Gene-environment interactions in holoprosencephaly

Mingi Hong¹, Hsiao Fan Lo¹, and Robert S. Krauss¹

¹Cell, Developmental, and Degenerative Biology, Icahn School of Medicine at Mount Sinai

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.