



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Molecular mimicry between SARS-CoV-2 and human proteins

### ARTICLE INFO

#### Keywords

Severe acute respiratory syndrome coronavirus

2

Molecular mimicry

Autoimmunity

#### To the Editor,

COVID-19 resemble immune dysregulation conditions, with hyperactivated immune system and cytokine storm [1,2]. In relation, molecular mimicry is drawing attention among possible mechanisms of autoimmune phenomena in COVID-19 [3–10]. Kanduc and Shoenfeld [11–16] searched related potential adverse events and peptide sharing between proteins of human and such pathogens, including SARS-CoV-2 [12–14]. In line with those studies, here it is aimed to draw attention to 7–9 residue matches in several known human proteins with a 15mer palindromic SARS-CoV-2 peptide (Table 1). Respective aligned sequences are predicted to contain peptides that both bind strongly to the same MHC supertype representative, based on predictions by NetMHCcons 1.1 and/or NetCTLpan 1.1 tools [17,18].

Associated diseases of some of those proteins listed in Table 1 are obtained from the human gene database GeneCards [20]. Accordingly, associated diseases of neuronal acetylcholine receptor subunit alpha-2 associated diseases involve Epilepsy and Nocturnal Frontal Lobe, 4, and Autosomal Dominant Nocturnal Frontal Lobe Epilepsy; that of Arginyl-tRNA synthetase-like involve Pontocerebellar Hypoplasia 6, Type 6 and Type 1; that of Tsukushin involve Barre-Lieou Syndrome and Spondylolisthesis; that of Golgi pH regulator B involve Chromosome 1Q21.1 Deletion Syndrome, 1.35-Mb and Hemochromatosis, Type 2A; that of Phospholipid phosphatase-related protein type 5 involve deafness, Autosomal Dominant 1, and Bardet-Biedl Syndrome 10; that of Solute carrier family 15 member 5 involve Dicarboxylic Aminoaciduria and Hydranencephaly; that of Adenosine receptor A2b involve Priapism and Cholera; that of Slit homolog 2 protein involve Cakut and Crohn's Colitis; that of Solute carrier family 35 member B1 involve Dicarboxylic Aminoaciduria and Hydranencephaly; that of Metabotropic glutamate receptor 5 involve Fragile X Syndrome and Fragile X-Associated Tremor/Ataxia Syndrome; that of Protein crumbs homolog 1 involve Leber Congenital Amaurosis 8 and Retinitis Pigmentosa 12. Relationships of those proteins with autoimmunity can be mentioned further. E.

deregulation is connected to pathological conditions like cancer, bacterial infection, fibrosis, neurogenerative diseases, muscular dystrophy, and rheumatoid arthritis [21]. Besides, elevated plasmin(ogen) was suggested to be a risk factor for COVID-19 susceptibility [22]. Plasminogen receptor KT is a membrane protein, expression of which increases on the surface upon inflammatory stimuli, like in case of several other plasminogen receptors [21]. Its contribution to the inflammatory diseases, together with the cell-surface associated plasmin activity, is yet to be elucidated, particularly in conditions where macrophages play a preeminent role in the pathogenesis, for being highly expressed at the proinflammatory macrophages [21]. Examples of such diseases are microglial cells and neuroinflammatory disease, Kupfer cells and hepatotoxic injury, Mi-type adipose tissue macrophage and obesity [21]. Another one, adenosine receptor A2b was suggested to play a role in inflammation [23], and immunoglobulin heavy chain variable 5–51, was reported to be among the modulated-genes in the patients with systemic sclerosis, which is characterized by immune system alterations, for being an autoimmune connective tissue disease [24]. Immunoglobulin heavy chain variable 5–51 is also among the 115 genes that are co-occurring with the disease autoimmune hemolytic anemia, in the abstracts of biomedical publications from the DISEASES Text-mining Gene-Disease Association Evidence Scores dataset [25]. Last, antibodies against metabotropic glutamate receptor 5 is among the antibodies that are possibly associated with autoimmune encephalitis [26,27]. Inhibitors of metabotropic glutamate 5 receptor were offered as a therapeutic strategy to fight against COVID-19 [28], and it was suggested that the therapeutic effect would be acting through interfering with the viral hijacking of the host protein synthesis [28]. It is worth to mention in the end that, other than one immunoglobulin heavy chain junction region (sequence ID MCG41834.1), the highest statistical significance in the alignments are observed for the peptides of slit homolog 2 protein and the solute carrier family proteins, among the proteins that are mentioned above.

g., plasminogen activation system has important functions, and its

<https://doi.org/10.1016/j.autrev.2021.102791>

Received 2 December 2020; Accepted 8 December 2020

Available online 18 February 2021

1568-9972/© 2021 Elsevier B.V. All rights reserved.

