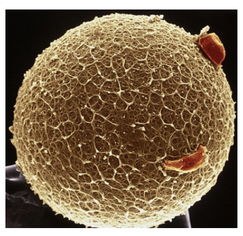
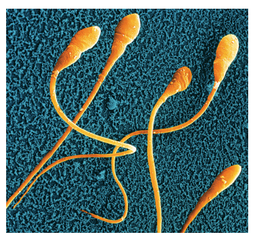
Escher Fund for Autism — Humans start as molecules

Investigating the Missing Heritability of Autism

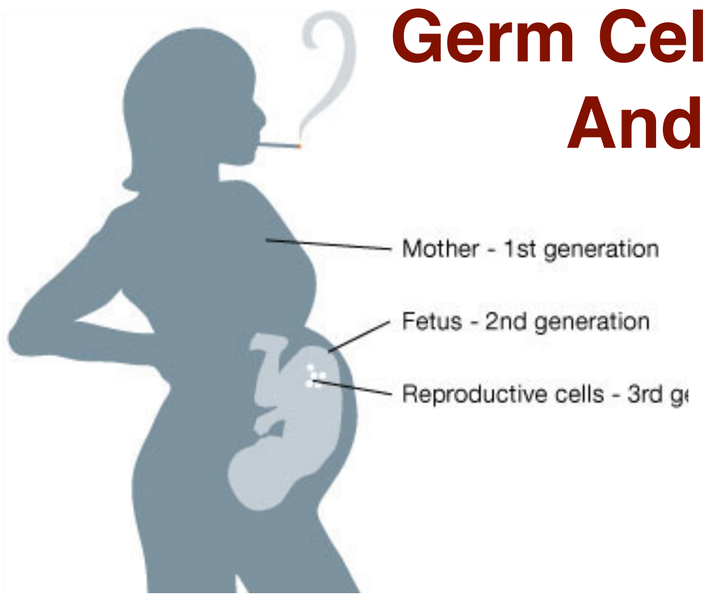
Not All Heritability is Genetic

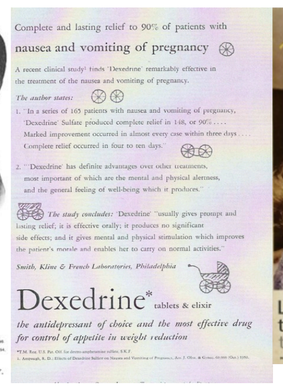
Autism is strongly heritable, but not strongly genetic. We hypothesize that to a large extent the missing heritability lies not in "common variation" but instead **germline dysregulation** of environmentally sensitive epigenome and chromatin.

Germ cells — eggs, sperm, and their precursors — contain **countless non-genetic modifications** that control how genes function. These marks can be susceptible to perturbation in critical windows, including **early gametogenesis**.

Decades of Intensive Germ Cell Exposures… And No Follow-Up



Pregnancy exposures affect three generations simultaneously. Pregnancy drugs and smoking proliferated in the 1950s, 60s, and 70s, possibly inducing unforeseen derangements in fetal germline, giving rise to **brain and behavioral abnormality in a subset of the grandchild generation**. Yet today, heritable effects are presumed "genetic"; germline impacts remain un-studied.



Behavioral Pathology/Abnormal Brain Function Can Be Induced by Germ Cell Toxicant Exposures

Tobacco, Tobacco Components

- **Nicotine** exposure in male mice produces behavioral impairment (hyperactivity, attention deficit, and cognitive inflexibility) in multiple generations of descendants. (McCarthy et al., 2018)
- Paternal exposure to **cannabinoids** during rat adolescence induces stress vulnerability in the offspring. (Andalouss et al., 2018)
- **Grandmaternal smoking** linked to autism and autism trait risk in grandchildren through the female line. (Golding et al., Sci Rep 2017)
- Prevalence of intellectual disability, based on occurrence of **tobacco-induced male germline mutation**, estimated to be millions worldwide. (Beal et al., 2017)
- Tobacco smoke component **benzo[a]pyrene** increases levels of germline and somatic mosaicism in offspring, particularly in the brain. (Meier et al., 2017)
- Grandpups of gestating mice exposed to **nicotine** exhibited ADHD-like behaviors. (Zhu et al., 2015)

Synthetic Steroid Hormone Drugs

- Significantly elevated odds for ADHD in grandchildren of women who took **synthetic estrogen diethylstilbestrol (DES)** during pregnancy. (Kioumourtzoglou et al., JAMA Peds 2018)
- Paternal **corticosterone** treatment in mice exerted effects on offspring brain serotonergic function. (Rawat et al,. 2018)
- Exogenous **thyroid hormone** influences brain gene expression programs and behaviors in later generations by altering germ line epigenetic information. (Martinez et al., 2018)
- Gestational treatment with **betamethasone** in guinea pigs at a clinically relevant dose resulted in various generational (through F3) pathology including altered cortisol response to stress, altered expression of genes in the prefrontal cortex and hypothalamic paraventricular nucleus. (Moisiadis et al., 2017)
- **Dexamethasone** administered in the clinical range to gestating ewes have multigenerational effects on HPA activity. (Long et al., 2013)
- Gestational treatment with **betamethasone** modified HPA function and behavior in the F2 grandpup generation in guinea pigs borne of exposed germ cells. (Iqbal, et al., 2012)

Hormone-Disrupting Chemicals

- Exposure of rats to EDCs **vinclozolin and PCBs** at the germ cell stage led to differences in the physiological and socio-sexual phenotype in offspring, especially in males. (Krishnan et al., 2018)
- Gestational exposure to **vinclozolin and PCBs** in rats resulted in transgenerational inheritance of epimutations in brain and sperm. (Gillette et al., 2018)
- Transgenerational effects of **BPA** on gene expression and DNA methylation of imprinted genes in the mouse brain. (Drobná et al. 2018)
- A single exposure to **vinclozolin** altered the physiology, behavior, metabolic activity, and transcriptome in discrete brain nuclei in descendant male rats, causing them to respond differently to chronic restraint stress. (Crews et al., 2012)
- Gestational exposure to **BPA** produces multigenerational alterations in genes and behavior in mice. (Wolstenholme et al, 2012)
- **Vinclozolin** exposure during fetal gonadal sex determination in rats results in alterations to epigenetic reprogramming of the male germline and offspring brain transcriptome. (Skinner et al., 2008)
- Females three generations removed from the original **vinclozolin** exposure discriminate and prefer males who do not have a history of exposure, in rats, a socio-sexual phenomenon. (Crews et al. 2007)

General Anesthetic Gases

- Neonatal exposure to the widely used general anesthetic agent **sevoflurane** can affect the 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)
- General anesthetic agent **enflurane** administered to male mice was found to adversely induce learning retardation of their offspring. (Tang et al., 1985)
- Learning retardation was seen in F2 mouse offspring of F1 parents exposed to general anesthetic **halothane** in utero—in other words, mental impairment in the grandpups of the exposed gestating dams. (Chalon et al., 1981)

Morphine

- **Morphine** in F1 adolescent female rats, prior to conception, increases the rewarding effects of cocaine in F2 male and female offspring. Sex-specific alterations in endogenous opioids and hypothalamic physiology were observed. (Vassoler et al., 2018)
- **Morphine** exposure to the F1 parent rat before conception induced intergenerational effects via dysregulation of HPA axis which results in anxiety in the adult male offspring. (Sabzevari et al., 2018)

Green = Escher Fund for Autism Grantee

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