Article published online: 2023-05-02

Exposure to SARS-CoV-2 and Infantile Diseases

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Glob Med Genet 2023;10:72–78.

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Abstract

Background and Aim Immune response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in newborns and children after prophylactic immunization is currently a relevant research topic. The present study analyzes the issue by examining the possibility that the anti-SARS-CoV-2 immune responses are not uniquely directed against the virus but can—via molecular mimicry and the consequent cross-reactivity—also hit human proteins involved in infantile diseases.

Methods Human proteins that—if altered—associate with infantile disorders were searched for minimal immune pentapeptide determinants shared with SARS-CoV-2 spike glycoprotein (gp). Then, the shared pentapeptides were analyzed for immunologic potential and immunologic imprinting phenomena.

Results Comparative sequence analysis shows that: (1) numerous pentapeptides (namely, 54) are common to SARS-CoV-2 spike gp and human proteins that, when altered, are linked to infantile diseases; (2) all the shared peptides have an immunologic potential since they are present in experimentally validated SARS-CoV-2 spike gp-derived epitopes; and (3) many of the shared peptides are also hosted in infectious pathogens to which children can have already been exposed, thus making immunologic imprint phenomena feasible.

Conclusion Molecular mimicry and the consequent cross-reactivity can represent the mechanism that connects exposure to SARS-CoV-2 and various pediatric diseases, with a fundamental role of the immunologic memory and the history of the child's infections in determining and specifying the immune response and the pathologic autoimmune sequela.

Keywords

- SARS-CoV-2 spike gp
- molecular mimicry
- peptide sharing
- cross-reactivity
- immunologic imprinting
- autoimmune
- infantile diseases

Introduction

Recently, researchers and clinicians called attention on the issue of vaccinating newborns and children against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to protect from coronavirus disease 2019 (COVID-19). Pros and cons have been examined and discussed in light of the following data:

- Children account only for 1.7 to 2% of the diagnosed cases of COVID-19.[1]
- COVID-19 in children shows a milder disease course and better prognosis than adults. Mortality is extremely low.[2]
- COVID-19 is deadlier for aged people than for other age groups.[3]
- Severe manifestations of COVID-19 in adults comprehend dyspnea, respiratory failure, pneumonitis, thromboembolic events, cardiogenic shock, renal injury, ischemic strokes, encephalitis, and cutaneous eruptions.[4]
- In contrast, severe manifestations of COVID-19 in children appear to be associated only with an uncommon, somewhat serious but tractable inflammatory disorder, that is,

DOI https://doi.org/10.1055/s-0043-1768699.
ISSN 2699-9404.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

the so-called multisystem inflammatory syndrome in children (MIS-C). MIS-C is rarest and rarely is fatal. Indeed, Ergenc et al[5] reported that among 1,340 patients aged between 0 and 216 months and diagnosed with COVID-19, only 6 patients had MIS-C, which corresponds to a MIS-C incidence of 0.4%. None of the patients died. In parallel, Payne et al[6] reported that MIS-C incidence per 1,000,000 SARS-CoV-2 infections was 316.

- Moreover, and crucially, an analysis of the potential risk of autoimmune cross-reactivity[7–17] lacks while it should be compulsorily included in the benefit–risk assessment of SARS-CoV-2 vaccination in children.

Then, the present study aims at exploring (or excluding) the possibility that molecular mimicry and the consequent potential cross-reactivity may exist between SARS-CoV-2 and human proteins that are linked, when altered, to infantile diseases, so that targeting the viral antigen via vaccination might equate to hit human proteins linked to childhood pathologies.

Materials and Methods

Peptide sharing between SARS-CoV-2 spike glycoprotein (gp) (NCBI, GenBank Protein Accession Id = QHD43416.1) from SARS-CoV-2 and human proteins related to childhood diseases was analyzed as previously detailed[9,10] using the pentapeptide as minimal immune determinant unit. Pentapeptides were used as sequence probes since a peptide grouping composed of five amino acid (aa) residues defines a minimal immune unit that can (1) induce highly specific antibodies and (2) determine antigen–antibody-specific interaction.[18,19] A library of 372 human proteins linked—when altered—to pediatric diseases was obtained from UniProt database (www.uniprot.org)[20] using the keyword "infantile." The 372 proteins are listed in ►**Supplementary Table S1** (online only).

CoV controls were as follows, with NCBI:txid number in parentheses: Middle East respiratory syndrome (MERS)-CoV (1335626); human (H) CoV-229E (11137); HCoV-NL63 (277944).

