ELUCIDATING AN ADVERSE OUTCOME PATHWAY OF MICROCEPHALY FOR USE IN COMPUTATIONAL TOXICOLOGY

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While evidence now supports a causal link between maternal Zika viral infection and microcephaly, genetic errors and chemical stressors may also precipitate this malformation through disruption of neuroprogenitor cell (NPC) proliferation, migration and differentiation in the early developing brain. Here, we present an Adverse Outcome Pathway (AOP) framework for microcephaly that can be used to help unravel the complexity of its pathogenesis. Publically available databases were used in conjunction with U.S. EPA developed tools to isolate relevant genes and pathways associated with this clinical diagnosis. The Mammalian Phenotype Browser database contains 85 gene associations for the phenotype 'microcephaly' (MP:0000433). Since reductions in cortical surface area and ventricular dilations are main features of the microcephalic brain, we searched for these features in prenatal developmental toxicity studies from EPA's ToxRefDB database. This query identified 75 chemicals that caused either reductions in fetal brain size/mass (40) or dilated brain ventricles/hydrocephaly (39). Since the minimal overlap in chemicals (4) that elicited both pathologies suggests that mechanistically diverse pathways converge on these apical endpoints. Lastly, a high-throughput literature mining tool was built to query PubMed for references and construct a MicrocephalyConnections knowledgebase of relevant information for gene, chemical, or viral effects on development. The knowledgebase was used to elucidate an AOP for primary autosomal microcephaly (MCPH) that links evidence for molecular/subcellular changes in microcephalin (*MCHP1*) and abnormal spindle-like microcephaly (*ASPM*) function to cellular/tissue level changes leading to hypocellularity of the embryonic ventricular zone. This putative AOP pinpoints mitotic spindle orientation as a key determinant of NPC pool size at the onset of neurogenesis, whereby the logistical dynamics of microtubule assembly in the centrosome are synchronized to the cell cycle. Ongoing research is investigating the extent to which an AOP for *MCPH1*-microcephaly co-opts a network for chemical- or viral- induced microcephaly by modeling ToxCast data and literature associated with the 75 ToxRefDB chemicals that invoke fetal brain pathologies. (This abstract does not necessarily reflect EPA policy).