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DNA Methylation in Huntington's Disease: Implications for Transgenerational Effects

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Abstract

Huntington's disease (HD) is a devastating, neurodegenerative disorder caused by a CAG repeat mutation in the *HTT* gene. A growing body of evidence suggests that epigenetic modifications play a key role in HD pathogenesis. Expression of the disease protein, huntingtin, leads to extensive transcriptional dysregulation due to disruption of histone-modifying complexes and altered interactions with chromatin-related factors. Such epigenetic mechanisms also readily respond to environmental factors, which are now thought to influence the risk, onset and progression of neurodegenerative disorders, including HD. DNA methylation is an epigenetic modification that has been studied intensively, however, its role in HD is just emerging. In this review, DNA methylation differences associated with HD will be summarized, as well as the role of environmental factors to alter DNA methylation in a manner that could alter disease phenotypes. Further, transgenerational epigenetic inheritance will be discussed in the context of relevant environmental factors and their potential links to HD. The study of epigenetic states in HD presents an opportunity to gain new insights into risk factors and pathogenic mechanisms associated with HD, as well as to inform about treatment options.

Keywords

DNA methylation; epigenetic; transgenerational; neurodegenerative

I. Introduction

Over the past decade, there has been mounting interest in the roles of epigenetic factors in the pathological mechanisms of neurodegenerative diseases [1, 2]. This is especially true for Huntington's disease (HD), in which the disease protein, huntingtin (Htt) has been shown to alter a wide range of epigenetic marks, including histone modifications (i.e. acetylation, methylation and ubiquitination), and, more recently, DNA methylation [2, 3]. These changes are associated with transcriptional disruption and are thought to lead to ensuing disease phenotypes. Despite HD being a single gene disorder, there is enormous variability in disease onset and severity, even in patients with the identical CAG repeat number,

suggesting that other genetic and/or environmental factors can influence disease symptoms. Environmental triggers also cause epigenetic changes that can alter gene expression, and DNA methylation is one particular mark that can link such triggers to behavioral outcomes. This mini review will discuss DNA methylation alterations associated with HD, as well as pertinent environmental factors that can also change DNA methylation. Environmental-induced epigenetic changes can have long-term consequences that could persist in to subsequent generations. Hence, the idea that environmental-induced DNA alterations can elicit transgenerational effects will also be discussed, including a focus on histone deacetylase (HDAC) inhibitors.

2. DNA methylation

DNA methylation is one of the oldest known, and most intensely studied, epigenetic modifications in mammals and is a critical player in the proper regulation of gene expression and gene silencing [4]. Although DNA methylation of promoters clearly can alter gene expression, distal regulatory sites also have an important role in gene regulation [5]. DNA methylation involves the addition of a methyl group at the 5 position on the pyrimidine ring of cytosines, creating 5-methylcytosine (5-mC) [4]. These modifications primarily occur at cytosine-phosphate-guanine (CpG) islands. Recently, however, non-CpG methylation has received increased attention and might also be important for transcriptional regulation [6]. Apart from cytosines, there are also reports of guanine and adenine methylation, resulting in 7-methylguanine (7-mG) and 3-methyladenine (3-MA), respectively, and these may contribute to normal and aberrant regulation of transcription. The recent discovery of 5-hydroxymethylcytosine (5hmC), an oxidation product of 5mC and potential epigenetic modifier, has broadened the scope of these effects in neurodegenerative diseases [7].

The methylation reaction of cytosines is catalyzed by a class of enzymes called DNA methyltransferases (DNMTs), which transfer the methyl group from *S*-adenosylmethionine to the fifth position on the cytosine ring. Five members of the DNMT family have been identified in mammals: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L. However, DNMT2 and DNMT3L are not thought to function as cytosine methyltransferases, with DNMT3L being a catalytically-inactive member, and DNMT2 thought to control methylation of tRNA [8]. It is believed that DNA methylation patterns initiated during embryogenesis and development occur via *de novo* DNMTs (DNMT3a and DNMT3b), which catalyze the methyl transfer onto an unmethylated DNA template [9]. DNMT1, on the other hand, is the “maintenance” methylation enzyme, which copies DNA marks from a hemi-methylated template and which has major importance preserving methylation patterns in adult tissues, including post mitotic cells in the brain. DNMTs are expressed throughout neural development and promote neuronal survival and plasticity. Recent studies have revealed that mutations associated with abnormal DNMT1 protein folding and impaired functions of the *DNMT1* gene lead to hereditary neurodegeneration [10, 11].

