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Review

Beyond CAG Repeats: The Multifaceted Role of Genetics in Huntington Disease

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Abstract: Huntington disease (HD) is a dominantly inherited neurodegenerative disorder caused by a CAG expansion on the huntingtin (*HTT*) gene and is characterized by progressive motor, cognitive, and neuropsychiatric decline. Recently, new genetic factors besides CAG repeats have been implicated in the disease pathogenesis. Most genetic modifiers are involved in DNA repair pathways and, as the cause of the loss of CAA interruption in the *HTT* gene, they exert their main influence through somatic expansion. However, this mechanism might not be the only driver of HD pathogenesis, and future studies are warranted in this field. The aim of the present review is to dissect the many faces of genetics in HD pathogenesis, from cis- and trans-acting genetic modifiers to RNA toxicity, mitochondrial DNA mutations, and epigenetics factors. Exploring genetic modifiers of HD onset and progression appears crucial to elucidate not only disease pathogenesis, but also to improve disease prediction and prevention, develop biomarkers of disease progression and response to therapies, and recognize new therapeutic opportunities. Since the same genetic mechanisms are also described in other repeat expansion diseases, their implications might encompass the whole spectrum of these disorders.

Keywords: gene modifiers; DNA mismatch repair; loss of interruption; somatic mutations; somatic instability; RNA toxicity; mtDNA; epigenetics

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1. Introduction

Huntington disease (HD) is a dominantly inherited neurodegenerative disorder characterized by motor, cognitive, and neuropsychiatric features [1]. It is caused by an expanded CAG repeat in exon 1 of the huntingtin (*HTT*) gene [2]. The CAG repeat length explains around 50–70% of the variability in the age at onset (AAO) of HD [3,4]. In fact, two individuals with an identical CAG repeat length can develop HD symptoms decades apart [5]. This is particularly evident in individuals carrying reduced penetrance alleles ranging from 36 to 39 CAG, who might develop HD at very late ages [6].

The unexplained variability in HD onset and pathogenesis underscores the presence of additional genetic factors that exert a crucial influence [7–9]. This highlights the necessity for further investigation into the intricate genetic landscape contributing to HD.

In the last few years, dramatic advances in sequencing technology and the availability of larger patient cohorts have moved the HD genetic field forward, identifying modifiers on chromosomes 8 and 15 mainly involved in the DNA mismatch repair pathway [10–12]. In addition, cis-acting factors in the *HTT* locus have also been discovered [13] which can modulate disease frequency [14,15] and expressivity [16,17]: particularly, the loss of the CAA interruption variant has raised great interest, especially in carriers of reduced penetrance alleles [18–22].

Genetic modifiers exert their main effect through somatic expansions of the CAG triplet, which appears to be a key driver of HD pathogenesis. Indeed, the *HTT* CAG displays somatic instability, which is greater in the brain and in areas most affected by HD (i.e., particularly the caudate) [8,23–26]. Research of surrogates of somatic expansion in peripheral tissues is mandatory, as it has been demonstrated that higher blood DNA CAG somatic expansions are associated with worse outcomes [27]. RNA-related pathology, mitochondrial DNA mutations, and epigenetic alterations are emerging aspects in HD genetics research that might contribute to the disentangling of the disease pathogenesis, as well as the identification of potential biomarkers of early disease stages and disease progression, and therapeutic targets [28,29].

In this review, we first provide an overview of the complex role of genetics in HD, in addition to the expanded CAG repeat mutation. We describe gene modifiers including cis- and trans-acting candidate genetic alterations that are thought to have a relevant role in HD AAO and progression.

As the ultimate objective to further improve knowledge in this field, we focus on targets for therapeutic interventions. The contribution of genetics to the development of therapies is fundamental if we consider that drug trials supported by genetics can potentially double clinical success rates [30,31] and two-thirds of 2021 FDA-approved drugs are supported by human genetics evidence [32].

Finally, the implications of pharmaceutical research into genetic modifiers of HD can be extrapolated to encompass other CAG/polyglutamine expansion disorders that share genetic similarities with HD, as will also be elucidated in this review.

2. *Cis*-Acting Genetic Modifiers

The typical sequence of the *HTT* repeat tract accounts for a number of CAG repeats, followed downstream by a 12-base-pair interrupting sequence (CAA-CAG-CCG-CCA) and a subsequent CCG tract.

According to the traditional view of the disease, HD pathogenesis has always been related to the toxic effect of the protein through the Poly-Q tract in the huntingtin protein. Since both CAG and CAA encode glutamine, a change in the final CAG-CAA sequence in the *HTT* locus was assumed to be irrelevant. Notwithstanding this, three concurrent genetic studies supported that CAG length is more predictive than polyglutamine length for HD AAO [12,18,19]. The Genome Wide Association Study (GWAS) on genetic modifiers from the GeM-HD consortium detected two association signals at the *HTT* locus influencing AAO [12]. The other two studies identified a variant characterized by the loss of the CAA-CAG sequence at the end of the *HTT* locus, thus extending the uninterrupted CAG length, leaving the polyglutamine length unchanged [12,18,19]. This variant was defined as the loss of interruption (LOI) and was associated with a hastened age of onset of approximately 9 years [19] Conversely, a duplication of the interruption was associated with the opposite effect, delaying the AAO.

Somatic repeat instability is the most probable mechanism mediating the LOI effect in low penetrance alleles since they were associated with increased somatic expansions in the blood and in the germline [19]. However, somatic instability might not be the only driver of the LOI. Indeed, possible alternative pathogenic processes have been suggested, such as repeat-associated non-AUG-dependent translation, CAG RNA toxicity (which will be described later in the text), and spliceosome dysregulation [33–36].

