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Article

From Viral Infections to Autistic Neurodevelopmental Disorders via Cross-Reactivity

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ABSTRACT

Objective: Genetic, epigenetic, and environmental factors such as infections have been proposed as potential causes of autism spectrum disorder (ASD). Searching for the molecular mechanism by which infections might contribute to the etiopathogenesis of ASD, we analyze here the hypothesis that immune responses to infectious agents may cross-react with human proteins that, when altered, relate to autistic neurodevelopmental spectrum disorders.

Methods: Viral and human proteins were analyzed for peptide sharing using the Pir Peptide Match resource.

Results: We find that: (i) an intense peptide overlap occurs between ASD–related viruses and ASD–related human proteins, and might underlie cross-reactivity scenarios following viral infections; (ii) viral peptide sharing also occurs with Y-linked proteins, in this way highlighting an additional potential cross-reactivity burden that would involve male subjects only; (iii) many shared peptides are also part of epitopes experimentally validated as immunopositive in the human host.

Conclusion: This study offers a cohesive set of data that suggests a contribution of immune cross-reactivity to the genesis of ASD.

Keywords: autism spectrum disorders; viral infections; peptide cross-reactivity; autism-related proteins; Y-linked proteins

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1 INTRODUCTION

There is a clinical and epidemiological consensus that infections may be causally involved in the neurodevelopmental and behavioural disturbances that characterize ASD [1–6]. Specifically, a main role in the pathophysiology of ASD has been repeatedly suggested for the activation of the immune system against the infectious agents [7–21] rather than to viral/microbial activities *per se*, such as, for example,

subversion of the host protein synthesis machinery [22], manipulation of membrane transport pathways [23], and up-regulation of HLA-E expression with, consequently, suppression of NK cell recognition [24–26].

However, how the immune system may be involved in ASD remains undetermined. The issue is further complicated by the fact that ASD are biased towards males, with ratios of 4:1 or higher [27–29], so that analyses of or hypotheses on ASD have to contemplate the male bias.

During last decades, in an attempt to further our understanding of infection-induced diseases, we analyzed sequence identities between viruses and humans [30,31]. We pursued the hypothesis that peptide commonality between microbial and human proteins might have the potential to trigger cross-reactions in the human host during infection, thus inducing autoimmune pathologic sequelae [30–37]. Here, we test such a hypothesis by analyzing viral pathogens that have been related to ASD [38–51]—namely Borna disease virus, Rubella virus, Measles virus, Influenza A virus, and Mumps virus—and searching for amino acid (aa) sequences common to (i) human proteins that, when altered, have been associated with autistic disorders, and (ii) proteins expressed by Y-linked genes.

2 METHODS

The viral proteomes analyzed in the present study are as follows, in order of aa length and with abbreviations, Taxonomy ID, number of proteins, and number of aa in parentheses: Parvovirus B19 (B19; 10798, 3 proteins, 2006 aa); Borna disease virus (BDV; 928296; 6 proteins; 3014 aa); Rubella virus (RUBV; 11041; 2 proteins; 3179 aa); Measles virus (MeV; 11235; 7 proteins; 4680 aa); Influenza A virus, H1N1 (211044; 13 proteins; 4788 aa); Mumps virus (MuV; 11171; 8 proteins; 4977 aa). Proteomes are described in detail at http://www.uniprot.org [52].

The primary sequence of viral proteins was dissected into hexapeptides overlapped by five residues each other. For example, BDV Envelope glycoprotein p57 (UniProt: P52638; 503 aa) was sequentially dissected into MQPSMS, QPSMSF, PSMSFL, SMSFLI, and so forth until its last hexapeptide LGRWQE, for a total of 498 hexapeptides. Then, each viral hexamer was probed for occurrences within human proteins characterized by being related to ASD or encoded by Y-linked genes.

A set of 138 ASD-related human proteins was randomly retrieved from UniProt database and NCBI (https://www.ncbi.nlm.nih.gov/gene) using 'autism' and 'autistic' as keywords and consisted of 138 proteins listed in Table S1. A set of 44 proteins expressed by Y-linked genes was assembled using data from Skaletsky *et al.* [53] and UniProt database, and are listed in Table S2. Proteins are indicated by UniProt entry and names.

The immunological potential of the peptide matching was analyzed using the Immune Epitope Database (IEDB; www.iedb.org) database [54]. Only epitopes that had been experimentally validated as immunopositive in the human host were considered. Data on brain protein expression were retrieved from https://www.proteinatlas.org/humanproteome [55,56].