**Table 1**

Human proteins that align with SARS-CoV-2 peptide CFLGYFCTCYFGLFC [19] with more than 7 residue matches. They are predicted to contain epitopes with at least 5 residue matches to the respective epitope regions in the query. Alignments are displayed as they are presented in the original file, but matching residues are written bold. Those residues in the predicted epitope parts are still bold if present. Yet they are further underlined if present in both query and subject epitopes. Gaps in the alignments are not shown in the epitopes. Numbers in front of the epitope pairs indicate the HLA allele and the predictor, as specified at the title row. However, only the epitopes predicted by NetMHCcons are displayed when significant predictions that are indicated at both 1 and 2, or 3 and 4, are present.

Alignments, top: query	1	HLA-A*24:02, NetMHCcons	3	HLA-A*02:01, NetMHCcons	Protein name
(Matches in bold)	2	HLA-A*24:02, NetCTLpan	4	HLA-A*01:01, NetCTLpan	Sequence ID (only the 1st)
<b>CFLGYFCTCYFGLFC</b>	1	<u>CFLGYFCTCYFGLF</u>			<b>hCG1995581, partial</b>
<b>CFSSYF—FLLFC</b>	2	<u>CFSSYFLLF</u>			EAW57092.1
<b>CFLGYFCTCYFGLF</b>	1	<u>CFLGYFCTCYFGLF</u>			<b>Immunoglobulin heavy chain junction region</b>
<b>CFVG—SC—FGLF</b>	2	<u>CFVGSFCGLF</u>			MON77051.1
<b>CFLGYFCTCYFGLF</b>	1	<u>CFLGYFCTCYFGLF</u>			<b>Neuronal acetylcholine receptor subunit alpha-2</b>
<b>CFLG—T—IGLF</b>	2	<u>CFLGTTGLF</u>			NP_001334636.1
<b>CFLGYFCTCYFGLF</b>	1	<u>CFLGYFCTCYFGLF</u>	3	<u>FLGYFCTCYFGL</u>	<b>arginyl-tRNA synthetase-like, isoform CRA_b, partial</b>
<b>CFL—FI—YFILF</b>	2	<u>CFLFIYFILF</u>		<u>FLFIYFILF</u>	EAW48585.1
<b>FLGYFCT—CYFGLFC</b>			4	<u>FLGYFCTCY</u>	<b>immunoglobulin heavy chain variable region, partial</b>
<b>FIGY—CSSTSCYTGFC</b>				<u>FIGYCSSTSCY</u>	CEF94348.1
<b>CFLGYFCTC—YFGLF</b>	1	<u>CFLGYFCTCYFGLF</u>			<b>unnamed protein product; E2IG4; tsukushin isoform b precursor</b>
<b>CFPG—CQCEVETFGLF</b>		<u>CFPGCQCEVETFGLF</u>			BAG52371.1; AAF09483.1; NP_001245139.1
<b>FLGYFCTCYFGLFC</b>			3	<u>FLGYFCTCYFGL</u>	<b>G protein-coupled receptor 89C, partial; Golgi pH regulator B; unnamed protein product; Golgi pH regulator A</b>
<b>FLGYF—FSIYC</b>			4	<u>FLGYFFSI</u>	CAI17085.1; NP_001337112.1; BAG63613.1; NP_001091082.2
<b>FLG—YFCTCYFGLF</b>			3	<u>FLGYFCTCYFGL</u>	<b>unnamed protein product; PAP2D protein, partial; Phospholipid phosphatase-related protein type 5</b>
<b>FLGIY—T—FGLF</b>				<u>FLGIYTFGL</u>	BAG58540.1; AAH40174.1; XP_011539140.1
<b>FLGYFCTCYFGLF</b>	1	<u>GYFCTCYFGLF</u>			<b>Solute carrier family 15 member 5</b>
<b>FLGYFSTC—LF</b>	2	<u>EYFSTCLF</u>			NP_001164269.1
<b>CFLGYFCTCYFGL</b>			3	<u>FLGYFCTCYFGL</u>	<b>Immunoglobulin heavy chain junction region</b>
<b>CALG—TCYVGL</b>				<u>ALGTCYVGL</u>	MOL37243.1
