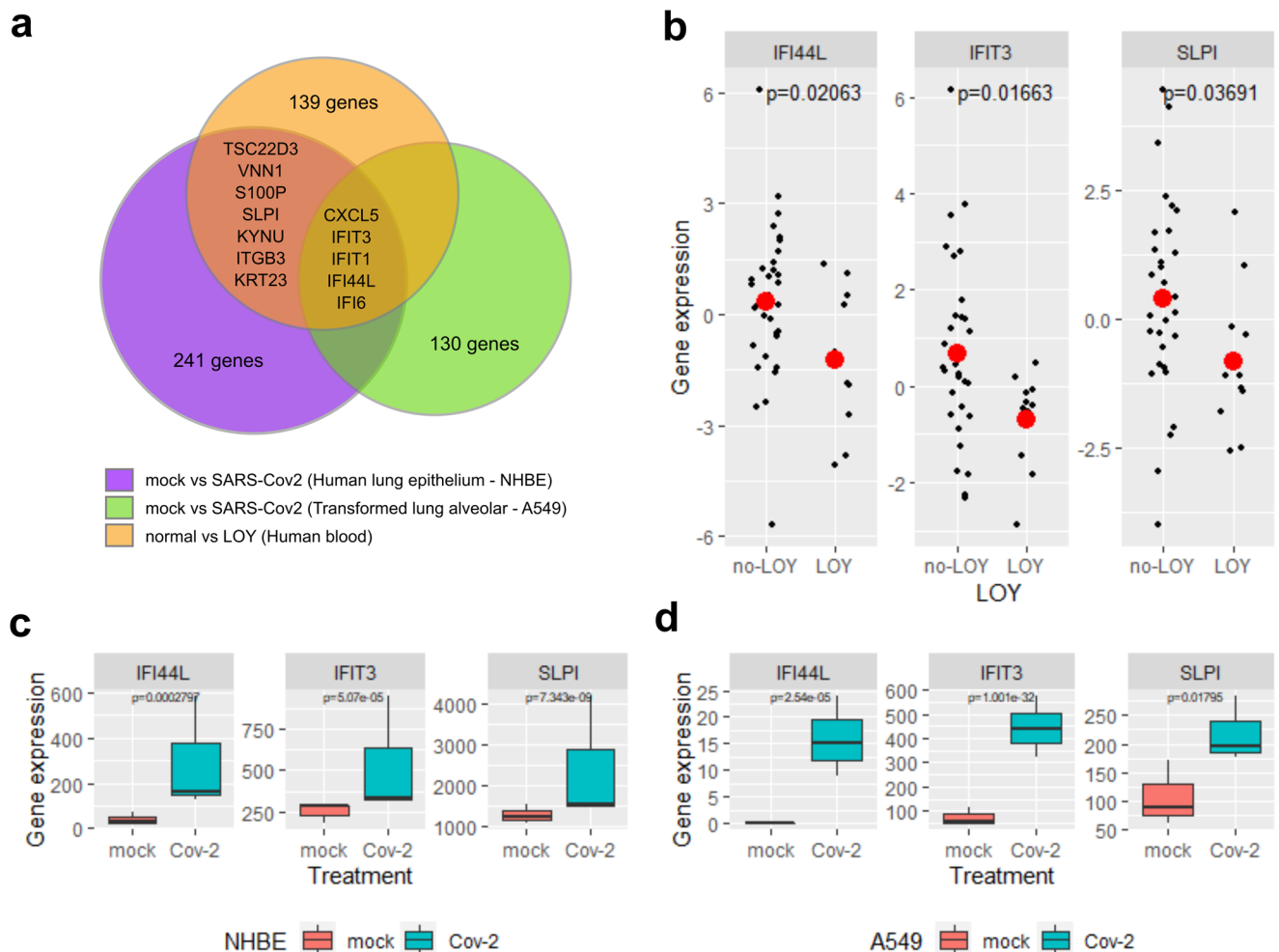


Fig. 5 | Transcriptomic overlap between LOY and SARS-CoV-2. **a** Overlap between top differentially expressed genes in individuals with LOY and deregulated genes in SARS-CoV-2 infected cells. Panels **b**, **c** and **d** show detailed gene expression patterns of some of these overlapping genes, including down-regulated in

individuals with LOY (**b**), and over-expressed in NHBE (**c**) and A549 (**d**) cell lines infected with SARS-CoV-2. Boxplots show the interquartile range, while error bars represent the spread of data around the median.

incidental infections and all cause early mortality^{12,16,18,28}, clonal hematopoiesis with mCA and/or XCM due to LOY is a risk factor for COVID-19 lethality with a combined odds ratio of 1.53. Despite some limitations of our study due to a relatively small sample size and the possibility of uncontrolled confounding factors, similar results have been recently reported in the UK biobank revealing increased risk for diverse incident infections and COVID-19 hospitalization in people with clonal hematopoiesis with chromosomal mosaicism^{16,28}. Our data indicate that these two types of chromosomal mosaicism underlie at least part of the aging-related and sex-biased severity and mortality of COVID-19. Therefore, identification of mCA and LOY in blood cells is likely to have an immediate clinical relevance in the management of aged patients with COVID-19.

Clonal hematopoiesis of indeterminate potential due to expansion of peripheral blood cells with acquired point mutations in a specific set of genes, is a similar condition that also increases with age and associates increased risk for cancer, cardiovascular disease, and decreased overall survival²⁹. A significant overlap after adjusting for age has been proven between detectable mCAs or LOY and mosaic gene mutations, suggesting a possible synergistic relationship between clonal hematopoiesis with gene mutations and acquired chromosomal rearrangements³⁰. Interestingly, a relationship between clonal hematopoiesis with gene mutations and risk of severe infections, including severe COVID-19, has also been recently documented³¹. However, although the increased severity and mortality of COVID-19 could be explained in part by the co-existence of clonal

hematopoiesis, the underlying mechanisms in individuals with LOY are likely different from those in individuals with mCAs or mosaic gene mutations.

The predisposing factors to autosomal events and LOY seem to be mostly unrelated, as no significant association has been found between both types of events in our cohort, their blood transcriptomic signatures do not overlap and the germline loci reported to predispose to autosomal mCAs and LOY are different^{16,19,21}. While only 10% of autosomal mCAs correspond to whole chromosome aneuploidies (mainly trisomies 8, 12 and 15 and monosomy 7) likely mediated by mitotic non-disjunction, this is the main mechanism for XCM and LOY. Mitotic non-disjunction of sister chromatids of the Y chromosome may be facilitated by the higher rate of cellular turnover of aging men. In mice, while the Y chromosome is stably transmitted during meiotic cell divisions, there is a high frequency of non-disjunction in mitosis, mainly in the earliest cleavage divisions³².

A possible pathogenetic mechanism that could be common to clonal mCAs and XCM is immunosenescence, which involves modifications of humoral and cellular immunity. One aspect of immunosenescence is a decline in the absolute number of peripheral blood lymphocytes with locus-dependent reduction of HLA class-I cell surface expression, related with increased risk of subsequent mortality³³. T-lymphocytes also play a central role in the effector and regulatory mechanisms of the adaptive immune response³⁴.

Many of the biochemical and transcriptomic alterations found in individuals with LOY have been already associated to poor prognosis for SARS-CoV-2 infection^{35,36}. Several genes located on the Y chromosome with relevant functions in the immune system have functional homologs on the X chromosome that escape X inactivation in females (Supplementary Data 4). Cells with XCM are likely haploinsufficient for many of those genes, which are downregulated in individuals with mosaic XCM due to LOY. In this regard, we observed low expression of *CSF2RA* in individuals with LOY, who also have low GM progenitors. *CSF2RA* codes for the alpha subunit of the heterodimeric receptor for colony stimulating factor 2, a cytokine that regulates the production, differentiation, and function of granulocytes and macrophages (GM-CSF), key cells for antigen presentation in infections, and is also critical for T cell function. GM-CSF increases IL-2R and IL-2 signaling, which can increase expansion of lymphocytes and IFN- γ production important for anti-viral response. Therefore, GM-CSF leads to enhanced protective responses³⁷. Loss or inactivation of both copies of the *CSF2RA* gene is associated with surfactant metabolism dysfunction-4 and pulmonary alveolar proteinosis, a primary immunodeficiency (OMIM 300770)³⁸. As Leukine[®] (sargramostim, rhu-GM-CSF) has been assessed in the SARPAC trial because of its potential positive effect on antiviral immunity and contribution to restore immune homeostasis in the lungs with inconclusive results (<https://clinicaltrials.gov/ct2/show/NCT04326920>), our data suggest that patients with LOY might be predictive of a poor response due to their low expression of one of the receptor subunits for GM-CSF (*CSF2RA*)³⁹.

Patients severely affected with COVID-19 have lower lymphocyte counts, especially T cells, higher leukocyte counts and neutrophil-lymphocyte-ratio, lower percentages of monocytes, eosinophils, and basophils, along with generally elevated levels of infection-related biomarkers and inflammatory cytokines, including IL-6. Helper, suppressor and regulatory T cells were all below normal levels in the severe group, with increased naive helper T cells and decreased memory helper T cells^{1,40}. We observed a significant overlap of deregulated genes in LOY individuals that participate in the immediate immune response elicited by SARS-CoV-2 virus infection. Some of these genes clearly activated in both studied cell types infected by SARS-CoV-2 are markedly under expressed in individuals with LOY (*SLPI*, *IFI6*, *IFIT1*, *IFIT3*, and *IFI44L*) (Fig. 5b–d). Secretory leukocyte protease inhibitor (SLPI) is a regulator of innate and adaptive immunity that protects the host from excessive inflammation in infectious disease, while the other four genes encode interferon induced proteins of the innate immune system that participate in the immediate host response to viral infections⁴¹. Dysfunctions of the adaptive immunity and interferon-mediated immediate host response in individuals with LOY are consistent with the observed sexual dimorphism in human immune system aging, and might underlie a poor immune response to SARS-CoV-2 infection⁴². This patterns along with the increased severity in older males, suggests that XCM due to LOY may be one underlying factor for susceptibility to COVID-19 in a proportion of patients.

