IRIS - Archivio Istituzionale dell'Università degli Studi di Sassari

Humoral immunity response to HERV-K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases

Questa è la versione Post print del seguente articolo:

Original
Humoral immunity response to HERV-K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases / Arru, G., Mameli, G., Deiana, G.A., Rassu, A.L., Piredda, R., Sechi, E., Caggiu, E., Bo, M., Nako, E., Urso, D., Mariotto, S., Ferrari, S., Zanusso, G., Monaco, S., Sechi, G., Sechi, L.A.. - In: EUROPEAN JOURNAL OF NEUROLOGY. - ISSN 1351-5101. - 25:8(2018), pp. 1076-1085. [10.1111/ene.13648]

Availability:
This version is available at: 11388/205521 since: 2021-02-25T13:39:33Z

Publisher:

Published
DOI:10.1111/ene.13648

Terms of use:

Chiunque può accedere liberamente al full text dei lavori resi disponibili come “Open Access”.

Publisher copyright

note finali coverpage

(Article begins on next page)

12 October 2026

DR. DANIELE URSO (Orcid ID : 0000-0002-4503-0110)

DR. SARA MARIOTTO (Orcid ID : 0000-0002-7806-3103)

PROF. LEONARDO ANTONIO SECHI (Orcid ID : 0000-0003-0566-2049)

Article type : Original Article

Humoral immunity response to HERV-K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases

Giannina Arru,[1°] Giuseppe Mameli,[2°] Giovanni Andrea Deiana,[1] Anna Laura Rassu,[1] Rosanna Piredda,[1] Elia Sechi,[1] Elisa Caggiu,[2] Marco Bo, [2] Enri Nako,[1] Daniele Urso,[1] Sara Mariotto,[3] Sergio Ferrari,[3] Gianluigi Zanusso,[3] Salvatore Monaco,[3] GianPietro Sechi [1*] and Leonardo A Sechi [2*]

1. Department of Clinical and Experimental Medicine, University of Sassari, Viale San Pietro 8, 07100 Sassari, Italy.

2. Department of Biomedical Sciences, University of Sassari, Viale San Pietro 43b, 07100 Sassari, Italy

3. Department of Neurosciences, University of Verona, Piazzale LA Scuro 10, 37134 Verona, Italy.

°The authors contributed equally to the paper.

*Correspondence and requests should be addressed to Leonardo A. Sechi and GianPietro Sechi

(email: sechila@uniss.it; gpsechi@uniss.it)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.13648

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Running title: Immunity response to HERV-K/W in neurological diseases.

Keywords: HERV-K, HERV-W, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer disease, humoral immunity

Conflict of interest: The authors declare no conflict of interest.

Abstract

Background and purpose: Human endogenous retroviruses-K/W seem play a role in fostering and exacerbation of some neurological diseases, including amyotrophic lateral sclerosis (ALS). Given these findings, we investigated the immunity response against HERV-K and HERV-W envelope surface (env-su) glycoprotein antigens in serum and cerebrospinal fluid (CSF) of ALS, multiple sclerosis (MS) and Alzheimer's disease (AD) patients, and in healthy controls (HCs).

Methods: Four antigenic peptides derived respectively from HERV-K and HERV-W env surface proteins were studied in twenty-one definite or probable ALS, twenty-six possible or definite relapsing-remitting (RR) MS, eighteen patients with AD and thirty-nine HCs. An indirect ELISA was set up to detect specific antibodies (Abs) against env surface peptides.

Results: Among the measured levels of Abs against the four different HERV-K peptide fragments, HERV-K env-su $_{19\text{-}37}$ only was significantly elevated in ALS compared to other groups, both in serum and CSF. Instead, among the Abs levels directed against the four different HERV-W peptide fragments, only HERV-W env-su $_{93\text{-}108}$ and HERV-W env-su $_{248\text{-}262}$ were significantly elevated, in serum and CSF of MS, compared to other groups. In ALS patients, the HERV-K env-su $_{19\text{-}37}$

This article is protected by copyright. All rights reserved.

antibodies levels were significantly correlated with clinical measures of disease severity, both in serum and CSF.

Conclusions: Increased circulating levels of Abs directed against the HERV-W env-su $_{93\text{-}108}$ and HERV-W env-su $_{248\text{-}262}$ peptide fragments could serve as possible biomarkers in patients with MS. Similarly, increased circulating levels of Abs directed against the HERV-K env-su$_{19\text{-}37}$ peptide fragment could serve as possible early novel biomarker in patients with ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive fatal neurodegenerative disorder, which leads to loss of cortical and spinal motor neurons [1]. Although several genetic forms of ALS have been documented, the etiology of the sporadic form of this pathology remains unknown [1]. Recently, in the pathophysiology of ALS, a possible retroviral implication has been hypothesized since some murine and human retroviruses can cause similar neurodegeneration, and in serum of patients with sporadic ALS high activity levels of the retroviral enzyme reverse transcriptase (RT) have been demonstrated [2-5]. In particular, the exogenous retrovirus human T-lymphotropic virus-1 (HTLV-1) has been detected by its RT activity in post-mortem brain tissue of Guamanian ALS patients [6], and human endogenous retroviral (HERV) sequences have been detected in motor neurons and other cells of the central nervous system (CNS) [6]. Such RT analysis does not identify the origin of the enzyme, but it indicates the possible involvement of HERV-encoded elements. Different research groups focused on HERV expression in ALS patients studying serum, muscle biopsy and brain specimens. Hadlock et al. showed that more than half of sporadic ALS patients presented serum IgG reactivity against the HERV-K (HML-2) gag protein [7]. These patients disclosed a 10-fold reduction of viral RNA in peripheral blood mononuclear

This article is protected by copyright. All rights reserved.

