

# GENETIC MODIFICATION OF THE ASSOCIATION BETWEEN DIOXIN EXPOSURE AND PUBERTAL ONSET IN A COHORT OF RUSSIAN BOYS

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**Background and Aims:** Dioxins are environmental pollutants with various reproductive toxicities, possibly including delayed pubertal onset. Dioxin susceptibility varies widely between animal species, but it is unknown whether genetic polymorphisms affect susceptibility in humans. In this prospective cohort of Russian boys, we assessed whether the observed associations between serum dioxin concentrations and pubertal onset differed by genotype.

**Methods:** 337 tagging single-nucleotide polymorphisms (SNPs) were selected from genes related either to dioxin metabolism or to pubertal development. Gene-environment interactions were assessed using two different statistical methods, considering both peripubertal and maternal serum dioxin concentrations, and pubertal onset defined both by testicular volume (TV) or genitalia staging (G2).

**Results:** The 408 boys were 8-9 years old at study entry, with a median serum TEQ of 21 pg/g lipid for boys and 25 pg/g lipid for their mothers. Using the first statistical method, in which SNPs are first screened for a significant marginal association with each outcome, two SNPs showed significant interactions with the sons' peripubertal serum dioxin concentration, after adjustment for multiple comparisons. One of the interactions was seen for TV pubertal onset, in the gene for estrogen receptor- $\alpha$  (ESR1). The other was for G2 pubertal onset in the SRC gene. Using the second method (i.e. including all SNPs regardless of marginal associations), significant interactions were seen for two SNPs in the glucocorticoid receptor (GR) after adjustment for multiple comparisons (both of them for G2 pubertal onset, with the sons' peripubertal serum dioxin concentration). No significant interactions were identified for maternal dioxin concentrations.

**Conclusions:** This is one of the first large studies to assess genetic susceptibility to dioxins. The findings suggest several genes which may modify the associations between dioxin and pubertal onset, although the results are sensitive to the choice of statistical method, and the method of assessment of pubertal onset.