In addition to depleted hematopoietic progenitor cells and possible immunodeficiency, individuals with LOY may have increased levels of circulating endothelial cells, which are known biomarkers for endothelial dysfunction and cardiovascular disease⁴³. In a mouse model with LOY, macrophages recruited to the heart showed aberrant profibrotic differentiation leading to cardiac fibrosis during aging⁴⁴. We observed up-regulation of *VWF* and *MYL9* in LOY. Pro-coagulant vWF promotes platelet adhesion and smooth muscle cell proliferation, and elevated levels of vWF have been associated with higher risk for thrombosis and cardiovascular disease⁴⁵. *MYL9* is a ligand for CD69 to form a net-like structure inside blood vessels in inflamed lungs and is also a risk factor for cardiovascular disease risk found over-expressed in aged versus young injured arteries⁴⁶. Through these mechanisms, LOY seems to contribute to COVID-19 lethality by its associated cardiovascular risk.

In summary, clonal detectable mCA & XCM are relatively common in aging individuals with much higher frequency in males due to somatic LOY. LOY is associated to decreased progenitors and stem cells, along with

immune system dysfunction and increased coagulation and cardiovascular risk, as revealed by biochemical and gene expression data. Our data indicate that this type of chromosomal mosaicism underlies at least part of the sex-biased severity and mortality of COVID-19 in aging patients. Given its potential relevance for modulating prognosis, therapeutic intervention, and immunization responses, we propose that evaluation of mCA/LOY by currently established methods should be implemented in both, retrospective studies and all prospective and currently ongoing clinical trials with different medications and vaccines for COVID-19. Testing for mCA/LOY at large scale in elderly people may also be helpful to evaluate vaccination response and to identify still unexposed people who may be especially vulnerable to severe COVID-19 disease.

Methods

Covid-19 infection, mortality data, mCA and LOY prevalence estimates

Accumulated data was obtained from the Spanish National Epidemiological Registry (<https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaARENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx>). Hospitalization rates, intensive care admission rates, and mortality stratified by age and sex was obtained from this report. Prevalence estimates of mCA and LOY by age were obtained from the general population^{14,21}.

EGCUT subjects, phenotype and genotype data

LOY and mCA were assessed in a total of 882 adult individuals belonging to the Estonian Gene Expression Cohort (EGCUT, www.biobank.ee) that comprises a large cohort of 53,000 samples of the Estonian Genome Center Biobank, University of Tartu⁴⁷. Detailed phenotypic information from all the individuals studied, including clinical analysis (blood cell counts and general biochemistry) and follow-up until June 2020, was available in ICD-10 codes. Patients selected in this study were genotyped using OmniX array. All individuals had genotyping success rate above 95%. All studies were performed in accordance with the ethical standards of the responsible committee on human experimentation, and with proper informed consent from all individuals tested.

SCOURGE subjects, phenotype and genotype data

A total of 9578 (5134 females and 4444 males) patients diagnosed with COVID-19 and recruited to the SCOURGE study were included in this study⁴⁸. Mean age was 62.58 years, 61.06 for females and 64.34 for males. Available phenotype data included age, sex, some clinical variables of past clinical history, several defined measures of COVID-19 severity and vital status (alive or dead) 90 days after diagnosis. The severity variables classified individuals in five levels called Asymptomatic (A), Mild (light: L), Moderate (M), Severe (G), and Critical (C). Additional information about pre-existing conditions as categorical variables was also available for most cases, including history of vascular disorders, cardiac problems, neurologic conditions, gastrointestinal disorders, onco-hematologic conditions, respiratory issues, and pulmonary thrombo-embolism. Blood DNA was genotyped using a customized Affymetrix SNP microarray⁴⁸. Genotype data passed quality controls for GWAS analysis. The whole SCOURGE project was approved by the Galician Ethical Committee Ref 2020/197, along with the Ethics and Scientific Committees of all participating centers.

Detection of mCA and LOY

The genotype CEL files from everyone were used to extract the log-R ratio (LRR) and B-allele (BAF) frequency from SNP probes. We used the *apt* software for quality control (QC) and the extraction of the array intensity signals. Following the QC pipeline with filters *axiom-dishqc-DQC* > 0.82 and *call-rate* > 0.97, we observed that all individuals could be included. The signals were obtained from CNV calling pipeline with default parameters *mapd-max* = 0.35 and *waviness-sd-max* = 0.1. We also called mosaicism in autosomes and chromosome X with the MAD algorithm⁴⁹. The method uses the fixed deviation from the expected BAF value of 0.5 for heterozygous SNPs (Bdev) to call allelic imbalances by using a segmentation procedure.

The segmentation was performed using the three different parameters of MAD: $T > 8$, $\alpha = 0.8$, $\text{minSegLength} > 100$. Some false positive alterations were detected in bad quality arrays. Therefore, curation via visual inspection, considering variability of LRR and BAF mean values in the segment, was performed by two independent investigators. Each mosaic alteration was classified as copy-loss, copy-gain or copy-neutral. The estimated percentage of abnormal cells was computed based on the B-deviation as previously reported¹⁰.

Mosaic LOY detection and quantification was performed using the *MADloy* tool which implements LOY calling using the mean LRR (mLRRY) and B-deviation derived-measures from chromosome Y across subjects⁵⁰. For each sample, *MADloy* first estimates the normalized mLRRY given by its ratio with the trimmed-mean of mLRRY values in the autosomes to discard regions with copy number alterations. B-deviation is calculated for the pseudoautosomal regions 1 and 2 (PAR1, 0–2.5 Mb on both Xp and Yp; PAR2, 300 kb on distal Xq and Yq, Mb 155 and 59, respectively), and the XY transposed region (88–92 Mb on X, 2.5–6.5 Mb on Y). The method is calibrated to detect mosaicism when the proportion of affected cells is above 10%. We then plotted the values of the mLRRY signals for males and females. A signal from chromosome Y in females is observed due to the background noise of the array and some cross-hybridization. While we observed variability of the mLRRY signal, numerous males were identified with extreme low values of mLRRY, suggesting loss of chromosome Y. We categorized the level of LOY status into three groups according to the magnitude of the decrease in mLRRY, believed to be a function of XCM/LOY cellularity.

Bulk transcriptome data

Gene expression was obtained with Illumina whole-genome expression BeadChips (HT12v3) from peripheral blood RNA in the EGCUT cohort. Low quality samples were excluded. All probes with primer polymorphisms were left out, leaving 34,282 probes. The expression dataset is publicly available at GEO (Gene Expression Omnibus) under the accession number GSE48348⁴⁵. In this dataset, a total of 11 individuals with LOY and 9 individuals with copy-neutral mCAs were identified. In order to consider the effect of aging on LOY/mCA detection and to have the maximum power, 32 age and gender-paired normal samples without LOY or mCA (3 controls per case) were selected for the transcriptomic analyses.

The effect of SARS-CoV-2 infection on gene expression was assessed in independent biological triplicates of two different cell lines that were mock treated or infected with SARS-CoV-2 (USA-WA1/2020). One corresponds to primary human lung epithelium (NHBE) and the other to transformed lung alveolar cells (A549). These data are available at GEO under the accession number GSE147507.

Statistical data analyses

Gene expression data was quantile-normalized to the median. We analyzed linear regression residuals of gene expression data on forty multi-dimensional scaling components, to correct for possible unwanted variability. Array quality was assessed using *arrayQualityMetrics* Bioconductor package. *genefilter* Bioconductor package was used to filter for features without annotation and/or exhibiting little variation and low signal across samples, leaving a total of 15,592 probes from 34,282. Differential expression (DE) between individuals with and without LOY was then performed using *limma* Bioconductor package. Significant DE genes were considered at false discovery rate (FDR) < 0.05 . Significant DE genes at $p < 0.001$ level was selected for Gene Ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analysis with *clusterProfiler* Bioconductor package. Over-representation of DE genes in the gene set obtained from the analysis of SARS-CoV-2 infected cell lines ($p < 0.001$ and $\log_2\text{-foldchange} > 0.5$) was performed using exact Fisher test. Cell-type composition of the 43 individuals with bulk transcriptomic data (11 LOY, 32 normal) was estimated using the 'xcell' method implemented in the *immunodeconv* R package⁵¹.

Association analysis between mCA or LOY status and clinical data, including blood cell counts and biochemical parameters, was assessed using linear models adjusted by age. All statistical analyses were performed using the statistical software R version 3.6.3 (<http://www.r-project.org>).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Transcriptomic data from EGCUT individuals are available at GEO repository under the accession number GSE48348. LOY and mCA status obtained from genomic data are available upon request.