LOI has implications at different levels. From a clinical point of view, although rare (0.9% to 2.5% in fully penetrant alleles [19], LOI is especially important to certain patient sub-populations, in particular in reduced penetrance allele carriers (i.e., CAG 36-39) [37,38]. Approximately a third of symptomatic carriers of low penetrance alleles harbor this variant [19,20]. As a consequence, LOI influence could be taken into account by genetic counseling guidelines in the future when patients carry low penetrance alleles [39]. At a diagnostic level, it should be considered that current diagnostic tests do not recognize them, since they only assess the length of amplified products and do not take DNA sequence into

account [40]. Thus, developing an LOI-specific PCR assay may complement genetic testing in the future. Finally, interruptions represent a potential therapeutic target, not only in HD but also for other repeat expansion disorders [41–43]. At present, different therapeutic approaches are under investigation to interfere with somatic repeat instability in preclinical studies; the CRISPR-Cas9 technique might be used to introduce additional interruptions into the CAG tract [44,45].

Future aims in this research field might be the investigation of LOI in different population groups other than Caucasians, such as individuals from Africa and Asia. The importance of studying genetically diverse populations in the context of the disease has been recently highlighted in people of African ancestry [15,17]. More in detail, atypical allele structures characterized by either a CCG-CCA proline loss downstream to the CAG repeat [17] or by a rare haplotype recombination [15] were observed in African disease alleles, whereas they were rare or missing in people with European ancestries. In these cases an association with an anticipation of an expected AAO of approximately 7.1 years in both African and European populations [17] and an increased frequency of juvenile cases in Middle East populations of African ancestries were observed [15,46]. Moreover, a linkage disequilibrium between the number of CAA and the number of CCA variants was reported, and a double loss was associated with a much earlier AAO. CCG-CCA loss seemed to act through a mechanism different from somatic instability since it was associated with reduced somatic expansion in blood DNA [17].

These recent findings demonstrate that not only the number of CAG repeats and the polyglutamine are involved in HD pathogenesis, but there might be also other factors, such as the downstream polyproline sequence which might affect the mRNA and the encoded protein. These alternative alleles warrant further investigation since they might influence the AAO, and analyzing them in parallel with CAG length will have a great impact on genetic counseling [17].

3. *Trans*-Acting Genetic Modifiers: DNA Mismatch Repair Pathway Genes

Several GWAS conducted in the last years on large international cohorts allowed the identification of other genetic factors influencing HD AAO besides CAG length (Table 1 and Figure 1). Many of them fall under the umbrella of DNA repair genes, and more specifically are involved in the mismatch repair pathway. The Genetic Modifiers of Huntington's Disease (GeM-HD) consortium's GWAS conducted on 4082 HD patients identified three significant modifying signals at two loci, one on chromosome 8 and the others on chromosome 15, associated with the AAO [10].

Two independent signals on chromosome 15 corresponded to the gene encoding *FAN1*, which is an endo- and exonuclease involved in interstrand DNA crosslink repair [47]. *FAN1* seems to be protective in HD: *FAN1* depletion in the neurons of animal models and in HD patients accelerates repeat expansion [48]. In fact, *FAN1* variants that cause protein decreases hastened the disease onset by more than 6 years earlier than would be expected from CAG length alone, and the others that increase *FAN1* expression delayed the disease onset by 1.4 years [48]. The current thinking is that *FAN1* suppresses somatic expansion at the *HTT* locus [49,50]. Two mechanisms have been shown to mediate somatic stability in *HTT*. The first is mediated by MLH1 binding [48,50,51]; indeed, FAN1 binds to MLH1, preventing its recruitment in the mismatch repair complex, thus stabilizing CAG repeat expansion [51]. The interaction between FAN1 and MLH1 is negatively regulated by phosphorylation of FAN1's S126 residue [48]. The second is related to FAN1's nuclease activity [52,53] which is activated by PCNA and RFC on DNA harboring triplet repeat extrusions [54]. McAllister and colleagues described *FAN1* mutations to be associated with a worse HD onset and a more severe phenotype. In particular, AAO-hastening SNPs (Single Nucleotide Polymorphisms) demonstrated reduced nuclease activity [53].

FAN1 is also involved in other neurogenerative diseases caused by repeat expansion, such as certain hereditary spinocerebellar ataxias and X fragile syndrome [55–57]. Therefore, the DNA repair pathway represents a common genetic mechanism underlying repeat

expansion disorders with potential broader therapeutic implications [58]. Moreover, there is also evidence of the involvement of *FAN1* in epilepsy, bipolar disorder, schizophrenia, and autism [58]. Future works are needed to assess the therapeutic tractability of *FAN1* in attenuating *HTT* somatic expansion. A possible therapeutic target under current investigation might be the aforementioned phosphorylation of FAN1-S126.

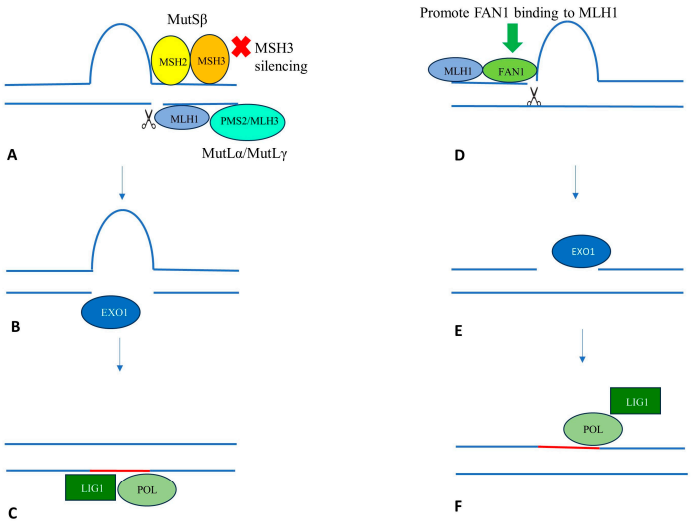

Figure 1. The role of DNA mismatch repair in repeat expansion and possible therapeutic targets. Left (**A**–**C**): MSH3 mediated repair at a CAG loopout, leading to repeat expansion. Right (**D**–**F**): FAN1 mediated repair preventing repeat expansion. FAN1 protects against repeat expansion through a mechanism that depends on its nuclease activity and binding to MLH1. See text for details.

