18

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Exploiting gene-environment interactions

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There is increasing evidence from epidemiological studies that genetic susceptibilities may modify the teratogenic effects of toxic chemicals. However, in contrast to tobacco smoke and folic acid intake, few epidemiological studies have addressed environmental chemicals, such as PCB-dioxins in regard to genetic susceptibility. The Hokkaido Study of Environment and Children's Health is a prospective cohort study on effects in children exposed to endocrine disrupting chemicals. Birth weight, length and head circumference were significantly lower among infants born to smoking mothers with the NQO1 wild genotype. For the CYP2E1 genotype, the estimated reduction in birth weight was 185 g ± 58 g ($p<0.01$) for the wildtype group (c1/c1). For the AhR R554K polymorphism, the concentrations of total non-ortho PCBs TEQ, total mono-ortho PCBs TEQ, total coplanar PCBs TEQ, and total TEQ of
the Arg/Arg genotype population were significantly lower than that of Arg/Lys and Lys/Lys populations ($p = 0.010$, $p = 0.005$, $p = 0.006$, $p = 0.023$, respectively). Significant adverse effects observed only in male infants included the association of birth weight with both total PCDF levels and total PCDF-TEQ levels. Further, wildtype CYP1A1 in mothers was significantly associated with a decreased risk hypospadias in their sons. Homozygosity for genotypes SRD5A2 and HRD17B3 increased the risk of hypospadias, thus suggesting that hormone metabolites might be critical for developing hypospadias, while xenobiotic-metabolizing enzymes, such as GSTM1 and T1, are not. Thus, complex interactions between exposure and predisposing factors of individual susceptibility may play an important role in the occurrence of abnormal intrauterine development and malformations.