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Genetic variants associated with SARS-CoV-2 infection also affect lung function and asthma severity

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A B S T R A C T

Background: Host genetic factors may be associated with COVID-19 unfavourable outcomes. The first genome-wide association study (GWAS) conducted in individuals with respiratory failure due to COVID-19 revealed susceptibility loci close to six genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*) and the ABO blood-group gene. We aimed to investigate how polymorphisms in those genes could relate to lung function and severe asthma in a Brazilian population.

Methods: DNA samples of 784 individuals following the ProAR (*Programa para Controle da Asma e Rinite Alérgica da Bahia*) were genotyped by the Multi-Ethnic Global Array panel with ~2 million polymorphisms (Illumina). Polymorphisms in *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, *XCR1* and the ABO blood-group gene were evaluated. Logistic regression for severe asthma, airway obstruction and lack of FEV_1 reversibility was performed using PLINK software 1.9, in the additive model and was adjusted for sex, age and PCA-1. Pairwise Linkage disequilibrium analyses were performed using Haploview 4.2. The haplotypes and gene score analyses were performed in the SNPstat tool. *In silico* functions of polymorphisms were analysed using rSNPbase and RegulomeDB plataforms.

Results: We identified the rs8176733 (G allele) and rs8176725 (A allele) in the ABO blood-group gene as risk factors for severe asthma, lower pulmonary obstruction and lack of FEV1 reversibility. Polymorphisms in CCR9 are risk factors for both severe asthma (A allele of rs34338823) and airway obstruction (A allele of rs6806802). The markers rs13079478 (A allele) and rs75817942 (A allele) in FYCO1 are related to more severe asthma and a lack of FEV1 reversibility, respectively. We identified the A allele of both rs35731912 and rs34338823 in LZTFL1 as risk factors for severe asthma. The marker rs6806802 (C allele) was associated with airway obstruction and rs7614952 (A allele), rs7625839 (G allele) and rs112509260 (A allele) are related to a lack of FEV1 reversibility. The A allele of rs2531747 in the SLC6A20 gene is also associated with severe asthma. Conversely, polymorphisms in XCR1 play a protective role in relation to severe asthma (A allele of rs2036295) and airway obstruction (A allele of rs2036295). Additionally, we found that individuals with a higher number of risk alleles have a greater risk of severe asthma, airway obstruction and FEV_1 reversibility.

Conclusion: Our study suggests that polymorphisms in genes associated with respiratory failure in SARS-CoV-2-infected individuals are associated with greater susceptibility to severe asthma and reduced lung function in subjects with asthma.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a systemic illness caused by the SARS-CoV-2 virus. In November 2022, there had been

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628,694,934 confirmed cases of COVID-19 and 6.576.088 deaths reported to the World Health Organisation (WHO) globally [WHO Coronavirus Disease Panel *(COVID-19) | WHO Coronavirus Disease panel (COVID-19)*]. Infected individuals can be asymptomatic or evolve to a serious condition quickly. A higher risk of critical outcomes was observed in the elderly, men and in patients with diabetes, obesity, cardiovascular diseases and chronic obstructive respiratory disease. However, the disease was fatal in a proportion of young people who presented no known risk factor for COVID-19 complications [1–6].

Host genetic factors may be involved in the fate of the affected individuals [7]. The global scientific community has made great efforts to determine genetic polymorphisms in individuals who die with COVID-19 [8,9]. The first genome-wide association study (GWAS) for COVID-19 showed that the loci at chromosome 3p21.31, containing six genes (*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6* and *XCR1*), and the loci at chromosome 9q34.2 (ABO blood-group gene) were risk regions for severe COVID-19 [10].

Both the *SLC6A20* and *ABO* loci are related to renin angiotensin system homeostasis [11–13]. The first encodes the sodium-dependent imino transporter 1 (SIT1), which interacts with the angiotensin-converting enzyme 2 (ACE2) receptor, which is the SARS-CoV-2 cell-surface receptor [11,12], while the second modulates ACE1 (angiotensin I-converting enzyme) (Gemmati et al., 2020. The ACE1/ACE2 pathway imbalance is related to inappropriate oxygenation, which leads to pulmonary edema, hyperproliferation and inflammation, contributing to severe respiratory failure [13]. ACE2 seems to play a protective role in human lung fibrosis [14,15]. Leucine Zipper Transcription Factor-like 1 (LZTFL1) is expressed in ciliated human bronchial epithelial cells. The upregulation of LZTFL1 is correlated with epithelial cell differentiation [16].

The *XCR1* gene encodes the receptor to X–C motif chemokine ligand [17]. XCR1 knockout mice showed a reduced Th2 response and reduced airway hyperresponsivity in a model of induced asthma [18]. The early phases of allergy-induced airway inflammation were associated with increased expression of CC motif chemokine receptor 9 (CCR9), which higher expression contributes to lung eosinophil recruitment [19].

The FYVE and Coiled-Coil Domain Autophagy Adaptor 1 (*FYCO1*) gene encodes a protein required to transport the autophagosomes to lysosomes during the autophagy process [20]. In the lungs, the expression of CXCR6 stimulates T cell activation [21]. Polymorphisms located in an intron of *FYCO1* and the 3'-UTR of *CXCR6i* were related to atopic dermatitis and eosinophil percentages in the blood, which implies a plausible role in allergic inflammation [22]; also, CXCR6 plays a role in the regulation of the recruitment of lung resident memory CD8 T-cells and has been associated with immune response to viruses. Considering that the genes linked to COVID-19 complications, including respiratory failure, are related to pulmonary and allergic conditions (Fig. 1), we investigated how polymorphisms in those genes could influence lung function and severe asthma in a Brazilian sample of subjects with asthma.

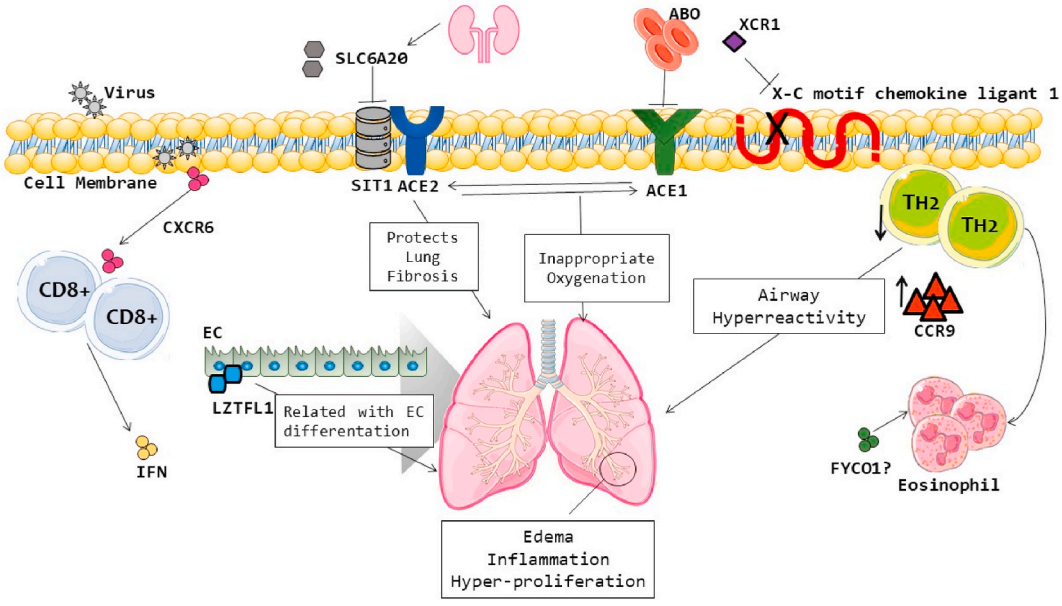

Fig. 1. The effects of the gene clusters associated with COVID-19 poor outcomes, and ABO blood group gene in human lungs. SLC6A20 is expressed in kidney and encodes the transporter SIT1, which interacts with ACE2, the SARS-CoV-2 cell-surface receptor and seems to play a protective role in human lung fibrosis. ABO receptors modulate the ACE1 levels. An imbalance between ACE1 and ACE2 is related to inappropriate oxygenation which leads to pulmonary edema, hyper-proliferation and inflammation, contributing to respiratory failure. LZTFL1 is expressed in ciliated human bronchial epithelial cells and its upregulation is correlated with epithelial cell differentiation. XCR1 encodes the receptor to XCL1. Lower expression of XCR1 reduced Th2 response and increase airway hyperreactivity leading to enhanced expression of CCR9 and consequent lung eosinophil recruitment. CXCR6 is involved in lung T cells activation and immune antiviral response with interferon production. The FYCO1 is related to eosinophil counts and immune allergic response. SLC6A20: Solute Carrier Family 6 Member 20; SIT1: sodium-dependent imino transporter 1; ACE2: angiotensin-converting enzyme 2; ACE1: Angiotensin I converting enzyme; LZTFL1: Leucine Zipper Transcription Factor-like 1, XCR1: X–C Motif Chemokine Receptor 1; XCL1: X–C motif chemokine ligand 1; CCR9: chemokine receptor 9; FYCO1: FYVE And Coiled-Coil Domain Autophagy Adaptor 1. CXCR6: CXCR6 – C-X-C motif chemokine receptor 6. IFN: interferon; EC: epithelial cells.

