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Blood Based Biomarkers in Test for Autism Suggest a Challenge to Proteostasis in Development of the Condition

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Abstract

Autism Spectrum Disorder (ASD) is of increasing prevalence and concern. The current diagnosis of ASD requires referral to an expert in child psychology and behavior to perform interviews and observational studies. There are often long delays and lengthy diagnosis period. There is currently no blood test for autism.

To develop a simple blood test for autism, we tested the hypothesis that a combination of spontaneous. modifications of plasma protein - glycation, oxidation and nitration, optimized by artificial intelligence machine learning may provide a diagnostic test of suitable accuracy and clinical chemistry to make it potentially available through the routine clinical diagnostics service. In our discovery phase study, published in Molecular Autism in 2018, we found that using support vector machine algorithm development, a combination of 3 advanced glycation endproducts(AGEs) - Nε-carboxymethyl-lysine (CML) and Nω-carboxymethylarginine (CMA) increased and 3-deoxyglucosone-derived hydroimidazolone (3DG-H) decreased in ASD, and one oxidation adduct - dityrosine (DT), increased in ASD, provided a pilot stage high accuracy blood test for autism. The accuracy was 88%, sensitivity 92%, specificity 84% and receiver operating characteristic area-under-the-curve AUROC 94%. The positive likelihood ratio was 5.8 and the negative likelihood ratio 0.10 indicating the test gave moderate evidence for the presence of autism and strong, often conclusive evidence for the absence of autism. In a subsequent validation study in a multi-centred, international clinical cohort of 450 case and control subjects, the features of the diagnostic algorithm were confirmed, and a similar high diagnostic accuracy was achieved.

The combination of these protein modifications suggested that ASD have a link to exposure to increased lipid peroxidation, protein crosslinking linked to gut mucosal immunity and increased removal of 3-deoxyglucosone-linked misfolded proteins. This is supported by recent studies of post-motem gene expression in the brain of subjects with autism suggesting a transcriptional response to increased misfolded proteins.

We conclude that data driven combination of selected plasma protein AGEs and DT produced diagnostic algorithms of high sensitivity and specificity suitable for the basis of a blood test for ASD. With the recent validation in a large independent cohort, this blood test offers the exciting possibility of an early diagnostic resource to support clinical experts in achieving a timely and accurate diagnosis of autism. We are now seeking clinical diagnostics company partners to bring this to market.