The classic dogma in the field has been that DNA methylation is an irreversible reaction. Although it is possible to reverse DNA methylation in replicating cells by passive demethylation by means of blocking DNMT1 activity during DNA synthesis, this mechanism would not work in post mitotic, differentiated cells. However, a growing body of

literature has provided evidence for active, replication-independent DNA demethylation [12]. Factors that have been linked to methyl group removal have remained more elusive, but include the ten-eleven translocation (TET) family enzymes and genes encoding Methyl-CpG binding domain protein 3 (*Mbd3*), Growth arrest and DNA-damage-inducible 45 (*Gadd45)* and RING finger protein 4 (*Rnf4*) [13–15].

3. HD and DNA methylation

Huntington's disease is a genetic, autosomal-dominant neurodegenerative disorder caused by a CAG repeat expansion in the coding region of the Huntingtin (*HTT*) gene. A CAG repeat number of 40 leads to the development of HD, while lengths below 35 repeats are generally considered non-pathological; 36–39 repeats show incomplete penetrance [16, 17]. The most characteristic symptom of HD is chorea, but other notable symptoms include cognitive and psychiatric deficits, which are often detectable prior to the appearance of motor abnormalities. HD is typically diagnosed during the 3rd–4th decade of life, however 5% of cases (with CAG repeats of >60) show juvenile onset [18].

The mutant *HTT* gene encodes a protein huntingtin (Htt) with an expanded polyglutamine domain. It remains unclear exactly how the mutant Htt protein leads to the degeneration of neurons and neuropathological manifestations [19], although epigenetic mechanisms have been a key feature implicated in pathology. Evidence indicates that mutant Htt has a widespread impact on gene expression, through interactions with specific transcription factors, interference with the core transcriptional machinery and posttranscriptional modifications of histones, directing the chromatin towards a more condensed state [3, 20]. Initial studies by Steffan and colleagues showed that Htt could bind the histone acetyltransferase domain of Creb-binding protein, leading to histone hypoacetylation [21]. These studies, and similar findings from other HD models [20, 22, 23], led to the idea that HDAC inhibitors may represent a relevant therapeutic strategy for HD (for review on this topic, see [2]). Additionally, studies have shown that mutant Htt can alter other histone modifications, including histone methylation [20, 24, 25]. More recent evidence has implicated DNA methylation changes in HD, which may also contribute to altered gene expression and neuronal dysfunction, as summarized below.

3.1. DNA methylation changes in HD

Several studies have reported changes in DNA methylation in association with expression of Htt protein in different HD model systems, as well as in human HD brain (Table 1). Using reduced representation bisulphate sequencing, Ng and colleagues found altered patterns of DNA methylation in mouse ST*Hdh*^{Q111} cells compared to WT^{Q7} cells [26]. Changes in DNA methylation were found at promoter, proximal and distal regulatory regions, with some sites increasing in methylation and others decreasing [26]. Further, these authors found that methylation changes at CpG-rich regions, which were largely located near the transcription start sites, were inversely correlated with gene expression and were enriched in categories of genes related to developmental processes, neuron migration, signal transduction, and cell differentiation. Similar results were found in a study from our lab using an array method in human fibroblasts from normal and HD patients [27].

Dysregulation of other methylated marks has also been studied on a global level in HD, and these may also contribute to the known transcriptional pathology of the disease. Genome-wide analysis of the 5hmC epigenetic mark showed lower levels in the striatum and cortex of YAC128 transgenic mice compared to WT controls, with the corresponding genes being related to neurogenesis, neuronal function and survival [28]. An HPLC-based method also detected differential levels of 7-mG in DNA samples from brains of two different HD mouse models, as well as in caudate DNA from HD patients [29]. Overall, it is clear that neither hyper-, nor hypomethylation is desired across the board for all genes, which highlights the need to investigate gene and CpG sequence-specific changes.

A genome-wide mapping study of the transcriptional mark, trimethyl-histone H3-lysine 4 (H3K4me3) in human HD cortex has led to the identification of an important site-specific DNA methylation change on the Hairy and enhancer of split 4 (*HES4*) gene promoter [30]. Loss of H3K4me3 at CpG-rich sequences on the *HES4* promoter was associated with excessive DNA methylation and altered expression of *HES4* and its target genes. Moreover, hypermethylation of the *HES4* promoter was correlated with measures of striatal degeneration and age-of-onset in a cohort of 25 HD brains [30].

Targeted gene-specific DNA methylation has also been studied in HD. Villar-Menedez and colleagues measured both 5mC and 5hmC contents in the 5′UTR region of the adenosine A2A receptor gene (*ADORA2A*) in the putamen of HD patients and in the striatum of R6/1 and R6/2 mice [31]. Their findings suggested that altered methylation patterns of the *ADORA2A* gene are linked to the pathological decrease of *ADORA2A* expression levels found in HD [31].

3.2. Altered DNA methylation-related gene expression in HD

Some studies have begun to explore a possible cause for DNA methylation difference by measuring expression of genes encoding DNMT enzymes in HD models. However, most of these studies showed decreased expression of DNMT genes (Table 1), which would correspond to lower levels of DNA methylation, and this was not always the case in the above-mentioned studies. Alternatively, reduced expression of genes encoding DNA demethylases could also account for increases in DNA methylation (see Table 1). One study found that *Dnmt1* expression was decreased two-fold in HD ST*Hdh*^{Q111} cells compared to WT^{Q7} cells [26]. Lowered *Dnmt1* expression in HD is supported by studies from our lab which demonstrated using real-time qPCR lower levels of *Dnmt1* in striatum and cortex of N171-82Q transgenic mice compared to littermate controls. Another study using human post-mortem brain found that *DNMT1* and *DNMT3A* were differentially co-expressed in a combined cohort of HD and Alzheimer's disease patients [32]. Different microarray datasets have also revealed decreased *Dnmt3a* expression in the striatum of R6/2 transgenic mice compared to WT controls [23, 33].

Decreased expression of *Gadd45a* has also been reported in striatum of R6/2 mice [33] and muscle from N171-82Q transgenic mice [27], although *Gadd45g*, was found to be increased in HD ST*Hdh*^{Q111} cells [26]. Finally, *Rnf4*, another gene associated with DNA demethylation, was also found to be differentially expression in HD mice from microarray studies [27, 33].

4. Environmental factors and HD disease symptoms

A review of the preclinical and clinical studies suggest that even though HD is a highly penetrant, single-gene disorder, an individual's environmental influences may significantly affect disease onset and progression [34]. Diagnosis of HD is based on clinical presentation of motor abnormalities. Age of onset is largely determined by CAG repeat number, although substantial variability remains after controlling for repeat length [35]. CAG repeat length only explains ~70% of the variability in age of onset, with up to 60% of the remaining variability being due to environmental factors [35]. Lifestyle factors, such as lack of activity, diet, stress and exposure to pollutants could contribute to the variability in the age of disease onset. Environment-mediated phenotypic changes can be considered from two different viewpoints. On one hand, environmental triggers such as stress and toxins, which are known to alter DNA methylation, could worsen disease phenotypes (Figure 1). On the other hand, the possibility that environmental interventions can protect against the effects of existing vulnerabilities (Figure 1), offers unprecedented avenues towards the enhancement of therapeutic strategies.

4.1. Negative regulators of disease phenotypes

The Venezuelan HD kindreds, which were instrumental to the localization [36] and identification [37] of the HD gene, represent the largest and best characterized HD population in the world. These kindreds have provided a wealth of genetically and phenotypically informative data about the disease. Members of the Venezuelan kindreds manifest a statistically significantly earlier age of onset (34.3 yrs) when compared to the American population (37.4 yrs) [35], although the life expectancy, in general, in Venezuela is not decreased. Most of this population of individuals live in extreme poverty, have poor diets, and are exposed to pollutants from the oil industry that also occupies much of the lake where they live. All of these environmental factors have been suggested to contribute to an earlier age of onset in these individuals [35].