Received: 18 February 2022; Accepted: 11 January 2024;

Published online: 19 February 2024

References

- Zhou, P. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **579**, 270–273 (2020).
- Verity, R. et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect. Dis.* **20**, 669–677 (2020).
- Williamson, E. J. et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430–436 (2020).
- Leong, H.-N. et al. SARS in Singapore-predictors of disease severity. *Ann. Acad. Med. Singap.* **35**, 326–331 (2006).
- Alghamdi, I. G. et al. The pattern of Middle east respiratory syndrome coronavirus in Saudi Arabia: A descriptive epidemiological analysis of data from the Saudi Ministry of Health. *Int. J. Gen. Med.* **7**, 417–423 (2014).
- Channappanavar, R. et al. Sex-based differences in susceptibility to severe acute respiratory syndrome Coronavirus infection. *J. Immunol.* **198**, 4046–4053 (2017).
- Takahashi, T. et al. Sex differences in immune responses that underlies COVID-19 disease outcomes. *Nature* **177**, 4375–4385 (2020).
- Jin, J.-M. et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front. Public Health* **8**, 152 (2020).
- Bastard, P. et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370**, eabd4585 (2020).
- COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. *Nature* **600**, 472–477 (2021).
- Rodríguez-Santiago, B. et al. Mosaic uniparental disomies and aneuploidies as large structural variants of the human genome. *Am. J. Hum. Genet.* **87**, 129–138 (2010).
- Jacobs, K. B. et al. Detectable clonal mosaicism and its relationship to aging and cancer. *Nat. Genet.* **44**, 651–658 (2012).
- Laurie, C. C. et al. Detectable clonal mosaicism from birth to old age and its relationship to cancer. *Nat. Genet.* **44**, 642–650 (2012).
- Machiela, M. J. et al. Characterization of large structural genetic mosaicism in human autosomes. *Am. J. Hum. Genet.* **96**, 487–497 (2015).
- Loh, P. R. et al. Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations. *Nature* **559**, 350–355 (2018).
- Zekavat, S. M. et al. Hematopoietic mosaic chromosomal alterations and risk for infection in 767891 individuals without blood cancer. *Nat. Med.* **27**, 1012–1024 (2021).
- Guo, X. et al. Mosaic loss of human Y chromosome: what, how and why. *Hum. Genet.* **139**, 421–446 (2020).
- Forsberg, L. A. et al. Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer. *Nat. Genet.* **46**, 624–628 (2014).
- Zhou, W. et al. Mosaic loss of chromosome Y is associated with common variation near TCL1A. *Nat. Genet.* **48**, 563–568 (2016).

20. Lofftfield, E. et al. Predictors of mosaic chromosome Y loss and associations with mortality in the UK Biobank. *Sci. Rep.* **8**, 12316 (2018).
21. Thompson, D. J. et al. Genetic predisposition to mosaic Y chromosome loss in blood. *Nature* **575**, 652–657 (2019).
22. Cáceres, A., Jene, A., Esko, T., Pérez-Jurado, L. A. & González, J. R. Extreme down-regulation of chromosome Y and cancer risk in men. *J. Natl Cancer Inst.* **112**, 913–920 (2020).
23. Cáceres, A., Jene, A., Esko, T., Pérez-Jurado, L. A. & González, J. R. Extreme down-regulation of chromosome Y and Alzheimer's disease in men. *Neurobiol. Aging* **90**, 150.e1–150.e4 (2020).
24. Machiela, M. J. et al. Female chromosome X mosaicism is age-related and preferentially affects the inactivated X chromosome. *Nat. Commun.* **7**, 11843 (2016).
25. Fuchs, M. M., Attenhofer Jost, C., Babovic-Vuksanovic, D., Connolly, H. M. & Egbe, A. Long-term outcomes in patients with Turner Syndrome: A 68-year follow-up. *J. Am. Heart Assoc.* **8**, e011501 (2019).
26. Wang, H. et al. Bioinformatic analysis identifies potential key genes in the pathogenesis of Turner Syndrome. *Front. Endocrinol.* **11**, 104 (2020).
27. González, J. R. et al. A robust estimation of mosaic loss of chromosome Y from genotype-array-intensity data to improve disease risk associations and transcriptional effects. *BMC Bioinforma.* **21**, 533 (2020).
28. Evans, M. A., Sano, S. & Walsh, K. Cardiovascular disease, aging, and clonal hematopoiesis. *Annu Rev. Pathol.* **15**, 419–438 (2020).
29. Lin, S. H. et al. Mosaic chromosome Y loss is associated with alterations in blood cell counts in UK Biobank men. *Sci. Rep.* **10**, 3655 (2020).
30. Gao, T. et al. Interplay between chromosomal alterations and gene mutations shapes the evolutionary trajectory of clonal hematopoiesis. *Nat. Commun.* **12**, 338 (2021).
31. Bolton, K. L. et al. Clonal hematopoiesis is associated with risk of severe Covid-19. *Nat. Commun.* **12**, 5975 (2021).
32. Bean, C. J., Hunt, P. A., Millie, E. A. & Hassold, T. J. Analysis of a malsegregating mouse Y chromosome: evidence that the earliest cleavage divisions of the mammalian embryo are non-disjunction-prone. *Hum. Mol. Genet.* **10**, 963–972 (2001).
33. Dai, X. & Guo, X. Decoding and rejuvenating human ageing genomes: Lessons from Mosaic chromosomal alterations. *Ageing Res. Rev.* **68**, 101342 (2021).
34. Rodríguez, I. J. et al. Immunosenescence study of T cells: a systematic review. *Front. Immunol.* **11**, 604591 (2021).
35. Wu, C., et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern. Med.* Mar 13;e200994. (2020).
36. Chen, G. et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J. Clin. Invest.* **130**, 2620–2629 (2020).
37. Autenshlyus, A. et al. The relationship between Cytokine Production, CSF2RA, and IL1R2 expression in Mammary Adenocarcinoma, tumor histopathological parameters, and lymph node metastasis. *Technol. Cancer Res. Treat.* **18**, 1533033819883626 (2019).
38. Suzuki, T. et al. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. *J. Exp. Med.* **205**, 2703–2710 (2008).
39. Bosteels, C. et al. Sargramostim to treat patients with acute hypoxic respiratory failure due to COVID-19 (SARPAC): A structured summary of a study protocol for a randomised controlled trial. *Trials* **21**, 491 (2020).
40. Wen, W. et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov.* **6**, 31 (2020).
41. Majchrzak-Gorecka, M., Majewski, P., Grygier, B., Murzyn, K. & Cichy, J. Secretory leukocyte protease inhibitor (SLPI), a multifunctional protein in the host defense response. *Cytokine Growth Factor Rev.* **28**, 79–93 (2016).
42. Márquez, E. J. et al. Sexual-dimorphism in human immune system aging. *Nat. Commun.* **11**, 751 (2020).
43. Farinacci, M. et al. Circulating endothelial cells as biomarker for cardiovascular diseases. *Res Pr. Thromb. Haemost.* **3**, 49–58 (2019).
44. Sano, S. et al. Hematopoietic loss of Y chromosome leads to cardiac fibrosis and heart failure mortality. *Science* **377**, 292–297 (2022).
45. Shehadeh, L. A., Webster, K. A., Hare, J. M. & Vazquez-Padron, R. I. Dynamic regulation of vascular myosin light chain (MYL9) with injury and aging. *PLoS One* **6**, e25855 (2011).
46. Kimura, M. Y., Koyama-Nasu, R., Yagi, R. & Nakayama, T. A new therapeutic target: The CD69-Myl9 system in immune responses. *Semin. Immunopathol.* **41**, 349–358 (2019).
47. Leitsalu, L. et al. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J. Epidemiol.* **44**, 1137–1147 (2015).
48. Cruz, R. et al. Novel genes and sex differences in COVID-19 severity. *Hum. Mol. Genet.* **31**, 3789–3806 (2022).
49. González, J. R. et al. A fast and accurate method to detect allelic genomic imbalances underlying mosaic rearrangements using SNP array data. *BMC Bioinforma.* **12**, 166 (2011).
50. Spiel, A. O., Gilbert, J. C. & Jilma, B. Von Willebrand Factor in Cardiovascular Disease. *Circulation* **117**, 1449–1459 (2008).
51. Tsoucas, D. et al. Accurate estimation of cell-type composition from gene expression data. *Nat. Commun.* **10**, 1–9 (2019).

Acknowledgements

We thank Gemma Moncunill, Lluís Armengol and Jozef Gecz for their critical reading of initial versions of this manuscript. The authors acknowledge support from the Catalan Department of Economy and Knowledge (SGR2017/1974, SGR2017/801), the Spanish Ministry of Science “Programa de Excelencia María de Maeztu” (MDM-2014-0370) and “Centro de Excelencia Severo Ochoa” (CEX2018-000806-S), the Fondo Europeo de Desarrollo Regional, UE (RTI2018-100789-B-I00) and the Estonian Research Council (PUT1660). The SCOURGE study has been funded by Instituto de Salud Carlos III (COV20_00622) and cofunded by European Union (ERDF) “A way of making Europe”; additional funding was received from Amancio Ortega Foundation and Banco de Santander. Authors also receive support from the Generalitat de Catalunya through the CERCA Program.

Author contributions

Conceptualization, L.A.P.J. and J.R.G.; Funding acquisition, L.A.P.J., TE (EGCUT), P.L. and Acar (SCOURGE) and J.R.G.; Data provider, T.E., M.L.d.H., I.Q., R.C., P.L., Acar, and SCOURGE Cohort Group; Data analysis: J.R.G., Acac, L.B.D. and L.A.P.J.; Methodology, Acac and J.R.G.; Project administration, L.A.P.J., P.L. and J.R.G.; Software, L.B.D. and J.R.G.; Validation, L.A.P.J. and Acac; Supervision and visualization, L.A.P.J. and J.R.G.; Writing original draft, L.A.P.J.; Writing review & editing, L.A.P.J., Acac and J.R.G.. L.A.P.J., Acac and J.R.G. contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Competing interests

LAPJ is founding partner and scientific advisor of qGenomics laboratories. The other authors declare no competing interests.

Ethics approval and consent to participate

All studies were performed in accordance with the ethical standards of the responsible committee on human experimentation, and with proper informed consent from all individuals tested.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s42003-024-05805-6>.

Correspondence and requests for materials should be addressed to Luis A. Pérez-Jurado or Juan R. González.

