

Invited Address

J.P. Curley
R. Mashoodh

Department of Psychology
Columbia University
Room 406 Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027
E-mail: jc3181@columbia.edu

Parent-of-Origin and Trans-Generational Germline Influences on Behavioral Development: The Interacting Roles of Mothers, Fathers, and Grandparents

ABSTRACT: Mothers and fathers do not contribute equally to the development of their offspring. In addition to the differential investment of mothers versus fathers in the rearing of offspring, there are also a number of germline factors that are transmitted unequally from one parent or the other that contribute significantly to offspring development. This article shall review four major sources of such parent-of-origin effects. Firstly, there is increasing evidence that genes inherited on the sex chromosomes including the nonpseudautosomal part of the Y chromosome that is only inherited from fathers to sons, contribute to brain development and behavior independently of the organizing effects of sex hormones. Secondly, recent work has demonstrated that mitochondrial DNA that is primarily inherited only from mothers may play a much greater than anticipated role in neurobehavioral development. Thirdly, there exists a class of genes known as imprinted genes that are epigenetically silenced when passed on in a parent-of-origin specific manner and have been shown to regulate brain development and a variety of behaviors. Finally, there is converging evidence from several disciplines that environmental variations experienced by mothers and fathers may lead to plasticity in the development and behavior of offspring and that this phenotypic inheritance can be solely transmitted through the germline. Mechanistically, this may be achieved through altered programming within germ cells of the epigenetic status of particular genes such as retrotransposons and imprinted genes or potentially through altered expression of RNAs within gametes. © 2010 Wiley Periodicals, Inc. Dev Psychobiol

Keywords: parent-of-origin effects; sex chromosomes; mitochondrial DNA; genomic imprinting; epigenetic; trans-generational inheritance

INTRODUCTION

Mothers and fathers do not contribute equally to the development of their offspring, but rather there are several ways in which one parent or the other can differentially influence their offspring: collectively, these are termed parent-of-origin effects. One major source of variation in the respective influence of each parent comes in the form of differential parental care. In mammals for instance, offspring develop within the in utero environment of the

Received 6 November 2009; Accepted 16 December 2009

Correspondence to: J.P. Curley

Contract grant sponsor: Office of the Director, National Institutes of Health

Contract grant number: DP2OD001674

Contract grant sponsor: National Sciences and Engineering Research Council of Canada

Published online in Wiley InterScience
(www.interscience.wiley.com). DOI 10.1002/dev.20430

© 2010 Wiley Periodicals, Inc.

mother and for the majority of mammals it is also the mother that provides most postnatal care (Clutton-Brock, 1991). Therefore, the opportunity for males in most mammalian species to influence their offspring's development is far smaller than it is for females. However, in addition to differential parenting, there are a number of other potential mechanisms that are inherited via the germline through which mothers and fathers can have a disproportionate influence on their offspring.

A useful way of screening for the differential influence of mothers and fathers on the development of their offspring is to examine the phenotypes of hybrids produced from the reciprocal mating of two separate species, subspecies or strains of animals. There have been several occurrences of such reciprocal hybrids being produced both naturally and artificially in the wild and in captivity, especially amongst the rodentia, equidae, and felidae (Gray, 1972). Differences in growth are typically observed in such hybrids, for instance offspring from Shire horse mares and Shetland pony sires are larger than those from Shetland pony mares and Shire horse sires (Walton & Hammond, 1938). Likewise, in voles, crossing of *Peromyscus maniculatus* females and *Peromyscus polionotus* males, who are similar in size, produces smaller offspring than the reciprocal cross (Vrana et al., 2000). Behavioral changes have also been observed in hybrids, such as the temperament differences commonly reported between hinnies (donkey mother and horse father) and mules (horse mother and donkey father) (Gray, 1972). In the laboratory, the reciprocal breeding of various inbred and outbred rodent strains and species has been extremely useful in screening for parent-of-origin effects on behavioral and physiological phenotypes such as emotional reactivity (Calatayud & Belzung, 2001; Carola, Frazzetto, & Gross, 2006; Roy, Merali, Poulter, & Anisman, 2007), maternal care (Calatayud, Coubar, & Belzung, 2004; Carola et al., 2008; Shoji & Kato, 2009), infanticide (Perrigo et al., 1993), aggression (Carlier, Roubertoux, & Pastoret, 1991; Platt & Maxson, 1989), sex (McGill & Manning, 1976), forced ethanol intake (Gabriel & Cunningham, 2008), calcium taste preference (Tordoff, Reed, & Shao, 2008), activity (Dohm, Richardson, & Garland, 1994; Massett & Berk, 2005; Price & Loomis, 1973), cerebellar development (Cooper, Benno, Hahn, & Hewitt, 1991), peripheral nerve conductivity (Hegmann & White, 1973), central estrogen receptor α distribution (Kramer, Carr, Schmidt, & Cushing, 2006), and puberty onset (Zhou et al., 2007).

Though it is clear from these studies that parent-of-origin effects exist, it is extremely challenging to delineate which mechanisms may be partially or fully responsible for each of these phenotypes. In most studies of reciprocal hybrids it has been assumed that the observed phenotypic

differences must be due to differences in maternal environment during gestation and/or lactation. Some studies have attempted to control for such maternal environmental effects by performing ovarian, blastocyst, or embryo transfers. In some cases this has shown that the observed parent-of-origin effects are indeed likely due to differential maternal rearing environments. For instance, males produced by mating fathers from the highly aggressive NZB strain and mothers from the less aggressive CBA strain are more aggressive than males produced by the reciprocal mating (Carlier et al., 1991). Significantly, this was only true when offspring were reared by their biological mothers, as no difference existed between reciprocal hybrids that were conceived in and born to F1 females who had undergone ovarian grafts of either NZB or CBA ovaries. However, other studies have clearly demonstrated that there must be other parent-of-origin mechanisms at play. For instance, reciprocal hybrid mice produced from mating either C57BL/6 and CBA/Ca strains or C57BL/6 and DBA strains were found to avoid the urine of their genetic maternal strain in an odor preference test even after they had all been embryo transferred to CD1 dams (Isles, Baum, Ma, Keverne, & Allen, 2001; Isles et al., 2002). These findings amongst others have led to an increased appreciation that there exist genetic and epigenetic mechanisms through which males and females can contribute uniquely to their offspring's development. In this article we shall discuss (1) sex chromosomes, (2) mitochondrial DNA, (3) genomic imprinting and (4) environmentally induced germline effects as particular examples of this inherited differential influence of mothers and fathers.

SEX CHROMOSOMES

In mammals, autosomes and the X chromosomes are inherited from both mothers and fathers but there is an unequal inheritance of the nonpseudoautosomal region of the Y chromosome (Y_{NPAR}) which is transmitted exclusively from fathers to sons. This is in contrast to the small pseudoautosomal region (PAR) of the Y chromosome which recombines during meiosis and exchanges information with the X chromosome. Furthermore, in females, a large proportion of one copy of the X chromosome in each cell lineage is randomly inactivated with respect to parental origin; although across species the proportion of genes that escape this inactivation varies (Brown & Greally, 2003). There are several lines of evidence to suggest that genes carried by the X chromosome and the Y_{NPAR} are involved in regulating specific aspects of brain function and behavior independently of changes in the organization and

activation of sexual differentiation that is activated by the *Sry* (testes determining factor) gene carried by the Y chromosome. Firstly, sex differences in gene expression are evident in the embryonic brain even before sexual differentiation has started to occur (Burgoyne et al., 1995; Dewing, Shi, Horvath, & Vilain, 2003). Secondly, humans that possess an abnormal number of sex chromosomes such as in Turner's syndrome (XO) and Klinefelter's syndrome (XXY) are characterized in part by altered behavioral phenotypes (Davies & Wilkinson, 2006). Finally, since the 1980s particular lines of mice and rats have been selectively bred such that they only differ with respect to the strain-of-origin of the Y_{NPAR} . These mice are produced by mating males of strain A with females of strain B and then mating male offspring of these hybrids with strain B females for several generations. Using these congenic strains, variations in inter-male aggression, hippocampal morphology, corticosterone release and serotonin functioning have been demonstrated to be associated with the strain-of-origin of the Y_{NPAR} , though the degree to which this occurs is dependent upon other factors such as the genetic background of the autosomes and PAR as well as the maternal environment (Guillot, Carlier, Maxson, & Roubertoux, 1995; Guillot, Sluyter, Laghmouch, Roubertoux, & Crusio, 1996; Miczek, Maxson, Fish, & Faccidomo, 2001; Tordjman et al., 1995).

A more recent approach to studying sex chromosome effects has been the production of mice known as the "four core genotypes" (Arnold, 2009; Arnold & Chen, 2009). These mice were created by inducing a mutation in the *Sry* gene followed by the reinsertion of a functional *Sry* transgene driven by its own promoter onto an autosome, thus enabling gonadal sex to be determined independently of sex chromosome complement. Hence there exists four possibilities: XX gonadal females (XXF), XY gonadal females (XYF), XY gonadal males (XYM), and XX gonadal males (XXM), and comparisons can be made between groups to examine effects of sex hormones (XXF vs. XXM and XYF vs. XYM) or the effects of sex chromosomes independent of the organizational and activational effects of gonadal hormones (XXF vs. XYF and XXM vs. XYM) on behavioral development. Investigations of these mice (who are typically gonadectomized prior to testing) have revealed that genes on the sex chromosomes other than *Sry* are responsible for variation in the response to thermal and chemical nociceptive stimuli (Gioiosa et al., 2008), learning of addictive habits (Quinn, Hitchcott, Umeda, Arnold, & Taylor, 2007), social interactions (McPhie-Lalmansingh, Tejada, Weaver, & Rissman, 2008), aggression and parental behavior (Gatewood et al., 2006). Interestingly, these effects appear to be highly specific as no effects of sex chromosome complement on other behaviors including

olfactory and anxiety-like behavior have been found (Arnold, 2009). Within the brain, sex chromosome complement has also been shown to modulate the density of vasopressin fibers in the lateral septum (Gatewood et al., 2006) and the expression of tyrosine hydroxylase positive neurons in the embryonic mesencephalon (Carruth, Reisert, & Arnold, 2002). Interestingly, differences in the brain expression of several genes including those encoding histone demethylases and ubiquitin enzymes between XX and XY mice are also independent of their gonadal sex, suggesting that altered brain development through epigenetic processes may be related to the inheritance of sex chromosomes (Xu, Deng, Watkins, & Disteché, 2008; Xu, Taya, Kaibuchi, & Arnold, 2005). Recently, it has been shown that mRNA expression of the prodynorphin gene, which encodes the dynorphin precursor molecule, is X-linked and shows a higher expression in the striatum of XX versus XY individuals (Chen, Grisham, & Arnold, 2009). This is found regardless of sex or circulating gonadal hormones suggesting that the X chromosome may indirectly influence adult dopaminergic functioning. Evidence that the Y chromosomes may also regulate adult dopaminergic functioning has also been recently provided by the finding that *Sry* is actually expressed in TH positive neurons of the substantia nigra (Dewing et al., 2006).