3 RESULTS AND DISCUSSION

We selected and analyzed five proteomes belonging to infectious agents that have been reported as related to or concomitant with ASD. That is, BDV [38–40], RUBV [41–46], MeV [41,47,48], Influenza A virus [49–51], MuV [41]. As a control, we used Parvovirus B19. B19 is the etiological agent of the infantile fifth disease, preferentially targets the erythroblasts in the bone, and does not appear to be related to ASD [57].

Hexapeptides were used as operational minimal immune determinants in light of a vast scientific literature that documents the crucial roles exerted by peptides 5–6 aa long in immunogenicity and antigenicity [58–85].

3.1 Hexapeptide sharing between B19, BDV, RUBV, MeV, influenza A virus, and MuV proteomes, and human proteins related to ASD

Table 1 quantitatively describes the hexapeptide sharing between B19, BDV, RUBV, MeV, Influenza A virus, and MuV, and the set of the 138 human proteins related to autism (see Table S1). It can be seen that all of the analyzed viruses share hexamers with human proteins related to ASD. Even if at a lesser extent, the peptide commonality also involves the control B19 virus.

Qualitatively, the viral hexapeptide distribution among the ASD-related proteins is described in Table 2. At first glance, space does not permit a match-by-match discussion of the vast peptide sharing illustrated in Tables 1 and 2. In synthesis, three main points emerge. Firstly, 96 hexapeptides belonging to the 6 analyzed viral pathogens also occur in 76 out of 138 human proteins associated with ASD, in this way indicating a non-stochastical clustering of peptide matches in 55% of the analyzed human proteins.

Table 1. Quantitation of the Hexapeptide Sharing between B19, BDV, RUBV, MeV, Influenza A Virus, and MuV Proteomes and ASD-Related Proteins.

Virus [1]	Number of Shared Hexapeptides	Number of ASD-Related Proteins Involved in the Sharing
B19	12	10
BDV	19	16
RUBV	28	28
MeV	32	26
Influenza A virus	18	18
MuV	33	28

[1] Viruses described under Methods and listed according to aa length.

Table 2. Hexapeptide Sharing between B19, BDV, RUBV, MeV, Influenza A Virus, and MuV Proteomes and ASD-Related Human Proteins.

Virus	Shared Peptides [1]	Human Protein Related to ASD [2]
B19	LSSSSS	ANK3. Ankyrin-3
	ALSSSSS; GAGGGG	ARI1B. AT-rich interactive domain-containing protein 1B
	PGLNPR	CTTB2. Cortactin-binding protein 2
	GLQSFV	HUWE1. E3 ubiquitin-protein ligase HUWE1
	AGPPQS	MAGA4. Melanoma-associated antigen 4
	IQILKD	NAC2. Sodium/calcium exchanger 2
	GESFVG	NHS. Nance-Horan syndrome protein
	SSTPIP	POGZ. Pogo transposable element with ZNF domain
	GAGGGG	PPR3F. Protein phosphatase 1 regulatory subunit 3F
	SSVASKL	SCN2A. Sodium channel protein type 2 subunit alpha
BDV	VNVTFM	AGRG2. Adhesion G-protein coupled receptor G2
	VELETP	ANK3. Ankyrin-3
	LEDEED	ARX. Homeobox protein ARX
	ADLDMD; SLLIGV	CHD8. Chromodomain-helicase-DNA-binding protein 8
	IQGLLD	CUL3. Cullin-3
	SVGVKP	HDAC4. Histone deacetylase 4
	HSYVEL	HNRH2. Heterogeneous nuclear ribonucleoprotein H2
	FHASLL	K1210. Acrosomal protein KIAA1210
	RLTVLVP	KIRR3. Kin of IRRE-like protein 3
	DPDFND; LLKKLL	MARK1. Serine/threonine-protein kinase MARK1
	EVSFCL	NPRL3. GATOR complex protein NPRL3
	AKLVLL	S12A5. Solute carrier family 12 member 5
	TSSHSS	SETD2. Histone-lysine N-methyltransferase SETD2
	HLPALT; LKSSSL	SHAN3. SH3 and multiple ankyrin repeat domains protein 3
	LKSSSL	TSC2. Tuberin
	GPDAGP	V1AR. Vasopressin V1a receptor