Accepted Article

cells, suggesting an effective and ongoing immune response against HERV-K [7]. Increased env and gag expression levels have been reported for HERV-W in ALS muscle biopsies [8], and for HERV-K pol in ALS post-mortem brain tissue [9]. In a recent study, Li et al. demonstrated that HERV-K env protein is able to induce damage in human motor neurons [10]. Moreover, in motor neurons of transgenic animals the amplified HERV-K env gene expression led to progressive motor dysfunction, decreased synaptic activity in pyramidal neurons, and DNA damage [10]. The authors concluded that increased HERV-K expression in neurons of patients with ALS might contribute to neurodegeneration and disease pathogenesis. On the other hand, HERV-W env protein expression has been found in association with multiple sclerosis (MS) and seems to correlate with the course and prognosis of the disease [11]. In MS, this envelope protein may act as a super-antigen that activates a pro-inflammatory and immune-mediated cascade fostering MS [11-14]. Of note, the specific humoral immune response against HERV-W env-su glycoprotein antigens found in MS is widely missing in neuromyelitis optica spectrum disorder [15]. In the present study, we investigated the IgG antibody response against four antigenic peptides derived respectively from HERV-K and HERV-W env surface proteins in serum and cerebrospinal fluid (CSF) of patients with ALS, MS, Alzheimer's disease (AD) and in serum of healthy controls (HCs). Moreover, in ALS patients, the levels of the four HERV-K antibodies evaluated in serum and CSF have been correlated with clinical measures of disease severity.

Results

Serum analysis, CSF analysis, CSF/Serum Albumin ratio and IgG index.

Serum inflammatory laboratory parameters as erythrocyte sedimentation rate, C-reactive protein and complete blood count were within normal limits in the 3 groups, as also the results of cytochemical analysis of CSF, including the white blood cell count. Two or more CSF-restricted oligoclonal bands

This article is protected by copyright. All rights reserved.

Accepted Article

(OCB) were detected in all MS patients (100%) and none (0%) in patients with ALS and AD, thus any correlation between OCB and the occurrence of disease specific antibodies in patients with ALS and MS seems unlikely.

For all samples, IgG index as the marker of intrathecal IgG synthesis, CSF/serum albumin ratio (Q Alb) as a marker of blood-brain barrier (BBB) integrity and percentage of samples with different type of BBB damage were calculated and shown in Table 1 (supplementary file). No statistically significant damage was observed at BBB in MS patients compared to other groups, as evidenced by the IgG index and the CFS/albumin ratio.

Elisa

Antibodies (Abs) against HERV-K env-su$_{19-37}$ were found in the sera of 81% ALS patients, whereas only 3% of HCs were positive and none of MS and AD patients (AUC=0.96, p<0.0001, ALS vs MS and ALS vs AD, p<0.0001) (Fig. 1A). Abs against HERV-K env-su $_{19-37}$ were found in CSF of 86% ALS, 50% of MS and 39% of AD (AUC=0.75, ALS vs MS p=0.0026; ALS vs AD p<0.00014) (Fig. 1B). Regarding HERV-K env-su $_{109-126}$ peptide, 95% of ALS patients, 69% of MS, 72% of AD and 0% of HCs were positive for Abs in sera (AUC=0.997, p<0.0001, ALS vs MS and ALS vs AD, p <0.0001) (Fig. 1C), whereas 81% of ALS patients, 42% of MS, and 56% among AD patients reacted against HERV-K env-su $_{109-126}$ in CSF, (AUC=0.65, no statistical differences were observed between ALS vs MS or ALS vs AD) (Fig. 1D). No differences between ALS, MS and AD were observed when antibodies against HERV-K env-su$_{164-186}$ were searched in sera of ALS patients (62%), MS (42%), AD (56%) and in 5% of HCs (AUC=0.73, p=0.0018) (Fig. 1E). The same trend was observed in CSF where 43% of ALS, 81% MS, and 56% AD patients showed Abs positivity against HERV-K env-su$_{164-186}$ (AUC=0.63) (Fig. 1F).

Regarding HERV-K env-su$_{205-226}$, 71% of ALS patients, 85% of MS, 100% of AD and 10% of HCs were positive for Abs in sera (AUC=0.90, p<0.0001) (Fig. 1G) and 57% of ALS, 50% of MS, and 28% of AD patients showed CSF Ab positivity against HERV-K env-su$_{205-226}$ (AUC=0.53) (Fig. 1H).

This article is protected by copyright. All rights reserved.

Abs positivity against HERV-W env-su$_{93-108}$ peptide was searched as well and we found 62% of MS patients positive whereas only 38% of ALS, 28% of AD and 21% of HCs were also positive (AUC=0.78, p<0.001, MS vs ALS, p =0.044, MS vs AD p =0.016) in serum (Fig. 2A). In CSF we observed the same trend where 62% of MS patients, 14% of ALS and 17% of AD were positive for Abs against HERV-W env-su $_{93-108}$ (AUC=0.7, p=0.0008, MS vs ALS, p =0.001; MS vs AD, p=0.034) (Fig. 2B). Regarding antibody reactivity against HERV-W env-su$_{129-143}$, 50% of MS patients, 10% of ALS, 44% of AD patients and 26% of HCs were positive in serum (AUC=0.67, p=0.0027, MS vs ALS, p=0.002, MS vs AD was not significant) (Fig. 2C); whereas no statistical differences were observed in CSF where 46% of MS patients, 33% ALS, and 22% of AD patients were positive (AUC = 0.53) (Fig. 2D). Abs positivity against HERV-W env-su$_{161-180}$ was found in 50% of MS patients, 43% of ALS, 44% of AD and 28% of HCs in serum (AUC=0.74, p=0.0027) (Fig. 2E), in CSF we observed a statistical difference among positivity in MS (58%), ALS (14%) but not in AD patients (28%) (AUC=0.7, p=0.058, MS vs ALS p=0.019, MS vs AD was not significant) (Fig. 2F). Finally, serum reactivity against HERV-W env-su$_{248-262}$ peptide was observed in 69% of MS patients, however only 5% of ALS, 6% of AD and 18% of HCs were positive (AUC=0.82, p<0.0001, MS vs ALS and MS vs AD p <0.0001) (Fig. 2G); a similar difference was found in CSF, where 65% of MS patients, 0% of ALS and 17 % of AD were positive for HERV-W env-su$_{248-262}$ (AUC=0.89, p<0.0001, MS vs ALS, p <0.0001; MS vs AD, p<0.0001), (Fig. 2H).

We also searched for the occurrence of a double positivity of autoantibodies in serum and CSF in the 3 groups, in order to find a peptide suitable to serve as possible serum biomarker also predictive of a CSF positivity. Sixteen out of 17 sera antibody positive to HERV-K env-su$_{19-37}$ were also positive in CSF (94%). This finding may indicate that this peptide could represent a possible serum biomarker in ALS pathology (p<0.0001), (Table 2).