Several other transgenic mice have also been created to study sex chromosome effects, although each has their own limitations. One example is the SF1 mutant mouse that contains a deletion in the steroidogenic factor 1 gene meaning that they do not develop gonads or adrenal glands. These mice can only survive following neonatal glucocorticoid treatment and adrenal tissue implantation but allow the behavioral effects of sex chromosomes (XX vs. XY) to be investigated in mice that lack any variation in gonadal hormones (Budefeld, Grgurevic, Tobet, & Majdic, 2008). These mice demonstrate gonadal-independent sex chromosome effects on the expression of nitric oxide synthase in the preoptic area and calbindin in the ventromedial hypothalamus, but no sex differences were found in aggressive behavior (Grgurevic, Budefeld, Rissman, Tobet, & Majdic, 2008). The Y_{POS} mouse is produced by backcrossing males of the poschiavinus substrain onto a C57BL background (Eicher, Washburn, Whitney, & Morrow, 1982). After repeatedly mating male offspring with C57BL females it was found that there was a significantly high proportion of females being produced, which were eventually determined to be genetic males that actually possessed ovarian tissue. This outcome appears to be related to a difference in levels of expression of the *Sry* gene between the two substrains, meaning that gonadal development is not completed in some XY individuals such that they become female. Comparing these XY gonadal females with XX gonadal

females indicates the presence of the Y chromosome significantly improved spatial abilities but did not influence anxiety-like or mating behavior (Canastar, Maxson, & Bishop, 2008; Stavnezer & Schrader, 2006). In another mouse model, a small region of the Y chromosome containing seven genes including *Sry* (the *Sxr* locus) is duplicated and can be translocated onto the X chromosome during meiosis in males. XX gonadal males that possess this extra region were found to be significantly better at retrieving pups and exhibited reduced infanticide in a test of paternal behavior compared to XY gonadal males, though they were still poorer at retrieving than XX females (Reisert et al., 2002). This suggests that genes on the Y chromosome may inhibit parental care, which has been confirmed by the finding that XYF mice were slower to retrieve pups than XXF mice in a similar test of parental behavior (Gatewood et al., 2006).

The contribution of genes expressed on the sex chromosome to behavioral phenotypes can also be investigated using mice with an adjusted number of sex chromosomes. For instance, XO females show increased anxiety-like behavior (Isles, Davies, Burrmann, Burgoyne, & Wilkinson, 2004) and deficits in visual attention (Davies, Humby, Isles, Burgoyne, & Wilkinson, 2007) compared to XX females and this effect appears to be related to X-linked genes that escape inactivation in the former and haplo-insufficiency of the PAR in the latter. Interestingly, a putatively maternally expressed gene (see genomic imprinting section later) on the X chromosome, *Xlr3b*, has also been revealed from studies of XO mice. Analysis of embryonic gene expression in the brain identified this gene as being differentially up-regulated in mice that received their X chromosome from the mother only. Although the function of this gene is currently unknown it is suggested that it may be partially responsible for the behavioral differences in attentional functioning observed in Turner's syndrome females dependent upon the parent-of-origin of the X chromosome (Skuse et al., 1997), as XO mice with a maternal X were found to be less flexible during trials of reversal learning than XO mice with an X chromosome of paternal origin (Davies et al., 2005). $XY Y^-$ males that possess two copies of the Y chromosome but only one copy of the *Sry* gene demonstrate improved sexual behavior compared to XY males, whereas XXY males are significantly poorer at both sexual behavior and learning in a simple tone-food conditioning task compared to XY males (Lue et al., 2005; Park et al., 2008). Taken together, these various mouse models provide overwhelming evidence for the roles of individual genes on the X, Y_{PAR} , and Y_{NPAR} in the development of sex differences in behavior independent of the organizational effects of gonadal hormones.

MITOCHONDRIAL DNA

In addition to DNA contained within the nucleosome, almost all eukaryotes possess DNA in mitochondria, a vestige of these organelles' proteobacteria ancestry. Within most animals this mitochondrial DNA (mtDNA) is double stranded, between 15 and 20 kb long, circular, intron-less, and contains typically 37 genes that encode ribosomal RNAs, transfer RNAs and subunits of the oxidative phosphorylation pathway which are required for the regulation of energy metabolism. Across different cell types there is great variation in mtDNA copy number, with somatic cells typically containing up to 4,000 copies whereas maternal oocytes may contain as many as 200,000 and sperm as few as 100 (White, Wolff, Pierson, & Gemmell, 2008). This disparity in number between mtDNA of maternal and paternal origin coupled with the fact that during the formation of the inner cell mass in embryogenesis there is a "mitochondrial bottleneck" where the total number of copies of mtDNA may be reduced to only 100 or so led to the acceptance that mtDNA is exclusively maternally inherited. This dramatic reduction in mtDNA number during embryogenesis followed by the rapid expansion during oogenesis dictates that only a very small subset of maternal mtDNAs will be passed on to future generations (White et al., 2008). Moreover, in several species there appears to be specific nuclear encoded proteins within maternal oocytes that identify and remove ubiquitin-labeled mtDNA of paternal origin from progressing beyond the early pronucleus stage thus ensuring a matrilineal inheritance (Kaneda et al., 1995; Shitara, Hayashi, Takahama, Kaneda, & Yonekawa, 1998; Sutovsky et al., 2000). However, more recently there have been reports that occasionally some mtDNA of paternal origin is transmitted to offspring which is known as "paternal leakage" (Wolff & Gemmell, 2008). Currently, this has only been described in a few species so much is yet to be understood as to its overall significance and frequency of occurrence among mammals.

There are several studies indicating that genomic variation in these 37 mitochondrial genes play a role in regulating brain function, including brain size (Roubertoux et al., 2003), neuro-protection from ageing of dopaminergic neurons in the substantia nigra (Bender et al., 2006; Kravtsov et al., 2006), synaptic transmission (Billups & Forsythe, 2002) and calcium signaling in hippocampal neurons (Kubota et al., 2006). Moreover, as mitochondria play a crucial role in regulating apoptotic and metabolic pathways in neurons, where mitochondria copy number is especially high, it is not surprising that polymorphic variation in mtDNA has been associated with the increased likelihood of developing various psychiatric disorders (Shao et al., 2008) including Alzheimer's disease (Elson et al., 2006), schizophrenia

(Martorell et al., 2006), bipolar disorder (Rollins et al., 2009), autism (Weissman et al., 2008), and Parkinson's disease (Bender et al., 2006) as well as variations in human personality traits (Kato et al., 2004) and cognitive ability (Byrne et al., 2009; Thomas, Miller, & Mascie-Taylor, 1998).

The involvement of mtDNA in the regulation of behavior has also been investigated in animal models. One approach has been to produce reciprocal F1 mice from two inbred strains and then to backcross the female offspring to the paternal strain, and to repeat this backcrossing for at least 30 generations. This breeding strategy eventually creates mice that are identical to their paternal progenitor strain with respect to nuclear genes but contain the mtDNA of their maternal progenitor strain (Roubertoux et al., 2003). One such study using NZB and CBA mouse strains found that the cognitive and learning performance of mice resembled that typically exhibited by the strain-of-origin of their mtDNA, an effect that was more pronounced as the mice aged (Roubertoux et al., 2003). The effect appears to be highly specific, as no differences were observed between mice that differed only in the origin of their mtDNA with respect to anxiety-like behavior, aggression or maternal care, and mixed results were found with exploratory behavior. Using the same breeding strategy, alterations in physical activity and hearing abilities have also been ascribed to the maternal origin of mtDNA (Johnson, Zheng, Bykhovskaya, Spirina, & Fischel-Ghodsian, 2001; Nagao et al., 1998). In a separate study using a similar breeding design, C57BL male mice were bred with females from 12 different strains and 4 subspecies of mice who all contained polymorphic variation in their mtDNA. With successive backcrossing of female offspring with C57BL males, eventually 16 separate mtDNA variants were produced all of which were identical with respect to their nuclear genome (Yu et al., 2009). A phenotypical analysis of these conplastic strains found that mtDNA variation, in particular of the ATP-ase subunit-8 gene, contributed significantly to variation in anxiety-related behavior as well as alterations in corticosterone release and monoamine activation following repeated social defeat stress (Gimsa, Kanitz, Otten, & Ibrahim, 2009). These studies are supportive of a maternal inheritance of behavior related to mtDNA inheritance, although the possibility that they may be due to other maternally inherited cytoplasmic factors cannot be completely eliminated.

A second approach to study the role of mtDNA in behavior has been to create transgenic mice with altered mtDNA functioning. For instance, mice that possess a neural-specific mutated copy of mtDNA polymerase gene are unable to repair mtDNA mutations, meaning that nonfunctional mtDNA accumulates with increasing age (Kasahara et al., 2006). Although these mice do not

display altered learning behavior, they do exhibit an altered startle response, depressed locomotor activity, disruption of circadian rhythmicity and hormonal cycling and antidepressant-induced hyperactivity as well as altered concentrations of brain monoamines (Kasahara, Kubota, Miyauchi, Ishiwata, & Kato, 2008; Kasahara et al., 2006). Interestingly, another transgenic mouse that expresses a high proportion of nonfunctional mtDNA exhibits deficits in spatial memory as well as deafness (Nakada et al., 2006; Tanaka et al., 2008). One further example is the xenomitochondrial mouse, in which mtDNA from closely related *Mus* species is inserted into embryonic stem cells of *Mus musculus*. The resulting female chimeric mice are able to successfully transmit the adopted foreign mtDNA to their offspring in a minority of cases, enabling the production of lineages that carry mtDNA from different species (McKenzie, Chiotis, Pinkert, & Trounce, 2003). Although these mice have yet to be behaviorally screened, it has already been shown that they have altered metabolic functioning (McKenzie et al., 2003; Pinkert & Trounce, 2007). Thus, it appears from the available animal and human data that maternally inherited variations in the sequence of mtDNA can lead to altered brain development and behavior, and that there is also good evidence that with increasing age disruptions to the mtDNA accumulates and can account for changes in neural functioning and behavior.

GENOMIC IMPRINTING

For the vast majority of autosomal nuclear genes, both the mother and father pass on functionally active copies to their offspring. This is not the case for a subset of mammalian genes (approximately 80–100 depending upon species) whereby one parent actively silences their own gene meaning that there is a parent-of-origin specific monoallelic expression of the gene in the offspring (Keverne, Fundele, Narasimha, Barton, & Surani, 1996). Significantly, the expression of these imprinted genes is not dependent upon the sex of the individual inheriting the gene, but on the sex of the individual passing on the gene. Thus a paternally expressed gene is silenced when passed through a mother to both her sons and daughters (the copy being inherited from the father is active) and will only become active again in the grandchildren of her sons but not of her daughters. This process, known as genomic imprinting, is achieved mechanistically through the establishment of epigenetic marks (typically involving DNA methylation, chromatin modifications, and non-coding RNAs) of chromosomal control regions adjacent to these genes (imprinting control centers) during gametogenesis, which are then maintained through somatic development (Reik, Dean, & Walter, 2001).

This parent-of-origin specific gene expression was discovered in the early 1980s when it was established that mammalian embryos that consisted exclusively of either two paternal haploid (androgenetic—AG) genomes or two maternal haploid (parthenogenetic—PG) genomes were not viable (Barton, Surani, & Norris, 1984; McGrath & Solter, 1984). However, chimeric mice that contain both wild-type cells and either PG or AG cells are viable and show differential patterns of brain development (Allen et al., 1995). Using a lacZ reporter gene, it was observed that PG cells were preferentially located in the developing neocortex, striatum, hippocampus, and olfactory receptor neurons but from very early stages of embryonic development (E9) they were absent from the basal forebrain plate and continued to be absent from limbic areas of the brain postnatally. Conversely, AG cells were located preferentially in the mediobasal forebrain but were almost completely missing from telencephalic structures. Consequently, chimeras with PG cells have enlarged brains whereas those with AG cells have small brains relative to body size. This distribution of cells suggests that imprinted genes that are expressed when inherited from the mother are involved in cognitive processes, whereas those that are expressed when inherited from the father are involved in behaviors regulated by the hypothalamus and limbic system. Behaviorally, PG mice were observed to have elevated levels of inter-male aggression compared to wild-type mice and this increase was correlated with the percentage of PG cells present in the chimeras (Allen et al., 1995).