Table 2. *Cont.*

Virus	Shared Peptides [1]	Human Protein Related to ASD [2]
RUBV	DANAVT	ANK3. Ankyrin-3
	QQVALL	ANR11. Ankyrin repeat domain-containing protein 11
	QQPQPP	ARI1B. AT-rich interactive domain-containing protein 1B
	RPRPPR	AUTS2. Autism susceptibility gene 2 protein
	ASCPAG	BICC1. Protein bicaudal C homolog 1
	EDYRALR	CCD22. Coiled-coil domain-containing protein 22
	RGGSAP	CTND2. Catenin delta-2
	EALRAR	CTTB2. Cortactin-binding protein 2
	AVTAAV	DEPD5. GATOR complex protein DEPDC5
	AVGGGP	DMPK. Myotonin-protein kinase
	LRELGS	ERBB2. Receptor tyrosine-protein kinase erbB-2
	AEVRPP	FOXP1. Forkhead box protein P1
	AYGRAL	GBRB1. Gamma-aminobutyric acid receptor subunit beta-1
	PWLFAE	IGSF1. Immunoglobulin superfamily member 1
	PPPAPV	MAP1B. Microtubule-associated protein 1B
	AAGHTE	MXRA5. Matrix-remodeling-associated protein 5
	TCSPAS	MYO16. Unconventional myosin-XVI
	RCTLPI	NPRL2. GATOR complex protein NPRL2
	EPATLL	NRX1A. Neurexin-1
	AVAPRR	PPR3F. Protein phosphatase 1 regulatory subunit 3F
	AVTAAV	REEP3. Receptor expression-enhancing protein 3
	ACICEI	S12A5. Solute carrier family 12 member 5
	QTPAPK	SETD2. Histone-Lys N-methyltransferase SETD2
	AALEEG	SETD5. SET domain-containing protein 5
	PPPPAP	SHAN3. SH3 and multiple ankyrin repeat domains protein 3
	LRGAIA	SL9A9. Sodium/hydrogen exchanger 9
	AAAPAP	STK39. STE20/SPS1-related proline-alanine-rich protein kinase
	SLSVPA	TSC2. Tuberin
MeV	SRGDIN	ANK3. Ankyrin-3
	RLHRAAI	ANR11. Ankyrin repeat domain-containing protein 11
	PGAPAG	APCL. Adenomatous polyposis coli protein 2
	LLGRVR	CCD22. Coiled-coil domain-containing protein 22
	ILSQGN	CHD8. Chromodomain-helicase-DNA-binding protein 8
	VELLIS	CTTB2. Cortactin-binding protein 2
	KGTGSR	CUL3. Cullin-3
	LKLAAL; **RLLDRLVR**	DIA1. Deleted in autism protein 1
	LVPQVR	DIA1R. Deleted in autism-related protein 1
	LVDVFL	GLT13. Polypeptide N-acetylgalactosaminyltransferase 13
	FIVSNI	GPHRA. Golgi pH regulator A
	LDLLLN	HERC2. E3 ubiquitin-protein ligase HERC2
	LLEVVQ; GRALAE	HUWE1. E3 ubiquitin-protein ligase HUWE1
	PTSSVG	K1210. Acrosomal protein KIAA1210
	TLVSGS	MARK1. Serine/threonine-protein kinase MA RK1
	SIQALS	MXRA5. Matrix-remodeling-associated protein 5
	KEEDEG	MYT1L. Myelin transcription factor 1-like protein
	VSNAAL	NHS. Nance-Horan syndrome protein
	ELAPYP	PQBP1. Polyglutamine-binding protein 1
	TGSSVE	SCN1A. Sodium channel protein type 1 subunit alpha
	TGSSVE; ELLESS	SCN3A. Sodium channel protein type 3 subunit alpha
	PTLKKL	SETD2. Histone-lysine N-methyltransferase SETD2
	VYSPSR	SETD5. SET domain-containing protein 5
	ISIQAL	T4S20. Transmembrane 4 L6 family member 20
	EVDGDV	TBL1R. F-box-like/WD repeat-containing protein TBL1XR1
	ELLRLQ; VYWLTI	TEN1. Teneurin-1

