Dysregulation of IncRNAs in autoimmune neuropathies

Mahdi Gholipour¹, Mohammad Taheri², Jafar Mehvari Habibabadi³, Naghme Nazer⁴, Arezou Sayad¹* & Soudeh Ghafouri-Fard¹*

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome (GBS) are inflammatory neuropathies with different clinical courses but similar underlying mechanisms. Long non-coding RNAs (lncRNAs) might affect pathogenesis of these conditions. In the current project, we have selected HULC, PVT1, MEG3, SPRY4-IT1, LINC-ROR and DSCAM-AS1 lncRNAs to appraise their transcript levels in the circulation of CIDP and GBS cases versus controls. Expression of HULC was higher in CIDP patients compared with healthy persons (Ratio of mean expression (RME) = 7.62, SE = 0.72, P < 0.001). While expression of this lncRNA was not different between female CIDP cases and female controls, its expression was higher in male CIDP cases compared with male controls (RME = 13.50, SE = 0.98, P < 0.001). Similarly, expression of HULC was higher in total GBS cases compared with healthy persons (RME = 4.57, SE = 0.65, P < 0.001) and in male cases compared with male controls (RME = 5.48, SE = 0.82, P < 0.001). Similar pattern of expression was detected between total cases and total controls. PVT1 was up-regulated in CIDP cases compared with controls (RME = 3.04, SE = 0.51, P < 0.001) and in both male and female CIDP cases compared with sex-matched controls. Similarly, PVT1 was up-regulated in GBS cases compared with controls (RME = 2.99, SE = 0.55, P < 0.001) and in total patients compared with total controls (RME = 3.02, SE = 0.43, P < 0.001). Expression levels of DSCAM-AS1 and SPRY4-IT1 were higher in CIDP and GBS cases compared with healthy subjects and in both sexes compared with gender-matched healthy persons. Although LINC-ROR was up-regulated in total CIDP and total GBS cases compared with controls, in sex-based comparisons, it was only up-regulated in male CIDP cases compared with male controls (RME = 3.06, P = 0.03). Finally, expression of MEG3 was up-regulated in total CIDP and total GBS cases compared with controls, but not in sex-based comparisons. Although SPRY4-IT could differentiate CIDP cases from controls with AUC = 0.84, sensitivity = 0.63 and specificity = 0.97. AUC values of DSCAM-AS1, MEG3, HULC, PVT1 and LINC-ROR were 0.80, 0.75, 0.74, 0.73 and 0.72, respectively. In differentiation between GBS cases and controls, SPRY4-IT and DSCAM-AS1 has the AUC value of 0.8. None of lncRNAs could appropriately differentiate between CIDP and GBS cases. Combination of all lncRNAs could not significantly enhance the diagnostic power. Taken together, these lncRNAs might be involved in the development of CIDP or GBS.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome (GBS) are inflammatory neuropathies with different clinical courses. While CIDP has a slowly progressive onset¹, GBS has an acute-onset with ascending pattern of neuropathy². Both conditions are associated with dysregulation of immune response³,⁴. In GBS, such responses are believed to be triggered by infectious conditions in the respiratory or gastrointestinal tract leading to a functional failure in the blood–nerve barrier and damage of myelin sheaths and/or nerve fibers⁵. Almost all aspects of immune function including humoral responses, complement, T cells and macrophages participate in the pathogenesis of these immune-mediated neuropathies⁶. However, the underlying cause of such extensive immune dysregulation is not thoroughly identified⁷. Long non-coding RNAs (lncRNAs) have central influences on the activity of immune system⁸,⁹. Contribution of a number of these transcripts in the pathogenesis of CIDP and GBS has been recently verified by our group⁵. However, the role of several members of lncRNAs in autoimmune neuropathies needs to be elucidated. In the current project, we have selected HULC, PVT1, MEG3, SPRY4-IT1, LINC-ROR and DSCAM-AS1 lncRNAs to appraise their transcript levels.