Further evidence for a strong role of these genes in brain and behavioral development comes from analysis of their expression patterns. Approximately 90% of all imprinted genes have been found to be expressed in the brain, although the exact spatio-temporal patterning of this expression has yet to be elucidated for most of these genes (Davies, Lynn, Relkovic, & Wilkinson, 2008; Wilkinson, Davies, & Isles, 2007). Nevertheless, for a small subset of imprinted genes, a thorough behavioral and neural analysis has been possible utilizing transgenic mice with targeted mutations (see Tab. 1). From these studies, there appears to be converging evidence that paternally expressed genes do indeed contribute to the development of the brain and in particular of the hypothalamus and also to physiological processes and behaviors that are coordinated by this brain region. This was predicted by the early AG chimera work, but interestingly paternally expressed genes appear to achieve this despite encoding gene products with distinct cellular functions. Furthermore, the transcriptional activation of both maternally and paternally expressed genes is not confined to the areas suggested from chimeric work and indeed both types of imprinted gene appear to be important in the regulation of cognitive behaviors (Davies

et al., 2008). Continued investigation of the brain expression and behavioral phenotypes associated with other imprinted genes is required in order to shed light on why genes involved in neural development have come to utilize this unique form of gene regulation. This work will also help in our understanding of several psychiatric disorders that demonstrate either complete or partial parent-of-origin inheritance such as Prader–Willi and Angelmann syndromes, Silver–Russell syndrome, schizophrenia, autism, and bipolar disorder (Davies et al., 2008; Wilkinson et al., 2007).

ENVIRONMENTALLY INDUCED GERMLINE EFFECTS

Evidence for the Nongenomic Transmission of Environmentally Induced Phenotypes through the Germline

Historically there has been little support for the Lamarckian notion that environmental influences experienced by a parent during their own lifetime (prior to mating) have the potential to influence the development of future offspring via germline inherited factors. More recent work has provided several strands of evidence suggesting that this type of inheritance can and does indeed occur. There is increasing human data demonstrating that the lifestyles of fathers (e.g., smoking, alcohol intake) before birth is directly related to several indices of behavioral development in children even after accounting for postnatal factors (Savitz, Schwingl, & Keels, 1991; Tarter, Jacob, & Bremer, 1989). There is even evidence that the experiences of grandparents may be important as the early growth rates of grandfathers and grandmothers are associated with the risk of grandsons and granddaughters respectively developing metabolic disorders (Kaati, Bygren, Pembrey, & Sjostrom, 2007; Pembrey et al., 2006). This has also been predicted by evolutionary biologists, who posit that it would be adaptive for individuals to develop according to their likely future environment from signals received from their parents (Bonduriansky & Head, 2007; Uller, 2008). In mammals, there are many examples of how variations in the environment (e.g., diet, stress) experienced by one generation can be passed down to future generations via the matriline (Jablonka & Raz, 2009). There are many possible routes of transmission through which such observed effects occur. For instance, changes in the in utero environment or postnatal care may induce long-term changes in physiology and behavior, which are perpetuated each generation or the observed phenotypic inheritance may also be encoded in the germline (Champagne & Curley, 2009). However, for the males

Table 1. Behavioral Phenotypes of Mice Lacking a Functional Copy of Various Imprinted Genes

Gene	Gene Function	Characteristics of Gene Knockout Mice	Refs.
Paternally expressed			
Peg3	Zinc finger protein transcription factor; apoptosis	Reduced oxytocin neurons and receptor binding; altered hypothalamic mRNA expression of orexin, NPY, POMC and MCH; deficits in maternal and sexual behavior, olfaction, feeding, pup suckling, energy metabolism, puberty onset, circadian rhythms and anxiety-like behavior.	Curley, Barton, Surani, and Keverne (2004), Curley et al. (2005), Champagne, Curley, Swaney, Hasen, and Keverne (2009), Li et al. (1999), Swaney, Curley, Champagne, and Keverne (2007, 2008), Broad, Curley, and Keverne (2009)
Peg1/Mest	Putative α/β hydrolase enzyme	Females show deficits in pup retrieval, nest building and placentophagia.	Lefebvre, Viville, Barton, Ishino, and Surani (1997)
Mage12	Belongs to MAGE/necdin family of proteins; cell-cycle regulation and apoptosis	Altered circadian activity, feeding, olfaction, metabolism, and anxiety-like behavior; infanticide, delayed puberty onset and impaired male reproductive behavior; reduced brain volume; decreased levels of serotonin and 5-hydroxyindoleacetic acid, and decreased dopamine and orexin	Kozlov et al. (2007), Bischof, Stewart, and Wevrick (2007), Mercer et al. (2009), Mercer and Wevrick (2009)
Gnasx1	Subunit of the G-protein $G\alpha$	Pups have suckling deficits	Plagge et al. (2004)
Sgce	Trans-membrane glycoprotein	Deficits in motor activity, elevated anxiety-like and depressive-like behavior, higher levels of dopamine metabolites and lower levels of serotonin metabolites	Yokoi, Dang, Li, and Li (2006)
mbii52	snRNA	Increased editing of the serotonin 5HT2C receptor pre-RNA and disruptions to 5HT2C receptor-mediated behaviors (impulsive responding, reactivity to palatable foodstuffs and locomotor activity)	Doe et al. (2009)
Ndn	MAGE/necdin protein family, cell-cycle regulation and apoptosis	Differential survival of forebrain GABA neurons and hypothalamic oxytocin and gonadotropin-releasing hormone neurons; increased skin picking behavior and increased spatial memory and pain tolerance	Andrieu et al. (2006), Kuwajima, Nishimura, and Yoshikawa (2006), Muscatelli et al. (2000)
Ras-GRF1	Nucleotide exchange factor	Deficits in long-term potentiation, and contextual fear memory (though monoallelic expression of the gene may be confined to the preweaning phase only, as adults show biallelic expression)	Arai, Li, Hartley, and Feig (2009), Drake, Park, Shirali, Cleland, and Soloway (2009), Fernandez-Medarde et al. (2007), Giese et al. (2001)
Maternally expressed			
Nesp55	Neuro-endocrine secretory protein 55	Altered reactivity to a novel environment	Plagge et al. (2005)
Ube3a	E6-AP ubiquitin ligase involved in regulating apoptosis by promoting p53 degradation	Impairments in spatial and context-dependent learning, long-term potentiation, the neurodevelopment of motor skills and fluid consumption behavior as well as being prone to seizures	Heck, Zhao, Roy, LeDoux, and Reiter (2008), Jiang et al. (1998), Miura et al. (2002)

of the majority of mammalian species, who do not provide any further investment to offspring following mating, their only opportunity to pass on information regarding the environment may be through germ cells (Bonduriansky & Head, 2007). Therefore while it is methodologically very challenging to determine if an environmentally induced trans-generational inheritance of phenotype down the matriline is actually encoded within the germline, the demonstration of such a phenotypic transmission down the patriline is more conclusive of an inherited germline effect. For this reason, in this section we shall primarily concentrate on data demonstrating paternal nongenomic inheritance of phenotype and describe potential epigenetic mechanisms through which this may operate.

The first approach to studying paternal germline effects has been to manipulate directly some aspect of the male's environment such that phenotypic variation is induced, and to then observe if these effects or other novel effects are transmitted to his offspring. Some of the best evidence for such paternal transmission comes from work that has directly mirrored the findings from the human literature that paternal alcohol and drug exposure can plastically shape offspring development. For instance, rat and mouse offspring sired by alcohol-exposed males show reduced litter size, reduced birth weight, developmental retardation, increased mortality, compromised immunity and a host of behavioral abnormalities including impaired discrimination on spatial tasks and altered aggressive, risk-taking and anxiety-like behavior (Abel, 2004; Ledig et al., 1998; Meek, Myren, Sturm, & Burau, 2007; Wozniak, Cicero, Kettinger, & Meyer, 1991). Further evidence for paternal transmission comes from findings that cocaine-exposed fathers sire offspring that perform poorly on tests of visuo-spatial attention, spatial working memory and spontaneous alternation and have a reduced cerebral volume (Abel, Moore, Waselewsky, Zajac, & Russell, 1989; He, Lidow, & Lidow, 2006). Similar effects on offspring development and behavior have been reported for fathers exposed to various other drugs and toxins including opiates, cyclophosphamide, ethylene dibromide, lead and other miscellaneous chemicals with some of these effects being transmitted to second and third generations (Hales & Robaire, 2001). It should be noted though that the strength of these effects are dependent upon the duration and dosage of exposure as well as species and offspring sex. Moreover, these effects are sensitive to the time at which the paternal exposure commenced and was completed although the majority of studies exposed postweaning animals.

A class of pharmacological agents that have been shown to induce phenotypic changes in offspring through the patriline are endocrine disruptors and in particular the anti-androgenic compound vinclozolin. Significantly,

these effects are sensitive to the time of exposure, with exposure having to occur in males during a small window in late embryogenesis. Males who are born to vinclozolin exposed late-gestation dams have been shown to have an increased risk of tumor formation, kidney disease, immune abnormalities and infertility, all of which were transmitted through the male germline across four subsequent generations (Anway, Cupp, Uzumcu, & Skinner, 2005; Anway & Skinner, 2008). Interestingly, it has also been reported that for up to three generations postexposure the gene expression of nearly 400 genes were altered in the hippocampus and amygdala of male offspring whereas in female offspring the expression of nearly 1,500 genes was changed (Skinner, Anway, Savenkova, Gore, & Crews, 2008). These genes were predominantly those involved in the regulation of axon guidance and long-term potentiation and could thus alter brain development. Significantly, the behavior of these mice was also altered with females and males showing elevated and decreased anxiety-like behavior respectively. These phenotypic alterations have been observed for as many as four generations, indicating that these effects must have been incorporated into the germline (Anway, Rekow, & Skinner, 2008). As F0 pregnant dams were exposed to the vinclozolin, not only were their F1 male offspring exposed but so were the developing germ cells of their F2 grand-offspring within their offspring. Therefore, as F3 individuals also inherited phenotypic changes and were not directly exposed to the endocrine disruptor it can be said that the effect is truly a trans-generational epigenetic inheritance (i.e., one that has been incorporated into the germline).

Few studies have addressed whether altering a male's physical or social environment can lead to differential developmental outcomes in his offspring. One early study that did find such an effect reported that males who were housed in small cages for 8 weeks before mating (and consequently experienced a decreased oxygen and increased carbon dioxide composition relative to those males in standard cages) had female offspring who consistently had elevated blood hemoglobin levels (Kahn, 1970). In rats, male offspring born to pregnant dams who are exposed to chronic levels of dexamethasone suffer various metabolic and stress-related insults, and significantly when they are mated with control dams their offspring also demonstrate reduced birth weight, glucose intolerance and altered hepatic enzyme activity (Drake, Walker, & Seckl, 2005). Although this study artificially manipulated the levels of glucocorticoids in pregnant F0 dams, similar increases in these steroids are observed during studies of prenatal stress. Differences in male diet in the period before mating have also been associated with altered offspring outcome. For instance, males that undergo a 24 hr complete fast 2 weeks before mating

have offspring with reduced serum glucose and altered levels of corticosterone and IGF1 (Anderson et al., 2006). Males who eat a diet consisting of betel nuts (which contain nitrosamines) prior to mating also have offspring that develop diabetes and metabolic syndrome; a phenotype which can be passed for at least three generations down the patriline (Boucher, Ewen, & Stowers, 1994). Similarly, F1 sons of female mice that are 50% calorically restricted during late gestation but fed ad libitum throughout their own life develop metabolic syndrome and indeed their own F2 offspring also exhibit impaired glucose tolerance (Jimenez-Chillaron et al., 2009). Mechanistically, this may be achieved through altered epigenetic regulation of genes regulating metabolic pathways (notably F2 males have reduced expression in epididymal fat tissues of the paternally expressed *Pref1* gene which is an inhibitor of adipogenesis, though there was no change to the DNA methylation of its promoter). However, there may also be an additive effect of the increased adiposity during adulthood of F1 males affecting spermatogenesis. Interestingly, in another study, when the fertilized eggs of adult females born to calorically restricted dams were embryo transferred to control dams, the inheritance of metabolic syndrome was still observed suggesting that this transmission may occur via alterations in the germline of both parents (Thamotharan et al., 2007). Therefore, while not altering behavioral phenotypes per se these metabolic studies are illustrative that alterations to the physical environment are able to exert trans-generational effects via the paternal lineage.