The chromosome 8 signal observed in GeM-HD GWAS was associated with an anticipated AAO of 1.6 years earlier than expected and could correspond to *RRM2B* or *UBR5* loci. These genes are involved in the following functions implicated in HD pathogenesis: mitochondrial regulation, DNA maintenance, oxidative stress, and proteostasis.

Another study [59] confirmed the signals identified on chromosomes 8 and 15 and also found a locus at *MLH1* on chromosome 3, associated with a delay in disease onset of 0.7 years. Dominant loss of function mutations of *MLH1* are associated with Lynch syndrome [60], the most common cause of hereditary colorectal cancer; moreover, the *MLH1* gene is associated with brain CAG instability in the *Htt* knock-in mouse [61].

The GWAS study conducted on 216 and 1773 participants from the TRACK-HD and REGISTRY studies, respectively, identified an association at chromosome 5, which corresponds to *MSH3*, associated with slower disease progression [11]. As with *FAN1* and *MLH1*, *MSH3* is also involved in the DNA mismatch repair pathway [62–64] and is the first identified genetic modifier of the rate of progression in HD. In particular, Moss and colleagues demonstrated that each copy of the minor allele at the lead SNP in *MHS3* was associated with a reduction in the change in the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score and Total Functional Capacity (0.4 and 0.12 units per year, respectively). *MSH3* involvement has been demonstrated also in myotonic dystrophy type 1 [65], further underlying the common genetic background of triplet diseases. O'Reilly and collaborators have recently characterized a fully chemically modified short interfering RNA (siRNA) capable of silencing *MSH3* in both in vitro and in vivo models [66]. The application of siRNA to downregulate *MSH3* proved highly effective in inhibiting the expansion of CAG repeats within the striatum in two distinct HD murine models. This discovery presents a promising therapeutic avenue for individuals afflicted by HD and other disorders characterized by repeat expansion mutations.

Interestingly, Lee and colleagues suggested that genetic modifiers might preferentially affect motor or cognitive functions [67]. For instance, *MSH3* could mainly impact the cognitive domain, whereas *FAN1* could impact motor function. As a consequence, these

genetic modifiers might act differentially on the neuronal networks underlying diverse clinical outcomes.

In 2019, an extended GWAS study involving over 9000 HD patients from the REGISTRY and Enroll-HD cohorts confirmed the findings of the previous GeM-HD GWAS and also identified new HD onset-associated loci, corresponding to other DNA repair genes *PMS1*, *MSH3*/*DHFR*, *PMS2*, and *LIG1*, as well as *TCERG1* and *CCDC82* [12]. Interestingly, *PMS1* has been found to be a target of splice modulators, small molecules that are being investigated in HD clinical trials to reduce HTT levels, providing alternative targets to prevent CAG somatic expansion [68].

The results of these genetic studies point out the central role of the mismatch DNA repair pathway in HD pathogenesis (Figure 1). Expanded repeat sequences can form secondary structures, such as hairpins and large loops, that might induce the mismatch repair complex to act erroneously, leading to somatic expansions. In more detail, MutSβ (MSH2-MSH3) recognizes these structures and recruits MutLα (MLH1-PMS2) or MutLγ (MLH1-MLH3), endonucleases that co-ordinate excision [69]. The MutL complex erroneously creates a break in the strand opposite the loop. The polymerase then uses the strand with the loop as the template strand, thus determining the elongation of the repeat sequence. On the contrary, MutSα (MHS2-MSH3) seems not to be involved in CAG instability, since it recognizes small DNA loops, rather than the longer loops targeted by MutSβ.

MSH2, MSH6, or MLH1 depletion may cause cancer in humans, while MSH3 loss of function does not affect lifespan or cause cancer in mice [70]. Therefore, small molecules or ASOs against MSH3 might represent fruitful strategies for potential therapies for HD [71].

DNA-repair genes represent promising candidates for future therapies, and in preclinical development, MSH3 is the most encouraging target [62,72]. Moreover, since slipped DNAs occur during somatic repeat expansions, small molecules that specifically bind to these structures are under development [36].

Table 1. Genetic modifiers implicated in HD onset and progression.

Genes	Effect
FAN1	FAN1 depletion in animal models and humans accelerates repeat expansion [48]. Increased expression promotes CAG repeat stability and is associated with delayed disease onset [49,50,55]. Variants that delay or hasten disease onset [10,53].
MLH1	The MLH1 gene is associated with brain CAG instability in Htt knock-in mice [61]. MLH1 delays disease onset [59].
MSH3	Promotes somatic CAG expansions, thus contributing to an earlier onset [62–64]. Variants are implicated in disease progression [11].
PMS1, PMS2, LIG1	Variants alter disease onset [12].

4. Somatic Mutations and Mosaicism

Whereas inherited mutations are transmitted across generations, somatic mutations occur post-zygotically. They can develop throughout the entire life of an individual, leading to somatic mosaicism, a condition in which only some cells of an individual harbor the mutation [73,74]. Their role in contributing to disease pathogenesis has been first described in cancer. Recently, thanks to technical improvements such as single-cell and whole-genome sequencing, growing evidence has supported their involvement also in neurodevelopmental disorders [75,76], such as in brain malformations associated with epilepsy and intellectual disabilities [77]. Besides these conditions, it has been demonstrated that somatic mutations are involved also in normal brain aging [78] and neurodegenerative disorders [79].