Methodologically, the SARS-CoV-2 spike gp primary aa sequence was dissected into pentapeptides offset each other by one residue (i.e., MFVFL, FVFLV, VFLVL, FLVLL, and so forth) and the resulting viral pentapeptides were analyzed for occurrences within the human proteins related to infantile diseases. Peptide Match and Peptide Search programs available at www.uniprot.org[20] were used.

The immunologic potential of the peptides shared between SARS-CoV-2 spike gp and proteins related to childhood diseases was analyzed by searching the Immune Epitope Database (IEDB, www.iedb.org/)[21] for immunoreactive SARS-CoV-2 spike gp-derived epitopes hosting the shared pentapeptides.

Finally, pentapeptides common to SARS-CoV-2 spike gp–derived epitopes and human proteins related to infantile diseases were additionally controlled for occurrences in the following bacterial pathogens listed with NCBI:txid number in parentheses: *Bordetella pertussis* (257313), *Corynebacterium diphtheriae* (257309), *Clostridium tetani* (212717), *Haemophilus influenzae* (71421), and *Neisseria meningitides* (122586).

Results and Discussion

Molecular Mimicry between SARS-CoV-2 Spike gp and Human Proteins Related to Infantile Diseases

►**Table 1** shows that SARS-CoV-2 spike gp shares a high number of minimal immune determinants (namely, 54) with 43 human proteins that associate with infantile disorders when altered, mutated, or, however, improperly functioning. The following points emerge from ►**Table 1**:

- The unexpectedly high molecular mimicry described in ►**Table 1** and the consequent potential cross-reactivity support the hypothesis that several diseases might occur in children following exposure to the SARS-CoV-2 antigen.
- Mathematically, the vastness of the common molecular platform stands out when one considers that the probability for 2 proteins to share 1 pentapeptide on the basis of the 20 aa and neglecting the relative aa abundance is equal to 1 out of 20 raised to 5. That is, it is equal to 0.0000003125.

Table 1 Peptide sharing between SARS-CoV-2 spike gp and human proteins related to infantile diseases

Peptides[a]	Human proteins, pathologies, and references[b]
TECSN	*ANTR2. Anthrax toxin receptor 2* Juvenile hyaline fibromatosis and infantile systemic hyalinosis[22]
GAGAAA	*ARX. Homeobox protein ARX* Lissencephaly associated with abnormal genitalia[23]
DIAAR	*AT1A2. Sodium/potassium-transporting ATPase subunit α-2* Alternating hemiplegia of childhood. Epilepsy[24,25]
SFELL	*CLN6. Ceroid-lipofuscinosis neuronal protein 6* Seizures, dementia, visual loss, and/or cerebral atrophy[26]
NSVAY	*CO1A1. Collagen α-1(I) chain* Osteogenesis imperfecta/Ehlers–Danlos' syndrome[27]
TLLAL	*COX15. Cytochrome c oxidase assembly protein homolog* Microcephaly, encephalopathy, hypertrophic cardiomyopathy, lactic acidosis, respiratory distress, hypotonia and seizures[28]
FLLKY	*CTNS. Cystinosin* Late-onset juvenile or adolescent nephropathic cystinosis[29]
NLLLQ, VPVAI, AGTIT	*DPOG1. DNA polymerase subunit gamma-1* Juvenile-onset Alpers' syndrome and status epilepticus[30]

(*Continued*)

Table 1 (*Continued*)