¹Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ³Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. ⁴Department of Electrical Engineering, Sharif University of Technology, Tehran, Iran. ⁵email: mohammad_823@yahoo.com; ar.sayad@yahoo.com; s.ghafourifard@sbmu.ac.ir
levels in the circulation of CIDP and GBS cases versus controls. The reason for selection of these lncRNAs was their roles in modulation of immune responses. HULC has been identified as one of important factors in induction of pro-inflammatory responses in the course of lipopolysaccharide-associated sepsis in endothelial cells\(^9\). PVT1 has been shown to modulate the immunosuppression function of granulocytic myeloid-derived suppressor cells in animal models\(^12\). MEG3 has been reported to induce imbalance between regulatory T cells and Th17 cells\(^12\). SPRY4-IT1 interacts with ERRα\(^13\), a nuclear receptor which regulates innate immunity\(^14\). LINC-ROR has functional interaction with TGF-β to regulated hypoxia-induced cellular cascades\(^15\). Finally, DSCAM-AS1 has been shown to regulate several genes which are implicated in inflammatory responses\(^16\). These lncRNAs regulate immune reactions via different routes.

### Materials and methods

#### Recruitment of GBS/CIDP cases and normal controls.
A total of 32 CIDP patients with typical type (11 females, 21 males), 25 GBS patients (7 females, 18 males), and 58 healthy individuals (20 females and 38 males) participated in the current investigation. CIDP cases had symmetric muscle weakness which affected both proximal and distal muscles. The course of disorder was compliant with a motor-predominant neuropathy. Patients were assessed using the guidelines stated by American Academy of Neurology\(^17\) and National Institute of Neurological Disorders and Stroke\(^18\). In addition, electrophysiological criteria were used for diagnosis of GBS\(^19\). Blood samples were obtained when patients entered the remission phase and were not on any treatment. All were responsive to corticosteroids or IV Ig treatment. No concomitant treatment was used for these patients. None of them had any comorbid condition. Persons recruited as controls had no recent or chronic infection, malignant condition, or any systemic diseases. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.575) and the study protocol is performed in accordance with the relevant guidelines. Informed consent forms were signed by all recruited persons.

#### Expression assay.
Three milliliters of the peripheral blood of all recruited people were obtained for RNA extraction. This phase was performed using the GeneAll kit (Seoul, Korea). The retrieved RNA was then transcribed to cDNA using the kit prepared by the Thermo Fisher Scientific Company (Brussels, Belgium). Expression levels of mentioned lncRNAs were measured in GBS and CIDP cases versus healthy persons using the Ampliqon master mix (Odense, Denmark). Reactions were executed in the Step One Plus Real-Time PCR system (Applied Biosystems, Foster city, CA, USA). Table 1 shows the characteristics of primers designed for amplification of HULC, PVT1, MEG3, SPRY4-IT1, LINC-ROR and DSCAM-AS1.

#### Statistical methods.
Expression of selected lncRNAs were analyzed in the R V.3.4 software\(^20\). Transcript magnitudes of these lncRNAs in comparison with the levels of B2M gene were measured from Ct and efficiency values. The obtained figures were log2 transformed. The significance of difference in mean values of transcript intensities of lncRNAs was judged using the t-test. Correlations between expression quantities were appraised using Spearman correlation test. Receiver operating characteristic (ROC) curves were plotted to quantify the diagnostic values of expression levels of lncRNAs. Youden's J statistic was used to determine the optimum threshold. Area under curve (AUC) values were quantified.

#### Ethics approval and consent to participant.
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical com-

### Table 1. Characteristics of primers designed for amplification of HULC, PVT1, MEG3, SPRY4-IT1, LINC-ROR and DSCAM-AS1.