Substance abuse is a risk factor for other neurodegenerative disorders [38]; however, whether substance abuse influences HD age of onset is not well established. One recent study investigated the relationships between alcohol, drug, and tobacco abuse and HD age of onset and found that alcohol and drug abuse were associated with earlier age of HD onset in women, with a trend towards an association with tobacco use, as well [39]. Smoking has also been found to be significantly associated with manifest HD in patients with intermediate CAG repeat length mutations [40].

Stress is known to exacerbate symptoms in several neurodegenerative diseases, and evidence from HD patients and mouse models supports a similar finding for HD. In patients, individuals with HD experience higher levels of stress than the general population [41, 42]. In a 5-year longitudinal study on psychological distress after predictive testing for HD, several measures related to increased stress and anxiety were found in gene-positive individuals [43]. Further, levels of the stress hormone, cortisol, were found to be higher in HD patients compared with controls [44]. Studies in mouse models have provided more detailed effects of stress on disease phenotypes. Mo and colleagues provide an excellent

review on this topic [34]. Such detailed clinical studies on stress have not yet been done in HD families, but should be guided by these important animal findings.

4.2. Positive mediators of disease phenotypes

Environmental enrichment, which enhances mental and physical activity levels, has been found to induce beneficial effects in rodent models of neurodegenerative diseases including HD (reviewed in [45]). Translation of these findings to clinical benefit has been less clear, however, recent studies have shown that physical activity can stave off symptoms in HD [46, 47]. Accordingly, a passive lifestyle of sedentary activities (e.g. watching television) was found to be correlated with an earlier age of onset [48].

Of course any drug therapy that improves symptoms in HD patients can be considered a positive environmental regulator. Since the identification of the HD gene in 1993, there have been enormous advancements in the diagnosis and understanding of the molecular and pathophysiological features of the disorder. However, there is currently no satisfactory treatment or cure for this disease. There is only one U.S. FDA-approved agent for the symptomatic management of HD, tetrabenazine [49]. The evidence for epigenetic disruptions, notably histone hypoacetylation, as a pathogenic mechanism in HD, has provided a rationale for the use of HDAC inhibitors as a novel therapeutic approach. Broadly-acting inhibitors, such as SAHA, phenylbutyrate and sodium butyrate, have been shown to impart beneficial effects in HD model systems [2]. Studies from our own lab have focused on the use of selective HDAC inhibitors as a potential therapeutic option in HD, whereby we have demonstrated beneficial effects of a novel class of HDAC inhibitors, which selectively target HDACs 1 and/or 3, in different HD mouse models [23, 27, 50].

5. Relevant environmental factors and DNA methylation

Environmental triggers exert their influence on behavior via epigenetic mechanisms. Interestingly, studies have demonstrated altered methylation patterns of DNA in response to many environmental factors that may be relevant to HD, as considered above. These include, stress, pollutants, substance abuse, physical activity and therapeutic drugs. The literature on these environmental factors and their ability to alter DNA methylation is extensive, and several excellent reviews have been previously published, as will be indicated below.

A comprehensive review of the role of environmental chemicals and pollutants on DNA methylation changes has been recently published [51]. In drugs of abuse, DNA methylation changes have been reported at particular genes of interest in response to cocaine, for example, [52], but there has not yet been a genome-wide mapping of such regulation. Alcohol abuse and cigarette smoking have certainly been associated with altered DNA methylation, including global DNA hypermethylation [53, 54].

It is well-known that stress during development and adulthood can confer long-term neurobiological and behavioral consequences, and now work from animal models provides evidence to support a role for DNA methylation in these effects (for review, see [55]). For example, exposure to chronic, unpredictable stressors in rats produces global and gene-specific hypermethylation in different regions of the brain [55]. Importantly, psychosocial

stress, which could be compared more to what HD patients experience, was found to induce long-term demethylation of the corticotropin releasing hormone genomic region [56].

Data linking exercise and altered DNA methylation suggests that there may be a possible epigenetic mechanism with regards to their protective effects [57]. One study found that individuals with physical activity ~30 min/day had a significantly higher level of global genomic DNA methylation compared to those with physical activity ≤ 10 min/day [58]. A similar genome-wide study on elderly individuals found that DNA methylation was significantly correlated with self-reported activity level [59].

