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# Using bioinformatic protein sequence similarity to investigate if SARS CoV-2 infection could cause an ocular autoimmune inflammatory reactions?

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ABSTRACT

Although severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection have emerged globally, findings related to ocular involvement and reported cases are quite limited. Immune reactions against viral infections are closely related to viral and host proteins sequence similarity. Molecular Mimicry has been described for many different viruses; sequence similarities of viral and human tissue proteins may trigger autoimmune reactions after viral infections due to similarities between viral and human structures. With this study, we aimed to investigate the protein sequence similarity of SARS CoV-2 with retinal proteins and retinal pigment epithelium (RPE) surface proteins. Retinal proteins involved in autoimmune retinopathy and retinal pigment epithelium surface transport proteins were analyzed in order to infer their structural similarity to surface glycoprotein (S), nucleocapsid phosphoprotein (N), membrane glycoprotein (M), envelope protein (E), ORF1ab polyprotein (orf1ab) proteins of SARS CoV-2. Protein similarity comparisons, 3D protein structure prediction, T cell epitopes-MHC binding prediction, B cell epitopes-MHC binding prediction and the evaluation of the antigenicity of peptides assessments were performed. The protein sequence analysis was made using the Pairwise Sequence Alignment and the LALIGN program. 3D protein structure estimates were made using Swiss Model with default settings and analyzed with TM-align web server. T-cell epitope identification was performed using the Immune Epitope Database and Analysis (IEDB) resource Tepitool. B cell epitopes based on sequence characteristics of the antigen was performed using amino acid scales and HMMs with the BepiPred 2.0 web server. The predicted peptides/epitopes in terms of antigenicity were examined using the default settings with the VaxiJen v2.0 server. Analyses showed that, there is a meaningful similarities between 6 retinal pigment epithelium surface transport proteins (MRP-4, MRP-5, RFC1, SNAT7, TAUT and MATE) and the SARS CoV-2 E protein. Immunoreactive epitopic sites of these proteins which are similar to protein E epitope can create an immune stimulation on T cytotoxic and T helper cells and 6 of these 9 epitopic sites are also vaxiJen. These result imply that autoimmune cross-reaction is likely between the studied RPE proteins and SARS CoV-2 E protein. The structure of SARS CoV-2, its proteins and immunologic reactions against these proteins remain largely unknown. Understanding the structure of SARS CoV-2 proteins and demonstration of similarity with human proteins are crucial to predict an autoimmune response associated with immunity against host proteins and its clinical manifestations as well as possible adverse effects of vaccination.

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**Abbreviations**

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| SARS CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| S | Surface glycoprotein |
| N | Nucleocapsid phosphoprotein |
| M | Membrane glycoprotein |
| E | Envelope protein |
| Orf1ab | ORF1ab polyprotein |
| RPE | Retinal pigment epithelium |
| IQR | Interquartile range |
| PPS | Protein-protein similarities |
| AIRs | Autoimmune retinopathies |
| APMPPE | Acute posterior multifocal placoid pigment epitheliopathy |
| VKH | Vogt-Koyanagi-Harada |

## 1. Introduction

Coronavirus disease 2019 (COVID-19) originated in Wuhan City, China in 2019 and has spread rapidly to all Chinese provinces and globally. COVID-19 is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) (Kannan et al., 2020). More than 71 million people have been infected worldwide (as of Dec 15, 2020), resulting in more than 1,5 Million deaths (covid19,). Following official reporting of the first case in January, the number of confirmed cases reached nearly 73,000 and 1870 deaths occurred in February in China (Shanmugaraj et al., 2020). However, despite high progression rate and increasing number of cases within the last 1 year, understanding of the molecular and pathologic mechanisms of the disease have been improved, but the pathogenesis of the disease has not been fully elucidated. Moreover, underlying mechanisms of the immune response to SARS CoV-2 infection are still not clear. Extensive research is ongoing with the aim to quickly develop an effective vaccine and treatment strategies.

While the exact pathogenesis remained elusive, case reports documenting clinical findings associated with SARS CoV-2 infection have emerged globally. However, only a few studies of ocular manifestations of the disease have been reported so far. In the first case series, the symptoms of conjunctivitis were described, however also retinal involvement has been found in the second series (Wu et al., 2020; Marinho et al., 2020; Abrishami et al., 2020; Chen et al., 2020). Both publications presented ocular findings but failed to provide an explanation for etiology and pathogenesis. In the study conducted by Pirraglia et al., in patients with SARS CoV-2 pneumonia, while conjunctival involvement was reported, but there was no retinal involvement and the authors speculate that SARS CoV-2 might not pass through the blood-retinal barrier (Pirraglia et al., 2020). In addition, in a study conducted by Löffler et al. it was shown that there was no typical viral involvement other than conjunctival inflammatory cell infiltration among patients who died due to SARS CoV-2. It was also emphasized that this was not different from the usual postmortem findings and they speculated that ophthalmic tissues is not a target tissue for SARS CoV-2 infection (Löffler et al., 2020). However, Casagrande et al. demonstrated SARS CoV-2 RNA in human retinal biopsies of deceased SARS CoV-2 patients (Casagrande et al., 2020). And this result is consistent with the study of the presence of ACE2 in the retina conducted by Senanayake et al. (2007), and the fact that SARS CoV-2 may cause retinal involvement (Senanayake et al., 2007). Besides, Bettach et al. reported bilateral anterior uveitis accompanied with the diagnosis of multisystem inflammatory syndrome secondary to SARS CoV-2 infection and they claimed that the ocular inflammatory findings were related to SARS CoV-2 infection. At the same time, they emphasized that these findings are similar to the Kawasaki-like multisystem inflammatory syndrome, which develops secondary to SARS CoV-2 infection in children and adolescents (Bettach et al., 2020).