SEPVL	*FRMD7. FERM domain-containing protein 7* Infantile nystagmus syndrome[31]
EDLLF, **LQELGK**	*GLSK. Glutaminase kidney isoform, mitochondrial* Neonatal epileptic encephalopathy[32]
SSVLN	*HCN1. Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1* Infantile epileptic encephalopathy[33]
YLQPR	*MTU1. Mitochondrial tRNA-specific 2-thiouridylase 1* Mitochondrial infantile liver disease[34]
SLLIV	*NALCN. Sodium leak channel nonselective protein* Hypotonia, speech impairment, intellectual disability, pyramidal signs, and chronic constipation[35]
IAGLI, VDCAL, LLQYG	*NBAS. Neuroblastoma-amplified sequence* Growth retardation, senile face, and optic atrophy[36]
GVVFL	*NEUR1. Sialidase-1* Sialidosis: cherry red macular spots in childhood, progressive debilitating myoclonus, insidious visual loss[37]
VCGPK, NASVV	*NPC1. NPC intracellular cholesterol transporter 1* Infantile Niemann–Pick type C disease[38]
LVLLPL	*NPT2A. Sodium-dependent phosphate transport protein 2A* Hypercalcemia, failure to thrive, vomiting, nephrocalcinosis[39]
GGFNF, AGAAA	*NUP62. Nuclear pore glycoprotein p62* Infantile bilateral striatal necrosis[40]
EMIAQ, LVDLP	*OPA1. Dynamin-like 120 kDa protein, mitochondrial* Lethal encephalopathy, cardiomyopathy optic atrophy[41]
KSFTV	*PCD19. Protocadherin-19* Seizure, cognitive impairment, and delayed development of variable severity. Mainly affects females[42]
EVRQI, KVTLA	*PEX1. Peroxisome biogenesis factor 1* The peroxisome biogenesis disorders include: Zellweger's syndrome, neonatal adrenoleukodystrophy, infantile Refsum's disease, and rhizomelic chondrodysplasia punctata[43]
SASFS, **FLVLLP**	*PEX12. Peroxisome assembly protein 12* See above[43]
VLLPL	*PEX26. Peroxisome assembly protein 26* See above[43]
LHSTQD	*PEX6. Peroxisome assembly factor 2* See above[43]
LIAIV	*PIGP. Phosphatidylinositol N-acetylglucosaminyltransferase subunit P* Developmental and epileptic encephalopathy[44]
LQPEL	*PRRT2. Proline-rich transmembrane protein 2* Recurrent and brief attacks of abnormal involuntary movements, triggered by sudden voluntary movement[45]
QIAPG	*PTH2. Peptidyl-tRNA hydrolase 2, mitochondrial* Global developmental delay, hypotonia, hearing loss, ataxia, hyporeflexia, hypothyroidism, and pancreatic insufficiency[46]

Table 1 (*Continued*)

DLFLP	*RMND1. Required for meiotic nuclear division protein 1* Neonatal hypotonia and lactic acidosis. Affected individuals may have respiratory insufficiency, seizures[47]
KRVDF	*RPB1. DNA-directed RNA polymerase II subunit RPB1* Hypotonia and intellectual and behavioral abnormalities[48]
PGDSS	*SC6A3. Sodium-dependent dopamine transporter* Infantile parkinsonism-dystonia[49]
NLAAT	*SCN1A. Sodium channel protein type 1 subunit α* Generalized epilepsy with febrile seizures persisting beyond the age of 6 y and/or a variety of afebrile seizure types[50]
NLAAT	*SCN2A. Sodium channel protein type 2 subunit α* Benign infantile epilepsy[51]
NLAAT	*SCN3A. Sodium channel protein type 3 subunit α* Epilepsy with focal seizures arising from temporal, frontal, parietal, occipital lobes[52]
NLAAT, DPLSE	*SCN8A. Sodium channel protein type 8 subunit α* Delayed cognitive and motor development, attention deficit disorder, and cerebellar ataxia[53]
VVLSF, NLDSK	*SIAT6. CMP-N-acetylneuraminate-β-1,4-galactoside α-2,3-sialyltransferase* Significantly below average general intellectual functioning associated with impairments in adaptive behavior[54]
LQPRT	*SIAT9. Lactosylceramide α-2,3-sialyltransferase* Salt and pepper syndrome with seizures, psychomotor delay, cortical blindness. Patches of skin hypo- or hyperpigmentation[55]
QSLLI	*SLF2. SMC5-SMC6 complex localization factor protein 2* Infantile-onset spinocerebellar ataxia[56]
GRLQS	*SPTN2. Spectrin β chain, nonerythrocytic 2* Spinocerebellar ataxia[57]
SASFST	*STXB1. Syntaxin-binding protein 1* Developmental and epileptic encephalopathy[58]
FIAGL	*SUCA. Succinate-CoA ligase subunit α, mitochondrial* Infantile onset of hypotonia, lactic acidosis, severe psychomotor retardation, progressive neurologic deterioration[59]
LADAG	*SYLC. Leucine–tRNA ligase, cytoplasmic* Infantile liver failure syndrome[60]
LPLVS	*SZT2. KICSTOR complex protein SZT2* Developmental and epileptic encephalopathy[61]
DSLSS	*TPP1. Tripeptidyl-peptidase 1* Spinocerebellar ataxia[62]

Abbreviations: gp, glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Hexapeptides derived from overlapping pentapeptides are given in bold.

[b]Human proteins given by UniProt entry and name are in italic. Further details and references on related pathologies are available in PubMed, OMIM, and UniProt databases.

- Such unexpected massive peptide commonality between SARS-CoV-2 antigen gp and the human proteome indicates and confirms a strict phenetic relationship between viruses and the origin of eukaryotic cells according to the endosymbiotic theory.[63]
- Pathologically, the diseasome that might occur via cross-reactivity includes severe disorders such as nephropathies, seizures, cardiomyopathies, parkinsonism-dystonia, global developmental delay, hypotonia, hearing loss, ataxia, hyporeflexia, hypothyroidism, pancreatic insufficiency, and lethal encephalopathy, inter alia.