Studies have shown that inhibition of HDAC enzymes could lead to DNA demethylation. Early studies showed that the histone deacetylase inhibitor, sodium butyrate, could trigger replication-independent DNA demethylation in P3HR-1 cells [60]. Since then, several papers have also provided evidence that HDAC inhibition can result in DNA demethylation [61, 62]. In our studies, we found that HDAC inhibition caused alterations in the expression of numerous DNA methylation-related genes [27]. Overall, the exact correlations between DNA methylation-related gene expression changes and global DNA methylation differences in a given system are not straightforward, which, again, underscores the need to investigate gene- and locus-specific methylation changes.

6. Transgenerational epigenetic inheritance

DNA methylation levels are dynamic during the epigenetic remodeling that takes place early in embryogenesis. After fertilization, the paternal and maternal alleles are demethylated, in part, to develop the pluripotent state of the embryonic stem cells; methylation is then re-established progressively, starting in the early post-conception period [63, 64]. Aside from imprinted genes, which retain the methylation profile of the parent of origin, it is now known that methylation clearing is not complete after fertilization, allowing a window of opportunity for other methylation marks to be maintained. Transgenerational epigenetic inheritance is the idea that epigenetic marks (i.e., DNA methylation, histone modifications) can be acquired in one generation (F0 generation), and then passed on to subsequent generations (F1, F2, F3, etc).

Epigenetic transgenerational inheritance of altered phenotypes has been observed in many species, such as worms, flies, plants, rodents and humans [65–69], suggesting that ancestral environmental exposure can influence disease epidemiology. Importantly, studies have demonstrated transgenerational effects via paternal transmission, even in humans [68, 69], and these can be detected in the F1 generation (compared to maternal transmission which requires testing of F2 and F3 generations). For paternal inheritance, environmentally induced epigenetic transgenerational inheritance requires epimutations to be present in sperm cells, because only these cells are passed on to the next generation. The best-characterized molecular mechanism for epigenetic changes to be transmitted through the germ cells involves changes in DNA methylation. These differential DNA methylation marks appear to become “imprinted-like,” such that they are not reset during germ cell specification and fertilization.

Some of the earliest literature on transgenerational effects in mammals comes from exposure to pesticides and toxins. Transgenerational effects of toxins, such as dioxins, pesticides, or hydrocarbons, has been found to be mediated via both the maternal and paternal germlines (see [70] for review). These factors impart negative effects of offspring, including increased risk for certain types of cancers, metabolic abnormalities and endocrine problems. More recently, studies have demonstrated transgenerational inheritance for environmental factors that may be relevant for HD, including stress, drugs of abuse and therapeutic drugs. Provocative studies have implicated heritability of cocaine-induced phenotypes [71]. Evidence for transgenerational effects due to stress and HDAC inhibitors is discussed in further detail below.

6.1 Paternal transgenerational effects of stress

Animal models of parental stress have examined transgenerational effects on offspring (reviewed in [55]). Males that experienced maternal separation during infancy were found to pass on their depressive-like phenotype to F1 and F2 generations of offspring [72]. These effects were linked to altered methylation of distinct genes (*MeCP2*, *CB1*, and *CRFR2*) in their sperm, with their offspring showing similar methylation patterns in brain tissue [72]. Similar studies demonstrated that offspring born to male mice exposed to social defeat stress exhibited increased anxiety- and depressive-like behaviors [73]. Males, stressed via being placed on an elevated platform, gave rise to offspring who showed behavioral deficits in association with altered DNA methylation in the frontal cortex and hippocampus [74]. Another group administered synthetic glucocorticoids (artificial stress) to males prior to conception, which resulted in global increases in non-CG methylation in their sperm [75]; the F1 generation from these males displayed significant differences in the expression of various stress-related genes [75].