However, there still has been no research on (-auto-)immune events that may be triggered by SARS CoV-2 viral proteins which could explain ophthalmic effects including any findings on the retinal structures.

A number of studies have previously shown that autoimmune reactions triggered by antigens from microorganisms may develop during infections related to pathogen-protein sequence similarity (Fujinami et al., 1983; Wildner and Diedrichs-Möhring, 2003; Wildner and Diedrichs-Möhring, 2004; Venigalla SSK et al., 2020). A similar process was shown to occur during viral infections and following immunization with vaccines developed against viruses (Wildner and Diedrichs-Möhring, 2005; Garip et al., 2009; Stübgen, 2013; Fraunfelder et al., 2010; Geier and Geier, 2015; Salemi and D'Amelio, 2010). As a basic pathogenesis, it is emphasized that there is a protein sequence similarity between host antigens and microorganisms or viral proteins used for vaccination (Fujinami et al., 1983; Wildner and Diedrichs-Möhring, 2003, 2004; Schattner, 2005; Escott et al., 2013; Stangos et al., 2006; Fine et al., 2001). However, the number of sequence similarities studies on SARS-COV2 infection is very limited, and the study conducted by Root-Bernstein on olfactory receptors constitutes the only example (Root-Bernstein, 2020). And still no definitive information in terms of ocular tissues is available on whether such an autoimmune process exists in the course of SARS CoV-2 infection. Additionally, it is not clear whether a vaccines against SARS CoV-2 may triger an autoimmune reaction. Although the protein structures of SARS CoV-2 were determined through sequence analyses and a number of vaccine studies focusing on these proteins were initiated, long-term effects of immunization with recombinant vaccines containing these proteins or of potential immune responses against these proteins cannot be predicted (Yoshimoto, 2020). Until now, no information has been presented about the sequence similarity between retinal proteins that are known targets for autoimmunity or RPE surface proteins responsible for the fluid transport process and SARS-CoV-2 proteins.

Our here presented study aimed to investigate the protein sequence and structural similarity of SARS CoV-2 surface glycoprotein (S), nucleocapsid phosphoprotein (N), membrane glycoprotein (M), envelope protein (E) and ORF1ab polyprotein (orf1ab) with retinal proteins and RPE surface proteins. Thus, it was aimed to obtain results that may help to predict whether there might be any theoretical risk of ocular immune reaction in relation to the infection with SARS CoV-2 or in relation to a vaccination that used any of the here studied surface proteins of SARS CoV-2.

## 2. Methods

In this study, retinal proteins involved in autoimmune retinopathy and retinal pigment epithelium surface transport proteins were analyzed to determine their structural similarity to the S, N, M, E, ORF1ab proteins of SARS CoV-2.11 retinal proteins showing antigenic mimicry to viral and bacterial agents and discussed to be responsible for non-paraneoplastic autoimmune retinopathy by Grewal et al. were included in the study for the protein sequence paired analysis, 3D protein structure prediction, T cell epitopes-MHC binding prediction, B cell epitopes-MHC binding prediction and the evaluation of the antigenicity of peptides. At the same time, since the influence of autoimmune uveitic reactions and autoimmune diseases cell surface proteins are crucial and immune cells recognize cell surface proteins as foreign antigens, 12 RPE surface transport proteins, which are settled in the plasma membrane, were included in the study. (Grewal et al., 2014; Hellinen et al., 2019; Uhl et al., 2014; Macher and Yen, 2007). Protein similarity comparison assessments performed during the analysis period was made using the Pairwise Sequence Alignment method (Li et al., 2014). 3D protein structure estimates were made using Swiss Model (https://swissmodel.expasy.org/) with default settings and analyzed with TM-align web

server (Zhang and Skolnick, 2005). T-cell epitope identification was performed using the Immune Epitope Database and Analysis (IEDB) resource Tepitool (http://tools.iedb.org/tepitool/)(Paul et al., 2016). B cell epitopes based on sequence characteristics of the antigen was performed using amino acid scales and HMMs with the BepiPred 2.0 web server (http://tools.iedb.org/bcell/)(Jespersen et al., 2017). The predicted peptides/epitopes in terms of antigenicity were examined using the default settings with the VaxiJen v2.0 server (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html)(; Doytchinova and Flower, 2007, 2008). Viral proteins that are primary proteins enabling attachment of SARS CoV-2 to the host cells or its replication were chosen for the purposes of this analysis (Chen et al., 2020).

The peptide sequences of the S, N, M, E and ORF1ab proteins of SARS CoV-2 were identified using the NCBI database (https://www.ncbi.nlm.nih.gov/) and reference sequences shown in Table 1 were selected.

Data on ocular proteins to be used for comparison were obtained from the Uniprot database (https://www.uniprot.org/). Reference sequences presented in Table 2 were included in the study.

The LALIGN program (https://embnet.vital-it.ch/software/LALIGN_form.html) was used to determine percent similarity between the proteins that are expressed by SARS CoV-2 and eye-related proteins. Information on the algorithm used by the LALIGN program is provided in an article published by Xiaoqiu and Webb (1991).

3D protein structure estimates were made in PDB format, firstly all proteins were converted to PDB file format using Swiss Model (https://swissmodel.expasy.org/) with default settings and analyzed with TM-align web server. TM-align is an algorithm for sequence independent protein structure comparisons. TM-align first generates optimized residue-to-residue alignment based on structural similarity using heuristic dynamic programming iterations. An optimal superposition of the two structures built on the detected alignment, as well as the TM-score value which scales the structural similarity, will be returned. TM-score has the value in (0–1] where 1 indicates a perfect match between two structures. Following strict statistics of structures in the PDB, scores below 0.2 correspond to randomly chosen unrelated proteins while those higher than 0.5 assume generally the same fold in SCOP/CATH Zhang and Skolnick, 2005).