A second approach to demonstrating paternal effects is to examine the behavioral development of offspring sired by isogenic males who exhibit natural individual variations in some aspects of their phenotype. One example of this is animal studies that have tested the effect of paternal age on altered offspring development. Rat offspring born to males aged over 22 months are significantly poorer at acquiring a conditioned avoidance response compared to offspring sired by younger males although no differences in anxiety-like behavior are observed (Auroux, 1983). In mice, male and female offspring born to sires who are over 120 weeks of age are found to have reduced longevity, diminished reproductive success, retarded sensorimotor development, inhibited adult spontaneous activity and impaired passive-avoidance learning compared to mice born to younger sires (Garcia-Palomares, Navarro, et al., 2009; Garcia-Palomares, Pertusa, et al., 2009). Interestingly, the spontaneous activity of both sexes and the learning capacity of males have also been found to be higher in offspring born to adult mouse sires (12–16 weeks) compared to postpubertal sires (6 weeks) (Auroux, Nawar, Naguib, Baud, & Lapaquellerie, 1998). This is suggestive of an inverted U-shaped relationship between

paternal age and offspring quality, a phenomenon that has been corroborated by studies investigating the relationship between paternal age and outcomes such as intelligence and neural tube defects in human populations (Auroux et al., 2009; Auroux et al., 1989; Malaspina et al., 2005; McIntosh, Olshan, & Baird, 1995).

Another experimental method is to prescreen genetically identical male mice for differences in phenotype and then to see if these differences are inherited by their offspring. The underlying assumption to this approach is that the phenotypic variation is likely caused by variations in the epigenetic regulation of gene expression between sires that is then transmitted to offspring via the germline. In one such study, Balb/c male mice were screened prior to mating for their emotional reactivity in an open-field test and it was subsequently found that their female offspring had behavioral differences in the same test as well as altered hippocampal volumes that significantly correlated with the behavioral differences of their fathers (Alter et al., 2009). This association between the behavior of daughters and fathers still holds true even after accounting for multiple potential mediators including maternal care, litter characteristics and the length of time the father was present with the mother during mating. This is a very important set of controls because an often overlooked component to all paternal effect studies is that they may actually be indirectly mediated via the mother. For instance, if females perceive differences in the phenotypic quality of males (which may be induced by exposure to drugs, vary with age or just naturally occur), then they may differentially invest resources (either prenatally or postnatally including changes in maternal care) into their offspring dependent upon their own reproductive life history. Evolutionary biologists refer to this theoretical maternal adjustment in relation to male quality as the differential allocation or compensation hypotheses (Burley, 1988; Gowaty et al., 2007). There are several experimental tests of these hypotheses including in house mice where, for instance, individuals show differences in fitness and behavior if they are the offspring of females who mated with sires that they preferred or did not prefer in a mate choice test (Drickamer, Gowaty, & Holmes, 2000). What will be required for future studies to conclusively demonstrate that paternal effects on behavior are not indirectly mediated via the mother will be to conduct in vitro fertilization and embryo transfer using sperm from males in each of the above studies.

Potential Mechanisms for the Nongenomic Transmission of Environmentally Induced Phenotypes through the Germline

The epigenetic state of the genome undergoes extensive reprogramming (active and passive demethylation as well

as reorganization of histone modifications) between generations, both in the gametes of each parent and in the early developing embryo (Reik et al., 2001). These events then enable cell lineage-specific and sex-specific placement of methylation marks, and also allow the erasure of methylation marks that have accumulated during the lifespan of the parents (see Fig. 1). Together, epigenetic programming and reprogramming events during this developmental period ensure the totipotency of the developing zygote, and favor the notion that embryonic development begins with an epigenetically “clean slate”. However, the incomplete reprogramming of epigenetic modifications may potentiate the trans-generational inheritance of phenotypes. As discussed earlier, exposure of F0 gestating rats to the endocrine disrupter vinclozolin during late gestation (ED 12–15) increases the incidence of various pathologies in F1 offspring, and these pathologies are transmitted through the paternal, but not maternal, lineage for up to four subsequent generations of offspring (Anway et al., 2005; Anway, Leathers, & Skinner, 2006; Crews et al., 2007; Skinner et al., 2008). Significantly, this transmission is associated with altered DNA methylation of several coding and noncoding gene sequences including

imprinted genes in the sperm cells of the F2 and F3 generations (Anway et al., 2005; Stouder & Paoloni-Giacobino, in press). It is interesting to note that the timing of de novo methylation during gametogenesis of F1 germ cells, following the genome-wide erasure of methylation marks, is sex-specific. In the rodent, demethylation of these primordial germ cells occurs around ED12 in both sexes. In the male, remethylation follows shortly thereafter on ED16 and continues until the day of birth. In females, this process is delayed until oogenesis occurs during the postnatal period (La Salle et al., 2004). Thus, it is likely that the timing of environmental experiences will determine the likelihood of males or females transmitting epigenetic changes to their offspring.

A second possibility is that environmental exposures occurring even beyond the period of primordial germ cell development could lead to heritable changes in the epigenome of germ cells. For this to occur, environmental exposures must induce changes in both somatic and germline tissues and these acquired marks must then avoid the erasure and reprogramming events that occur during embryogenesis. With regard to the first issue, there is ample evidence to suggest that epigenetic changes can occur in both tissues in tandem. For instance, stochastic

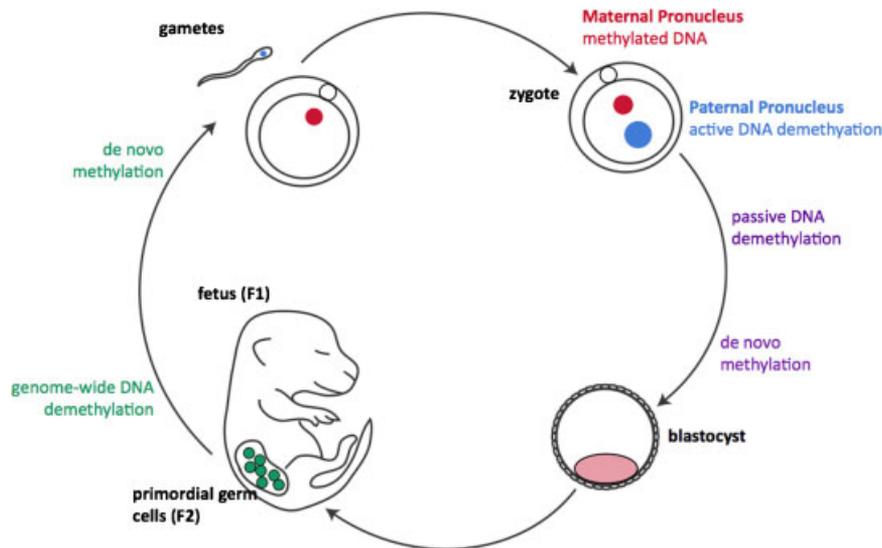


FIGURE 1 Epigenetic modifications undergo reprogramming during two critical phases of the life cycle. The first is during gametogenesis during which the primordial germ cells (PGCs; which develop into the mature gametes) are derived from somatic tissue of the developing zygote. PGCs undergo genome-wide DNA demethylation in the embryo between ED11.5 and ED12.5. Remethylation of the male primordial germ line begins around ED16 and is complete by the day of birth. In females, the process of remethylation is both delayed and protracted, with DNA remethylation taking place only after birth and continuing throughout oocyte development. The second wave of reprogramming occurs at fertilization during which the paternal genome is actively demethylated. During early cell divisions the genome of the embryo (except for imprinted genes) undergoes passive DNA demethylation until blastulation. Following blastulation, de novo DNA methylation occurs shortly before the differentiation of placental and somatic tissue derivatives. (Figure modified from Morgan, Santos, Green, Dean, & Reik, 2005).

changes (e.g., those that accrue with increasing parental age) in DNA methylation occur in all tissues including the gametes and are likely due to copy errors of epigenetic marks made during cell division (Flanagan et al., 2006; Fraga et al., 2005; Oakes, Smiraglia, Plass, Trasler, & Robaire, 2003). Furthermore, it has been shown that chronic exposures to environmental variables such as alcohol, induce gene expression and chromatin remodeling and changes in CpG methylation at various genes in both the brain and periphery (Carlson & Quinn, 2007; Ouko et al., 2009; Pandey, Ugale, Zhang, Tang, & Prakash, 2008). Moreover, this exposure has also been shown to alter the expression of the proteins and enzymes that regulate the epigenetic machinery of the cells in the germline. For example, alcohol intake has been shown to decrease the mRNA levels of DNA-methyltransferases (DNMTs, the enzymes responsible for DNA methylation) in the sperm cells of adult male rats leading to hypomethylation and increased gene expression (Bielawski, Zaher, Svinarich, & Abel, 2002; Ouko et al., 2009) whereas adult male mice exposed to chronic cocaine showed reduced DNMT1 and increased DNMT3 mRNA expression in cells of the seminiferous tubules of the testes (He et al., 2006).

Even acknowledging therefore that environmental experiences subsequent to primordial germ cell development could alter the epigenetic status of genes, it remains to be tested in most instances whether these altered epigenetic marks are inherited or are erased following fertilization in the subsequent generation. A key question of this research, therefore, is identifying genes that are more likely to transmit their altered epigenomes to their offspring by either avoiding having their epigenetic marks from being erased postfertilization or by enabling these marks to be reestablished. Two particular groups of genes that have emerged as strong candidates for these mediators are imprinted genes and retrotransposons. As discussed earlier in this review, imprinted genes typically are silenced in a parent-of-origin manner through DNA methylation. Interestingly, it has been established that the expression and methylation status of these genes in sperm can be altered through environmental influences such as exposure to alcohol in humans (Ouko et al., 2009). Similar changes have also been observed in the sperm of mice who were conceived through artificial reproductive technologies and significantly the altered methylation patterns of particular imprinted genes (*Snrpn* and *H19*) were observed in the sperm of F2 males demonstrating that these changes had avoided reprogramming and been trans-generationally inherited (Stouder, Deutsch, & Paoloni-Giacobino, 2009). Retrotransposable elements are another group of genes that may be able to retain the epigenetic marks of their parent, from fertilization through embryonic development to adulthood (Lane

et al., 2003). Transposable and retrotransposable elements comprise approximately 45% of the human genome and are remnants of ancestral infections that became incorporated into the DNA of the germline. Most transposons and retrotransposons have accumulated a sufficient number of mutations to render them functionless. They do, however, possess functionally competent promoters, which tend to be silenced by extensive methylation during embryogenesis. Since it is known that specific types of transposons, for instance intracisternal-A particles (IAPs, a long-terminal repeat retrotransposon) are resistant to postfertilization demethylation, and that differential methylation of these regions can result in the transcriptional regulation of neighboring genes, it has been proposed that stochastic patterns of epigenetic variation arising within these regions may contribute to heritable phenotypic variability (Whitelaw & Martin, 2001).

By measuring the stochastic variation in IAP methylation status, that arises even in isogenic littermates, it is possible to correlate levels of methylation and its resulting gene product with some observable phenotype. For instance, an IAP element inserted into the 5' region of the *Axin*^{Fu} allele (a gene responsible for embryonic axis formation), when methylated will result in the expression of aberrant gene transcripts and a kinked-tail phenotype (Rakyan et al., 2003). Interestingly, methylation status of the IAP is correlated with the degree of tail kink, and both phenotype and methylation status can be inherited by offspring through both maternal and paternal lineages. Similarly, the insertion of an IAP element into an exon of the agouti gene (*A^{Vy}*) results in a number of phenotypic effects including a range of coat color pigmentations. Like in the *Axin*^{Fu} mouse, the epigenetic state of *A^{Vy}* can be modified by environmental factors such as diet and is inherited by offspring (Cropley, Suter, Beckman, & Martin, 2006; Morgan, Sutherland, Martin, & Whitelaw, 1999). Interestingly, in one study, the epigenetic phenotype was found to be inherited via both 129 and C57B6 mothers regardless of the strain of the father, but only inherited from fathers (either 129 or C57B6) when the mother was of the 129 but not the C57B6 strain. There therefore appears to be strain-specific (and therefore genetic background contributions to) the ability of egg cells to erase and/or reestablish IAP methylation marks (Rakyan et al., 2003).

