**Investigating the gene-environment interaction between autism-associated WAC gene and perfluoroctane sulfonate exposure**

Tislerics, Elena1; Barot, Janki1; Napissara Boonpraman1,2​; Kuhn, Nathan C.1; and Sammi, Shreesh Raj1,2​

1Department of Translational Neuroscience, Michigan State University, Grand Rapids Research Center, 400 Monroe Ave NW, Grand Rapids, MI, USA 49503​

2Department of Neuroscience, Michigan State University, Giltner Hall, 293 Farm Lane, East Lansing, MI, USA 48824

Autism Spectrum Disorder (ASD) is a neurological syndrome characterized by a broad spectrum of behavioral impairments. While multiple genetic and environmental factors are attributed to its cause, a confirmed mechanism has yet to be identified. Given that the symptoms of ASD are mostly neurobehavioral in nature, we investigated an ASD-associated gene, WAC, for its effect on cholinergic and dopaminergic-associated behavior, followed by further testing with perfluoroctane sulfonate (PFOS) exposure. PFOS is a type of perfluoroalkyl substance (PFAS) widely used in consumer and industrial applications. Perfluorooctanesulfonic acid (PFOS), like other per- and polyfluoroalkyl substances (PFASs), resists degradation and persists in soil, air, and groundwater, leading to toxic effects on the environment and human health.

Studies on *C. elegans* with ASD-associated *wac* gene deletion (*wac-1.1* and *wac-1.2*) exhibited enhanced acetylcholine-associated behavior and curtailed dopamine-associated behavior, as indicated by aldicarb and 1-nonanol assays. No alteration in acetylcholine levels or acetylcholinesterase activity was observed. Upon further investigation, we found that the elevated cholinergic transmission was due to the enhanced nicotinic acetylcholine receptor (nAChR) activity. This enhanced activity was plausibly due to the upregulation of the lev-1 gene, although a feedback-counterbalancing response was also observed in the form of downregulated genes, *acr-2, unc-17, unc-63,* and *unc-50.* This study aims to examine the effect of PFOS exposure on wild-type and *wac* mutant worms to understand better the risks associated with PFOS exposure, help shed light on its mechanism, and examine whether PFOS is a likely contributing factor in ASD, with potential implications pertaining to human health.