T-cell epitope identification was performed using the IEDB analysis resource Tepitool (http://tools.iedb.org/tepitool/)(Paul et al., 2016). It provides an estimation of peptides that bind to MHC class I and class II molecules using the Tepitool, NetMHCpan, and NetMHCIIpan methods (Karosiene et al., 2013; Nielsen et al., 2007, 2008; Hoof et al., 2009). The tool is designed as a 6-step wizard. Each field (excluding sequences and alleles) is analyzed by filling with the default recommended settings for estimation and selection of optimum peptides.

A collection of methods to predict linear B cell epitopes based on sequence characteristics of the antigen was performed using amino acid scales and HMMs with the BepiPred 2.0 web server (http://tools.iedb.org/bcell/). BepiPred 2.0 employs the hidden Markov model combined with amino acid propensity scales to predict epitope data derived from crystal structures by assessing surface accessibility, helix probability, sheet probability, and coil probability (Jespersen et al., 2017.

The predicted peptides in terms of antigenicity were examined using the default settings with the VaxiJen v2.0 server (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html). VaxiJen v2.0 is a feely accessible server which functions on the auto and cross variance (ACC) transformation of proteins and convert them into uniform vectors of principal amino acid properties Doytchinova and Flower, 2007; Doytchinova and Flower, 2008).

### 2.1. Statistical analyses

Descriptive statistics were provided as mean and standard deviation for numerical data, for normally distributed data, and median interquartile range (IQR 1st, 3rd) for non-normally distributed data. Jamovi 1.20 (www.jamovi.org/; Vienna, Austria) was used for statistical analyses.

## 3. Results

The results of our analyses evaluating the sequence identity and similarity between SARS CoV-2 and retinal and RPE related proteins are shown in Table 3. The analyses showed that the identity among studied proteins was less than 70%. Overall, median percentages of identity and similarity between each SARS CoV-2 protein and individual retinal proteins and retinal pigment epithelium surface transport proteins were as follows: S protein median identity 27% (IQR 23.5–32.7), similarity 55.9% (IQR 52–59.8), E protein median identity 33.3% (IQR 28.3–40.5), similarity 64.6% (IQR 61.3–80), M protein median identity 26.7% (IQR 25–32.5), similarity 59.1% (IQR 56.8–66.7), N protein identity 27.6% IQR (26.1–30.8), similarity 56% (IQR 53–62.7), ORF1ab protein median identity 24.3% (IQR 22.6–30.6), similarity 56.2% (IQR 53.8–62.6) (Table 3). Table 4 shows percent identity and similarity between the sequences of SARS CoV-2 proteins and retinal and RPE related proteins individually.

According to the homology table, 3D structures of eye-related proteins and SARS CoV-2 (S, M, N, E, and ORF1ab) proteins were estimated using the Swiss model (https://swissmodel.expasy.org/). The model with the best GMQE and QMEAN values was selected according to the 3D structure estimation. Afterward, models of SARS CoV-2 proteins were compared with eye-related protein models in the program TM-align (https://zhanglab.ccmb.med.umich.edu/TM-align/). When the 3D structure comparison was examined, a meaningful result could not be reached as a structural similarity for those whose TM-align score was below 0.5. However, we identified a low structural similarity between the Envelope (E) protein and multidrug resistance –associate protein 4 (MRP-4), multidrug resistance –associate protein 5 (MRP-5), replication factor C subunit 1 (RFC1), putative sodium-coupled neutral amino acid transporter 7 (SNAT7), sodium-and chloride-dependent taurine transporter (TAUT), and multidrug and toxin extrusion protein 1 (MATE1) proteins for which the TM-align score is above 0.5 (Table 5).

Regions of the envelope protein forming similar structural folds with the MRP-4, MRP-5, RFC1, SNAT7, TAUT, and MATE1 proteins were selected and aligned with the MUSCLE (https://www.ebi.ac.uk/Tools/msa/muscle/) program. As a result of the alignment, the FVVFLLVTLAILTALRLCAY conserved region of the envelope protein was obtained. The protected area was scanned with the IEDB database (http://tools.iedb.org/main/) in terms of the potential for inducing an immune response from T and B cell. As a result of the screening, 7 peptides from MHC class I (Table 6) that stimulate different allele groups in T cell response, and 2 peptides from MHC class II (Table 7) were identified. In addition, the predicted peptides were analyzed using the

**Table 1**
Genes expressed by SARS CoV-2.

| Collection Date | Number | Gene Symbol | Gene Product Name | Genbank ID | ID Link |
|---|---|---|---|---|---|
| March 17, 2020 | 7096 aa | Orf1ab | RNA-dependent RNA polymerase | QIZ16507.1 | https://www.ncbi.nlm.nih.gov/protein/QIZ16507.1/ |
| March 17, 2020 | 1273 aa | S | Surface glycoprotein | QIZ16509.1 | https://www.ncbi.nlm.nih.gov/protein/QIZ16509.1/ |
| March 17, 2020 | 419 aa | N | nucleocapsid phosphoprotein | QIZ16517.1 | https://www.ncbi.nlm.nih.gov/protein/QIZ16517.1/ |
| March 17, 2020 | 222 aa | M | membrane glycoprotein | QIZ16512.1 | https://www.ncbi.nlm.nih.gov/protein/QIZ16512.1/ |
| March 17, 2020 | 75 aa | E | envelope protein | QIZ16511.1 | https://www.ncbi.nlm.nih.gov/protein/QIZ16511.1/ |