Table 2. *Cont.*

Virus	Shared Peptides [1]	Human Protein Related to ASD [2]
Influenza A virus	VPLHQS	ADNP2. Activity-dependent neuroprotector homeobox protein 2
	RTLLAK	APCL. Adenomatous polyposis coli protein 2
	AGVESA	BICC1. Protein bicaudal C homolog 1
	AADADT; TGNLQT	CADM1. Cell adhesion molecule 1
	ERELVR	CUL3. Cullin-3
	TATKRI	DEPD5. GATOR complex protein DEPDC5
	EEEVLT	DMPK. Myotonin-protein kinase
	GKVTKS	EF1A2. Elongation factor 1-alpha 2
	AGSSEQ	HUWE1. E3 ubiquitin-protein ligase HUWE1
	LKAEIA	MYO16. Unconventional myosin-XVI
	KLRTQI	MYT1L. Myelin transcription factor 1-like protein
	TRSGGN	NRX1A. Neurexin-1
	TRSGGN	NRX1B. Neurexin-1-beta
	EDFVRQ	NSE3. Non-structural maintenance of chromosomes element 3 homolog
	LASLLE	SHAN3. SH3 and multiple ankyrin repeat domains protein 3
	KNDLLE	SLIK2. SLIT and NTRK-like protein 2
	LGKCNI	TEN1. Teneurin-1
	LLQNSQ	ULK4. Serine/threonine-protein kinase ULK4
MuV	TLMGAE	AGRA2. Adhesion G protein-coupled receptor A2
	PSAGMQN	ARI1B. AT-rich interactive domain-containing protein 1B
	NLVARK	CAC1H. Voltage-dependent T-type calcium channel subunit alpha-1H
	ASNIVG; GEEGSI	CADM1. Cell adhesion molecule 1
	KTLSNL	CCD22. Coiled-coil domain-containing protein 22
	LGELVR	CYFP1. Cytoplasmic FMR1-interacting protein 1
	ASAVGV	DIA1R. Deleted in autism-related protein 1
	HIRLAD	DMPK. Myotonin-protein kinase
	DDLIRY	FAN1. Fanconi-associated nuclease 1
	DNRVAD	GBRB1. Gamma-aminobutyric acid receptor subunit beta-1
	DNRVAD	GBRB3. Gamma-aminobutyric acid receptor subunit beta-3
	LELSEA	HECAM. Hepatocyte cell adhesion molecule
	SQSSSS; EIKAAS	HUWE1. E3 ubiquitin-protein ligase HUWE1
	KGASVS	K1210. Acrosomal protein KIAA1210
	LVTCLG	MAGA4. Melanoma-associated antigen 4
	RINNSQ	MEF2C. Myocyte-specific enhancer factor 2C
	HLYLAE	MXRA5. Matrix-remodeling-associated protein 5
	ANNHGI; SLFNSG	MYO16. Unconventional myosin-XVI
	ASPSSG; AGNISA	NHS. Nance-Horan syndrome protein
	SLIPPE	NPRL3. GATOR complex protein NPRL3
	RTCFRI	SCN1A. Sodium channel protein type 1 subunit alpha
	EEEEEL	SETD2. Histone-Lys N-methyltransferase SETD2
	LSPLKK; SLPSAG	SETD5. SET domain-containing protein 5
	PLSLAA	SHAN3. SH3 and multiple ankyrin repeat domains protein 3
	ISIQAL	T4S20. Transmembrane 4 L6 family member 20
	TLSTSI	TROP. Trophinin
	SLLEME	TSH3. Teashirt homolog 3
	ERRVAS	XPC. DNA repair protein complementing XP-C cells

[1] Hepta- and octapeptides formed by overlapping hexapeptides given bold. [2] Details and references on human proteins at www.uniprot.org.

Secondly, in light of the fact that the probability of a hexapeptide occurring once in a protein is 1 out of 20^6, the viral vs human peptide overlap reported in Table 2 largely exceeds mathematical expectation. As a note *a latere*, we observe that this unexpected high peptide matching may be explained by the evolutionary role played by viruses in the origin of the eukaryotic nucleus [86].

Then, as a third point, it was found that human proteins related to ASD and sharing peptides with the analyzed viruses are mostly expressed in the brain. Limiting our analysis to a few examples—*i.e.*, ARI1B, CTTB2, HUWE1, SETD2, and SHAN3 proteins—we find that:

- AT-rich interactive domain-containing protein 1B (ARI1B) shares the viral peptides ALSSSSS, GAGGGG, QQPQPP, and PSAGMQN (Table 1). ARI1B has been detected in embryonic stem cells [87] where it is involved in transcriptional repression [88]. ARI1B has essential roles in dendritic arborization and spine morphology of developing pyramidal neurons [89]. Haploinsufficiency of ARID1B has been related to corpus callosum abnormalities, intellectual disability, speech impairment, and autism [90,91].
- Cortactin-binding protein 2 (CTTB2) shares the viral peptides PGLNPR, EALRAR, and VELLIS (Table 2). CTTB2 regulates the dendritic spine distribution of cortactin in hippocampal neurons [92]. Of note, dendritic spines are the major locations of excitatory synapses in mammalian brains [93].
- The ubiquitin ligase HUWE1 shares the viral peptides GLQSFV, AGSSEQ, SQSSSS, EIKAAS, LLEVVQ, and GRALAE (Table 2). HUWE1 promotes neurogenesis [94,95]. HUWE1-dependent degradation of the transcriptional regulator atonal homolog 1 (Atoh1) is required for normal differentiation of cerebellar granule neuron progenitor cells [96].
- Histone-Lys N-methyltransferase SETD2 shares the viral peptides TSSHSS, QTPAPK, EEEEEL, and PTLKKL (Table 2). SETD2 is the main enzyme generating histone H3 trimethylation at lysine 36, a specific tag for epigenetic transcriptional regulation. SETD2 mutation was detected in a child with autism, intellectual disabilities and epilepsy [97]. SETD2 alterations may lead to alterations of epigenetic mechanisms that are critical in neural development [98].
- SH3 and multiple ankyrin repeat domains protein 3 (SHAN3) shares the viral peptides HLPALT, LKSSSL, PPPPAP, LASLLE, and PLSLAA (Table2). SHAN3 is a postsynaptic density protein that contributes to orchestrate the dendritic spine and synapse formation, has a critical role in neuronal morphogenesis in placodal neurons [99], and participates in the regulation of developing neurons growth cone motility and the NMDA receptor-signaling [100].