The CAG repeat causing HD shows great meiotic instability and frequently increases in length across generations [80,81]. The risk of expansion is higher in spermatogenesis than

in oogenesis. This may contribute to partially explain pediatric-onset HD cases inherited by affected fathers [81,82], and the occurrence of de novo mutations from paternal intermediate alleles [83].

CAG repeat expansion is highly unstable not only in germline but also in somatic cells, thus determining somatic mosaicism. The tissue specificity of somatic repeat instability has been described in both mice models and in humans, with the striatum and cerebral cortex displaying the highest levels of somatic expansions [84–90]. Brain somatic CAG instability is associated with an earlier age at onset [90] and mounting evidence suggests that the degree of somatic repeat length in undifferentiated neurons better explains the AAO than the germline repeat [72].

Somatic instability can be investigated in peripheral tissues [27] whose alterations might mirror what happens in the brain. In a large study of nearly 750 HD mutation carriers, somatic expansions in the blood correlated with worse clinical outcomes, encompassing an earlier AAO, worse baseline motor scores, and higher disease progression scores [18]. Variants in several DNA repair genes are associated with somatic expansion, both in HD animal models [61,62,91] and HD patients [12,18,64]. Therefore, it seems reasonable that their effect might be mediated through somatic expansion of the CAG repeat. However, other factors might also contribute to drive somatic instability. A possible candidate is oxidative stress since it could modify instability rates [92]. Somatic expansions in blood samples increase with age, whereas they are minimal in fetal mutation carriers [93]. As a consequence, these findings support a computational, simulational approach proposed by Kaplan et al. to explain the onset and progression of HD [94]. According to this view, disease onset occurs once the repeat sequence has increased in length beyond a cell type-specific pathological threshold in a critical proportion of vulnerable cells to trigger toxicity and dysfunction, leading eventually to cell death [94,95]. The threshold for each specific cell type is yet to be determined. By performing quantitative analyses of CAG instability across several central nervous system (CNS) regions and peripheral post mortem tissues of HD individuals, Pinto et al. demonstrated that *HTT* CAG repeat expansion indeed occurs in all tissues analyzed, though to different extents [25]. The greatest instability was found in multiple cortical regions and neostriatum in the CNS, and liver in the periphery, the latter of which indeed affected children with highly expanded and unstable mutations [96].

The presence of CAG instability also in peripheral cells opens new ways to further investigate triplet mosaicism. Furthermore, given the central role of somatic expansions in disease progression, targeting repeat instability might have extremely relevant, even though challenging, therapeutic implications in triplet disorders [97].

Altogether, the above considerations lend support to the following hypotheses: (1) the inherited expanded *HTT*-CAG repeats undergo further expansion somatically toward a critical threshold length in vulnerable cell types [91], thus extensively and progressively affecting HD biology in a length-dependent manner [98]; (2) when the expanded CAG threshold length is reached, a mechanism is triggered that affects HD progression [94,98]; (3) in cis haplotypes may affect HD frequency and toxicity of mutant HTT in axons [13–15]; (4) factors in trans to expanded *HTT*-CAG repeats may act as disease modifiers [9–12].

5. RNA-Related Pathology

Although a great number of works demonstrated that the mHTT protein affects many cellular functions, leading to cell death and neurodegeneration, an increasing body of evidence indicates that also the mHTT RNA may contribute to toxicity [34].

Normally, two alternatively spliced transcripts emanate from the *HTT* gene. These transcripts vary in the length of their 3′ untranslated region (UTR) by 3 kilobases (kb), producing an identical HTT protein. The extended transcript is primarily observed in the brain, whereas the other variant has a broader expression throughout various tissues [99]. However, a well-documented feature of HD is that HTT pre-mRNA splicing can be altered, leading to the production of different isoforms of the huntingtin protein [100,101]. Among the multiple shorter versions of the HTT, exon 1 is the most toxic N-terminal

fragment [102,103]. This short exon 1 transcript (HTT1a) was described in mice models and post mortem brains of subjects with HD [104]; its level is proportional to the CAG repeat length, it is only seen in mutant alleles, and it produces the pathogenic and highly aggregation-prone exon 1 huntingtin protein [105]. In mice models expressing the human *HTT* gene (YAC128 mice), HTT1a was found both in large nuclear RNA clusters and as single transcripts in the cytoplasm [106]. The levels of exon 1 HTT in YAS128 mice correlated with HTT aggregation, suggesting the hypothesis that exon 1 HTT initiates the aggregation process. These findings might have profound therapeutic implications, underlying the importance of specifically targeting the exon 1 protein instead of the full-length HTT mRNA.

Another characteristic of RNA pathology in HD is related to the production of toxic RNA species. Indeed, repeat-containing RNAs may agglomerate in the nucleus as foci or undergo aberrant repeat-associated non-AUG (RAN) translation. RAN translation refers to a phenomenon in which RNA sequences containing repetitive elements are translated into proteins without the requirement of a traditional start codon (ATG) that usually initiates protein translation. As a result, short, abnormal proteins with repeated amino acid sequences are produced. This process was documented in certain genetic disorders associated with repeat expansion, such as HD, myotonic dystrophy, and amyotrophic lateral sclerosis [33,107,108]. In HD, these elements accumulate most abundantly in regions associated with HD pathology, such as the striatum, the white matter, and the cerebellum in juvenile HD [108]. RNA translation adds a further layer of complexity to the molecular mechanisms underlying HD and other neurodegenerative diseases. The abnormal proteins generated through RAN translation might contribute to cellular dysfunction and toxicity, ultimately contributing to neurodegeneration [109,110]. However, another study showed that HD knock-in mice lack RAN-mediated toxicity [111]; thus, the role of this form of translation in HD pathogenesis requires further confirmation.