Peer review information *Communications Biology* thanks Soichi Sano and Xihan Guo for their contribution to the peer review of this work. Primary Handling Editors: Eve Rogers and Manuel Breuer. A peer review file is available.

Reprints and permissions information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2024

¹Genetics Unit, Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain. ²Genetics Service, Hospital del Mar & Hospital del Mar Research Institute (IMIM), Barcelona, Spain. ³Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), ISCIII, Barcelona, Spain. ⁴Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain. ⁵Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. ⁶Estonian Genome Science Centre, University of Tartu, Tartu, Estonia. ⁷Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. ⁸Centro Nacional de Genotipado (CEGEN), Universidade de Santiago de Compostela, Santiago de Compostela, Spain. ⁹Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, Spain. ¹⁰Centro Singular de Investigación en Medicina Molecular y Enfermedades Crónicas (CIMUS), Universidade de Santiago de Compostela, Santiago de Compostela, Spain. ¹¹Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz-IDIPAZ, Madrid, Spain. ¹²ERN-ITHACA-European Reference Network, Paris, France. ¹³Fundación Pública Galega de Medicina Xenómica, Sistema Galego de Saúde (SERGAS), Santiago de Compostela, Spain. ¹⁴Department of Mathematics, Universitat Autònoma de Barcelona, Bellaterra, Spain. ^{27,29}These authors contributed equally: Luis A. Pérez-Jurado, Alejandro Cáceres. ✉ e-mail: luis.perez@upf.edu; juan.gonzalez@isglobal.org

SCOURGE Cohort Group

Javier Abellán^{15,16}, René Acosta-Isaac¹⁷, Jose María Aguado^{18,19,20,21}, Carlos Aguilar²², Sergio Aguilera-Albesa^{23,24}, Abdolrah Ahmadi Sabbagh²⁵, Jorge Alba²⁶, Sergiu Albu^{27,28,29}, Karla A. M. Alcalá-Gallardo³⁰, Julia Alcoba-Florez³¹, Sergio Alcolea Batres³², Holmes Rafael Algarin-Lara^{33,34}, Virginia Almadana³⁵, Kelliane A. Medeiros^{36,37}, Julia Almeida^{38,39}, Berta Almoguera^{3,40}, María R. Alonso⁴¹, Nuria Álvarez⁴¹, Rodolfo Álvarez-Sala Walther³², Yady Álvarez-Benítez^{33,34}, Felipe Álvarez-Navia^{42,43}, Katiusse A. dos Santos⁴⁴, Álvaro Andreu-Bernabeu^{20,45}, María Rosa Antonijoan⁴⁶, Eleno Martínez-Aquino⁴⁷, Eunáte Arana-Arri^{48,49}, Carlos Aranda^{50,51}, Celso Arango^{20,45,52}, Carolina Araque^{53,54}, Nathalia K. Araujo⁵⁵, Ana C. Arcanjo^{56,57,58}, Ana Arnaiz^{59,60}, Francisco Arnalich Fernández⁶¹, María J. Arranz⁶², José Ramón Arribas López⁶¹, María-Jesús Artiga⁶³, Yubelly Avello-Malaver⁶⁴, Carmen Ayuso^{3,40}, Belén Ballina Martín²⁵, Raúl C. Baptista-Rosas^{65,66,67}, Ana María Baldion⁶⁴, Andrea Barranco-Díaz³⁴, María Barreda-Sánchez^{68,69}, Viviana Barrera-Penagos⁶⁴, Moncef Belhassen-García^{43,70}, David Bernal-Bello⁷¹, Enrique Bernal⁶⁸, Joao F. Bezerra⁷², Marcos A. C. Bezerra⁷³, Natalia Blanca-López⁷⁴, Rafael Blancas⁷⁵, Lucía Boix-Palop⁷⁶, Alberto Borobia⁷⁷, Elsa Bravo⁷⁸, María Brion^{79,80}, Óscar Brochado-Kith⁸¹, Ramón Brugada^{80,82,83,84}, Matilde Bustos⁸⁵, Alfonso Cabello⁸⁶, Alejandro Cáceres^{4,5,27,29}, Juan J. Cáceres-Agra⁸⁷, Esther Calbo⁷⁶, Enrique J. Calderón^{6,88,89}, Shirley Camacho⁹⁰, Francisco C. Ceballos⁸¹, Yolanda Cañadas⁵¹, Cristina Carbonell^{42,43}, Servando Cardona-Huerta⁹¹, María Sánchez-Carpintero Abad^{50,51}, Carlos Carpio Segura³², José Antonio Carrillo-Avila⁹², Marcela C. Campos⁵⁶, Carlos Casasnovas^{3,93,94}, Luis Castaño^{3,48,95,96,97}, Carlos F. Castaño^{50,51}, Jose E. Castelao⁹⁸, Aranzazu Castellano Candalija⁹⁹, María A. Castillo⁹⁰, Walter G. Chaves-Santiago^{54,100}, Sylena Chiquillo-Gómez^{33,34}, Marco A. Cid-López³⁰, Óscar Cienfuegos-Jiménez⁹¹, Rosa Conde-Vicente¹⁰¹, Gabriela C. R. Cunha¹⁰², M. Lourdes Cordero-Lorenzana¹⁰³, Dolores Corella^{104,105}, Almudena Corrales^{106,107}, Jose L. Cortés-Sánchez^{91,108}, Marta Corton^{3,40}, Karla S. C. Souza¹⁰⁹, Fabiola T. C. Silva⁵⁶, Raquel Cruz^{3,8,9,10}, Luisa Cuesta¹¹⁰, Nathali A. C. Tavares¹¹¹, Maria C. C. Carvalho¹¹², David Dalmau^{62,76}, Raquel C. S. Dantas-Komatsu¹¹³, M. Teresa Darnaude¹¹⁴, Raimundo de Andrés¹¹⁵, Carmen de Juan¹¹⁶, Juan J. de la Cruz Troca^{6,117,118}, Carmen de la Horra⁸⁹, Ana B. de la Hoz⁴⁸, Alba De Martino-Rodríguez^{119,120}, Marina S. Cruz¹²¹, Julianna Lys de Sousa Alves Neri¹²², Victor del Campo-Pérez¹²³, Juan Delgado-Cuesta¹²⁴, Aranzazu Diaz de Bustamante¹¹⁴, Anderson Díaz-Pérez³⁴, Beatriz Dietl⁷⁶, Sílvia Diz-de Almeida^{3,10}, Manoella do Monte Alves^{125,126}, Elena Domínguez-Garrido¹²⁷, Lidia S. Rosa¹²⁸, Andre D. Luchessi¹²⁹, Jose Echave-Sustaeta¹³⁰, Rocío Eiros¹³¹, César O. Enciso-Olivera^{53,54}, Gabriela Escudero¹³², Pedro Pablo España¹³³, Gladys Estigarribia Sanabria¹³⁴,