| Gene      | Primer sequence       | Primer length | Product size |
|-----------|-----------------------|---------------|--------------|
| HULC      | Forward primer: ACGTGAGGATAAAGCGAAGGC | 20            | 75           |
|           | Reverse primer: AGAGTTCTCCTCATGCTGTCG | 20            |              |
| PVT1      | Forward primer: CCCGAATCTAGCATTCATCCTC | 19            | 131          |
|           | Reverse primer: GGTGTGACTCATCTATATTCAA | 21            |              |
| MEG3      | Forward primer: TGCCATAGGAGGAGGTGAT | 18            | 111          |
|           | Reverse primer: GAGATGTGGTGTGGAGAAATA | 19            |              |
| SPRY4-IT1 | Forward primer: ACGCACTAATTACAGCAGA | 20            | 115          |
|           | Reverse primer: GATGATAGACTCTTCTCA | 18            |              |
| LINC-ROR  | Forward primer: TATATTGAGATACACCTTT | 20            | 170          |
|           | Reverse primer: AGGAACCTGCTACACCGTTTC | 20            |              |
| DSCAM-AS1 | Forward primer: TCAGTGCTGCTACAGGGGAT | 20            | 118          |
|           | Reverse primer: GAGGAAGGCCAGAGAAGGA | 20            |              |
| R2M       | Forward primer: AGATGATATGCTGGCGGTG | 20            | 105          |
|           | Reverse primer: GCCGACATCTTCAAACCTCAA | 20            |              |
Table 2. Demographic and clinical data of patients.

|               | Age (mean ± SD, Y) | GBS | CIDP |
|---------------|--------------------|-----|-----|
|               | 49.72 ± 14.6       | 50.5 ± 15.8 |
| Prolonged F waves (%) | 70          | 90 |
| Prolonged distal motor latency (%) | 85          | 58 |
| Slowed conduction velocity (%) | 87          | 67 |
| Conduction block (%) | 65          | 30 |

Table 3. Detailed parameters of expression analysis of IncRNAs in patients and controls.