Immunologic Potential of the Peptide Sharing between SARS-CoV-2 Spike gp and Human Proteins Related to Infantile Diseases

The cross-reactivity potential of the peptide sharing described in ►**Table 1** appears to be supported by inspection of IEDB (www.iedb.org).[21] Indeed, all the 54 minimal immune determinants common to SARS-CoV-2 spike gp and human proteins related to infantile diseases occur and repeatedly recur in 839 SARS-CoV-2 spike gp–derived epitopes, of which ►**Table 2** displays only a synopsis in the interest of brevity. In essence, ►**Table 2** validates, likely enough, the cross-reactivity hypothesis at the basis of the present study.

Specificity of the Peptide Sharing between SARS-CoV-2 Spike gp and Human Proteins Linked to Infantile Diseases

To control the specificity of the peptide sharing between SARS-CoV-2 spike gp and human proteins linked to childhood diseases (►**Table 1**), the 54 shared pentapeptides were analyzed for occurrences in other coronaviruses not associated with particular pediatric complications, that is, MERS-CoV, HCoV-OC43, and HCoV-229E. Results are shown in ►**Table 3** that provides evidence that the intense peptide overlap between SARS-CoV-2 spike gp and human proteins related to childhood diseases is highly specific. *De facto*, almost all the 54 shared pentapeptides are absent in the CoV controls, that is, in the pathogenic MERS-CoV[64] as well as in the scarcely pathogenic HCoV-OC43 and HCoV-229E that cause only mild symptoms.[65]

Occurrence in Bacteria of Peptides Common to SARS-CoV-2 Spike gp and Proteins Linked to Infantile Diseases

To further control the specificity of the peptide sharing between SARS-CoV-2 spike gp and human proteins linked to childhood diseases, comparative sequence analyses were extended to the bacterial pathogens *B. pertussis*, *C. diphtheriae*, *C. tetani*, *H. influenzae*, and *N. meningitides*—that is, bacteria to which children may be exposed also following current vaccinal routes—were analyzed. Results are displayed in ►**Table 4**.

It can be seen that many of the 54 peptides shared between SARS-CoV-2 spike gp and human proteins linked to infantile diseases also occur in the analyzed microbial organisms, thus highlighting that, contrary to expectations, while practically no phenetic similarity exists between SARS-CoV-2 spike gp and the control CoVs (►**Table 3**), a high level of similarity exists between SARS-CoV-2 spike gp and bacterial pathogens to which children have been exposed via passive/active infection and by which the immune system has already been imprinted (►**Table 4**).

Table 2 Immunoreactive SARS-CoV-2 spike gp-derived epitopes containing pentapeptides shared between SARS-CoV-2 spike gp and human proteins linked to infantile diseases: a synopsis

IEDB ID[a]	Epitope sequence[b]	IEDB ID[a]	Epitope sequence[b]
3589	aphGVVFLhv	1325536	tLADAGfik
4321	asaNLAATk	1327418	vydpLQPELdsf
16156	FIAGLIAIV	1327824	wtAGAAAyy
23200	GVVFLhvty	1327836	wtfGAGAAl
36724	litGRLQSl	1329248	dEMIAQytsal
37289	llfnKVTLA	1330227	tqDLFLPff
37724	LLQYGsfct	1330420	aphGVVFL
50166	pyrvVVLSF	1330526	lynSASFSTf
51999	qpyrvVVLSF	1331519	EDLLFn
57592	SEPVLkgvkl	1332003	fvFLVLLPL
57792	sfiEDLLFnk	1332424	itGRLQSlqty
59161	slidLQELGK	1332664	lltdEMIAQy
71996	vydpLQPEL	1332702	LQELGKyeqy
1074967	lepLVDLPi	1332727	ltdEMIAQyt
1075065	stqDLFLPff	1332785	mfvFLVLLPLVSs
1309147	YLQPRTfll	1333450	SASFSTfkcy
1310623	ltdEMIAQy	1333520	SFELLhapatv
1311673	EVRQIAPGqt	1333523	sfiEDLLF
1311846	SFELL	1333568	sKRVDFcgkgy
1313244	nSASFSTfk	1333801	sTECSNLLLQy
1314425	alDPLSEtk	1333812	stqDLFLPf
1315940	epLVDLPi	1333921	tdEMIAQy
1316323	fdeddSEPVL	1334182	vgYLQPRTf
1317916	gYLQPRTfll	1390229	VDCALDPLSEtkctlks
1320443	lgaeNSVAY	1541124	KRVDFcgk
1321078	LPLVSsqcv	1546420	fiEDLLFnk
1322298	NASVVniqk	1547648	gYLQPRTFl
1323200	QELGKyeqy	1593850	YLQPRifll
1323249	QIAPGqtgk	1597683	fiEDLLFnkv
1323750	rasaNLAATk	1625440	ssvLHSTQ
1325401	TECSNLLLQy	1659240	fvFLVLLPLv

