Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man

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Abstract

Mental illness remains the greatest chronic health burden globally with few inroads having been made despite significant advances in genomic knowledge in recent decades. The field of psychiatry is constantly challenged to bring new approaches and tools to address and treat the needs of vulnerable individuals and subpopulations, and that has to be supported by a continuous growth in knowledge. The majority of neuropsychiatric symptoms reflect complex gene-environment interactions, with epigenetics bridging the gap between genetic susceptibility and environmental stressors that trigger disease onset and drive the advancement of symptoms. It has more recently been demonstrated in preclinical models that epigenetics underpins the transgenerational inheritance of stress-related behavioural phenotypes in both paternal and maternal lineages, providing further supporting evidence for heritability in humans. However, unbiased prospective studies of this nature are practically impossible to conduct in humans so preclinical models remain our best option for researching the molecular pathophysiology underlying many neuropsychiatric conditions. While rodents will remain the dominant model system for preclinical studies (especially for addressing complex behavioural phenotypes), there is scope to expand current research of the molecular and epigenetic pathologies by using invertebrate models. Here, we will discuss the utility and advantages of two alternative model organisms—Caenorhabditis elegans and Drosophila melanogaster—and summarise the compelling insights of the epigenetic regulation of transgenerational inheritance that are potentially relevant to human psychiatry.

Key Words: Transgenerational inheritance; Epigenetics; Invertebrate models; Caenorhabditis elegans; Drosophila melanogaster; Environmental stress
INTRODUCTION

Advances in genomic technologies have led to a rapid increase in the number of known genomic variants linked to human psychiatric illnesses. However, we still know little of the molecular and genetic functions of many of these genes or their mode of inheritance. The wealth of genetic information and experimental techniques associated with laboratory model organisms that have not been traditionally utilised for analysis of psychiatric illnesses provide an untapped resource that promise to revolutionise our understanding of these conditions.

At the turn of the 18th century, the French naturalist Jean-Baptiste Lamarck proposed that environmentally adaptive traits could be acquired by an individual over a lifetime and, more importantly, inherited by their progeny. It was not until the 21st century that Lamarckian theory re-emerged from the shadows of Darwin’s theory of natural selection and the principles of genetic inheritance. This recent revival has been driven by growing evidence of unusual inheritance patterns across a wide number of species, which collectively indicate the presence of biological mechanisms that govern how the physical environment, diet and individual experiences not only influence our individual constitution, but the health of our descendants as well. In the past decade, preclinical studies of mammalian models of human disease have uncovered robust evidence of transgenerational shifts in health. However, alternative animal models should be considered as a means of conducting more time- and cost-effective transgenerational research. Here, we summarise recent advances in transgenerational epigenetic inheritance stemming from non-mammalian models that have revealed epigenetic processes potentially relevant to psychiatry. We hope to convince readers that research based on these non-mammalian organisms have the capacity to provide novel insights into the molecular pathologies of different neuropsychiatric conditions.

Epigenetic inheritance drives the adaptation of phenotypic traits and plays a significant role in directing human health outcomes across generations. For example, the accumulation of specific epigenetic modifications is proposed to contribute to the increasing prevalence of cardiovascular and metabolic diseases[1,2]. Separately, epigenetic modifications have been demonstrated in the transgenerational transmission of risk for mental illness, and possibly contributing to the increasing prevalence of a range of psychiatric disorders[3-6]. However, non-mammalian models have also contributed by extending our understanding of the molecular pathologies in human disease. For example, studies of the nematode Caenorhabditis elegans (C. elegans) have not only provided us enlightening perspectives on the molecular regulation of aging[7,8] but also revealed how stress and nutrition are transgenerational modifiers of progeny survival[9-11].

Briefly, transgenerational inheritance broadly describes the process of a parental generation undergoing experiences and exposures that are subsequently linked to altered phenotypes and behaviours in future generations (in F2s at the very least). Note that the phrase ‘intergenerational inheritance’ describes transmission that is
limited (or only studied up till) to the very next F1 generation (see Figure 1 for further patrilineal and matrilineal distinctions). While the full spectrum of biological processes underlying transgenerational inheritance is yet to be fully elucidated, a multiplex of epigenetic modifications has been implicated. Importantly, epigenetic inheritance specifically excludes the reorganisation of genome sequence through DNA mutations, and some epigenetic marks are species-specific (further emphasizing the importance of multi-species research). The most widely studied epigenetic modifications include DNA methylation, histone protein modifications (such as methylation, acetylation), as well as short and long non-coding RNAs (snRNAs and lncRNAs, respectively) that moderate transcriptional activity. Due to space constraints, we refer readers to the following reviews that comprehensively discuss the biochemistry of epigenetic modifications relevant to the neuropsychiatric field[12-16]. The epigenome is subject to modification following exposure to stressors that challenge survival, ranging from environmental (exposure to toxic chemicals)[17] to physical (heat stress) to psychological (fear of predation)[18,19]. We now know that offspring can inherit a range of epigenetic modifications that alters their physical or behavioural traits. Over the past decade, preclinical studies of rodent models of chronic stress[20,21] and trauma[22-24] have demonstrated this phenomenon, but could alternative non-mammalian models of stress offer further insight into the relevant epigenetic pathways? These tools offer the field of psychiatry the opportunity to clarify the extent to which the risk for mental illness may be moderated by parental or ancestral exposures to such stressors and life events, and understand the molecular mechanisms mediating such forms of transgenerational inheritance. Epidemiological studies have reported a range in heritability of neuropsychiatric disorders (although readers should note that there have been relatively few studies given the challenges of conducting such large-scale research). For example, a high degree of heritability (81%) was initially estimated for schizophrenia (SZ) based on twin studies[25], while subsequent estimates based on the Danish and Swedish populations were comparatively lower at approximately 60%[26,27]. Those latter studies also estimated that heritability of bipolar disorder (BP) was similar to SZ. However, the potential that epigenetic inheritance moderates the heritability of certain neuropsychiatric conditions has yet to be thoroughly investigated. Of course, in contrast, other psychiatric disorders such as alcohol dependence or major depression display low-moderate degrees of heritability[28] so while those disorders may involve aspects of epigenetic pathology, it is less likely that epigenetic inheritance would be a significant causal factor.

While studies of C. elegans and Drosophila melanogaster (D. melanogaster) may be initially dismissed as far removed from relevance to human physiology, and although most preclinical drug testing is performed with rodent models, these invertebrate model systems provide alternative approaches to conducting complementary research of common epigenetic mechanisms and biochemical processes that may be fundamental to neuropsychiatric pathologies. One should not forget that mammalian transgenerational research can trace its roots to historically rich and revealing studies of plants. Some of the earliest evidence for the phenomenon include Barbara McClintock’s ground-breaking studies of retrotransposition in maize and the transgenerational inheritance of transponon phases. While we tend to associate ‘stress’ with the notion of psychosocial stress, this term can be used to encompass any extrinsic condition that disturbs the normal function of the biological system, or a condition that decreases fitness, including thermal stress, desiccation, UV stress, starvation, chemical exposure and overcrowding. In using alternative animal models, it is crucial that etiologically relevant stressors are applied in the appropriate manner. Heat stress is well known to impact a wide range of physiological and behavioural parameters, which can result in gastrointestinal dysfunction[29], increased blood pressure and disordered metabolic function[30]. In particular, elevated temperatures cause profound disruptions to various aspects of reproduction in both mammals and invertebrates including mating behaviours[31,32], spermatogenesis and oogenesis, egg/foetal development and viability, and offspring body size[33,34]. With mounting concerns about climate change, and recent increases in unusual climate events, understanding how we adapt to such environmental changes and the implications for global population health trends have become more important than ever. A recent systematic review of the impacts of climate change on mental health reported on the complexities in attempting to consolidate the data, but highlighted more common psychopathologies such as anxiety and trauma[35]. It is unclear if and how climatic factors could influence human health outcomes through epigenetic modifications. Understandably, designing and conducting human studies of this nature would be highly challenging due to the inherent complexities e.g. having to account for geographical and ethnic diversities. However, research based in the primary
production industries may be an unexpected source of early clues as to how these occur. After all, developing the knowledge to control the effects of heat stress has been crucial to the field of agriculture for maximising crop yield[36,37] and maintaining livestock fecundity and fitness[38,39].

There are mounting calls to recognize that ancestral health is a significant contributing factor of current day human health and phenotypes, and this would require maintaining detailed individual medical records for longitudinal epidemiological studies. On a large scale, such a perspective shift would aid us in identifying the determinants of public health issues and evaluating possible interventions and treatments. Furthermore, elucidating the mechanisms driving environmentally-induced epigenetic changes linked to specific aspects of health and disease may promote a shift towards the development of personalised treatments and drugs based on these signatures[40]. With numerous epigenetic processes conserved from invertebrates to humans, it is unsurprising that many fundamental epigenetic processes are also shared by humans and non-mammalian animals. Therefore, there is valid argument for utilising non-mammalian species as viable alternative animal models to investigate environmentally induced changes in human health, stress response and behavioural adaptations. We will now summarise recent evidence from transgenerational studies of key two non-mammalian models—C. elegans and D. melanogaster—focussing on environmental stressors and highlight their potential utility for investigating the molecular pathologies of psychiatric conditions.

**EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF C. ELEGANS RELEVANT TO PSYCHIATRY**

In contrast to mammalian models where multigenerational studies are impeded by long generational times, logistical difficulties and confounding factors, invertebrate models breed rapidly with large progeny cohorts, making them ideal models for performing multi-generational studies. There are the obvious limitations of C. elegans as a model, primarily that it is a relatively simple organism lacking many organ systems found in vertebrates. However, the C. elegans genome possesses homologs of about two-thirds of all human disease genes. Thus, it is widely used as a model system for studying aging, age-related diseases[41] and neurogenerative conditions[42].

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Figure 1 Differences between the definition of transgenerational and intergenerational inheritance through the male and female germ lines.
Transgenerational studies of *C. elegans* could therefore provide insight into the molecular pathologies and epigenetic modifications that could be accumulating across generations in humans. Here, we will summarise recent advances in our understanding of the transgenerational responses of *C. elegans* involving thermal stress and starvation and highlight their relevancy to human psychopathologies (Table 1).

The most impressive finding to-date was that exposure of a single progenitor generation to an elevated rearing temperature (25 °C instead of 20 °C) caused transcriptome-wide expression changes that persisted for a further seven generations after temperature normalisation[43]. Importantly, it was identified that the ancestral exposure to a higher temperature was associated with a reduction in the repressive histone modification H3K9me3 (trimethylation of lysine 9 residue in histone H3) in both oocytes and sperm, before onset of zygotic transcription. What could be of importance to the psychiatry field was the revelation that there was de-repression of endogenously repressed repeat sequences, and increased expression of two DNA transposons remained for up to five generations. The role of repetitive elements in human health and disease is still unclear but they have been speculated to be potential etiological factors for SZ, BP and major depressive disorder (MDD)[44], despite a present lack of consistent evidence. For example, there has only been a single report of a repetitive element insertion in three monozygotic twin pairs discordant for SZ[45] but similar observations have not been detected in other studies. However, subsequent studies have reported elevated levels of Class I retrotransposon RNA in cerebrospinal fluid, whole blood and serum samples from SZ patients[46–48]. It should be noted that these latter studies were conducted by the same research group and further independent verification is still required. At the present time, there are also no available rodent models of abnormal repetitive element expression so determining its relevance to neuropsychiatric pathologies is impossible. *C. elegans* would therefore be a prime model organism to investigate environmental factors associated with the aforementioned psychiatric conditions, with the dysregulation of repetitive element expression as a primary outcome measurable. Such studies would either cement their causal roles or establish them as secondary molecular pathologies.

Separately, another repressive histone mark linked to *C. elegans* lifespan[49], dimethylation of lysine 9 residue in histone H3 (H3K9me2), has also been implicated in various psychiatric conditions. Increased levels of H3K9me2 were found in post mortem SZ brains and in peripheral blood cells[50]. However, the directionality of this change in expression may vary depending on the specific psychopathology, according to evidence from rodent studies. For example, stress-induced depression was associated with reduced H3K9me2 occupancy at the oxytocin and arginine vasopressin gene promoters, both of which were normalised by physical exercise[51]. Thus, the outcomes linked to the manipulation of H3K9me2 levels are also gene specific. This is further exemplified by the capacity for Cdk-5 targeted H3K9me2 to attenuate cocaine-induced locomotor behaviour and conditioned place preference[52]. These clearly showcase the complexity to epigenetic regulation of gene transcription and the significant challenges faced when attempting to treat psychiatric conditions by targeting a single histone modification. However, armed with precise knowledge of the molecular pathologies, aiming to modify negative behaviours in addiction through gene-targeted histone modification could be an intriguing prospect for the future.