Regarding HERV-W env peptides both HERV-W env-su$_{93-108}$ and HERV-W env-su$_{248-262}$ peptides could serve as possible biomarkers of disease in MS but not in ALS and AD. A double positivity in serum and CSF was found in 75 % of HERV-W env-su$_{93-108}$ and 83% of HERV-W env-su$_{248-262}$ (p<0.0001) (Table 2).

This article is protected by copyright. All rights reserved.

Accepted Article

Correlation analyses

A correlation analysis was performed to establish the association between the antibody positivity toward the selected peptides in serum and CSF in the different pathologies. In patients with ALS, we found a very good correlation between Abs HERV-K env-su$_{19-37}$ peptide in serum compared to CSF (R^2=0.6; P<0.002) (Fig 3A). Instead, no correlation was found in serum and CSF for this peptide in MS and AD. (Figs 3B and C). A positive result was also observed for antibodies against HERV-K env-su$_{109-126}$ in serum compared to CSF in patients with ALS (R^2=0.33; p=0.03), but not in MS and AD (Fig 3D, E and F), whereas the antibody correlation against HERV-K env-su$_{164-186}$ between serum and CSF was significant in ALS (R^2=0.4; p=0.003) (Fig 3G). Finally, antibody response against HERV-K env-su$_{205-226}$ peptide was also slightly correlated in serum and CSF of ALS and MS patients (R^2=0.2; p=0.04), (Fig 3L and M). These results indicate a good correlation of HERV-K peptides Abs response in serum and CSF in ALS patients compared to other groups.

As previously shown, analysis of HERV-W correlation showed a positivity only in MS patients regarding the HERV-W env-su$_{93-108}$ Abs in serum and CSF (R^2=0.27; p=0.05) (Fig 4A, B and C). No correlation for antibodies against the other two peptides analysed, HERV-W env-su$_{129-143}$ and HERV-W env-su$_{161-180}$ was observed in the 3 groups (Fig 4D, E, F,G, H and I). A good correlation between serum and CSF was found for the antibody response against HERV-W env-su $_{248-262}$ in MS compared to ALS and AD (R^2=0.43; p=0.004) (Fig. 4L, M and N).

Another correlation analyses was performed to establish the association between the antibody positivity of the HERV-K env surface selected peptides in serum/CSF of ALS patients and ALS functional rating scale revised (ALSFRS). We found a good correlation between Abs HERV-K env-su$_{19-37}$ peptide compared to ALSFRS in serum (R^2=0.45; p=0.003) (Fig 5A) and CSF (R^2=0.41; p=0.004) (Fig 5B). No significant correlation was found for the antibody response against the other HERV-K env surface peptides evaluated in serum and CSF of ALS patients compared to ALSFRS. (Figs 5C-5H).

This article is protected by copyright. All rights reserved.

Accepted Article

Peptide IgG-specific antibody index (AI) in the 3 groups.

Antibody Index (AI) for all patients was calculated according to the following formula AI = QIgG[spec]/Qlim [22,24]. A high number of positive samples against the selected peptides in all groups showed an AI > 1.5 suggesting an intratecal IgG-specific antibody production against HERV-K and HERV-W env peptides, as shown in Table 3 (supplementary file).

HERV-K peptides as possible biomarker for ALS

We collected and analysed serum samples of ALS patients resulted positive to IgG against HERV-K surface peptides, before or contemporary to clinical/EMG diagnosis. HERV-K env su_{19-37} was recognized in all samples whereas Abs against HERV-K $env_{109-126}$ in 93% of samples (Table 4, supplementary file).

Discussion

Currently, no specific biomarkers are available for differential diagnosis of ALS and other neurological disorders. Thus, diagnostic and prognostic biomarkers for ALS remain a major unmet clinical need.

Although the cause of neurodegeneration in ALS remains unknown, recently the Avindra Nath research group showed that the env glycoprotein of HERV-K might contribute to neurodegeneration and disease pathogenesis [9,10,25]. In particular, sustained activation of HERV-K in the CNS of sporadic ALS patients, due to still now unknown etiological factors, might induce an innate cellular immune response, amplify neuro-inflammation and, ultimately, promote neuronal injury [5,9,10]. These authors documented also that, in some patients with HIV-associated motor neuron disease, HERV-K activation might be responsive to antiretroviral therapy [26]. However, definite proof that in

This article is protected by copyright. All rights reserved.

Accepted Article

ALS, HERV-K expression has really a pathogenic role and is not simply an epiphenomenon of HIV infection, is still lacking [27].

Considering these findings, we investigated the HERV-K and HERV-W env antigen-specific humoral immunity response in serum and CSF of patients with suspected ALS, MS and AD, with the aim to identify a possible biomarker able to support and facilitate an early diagnosis of ALS. In particular, we explored an immunological IgG response against HERV-K and HERV-W env surface peptides in serum and CSF in patients with ALS, MS and AD. We evaluated the humoral immune response in the form of IgG antibodies against peptides previously identified by in silico analysis that allowed us to select different antigenic peptides from HERV-K and HERV-W env surface proteins.

Only one of HERV-K peptides was able to induce a significant humoral immune response in serum and CSF of ALS patients. On the other hand, two HERV-W peptides were able to induce a significant humoral immune response in serum and CSF in MS patients.

We also investigated the presence of intrathecal immune response against HERV-K and HERV-W surface env peptides. To check the BBB integrity, IgG index (as a marker of intrathecal IgG synthesis) and CSF/serum albumin ratio (Q Alb) were evaluated. Results showed a specific intrathecal IgG synthesis against the HERV-K and HERV-W peptides (AI >1.5) and the integrity of BBB in the majority of patients in the three groups. ELISA analysis showed that IgGs against the HERV-K env-$su_{19\text{-}37}$ peptide was higher in cases with ALS compared to the other groups, in both CSF and serum. Of note, a higher serum/CSF correlation was found between the levels of IgGs against all HERV-K peptides. This result was confirmed by serum and CSF comparison, since only HERV-K env-$su_{19\text{-}37}$ was significantly positive in both. With regard to HERV-W, the indirect ELISA showed that HERV-W env-$su_{93\text{-}108}$ and env-$su_{248\text{-}262}$ peptides were able to induce a higher IgG response in MS cases compared to ALS and AD patients. As observed in previous studies, these findings suggest a possible pathophysiological role of HERV-W family in MS [28-30], and indicate the potential use of these antibodies as humoral biomarkers in patients with MS [14, 15].