2. Methods

2.1. Study population

A total of 784 subjects with mild-moderate or severe asthma, with ages ranging from 18 to 90 years and of both genders from ProAR (Programa para Controle da Asma e Rinite Alérgica da Bahia), Salvador, Brazil was included in this study. The study was approved by the Ethics Committee (reference number CONEP -nº 450/10) with an amendment on biorepository approved by the Ethics Committee of MCO/UFBA (Maternidade Climério de Oliveira - Federal University of Bahia) n°095/2012. Informed consent was obtained from all participants through a written document.

2.2. Asthma definition

The diagnosis of asthma was made by two experts using the criteria of the Global Initiative against Asthma (GINA, 2006); individuals aged ≥18 years old were included and the diagnosis of asthma was confirmed by an audit. The clinical history, pulmonary function tests to diagnose airflow obstruction and chest radiography were used as parameters to exclude other lung diseases. After that, subjects were divided into case and control groups. Information about the age of onset of symptoms of asthma, adherence to treatment according to patient reports and pharmacy records, the proper use of inhalers, medications used, emergency room visits, hospitalisations, intensive care admissions, comorbidities, exposure to indoor air pollution, heart rate, weight, height, pulse oximetry, blood pressure, waist, hip and neck circumferences and nasal peak inspiratory flow were used to defined the groups as previously described by Cruz A. Alvaro (2019) [23]. Also, the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ) were applied for all subjects [23]. For this study, we included 401 patients with severe asthma presenting daily symptoms, asthma exacerbations, limitations in physical activity and FEV_1 ≤60%. In the control group, we included 431 patients with mild to intermittent asthma. Individuals with other respiratory diseases, a history of stroke, neurological disease, congestive heart failure (CHF), myopathies, psychiatric disorders and advanced neoplasia were excluded from the study. Also, subjects with untreated severe asthma, difficult-to-treat severe asthma and treatment-resistant severe asthma were included in the asthma severity group as recommended by the WHO 2019 [23,24].

2.3. Asthma control

Asthma control was assessed considering the week prior to the date of clinical evaluation and reflects the response to the treatment that each patient is using. Asthma was considered uncontrolled if the patient had three or more of the following characteristics: symptoms more than twice a week, activity limitations, nocturnal symptoms and FEV_1 or Peak Expiratory Flow <80% of predicted. The patient was also considered uncontrolled if there had been exacerbation of asthma in the previous week (GINA, 2008).

2.4. Pulmonary function

Spirometry was performed using the Koko® Spirometer (Ferraris Medical, USA) for the measurement of FEV_1, FVC and the FEV_1/FVC ratio before and 15 min after inhaling 400 mcg of bronchodilator (salbutamol), as recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) (Pellegrino, 2005; Graham et al., 2019). Airway obstruction was assessed as the FEV_1/FVC ratio lower than lower limit of normal (LLN) and FEV_1 bronchodilator responsiveness was determined by the increase in FEV_1 post-bronchodilator less than 12% and 200 ml (Pellegrino et al., 2005). The reference equation used for the Brazilian population was according to Pereira (2008).

2.5. Genomic DNA extraction

Venous blood was collected for blood cell counts and to extract genomic DNA according to the Flexigene DNA Kit protocol.

2.6. Genotyping

Genotyping was performed on the samples of the included subjects, using the Multi-Ethnic Global Array panel standardised by Illumina. The database contains more than 2 million polymorphisms distributed across the autosomes. Genetic information was extracted using GRCh38.p13 genomic version. This is a candidate gene study including SNPs in the *ABO* (chr9:133250401-133275201), *CXCR6* (chr3:45940688-45948354), *XCR1* (chr3: 46016990–46086773), *CCR9* (chr3:45886504-45903177), *SLC6A20* (chr3: 45755449–45796553), *FYCO1* (chr3:45917903-45995824) and *LZTFL1* (chr3: 45823316–45916037) genes, as well as all SNPs in the regions 500 kb downstream and upstream of the 5′ and 3′ UTR limits for each gene. The quality control parameters were a genotype call rate >98%, Hardy-Weinberg equilibrium (HWE) > 0.05 and minor allele frequency (MAF) > 0.01.

2.7. Statistical analysis

Logistic regression was applied to estimate the odds ratio (OR), p-value, permutational-p-value, correction of the p-value by Bonferroni test and 95% confidence interval (CI) for the association between SNPs, severe asthma and lung function abnormalities

(reversibility of FEV_1 and airway obstruction). A bivariate test was performed to define the co-variants, so the analyses were adjusted for sex, age and ancestry markers. The principal components (PCs) were calculated based on genotypes of PROAR subjects and using the R Bioconductor GENESIS package of genotypes as a reference, as described by Daya et al. (2019) [25]. All analysis were performed using the additive genetic model, to observe the dose effect of each allele. A p-value and permutational p-value lower than 0.05 were considered statistically significant. The permutation test was performed to test the null hypothesis, with a difference in values being expected under the null hypothesis. Permutation procedures provide a computationally intensive approach to generating significance levels empirically. This type of test is used to relax assumptions about the normality of continuous phenotypes and Hardy-Weinberg equilibrium, dealing with rare alleles and small sample sizes, providing a framework for correction for multiple testing and controlling for identified substructures or familial relationships by permuting only within the cluster. All of the above analyses and haplotype frequencies were performed using the software PLINK (version 1.9). Pairwise Linkage Disequilibrium (LD) figures for cases and controls were created with Haploview 4.2. Haplotype frequencies and associations with responses were performed using Snpstat toll.

The genetic risk score was used to determine the way in which the presence of increasing numbers of risk alleles affect the outcomes evaluated (severe asthma or lung function) as previously described by Silva et al., 2019 [26]. The risk score was attributed according to the presence of risk alleles. These analyses were performed using the Snpstat online tool. The graphs were created using the GraphPad Prism 8.0 software.

2.8. In silico analysis

The SNP functions were obtained using the NCBI (https://www.ncbi.nlm.nih.gov/) online platform, which provides extensive information about polymorphisms. Information about SNP positions, chromosomal location, allele frequency of each allele variation, whether the SNPs are intronic, exonic or close to a gene, whether they are missense variants and which amino acids are altered was taken from this platform.

To access the possible regulatory role of each polymorphism in the *ABO*, *CXCR6*, *XCR1*, *CCR9*, *SLC6A20*, *FYCO1* and *LZTFL1* genes, we used the rSNPBase (http://rsnp.psych.ac.cn/), which provides annotations about proximal, distal, miRNA and post-transcriptional regulation. The results are given as "Yes" or "No" for each parameter. Thus, 1) *proximal regulation* indicates SNPs that are involved in proximal transcriptional regulation, 2) *distal regulation* denotes SNPs that are involved in distal transcriptional regulation, 3) *microRNA regulation* describes SNPs within mature miRNA and 4) *RNA binding proteins* are SNPs involved in RNA binding protein-mediated post-transcriptional regulation.

The RegulomeDB (https://regulomedb.org/) is an online tool for the interpretation of putative regulatory potential and function of polymorphisms through computational predictions and manual annotations (Boyle et al., 2012). Greater evidence for a variant to be located in a functional region is shown by lower scores in the RegulomeDB as follows: *1a to 1f* scores show SNVs that are likely to affect binding and linked to the expression of a target gene, *2a to 2c* scores are SNVs which are likely to affect binding, scores *3a and 3b* are less likely to affect binding, scores *4, 5* and *6* denote SNVs that may have minimal binding evidence and a score of *7* indicates that there are no data about the function of a certain SNV (Boyle et al., 2012). Also, the RegulomeDB probability score ranges from 0 to 1, with scores closer to 1 indicating that this is probably a regulatory variant.

3. Results

3.1. Characteristics of the study population

Table 1 summarises the clinical characteristics of the study population: 50.9% of individuals had mild-moderate asthma, while 49.1% had severe asthma. The number of females was higher than males in both groups. The mean age was 36 years for individual mild-moderate asthma and 50 years for individuals with severe asthma. Uncontrolled asthma was more frequent in the group with severe asthma (see Table 2).

Table 1
Population of study and demographic characteristics.

N(%)		Mild-moderate asthma	Severe asthma	p-value
		399(50,9)	385(49,1)	
Sex				
	Female	297(50)	297(50)	.084
	Male	86(55,5)	69(44,5)	
Age				
	(Média±DP)	36 ± 12	50 ± 14	.674
Asthma control				
	Controlled	113(69,8)	40(30,2)	.000
	Partial Controlled	232(51,6)	218(48,4)	
	Uncontrolled	54(29,8)	127(70,2)	

3.2. SNPs included in study after quality control

After quality control (QC), a total of 160 SNPs were included in the present study, among them, 62 SNPs were in the *ABO* gene, 4 were in the *CXCR6* gene, 5 were in the *CCR9* gene, 27 were in the *LZTFL1* gene, 24 were in the *SCL6A20* gene, 12 were in the *XCR1* gene and 26 SNPs were in the *FYCO1* gene.