Besides DNA, both sperm cells and oocytes must transmit various cytoplasmic RNAs (e.g., mRNAs, siRNAs, piRNAs, and microRNAs) and proteins that are essential for initiating development following fertilization (Amanai, Brahmajoshiyula, & Perry, 2006; Lalancette, Miller, Li, & Krawetz, 2008). Although sperm RNA content is much lower than in the oocyte, sperm cells do transmit much of their RNA to the oocyte at fertilization (Ostermeier, Miller, Huntriss, Diamond, & Krawetz,

2004). While many of the RNAs contained in sperm are degraded during the early phases of embryogenesis, some RNAs are retained and even play critical roles in oocyte activation and signaling in the early zygote (Hayashi, Yang, Christenson, Yanagimachi, & Hecht, 2003). Interestingly, there is evidence that RNAs carried by mouse sperm and eggs may epigenetically alter the phenotype of offspring (Rassoulzadegan et al., 2006; Wagner et al., 2008). In one study, a reporter cassette was used to disrupt the *Kit* gene, which codes for a receptor tyrosine kinase critical for a number of developmental processes (Rassoulzadegan et al., 2006). While homozygosity at this locus is lethal, mice that are heterozygotes have distinctive white pigmentations on their feet and tail tips. Surprisingly, crosses of the heterozygotes resulted in an unexpectedly large number of offspring with the white pigmentations than would be predicted by Mendelian inheritance. When genotyped, many of the offspring from these crosses appeared to be genotypically wild type despite their mutant phenotype, and this “paramutation” could be transmitted through both male and female lineages. Further, it was shown that these offspring, like their heterozygote parents, showed decreased levels of *Kit* mRNAs and an accumulation of various abnormal RNA molecules in the testes and mature sperm. This has led to the hypothesis that RNAs may be transmitting the phenotype across generations. Subsequent experiments showed that injection into fertilized eggs of *Kit* mRNA prepared from heterozygotes or microRNAs that induce the degradation of *Kit* produced similar phenotypes.

In another study, a microRNA important for brain development (miR-124) was injected directly into one-cell embryos and implanted into pseudopregnant recipient females. The resulting offspring showed a marked increase in growth rate, which was detectable from the blastocyst stage onwards (Grandjean et al., 2009). Further, injection of a heart-specific microRNA (miR-1) resulted in offspring with cardiac hypertrophy (Wagner et al., 2008). In both cases, offspring born to these females showed developmental and adult up-regulation of a number of genes known to be targeted by the respective RNAs and in some cases were associated with chromatin modification of those genes. Further, these phenotypes were transmitted via the sperm through the same mechanisms as the *Kit* mutant phenotype (Grandjean et al., 2009; Wagner et al., 2008). It is important to note that these phenotypes arise through paternal and maternal lineages, suggesting that the same mechanisms of RNA-mediated inheritance occur through the female gametes. It remains to be seen if similar mechanisms are important in the transmission of environmentally induced phenotypic changes. However, given that RNA expression in gametes can vary as a function of both age (Hamatani et al., 2004) and lifestyle variables such as smoking (Linschooten

et al., 2009), there is the intriguing possibility that RNA changes that occur in egg and sperm cells following particular experiences may be transmitted to future generations and alter development.

CONCLUSION

Unequivocally, mothers and fathers do not contribute equally to the development of their offspring. Moreover, this differential influence is also not simply limited to variations in the amount of parental investment provided by one sex or another, although in mammals this certainly does lead to the predominant influence on offspring of mothers compared to fathers. Instead, there are several mechanisms through which mothers and fathers are able to pass on through their germline unique influences on their offspring. In the case of genetic sequence differences in mitochondrial DNA which are almost exclusively inherited via the matriline, the overall contribution to brain development is likely to be small but nevertheless significant. Indeed, there is increasing evidence that mtDNA variation may play an important role in the development of cognitive capacity and several mental disorders. Another source of genetic differences inherited differentially from parents arises from genes residing on the sex chromosomes. In particular, our understanding that genes on the X chromosome and Y_{PAR} and Y_{NPAR} (inherited down patriline) regions of the Y chromosome can contribute to behavioral sexual differentiation independently of the organizing effects of sex hormones has advanced greatly. In addition to these inherited genetic factors, there are also inherited differences in the epigenetic regulation of genes. This has been explored most with imprinted genes, whereby certain genes are silenced when inherited from one parent versus another. Both maternally and paternally expressed genes have been shown to play a very significant role in brain development and behaviors, particularly those that are regulated by the hypothalamus. Finally, there is an increasing acceptance and appreciation that the differential epigenetic regulation of other genomic regions such as retrotransposons may also be inherited through the germline. These altered epigenomic patterns may arise through stochastic variation, age-related degradation or may even be induced by the environmental experiences of parents. However, much about this inheritance has yet to be determined. For instance, it is still unknown as to how many and which type of genomic regions are able to avoid the erasure of their epigenetic status when inherited, what time points during an individual's lifetime their germline may be susceptible to epigenetic change (e.g., primordial germ cell development vs. gametogenesis) or indeed if there are other mechanisms (e.g., RNA-

mediated) that may be able to transmit these environmentally induced phenotypes through gametes. In conclusion, these studies show that the transmissible influence of mothers and fathers to their offspring's development is not related simply to the inheritance of autosomal genetic differences, but that there are many other routes through which each parent can effect this process. Moreover, these factors are inherited from generation to generation, such that offspring development is not simply a product of the experiences of their parents but also potentially of their grandparents and even earlier generations.

NOTES

We would like to thank George Michel, Frances Champagne, and Barry Keverne for their encouragement and helpful comments in the preparation of this article.

REFERENCES

- Abel, E. (2004). Paternal contribution to fetal alcohol syndrome. *Addiction Biology*, 9(2), 127–133.
- Abel, E. L., Moore, C., Waselewsky, D., Zajac, C., & Russell, L. D. (1989). Effects of cocaine hydrochloride on reproductive function and sexual behavior of male rats and on the behavior of their offspring. *Journal of Andrology*, 10(1), 17–27.
- Allen, N. D., Logan, K., Lally, G., Drage, D. J., Norris, M. L., & Keverne, E. B. (1995). Distribution of parthenogenetic cells in the mouse brain and their influence on brain development and behavior. *Proceedings of the National Academy of Science of the United States of America*, 92(23), 10782–10786.
- Alter, M. D., Gilani, A. I., Champagne, F. A., Curley, J. P., Turner, J. B., & Hen, R. (2009). Paternal transmission of complex phenotypes in inbred mice. *Biological Psychiatry*, 66, 1061–1066.
- Amanai, M., Brahmajosyula, M., & Perry, A. C. (2006). A restricted role for sperm-borne microRNAs in mammalian fertilization. *Biology of Reproduction*, 75(6), 877–884.
- Anderson, L. M., Riffle, L., Wilson, R., Travlos, G. S., Lubomirski, M. S., & Alvord, W. G. (2006). Preconceptional fasting of fathers alters serum glucose in offspring of mice. *Nutrition*, 22(3), 327–331.
- Andrieu, D., Meziane, H., Marly, F., Angelats, C., Fernandez, P. A., & Muscatelli, F. (2006). Sensory defects in Neeidin deficient mice result from a loss of sensory neurons correlated within an increase of developmental programmed cell death. *BMC Developmental Biology*, 6, 56.
- Anway, M. D., Cupp, A. S., Uzumcu, M., & Skinner, M. K. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*, 308(5727), 1466–1469.
- Anway, M. D., Leathers, C., & Skinner, M. K. (2006). Endocrine disruptor vinclozolin induced epigenetic trans-generational adult-onset disease. *Endocrinology*, 147(12), 5515–5523.
- Anway, M. D., Rekow, S. S., & Skinner, M. K. (2008). Comparative anti-androgenic actions of vinclozolin and flutamide on transgenerational adult onset disease and spermatogenesis. *Reproductive Toxicology*, 26(2), 100–106.
- Anway, M. D., & Skinner, M. K. (2008). Transgenerational effects of the endocrine disruptor vinclozolin on the prostate transcriptome and adult onset disease. *The Prostate*, 68(5), 517–529.
- Arai, J. A., Li, S., Hartley, D. M., & Feig, L. A. (2009). Transgenerational rescue of a genetic defect in long-term potentiation and memory formation by juvenile enrichment. *Journal of Neuroscience*, 29(5), 1496–1502.
- Arnold, A. P. (2009). Mouse models for evaluating sex chromosome effects that cause sex differences in non-gonadal tissues. *Journal of Neuroendocrinology*, 21(4), 377–386.
- Arnold, A. P., & Chen, X. (2009). What does the “four core genotypes” mouse model tell us about sex differences in the brain and other tissues? *Frontiers in Neuroendocrinology*, 30(1), 1–9.
- Auroux, M. (1983). Decrease of learning capacity in offspring with increasing paternal age in the rat. *Teratology*, 27(2), 141–148.
- Auroux, M., Nawar, N. N., Naguib, M., Baud, M., & Lapaquellerie, N. (1998). Post-pubescent to mature fathers: Increase in progeny quality? *Human Reproduction*, 13(1), 55–59.
- Auroux, M., Volteau, M., Ducot, B., Wack, T., Letierce, A., Meyer, L., et al. (2009). Progeny's mental aptitudes in man: Relationship with parental age at conception and with some environmental factors. *Comptes Rendus Biologies*, 332(7), 603–612.
- Auroux, M. R., Mayaux, M. J., Guihard-Moscato, M. L., Fromantin, M., Barthe, J., & Schwartz, D. (1989). Paternal age and mental functions of progeny in man. *Human Reproduction*, 4(7), 794–797.
- Barton, S. C., Surani, M. A., & Norris, M. L. (1984). Role of paternal and maternal genomes in mouse development. *Nature*, 311(5984), 374–376.
- Bender, A., Krishnan, K. J., Morris, C. M., Taylor, G. A., Reeve, A. K., Perry, R. H., et al. (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nature Genetics*, 38(5), 515–517.
- Bielawski, D. M., Zaher, F. M., Svinarich, D. M., & Abel, E. L. (2002). Paternal alcohol exposure affects sperm cytosine methyltransferase messenger RNA levels. *Alcoholism, Clinical and Experimental Research*, 26(3), 347–351.
- Billups, B., & Forsythe, I. D. (2002). Presynaptic mitochondrial calcium sequestration influences transmission at mammalian central synapses. *Journal of Neuroscience*, 22(14), 5840–5847.
- Bischof, J. M., Stewart, C. L., & Wevrick, R. (2007). Inactivation of the mouse Magel2 gene results in growth abnormalities similar to Prader-Willi syndrome. *Human Molecular Genetics*, 16(22), 2713–2719.
- Bonduriansky, R., & Head, M. (2007). Maternal and paternal condition effects on offspring phenotype in *Telostylinus*

