IDENTIFICATION OF PROTEINS WITH VARIABLE LEVELS OF POST-TRANSLATIONAL MODIFICATIONS IN HUMAN TEMPORAL LOBE EPILEPSY

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Comparative mass spectrometry analysis of hippocampal tissue samples from patients with sclerotic and non-sclerotic temporal lobe epilepsy and nonepileptic patients was undertaken to identify differences in the levels of protein post-translational modifications (PTMs). The original proteomic data obtained by Mathoux et al. [DOI: 10.1172/jci.insight.188612] and deposited in the PRIDE repository (PXD064519) were used in this work. Our reanalysis of the comparative proteomic data identified 53 proteins with PTMs (phosphorylation, methylation, acetylation, and citrullination) that exhibited significant changes in the levels of individual modified peptides. According to the published original data, all 53 proteins are involved in processes associated with neurological diseases in general and epileptogenesis in particular. The analysis identified PTMs of proteins that could play an important role in the pathogenesis of neurological diseases.

Keywords: post-translational modifications; epilepsy; bioinformatics

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INTRODUCTION

This study continues our previous work [1, 2] on bioinformatic reanalysis of data deposited in the PRIDE repository [3]. Usually, authors of large-scale experimental studies using mass spectrometry (MS) plan the experiment and subsequent data analysis to obtain the desired data as accurately and efficiently as possible. However, the initial experimental data contain significant information that can be extracted by processing the data with different parameters or using different methods. For example, in many studies on protein identification or comparison of protein spectra in health and disease, the authors either completely ignore the entire spectrum of post-translational modifications (PTMs) or consider only a subset of them, based on their own understanding of the problem. At the same time, the role of PTMs is difficult to overestimate [4, 5], and information about their presence can be of interest in the context of forming hypotheses about the role of various PTMs in pathology or planning more specialized experiments to confirm the obtained information. Data on changes in the abundance of specific observed PTMs are also of interest. Modern whole-proteome profiling technologies using MS provide highly accurate and reproducible quantitative data on each specific ion, even without preliminary enrichment of modified proteins/peptides and without the use of isotopic labels [6].

Nervous system diseases are among the top three groups of diseases in which the development of the pathological process is influenced by PTM impairments [7]. Temporal lobe epilepsy (TLE) is one of the most common chronic nervous system diseases in adults [8]. The predominant pathological change in epilepsy, especially in TLE, is hippocampal sclerosis; however, the pathophysiological mechanism of epileptic damage to hippocampal tissue remains unclear [9].

In this study, we have analyzed a dataset deposited in the PRIDE repository [3] with the identifier PXD064519. In the original study [8], a comprehensive comparative analysis of the profiling of an internal modification of mRNA, N^6 adenosine methylation (m6A), was conducted on hippocampal tissue samples from mice and humans with drug-resistant temporal lobe epilepsy. The authors of [8] demonstrated that metabolic and autophagic pathways, which could be directly related to m6A processing, were impaired in epileptic tissues. For the proteomic analysis of human hippocampal samples, a variable modification with N-terminal acetylation of the protein was selected, but quantitative changes were carried out at the level of whole proteins. Since authors did not consider other physiological PTMs, so we reanalyzed the original data [8] to identify proteins with different PTM levels in the experimental and control samples.

MATERIALS AND METHODS

The authors of the original study [8] used postoperative human hippocampal tissues removed due to sclerotic (S) (n=7) and non-sclerotic (NS) (n=7) temporal lobe epilepsy, as well as control (C) samples taken during autopsy from patients without

epilepsy (n=10). The stages of tissue sample extraction from patients with epilepsy, obtaining control samples, sample preparation and proteomic analysis are described in details by the authors of the original experimental work [8].

In our study, peptide identification based on raw files was performed again using the PEAKS Studio 13 program [10]. The search was performed using the amino acid sequences of human proteins (*Homo sapiens*, UniProtKB/Swiss-Prot release 2025_04, 83587 records [11]) using the following search parameters: cleaving enzyme was trypsin; the peptide mass tolerance was 10 ppm; the fragment mass tolerance was 0.02 Da; the max missed trypsin site cleavage was set as 2; the number of variable modifications per peptide was 2 (peptides with a single modification under study were considered in the final analysis). Carbamidomethylation of cysteine was chosen as a fixed modification, and the variable modifications included: (1) methionine oxidation (not considered significant), (2) phosphorylation of serine, threonine, and tyrosine, (3) methylation of lysine, arginine, and histidine, (4) acetylation of lysine and the N-terminal peptide of the protein, (5) citrullination of asparagine. All options for additional filtering and formation of chimeric spectra were disabled. Modifications of lysine and arginine residues were considered only if the modified residue was not the first or last residue in the peptide. The false discovery rate (FDR) for the final selection of identified peptides was 0.1%. Identification was performed for each sample independently.

Using chromatographic data from raw files, the entire space of primary ions was aligned and the area under the peak for each of the primary ions was normalized (Normalized abundance, NA) using the Progenesis LC-MS program [12]. The peptide identification data were imported into the Progenesis LC-MS project, combining the alignment results with the peptide identification results for subsequent comparison of quantitative data from hippocampal samples.

During analysis of the significance of changes in peptide levels with PTM, results of the analysis of variance (ANOVA) performed by computational algorithms implemented in Progenesis LC-MS were evaluated. Changes in modified peptide levels were considered significant at the Anova p-value < 0.05 and a Max fold change ≥ 2. The Max fold change is a measure that describes the changes in the mean NA value between the control (C) and study groups (S, NS); for example, for two values of NA_C and NA_S, the range of change in NA_S relative to NA_C is NA_S/NA_C.

RESULTS AND DISCUSSION

After alignment and normalization of the raw data in Progenesis LC-MS and integration with peptide identification results, 212,985 primary ions were selected, of which 22,354 were identified. A total of 15,576 peptide sequences for 2,560 proteins were identified. The final selection was made for proteins for which at least six peptides were quantified by Progenesis LC-MS. A table with the full set of identification data is given in the Supplementary Materials.

Identified peptides with PTMs that met the conditions “Anova p-value < 0.05” and “Max fold change ≥ 2” during evaluation of the NA mean differences between the study groups and the control are listed in Table 1. No peptides with histidine methylation were identified under the given selection parameters. If a peptide is listed more than once in the table, the data are presented for ions of different charges. Direct data summation is possible, since the distribution of the peptide between ions of different charges does not depend on its concentration in the sample [13], but since in each specific case there is no certainty that all ionic states have been identified, this may be a source of error in the interpretation of the results.

Table 1 shows the lack of significant quantitative changes in the total protein content only for peptides nos. 61, 69, and 71 with methylation of the lysine residue and two N-terminal acetylations, respectively. For other peptides the change in the average NA of the peptide between the experiment (NS and S) and the control (C) differed from the same parameter for the protein by at least 1.2 times. For example, for the peptide AEEAKDEPPSEGEAEEEEK (no. 9, P07196) with phosphorylation at the serine residue, this difference was 139.4 times. However, in this case, this effect is probably due to the fact of missed tryptic cleavage site; in addition it contains a large number of negatively charged residues (see below the section devoted to the discussion of Figures 1 and 2). For peptides nos. 1–3, 25–38, 47, 52, 67, and 68, an increase in quantity was observed in the experiment, while an insignificant decrease in quantity was observed for the protein itself in most cases. The opposite relationship was found for peptides nos. 10, 11, 19, 62, 63, 78–85, 88, and 89; there was a decrease in quantity in the experiment and an insignificant increase in quantity for the whole protein. For example, for the SKDGTGSDDK peptide (no. 62, P10636, microtubule-associated tau protein) with methylation at the lysine residue, the average NA in the experiment was 4031.4 times lower than in the control, while the amount of the protein itself in the experiment was slightly higher than in the control. Methylation of the tau protein is critical for its physiological state and can compete with other PTMs. Global methylation in neurons, microglia, and astrocytes is involved in numerous cellular functions [14].