3.3. Polymorphisms linked to SARS-CoV-2 infection are also associated with severe asthma

Among the subjects with asthma, we compared those with mild to moderate asthma with individuals with severe asthma. Regarding ABO variants, the A allele of rs8176693 (OR: 1.56; 95%CI: 1.10–2.25; p-value: 0.02), the A allele of rs8176725 (OR: 1.41; 95%CI: 1.03–1.93; p-value: 0.03) and the G allele of rs8176733 (OR: 1.41; 95%CI: 1.03–1.92; p-value: 0.03) were a risk factor for severe asthma (Table 2). Also, in *CCR9*, the A allele of rs34338823 (OR:1.77; 95%CI: 1.01–3.13; p-value: 0.04) was positively associated with severe asthma (Table 2). In addition, the A allele of rs13079478 (OR:1.88; 95%CI: 1.10 − 3.28; p-value: 0.02) in *FYCO1* was also a risk factor for severe asthma (Table 2). Moreover, we found within *LZTFL* that the A allele of rs35731912 (OR: 1.76; 95%CI: 1.04–2.99; p-value: 0.03) and the A allele of rs34338823 (OR: 1.78; 95%CI: 1.01–3.13; p-value: 0.04) were positively associated with severe asthma (Table 2). Finally, the A allele of rs2531747 (OR: 1.30; 95%CI: 1.03–1.70; p-value: 0.04) in SCL6A20 was a risk factor for severe asthma as well as a protective factor for severe asthma, as was the A allele of rs2036295 (OR: 0.74; 95%CI: 0.57–0.96; p-value: 0.02) in the *XCR1* gene. We did not find any significant association between SNPs in *CXCR6* and severe asthma (see Table 3).

3.4. Polymorphisms linked to SARS-CoV-2 infection may be related to lung function in asthma

We analysed lung function parameters in subjects with asthma, such as airway obstruction and response to FEV_1. In the context of airway obstruction, we found the G allele of rs8176733 (OR: 1.63; 95%CI: 1.04–2.55; p-value: 0.03) and the A allele of rs8176725 (OR:1.62; 95%CI: 1.04–2.54; p-value: 0.03) in *ABO* to be susceptibility factors (Table 3). Moreover, in *CCR9*, the A allele of rs6806802 (OR: 1.82; 95%CI: 1.04–3.21; p-value: 0.03) was positively associated with airway obstruction (Table 3). In addition, for *LZTFL*, the C allele of rs6806802 (OR: 1.82; 95%CI: 1.04–3.20; p-value: 0.03) was a risk factor for airway obstruction (Table 3). SNPs in *XCR1*, *CXCR6* and *SLC6A20* were not associated with the airway obstruction. In addition, we analysed the response to FEV_1 in our sample of subjects with asthma and found the G allele of rs8176733 (OR: 0.72; 95%CI: 0.06–0.94; p-value: 0.02), the A allele of rs8176725 (OR: 0.71; 95%CI: 0.04–0.86; p-value: 0.02), the A allele of rs8176722 (OR: 0.72; 95%CI: 0.04–0.86; p-value: 0.02) and the G allele of rs8176720 (OR: 0.80; 95%CI: 0.25–0.96; p-value: 0.02) in ABO to be negatively associated with response to FEV1. On the other hand, the G allele of rs8176692 (OR:2.20; 95%CI: 1.16–3.14; p-value: 0.01) and the G allele of rs2073824 (OR:1.35; 95%CI: 1.10–1.65; p-value <0.01) were positively associated with response to FEV_1 (Table 3). Also, in *FYCO1*, the A allele of rs75817942 (OR: 2.14; 95%CI: 1.01–4.55; p-value: 0.04) was inversely associated with FEV_1 reversibility (Table 4). On the other hand, in *LZTFL*, the A allele of rs7614952 (OR: 0.53; 95%CI: 0.09–0.59; p-value: 0.04), the G allele of rs7625839 (OR: 0.32; 95%CI: 0.06–0.53; p-value: 0.04) and the A allele of rs112509260 (OR: 0.19; 95%CI: 0.14–0.98; p-value: 0.04) (Table 3) were negatively associated with response to FEV_1. For *SLC6A20*, *CXCR6*, *CCR9* and *XCR1,* we found no significant associations (seeTable 4 and 5.

3.5. Haplotype association and linkage disequilibrium

We selected the risk allele of each SNP that was associated with severe asthma, airway obstruction or response to FEV_1 and performed a haplotype analysis and linkage disequilibrium approach. For the ABO gene, we found a combination of the G allele of rs8176733, the A allele of rs817625 and the A allele of rs8176793 (GAA) at a frequency of 0.12% in our population; this was associated with severe asthma (OR:1.77; 95%CI: 1.42–2.41; p-value: 0.04) (Supplementary Table 2). For *ABO* genes and the risk of lung obstruction, we did not find any association (Table 5). Also, the haplotype combination of the A allele of rs8176733, the G allele of rs8176725, the C allele of rs8176722, the G allele of rs2073824, the A allele of rs8176710, the A allele of rs8176692 and the G allele of rs8176720 (AGCGAAG), with a frequency of 2% in our population, was associated with response to FEV_1 (OR: 1.48; 95%CI: 1.31–1.88)

Table 2
Significant association between SNPs in *ABO*, *CCR9*,*FYCO1*,*LZTFL1*,*SLC6A20* and *XCR1* genes and asthma severity, adjusted by sex, age and PC1.

Asthma Severity						
Gene	SNP††	A1¥¥	OR¥¥¥	95%CI†	p-value	Perm††
ABO	rs8176693	A	1.55	1.07-2.24	0.01	0.01
	rs8176725	A	1.41	1.03-1.93	0.03	0.03
	rs8176733	G	1.41	1.03-1.92	0.03	0.03
CCR9	rs34338823	A	1.77	1.01–3.13	0.04	0.03
FYCO1	rs13079478	A	1.88	1.08-3.28	0.02	0.02
LZTFL1	rs35731912	A	1.76	1.04-2.99	0.03	0.02
	rs34338823	A	1.77	1.01–3.13	0.04	0.03
SLC6A20	rs2531747	A	1.30	1.03-1.70	0.04	0.03
XCR1	rs2036295	A	0.74	0.57-0.96	0.02	0.02

† † Single nucleotide polymorphism;¥¥ Minor Allele; ¥¥¥Odds ratio; †Confidence Interval; ††Permutational p-value.

Table 3
Significant association between SNPs in *ABO*, *CCR9*, *FYCO1*, *LZTFL1*, *SLC6A20* and *XCR1* genes and lung obstruction and lack of FEV reversibility, adjusted by sex, age and PC1.

Lung Obstruction						
Gene	SNP††	A1¥¥	OR¥¥¥	95%CI†	p-value	Perm††
ABO	rs8176733	G	1.63	1.04-2.55	0.03	0.03
	rs8176725	A	1.62	1.04-2.54	0.03	0.04
CCR9	rs6806802	C	1.82	1.04-3.20	0.03	0.01
LZTFL1	rs6806802	C	1.82	1.04-3.20	0.03	0.03
XCR1	rs2036295	A	0.74	0.57-0.96	0.02	0.02
Lack of FEV reversibility						
ABO	rs2073824	G	0.74	0.60-0.90	<0.01	<0.01
	rs8176710	T	3.75	1.39-1.43	0.01	0.01
	rs8176692	G	0.45	0.24-0.85	0.01	0.01
	rs8176733	G	1.28	1.26-1.95	0.02	0.02
	rs8176725	A	1.29	1.23-1.96	0.02	0.02
	rs8176722	A	1.28	1.23-1.96	0.02	0.02
	rs8176720	G	1.20	1.24-1.97	0.02	0.04
FYCO1	rs75817942	A	2.14	1.01–4.55	0.04	0.04
LZTFL	rs7614952	A	1.78	1.62-1.99	0.04	0.03
	rs7625839	G	1.81	1.65-1.94	0.04	0.06
	rs112509260	A	1.47	1.23-1.98	0.04	0.04

† † Single nucleotide polymorphism;¥¥ Minor Allele; ¥¥¥Odds ratio; †Confidence Interval; ††Permutational p-value.

Table 4
Haplotype analysis between rs8176733, rs8176725 and rs8176793 in *ABO* gene on risk of asthma severity.

Haplotypes in *ABO* and asthma severity						
	rs8176733 †	**rs8176725 †**	**rs8176793 †**	Freq †	**OR (95% CI) ¥**	**P-value**
1	A	G	C	0.85	1.00	—
2	G	A	A	0.12	1.77 (1.42 - 2.41)	00.4
3	G	A	C	0.03	0.00 (0.00-0.00)	0.89
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.09						

†Single nucleotide polymorphism in *ABO* gene;†Frequency of haplotypes;¥Odds ratio and confidential interval.

Table 5
Haplotype analysis between rs8176733 and rs8176725 in *ABO* gene on risk of lung obstruction Haplotypes in *ABO* and Lung obstruction.

	rs8176733 †	rs8176725 †	Freq †	OR (95% CI) ¥	P-value
1	A	A	0.55	1.15 (1.04 - 2.18)	0.71
2	G	A	0.22	1.06 (1.79 - 2.42)	0.54
3	A	G	0.12	1.95 (1.68 - 2.97)	0.20
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.86					

†Single nucleotide polymorphism in *ABO* gene;†Frequency of haplotypes;¥Odds ratio and confidential interval.

(Supplementary Table 3). The linkage disequilibrium (LD) between SNPs in ABO showed that rs3426669, rs199969472 and rs7849280 are in perfect linkage disequilibrium and form a block, while rs657152, rs676996 and rs529565 are in high LD and also form a block and rs8176733 is in perfect LD with rs8176725 (Fig. 2A) (see Table 6).

