Choline Metabolism Gene-Exposure Interactions in Fetal Alcohol-related Memory Deficits

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Objectives: Animal and human studies have demonstrated the potential for the essential nutrient choline to ameliorate teratogenic effects of prenatal alcohol exposure (PAE), including growth and recognition memory deficits. We hypothesized that the presence of maternal SNPs in choline metabolism-related genes may modify fetal vulnerability to PAE.

Methods: Mothers from two prenatally recruited birth cohorts in Cape Town, South Africa (discovery cohort: $n = 149$; validation cohort: $n = 153$) were genotyped for 315 SNPs in choline metabolism-related genes. Primary outcomes were: height/length z-scores (disc. at age 9 yr; val. at 5 yr) and recognition memory (disc. = CVLT-C recognition discrimination score, age 9 yr; val. = Fagan Test of Infant Intelligence novelty preference score, 6.5 and 12 mo). Linear regression models were constructed using OLS: outcome $\sim$ PAE + gene dose (# effective alleles) + PAE x gene dose; significance of PAE-gene interaction was tested using a 2-sided Wald test on the PAE-gene dose interaction term with Benjamini-Hochberg (BH) multiple testing correction.

Results: PAE (drinking days/wk) was related to shorter height (disc. B(95% CI) = $-.11(-.18, -.01)$; val. B = $-.12(-.20, -.04)$ and poorer recognition memory (disc. B = $-.11(-.26, -.02)$; val. B = $-.11(-.19, -.03)$). Gene-PAE interaction for recognition memory was seen in both cohorts for rs12262538 (discovery BH-adj. $p = .0015$; validation unadj. $p = .004$); for rs1043261, discovery BH-adj. $p = .0235$ and validation unadj. $p = .0903$. No gene-PAE interactions were seen for height. rs12262538 is in the 5' flanking region near the Stearoyl-CoA Desaturase (*SCD*) gene. rs1043261 is in the 3' flanking region near the choline dehydrogenase (*CHDH*) gene.

Conclusions: We identified two maternal SNPs that may confer higher fetal risk for teratogenic effects of PAE. These findings support the potential protective role of choline in fetal alcohol spectrum disorders prevention.