<b>FLGYFCTCY—FGLF</b>			3	<u>FLGYFCTCYFGL</u>	<b>Phospholipid phosphatase-related protein type 2</b>
<b>FLG—VYSFGLF</b>				<u>FLGVYSFGL</u>	XP_024307423.1
<b>CFLGYFCTCYFGL</b>	1	<u>CFLGYFCTCYFGLF</u>	3	<u>FLGYFCTCYFGL</u>	<b>Immunoglobulin heavy chain junction region</b>
<b>CYLGW—YFDL</b>	2	<u>CYLGWYFDL</u>		<u>YLGWYFDL</u>	MCC33910.1
<b>CFLGYFCTCYFGL</b>			3	<u>FLGYFCTCYFGL</u>	<b>Immunoglobulin heavy chain junction region</b>
<b>CFLHY—YYGL</b>				<u>FLHYYYGL</u>	MOQ87140.1
<b>FLGYFCTCYFGLF</b>	1	<u>GYFCTCYFGLF</u>			<b>Adenosine receptor A2b</b>
<b>FLGY—MVYFNFF</b>	2	<u>GYMVYFNFF</u>			EAX04485.1
<b>FLGYFCTCYFGLF</b>			3	<u>FLGYFCTCYFGL</u>	<b>[Protein ADP-ribosylarginine] hydrolase-like protein 1</b>
<b>FLGSLCT—ALF</b>				<u>FLGSLCTAL</u>	NP_954631.1
<b>FLGYFCTCYFGLF</b>	2	<u>GYFCTCYFGLF</u>	3	<u>FLGYFCTCYFGL</u>	<b>Transmembrane protein 250</b>
<b>FLLYF—SC—SLF</b>		<u>LYFSCSLF</u>		<u>FLLYFSCSL</u>	NP_001243455.1
<b>FLGYFCTCYFGL</b>	1	<u>GYFCTCYFGLF</u>			<b>chromosome 9 open reading frame 46; Plasminogen receptor (KT)</b>
<b>FLKYFGT—FFGL</b>	2	<u>KYFGTFGL</u>			EAW58764.1; XP_005251569.1
<b>FL—GYFCTCYFGL</b>	1	<u>GYFCTCYFGLF</u>	3	<u>FLGYFCTCYFGL</u>	<b>Immunoglobulin heavy chain junction region</b>
<b>FLTGYATPYFDL</b>	2	<u>GYATPYFDL</u>	4	<u>FLTGYATPYFDL</u>	MOM08080.1
<b>LGYFCT—CYFGLF</b>	1	<u>GYFCTCYFGLF</u>			<b>Immunoglobulin heavy chain junction region</b>
<b>LGY—CSSTSCYFGFF</b>	2	<u>GYCSSTSCYFGFF</u>			MCG41834.1
<b>GYFCTC—YFGLFC</b>	1	<u>GYFCTCYFGLF</u>			<b>Slit homolog 2 protein</b>
<b>GYTCICPEGYSGLFC</b>		<u>GYTCICPEGYSGLFC</u>			XP_011512212.2
<b>FLGYFCTCYFGL</b>			3	<u>FLGYFCTCYFGL</u>	<b>Immunoglobulin heavy chain junction region</b>
<b>FLGY—YYGL</b>				<u>FLGYYYGL</u>	MOP50498.1
<b>CFLGYFCTCYF</b>	2	<u>CFLGYFCTCYF</u>	4	<u>FLGYFCTCY</u>	<b>unnamed protein product; Solute carrier family 35 member B1</b>
<b>CFLGVF—VCYF</b>		<u>CFLGVFVCYF</u>		<u>FLGVFVCY</u>	BAG58831.1; XP_011522481.1
<b>LGYFCTCYFGL</b>	2	<u>GYFCTCYFGL</u>			<b>Chain A, Metabotropic glutamate receptor 5, Lysozyme and Endolysin</b>
<b>LGYLCT—FXL</b>		<u>GYLCTFXL</u>			4O09_A and 6FFH_A
<b>LGYFCTCYFGL</b>			4	<u>FLGYFCTCY</u>	<b>Immunoglobulin gamma 2 heavy chain variable region, partial</b>
<b>LGTF—TYYYGL</b>				<u>LGTFYYYY</u>	ADM43945.1
<b>GYFCTCYFGLF</b>	1	<u>GYFCTCYFGLF</u>			<b>hypothetical protein; Protein crumbs homolog 1</b>
<b>GYSLC—FGNF</b>	2	<u>GYSLCFGNF</u>			CAE45845.1; XP_011507671.1
<b>GYFCTCYFGL</b>	2	<u>GYFCTCYFGL</u>			<b>Immunoglobulin heavy chain junction region</b>
<b>GYFY—YFGL</b>		<u>GYFYFGL</u>			MOL71978.1
<b>GYFCTCYFGL</b>	2	<u>GYFCTCYFGL</u>			<b>Immunoglobulin heavy chain junction region</b>
<b>GYFTTGYFDL</b>		<u>GYFTTGYFDL</u>			MOM22920.1
<b>GYFCTCYF</b>	1	<u>GYFCTCYFGLF</u>			<b>hCG2028737</b>
<b>GYFCTNYF</b>	2	<u>GYFCTNYF</u>			EAW73174.1

