Title: Plasma Metabolomics Analysis of Children with Down Syndrome, Autism Spectrum Disorder, And Idiopathic-Developmental Delays Reveals Similar Metabolic Alterations

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Introduction: Down syndrome (DS) has a known genetic origin caused by abnormal cell division of chromosome 21 (HSA21). However, little is known about its etiology apart from an increased risk with advanced maternal age (Yoon et al., 1996). Paradoxically, individuals with DS are protected from some medical conditions, but are highly predisposed to others directly linked to trisomy HSA21 (van Schrojenstein Lantman-de Valk, Haveman, & Crebolder, 1996) (e.g. overexpression of amyloid protein resulting in increased Alzheimer’s risk (Patterson et al., 1988), and overexpression of superoxide dismutase 1 contributing to underlying oxidative stress in DS (Pagano & Castello, 2012; Wojtovich, Smith, Haynes, Nehke, & Brookes, 2013). Furthermore, gene products of HSA21 may also be interacting with genes/proteins on other chromosomes, resulting in widespread metabolic consequences. Indeed, although developmental delays are a group of conditions specifically affecting learning, language, behavior, and sometimes physical impairment, evidence suggest that developmental delays may also be present with disturbances in metabolism (Kaddurah-Daouk & Krishnan, 2009). Unlike DS, with a known singular chromosomal origin, autism spectrum disorder (ASD), which has a complex gene-environmental origin, has also been associated with a number of metabolic abnormalities (Adams et al., 2011). In this project, we assessed similarities and differences between DS and ASD children based on a broad screen for metabolic impairments.

Method: All children in the present study including children with Autism Spectrum Disorder (ASD; n=184), Down syndrome (DS; n=39), idiopathic developmental delay (i-DD; n=78), and typically developed controls (TD; n=200) were from a subset of the Childhood Autism Risk from Genetics and Environment (CHARGE) Study (Hertz-Picciotto et al., 2006). Blood plasma metabolome profiles were obtained using Nuclear Magnetic Resonance (NMR) spectroscopy, and analyzed in an untargeted manner using Chenomx NMR Suite 8.1 to identify and quantify 50 metabolites in each sample that included amino acids, organic acids, sugars and other compounds. Multiple linear regression (MLR) was performed for each metabolite to assess the association between neurodevelopmental outcome (independent variables) and plasma metabolites (dependent). Typically developed (TD) children were used as a reference group for neurodevelopmental outcome. The final models were adjusted for child’s race/ethnicity, sex, and minutes fasted.

Result: Significant associations were found between 13 plasma metabolites and neurodevelopment when comparing ASD, i-DD, and DS cases to TD controls after controlling for false discovery rate. Compared to TD children, children with DS had significantly higher levels of lipid metabolites ( carnitine and O-acetylcarnitine), homocysteine metabolism metabolites (N-N-dimethylglycine and choline), the TCA cycle metabolite 2-oxoglutarate, creatinine and dimethyl sulfone. Children with ASD had significantly higher levels of the amino acid glycine and the urea cycle metabolite ornithine compared to TD controls. Children with i-DD had higher levels of plasma lactate and TCA cycle metabolites (2-oxoglutarate, cis-aconitate, and succinate), as well as lower levels of ascorbate compared to TD controls.

Discussion: Although the origins of these developmental disabilities vary, we observed commonalities in metabolic pathways related to mitochondrial dysfunction, alterations in one carbon metabolism, homocysteine/glutathione metabolism and the TCA cycle; however the direction of change, and specific metabolites varied by diagnosis. These results suggest alterations in metabolic pathways of the mitochondria may contribute to the metabolic pathophysiology of these neurodevelopmental disorders.

References/Citations:

