GENETIC FACTORS UNDERLYING SUSCEPTIBILITY TO PRENATAL ALCOHOL AND CANNABINOID EXPOSURE

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Genetic factors play a significant role in determining an individual's susceptibility to developmental teratogen exposure, in particular abnormalities involving the early development of the craniofacies. In our mouse model, both alcohol and cannabinoids induce craniofacial abnormalities similar to fetal alcohol syndrome. Both drugs inhibit the sonic hedgehog (Shh) pathway, which controls cell proliferation and migration for craniofacial development, through different mechanisms. In the same mouse model, we have identified numerous candidate genes that modify susceptibility to alcohol by comparing mouse strains with a spectrum of abnormalities, namely the C57BL/6J strain (highly susceptible) and the closely related C57BL/6N strain (moderately susceptible). This current work describes the discovery of a mouse strain (129S1) that is completely resistant to developing the characteristic craniofacial abnormalities associated with early embryonic alcohol exposure, despite the fact that it presented with a significantly higher blood alcohol concentration following early embryonic alcohol exposure as compared to the C57 strains. We also discovered that the 129S1 stain is resistant to cannabinoids and other Shh pathway antagonists, which are also highly teratogenic to the face. To explore potential differences between strains accounting for this differential susceptibility, we identified gene regulation differences between the 129S1 and C57BL/6J strains in Shh-related genes. In addition to identifying individual candidate genes that can be tested in human populations, these data identify cellular and molecular pathways that are possibly involved in prenatal drug-related pathogenic mechanisms of action as well as potential druggable pathways that may serve to help ameliorate the effects of prenatal teratogen exposure.