**References**

[1] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020 Mar; 395(10229):1033–4. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).

[2] Shoenfeld Y. Corona (COVID-19) time musings: our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. *Autoimmun Rev* 2020 June;19(6):102538. <https://doi.org/10.1016/j.autrev.2020.102538>.

[3] Cappello F. Is COVID-19 a proteiform disease inducing also molecular mimicry phenomena? *Cell Stress Chaperones* 2020 May;25(3):381–2. <https://doi.org/10.1007/s12192-020-01112-1>.

- [4] Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. *J Clin Neurosci* 2020 June;76:233–5. <https://doi.org/10.1016/j.jocn.2020.04.062>.
- [5] Cappello F. COVID-19 and molecular mimicry: the Columbus' egg? *J Clin Neurosci* 2020 July;77:246. <https://doi.org/10.1016/j.jocn.2020.05.015>.
- [6] Lucchese G, Flöel A. Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. *Autoimmun Rev* 2020 May;19:102556. <https://doi.org/10.1016/j.autrev.2020.102556>.
- [7] Lucchese G, Flöel A. SARS-CoV-2 and Guillain-Barré syndrome: molecular mimicry with human heat shock proteins as potential pathogenic mechanism. *Cell Stress Chaperones* 2020 July;25:731–5. <https://doi.org/10.1007/s12192-020-01145-6>.
- [8] Angileri F, Legare S, Gammazza AM, de Macario EC, Macario AJL, Cappello F. Molecular mimicry may explain multi-organ damage in COVID-19. *Autoimmun Rev* 2020 June;19:102591. <https://doi.org/10.1016/j.autrev.2020.102591>.
- [9] Lyons-Weiler J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. *J Transl Autoimmun* 2020;3: 100051. <https://doi.org/10.1016/j.jtauto.2020.100051>.
- [10] Kanduc D. From anti-SARS-CoV-2 immune responses to COVID-19 via molecular mimicry. *Antibodies* 2020;9:33. <https://doi.org/10.3390/antib9030033>.
- [11] Kanduc D, Shoenfeld Y. From HBV to HPV: designing vaccines for extensive and intensive vaccination campaigns worldwide. *Autoimmun Rev* 2016 Aug;15: 1054–61. <https://doi.org/10.1016/j.autrev.2016.07.030>.
- [12] Kanduc D, Shoenfeld Y. Inter-pathogen peptide sharing and the original antigenic sin: solving a paradox. *Open Immunol J* 2018 Aug;8:16–27. <https://doi.org/10.2174/1874226201808010016>.
- [13] Kanduc D, Shoenfeld Y. Human papillomavirus epitope mimicry and autoimmunity: the molecular truth of peptide sharing. *Pathobiology* 2019 Oct;86(5–6): 285–95. <https://doi.org/10.1159/000502889>.
- [14] Kanduc D, Shoenfeld Y. On the molecular determinants of the SARS-CoV-2 attack. *Clin Immunol* 2020 Apr;215:108426. <https://doi.org/10.1016/j.clim.2020.108426>.
- [15] Kanduc D, Shoenfeld Y. Medical, genomic, and evolutionary aspects of the peptide sharing between pathogens, primates, and humans. *Glob Med Genet* 2020 Aug;7: 64–7. <https://doi.org/10.1055/s-0040-1716334>.
- [16] Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol Res* 2020 Sep;68:310–3. <https://doi.org/10.1007/s12026-020-09152-6>.