In summary, RNA plays a critical role in the development and progression of HD. The expanded CAG repeat within the *HTT* gene leads to various RNA-related abnormalities, including altered transcription, RNA processing, and the generation of toxic RNA species. Harnessing the understanding of these RNA-related mechanisms has led to the development of potential therapeutic strategies aimed at mitigating the effects of the disease. For instance, pharmaceutical companies have been developing *HTT*-lowering therapies, aiming at specifically targeting and leading to HTT mRNA degradation including small interfering RNA molecules (siRNAs) and antisense oligonucleotides (ASOs). These therapies aim to finally reduce the production of the toxic proteins, potentially slowing down or halting the progression of the disease [1,71].

6. Mitochondrial Mutations

Robust evidence demonstrates that mitochondrial dysfunction plays a central role in normal aging and neurodegenerative diseases [112,113]. Mitochondrial DNA (mtDNA), compared to nuclear DNA (nDNA), is 10 times more susceptible to mutations and plays a key role in the development and progression of neurodegenerative disorders, including HD [114]. Additionally, it is worth noting that the repair mechanisms for mtDNA and nDNA differ [115] and there is still a dearth of studies focusing on the assessment of mtDNA repair machinery [116].

Mitochondrial alterations are well documented in HD [117,118] and several molecular mechanisms have been hypothesized to connect mHTT to mitochondrial dysfunction [119]. Disentangling these mechanisms is of particular interest since promoting mitochondrial function might represent a complementary approach to target the causative gene mutation in HD. Mitochondria are crucial for energy metabolism and their proteins are encoded by both nDNA and mtDNA. mtDNA damage has been described in the brain of HD mouse models [120,121], adult HD [122,123], and pediatric HD patients [124]. Moreover, nDNA and mtDNA alterations have been reported also in peripheral tissues, suggesting a possible role as easily accessible biomarkers of disease progression and therapeutic monitoring. In

this field, several open issues should be addressed, namely which kind of peripheral cell is the most promising (e.g., different subpopulations of leukocytes), the different roles as potential biomarkers of nDNA and mtDNA, and the correlation with scores of disease severity and disease progression.

Different works have described alterations in mtDNA amounts in leukocytes of HD patients [125–128]. However, the results of the first studies were not conclusive, showing both a depletion [125,127,128] and an increase in the mtDNA copy number [126,129]. An opposed alteration in mtDNA amount between leukocytes and fibroblasts in the same patients was reported [129]. These discrepancies could have been due to differences in the size of populations, techniques, or type of cells considered. Moreover, an association between mtDNA alterations and disease severity was not clearly defined. On the other hand, results from another study conducted on peripheral blood mononuclear cells (PBMC) of 36 HD patients were further in contrast to the works aforementioned [130]. Askeland and colleagues found a reduction in genes associated with aerobic metabolism in PBMC of HD patients, thus suggesting mitochondrial dysfunction. However, they showed reduced mtDNA damage in HD patients compared to healthy controls, whereas nDNA was severely damaged in patients. An inverse correlation between nDNA damage and total functional capacity (TFC) was described.

A study conducted on a large population of 1549 HD patients shed more light on this research field [28]. A significant increase in mtDNA heteroplasmies of predicted pathogenicity was found in the lymphoblast of HD patients, which correlated with HD stage and disease severity, determined by motor and cognitive scores and TFC. Moreover, with a 6-year longitudinal follow-up of a subgroup of 169 HD patients, the authors found that the expansion of pathogenic mtDNA heteroplasmies was correlated with disease progression, evaluated by means of decline in TFC, motor score, and symbol digit modality test results.

In conclusion, mtDNA alterations in peripheral tissues could provide an accessible biomarker of disease progression in HD. The implications might be even broader in the field of triplet disorders since the observations have been extended also to other polyglutamine diseases [127].

7. Epigenetics

Epigenetics describes heritable modifications that alter the accessibility of DNA and regulate gene transcription without changing the underlying DNA sequence. Methylation is the most studied epigenetic alteration and consists of the binding of a methyl group to CpG dinucleotide in the promoter region of a gene, thus reducing its transcription.

Various DNA methylation alterations in neurological diseases are associated with disease activity, disease progression, and clinical outcomes, and may have a prognostic or diagnostic value [131]. Different works underlined the potential role of methylation in HD, both in animal models and in humans. Through the analysis of the cortex DNA methylation profiles in HD patients, De Souza and colleagues found an association between DNA methylation and the age of disease onset [132]. However, they failed to identify any HD-associated DNA methylation changes at probe sites.

Transcriptional dysregulation is a major characteristic of early HD, preceding neuronal death, demonstrated both in human post mortem tissues and mouse models [23,133]. The polyglutamine-expanded *HTT* might be directly involved in these expression changes. Indeed, in cell lines derived from mouse striatal neurons, the presence of mutant HTT was associated with significant changes in DNA methylation, with the downregulation of the expression of genes associated with neurogenesis, and neuronal differentiation, such as SOX2, PAX6, and NES [134]. mHTT might be involved in the regulation of DNA methyltransferases [134,135] and it could also bind directly to DNA, thus driving the recruitment of epigenetic modifiers [136]. In primary neuronal models of HD, mHTT increased the levels of DNA methylation in the promoters of BDNF, an essential neurotrophic factor [137].

Conversely, pharmacological inhibition of DNA methyltransferase decreased methylation, thus restoring BDNF transcription.

If on one hand there is evidence that polyglutamine-expanded HTT is associated with transcription regulation of key genes, on the other hand, the epigenetic status in and around the CAG repeat also plays a relevant role. To the best of our knowledge, at present, the largest study on DNA methylation in HD was conducted by Lu and colleagues in seven DNA sources from three species, namely human, mouse, and sheep models [29]. First of all, they demonstrated that manifest HD, but not premanifest, was associated with increased epigenetic age in human blood DNA. This is in line with previous evidence from human brain samples [138]. Secondly, epigenome-wide association studies found that HTT is the main locus involved in all three species. This finding might help to explore disease pathogenesis. Moreover, investigating whether methylation at this locus contributes to drive somatic expansion would be of great interest in research. Finally, methylation levels at three loci (PEX14, GRIK4, and COX4I2) were significantly associated with motor progression in manifest HD.

