Tuesday, March 1, 8:00AM-12:00PM
Plenary Session

Teratogen Update
Moderator: Angela Lin, MassGeneral Hospital for Children, and the Massachusetts Birth Defects Monitoring Program, DPH, Boston, MA

Of Mice and Men: Studying Gene-Environment Interactions Using Animal Models
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We have long appreciated the fact that not all infants exposed *in utero* to select environmental teratogens-ethanol, thalidomide, Vitamin A-were adversely affected and expressed a recognizable phenotype associated with the teratogenic exposure. This suggests that certain mother-infant pairs possess genetic traits that push them close to the threshold of abnormal development, making them more susceptible when stressed *in utero* by environmental contaminants. Our whole thinking about the 'maternal environment' has expanded of late, moving from the more typical categorization of exposures involving air and water pollution, occupational exposures, diet, stress and infectious pathogens, to the realization that these compounds work collectively at times and in multiple pathways to interrupt normal development. We now recognize that teratogenic effects are often mediated via compounds/molecules that the mother's body generates in response to these environmental stimuli, and that in many cases, these compounds accumulate over a lifetime.

Very little human data exists which convincingly demonstrates an interaction between a specific gene and an environmental exposure, and much less exists reflecting the real world situation where multiple genes are identified that interact with multiple environmental factors to reveal true risks for an adverse pregnancy outcome. The best human data exists concerning the risks for craniofacial malformations secondary to gene (TGFa) and environment (maternal cigarette smoking and multi-vitamin status) interactions. Mothers who smoke more than 20 cigarettes a day and did not take a vitamin supplement containing folic acid and whose infant had the uncommon allele for TGFa had ten-times the risk for having a cleft palate than did infants with the common TGFa allele whose mother's did not smoke and took a vitamin supplement.

We have attempted to extend such a modeling paradigm to mouse studies of known human neural tube teratogens, such as the anti-epileptic drug Depakene (Valproic acid) and the environmental teratogen, arsenic. Using inbred mouse stains that are genetically susceptible to VPA-induced neural tube defects (SWV) and genetically modified knockout mouse models where the gene (Folr1, Folr2) transporting folic acid into cells has been ablated, we have attempted to learn more about the underlying mechanisms between these environmental factors and specific genes that disrupt the process of neural tube closure. The mouse, with its well-understood biology and genome, lends itself particularly well to these types of investigations. I will review these animal studies and during the course of the presentation, I will cover how a heretofore-unexpected gene family has been identified that appears to regulate infant susceptibility to Depakene-induced birth defects.

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