Figure 1 shows examples of the NA distribution for four peptides for each sample from the experimental (NS and S) and control groups. For comparison, data

Table 1. Identified peptides with PTM that meet the conditions of Anova *p*-value < 0.05 and Max fold change ≥ 2 when assessing the average NA between the study groups (S, NS) and the control (C)

Protein ID (UniProt)	Protein name (UniProt)	#	Sequence of modified peptide	Anova *p*-value of the peptide	Max fold change of the peptide	Group with the highest and lowest NA mean value of the peptide		Max fold change of the protein	Group with the highest and lowest NA mean value of the protein	
Phosphorylation (S,T,Y+79.97)										
O00264	Membrane-associated progesterone receptor component 1	1	EGEEPTVY**S**DEEEPKDESARK	0.0488	2.1	NS	C	1.5	C	S
O15075	Serine/threonine-protein kinase DCLK1	2	SPSP**S**PTSPGSLRK	0.0039	2.8	NS	C	1.2	C	S
		3	SSQHGG**S**STSLASTK	0.0004	31.2	S	C			
O75363	Breast carcinoma-amplified sequence 1	4	TI**T**PPEPEPTGAPQK	0.0007	4.7	NS	C	2.1	NS	C
P00558	Phosphoglycerate kinase 1	5	ITLPVDFV**T**ADK	0.0001	15.6	C	S	1.2	C	S
P02671	Fibrinogen alpha chain	6	AD**S**GEGDFLAEGGGVR	1.99E-06	482.7	S	C	5.4	S	C
P05060	Secretogranin-1	7	WAEGGGH**S**RER	0.0022	17.6	C	S	1.2	S	NS
P07196	Neurofilament light polypeptide	8	AEEAKDEPP**S**EGEAEEEEK	1.07E-06	32.9	NS	C	1.2	NS	C
		9	AEEAKDEPP**S**EGEAEEEEK	6.96E-06	167.3	NS	C			
P07197	Neurofilament medium polypeptide	10	KAE**S**PVKEEAVAEVVT	1.69E-06	15.3	C	NS	1.5	NS	C
		11	SDQAEEGG**S**EK	0.0063	105.6	C	S			
P12036	Neurofilament heavy polypeptide	12	EEAR**S**PADKFPEK	0.0075	3.2	NS	C	1.3	NS	C
P07900	Heat shock protein HSP 90-alpha	13	DKEV**S**DDEAEEKEDKEEEK	0.0122	2.0	C	NS	1.3	C	S
		14	ERDKEV**S**DDEAEEK	3.35E-06	2.6	C	S			
		15	ERDKEV**S**DDEAEEK	0.0001	2.3	C	NS			
		16	ERDKEV**S**DDEAEEKEDKEEEK	0.0200	2.2	C	NS			
		17	ERDKEV**S**DDEAEEKEDKEEEK	0.0131	2.2	C	NS			
		18	ERDKEV**S**DDEAEEKEDKEEEK	0.0129	2.2	C	NS			
P11137	Microtubule-associated protein 2	19	ET**S**PESSLIQDEIAVK	0.0471	2.1	C	S	1.3	S	C
		20	KET**S**PESSLIQDEIAVK	0.0375	3.1	S	C			
		21	GHDLSPLASDILTNT**S**GSMDEGDDYLPATTPALEK	0.0015	81.6	S	C			
		22	GHDLSPLASDILTNT**S**GSMDEGDDYLPATTPALEK	0.0100	10.13	S	C			
		23	KTEVQAH**S**PSRK	0.0073	2.6	S	C			
		24	KTEVQAH**S**PSRK	0.0400	3.4	S	C			

Table 1. Identified peptides with PTM that meet the conditions of Anova *p*-value < 0.05 and Max fold change ≥ 2 when assessing the average NA between the study groups (S, NS) and the control (C) (continued)

Protein ID (UniProt)	Protein name (UniProt)	#	Sequence of modified peptide	Anova *p*-value of the peptide	Max fold change of the peptide	Group with the highest and lowest NA mean value of the peptide		Max fold change of the protein	Group with the highest and lowest NA mean value of the protein	
P46821	Microtubule-associated protein 1B	25	AD**S**RESLKPAAKPLPSK	0.0099	2.6	S	C	1.1	C	NS
		26	**S**PSDSGYSYETIGK	2.77E-07	14.7	NS	C			
		27	TTK**T**PEDGDYSYEIIEK	0.0020	30.4	NS	C			
		28	TTR**T**PEEGGYSYDISEK	1.10E-09	34.3	NS	C			
		29	TTR**T**PEEGGYSYDISEK	0.0003	69.3	NS	C			
		30	TT**S**PPEVSGYSYEK	0.0046	2.6	NS	C			
		31	VLSPLR**S**PPLIGSESAYESFLSADDK	0.0001	3.7	S	C			
P78559	Microtubule-associated protein 1A	32	AELEEMEEVHP**S**DEEEEDATK	0.0096	22.6	NS	C	1.1	C	NS
		33	CL**S**PDDSTVK	0.0002	3.0	S	C			
		34	DRGLD**S**GAETEEEK	0.0356	4.6	NS	C			
		35	DRGLD**S**GAETEEEK	0.0003	7.8	S	C			
		36	ELSSEPQ**T**PPAQK	0.0001	33.4	S	C			
		37	SHWDDS**T**SDSELEK	1.49E-11	67.0	NS	C			
P08559	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	38	YHGH**S**MSDPGVSYR	3.29E-05	3.6	S	C	1.4	C	S
P09543	2',3'-cyclic-nucleotide 3'-phosphodiesterase	39	KM**S**SSGAK	0.0355	3.9	NS	C	1.6	NS	C
P16949	Stathmin	40	**S**HEAEVLK	0.0002	5.4	S	C	2.1	NS	C
P17677	Neuromodulin	41	AGE**T**PSEEK	0.0464	3.5	S	C	1.3	S	NS
P20916	Myelin-associated glycoprotein	42	NV**T**ESPSFSAGDNPPVLFSSDFR	0.0013	48.0	NS	C	2.2	NS	C
Q96JE9	Microtubule-associated protein 6	43	VMIPTAPHTEYIES**S**P	0.0002	3.3	NS	C	1.2	NS	C
P13591	Neural cell adhesion molecule 1	44	AAFSKDE**S**KEPIVEVR	2.03E-06	3.3	NS	C	1.1	S	NS
P16157	Ankyrin-1	45	RD**S**RDVDEEK	6.32E-07	9.5	S	C	3.7	S	C
		46	RD**S**RDVDEEK	1.01E-05	4.5	S	C			
P28482	Mitogen-activated protein kinase 1	47	VADPDHDHTGFLTE**Y**VATR	0.0003	8.3	S	C	1.3	C	S

Table 1. Identified peptides with PTM that meet the conditions of Anova *p*-value < 0.05 and Max fold change ≥ 2 when assessing the average NA between the study groups (S, NS) and the control (C) (continued)