Post-translational histone modifications (e.g., acetylation) are also epigenetic events that have been well studied in HD. For instance, a reduction in histone acetylation and in specific loci has been documented in several HD models and human HD biosamples [24]. In addition, there is also evidence that many RNA species can contribute to HD pathogenesis which has been described elsewhere [139,140]. One of these species, i.e., lncRNAs, RNA molecules exceeding 200 nucleotides in length, have been observed to exhibit notably higher expression in the brain, playing intricate roles in a multitude of cellular processes, including functions pertaining to transcriptional regulation and chromatin modulation.

In conclusion, assessing the diagnostic relevance of epigenetic regulations in HD through DNA methylation and RNA species might represent an attractive target for future therapeutic intervention.

8. Conclusions and Future Perspectives

The field of genetic modification research has expanded enormously in the last years, significantly enhancing our comprehension of somatic instability as the pivotal driver of HD pathogenesis. This newfound knowledge not only holds profound implications for advancing our understanding of other repeat expansion disorders but also offers a wide range of therapeutic prospects for these diseases. In the near future, it is imperative to delve into alternative pathways of pathogenesis that extend beyond somatic instability and to explore the involvement of other genetic factors such as the ones discussed in this review. These avenues of investigation not only promise to disentangle HD pathogenesis but also present opportunities for the development of disease progression biomarkers and innovative therapeutic targets. The multifaceted nature of HD genetics demands a comprehensive approach, and continued extensive research on genetic modifiers holds the key to unlocking new horizons in our quest to cure this devastating disorder.