|               | SE | RME | P Value | 95% CI | SE | RME | P Value | 95% CI | SE | RME | P Value | 95% CI |
|---------------|----|-----|---------|--------|----|-----|---------|--------|----|-----|---------|--------|
|**HULC**       |    |     |         |        |    |     |         |        |    |     |         |        |
| Total         | 32/58 | 0.72 | 7.62    | 0.00   | 1.49 | 4.37 | 0.51 | 3.04 | 0.00 | 0.58 | 2.63 | 0.77 | 13.52 | 0.00 | 2.23 | 5.28 |
| F             | 11/20 | 0.93 | 2.57    | 0.16   | -0.56 | 3.28 | 0.58 | 2.99 | 0.02 | 0.35 | 2.81 | 1.08 | 6.94 | 0.02 | 0.58 | 5.01 |
| M             | 21/38 | 0.98 | 13.50   | 0.00   | 1.77 | 5.74 | 0.73 | 3.07 | 0.03 | 0.16 | 3.08 | 1.02 | 19.19 | 0.00 | 2.21 | 6.31 |
| GBS/Control   | 25/58 | 0.65 | 4.57    | 0.00   | 0.90 | 3.49 | 0.55 | 2.99 | 0.01 | 0.47 | 2.70 | 0.73 | 11.70 | 0.00 | 2.09 | 5.01 |
| F             | 7/20  | 0.94 | 3.89    | 0.05   | -0.03 | 3.95 | 0.76 | 3.31 | 0.06 | -0.05 | 3.51 | 0.93 | 26.07 | 0.00 | 2.79 | 6.62 |
| M             | 18/38 | 0.82 | 5.48    | 0.00   | 0.81 | 4.10 | 0.74 | 2.79 | 0.05 | -0.02 | 2.98 | 0.95 | 8.66 | 0.00 | 1.20 | 5.03 |
| CIDP/GBS      | 32/25 | 0.71 | 1.67    | 0.31   | -0.70 | 2.17 | 0.62 | 1.02 | 0.97 | -1.21 | 1.26 | 0.75 | 11.60 | 0.00 | -1.30 | 1.72 |
| F             | 11/7  | 0.97 | 0.66    | 0.55   | -2.66 | 1.47 | 0.89 | 0.90 | 0.87 | -2.09 | 1.79 | 0.92 | 2.27 | 0.06 | -3.87 | 0.05 |
| M             | 21/18 | 0.95 | 2.46    | 0.18   | -0.63 | 3.23 | 0.81 | 1.10 | 0.87 | -1.51 | 1.78 | 0.98 | 2.22 | 0.25 | -0.84 | 3.14 |
| All Patients/Control | 57/58 | 0.60 | 6.09    | 0.00   | 1.43 | 3.79 | 0.43 | 3.02 | 0.00 | 0.74 | 2.45 | 0.65 | 12.69 | 0.00 | 2.38 | 4.95 |
| F             | 18/20 | 0.80 | 3.02    | 0.06   | -0.04 | 3.23 | 0.48 | 3.11 | 0.00 | 0.66 | 2.62 | 0.94 | 11.61 | 0.00 | 1.63 | 5.45 |
| M             | 39/38 | 0.78 | 8.90    | 0.00   | 1.60 | 4.71 | 0.61 | 2.94 | 0.01 | 0.35 | 2.76 | 0.86 | 13.29 | 0.00 | 2.01 | 5.45 |
|**SPRY4–IT1**  |    |     |         |        |    |     |         |        |    |     |         |        |
| Total         | 32/58 | 0.76 | 25.02   | 0.00   | 3.13 | 6.16 | 0.76 | 6.55 | 0.00 | 1.19 | 4.23 | 0.85 | 10.96 | 0.00 | 1.74 | 5.17 |
| F             | 11/20 | 0.93 | 31.54   | 0.00   | 3.03 | 6.93 | 1.06 | 3.00 | 0.15 | -0.58 | 3.76 | 1.22 | 13.12 | 0.01 | 1.13 | 6.30 |
| M             | 21/18 | 0.95 | 22.14   | 0.00   | 2.34 | 6.59 | 1.02 | 9.86 | 0.00 | 1.26 | 5.35 | 1.12 | 9.96 | 0.01 | 1.04 | 5.59 |
| GBS/Control   | 25/58 | 0.64 | 9.96    | 0.00   | 2.04 | 4.60 | 0.75 | 3.06 | 0.03 | 0.12 | 3.11 | 0.77 | 5.13 | 0.00 | 0.81 | 3.90 |
| F             | 7/20  | 0.89 | 27.37   | 0.00   | 2.85 | 6.70 | 1.22 | 5.04 | 0.07 | -0.26 | 4.93 | 0.96 | 23.12 | 0.00 | 2.45 | 6.61 |
| M             | 18/38 | 0.86 | 6.36    | 0.00   | 0.94 | 4.39 | 0.95 | 2.58 | 0.16 | -0.55 | 3.28 | 1.01 | 2.54 | 0.19 | -0.70 | 3.39 |
| CIDP/GBS      | 32/25 | 0.69 | 2.51    | 0.06   | -0.05 | 2.70 | 0.72 | 2.14 | 0.14 | -0.35 | 2.55 | 0.95 | 2.14 | 0.25 | -0.81 | 3.00 |
| F             | 11/7  | 1.07 | 1.15    | 0.85   | -2.06 | 2.47 | 1.17 | 0.60 | 0.54 | -3.29 | 1.80 | 1.34 | 0.57 | 0.55 | -3.67 | 2.03 |
| M             | 21/18 | 0.89 | 3.48    | 0.05   | -0.01 | 3.61 | 0.91 | 3.82 | 0.04 | 0.09 | 3.78 | 1.23 | 3.92 | 0.12 | -0.53 | 4.47 |
| All Patients/Control | 57/58 | 0.63 | 16.70   | 0.00   | 2.82 | 5.31 | 0.67 | 4.69 | 0.00 | 0.90 | 3.56 | 0.67 | 7.86 | 0.00 | 1.65 | 4.30 |
| F             | 18/20 | 0.74 | 29.85   | 0.00   | 3.40 | 6.40 | 0.96 | 3.67 | 0.06 | -0.08 | 3.83 | 0.90 | 16.36 | 0.00 | 2.20 | 5.87 |
| M             | 39/38 | 0.87 | 12.45   | 0.00   | 1.89 | 5.38 | 0.89 | 5.31 | 0.01 | 0.63 | 4.19 | 0.89 | 5.30 | 0.01 | 0.64 | 4.17 |

Results

Table 2 demonstrates demographic and clinical data of patients.

