IL6 receptor^{358} Ala variant and trans-signaling are disease modifiers in amyotrophic lateral sclerosis

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Neurol Neuroimmunol Neuroinflamm 2019;6:e631. doi:10.1212/NXI.0000000000000631

Abstract

Objective
To test the hypothesis that patients with amyotrophic lateral sclerosis (ALS) inheriting the common interleukin 6 receptor (IL6R) coding variant (Asp^{358} Ala, rs2228145, C allele) have associated increases in interleukin 6 (IL6) and IL6R levels in serum and CSF and faster disease progression than noncarriers.

Methods
An observational, case-control study of paired serum and CSF of 47 patients with ALS, 46 healthy, and 23 neurologic disease controls from the Northeastern ALS Consortium Biofluid Repository (cohort 1) was performed to determine serum levels of IL6, sIL6R, and soluble glycoprotein 130 and compared across groups and IL6R genotype. Clinical data regarding disease progression from a separate cohort of 35 patients with ALS from the Wake Forest ALS Center (cohort 2) were used to determine change in ALSFRS-R scores by genotype.

Results
Patients with ALS had increased CSF IL6 levels compared with healthy (p < 0.001) and neurologic (p = 0.021) controls. Patients with ALS also had increased serum IL6 compared with healthy (p = 0.040) but not neurologic controls. Additive allelic increases in serum IL6R were observed in all groups (average increase of 52% with the presence of the IL6R C allele; p < 0.001). However, only subjects with ALS had significantly increased CSF sIL6R levels compared with controls (p < 0.001). When compared across genotypes, only patients with ALS inheriting the IL6R C allele exhibit increased CSF IL6. ALSFRS-R scores decreased more in patients with ALS with the IL6R C allele than in those without (p = 0.019).

Conclusions
Theses results suggest that for individuals inheriting the IL6R C allele, the cytokine exerts a disease- and location-specific role in ALS. Follow-up, prospective studies are necessary, as this subgroup of patients may be identified as ideally responsive to IL6 receptor–blocking therapies.
Northeastern ALS Consortium; peripherally at the neuromuscular junction (NMJ), and for diseases associated with IL6 signaling. IL6 metabolism, differences diverse cellular mechanisms including cell growth, functions, IL6 trans-signaling may be an important modifier of the variability in increased sIL6R plasma levels accounted for by the C allele.10–12 In individuals inheriting the IL6R C allele, increased shedding of the receptor enhances both localized and systemic IL6 trans-signaling in the presence of IL6. Given the role of IL6 signaling in mediating multiple cell functions, IL6 trans-signaling may be an important modifier for diseases associated with IL6 signaling.13–17

To determine whether IL6 trans-signaling could have a potential role in ALS, IL6 and sIL6R levels were measured in paired samples of serum and CSF collected at a single time point in a cohort of patients with ALS and compared with healthy (HCs) and disease controls (DCs) and across IL6R variant groups. Our results suggest that the IL6R C allele influences IL6 signaling in the CNS of patients with ALS. In a second cohort of subjects with ALS with more defined clinical data, the presence of the IL6R C allele was associated with faster disease progression. These results suggest that identifying patients who possess the IL6R C allele may provide insight for predicting disease progression and identifying those who might benefit most from IL6R-blocking therapies. Follow-up studies are warranted.

Methods

Subjects
All subjects were unrelated persons of self-reported European ancestry. Genetic status regarding disease causative mutations (e.g., SOD1) was unknown. Cohort 1 consisted of paired samples of serum and CSF collected at a single time point from patients with ALS, DCs, and healthy subjects. All samples for cohort 1 were obtained from the Northeastern ALS Consortium (NEALS) multicenter biorepository. Subjects with ALS were diagnosed as probable or definite by the El Escorial criteria; diseased controls were diagnosed with a degenerative or inflammatory neurologic disorder that may mimic ALS such as MS, myasthenia gravis, and hereditary spastic paraplegia.18 CSF and blood samples were collected by lumbar and venipuncture, respectively. Cohort 2 included male and female patients, 18 years and older with a probable or definite diagnosis of ALS18 without other potentially confounding neurologic diseases as determined by 2 independent neuromuscular disease specialists. Clinical data for these subjects were collected at the Wake Forest ALS Center during routine clinical practice, deidentified, and entered into the Wake Forest ALS biorepository database.