This article is protected by copyright. All rights reserved.

Of note, in this study we exclusively evaluated levels of total IgG antibodies anti-HERV-K and anti-HERV-W peptides, thus which IgG subclasses were predominant in patients with ALS and MS remain to be determined. This is an important issue considering recent data indicating that IgG4 antibodies fulfil a protective role dampering the more harmful effects of IgG1 when directed against to same epitopes [31]. Given these findings, it should also be considered the possibility that the immune response we observed might actually have a protective role in these diseases.

In conclusion, our results are useful both to better understanding the putative role of endogenous retroviruses in neurodegenerative and autoimmune diseases, and to indicate novel therapeutic strategies for some ALS patients such as the possible utility of specific immune treatment. Moreover, the selective increase of circulating levels of the HERV-K env-su_{19-37} antibody in serum and CSF may have prognostic significance and serve as early novel candidate biomarkers for ALS.

Acknowledgments

The study was supported by a project of Prof Leonardo A. Sechi financed by AriSLA, project IRKALS, immune response against HERV_in ALS patients, 2017.

Author contribution statement.

GA and GM, conceived and performed the experiments, analyze the data and wrote the manuscript. GAD, ALR, RP, EN, GZ, EC, MB, DU and GMP collected samples and analyze the data, ES, SM, SF analyzed the data and contributed to the writing of the manuscript. GPS analyzed the data and contributed to the writing of the manuscript. LAS conceived the study, analyzed the data and contributed to the writing of the manuscript.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Figures Legend.

Figure 1. Antibody OD measured by indirect ELISA. 21 ALS patients, 26 MS, 18 AD and 39 HC were screened for their reactivity against plate-coated with HERV-K env $_{19\text{-}37}$, HERV-K env $_{109–126}$, HERV-K env $_{164–186}$ and HERV-K env $_{205–226}$ peptides in serum (A, C, E, G) and CSF (B, D, F, H). Scatter plots present median values with interquartile range. Area under ROC curve (AUC) as well as p value are displayed in the top-right corner. Differences with $p<0.05$ were considered statistically significant. Cut-off values for positivity, calculated by ROC analysis are indicated by dashed lines.

Figure 2. Antibody OD measured by indirect ELISA 21 ALS patients, 26 MS, 18 AD, and 39 HC were screened for their reactivity against plate-coated with HERV-W env $_{93\text{-}108}$, HERV-W env $_{129–143}$, HERV-W env $_{161–180}$ and HERV-W env $_{248–262}$ peptides in serum (A, C, E, G) and CSF (B, D, F, H). Scatter plots present median values with interquartile range. Area under ROC curve (AUC) as well as p value are displayed in the top-right corner. Differences with $p<0.05$ were considered statistically significant. Cut-off values for positivity, calculated by ROC analysis are indicated by dashed lines.

Figure 3. Scatter plot showing the correlations between IgG against HERV-K env $_{19\text{-}37}$ in CSF with HERV-K env $_{19\text{-}37}$ in serum of ALS, MS and AD (A, B, C). IgG against HERV-K env $_{109\text{-}126}$ in CSF with HERV-K env $_{109\text{-}126}$ in serum of ALS, MS and AD (D, E, F). IgG against HERV-K env $_{164\text{-}186}$ in CSF with HERV-K env $_{164\text{-}186}$ in serum of ALS, MS and AD (G, H, I). IgG against HERV-K env $_{205\text{-}226}$ in CSF with HERV-K env $_{205\text{-}226}$ in serum of ALS, MS and AD (L, M, N). The abscissa in all panels represent antibody OD in serum, the ordinate represent antibody OD in CSF.

This article is protected by copyright. All rights reserved.

Figure 4. Scatter plot showing the correlations between IgG against HERV-W env $_{93-108}$ in CSF with HERV-W env $_{93-108}$ in serum of ALS, MS and AD (A, B, C). IgG against HERV-W env $_{129-143}$ in CSF with HERV-W env $_{129-143}$ in serum of ALS, MS and AD (D, E, F). IgG against HERV-W env $_{161-180}$ in CSF with HERV-W env $_{161-180}$ in serum of ALS, MS and AD (G, H, I). IgG against HERV-W env $_{248-262}$ in CSF with HERV-W env $_{248-262}$ in serum of ALS, MS and AD (L, M, N). The abscissa in all panels represent antibody OD in serum, the ordinate represent antibody OD in CSF.

Figure 5. Scatter plot showing the correlations between IgG against HERV-K env $_{19-37}$ in serum and CSF of ALS patients compared to ALS functional rating scale revised (ALSFRS) (A, B). IgG against the other HERV-K env surface peptides (HERV-K env $_{109-126,}$ HERV-K env $_{164-186,}$ HERV-K env $_{205-226}$) in serum and CSF of ALS patients compared to (ALSFRS) (C, D, E, F, G, H).

Table 2. The table shows ALS, MS-AD samples serum-CSF double positive for the HERV-K and HERV-W peptides. P value was calculated by Fisher's exact test.

Peptide name	**ALS double positive CSF-SERUM (%)**	**MS-AD double positive CSF-SERUM (%)**	**P value**
HERV-K SU $_{19-37}$	94%	0%	P<0.0001
Peptide name	**MS double positive CSF-SERUM (%)**	**ALS-AD double positive CSF-SERUM (%)**	**P value**
HERV-W SU $_{93-108}$	75%	31%	P<0.0001
HERV-W SU $_{248-262}$	83%	0%	P<0.0001

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

References (for online only E-extra publication)

1. Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, Shaw PJ. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. Nat Rev Neurol 2016; 7: 616–630.

2. Steele AJ, Al-Chalabi A, Ferrante K, et al. Detection of serum reverse transcriptase activity in patients with ALS and unaffected blood relatives. Neurology 2005; 64: 454–458 .

3. MacGowan DJ, Scelsa SN, Imperato TE, et al. A controlled study of reverse transcriptase in serum and CSF of HIV-negative patients with ALS. Neurology 2007; 68: 1944–1946.