For *CCR9*, we found a haplotype between the G allele of rs34338823, the G allele of rs115227401, the C allele of rs6806802, the A allele of rs72884922 and the G allele of rs2236938 (GGCAG) with a frequency of 0.07% in our population, which was associated with airway obstruction (OR: 2.10; 95%CI: 1.19–3.73; p-value: 0.01) (Table 8). Also, the A allele of rs34338823, the G allele of rs115227401, the A allele of rs6806802, the A allele of rs72884922 and the G allele of rs2236938 (AGAAG) were associated with severe asthma (OR: 1.95; 95%CI: 1.09–3.48; p-value: 0.02) with a frequency of 0.03% in our population (Table 7). In addition, the G allele of rs34338823, the A allele of rs115227401, the A allele of rs6806802, the A allele of rs72884922 and the A allele of rs2236938 (GAAAA), found in 0.03% of our population, were also a risk factor for severe asthma (OR: 2.02; 95%CI: 1.05–3.87; p-value: 0.03). Furthermore, the combination of the G allele of rs34338823, the G allele of rs115227401, the A allele of rs6806802, the C allele of rs72884922 and the G allele of rs2236938 (GGACG) with a frequency of 0.01% was associated with a risk of severe asthma (OR: 2.84; 95%CI: 1.18–6.85; p-value: 0.02) (Supplementary Table 4). However, polymorphisms in CCR9 were not associated with a risk of lung obstruction and lack of FEV reversibility (Supplementary Table 5 and Table 6). Also, SNPs in *CCR9* are not in LD (Fig. 2d) (see Table 8) (see Table 9) (see Table 7).

For *LZTFL1*, the combination of the A allele of rs7614952, the C allele of rs6806802, the G allele of rs35731912 and the G allele of rs34338823 (ACGG), with a frequency of 0.07% in our population, was positively associated with airway obstruction (OR: 1.85; 95%

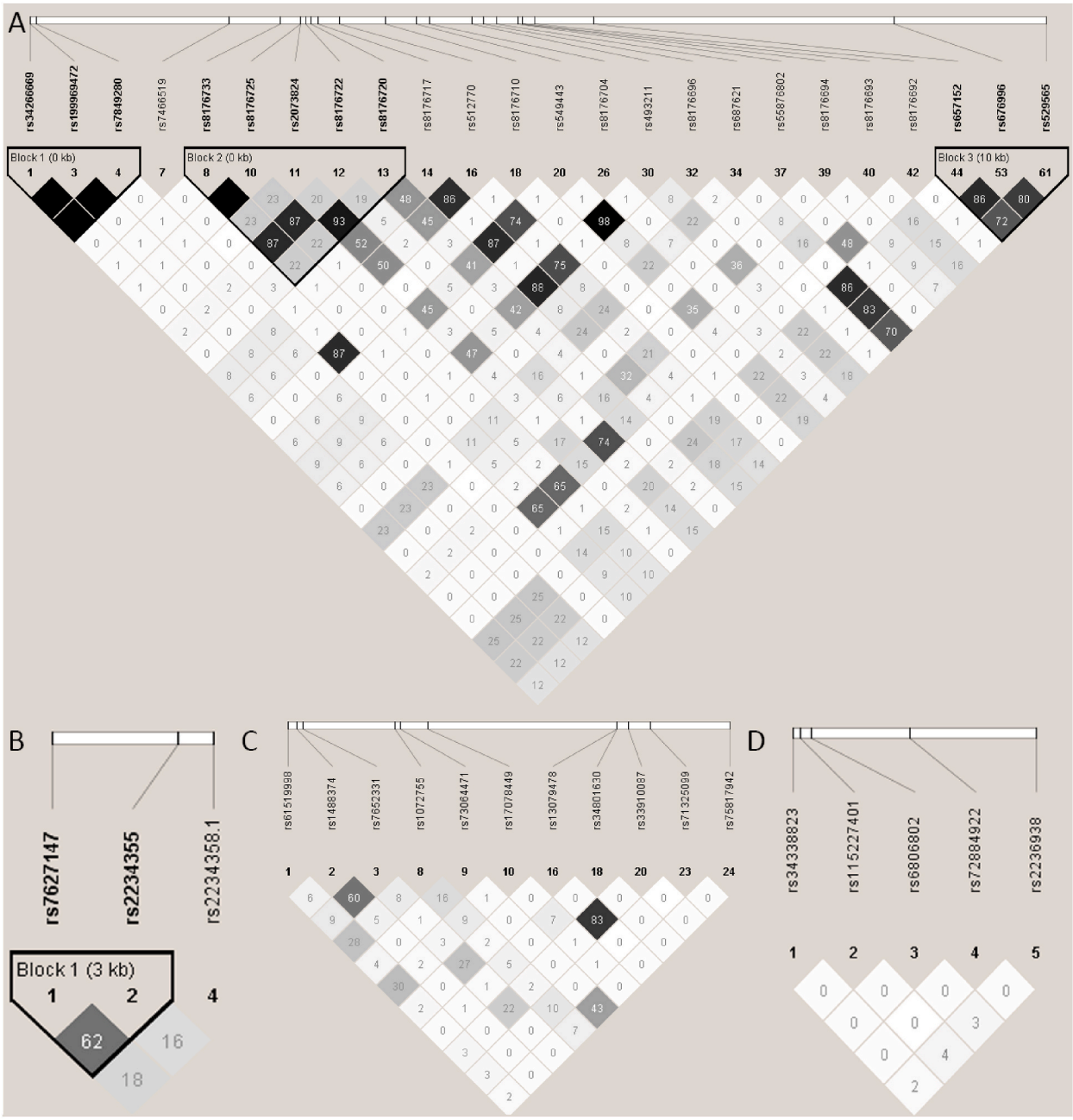

Fig. 2. Linkage of Disequilibrium plots of SNPs of *ABO, CXCR6, FYCO1*and *CCR9* genes. The top horizontal bar illustrates the location of SNPs on a physical scale. The colour of squares shows the strength of pairwise r^2 values on a scale where black indicates perfect LD ($r^2 = 1$), shades of grey suggests imperfect LD ($0 < r^2 < 1$) and white implies perfect equilibrium ($r^2 = 0$). The r^2 LD value is also indicated within each square. (a) LD in twenty-four SNPs of *ABO* in chromosome 9; (b) LD in three SNPs of *CXCR6*in chromosome 3; (c) LD in eleven SNPs of *FYCO1* in chromosome 3 and (d) LD in five SNPs of *CCR9* in chromosome 3.

CI: 1.07–3.20; p-value: 0.02) (Table 10). We also found that the A allele of rs7614952, the A allele of rs6806802, the A allele of rs35731912 and the A allele of rs34338823 (AAAA), at a frequency of 0.02% in our population, were positively associated with severe asthma (Table 11) (OR: 2.20; 95%CI: 1.11–4.36; p-value: 0.02) (Supplementary Table 7). We found no associations between SNPs in those genes and risk of lung obstruction or lack of FEV reversibility (Table 12 and Supplementary Table 8 and Table 9) and none of those SNPs were in LD (Fig. 3a) (see Table 11) (seeTable 12) (see Table 13) (see Table 10).

In the haplotype analysis for *SCL6A*20, the haplotype combination of the G allele of rs73062389, the G allele of rs2271615, the A allele of rs143463150 and the A allele of rs2531747 (GGAA), with a frequency of 0.08%, was directly associated with response to FEV1

Table 6
Haplotype analysis between rs8176733, rs8176725, rs8176722, rs2073824, rs8176710, rs8176692 and rs8176720 in *ABO* gene on risk of lack of FEV reversibility.

Haplotypes in *ABO* and Lack of FEV reversibility										
	rs8176733†	rs8176725†	rs8176722†	rs2073824†	rs8176710 †	rs8176692 †	rs8176720†	**Freq¶**	**OR (95% CI)¥**	**P-value**
1	A	G	C	G	A	A	A	0.55	1.00	—
2	A	G	C	A	A	A	G	0.22	0.88 (0.68 - 1.14)	0.32
3	G	A	A	G	A	A	G	0.11	0.98 (0.71 - 1.37)	0.91
4	A	G	C	G	T	A	G	0.02	0.57 (0.30 - 1.06)	0.07
5	A	G	C	G	A	A	G	0.02	0.52 (0.28 - 0.98)	0.04
6	G	A	C	A	A	A	G	0.01	1.13 (0.48 - 2.65)	0.79
7	A	G	C	A	A	A	G	0.03	1.70 (0.59 - 4.93)	0.32
*	*	*	*	*	*	*	*	0.01	0.90 (0.48 - 1.69)	0.75
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.86										

†Single nucleotide polymorphism in *ABO* gene;¶Frequency of haplotypes;¥Odds ratio and confidential interval * rare haplotype in population.

Table 7
Haplotype analysis between rs34338823, rs115227401, rs6806802, rs72884922 and rs2236938in *CCR9* gene on risk of asthma severity.

Haplotypes in *CCR9* and asthma severity								
	rs34338823	rs115227401	rs6806802	rs72884922	rs2236938	Freq¶	OR (95% CI)¥	P-value
1	G	G	A	A	G	0.55	1.00	—
2	G	G	A	A	A	0.28	1.15 (0.86 - 1.53)	0.36
3	G	G	C	A	G	0.07	1.44 (0.90 - 2.29)	0.13
4	A	G	A	A	G	0.03	1.95 (1.09 - 3.48)	0.02
5	G	A	A	A	A	0.02	2.02 (1.05 - 3.87)	0.03
6	G	G	A	C	G	0.55	2.84 (1.18 - 6.85)	0.02
*	*	*	*	*	*	0.01	1.00	—
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.03								

†Single nucleotide polymorphism in *CCR9* gene;¶Frequency of haplotypes;¥Odds ratio and confidential interval.