María Carmen Fariñas^{59,60,135}, Ramón Fernández^{59,136}, Lidia Fernández-Caballero^{3,40}, Ana Fernández-Cruz¹³⁷,
 Silvia Fernández-Ferrero²⁵, Yolanda Fernández Martínez²⁵, María J. Fernandez-Nestosa¹³⁸, Uxía Fernández-Robelo¹³⁹,
 Amanda Fernández-Rodríguez⁸¹, Marta Fernández-Sampedro^{59,60,135}, Ruth Fernández^{3,40}, Tania Fernández-Villa¹⁴⁰,
 Carmen Fernández-Capitán⁹⁹, Antonio Augusto F. Carioca¹⁴¹, Patricia Flores-Pérez¹⁴², Lácides Fuenmayor-Hernández³⁴,
 Marta Fuertes-Núñez²⁵, Victoria Fumadó¹⁴³, Ignacio Gadea¹⁴⁴, Lidia Gagliardi^{50,51}, Manuela Gago-Domínguez^{9,13},
 Natalia Gallego¹¹, Cristina Galoppo¹⁴⁵, Ana García-Soidán¹⁴⁶, Carlos García-Cerrada^{15,16}, Aitor García-de-Vicuña^{48,95},
 Josefina García-García⁶⁸, Irene García-García⁷⁷, Carmen García-Ibarbia^{59,60,135}, Andrés C. García-Montero¹⁴⁷, Leticia García^{50,51},
 Mercedes García^{50,51}, María Carmen García Torrejón^{16,148}, Inés García^{3,40}, Elisa García-Vázquez⁶⁸, Emiliano Garza-Frias⁹¹,
 Angela Gentile¹⁴⁵, Belén Gil-Fournier¹⁴⁹, Jéssica N. G. de Araújo¹⁵⁰, Mario Gómez-Duque^{54,100}, Javier Gómez-Arre^{119,120},
 Luis Gómez Carrera³², María Gómez García⁸, Ángela Gómez Sacristán¹⁵¹, Juan R. González^{4,5,6,14}, Anna González-Neira⁴¹,
 Beatriz González Álvarez^{119,120}, Fernán González Bernaldo de Quirós¹⁵², Rafaela González-Montelongo¹⁵³,
 Javier González-Peñas^{20,45,52}, Manuel Gonzalez-Sagrado¹⁰¹, Hugo Gonzalo-Benito¹⁵⁴, Oscar Gorgojo-Galindo¹⁵⁵,
 Miguel Górgolas⁸⁶, Florencia Guaragna¹⁴⁵, Jessica G. Chau⁵⁴, Encarna Guillén-Navarro^{68,156,157,158}, Beatriz Guillén-Guío¹⁰⁶,
 Pablo Guisado-Vasco¹³⁰, Luz D. Gutiérrez-Castañeda^{54,159}, Juan F. Gutiérrez-Bautista¹⁶⁰, Sara Heili-Frades¹⁶¹,
 Rafael H. Jacomo¹⁶², Estefania Hernández¹⁶³, Cristina Hernández-Moro²⁵, Luis D. Hernández-Ortega^{164,165},
 Guillermo Hernández-Pérez⁴², Rebeca Hernández-Vaquero¹⁶⁶, Belén Herráez⁴¹, M. Teresa Herranz⁶⁸, María Herrera^{50,51},
 María José Herrero^{167,168}, Antonio Herrero-González¹⁶⁹, Juan P. Horcajada^{28,170,171,172}, Natale Imaz-Ayo⁴⁸,
 Mainer Intxausti-Urrutibeaskoa¹⁷³, Antonio Íñigo-Campos¹⁵³, María Íñiguez¹⁷⁴, Rubén Jara⁶⁸, Ángel Jiménez^{50,51},
 Ignacio Jiménez-Alfaro¹⁷⁵, Pilar Jiménez¹⁶⁰, María A. Jiménez-Sousa⁸¹, Iolanda Jordan^{6,176,177}, Rocío Laguna-Goya^{178,179},
 Daniel Laorden³², María Lasa-Lázaro^{178,179}, María Claudia Lattig^{90,180}, Ailen Lauriente¹⁴⁵, Anabel Liger Borja¹⁸¹, Lucía Llanos¹⁸²,
 Amparo López-Bernús^{42,43}, Miguel López de Heredia³, Esther Lopez-García^{6,117,118,183}, Eduardo López-Granados^{3,184,185},
 Rosario Lopez-Rodríguez^{3,40}, Miguel A. López-Ruz^{186,187,188}, Leonardo Lorente¹⁸⁹, José M. Lorenzo-Salazar¹⁵³, José E. Lozano¹⁹⁰,
 María Lozano-Espinosa¹⁸¹, Ignacio Mahillo^{107,191,192}, Esther Mancebo^{178,179}, Carmen Mar¹³³, Cristina Marcelo Calvo⁹⁹,
 Alba Marcos-Delgado¹⁹³, Miguel Marcos^{42,43}, Alicia Marín-Candón⁷⁷, Pablo Mariscal-Aguilar³², Laura Martin-Pedraza⁷⁴,
 Marta Martin-Fernandez¹⁹⁴, Caridad Martín-López¹⁸¹, José-Ángel Martín-Oterino^{42,43}, María Dolores Martín¹⁹⁵, Vicente Martín^{6,193},
 María M. Martín¹⁹⁶, María Martín-Vicente⁸¹, Amalia Martínez¹⁹⁷, Óscar Martínez-González⁷⁵, Ricardo Martínez¹⁶³,
 Pedro Martínez-Paz¹⁵⁴, Covadonga M. Díaz-Caneja^{20,45,52}, Óscar Martínez-Nieto^{64,180}, Iciar Martínez-López^{198,199},
 Michel F. Martínez-Reséndez⁹¹, Silvia Martínez^{59,135}, Juan José Martínez^{3,94}, Ángel Martínez-Pérez²⁰⁰, Andrea Martínez-Ramas^{3,40},
 Violeta Martínez-Robles²⁵, Laura Marzal^{3,40}, Juliana F. Mazzeu^{201,202,203}, Francisco J. Medrano^{6,88,89}, Xose M. Meijome^{204,205},
 Natalia Mejuto-Montero²⁰⁶, Ingrid Mendes³, Alice L. Duarte¹⁰⁹, Ana Méndez-Echevarría²⁰⁷, Humberto Mendoza Charris^{34,78},
 Eleuterio Merayo Macías²⁰⁸, Fátima Mercadillo²⁰⁹, Arie R. Mercado-Sesma^{164,165}, Pablo Mínguez^{3,40}, Elena Molina-Roldán²¹⁰,
 Antonio J. J. Molina¹⁹³, Juan José Montoya¹⁶³, Susana M. T. Pinho^{36,211,212}, Patricia Moreira-Escriche¹¹⁶, Xenia Morelos-Arnedo^{34,78},
 Rocío Moreno³, Víctor Moreno Cuerda^{15,16}, Antonio Moreno-Docón⁶⁸, Junior Moreno-Escalante³⁴, Alberto Moreno Fernández⁹⁹,
 Patricia Muñoz García^{20,107,213}, Pablo Neira¹⁴⁵, Julián Nevado^{3,11,12}, Israel Nieto-Gañán¹⁴⁶, Vivian N. Silbiger¹²⁹,
 Rocío Nuñez-Torres⁴¹, Antònia Obrador-Hevia^{214,215}, J. Gonzalo Ocejo-Vinyals^{59,135}, Virginia Olivar¹⁴⁵, Silviene F. Oliveira^{56,203,216,217},
 Lorena Ondo^{3,40}, Alberto Orfao^{38,39}, Eva Ortega-Paino⁶³, Luis Ortega²¹⁸, Rocío Ortiz-López⁹¹, Fernando Ortiz-Flores^{59,135},
 José A. Oteo^{26,174}, Manuel Pacheco¹⁶³, Fredy Javier Pacheco-Miranda³⁴, Irene Padilla-Conejo²⁵, Sonia Panadero-Fajardo⁹²,
 Mara Parellada^{20,45,52}, Roberto Pariente-Rodríguez¹⁴⁶, Vicente Friaiza^{6,89}, Estela Paz-Artal^{178,179,219}, Germán Peces-Barba^{107,220},
 Miguel S. Pedromingo Kus²²¹, Celia Perales¹⁴⁴, Ney P. C. Santos²²², Genilson P. Guegel²²³, María Jazmín Pérez¹⁴⁵,
 Alexandra Pérez^{80,82}, Patricia Pérez-Matute¹⁷⁴, César Pérez²²⁴, Gustavo Pérez-de-Nanclares^{48,95}, Felipe Pérez-García^{225,226},
 Patricia Pérez²²⁷, Luis A. Pérez-Jurado^{1,2,3,279}, M. Elena Pérez-Tomás⁶⁸, Teresa Perucho²²⁸, Lisbeth A. Pichardo²⁵,
 Adriana P. Ribeiro^{36,37,212}, Mel-lina Pinsach-Abuin^{80,82}, Luz Adriana Pinzón^{54,100}, Jeane F. P. Medeiros²²⁹, Guillermo Pita⁴¹,
 Francesc Pla-Juncà^{3,230}, Laura Planas-Serra^{3,94}, Ericka N. Pompa-Mera²³¹, Gloria L. Porras-Hurtado¹⁶³, Aurora Pujol^{3,94,232},
 María Eugenia Quevedo-Chávez^{33,34}, María Angeles Quijada^{46,233}, Inés Quintela⁸, Soraya Ramiro-León¹⁴⁹,
 Pedro Rascado Sedes²³⁴, Joana F. R. Nunes⁵⁶, Delia Recalde^{119,120}, Emma Recio-Fernández¹⁷⁴, Salvador Resino⁸¹,
 Renata R. Sousa²¹², Carlos S. Rivadeneira-Chamorro⁵⁴, Diana Roa-Agudelo⁶⁴, Montserrat Robelo Pardo²³⁴,
 Marianne R. Fernandes^{222,235}, María A. Rodríguez-Hernández⁸⁵, Agustí Rodríguez-Palmero^{94,236}, Emilio Rodríguez-Ruiz^{9,234},
 Marilyn Johanna Rodriguez⁵⁴, Fernando Rodríguez-Artalejo^{6,117,118,183}, Marena Rodríguez-Ferrer³⁴,
 Carlos Rodríguez-Gallego^{237,238}, José A. Rodríguez-García²⁵, Belén Rodríguez Maya¹⁵, Antonio Rodríguez-Nicolas¹⁶⁰,
 German Ezequiel Rodríguez-Novoa¹⁴⁵, Paula A. Rodriguez-Urrego⁶⁴, Federico Rojo^{239,240}, Andrea Romero-Coronado³⁴,
 Rubén Morilla^{89,241}, Filomeno Rondón-García²⁵, Antonio Rosales-Castillo²⁴², Cladelis Rubio²⁴³, María Rubio Olivera^{50,51},
 Francisco Ruiz-Cabello^{160,187,244}, Eva Ruiz-Casares²²⁸, Juan J. Ruiz-Cubillan^{59,135}, Javier Ruiz-Hornillos^{51,245,246}, Montserrat Ruiz^{3,94},
 Pablo Ryan^{247,248,249}, Hector D. Salamanca^{53,54}, Lorena Salazar-García⁹⁰, Giorgina Gabriela Salgueiro-Origlia⁹⁹, Anna Sangil⁷⁶,
 Olga Sánchez-Pernaute²⁵⁰, Pedro-Luis Sánchez^{43,131}, Antonio J. Sánchez López²⁵¹, Clara Sánchez-Pablo¹³¹,

