The Transgenerational Transmission of Stress-Induced Traits Through Epigenetic Alterations

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Abstract

Lamarckian pathways of inheritance are often grossly overlooked. This paper reviews the transgenerational transmission of traits via stress-induced epigenetic alterations. The prevalence of this transmission is investigated in humans as well as other animals. Stress-induced DNA methylation, histone modifications and non-coding RNAs can all manifest itself into altered phenotypes of subsequent generations. Increased activity of the HPA axis in the offspring of stress-affected individuals is a recurrent finding. Furthermore, potential adaptive capabilities of this transgenerational modification will be discussed, in an attempt to hypothesize the benefits of Lamarckian inheritance.

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Introduction

French naturalist Jean-Baptiste Lamarck is perhaps best remembered for his endorsement of the view that evolution operates through the heritage of acquired traits. This view is now seen by many as the antithesis of the highly regarded Darwinian theory of evolution, and with this development his legacy has been tarnished. Lamarckian views of evolution have been consistently mocked throughout history. French zoologist George Cuvier even marked Lamarck's death as an occasion on how not to perform science (Burkhardt, 2013), which served as an illustrative example of the limited admiration many scientists had for one of the founding fathers of evolution. With the rise of neo-Darwinism, the Lamarckian perspective was completely rejected and the transgenerational transmission of traits has long been fully attributed to a combination of Mendelian genetics and mutations. Throughout the course of the 20th century, however, this view was challenged by a mounting number of discoveries which cannot be attributed to classical genetics. In 1956, embryologist Conrad Waddington managed to demonstrate that acquired traits can be inherited, by showing that the trait of artificially enlarged halteres of *Drosophila Melanogaster* was actually transmitted to offspring of the treated individuals (Waddington, 1956). Waddington coined the term 'epigenetics' to describe all the developmental processes, unrelated to the genotype, that shape the final phenotypical product (Felsenfield, 2014). These days epigenetics is loosely defined as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence"(Russo et al., 1996). Epigenetics is now a popular topic of interest amongst evolutionary biologists, with Pubmed providing tens of thousands of hits for the topic; genetic sequences are no longer seen as the sole medium of the transgenerational transfer of phenotypic traits.

In recent times, a myriad of findings have revealed that stress, or lack thereof, can alter the expression of genes via epigenetic influence (Champagne, 2008). Additionally, it has been revealed that these traits can then be passed on to the progeny of the affected individual (Champagne, 2008). A number of experiments have looked at the epigenetic consequences of stress and what these entail for subsequent generations. For instance, it has been shown that the epigenetic influence of stress can influence the gestational length of multiple generations and with it the health of newborns (Yao et al., 2014). Another study found that traumatic stress in mice can alter behavioural and metabolic responses in the offspring of the traumatized individuals (Gapp et al., 2014). Even in humans, it has been demonstrated that experiencing traumas can cause an increased susceptibility to stress and depression, for the affected mother as well as her children (Perroud et al., 2014). These insights drastically alter the perception of how transgenerational phenotypic transmission operates, and sparks the interest for a number of questions. The practical application of this knowledge is easily conjured, since it further stresses the medical importance of psychological health.

This paper aims to review the significance of the transgenerational impact of stress. The main research question reads: "what epigenetic mechanisms cause transgenerational alterations induced by stress?". Other questions that will be answered are: "what are the phenotypical consequences of stress-induced epigenetic inheritance?" and "what evolutionary reasons might exist for the existence of epigenetic inheritance?". The paper will conclude by summarising the findings and a discussion of their relevance.

The Mechanisms Behind Transgenerational Epigenetics

In this section, the aim is to cover the technical side of transgenerational epigenetic inheritance. The functioning of these mechanisms will be analysed, proceeded by a look into how these mechanisms are allowed to influence subsequent generations. There are a number of mechanisms that cause the epigenetic transmission of traits to daughter cells, only three of which have been established to be heritable through the germline. These are also the most well-known and established epigenetic mechanisms, namely: DNA methylation, histone modifi-

cation and non-coding RNAs. These three epigenetic mechanisms will be discussed separately.

DNA Methylation

DNA methylation is the post-synthetic addition of methyl groups to the 5-position of cytosines, forming 5-methylcytosine (Champagne et al., 2007), a process mediated by methyltransferases (Champagne, 2010). This methylation alters the major groove structure of the DNA, which affects protein-binding to the DNA (Jones, 2001). In animals this methylation occurs primarily at CpG dinucleotides; in mammals it does so almost exclusively (Champagne et al., 2007; Bird, 2002). Clusters of these CpGs are called CpG islands. They serve as strong promoters for transcription. The methylation of this area inhibits transcription factors from binding to the DNA, resulting in gene silencing (Champagne, 2008), a function which can be used to, for instance, silence parasitic DNAs (Champagne et al., 2007). DNA methylation patterns are inherited by daughter cells (Champagne & Meaney, 2010), making them a rather stable epigenetic change.

Usually, 5-methylcytosine is a target for deamination by DNA repair enzymes. However, since 5-methylcytosine is prone to convert to thymine or methylated guanine - functional compounds which aren't identified by DNA repair enzymes as damage - they are often exempt from deamination (Bateson, 2012). This makes CpG islands important sites for methylation. DNA methylation can also disturb the normal functioning of DNA repair genes and apoptosis (Meng et al., 2015; Meng et al., 2011), enabling establishment in the genome. During germline and embryonic reprogramming, DNA is met with extensive demethylation, but it has been demonstrated that some loci are able to avoid demethylation (Hajkova et al., 2002). Exactly how methylation patterns persist through reprogramming is still unclear. It has, however, been shown that the enzyme *DNA Methyltransferase 1* (DNMT1) - an enzyme responsible for catalysing the methylation of CpGs - is vital for this avoidance (Messerschmidt et al., 2014). It seems that some areas of the genome are specifically exempt from demethylation, perhaps to meet specific requirements of adaption (Feil, 2009). Hypomethylation of sperm DNA is consistent with hypomethylation of embryonic cells in humans, suggesting that there is a mechanism in place which allows this transgenerational transmission to take place (Hammoud et al., 2009).

Histone Modification

Chromatin consists of DNA wrapped around histone proteins. The state of this protein determines whether DNA is exposed and can come in contact with RNA polymerase and transcription factors (Champagne & Meaney, 2010) Thus, histone proteins play a role in the expression and silencing of DNA.

Histones can be modified through a number of chemical processes such as methylation, acetylation and phosphorylation (Bannister & Kouzarides, 2011). This can affect the chromatin structure and with it the DNA availability. Histone acetylation is typically associated with increased transcriptional activity, whereas histone methylation is associated with transcriptional repression (Champagne, 2010). The rapid change in DNA availability caused by altered histone conformation make histone modifications primary players in the field of epigenetics. Multiple studies have shown that histone modifications can have transgenerational effects. One study showed that stress-induced chromatin modification in *Drosophila Melanogaster*, caused a change in eye pigment, which was transmitted across generations (Seong et al., 2011). Another study on *Drosophila Melanogaster* showed that toxic stress, which caused transgenerational epigenetic alterations of development, was partly induced by the alteration of histone regulators (Stern et al., 2012). Even though the great majority of histones are replaced by protamines in mature spermatozoa (99% in humans, 85% in mice; Brunner et al., 2014), transmission of chromatin states can occur through both the paternal and maternal lineage. How histone marks are not completely renewed through the germline still remains partly unclear. Germline reprogramming causes histone modifications to be reset, and in mammals, reprogramming also occurs in the zygote after fertilization (Heard & Martienssen, 2014). However, new insights into the mechanism are developing. The

alteration of chromatin marks could result in the generation of non-coding RNAs which are transmitted through the germline, these non-coding RNAs could then induce the same chromatin marks in the somatic cells which were made in the parental cells (Lim & Brunet, 2013). In humans and mice, certain histone marks are protected from replacement by protamine, causing modifications to persist into the germline (Brykczynska et al., 2010; Hammoud et al., 2009). In *C. Elegans*, deficiencies in histone regulators could be caused by histone markings, which then result in alterations of the histone structure in the germline (Lim & Brunet, 2013). Protamines can also be influenced by the histones they are replacing and vice versa, causing epigenetic changes to be transferrable at specific loci (Lim & Brunet, 2013). In humans, histone modifications are particularly present at certain developmental loci. Trimethylation of the H3K27 protein (H3K27me3) is particularly enriched at developmental promoters repressed in early embryos (Hammoud et al., 2009). While trimethylation of the H3K4 protein (H3K4me3) showed a significant correlation with promoters which are activated in early embryos (Teperek etl al., 2016). H3K27me3 is also an established marker of transgenerational inheritance in *Drosophila Melanogaster* (Ciabrelli et al., 2017). These findings show that histone modifications might actually play a crucial role in embryonic development.