Standard protocol approvals, registrations, and patient consents
All subjects provided informed consent as required by the respective institutional review boards.

Serum and CSF samples
The NEALS biorepository provided deidentified samples with a separate document containing clinical information and subject IDs. Before assays, thawed aliquots were cleared by 10-minute centrifugation at 18,000g at 4°C. Protein concentrations for serum and CSF were determined using bichloronic acid assay total protein assay (Thermo Scientific, 23,225) to assure that sample protein content fell within the normal range for adults (serum 6.4–8.3 g/dL; CSF15–45 mg/dL) and did not differ between groups (data not shown).
Statistical analyses

Serum and CSF IL6 levels were winsorized to within 2 SDs of the mean of the cohort as a whole to limit the influence of outlying values (4 CSF values and 5 serum values winsorized; table e-1, links.lww.com/NXI/A152). IL6 raw values were natural log transformed to normalize the distribution before any parametric comparisons; sIL6R and sgp130 were well approximated by the normal distribution and did not require transformation.

Significant age differences had previously measured between ALS and control groups’ serum IL6 levels ($p < 0.001$, $\rho = 0.12$, Spearman correlation). Therefore, age was a covariate in all serum IL6 analyses involving generalized linear models (GLM) to test for associations (table e-2, links.lww.com/NXI/A152). The data’s fit to the model’s distributional assumptions of conditional normality and homogeneity of variance were examined. Estimated least square means and standard errors were computed for summarizing data and individual comparisons. All comparisons were determined before data analysis to be as follows: ALS vs HC, ALS vs DC (whole group, within AA genotype, or within °C genotypes), and AA vs °C (within ALS, HC, or DC groups; see table e-3, links.lww.com/NXI/A152). As these were planned comparisons, tests for pairwise differences were performed using the Fisher protected least significant difference multiple comparison procedure. The Student 2-way $t$ test was used on the $\Delta$FS values. Corresponding effect sizes were estimated via Cohen’s D statistic.

Data availability

Data not provided in the article because of space limitations will be shared upon request of other investigators for purposes of replicating procedures and results.

Results

Subject characteristics

Cohort 1 consisted of serum and CSF samples provided by the NEALS repository and comprised 47 subjects with ALS, 46 HCs, and 23 subjects with neurologic diseases that mimic ALS. Demographics for each sample included age, sex, race, and disease duration (ALS and DCs; table). Two subjects with ALS and 11 neurologic DCs did not have disease duration information. Significant differences in age existed between the ALS and control groups; therefore, this factor was controlled for in subsequent analyses when appropriate, as described in Methods. Cohort 2 consisted of 35 subjects with ALS, all of whom had contributed DNA samples along with detailed demographic and clinical data from their initial visit to the Wake Forest ALS Clinic (table).

Serum IL6 levels are elevated in subjects with ALS and DCs compared with HCs, but only subjects with ALS exhibit increased CSF levels.

Both ALS and DC individuals exhibited elevated serum IL6 compared with HCs (figure 1A). CSF IL6 levels were significantly higher in subjects with ALS compared with both HCs and
DCs (figure 1B). There were no observed differences between CSF and serum sIL6R levels between groups (Figure 1, C and D). Together, these data indicate a possible CNS-specific role for IL6 in ALS. Although the concentrations of IL6 were comparable between serum and CSF, serum levels of sIL6R and its naturally occurring, soluble gp130 (sgp130) were consistently ten-fold higher than the CSF levels in all groups. We found no significant differences in sgp130 in either serum or CSF between groups (figure 1, E and F). These results suggest that in ALS, sgp130 does not compensate for the observed increases in IL6.