Expression of HULC was higher in CIDP patients compared with controls (Ratio of mean expression (RME) = 7.62, SE = 0.72, P < 0.001). While expression of this lncRNA was similar between female CIDP

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cases and female controls, its expression was up-regulated in male CIDP cases compared with male controls (RME = 13.50, SE = 0.98, P < 0.001). Similarly, expression of HULC was higher in total GBS cases compared with controls (RME = 4.57, SE = 0.65, P < 0.001) and in male cases compared with male controls (RME = 5.48, SE = 0.82, P < 0.001). Similar pattern of expression was detected between total cases and total controls. PVT1 was up-regulated in CIDP cases compared with controls (RME = 3.04, SE = 0.51, P < 0.001) and in both male and female CIDP cases compared with sex-matched healthy persons. Similarly, PVT1 was up-regulated in GBS cases compared with controls (RME = 2.99, SE = 0.55, P < 0.001) and in total patients compared with total controls (RME = 3.02, SE = 0.43, P < 0.001). Expression levels of DSCAM-AS1 and SPRY4-IT1 were higher in CIDP and GBS cases compared with controls and in both sexes compared with gender-matched healthy subjects. Although LINC-ROR was up-regulated in total CIDP and total GBS cases compared with controls, in sex-based comparisons, it was only up-regulated in male CIDP cases compared with male controls (RME = 3.06, P = 0.03). Finally, expression of MEG3 was up-regulated in all subgroups of patients versus controls except for male GBS controls (Table 3).

Figure 1 displays expression amounts of selected lncRNAs in study subgroups. Mean values and interquartile range are displayed. Purple dots show each expression level. Black dot represents outliers. (This figure has been depicted by R software).

Significant pairwise correlations have been identified between lncRNAs expressions with the most robust one being HULC/DSCAM-AS1 and HULC/SPRY4-IT pairs (r = 0.86 and 0.85 respectively) (Fig. 2).

Among healthy controls, the most robust correlations have been reported between HULC/DSCAM-AS1 and HULC/LINC-ROR pairs (r = 0.84 for both pairs) (Fig. 3).

Finally, diagnostic power of lncRNAs for distinguishing patients from healthy subjects was assessed (Fig. 4). SPRY4-IT could differentiate CIDP cases from controls with AUC = 0.84, sensitivity = 0.63 and specificity = 0.97. AUC values of DSCAM-AS1, MEG3, HULC, PVT1 and LINC-ROR were 0.80, 0.75, 0.74, 0.73 and 0.72, respectively. In differentiation between GBS cases and controls, SPRY4-IT and DSCAM-AS1 has the AUC value of 0.8. None of lncRNAs could appropriately differentiate between CIDP and GBS cases. Combination of all lncRNAs could not significantly enhance the diagnostic power (Table 4).

Discussion
LncRNAs have been shown to take part in the pathogenesis of immune-related conditions. Up-regulation of lncRNAs has been reported in a number of these conditions. For instance, expression levels of HOXATIR, LUST, anti-NOS2A, MEG9, SNHG4, TUG1, and NEAT1 have been shown to be increased in blood exosomes of patients with rheumatoid arthritis (RA) compared with exosomes retrieved from normal blood samples. The same study has reported up-regulation of mentioned lncRNAs in addition to H19 antisense, HARI8 and GAS5 in peripheral blood mononuclear cells of these patients. ENST00000483588 is another lncRNA which has been shown to be up-regulated in fibroblast-like synoviocytes of patients with RA. A number of selected lncRNAs in the current

Figure 1. Expression levels of lncRNAs in study subgroups. Mean values and interquartile range are displayed. Purple dots show each expression level. Black dot represents outliers. (This figure has been depicted by R software).
project have been previously shown to be up-regulated in immune-mediated conditions. For instance, PVT1 has been reported to be up-regulated in fibroblast-like synoviocytes of RA models parallel with down-regulation of sirt6, a putative target for this lncRNA. PVT1 silencing or sirt6 over-expression could suppress cell proliferation and inflammation, while inducing cell apoptosis23. MEG3 has been demonstrated to regulate RA pathogenesis through targeting NLRC524. LINC-ROR, MEG3, SPRY4-IT1 and UCA1 have been among lncRNA with higher expression in patients with schizophrenia compared with normal subjects25.