- angusticollis (Diptera: Neriidae). *Journal of Evolutionary Biology*, 20(6), 2379–2388.
- Boucher, B. J., Ewen, S. W., & Stowers, J. M. (1994). Betel nut (*Areca catechu*) consumption and the induction of glucose intolerance in adult CD1 mice and in their F1 and F2 offspring. *Diabetologia*, 37(1), 49–55.
- Broad, K. D., Curley, J. P., & Keverne, E. B. (2009). Increased apoptosis during neonatal brain development underlies the adult behavioral deficits seen in mice lacking a functional paternally expressed gene 3 (Peg3). *Developmental Neurobiology*, 69(5), 314–325.
- Brown, C. J., & Greally, J. M. (2003). A stain upon the silence: Genes escaping X inactivation. *Trends in Genetics*, 19(8), 432–438.
- Budefeld, T., Grgurevic, N., Tobet, S. A., & Majdic, G. (2008). Sex differences in brain developing in the presence or absence of gonads. *Developmental Neurobiology*, 68, 981–995.
- Burgoyne, P. S., Thornhill, A. R., Boudrean, S. K., Darling, S. M., Bishop, C. E., & Evans, E. P. (1995). The genetic basis of XX-XY differences present before gonadal sex differentiation in the mouse. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 350(1333), 253–260.
- Burley, N. (1988). The differential allocation hypothesis—An experimental test. *The American Naturalist*, 132, 611–628.
- Byrne, E. M., McRae, A. F., Duffy, D. L., Zhao, Z. Z., Martin, N. G., Wright, M. J., et al. (2009). Association study of common mitochondrial variants and cognitive ability. *Behavior Genetics*, 39(5), 504–512.
- Calatayud, F., & Belzung, C. (2001). Emotional reactivity in mice, a case of nongenetic heredity? *Physiology & Behavior*, 74(3), 355–362.
- Calatayud, F., Coubard, S., & Belzung, C. (2004). Emotional reactivity in mice may not be inherited but influenced by parents. *Physiology & Behavior*, 80(4), 465–474.
- Canastar, A., Maxson, S. C., & Bishop, C. E. (2008). Aggressive and mating behaviors in two types of sex reversed mice: XY females and XX males. *Archives of Sexual Behavior*, 37(1), 2–8.
- Carlier, M., Roubertoux, P. L., & Pastoret, C. (1991). The Y chromosome effect on intermale aggression in mice depends on the maternal environment. *Genetics*, 129(1), 231–236.
- Carlson, S. M., & Quinn, T. P. (2007). Ten years of varying lake level and selection on size-at-maturity in sockeye salmon. *Ecology*, 88(10), 2620–2629.
- Carola, V., Frazzetto, G., & Gross, C. (2006). Identifying interactions between genes and early environment in the mouse. *Genes, Brain, and Behavior*, 5(2), 189–199.
- Carola, V., Frazzetto, G., Pascucci, T., Audero, E., Puglisi-Allegra, S., Cabib, S., et al. (2008). Identifying molecular substrates in a mouse model of the serotonin transporter \times environment risk factor for anxiety and depression. *Biological Psychiatry*, 63(9), 840–846.
- Carruth, L. L., Reisert, I., & Arnold, A. P. (2002). Sex chromosome genes directly affect brain sexual differentiation. *Nature Neuroscience*, 5(10), 933–934.
- Champagne, F. A., & Curley, J. P. (2009). The trans-generational influence of maternal care on offspring gene expression and behavior in rodents. In: D. Maestripietri & J. M. Matteo (Eds.), *The role of maternal effects in mammalian evolution and adaptation*. Chicago: Chicago University Press.
- Champagne, F. A., Curley, J. P., Swaney, W. T., Hasen, N. S., & Keverne, E. B. (2009). Paternal influence on female behavior: The role of Peg3 in exploration, olfaction, and neuroendocrine regulation of maternal behavior of female mice. *Behavioral Neuroscience*, 123(3), 469–480.
- Chen, X., Grisham, W., & Arnold, A. P. (2009). X chromosome number causes sex differences in gene expression in adult mouse striatum. *European Journal of Neuroscience*, 29(4), 768–776.
- Clutton-Brock, T. H. (1991). *The evolution of parental care*. Princeton, NJ: Princeton University Press.
- Cooper, P. A., Benno, R. H., Hahn, M. E., & Hewitt, J. K. (1991). Genetic analysis of cerebellar foliation patterns in mice (*Mus musculus*). *Behavior Genetics*, 21(4), 405–419.
- Crews, D., Gore, A. C., Hsu, T. S., Dangleben, N. L., Spinetta, M., Schallert, T., et al. (2007). Transgenerational epigenetic imprints on mate preference. *Proceedings of the National Academy of Science of the United States of America*, 104(14), 5942–5946.
- Cropley, J. E., Suter, C. M., Beckman, K. B., & Martin, D. I. (2006). Germ-line epigenetic modification of the murine *A_{vy}* allele by nutritional supplementation. *Proceedings of the National Academy of Science of the United States of America*, 103(46), 17308–17312.
- Curley, J. P., Barton, S., Surani, A., & Keverne, E. B. (2004). Coadaptation in mother and infant regulated by a paternally expressed imprinted gene. *Proceedings. Biological Science*, 271(1545), 1303–1309.
- Curley, J. P., Pinnock, S. B., Dickson, S. L., Thresher, R., Miyoshi, N., Surani, M. A., et al. (2005). Increased body fat in mice with a targeted mutation of the paternally expressed imprinted gene Peg3. *The FASEB Journal*, 19(10), 1302–1304.
- Davies, W., Humby, T., Isles, A. R., Burgoyne, P. S., & Wilkinson, L. S. (2007). X-monosomy effects on visuospatial attention in mice: A candidate gene and implications for Turner syndrome and attention deficit hyperactivity disorder. *Biological Psychiatry*, 61(12), 1351–1360.
- Davies, W., Isles, A., Smith, R., Karunadasa, D., Burrmann, D., Humby, T., et al. (2005). *Xlr3b* is a new imprinted candidate for X-linked parent-of-origin effects on cognitive function in mice. *Nature Genetics*, 37(6), 625–629.
- Davies, W., Lynn, P. M., Relkovic, D., & Wilkinson, L. S. (2008). Imprinted genes and neuroendocrine function. *Frontiers in Neuroendocrinology*, 29(3), 413–427.
- Davies, W., & Wilkinson, L. S. (2006). It is not all hormones: Alternative explanations for sexual differentiation of the brain. *Brain Research*, 1126(1), 36–45.
- Dewing, P., Chiang, C. W., Sinchak, K., Sim, H., Fernagut, P. O., Kelly, S., et al. (2006). Direct regulation of adult brain function by the male-specific factor SRY. *Current Biology*, 16(4), 415–420.

- Dewing, P., Shi, T., Horvath, S., & Vilain, E. (2003). Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. *Brain Research. Molecular Brain Research*, 118(1–2), 82–90.
- Doe, C. M., Relkovic, D., Garfield, A. S., Dalley, J. W., Theobald, D. E., Humby, T., et al. (2009). Loss of the imprinted snoRNA mbii-52 leads to increased 5hr2c pre-RNA editing and altered 5HT2CR-mediated behaviour. *Human Molecular Genetics*, 18(12), 2140–2148.
- Dohm, M. R., Richardson, C. S., & Garland, T. Jr. (1994). Exercise physiology of wild and random-bred laboratory house mice and their reciprocal hybrids. *American Journal of Physiology*, 267(4 Pt 2), R1098–R1108.
- Drake, A. J., Walker, B. R., & Seckl, J. R. (2005). Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 288(1), R34–R38.
- Drake, N. M., Park, Y. J., Shirali, A. S., Cleland, T. A., & Soloway, P. D. (2009). Imprint switch mutations at Rasgrf1 support conflict hypothesis of imprinting and define a growth control mechanism upstream of IGF1. *Mammalian Genome* 20, 654–663.
- Drickamer, L. C., Gowaty, P. A., & Holmes, C. M. (2000). Free female mate choice in house mice affects reproductive success and offspring viability and performance. *Animal Behavior*, 59(2), 371–378.
- Eicher, E. M., Washburn, L. L., Whitney, J. B., III, & Morrow, K. E. (1982). Mus poschiavinus Y chromosome in the C57BL/6J murine genome causes sex reversal. *Science*, 217(4559), 535–537.
- Elson, J. L., Herrstadt, C., Preston, G., Thal, L., Morris, C. M., Edwardson, J. A., et al. (2006). Does the mitochondrial genome play a role in the etiology of Alzheimer's disease? *Human Genetics*, 119(3), 241–254.
- Fernandez-Medarde, A., Porteros, A., de las Rivas, J., Nunez, A., Fuster, J. J., & Santos, E. (2007). Laser microdissection and microarray analysis of the hippocampus of Ras-GRF1 knockout mice reveals gene expression changes affecting signal transduction pathways related to memory and learning. *Neuroscience*, 146(1), 272–285.
- Flanagan, J. M., Pependikyte, V., Pozdniakovaite, N., Sobolev, M., Assadzadeh, A., Schumacher, A., et al. (2006). Intra- and interindividual epigenetic variation in human germ cells. *American Journal of Human Genetics*, 79(1), 67–84.
- Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., et al. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Science of the United States of America*, 102(30), 10604–10609.
- Gabriel, K. I., & Cunningham, C. L. (2008). Effects of maternal strain on ethanol responses in reciprocal F1 C57BL/6J and DBA/2J hybrid mice. *Genes, Brain, and Behavior*, 7(3), 276–287.
- Garcia-Palomares, S., Navarro, S., Pertusa, J. F., Hermenegildo, C., Garcia-Perez, M. A., Rausell, F., et al. (2009). Delayed fatherhood in mice decreases reproductive fitness and longevity of offspring. *Biology of Reproduction*, 80(2), 343–349.
- Garcia-Palomares, S., Pertusa, J. F., Minarro, J., Garcia-Perez, M. A., Hermenegildo, C., Rausell, F., et al. (2009). Long-term effects of delayed fatherhood in mice on postnatal development and behavioral traits of offspring. *Biology of Reproduction*, 80(2), 337–342.
- Gatewood, J. D., Wills, A., Shetty, S., Xu, J., Arnold, A. P., Burgoyne, P. S., et al. (2006). Sex chromosome complement and gonadal sex influence aggressive and parental behaviors in mice. *Journal of Neuroscience*, 26(8), 2335–2342.
- Giese, K. P., Friedman, E., Telliez, J. B., Fedorov, N. B., Wines, M., Feig, L. A., et al. (2001). Hippocampus-dependent learning and memory is impaired in mice lacking the Ras-guanine-nucleotide releasing factor 1 (Ras-GRF1). *Neuropharmacology*, 41(6), 791–800.
- Gimsa, U., Kanitz, E., Otten, W., & Ibrahim, S. (2009). Behavior and stress reactivity in mouse strains with mitochondrial DNA variations. *Annals of the New York Academy of Sciences*, 1153, 131–138.
- Gioiosa, L., Chen, X., Watkins, R., Klanfer, N., Bryant, C. D., Evans, C. J., et al. (2008). Sex chromosome complement affects nociception in tests of acute and chronic exposure to morphine in mice. *Hormones and Behavior*, 53(1), 124–130.
- Gowaty, P. A., Anderson, W. W., Bluhm, C. K., Drickamer, L. C., Kim, Y. K., & Moore, A. J. (2007). The hypothesis of reproductive compensation and its assumptions about mate preferences and offspring viability. *Proceedings of the National Academy of Science of the United States of America*, 104(38), 15023–15027.
- Grandjean, V., Gounon, P., Wagner, N., Martin, L., Wagner, K. D., Bernex, F., et al. (2009). The miR-124-Sox9 paramutation: RNA-mediated epigenetic control of embryonic and adult growth. *Development*, 136(21), 3647–3655.
- Gray, A. P. (1972). *Mammalian hybrids: A check-list with bibliography*. Slough: Commonwealth Agricultural Bureaux.
- Grgurevic, N., Budefeld, T., Rissman, E. F., Tobet, S. A., & Majdic, G. (2008). Aggressive behaviors in adult SF-1 knockout mice that are not exposed to gonadal steroids during development. *Behavioral Neuroscience*, 122(4), 876–884.
- Guillot, P. V., Carlier, M., Maxson, S. C., & Roubertoux, P. L. (1995). Intermale aggression tested in two procedures, using four inbred strains of mice and their reciprocal congenics: Y chromosomal implications. *Behavior Genetics*, 25(4), 357–360.
- Guillot, P. V., Sluyter, F., Laghmouch, A., Roubertoux, P. L., & Crusio, W. E. (1996). Hippocampal morphology in the inbred mouse strains NZB and CBA/H and their reciprocal congenics for the nonpseudautosomal region of the Y chromosome. *Behavior Genetics*, 26(1), 1–5.
- Hales, B. F., & Robaire, B. (2001). Paternal exposure to drugs and environmental chemicals: Effects on progeny outcome. *Journal of Andrology*, 22(6), 927–936.
- Hamatani, T., Falco, G., Carter, M. G., Akutsu, H., Stagg, C. A., Sharov, A. A., et al. (2004). Age-associated alteration of gene expression patterns in mouse oocytes. *Human Molecular Genetics*, 13(19), 2263–2278.

