New biomarker candidate for amyotrophic lateral sclerosis

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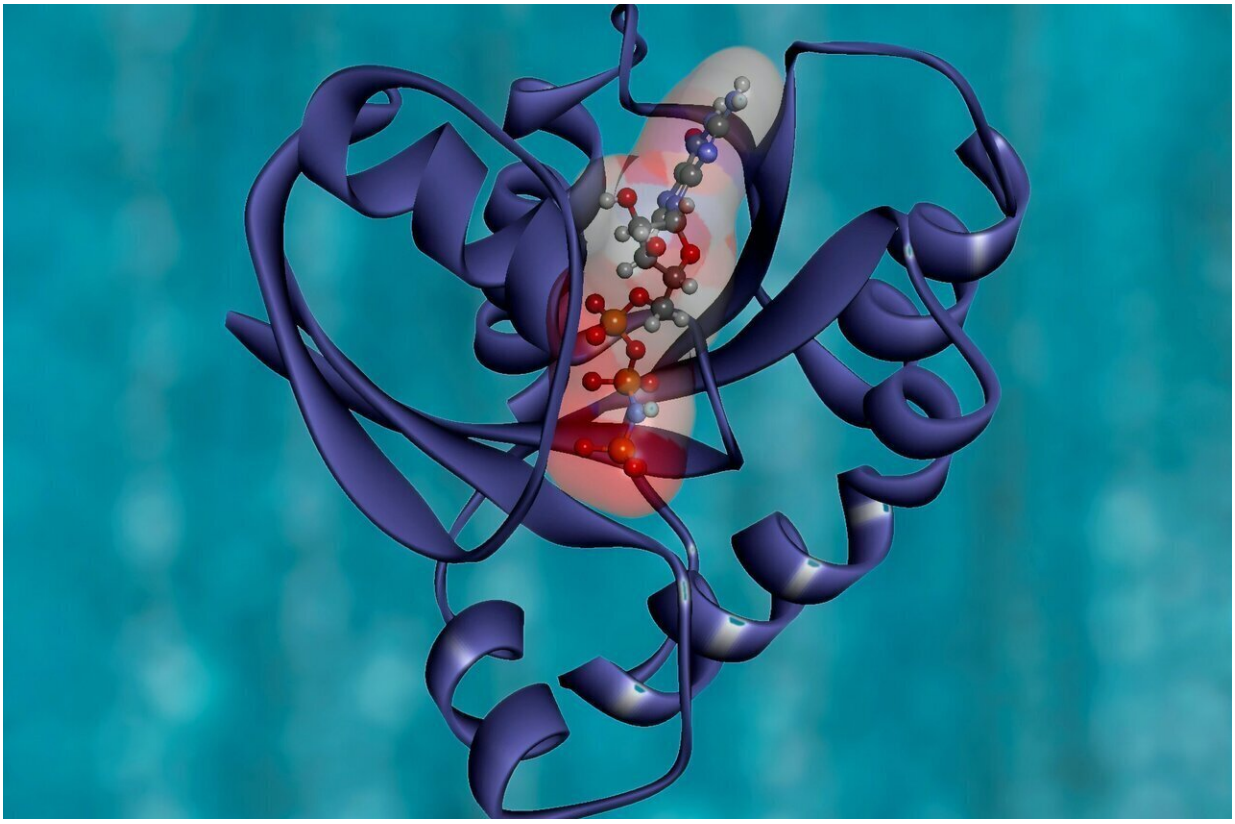

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ALS is a fatal neurodegenerative disease causing a rapid loss of motor function, which usually results in a serious condition with early death within a few years. So far, early and precise diagnosis of the disease has

been difficult. Stephen Hawking was one of the most prominent patients. In summer 2014, the disease gained media attention through a large-scale fundraising campaign, the so-called Ice Bucket Challenge.

To date, one of the most important challenges in ALS diagnostics is to exclude other mimicking diseases and to reliably verify an exact diagnosis. In ALS, the TDP-43 protein in particular plays a pivotal role. It forms small inclusions in nerve cells. TDP-43 inclusions appear to have a crucial pathomechanistic significance and are the neuropathological markers in sporadic and many genetic ALS cases. They have been detected in numerous brain autopsies of ALS patients. In this study, the Bochum researchers and their colleagues showed that pathologically misfolded forms of the protein also occur in solution in the nerve fluid and can be specifically analyzed there.

Dr. Rene Günther, one of the lead authors of the study and head of the research group and specialist outpatient clinic for motor neuron diseases at the Department of Neurology of the Carl Gustav Carus University Hospital at the Technical University of Dresden, explains: "Biomarker research plays a crucial role in improving early detection and securing the diagnosis of amyotrophic lateral sclerosis. In addition, biomarkers are a basis for successful drug testing and therapy development in this dramatically progressing and difficult to treat disease. So far, only disease-unspecific biomarkers are available. In our pilot study, we successfully identified conformational changes of TDP-43 proteins in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis for the first time using this innovative method."

Pilot study shows potential

The team led by Lars Tönges and Klaus Gerwert succeeded in securing a diagnosis of the disease based on the altered structure of the protein TDP-43. In the process, the researchers showed that the proteins fold

from predominantly disordered and helical structures to so-called ß-sheets. These shapes promote damage assemblies and deposits of the protein in nerve cells. In the analysis, 36 ALS patients were distinguished from 30 Parkinson's patients by means of the TDP-43 signal with a sensitivity of 89 percent and a specificity of 77 percent. In addition, a control group with neurologically inconspicuous patients was differentiated with a sensitivity of 89 percent and a specificity of 83 percent. By analyzing TDP-43, the researchers were thus able to exclude other diseases that affect motor function, such as Parkinson's disease. These results will be verified and validated in a larger study.

Klaus Gerwert's immuno-infrared sensor has already been used in earlier studies to detect pathologically altered proteins in the blood of patients with Alzheimer's disease before symptoms occur. In this case, the technology has been optimized and refined for use in the cerebrospinal fluid of patients with ALS. This shows that the potential of the method for other neurological diseases should also be explored. In close collaboration with Professor Ralf Gold, director of the Department of Neurology at St. Josef-Hospital Bochum and Head of Research at the Prodi Department of Experimental Medicine, further projects are currently being undertaken to gain a better understanding of neurological disease processes.

Léon Beyer, one of the lead authors of the study and Ph.D. student at the Prodi Biospectroscopy Department, says: "This achievement may provide new insight into the mechanisms of the disease. Compared to other methods that reflect concentrations of certain proteins, our infrared sensor technology gives insights into molecular events and may therefore become a crucial tool in the future for diagnosing and for developing clinical therapies. First and foremost, however, it will contribute greatly to a more precise understanding of diseases."

In the future, the results of validation studies should provide information

on whether the pathologically modified TDP-43 proteins can be used in clinical applications to facilitate earlier and more precise diagnoses and to gain new molecular insights.

More information: Léon Beyer et al. TDP-43 as structure-based biomarker in amyotrophic lateral sclerosis, *Annals of Clinical and Translational Neurology* (2020). DOI: 10.1002/acn3.51256

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