Table 8
Haplotype analysis between rs34338823, rs115227401, rs6806802, rs72884922 and rs2236938 in *CCR9* gene on risk of lung obstruction.

Haplotypes in *CCR9* and Lung obstruction								
	rs34338823	rs115227401	rs6806802	rs72884922	rs2236938	Freq¶	OR (95% CI)¥	P-value
1	G	G	A	A	G	0.54	1.00	—
2	G	G	A	A	A	0.28	1.35 (0.89 - 2.05)	0.16
3	G	G	C	A	G	0.07	2.10 (1.19 - 3.73)	0.01
4	A	G	A	A	G	0.04	0.85 (0.30 - 2.41)	0.76
5	G	A	A	A	A	0.03	0.51 (0.12 - 2.11)	0.35
6	G	G	A	C	G	0.01	0.55 (0.07 - 4.14)	0.56
*	*	*	*	*	*	0.00	1.18 (0.13 - 10.28)	0.88
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.15								

†Single nucleotide polymorphism in *CCR9* gene;¶Frequency of haplotypes;¥Odds ratio and confidential interval.

Table 9
Haplotype analysis between rs34338823, rs115227401, rs6806802, rs72884922 and rs2236938 in *CCR9* gene on risk of lack of FEV reversibility.

Haplotypes in *CCR9* and Lack of FEV reversibility								
	rs34338823	rs115227401	rs6806802	rs72884922	rs2236938	Freq¶	OR (95% CI)¥	P-value
1	G	G	A	A	G	0.54	1.00	—
2	G	G	A	A	A	0.28	1.09 (0.84 - 1.40)	0.53
3	G	G	C	A	G	0.07	0.87 (0.58 - 1.28)	0.48
4	A	G	A	A	G	0.04	1.01 (0.60 - 1.72)	0.96
5	G	A	A	A	A	0.03	0.68 (0.40 - 1.18)	0.17
6	G	G	A	C	G	0.01	1.96 (0.68 - 5.66)	0.21
*	*	*	*	*	*	0.00	1.57 (0.32 - 7.72)	0.58
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.53								

†Single nucleotide polymorphism in *CCR9* gene;¶Frequency of haplotypes;¥Odds ratio and confidential interval.

Table 10
Haplotype analysis between rs7614952, rs6806802,rs35731912and rs34338823 in *LZTFL1* gene on risk of lung obstruction.

Haplotypes in *LZTFL1* and Lung obstruction							
	rs7614952	**rs6806802**	**rs35731912**	**rs34338823**	**Freq[¶]**	**OR (95% CI)[¥]**	**P-value**
1	A	A	G	G	0.81	1.00	—
2	A	C	G	G	0.07	1.85 (1.07 - 3.20)	0.02
3	C	A	G	G	0.03	0.62 (0.19 - 2.00)	0.43
4	A	A	A	A	0.02	1.16 (0.41 - 3.26)	0.78
5	A	A	A	G	0.02	0.72 (0.17 - 2.98)	0.65
*	A	A	G	A	0.01	0.00 (0.16- 6.60)	1.00
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.08							

(OR: 1.54; 95%CI: 1.33–1.94; p-value: 0.00). Also, the G allele of rs73062389, the G allele of rs2271615, the A allele of rs143463150 and the G allele of rs2531747 (GGAG), with a frequency of 0.06% in our population, were positively associated with the same outcome (OR: 1.64; 95%CI: 1.32–1.77; p-value: 0.01). The G allele of rs73062389, the G allele of rs2271615, the A allele of rs143463150 and the G allele of rs2531747 (GGAG), found in 0.03% of our population, was positively associated with response FEV_1 (OR: 1.54; 95%CI: 1.25–1.85; p-value: 0.00) (Table 15), which is the same to say it is directly associated with FEV_1 reversibility to bronchodilators. We found no other associations for these gene (Table 13 and Table 14). Also, the SNPs in this gene are not in linkage disequilibrium (Fig. 3b) (see Table 14) (see Table 15) (see Table 16).

No allele combination in *FYCO1 and* CXCR6 was associated with severe asthma, response to FEV_1 or airway obstruction (Supplementary Tables 10 and 11 and 12); moreover, none of those SNPs are in LD (Fig. 2C and B).

In *XCR1*, the haplotype formed by the C allele of rs6764042, the A allele of rs2230322, the A allele of rs6780163, the A allele of rs62242833, the C allele of rs60813993, the G allele of rs7646264, the A allele of rs2036295, the G allele of rs1500005, the G allele of rs9311384, the T allele of rs138967191, the A allele of rs9838450 and the G allele of rs902760 (CAAACG AGGTAG), with a frequency of 0.02% in our population, was negatively associated with severe asthma (OR: 0.23; 95%CI: 0.06–0.79; p-value: 0.02), but not with the risk of lung obstruction or lack of FEV reversibility. For LD analysis, rs6764042 and rs6780163 are in high linkage disequilibrium (Supplementary Tables 13 to 20). Also, rs6764042 is in high LD with rs7646264 and rs7646264 is in LD with rs6780163 (Fig. 3c).

A cluster of alleles can increase the susceptibility to severe asthma, airway obstruction and response to FEV_1

The polygenic risk score was produced using the risk alleles for the SNPs in the *ABO*, *CCR9*, *XCR1*, *SLC6A20*, *FYCO1* and *LZTFL1* genes, which were described here as being significantly associated with severe asthma, airway obstruction and response to FEV_1. We found that the greater the number of risk alleles, the greater the risk of severe asthma, airway obstruction and response to FEV_1. The number of scores represents the number of risk alleles; thus, "score 1" means "1 risk allele", "score 2" represents "2 risk alleles" and so forth.

For severe asthma, each increase in risk allele is followed by an increase in OR in a dose-dependent manner ["Score 1" (OR: 2.18; 95%CI: 1.12–4.15; p-value: 0.04); "Score 2" (OR: 3.11; 95%CI: 1.56–5.16; p-value: 0.03); "Score 3" (OR: 3.72; 95%CI: 1.90–6.15; p-value: 0.03); "Score 4" (OR: 4.50; 95%CI: 3.01–8.15; p-value: 0.05); "Score 5" (OR: 6.30; 95%CI: 2.30–14.23; p-value: 0.01); and "Score 6" (OR: 7.56; 95%CI: 3.53–16.23; p-value: 0.001) (Fig. 4a)].

In regard to airway obstruction, the same dose-response effect was found ["Score 1" (OR: 1.86; 95%CI: 1.32–2.15; p-value: 0.05); "Score 2" (OR: 1.96; 95%CI: 1.02–2.19; p-value: 0.04); "Score 3" (OR: 1.99; 95%CI: 1.60–3.50; p-value: 0.05); "Score 4" (OR: 2.18; 95%CI: 2.60–3.99; p-value: 0.04); "Score 5" (OR: 3.18; 95%CI: 1.40–4.00; p-value: 0.01); and "Score 6" (OR: 4.13; 95%CI: 1.50–6.89; p-value: 0.05) (Fig. 4b)].

For response to FEV_1, the same increased trend was found for the greater the number of risk alleles ["Score 1" (OR: 0.70; 95%CI: 0.18–0.95; p-value: 0.05); "Score 2" (OR: 0.60; 95%CI: 0.20–0.79; p-value: 0.05); "Score 3" (OR: 0.55; 95%CI: 0.35–0.84; p-value: 0.03); "Score 4" (OR: 0.50; 95%CI: 0.31–0.83; p-value: 0.04); "Score 5" (OR: 0.37; 95%CI: 0.45–0.89; p-value: 0.04); and "Score 6" (OR: 0.30; 95%CI: 0.13–0.85; p-value: 0.02) (Fig. 4c)] (Supplementary Tables 13 and 20).

3.6. In silico regulatory SNPs functions

In order to determine the putative regulatory potential of polymorphisms in the studied genes, we evaluated in the regulatory feature *in silico* using the rSNPBase and RegulomeDb tools. Using the rSNPbase tool, we showed that some polymorphisms can interfere with regulatory elements associated with DNA accessibility (proximal regulation). Other SNPs can act in distal regulation, which means that they modify chromatin interactions (with the exception of rs796972949). None of the included SNPs seem to modify miRNA regulation (RNA expression levels). Also, some polymorphisms have a role in the post-transcriptional RNA binding. The RegulomeDb analysis showed that most of the SNPs acts as regulatory factors (Scores close to 1) and that all SNPs may interfere to some level, impacting gene expression (Scores 1 to 5), with the exception of rs71325099 and rs6806802 (Score 7).The rSNPbase information as well as RegulomeDb score for each SNP is summarised in Supplementary Table 1.