Non-Coding RNAs

Small non-coding RNAs (sncRNAs) are RNA molecules which are not translated into proteins. They are particularly important in paternal germline transmission (Johnson et al., 2010), but have also been found in oocytes (Tam et al., 2010). Machinery that regulates RNA interference (RNAi) is important for the heritability of non-coding RNAs, as well as the transgenerational maintenance of chromatin states (Bannister & Kouzarides, 2011). Some examples of non-coding RNA which play a role in transgenerational inheritance are small interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), and miRNAs (Lim & Brunet, 2013). Transcriptional regulation by these RNAs occurs through various mechanisms: destabilization and degradation of mRNA, translation repression, histone modifications and DNA methylation (Fedoroff, 2012; Kaikkonen et al., 2011; Kim et al., 2008).

Precisely how scnRNAs are able to induce transgenerational has yet to be fully established. The theory of the Weismann barrier states that hereditary information can only be passed from germ cells to somatic cells and not the other way around. However, this view has been challenged by findings proving that somatically induced epigenetic changes can be recovered in germ cells (Ligtenberg et al., 2008; Bucher et al., 2002). Additionally, somatic information in the form of silencing RNAs, has been shown to be heritable across multiple generations (Alcazar et al., 2008; Barolomei, 2009). Through a complex interaction with DNA methylation and the modification of chromatin structures, sncRNAs have exhibited multigenerational changes of the genome (Quérin et al., 2013; Holoch et al., 2015; Ashe et al., 2012).

The interplay between the three discussed mechanisms seems to be very important for allowing effective transgenerational impact. There are a number of intergenerational barriers in place to be crossed. Successful transmission seems to be an exception rather than the rule.

The Lasting Epigenetic Influence of Stress

Here, the epigenetic consequences and the phenotypical effects of stress will be reviewed. Throughout the course of the 21st century it has become apparent that, through epigenetics, stressful experiences can have a number of lasting influences on an organism. It appears that if these stressful experiences occur early in life, their impact can be especially profound. The transgenerational effects of stress have shown to be exhibited in a number of different species ranging from *Drosophila Melanogaster* to *Homo Sapiens*. Here the focus will lie largely on research done on rodents and humans.

Stress Epigenetics in Animals

A number of experiments have looked at the epigenetic effects of poor parental care in rodents, and the stress and trauma associated with it. A 2009 study showed that early maltreatment of rat pups resulted in a lasting decreased expression of the *brain derived neurotropic factor* (BDNF) gene in the prefrontal cortex as well as the hippocampus (Roth et al., 2009). This altered expression was caused by the methylation of the BDNF gene, which is an established biomarker for a number of psychiatric disorders (Zheleznyakova et al., 2016; Ikegame et al., 2013). Cross-fostering of these offspring did not erase the methylation patterns, ruling out the possibility of behavioural transmission. Administration of zebularine, a compound which reduces DNA methylation, has been demonstrated to increase BDNF expression. This provides further evidence for the contribution of epigenetics in the prolonged effects of stressful experiences.

Furthermore, it has been shown that low levels of licking and grooming (LG) during maternal care caused lasting elevations in ACTH and corticosterone induced by stress, as well as reduced *glucorticoid receptor* (GR) mRNA in the hippocampus and increased *corticotrophin realising hormone* (CRH) in the hypothalamus (Champagne, 2008). A dampened ability to limit the release of CRH and ACTH suggests elevated activity of the *hypothalamic-pituitary-adrenal* (HPA) axis (Champagne, 2008). Decreased levels of GR mRNA cause a decreased ability to reach baseline levels of corticosterone in response to stress (Champagne, 2008). Pups raised by low LG mothers showed differences in DNA methylation, histone acetylation and binding of transcription factors to the GR promoter. Infusion of a histone deacetylase inhibitor removed these differences between high-LG and low-LG pups (Weaver et al., 2008). This suggests a relationship between epigenetics, GR expression and the effects of maternal care on the stress responses in offspring. Low-LG pups also exhibited lower mRNA expression of the *Nuclear Receptor Subfamily 3 Group C Member 1* (NR3C1) gene which, just like higher methylation of this gene, leads to lower expression of GR (Weaver et al., 2004). It has been determined that LG behaviour and its effects on exploratory behaviour can be transmitted transgenerationally (Champagne & Meaney, 2007), meaning the offspring of low-LG raised pups are also affected.

