Escher Fund for Autism — Humans start as molecules

GermlineExposures.org Contact: jill.escher@gmail.com

Investigating Heritable Impacts of Germ Cell Toxicant Exposures

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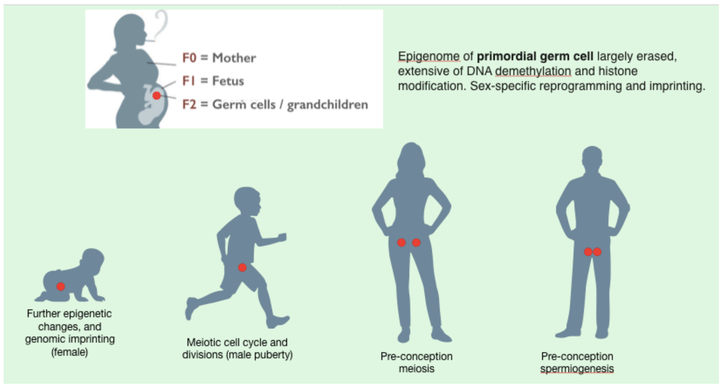
Germ Cell Toxicants and Adverse Progeny Outcomes (APOs)

Germ cells can be exquisitely vulnerable to toxicants



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.**

Research in humans is finding APOs of pregnancy synthetic drugs and smoking that boomed in the post-war era:

Grandmaternal pregnancy diethylstilbestrol (DES)

- APOs in grandsons: genital tract defects such as hypospadias
- APOs in granddaughters: menstrual irregularity, possible infertility, ovarian cancer, preterm birth, and possibly ectopic pregnancy (Titus-Ernstoff et al. 2006; Tournaire et al. 2016; Titus et al. 2018)
- NEW: grandchild APO of attention deficit hyperactivity disorder (ADHD) (Kioumourtzoglou et al. 2018)

Grandmaternal pregnancy smoking

- APOs of autism and autism trait risk in grandchildren through the female line. (Golding et al. 2017)
- APO of ADHD via exposed mother (Yim et al. unpublished).
- APOs of asthma and allergies (Li et al. 2005; Miller et al. 2014; Magnus et al. 2015; Accordini et al. 2018; Lodge et al. 2018)
- Tobacco smoke also a likely human germ cell mutagen (DeMarini 2012), with likely widespread population impacts on intellectual health of offspring of exposed sperm (Beal et al. 2017)

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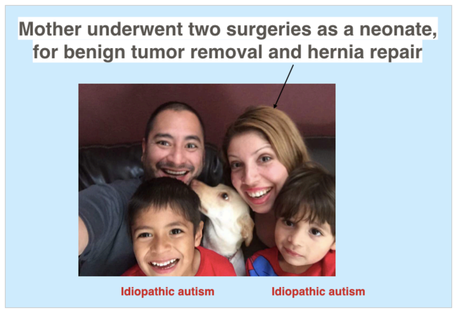
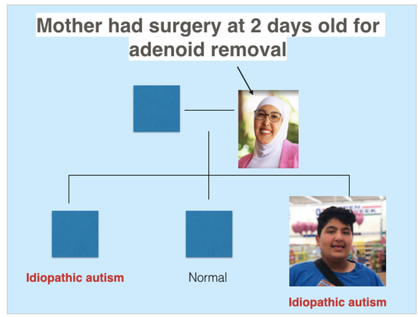
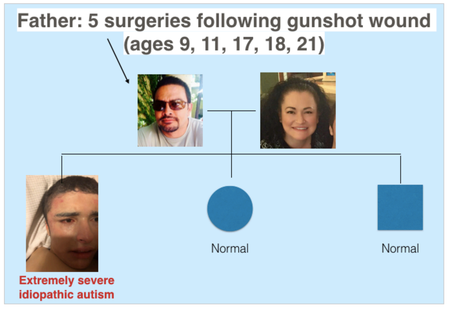
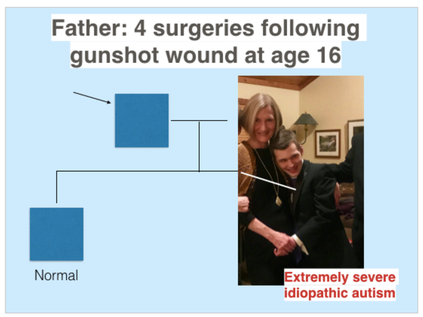
Spotlight: APOs of Early Germ Cell Exposure to General Anesthesia (GA)

Family histories raise red flags concerning neurodevelopment 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).









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 gases 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.

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

Recent Publications, Selected

Original Research

Golding J, Ellis G, Gregory S, Birmingham K, Iles-Caven Y, Rai D, Pembrey M.I. 2017. **Grand-maternal smoking in pregnancy and grandchild's autistic traits and diagnosed autism**. *Sci Rep* 7:46179.

Kioumourtzoglou M, Coull BA, O'Reilly ÉJ, Ascherio A, Weisskopf MG. 2018. **Association of Exposure to Diethylstilbestrol During Pregnancy With Multigenerational Neurodevelopmental Deficits**. *JAMA Pediatr* 172:7;670-677.

McCarthy, DM, Deirdre M. McCarthy, Morgan TJ, Lowe SE, Williamson MJ, Spencer TJ, Biederman J, Bhide PG. 2018. **Nicotine exposure of male mice produces behavioral impairment in multiple generations of descendants**. *PLOS Biol* 16(10):e2006497.

Commentary

Escher J. 2018. **Bugs in the program: can pregnancy drugs and smoking disturb molecular reprogramming of the fetal germline, increasing heritable risk for autism and neurodevelopmental disorders?** *Environ Epigen* 4:2;dvy001.

Escher J, Robotti S. 2019. **Pregnancy drugs, fetal germline epigenome, and risks for next-generation pathology: a call to action**. *Environ Mol Mutagen*, in press.

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

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.**