



Metabolic Pathway Analysis Of Prenatal Combined Exposure To Heavy Metals And Phthalates Related to Child Motor Development

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Abstract
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INTRODUCTION

Several environmental compounds have been found to interact with child neurodevelopment. It is important to identify the compounds that have the highest influence on given population groups. This raises the question on which is the category of environmental compounds in the Polish population that relates to child psychomotor development.



METHODOLOGY

- Urine and cord blood samples of pregnant women exposed to environmental contaminants (phthalates, Pb, Hg)
 - Urinary concentrations of phthalates
 - Cord blood Pb
 - Hair Hg
- Child Psychomotor development at the age of 2 years by the Bayley Scales
- EWAS analysis
- LC MS/MS (Thermo Orbitrap) for metabolites identification
- Agilent Genespring / Mass Profiler Pro for pathway identification

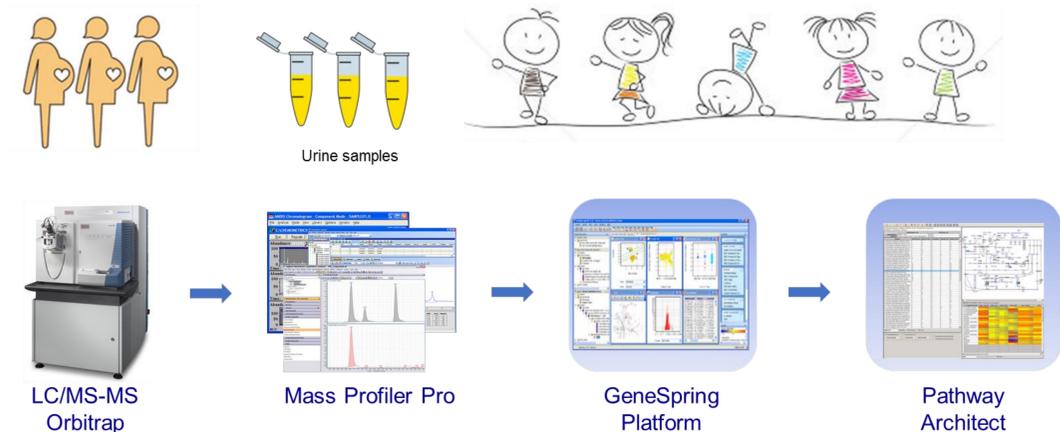


Figure 1. Conceptual methodological approach

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RESULTS & DISCUSSION

Exposure levels to both phthalate metabolites and metals were far below the respective biomonitoring equivalent values, while from the EWAS analysis, it was found that child motor development was inversely associated with natural log concentrations of 3OH-MnBP, the sum of DEHP and DnBP metabolites, in the urine, as well as the Pb in blood and the Hg in hair collected from mothers. With regard to post-natal exposure, the only statistically significant associated association was the inverse correlation of Hg (log10p=1.9) in hair and cognitive functions for females.

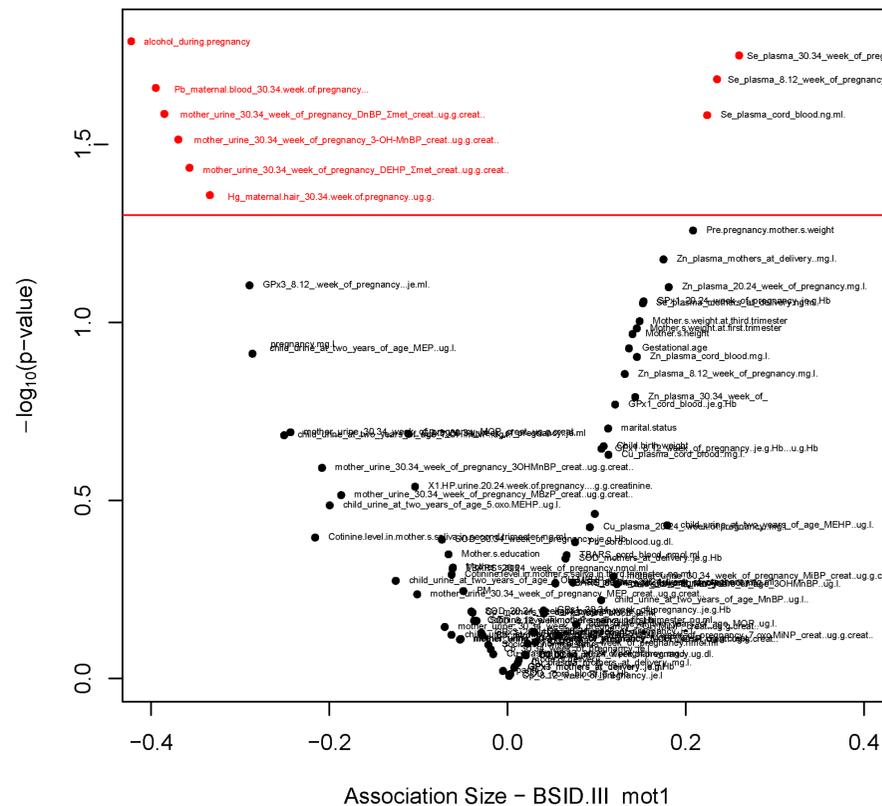


Figure 2. Child motor development EWAS analysis

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The most significantly perturbed metabolic pathways include carbohydrate, amino acid, lipid, and purine metabolism. Metabolic pathway analysis revealed that alterations in phthalate metabolites are related to the TCA cycle, suggesting impaired mitochondrial respiration; the latter is central to energy metabolism and cellular signaling and plays fundamental roles in synthesis of nucleotides and active transport processes.

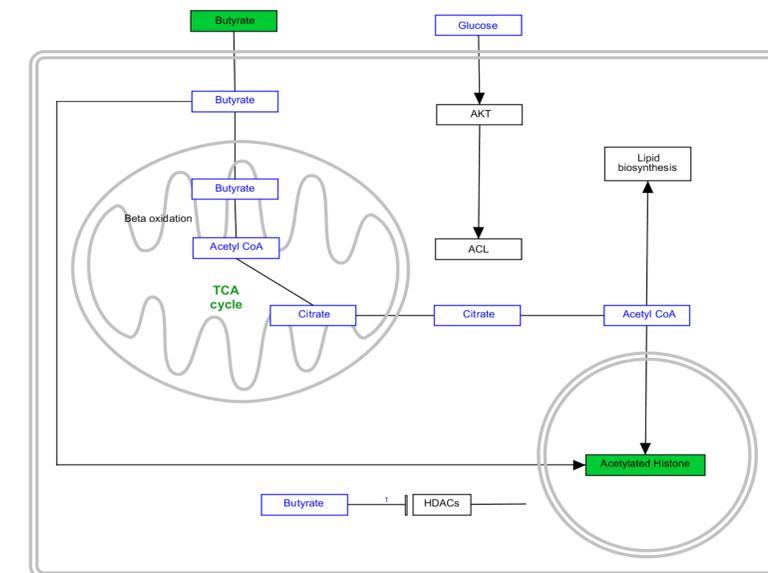


Figure 3. TCA metabolic pathway perturbation due to phthalates exposure

Exposure to metals (Hg, Pb) induce oxidative stress, directly affecting mitochondria. Inhibition of mitochondrial oxidative phosphorylation could also cause a defective mitochondrial energy production during the process of fetus formation and development that are reflected in early life motor development.

CONCLUSIONS

The key finding of the study is that although phthalates and metals affect mitochondrial respiration through different mechanisms (endocrine disruption and oxidative stress respectively), this synergistic effect is essential for the deployment of neurodevelopmental defects.

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