**Table 2**
Eye-related proteins.

| Number | Gene Symbol | Gene Product Name | Genbank ID | ID Link |
|---|---|---|---|---|
| 200aa | RCVRN | Recoverin | NP_002894.1 | https://www.uniprot.org/uniprot/P35243 |
| 405aa | SAG | S-arrestin | NP_000532.2 | https://www.uniprot.org/uniprot/P10523 |
| 1247aa | RBP3 | Retinol-binding protein 3 | NP_002891.1 | https://www.uniprot.org/uniprot/P10745 |
| 542aa | TULP1 | Tubby-related protein 1 | NP_003313.3 | https://www.uniprot.org/uniprot/O00294 |
| 640aa | HSPA1A | Heat shock 70 kDa protein 1A | AAD21816.1 | https://www.uniprot.org/uniprot/P0DMV8 |
| 335aa | GAPDH | Glyceraldehyde-3-phosphate dehydrogenase | NP_001276674.1 | https://www.uniprot.org/uniprot/P04406 |
| 260aa | CA2 | Carbonic anhydrase 2 | NP_000058.1 | https://www.uniprot.org/uniprot/P00918 |
| 350aa | GNAT1 | Guanine nucleotide-binding protein G(t) subunit alpha-1 (alpha transducine −1) | NP_000163.2 | https://www.uniprot.org/uniprot/P11488 |
| 585aa | BEST1 | Bestrophin-1 | NP_004174.1 | https://www.uniprot.org/uniprot/O76090 |
| 348aa | RHO | Rhodopsin | NP_000530.1 | https://www.uniprot.org/uniprot/P08100 |
| 304aa | MBP | Myelin basic protein | NP_001020272.1 | https://www.uniprot.org/uniprot/P02686 |
| 1325aa | ABCC4 | Multidrug resistance-associated protein 4 | NP_005836.2 | https://www.uniprot.org/uniprot/O15439 |
| 164aa | MDR1 | p-glycoprotein | AAR99172.1 | https://www.uniprot.org/uniprot/Q6RVA0 |
| 1531aa | ABCC1 | Multidrug resistance-associated protein 1 | NP_004987.2 | https://www.uniprot.org/uniprot/P33527 |
| 1437aa | ABCC5 | Multidrug resistance-associated protein 5 | NP_005679.2 | https://www.uniprot.org/uniprot/O15440 |
| 507aa | LAT1 | Sodium-independent neutral amino acid | BAB70708.1 | https://www.uniprot.org/uniprot/Q96QB2 |
| 1148aa | RFC1 | Replication factor C subunit 1 | NP_001191676.1 | https://www.uniprot.org/uniprot/P35251 |
| 635aa | SLC5A6 | Sodium-dependent multivitamin transporter | NP_066918.2 | https://www.uniprot.org/uniprot/Q9Y289 |
| 462aa | SLC38A7 | Putative sodium-coupled neutral amino acid transporter 7 | NP_001356537.1 | https://www.uniprot.org/uniprot/Q9NVC3 |
| 721aa | SLC6A6 | Sodium- and chloride-dependent taurine transporter | NP_001127839.2 | https://www.uniprot.org/uniprot/P31641 |
| 570aa | SLC47A1 | Multidrug and toxin extrusion protein 1 | NP_060712.2 | https://www.uniprot.org/uniprot/Q96FL8 |
| 500aa | SLC16A1 | Monocarboxylate transporter 1 | NP_001159968.1 | https://www.uniprot.org/uniprot/P53985 |
| 541aa | SLC1A5 | Neutral amino acid transporter B (0) | NP_005619.1 | https://www.uniprot.org/uniprot/Q15758 |

**Table 3**
Percent identity and similarity between retinal/retinal pigment epithelium surface proteins and SARS CoV-2 proteins.

| SARS CoV-2 proteins | Median Identity | Median Similarity |
|---|---|---|
| S protein | 27% (IQR 23.5–32.7) | 55.9% (IQR 52–59.8) |
| E protein | 33.3% (IQR 28.3–40.5) | 64.6% (IQR 61.3–80) |
| M protein | 26.7% (IQR 25–32.5) | 59.1% (IQR 56.8–66.7) |
| N protein | 27.6% (IQR 26.1–30.8) | 56% (IQR 53–62.7) |
| ORF1ab protein | 24.3% (IQR 22.6–30.6) | 56.2% (IQR 53.8–62.6) |

vaxiJen server (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html) in terms of antigenicity, and 6 of the 9 peptides showed antigenic properties.

Since the Specificity/Sensitivity ratio is below 0.5 for a potential B cell response, the appropriate epitope could not be predicted.

## 4. Discussion

In the current study, no significant structural similarity were found between retinal proteins involved in autoimmune retinopathy and SARS CoV-2 S, E, M, N, ORF1ab proteins (Xiaoqiu and Webb, 1991; (Madeira et al., 2019). The results of the protein sequence analyses showed that identity among studied proteins was less than 70%. However, 6 RPE surface transport proteins; MRP-4, MRP-5, RFC1, SNAT7, TAUT and MATE1 were found structurally similar to Envelope (E) protein. In terms

**Table 4**
Percent identity and similarity between the sequences of SARS CoV-2 proteins and retinal and RPE related proteins analyzed by the LALIGN program. **aa*:** Amino acid overlap.