6.2 Paternal transgenerational effects of HDAC inhibitors

A large body of literature has demonstrated preclinical efficacy of HDAC inhibitors in different HD mouse models [2, 23, 27, 50].. Given their beneficial effects in rodent models, we further investigated these compounds for their persistent epigenetic effects. DNA methylation changes elicited by the HDAC inhibitor, HDACi 4b, were detected in HD patient fibroblasts, as well as in germ line tissue (i.e. sperm) from male N171-82Q transgenic mice [27]. One gene in particular, Lysine (K)-specific demethylase 5D (*Kdm5d*), which was hypermethylated at several CpG loci of the *Kdm5d* gene in mouse sperm DNA from HDACi 4b treated male HD mice, showed altered expression, not only in the parent mice directly exposed to the inhibitor, but also in the cortex of their male transgenic F1 offspring [27]. When tested in a battery of behavioral assays, these F1 offspring showed improved disease phenotypes compared to F1 transgenic offspring from vehicle-treated parent mice. Among the novel aspects of these findings was the fact that HDAC inhibitors could impart beneficial effects on disease phenotypes to offspring in a transgenerational manner. This was the first study to report beneficial transgenerational effects on disease phenotypes in mammals.

7. Conclusions

This review has summarized evidence for epigenetic modifications linking mutant Htt expression and environmental exposures to behavioral outcomes. Environmental influences over a lifetime, including drug exposure, exercise, and stress, can influence disease symptoms in HD, either in a beneficial or detrimental manner. It is possible that the methylation changes elicited by these factors might converge on the same targets as Htt, and would provide a direct mechanism for their effects on disease phenotypes. An intriguing concept involves the idea that these environmental factors can leave their mark not only in the generations directly exposed to these triggers, but also in subsequent generations of offspring. Although the molecular processes involved in epigenetic inheritance of environmental exposures are still not fully identified, understanding the potential for transgenerational effects hold a great promise for the determination of disease susceptibility and the potential beneficial long-term effects of drug treatments.

Abbreviations

HD	Huntington’s disease
Htt	huntingtin
DNMT	DNA methyltransferase
HDAC	histone deacetylase

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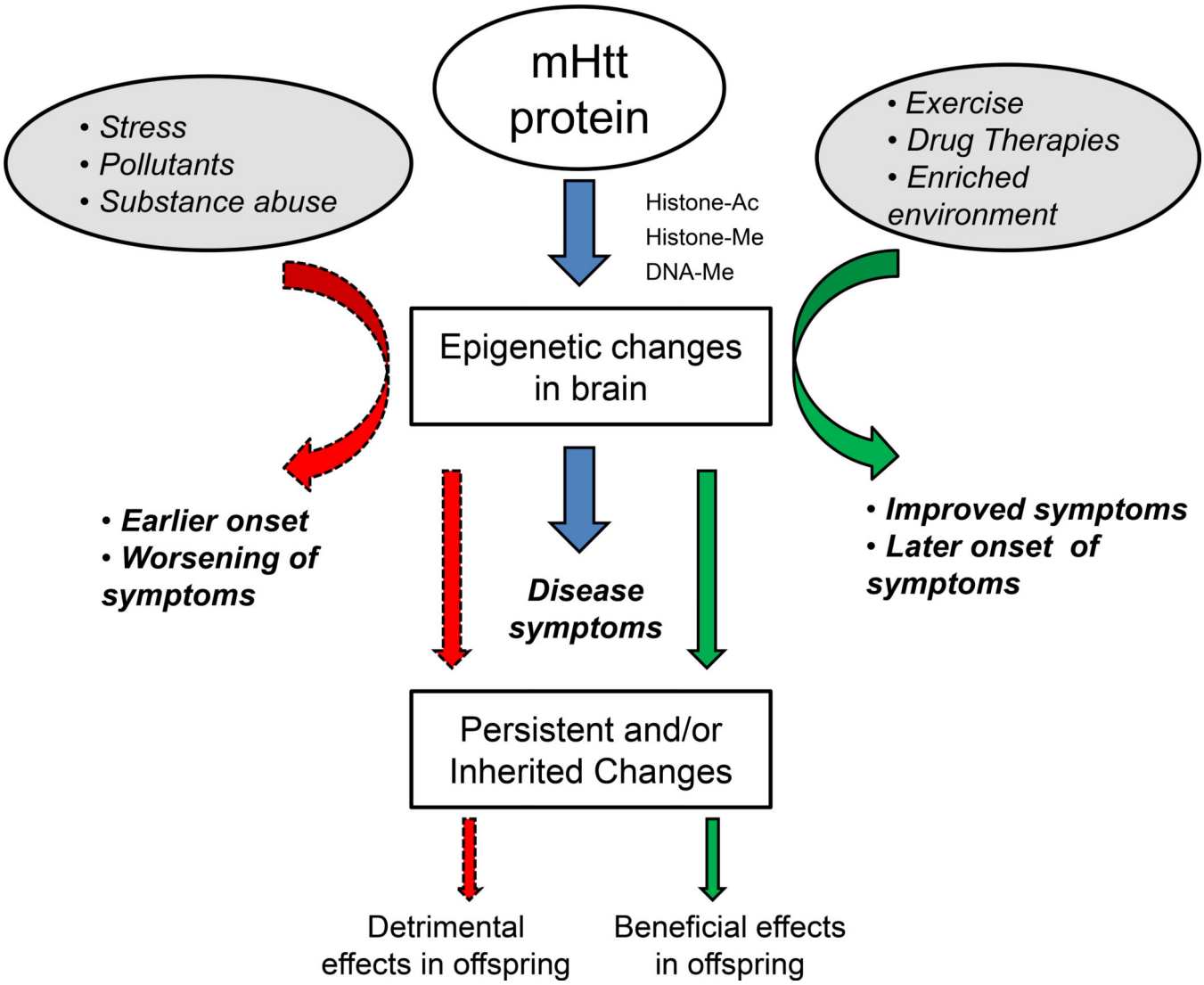

