

Request for Proposals: The Genetics of Autism

20th Century Maternal Smoking: Induced Fetal Germline Perturbations in the Etiology of Autism and Neurodevelopmental Disorders

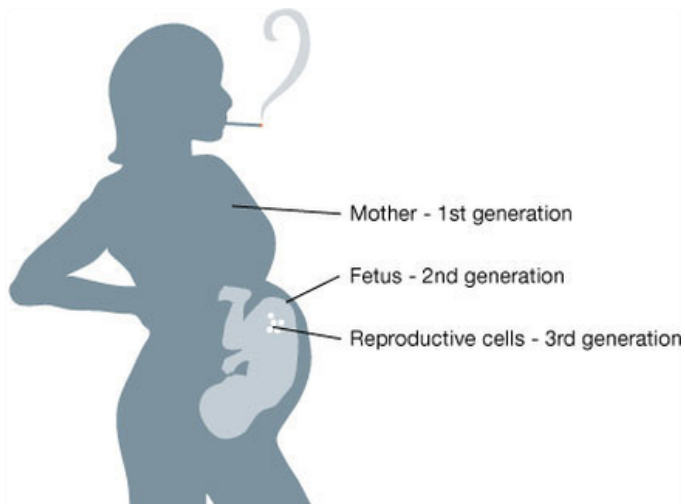
Application deadline: February 27, 2015; \$25,000 grant available

Background:

The past three decades have seen a staggering increase in the number of children diagnosed with the neurodevelopmental disability of autism. In California, substantially disabling autism cases served by the Department of Developmental Services have soared more than 2,000% since the early 1980s, now surpassing 73,000 cases, prompting what many see as perhaps the greatest public health crisis in the state's history, as virtually all these individuals have severe functional limitations and will require lifelong care.

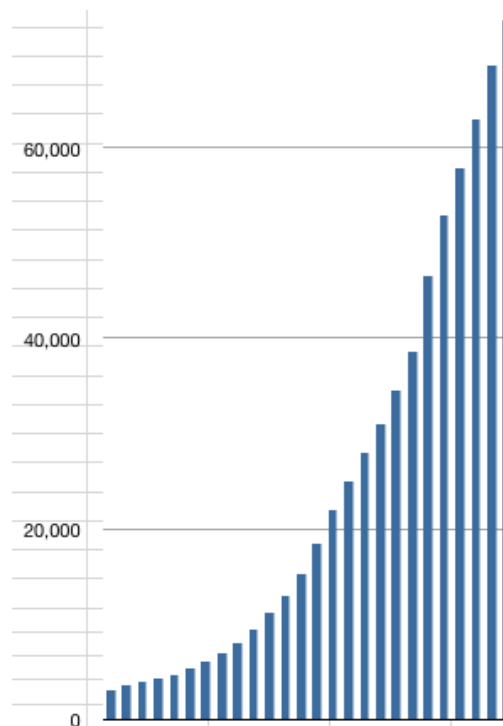
The skyrocketing rates of profound disability have baffled families, scientists and practitioners, because though autism appeared to be strongly heritable (among siblings, not parent-to-child), the idea of a "genetic epidemic" made little sense in light of the understanding

Smoking Affects Mother, Fetus, Germline



A pregnancy exposure affects three generations simultaneously: **for the grandchild generation, the perturbation occurs at the root genetic or epigenetic level.**

California DDS Autism Cases, 1989-2014



California DDS autism cases (limited to "substantially disabling" autism) have **skyrocketed from 3,262 in 1989 to more than 73,000 today.**

Source: California Department of Developmental Services, data as of September 2014

that genes could not change so dramatically in the course of a single generation.

It has come to light, however, that heritability includes *de novo* mutation of germline in addition to induced dysregulation of environmentally sensitive “epigenome.” Germ cells — eggs, sperm, and their precursors — contain countless millions of epigenetic marks that control how genes function, and these marks can be susceptible to perturbation in critical windows, including early gametogenesis, a time of dynamic and widespread epigenetic remodeling of chromatin. Disruption of germline epigenetics can cause permanent dysregulation of sensitive genes, including imprinted genes, leading to pathology in offspring.

“Over 1,000 harmful products are contained in cigarette smoke, apart from nicotine. Cigarette smoke is a mutagen, because it can produce chemical changes in the DNA.”



—Professor Pradeep Bhide, from GermlineExposures.org

In short, it is now understood that maternal smoking — like other toxic exposures of pregnancy — can affect three generations simultaneously: the soma of the mother (F0), the soma of the fetus (F1), and the germ cells of the fetus, which become the F2, or grandchildren of the F0. If the F2 generation is perturbed, it would be at the root genetic or epigenetic level.