Abbreviations: gp, glycoprotein; IEDB, Immune Epitope Database; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Epitopes listed according to the IEDB ID number. Details and references for each epitope are available at www.iedb.org/.[21]
[b]Shared peptides are given capitalized.

Table 3 Quantitation of the pentapeptide sharing between CoVs spike gps and human proteins linked to childhood diseases

Spike gp from:	Number of shared pentapeptides
SARS-CoV-2	54
MERS-CoV	–
hCoV-229E	–
hCoV-NL63	2

Abbreviations: CoV, coronavirus; gp, glycoprotein; h, human; MERS, Middle East respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4 Occurrences in bacterial pathogens of pentapeptides shared between SARS-CoV-2 spike gp and human proteins linked to infantile diseases

Organism	Shared pentapeptides
B. pertussis	AGAAA, AGTIT, DIAAR, DSLSS, FIAGL, FLVLL, GAGAA, GVVFL, KVTLA, LADAG, LIAIV, LPLVS, LQELG, LVDLP, NASVV, NLAAT, QELGK, SLLIV, VLLPL
C. diphtheriae	AGAAA, AGTIT, GAGAA, LADAG, VPVAI
C. tetani	AGAAA, AGTIT, DLFLP, EVRQI, FIAGL, LLQYG, LQELG, NASVV, SSVLN
H. influenzae	AGAAA, AGTIT, DIAAR, EVRQI, GAGAA, GGFNF, GVVFL, IAGLI, KRVDF, LADAG, LIAIV, LPLVS, LQELG, LVDLP, LVLLP, NASVV, NLAAT, NLDSK, NLLLQ, NSVAY, QELGK, QIAPG, QSLLI, SFELL, SLLIV, SSVLN, TLLAL, VLLPL, VPVAI, VVLSF
N. meningitidis	AGAAA, ASFST, EVRQI, FIAGL, FLVLL, GAGAA, KRVDF, LADAG, LQELG, LQPEL, NLDSK, QELGK, TLLAL, VLLPL, VVLSF

Abbreviations: gp, glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Then, as highlighted in the literature,[66–72] the interpathogen peptide commonality can add a further potential burden to the molecular mimicry phenomenon described in ►**Table 1**. Indeed, a fundamental property of the immune system is the memory for immune determinants previously encountered so that, as a rule, the immune system reacts by recalling memory of the responses toward past infections rather than producing *ex novo* responses toward the recent ones.

Consequently, in the case under study here, the following sequence of events may unfold:

- A primary response to SARS-CoV-2 can actually occur as a secondary (or even tertiary) response against pathogens previously encountered and memorized by the immune system. That is, anamnestic secondary antibacterial responses can occur after exposure to SARS-CoV-2. Such anamnestic secondary antibacterial responses will be of considerable proportions given the extent of the viral versus bacterial peptide overlap described in ►**Table 4**.
- SARS-CoV-2 antigen will not be affected in that the immunologic memory deflects the immune response toward the already encountered peptides, that is, the bacterial peptide platform detailed in ►**Table 4**.
- However, also the attack against the early sensitizing bacterial pathogens can fail by being the early sensitizing bacterial pathogens no more present in the organism.
- Then, the ultimate result might be that the anamnestic, high affinity, high avidity, and extremely potent secondary immune response elicited by the lastly encountered pathogen—that is, SARS-CoV-2—can hit the only available targets, that is, the common immune determinants that in this instance are present in the human proteins related to infantile diseases (►**Table 1**).

According to this sequence of events, molecular mimicry and immunologic memory might explain also the different pathological outcomes of the autoimmune responses—from mild symptoms to even lethal pathologies—that may follow exposure to SARS-CoV-2. In practice, the history of infections/immunization of each child is the main factor dictating the onset and the severity of the pathologies outlined in ►**Table 1**.