María Concepción Sánchez-Prados³², Javier Sánchez-Real²⁵, Jorge Sánchez-Redondo^{15,252}, Cristina Sancho-Sainz¹⁷³, Esther Sande²²⁴, Arnoldo Santos²²⁴, Agatha Schlüter^{3,94}, Sonia Segovia^{230,253,254}, Alex Serra-Llovich⁶², Fernando Sevil-Puras²², Marta Sevilla-Porras^{3,11}, Miguel A. Sicolo^{255,256}, Cristina Silván-Fuentes³, Vitor M. S. Moraes²⁵⁷, Vanessa S. Souza¹⁰², Jordi Solé-Violán^{107,258}, José Manuel Soria²⁰⁰, Jose V. Sorli^{104,105}, Nayara S. Silva²⁵⁹, Juan Carlos Souto¹⁷, John J. Sprockel^{54,100}, José Javier Suárez-Rama⁸, David A. Suárez-Zamora⁶⁴, Xiana Taboada-Fraga²⁰⁶, Eduardo Tamayo^{155,260}, Alvaro Tamayo-Velasco²⁶¹, Juan Carlos Taracido-Fernández¹⁶⁹, Romero H. T. Vasconcelos¹¹¹, Carlos Tellería^{119,120}, Thássia M. T. Carratto²⁵⁷, Jair Antonio Tenorio-Castaño^{3,11,12}, Alejandro Teper¹⁴⁵, Izabel M. T. Araujo¹⁰⁹, Juan Torres-Macho²⁶², Lilian Torres-Tobar²⁶³, Ronald P. Torres-Gutiérrez²²¹, Jesús Troya²⁴⁷, Miguel Urioste²⁰⁹, Juan Valencia-Ramos²⁶⁴, Agustín Valido^{35,265}, Juan Pablo Vargas-Gallo^{266,267}, Belén Varón²⁶⁸, Tomas Vega²⁶⁹, Santiago Velasco-Quirce²⁷⁰, Valentina Vélez-Santamaría^{93,94}, Virginia Víctor^{50,51}, Julia Vidán-Estévez²⁵, Gabriela V. Silva¹⁰⁹, Miriam Vieitez-Santiago^{59,135}, Carlos Vilches²⁷¹, Lavinia Villalobos²⁵, Felipe Villar²²⁰, Judit Villar-García^{272,273,274}, Cristina Villaverde^{3,40}, Pablo Villoslada-Blanco¹⁷⁴, Ana Virseda-Berduces⁸¹, Tatiana X. Costa²⁷⁵, Zuleima Yáñez³⁴, Antonio Zapatero-Gaviria²⁷⁶, Ruth Zarate²⁷⁷, Sandra Zazo²³⁹, Carlos Flores^{106,107,153,238}, José A. Riancho^{59,60,135}, Augusto Rojas-Martínez²⁷⁸, Pablo Lapunzina^{3,11,12} & Ángel Carracedo^{3,8,9,10,13}

¹⁵Hospital Universitario Mostoles, Medicina Interna, Madrid, Spain. ¹⁶Universidad Francisco de Vitoria, Madrid, Spain. ¹⁷Haemostasis and Thrombosis Unit, Hospital de la Santa Creu i Sant Pau, IIB Sant Pau, Barcelona, Spain. ¹⁸Unit of Infectious Diseases, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. ¹⁹Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002), Instituto de Salud Carlos III, Madrid, Spain. ²⁰School of Medicine, Universidad Complutense, Madrid, Spain. ²¹Centre for Biomedical Network Research on Infectious Diseases, Instituto de Salud Carlos III, Madrid, Spain. ²²Hospital General Santa Bárbara de Soria, Soria, Spain. ²³Pediatric Neurology Unit, Department of Pediatrics, Navarra Health Service Hospital, Pamplona, Spain. ²⁴Navarra Health Service, NavarraBioMed Research Group, Pamplona, Spain. ²⁵Complejo Asistencial Universitario de León, León, Spain. ²⁶Hospital Universitario San Pedro, Infectious Diseases Department, Logroño, Spain. ²⁷Fundación Institut Guttmann, Institut Universitari de Neurorehabilitació ofunde a la UAB, Hospital de Neurorehabilitació, Barcelona, Spain. ²⁸Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. ²⁹Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Barcelona, Spain. ³⁰Hospital General de Occidente, Guadalajara, Mexico. ³¹Microbiology Unit, Hospital Universitario N. S. de Candelaria, Santa Cruz de Tenerife, Spain. ³²Hospital Universitario La Paz-IDIPAZ, Servicio de Neumología, Madrid, Spain. ³³Camino Universitario Adelita de Char, Mired IPS, Barranquilla, Colombia. ³⁴Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia. ³⁵Hospital Universitario Virgen Macarena, Neumología, Seville, Spain. ³⁶Hospital das Forças Armadas, Brasília, Brazil. ³⁷Exército Brasileiro, Brasília, Brazil. ³⁸Departamento de Medicina, Universidad de Salamanca, Salamanca, Spain. ³⁹Centro de Investigación del Cáncer (IBMCC) Universidad de Salamanca – CSIC, Salamanca, Spain. ⁴⁰Department of Genetics & Genomics, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ⁴¹Spanish National Cancer Research Centre, Human Genotyping-CEGEN Unit, Madrid, Spain. ⁴²Hospital Universitario de Salamanca-IBSAL, Servicio de Medicina Interna, Salamanca, Spain. ⁴³Universidad de Salamanca, Salamanca, Spain. ⁴⁴Universidade Federal do Rio Grande do Norte, Programa de Pós-Graduação em Ciências Farmacêuticas, Natal, Brazil. ⁴⁵Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón (iSGM), Madrid, Spain. ⁴⁶Clinical Pharmacology Service, Hospital de la Santa Creu i Sant Pau, IIB Sant Pau, Barcelona, Spain. ⁴⁷Servicio de Medicina Interna, Sanatorio Franchin, Buenos Aires, Argentina. ⁴⁸Biocruces Bizkaia HRI, Bizkaia, Spain. ⁴⁹Cruces University Hospital, Osakidetza, Bizkaia, Spain. ⁵⁰Hospital Infanta Elena, Valdemoro, Madrid, Spain. ⁵¹Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ⁵²Centre for Biomedical Network Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain. ⁵³Fundación Hospital Infantil Universitario de San José, Bogotá, Colombia. ⁵⁴Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia. ⁵⁵Universidade Federal do Rio Grande do Norte, Departamento de Análises Clínicas e Toxicológicas, Natal, Brazil. ⁵⁶Departamento de Genética e Morfologia, Instituto de Ciências Biológicas, Universidade de Brasília, Brasília, Brazil. ⁵⁷Colégio Marista de Brasília, Brasília, Brazil. ⁵⁸Associação Brasileira de Educação e Cultura, Ribeirão Preto, Brazil. ⁵⁹IDIVAL, Santander, Spain. ⁶⁰Universidad de Cantabria, Santander, Spain. ⁶¹Hospital Universitario La Paz-IDIPAZ, Servicio de Medicina Interna, Madrid, Spain. ⁶²Fundació Docència I Recerca Mutua Terrassa, Barcelona, Spain. ⁶³Spanish National Cancer Research Center, CNIO Biobank, Madrid, Spain. ⁶⁴Fundación Santa Fe de Bogota, Departamento Patología y Laboratorios, Bogotá, Colombia. ⁶⁵Hospital General de Occidente, Zapopan, Jalisco, Mexico. ⁶⁶Centro Universitario de Tonalá, Universidad de Guadalajara, Tonalá, Jalisco, Mexico. ⁶⁷Centro de Investigación Multidisciplinario en Salud, Universidad de Guadalajara, Tonalá, Jalisco, Mexico. ⁶⁸Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), Murcia, Spain. ⁶⁹Universidad Católica San Antonio de Murcia (UCAM), Murcia, Spain. ⁷⁰Hospital Universitario de Salamanca-IBSAL, Servicio de Medicina Interna-Unidad de Enfermedades Infecciosas, Salamanca, Spain. ⁷¹Hospital Universitario de Fuenlabrada, Department of Internal Medicine, Madrid, Spain. ⁷²Escola Técnica de Saúde, Laboratório de Vigilância Molecular Aplicada, Recife, Brazil. ⁷³Federal University of Pernambuco, Genetics Postgraduate Program, Recife, Pernambuco, Brazil. ⁷⁴Hospital Universitario Infanta Leonor, Servicio de Alergia, Madrid, Spain. ⁷⁵Hospital Universitario del Tajo, Servicio de Medicina Intensiva, Toledo, Spain. ⁷⁶Hospital Universitario Mutua Terrassa, Barcelona, Spain. ⁷⁷Hospital Universitario La Paz-IDIPAZ, Servicio de Farmacología, Madrid, Spain. ⁷⁸Alcaldía de Barranquilla, Secretaría de Salud, Barranquilla, Colombia. ⁷⁹Instituto de Investigación Sanitaria de Santiago (IDIS), Xenética Cardiovascular, Santiago de Compostela, Spain. ⁸⁰Centre for Biomedical Network Research on Cardiovascular Diseases (CIBERCv), Instituto de Salud Carlos III, Madrid, Spain. ⁸¹Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología (CNM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain. ⁸²Cardiovascular Genetics Center, Institut d'Investigació Biomèdica Girona (IDIBGI), Girona, Spain. ⁸³Medical Science Department, School of Medicine, University of Girona, Girona, Spain. ⁸⁴Hospital Josep Trueta, Cardiology Service, Girona, Spain. ⁸⁵Institute of Biomedicine of Seville (IbIS), Consejo Superior de Investigaciones Científicas (CSIC)- University of Seville- Virgen del Rocío University Hospital, Seville, Spain. ⁸⁶Division of Infectious Diseases, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ⁸⁷Intensive Care Unit, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain. ⁸⁸Departamento de Medicina, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla, Spain. ⁸⁹Instituto de Biomedicina de Sevilla, Sevilla, Spain. ⁹⁰Universidad de los Andes, Facultad de Ciencias, Bogotá, Colombia. ⁹¹Tecnológico de Monterrey, Monterrey, Mexico. ⁹²Andalusian Public Health System Biobank, Granada, Spain. ⁹³Neuromuscular Unit, Neurology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain. ⁹⁴Bellvitge Biomedical Research Institute (IDIBELL), Neurometabolic Diseases Laboratory, L'Hospitalet de Llobregat, Spain. ⁹⁵Osakidetza, Cruces University Hospital, Barakaldo, Spain. ⁹⁶Centre for Biomedical Network Research on Diabetes and Metabolic Associated Diseases (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain. ⁹⁷University of Pais Vasco, UPV/EHU, Bilbao, Spain. ⁹⁸Oncology and Genetics Unit, Instituto de Investigación Sanitaria Galicia Sur, Xerencia de Xestión Integrada de Vigo-Servizo Galego de Saúde, Vigo, Spain. ⁹⁹Hospital Universitario La Paz, Hospital Carlos III, Madrid, Spain. ¹⁰⁰Hospital de San José, Sociedad de Cirugía de Bogotá, Bogotá, Colombia. ¹⁰¹Hospital Universitario Río Hortega, Valladolid, Spain. ¹⁰²Programa de Pós Graduação em Ciências da Saúde, Faculdade de Medicina,