Another study found that early life stress in mice resulted in the increased secretion of corticosterone, altering stress coping and memory (Murgatroyd et al., 2007). This was caused by hypomethylation of key CpG areas of the *arginine vasopressin* (AVP) gene. These CpG areas are used for the binding of methyl CpG-binding protein 2 (MeCP2) which regulate the transcription of the gene. This hypomethylation caused increased expression of AVP and therefore hyperactivity of the HPA axis. This effect was reversed by applying an AVP receptor antagonist, normalizing HPA axis activity. Just like CRH, AVP is responsible for the activation of the *Pro-opiomelanocortin* (POMC) gene which results in the cleavage and release of ACTH from the pituitary. ACTH then activates the release of cortisol by the adrenal gland (Provençal & Binder, 2015).

A 2014 study exposed newborn mice to a combination of unpredictable maternal separation and unpredictable maternal stress (MSUS) (Gapp et al., 2014). This resulted in several epigenetic changes at the *mineralocorticoid receptor* (MR) gene which remained present through several generations. Such as reduced MR mRNA and decreased acetylation and methylation of several histone proteins. Furthermore, DNA methylation in sperm cells of F1 males was significantly increased at several CpGs across the MR promoter region.

Another 2014 study even demonstrated that adverse outcomes of chronic stress progressively worsened up to the F2 generation (Yao et al., 2014). Pregnant mice were exposed to daily periods of stress in the form of restraint and forced swimming. Offspring of these mice exhibited significantly shorter gestational length, elevated blood glucose levels, lower gestational weight gain, impeded offspring growth, less tail-chasing and delayed sensorimotor development of offspring. Most of these effects were magnified in the F2 generation and still present in the F3 generation. Drastic changes in the miRNA profiles of somatic tissues were

observed, especially in the F2 generation. Ten different miRNAs in the frontal cortex depicted altered expression in stress-affected individuals. Several of these miRNAs were related to transcription regulators and chromatin organization. Furthermore, a number of target genes were shown to be involved in endocrine functioning. Some placental miRNA's were also altered in the F2 generation of stress-affected individuals.

But apart from chronic stress, acute stress in early life can also depict some transgenerational epigenetic effects. A study carried out in chickens showed that exposure to stressful situations early in life resulted in several transgenerational effects (Goerlich et al., 2012). Chicks were exposed to three intermittent periods of social isolation. These periods lasted for one, two and three hours and occurred once a week. In these periods they were also marked by water and food deprivation and a 10^{o}C drop in temperature. This affected the offspring of these stress-affected chickens in a number of ways. For female offspring it resulted in an increased body mass and males exhibited a significantly lower corticosterone response in reaction to stress. Both sexes showed altered gene expressions across multiple generations, likely caused by epigenetic influence. Stress-specific genes like *early growth response 1 (EGR1)* and *corticotropin releasing hormone receptor 1 (CRHR1)* were both upregulated by the stress exposure. A recent study demonstrated compelling evidence for the substantial role of small non-coding RNAs in the transgenerational transmission of traits via the paternal lineage (Gapp et al., 2014). First it was shown that the early-life trauma (MSUS) resulted in the depiction of several metabolic changes and depressive-like behaviours for the victims and their offspring. After which they showed that MSUS affected individuals showed an altered expression of several miRNAs present in sperm. The alteration of the expressions of these miRNAs was artificially replicated for mice via injection of corticosterone, mimicking a natural stress response. Finally, they demonstrated that injected these sperm miRNAs into the fertilized oocytes of wild-type mice. Showing that offspring born from these oocytes demonstrated comparable metabolic changes and depressive-like behaviours depicted by the MSUS affect individuals.

The role of miRNA in the paternal transmission of stress has been further established by another study (Rodgers et al., 2015). Here they identified nine miRNAs previously established to be increased in stressed individuals, which seemed to cause reduced reactivity of the HPA axis in their offspring. These nine miRNAs were injected into zygotes and the developmental impact was examined. Decreased reactivity of the HPA axis was noted and plasma corticosterone levels were reduced in the offspring. Furthermore, the targeted degradation of stored maternal mRNA transcripts was witnessed. It was concluded that the altered stress reactivity was caused by a combination of the miRNAs and the *ubiquitin protein ligase E3a* (Ube3a) and *Sirtuin 1* (Sirt1) gene. Both these gene are responsible for chromatin remodelling, possible allowing further epigenetic alterations to take place.

Research into the transgenerational impact of stress in rodents has produced some intriguing results. Whether these examples are simply anomalies or evidence for Lamarckian inheritance has yet to be determined. Either way, the emergence of the phenomena has been properly documented and is clearly worth the investigation. The next section will look into the appearance of similar occurrences in humans.

