The Importance of Diagnostic and Prognostic Biomarker Identification and Classification Towards Understanding ALS Pathogenesis

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Abstract

ALS is increasingly perceived as a multisystem neurodegenerative disorder, and the identification of a panel of biomarkers that accurately reflect features of pathology is a priority, not only for diagnostic purposes but also for prognostic or predictive applications [1]. Thus, as a multisystemic disease, it is likely that a panel of biomarkers will be needed to fully capture the features of ALS pathology. Taking also into consideration the fact that its causes remain unknown to their majority, it remains a complex disease driven by a combination of several systemic parameters [2]. Beyond the monogenic causes, representing the 15% of the ALS cases, which list up to 30 gene mutations with the most frequent being C9orf72, SOD1, FUS, and TARDBP/TDP43 [3–5], much research is being done to identify and associate possible causes for the 80% of ALS cases (sALS and fALS combined) which at the moment are not explained by a known mutation [2, 4]. ALS sporadic cases are related to a multigenic component, and/or involve epigenetic modification, and/or result from DNA damage, environmental risk factors, behavioural factors, oxidative stress or viral infections leading to cellular dysfunctions [4, 6–10]. ALS diagnosis is lengthy and there is a typical diagnostic delay of 9–15 months from onset to diagnostic confirmation based on clinical and electrophysiological criteria as well as the exclusion of diseases with similar behaviour to ALS. Three major exclusion criteria are involved in the diagnosis process: the Revised El Escorial Criteria (REEC), the Airlie House Criteria (AHC) and the Awaji Criteria [11, 12]. Taking into consideration that the average survival is 2–4 years, it makes it urgent for the researchers to improve diagnostic speed and accuracy for ALS [13, 14]. In the absence of a reliable diagnostic test for ALS, biomarkers are a strong weapon not only for its diagnosis but also for understanding the pathomechanism as well as a basis for the development of therapeutics. Recent global research has accepted the fact that biomarkers will facilitate the combination of therapeutics with diagnostics and will thus play an important role in the development of personalized medicine [15]. This paper proposes a combination of diagnostic and prognostic biomarkers to meet the scope of global research. Thus, biomarkers specific to ALS pathology need to be identified towards the development of a reliable fast diagnostic test, while at the same time prognostic biomarkers should also be identified to monitor the status of the pathology as various candidates may serve both purposes. Finally,

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P. Vlamos (ed.), *GeNeDis 2020*, Advances in Experimental Medicine and Biology 1339,
https://doi.org/10.1007/978-3-030-78787-5_16

since different sub-cohorts of ALS patients respond differently to treatments [16], the identification of ALS biomarkers will contribute to a better understanding of the disease pathogenesis and permit targeted drug development and patient stratification leading to more efficient clinical trials.

Keywords

ALS · Biomarkers · Diagnostic biomarkers · Prognostic biomarkers · Personalized medicine

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