| Genbank ID | Gene Product Protein Name | Number | Comparison | Genbank ID | Eye-related Protein Name | Number | Identity % | Similar % | Overlap |
|---|---|---|---|---|---|---|---|---|---|
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_002894.1 | Recoverin | 200aa | 33.3 | 61.5 | 39aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 37.9 | 51.7 | 29aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 37.5 | 87.5 | 16aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 66.7 | 77.8 | 9aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 30.8 | 61.5 | 26aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_000532.2 | S-arrestin | 405aa | 22.7 | 59.1 | 66aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 19.6 | 52.5 | 179aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 22.7 | 59.1 | 66aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 25.7 | 60 | 35aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 24.3 | 62.2 | 37aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_002891.1 | Retinol-binding protein 3 | 1247aa | 32.5 | 57.5 | 40aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 25.6 | 56.1 | 82aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 25.5 | 49.1 | 55aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 30.5 | 52.5 | 59aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 29.3 | 53.7 | 41aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_003313.3 | Tubby-related protein 1 | 542aa | 45 | 70 | 20aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 23.2 | 52.2 | 69aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 27.8 | 66.7 | 18aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 22.4 | 56 | 125aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 60 | 100 | 5aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | AAD21816.1 | Heat shock 70 kDa protein 1A | 640aa | 21.6 | 72.5 | 51aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 22.1 | 55.9 | 68aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 35.3 | 64.7 | 17aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 24.1 | 58.6 | 58aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 60 | 80 | 10aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001276674.1 | Glyceraldehyde-3-phosphate | 335aa | 24.3 | 55.2 | 181aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | dehydrogenase | | 27.9 | 60.5 | 43aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 30.8 | 76.9 | 26aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 25 | 53.1 | 64aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 33.3 | 80 | 15aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_000058.1 | Carbonic anhydrase 2 | 260aa | 41.4 | 65.5 | 29aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 27.3 | 51.5 | 66a |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 40.9 | 59.1 | 22aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 26.5 | 50 | 68aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 33.3 | 60 | 15aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_000163.2 | Guanine nucleotide-binding protein G(t) | 350aa | 26.7 | 53.3 | 75aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | subunit alpha-1 (Alpha transducine-1) | | 61.2 | 24.5 | 49aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 43.5 | 69.6 | 23aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 25.8 | 48.4 | 31aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 40 | 90 | 10aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_004174.1 | Bestrophin-1 | 585aa | 24.7 | 55.3 | 85aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 30.3 | 48.5 | 66aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 26.2 | 57.1 | 42aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 32.4 | 52.9 | 34aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 40.9 | 54.5 | 22aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_000530.1 | Rhodopsin | 348aa | 19.7 | 52.8 | 127aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 39.3 | 60.7 | 28aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 20.8 | 58.3 | 72aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 27.6 | 69 | 29aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 24.3 | 62.2 | 37aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001020272.1 | Myelin Basic Protein | 304aa | 42.9 | 66.7 | 21aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 23.1 | 55.8 | 52aa |

(*continued on next page*)

**Table 4** (*continued*)

| Genbank ID | Gene Product Protein Name | Number | Comparison | Genbank ID | Eye-related Protein Name | Number | Identity % | Similar % | Overlap |
|---|---|---|---|---|---|---|---|---|---|
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 21.7 | 56.5 | 69aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 28.1 | 50.9 | 57aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 44.4 | 77.8 | 9aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_005836.2 | Multidrug resistance-associated protein | 1325aa | 23.5 | 48.5 | 196aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | 4 | | 39.3 | 75 | 28aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 25.8 | 54.6 | 97aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 27.7 | 63.8 | 47aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 23.6 | 60 | 55aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | AAR99172.1 | p-glycoprotein | 164aa | 28.1 | 56.2 | 64aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 33.3 | 61.9 | 21aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 25.9 | 63 | 27aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 43.8 | 56.2 | 16aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 55.6 | 77.8 | 9aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_004987.2 | Multidrug resistance-associated protein | 1531aa | 23.4 | 62.5 | 64aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | 1 | | 21.4 | 60.7 | 84aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 23.7 | 53.2 | 139aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 28.6 | 66.1 | 56aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 29.2 | 64.6 | 48aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_005679.2 | Multidrug resistance-associated protein | 1437aa | 25.7 | 51.4 | 70aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | 5 | | 28.9 | 56.6 | 76aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 26.7 | 66.7 | 45aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 30 | 55 | 60aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 40 | 62.9 | 35aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | BAB70708.1 | Sodium-independent neutral amino acid | 507aa | 22.5 | 53.9 | 102 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 26.6 | 58.2 | 79aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 34.6 | 57.7 | 52aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 26.8 | 54.9 | 71aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 29.2 | 62.5 | 48aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001191676.1 | Replication factor C subunit 1 | 1148aa | 22.9 | 61.5 | 109aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 32.1 | 67.9 | 28aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 27.3 | 67.3 | 55aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 31.1 | 62.2 | 45aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 44.4 | 88.9 | 9aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_066918.2 | Sodium-dependent multivitamin | 635aa | 22.3 | 50.3 | 193aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | transporter | | 25 | 57.1 | 112aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 29.4 | 88.2 | 17aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 36.8 | 63.2 | 19aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 38.9 | 94.4 | 18aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001356537.1 | Putative sodium-coupled neutral amino | 462aa | 28.8 | 62.7 | 59aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | acid transporter 7 | | 22.2 | 50.8 | 63aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 24.5 | 61.2 | 49aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 26.7 | 53.3 | 90aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 27.8 | 61.1 | 36aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001127839.2 | Sodium- and chloride-dependent taurine | 721aa | 19.1 | 53.6 | 194aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | transporter | | 23.9 | 54.3 | 46aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 32.5 | 57.5 | 40aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 25 | 55 | 40aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 24.6 | 54.1 | 61aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_060712.2 | Multidrug and toxin extrusion protein 1 | 570aa | 20.3 | 56 | 182aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 35.9 | 59 | 39aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 32.5 | 57.5 | 40aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 28.6 | 65.7 | 35aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 25.7 | 65.7 | 35aa |

(*continued on next page*)

**Table 4** (*continued*)

| Genbank ID | Gene Product Protein Name | Number | Comparison | Genbank ID | Eye-related Protein Name | Number | Identity % | Similar % | Overlap |
|---|---|---|---|---|---|---|---|---|---|
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_001159968.1 | Monocarboxylate transporter 1 | 500aa | 39.3 | 67.9 | 28aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 27 | 48.6 | 37aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 26.4 | 54.7 | 53aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 27 | 52.4 | 63aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 36.4 | 90.9 | 11aa |
| QIZ16507.1 | ORF1ab polyprotein | 7096 aa | <=> | NP_005619.1 | Neutral amino acid transporter B (0) | 541aa | 23.3 | 55 | 129aa |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | | 26.7 | 55.6 | 45aa |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | | 19.7 | 46.5 | 71aa |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | | 41.4 | 58.6 | 29aa |
| QIZ16511.1 | envelope protein | 75 aa | | | | | 34.5 | 65.5 | 29aa |