CIDP and GBS disorders are two immune-mediated conditions in which lncRNAs might contribute. We measured expression of amounts of six immune-related lncRNAs in the circulation of these patients versus healthy controls. Expression of HULC was higher in CIDP patients compared with controls. While expression of this lncRNA was not different between female CIDP cases and female controls, its expression was higher in male CIDP cases compared with male controls. Similarly, expression of HULC was higher in total GBS cases compared with controls and in male cases compared with male controls. Similar pattern of expression was detected between total cases and total controls. HULC has been shown to regulate immune responses through miR-128-3p/RAC1 axis26. In line with our observations, miR-128-3p has been shown to be down-regulated in cerebrospinal fluid of animal models of GBS27. RAC1 regulates a number of inflammatory pathways such as STAT3 and NF-κB28. NF-κB pathway has a documented effect in the pathogenesis of immune-related neuropathies29. Therefore, HULC/miR-128-3p/RAC1 axis might also been involved in the pathogenesis of CIDP and GBS.

PVT1 was up-regulated in CIDP cases compared with controls and in both male and female CIDP cases compared with sex-matched controls. Similarly, PVT1 was up-regulated in GBS cases compared with controls and in total patients compared with total controls. Contrary to this finding, we have previously reported down-regulation of PVT1 in the peripheral blood of patients with multiple sclerosis30. Therefore, this lncRNA might have distinctive effects in these two inflammatory conditions. Expression levels of DSCAM-AS1 and SPRY4-IT1 were higher in CIDP and GBS cases compared with controls and in both sexes compared with sex-matched controls. Therefore, these lncRNAs have a consistent pattern of expression among CIDP and GBs patients potentiating them as biomarkers for these conditions.

Although LINC-ROR was up-regulated in total CIDP and total GBS cases compared with controls, in sex-based comparisons, it was only up-regulated in male CIDP cases compared with male controls indicating the
possible interactions between this lncRNA and sex-related parameters, since there was no gender-based difference in phenotype of the patients in terms of severity of illness.

Finally, expression of \( \text{MEG3} \) was up-regulated in all subgroups of patients versus controls except for male GBS controls. Expression of \( \text{MEG3} \) has been shown to be elevated in CD4+ T cells of patients with immune thrombocytopenic purpura. Expression of this lncRNA has been reduced in CD4+ T cells cultured with dexamethasone12. Functionally, \( \text{MEG3} \) inhibits Foxp3 expression and increases ROR\( \gamma \)t expression, thus inducing imbalance between regulatory T cells and Th17 cells12. The imbalance between these subsets of T cells might participate in the pathogenesis of GBS or CIDP as previous studies have shown the therapeutic effects of regulatory T cells in animal models of GBS31.

The correlations between expression levels of mentioned lncRNAs were not meaningfully different between patients and controls based on the measured correlation coefficients. \( \text{SPRY4-IT} \) and \( \text{DSCAM-AS1} \) could differentiate CIDP cases from controls with appropriate diagnostic power values. Similarly, these lncRNAs had high power in differentiation between GBS cases and controls. Since expression levels of lncRNAs were almost similar between CIDP cases and GBS cases, none of lncRNAs could appropriately differentiate between CIDP and GBS cases. Combination of all lncRNAs could not significantly enhance the diagnostic power. Taken together, these lncRNAs might be involved in the development of CIDP or GBS. These transcripts might be regarded as marker for these immune-related conditions as well. Future studies should appraise expression of these transcripts in other immune-related conditions to evaluate their suitability as diagnostic markers for GBS/CIDP.
Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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A.S. and S.G.F. wrote the draft and revised it. M.T. and M.G. performed the experiment. N.N. and J.M.H. analyzed the data. All authors contributed equally and fully aware of submission.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to M.T., A.S. or S.G.-F.
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