Fig 1.

Summary of environmental factors that can affect epigenetic changes in the brain and how these lead to altered behavior that might be inherited. Mutant huntingtin protein (mHtt) is known to alter several epigenetic mechanisms, including histone acetylation (Histone-Ac), histone methylation (Histone-Me) and DNA methylation (DNA-Me). These lead to epigenetic changes in the brain and ensuing disease symptoms. Many environmental factors, such as those listed, are known to improve or worsen disease symptoms in HD mouse models and humans. These factors can also influence epigenetic factors, such as DNA methylation, leading to persistent changes and could have detrimental or beneficial effects in offspring.

Table 1

DNA methylation changes related to Huntington's disease (HD).

Methylation change:	**Source:**	**HD Model:**	**Type:**	**Ref #:**
5-mC	Fibroblasts	Human	Genome-wide	27
5-mC	STHdhQ111 cells	Cells	Genome-wide	26
5-mC	Cortex	Human	*HES4 promoter*	30
5-mC/5-hmC	Putamen	Human	*ADORA2A* promoter	31
5-mC/5-hmC	Striatum	R6/1, R6/2 mice	*Adora2a* promoter	31
5-hmC	Striatum and cortex	YAC128 mice	Genome-wide	28
7-mG	Brain	R6/2, CAG140 KI mice	Genome-wide	29
7-mG	Cortex	Human	Genome-wide	29
Gene expression change:	**Source:**	**HD Model:**	**Direction of change:**	**Ref #:**
Dnmt3a	Striatum	R6/2 mice	down	23,033
Dnmt1	STHdhQ111 cells	Cells	down	26
Dnmt1	Striatum	N171-82Q mice	down	*
DNMT1	Cortex	Human	disrupted coexpression	32
DNMT3A	Cortex	Human	disrupted coexpression	32
Gadd45a	Striatum	R6/2 mice	down	33
Gadd45b	Muscle	N171-82Q mice	down	27
Gadd45g	STHdhQ111 cells	Cells	up	26
Rnf4	Striatum	R6/2 mice	down	33
Rnf4	Muscle	N171-82Q mice	up	27

5-methylcytosine, 5-mC; 5-hydroxymethylcytosine, 5-hmC;7-methyguanine, 7-mG DNA methyltransferase 1, Dnmt1; DNA methyltransferase 3a, Dnmt3a; RING finger protein 4 (RNF4)
Growth arrest and DNA-damage-inducible, alpha, Gadd45a; Growth arrest and DNA-damage-inducible, beta, Gadd45b;
Growth arrest and DNA-damage-inducible, beta, Gadd45b.

*unpublished findings.