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References

1. Tabrizi, S.J.; Flower, M.D.; Ross, C.A.; Wild, E.J. Huntington Disease: New Insights into Molecular Pathogenesis and Therapeutic Opportunities. *Nat. Rev. Neurol.* **2020**, *16*, 529–546. [CrossRef]
2. MacDonald, M.E.; Ambrose, C.M.; Duyao, M.P.; Myers, R.H.; Lin, C.; Srinidhi, L.; Barnes, G.; Taylor, S.A.; James, M.; Groot, N.; et al. A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* **1993**, *72*, 971–983. [CrossRef]
3. Andrew, S.E.; Goldberg, Y.P.; Kremer, B.; Telenius, H.; Theilmann, J.; Adam, S.; Starr, E.; Squitieri, F.; Lin, B.; Kalchman, M.A.; et al. The Relationship between Trinucleotide (CAG) Repeat Length and Clinical Features of Huntington's Disease. *Nat. Genet.* **1993**, *4*, 398–403. [CrossRef]
4. Keum, J.W.; Shin, A.; Gillis, T.; Mysore, J.S.; Abu Elneel, K.; Lucente, D.; Hadzi, T.; Holmans, P.; Jones, L.; Orth, M.; et al. The HTT CAG-Expansion Mutation Determines Age at Death but Not Disease Duration in Huntington Disease. *Am. J. Hum. Genet.* **2016**, *98*, 287–298. [CrossRef]
5. Squitieri, F. Neurodegenerative Disease: "fifty Shades of Grey" in the Huntington Disease Gene. *Nat. Rev. Neurol.* **2013**, *9*, 421–422. [CrossRef]
6. Phenotypic Characterization of Individuals with 30–40 CAG Repeats in the Huntington Disease (HD) Gene Reveals HD Cases with 36 Repeats and Apparently Normal Elderly Individuals with 36–39 Repeats—PubMed. Available online: https://pubmed.ncbi.nlm.nih.gov/8659522/ (accessed on 20 April 2024).
7. Djoussé, L.; Knowlton, B.; Hayden, M.; Almqvist, E.W.; Brinkman, R.; Ross, C.; Margolis, R.; Rosenblatt, A.; Durr, A.; Dode, C.; et al. Interaction of Normal and Expanded CAG Repeat Sizes Influences Age at Onset of Huntington Disease. *Am. J. Med. Genet. A* **2003**, *119A*, 279–282. [CrossRef]
8. Wexler, N.S.; Lorimer, J.; Porter, J.; Gomez, F.; Moskowitz, C.; Shackell, E.; Marder, K.; Penchaszadeh, G.; Roberts, S.A.; Gayán, J.; et al. Venezuelan Kindreds Reveal That Genetic and Environmental Factors Modulate Huntington's Disease Age of Onset. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 3498–3503. [CrossRef]
9. Gusella, J.F.; Macdonald, M.E.; Lee, J.M. Genetic Modifiers of Huntington's Disease. *Mov. Disord.* **2014**, *29*, 1359–1365. [CrossRef]
10. Lee, J.M.; Wheeler, V.C.; Chao, M.J.; Vonsattel, J.P.G.; Pinto, R.M.; Lucente, D.; Abu-Elneel, K.; Ramos, E.M.; Mysore, J.S.; Gillis, T.; et al. Identification of Genetic Factors That Modify Clinical Onset of Huntington's Disease. *Cell* **2015**, *162*, 516–526. [CrossRef]
11. Moss, D.J.H.; Tabrizi, S.J.; Mead, S.; Lo, K.; Pardiñas, A.F.; Holmans, P.; Jones, L.; Langbehn, D.; Coleman, A.; Santos, R.D.; et al. Identification of Genetic Variants Associated with Huntington's Disease Progression: A Genome-Wide Association Study. *Lancet Neurol.* **2017**, *16*, 701–711. [CrossRef]
12. Lee, J.M.; Correia, K.; Loupe, J.; Kim, K.H.; Barker, D.; Hong, E.P.; Chao, M.J.; Long, J.D.; Lucente, D.; Vonsattel, J.P.G.; et al. CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset. *Cell* **2019**, *178*, 887–900.e14. [CrossRef]
13. Squitieri, F.; Andrew, S.E.; Goldberg, Y.P.; Kremer, B.; Spence, N.; Zelsler, J.; Nichol, K.; Theilmann, J.; Greenberg, J.; Goto, J.; et al. DNA Haplotype Analysis of Huntington Disease Reveals Clues to the Origins and Mechanisms of CAG Expansion and Reasons for Geographic Variations of Prevalence. *Hum. Mol. Genet.* **1994**, *3*, 2103–2114. [CrossRef]
14. Brady, S.T.; Mesnard-Hoaglin, N.A.; Mays, S.; Priego, M.; Dziechciowska, J.; Morris, S.; Kang, M.; Tsai, M.Y.; Purks, J.L.; Klein, A.; et al. Toxic effects of mutant huntingtin in axons are mediated by its pro line-rich domain. *Brain* **2024**, *147*, 2098–2113. [CrossRef]
15. Squitieri, F.; Mazza, T.; Maffi, S.; De Luca, A.; AlSalmi, Q.; AlHarasi, S.; Collins, J.A.; Kay, C.; Baine-Savanhu, F.; Landwhermeyer, B.G.; et al. Tracing the Mutated HTT and Haplotype of the African Ancestor Who Spread Huntington Disease into the Middle East. *Genet. Med.* **2020**, *22*, 1903–1908. [CrossRef]
16. Becanovic, K.; Nørremølle, A.; Neal, S.J.; Kay, C.; Collins, J.A.; Arenillas, D.; Lilja, T.; Gaudenzi, G.; Manoharan, S.; Doty, C.N.; et al. A SNP in the HTT Promoter Alters NF-KB Binding and Is a Bidirectional Genetic Modifier of Huntington Disease. *Nat. Neurosci.* **2015**, *18*, 807–816. [CrossRef]
17. Dawson, J.; Baine-Savanhu, F.K.; Ciosi, M.; Maxwell, A.; Monckton, D.G.; Krause, A. A Probable Cis-Acting Genetic Modifier of Huntington Disease Frequent in Individuals with African Ancestry. *HGG Adv.* **2022**, *3*, 100130. [CrossRef]
18. Ciosi, M.; Maxwell, A.; Cumming, S.A.; Hensman Moss, D.J.; Alshammari, A.M.; Flower, M.D.; Durr, A.; Leavitt, B.R.; Roos, R.A.C.; Holmans, P.; et al. A Genetic Association Study of Glutamine-Encoding DNA Sequence Structures, Somatic CAG Expansion, and DNA Repair Gene Variants, with Huntington Disease Clinical Outcomes. *EBioMedicine* **2019**, *48*, 568–580. [CrossRef]
19. Wright, G.E.B.; Collins, J.A.; Kay, C.; McDonald, C.; Dolzhenko, E.; Xia, Q.; Bečanović, K.; Drögemöller, B.I.; Semaka, A.; Nguyen, C.M.; et al. Length of Uninterrupted CAG, Independent of Polyglutamine Size, Results in Increased Somatic Instability, Hastening Onset of Huntington Disease. *Am. J. Hum. Genet.* **2019**, *104*, 1116–1126. [CrossRef]
20. Findlay Black, H.; Wright, G.E.B.; Collins, J.A.; Caron, N.; Kay, C.; Xia, Q.; Arning, L.; Bijlsma, E.K.; Squitieri, F.; Nguyen, H.P.; et al. Frequency of the Loss of CAA Interruption in the HTT CAG Tract and Implications for Huntington Disease in the Reduced Penetrance Range. *Genet. Med.* **2020**, *22*, 2108–2113. [CrossRef]
21. Ingannato, A.; Bagnoli, S.; Bessi, V.; Ferrari, C.; Mazzeo, S.; Sorbi, S.; Nacmias, B. Intermediate Alleles of HTT: A New Pathway in Longevity. *J. Neurol. Sci.* **2022**, *438*, 120274. [CrossRef]
22. Moschini, V.; Mazzeo, S.; Bagnoli, S.; Padiglioni, S.; Emiliani, F.; Giacomucci, G.; Morinelli, C.; Ingannato, A.; Freni, T.; Belloni, L.; et al. CAG Repeats Within the Non-Pathological Range in the HTT Gene Influence Personality Traits in Patients With Subjective Cognitive Decline: A 13-Year Follow-Up Study. *Front. Psychiatry* **2022**, *13*, 826135. [CrossRef]