4. McCormick AL, Brown RH Jr, Cudkowicz ME, Al-Chalabi A, Garson JA. Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. Neurology 2008; 70: 278–283.

5. Douville RN, Nath A. Human endogenous retroviruses and the nervous system. Handb Clin Neurol 2014; 123: 465-485.

6. Viola MV, Frazier M, White L, Brody J, Spiegelman S. RNA-instructed DNA polymerase activity in a cytoplasmic particulate fraction in brains from Guamanian patients. J Exp Med 1975; 142: 483–494.

7. Hadlock KG, Miller RG, Jin X, et al. Elevated rates of antibody reactivity to HML-2/HERV-K but not other endogenous retroviruses in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004; 5 (Suppl.2): 63.

8. Oluwole OSA, Yao Y, Conradi S, Kristensson K, Karlsson H. Elevated levels of transcripts encoding a human retroviral envelope protein (syncytin) in muscles from patients with motor neuron disease. Amyotroph Lateral Scler 2007; 8: 67–72.

9. Douville R, Liu J, Rothstein J, Nath A. Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis. Ann Neurol 2011; 69: 141–151.

10. Li W, Lee MH, Henderson L, et al. Human endogenous retrovirus-K contributes to motor neuron disease. Sci Transl Med 2015; 7: ra153.

11. Mameli G, Madeddu G, Mei A, et al. Activation of MSRV-type endogenous retroviruses during infectious mononucleosis and Epstein-Barr virus latency: the missing link with multiple sclerosis? PLoS One 2013; 8:e78474.

This article is protected by copyright. All rights reserved.

12. Arru G, Leoni S, Pugliatti M, et al. Natalizumab inhibits the expression of human endogenous retroviruses of the W family in multiple sclerosis patients: a longitudinal cohort study. Mult Scler 2014; 20:174-182.

13. Arru G, Caggiu E, Leoni S, et al. Natalizumab modulates the humoral response against HERVWenv73-

88 in a follow-up study of Multiple Sclerosis patients. J Neurol Sci 2015; 357:106-108.

14. Mameli G, Cossu D, Cocco E, et al. Epitopes of HERV-W env induce antigen-specific humoral immunity in multiple sclerosis patients. J Neuroimmunol 2015; 280: 66-68.

15. Arru G, Sechi E, Mariotto S, et al. Antibody response against HERV-W env surface peptides differentiates multiple sclerosis and neuromyelitis optica spectrum disorder. Mult Scler J Exp Transl Clin 2017; 1-6. DOI. 101177/2055217317742425.

16. Brooks BR, Miller RG, Swash M, Munsat TL World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1: 293-299.

17. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302.

18. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999; 169: 13-21.

19. Kimura F, Fujimura C, Ishida S, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 2006; 66: 265-267.

20. Mameli G, Cossu D, Cocco E, et al. Epstein-Barr virus and Mycobacterium avium subsp. paratuberculosis peptides are cross recognized by anti-myelin basic protein antibodies in multiple sclerosis patients. J Neuroimmunol 2014; 270: 51-55.

21. Cossu D, Masala S, Frau J, et al. Antigenic epitopes of MAP2694 homologous to T-cell receptor gamma-chain are highly recognize in multiple sclerosis Sardinia patients. Mol Immunol 2014; 57: 138–140.

22. Reiber H. & Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. Clin Chem 1991; 37:1153-

This article is protected by copyright. All rights reserved.

Accepted Article

1160.

23. Castellazzi M, Contini C, Tamborino C, et al. Epstein Barr virus-specific intrathecal oligoclonal IgG production in relapsing-remitting multiple sclerosis is limited to a subset of patients and is composed of low-affinity antibodies. J Neuroinflammation 2014; 11: 188.

24. Mameli G, Cocco E, Frau J, Marrosu MG, Sechi LA. Epstein Barr Virus and Mycobacterium avium subsp. paratuberculosis peptides are recognized in sera and cerebrospinal fluid of MS patients. Sci Rep 2016; 6:22401.

25. Alfahad T, Nath A. Retroviruses and amyotrophic lateral sclerosis. Antiviral Res 2013; 99: 180-187.

26. Bowen LN, Tyagi R, Li W, et al. HIV-associated motor neuron disease: HERV-K activation and response to antiretroviral therapy. Neurology 2016; 87:1756-1762.

27. Berger JR, Power C. Closing in on an infectious etiology of motor neuron disease. Neurology 2016; 87: 1750-1751.

28. Van Horssen J, Van der Pol S, Nijland P, Amor S, Perron H. Human endogenous retrovirus W in brain lesions: Rationale for targeted therapy in multiple sclerosis. Multiple Sclerosis and Related Disorders 2016; 8:11–18.

29. Garcia-Montojo M, Dominguez Mozo M, Arias Leal A, et al. The DNA Copy Number of Human Endogenous Retrovirus-W (MSRV-Type) Is Increased in Multiple Sclerosis Patients and Is Influenced by Gender and Disease Severity. PloS One 2013; 8: 1.