Conclusion

The present study investigates the possible adverse events that might occur in newborns and children following exposure to SARS-CoV-2. Based on the extensive peptide sharing between SARS-CoV-2 gp antigen and human proteins related to infantile diseases, supported by epitopic data that confer a high immunoreactivity to the peptide sharing, and given the possibility of immunologic imprinting phenomena, this study leads to predict that exposing newborns and children to SARS-CoV-2 might associate with infantile severe diseases such as growth retardation, abnormal genitalia, epilepsy, seizures, cardiomyopathies, hypotonia, visual loss, hypercalcemia, ataxia, infantile parkinsonism-dystonia, below average general intellectual functioning, encephalopathies, and inter alia. Then, the present data suggest that extreme caution be exercised in planning and implementing a mass anti-SARS-CoV-2 vaccination of infants and children.

Funding
None.

Conflict of Interest
None declared.

References

1 Kapustova L, Petrovicova O, Banovcin P, et al. COVID-19 and the differences in physiological background between children and adults and their clinical consequences. Physiol Res 2021;70(S2): S209–S225
2 Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(06):1088–1095

3 Islam MS, Larpruenrudee P, Saha SC, et al. How severe acute respiratory syndrome coronavirus-2 aerosol propagates through the age-specific upper airways. Phys Fluids 2021;33(08):081911
4 Ladani AP, Loganathan M, Kolikonda MK, Lippmann S. COVID-19 Legacy. South Med J 2021;114(12):751–759
5 Ergenc Z, Kepenekli E, Çetin E, et al. Incidence of multisystem inflammatory syndrome in children and the comorbidity scores in pediatric coronavirus disease 2019 cases. Pediatr Int (Roma) 2022;64(01):e15084
6 Payne AB, Gilani Z, Godfred-Cato S, et al; MIS-C Incidence Authorship Group. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 2021;4(06):e2116420
7 Chen Y, Xu Z, Wang P, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology 2022;165(04):386–401
8 Churilov LP, Kanduc D, Ryabkova VA. COVID-19: adrenal response and molecular mimicry. Isr Med Assoc J 2021;23(10):618–619
9 Kanduc D. From anti-SARS-CoV-2 immune responses to COVID-19 via molecular mimicry. Antibodies (Basel) 2020;9(03):33
10 Kanduc D. From anti-SARS-CoV-2 immune response to the cytokine storm via molecular mimicry. Antibodies (Basel) 2021;10 (04):36
11 Angileri F, Legare S, Marino Gammazza A, Conway de Macario E, Jl Macario A, Cappello F. Molecular mimicry may explain multi-organ damage in COVID-19. Autoimmun Rev 2020;19(08): 102591
12 Garg RK, Paliwal VK. Spectrum of neurological complications following COVID-19 vaccination. Neurol Sci 2022;43(01):3–40
13 Gambichler T, Boms S, Susok L, et al. Cutaneous findings following COVID-19 vaccination: review of world literature and own experience. J Eur Acad Dermatol Venereol 2022;36(02):172–180
14 Mehta SK, Sunder A. Getting paralysed after COVID: Guillain-Barre syndrome. J Family Med Prim Care 2021;10(07):2706–2708
15 Moody R, Wilson K, Flanagan KL, Jaworowski A, Plebanski M. Adaptive immunity and the risk of autoreactivity in COVID-19. Int J Mol Sci 2021;22(16):8965
16 Chittal A, Rao S, Lakra P, Nacu N, Haas C. A case of COVID-19 vaccine-induced thrombotic thrombocytopenia. J Community Hosp Intern Med Perspect 2021;11(06):776–778
17 Shi H, Zuo Y, Navaz S, et al. Endothelial cell-activating antibodies in COVID-19. Arthritis Rheumatol 2022;74(07):1132–1138
18 Kanduc D. Hydrophobicity and the physico-chemical basis of immunotolerance. Pathobiology 2020;87(04):268–276
19 Kanduc D. The role of proteomics in defining autoimmunity. Expert Rev Proteomics 2021;18(03):177–184
20 UniProt Consortium. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res 2019;47(D1):D506–D515
21 Vita R, Mahajan S, Overton JA, et al. The Immune Epitope Database (IEDB): 2018 update. Nucleic Acids Res 2019;47(D1):D339–D343
22 Hanks S, Adams S, Douglas J, et al. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet 2003; 73(04):791–800