**IL6R C allele accounts for serum sIL6R levels in all groups**

The IL6C allele occurs at a frequency of ~10% in African, ~40% in European, ~30% in East Asian, and ~50% in Native American ancestries (reference 13, NCBI dbSNP). To investigate the role of the IL6R C allele on sIL6R levels and the potential influence of trans-signaling in ALS, we evaluated the distribution of the IL6R C allele in all subjects (table; those with AC or CC genotype will be referred to as *C). When contrasting subjects with ALS with control sets in cohort 1, the allele frequencies were comparable (ALS minor allele frequency (MAF) = 0.394 and p = 0.91, healthy MAF = 0.380 and p = 0.98, DC MAF = 0.386 and p = 0.81). Similar results were also observed in cohort 2 (table). Importantly, both within each cohort across groups (table e-1, links.lww.com/NXI/A152) and across the 2 cohorts, the IL6R C allele frequencies (MAF) were comparable and consistent with previous reports (0.387 and 0.417 for cohorts 1 and 2, respectively). Both cohorts were consistent with Hardy-Weinberg equilibrium proportions (p = 0.72 and p = 0.61 for cohorts 1 and 2, respectively). Univariate analysis found no association between the IL6R C allele and sex (p = 0.77), age at onset (p = 0.55), or disease duration (p = 0.19). These results suggest that the presence of the C allele does not predispose individuals to ALS. As expected for an additive genetic model, in all groups, the IL6R C allele was associated with increased (52%) serum sIL6R (figure 2A). Only in subjects with ALS were CSF sIL6R levels significantly increased (23%) with the presence of the C allele (figure 2C). Similar results were also observed in cohort 2 (table). Importantly, both within each cohort across groups (table e-1, links.lww.com/NXI/A152) and across the 2 cohorts, the IL6R C allele frequencies (MAF) were comparable and consistent with previous reports (0.387 and 0.417 for cohorts 1 and 2, respectively). Both cohorts were consistent with Hardy-Weinberg equilibrium proportions (p = 0.72 and p = 0.61 for cohorts 1 and 2, respectively). Univariate analysis found no association between the IL6R C allele and sex (p = 0.77), age at onset (p = 0.55), or disease duration (p = 0.19). These results suggest that the presence of the C allele does not predispose individuals to ALS. As expected for an additive genetic model, in all groups, the IL6R C allele was associated with increased (52%) serum sIL6R (figure 2A). Only in subjects with ALS were CSF sIL6R levels significantly increased (23%) with the presence of the C allele (figure 2C). Suggesting potential for CSF trans-signaling to be correlated in a genotypic manner with occurrence of ALS-specific pathologic processes in *C individuals.

**Subjects with ALS with the IL6R C allele have increased IL6 in the CSF**

Univariate analysis was used to check for potential correlations between CSF or serum IL6, sIL6R, sgp130, and demographics. Sex and duration of symptoms were unrelated to any measure; however, serum IL6 was positively correlated with age (IL6 p < 0.001, p = 0.12, Spearman correlation). We next investigated whether the presence of the IL6R C allele contributed to differences in IL6 levels in subjects with ALS in cohort 1. There was no significant difference in IL6 levels between subjects with ALS with and without the C allele (figure 2C). Serum IL6 was higher in subjects with *C ALS compared with *C HCs (figure 2C).

**Table Demographic and clinical information (cohorts 1 and 2)**

<table>
<thead>
<tr>
<th>NEALS biorepository (Cohort 1)</th>
<th>Subjects with ALS</th>
<th>DCs</th>
<th>HCs</th>
<th>Significant differences</th>
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<tbody>
<tr>
<td>Number (% male)</td>
<td>47 (70)</td>
<td>23</td>
<td>46</td>
<td>Sex: ALS v NC p = 0.04a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALS v HC p = 0.17a</td>
</tr>
<tr>
<td><strong>Age at draw (y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>56.9</td>
<td>49.9</td>
<td>46.8</td>
<td>ALS v NC p = 0.021b</td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>48</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>31–78</td>
<td>27–72</td>
<td>25–77</td>
<td>ALS v HC p &lt; 0.001b</td>
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<td><strong>Disease duration at draw (mo)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>18</td>
<td>96</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td>73</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Range</td>
<td>1–62</td>
<td>3–258</td>
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<td></td>
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<tr>
<td><strong>Genotype (number (% of group))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>18 (38)</td>
<td>9 (39)</td>
<td>18</td>
<td>ALS v DC p = 0.95a</td>
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<tr>
<td>*C (CC, CA)</td>
<td>29 (62)</td>
<td>14</td>
<td>28</td>
<td>ALS v HC p = 0.93a</td>
</tr>
</tbody>
</table>