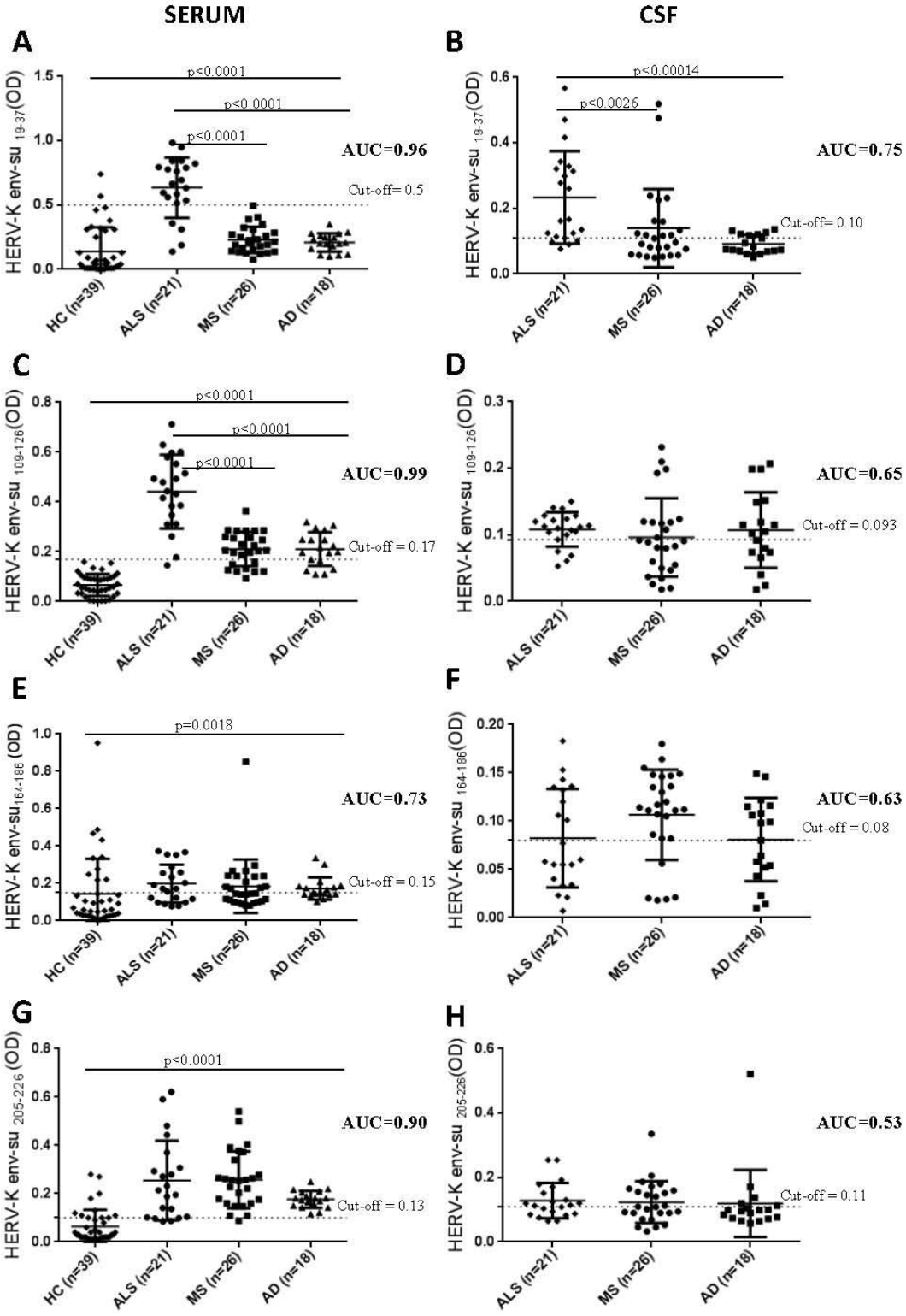
30. Perron H, Germi R, Bernard C, et al. Human endogenous retrovirus type W envelope expression in blood and brain cells provides new insights into multiple sclerosis disease. Mult Scler 2012; 18: 1721–1736.

31. Trampert DC, Hubers LM, van de Graaf SFJ, Beuers U. On the role of IgG4 in inflammatory conditions: lessons for IgG4-related disease. Biochim Biophys Acta 2017; S0925-4439 (17) 30273-9. DOI: 10.1016/J.bbadis.

Accepted Article

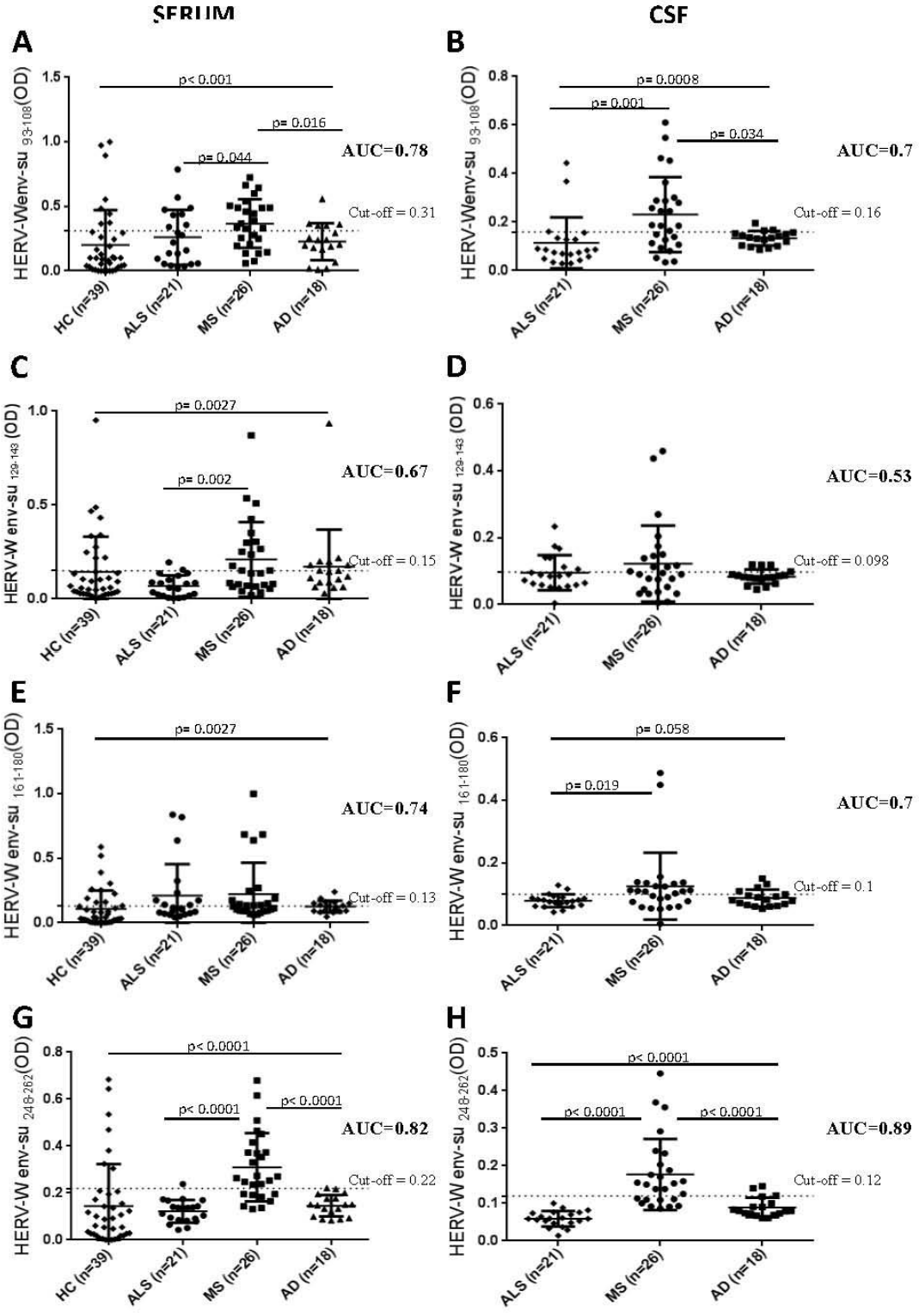
This article is protected by copyright. All rights reserved.