3.2 Hexapeptide sharing between B19, BDV, RUBV, MeV, influenza A virus, and MuV proteomes and human Y-chromosomal proteins

The human Y chromosome contains a male-specific non-recombining region with 27 protein-coding genes (Table S2) [53]. The peptide sharing between the analyzed viruses and the Y-chromosomal proteins is shown in Table 3. It can be seen that 7 Y-linked proteins namely: KDM5D (SMCY), PC11Y, TBL1Y, TXNG2, USP9Y, UTY (KDM6C), and ZFY—share hexa-/heptapeptides with all of the potential viral pathogens analyzed here, B19 excluded (Table 3).

The 7 Y-linked proteins are widely expressed in the brain. Specifically:

- lysine-specific demethylase 5D (KDM5D aka protein SMCY aka H-Y antigen) specifically demethylates trimethylated histone H3 lysine 4 (H3K4me3) [101] and is associated with gene activation [102]. H3K4me3 is expressed in neonatal male cortex/hippocampus at levels more than 3,000 times higher than in females as shown by reverse transcription with quantitative PCR (RT-qPCR) [103]. Male-specific KDM5D expression has been detected in post-mortem human brain [104];
- protocadherin-11 Y-linked protein (PC11Y) is involved in cell-cell interactions and is critical in the development of the central nervous system. PC11Y is expressed strongly in fetal brain and brain (cortex, amygdala, thalamus, substantia nigra, hippocampus, caudate nucleus and corpus callosum) [105,106];
- transducin beta-like protein 1Y (TBL1Y) is expressed in fetal brain and prostate [53]. TBL1Y may contribute to the variation in male-specific phenotypes [107]. Recently, a role of TBL1Y during cardiac differentiation of human embryonic stem cells has been proposed. It was seen that a reduced TBL1Y cellular level influenced cardiac differentiation and increased the probability of impaired contractions [108]. Then, it is pertinent to recall that subjects with autism are at risk for heart problems [109–111];
- putative gamma-taxilin 2 (TXNG2) is ubiquitously expressed [53];

- ubiquitin carboxyl-terminal hydrolase FAF-Y (USP9Y) might stabilize through de-ubiquitination a specific target protein that is important for male germ cell development [112,113]. USP9Y expression has been found in post-mortem human brain [104] and during neurodevelopment in mouse brain [113];
- histone demethylase UTY (also known as KDM6C) catalyzes demethylation of histone H3 lysine 27 (H3K27) [114] that, in the trimethylated form (H3K27me3), is involved in gene silencing [115]. In the mouse brain, UTY has a male-specific high expression in the paraventricular nucleus of the hypothalamus [116]. UTY has been detected in post-mortem human brain [104];
- the transcriptional activator zinc finger Y-chromosomal protein (ZFY) is transcribed in hypothalamus, and frontal and temporal cortex of adult human brain [117].

Table 3. Hexapeptide Sharing between B19, BDV, RUBV, MeV, Influenza A Virus, and MuV Proteomes and Y-Chromosomal Proteins.

Virus	Shared Peptides [1]	Y-Chromosomal Protein [2]
B19	-	-
BDV	PSRGDS	PC11Y. Protocadherin-11 Y-linked
	SLVDSL	USP9Y. Probable ubiquitin carboxyl-terminal hydrolase FAF-Y
RUBV	SPGLLR	KDM5D. SMCY. Lysine-specific demethylase 5D. SMCX
	IVAVIP	TBL1Y. F-box-like/WD repeat-containing protein TBL1Y
	RAIQKII	USP9Y. Probable ubiquitin carboxyl-terminal hydrolase FAF-Y
	DAAVAA	ZFY. Zinc finger Y-chromosomal protein
MeV	KLAALC	TXNG2. Putative gamma-taxilin 2
	DKKVDT	USP9Y. Probable ubiquitin carboxyl-terminal hydrolase FAF-Y
Influenza A virus	SSIGKV	UTY. KDM6C. Histone demethylase UTY
MuV	**SKTFLKK**	KDM5D. SMCY. Lysine-specific demethylase 5D.
	LQHLEQ	UTY. KDM6C. Histone demethylase UTY

[1] Heptapeptides formed by 2 overlapping hexapeptides given bold. [2] Details on Y-chromosomal proteins at www.uniprot.org and in Ref. [53].