Based on what we are learning from epigenetics and mutagenesis, reproductive and germ cell biology, and the science of endocrine disruption and toxicology, could widespread F0 maternal smoking of the 1950s, 60s, and 70s have caused unforeseen derangements to some fetal germline (the F2 within F1), giving rise to developmental or behavioral abnormality in a subset of the grandchild generation?

While the sponsor is interested in a wide array of gestational toxicants, particularly the many powerful synthetic pregnancy drugs of the 20th century, this particular RFP is limited to investigations of intergenerational effects of maternal cigarette smoking, a pervasive, intensive toxic exposure and an established mutagen and epimutagen.

To apply:

(1) Project description: Please provide an overview, in 500 words or less, of your proposed project, including methods. Some examples of relevant projects:

- **Animal models:** Given F0 cigarette smoking, what are F1 fetal germline and F2 behavioral outcomes?
- **Case studies of ASD families** with parental prenatal smoking exposure: Genetic and epigenetic analysis of parents exposed in utero to maternal smoking, and same for their children.

• **Epidemiology:** Given a cohort of pregnancies for which there are reliable prenatal medical records dating from circa 1960s, are F2 developmental outcomes different when the F0 grandmother had smoked, compared to controls?

• **Human semen analysis:** Analysis of human F1 semen where there is known F0 pregnancy smoking, as compared to controls. Also in cases where F1 had fathered children with ASD.

• **Meetings, symposia, or publications:** Sessions at scientific meetings or conference panels or symposia about this topic; articles or publications that help educate the science, regulatory, or lay community about fetal germline disruption.

Please note:

Abnormal molecular outcomes of interest may include but are not limited to: abnormal methylation of male or female germline, or other epigenetic marks, de novo mutation in male or female germline, or any other genetic variation not descended from the parental DNA.

Abnormal phenotypic outcomes of interest may include but are not limited to: Autism spectrum disorders, Aspergers, PDD-NOS, ADHD/ ADD, Sensory processing disorders, Learning disabilities, Social development disorders, Communication disorders, Behavioral/conduct disorders, and Mental illness.

Effects of second-hand smoke: in addition to direct germline exposure through maternal smoking, may also be considered.

History of maternal smoking: it is preferred that a project include a brief overview of the history of maternal smoking in the United States.

Critical windows: It is preferred that projects look at impacts on germline development and epigenetic reprogramming during the period of embryogenesis and fetal development, beginning with the specification of the primordial germ cells. However, projects investigating other critical windows such as periconception and/or spermatogenesis will also be considered.

(2) **Collaborators.** CVs can be emailed or linked separately. Interdisciplinary work, for example, involving a toxicologist, geneticist or epigeneticist, developmental or reproductive biologist, and historian, is preferred.

(3) **Line item description of how grant money would be used.** *The applicant must stipulate that max 5% of grant funds will support indirect costs.*

(4) **Timeline:** Projects must be completed within a year of the grant.

(5) Amount of request: \$25,000 is the maximum, but requests for smaller amounts will also be considered and may be given priority. This grant may be used to augment or leverage other awards or projects. We realize this amount may only be enough to fund a small pilot or “proof of principle” project.

(6) Tax status of requestor: Grants can be given through 501c3 or otherwise qualifying nonprofit organizations or institutions only.

Depending on grantee progress, further support may be available.

Deadline to submit proposals to jill.escher@gmail.com is February 27, 2015. Applicants are free to email comments or questions prior to submitting a proposal.



About the Escher Fund for Autism

The Escher Fund for Autism (“Humans Start as Molecules”) sponsors the science education website germlineexposures.org and promotes

and funds research into the hypothesis that adverse fetal exposures, along with exposures during other critical windows of germline synthesis, can induce molecular derangement of vulnerable fetal germline, giving rise to pathologies in the next generation.

The founder is the mother of two children with nonverbal autism. The story of her discovery of *in utero* exposure to multiple synthetic hormone drugs is [here](#). Though a forgotten history to most of today’s autism researchers, these powerful chemicals, along with many other drugs, were used prolifically during 1950s, 60s, and 70s to treat pregnancies considered “at risk” and many other real and perceived problems of pregnancy. This era also saw unprecedented rates of maternal smoking.

Family surveys conducted by the Escher Fund suggest that *in utero* exposure to drugs or smoking sustained by parents (when they were fetuses) and their nascent germline during the 1950s, 60s, and 70s may be a substantial causative factor in the surging rates of autism and related neurodevelopmental disorders in their offspring.

Past grantees of the Escher Fund for Autism, along with its sister fund, the Escher Family Fund, have included University of California San Francisco, University of Copenhagen, Brown University, University of Chicago, University of California Davis, Autism Speaks, Rockefeller University, and Stanford University, along with dozens of autism service organizations.