Accepted Article



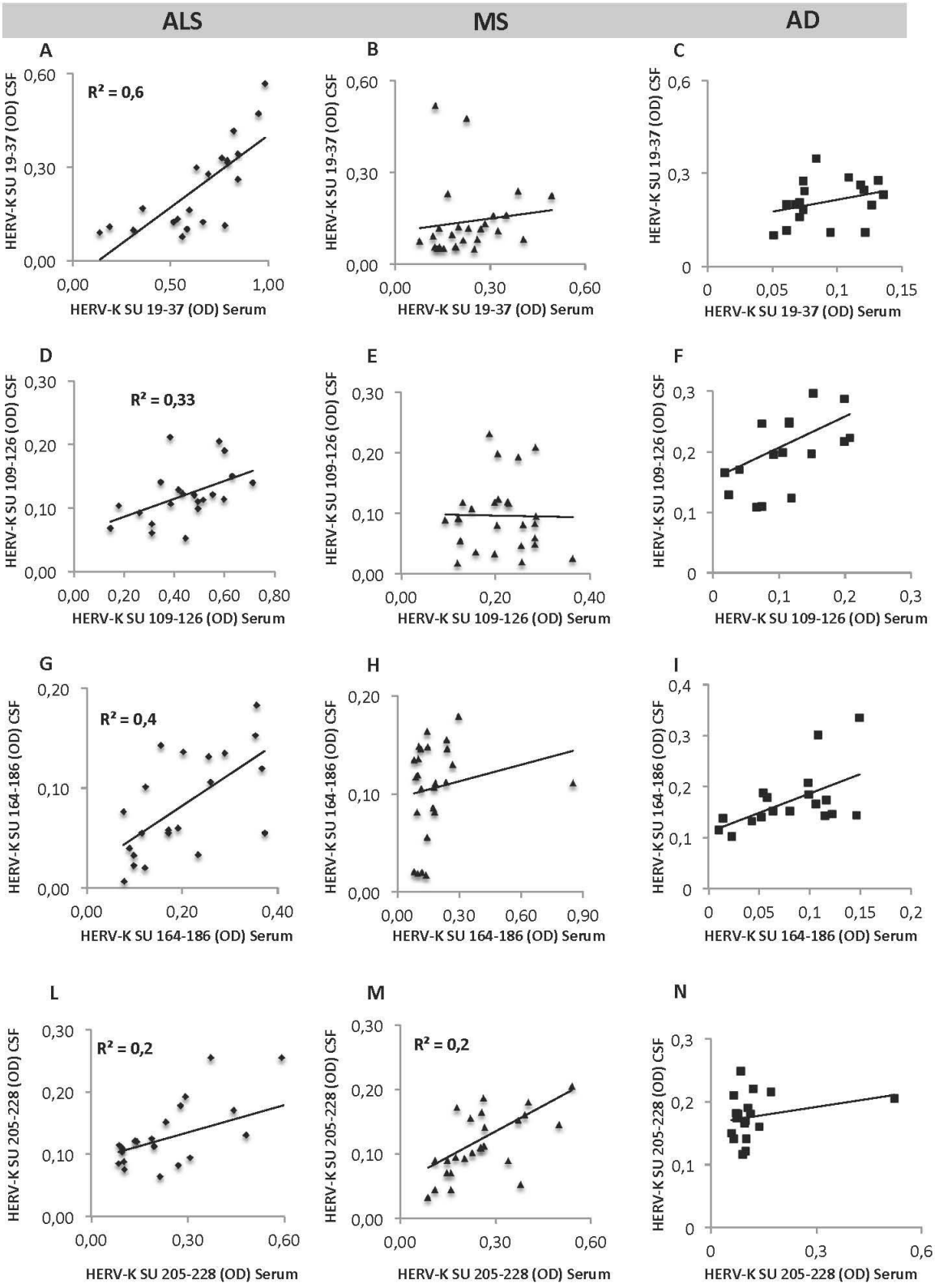
This article is protected by copyright. All rights reserved.