Universidade de Brasília, Brasília, Brazil. ¹⁰³Servicio de Medicina ofounded, Complejo Hospitalario Universitario de A Coruña (CHUAC), Sistema Galego de Saúde (SERGAS), A Coruña, Spain. ¹⁰⁴Valencia University, Preventive Medicine Department, Valencia, Spain. ¹⁰⁵Centre for Biomedical Network Research on Physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain. ¹⁰⁶Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain. ¹⁰⁷Centre for Biomedical Network Research on Respiratory Diseases (CIBERES), Instituto de Salud Carlos III, Madrid, Spain. ¹⁰⁸Otto von Guericke University, Department of Microgravity and Translational Regenerative Medicine, Magdeburg, Germany. ¹⁰⁹Universidade Federal do Rio Grande do Norte, Departamento de Análises Clínicas e Toxicológicas, Natal, Brazil. ¹¹⁰Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón (IISGM), Madrid, Spain. ¹¹¹Hospital Universitario Lauro Wanderley, João Pessoa, Brazil. ¹¹²Programa de Pós Graduação em Ciências Farmacêuticas (PPGCF), Natal, Brazil. ¹¹³Universidade Federal do Rio Grande do Norte, Programa de Pós-graduação em Ciências da Saúde, Natal, Brazil. ¹¹⁴Hospital Universitario Mostoles, Unidad de Genética, Madrid, Spain. ¹¹⁵Internal Medicine Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹¹⁶Hospital Universitario Severo Ochoa, Servicio de Medicina Interna, Madrid, Spain. ¹¹⁷Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain. ¹¹⁸IdiPaz (Instituto de Investigación Sanitaria Hospital Universitario La Paz), Madrid, Spain. ¹¹⁹Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza, Spain. ¹²⁰Instituto Investigación Sanitaria Aragón (IIS-Aragon), Zaragoza, Spain. ¹²¹Universidade Federal do Rio Grande do Norte, Programa de Pós-Graduação em Ciências da Saúde, Natal, Brazil. ¹²²Universidade Federal do Rio Grande do Norte, Programa de Pós Graduação em Nutrição, Natal, Brazil. ¹²³Preventive Medicine Department, Instituto de Investigación Sanitaria Galicia Sur, Xerencia de Xestión Integrada de Vigo-Servizo Galego de Saúde, Vigo, Spain. ¹²⁴Hospital Universitario Virgen del Rocío, Servicio de Medicina Interna, Seville, Spain. ¹²⁵Universidade Federal do Rio Grande do Norte, Departamento de Infectologia, Natal, Brazil. ¹²⁶Hospital de Doenças Infecciosas Giselda Trigueiro, Rio Grande do Norte, Natal, Brazil. ¹²⁷Unidad Diagnóstico Molecular. Fundación Rioja Salud, Logroño, Spain. ¹²⁸Faculdade de Ciências da Saúde, Universidade de Brasília, Brasília, Brazil. ¹²⁹Universidade Federal do Rio Grande do Norte, Departamento de Análises Clínicas e Toxicológicas, Natal, Brazil. ¹³⁰Hospital Universitario Quironsalud Madrid, Madrid, Spain. ¹³¹Hospital Universitario de Salamanca-IBSAL, Servicio de Cardiología, Salamanca, Spain. ¹³²Hospital Universitario Puerta de Hierro, Servicio de Medicina Interna, Majadahonda, Spain. ¹³³Biocruces Bizkaia Health Research Institute, Galdakao University Hospital, Osakidetza, Barakaldo, Spain. ¹³⁴Instituto Regional de Investigación en Salud-Universidad Nacional de Caaguazú, Caaguazú, Paraguay. ¹³⁵Hospital U M Valdecilla, Santander, Spain. ¹³⁶Fundación Asilo San Jose, Santander, Spain. ¹³⁷Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Hospital Universitario Puerta de Hierro, Instituto de Investigación Sanitaria Puerta de Hierro – Segovia de Arana, Madrid, Spain. ¹³⁸Universidad Nacional de Asunción, Facultad de Politécnica, San Lorenzo, Paraguay. ¹³⁹Urgencias Hospitalarias, Complejo Hospitalario Universitario de A Coruña (CHUAC), Sistema Galego de Saúde (SERGAS), A Coruña, Spain. ¹⁴⁰Grupo de Investigación en Interacciones Gen-Ambiente y Salud (GILGAS) – Instituto de Biomedicina (BIOMED), Universidad de León, León, Spain. ¹⁴¹Universidade de Fortaleza, Natal, Brazil. ¹⁴²Hospital Universitario Niño Jesús, Pediatrics Department, Madrid, Spain. ¹⁴³Unitat de Malalties Infeccioses I Importades, Servei de Pediatria, Infectious and Imported Diseases, Pediatric Unit, Hospital Universitari Sant Joan de Déu, Barcelona, Spain. ¹⁴⁴Microbiology Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁴⁵Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina. ¹⁴⁶Department of Immunology, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain. ¹⁴⁷University of Salamanca, Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain. ¹⁴⁸Hospital Infanta Elena, Servicio de Medicina Intensiva, Valdemoro, Madrid, Spain. ¹⁴⁹Hospital Universitario de Getafe, Unidad de Genética, Madrid, Spain. ¹⁵⁰Programa de pós-graduação em biotecnologia – Rede Nordeste de Biotecnologia (RENORBIO), Universidade Federal do Rio Grande do Norte, Natal, Brazil. ¹⁵¹Pneumology Department, Hospital General Universitario Gregorio Marañón (IISGM), Madrid, Spain. ¹⁵²Ministerio de Salud Ciudad de Buenos Aires, Buenos Aires, Argentina. ¹⁵³Genomics Division, Instituto Tecnológico y de Energías Renovables, Santa Cruz de Tenerife, Spain. ¹⁵⁴Hospital Clínico Universitario de Valladolid, Unidad de Apoyo a la Investigación, Valladolid, Spain. ¹⁵⁵Universidad de Valladolid, Departamento de Cirugía, Valladolid, Spain. ¹⁵⁶Sección Genética Médica – Servicio de Pediatría, Hospital Clínico Universitario Virgen de la Arrixaca, Servicio Murciano de Salud, Murcia, Spain. ¹⁵⁷Departamento Cirugía, Pediatría, Obstetricia y Ginecología, Facultad de Medicina, Universidad de Murcia (UMU), Murcia, Spain. ¹⁵⁸Grupo Clínico Vinculado, Centre for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain. ¹⁵⁹Hospital Universitario Centro Dermatológico Federico Lleras Acosta, Bogotá, Colombia. ¹⁶⁰Hospital Universitario Virgen de las Nieves, Servicio de Análisis Clínicos e Inmunología, Granada, Spain. ¹⁶¹Intermediate Respiratory Care Unit, Department of Neumology, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁶²Sabin Medicina Diagnóstica, Santa Catarina, Brazil. ¹⁶³Clinica Comfamiliar Risaralda, Pereira, Colombia. ¹⁶⁴Centro Universitario de Tonalá, Universidad de Guadalajara, Guadalajara, Mexico. ¹⁶⁵Centro de Investigación Multidisciplinario en Salud, Universidad de Guadalajara, Guadalajara, Mexico. ¹⁶⁶Unidad de Cuidados, Intensivos Hospital Clínico Universitario de Santiago (CHUS), Sistema Galego de Saúde (SERGAS), Santiago de Compostela, Spain. ¹⁶⁷IIS La Fe, Plataforma de Farmacogenética, Valencia, Spain. ¹⁶⁸Universidad de Valencia, Departamento de Farmacología, Valencia, Spain. ¹⁶⁹Data Analysis Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁷⁰Hospital del Mar, Infectious Diseases Service, Barcelona, Spain. ¹⁷¹Institut Hospital del Mar d'Investigacions Mèdiques (IIMM), Barcelona, Spain. ¹⁷²CEXS-Universitat Pompeu Fabra, Spanish Network for Research in Infectious Diseases (REIPI), Barcelona, Spain. ¹⁷³Biocruces Bizkaia Health Research Institute, Basurto University Hospital, Osakidetza, Basurto, Spain. ¹⁷⁴Infectious Diseases, Microbiota and Metabolism Unit, Center for Biomedical Research of La Rioja (CIBIR), Logroño, Spain. ¹⁷⁵Ophthalmology Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁷⁶Hospital Sant Joan de Deu, Pediatric Critical Care Unit, Barcelona, Spain. ¹⁷⁷Paediatric Intensive Care Unit, Agrupación Hospitalaria Clínica-Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain. ¹⁷⁸Hospital Universitario 12 de Octubre, Department of Immunology, Madrid, Spain. ¹⁷⁹Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Transplant Immunology and Immunodeficiencies Group, Madrid, Spain. ¹⁸⁰SIGEN Alianza Universidad de los Andes – Fundación Santa Fe de Bogotá, Bogotá, Colombia. ¹⁸¹Hospital General de Segovia, Medicina Intensiva, Segovia, Spain. ¹⁸²Clinical Trials Unit, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁸³IMDEA-Food Institute, CEI UAM + CSIC, Madrid, Spain. ¹⁸⁴Hospital Universitario La Paz-IDIPAZ, Servicio de Inmunología, Madrid, Spain. ¹⁸⁵La Paz Institute for Health Research (IdiPAZ), Lymphocyte Pathophysiology in Immunodeficiencies Group, Madrid, Spain. ¹⁸⁶Hospital Universitario Virgen de las Nieves, Servicio de Enfermedades Infecciosas, Granada, Spain. ¹⁸⁷Instituto de Investigación Biosanitaria de Granada (ibs GRANADA), Granada, Spain. ¹⁸⁸Universidad de Granada, Departamento de Medicina, Granada, Spain. ¹⁸⁹Intensive Care Unit, Hospital Universitario de Canarias, La Laguna, Spain. ¹⁹⁰Dirección General de Salud Pública, Consejería de Sanidad, Junta de Castilla y León, Valladolid, Spain. ¹⁹¹Fundación Jiménez Díaz, Epidemiology, Madrid, Spain. ¹⁹²Universidad Autónoma de Madrid, Department of Medicine, Madrid, Spain. ¹⁹³Instituto de Biomedicina (BIOMED), Universidad de León, León, Spain. ¹⁹⁴Universidad de Valladolid, Departamento de Medicina, Valladolid, Spain. ¹⁹⁵Preventive Medicine Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ¹⁹⁶Intensive Care Unit, Hospital Universitario N. S. de Candelaria, Santa Cruz de Tenerife, Spain. ¹⁹⁷Hospital Universitario Infanta Leonor, Servicio de Medicina Intensiva, Madrid, Spain. ¹⁹⁸Unidad de Genética y Genómica Islas Baleares, Palma de Mallorca, Spain. ¹⁹⁹Hospital Universitario Son Espases, Unidad de Diagnóstico Molecular y Genética Clínica, Palma de Mallorca, Spain. ²⁰⁰Genomics of Complex Diseases Unit, Research Institute of Hospital de la Santa Creu i Sant Pau, IIB Sant Pau, Barcelona, Spain. ²⁰¹Faculdade de Medicina, Universidade de Brasília, Brasília, Brazil. ²⁰²Programa de Pós-Graduação em Ciências Médicas, Universidade de Brasília, Brasília, Brazil. ²⁰³Programa de Pós-Graduação em Ciências da Saúde, Universidade de Brasília, Brasília, Brazil. ²⁰⁴Hospital El Bierzo, Gerencia de Asistencia Sanitaria del Bierzo (GASBI), Gerencia Regional de Salud (SACYL),