3.3 Immunologic potential of the viral peptides shared with human proteins related to ASD or expressed by Y-linked genes

The viral vs human peptide overlap illustrated in Tables 1–3 also has an immunologic potential. Indeed, Table 4 shows that many shared peptides are part of immunopositive epitopes cataloged at IEDB [54].

Table 4. Immunopositive Epitopes Containing Sequences Shared between B19, BDV, RUBV, MeV, Influenza A Virus, and MuV Proteomes and ASD-Related or Y-Linked Proteins.

IEDB ID [1]	EPITOPES [2]	IEDB ID [1]	EPITOPES [2]	IEDB ID [1]	EPITOPES [2]
1848	aiakledakelless	87732	qtpapkpsrappqqpqpprmqtgr	437698	gpgripppppapy
4375	asdvetaeggeihellrlq	87776	ragltagasqsrrprppr	438262	iplppppapety
4376	asdvetaeggeihellrlqsr	97279	eqmagsseqaaeameia	442782	argaalalllfg
11286	edakellessdqilr	97289	etyvlsiipsgplkaeiaqkledvfagkn	451565	aaapapapa
12901	ekvtgtdleliqilkdhyni	97293	evltgnlqtlkirvhegyeeftmvgrratailr	451566	aaapappaa
13126	elklaalchgedsit	97452	lkndllenlq	452570	apaaapapa
14641	evdgdvklssnlvil	97554	plkaeiaqrledvfagk	461930	aevdgdvkl
19737	gggagaggagaggggr	97694	tlelrsgywairtrsggn	462034	grlvpqvrvid
20971	gllaccakclyylrgaiapr	97740	vlasttakameqmagsseqa	470109	rprpprpepppglm

Table 4. *Cont.*

IEDB ID [1]	EPITOPES [2]	IEDB ID [1]	EPITOPES [2]	IEDB ID [1]	EPITOPES [2]
20972	gllacsakclyyLRGAIApr	97766	wairTRSGGNtnqqrasa	470110	RPRPPPRpepppglma
21686	gpLKAEIAqrle	97779	ymlERELVRktrflpva	476328	atlpsSPGLLR
21912	gqlsdhphALSSSSShaepr	106084	rprspsSQSSSSgspprrp	489419	yLLKKLLql
22542	gstkscarTLVSGSf	119022	sSQSSSSgspprrpppgrrpffhpvgeadyfeyhqe	504031	prspsSQSSSSgspprrppp
35591	lelrsrywairTRSGGNtnqqras	119788	cPLSLAAqld	507907	RPRPPPRpldshl
36538	liglIaiagiRLHRAAIytaeihk	120221	ssssaggggGAGGGGggggsgg	508324	spKGASVSi
37232	LLEVVQsdqsqsgltfasr	127270	tyvlsivpsgpLKAEIAqrl	509573	eAAAPAPtv
37300	llfsllgLSSSSSis	127692	ifkiekGKVTKSielna	509875	lpLSSSSSv
39061	lrdpisaeISIQALS	128243	AGSSEQaaeamevasqa	517071	gPGAPAGaqpaqpp
40581	lvsgsfgnrflLSQGNli	128743	glKNDLLEnlqayqkrm	517072	gPGAPAGaqpaqpps
40826	lyksnhnnVYWLTIp	129032	kameqmAGSSEQaaeam	534817	yivtdqkPLSLAA
43219	nalypMSPLLQeclr	129920	sivpsgpLKAEIAqrle	534818	yivtdqkPLSLAAg
46150	ntlelrsrywairTRSGGNt	130187	vaymlERELVRktrflp	540558	ptILSQGNrfcapder
48376	pLKAEIAqrledv	131276	wheaqpSPGLLR	540650	yaiggsasptILSQGN
48856	ppppeerqetrsQTPAPKps	143551	stlelrsrywairTRSGGNt	540949	agglggGAGGGGdhad
52333	qshgqlsdhphALSSSSSha	145868	lelrsrywairTRSGGNt	544452	ppgapsapAAAPAPaa
52523	qtgRGGSAPrpelgpptn	150995	hLGKCNIagwilgnp	549187	llqEEEEEL
52588	QTPAPKpsrappQQPQPPrmqtgrg	164390	sstglKNDLLEnlqayqk	552594	htkLSSSSSitltlp
53963	rgrgrgekrprspsSQSSSS	170345	anptILSQGNrf	562078	aLLEVVQsggkniel
54638	RLLDRLVRl	173446	tILSQGNrfhap	569127	grLKAEIAr
54946	rmqtgRGGSAPrpelgpptnpfqaava	179908	smDAAVAAl	571902	eELLRLQql
55937	rsQTPAPKpsrappQQPQPPrmqt	181520	ynpytrsIQILKD	574167	kLLEVVQpcl
56752	saeISIQALSyalgg	182182	irlradTLMGAElaarpeyr	592219	gdpeeeeEEEEELvd
58175	sgplkaeiaqkledvfagkn	188697	klcklrgvaplhlgkcniag	593877	aagaalalalw
58176	sgplkaeiaqrle	202816	ataavtaavk	594430	assppagpppppapalvg
58177	sgplkaeiaqrledv	227311	krprspssqssssgs	599581	Ltvlvprvw
59546	slvgidpfkllqnsqvyslirp	227587	ssqssssgspprrpp	601005	rlrelgslvw
59548	slvgidpfrllqnsqvfsli	239959	lagaggggaavtv	601256	rsvssqssssvs
60889	ssaglkndllenlqayqkrm	245808	aakapapkaaapapk	614836	dsssvaskv
63973	tgtdleliqilkdhynisld	252233	akapapkaaapapka	620205	kslligvfk
67496	tyvlsiipsgplkaeiaqrl	255133	apapkaaapapkaaa	621015	lelseavlptmta
72315	wdleatgaciceipt	255442	apkaaapapkaaaaa	629659	avppppapl
79398	srappppeerqesrsqtpapkpsrapp	316384	kapapkaaapapkaa	632869	islippeerw
79399	srappqqpqpprmqtgrggsaprpelg	348636	papkaaapapkaaaa	638702	vpvavtaav
79544	fapwdleatgaciceiptdv	419951	margaalal	641923	dyfkdlcgpdagpig
79784	dpfrllqnsqvys	434859	argaalalllf	645191	iqriplppppapety
79844	gplkaeiaqrled	434943	artllaknl	650955	tpkdqfiiaygglrgaia