- Hayashi, S., Yang, J., Christenson, L., Yanagimachi, R., & Hecht, N. B. (2003). Mouse preimplantation embryos developed from oocytes injected with round spermatids or spermatozoa have similar but distinct patterns of early messenger RNA expression. *Biology of Reproduction*, 69(4), 1170–1176.
- He, F., Lidow, I. A., & Lidow, M. S. (2006). Consequences of paternal cocaine exposure in mice. *Neurotoxicology and Teratology*, 28(2), 198–209.
- Heck, D. H., Zhao, Y., Roy, S., LeDoux, M. S., & Reiter, L. T. (2008). Analysis of cerebellar function in Ube3a-deficient mice reveals novel genotype-specific behaviors. *Human Molecular Genetics*, 17(14), 2181–2189.
- Hegmann, J. P., & White, J. E. (1973). Nervous system function: Maternal effects on conduction velocity in mice. *Behavioral Biology*, 8(6), 815–818.
- Isles, A. R., Baum, M. J., Ma, D., Keverne, E. B., & Allen, N. D. (2001). Urinary odour preferences in mice. *Nature*, 409(6822), 783–784.
- Isles, A. R., Baum, M. J., Ma, D., Szeto, A., Keverne, E. B., & Allen, N. D. (2002). A possible role for imprinted genes in inbreeding avoidance and dispersal from the natal area in mice. *Proceedings. Biological sciences*, 269(1492), 665–670.
- Isles, A. R., Davies, W., Burrmann, D., Burgoyne, P. S., & Wilkinson, L. S. (2004). Effects on fear reactivity in XO mice are due to haploinsufficiency of a non-PAR X gene: Implications for emotional function in Turner's syndrome. *Human Molecular Genetics*, 13(17), 1849–1855.
- Jablonka, E., & Raz, G. (2009). Transgenerational epigenetic inheritance: Prevalence, mechanisms, and implications for the study of heredity and evolution. *The Quarterly Review of Biology*, 84(2), 131–176.
- Jiang, Y. H., Armstrong, D., Albrecht, U., Atkins, C. M., Noebels, J. L., Eichele, G., et al. (1998). Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. *Neuron*, 21(4), 799–811.
- Jimenez-Chillaron, J. C., Isganaitis, E., Charalambous, M., Gesta, S., Pentinat-Pelegrin, T., Faucette, R. R., et al. (2009). Intergenerational transmission of glucose intolerance and obesity by in utero undernutrition in mice. *Diabetes*, 58(2), 460–468.
- Johnson, K. R., Zheng, Q. Y., Bykhovskaya, Y., Spirina, O., & Fischel-Ghodsian, N. (2001). A nuclear-mitochondrial DNA interaction affecting hearing impairment in mice. *Nature Genetics*, 27(2), 191–194.
- Kaati, G., Bygren, L. O., Pembrey, M., & Sjöström, M. (2007). Transgenerational response to nutrition, early life circumstances and longevity. *European Journal of Human Genetics*, 15(7), 784–790.
- Kahn, A. J. (1970). Alteration of paternal environment prior to mating: Effect on hemoglobin concentration in offspring of CF1 mice. *Growth*, 34(2), 215–220.
- Kaneda, H., Hayashi, J., Takahama, S., Taya, C., Lindahl, K. F., & Yonekawa, H. (1995). Elimination of paternal mitochondrial DNA in intraspecific crosses during early mouse embryogenesis. *Proceedings of the National Academy of Science of the United States of America*, 92(10), 4542–4546.
- Kasahara, T., Kubota, M., Miyauchi, T., Ishiwata, M., & Kato, T. (2008). A marked effect of electroconvulsive stimulation on behavioral aberration of mice with neuron-specific mitochondrial DNA defects. *PLoS ONE*, 3(3), e1877.
- Kasahara, T., Kubota, M., Miyauchi, T., Noda, Y., Mouri, A., Nabeshima, T., et al. (2006). Mice with neuron-specific accumulation of mitochondrial DNA mutations show mood disorder-like phenotypes. *Molecular Psychiatry*, 11(6), 577–593, 523.
- Kato, C., Umekage, T., Tochigi, M., Otowa, T., Hibino, H., Ohtani, T., et al. (2004). Mitochondrial DNA polymorphisms and extraversion. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 128(1), 76–79.
- Keverne, E. B., Fundele, R., Narasimha, M., Barton, S. C., & Surani, M. A. (1996). Genomic imprinting and the differential roles of parental genomes in brain development. *Brain Research. Developmental Brain Research*, 92(1), 91–100.
- Kozlov, S. V., Bogenpohl, J. W., Howell, M. P., Wevrick, R., Panda, S., Hogenesch, J. B., et al. (2007). The imprinted gene *Mage12* regulates normal circadian output. *Nature Genetics*, 39(10), 1266–1272.
- Kramer, K. M., Carr, M. S., Schmidt, J. V., & Cushing, B. S. (2006). Parental regulation of central patterns of estrogen receptor alpha. *Neuroscience*, 142(1), 165–173.
- Kraysberg, Y., Kudryavtseva, E., McKee, A. C., Geula, C., Kowall, N. W., & Khrapko, K. (2006). Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. *Nature Genetics*, 38(5), 518–520.
- Kubota, M., Kasahara, T., Nakamura, T., Ishiwata, M., Miyauchi, T., & Kato, T. (2006). Abnormal Ca²⁺ dynamics in transgenic mice with neuron-specific mitochondrial DNA defects. *Journal of Neuroscience*, 26(47), 12314–12324.
- Kuwajima, T., Nishimura, I., & Yoshikawa, K. (2006). *Neccin* promotes GABAergic neuron differentiation in cooperation with *Dlx* homeodomain proteins. *Journal of Neuroscience*, 26(20), 5383–5392.
- La Salle, S., Mertineit, C., Taketo, T., Moens, P. B., Bestor, T. H., & Trasler, J. M. (2004). Windows for sex-specific methylation marked by DNA methyltransferase expression profiles in mouse germ cells. *Developmental Biology*, 268(2), 403–415.
- Lalancette, C., Miller, D., Li, Y., & Krawetz, S. A. (2008). Paternal contributions: New functional insights for spermatozoal RNA. *Journal of Cellular Biochemistry*, 104(5), 1570–1579.
- Lane, N., Dean, W., Erhardt, S., Hajkova, P., Surani, A., Walter, J., et al. (2003). Resistance of IAPs to methylation reprogramming may provide a mechanism for epigenetic inheritance in the mouse. *Genesis*, 35(2), 88–93.
- Ledig, M., Misslin, R., Vogel, E., Holownia, A., Copin, J. C., & Tholey, G. (1998). Paternal alcohol exposure: Developmental and behavioral effects on the offspring of rats. *Neuropharmacology*, 37(1), 57–66.
- Lefebvre, L., Viville, S., Barton, S. C., Ishino, F., & Surani, M. A. (1997). Genomic structure and parent-of-origin-specific

- methylation of Peg1. *Human Molecular Genetics*, 6(11), 1907–1915.
- Li, L., Keverne, E. B., Aparicio, S. A., Ishino, F., Barton, S. C., & Surani, M. A. (1999). Regulation of maternal behavior and offspring growth by paternally expressed Peg3. *Science*, 284(5412), 330–333.
- Linschooten, J. O., Van Schooten, F. J., Baumgartner, A., Cemeli, E., Van Delft, J., Anderson, D., et al. (2009). Use of spermatozoal mRNA profiles to study gene-environment interactions in human germ cells. *Mutation Research*, 667(1–2), 70–76.
- Lue, Y., Jentsch, J. D., Wang, C., Rao, P. N., Hikim, A. P., Salameh, W., et al. (2005). XXY mice exhibit gonadal and behavioral phenotypes similar to Klinefelter syndrome. *Endocrinology*, 146(9), 4148–4154.
- Malaspina, D., Reichenberg, A., Weiser, M., Fennig, S., Davidson, M., Harlap, S., et al. (2005). Paternal age and intelligence: Implications for age-related genomic changes in male germ cells. *Psychiatric Genetics*, 15(2), 117–125.
- Martorell, L., Segues, T., Folch, G., Valero, J., Joven, J., Labad, A., et al. (2006). New variants in the mitochondrial genomes of schizophrenic patients. *European Journal of Human Genetics*, 14(5), 520–528.
- Masset, M. P., & Berk, B. C. (2005). Strain-dependent differences in responses to exercise training in inbred and hybrid mice. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 288(4), R1006–R1013.
- McGill, T. E., & Manning, A. (1976). Genotype and retention of the ejaculatory reflex in castrated male mice. *Animal Behavior*, 24(3), 507–518.
- McGrath, J., & Solter, D. (1984). Completion of mouse embryogenesis requires both the maternal and paternal genomes. *Cell*, 37(1), 179–183.
- McIntosh, G. C., Olshan, A. F., & Baird, P. A. (1995). Paternal age and the risk of birth defects in offspring. *Epidemiology*, 6(3), 282–288.
- McKenzie, M., Chiotis, M., Pinkert, C. A., & Trounce, I. A. (2003). Functional respiratory chain analyses in murid xenomitochondrial cybrids expose coevolutionary constraints of cytochrome b and nuclear subunits of complex III. *Molecular Biology and Evolution*, 20(7), 1117–1124.
- McPhie-Lalmansingh, A. A., Tejada, L. D., Weaver, J. L., & Rissman, E. F. (2008). Sex chromosome complement affects social interactions in mice. *Hormones and Behavior*, 54(4), 565–570.
- Meek, L. R., Myren, K., Sturm, J., & Burau, D. (2007). Acute paternal alcohol use affects offspring development and adult behavior. *Physiology & Behavior*, 91(1), 154–160.
- Mercer, R. E., Kwolek, E. M., Bischof, J. M., van Eede, M., Henkelman, R. M., & Wevrick, R. (2009). Regionally reduced brain volume, altered serotonin neurochemistry, and abnormal behavior in mice null for the circadian rhythm output gene *Mage12*. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* 150B, 1085–1099.
- Mercer, R. E., & Wevrick, R. (2009). Loss of *mage12*, a candidate gene for features of Prader-Willi syndrome, impairs reproductive function in mice. *PLoS ONE*, 4(1), e4291.
- Miczek, K. A., Maxson, S. C., Fish, E. W., & Faccidomo, S. (2001). Aggressive behavioral phenotypes in mice. *Behavioural Brain Research*, 125(1–2), 167–181.
- Miura, K., Kishino, T., Li, E., Webber, H., Dikkes, P., Holmes, G. L., et al. (2002). Neurobehavioral and electroencephalographic abnormalities in *Ube3a* maternal-deficient mice. *Neurobiology of Disease*, 9(2), 149–159.
- Morgan, H. D., Sutherland, H. G., Martin, D. I., & Whitelaw, E. (1999). Epigenetic inheritance at the agouti locus in the mouse. *Nature Genetics*, 23(3), 314–318.
- Morgan, H. D., Santos, F., Green, K., Dean, W., & Reik, W. (2005). Epigenetic reprogramming in mammals. *Human Molecular Genetics*, 14, R47–R58.
- Muscattelli, F., Abrous, D. N., Massacrier, A., Boccaccio, I., Le Moal, M., Cau, P., et al. (2000). Disruption of the mouse *Necdin* gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. *Human Molecular Genetics*, 9(20), 3101–3110.
- Nagao, Y., Totsuka, Y., Atomi, Y., Kaneda, H., Lindahl, K. F., Imai, H., et al. (1998). Decreased physical performance of congenic mice with mismatch between the nuclear and the mitochondrial genome. *Genes & Genetic Systems*, 73(1), 21–27.
- Nakada, K., Sato, A., Yoshida, K., Morita, T., Tanaka, H., Inoue, S., et al. (2006). Mitochondria-related male infertility. *Proceedings of the National Academy of Science of the United States of America*, 103(41), 15148–15153.
- Oakes, C. C., Smiraglia, D. J., Plass, C., Trasler, J. M., & Robaire, B. (2003). Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. *Proceedings of the National Academy of Science of the United States of America*, 100(4), 1775–1780.
- Ostermeier, G. C., Miller, D., Huntriss, J. D., Diamond, M. P., & Krawetz, S. A. (2004). Reproductive biology: Delivering spermatozoan RNA to the oocyte. *Nature*, 429(6988), 154.
- Ouko, L. A., Shantikumar, K., Knezovich, J., Haycock, P., Schnugh, D. J., Ramsay, M. (2009). Effect of alcohol consumption on CpG methylation in the differentially methylated regions of H19 and IG-DMR in male gametes: Implications for fetal alcohol spectrum disorders. *Alcoholism, Clinical and Experimental Research*, 33(9), 1615–1627.
- Pandey, S. C., Ugale, R., Zhang, H., Tang, L., & Prakash, A. (2008). Brain chromatin remodeling: A novel mechanism of alcoholism. *Journal of Neuroscience*, 28(14), 3729–3737.
- Park, J. H., Burns-Cusato, M., Dominguez-Salazar, E., Riggan, A., Shetty, S., Arnold, A. P., et al. (2008). Effects of sex chromosome aneuploidy on male sexual behavior. *Genes, Brain, and Behavior*, 7(6), 609–617.
- Pembrey, M. E., Bygren, L. O., Kaati, G., Edvinsson, S., Northstone, K., Sjöström, M., et al. (2006). Sex-specific, male-line transgenerational responses in humans. *European Journal of Human Genetics*, 14(2), 159–166.
- Perrigo, G., Belvin, L., Quindry, P., Kadir, T., Becker, J., van Look, C., et al. (1993). Genetic mediation of infanticide and parental behavior in male and female domestic and wild stock house mice. *Behavior Genetics*, 23(6), 525–531.

