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Maternal metabolic profile predicts high or low risk of an autism pregnancy outcome

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ABSTRACT

Background: Currently there is no test for pregnant mothers that can predict the probability of having a child that will be diagnosed with autism spectrum disorder (ASD). Recent estimates indicate that if a mother has previously had a child with ASD, the risk of having a second child with ASD is ~18.7% (High Risk) whereas the risk of ASD in the general population is ~1.7% (Low Risk).

Methods: In this study, metabolites of the folate-dependent transmethylation and transsulfuration biochemical pathways of pregnant mothers were measured to determine whether or not the risk of having a child with autism could be predicted by her metabolic profile. Pregnant mothers who have had a child with autism before were separated into two groups based on the diagnosis of their child whether the child had autism (ASD) or not (TD). Then these mothers were compared to a group of control mothers who have not had a child with autism before. A total of 107 mothers were in the High Risk category and 25 mothers in the Low Risk category. The High Risk category was further separated into 29 mothers in the ASD group and 78 mothers in the TD group.

Results: The metabolic results indicated that among High Risk mothers, it was not possible to predict an autism pregnancy outcome. However, the metabolic profile was able to predict with approximately 90% sensitivity and specificity whether a mother fell into the High Risk group (18.7% risk) or Low Risk group (1.7% risk).

Conclusions: Based upon these measurements it is not possible to determine during a pregnancy if a child will be diagnosed with ASD by age 3. However, differences in the folate-dependent

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transmethylation and transsulfuration metabolites are indicative of the risk level (High Risk of 18.7% vs. Low Risk of 1.7%) of the mother for having a child with ASD.

1. Introduction

Progress in early diagnosis and treatment of autism spectrum disorder has been hindered by the lack of understanding of the underlying pathogenesis of the disorder which is a necessary prerequisite for the design of effective treatment and prevention strategies. Although gene-environment interactions are thought to be involved, as of yet none have been reproducibly identified. The metabolic basis for autism has received much less research attention despite the fact that chronic biochemical imbalance is often a primary factor in the development of complex diseases and has been implicated in the pathogenesis of multiple other neurobehavioral disorders (Andreazza et al., 2009; Dean et al., 2009; Gysin et al., 2007; Mattson & Shea, 2003; Smythies, Gottfries, & Regland, 1997). A targeted candidate pathway approach to autism pathogenesis offers advantages over untargeted genomic/proteomic approaches by providing a reflection of the combined influence of genes and environment on a defined metabolic phenotype.

In this study, we target the tetrahydrofolate (THF)-dependent methionine transmethylation and transsulfuration (TM/TS) pathways for glutathione (GSH) synthesis in pregnant mothers at high risk of having a second child with autism (Fig. 1). The vital importance of these three interconnected pathways during gestation is underscored by their essentiality for error-free DNA synthesis and repair, cell proliferation, and immune potential (Pathway 1); for essential cellular methylation reactions including DNA, RNA, proteins, phospholipids, and neurotransmitters (Pathway 2); and for the maintenance of glutathione (GSH) redox homeostasis for cell signaling, detoxification, stress response, cell cycle progression and apoptosis (Pathway 3). Because these three pathways regulate the distribution of precursors for DNA synthesis (proliferation), DNA/histone methylation (epigenetics) and glutathione synthesis (antioxidant/detoxification potential), the homeostatic balance between these pathways is essential to support normal cell programming and ontogeny during prenatal and post-natal development (Chmurzynska, 2010; Rassin, Sturman, & Gaull, 1981; Zeisel, 2009). Viewed in the context of systems biology, these are clearly core metabolic pathways that represent “hubs” for the regulation of gene expression and redox signaling during rapid fire shifts between proliferation, differentiation and cell death during fetal development. The biochemical details of these pathways details are included in the Fig. 1 legend.

Alterations in the prenatal intrauterine metabolic environment can have a profound influence on fetal brain development and

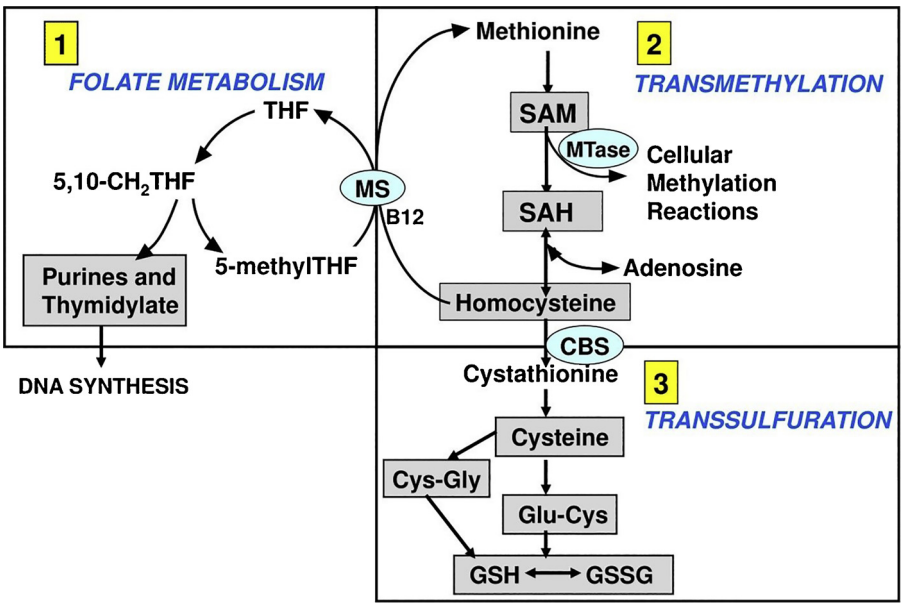

Fig. 1. Diagram of tetrahydrofolate (THF) – dependent methionine transmethylation and transsulfuration for glutathione (GSH) synthesis. THF is the metabolically active form of folate that is converted to 5-methylTHF, the primary methyl donor for methionine transmethylation. The essential amino acid methionine is regenerated and conserved by the B12-dependent transfer of a methyl group from 5-methyl THF to homocysteine in the central methionine synthase (MS) reaction. Methionine is then activated to S-adenosylmethionine (SAM), the methyl donor for multiple essential methyltransferase (MTase) reactions. The ratio of the methyl-donor SAM to the product-inhibitor S-adenosylhomocysteine (SAH) is a reflection of transmethylation pathway efficiency and cellular methylation potential. The reversible hydrolysis of SAH to homocysteine and adenosine by the SAH hydrolase (SAHH) reaction completes the methionine cycle. Homocysteine can then be remethylated to methionine or irreversibly removed from the methionine cycle by cystathionine beta synthase (CBS). This reaction initiates the transsulfuration pathway for the synthesis of cysteine and glutathione. GSH is the active reduced form of glutathione and GSSG is the inactive oxidized form. Glutamylcysteine (Glu-Cys) is the metabolic precursor for GSH and Cystinylglycine (Cys-Gly) is an intermediate in an alternate pathway for GSH synthesis.