**Table 5**
Results of SARS CoV-2 and eye related protein showing folding similarities.

| Genbank ID | Gene Product Protein Name | Number | Genbank ID | Eye Related Protein Name | Number | TM-align Score Result | |
|---|---|---|---|---|---|---|---|
| | | | | | | Eye Related Protein | Covid Related Protein |
| | | | | | | 0.16453 | 0.29748 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.18024 | 0.19398 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.04503 | 0.33477 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.05804 | 0.34955 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.03568 | **0.54718** |
| QIZ16507.1 | orf1ab polyprotein | 7096 aa | NP_005679.2 | Multidrug resistance-associated protein 5 | 1437aa | 0.17338 | 0.23131 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.21403 | 0.17011 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.06409 | 0.33103 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.08345 | 0.34311 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.05235 | **0.54823** |
| QIZ16507.1 | orf1ab polyprotein | 7096 aa | NP_001191676.1 | Replication factor C subunit 1 | 1148aa | 0.24011 | 0.2113 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.26267 | 0.13535 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.09472 | 0.30317 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.11934 | 0.3119 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.09789 | **0.53043** |
| QIZ16507.1 | orf1ab polyprotein | 7096 aa | NP_001356537.1 | Putative sodium-coupled neutral amino acid transporter 7 | 462aa | 0.25991 | 0.18005 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.26218 | 0.103 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.13621 | 0.35986 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.15358 | 0.31457 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.11179 | **0.50902** |
| QIZ16507.1 | orf1ab polyprotein | 7096 aa | NP_001127839.2 | Sodium- and chloride-dependent taurine transporter | 721aa | 0.2012 | 0.19401 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.2403 | 0.13667 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.09516 | 0.32428 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.12354 | 0.35704 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.07981 | **0.528** |
| QIZ16507.1 | orf1ab polyprotein | 7096 aa | NP_060712.2 | Multidrug and toxin extrusion protein 1 | 570aa | 0.23032 | 0.1876 |
| QIZ16509.1 | surface glycoprotein | 1273 aa | | | | 0.29658 | 0.13646 |
| QIZ16512.1 | membrane glycoprotein | 222 aa | | | | 0.11147 | 0.33587 |
| QIZ16517.1 | nucleocapsid phosphoprotein | 419 aa | | | | 0.1327 | 0.33069 |
| QIZ16511.1 | envelope protein | 75 aa | | | | 0.10556 | **0.56509** |

of creating an immune response in T and B cell, 7 peptides (epitopes of similar proteins) for MHC class I (Cytotoxic T cell), and 2 peptides for MHC class II (T helper cell) were identified. In addition, 6 of these 9 peptides/epitopes showed antigenic properties according to vaxiJen analysing server (http://www.ddg pharmfac. net/vaxijen/VaxiJen/VaxiJen.html).

It is well established that structural and epitopic similarities among antigens from infectious microorganisms and host antigenic structures cause autoimmune diseases through cross-reactions between monoclonal antibodies that develop against these structures and host tissues (Fujinami et al., 1983). While the immune mechanism involved in these autoimmune reactions is not clear, the primary role of viral infections as trigger of autoimmune reactions has been suggested in some studies (Schattner and Rager-Zisman, 1990; Ludewig et al., 2004)). In other studies, viral antigenic epitopes have been demonstrated to be responsible for this process (Schattner and Rager-Zisman, 1990; Tauriainen et al., 2003). It has been reported by previous studies that host response to viral epitopes which are similar to host antigens has a major role in autoimmune processes and that cytotoxic T-cells cross-reacting to these antigens mediate immune damage in the eye (Zhao et al., 1998). The sharing of a linear amino acid sequence or a conformation fit between a microbe and a host 'self' determinant was described to be the initial stage of molecular mimicry (Oldstone, 1998).

SARS- CoV-2 infection which first appeared in December 2019 and

**Table 6**
The selected cytotoxic T lymphocytes (CTL) epitopes of SARS CoV-2 based on binding affinity. This server is meant to predict MHC I binding with accuracy of 90–95%.

| MHC Class I Peptide | IC50 | Allele | VaxiJen |
|---|---|---|---|
| TLAILTALR | 10.31 | HLA-A*68:01 | 0.7223 (Probable ANTIGEN). |
| | 71.35 | HLA-A*33:01 | |
| | 71.73 | HLA-A*31:01 | |
| FLLVTLAIL | 14.58 | HLA-A*02:01 | 0.9645 (Probable ANTIGEN). |
| | 31.6 | HLA-A*02:03 | |
| | 38.97 | HLA-A*02:06 | |
| VTLAILTAL | 35.21 | HLA-A*02:06 | 0.6140 (Probable ANTIGEN). |
| | 220.54 | HLA-A*32:01 | |
| | 366.74 | HLA-A*68:02 | |
| | 413.73 | HLA-A*02:01 | |
| LTALRLCAY | 51.96 | HLA-B*15:01 | 0.2825 (Probable NON-ANTIGEN). |
| | 74.27 | HLA-A*30:02 | |
| | 147.23 | HLA-A*01:01 | |
| | 283.48 | HLA-A*26:01 | |
| FVVFLLVTL | 73.1 | HLA-A*02:06 | 0.7403 (Probable ANTIGEN). |
| | 178.61 | HLA-A*68:02 | |
| | 305.67 | HLA-A*02:01 | |
| | 404.63 | HLA-A*02:03 | |
| VFLLVTLAI | 328.04 | HLA-A*23:01 | 0.8134 (Probable ANTIGEN). |
| ILTALRLCA | 329.7 | HLA-A*02:03 | 0.1234 (Probable NON-ANTIGEN). |

