**Investigating Heritable Impacts of Germ Cell Toxicant Exposures**

Jill Escher, JD, MA, Escher Fund for Autism, San Jose, California*

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**Germ Cell Toxicants and Adverse Progeny Outcomes (APOs)**

Germ cells can be exquisitely vulnerable to toxicants.

![Image](1)

Germ cells' genes, chromatin and non-genetic marks may be susceptible to perturbation during critical windows of reprogramming. Unfortunately, this aspect of biological vulnerability is largely overlooked in toxicology, research, and regulation.

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**Spotlight: APOs of Early Germ Cell Exposure to General Anesthesia (GA)**

Family histories raise red flags concerning neurodevelopmental derangement caused by early or intensive germ cell to GA (see below for examples, but no studies on this question have been conducted in humans to date. In the U.S., up to 75,000 pregnant women and 6 million children (1.5 million infants) are exposed per year (Gluncic et al., 2019).

![Image](2)

**Mammal models demonstrate GA-induced APO of mental impairment:**

- Neonatal sevoflurane linked to APO of abnormal brains and behavior of the next generation of rat males through epigenetic modification of Kcc2 expression, while F1 females are at diminished risk. (Ju et al., 2018)
- Enflurane in male mice induced learning retardation in offspring. (Tang et al., 1985)
- In utero halothane induced learning retardation in mouse grandpups. (Chalon et al., 1981)
- GA is genotoxic, neurotoxic and germ-cell toxic:
  - Early GA induces learning impairments, brain abnormalities, behavioral abnormality (Gluncic et al., 2019)
  - Early GA induces neuronal apoptosis, impaired synaptogenesis and incomplete neuronal migration (ectopic neurons) (Gluncic et al. 2019)
  - GA gases have been shown to be powerful modulators of chromatin remodeling and epigenetic function that induce a wide variety of morpho-functional effects when administered during critical periods of brain development (Vutskits et al. 2018)
  - GA genes are genotoxic, causing DNA damage (Yilmaz et al. 2016)
  - For example, even brief exposure to the GA agent isoflurane led to widespread changes in genetic control in the amygdala six hours after exposure (Pan et al. 2006)

**Ascertainment of APOs of GA is an urgent question for public health, with potentially strong relevance to etiology of autism spectrum disorders.**

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**We Fund and Advocate for Research on APOs of Germ Cell Exposures**

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**Recent Publications, Selected**

**Original Research**


**Commentary**

Escher J. 2018. Bugs in the program: can pregnancy drugs and smoking disturb molecular reprogramming of the fetal germine, increasing heritable risk for autism and neurodevelopmental disorders? *Environ Epigen* 4:2;dyx001.


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**Recent Grants, Selected**

University of California, San Diego: Sebat Lab, for investigation of grandmaternal smoking in a genetics cohort of progeny with autism.

Harvard University: Shioda Lab, for the in vitro investigation of epigenetic perturbation of induced pluripotent germ cell-like cells caused by xenobiotics.

Columbia University: Alan Brown MD, MPH, for the investigation of F2 autism and related outcomes in a human cohort in Finland where a parent had been born by Cesarean section under general anesthesia.

Syracuse University: Pепling Lab, for the investigation of F2 behavioral outcomes of F1 early life exposure to general anesthetic gas halothane.

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**Summary**

Heritable contents of germ cells are vulnerable to toxicant exposure. Yet this dimension of risk is barely considered in toxicology, research, and regulation.

Many pathologies increasing in prevalence today (eg, autism, ADHD, asthma, allergies) may be APOs of long-ago germ cell exposures such as tobacco, GA, and synthetic steroids.

Given the regrettable oversight in conventional research, private strategic philanthropy can play a critical role in bringing this crucial dimension of risk to light.