**WF ALS Center biorepository (Cohort 2) | Subjects with ALS (figure 4)**

| Number (% male)                | 35 (56%)         |
| **Age at sample collection (y)** |                  |     |     |                         |
| Mean                           | 65.3             |
| Median                         | 64.5             |
| Range                          | 41.8–83.6        |
| **Disease duration (mo)**      |                  |     |     |                         |
| Mean                           | 8.2              |
| Median                         | 9.4              |
| Range                          | 3.4–11.5         |
| **Genotype n (% of total)**    |                  |     |     |                         |
| AA                             | 16 (45%)         |
| *C                             | 19 (55%)         |

ALS = amyotrophic lateral sclerosis; DC = disease control; HC = healthy control; IL6R = interleukin 6 receptor; NEALS = Northeastern ALS Consortium.

a Significance determined by χ2.
b Significance determined by the Fisher exact test.
We and others have reported that IL6 is increased in the CSF of subjects with ALS compared with control populations. Our results here suggest that this observed increase is not present in every subject but rather is driven by C subjects, thus indicating the potential that IL6 trans-signaling could be active in ALS CSF and dependent on inheriting the IL6R C allele. In both serum and CSF, there were no significant differences in sgp130 between affected and unaffected subjects (data not shown).

Subjects with ALS who inherit the IL6R C allele exhibit faster disease progression

We next questioned whether the presence of the C allele is associated with accelerated ALS disease progression. Because there were no disease progression data available for cohort 1, and to investigate whether the presence of the C allele resulted in faster disease progression compared with patients without the variant, we turned to an independent sample (cohort 2) that included clinical outcomes, although paired CSF and serum samples were not available. Subjects in cohort 2 had reliable information regarding symptom onset with diagnosis and clinic visits within 1 year of onset. We limited our progression comparison to those subjects who were diagnosed within 1 year of their first symptom to most accurately obtain disease onset time. Thus, we were able to assess early stages of disease as secondary pathologic outcomes where IL6 may be a contributing factor (e.g., lung inflammatory responses and advanced muscle atrophy), have either not yet occurred, or would be less significantly progressed. Functional decline (ALSFRS-R progression rate) as measured by the ΔFS of patients diagnosed within the first year after symptom onset revealed that patients with the IL6R C allele have greater loss of function than those without (figure 3). There was no difference in the number of patients with bulbar or spinal onset between the 2 compared groups (p = 0.68).

Discussion

ALS is a fatal disease with a short survival time after diagnosis, an extensive clinical diagnostic process, and few treatment options. To further our understanding of which factors influence disease progression and severity, we completed
a retrospective study of 2 cohorts of subjects with ALS and controls. Our results from cohort 1 show that only subjects with ALS with the $IL6R^C$ allele have increased IL6 and IL6R in CSF compared with HCs and neurologic DCs. The additive nature of the allele appears to be magnified only in CSF of patients with ALS and not in controls. From cohort 2, we found that individuals inheriting the $IL6R^C$ allele exhibit faster disease progression. The $IL6R^C$ allele regulates IL6 signaling mechanisms reported to influence several disease pathologies. Knowledge that a specific subgroup of patients with ALS, such as those carrying the $IL6R^C$ allele, will experience faster decline can contribute to earlier, informed diagnosis and application of patient-specific treatments and interventions (e.g., noninvasive ventilation) to improve quality of life. These results of the current study may have clinical significance and serve as a foundation for future, prospective studies to determine whether IL6R genotype and CNS signaling modify disease progression and are targets of therapeutic intervention with IL6R-blocking agents.