4. Discussion

Asthma and COVID-19 are both diseases that can affect lung function [27]; there are some common clinical manifestations between

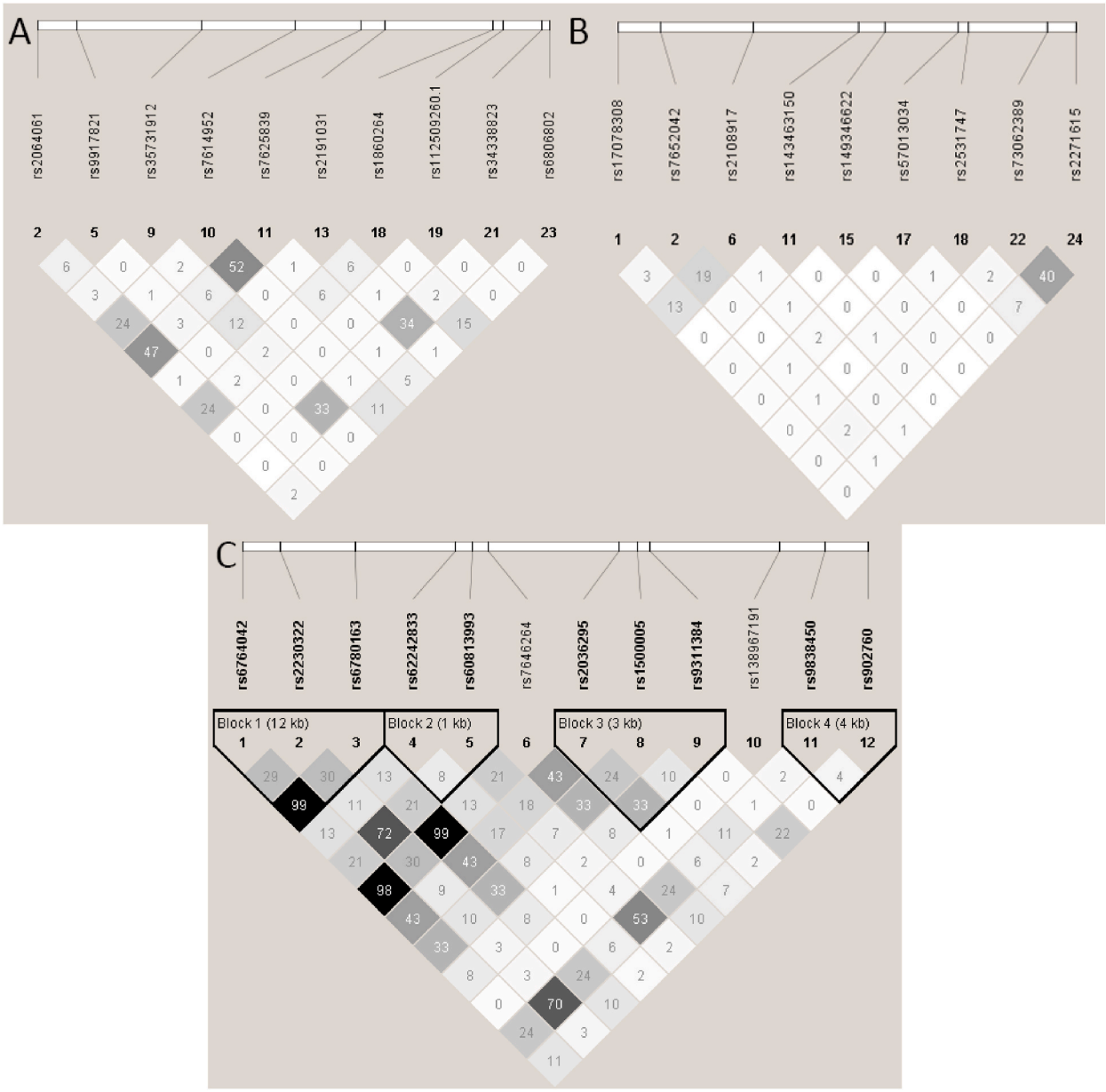

Fig. 3. Linkage of Disequilibrium plots of SNPs of *LZTFL1, SCL6A20* and *XCR1*genes. The top horizontal bar illustrates the location of SNPs on a physical scale. The colour of squares shows the strength of pairwise r^2 values on a scale where black indicates perfect LD ($r^2 = 1$), shades of grey suggests imperfect LD ($0 < r^2 < 1$) and white implies perfect equilibrium ($r^2 = 0$). The r^2 LD value is also indicated within each square. (a) LD in ten SNPs of *LZTFL1*in chromosome 3; (b) LD in nine SNPs of *SCL6A20* in chromosome 3 and (c) LD in twelve SNPs of *XCR1* in chromosome 3.

them, like cough, shortness of breath and chest tightness (AAFA.org., 2020; Liu et al., 2020). Although there is no clear evidence proving that asthma increases susceptibility to SARS-CoV-2 infection [28], once infected, subjects with more severe forms of asthma may develop worse outcomes for COVID-19 19 [30–33]. Subjects with asthma are most susceptible to developing inflammatory exacerbations in response to a viral infection [29] and some asthmatics do not have an efficient response against viruses, due to a failure in the innate immune antiviral response and delays in the production of IFN by airway epithelial cells, which may lead to exacerbations [30].

The immunological mechanism of protection against SARs-CoV-2 mainly involves IFN-I responses and the viral RNA and translated proteins activate NF-kB in epithelial cells [31,32]. Also, the host immune system reacts to cells injured by the virus [33]. The presence of SARs-CoV-2 in the lung can trigger proinflammatory cytokines like IFN-γ, IL-1Rα, IL-2Rα, IL-6 and the active inflammasome, leading to a "cytokine storm syndrome", which is associated with worse outcomes [34,35]. Studies have associated the presence of inflammatory cells as a risk factor with airway remodelling during asthma attacks Fehrenbach et al., 2017; Global Initiative for Asthma, 2020;

Table 11
Haplotype analysis between rs7614952, rs6806802,rs35731912 and rs34338823 in *LZTFL1* gene on risk of asthma severity.

Haplotypes in *LZTFL1* and asthma severity							
	rs7614952	**rs6806802**	**rs35731912**	**rs34338823**	**Freq[1]**	**OR (95% CI)[¥]**	**P-value**
1	A	A	G	G	0.82	1.00	—
2	A	C	G	G	0.07	1.30 (0.83 - 2.04)	0.25
3	C	A	G	G	0.04	1.10 (0.61 - 1.99)	0.75
4	A	A	A	A	0.02	2.20 (1.11 - 4.36)	0.02
5	A	A	A	G	0.01	1.39 (0.62 - 3.13)	0.43
*	A	A	G	A	0.01	1.21 (0.45 - 3.23)	0.7
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.29							

Table 12
Haplotype analysis between rs7614952, rs6806802,rs35731912 and rs34338823 in *LZTFL1* gene on risk of lack of FEV reversibility.

Haplotypes in *LZTFL1* and Lack of FEV reversibility							
	rs7614952	**rs6806802**	**rs35731912**	**rs34338823**	**Freq[1]**	**OR (95% CI)[¥]**	**P-value**
1	A	A	G	G	0.81	1.00	—
2	A	C	G	G	0.07	0.85 (0.58 - 1.25)	0.41
3	C	A	G	G	0.03	0.96 (0.55 - 1.67)	0.89
4	A	A	A	A	0.02	1.03 (0.54 - 1.96)	0.94
5	A	A	A	G	0.02	0.97 (0.47 - 1.98)	0.93
*	A	A	G	A	0.01	0.91 (0.39 - 2.14)	0.83
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.98							

Table 13
Haplotype analysis betweenrs73062389, rs2271615, rs143463150 andrs2531747in *SLC6A20* gene on risk of asthma severity.

Haplotypes in *SLC6A20* and asthma severity							
	rs73062389	**rs2271615**	**rs143463150**	**rs2531747**	**Freq[1]**	**OR (95% CI)[¥]**	**P-value**
1	G	G	A	G	0.80	1.00	—
2	G	G	A	A	0.03	1.37 (0.82 - 2.27)	0.23
3	G	G	A	G	0.07	0.84 (0.47 - 1.53)	0.58
4	G	G	A	A	0.04	0.75 (0.28 - 1.98)	0.56
5	G	G	A	G	0.02	0.49 (0.18 - 1.37)	0.18
*	G	C	A	G	0.01	0.41 (0.06 - 2.89)	0.37
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.58							

Table 14
Haplotype analysis betweenrs73062389, rs2271615, rs143463150 andrs2531747 in *SLC6A20* gene on risk of lung obstruction.

Haplotypes in *SLC6A20* and Lung Obstruction							
	rs73062389	**rs2271615**	**rs143463150**	**rs2531747**	**Freq[1]**	**OR (95% CI)[¥]**	**P-value**
1	G	G	A	G	0.83	1.00	—
2	G	G	A	A	0.06	0.95 (0.45 - 2.01)	0.90
3	G	G	A	G	0.04	1.01 (0.48 - 2.12)	0.99
4	G	G	A	A	0.04	0.85 (0.29 - 2.50)	0.77
5	G	G	A	G	0.03	0.20 (0.03 - 1.48)	0.12
*	G	C	A	G	0.00	0.00 (-Inf - Inf)	1
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.74							

Sandberg et al., 2000). Moreover, in atopic asthma, the allergic response suppresses antiviral immunity (Lindsley et al., 2020; Riggioni et al., 2020; Roisman et al., 1999). In addition, subjects with more severe forms of asthma are often treated with oral glucocorticoids and these medications are related to increased virus load in the initial phases of respiratory infections; however, these same medications, while used in the inflammatory, second phase of COVID-19, increase survival survival [31,36,37]. In the present study, we explored how polymorphisms in genes previously associated with COVID-19 severe respiratory failure are linked to lung function among subjects with asthma [38].

In our study, we showed for the first time that polymorphisms in genes related to COVID-19 are associated with severe asthma and poor lung function in a Brazilian population. The *ABO* gene was previously described to be associated with SARS-CoV-2 respiratory failure in a European population [38]. In our study, we found some polymorphisms in the *ABO* gene that were associated with severe asthma, airway obstruction and poor FEV_1 reversibility to bronchodilators. In the GWAS for SARS-CoV-2 respiratory failure, the

Table 15
Haplotype analysis betweenrs73062389, rs2271615, rs143463150 andrs2531747 in *SLC6A20* gene on risk of lack of FEV reversibility.