23 Kato M, Das S, Petras K, et al. Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum Mutat 2004;23(02):147–159
24 Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol 2004;55(06):884–887
25 Deprez L, Weckhuysen S, Peeters K, et al. Epilepsy as part of the phenotype associated with ATP1A2 mutations. Epilepsia 2008;49 (03):500–508
26 Gao H, Boustany RM, Espinola JA, et al. Mutations in a novel CLN6-encoded transmembrane protein cause variant neuronal ceroid lipofuscinosis in man and mouse. Am J Hum Genet 2002;70(02): 324–335
27 Cabral WA, Makareeva E, Colige A, et al. Mutations near amino end of alpha1(I) collagen cause combined osteogenesis imperfecta/Ehlers-Danlos syndrome by interference with N-propeptide processing. J Biol Chem 2005;280(19): 19259–19269
28 Alfadhel M, Lillquist YP, Waters PJ, et al. Infantile cardioencephalopathy due to a COX15 gene defect: report and review. Am J Med Genet A 2011;155A(04):840–844
29 Attard M, Jean G, Forestier L, et al. Severity of phenotype in cystinosis varies with mutations in the CTNS gene: predicted effect on the model of cystinosin. Hum Mol Genet 1999;8(13): 2507–2514
30 Uusimaa J, Hinttala R, Rantala H, et al. Homozygous W748S mutation in the POLG1 gene in patients with juvenile-onset Alpers syndrome and status epilepticus. Epilepsia 2008;49(06): 1038–1045
31 Bai D, Shi W, Qi Z, et al. Clinical feature and waveform in infantile nystagmus syndrome in children with FRMD7 gene mutations. Sci China Life Sci 2017;60(07):707–713
32 Rumping L, Büttner B, Maier O, et al. Identification of a loss-of-function mutation in the context of glutaminase deficiency and neonatal epileptic encephalopathy. JAMA Neurol 2019;76(03): 342–350
33 Nava C, Dalle C, Rastetter A, et al; EuroEPINOMICS RES Consortium. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet 2014;46(06):640–645
34 Gaignard P, Gonzales E, Ackermann O, et al. Mitochondrial infantile liver disease due to TRMU gene mutations: three new cases. JIMD Rep 2013;11:117–123
35 Al-Sayed MD, Al-Zaidan H, Albakheet A, et al. Mutations in NALCN cause an autosomal-recessive syndrome with severe hypotonia, speech impairment, and cognitive delay. Am J Hum Genet 2013; 93(04):721–726
36 Maksimova N, Hara K, Nikolaeva I, et al. Neuroblastoma amplified sequence gene is associated with a novel short stature syndrome characterised by optic nerve atrophy and Pelger-Huët anomaly. J Med Genet 2010;47(08):538–548
37 Bonten E, van der Spoel A, Fornerod M, Grosveld G, d'Azzo A. Characterization of human lysosomal neuraminidase defines the molecular basis of the metabolic storage disorder sialidosis. Genes Dev 1996;10(24):3156–3169
38 Blom TS, Linder MD, Snow K, et al. Defective endocytic trafficking of NPC1 and NPC2 underlying infantile Niemann-Pick type C disease. Hum Mol Genet 2003;12(03):257–272
39 Magen D, Berger L, Coady MJ, et al. A loss-of-function mutation in NaPi-IIa and renal Fanconi's syndrome. N Engl J Med 2010;362 (12):1102–1109
40 Basel-Vanagaite L, Muncher L, Straussberg R, et al. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. Ann Neurol 2006;60(02):214–222
41 Spiegel R, Saada A, Flannery PJ, et al. Fatal infantile mitochondrial encephalomyopathy, hypertrophic cardiomyopathy and optic atrophy associated with a homozygous OPA1 mutation. J Med Genet 2016;53(02):127–131
42 Depienne C, Bouteiller D, Keren B, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. PLoS Genet 2009;5(02):e1000381
43 Yik WY, Steinberg SJ, Moser AB, Moser HW, Hacia JG. Identification of novel mutations and sequence variation in the Zellweger syndrome spectrum of peroxisome biogenesis disorders. Hum Mutat 2009;30(03):E467–E480
44 Johnstone DL, Nguyen TT, Murakami Y, et al; Care4Rare Canada Consortium. Compound heterozygous mutations in the gene PIGP are associated with early infantile epileptic encephalopathy. Hum Mol Genet 2017;26(09):1706–1715
45 Li M, Niu F, Zhu X, et al. PRRT2 mutant leads to dysfunction of glutamate signaling. Int J Mol Sci 2015;16(05):9134–9151
46 Hu H, Matter ML, Issa-Jahns L, et al. Mutations in PTRH2 cause novel infantile-onset multisystem disease with intellectual