Serum levels of IL6 can easily fluctuate within 12 pg/mL range due to environmental factors unrelated to disease, such as age, adiposity, recent exercise, tobacco consumption, or comorbid inflammatory conditions. Variability in serum IL6 levels must also be interpreted in context of a disease, especially one like ALS where secondary disease processes may occur coincident with decreased functionality.

Patients inheriting the $IL6R^C$ allele present with elevated serum IL6 at disease onset compared with AA patients because sIL6R extends the half-life of circulating IL6. Early in disease, MN degeneration and muscle atrophy stimulate production of IL6. However, throughout the disease...
course, other peripheral mechanisms can produce IL6, such as aspiration pneumonia or hypoxia resulting from decreased bulbar muscle and lung function limiting the diagnostic or prognostic value of the measure. Although IL6 levels may be partially dependent on IL6R genotype and subject age, extensive individual clinical characterization accounting for the aforementioned IL6-stimulating factors is necessary for appropriate interpretation.

Unlike in the periphery, levels of CSF IL6 likely reflect CNS-specific processes and are less influenced by acute peripheral undulations. Although there may be a specific transport mechanism for IL6 across the blood-brain barrier (BBB) that has only been minimally investigated in animals, we found no correlation between serum and CSF IL6 levels (figure e-1, links.lww.com/NXI/A152) underlining that CSF IL6 levels are not simply a reflection of serum IL6 at any given time. In addition, measurements of the albumin quotient (CSF: serum albumin) indicate that there is no BBB disruption in subjects with ALS as a whole or within IL6R variant groups (data not shown).

To determine whether CSF IL6 is potentially a diagnostic biomarker, we estimated by the area under the corresponding receiver operating characteristic curve for cohort 1 (data not shown). When age is included as a covariate, CSF IL6 was an informative biomarker, with an area under curve (AUC) of 0.75, sensitivity of 76.6%, and specificity of 70.6% (data not shown). Given the less variable nature of CSF IL6, a normal IL6 CSF level could be a good biomarker to exclude an ALS diagnosis and is at least comparable to other recently reported CSF diagnostic biomarkers neurofilament (NF) light (AUC = 0.78, 76% sensitivity, and 73% specificity) or phosphorylated NF heavy (AUC = 0.87, 84% sensitivity, and 83% specificity). Considering that patients with ALS with the C allele exhibited the highest levels of CSF IL6, we further estimated the ability of CSF IL6 to discriminate between ALS and HCs or DCs using a separate receiver operating characteristic only including subjects with the C allele, with age as a covariate. In this case, CSF IL6 as a diagnostic tool has superior sensitivity (AUC = 0.82, 90% sensitivity, and 69% specificity).

Because cohort 1 did not include clinical data, we were not able to evaluate whether CSF IL6 levels associate with disease progression as reported to chitotriosidase-1 (CHIT-1), a biomarker associated with microglial activation in ALS.

Figure 4 In amyotrophic lateral sclerosis (ALS), interleukin 6 (IL6) trans-signaling effects on motor neurons may shift the balance from trophic activity to promoting a toxic environment.
A prospective study evaluating IL6R genotype, CSF levels of IL6, CHIT-1, and NF could provide insight into how biomarkers of glial activation and neuronal responses correlate with disease symptomology and progression.

As CSF IL6 levels are highest in *C patients, elevated IL6 trans-signaling would be expected. The source of CSF IL6 may be activated microglia and astrocytes. Although as shown in animal models, activation/IL6 levels may vary throughout disease,36,37 in the presence of circulating CSF IL6R observed in *C ALS patients, sIL6R/IL6 complexes could enhance activation via trans-signaling mechanisms to further promote MN dysfunction and degeneration.9,38,39 Indeed, as high levels of CSF CHIT-1, a biomarker of microglial activation are associated with faster disease progression,40 we hypothesize that *C patients who experience elevated CNS IL6 trans-signaling may be associated with increased glial activation and experience a more rapid disease progression. A change in the ALSFRS-R score of ≥3 points is an indicator of a substantial decline in function.40 In our data set, only 3 of 16 (19%) AA patients met this threshold (1.3 points lost per month; dotted line, figure 3) as opposed to 8 of 19 (42%) *C patients. Future studies that include assessment of IL6R genotype, CSF IL6R and IL6, and clinical progression will provide more insights into this hypothesis.