Protein ID (UniProt)	Protein name (UniProt)	#	Sequence of modified peptide	Anova *p*-value of the peptide	Max fold change of the peptide	Group with the highest and lowest NA mean value of the peptide		Max fold change of the protein	Group with the highest and lowest NA mean value of the protein	
P29966	Myristoylated alanine-rich C-kinase substrate	48	GEPAAAAAPEAGA**S**PVEK	0.0002	3.9	S	C	1.5	S	C
P35611	Alpha-adducin	49	AAVVT**S**PPPTTAPHK	0.0055	3.3	S	C	1.1	S	C
		50	QKG**S**EENLDEAR	0.0002	4.5	NS	C			
P63010	AP-2 complex subunit beta	51	HLPIHHGS**T**DAGDSPVGTTTATNLE	2.37E-10	46.3	C	NS	1.2	C	NS
Q01082	Spectrin beta chain, non-erythrocytic 1	52	AQTLPTSVVTITSES**S**PGKR	4.61E-07	5.1	NS	C	1.3	C	NS
Q08495	Dematin	53	ST**S**PPPSPEVWADSR	0.0003	4.0	NS	C	2.5	NS	C
Q15121	Astrocytic phosphoprotein PEA-15	54	DIIRQP**S**EEEIIK	2.45E-09	3.4	NS	C	1.3	NS	S
		55	LTRIP**S**AK	0.0020	3.6	NS	C			
Q7Z6L0	Proline-rich transmembrane protein 2	56	AHSGHPG**S**PR	0.0005	7.9	S	C	1.0	S	NS
Q96GW7	Brevican core protein	57	DVLEGD**S**SEDR	0.0372	4.4	C	NS	1.2	C	NS
Q9UEY8	Gamma-adducin	58	IEEVLSPEGSPSK**S**PSK	0.0001	5.5	S	C	1.1	S	C
Q9UK76	Jupiter microtubule associated homolog 1	59	RNS**S**EASSGDFLDLK	1.97E-05	11.3	NS	C	2.1	NS	C
Q9Y2J0	Rabphilin-3A	60	WHQLQNENHVS**S**D	0.0185	2.3	C	NS	1.3	C	NS
Methylation (K,R+14.02)										
O60664	Perilipin-3	61	TVCDAAE**K**GVR	0.0243	2.0	NS	C	2.1	NS	C
P10636	Microtubule-associated protein tau	62	S**K**DGTGSDDK	0.0140	4031.4	C	NS	1.2	S	C
		63	S**K**DGTGSDDKK	0.0372	125.0	C	S			
Q13554	Calcium/calmodulin-dependent protein kinase type II subunit beta	64	YPPFWDEDQH**K**LYQQIKAGAYDFPSPEWDTVTPEAK	0.0006	26.9	C	NS	1.9	C	NS
Q16555	Dihydropyrimidinase-related protein 2	65	IVAPPGG**R**ANITSLG	0.0010	3.5	S	C	1.1	NS	S
Acetylation (K,N-term+42.01)										
Q7L266	Isoaspartyl peptidase/L-asparaginase	66	GAQ**K**TDCQK	2.16E-05	2.5	S	C	1.3	S	C
Q9NVA2	Septin-11	67	DDSY**K**PIVEYIDAQFEAYLQEELKIK	0.0210	4.5	S	C	1.1	C	S

Table 1. Identified peptides with PTM that meet the conditions of Anova *p*-value < 0.05 and Max fold change ≥ 2 when assessing the average NA between the study groups (S, NS) and the control (C) (continued)

Protein ID (UniProt)	Protein name (UniProt)	#	Sequence of modified peptide	Anova *p*-value of the peptide	Max fold change of the peptide	Group with the highest and lowest NA mean value of the peptide		Max fold change of the protein	Group with the highest and lowest NA mean value of the protein	
Q9ULV4	Coronin-1C	68	LHER**K**CEPIIMTVPR	0.0004	4.8	NS	C	1.4	C	NS
P04040	Catalase	69	**A**DSRDPASDQMQHWK	4.00E-05	3.8	NS	C	3.4	NS	C
P07197	Neurofilament medium polypeptide	70	**S**YTLDSLGNPSAYRR	0.0050	2.7	NS	C	1.5	NS	C
P16949	Stathmin	71	**A**SSDIQVK	0.0166	2.2	NS	C	2.1	NS	C
P17252	Protein kinase C alpha type	72	**A**DVFPGNDSTASQDVANR	0.0247	2.4	C	S	1.6	C	NS
P27816	Microtubule-associated protein 4	73	**A**DLSLADALTEPSPDIEGEIKR	1.50E-06	24.8	S	C	1.7	NS	C
Q16352	Alpha-internexin	74	**S**FGSEHYLCSSSSYR	0.0004	2.6	S	C	1.3	NS	C
		75	**S**FGSEHYLCSSSSYRK	0.0021	2.1	S	C			
Q9BY11	Protein kinase C and casein kinase substrate in neurons protein 1	76	**S**SSYDEASLAPEETTDSFWEVGNYKR	0.0003	3.3	C	NS	1.3	C	NS
Q9NQ66	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase beta-1	77	**A**GAQPGVHALQLKPVCVSDSLK	0.0447	2.4	C	NS	1.2	C	NS
Q9Y2J2	Band 4,1-like protein 3	78	**T**TESGSDSESKPDQEAEPQEAAGAQGR	1.50E-05	79.8	C	S	1.3	NS	C
Citrullination (R+0.98)										
O94811	Tubulin polymerization-promoting protein	79	AISSPTVS**R**LTDTTK	0.0057	5.3	C	S	1.3	NS	C
		80	AISSPTVS**R**LTDTTK	2.00E-06	5.3	C	S			
		81	E**R**FDPSGK	0.0224	2.5	C	NS			
P09543	2',3'-cyclic-nucleotide 3'-phosphodiesterase	82	STLA**R**VIVDK	5.99E-07	27.5	C	NS	1.6	NS	C
		83	TLFIL**R**GLPGSGK	0.0042	110.0	C	NS			
		84	TLFIL**R**GLPGSGK	4.00E-05	33.8	C	NS			
P12277	Creatine kinase B-type	85	VLTPELYAEL**R**AK	0.0179	2.3	C	NS	1.1	S	C
P50993	Sodium/potassium-transporting ATPase subunit alpha-2	86	ILD**R**CSTILVQGK	0.0058	2.5	C	S	1.2	C	NS
Q13885	Tubulin beta-2A chain	87	GHYTEGAELVDSVLDVV**R**K	0.0354	3.7	C	S	1.2	C	NS
Q8TAM6	Ermin	88	GHQAAEIEWLGF**R**K	2.06E-05	4.6	C	S	3.9	NS	C
Q9H4G4	hogenesis-related protein 1	89	EAQQYSEALAST**R**ILK	4.73E-06	9.7	C	S	1.9	NS	C