A recent study examined a more severe temperature perturbation through acute heat shock (34 °C for 5 min) and discovered that this caused maternal neurons to release the neurotransmitter 5-HT, which facilitated transcription factor heat shock factor 1 (HSF-1)-mediated mRNA production in soon-to-be fertilized germ cells[9]. The authors proposed that this timely activation of HSF-1 in germ cells ensures viability and future stress tolerance since embryos that arose from heat-shocked mothers contained an excess of protective mRNA and their F1 progeny were more resilient to subsequent temperature insults. It was found that HSF-1 recruited the histone chaperone FACTilates Chromatin Transcription (FACT) complex to alter histone dynamics and promote transcription of the heat shock protein Hsp70. Interestingly, several studies have identified an accumulation of Hsp70 associated with MDD. In a study of post-mortem brain samples from patients with MDD, Hsp70 was significantly elevated in the dorsolateral prefrontal cortex, while antidepressant treatment did not have any modulatory effect[53]. Separately, elevated serum Hsp70 levels were reportedly predictive of premenopausal women who would go on to develop MDD [54], although Hsp70 levels subsequently decreased for women who did not develop MDD. Collectively, this suggests that Hsp70 could be a useful biomarker for MDD risk but it remains to be verified in a younger, or even a healthy, population.
Table 1: Studies of transgenerational epigenetic inheritance in Caenorhabditis elegans of relevance to neuropsychiatric conditions and mammalian preclinical models

| Type of stress (if applicable to study) | Transgenerational shifts in progeny phenotypes | Epigenetic modifications implicated in the inheritance process | Psychiatric conditions with similar epigenetic pathology |
|--------------------------------------|-----------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|
| Elevated temperature                 | Temperature-induced transcriptome changes potentially up to F14 generation | Heat shock reduces H3K9me3 to facilitate de-repression of endogenously repressed repeats (DNA transposons) | Repetitive elements as etiological factors for schizophrenia (SZ), bipolar disorder and major depression (review) |
| Heat shock                           | Maternal heat shock altered survival of F1 progeny through 5-HT dependent HSF-1 recruitment to heat shock protein gene promoters. Persistence of phenotypic changes not investigated | Histone H3 occupancy at hsp70 genes decreased following heat shock | MDD associated with increased hsp70 expression in post mortem dorsolateral prefrontal cortex |
| NA                                   | NA                                            | Transgenerational inheritance of H3K36me3 is regulated by two distinct histone methyltransferases, MES-4 and MET-1 | Elevated serum HSP70 levels predicted development of MDD for premenopausal women. Serum HSP70 decreased over time for women who did not develop MDD |
| NA                                   | NA                                            | Lifespan regulated by the H3K9me2 methyltransferase MET-2 | Decreased Hsp70 expression in CA4 associated with complete seizure remission for temporal lobe epilepsy |
| NA                                   | Decline in fertility                          | H3K4me2 demethylase spr-5                                      | H3K36me3 implicated in SZ susceptibility SNPs. But histone lysine methyltransferases yet to be investigated in the context of SZ |
| Heavy metal (arsenite) stress        | Increased resistance to oxidative stress up to F2 generation; no change in reproduction or lifespan | H3K4me3 complex components (wdr-5.1, ash-2, set-2), and transcription factors daf-16 and hsf-1 | Reduced H3K9me2 at oxytocin and arginine vasopressin gene promoters in a rodent model of stress-induced depression. Rescued by physical exercise |
|                                      |                                               | Increased H3K4me3 associated with three synapsin gene variants in bipolar disorder and major depression | KDM5C gene that encodes the H3K4me2/3 histone demethylase linked to autism and intellectual disability |

Ref. [Klosin et al. 2017], [Kreher et al. 2018], [Lee et al. 2019], [Greer et al. 2014], [Kishimoto et al. 2017], [Su et al. 2020], [Vallianatos et al. 2018], [Crucea et al. 2013], [Girdhar et al. 2014].
| Event                      | Outcome                                                                 | Reference                              |
|---------------------------|--------------------------------------------------------------------------|----------------------------------------|
| Hyperosmotic stress       | Increased resistance to oxidative stress up to F2 generation             | Kishimoto et al. [10], 2017            |
| Larval starvation         | Increased resistance to oxidative stress up to F2 generation             | Kishimoto et al. [10], 2017            |
| Larval starvation         | NA                                                                        |                                        |
| Starvation                | Increased longevity of progeny up to F3 generation                        |                                        |

**Small RNAs regulating expression of genes involved in nutrition, metabolic health and lipid transport**

| Event                      | Outcome                                                                 | Reference                              |
|---------------------------|--------------------------------------------------------------------------|----------------------------------------|
| Starvation                | Inheritance of small RNAs through at least 3 generations.                | Rechavi et al. [11], 2014              |
| Starvation                | miRNAs and rRNAs make up the majority of exRNAs in human plasma         | Danielson et al. [91], 2017             |
| Starvation                | Small RNAs regulating expression of genes involved in nutrition, metabolic health and lipid transport | Yan et al. [94], 2020                  |
| Starvation                | exRNAs are potentially involved in the paternal intergenerational influence on offspring metabolic health (mouse model) | van Steenswyk et al. [95], 2020        |

**Relevance to human health presently unclear**

**Increased H3K4me3 associated with increased Otxr gene expression in a rat model of methamphetamine addiction**

**Increased H3K4me3 linked to PTSD**

**Increased H3K4me3 implicated in SZ susceptibility SNPs**

**Increased resistance to oxidative stress deficiencies in MDD, BP and SZ through antioxidant treatments such as N-acetylcysteine**

**Increased longevity of progeny up to F3 generation**

**Increased resistance to oxidative stress up to F2 generation**

**Increased H3K4me3 associated with increased oxidative stress in induced pluripotent stem cells derived from schizophrenia patients**

**Collectively, it emphasizes the conserved association between heat shock proteins, oxidative stress and neuronal damage. However, the precise regulatory roles that histone H3 and H4 proteins provide independently to the overall oxidative stress response remain unclear and warrants further investigation.**

**Mitochondrial dysfunction and the accumulation of oxidative stress are crucial factors in the pathophysiology of MDD**

**Thus, there is strong interest in targeting oxidative stress deficiencies in MDD, BP and SZ through antioxidant treatments such as N-acetylcysteine.**

**Future studies could use C. elegans to explore the efficacies of various antioxidant compounds in treating heat shock-induced oxidative stress, as well as their underlying modes of action. Studies could also be extended to heat shocking C. elegans pre-treated with antioxidants to better understand the epigenetic regulation of 5-HT neurotransmission.**
The dysregulation of transcriptional activity is widely reported in a swathe of psychiatric conditions but the causes have yet to be precisely identified. For example, H3K4me3 has been implicated in the pathophysiology of SZ, BP, and MDD, with increased H3K4me3 is associated with three synapsin gene variants in BP and MDD[63] while SZ risk variants are over-represented in association with H3K4me3 in human frontal lobe samples[64]. The latter is a consistent with a separate study examining H3K4me3 association with SZ susceptibility SNPs[65]. While there have been several independent GWAS studies of SZ, there has yet to be an attempt to reconcile the genomic data with epigenetic variation. That would undoubtedly be a tremendous undertaking, but it could further streamline and identify more robust gene candidates in our attempts to pinpoint the primary molecular pathologies underlying SZ. C. elegans could be used to first establish the molecular consequences of such an abnormal epigenetic landscape and resulting transcriptional dysregulation (matched to existing human data), before further behavioural studies are extended to mammalian models. Incidentally, H3K4me3 was identified by Kishimoto et al[10] as being involved with the transgenerational adaptations to other forms of environmental stressors aside from thermal stress, namely heavy metal exposure, hyperosmotic conditions, and transient starvation[10]. Following progenitor exposure to all three stressors, there were consistent increases in progeny fitness up till the F2 generation; however only the epigenetic mechanism mediating adaptation to arsenite exposure was further investigated. Unlike the repressive histone modifications mentioned above, H3K4me3 predominantly marks transcriptional start sites and is part of a regulatory complex that facilitates access and assembly of RNA polymerase[2][66,67]. Kishimoto et al[10] reported that the genetic components (set-2, dhr-14, and sid-2) of the H3K4me3 regulatory complex were required for manifesting the transgenerational adaptations, implicating histone H3-dependent gene transcription in transgenerational inheritance. Therefore, future work on H3K4me3-regulation transcriptional activity could provide new insight into the molecular pathways affected in SZ, BP and MDD by targeting C. elegans homologs of human risk genes for more specific investigations.

Finally, in a rat model of methamphetamine addiction, there was greater H3K4me3 association with the oxytocin receptor gene that corresponded to increased Oxtr gene expression[68]. As discussed above, strategies to treat addiction-related molecular pathologies by targeting histone modifications will be challenged by having to account for both active and repressive histone marks. The viability of such interventions and their molecular consequences would be ideally first tested in C. elegans before proceeding to trials in mammalian models.

Malnutrition and starvation at different stages of life have a dramatic impact on mental health. For example, famine exposure in utero was associated with an increased risk for mental illness in females, though surprisingly with no apparent significant effect on males[69]. Developmental malnutrition driven by abnormalities in oxidative stress pathways has been linked to an increased risk for SZ and other psychiatric illness later-in-life[70]. Nutrition ultimately dictates metabolic health and more recent studies reported that fasting insulin levels and body mass index at different ages were predictive of at-risk status for psychosis or depression[71], while fasting blood glucose and serum lipid levels predicted suicide attempters in young patients with MDD[72]. At the opposite end of the age spectrum, geriatric deficiencies in micronutrients such as folic acid, thiamine or cobalamin have been linked to worsened mental health symptoms[73,74]. However, careful regulation of nutrition through caloric restriction or fasting has been proposed to be effective in improving symptoms of MDD[75], indicating that dietary interventions where appropriate would benefit patients. This could be particularly important in conditions whereby medications could have unavoidable metabolic side effects[76]. While epidemiological data flags the importance of nutrition for mental health, we continue to have a very poor understanding of this interactive relationship in the absence of evidence of causality and the underlying molecular mechanisms. Human studies of that nature would be severely limited by inherent genetic and cultural heterogeneities within populations, and there would be strong ethical arguments against the manipulation of subjects' diets. These issues are circumvented in studies of C. elegans wherein genetic homogeneity is controlled and dietary manipulations are feasible, although as C. elegans feed upon bacteria subtle dietary manipulations may be more easily accomplished using the chemically controlled diets that have been formulated for D. melanogaster. Transgenerational studies of starvation in C. elegans have already been conducted with clear evidence of downstream impacts on progeny fitness. More importantly, these studies have identified epigenetic mechanisms regulating the transgenerational adaptations, and these could potentially be regulating the molecular pathologies driving the malnutrition-related increase in risk for mental illness.
Kishimoto et al[10] reported that progenitor larval starvation triggered increased resistance to oxidative stress of two generations of progeny[10] but did not pursue the underlying epigenetic mechanisms and their associated molecular adaptations. However, previously, it was reported that starvation during the early L4 Larval stage altered the expression of 13 miRNAs in C. elegans[77]. Of the 13, only 2 were downregulated while the miRNAs of the miR-35 family were most highly upregulated. Being a simple organism, there are only 302 known miRNAs in C. elegans compared to over 2000 human miRNAs, so studying their role in transgenerational inheritance and phenotype adaptations is comparatively straightforward. miRNAs are now established to be dysregulated in different human conditions and are the subjects of interest for severe stress-related anxiety disorders such as post-traumatic stress disorder and SZ, as prognostic biomarkers and therapeutic targets. However, their role as epigenetic regulators of pathogenesis are unclear and systematic profiling of individual miRNAs to neuronal circuitry could be one approach to identifying their potential pathogenic roles in psychiatric conditions.

In a cohort study of military combat veterans, 8 differentially expressed blood miRNAs were associated with the diagnosis of post-traumatic stress disorder (PTSD) [78], and their predicted gene targets were implicated in neurotransmission and maintenance of the neural circuitry. Indeed, multiple functional magnetic resonance imaging studies have clearly demonstrated that brain function is compromised in PTSD[79,80]. There is initial evidence to suggest that paternal PTSD may also have the capacity to influence the neural function and behaviour of progeny, and that this is through the inheritance of sperm-borne miRNAs. In the social defeat mouse model of PTSD, both male and female progeny displayed significant anxiety and depression-related behaviours despite themselves not having been subject to stressful interventions[81,82]. It was later independently reported that modelling paternal early life trauma alters sperm miRNAs and exerts significant intergenerational alterations of target genes in the brains of progeny (e.g. cttnb1, catenin β1 in the hippocampus)[22].