Accepted Article



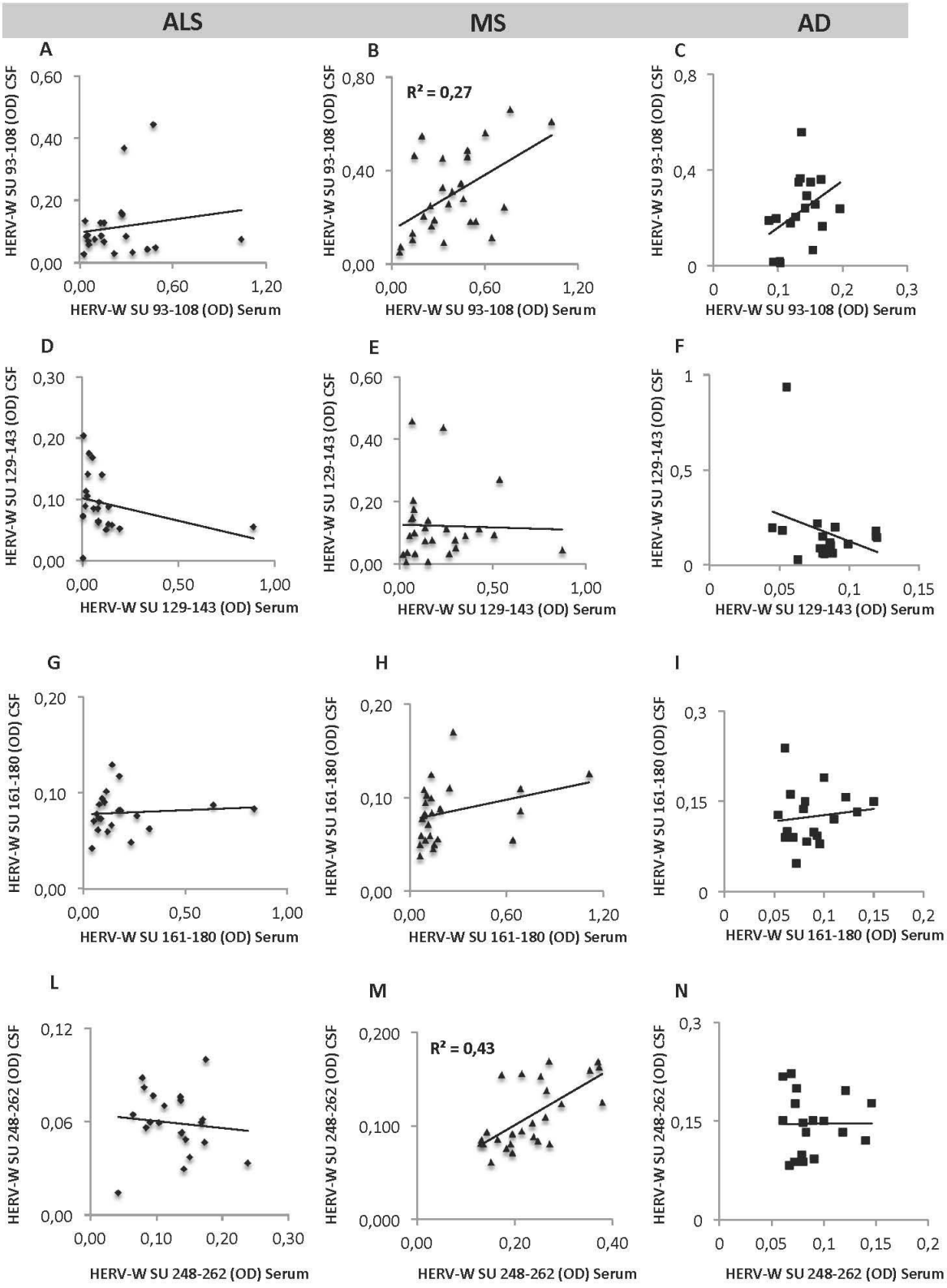
This article is protected by copyright. All rights reserved.

Accepted Article



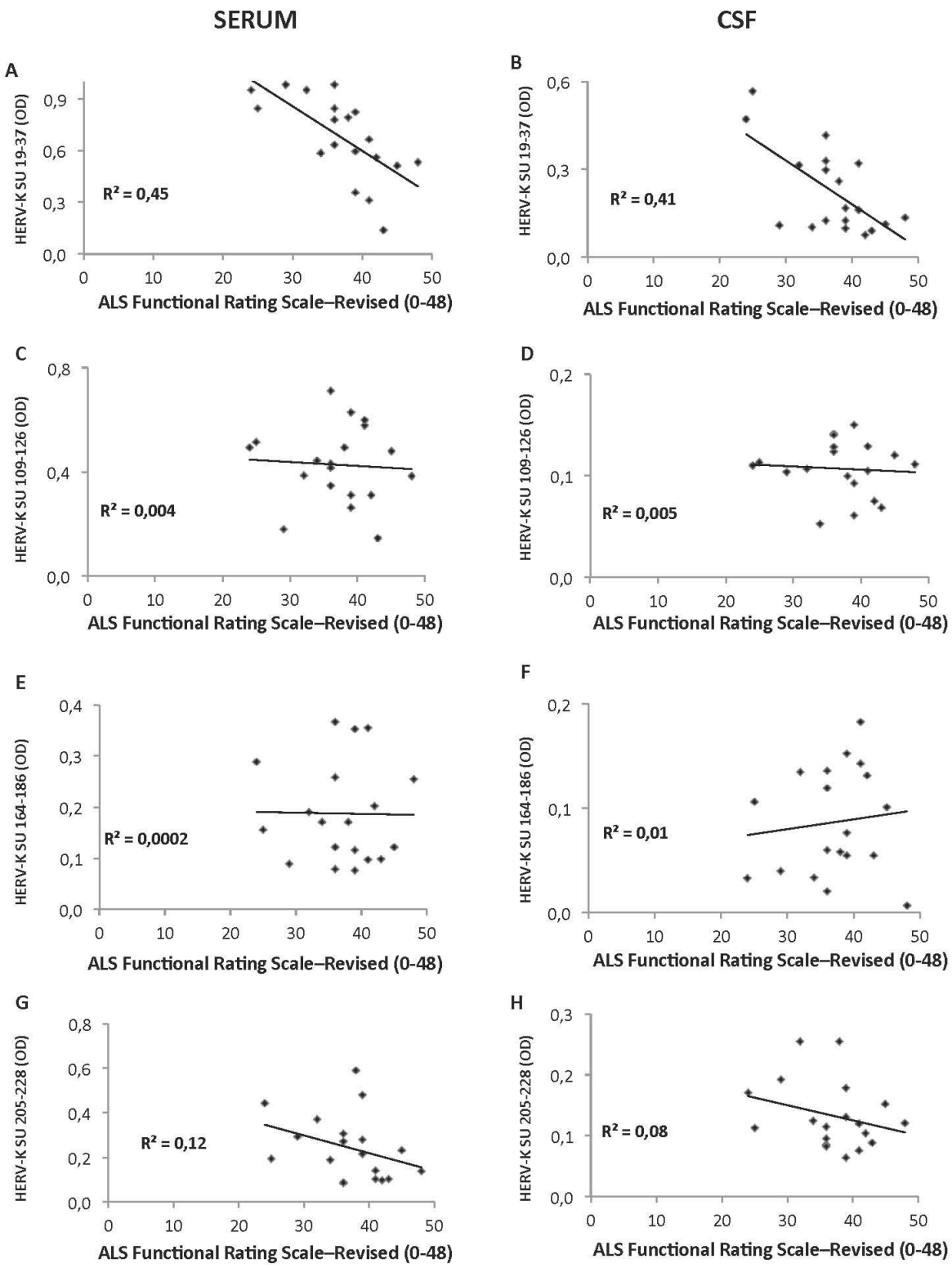
This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.