

INTERACTIONS BETWEEN DISINFECTION BY PRODUCTS IN DRINKING WATER AND GENETIC SUSCEPTIBILITY VARIANTS IN RELATION TO ADVERSE REPRODUCTIVE OUTCOMES (THE HIWATE STUDY)

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Background and Aims: The Hiwate project (Heath Impacts of Long-Term Exposure to Disinfection By-Products in Drinking Water) studied the relation between prenatal exposure to DBPs (Disinfection by-products) in drinking water and adverse reproductive outcomes, without finding evidence of any effect. This lack of association could be partially caused by differences in genetic background. Thus, a gene*environment (G*E) interaction study was undertaken within Hiwate project.

Methods: A nested case control study was designed using samples (maternal and child DNA) from four European birth cohorts (INMA, KAUNAS, PELAGIE and RHEA). Forty-nine Single Nucleotide Polymorphisms (SNPs) and 4 Copy Number Variants (CNVs) in DBP detoxification genes (CYP1A cluster, CYP2A6, CYP2E1, CYP3A cluster, GSTP1, GSTT1 cluster, GSTZ1, GSTM1 and GSTM4) were successfully genotyped using Illumina and MLPA, respectively, blindly to the case-control status. Prenatal exposure to total trihalomethanes (tTHMs), the most abundant DBP group, was considered continuous in models. Main genetic effects were initially explored under an additive genetic model, and those with a p -val <0.2 (in mothers or children) were included in the G*E analysis.

Results: In total, 270/228 (mother/child DNAs) preterm cases, 368/377 small for gestational age (SGA) cases, and 416/429 controls were analyzed. A SNP in CYP1A cluster (in child DNA), and two SNPs in GSTZ1 (in maternal and/or child DNA) showed an interaction with tTHMs in relation to preterm (p int ≤ 0.052). Regarding SGA, mothers with 0 copies of the GSTT1 CNV tended to have children more susceptible to be SGA after prenatal exposure to tTHMs (p int=0.050). None of the interactions were statistically significant after correction for multiple testing.

Conclusions: Genetic variants in the CYP1A cluster, GSTZ1 and GSTT1 may modulate the effect of prenatal exposure to DPBs on reproductive outcomes. Although biologically plausible, the findings should be interpreted with caution because effects were small and only marginally significant.