Our own studies have extended that line of evidence by demonstrating the transgenerational effects of paternal stress exposure and altered sperm miRNAs resulting in significant expression differences of the imprinted gene insulin-like growth factor 2, 

\[\text{lgf2}\]

in the hippocampus of two generations of progeny[21]. While their downstream target genes may have been discovered to be dysregulated, there is still some controversy regarding the intergenerational inheritance of sperm miRNAs because having altered levels of miRNAs in sperm does not translate to those same miRNAs being dysregulated in offspring brains[23]. Despite the transgenerational implications of paternal PTSD on brain function of their children remaining unknown at this time, a bigger unresolved question is how traumatic stress alters miRNA expression, with one possibility being dysregulation of histone protein modifications and altered chromatin state. Unlike PTSD, which is caused by an external trigger, miRNAs appear to be co-regulated with susceptibility risk genes in SZ. For example, one study has reported an over-representation of miR-9-5p-targeted risk genes while miR-9-2 is located in a genomic region strongly associated with SZ[83]. Given the strong environmental component to both PTSD and SZ, continuing research into stress-induced miRNA changes in C. elegans could be used to further our understanding of the relevant environment x gene interactions underlying the molecular pathogenesis of PTSD and SZ. Other miRNAs have been implicated in stress-related disorders such as members of the miR-34 family, which are differentially expressed in induced pluripotent stem cells derived from SZ patients[41,84]. Among these, and consistent with the neurodevelopmental hypothesis of SZ[85], miR-34a is a key regulator of p73 expression, a p53-family member that is implicated in neuronal differentiation[86]. However, causal evidence is lacking to demonstrate that miR-34a is an epigenetic conduit for environmental stress to impact on brain development resulting in a schizotypy brain phenotype. One feasible experiment to propose would be ablating expression of the C. elegans homolog of miR-34a or the miR-34 family and study the impacts on neuronal differentiation, development and circuit maturation.

Interestingly, Rechavi et al[11] report that progenitor larval starvation was associated with extended longevity in three generations of progeny through the inheritance of small RNAs that regulate genes involved in nutrition, metabolic health and lipid transport[11]. It has been demonstrated in C. elegans that extracellular RNAs (exRNAs) are transported from one generation to the next through intracellular vesicles or even as unpackaged extracellular material[87]. The transgenerational effects of paternal stress exposures[21-23] involve altered small non-coding RNA content of sperm transmitted in microvesicles within the male reproductive organs[88,89], but so far this has only been demonstrated in mouse models[90]. Perhaps not so coincidentally, miRNAs are one of two major exRNA species in human plasma (the other
being ribosomal RNAs. Their presence and relative stability have led to an emerging recognition of their promise as ‘liquid biopsies’ for diseases, but while early adoption has targeted metabolic pathology, the correlation of biofluid exRNA levels with psychiatric conditions remain untested. Interestingly, it was reported that chronic injection of serum from a mouse model of trauma into healthy controls was sufficient to recapitulate the intergenerational impact on offspring metabolism. However, miRNA profiling of the serum content was not performed in that study. Very recently, an investigation profiling exRNAs isolated from the plasma of elderly individuals up to 15 years prior to death revealed that the early presence and progressive increase of phosphoglycerate dehydrogenase (PHGDH) exRNA predicted eventual diagnosis of Alzheimer’s disease (confirmed with post mortem pathology testing). Studies of C. elegans could be used to first determine how stress triggers an elevation of circulating exRNAs. Subsequently, given that biofluid screening of exRNAs is already being used to aid diabetes and AD diagnoses, there appears to be untapped potential for this methodology as a presymptomatic screening tool in psychiatry.

Overall, recent studies have demonstrated the complexity of epigenetic responses implicated in the transgenerational responses to progenitor stress exposure. These include histone modifications, dysregulation of DNA repetitive elements and altered expression of non-coding RNAs. These are also molecular processes shared by humans and have been identified as molecular pathologies of various psychiatric conditions. Thus, studying the epigenetic response of C. elegans to etiologically relevant environmental stressors and the corresponding physiological and behavioural responses will continue to provide further insight into human molecular psychiatry.

EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF D. MELANOGASTER RELEVANT TO PSYCHIATRY

D. melanogaster has been established as an invertebrate model organism for studying human neurological disorders due to the remarkable evolutionary conservation of multiple human disease-causing genes. D. melanogaster have a higher degree of concordance with humans than C. elegans, with 75% of human diseases estimated to have a D. melanogaster homologue. While also displaying sexual dimorphism in its physiology and behaviour, D. melanogaster have a generational time of only 10-12 d as opposed to approximately 6-9 wk for mice. Thus, in a protracted timeframe and at much lower cost compared to using rodents, multi-generational studies can also be performed to assess transgenerational effects and adaptations of D. melanogaster offspring to various environmental stressors. Additionally, a wide range of established transgenic strains, gene manipulation techniques and tools are readily available.

Here, we refer readers to several broad reviews discussing the utility of D. melanogaster research in advancing the understanding of the complex genetic basis for human traits, psychiatric disorders, neurodegeneration, and for drug discovery and screening. Of course, the significant limitations of modelling complex neuropsychiatric conditions in D. melanogaster must also be acknowledged. Despite the relative ease in genetic manipulation, neuropsychiatric conditions such as SZ are driven by a combination of multiple genetic and environmental factors, and cannot be simply reduced to and reproduced in single, double or even triple transgenic knockout strains. Furthermore, the myriad of behavioural symptoms requires higher brain function to manifest, for which only mammalian models could be considered as appropriate. However, these reasons should certainly not diminish the utility value of D. melanogaster as a high throughput screening tool for basic neuropsychological, molecular or epigenetic markers of disease. Most recently, D. melanogaster have even been used to model insomnia in order to examine the effectiveness of sleep restriction therapy. However, despite these advantages, transgenerational studies in D. melanogaster aimed at examining mechanisms of epigenetic inheritance remain relatively sparse. Yet, the limited research has produced some compelling evidence, nonetheless. In this section, we will summarise key findings by highlighting the transgenerational outcomes of environmental and chemical stress exposures on offspring phenotypes paired with the reported epigenetic processes implicated. We will then flag the neuropsychiatric conditions for which further D. melanogaster research could potentially shed new light on the pathological origins.

D. melanogaster are sensitive to the climate and temperature fluctuations and have been instrumental in advancing our understanding of the heat stress response. Heat stress-associated deleterious effects on physiology and behaviour are...
largely attributed to its denaturing effect on proteins, which undergo abnormal folding, entanglement and unspecific aggregation[104]. In addition to the disruption of singular proteins, heat stress can also disrupt other cellular mechanisms with the culmination of these individual disruptions being cell death[105]. The ubiquitous and highly conserved heat shock response is a complex cascade of different processes, the most central being the transcriptional up-regulation of genes coding for the family of heat shock proteins that were in fact first discovered in *D. melanogaster*[106,107]. In addition to the metabolic and physiological effects on the exposed organism[108,109], selective thermal variations can dramatically shift *D. melanogaster* physical phenotypes such as flight ability over generations (impaired by F2 generation and maintained till the F4 generation) in a sex-dependent manner[110,111]. Thus, imposing a suboptimal ambient environment for survival either by changing the housing temperature or through a transient shift of temperature represents the most etiologically relevant approaches to stressing *D. melanogaster*. These encapsulate studies of both cold tolerance[112] and heat tolerance (discussed in detail below, Table 2), and these allow us to investigate how genetic variation dictates response to the environment or *vice versa*. Research into the transgenerational effects of heat stress in *D. melanogaster* have yielded intriguing and robust evidence of altered offspring physiology and heat stress responses. More importantly, those studies have also revealed epigenetic mechanisms that are of particular interest to psychiatry. Perhaps the most compelling demonstrations of environment-directed modifications of *D. melanogaster* epigenetics resulting in altered gene expression are the transgenerational studies of *white* gene expression following heat stress. The X chromosome residing *white* gene encodes for an ATP-binding cassette transporter that facilitates transport of the eye pigment precursors, guanine and tryptophan (red and brown pigment precursors, respectively) into the developing eyes during pupation[113]. Repression of *white* achieved by inserting the cellular memory module Fab-7 upstream of *white* to enhance chromatin silencing results in the loss of eye pigmentation[114]. Importantly, the Fab-7-mediated silencing process involves recruitment of *Polycomb* Group (PcG) proteins, which are essential in the propagation of chromatin structures and regulate gene silencing through S-phase of the cell cycle[115-117]. The mere developmental exposure to a mildly stressful temperature of 29 °C (typical housing temperature is 25 °C) suppressed Fab-7 expression, resulting in the de-repression of *white* and recovery of red eye pigmentation[118]. Importantly, that de-repression event was heritable down both male and female germ lines up till the F4 generation. That “founder effect” and maintenance of a de-repressed state across multiple generations indicates that inheritance of the temperature-modified chromatin state is maintained by the PcG protein complex. Of relevance to the human epigenome, the PcG protein complexes catalyse the formation and maintenance of the inactive histone mark H3K27me3[118], which as previously mentioned, is widely associated with neuropsychiatric conditions with abnormal histone modification patterns and aberrant gene transcriptional profiles[119]. Yet, the regulation of differentially expressed genes by PcG protein complexes in neuropsychiatric conditions has not been reported. While PcG protein complex function has been of great interest to the oncology field given the tell-tale features of DNA hypermethylation and aberrant transcriptional silencing of tumour suppressor genes[120], a causative role in psychiatric disorders has yet to be established. PcG protein complexes serve as a master regulator of active gene transcription so understanding the intricacies of PcG regulation of chromatin states will be essential if targeting aberrant histone modifications are to be a major therapeutic focus of the future. Aside from changes at the *white* gene locus, the multi-generational effects of heat shock on other behavioural (social interaction, mating) and physiological (metabolic and endocrine health) parameters in *D. melanogaster* are yet to be comprehensively studied. It would be very interesting to investigate if PcG protein complexes also have the capacity to affect the social behaviour, cognition and physical attributes of *D. melanogaster* by manipulating the extent of histone methylation associated with neuropsychiatric risk genes.

Interestingly, and in contrast to the stable inheritance pattern mediated by PcG protein complexes, heat shock-induced de-repression of *white* gene expression involving disruption of the heterochromatin assembly was maintained through three generations of embryos but contingent on repeated exposure of the offspring themselves to heat stress[121]. In that study, the transgenerational effects of heat shock were associated with increased phosphorylation of ATF-2, a member of the CREB/ATF family of transcription factors. Interestingly, levels of phosphorylated ATF-2 are reported to be increased in the ventral parieto-occipital region of post-mortem human brains when comparing between medicated and unmedicated patients with depression[122]; it is unknown if pATF-2 Levels could be predictive of a familial
| Type of stress (if applicable to study) | Transgenerational shifts in progeny phenotypes | Epigenetic processes implicated in the inheritance process | Ref. | Potentially relevant psychiatric conditions | Ref. |
|----------------------------------------|-----------------------------------------------|----------------------------------------------------------|------|---------------------------------------------|------|
| Thermal stress (selection based on intolerance to heat stress) | Reduced ability to fly by F2 generation, maintain through to F4 generation | Epigenetic mechanism not investigated; aspects of stress physiology that affect flight still unclear | Krebs and Thompson [111], 2006 | Relevance to human health presently unclear. | |
| Mild heat stress (embryos maintained at 29 °C) | De-suppression of white gene up to F4 generation | Disruption of polycomb group (PcG) protein complex affecting H3K27me3 | Bantignies et al [114], 2003 | Despite multiple reports of altered H3K27me3, the involvement of PcG protein complexes in human psychopathologies has not been established | |
| Heat shock (flies exposed to 37 °C for 1 h) | De-suppression of white gene sustained up to F3 generation required repeated exposure to the same paternal stressor. Gradual return to normal upon removal of heat shock | Disruption of pATF-2 mediated heterochromatin assembly | Seong et al [121], 2011 | Rat model of chronic stress reported increased ATF-2 gene expression in the frontal cortex of chronically stressed rats, which is decreased following chronic antidepressant treatment | Laifenfeld et al [122], 2004 |
| Heat stress (flies raised at 29 °C) | Suppression of BX2 transgene cluster over multiple (50) generations | Paramutation of BX2 via maternally inherited piRNAs, triggered by heat stress which resulted in active transcription of piRNAs within that gene locus | de Vanssay et al [126], 2012 | Paramutation is not regarded as an established epigenetic process in mammals | |
| Forced cohabitation with predator or | Stressed females shift behaviour to laying eggs on | Maternal inheritance of chromosome III and NPF | Bozler et al [136], 2019 | Dysregulation of NPY levels in the brain is a key pathophysiology of drug | Gonçalves et al [181], 2016 |

Table 2: Studies of transgenerational epigenetic inheritance in Drosophila melanogaster of potential relevance to psychiatric conditions and mammalian preclinical models.
endoparasitoid wasps

food rich in ethanol, and that preference is inherited through five generations  

Drosophila homolog of NPY (NPY) gene locus, reduced NPY expression in the fan shaped body of the adult brain drives ethanol preference  

addiction. Manipulation of NPY neurotransmission has potentially beneficial behavioural outcomes, depending on the drug in question

NPY is implicated in human alcohol misuse disorders  

Mayfield et al [137], 2002

NPY is also implicated in rodent models of alcohol misuse disorder  

Mettagui-Tabar et al [138], 2005

Restraint stress

Paternal restraint stress affects epigenome, transcriptome and metabolome of F1 progeny  

Stress-induced up-regulation of Upp3 (Drosophila homolog of IL-6) in somatic cells and testes, activating JAK/STAT pathway  

Metabolic dysregulation in the F1 offspring derived from male breeders exposed to early postnatal stress  

van Steenwyk et al [146]. 2018; van Steenwyk et al [93], 2020

Subsequent p38 activation results in dATF-2 deactivation in germ cells leading to decreased H3K9me2 (repressive mark) at target genes. Repressive histone marks inherited by F1 progeny  

Review of epigenetic mechanisms proposed to underlie intergenerational transmission of paternal trauma  

Yehuda and Lehner [182], 2018

Childhood adversity associated with altered DNA methylation of HPA axis and immune system genes; potentially inherited by offspring  

Bick et al [154], 2012

Methylphenidate (MPH) treatment

Behavioural response to MPH is genetically variable and intergenerational effects can be observed in F1 offspring  

Mechanism is unknown but MPH resulted in alterations to expression of many histone modifying genes  

ADHD is highly heritable, but the reasons are unclear despite the identification of candidate genes. Future studies should attempt to identify transgenerationally heritable epigenetic modifications as the basis for genetic vulnerability  

Mattison et al [155], 2011

Mechanism is unknown  

Rohde et al [156], 2019

Non-human primate studies indicate that MPH treatment affects normal puberty. The transgenerational implications of this finding for humans needs to be followed-up  

PTC: Premature termination codon; IL: Interleukin.
have the capacity to inhibit heterochromatin formation[125].