Stress Epigenetics in Humans

Understandably, the literature for transgenerational epigenetic of stress in humans is a mere fraction of the literature available for rodents. However, exploring the magnitude of these effects in humans does further stress the practical applicability of this knowledge. For this reason the following section will be devoted to studies performed with human participants.

Most studies available for humans have investigated the transgenerational impact of traumatic events. A 2014 study examined the epigenetic effects of PTSD on witnesses of the Rwandan genocide and their children (Perroud et al., 2014). Showing that both displayed changes of the HPA axis. Both showed lower levels of cortisol and GR, but higher levels of MR than their non-

exposed counterparts. Both exposed groups had higher methylation of CpGs within the *Nuclear Receptor Subfamily 3 Group C Member 2* (NR3C2) coding sequence, and higher methylation of the NR3C1 exon. The NR3C1 gene and NR3C2 gene are associated with expression of the GR and MR respectively (Genecards, 2018). Increased methylation of the NR3C1 gene has also been reported in victims of childhood abuse (McGowan et al., 2009). This demonstrates that the transgenerational impact of stress has a biological basis, rather than simply being behaviourally transmitted.

More recently a study was done on the transgenerational effects of holocaust exposure (Yehuda et al., 2016). It was concluded that Holocaust survivors had a 10% increase in the methylation of the FBKP5 gene. The *FK506 Binding Protein 5* (FBPK5) gene is partly responsible for the regulation of glucocorticoid sensitivity and has been documented to exhibit dampened expression in individuals suffering from PTSD or depression. Descendants of the holocaust survivors showed different methylation of the same sites of the FBPK5 gene but decreased methylation instead of more. Methylation of the FBPK5 gene causes increased activation of GR, thereby reducing its sensitivity and impairing negative feedback regulation of the receptor. This prolongs the cortisol response in stressful situations (Klengel et al., 2014).

Another study looked at the effects on the children of mothers who were exposed to intimate partner violence (IPV) during their gestational period (Radtke et al., 2011). It was demonstrated that prenatal exposure to IPV resulted in an increased methylation of the GR promotor in the blood. Prenatal stress has been linked to persistently alter the regulation of the HPA axis throughout adult life.

Evolutionary Benefits of Transgenerational Inheritance of Traits

The role of epigenetics mechanisms and their positive influence on adaptability has been well established. To list of few functions: epigenetics cause increased plasticity of the immune response (Kondilis-Mangum & Wade, 2013), DNA methylation plays a critical role in the conditioning of fear and memory (Levenson et al., 2006; Miller & Sweatt, 2007), and both DNA methylation and histone acetylation play a vital role in the normal development of a foetus. Both targeted deletion of the histone acetyltransferase Gcn5 gene and deletion of DNMT1 have lethal consequences in mice embryo (Li et al., 1993; Bu et al, 2007). Epigenetic mechanisms maintain patterns of parent-of-origin expression, exhibited by maternally or paternally imprinted genes. Apt silencing of either maternal or paternal alleles play an essential role in the proper development of a newborn (Biniszkiewicz et al., 2002; Jackson-Grusby et al., 2001). Clearly, the vital function of epigenetics has been demonstrated. However, the evolutionary role of the transgenerational transfer of epigenetic markers is not as irrefutably proven.

The potential advantages of epigenetic inheritance are easily imagined. Adaption could theoretically occur throughout an entire population in a single generation, opposed to a beneficial mutation, which is limited to a single individual, and often takes a large number of generations to be pronounced in a population. Especially in a highly dynamic environment with short-lived environmental changes, transgenerational epigenetics could be hugely beneficial for organisms due to its rapid emergence and easy reversibility. Some intra-species population differences in epigenetic marks have been discovered in both mice and humans (Heyn et al., 2013; Oey et al., 2015). These environmentally specific patterns would imply an adaptive aspect to epigenetics. However, evidently, there are many systems in place aimed at specifically eradicating the possibility of germ line transmission. Demethylation events, germline reprogramming and embryonic reprogramming are all in place to prevent the transgenerational transfer of acquired traits. This would suggest that examples of transgenerational transfer are simply errors caused by the malfunctioning of these biological systems. However, some examples seem to be too consistent, specific or beneficial for this to be the case. In zebrafish, for example, the paternal germline is specifically exempt from demethylation, leaving seemingly deliberate room for transgenerational epigenetic inheritance (Jiang et al.,