Although the limitations of this study prevent mechanistic evaluation, the potential role of IL6 signaling in ALS should be considered to provide perspective for current results and design of future studies. IL6 signaling has distinct, localized roles (e.g., peripheral muscle/NMJ, diaphragm and lung, and spinal cord/brain) throughout ALS disease progression, with some potentially being beneficial and others exacerbating disease progression (figure 4). To discover and use effective treatments, it is crucial to better understand physiologic causes of variability in ALS disease progression. The possibility that *C patients experience faster progression, possibly mediated by CNS IL6 trans-signaling, merits further investigation and consideration in future therapeutic trials of IL6R-blocking strategies.

**Study limitations**

As an observational and correlative study, there are several limitations. First, the 2 cohorts were not collected under identical recruitment schemes, thus availability of samples and phenotypic data was not consistent. As a result, it was not possible to perform the same assays in each cohort because cohort 1 did not include clinical or outcome data. Although containing clinical data, cohort 2 did not include paired serum and CSF samples. The difference in cohort design did not allow comparative, longitudinal data to be collected to make direct comparisons for disease progression in the same cohort. For this reason, we caution the reader not to conflate results presented from each cohort. In addition, ALS is a highly heterogeneous in demographics and clinical phenotypes. As such, it is imperative to replicate the above findings in a larger cohort of patients where longitudinal clinical indicators of disease and multiple biological samples are collected simultaneously.

**Study funding**

This work was supported by Hope for Tomorrow, a gift in the memory of Murray Sherman, the WFHS Brian White Fund, and the Tab A. Williams Funds at Wake Forest School of Medicine. Matched CSF and serum samples for the first cohort in this study were provided by the Northeastern ALS Biofluid Repository and were collected as part of the Multi-Center Validation of Biomarkers for Motor Neuron Disease Project (SRC1NS068179, Bowser and Cudkowicz). MWK is supported by the Argenta Scholarship at WFSM.

**Disclosure**

Drs. Milligan, Hawkins, Langefeld, Caress, Cartwright, Cudkowicz, Bowser, Martin, Robinson, Mr. Arounleut, Ms. Strupe, and Ms. Wosiiski-Kuhn report no disclosures. Go to Neurology.org/NN for full disclosures.

**Publication history**

Received by Neurology: Neuroimmunology & Neuroinflammation April 26, 2019. Accepted in final form August 28, 2019.

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**Appendix Authors**

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<th>Location</th>
<th>Role</th>
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<tr>
<td>Marlena Wosiski-Kuhn</td>
<td>Wake Forest School of Medicine, Winston-Salem, NC</td>
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<td>Worked with PIs to design and conceptualize the study; conducted laboratory procedures; analyzed and interpreted the data; and drafted and finalized original submission for intellectual content.</td>
</tr>
<tr>
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<td>Major role in preliminary data collection and conceptualization of the study and revised the manuscript for intellectual content.</td>
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<tr>
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### References

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*Neurol Neuroimmunol Neuroinflamm* 2019;6;e631
DOI 10.1212/NXI.0000000000000631

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IL6 receptor\textsuperscript{358} Ala variant and trans-signaling are disease modifiers in amyotrophic lateral sclerosis

Neurol Neuroimmunol Neuroinflamm 2020;7:e650. doi:10.1212/NXI.0000000000000650

In the article “IL6 receptor\textsuperscript{358} Ala variant and trans-signaling are disease modifiers in amyotrophic lateral sclerosis” by Wosiski-Kuhn et al.,\textsuperscript{1} first published online October 14, 2019, the y-axis label in figure 1C should be “Serum sIL6R (ng/mL).” In figure 1E, the y-axis label should be “Serum sgp130 (ng/mL).” In figure 2A, the y-axis label should be “Serum sIL6R (ng/mL).” The editorial office regrets the errors.

Reference