Studies of heat stress have also uncovered other heat-induced epigenetic responses involving paramutation and the resulting transgenerational inheritance of small non-coding RNAs via the maternal lineage. de Vanssay et al[126] described a paramutation event involving P-transposable-element repression in the germ line (termed trans-silencing effect, TSE) that converted other homologous clusters typically incapable of TSE into strong silencers[126]. The transgenerational effects of this paramutation persisted through 50 generations of progeny and was found to specifically require aubergine gene-mediated piRNA biogenesis but not Dicer-2 mediated siRNA production. Interestingly, this paramutation is triggered by heat stress and the pattern of piRNA up-regulation is transmitted via the maternal lineage[127]. Thus, one of the persistent epigenetic modifications in response to stress in humans could be the emergence of actively transcribed piRNA loci. While piRNAs are not a core focus of molecular psychiatry, piRNAs have started to gain attention in the domain of neurodegenerative diseases after having been found to be differentially expressed in prefrontal cortical tissue of post-mortem AD brains[128]. That has led to questions of their role in disease pathogenesis and the possibility of using them as a reliable biomarker for human disease. In support of the latter notion, miRNA and piRNA profiling of human cerebrospinal fluid-derived exosomes has more recently been proposed to have utility in diagnosing AD, as well as predicting the conversion from mild cognitive impairment to AD dementia[129]. There is sexual dimorphism in the clinical manifestation of AD with more women than men being diagnosed and maternal transmission is more frequently observed than paternal transmission[130], but the potential involvement of maternally inherited miRNAs or piRNAs to confer AD risk is completely unknown at this time. In D. melanogaster it has been established that piRNAs are maternally inherited and aging is associated with an increased presence of novel heterochromatic-only secondary piRNAs[131-134]. However, evidence of a similar pattern of inheritance role in humans has yet to be discovered. Our understanding of piRNA in the context of psychiatry and behaviour is barely in its infancy, and there remains much to be uncovered regarding the piRNA pathogenesis and its direct consequences across the range of neuropsychiatric diseases. Perhaps further studies in D. melanogaster can uncover novel piRNA-mediated disease mechanisms for psychiatry conditions that are skewed to maternal transmission.

Predator stress is another form of environmental stress that applies to D. melanogaster and studies have revealed that it is sufficiently severe to induce shifts in reproductive behaviours. Females housed in cohabitation conditions with endoparasitoid wasps develop a preference to lay eggs on ethanol-rich food as ethanol protects the larvae from wasp infection[135]. That change in oviposition behaviour was found to be driven by neuropeptide F (the D. melanogaster homolog of Neuropeptide Y, NPY) and persisted despite removal of the endoparasitoid wasps. More impressively, a recent study reported that exposure to predatory wasps is also an environmental stressor that triggers a similar transgenerational modification of egg laying behaviour over five generations[136]. That shift towards ethanol-rich substrates was established to be superficially maternally transmitted and involved inheritance of Chromosome III within which resides the NPF gene that is differentially expressed in the fan shaped body of the adult female brain. Here, it is worth noting that NPY is of major interest to substance misuse disorders and has been implicated in human alcohol use disorder[137-139] as well as in rodent models[140-142]. Since genetic vulnerability remains the core disease-causing factor for humans, and given that unbiased genetic screening, QTL analyses or GWAS studies are easily paired with functional studies in D. melanogaster[143,144], the latter presents as a viable alternative organism to study gene-environment interactions and the triggers that drive alcoholism, with perhaps the next step being a pursuit of the epigenetic mechanisms underlying those pathologies.

Interestingly, by using restraint stress to model strong psychological stress, Seong et al[145] found that paternal stress altered the epigenome, transcriptome, and metabolome in a dATF2 pathway-dependent manner[145]. A host of genes involved in metabolic health (amino acid metabolism, glycolysis, TCA cycle) were differentially expressed in the F1 offspring, which is consistent with the observations of similar paternal stress studies in mice[93,146]. The intergenerational effects in D. melanogaster were proposed to be caused by stress-induced up-regulation of Upd3 gene in the testes [the D. melanogaster homolog of the pro-inflammatory cytokine Interleukin-6 (IL-6)], which was confirmed by overexpression studies of Upd3 in paternal somatic cells with corresponding studies of the offspring outcomes. The overall intergenerational effects were proposed to be mediated by stress-induced increases in Upd3 that causes abnormal phosphorylation of dATF-2 in D. melanogaster germ cells, resulting in decreased H3K9me2 repressive marks that are inherited by the F1 offspring to
ultimately disrupt heterochromatin assembly and gene transcription. In humans, it remains to be clarified whether IL-6 (or other pro-inflammatory cytokines) correlates with sperm DNA damage[147,148]. However, it is well-established that inflammation has a significant role in the pathogenesis of various neuropsychiatric conditions including MDD[149-151] and SZ[152,153]. It would be interesting to elucidate the relationship of SNPs and risk gene loci with H3K9me2 repressive marks, and its contribution to the development of those conditions especially in familial cases. Additionally, given initial evidence suggesting that traumatic stress has long-term epigenetic consequences including altering the DNA methylation patterns of genes relevant to HPA axis function and the immune (inflammation) response[154], future D. melanogaster studies should also focus on DNA methylation as a key epigenetic mechanism mediating the transgenerational inheritance of stress-induced pathologies.

Methylphenidate (Ritalin) is a frontline prescription psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The increasing frequency of prescription has been the cause for concern regarding over-prescription and overdiagnosis. Methylphenidate treatment has been reported to result in significant developmental delay to puberty with hormonal imbalance in non-human primates[155]. While the impacts on spermatogenesis or sperm health were not investigated in that study, separate work on the major metabolite of methylphenidate, ritalinic acid, has found a significant increase of human sperm motility and viability in vitro[156]. However, any effects of long-term methylphenidate treatment on pubertal growth, sperm development in vivo and the sperm epigenome are unknown presently. D. melanogaster studies have contributed tremendously to advancing our understanding of the genetics of neuropsychiatric conditions. A prime example is they have been used to identify ADHD candidate genes[157] and to determine the transcriptomic response to methylphenidate, which correlate to their locomotor responses to drug treatment[158]. The latter study also identified putative candidate genes through whole genome transcriptomic analysis that accounted for the variability in drug response. Collectively, that body of work establishes D. melanogaster as a valid organism to further probe the transgenerational effects of methylphenidate exposure on male reproductive health and progeny behaviours. The aetiology of ADHD remains poorly understood but epidemiological data indicates approximately 80% heritability for both adults and children[159,160] despite only 22% of the disease liability being linked to common gene variants[161]. Given that knockdown of D. melanogaster homologues of ADHD candidate genes produces abnormal locomotor phenotypes that are also responsive to treatment by ADHD prescription compounds[162,163], D. melanogaster would continue to serve as an ideal organism for future investigations into the epigenetic factors underlying the high degree of heritability of ADHD.

Recently, one study investigating new therapeutic options for treating frontotemporal dementia (FTLD)[164] explored the use of aminoglycosides—a class of gram-negative bacilli antibiotics that have the capacity to induce eukaryotic ribosomal readthrough of premature termination codon (PTC) sequences to yield a full-length protein. Aminoglycosides have successfully been used to treat various diseases involving PTC mutations such as cystic fibrosis[165], Duchenne muscular dystrophy[166] and Rett syndrome[167], but have yet to be employed for neuropsychiatric conditions. In using a cell culture screening assay to conduct proof-of-principle studies with non-sense mutations of progranulin associated with FTLD, Kuang et al[164] identified two aminoglycosides that rescued the expression of the progranulin. It is worth noting that one of those aminoglycosides, G418 (also known as geneticin), has previously been reported to exert transgenerational effects on maternal Polycomb levels in D. melanogaster F2 embryos that persisted into the F3 generation[168]. Importantly, G418 exposure lead to growth retardation and delay in pupation times. While the transgenerational implications of G418 would be minimal since FTLD is associated with advanced aging, we believe it is important that readers be aware of such potential risks to offspring should aminoglycosides continue to be explored as therapeutic options for conditions in a younger fertile population.

**CONCLUSION**

Looking towards the future, improving the prospects for neuropsychiatric patients requires the field of psychiatry to have a more comprehensive understanding of the causes of various conditions, especially regarding how basic molecular and epigenetic pathologies interact and contribute to the overall disease phenotype. A major step
would be the incorporation of epigenome profiling since it is the key molecular intermediary linking genetics (susceptibility) to the environment (stress-related triggers). In highlighting the key findings of studies of C. elegans and D. melanogaster, we hope readers can come to appreciate the value of conducting basic research employing these two key non-mammalian organisms to potentially uncover novel molecular and epigenetic pathologies. Multiple stress-induced epigenetic modifications that affect the individual have significance in a variety of human neurological conditions, but further findings that progeny are also transgenerationally affected will have broader implications for health projections for future generations. At a time when stress (physical and mental) is prevalent and largely unavoidable, there is great urgency to understand the current mental health crisis and work towards new approaches for treatment and prevention. Of course, it is openly acknowledged that those molecular and neuronal circuitries can be interrogated in a rapid manner in complex human behavioural responses and adaptations related to psychopathologies.

Complex human behavioural responses and adaptations related to psychopathologies cannot be modelled in simple organisms. However, many fundamental molecular mechanisms that regulate neuronal behaviour have been conserved across phyla, and those molecular and neuronal circuitries can be interrogated in a rapid manner in simple model organisms. Therefore, invertebrate research should be regarded as being tremendously beneficial and highly complementary to human and mammalian model research, and further investments should be made in this regard. An expanded combination of clinical studies, rodent models and molecular studies in model organisms provides an extremely powerful multi-tiered approach to understanding the molecular basis of psychiatric disorders. Focusing on the epigenetic pathologies associated with neuropsychiatric conditions will undoubtedly lead to the development of novel approaches for treatment.