Haplotypes in *SLC6A20* and Lack of FEV reversibility							
	rs73062389	**rs2271615**	**rs143463150**	**rs2531747**	**Freq[1]**	**OR (95% CI)[¥]**	**P-value**
1	G	G	A	G	0.83	1.00	—
2	G	G	A	A	0.06	0.46 (0.29 - 0.74)	>0.01
3	G	G	A	G	0.04	0.36 (0.22 - 0.57)	>0.01
4	G	G	A	A	0.02	1.09 (0.44 - 2.71)	0.85
5	G	G	A	G	0.03	0.46 (0.25 - 0.84)	0.01
*	G	C	A	G	0.01	2.06 (0.45 - 9.35)	0.35
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: >0.01							

Table 16
Haplotype analysis betweenrs13079478, rs7652331, rs33910087, rs17078449, rs61519998, rs34801630 and rs75817942in *FYCO1* gene on risk of lack of FEV reversibility.

Haplotypes in *FYCO1* and Lack of FEV reversibility										
	rs13079478	**rs7652331**	**rs33910087**	**rs17078449**	**rs61519998**	**rs34801630**	**rs75817942**	**Freq**	**OR (95% CI)**	**P-value**
1	C	G	G	G	T	G	G	0.20	1.00	—
2	C	G	G	G	A	G	G	0.20	1.31 (0.93 - 1.85)	0.13
3	C	G	G	A	T	G	G	0.11	1.17 (0.77 - 1.78)	0.46
4	C	A	G	G	A	G	G	0.09	0.83 (0.55 - 1.26)	0.38
5	C	G	G	G	A	G	G	0.09	0.75 (0.50 - 1.13)	0.17
6	C	G	G	G	A	A	G	0.05	0.91 (0.55 - 1.51)	0.72
7	C	G	G	G	A	G	G	0.04	0.85 (0.51 - 1.41)	0.52
8	C	G	G	A	T	A	G	0.04	0.99 (0.57 - 1.70)	0.96
9	A	A	A	G	A	G	G	0.04	0.99 (0.56 - 1.74)	0.97
10	C	G	G	G	A	G	G	0.03	0.88 (0.50 - 1.56)	0.67
11	C	G	G	G	A	G	A	0.03	2.03 (0.93 - 4.43)	0.07
*	*	*	*	*	*	*	*	0.02	1.29 (0.58 - 2.87)	0.53
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.18										

Table 17
Haplotype analysis betweenrs13079478, rs7652331, rs33910087, rs17078449, rs61519998, rs34801630 and rs75817942 in *FYCO1* gene on risk of asthma severity.

Haplotypes in *FYCO1* and asthma severity										
	rs13079478	**rs7652331**	**rs33910087**	**rs17078449**	**rs61519998**	**rs34801630**	**rs75817942**	**Freq**	**OR (95% CI)**	**P-value**
1	C	G	G	G	T	G	G	0.20	1.00	—
2	C	G	G	G	A	G	G	0.20	1.10 (0.76 - 1.60)	0.60
3	C	G	G	A	T	G	G	0.10	0.85 (0.52 - 1.39)	0.53
4	C	A	G	G	A	G	G	0.09	1.00 (0.61 - 1.64)	0.99
5	C	G	G	G	A	G	G	0.08	1.19 (0.73 - 1.93)	0.49
6	C	G	G	G	A	A	G	0.05	1.08 (0.60 - 1.92)	0.81
7	C	G	G	G	A	G	G	0.05	0.73 (0.38 - 1.40)	0.35
8	C	G	G	A	T	A	G	0.05	1.28 (0.71 - 2.29)	0.41
9	A	A	A	G	A	G	G	0.03	0.47 (0.20 - 1.11)	0.08
10	C	G	G	G	A	G	G	0.03	1.79 (0.98 - 3.28)	0.05
11	C	G	G	G	A	G	A	0.0364	0.88 (0.42 - 1.85)	0.74
*	*	*	*	*	*	*	*	0.0232	0.35 (0.10 - 1.29)	0.12
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.13										

Table 18
Haplotype analysis between rs13079478, rs7652331, rs33910087, rs17078449, rs61519998, rs34801630 and rs75817942 in *FYCO1* gene on risk of lung obstruction.

Haplotypes in *FYCO1* and Lung obstruction										
	rs13079478	**rs7652331**	**rs33910087**	**rs17078449**	**rs61519998**	**rs34801630**	**rs75817942**	**Freq**	**OR (95% CI)**	**P-value**
1	C	G	G	G	T	G	G	0.20	1.00	—
2	C	G	G	G	A	G	G	0.20	0.83 (0.48 - 1.46)	0.52
3	C	G	G	A	T	G	G	0.11	1.07 (0.56 - 2.05)	0.83
4	C	A	G	G	A	G	G	0.09	1.23 (0.64 - 2.38)	0.54
5	C	G	G	G	A	G	G	0.09	0.84 (0.40 - 1.76)	0.65
6	C	G	G	G	A	A	G	0.05	0.65 (0.24 - 1.76)	0.39
7	C	G	G	G	A	G	G	0.04	0.86 (0.35 - 2.14)	0.74
8	C	G	G	A	T	A	G	0.04	0.29 (0.07 - 1.31)	0.11
9	A	A	A	G	A	G	G	0.04	0.67 (0.23 - 1.97)	0.46
10	C	G	G	G	A	G	G	0.03	0.53 (0.16 - 1.80)	0.31
11	C	G	G	G	A	G	A	0.03	0.81 (0.27 - 2.42)	0.71
*	*	*	*	*	*	*	*	0.02	0.92 (0.25 - 3.39)	0.90
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.74										

Table 19
Haplotype analysis between rs6764042, rs2230322, rs6780163, rs62242833, rs60813993, rs7646264 and rs2036295in *XCR1* gene on risk of asthma severity.

Haplotypes in *XCR1* and asthma severity										
	rs6764042	**rs2230322**	**rs6780163**	**rs62242833**	**rs60813993**	**rs7646264**	**rs2036295**	**Freq**	**OR (95% CI)**	**P-value**
1	A	A	C	A	C	A	G	0.70	1.00	—
2	C	A	A	G	C	G	A	0.09	0.78 (0.53 - 1.15)	0.21
3	C	G	A	A	A	G	A	0.06	0.90 (0.61 - 1.32)	0.59
4	A	A	C	A	C	A	G	0.06	0.79 (0.45 - 1.39)	0.41
5	C	G	A	A	C	G	G	0.02	0.83 (0.42 - 1.64)	0.60
6	A	A	C	A	C	A	A	0.03	0.66 (0.32 - 1.39)	0.28
7	C	A	A	A	C	G	A	0.02	0.23 (0.06 - 0.79)	0.02
8	C	A	A	A	C	G	G	0.02	0.74 (0.31 - 1.76)	0.50
9	C	G	A	A	A	G	G	0.01	0.44 (0.13 - 1.48)	0.18
10	A	A	C	G	C	A	G	0.01	0.30 (0.08 - 1.18)	0.08
11	A	A	C	A	C	A	G	0.01	0.78 (0.23 - 2.60)	0.68
*	A	A	C	A	C	A	G	0.00	1.00	—
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.23										

Table 20
Haplotype analysis between rs6764042, rs2230322, rs6780163, rs62242833, rs60813993, rs7646264 and rs2036295in *XCR1* gene on risk of lung obstruction.

Haplotypes in *XCR1* and Lung Obstruction										
	rs6764042	**rs2230322**	**rs6780163**	**rs62242833**	**rs60813993**	**rs7646264**	**rs2036295**	**Freq**	**OR (95% CI)**	**P-value**
1	A	A	C	A	C	A	G	0.70	1.00	—
2	C	A	A	G	C	G	A	0.09	1.00 (0.56 - 1.77)	0.99
3	C	G	A	A	A	G	A	0.06	1.06 (0.60 - 1.88)	0.84
4	A	A	C	A	C	A	G	0.06	0.36 (0.11 - 1.24)	0.11
5	C	G	A	A	C	G	G	0.02	0.91 (0.34 - 2.43)	0.86
6	A	A	C	A	C	A	A	0.03	0.79 (0.27 - 2.32)	0.67
7	C	A	A	A	C	G	A	0.02	0.24 (0.03 - 1.86)	0.17
8	C	A	A	A	C	G	G	0.02	0.65 (0.18 - 2.30)	0.5
9	C	G	A	A	A	G	G	0.01	1.00 (0.29 - 3.51)	1
10	A	A	C	G	C	A	G	0.01	0.93 (0.21 - 4.23)	0.93
11	A	A	C	A	C	A	G	0.01	1.88 (0.51 - 6.96)	0.34
*	A	A	C	A	C	A	G	0.00	1.00	—
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.48										

authors found some SNPs on 9q34.2, in the region of the *ABO* gene, to be associated with COVID-19 complications; rs657152 was the most commonly associated SNP with severe respiratory features in COVID-19, while rs687621 and rs647800 were also associated with this [38]. In our study, none of these SNPs were associated with the asthma and lung function outcomes evaluated.

Polymorphisms in the *ABO* gene have already been associated with best survival in *Plasmodium falciparum* in an African population [39] and the ABO histo-blood group was considered a risk factor for asthma [40–43] and an increase risk of infection in COVID-19

Table 21
Haplotype analysis between rs6764042, rs2230322, rs6780163, rs62242833, rs60813993, rs7646264 and rs2036295in *XCR1* gene on risk of lack of FEV reversibility.