disability, microcephaly, progressive ataxia, and muscle weakness. Ann Clin Transl Neurol 2014;1(12):1024–1035
47 Garcia-Diaz B, Barros MH, Sanna-Cherchi S, et al. Infantile encephaloneuromyopathy and defective mitochondrial translation are due to a homozygous RMND1 mutation. Am J Hum Genet 2012;91(04):729–736
48 Haijes HA, Koster MJE, Rehmann H, et al. De novo heterozygous POLR2A variants cause a neurodevelopmental syndrome with profound infantile-onset hypotonia. Am J Hum Genet 2019;105 (02):283–301
49 Kurian MA, Zhen J, Cheng SY, et al. Homozygous loss-of-function mutations in the gene encoding the dopamine transporter are associated with infantile parkinsonism-dystonia. J Clin Invest 2009;119(06):1595–1603
50 Harkin LA, McMahon JM, Iona X, et al; Infantile Epileptic Encephalopathy Referral Consortium. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130(Pt 3):843–852
51 Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. Lancet 2002;360(9336):851–852
52 Vanoye CG, Gurnett CA, Holland KD, George AL Jr, Kearney JA. Novel SCN3A variants associated with focal epilepsy in children. Neurobiol Dis 2014;62:313–322
53 Trudeau MM, Dalton JC, Day JW, Ranum LP, Meisler MH. Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a patient with cerebellar atrophy, ataxia, and mental retardation. J Med Genet 2006;43(06):527–530
54 Hu H, Eggers K, Chen W, et al. ST3GAL3 mutations impair the development of higher cognitive functions. Am J Hum Genet 2011;89(03):407–414
55 Simpson MA, Cross H, Proukakis C, et al. Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase. Nat Genet 2004;36(11): 1225–1229
56 Nikali K, Saharinen J, Peltonen L. cDNA cloning, expression profile and genomic structure of a novel human transcript on chromosome 10q24, and its analyses as a candidate gene for infantile onset spinocerebellar ataxia. Gene 2002;299(1-2):111–115
57 Jacob FD, Ho ES, Martinez-Ojeda M, Darras BT, Khwaja OS. Case of infantile onset spinocerebellar ataxia type 5. J Child Neurol 2013; 28(10):1292–1295
58 Saitsu H, Kato M, Mizuguchi T, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet 2008;40(06):782–788
59 Ostergaard E, Christensen E, Kristensen E, et al. Deficiency of the alpha subunit of succinate-coenzyme A ligase causes fatal infantile lactic acidosis with mitochondrial DNA depletion. Am J Hum Genet 2007;81(02):383–387
60 Casey JP, McGettigan P, Lynam-Lennon N, et al. Identification of a mutation in LARS as a novel cause of infantile hepatopathy. Mol Genet Metab 2012;106(03):351–358
61 Basel-Vanagaite L, Hershkovitz T, Heyman E, et al. Biallelic SZT2 mutations cause infantile encephalopathy with epilepsy and dysmorphic corpus callosum. Am J Hum Genet 2013;93(03): 524–529
62 Sun Y, Almomani R, Breedveld GJ, et al. Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is caused by variants in TPP1, the gene involved in classic late-infantile neuronal ceroid lipofuscinosis 2 disease (CLN2 disease). Hum Mutat 2013;34(05): 706–713
63 Kanduc D. The comparative biochemistry of viruses and humans: an evolutionary path towards autoimmunity. Biol Chem 2019; 400(05):629–638
64 Choudhry H, Bakhrebah MA, Abdulaal WH, et al. Middle East respiratory syndrome: pathogenesis and therapeutic developments. Future Virol 2019;14(04):237–246
65 Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of Coronaviruses. Trends Microbiol 2016;24 (06):490–502
66 Francis T, Salk JE, Quilligan JJ. Experience with vaccination against influenza in the spring of 1947: a preliminary report. Am J Public Health Nations Health 1947;37(08):1013–1016
67 Lucchese G, Kanduc D. The Guillain–Barrè peptide signatures: from Zika virus to Campylobacter, and beyond. Virus Adapt Treat 2017;9:1–11
68 Lucchese G, Kanduc D. Minimal immune determinants connect Zika virus, human cytomegalovirus, and *Toxoplasma gondii* to microcephaly-related human proteins. Am J Reprod Immunol 2017;77(02):e12608
69 Kanduc D. Anti-SARS-CoV-2 immune response and sudden death: Titin as a link. Adv Stud Biol 2021;13:37–44
70 Kanduc D. Thromboses and hemostasis disorders associated with COVID-19: the possible causal role of cross-reactivity and immunological imprinting. Glob Med Genet 2021;8(04):162–170
71 Davenport FM, Hennessy AV, Francis T Jr. Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus. J Exp Med 1953;98(06): 641–656
72 Fevang B, Wyller VBB, Mollnes TE, et al. Lasting immunological imprint of primary Epstein-Barr virus infection with associations to chronic low-grade inflammation and fatigue. Front Immunol 2021;12:715102