[1] Epitopes listed according to the IEDB ID number. [2] Peptide sequences shared between viruses and human proteins in capital letters.

Again, the high number of epitopes containing the shared peptide sequences precludes a detailed epitope-by-epitope discussion. However, a special attention has to be drawn to the peptide RLLDRLVR shared between MeV and the human Deleted in Autism protein 1 (DIA1). In fact, the peptide RLLDRLVR corresponds to the epitope IEDB ID 54638 (Table 4) that was shown to be responsive in 80% of 5 HLA-A2–positive adults revaccinated with measles-mumps-rubella vaccine [118].

Another point calling for attention is that hexapeptide analyses underestimate by one order of magnitude the potential cross-reactivity that may be evoked by immune responses following infections. As a matter of fact, also a pentapeptide can represent a minimal immune unit endowed with immunogenicity and antigenicity [58–86]. And, in addition, discontinuous pentapeptide epitopes have been reported in IEDB database such as the Influenza A hemagglutinin conformational epitope $P^{134}S^{137}K^{177}Y^{180}T^{183}$ (IEDB ID: 164481). Hence, expanding the similarity analyses to (dis)continuous pentapeptides would generate a viral vs human cross-reactivity scenario even more massive than that displayed in Tables 1-4.

3.4 ASD-related and Y-chromosomal proteins involved in the viral peptide overlap: expression in the human brain

Taken together, Tables 1-4 factually support the hypothesis that, following active infections by the viral pathogens analyzed here, the consequent anti-viral immune responses might cross-react with ASD-related and/or Y-linked proteins expressed in the human brain. However, it is incumbent to observe that the brain expression data reported above have been mainly obtained in animal models, and using microarray analyses, quantitative real-time PCR, and in situ hybridization technologies. Actually, it is well-known that transcript abundances only partially predict protein abundances [119,120]. Consequently, since a *conditio sine qua non* for a cross-reaction to occur is a sufficient level of antigenemia, the Human Protein Atlas resource (https://www.proteinatlas.org/) [55,56] was searched for data on the expression level in the brain of the proteins discussed above. Results are reported in Fig. 1 that shows that the ASD-related proteins ARI1B, CTTB2, HUWE1, and SHAN3 have an expression level from medium to high in the nervous system cells (panel A) and that, among the Y-chromosomal proteins, TBL1Y has a high protein expression level in almost all nervous system cells (panel B). Expression in peripheral nerve cells was low or absent. Data on KDM5D, USP9Y, and TXNG2 proteins were pending or not available at the time of the present study.