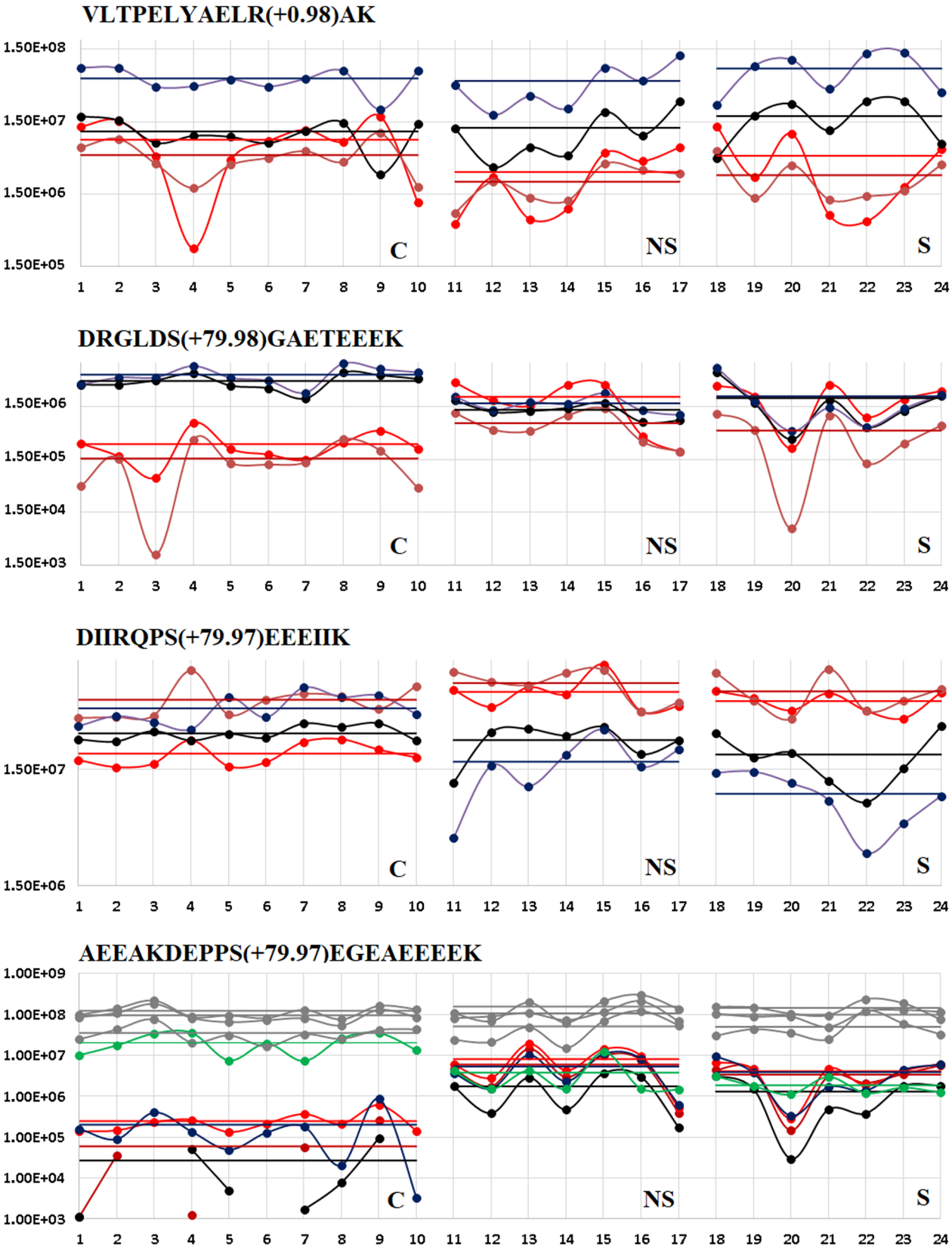

Figure 1. An example demonstrating NA changes between groups of samples (C, NS, and S) for four peptides. The abscissa axis shows sample numbers and the ordinate axis shows NA values (a logarithmic scale). Data for the 2+ ion of the modified peptide are shown in maroon, while 2+ ions are shown in red. Similarly, the 2+ and 3+ ions of the unmodified form of the same peptide are shown in black and blue. In the diagram for the peptide AEEAKDEPPS(+79.97)EGEAEEEEK, three 2+ ions of the same protein, lacking PTMs and missed tryptic cleavage sites are shown in gray. The 2+ ion of the peptide DEPPSEGEAEEEEK is shown in green.

are presented for both the modified form of the peptide and the unmodified form detected in the same sample. The proportion of the VLTPELYAELR(+0.98)AK peptide in the control group is comparable to the amount of the VLTPELYAELRAK peptide (without PTM), while in the NS and S groups, the amount of the peptide with PTM decreases. It should be noted that the VLTPELYAELRAK peptide obviously represents the "undercut" version of the peptide VLTPELYAELR; in the sample it was also identified with comparable NA values (6.5×10^8 for 2+ ions and 2.8×10^6 for 3+ ions). Another variant is the DRGLDS(+79.98)GAETEEEK peptide, where the control contained less phosphorylated peptide than the experimental groups, in which their abundance was basically equal. As in the previous case, the 2+ ion was registered in the samples for the GLDSGAETEEEK peptide (NA ~ 6.6×10^5). Considering that during trypsin hydrolysis one would expect that the number of "undercut" peptides (with missed tryptic cleavage sites) should be less than the peptides corresponding to complete tryptic hydrolysis, it is likely that a significant portion of the peptides has not been registered possibly due to the peptide ionization charge of 1+ charge (such ions were not registered in [8]). The peptide DIIRQPS(+79.97)EEEIIK is interesting due to the fact that the QPSEEEIIK peptide was not identified in any form; in this context, it should be noted that the identified phosphorylated peptide YKDIIRQPS(+79.97)EEEIIK (3+ ion, NA ~ 8.5×10^5) obviously originated due to two missed tryptic cleavages. However, no significant difference in its level was observed between the groups, although the same trend was noted: less phosphorylated peptide presented in the control group. All three peptides contain a large number of negatively charged amino acid residues, which may influence ionization.

Finally, let's consider the peptide AEEAKDEPPS(+79.97)EGEAEEEEK, discussed above. Excluding possible sample preparation differences in different groups, as well as alignment and identification errors, we have no reasonable explanation for why the amount of peptide with one missed tryptic cleavage site in both the phosphorylated form and without PTM is so much lower in the control group than in the NS and S groups. This issue requires targeted experimental verification. If we consider not the absolute NA values, but the ratio of NA values for 3+ ions for the peptide with PTM and the peptide without PTM (Fig. 2), the difference in mean values is insignificant (insufficient 2+ ion detection precludes an adequate comparison). For the remaining three peptides used in the example, the results are consistent with the data for absolute values. Unfortunately, it is not always possible to use this ratio, since the unmodified peptide may not be registered, as, for example, in cases of acetylation, methylation, or citrullination, when the unmodified peptide, in contrast to the modified one, is subject to trypsin hydrolysis, and the number of possibly missed tryptic cleavage sites can vary greatly from sample to sample.

The majority of peptides listed in Table 1 have phosphorylation as a PTM. For example, two peptides of the astrocytic phosphoprotein PEA-15 (PEA15; Q15121) phosphorylated at serine residues (DIIRQPSEEEIIK — S116, LTRIPSAK — S104) were identified. PEA15 is a small phosphoprotein that is involved in epileptogenesis; it protects astrocytes from apoptosis, and modulates cell survival and proliferation. These functions depend on differential phosphorylation, which regulates proliferative and/or apoptotic signals in astrocytes after status epilepticus [15]. Another example includes representatives of the family of microtubule-associated proteins (MAPs) (P10636, P11137, P27816, P46821, P78559, Q96JE9), which play an important role in brain development processes, particularly the formation of neurons and synapses, as well as myelination. Destabilization of microtubules affects brain functions associated with neurodegenerative and mental disorders, such as cognitive impairment, memory problems, and attention [16]. Phosphorylation of MAPs in response to various extracellular signals regulates neuronal functions [17]. In Table 1, there are four out of six MAPs (P11137, P46821, P78559, Q96JE9), containing peptides with phosphorylated residues. The cytoskeletal adapter protein, dematin (Q08495), is also an example of protein whose activity is regulated by phosphorylation. Dematin binds and assembles actin filaments and also acts as a major regulator of calcium mobilization [18]. Jupiter microtubule-associated protein homolog 1 (Q9UK76) is highly expressed in many human tissues, particularly in the brain; it contains phosphorylation sites and their phosphorylation promotes cell cycle progression and modulates DNA replication and repair processes [19].