2015; Potok et al., 2013). The offspring of rats affected by fibrogenic liver damage showed increased H3K27me3 at PPARg chromatin (Seki, 2013). PPARg is a receptor which inhibits fibrogenesis (Zardi et al., 2013), allowing the possibility that these chromatin modifications are in place to protect offspring from the same dangers their parents faced. Furthermore, offspring of mice affected by early-life MSUS trauma exhibited improved goal-directed behaviour, as well as better behavioural flexibility (Gapp et al., 2014). Epigenetic regulation of the previously mentioned, BDNF gene was determined to be used for inducing fear memory (Lubin et al., 2008). Perhaps the transgenerational effects of DNA methylation of the BDNF gene exist because they offer rapid adaption to a fearful stimulus. It has already been documented that mice fear smells that their parents associated with fear (Dias & Ressler, 2013). The previously discussed study on Holocaust survivors also shows that while the victims themselves suffered from increased methylation and therefore dampening of the FBPK5 gene, their offspring actually exhibited less methylation of the same areas. This could indicate an adaptive mechanism, aimed at desensitizing the offspring against the potential trauma they might also experience. In plants such an adaptive response to stress, through epigenetic germline transmission, has been observed (Boyko & Kovalchuk, 2011). To infer that therefore a similar system could be in place for animals is nothing more than surmise, but the possibility is definitely still out there. It does seem that transgenerational epigenetic can serve as an adaptive advantage. This allows for the possibility that these transmissions are not mere anomalies allowed by the flawed nature of biological mechanisms.

Conclusion

This paper has explored the scope of the transgenerational epigenetic impact of stress. A number of mechanisms and consequences have been extrapolated from the available literature. Reduced mRNAs and increased methylation of certain promoter areas like MR and GR have proven to be a recurrent finding. Methylation of genes like the FBPK5, NR3C1 and NR3C2 gene, which regulate the expression and sensitivity of the MR and GR have also shown to result from the transgenerational effects of stress. Furthermore, increased secretion of ACTH by increased activity of CRH and AVP has been reported, which elevates the activity of the HPA axis. CRHR1 also demonstrated increased activity, further bolstering this effect. The elevation of HPA axis activity seems to be a pivotal consequence of ancestral stress exposure. Methylation of the BDNF gene, which can result in multiple psychopathological conditions, has also been identified multiple times as a symptom. As well as altered expression of the Ube3a and Sirt1 gene which are both responsible for chromatin remodelling. Alteration of the HPA axis activity via a variety of epigenetic mechanism seems to be a change induced by stress experienced by previous generations. Other consequences include weight gain, dampened corticosterone response, various behavioural issues and altered plasma glucose levels. The most compelling origin of the transgenerational impact of stress has been via miRNAs transmitted through sperm. Methylation and histone modification induced in the progeny are also apparent but are often caused by miRNAs.

It is possible that the existence of the transgenerational impact of stress is allowed because it allows for the rapid adaption to a dynamic environment. It has been shown that some transgenerational epigenetic effects are highly consistent and provide important developmental functions, like the trimethylation the H3K27 protein. However, for the specific case of stress-induced epigenetic changes this has yet to be established. Examples of stress-induced transgenerational effects affecting the progeny in a potentially useful manner have been established, but it is too soon to draw any concurrent conclusions on the matter.

Discussion

Although compelling evidence for the transgenerational epigenetic impact of stress is available, the extent of this phenomenon is still up for discussion. Most of the research performed on the matter has been on rodents, and some have questioned the magnitude of its impact. For instance, it has been shown that IVF-born mice

barely exhibited any of the effects attributed to epigenetic transgenerational effects of stress (Dietz et al., 2011). A very recent study failed to find any classical epigenetic alterations in the offspring of stress-affected rats, even though they did exhibit the phenotype (Carier et al., 2018). It is possible that a number of findings have been affected by variables not accounted for. Especially in humans, the occurrence has been demonstrated to be far from consistent. One of the most iconic examples of transgenerational epigenetics in humans - the Dutch Famine Birth Cohort study (Lumey et al., 1995) - has later been largely refuted by the same author (Stein & Lumey, 2000). It is quite obvious that there is still much to learn about transgenerational epigenetics and its propagation by stress. The field of transgenerational epigenetics is exciting and promising and it's hard to deny the potential evolutionary benefit of such a mechanism. That being said, more discoveries need to be unveiled before Lamarckism can truly become accepted as a fundamental force of evolution.

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