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Gene-environment interactions in holoprosencephaly

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Complex gene-environment interactions are thought to underlie many developmental defects, and potential teratogens may be environmental modifiers of predisposing mutations. Fetal alcohol is teratogenic, inducing a variety of structural defects in developing humans and animals exposed in utero. Among the developmental defects alcohol has been implicated in is holoprosencephaly (HPE), a failure to define the midline of the forebrain and/or midface. HPE is associated with heterozygous mutations in the Hedgehog (Hh) pathway, but clinical presentation is highly variable, and many mutation carriers are unaffected. This scenario appears to be explained by a "mutation-plus-modifier" model. We have developed a gene-environment interaction model of HPE in mice with a mutation of the Hh coreceptor, Cdon. While individual loss of *Cdon* or in utero exposure to alcohol did not cause HPE in 129S6 mice, the two together produced defects in early midline patterning, inhibition of Hh signaling in the developing forebrain, and a broad spectrum of HPE phenotypes. Alcohol itself, rather than a consequence of its metabolism, is the HPE-inducing teratogen, indirectly inhibiting Hh signaling. Other Hh pathway inhibitors may also promote HPE. Δ9-tetrahydrocannabinol (THC), an abundant psychotropic component of Cannabis, has been reported to inhibit Hh signaling. We find that Hh-dependent induction of the pathway target genes, *Gli1* and *Ptch1*, is inhibited by THC. Additionally, THC exposure in utero causes HPE in *Cdon* mutant mice. Cannabis is often used by pregnant women. It is therefore an important public health issue to investigate whether THC is a risk factor for HPE in humans.