- Pinkert, C. A., & Trounce, I. A. (2007). Generation of transmitochondrial mice: Development of xenomitochondrial mice to model neurodegenerative diseases. *Methods in Cell Biology*, 80, 549–569.
- Plagge, A., Gordon, E., Dean, W., Boiani, R., Cinti, S., Peters, J., et al. (2004). The imprinted signaling protein XL alpha s is required for postnatal adaptation to feeding. *Nature Genetics*, 36(8), 818–826.
- Plagge, A., Isles, A. R., Gordon, E., Humby, T., Dean, W., Gritsch, S., et al. (2005). Imprinted Nesp55 influences behavioral reactivity to novel environments. *Molecular and Cellular Biology*, 25(8), 3019–3026.
- Platt, T. H., & Maxson, S. C. (1989). Effects of the heterosomes and maternal environments on aggressive behavior in *Mus musculus*. *Behavioral and Neural Biology*, 52(2), 222–238.
- Price, E. O., & Loomis, S. (1973). Maternal influence on the response of wild and domestic Norway rats to a novel environment. *Developmental Psychobiology*, 6(3), 203–208.
- Quinn, J. J., Hitchcott, P. K., Umeda, E. A., Arnold, A. P., & Taylor, J. R. (2007). Sex chromosome complement regulates habit formation. *Nature Neuroscience*, 10(11), 1398–1400.
- Rakyan, V. K., Chong, S., Champ, M. E., Cuthbert, P. C., Morgan, H. D., Luu, K. V., et al. (2003). Transgenerational inheritance of epigenetic states at the murine Axin(Fu) allele occurs after maternal and paternal transmission. *Proceedings of the National Academy of Science of the United States of America*, 100(5), 2538–2543.
- Rassoulzadegan, M., Grandjean, V., Gounon, P., Vincent, S., Gillot, I., & Cuzin, F. (2006). RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. *Nature*, 441(7092), 469–474.
- Reik, W., Dean, W., & Walter, J. (2001). Epigenetic reprogramming in mammalian development. *Science*, 293(5532), 1089–1093.
- Reisert, I., Karolczak, M., Beyer, C., Just, W., Maxson, S. C., & Ehret, G. (2002). Sry does not fully sex-reverse female into male behavior towards pups. *Behavior Genetics*, 32(2), 103–111.
- Rollins, B., Martin, M. V., Sequeira, P. A., Moon, E. A., Morgan, L. Z., Watson, S. J., et al. (2009). Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder. *PLoS ONE*, 4(3), e4913.
- Roubertoux, P. L., Sluyter, F., Carlier, M., Marcet, B., Maarouf-Veray, F., Cherif, C., et al. (2003). Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice. *Nature Genetics*, 35(1), 65–69.
- Roy, V., Merali, Z., Poulter, M. O., & Anisman, H. (2007). Anxiety responses, plasma corticosterone and central monoamine variations elicited by stressors in reactive and nonreactive mice and their reciprocal F1 hybrids. *Behavioural Brain Research*, 185(1), 49–58.
- Savitz, D. A., Schwingl, P. J., & Keels, M. A. (1991). Influence of paternal age, smoking, and alcohol consumption on congenital anomalies. *Teratology*, 44(4), 429–440.
- Shao, L., Martin, M. V., Watson, S. J., Schatzberg, A., Akil, H., Myers, R. M., et al. (2008). Mitochondrial involvement in psychiatric disorders. *Annals of Medicine*, 40(4), 281–295.
- Shitara, H., Hayashi, J. I., Takahama, S., Kaneda, H., & Yonekawa, H. (1998). Maternal inheritance of mouse mtDNA in interspecific hybrids: Segregation of the leaked paternal mtDNA followed by the prevention of subsequent paternal leakage. *Genetics*, 148(2), 851–857.
- Shoji, H., & Kato, K. (2009). Maternal care affects the development of maternal behavior in inbred mice. *Developmental Psychobiology*, 51(4), 345–357.
- Skinner, M. K., Anway, M. D., Savenkova, M. I., Gore, A. C., & Crews, D. (2008). Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. *PLoS ONE*, 3(11), e3745.
- Skuse, D. H., James, R. S., Bishop, D. V., Coppin, B., Dalton, P., Aamodt-Leeper, G., et al. (1997). Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature*, 387(6634), 705–708.
- Stavnezer, J., & Schrader, C. E. (2006). Mismatch repair converts AID-instigated nicks to double-strand breaks for antibody class-switch recombination. *Trends in Genetics*, 22(1), 23–28.
- Stouder, C., & Paoloni-Giacobino, A. (in press). Transgenerational effects of the endocrine disruptor vinclozolin on the methylation pattern of imprinted genes in the mouse sperm. *Reproduction*.
- Stouder, C., Deutsch, S., & Paoloni-Giacobino, A. (2009). Superovulation in mice alters the methylation pattern of imprinted genes in the sperm of the offspring. *Reproductive Toxicology*, 28(4), 536–541.
- Sutovsky, P., Moreno, R. D., Ramalho-Santos, J., Dominko, T., Simerly, C., & Schatten, G. (2000). Ubiquitinated sperm mitochondria, selective proteolysis, and the regulation of mitochondrial inheritance in mammalian embryos. *Biology of Reproduction*, 63(2), 582–590.
- Swaney, W. T., Curley, J. P., Champagne, F. A., & Keverne, E. B. (2007). Genomic imprinting mediates sexual experience-dependent olfactory learning in male mice. *Proceedings of the National Academy of Science of the United States of America*, 104(14), 6084–6089.
- Swaney, W. T., Curley, J. P., Champagne, F. A., & Keverne, E. B. (2008). The paternally expressed gene *Peg3* regulates sexual experience-dependent preferences for estrous odors. *Behavioral Neuroscience*, 122(5), 963–973.
- Tanaka, D., Nakada, K., Takao, K., Ogasawara, E., Kasahara, A., Sato, A., et al. (2008). Normal mitochondrial respiratory function is essential for spatial remote memory in mice. *Mol Brain*, 1(1), 21.
- Tarter, R. E., Jacob, T., & Bremer, D. L. (1989). Specific cognitive impairment in sons of early onset alcoholics. *Alcoholism, Clinical and Experimental Research*, 13(6), 786–789.
- Thamotharan, M., Garg, M., Oak, S., Rogers, L. M., Pan, G., Sangiorgi, F., et al. (2007). Transgenerational inheritance of the insulin-resistant phenotype in embryo-transferred intrauterine growth-restricted adult female rat offspring. *American Journal of Physiology. Endocrinology and Metabolism*, 292(5), E1270–E1279.

- Thomas, M. G., Miller, K. W. P., & Mascie-Taylor, C. G. N. (1998). Mitochondrial DNA and IQ in Europe. *Intelligence*, 26, 167–173.
- Tordjman, S., Roubertoux, P. L., Carlier, M., Moutier, R., Anderson, G., Launay, M., et al. (1995). Linkage between brain serotonin concentration and the sex-specific part of the Y-chromosome in mice. *Neuroscience Letters*, 183(3), 190–192.
- Tordoff, M. G., Reed, D. R., & Shao, H. (2008). Calcium taste preferences: Genetic analysis and genome screen of C57BL/6J x PWK/PhJ hybrid mice. *Genes, Brain, and Behavior*, 7(6), 618–628.
- Uller, T. (2008). Developmental plasticity and the evolution of parental effects. *Trends in Ecology & Evolution*, 23(8), 432–438.
- Vrana, P. B., Fossella, J. A., Matteson, P., del Rio, T., O'Neill, M. J., & Tilghman, S. M. (2000). Genetic and epigenetic incompatibilities underlie hybrid dysgenesis in *Peromyscus*. *Nature Genetics*, 25(1), 120–124.
- Wagner, K. D., Wagner, N., Ghanbarian, H., Grandjean, V., Gounon, P., Cuzin, F, et al. (2008). RNA induction and inheritance of epigenetic cardiac hypertrophy in the mouse. *Developmental Cell*, 14(6), 962–969.
- Walton, A., & Hammond, J. (1938). The maternal effects on growth and conformation in Shire horse–Shetland pony crosses. *Proceedings of the Royal Society B*, 125, 311–335.
- Weissman, J. R., Kelley, R. I., Bauman, M. L., Cohen, B. H., Murray, K. F., Mitchell, R. L., et al. (2008). Mitochondrial disease in autism spectrum disorder patients: A cohort analysis. *PLoS ONE*, 3(11), e3815.
- White, D. J., Wolff, J. N., Pierson, M., & Gemmell, N. J. (2008). Revealing the hidden complexities of mtDNA inheritance. *Molecular Ecology*, 17(23), 4925–4942.
- Whitelaw, E., & Martin, D. I. (2001). Retrotransposons as epigenetic mediators of phenotypic variation in mammals. *Nature Genetics*, 27(4), 361–365.
- Wilkinson, L. S., Davies, W., & Isles, A. R. (2007). Genomic imprinting effects on brain development and function. *Nature Reviews. Neuroscience*, 8(11), 832–843.
- Wolff, J. N., & Gemmell, N. J. (2008). Lost in the zygote: The dilution of paternal mtDNA upon fertilization. *Heredity*, 101(5), 429–434.
- Wozniak, D. F., Cicero, T. J., Kettinger, L., III, & Meyer, E. R. (1991). Paternal alcohol consumption in the rat impairs spatial learning performance in male offspring. *Psychopharmacology (Berlin)*, 105(2), 289–302.
- Xu, J., Deng, X., Watkins, R., & Disteché, C. M. (2008). Sex-specific differences in expression of histone demethylases Utx and Uty in mouse brain and neurons. *Journal of Neuroscience*, 28(17), 4521–4527.
- Xu, J., Taya, S., Kaibuchi, K., & Arnold, A. P. (2005). Sexually dimorphic expression of Usp9x is related to sex chromosome complement in adult mouse brain. *European Journal of Neuroscience*, 21(11), 3017–3022.
- Yokoi, F., Dang, M. T., Li, J., & Li, Y. (2006). Myoclonus, motor deficits, alterations in emotional responses and monoamine metabolism in epsilon-sarcoglycan deficient mice. *Journal of Biochemistry*, 140(1), 141–146.
- Yu, X., Gimsa, U., Wester-Rosenlof, L., Kanitz, E., Otten, W., Kunz, M., et al. (2009). Dissecting the effects of mtDNA variations on complex traits using mouse conplastic strains. *Genome Research*, 19(1), 159–165.
- Zhou, Y., Zhu, W., Guo, Z., Zhao, Y., Song, Z., & Xiao, J. (2007). Effects of maternal nuclear genome on the timing of puberty in mice offspring. *Journal of Endocrinology*, 193(3), 405–412.