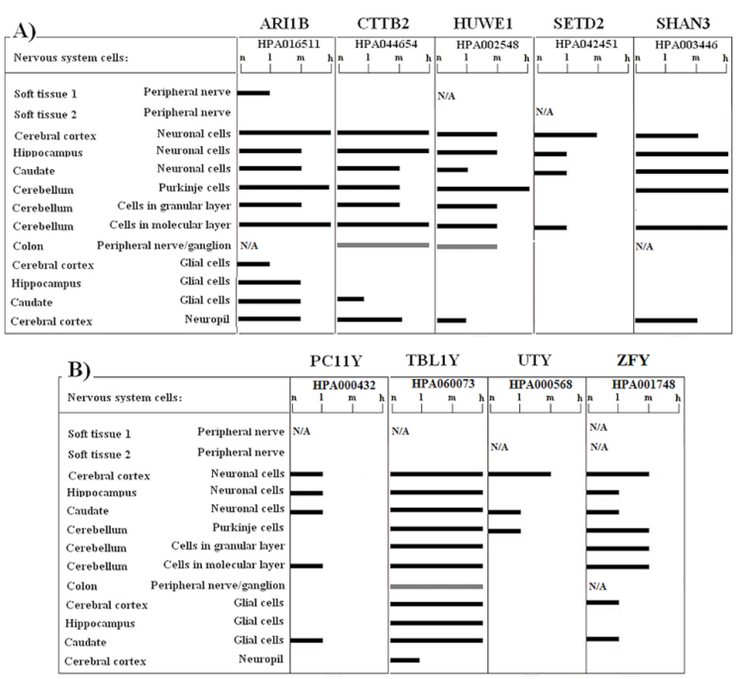

Fig. 1 Expression in the human brain of (A) ASD-related proteins ARI1B, CTTB2, HUWE1, SETD2, and SHAN3, and (B) Y-chromosomal proteins PC11Y, TBL1Y, UTY, and ZFY. Estimates of the protein expression are—n: not detected; l: low; m: medium; h: high. Grey bars refer to expression in peripheral nerve/ganglion. Antibodies are described at www.proteinatlas.org. Images and data from www.proteinatlas.org [55,56]. Further details at www.proteinatlas.org.

4 CONCLUSIONS

ASD is of unknown etiology. Genetic components such as mutations [121], epigenetic disorders such as altered methylaton [122], abnormal cytokine profile where inflammatory signals dominate [15], and environmental factors such as pollutants [123] or immune responses to infections [7–21] appear to contribute to ASD. However, whichever it may be the invoked causal factor, the mechanism(s) at the basis of ASD remain unsettled.

Here, we hypothesized that immune responses against infectious viral agents might have the potential to cross-react with proteins that, when altered, are related to autism. Actually, Tables 1, 2 and 4, and Fig. 1A document an ample and potentially immunologic peptide matching of B19, BDV, RUBV, MeV, Influenza A virus, and MuV with ASD-related proteins, thus supporting the possibility of a causal connection between infection and neurodevelopmental diseases through cross-reactivity. Very much the same consideration applies to data from Tables 3 and 4, and Fig. 1B that highlight peptide overlaps between viral and Y-chromosomal proteins. In this case, the potential cross-reactivity burden specifically involves male subjects, so determining a higher male susceptibility to neurodevelopmental disorders.

It has to be underlined that ASD comprehends autism, childhood disintegrative disorder and Asperger syndrome that are characterized, in different combinations and at various level of intensity, by symptoms such as impaired capacity for interactions, a restricted repertoire of interests, stereotyped repetitive activities, and decreased intellectual ability [1]. Hence, the here described numerous brain proteins involved in the peptide matching and in the consequent potential cross-reactions might explain the multitude of symptoms that characterize ASD. In addition, the ASD symptomatology and severity may have spatial-temporal patterns, with, for example, in utero infections involving the maternal immune system. In this regard, as a final caveat, it has to be kept in the due account the observation that the maternal immune response in the absence of virus and obtained by using the synthetic double-stranded RNA poly (I:C) is sufficient to cause behavioral changes in the offspring [124]. Moreover, the infection outcome in children and adults may depend on previous immune responses following previous encounters with the pathogens [125,126].

In sum, the data support our previous studies [30–37], offer the immune cross-reactivity paradigm as a possible approach for studying autism and neuropsychiatric disorders, and strongly warrant further collaborative research efforts to determine the impact of viral vs human cross-reactivity in the etiology of ASD.

AUTHOR CONTRIBUTIONS

DK proposed the original idea, developed sequence analyses and wrote the manuscript. AP contributed to the clinical analysis and discussion of the data, and to the writing of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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