- [17] Karosiene E, Lundegaard C, Lund O, Nielsen M. NetMHCcons: a consensus method for the major histocompatibility complex class I predictions. *Immunogenetics* 2012 Mar;64(3):177–86. <https://doi.org/10.1007/s00251-011-0579-8>.
- [18] Stranzl T, Larsen MV, Lundegaard C, Nielsen M. NetCTLpan. Pan-specific MHC class I pathway epitope predictions. *Immunogenetics* 2010 Jun;62(6):357–68. <https://doi.org/10.1007/s00251-010-0441-4>.
- [19] Adiguzel Y. Peptides of *H. sapiens* and *P. falciparum* that are predicted to bind strongly to HLA-A\*24:02 and homologous to a SARS-CoV-2 peptide. *Arxiv* 2021. arxiv: 2101.07356.
- [20] Stelzer G, Rosen R, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards suite: from gene data mining to disease genome sequence analysis. *Curr Protoc Bioinformatics* 2016;54:1.30.1–1.30.33. <https://doi.org/10.1002/cpbi.5>.
- [21] Flick MJ, Bugge TH. Plasminogen-receptor  $\alpha_2$ : Plasminogen activation and beyond. *J Thromb Haemost* 2017;15:150–4. <https://doi.org/10.1111/jth.13541>.
- [22] Ji H-L, Zhao R, Matalon S, Matthey MA. Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. *Physiol Rev* 2020;100:1065–75. <https://doi.org/10.1152/physrev.00013.2020>.
- [23] Ham J, Rees A. The Adenosine A2b Receptor: Its Role in Inflammation. *Endocrine Metabolic & Immune Disorders - Drug Targets (Formerly Current Drug Targets - Immune Endocrine & Metabolic Disorders)* 2009. p. 244–54. <https://doi.org/10.2174/187153008786848303>.
- [24] Dolcino M, Pelosi A, Fiore PF, Patuzzo G, Tinazzi E, Lunardi C, et al. Gene profiling in patients with systemic sclerosis reveals the presence of oncogenic gene signatures. *Front Immunol* 2018;9:449. <https://doi.org/10.3389/fimmu.2018.00449>.
- [25] Rouillard AD, Gundersen GW, Fernandez NF, Wang Z, Monteiro CD, McDermott MG, et al. The harmonizome: a collection of processed datasets gathered to serve and mine knowledge about genes and proteins. *Database* 2016: baw100. <https://doi.org/10.1093/database/baw100>.
- [26] Spatola M, Sabater L, Planaguma J, Iizuka T, Pruss H, Martinez-Hernandez E, et al. Clinical findings, IgG subclass, and antibody effects in encephalitis associated with metabotropic glutamate receptor 5 (mGluR5) antibodies. *Neurology* 2018;90: P5.390.
- [27] Christ M, Müller T, Bien C, Hagen T, Naumann M, Bayas A. Autoimmune encephalitis associated with antibodies against the metabotropic glutamate receptor type 1: case report and review of the literature. *Ther Adv Neurol Disord* 2019;12: 1–11. <https://doi.org/10.1177/1756286419847418>.
- [28] Westmark CJ, Kiso M, Halfmann P, Westmark PR, Kawaoka Y. Repurposing fragile X drugs to inhibit SARS-CoV-2 viral reproduction. *Front Cell Dev Biol* 2020;8:856. <https://doi.org/10.3389/fcell.2020.00856>.

Yekbun Adiguzel\*

Department of Biophysics, School of Medicine, Altinbas University,  
Kartaltepe Mah. Incirli Cad. No11, 34147 Bakirkoy, Istanbul, Turkey

\* Corresponding author at: Department of Biophysics, School of  
Medicine, Altinbas University, Istanbul, Turkey.  
E-mail address: [yekbun.adiguzel@altinbas.edu.tr](mailto:yekbun.adiguzel@altinbas.edu.tr).