Table 1 also contains a group of cytoskeletal proteins expressed in nerve cells and involved in maintaining their stability and proper conductivity. For example, proteins of the neurofilament family (P07196, P07197, P12036) are the main cytoskeletal proteins in neuronal axons. Interactions between neurofilaments and other cytoskeletal proteins regulate axon diameter and axoplasmic transport. Dysregulation of neurofilaments can lead to neuronal death and the development of epilepsy, as well as other diseases of the nervous system [20]. Stathmin (P16949) is an evolutionarily conserved protein involved in the regulation of microtubule dynamics. Increased stathmin levels and decreased microtubule stability, particularly in the insular cortex and hippocampus, may play an important role in the development of epileptic fear [21]. The protein septin-11 (Q9NVA2) is co-localized with microtubules and stress fibers in various epithelial cell lines, and changes in septin-11 solubility may disrupt cytoskeletal function and lead to cellular toxicity, a mechanism established for proteinopathies in neurodegenerative diseases [22].

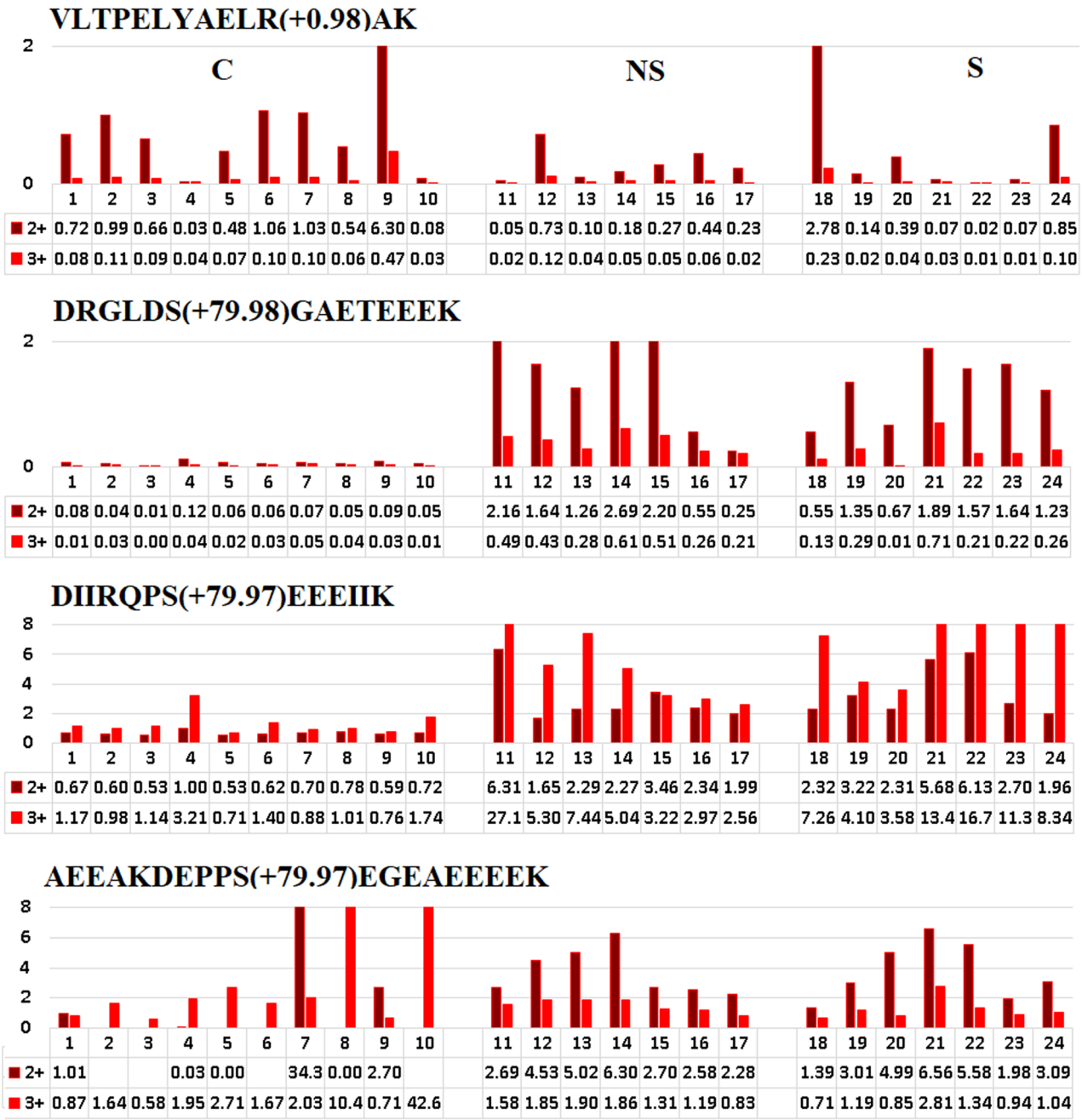

Figure 2. An example demonstrating changes in the ratio of NA values for 2+ and 3+ ions for a peptide with PTM and a peptide without PTM. The abscissa axis shows sample numbers, and the ordinate axis shows NA values.

Another cytoskeletal component, coronin-1 (Q9ULV4), is actively expressed in the adult central nervous system, binds F-actin, and plays an important role in cell migration and brain morphogenesis [23].

Another group includes proteins involved in neurogenesis, cell signaling, and other neuronal regulatory mechanisms. For example, the P13591 protein (neural intercellular adhesion molecule 1) provides recognition and adhesion of neurons; it participates in axon growth, neuronal synaptic reconstruction, and neuronal migration processes. Thus, the P13591 protein promotes neurogenesis and synaptic plasticity, for example, after a brain injury. In rats with epilepsy, it plays an important role in the impairment of spatial memory [24]. Secretogranin-1 (P05060) interacts and is secreted together with various hormones; it regulates the level of intracellular calcium, cellular signaling, in various (including hippocampal) cells; this is important in the context of various neurological diseases, such as Alzheimer's disease, epilepsy, and schizophrenia [25]. Proline-rich transmembrane protein 2 (Q7Z6L0) is responsible for neuronal stability; it negatively affects intrinsic excitability by causing pleiotropic paroxysmal syndromes, including epilepsy, kinesigenic dyskinesia, episodic ataxia, and migraine [26]. The synaptic protein rabphilin 3A (Q9Y2J0) is indirectly responsible for synaptic plasticity and

cognitive functions. Disturbances in the *RPH3A* gene, encoding rabphilin 3A, are associated with developmental disorders of the nervous system, manifested either as drug-resistant epilepsy with mental retardation or as autism spectrum disorder with learning disabilities [27]. Collapsin response mediator protein 2 (Q16555) is localized primarily in the nervous system, is highly conserved; it is required for stimulation of axon growth and maintenance of neuronal polarity in hippocampal neurons. A significant decrease in the level of this protein may indicate neurodegeneration, impaired neural plasticity and brain pathways in multiple system atrophy, and may be involved in the etiology of epilepsy and age-related cognitive decline [28]. Isoaspartyl peptidase/L-asparaginase (Q7L266) is an enzyme that may be involved in the formation of the neurotransmitter amino acid L-aspartate, which can act as an excitatory neurotransmitter in some areas of the brain, and also reduces the accumulation of some toxic peptides in the brain and other mammalian tissues [29]. Band 4.1-like protein 3 (Q9Y2J2) plays a critical role in oligodendrocyte differentiation, and its loss impairs oligodendroglial function and cell survival in mice. Biallelic variants of the gene encoding this protein cause impaired oligodendrocyte myelination, accompanied by seizures in patients [30]. Tubulin polymerization-promoting protein (O94811) is expressed exclusively in oligodendrocytes in the normal brain. Its nonphysiological levels are closely linked to the etiology of Parkinson's disease, multiple system atrophy, multiple sclerosis, and glioma [31]. Alpha-internexin (Q16352) is characterized by early expression, which may stabilize neurons and their processes and provide a scaffold for the co-assembly of other proteins during development. Alpha-internexin is the only expressed intermediate filament protein, suggesting a role for this protein in neuronal maturation and regeneration after injury [32].

Reactive oxygen species and oxidative stress are involved in the pathogenesis of some neurodegenerative diseases and brain injuries. Catalase (P04040), an enzyme responsible for hydrogen peroxide decomposition, remains an important target for antioxidant therapy [33]. Phosphoglycerate kinase-1 (P00558), a key enzyme in the glycolytic pathway, is involved in biological processes such as angiogenesis, autophagy, and DNA repair. Deficiency of phosphoglycerate kinase-1 leads to hemolytic anemia, rhabdomyolysis, myopathy, and central nervous system damage, including idiopathic stroke, stroke-like episodes, and epilepsy [34]. Iron-bound fibrinogen alpha chain (P02671) accelerates plasma coagulation in patients with various diseases accompanied by increased heme oxygenase activity; accumulates during the deposition of amyloid-β in nerve cells and blood vessels of the brain and affects the progression of Alzheimer's disease [35]. The alpha-2 subunit of Na^+/K^+-ATPase (P50993) is an enzymatic version of the sodium-potassium pump, which is responsible for various important cellular functions, such as maintaining cation balance and restoring the resting membrane potential in neurons [36]. Golgi-associated protein 1, associated with plant pathogenesis (Q9H4G4, GAPR-1), belongs to the superfamily of cysteine-rich proteins. It has been shown that this protein efficiently binds to prefibrillar oligomeric structures of β-amyloid in the early stages of fibril formation [37]. Protein kinase C alpha-type (P17252) is activated in response to a variety of stimuli and is translocated from the cytosol to specialized cellular compartments (nucleus, caveolae, etc.), where it is obviously involved in various cellular functions such as proliferation, apoptosis, differentiation, motility, and inflammation [38].

It should be noted that all other proteins from Table 1 not listed in this section are also considered in the literature and are directly involved in one or more important (patho)biological processes, such as neuroprotection, neurogenesis, neurodegeneration, epileptogenesis, seizure activity in epilepsy, atherogenesis in diseases of the nervous system, and mental illness in humans [9, 39–57].

In conclusion, our analysis resulted in identification of PTMs of proteins that may be important in the pathogenesis of neurological diseases. The obtained results require further verification, either using more accurate methods than label-free quantitative proteomic analysis, or using independent methods adapted to detect changes in PTM levels.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Supplementary materials are available in the electronic version at the journal site (pbmc.ibmc.msk.ru).

REFERENCES

1. *Skvortsov V.S., Ivanova Ya.O., Voronina A.I.* (2021) The bioinformatic identification of proteins with varying levels of post-translational modifications in experimental ischemic stroke in mice. Biomeditsinskaya Khimiya, **67**(6), 475–484. DOI: 10.18097/PBMC20216706475
2. *Voronina A.I., Miroshnichenko Yu.V., Skvortsov V.S.* (2024) Bioinformatic identification of proteins with altered PTM levels in a mouse line established to study the mechanisms of the development of fibromuscular dysplasia. Biomeditsinskaya Khimiya, **70**(4), 248–255. DOI: 10.18097/PBMC20247004248
3. *Martens L., Hermjakob H., Jones P., Adamski M., Taylor C., States D., Gevaert K., Vandekerckhove J., Apweiler R.* (2005) PRIDE: the proteomics identifications database. Proteomics, **5**(13), 3537–3545. DOI: 10.1002/pmic.200401303
4. *Salovska B., Liu Y.* (2023) Post-translational modification and phenotype. Proteomics, **23**(3–4), e2200535. DOI: 10.1002/pmic.202200535
5. *Yamaguchi K., Hu Y.-Y., Kawajiri K., Itakura M., Nakashima F., Shibata T., Uchida K.* (2025) Adductome-based identification of lysine monomethylation as a key post-translational protein modification in autoimmune diseases. J. Biol. Chem., **301**(10), 110684. DOI: 10.1016/j.jbc.2025.110684
6. *Tuli L., Tsai T.-H., Varghese R.S., Xiao J.F., Cheema A., Ressom H.W.* (2012) Using a spike-in experiment to evaluate analysis of LC-MS data. Proteome Sci., **10**, 13. DOI: 10.1186/1477-5956-10-13
7. *Ramazi S., Zahiri J.* (2021) Posttranslational modifications in proteins: resources, tools and prediction methods. Database (Oxford), **2021**, baab012. DOI: 10.1093/database/baab012
8. *Mathoux J., Wilson M.M., Srinivas S., Litovskich G., Villalba B.L., Tran C., Kesavan J., Harnett A., Auer T., Sanz-Rodriguez A., Alkhayyat M.Kh.A.E., Sullivan M., Liu Z., Huang Y., Lacey A., Delanty N., Cryan J., Brett F.M., Farrell M.A., O'Brien D.F., Casillas-Espinosa P.M., Jimenez-Mateos E.M., Glennon J.C., Canavan M., Henshall D.C., Brennan G.P.* (2025) N6-methyladenosine (m6A) dysregulation contributes to network excitability in temporal lobe epilepsy. JCI Insight, **10**(14), e188612. DOI: 10.1172/jci.insight.188612
9. *Chen Y., Nie Q., Song T., Zou X., Li Q., Zhang P.* (2025) Integrated proteomics and lipidomics analysis of hippocampus to reveal the metabolic landscape of epilepsy. ACS Omega, **10**(9), 9351–9367. DOI: 10.1021/acsomega.4c10085
10. *Ma B., Zhang K., Hendrie C., Liang C., Li M., Doherty-Kirby A., Lajoie G.* (2003) PEAKS: Powerful software for peptide *de novo* sequencing by tandem mass spectrometry. Rapid Commun. Mass Spectrom., **17**(20), 2337–2342. DOI: 10.1002/rcm.1196
11. *The UniProt Consortium* (2020) UniProt: The universal protein knowledgebase in 2021. Nucleic Acids Res., **49**(D1), D480–D489. DOI: 10.1093/nar/gkaa1100
12. Progenesis LC-MS version 4.0, Nonlinear Dynamics, Newcastle upon Tyne, UK.
13. *Skvortsov V.S., Alekseychuk N.N., Miroshnichenko Yu.V., Rybina A.V.* (2019) The prediction of the ion fraction of the peptide with selected charge in mass spectrometry with positive electrospray ionization. Biomedical Chemistry: Research and Methods, **2**(4), e00100. DOI: 10.18097/BMCRM00100
14. *Balmik A.A., Chinnathambi S.* (2021) Methylation as a key regulator of Tau aggregation and neuronal health in Alzheimer's disease. Cell Commun. Signal., **19**, 51. DOI: 10.1186/s12964-021-00732-z
15. *Park J.-Y., Kang T.-C.* (2018) The differential roles of PEA15 phosphorylations in reactive astrogliosis and astroglial apoptosis following status epilepticus. Neurosci. Res., **137**, 11–22. DOI: 10.1016/j.neures.2018.02.003
16. *Chang Q., Yang H., Wang M., Wei H., Hu F.* (2018) Role of microtubule-associated protein in autism spectrum disorder. Neurosci. Bull., **34**(6), 1119–1126. DOI: 10.1007/s12264-018-0246-2
17. *Sanchez C., Díaz-Nido J., Avila J.* (2000) Phosphorylation of microtubule-associated protein 2 (MAP2) and its relevance for the regulation of the neuronal cytoskeleton function. Prog. Neurobiol., **61**(2), 133–168. DOI: 10.1016/s0301-0082(99)00046-5
18. *Fritz D.I., Ding Y., Merrill-Skoloff G., Flaumenhaft R., Hanada T., Chishti A.H.* (2023) Dematin regulates calcium mobilization, thrombosis, and early Akt activation in platelets. Mol. Cell. Biol., **43**(6), 283–299. DOI: c10.1080/10985549.2023.2210033
19. *Li H., Fan S., Gong Z., Chan J.Y.K., Tong M.C.F., Chen G.G.* (2024) Role of hematological and neurological expressed 1 (HN1) in human cancers. Crit. Rev. Oncol. Hematol., **201**, 104446. DOI: 10.1016/j.critrevonc.2024.104446
20. *Xin Y., Lin G., Hua T., Liang J., Sun T., Wu X.* (2023) The altered expression of cytoskeletal and synaptic remodeling proteins during epilepsy. Open Life Sci., **18**, 20220595. DOI: 10.1515/biol-2022-0595
21. *Zhang L., Feng D., Tao H., De X., Chang Q., Hu Q.* (2015) Increased stathmin expression strengthens fear conditioning in epileptic rats. Biomed. Rep., **3**(1), 28–32. DOI: 10.3892/br.2014.386
22. *Gozal Y.M., Seyfried N.T., Gearing M., Glass J.D., Heilman C.J., Wuu J., Duong D.M., Cheng D., Xia Q., Rees H.D., Fritz J.J., Cooper D.S., Peng J., Levey A.I., Lah J.J.* (2011) Aberrant septin 11 is associated with sporadic frontotemporal lobar degeneration. Mol. Neurodegener., **6**, 82. DOI: 10.1186/1750-1326-6-82
23. *Thal D., Xavier C.-P., Rosentreter A., Linder S., Friedrichs B., Waha A., Pietsch T., Stumpf M., Noegel A., Clemen C.* (2008) Expression of coronin-3 (coronin-1C) in diffuse gliomas is related to malignancy. J. Pathol., **214**(4), 415–424. DOI: 10.1002/path.2308
24. *Kong Q., Min X., Sun R., Gao J., Liang R., Li L., Chu X.* (2016) Effects of pharmacological treatments on hippocampal NCAM1 and ERK2 expression in epileptic rats with cognitive dysfunction. Oncol. Lett., **12**(3), 1783–1791. DOI: 10.3892/ol.2016.4882
25. *Nicolay N.H., Hertle D., Boehmerle W., Heidrich F.M., Yeckel M., Ehrlich B.E.* (2007) Inositol 1,4,5 trisphosphate receptor and chromogranin B are concentrated in different regions of the hippocampus. J. Neurosci. Res., **85**(9), 2026–2036. DOI: 10.1002/jnr.21328
26. *Franchi F. Marte A., Corradi B., Sterlini B., Alberini G., Romei A., de Fusco A., Vogel A., Maragliano L., Baldelli P., Corradi A., Valente P., Benfenati F.* (2023) The intramembrane COOH-terminal domain of PRRT2 regulates voltage-dependent Na^+ channels. J. Biol. Chem., **299**(5), 104632. DOI: 10.1016/j.jbc.2023.104632
27. *Barzasi M., Spinola A., Costa A., Pavinato L., Brusco A., Marcello E., DiLuca M., Gardoni F.* (2025) Arg209Lys and Gln508His missense variants in Rabphilin 3A cause pre- and post-synaptic dysfunctions at excitatory glutamatergic synapses. Sci. Rep., **15**, 8698. DOI: 10.1038/s41598-025-93403-9

28. *Zhu J.X., Aswad D.W.* (2024) Isoaspartate formation and irreversible aggregation of collapsin response mediator protein 2: implications for the etiology of epilepsy and age-related cognitive decline. Amino Acids, **57**, 5. DOI: 10.1007/s00726-024-03435-0
29. *Cantor J.R., Stone E.M., Chantranupong L., Georgiou G.* (2009) The human asparaginase-like protein 1 hASRGL1 is an Ntn hydrolase with beta-aspartyl peptidase activity. Biochemistry, **48**(46), 11026–11031. DOI: 10.1021/bi901397h
30. *Werren E.A., Rodriguez Bey G., Majethia P., Kaur P., Patil S.J., Kekatpure M.V., Afenjar A., Qebibo L., Burglen L., Tomoum H., Demurger F., Duborg C., Siddiqui S., Tsan Y.-C., Abdullah U., Ali Z., Saadi S.M., Baig S.M., Houlden H., Maroofian R., Padiath Q.S., Bielas S.L., Shukla A.* (2024) Biallelic EPB41L3 variants underlie a developmental disorder with seizures and myelination defects. Brain, **147**(12), 4033–4042. DOI: 10.1093/brain/awae299
31. *Olah J., Bertrand P., Ovadi J.* (2017) Role of the microtubule-associated TPPP/p25 in Parkinson's and related diseases and its therapeutic potential. Expert Rev. Proteomics, **14**(4), 301–309. DOI: 10.1080/14789450.2017.1304216
32. *Liu X.-Y., Yang J.-L., Chen L.-J., Zhang Y., Yang M.-L., Wu Y.-Y., Li F.-Q., Tang M.-H., Liang S.-F., Wei Y.-Q.* (2008) Comparative proteomics and correlated signaling network of rat hippocampus in the pilocarpine model of temporal lobe epilepsy. Proteomics, **8**(3), 582–603. DOI: 10.1002/pmic.200700514
33. *Singhal A., Morris V.B., Labhasetwar V., Ghorpade A.* (2013) Nanoparticle-mediated catalase delivery protects human neurons from oxidative stress. Cell Death Dis., **4**(11), e903. DOI: 10.1038/cddis.2013.362
34. *Guimarães T.G., Parmera J.B., Castro M.A.A., Cury R.G., Barbosa E.R., Kok F.* (2024) X-Linked levodopa-responsive parkinsonism-epilepsy syndrome: a novel PGK1 mutation and literature review. Mov. Disord. Clin. Pract., **11**(5), 556–566. DOI: 10.1002/mdc3.13992
35. *Nielsen V.G., Jacobsen W.K.* (2016) Iron modulates the alpha chain of fibrinogen. Biometals, **29**(2), 235–238. DOI: 10.1007/s10534-016-9909-5
36. *Hernández-R J.* (1992) Na+/K(+)-ATPase regulation by neurotransmitters. Neurochem. Int., **20**(1), 1–10. DOI: 10.1016/0197-0186(92)90119-c
37. *Olrichs N.K., Mahalka A.K., Kaloyanova D., Kinnunen P.K., Bernd H.J.* (2014) Golgi-associated plant pathogenesis related protein 1 (GAPR-1) forms amyloid-like fibrils by interaction with acidic phospholipids and inhibits a aggregation. Amyloid, **21**(2), 88–96. DOI: 10.3109/13506129.2014.882304
38. *Nakashima S.* (2002) Protein kinase C alpha (PKC alpha): regulation and biological function. J. Biochem., **132**(5), 669–675. DOI: 10.1093/oxfordjournals.jbchem.a003272
39. *Petersen S.L., Intlekofer K.A., Moura-Conlon P.J., Brewer D.N., del Pino Sans J., Lopez J.A.* (2013) Novel progesterone receptors: neural localization and possible functions. Front. Neurosci., **7**, 164. DOI: 10.3389/fnins.2013.00164
40. *Fedotcheva T.A., Shimanovsky N.L.* (2025) Neurosteroids progesterone and dehydroepiandrosterone: molecular mechanisms of action in neuroprotection and neuroinflammation. Pharmaceuticals (Basel), **18**(7), 945. DOI: 10.3390/ph18070945
41. *Huang Z., Shen S., Han X., Li W., Luo W., Lin L., Xu M., Wang Y., Huang W., Wu G., Liang G.* (2023) Macrophage DCLK1 promotes atherosclerosis via binding to IKKβ and inducing inflammatory responses. EMBO Mol. Med., **15**(5), e17198. DOI: 10.15252/emmm.202217198
42. *Mastroeni D., Sekar S., Nolz J., Delvaux E., Lunnon K., Mill J., Liang W.S., Coleman P.D.* (2017) ANK1 is up-regulated in laser captured microglia in Alzheimer's brain; the importance of addressing cellular heterogeneity. PLOS One, **12**(7), e0177814. DOI: 10.1371/journal.pone.0177814
43. *Wang X., Chen G., Wan B., Dong Z., Xue Y., Luo Q., Wang D., Lu Y., Zhu L.* (2022) NRF1-mediated microglial activation triggers high-altitude cerebral edema. J. Mol. Cell Biol., **14**(5), mjac036. DOI: 10.1093/jmcb/mjac036
44. *Blondiaux A., Jia S., Annamneedi A., Çalışkan G., Nebel J., Montenegro-Venegas C., Wykes R.C., Fejtova A., Walker M.C., Stork O., Gundelfinger E.D., Dityatev A., Seidenbecher C.I.* (2023) Linking epileptic phenotypes and neural extracellular matrix remodeling signatures in mouse models of epilepsy. Neurobiol. Dis., **188**, 106324. DOI: 10.1016/j.nbd.2023.106324
45. *Sun Z.M., Chen Q., Li M.H., Ma W.N., Zhao X.Y., Huang Z.* (2019) Chronic phosphoproteomic in temporal lobe epilepsy mouse models induced by kainic acid. Beijing Da Xue Xue Bao Yi Xue Ban, **51**(2), 197–205. DOI: 10.19723/j.issn.1671-167X.2019.02.001
46. *Liu X.-B., Murray K.D.* (2012) Neuronal excitability and calcium/calmodulin-dependent protein kinase type II: location, location, location. Epilepsia, **53**(Suppl 1), 45–52. DOI: 10.1111/j.1528-1167.2012.03474.x
47. *Cai S., Li J., Wu Y., Jiang Y.J.* (2020) *De novo* mutations of TUBB2A cause infantile-onset epilepsy and developmental delay. Hum. Genet., **65**(7), 601–608. DOI: 10.1038/s10038-020-0739-5
48. *Schoonjans A.-S., Meuwissen M., Reyniers E., Kooy F., Ceulemans B.* (2016) PLCB1 epileptic encephalopathies; review and expansion of the phenotypic spectrum. Eur. J. Paediatr. Neurol., **20**(3), 474–479. DOI: 10.1016/j.ejpn.2016.01.002
49. *Fard M.K., van der Meer F., Sanchez P., Cantuti-Castelvetri L., Mandad S., Jäkel S., Fornasiero E.F., Schmitt S., Ehrlich M., Starost L., Kuhlmann T., Sergiou C., Schultz V., Wrzos C., Brück W., Urlaub H., Dimou L., Stadelmann C., Simons M.* (2017) BCAS1 expression defines a population of early myelinating oligodendrocytes in multiple sclerosis lesions. Sci. Transl. Med., **9**(419), eaam7816. DOI: 10.1126/scitranslmed.aam7816
50. *Hu S., Tang Y., Li X., Li W., Zeng Y., Jiang M., Chen R., Zheng P., Yang L., Song Z., Xie D., Chen Y., Yuan Y.* (2024) Hsp90aa1/JUN/Ccl2 regulatory axis mediates migration and differentiation of NSPCs, promoting the onset and progression of early post-ischemic stroke epilepsy. Neurobiol. Dis., **200**, 106635. DOI: 10.1016/j.nbd.2024.106635
51. *Gu C., Wang F., Zhang Y.-T., Wei S.-Z., Liu J.-Y., Sun H.-Y., Wang G.-H., Liu C.-F.* (2021) Microglial MT1 activation inhibits LPS-induced neuroinflammation via regulation of metabolic reprogramming. Aging Cell, **20**(6), e13375. DOI: 10.1111/acel.13375
52. *Ying Z., Najm I., Nemes A., Pinheiro-Martins A.P., Alexopoulos A., Gonzalez-Martinez J., Bingaman W.* (2014) Growth-associated protein 43 and progressive epilepsy in cortical dysplasia. Ann. Clin. Transl. Neurol., **1**(7), 453–461. DOI: 10.1002/acn3.69
53. *Xiao L., Chen W., Guo W., Li H., Chen R., Chen Q.* (2025) Exploring the mechanism of action of *Phyllanthus emblica* in the treatment of epilepsy based on network pharmacology and molecular docking. Medicine (Baltimore), **104**(7), e41414. DOI: 10.1097/MD.0000000000041414

54. *Fan B., Gu J.-Q., Yan R., Zhang H., Feng J., Ikuyama S.* (2013) High glucose, insulin and free fatty acid concentrations synergistically enhance perilipin 3 expression and lipid accumulation in macrophages. Metabolism, **62**(8), 1168–1179. DOI: 10.1016/j.metabol.2013.02.013
55. *Wesseling H., Rahmoune H., Tricklebank M., Guest P.C., Bahn S.* (2015) A targeted multiplexed proteomic investigation identifies ketamine-induced changes in immune markers in rat serum and expression changes in protein kinases/phosphatases in rat brain. J. Proteome Res., **14**(1), 411–421. DOI: 10.1021/pr5009493
56. *Tavakkoli A., Abnous K., Vahdati Hassani F., Hosseinzadeh H., Birner-Gruenberger R., Mehri S.* (2020) Alteration of protein profile in cerebral cortex of rats exposed to bisphenol A: a proteomics study. Neurotoxicology, **78**, 1–10. DOI: 10.1016/j.neuro.2020.01.013
57. *Wang T., Jia L., Lv B., Liu B., Wang W., Wang F., Yang G., Bu X., Yao L., Zhang B.* (2011) Human Ermin (hErmin), a new oligodendrocyte-specific cytoskeletal protein related to epileptic seizure. Brain Res., **1367**, 77–84. DOI: 10.1016/j.brainres.2010.10.003

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ИДЕНТИФИКАЦИЯ БЕЛКОВ С МЕНЯЮЩИМСЯ УРОВНЕМ ПОСТТРАНСЛЯЦИОННЫХ МОДИФИКАЦИЙ ПРИ ВИСОЧНОЙ ЭПИЛЕПСИИ У ЧЕЛОВЕКА

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Проанализированы масс-спектрометрические данные, полученные при анализе тканей гиппокампа пациентов склеротической и несклеротической височной эпилепсии и без неё для выявления различий в уровне посттрансляционных модификаций (ПТМ) белков. Исходные протеомные данные, полученные Mathoux и соавт. [DOI: 10.1172/jci.insight.188612], были депонированы в репозитории PRIDE (идентификатор PXD064519). В результате сравнительного протеомного анализа образцов отобрано 53 белка с ПТМ (фосфорилирование, метилирование, ацетилирование и цитруллинирование), имеющих существенные изменения в уровне отдельных модифицированных пептидов. Согласно литературным данным, все 53 белка вовлечены в процессы, связанные с неврологическими заболеваниями в целом или эпилептогенезом в частности. Проведённый анализ позволил выявить ПТМ белков, которые могут играть важную роль в патогенезе развития неврологических заболеваний.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: посттрансляционные модификации; эпилепсия; биоинформатика

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