Haplotypes in *XCR1* and Lack of FEV reversibility										
	rs6764042	**rs2230322**	**rs6780163**	**rs62242833**	**rs60813993**	**rs7646264**	**rs2036295**	**Freq**	**OR (95% CI)**	**P-value**
1	A	A	C	A	C	A	G	0.70	1.00	—
2	C	A	A	G	C	G	A	0.09	0.96 (0.68 - 1.36)	0.82
3	C	G	A	A	A	G	A	0.06	0.98 (0.69 - 1.39)	0.92
4	A	A	C	A	C	A	G	0.06	0.77 (0.48 - 1.23)	0.27
5	C	G	A	A	C	G	G	0.02	1.07 (0.59 - 1.93)	0.82
6	A	A	C	A	C	A	A	0.03	1.30 (0.68 - 2.48)	0.42
7	C	A	A	A	C	G	A	0.02	1.23 (0.63 - 2.40)	0.55
8	C	A	A	A	C	G	G	0.02	0.80 (0.42 - 1.53)	0.56
9	C	G	A	A	A	G	G	0.01	0.87 (0.41 - 1.81)	0.7
10	A	A	C	G	C	A	G	0.01	1.79 (0.61 - 5.28)	0.29
11	A	A	C	A	C	A	G	0.01	2.41 (0.61 - 9.61)	0.21
*	A	A	C	A	C	A	G	0.00	1.00	—
GLOBAL HAPLOTYPE ASSOCIATION P-VALUE: 0.23										

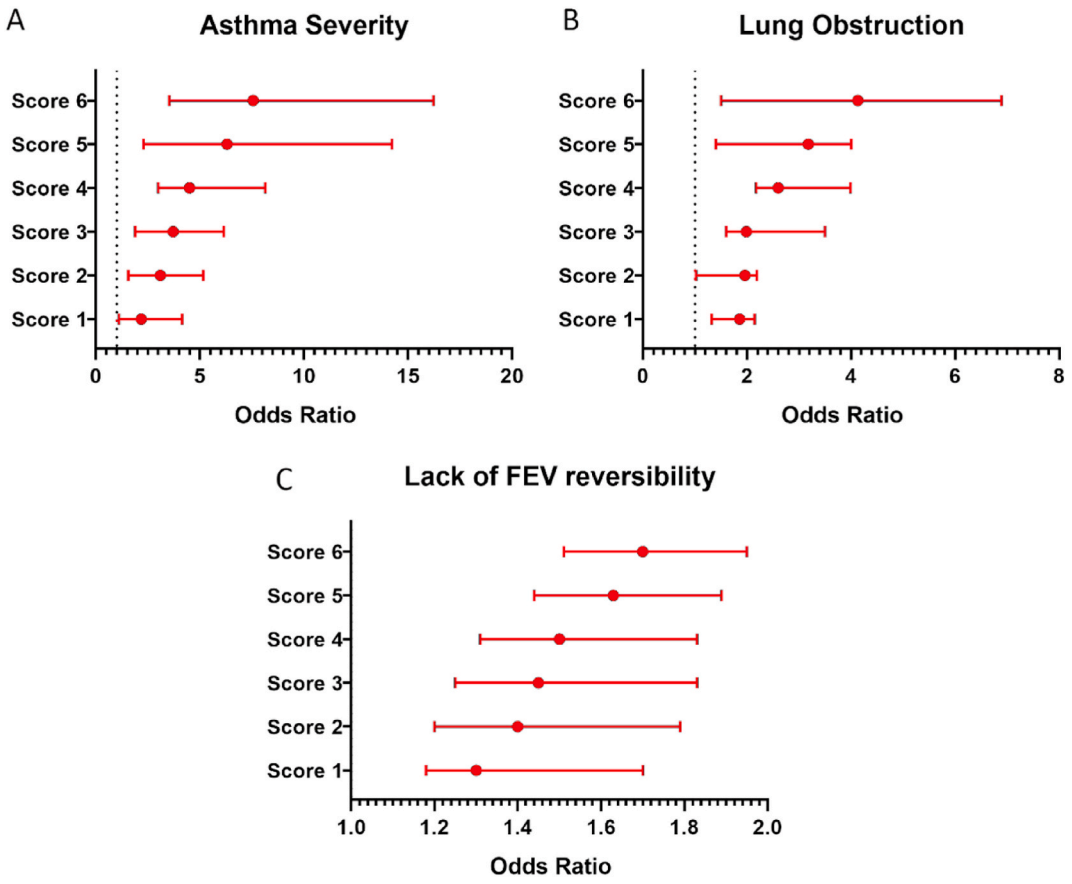

Fig. 4. Polygenic risk score using the risk alleles from SNPs in *ABO*, *CCR9*, *XCR1*, *SLC6A20*, *FYCO1* and *LZTFL1* genes associated with (a) asthma severity; (b) lung obstruction and (c) lack of FEVE reversibility.

[44]. In our study, we found polymorphisms in the *ABO* gene to be a risk factor for severe asthma, airway obstruction and poor FEV_1 reversibility. The ABO system is also related to thrombotic events and ABO antigens are expressed on mucosal epithelial cells and respiratory organs (Chen et al., 2005). It is therefore possible that polymorphisms in this gene play a role in coagulation homeostasis, leading to a worse prognosis of COVID-19 among subjects with severe asthma. Closely related to the ABO system, the *SCL6A20* gene seems to play a key role in the entry of SARS-CoV-2 into lung cells. A study of DNA methylation showed the *SLC6A20* gene to be a potential therapeutic target for malignant mesothelioma in the lungs [,10,11,45,46]. In the GWAS for COVID-19 respiratory failure, rs17213127 in *SLC6A2*0 had a strong association with the outcome (Ellinghaus et al., 2020b). In our study, we did not find this SNP to

be associated with severe asthma or lung function; however, some new polymorphisms in *SLC6A20* were associated with the risk of severe asthma (rs2531747 and rs2036295).

Part of the lung inflammation in asthma and COVID-19 infection is mediated by epithelial cells, which can release chemokines and cytokines involved in the immune response in lung inflammation asthma [51,52] [47]. In this context, *LZTFL1* has an important role in the differentiation of epithelial cells in lung tissue [47,48]. In our study, we also found polymorphisms in the *LZFL1* gene to be risk factors for airway obstruction, severe asthma and poor FEV_1 reversibility to bronchodilators. Two SNPs in this gene were previously reported to be risk factors for severe respiratory failure in COVID-19: rs35652899 and rs11385942(Ellinghaus et al., 2020b). In the process of airway inflammation, chemokines act in mutual biological pathways, like chemotaxis, angiogenesis and lung remodelling [49,50]. In our work, we analysed three genes that encode chemokines receptors (*CXCR6*, *XCR1* and *CCR9*). CXCR6 is associated with the presence of TCD8+ cells in the lung [51] and high levels of CXCR6 are a risk factor for COPD [50]. Although CXCR6 was previously associated with lung diseases, in our work we did not find any evidence of associations between polymorphisms in *CXCR6* and severe asthma, airway obstruction or FEV_1 reversibility. However, we found polymorphisms in *XCR1* and *CCR9* to be associated with severe asthma and lung function. *XCR1* encodes a chemokine receptor related to the G protein-receptor family. In addition, the CCR9 protein, encoded by the *CCR9* gene, is involved in leukocyte recruitment, closely linked to atopic asthma [19], and plays a role in eosinophil recruitment [52]. A previous study suggests that eosinophils play an important role in COVID-19 outcomes [53]. Moreover, *FYCO1* seems to have some influence in eosinophils levels, but the mechanism is still not clarified. In the present study, polymorphisms in *FYCO1* were associated with poor FEV_1 reversibility.

It was remarkable to notice, when we analysed the combination of risk alleles for each outcome in asthma or lung function, the degree of susceptibility in a dose-response fashion according to the number of risk alleles, indicating that the presence of multiple polymorphisms may play a key role in severe asthma. Moreover, severe asthma has already been associated with severe COVID-19 outcomes and hospitalisation [54]; also, this study showed that the phenotype of asthma and asthma exacerbation can be an important factor in the course of COVID-19 [61,62].

In the same way, a GWAS was performed to analyse asthma and COVID-19 hospitalisation and COVID-19 infection; the results showed a correlation between asthma and the two outcomes of COVID-19, where asthma was a protect factor against those COVID-19 outcomes. Also, asthma and COVID-19 share some genetic regions such as ABO loci [55]. Furthermore, a cohort study demonstrated an association between asthma and susceptibility to severe COVID-19; in this study, asthmatic subjects also have a higher risk of COVID-19 [64].

In conclusion, by exploring genetic variants in genes previously linked to severe respiratory failure in COVID-19 in a large sample of subjects with asthma, we demonstrated that some of these SNPs are also associated with severe asthma and abnormal lung function. Our results showed that there is a relationship between genes related to COVID-19 and asthma outcomes. The importance of the shared genetic predisposition to both diseases needs to be further clarified and should be considered in future studies.

Author contribution statement

Milca Silva: Candace Machado de Andrade: Bianca Sampaio Dotto Fiuza: Gabriela Pimentel Pinheiro: Cinthia Vila Nova Santana: Ryan dos S. Costa: Kathleen Barnes: Álvaro A. Cruz: Camila Alexandrina Figueiredo: Conceived and designed the experiments; Performed the experiments; Analysed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. </p>

4.1. Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of Competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19235.

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