REFERENCES

1. Eberle C, Kirchner MF, Herden R, Stichling S. Paternal metabolic and cardiovascular programming of their offspring: A systematic scoping review. PLoS One 2020; 15: e0244826 [PMID: 33382823 DOI: 10.1371/journal.pone.0244826]
2. Pereira SC, Crisóstomo L, Sousa M, Oliveira PF, Alves MG. Metabolic diseases affect male reproduction and induce signatures in gametes that may compromise the offspring health. Environ Epigenet 2020; 6: dvaa019 [PMID: 33324496 DOI: 10.1093/epd/dvaa019]
3. Bowers ME, Yehuda R. Intergenerational Transmission of Stress in Humans. Neuropsychopharmacology 2016; 41: 232-244 [PMID: 26279078 DOI: 10.1038/npp.2015.247]
4. Jawaid A, Roszkowski M, Mansuy JM. Transgenerational Epigenetics of Traumatic Stress. Prog Mol Biol Transl Sci 2018; 158: 273-298 [PMID: 30072057 DOI: 10.1016/bs.pmbts.2018.03.003]
5. Klengel T, Dias BG, Ressler KJ. Models of Intergenerational and Transgenerational Transmission of Risk for Psychopathology in Mice. Neuropsychopharmacology 2016; 41: 219-231 [PMID: 26283147 DOI: 10.1038/npp.2015.249]
6. Rompala GR, Homanics GE. Intergenerational Effects of Alcohol: A Review of Paternal Preconception Ethanol Exposure Studies and Epigenetic Mechanisms in the Male Germline. Alcohol Clin Exp Res 2019; 43: 1032-1045 [PMID: 30908630 DOI: 10.1111/acer.14029]
7. Cook DE, Zdraljevic S, Tanny RE, Seo B, Riccardi DD, Noble LM, Rockman MV, Alkema MJ, Braendle C, Kammenga JE, Wang J, Kruglyak L, Félix MA, Lee J, Andersen EC. The Genetic Basis of Natural Variation in Caenorhabditis elegans Telomere Length. Genetics 2016; 204: 371-383 [PMID: 27440956 DOI: 10.1534/genetics.116.191148]
8. Maklakov AA, Carlsson H, Denbaum P, Lind MI, Mautz B, Hinas A, Immler S. Antagonistically pleiotropic allele increases lifespan and late-life reproduction at the cost of early-life reproduction and individual fitness. Proc Biol Sci 2017; 284 [PMID: 28615498 DOI: 10.1098/rspb.2017.0376]
9. Das S, Ooi FK, Cruz Corchedo J, Fuller LC, Weiner JA, Prahlad V. Serotonin signaling by maternal neurons upon stress ensures progeny survival. Elife 2020; 9 [PMID: 32324136 DOI: 10.7554/eLife.55246]
10. Kishimoto S, Uno M, Okabe E, Nono M, Nishida E. Environmental stresses induce transgenerationally inheritable survival advantages via germline-to-soma communication in Caenorhabditis elegans. Nat Commun 2017; 8: 14031 [PMID: 28067237 DOI: 10.1038/s41467-017-00371-8]
11. Rechavi O, Houri-Ze’evi L, Anava S, Goh WSS, Kerk SY, Hannon GI, Hobert O. Starvation-induced transgenerational inheritance of small RNAs in C. elegans. Cell 2014; 158: 277-287 [PMID: 25018105 DOI: 10.1016/j.cell.2014.06.020]
12. Bale TL. Epigenetic and transgenerational reprogramming of brain development. Nat Rev Neurosci 2015; 16: 332-344 [PMID: 23921815 DOI: 10.1038/nrn3818]
13. Müller D, Grett G, da Silva BS, Charão MF, Rovaris DL, Bau CHD. The neuroendocrine modulation of global DNA methylation in neuropsychiatric disorders. Mol Psychiatry 2021; 26: 66-69 [PMID: 33995777 DOI: 10.1038/s41380-020-00924-y]
14. Saxena R, Babadi M, Namvaraghahighi H, Roullet F. Role of environmental factors and epigenetics...
in autism spectrum disorders. Prog Mol Biol Transl Sci 2020; 173: 35-60 [PMID: 32711816 DOI: 10.1016/bs.pmbts.2020.05.002]

15 Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci 2007; 8: 355-367 [PMID: 17453016 DOI: 10.1038/nrn2132]

16 Yao B, Christian KM, He C, Jin P, Ming GL, Song H. Epigenetic mechanisms in neurogenesis. Nat Rev Neurosci 2016; 17: 537-549 [PMID: 27334043 DOI: 10.1038/nrn.2016.70]

17 Nagy C, Turecki G. Transgenerational epigenetic inheritance: an open discussion. Epigenomics 2015; 7: 781-790 [PMID: 26344807 DOI: 10.2217/epl.15.46]

18 Brass KE, Herndon N, Gardner SA, Grindstaff JL, Campbell P. Intergenerational effects of paternal predator cue exposure on behavior, stress reactivity, and neural gene expression. Horm Behav 2020; 124: 104806 [PMID: 32534838 DOI: 10.1016/j.yhbeh.2020.104806]

19 Cuarenta A, Kigar SL, Henion IC, Chang L, Bakshi VP, Auger AP. Early life stress during the neonatal period alters social play and Linel during the juvenile stage of development. Sci Rep 2021; 11: 3549 [PMID: 33574362 DOI: 10.1038/s41598-021-82953-3]

20 Fennell KA, Busby RGG, Li S, Boddien C, Stanger SJ, Nixon B, Short AK, Hannan AJ, Pang TY. Limitations to intergenerational inheritance: subchronic paternal stress preconception does not influence offspring anxiety. Sci Rep 2020; 10: 16050 [PMID: 32994941 DOI: 10.1038/s41598-020-72560-z]

21 Short AK, Fennell KA, Perreau VM, Fox A, O'Bryan MK, Kim JH, Bredy TW, Pang TY, Hannan AJ. Elevated paternal glucocorticoid exposure alters the small noncoding RNA profile in sperm and modifies anxiety and depressive phenotypes in the offspring. Transl Psychiatry 2016; 6: e837 [PMID: 27300263 DOI: 10.1038/tp.2016.109]

22 Gapp K, Jawaid A, Sarkies P, Bobaek J, Pelczar P, Prados J, Farinelli L, Miska E, Mansuy IM. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci 2014; 17: 667-669 [PMID: 24728267 DOI: 10.1038/nmn.2013.395]

23 Rodgers AB, Morgan CP, Bronson SL, Revello S, Bale TL. Paternal stress exposure alters sperm microRNA content and reprograms offspring HPA stress axis regulation. J Neurosci 2013; 33: 9003-9012 [PMID: 23699511 DOI: 10.1523/JNEUROSCI.0914-13.2013]

24 Rodgers AB, Morgan CP, Leu NA, Bale TL. Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci U S A 2015; 112: 13699-13704 [PMID: 26483456 DOI: 10.1073/pnas.1508347112]

25 Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 2003; 60: 1187-1192 [PMID: 14662550 DOI: 10.1001/archpsyc.60.12.1187]

26 Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009; 373: 234-239 [PMID: 19150704 DOI: 10.1016/S0140-6736(09)60072-6]

27 Wray NR, Gottesman II. Using summary data from the danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front Genet 2012; 3: 118 [PMID: 22783273 DOI: 10.3389/fgene.2012.00118]

28 Pettersson E, Lichtenstein P, Larsson H, Song J. Attention Deficit/Hyperactivity Disorder Working Group of the IPSYCH-Broad-PGC Consortium, Autism Spectrum Disorder Working Group of the iPSYCH-Broad-PGC Consortium, Bipolar Disorder Working Group of the PGC, Eating Disorder Working Group of the PGC, Major Depressive Disorder Working Group of the PGC, Obsessive Compulsive Disorders and Tourette Syndrome Working Group of the PGC, Schizophrenia CLOZUK, Substance Use Disorder Working Group of the PGC, Agrawal A, Berglund AD, Bulik CM, Daly MJ, Davis LK, Demontis D, Edenberg HJ, Grove J, Gelernter J, Neale BM, Pardinas AF, Stahl E, Walters JTR, Walters R, Sullivan PF, Posthuma D, Polderman TJ. Genetic influences on eight psychiatric disorders based on family data of 4,408,646 full and half-siblings, and genetic data of 333,748 cases and controls. Arch Gen Psychiatry 2009; 66: 373-382 [PMID: 19150704 DOI: 10.1016/j.archgenpsychiatry.2008.11.013]

29 Gupta A, Chauhan NR, Chowdhury D, Singh A, Meena RC, Chakrabarti A, Singh SB. Heat stress modulated gastrointestinal barrier dysfunction: role of tight junctions and heat shock proteins. Scand J Gastroenterol 2017; 52: 1315-1319 [PMID: 28906161 DOI: 10.1080/00365521.2017.1377285]

30 Das R, Saino L, Verma N, Bhatti P, Saikia J, Intivari, Kumar R. Impact of heat stress on health and performance of dairy animals: A review. Vet World 2016; 9: 260-266 [PMID: 27057109 DOI: 10.14202/vetworld.2016.260-265]

31 Issac G, Maury C, Fletcher RM, Eady PE. Temperature-induced developmental plasticity in Plodia interpunctella: Reproductive behaviour and sperm length. J Evol Biol 2019; 32: 675-682 [PMID: 30916425 DOI: 10.1111/jeb.13447]

32 Miwa Y, Koganezawa M, Yamamoto D. Antennae sense heat stress to inhibit mating and promote escaping in Drosophila females. J Neurogenet 2018; 32: 353-363 [PMID: 30231794 DOI: 10.1080/01677063.2018.1513507]

33 Johnson JS, Abuajamieh M, Victoria Sanz Fernandez M, Seibert JT, Staakes SK, Keating AF, Ross JW, Selbys JT, Rhoads RP, Baumgard LH. The impact of in utero heat stress and nutrient restriction on progeny body composition. J Therm Biol 2015; 53: 143-150 [PMID: 26590467 DOI: 10.1016/j.jtherbio.2015.10.002]

34 Wang J, Liu X, Dong M, Sun X, Xiao J, Zeng W, Hu J, Li X, Guo L, Rong Z, He G, Sun J, Ning D, Chen D, Zhang Y, Zhang B, Ma W, Liu T. Associations of maternal ambient temperature exposures
during pregnancy with the placental weight, volume and PFR: A birth cohort study in Guangzhou, China. *Environ Int* 2020; 139: 105682 [PMID: 32248024 DOI: 10.1016/j.envint.2020.105682]

35 Cianconi P, Betôro S, Janiri L. The Impact of Climate Change on Mental Health: A Systematic Descriptive Review. *Front Psychiatry* 2020; 11: 74 [PMID: 32210846 DOI: 10.3388/fpsyg.2020.00074]

36 Hein NT, Ciampitti IA, Jagadish SVK. Bottlenecks and opportunities in field-based high-throughput phenotyping for heat and drought stress. *J Exp Bot* 2021; 72: 5102-5116 [PMID: 33474563 DOI: 10.1093/jxb/erab021]

37 Waqas MA, Wang X, Zafar SA, Noor MA, Hussain HA, Azher Navaz M, Farooq M. Thermal Stresses in Maize: Effects and Management Strategies. *Plants (Basel)* 2021; 10 [PMID: 33557079 DOI: 10.3390/plants10020293]

38 Morrell JM. Heat stress and bull fertility. *Theriogenology* 2020; 153: 62-67 [PMID: 32442741 DOI: 10.1016/j.theriogenology.2020.05.014]

39 van Wettere WHEJ, Kind KL, Gatford KL, Swinburn AM, Leu ST, Hayman PT, Kelly JM, Weaver AC, Kleemann DO, Walker SK. Review of the impact of heat stress on reproductive performance of sheep. *J Anim Sci Biotechnol* 2021; 12: 26 [PMID: 33583422 DOI: 10.1186/s40104-020-00537-z]

40 Pembrey M, Saffery R, Bygren LO; Network in Epigenetic Epidemiology; Network in Epigenetic Development, Health and Biomedical Research. Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research. *J Med Genet* 2014; 51: 563-572 [PMID: 25062846 DOI: 10.1136/jmedgenet-2014-102577]

41 Zhang S, Li F, Zhou T, Wang G, Li Z. *Caenorhabditis elegans* as a Useful Model for Studying Aging Mutations. *Front Endocrinol (Lausanne)* 2020; 11: 554994 [PMID: 33123086 DOI: 10.3389/fendo.2020.554994]

42 Briese M, Esmaeili B, Fraboulé S, Burt EC, Christodoulou S, Towers PR, Davies KE, Sattelle DB. Deletion of smn-1, the *Caenorhabditis elegans* ortholog of the spinal muscular atrophy gene, results in locomotor dysfunction and reduced lifespan. *Hum Mol Genet* 2009; 18: 97-104 [PMID: 18829666 DOI: 10.1093/hmg/dda214]

43 Klosin A, Casas E, Hidalgo-Carcedo C, Vavouri T, Lehner B. Transgenerational transmission of environmental information in *C. elegans*. *Science* 2017; 356: 320-323 [PMID: 28428426 DOI: 10.1126/science.aab6412]

44 Darby MM, Sabuncylan S. Repetitive elements and epigenetic marks in behavior and psychiatric disease. *Adv Genet* 2014; 86: 185-252 [PMID: 25172351 DOI: 10.1002/978-0-118-80222-3.00009-7]

45 Deb-Rınker P, Klempan TA, O’Reilly RL, Torresy EF, Singhy SM. Molecular characterization of a MSRV-like sequence identified by RDA from monogenic twin discordant for schizophrenia. *Genomics* 1999; 61: 133-144 [PMID: 10534399 DOI: 10.1006/geno.1999.5946]

46 Karlsson H, Bachmann S, Schröder J, McArthur J, Torreyy EF, Yolken RH. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. *Proc Natl Acad Sci U S A* 2001; 98: 4634-4639 [PMID: 11296294 DOI: 10.1073/pnas.061021998]

47 Karlsson H, Schröder J, Bachmann S, Bottmér C, Yolken RH. HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. *Mol Psychiatry* 2004; 9: 12-13 [PMID: 14571258 DOI: 10.1038/sj.mp.4001459]

48 Yao Y, Schröder J, Nelländer C, Bottmér C, Bachmamn S, Yolken RH, Karlsson H. Elevated levels of human endogenous retrovirus-W transcripts in blood cells from patients with first episode schizophrenia. *Genes Brain Behav* 2008; 7: 103-112 [PMID: 17559415 DOI: 10.1111.j.1601-183X.2007.00334.x]

49 Lee TW, David HS, Engstrom AK, Carpenter BS, Katz DJ. Repressive H3K9me2 protects lifespan against the transgenerational burden of COMPASS activity in *C. elegans*. *Elife* 2019; 8 [PMID: 31815663 DOI: 10.7554/eLife.48498]

50 Chase KA, Feiner B, Ramaker MJ, Hu E, Rosen C, Sharma RP. Examining the effects of the histone methyltransferase inhibitor BIX-01294 on histone modifications and gene expression in both a clinical population and mouse models. *PLoS One* 2019; 14: e0216463 [PMID: 31185023 DOI: 10.1371/journal.pone.0216463]