Ponferrada, Spain. ²⁰⁵Grupo INVESTEN, Instituto de Salud Carlos III, Madrid, Spain. ²⁰⁶Unidad de Cuidados Intensivos, Complejo Universitario de A Coruña (CHUAC), Sistema Galego de Saúde (SERGAS), A Coruña, Spain. ²⁰⁷Hospital Universitario La Paz-IDIPAZ, Servicio de Pediatría, Madrid, Spain. ²⁰⁸Hospital El Bierzo, Unidad Cuidados Intensivos, León, Spain. ²⁰⁹Spanish National Cancer Research Centre, Familial Cancer Clinical Unit, Madrid, Spain. ²¹⁰Instituto de Investigación Sanitaria San Carlos (IdISSC), Hospital Clínico San Carlos (HCSC), Madrid, Spain. ²¹¹Marinha do Brasil, Brasil, Brazil. ²¹²Universidade de Brasília, Brasília, Brazil. ²¹³Hospital General Universitario Gregorio Marañón (IiSGM), Madrid, Spain. ²¹⁴Unidad de Genética y Genómica Islas Baleares, Unidad de Diagnóstico Molecular y Genética Clínica, Hospital Universitario Son Espases, Palma de Mallorca, Spain. ²¹⁵Instituto de Investigación Sanitaria Islas Baleares (IdISBa), Palma de Mallorca, Spain. ²¹⁶Programa de Pós-Graduação em Biologia Animal (UnB), Brasília, Brazil. ²¹⁷Programa de Pós-Graduação Profissional em Ensino de Biologia (UnB), Brasília, Brazil. ²¹⁸Anatomía Patológica, Instituto de Investigación Sanitaria San Carlos (IdISSC), Hospital Clínico San Carlos (HCSC), Madrid, Spain. ²¹⁹Universidad Complutense de Madrid, Department of Immunology, Ophthalmology and ENT, Madrid, Spain. ²²⁰Department of Neumology, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ²²¹Hospital Nuestra Señora de Sonsoles, Ávila, Spain. ²²²Universidade Federal do Pará, Núcleo de Pesquisas em Oncologia, Belém, Pará, Brazil. ²²³Secretaria Municipal de Saude de Apodi, Natal, Brazil. ²²⁴Intensive Care Department, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ²²⁵Hospital Universitario Príncipe de Asturias, Servicio de Microbiología Clínica, Madrid, Spain. ²²⁶Universidad de Alcalá de Henares, Departamento de Biomedicina y Biotecnología, Facultad de Medicina y Ciencias de la Salud, Madrid, Spain. ²²⁷Inditex, A Coruña, Spain. ²²⁸GENYCA, Madrid, Spain. ²²⁹Universidade Federal do Rio Grande do Norte, Departamento de Análises Clínicas e Toxicológicas, Natal, Brazil. ²³⁰Neuromuscular Diseases Unit, Department of Neurology, Hospital de la Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. ²³¹Instituto Mexicano del Seguro Social (IMSS), Centro Médico Nacional Siglo XXI, Unidad de Investigación Médica en Enfermedades Infecciosas y Parasitarias, Mexico City, Mexico. ²³²Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain. ²³³Drug Research Centre, Institut d'Investigació Biomèdica Sant Pau, IIB-Sant Pau, Barcelona, Spain. ²³⁴Unidad de Cuidados Intensivos, Hospital Clínico Universitario de Santiago (CHUS), Sistema Galego de Saúde (SERGAS), Santiago de Compostela, Spain. ²³⁵Hospital Ophir Loyola, Departamento de Ensino e Pesquisa, Belém, Pará, Brazil. ²³⁶University Hospital Germans Trias I Pujol, Pediatrics Department, Badalona, Spain. ²³⁷Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain. ²³⁸Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ²³⁹Department of Pathology, Biobank, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ²⁴⁰Centre for Biomedical Network Research on Cancer (CIBERONC), Instituto de Salud Carlos III, Madrid, Spain. ²⁴¹Universidad de Sevilla, Departamento de Enfermería, Seville, Spain. ²⁴²Hospital Universitario Virgen de las Nieves, Servicio de Medicina Interna, Granada, Spain. ²⁴³Fundación Universitaria de Ciencias de la Salud, Grupo de Ciencias Básicas en Salud (CBS), Bogotá, Colombia. ²⁴⁴Universidad de Granada, Departamento Bioquímica, Biología Molecular e Inmunología III, Granada, Spain. ²⁴⁵Hospital Infanta Elena, Allergy Unit, Valdemoro, Madrid, Spain. ²⁴⁶Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain. ²⁴⁷Hospital Universitario Infanta Leonor, Madrid, Spain. ²⁴⁸Complutense University of Madrid, Madrid, Spain. ²⁴⁹Gregorio Marañón Health Research Institute (IiSGM), Madrid, Spain. ²⁵⁰Rheumatology Service, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital – Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain. ²⁵¹Biobank, Puerta de Hierro-Segovia de Arana Health Research Institute, Madrid, Spain. ²⁵²Universidad Rey Juan Carlos, Madrid, Spain. ²⁵³The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, England. ²⁵⁴Neuromuscular Unit, Neuro-pediatrics Department, Institut de Recerca Sant Joan de Déu, Hospital Sant Joan de Déu, Barcelona, Spain. ²⁵⁵Casa de Saúde São Lucas, Natal, Brazil. ²⁵⁶Hospital Rio Grande, Natal, Brazil. ²⁵⁷Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, São Paulo, Brazil. ²⁵⁸Intensive Care Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain. ²⁵⁹Universidade Federal do Rio Grande do Norte, Pós-graduação em Biotecnologia – Rede de Biotecnologia do Nordeste (Renorbio), Natal, Brazil. ²⁶⁰Hospital Clínico Universitario de Valladolid, Servicio de Anestesiología y Reanimación, Valladolid, Spain. ²⁶¹Hospital Clínico Universitario de Valladolid, Servicio de Hematología y Hemoterapia, Valladolid, Spain. ²⁶²Hospital Universitario Infanta Leonor, Servicio de Medicina Interna, Madrid, Spain. ²⁶³Sociedad de Cirugía de Bogotá, Hospital de San José, Bogotá, Colombia. ²⁶⁴University Hospital of Burgos, Burgos, Spain. ²⁶⁵Universidad de Sevilla, Seville, Spain. ²⁶⁶Fundación Santa Fe de Bogota, Instituto de servicios medicos de Emergencia y trauma, Bogotá, Colombia. ²⁶⁷Universidad de los Andes, Bogotá, Colombia. ²⁶⁸Quironprevención, A Coruña, Spain. ²⁶⁹Junta de Castilla y León, Consejería de Sanidad, Valladolid, Spain. ²⁷⁰Gerencia Atención Primaria de Burgos, Burgos, Spain. ²⁷¹Immunogenetics-Histocompatibility group, Servicio de Inmunología, Instituto de Investigación Sanitaria Puerta de Hierro – Segovia de Arana, Madrid, Spain. ²⁷²Hospital del Mar, Department of Infectious Diseases, Barcelona, Spain. ²⁷³Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. ²⁷⁴Universitat Autònoma de Barcelona, Department of Medicine, Barcelona, Spain. ²⁷⁵Maternidade Escola Janário Cicco, Natal, Brazil. ²⁷⁶Consejería de Sanidad, Comunidad de Madrid, Madrid, Spain. ²⁷⁷Centro para el Desarrollo de la Investigación Científica, Caaguazú, Paraguay. ²⁷⁸Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico.