Towards the Development of a Diagnostic Test for Autism Spectrum Disorder: Big Data Meets Metabolomics

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Keywords: autism spectrum disorder, fisher discriminant analysis, kernel partial least squares

Abstract:

Autism Spectrum Disorders (ASD) are a group of neurological disorders that present with limited social communication/interaction and restricted, repetitive behaviors/interests. The current estimate is that approximately 1.9% of children in the US are diagnosed with ASD. While this is a high prevalence and the economic burden by ASD is significant, there is still considerable debate regarding the underlying pathophysiology of ASD. Because of this lack of biological knowledge, autism diagnoses are restricted to observational behavioral and psychometric tools. This work takes a step towards the goal of incorporating bio-chemical data into ASD diagnosis by analyzing measurements of metabolite concentrations of the folate-dependent one-carbon metabolism and transulfuration pathways. Unlike traditional approaches that are based upon comparing differences in individual metabolite concentrations between children with and without an ASD diagnosis, we made use of multivariate classification via Fisher Discriminant Analysis and used Kernel Partial Least Squares regression to predict adaptive behavior. Although these results need to be replicated in independent studies, these analyses suggest combinations of metabolites in these path-ways as potential biomarkers for ASD.

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Towards the Development of a Diagnostic Test for Autism Spectrum Disorder: Big Data Meets Metabolomics

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ABSTRACT

Autism Spectrum Disorders (ASD) are a group of neurological disorders that present with limited social communication/interaction and restricted, repetitive behaviors/interests. The current estimate is that approximately 1.9% of children in the US are diagnosed with ASD. While this is a high prevalence and the economic burden by ASD is significant, there is still considerable debate regarding the underlying pathophysiology of ASD. Because of this lack of biological knowledge, autism diagnoses are restricted to observational behavioral and psychometric tools. This work takes a step towards the goal of incorporating biochemical data into ASD diagnosis by analyzing measurements of metabolite concentrations of the folate-dependent one-carbon metabolism and transulfuration pathways. Unlike traditional approaches that are based upon comparing differences in individual metabolite concentrations between children with and without an ASD diagnosis, we made use of multivariate classification via Fisher Discriminant Analysis and used Kernel Partial Least Squares regression to predict adaptive behavior. Although these results need to be replicated in independent studies, these analyses suggest combinations of metabolites in these pathways as potential biomarkers for ASD.

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INTRODUCTION

Autism Spectrum Disorders (ASD) are a group of neurological disorders that present with limited social communication and interaction and restricted, repetitive behaviors and interests [1]. The current estimate is that approximately 1.9% of children in the US are diagnosed with ASD [2]. While this is a high prevalence and the economic burden by ASD is significant [3], there is still considerable debate regarding the underlying pathophysiology of ASD. Because of this lack of biological knowledge, autism diagnoses are restricted to observational behavioral and psychometric tools. Subsequently, the average age at which children receive an ASD diagnosis is four years, while it is generally acknowledged that diagnosis between 18-24 months is possible [4]. Furthermore, disparities by race/ethnicity in estimated ASD prevalence as well as disparities in the age of earliest comprehensive evaluation and presence of a previous ASD diagnosis or classification, suggest that access to treatment and services might be lacking or delayed for some children. Thus, confirmation and expansion of the unique metabolic abnormalities in children with autism that accurately distinguishes them from typically developing children would not only strengthen diagnostic accuracy, but also provide insights into underlying pathophysiology and a personalized approach to treatment options.

METHODS

Stepping towards this goal of incorporating biochemical data into ASD diagnosis, we analyzed measurements of metabolite concentrations of the folate-dependent one-carbon metabolism and transulfuration pathways taken from blood samples of 83 participants with ASD and 76 age-matched typically developing peers. Fisher Discriminant Analysis enabled multivariate classification of the participants as on the spectrum or typically developing which results in 96.1% of all typically developing participants being correctly identified as such while still correctly identifying 97.6% of the ASD cohort [5]. Furthermore, kernel partial least squares was used to predict adaptive behavior, as measured by the Vineland Adaptive Behavior Composite score, where measurement of five metabolites of the pathways was sufficient to predict the Vineland score with an R^2 of 0.45 after cross-validation [5]. These results have been partially validated in a separate study involving 156 participants with an ASD diagnosis where over 88% of the participants were correctly identified as having an ASD diagnosis [6].

DISCUSSION

This computational study enhances the analysis obtained from traditional population-level statistics and suggest that folate-dependent one carbon metabolism and transsulfuration may play an integral role in ASD pathophysiology. Furthermore, the work highlights the contribution that systems approaches can make for clinical studies involving significant amount of data, some of which are often correlated and require multivariate analysis methods [7]. Although these results need to be replicated in independent studies, these analyses suggest combinations of metabolites in these pathways as potential biomarkers for ASD.

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REFERENCES

1. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, D.C.: American Psychiatric Association (2013)
2. Maenner MJ, Shaw KA, Baio J, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR Surveill Summ 2020*. 69:SS-4:1–12 (2020)
3. Leigh JP and Du J. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. *J Autism Dev Disord*, 45:12:4135–4139 (2015)
4. McPheeters ML, et al. Screening for Autism Spectrum Disorder in Young Children: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville, Maryland, 13-05185-EF-1 (2016)
5. Howsmon DP, Kruger U, Melnyk S, James SJ, and Hahn J. Classification and Adaptive Behavior Prediction of Children with Autism Spectrum Disorder based upon Multivariate Data Analysis of Markers of Oxidative Stress and DNA Methylation. *PLoS Computational Biology* 13:3:e1005385 (2017)
6. Howsmon DP, Vargason T, Rubin RA, Delhey L, Tippett M, Rose S, Bennuri SC, Slattery JC, Melnyk S, James SJ, Frye RE, and Hahn J. Multivariate Techniques Enable a Biochemical Classification of Children with Autism Spectrum Disorder versus Typically-Developing Peers: A Comparison and Validation Study. *Bioeng Translational Med* 3:2:156-165 (2018)
7. Vargason T, Grivas G, Hollowood-Jones KL, and Hahn J. Towards a Multivariate Biomarker-based Diagnosis of Autism Spectrum Disorder: Review and Discussion of Recent Advancements. *Seminars in Pediatric Neurology* 34:100803 (2020)