51 Kim TK, Lee JE, Kim JE, Park JY, Choi J, Kim H, Lee EH, Han PL. G9a-Mediated Regulation of OXT and AVP Expression in the Basolateral Amygdala Mediates Stress-Induced Lasting Behavioral Depression and Its Reversal by Exercise. *Mol Neurobiol* 2016; 53: 2843-2856 [PMID: 25863961 DOI: 10.1007/s12035-015-9160-z]

52 Heller EA, Hamilton PJ, Burek DD, Lombroso SI, Peña CJ, Neve RL, Nestler EJ. Targeted Epigenetic Remodeling of the Cdk5 Gene in Nucleus Accumbens Regulates Cocaine- and Stress-Evoked Behavior. *J Neurosci* 2016; 36: 4690-4697 [PMID: 27122028 DOI: 10.1523/JNEUROSCI.0113-16.2016]

53 Martin-Hernández D, Caso JR, Javier Meana J, Callado LF, Madrigal JLM, García-Bueno B, Leza JC. Intracellular inflammatory and antioxidant pathways in postmortem frontal cortex of subjects with major depression: effect of antidepressants. *J Neuroinflammation* 2018; 15: 251 [PMID: 30180869 DOI: 10.1186/s12974-018-1294-2]

54 Passam FA, Harlow BL, Soares CN, Otto MW, Cohen LS, Minuzzi L, Gelain DP, Moreira JCF, Frey BN. A longitudinal study of neurotrophic, oxidative, and inflammatory markers in first-onset depression in middle women. *Eur Arch Psychiatry Clin Neurosci* 2018; 268: 771-781 [PMID: 29909955 DOI: 10.1007/s00406-017-0993-y]

55 Ciano GR, Pott S, Janiri L. The Impact of Climate Change on Mental Health: A Systematic Descriptive Review. *Front Psychiatry* 2020; 11: 74 [PMID: 32210846 DOI: 10.3388/fpsyg.2020.00074]

56 Hein NT, Ciampitti IA, Jagadish SVK. Bottlenecks and opportunities in field-based high-throughput phenotyping for heat and drought stress. *J Exp Bot* 2021; 72: 5102-5116 [PMID: 33474563 DOI: 10.1093/jxb/erab021]

57 Waqas MA, Wang X, Zafar SA, Noor MA, Hussain HA, Azher Navaz M, Farooq M. Thermal Stresses in Maize: Effects and Management Strategies. *Plants (Basel)* 2021; 10 [PMID: 33557079 DOI: 10.3390/plants10020293]

58 Morrell JM. Heat stress and bull fertility. *Theriogenology* 2020; 153: 62-67 [PMID: 32442741 DOI: 10.1016/j.theriogenology.2020.05.014]
Sural S, Liang CY, Wang FY, Ching TT, Hsu AL. HSB-1/HSF-1 pathway modulates histone H4 in mitochondria to control mtDNA transcription and longevity. Sci Adv 2020; 6 [PMID: 33087356 DOI: 10.1126/sciadv.azc4452]

Liao PC, Lin HY, Yuh CH, Yu LK, Wang HD. The effect of neuronal expression of heat shock proteins 26 and 27 on lifespan, neurodegeneration, and apoptosis in Drosophila. Biochem Biophys Res Commun 2008; 376: 637-641 [PMID: 18786296 DOI: 10.1016/j.bbrc.2008.08.161]

Allen J, Caruncho HJ, Kalynchuk LE. Severe life stress, mitochondrial dysfunction, and depressive behavior: A pathophysiological and therapeutic perspective. Mitochondrion 2021; 56: 111-117 [PMID: 33220501 DOI: 10.1016/j.mito.2020.11.010]

Shao A, Lin D, Wang L, Tu S, Lenahan C, Zhang J. Oxidative Stress at the Crossroads of Aging, Stroke and Depression. Aging Dis 2020; 11: 1537-1566 [PMID: 33269106 DOI: 10.14333/AD.2020.0225]

Weger M, Alpern D, Cherix A, Ghosal S, Grosse J, Russeil J, Gruetter R, de Kloet ER, Deplancke B, Sandi C. Mitochondrial gene signature in the prefrontal cortex for differential susceptibility to chronic stress. Sci Rep 2020; 10: 18308 [PMID: 33110158 DOI: 10.1038/s41598-020-75326-9]

Tao Q, Miao Y, Li H, Yuan X, Huang X, Wang Y, Andressen OA, Fan X, Yang Y, Song X. Insulin Resistance and Oxidative Stress: In Relation to Cognitive Function and Psychopathology in Drug-Naïve, First-Episode Drug-Free Schizophrenia. Front Psychiatry 2020; 11: 537280 [PMID: 33329081 DOI: 10.3389/fpsyt.2020.537280]

Morris G, Walker AJ, Walder K, Berk M, Marx W, Carvalho AF, Maes M, Puri BK. Increasing Nrf2 activity as a Treatment Approach in Neuropsychiatry. Mol Neurobiol 2021; 58: 2158-2182 [PMID: 33412248 DOI: 10.1007/s12035-020-02212-w]

Fan C, Long Y, Wang L, Liu X, Liu Z, Lan T, Li Y, Yu SY. N-Acetylcysteine rescues Hippocampal Oxidative Stress-Induced Neuronal Injury via Suppression of p38/JNK Signaling in Depressed Rats. Front Cell Neurosci 2020; 14: 554613 [PMID: 33262669 DOI: 10.3389/fncel.2020.554613]

Crucencau C, Alda M, Nagy C, Freemantle E, Rouelle GA, Turecki G. H3K4 tri-methylation in synapsin genes leads to different expression patterns in bipolar disorder and major depression. Int J Neuropsychopharmacol 2013; 16: 289-299 [PMID: 22571925 DOI: 10.1017/S1461145712003636]

Girdhar K, Hoffman GE, Jiang Y, Brown L, Kundakovic M, Hauberg ME, Francoeur NJ, Wang YC, Shah H, Kavanagh DH, Zavrovsky E, Jacobov R, Wiseman JR, Johnson JS, Kassim BS, Liu X, Liu Z, Lan T, Li Y, Yu SY. N-Acetylcysteine rescues Hippocampal Oxidative Stress-Induced Neuronal Injury via Suppression of p38/JNK Signaling in Depressed Rats. Front Cell Neurosci 2020; 14: 554613 [PMID: 33262669 DOI: 10.3389/fncel.2020.554613]

Niu HM, Yang P, Chen HH, Hao RH, Dong SS, Yao S, Chen XF, Yan H, Zhang YJ, Chen YX, Jiang F, Yang T, Guo Y. Comprehensive functional annotation of susceptibility SNPs prioritized 10 genes for schizophrenia. Transl Psychiatry 2019; 9: 56 [PMID: 30705251 DOI: 10.1038/s41398-019-0395-5]

Benayoun BA, Pollina EA, Ucar D, Mahmoudi S, Karra K, Weng Z, Sieberts SK, Peters MA, Harris BT, Lipska BK, Sklar P, Roussos P, Akbarian S. Cell-specific histone modification maps in the human frontal lobe link schizophrenia risk to the neuronal epigenome. Nat Neurosci 2018; 21: 1126-1136 [PMID: 30038276 DOI: 10.1038/s41593-018-0187-0]

Huang C, Phillips MR, Zhang Y, Zhang J, Shi Q, Song Z, Ding Z, Pang S, Martorell R. Malnutrition in early life and adult mental health: evidence from a natural experiment. Soc Sci Med 2013; 97: 259-266 [PMID: 23314395 DOI: 10.1016/j.socscimed.2012.09.051]

Mihlaj E, Morsch MG, Trabace L. Early life and oxidative stress in psychiatric disorders: what can we learn from animal models? Curr Pharm Des 2015; 21: 1396-1403 [PMID: 25564390 DOI: 10.2174/1381612821666150105122422]

Perry BI, Stochi JP, Uthegrove R, Zammit S, Wareham N, Langenberg C, Winpenny E, Dunger D, Jones PB, Khandaker GM. Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations With Risks of Psychosis and Depression in Young Adults. JAMA Psychiatry 2021; 78: 416-425 [PMID: 33439216 DOI: 10.1001/jamapsychiatry.2020.4180]

Zhao K, Zhou S, Shi X, Chen J, Zhang Y, Fan K, Zhang X, Wang W, Tang W. Potential metabolic monitoring indicators of suicide attempts in first episode and drug naive young patients with major depressive disorder: a cross-sectional study. BMC Psychiatry 2020; 20: 387 [PMID: 32723375 DOI: 10.1186/s12888-020-02791-x]

Harris D, Haboubi N. Malnutrition screening in the elderly population. J R Soc Med 2005; 98: 411-414 [PMID: 16140852 DOI: 10.1258/jrsm.98.9.411]

Koster A, van Gool CH, Kempen GI, Penninx BW, Lee JS, Rubin SM, Tylusvky FA, Yaffe K, Newman AB, Harris TB, Pahor M, Ayonayon HN, van Eijk JT, Kritchevsky SB; Health ABC Study.
Late-life depressed mood and weight change contribute to the risk of each other. *Am J Geriatr Psychiatry* 2010; 18: 256-244 [PMID: 20224519 DOI: 10.1097/JGP.0b013e3181e58337]

Igwe O, Sone M, Matveychuk D, Baker GB, Dursun SM. A review of effects of calorie restriction and fasting with potential relevance to depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2020; 110206 [PMID: 33316333 DOI: 10.1016/j.pnpbp.2020.110206]

Cao H, Meng Y, Li X, Ma X, Deng W, Guo W, Li T. The metabolic effects of antipsychotics in the early stage of treatment in first-episode patients with schizophrenia: A real-world study in a naturalistic setting. *J Psychiatr Res* 2020; 129: 265-271 [PMID: 32827810 DOI: 10.1016/j.jpsychires.2020.07.038]

García-Segura L, Abreu-Googder C, Hernandez-Mendoza A, Dimitrova Dinkova TD, Padilla-Noriega L, Perez-Andrade ME, Miranda-Rios J. High-Throughput Profiling of Caenorhabditis elegans Starvation-Responsive microRNAs. *PLoS One* 2015; 10: e0142262 [PMID: 26554708 DOI: 10.1371/journal.pone.0142262]

Martin CG, Kim H, Yun S, Livingston W, Fetta J, Mysliwiec V, Baxter T, Gill JM. Circulating miRNA associated with posttraumatic stress disorder in a cohort of military combat veterans. *Psychiatry Res* 2017; 251: 261-265 [PMID: 28222310 DOI: 10.1016/j.psychres.2017.01.081]

Françati V, Vernetten E, Brenner JD. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. *Depress Anxiety* 2007; 24: 202-218 [PMID: 16960853 DOI: 10.1002/da.20208]

Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. *Expert Rev Neurother* 2011; 11: 275-285 [PMID: 21306214 DOI: 10.1586/ern.10.198]

Cunningham AM, Walker DM, Ramakrishnan A, Doyle MA, Bangor RT, Cates HM, Peña CJ, Issler O, Lardner C, Brownie C, Russo SJ, Shen L, Nestler EJ. Sperm transcriptional state associated with paternal transmission of stress phenotypes. *J Neurosci* 2021 [PMID: 34099514 DOI: 10.1523/JNEUROSCI.3192-20.2021]

Dietz DM, Laplant Q, Watts EL, Hodes GE, Russo SJ, Feng J, Oosting RS, Vioulou V, Nestler EJ. Paternal transmission of stress-induced pathologies. *Biol Psychiatry* 2011; 70: 408-414 [PMID: 21679926 DOI: 10.1016/j.biopsych.2011.05.005]

Hauberg ME, Roussos P, Grove J, Børglum AD, Mattheisen M. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Analyzing the Role of MicroRNAs in Schizophrenia in the Context of Common Genetic Risk Variants. *JAMA Psychiatry* 2016; 73: 369-377 [PMID: 26963595 DOI: 10.1001/jamapsychiatry.2015.3018]

Andolina D, Di Segni M, Bisicchia E, D’Alessandro F, Cestari V, Ventura A, Concepcion C, Puglisi-Allegra S, Ventura R. Effects of lack of microRNA-34 on the neural circuitry underlying the stress response and anxiety. *Neuropsychopharmacology* 2016; 41: 305-316 [PMID: 27026110 DOI: 10.1016/j.neuropharm.2016.03.044]

Owen MJ, O’Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. *Br J Psychiatry* 2011; 198: 173-175 [PMID: 21557874 DOI: 10.1192/bjp.bp.110.084354]

Agostini M, Tucci P, Killiick R, Candi E, Sayan BS, Rivetti di Val Cervo P, Nicotera P, McKeon F, Knight RA, Mak TW, Melino G. Neuronal differentiation by TAp73 is mediated by microRNA-34a regulation of synaptic protein targets. *Proc Natl Acad Sci U S A* 2011; 108: 21093-21098 [PMID: 22160687 DOI: 10.1073/pnas.1112061109]