**Table 7**
Helper T-Lymphocytes (HTL) epitopes are given in the table along with their scores predicted by IEDB MHC class II server.

| MHC Class II Peptide | Consensus percentile ≤ 20 | VaxiJen |
|---|---|---|
| LVTLAILTALRLCAY | 18 | 0.4070 (Probable NON-ANTIGEN). |
| FVVFLLVTLAILTAL | 20 | 0.5738 (Probable ANTIGEN). |

quickly spread all over the world is a viral infection and the immune mechanism involved or whether it may trigger autoimmune reactions is currently a field of intensive research. Recently, some suspected systemic or local autoimmune reactions related to SARS CoV-2 infection were reported. Pfeuffer et al. demonstrated Guillain-Barré syndrome (GBS) and its variants as a neurologic complication of SARS CoV-2 infection. In addition, Sadiq et al. and Galeotti at al. claimed that SARS CoV-2 infection might lead to autoimmune and autoinflammatory diseases, such as pediatric inflammatory multisystemic syndrome including Kawasaki-like disease (Pfeuffer et al., 2020; Sadiq et al., 2020; Galeotti at al., 2020). Furthermore, the AstraZeneca's Phase 3 vaccine trial was recently temporarily stopped after a participant, who received the Covid-19 vaccine, developed neurological symptoms, consistent with the severe spinal inflammatory condition transverse myelitis (statnews,). Despite all these findings, the target and details of such supposed autoimmune mechanisms are still not fully understood. At the same time, besides all these autoimmune clinical findings, there are still no reports showing that the SARS-CoV-2 infection affects the retina or the blood retinal barrier directly or antibody-related.

The structures of SARS CoV-2 proteins have been identified through sequence analyses (Li et al., 2014). Protein similarity between human proteins and SARS CoV-2 proteins is still under investigation. These research efforts aim to develop a medication for the treatment of SARS CoV-2 infection and a total of 332 protein-protein similarities (PPS) between SARS CoV-2 proteins and human proteins were identified in one study (Gordon et al., 2020). In addition, in another sequence similarity study conducted by Root-Bernstein, a similarity was found between olfactory receptors and SARS-Cov 2 proteins, and it was determined that the reaction of the body's Ig A against SARS-COV 2 with olfactory receptors resembling a transient anosmia (Root-Bernstein, 2020). However, no PPS results still were available for human retinal proteins and RPE surface proteins.

*Autoimmune retinopathies* (AIRs) comprise a wide spectrum of retinal degenerative disorders that includes the paraneoplastic and non-paraneoplastic AIRs (Adamus, 2018; Adamus et al., 2004; diagnosis,). The pathology of AIRs involves sequence similarities between retinal antigens and foreign antigens that enter the body. In paraneoplastic autoimmune retinopathy, there is a molecular similarity between retinal antigens and tumor antigens, whereas in non-paraneoplastic autoimmunity, the mimicry is between retinal antigens and antigens of infectious bacterial and viral agents (Grewal et al., 2014). Cross-reaction between antibodies against foreign antigens that are similar at the molecular level and retinal proteins is the key pathological process (Adamus, 2018; Ten Berge et al., 2016). Recognition of autoantigens once as foreign antigens constantly triggers an immune response and persistent immunologic stimulation by retinal autoantigens elicits a chronic retinal autoimmune reaction. This process results in retinal degeneration and impaired vision at a later stage (Novack and Leopold, 1998; Adamus, 2017; de Andrade et al., 2016). To date, no studies have focused on mimicry between structural proteins of SARS CoV-2 and human retinal proteins and retinal pigment epithelium surface transport proteins.

There are several retinal proteins that are involved in the development of retinal autoimmunity (Grewal et al., 2014). In non-paraneoplastic retinal autoimmunity, most commonly detected proteins include recoverin, alpha-enolase, carbonic anhydrase II and transducine (Ten Berge et al., 2016). Our findings did not show a significant similarity between these proteins and SARS CoV-2 proteins.

Currently, vaccination offers an effective and cost-effective solution to prevent numerous diseases. The main consideration for vaccination is to achieve a balanced immune response to the vaccine that can be kept under control. Therefore, current immunity should be monitored while carrying out vaccine trials. Achieving this balance also affects compliance to vaccination. The most important challenge that needs to be tackled with during this process is the occurrence of autoimmune events which are elicited by viral vaccines in particular (Wraith et al., 2003; Older et al., 1999; Shoenfeld and Aron-Maor, 2000). Similarity of viral peptide fragments used in vaccines and host proteins has been primarily implicated in autoimmune reactions (Fraunfelder et al., 2010; Escott et al., 2013; Stangos et al., 2006; Fine et al., 2001). This autoimmune mechanism mediates both systemic and ocular adverse effects (Fraunfelder et al., 2010; Geier and Geier, 2005; (Verstraeten et al., 2008); Mikaeloff et al., 2007;(Mikaeloff et al., 2009)Altman et al., 2008). Vaccine-associated ocular adverse effects were reported including manifestations of retinopathy and uveitis (Stübgen, 2013; Altman et al., 2008; Dolinova, 1974; Knopf, 1991; Islam et al., 2000; Esmaeli-Gutstein and Winkelman, 1999; Lee et al., 1994; Cunningham et al., 2019)). Uveitic reactions including iridocyclitis and vitritis can sometimes be observed following vaccination and sporadic cases of acute posterior multifocal placoid pigment epitheliopathy (APMPPE), a disease affecting the RPE, have also been reported (Brézin et al., 1993, 1995; Khalifa et al., 2010). Additionally, several cases of bilateral exudative

retinal detachment resembling Vogt-Koyanagi-Harada (VKH) syndrome were reported (Dansingani et al., 2015). In our protein similarity analyses, it was seen that, there is a meaningful similarities between 6 retinal pigment epithelium surface transport proteins (MRP-4, MRP-5, RFC1, SNAT7, TAUT and MATE) and SARS CoV-2 envelope (E) protein (Table 5). Each of these proteins has 9 epitopic site which is similar to protein E and 7 peptides (epitopes of similar proteins) can induce MHC class I (Cytotoxic T cell), 2 peptides can induce MHC class II (T helper cell)(Tables 6 and 7) by causing an immune stimulation of T cytotoxic and T helper. Besides, 6 of these 9 epitopic sites have predicted antigenic potential as analyzed using the VaxiJen server (https://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html). This implies that during any immune response against SARS CoV-2 envelope (E) protein, these proteins may be perceived as E protein and may be subjected to an immune response by being recognised MHC I T cytotoxic and MHC II T helper cells as if they are antigenic. This theorical findings are consistent with the study conducted by Lu et al., and they showed a similar strong T cell immune response in mice an after systemic E protein immunization (Lu et al., 2020).

In the similarity comparisons, when the sequence analysis results show at least 97% identity percentage, it indicates an ideal match. However, these high similarity results are not always frequently seen. Importantly, obtaining such theoretical result alone obviously does not imply that the two proteins are identical proteins. The main factor that allows the two protein sequences to be identified is not only identity percentage but also the continuous strect structure of the amino acid (aa) sequences compared. In addition, protein sequence analysis is a primary evaluation, and the final protein property is determined by secondary and tertiary protein structures. For example, in the study conducted by Massilamany et al., the MBP 8–101 epitope that develops cross-reactive T cell-derived autoimmunity of Acanthamoeba castellanii has an identity ratio of only 46% with 6 discontinuous aa but nevertheless, encephalomyelitis has been seen as a result of the immunization of SJL mice with NAD 108-120 epitope (Massilamany et al., 2011). According to the allergen criteria determined by FAO/WHO (http://fermi.utmb.edu/SDAP/sdap_who.html), it is required to have at least 5–6 aa similarity or 35% sequence similarity within 80 amino acids (aa). Similar relationship was emphasized in the study conducted by Kanduc, P. 2012. The sequence identity result of the study conducted by Massilamanay et al., shows 46.2% percentage with 5 Aa continuous strect structure with 6/13 aa overlap. This situation may explain the current epitopic similarity and immune response, but the most important aspect for determining immune similarity and cross responses is performing 3D similarity analysis of the proteins and then evaluating the relevant epitopic region by immune epitope analysis to better predict if it may trigger any immune response or not.

In our current study, the median identity rates are very low (Table 3) and continuous strech structure does not exceed 2 aa even in the highest identity result (Recoverin-N protein Pairing; 66.7% identity - 77.8% similarity Table 4). These results make the two protein sequence matching results invalid. But primary sequence analyses are only predictive tools used for the secondary and tertiary structures of proteins and contribute to prediction for further protein similarity studies (MacCarthy et al., 2019). In the analysis results of our current study, the 70% value that we mentioned is not a definite cut off value. This value constitutes the 66.7% value, which is the highest identical value determined during analysis and no identical and significant continuous strech structure was observed among analysis results below 66.7%. In addition, the antigenic properties of the sequence compared with the LALIGN program are interpreted by checking the E-value. As a result of the comparison, when the E-value value is lower than $<0.01$, the results are considered important and must be confirmed by further analysis. Although the E-value values were not significant in our study as well, we performed 3D analysis with Swiss –Model and TM-align and it was seen some meaningful results; there is a low structural similarity between the Envelope (E) protein and MRP-4, MRP-5, RFC1, SNAT7, TAUT and MATE1 proteins. Furthermore, when we performed immune epitope analysis for these proteins, we saw that they have epitopic sites similar to E protein and induce a T cell related immune response.

Our findings suggest that cross-reaction with selected retinal proteins associated immunologic process are not likely to occur secondary to immune response to SARS CoV-2 infection. However, some retinal pigment epithelium surface proteins (MRP-4, MRP-5, RFC1, SNAT7, TAUT and MATE) can create a cross reaction with SARS-CoV-2 E protein and also induce autoimmune reaction after vaccintion. This means RPE related clinical relevant ocular findings may occure and/or increase during SARS CoV-2 infection exist or after vactination.

Additionally, the multisystem inflammatory syndrome reported SARS CoV-2 and associated systemic vasculitis may appear as a sign of another autoimmune cross-reaction that may develop against proteins in the vascular endothelial structure during this infection. At the same time, it may be possible to have an autoimmune reaction against Myelin Oligodendrocyte Glycoprotein (MOG) related to transverse myelitis which has occurred during SARS CoV-2 vaccine phase studies. Therefore, sequence and protein similarity analysis with SARS CoV-2 proteins could shed light on the potential risk and retinal vascular endothelial protein similarity analysis with SARS CoV-2 proteins may be a next interesting area to study.

## 5. Conclusion

In conclusion, the structure of SARS CoV-2, its proteins and immunologic reactions against these proteins remain largely unknown. Understanding the structure of SARS CoV-2 proteins and demonstration of similarity of these proteins to the body proteins are crucial to predict an autoimmune response associated with immunity against host proteins and its clinical manifestations. The here presented study focused on five of the SARS CoV-2 proteins (S, N, M, E, orf1ab) on sequence similarities and presents the first study in this area, suggesting that autoimmune attacks against retinal structures in COVID-19 patients may theoretically occur based on the here identified similarities to RPE proteins.

More data are needed from the field of theoretical biology but obviously from clinical ophthalmological findings in infected patients.

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## Declaration of competing interest

None of the authors has a conflict of interest to disclose.

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