Marré J, Traver EC, Jose AM. Extracellular RNA is transported from one generation to the next in Caenorhabditis elegans. *Proc Natl Acad Sci U S A* 2016; 113: 12496-12501 [PMID: 27791108 DOI: 10.1073/pnas.1608951913]

Pang TYC, Short AK, Bredy TW, Hannan AJ. Transgenerational paternal transmission of acquired traits: Stress-induced modification of the sperm regulatory transcriptome and offspring phenotypes. *Curr Opin Behav Sci* 2017; 14: 140-147 [PMID: 29270445 DOI: 10.1016/j.cobeha.2017.02.007]

Trigg NA, Eamsns AL, Nixon B. The contribution of epididymosomes to the sperm small RNA profile. *Reproduction* 2019; 157: R209-R223 [PMID: 30780129 DOI: 10.1530/REP-18-0480]

Chan JC, Morgan CP, Adrian Leu N, Shetty A, Cisse YM, Nugent BM, Morrison KE, Jašarević E, Morgan CP, Adrian Leu N, Shetty A, Cisse YM, Nugent BM, Morrison KE, Jašarević E, Eamens AL, Nixon B. The contribution of epididymosomes to the sperm small RNA profile. *Biogerontology* 2020; 21(3): 291-301 [PMID: 32495146 DOI: 10.1007/s10522-020-09704-4]

Danielson KM, Rubio R, Abderazzaq F, Das S, Wang YE. High-Throughput Sequencing of Extracellular RNA from Human Plasma. *PloS One* 2017; 12: e0164644 [PMID: 28060806 DOI: 10.1371/journal.pone.0164644]

Shah R, Murthy V, Pacold M, Danielson K, Tanirverdi K, Larson MG, Hansper K, Pico A, Mick E, Reis J, de Ferrari S, Freinkman E, Levy D, Hoffmann U, Osganian S, Das S, Freedman JE. Extracellular RNAs Are Associated With Insulin Resistance and Metabolic Phenotypes. *Diabetes Care* 2017; 40: 546-553 [PMID: 28183786 DOI: 10.2337/dc16-1354]

van Steenwyk G, Gapp K, Jawaed A, Germain PL, Manuella F, Tanwar DK, Zamboni N, Gaur N, Efimova A, Thumfart KM, Miska EA, Mansuy IM. Involvement of circulating factors in the transmission of paternal experiences through the germline. *EMBO J* 2020; 39: e104579 [PMID: 33034389 DOI: 10.15252/embj.2020104579]

Yan Z, Zhou Z, Wu Q, Chen ZB, Koo EH, Zhong S. Presymptomatic Increase of an Extracellular RNA in Blood Plasma Associates with the Development of Alzheimer’s Disease. *Curr Biol* 2020; 30:

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**LATE-LIFE DEPRESSED MOOD AND WEIGHT CHANGE CONTRIBUTE TO THE RISK OF EACH OTHER.**

**TRANSGENERATIONAL PATERNAL TRANSMISSION OF ACQUIRED TRAITS: STRESS-INDUCED MODIFICATION OF THE SPERM REGULATORY TRANSCRIPTOME AND OFFSPRING PHENOTYPES.**

**EXTRACELLULAR RNA FROM HUMAN PLASMA.**

**REFERENCE:**

Jennifer S, smoke and alcohol consumption contribute to the risk of each other. *Am J Geriatr Psychiatry* 2010; 18: 256-244 [PMID: 20224519 DOI: 10.1097/JGP.0b013e3181e58337]

Hime GR et al. 
WJP | https://www.wjgnet.com
730 | October 19, 2021 | Volume 11 | Issue 10
Bredy TW, Sun YE, Kobor MS. How the epigenome contributes to the development of psychiatric disorders. *Dev Psychobiol* 2010; 52: 331-342 [PMID: 20127889 DOI: 10.1002/dev.20424]

Ohm JE, McGarvey KM, Yu X, Cheng L, Schuebel KE, Cope L, Mohammad HP, Chen W, Daniel VC, Yu W, Berman DM, Jenuwein T, Pruitt K, Shankis SJ, Watkins DN, Herman JG, Baylin SB. A stem cell-like chromatin pattern may predispose tumor suppressor genes to DNA hypermethylation and heritable silencing. *Nat Genet* 2007; 39: 237-242 [PMID: 17211412 DOI: 10.1038/ng1972]

Seong KH, Li D, Shimizu H, Nakamura R, Ishii S. Inheritance of stress-induced, ATF-2-dependent epigenetic change. *Cell* 2011; 145: 1049-1061 [PMID: 21703449 DOI: 10.1016/j.cell.2011.05.029]

Laienfeld D, Karry R, Grauer E, Klein E, Ben-Shacar D, AT2F, a member of the CREB/ATF family of transcription factors, in chronic stress and consequent to antidepressant treatment: animal models and human post-mortem brains. *Neuropsychopharmacology* 2004; 29: 589-597 [PMID: 14647483 DOI: 10.1038/sj.npp.1300357]

Sharma RP, Gavin DP, Chase KA. Heterochromatin as an incubator for pathology and treatment non-response: implication for neuropsychiatric illness. *Pharmacogenomics J* 2012; 12: 361-367 [PMID: 22249356 DOI: 10.1038/tjp.2011.64]

Zhu Y, Sun D, Jakovevski M, Jiang Y. Epigenetic mechanism of SETDB1 in brain: implications for neuropsychiatric disorders. *Transl Psychiatry* 2020; 10: 115 [PMID: 32321908 DOI: 10.1038/s41398-020-0797-7]

Feiner B, Chase KA, Melbourne JK, Rosen C, Sharma RP. Risperidone effects on heterochromatin: the role of kinase signaling. *Clin Exp Immunol* 2019; 196: 67-75 [PMID: 30714445 DOI: 10.1111/cei.13250]

de Vanssay A, Bougé AL, Boivin A, Hermant C, Teysset L, Delmarre V, Antoniewski C, Ronsseray S. Paramutation in Drosophila linked to emergence of a piRNA-producing locus. *Nature* 2012; 490: 112-115 [PMID: 22922650 DOI: 10.1038/nature11416]

Casier K, Delmarre V, Gueguen N, Hermant C, Vioëd E, Vaury C, Ronsseray S, Brasset E, Teysset L, Boivin A. Environmentally-induced epigenetic conversion of a piRNA cluster. *Elife* 2019; 8 [PMID: 30875295 DOI: 10.7554/elife.39842]

Qiu W, Guo X, Lin X, Yang Q, Zhang W, Zhang Y, Zuo L, Zhi Y, Li CR, Ma C, Luo X. Transcriptome-wide piRNA profiling in human brains of Alzheimer's disease. *Neurobiol Aging* 2017; 57: 170-177 [PMID: 28654860 DOI: 10.1016/j.neurobiolaging.2017.05.020]

Jain G, Stuendl A, Rao P, Berulava T, Pena Centeno T, Kaurani L, Burkhardt S, Delalle I, Kornhuber J, Hül M, Maier W, Peters O, Eisselmüller H, Schulte C, Deuschle C, Synofzik M, Wiltfang J, Mollenhauer B, Maetzler W, Schneider A, Fischer A. A combined miRNA-piRNA signature to detect Alzheimer's disease. *Transl Psychiatry* 2019; 9: 250 [PMID: 31591382 DOI: 10.1038/s41398-019-0579-2]

Heggel KA, Crook J, Thomas C, Graff-Radford N. Maternal transmission of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2012; 26: 364-366 [PMID: 22273801 DOI: 10.1097/WAD.0b013e3182187f72]

Blumenthal JP, Hartl DL. Evidence for maternally transmitted small interfering RNA in the repression of transposition in Drosophila virilis. *Proc Natl Acad Sci U S A* 2005; 102: 15965-15970 [PMID: 16247000 DOI: 10.1073/pnas.0508192102]

Brennecke J, Malone CD, Aravin AA, Sachidanandam R, Stark A, Hannon GJ. An epigenetic role for maternally transmitted small interfering RNA in the Drosophila P element transposon. *Science* 2008; 322: 1387-1392 [PMID: 19039138 DOI: 10.1126/science.1165171]

Grentzinger T, Armenise C, Brun C, Mugat B, Serrano V, Pelisson A, Chambeymon S. piRNA-mediated transgenerational inheritance of an acquired trait. *Genome Res* 2012; 22: 1877-1888 [PMID: 22555593 DOI: 10.1101/gr.136614.111]

Khrurana JS, Wang J, Xu J, Koppetsch BS, Thomson TC, Nowosielska A, Li C, Zamore PD, Weng Z, Theurkauf WE. Adaptation to P element transposon invasion in Drosophila melanogaster. *Cell* 2011; 147: 1551-1563 [PMID: 22196730 DOI: 10.1016/j.cell.2011.11.042]

Kacsoh BZ, Lynch ZR, Mortimer NT, Schlenke TA. Fruit flies mediate offspring after seeing parasitises. *Science* 2013; 339: 947-950 [PMID: 23430653 DOI: 10.1126/science.1229625]

Bozler J, Kacsoh BZ, Bosco G. Transgenerational inheritance of ethanol preference is caused by maternal NPF repression. *Elife* 2019; 8 [PMID: 31287057 DOI: 10.7554/elife.45391]

Mayfield RD, Lewohl JM, Dodd PR, Herlihy A, Liu J, Harris RA. Patterns of gene expression are altered in the frontal and motor cortices of human alcoholics. *J Neurochem* 2002; 81: 802-813 [PMID: 12065639 DOI: 10.1046/j.1471-4149.2002.00860.x]

Mottagui-Tabar S, Prince JA, Walestedt C, Zha G, Goldman D, Heilig M. A novel single nucleotide polymorphism of the neuropeptide Y (NPY) gene associated with alcohol dependence. *Alcohol Clin Exp Res* 2005; 29: 702-707 [PMID: 15957713 DOI: 10.1097/01.acl.0000164365.04061.b1]

Thorsell A, Mathé AA. Neuropeptide Y in Alcohol Addiction and Affective Disorders. *Front Endocrinol (Lausanne)* 2017; 8: 178 [PMID: 28824541 DOI: 10.3389/fendo.2017.00178]

Badia-Elder NE, Stewart RB, Powrozek TA, Murphy JM, Li TK. Effects of neuropeptide Y on sucrose and ethanol intake and on anxiety-like behavior in high alcohol drinking (HAD) and low alcohol drinking (LAD) rats. *Alcohol Clin Exp Res* 2003; 27: 894-899 [PMID: 12848099 DOI: 10.1097/01.ALC.0000071929.17974.DA]

Robinson SL, Marrero IM, Perez-Heydrich CA, Sepulveda-Orengo MT, Reissner KJ, Thiele TE. Medial prefrontal cortex neuropeptide Y modulates binge-like ethanol consumption in C57BL/6J
mice. *Neuropsychopharmacology* 2019; 44: 1132-1140 [PMID: 30647448 DOI: 10.1038/s41386-018-0310-7]

**Schröder JP**, Overstreet DH, Hodge CW. The neuropeptide-Y Y5 receptor antagonist L-152,804 decreases alcohol self-administration in inbred alcohol-prefering (iP) rats. *Alcohol* 2005; 36: 179-186 [PMID: 16377459 DOI: 10.1016/j.alcohol.2005.10.001]

**Chivilicek MM**, Titos I, Rothenfluh A. The Neurotransmitters Involved in Drosophila Alcohol-Induced Behaviors. *Front Behav Neurosci* 2020; 14: 607700 [PMID: 33384590 DOI: 10.3389/fibeh.2020.607700]

**Lathen DR**, Merrill CB, Rothenfluh A. Flying Together: *Drosophila* as a Tool to Understand the Genetics of Human Alcoholism. *Int J Mol Sci* 2020; 21 [PMID: 32932795 DOI: 10.3390/ijms21186649]

**Seong KH**, Ly NH, Katou Y, Yokota N, Nakato R, Murakami S, Hirayama A, Fukuda S, Kang S, Soga T, Shirahige K, Ishii S. Paternal restraint stress affects offspring metabolism via ATF-2 dependent mechanisms in Drosophila melanogaster germ cells. *Commun Biol* 2020; 3: 208 [PMID: 32367035 DOI: 10.1038/s42003-020-0935-z]

**van Steenwyk G**, Roszkowski M, Manuella F, Franklin TB, Mansuy IM. Transgenerational inheritance of behavioral and metabolic effects of paternal exposure to traumatic stress in early postnatal life: evidence in the 4th generation. *Environ Epigenet* 2018; 4: dyv023 [PMID: 30349741 DOI: 10.1093/epd/dyw023]

**Aghazarian A**, Huf W, Pflüger H, Klatte T. The association of seminal leukocytes, interleukin-6 and interleukin-8 with sperm DNA fragmentation: A prospective study. *Andrologia* 2019; 51: e13428 [PMID: 31642092 DOI: 10.1111/and.13428]

**Kopa Z**, Wenzel J, Papp GK, Haidl G. Role of granulocyte elastase and interleukin-6 in the diagnosis of male genital tract inflammation. *Andrologia* 2005; 37: 188-194 [PMID: 16266398 DOI: 10.1111/j.1439-0272.2005.06676.x]

**Hodes GE**, Ménard C, Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. *Neurobiol Stress* 2016; 4: 15-22 [PMID: 27981186 DOI: 10.1016/j.ynust.2016.03.003]

**Kakeda S**, Watanabe K, Katsuki A, Sugimoto K, Igata N, Ueda I, Igata R, Abe O, Yoshihara R, Korogi Y. Relationship between interleukin (IL)-6 and brain morphology in drug-naïve, first-episode major depressive disorder using surface-based morphometry. *Sci Rep* 2018; 8: 10054 [PMID: 29968776 DOI: 10.1038/s41598-018-28300-5]

**Ting EY**, Yang AC, Tsai SJ. Role of Interleukin-6 in Depressive Disorder. *Int J Mol Sci* 2020; 21 [PMID: 32235786 DOI: 10.3390/ijms21062194]

**Borovcanin MM**, Jovanovic I, Radosavljevic G, Pantić J, Minic Janicijevic S, Arsenijevic N, Lukic M. Interleukin-6 in Schizophrenia-Is There a Therapeutic Relevance? *Front Psychiatry* 2017; 8: 221 [PMID: 29163240 DOI: 10.3389/fpsyt.2017.00221]

**Chase KA**, Cone JJ, Rosen C, Sharma RP. The value of interleukin 6 as a peripheral diagnostic marker in schizophrenia. *BMC Psychiatry* 2016; 16: 152 [PMID: 27206977 DOI: 10.1186/s12888-016-0866-x]

**Bick J**, Naumova O, Hunter S, Barbot B, Lee M, Luthar SS, Raefski A, Grigorenko EL. Childhood adversity and DNA methylation of genes involved in the hypothalamus-pituitary-adrenal axis and immune system: whole-genome and candidate-gene associations. *Dev Psychopathol* 2012; 24: 1417-1425 [PMID: 23062307 DOI: 10.1017/S0954579412000806]

**Mattison DR**, Plant TM, Lin HM, Chen HC, Chen JJ, Twaddle NC, Doerge D, Slikker W Jr, Patton RE, Hotchkiss CE, Callicott RJ, Schrader SM, Turner TW, Kesner JS, Vitiello B, Petibone DM, Morris SM. Pubertal delay in male nonhuman primates (Macaca mulatta) treated with methylphenidate. *Proc Natl Acad Sci U S A* 2011; 108: 16301-16306 [PMID: 21930929 DOI: 10.1073/pnas.1102187108]

**Harlev A**, Henkel R, Samanta L, Agarwal A. Ritalinic Acid Stimulates Human Sperm Motility and Maintains Vitality *In Vitro. World J Mens Health* 2020; 38: 61-67 [PMID: 31081298 DOI: 10.5534/wjmwh.180.127]

**Rohde PD**, Madsen LS, Neumann Arvidson SM, Loeschcke V, Demontis D, Kristensen TN. Testing candidate genes for attention-deficit/hyperactivity disorder in fruit flies using a high throughput assay for complex behavior. *Fly (Austin)* 2016; 10: 25-34 [PMID: 26954469 DOI: 10.1080/19336934.2016.1158365]

**Rohde PD**, Jensen IR, Sarup PM, Ørsted M, Demontis D, Sørensen P, Kristensen TN. Genetic Signatures of Drug Response Variability in Drosophila melanogaster. *Genetics* 2019; 213: 633-650 [PMID: 31455722 DOI: 10.1534/genetics.119.302381]

**Banaschewski T**, Becker K, Scherag S, Franke B, Coghill D. Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *Eur Child Adolesc Psychiatry* 2010; 19: 237-257 [PMID: 20415962 DOI: 10.1007/s00787-010-0090-z]

**Faraone SV**, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, Rohde LA, Sonuga-Barke EJ, Tannock R, Franke B. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers* 2015; 1: 1520 [PMID: 27189265 DOI: 10.1038/nrd.2015.20]

**Demontis D**, Walters RK, Martin J, Mattheisen M, Als TD, Agebro E, Baldursson G, Belliveau R, Byßberg-Grauholm J, Bækvd-Hansen M, Cerrato F, Chamber A, Churchhouse D, Dumont AC, Eriksson N, Gandal M, Goldstein JI, Grasby KL, Grove J, Guðmundsson OØ, Hansen CS, Hauberg ME, Hollegaard MV, Howrigan DP, Huang H, Mäller JB, Martin AR, Martin NG, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poulbeau T, Poulsen JB, Ripke S, Robinson EB,
Satterstrom FK, Stefansson H, Stevens C, Turley P, Walters GB, Won H, Wright MJ; ADHD Working Group of the Psychiatric Genomics Consortium (PGC); Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium; 23andMe Research Team, Andreassen OA, Asherson P, Burton CL, Boomsma DI, Cornelis M, Franke B, Gelernter J, Geschwind D, Hakonarson H, Haavik J, Kranzler HR, Kuntsi J, Langley K, Leisch KP, Middeldorp C, Reif A, Rohde LA, Roussou P, Schachar R, Sklar P, Sonuga-Barke EJS, Sullivan PF, Thapar A, Tung JY, Waldman ID, Medland SE, Stefansson K, Nordenskjöld M, Hougaard DM, Mortensen PB, Daly MJ, Fanzone SV, Børglum AD, Neale BM. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2019; **51**: 63-75 [PMID: 30478444 DOI: 10.1038/s41588-018-0269-7]

van der Ven H, Harich B, Franke B, Schenck A. ADHD-associated dopamine transporter, latrophilin and neurofibrin share a dopamine-related locus marker in Drosophila. *Mol Psychiatry* 2016; **21**: 565-573 [PMID: 25962619 DOI: 10.1038/mp.2015.55]

van Swinderen B, Brembs B. Attention-like deficit and hyperactivity in a Drosophila memory mutant. *J Neurosci* 2010; **30**: 1003-1014 [PMID: 20089909 DOI: 10.1523/JNEUROSCI.4516-09.2010]

Kuang L, Hashimoto K, Huang EJ, Gentry MS, Zhu H. Frontotemporal dementia non-sense mutation of prion protein rescued by aminoglycosides. *Hum Mol Genet* 2020; **29**: 624-634 [PMID: 31913476 DOI: 10.1093/hmg/ddz280]

Howard M, Frizzell RA, Bedwell DM. Aminoglycoside antibiotics restore CFTR function by overcoming premature stop mutations. *Nat Med* 1996; **2**: 467-469 [PMID: 8597960 DOI: 10.1038/nmd.1996.467]

Howard MT, Anderson CB, Fass U, Khatri S, Gesteland RF, Atkins JF, Flanigan KM. Readthrough of dystrophin stop codon mutations induced by aminoglycosides. *Ann Neurol* 2004; **55**: 422-426 [PMID: 14991821 DOI: 10.1002/ana.20052]

Veesler M, Ben Zeev B, Nudelman I, Anikster Y, Simon AJ, Amariglio N, Rechavi G, Baasov T, Gak E. Ex vivo treatment with a novel synthetic aminoglycoside NB54 in primary fibroblasts from Rett syndrome patients suppresses MECP2 nonsense mutations. *PLoS One* 2011; **6**: e20733 [PMID: 21695138 DOI: 10.1371/journal.pone.0020733]

Stern S, Snir O, Mizrachi E, Galili M, Zeltsman I, Soen Y. Reduction in maternal Polyclomb levels contributes to transgenerational inheritance of a response to toxic stress in flies. *J Physiol* 2014; **592**: 2343-2355 [PMID: 24535443 DOI: 10.1113/jphysiol.2014.271445]

Misiak B, Ricceri L, Świądek MM. Transposable Elements and Their Epigenetic Regulation in Mental Disorders: Current Evidence in the Field. *Front Genet* 2019; **10**: 580 [PMID: 31293617 DOI: 10.3389/fgene.2019.00580]

Billingsley KJ, Lättekivi F, Planken A, Reimann E, Kurvits L, Kadastik-Eerme L, Kasterpalu KM, Bubb VJ, Quinn JP, Köks S, Tabu P. Analysis of repetitive element expression in the blood and skin of patients with Parkinson's disease identifies differential expression of satellite elements. *Sci Rep* 2019; **9**: 4369 [PMID: 30267520 DOI: 10.1038/s41598-019-40869-z]

Kandratavicius L, Hallak JE, Carlotti CG Jr, Assirati JA Jr, Leite JP. Hippocampal expression of heat shock proteins in mesial temporal lobe epilepsy with psychiatric comorbidities and their relation to seizure outcome. *Epilepsia* 2014; **55**: 1834-1843 [PMID: 25244257 DOI: 10.1111/epi.12787]

Kreher J, Takasaki T, Cockrum C, Sidoli S, Garcia BA, Jensen ON, Strome S. Distinct Roles of Two Histone Methyltransferases in Transmitting H3K36me3-Based Epigenetic Memory Across Generations in *Caenorhabditis elegans*. *Genetics* 2018; **210**: 969-982 [PMID: 30217796 DOI: 10.1534/genetics.118.301353]

Greer EL, Beece-Sims SE, Brookes E, Spadafora R, Zhu Y, Rothbart SB, Aristizábal-Corrales D, Chen S, Badeaux AI, Jin Q, Wang W, Strahl BD, Colaiácovo MP, Shi Y. A histone methylation network regulates transgenerational epigenetic memory in *C. elegans*. *Cell Rep* 2014; **7**: 113-126 [PMID: 24685137 DOI: 10.1016/j.celrep.2014.02.044]

Su Y, Liu X, Lian J, Deng C. Epigenetic histone modulations of PPARy and related pathways contribute to olanzapine-induced metabolic disorders. *Pharmacol Res* 2020; **155**: 104703 [PMID: 32068120 DOI: 10.1016/j.phrs.2020.104703]

Vaillantanos CN, Farrehi C, Friez MJ, Burmeister M, Keegan CE, Iwase S. Altered Gene-Regulatory Function of KDM5C by a Novel Mutation Associated With Autism and Intellectual Disability. *Front Mol Neurosci* 2018; **11**: 104 [PMID: 29675050 DOI: 10.3389/fnmol.2018.00104]

Zhao D, Lin M, Chen J, Pedroso E, Hrabovsky A, Fourcade HM, Zheng D, Lachman HM. MicroRNA Profiling of Neurons Generated Using Induced Pluripotent Stem Cells Derived from Patients with Schizophrenia and Schizoaffective Disorder, and 22q11.2 Del. *PLoS One* 2015; **10**: e0132387 [PMID: 26173148 DOI: 10.1371/journal.pone.0132387]

Gouris P, Skokou M, Polychronopoulos P, Soubasi E, Triantaphyllidou IE, Aravidis C, Sarela AI, Kosmaidou Z. Frontotemporal dementia, manifested as schizophrenia, with decreased heterochromatin on chromosome 1. *Case Rep Psychiatry* 2012; **2012**: 937518 [PMID: 23082270 DOI: 10.1155/2012/937518]

Kosower NS, Gerard L, Goldstein M, Parasol N, Zipser Y, Ragolsky M, Rozenwag S, Elbeketz E, Abramovitch Y, Lerer B. Constitutive heterochromatin of chromosome 1 and Duffy blood group alleles in schizophrenia. *Am J Med Genet* 1995; **60**: 133-138 [PMID: 7485247 DOI: 10.1002/ajmg.1320600209]

Kalichak F, de Alcantara Barcellos HH, Ildalencio R, Koakoski G, Soares SM, Pompermaier A,
Rossini M, Barcellos L.J.G. Persistent and transgenerational effects of risperidone in zebrafish. *Environ Sci Pollut Res Int* 2019; 26: 26293-26303 [PMID: 31286368 DOI: 10.1007/s11356-019-05890-9]

Yuan S, Oliver D, Schuster A, Zheng H, Yan W. Breeding scheme and maternal small RNAs affect the efficiency of transgenerational inheritance of a paramutation in mice. *Sci Rep* 2015; 5: 9266 [PMID: 25783852 DOI: 10.1038/srep09266]

Gonçalves J, Martins J, Baptista S, Ambrósio AF, Silva AP. Effects of drugs of abuse on the central neuropeptide Y system. *Addict Biol* 2016; 21: 755-765 [PMID: 25904345 DOI: 10.1111/adb.12250]

Yehuda R, Lehrner A. Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. *World Psychiatry* 2018; 17: 243-257 [PMID: 30192087 DOI: 10.1002/wps.20568]

Laumonnier F, Shoubridge C, Antar C, Nguyen LS, Van Esch H, Kleefstra T, Briault S, Fryns JP, Hamel B, Chelly J, Ropers HH, Ronce N, Blesson S, Moraine C, Gécz J, Raynaud M. Mutations of the UPF3B gene, which encodes a protein widely expressed in neurons, are associated with nonspecific mental retardation with or without autism. *Mol Psychiatry* 2010; 15: 767-776 [PMID: 19238151 DOI: 10.1038/mp.2009.14]