23. Cha, J.H.J. Transcriptional Signatures in Huntington's Disease. *Prog. Neurobiol.* **2007**, *83*, 228–248. [CrossRef]
24. Hyeon, J.W.; Kim, A.H.; Yano, H. Epigenetic Regulation in Huntington's Disease. *Neurochem. Int.* **2021**, *148*, 105074. [CrossRef]
25. Pinto, R.M.; Arning, L.; Giordano, J.V.; Razghandi, P.; Andrew, M.A.; Gillis, T.; Correia, K.; Mysore, J.S.; Grote Urtubey, D.M.; Parwez, C.R.; et al. Patterns of CAG Repeat Instability in the Central Nervous System and Periphery in Huntington's Disease and in Spinocerebellar Ataxia Type 1. *Hum. Mol. Genet.* **2020**, *29*, 2551–2567. [CrossRef]
26. Mätlik, K.; Baffuto, M.; Kus, L.; Deshmukh, A.L.; Davis, D.A.; Paul, M.R.; Carroll, T.S.; Caron, M.C.; Masson, J.Y.; Pearson, C.E.; et al. Cell-Type-Specific CAG Repeat Expansions and Toxicity of Mutant Huntingtin in Human Striatum and Cerebellum. *Nat. Genet.* **2024**, *56*, 383–394. [CrossRef]
27. Cannella, M.; Maglione, V.; Martino, T.; Ragona, G.; Frati, L.; Li, G.M.; Squitieri, F. DNA Instability in Replicating Huntington's Disease Lymphoblasts. *BMC Med. Genet.* **2009**, *10*, 11. [CrossRef]
28. Wang, Y.; Guo, X.; Ye, K.; Orth, M.; Gu, Z. Accelerated Expansion of Pathogenic Mitochondrial DNA Heteroplasmies in Huntington's Disease. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2014610118. [CrossRef]
29. Lu, A.T.; Narayan, P.; Grant, M.J.; Langfelder, P.; Wang, N.; Kwak, S.; Wilkinson, H.; Chen, R.Z.; Chen, J.; Simon Bawden, C.; et al. DNA Methylation Study of Huntington's Disease and Motor Progression in Patients and in Animal Models. *Nat. Commun.* **2020**, *11*, 4529. [CrossRef]
30. Nelson, M.R.; Tipney, H.; Painter, J.L.; Shen, J.; Nicoletti, P.; Shen, Y.; Floratos, A.; Sham, P.C.; Li, M.J.; Wang, J.; et al. The Support of Human Genetic Evidence for Approved Drug Indications. *Nat. Genet.* **2015**, *47*, 856–860. [CrossRef]
31. King, E.A.; Wade Davis, J.; Degner, J.F. Are Drug Targets with Genetic Support Twice as Likely to Be Approved? Revised Estimates of the Impact of Genetic Support for Drug Mechanisms on the Probability of Drug Approval. *PLoS Genet.* **2019**, *15*, e1008489. [CrossRef]
32. Ochoa, D.; Karim, M.; Ghoussaini, M.; Hulcoop, D.G.; McDonagh, E.M.; Dunham, I. Human Genetics Evidence Supports Two-Thirds of the 2021 FDA-Approved Drugs. *Nat. Rev. Drug Discov.* **2022**, *21*, 551. [CrossRef]
33. Zu, T.; Gibbens, B.; Doty, N.S.; Gomes-Pereira, M.; Huguet, A.; Stone, M.D.; Margolis, J.; Peterson, M.; Markowski, T.W.; Ingram, M.A.C.; et al. Non-ATG-Initiated Translation Directed by Microsatellite Expansions. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 260–265. [CrossRef]
34. Martí, E. RNA Toxicity Induced by Expanded CAG Repeats in Huntington's Disease. *Brain Pathol.* **2016**, *26*, 779–786. [CrossRef]
35. Schilling, J.; Broemer, M.; Atanassov, I.; Duernberger, Y.; Vorberg, I.; Dieterich, C.; Dagane, A.; Dittmar, G.; Wanker, E.; van Roon-Mom, W.; et al. Deregulated Splicing Is a Major Mechanism of RNA-Induced Toxicity in Huntington's Disease. *J. Mol. Biol.* **2019**, *431*, 1869–1877. [CrossRef]
36. Nakamori, M.; Panigrahi, G.B.; Lanni, S.; Gall-Duncan, T.; Hayakawa, H.; Tanaka, H.; Luo, J.; Otabe, T.; Li, J.; Sakata, A.; et al. A Slipped-CAG DNA-Binding Small Molecule Induces Trinucleotide-Repeat Contractions In Vivo. *Nat. Genet.* **2020**, *52*, 146–159. [CrossRef]
37. Wright, G.E.B.; Black, H.F.; Collins, J.A.; Gall-Duncan, T.; Caron, N.S.; Pearson, C.E.; Hayden, M.R. Interrupting Sequence Variants and Age of Onset in Huntington's Disease: Clinical Implications and Emerging Therapies. *Lancet Neurol.* **2020**, *19*, 930–939. [CrossRef]
38. Mazzeo, S.; Emiliani, F.; Bagnoli, S.; Padiglioni, S.; Conti, V.; Ingannato, A.; Giacomucci, G.; Balestrini, J.; Ferrari, C.; Sorbi, S.; et al. Huntingtin Gene Intermediate Alleles Influence the Progression from Subjective Cognitive Decline to Mild Cognitive Impairment: A 14-Year Follow-up Study. *Eur. J. Neurol.* **2022**, *29*, 1600–1609. [CrossRef]
39. Migliore, S.; Jankovic, J.; Squitieri, F. Genetic Counseling in Huntington's Disease: Potential New Challenges on Horizon? *Front. Neurol.* **2019**, *10*, 453. [CrossRef]
40. De Luca, A.; Morella, A.; Consoli, F.; Fanelli, S.; Thibert, J.R.; Statt, S.; Latham, G.J.; Squitieri, F. A Novel Triplet-Primed PCR Assay to Detect the Full Range of Trinucleotide CAG Repeats in the Huntingtin Gene (HTT). *Int. J. Mol. Sci.* **2021**, *22*, 1689. [CrossRef]
41. Nakamura, K.; Jeong, S.Y.; Uchihara, T.; Anno, M.; Nagashima, K.; Nagashima, T.; Ikeda, S.I.; Tsuji, S.; Kanazawa, I. SCA17, a Novel Autosomal Dominant Cerebellar Ataxia Caused by an Expanded Polyglutamine in TATA-Binding Protein. *Hum. Mol. Genet.* **2001**, *10*, 1441–1448. [CrossRef]
42. Nethisinghe, S.; Pigazzini, M.L.; Pemble, S.; Sweeney, M.G.; Labrum, R.; Manso, K.; Moore, D.; Warner, J.; Davis, M.B.; Giunti, P. PolyQ Tract Toxicity in SCA1 Is Length Dependent in the Absence of CAG Repeat Interruption. *Front. Cell. Neurosci.* **2018**, *12*, 200. [CrossRef]
43. Nolin, S.L.; Glicksman, A.; Tortora, N.; Allen, E.; Macpherson, J.; Mila, M.; Vianna-Morgante, A.M.; Sherman, S.L.; Dobkin, C.; Latham, G.J.; et al. Expansions and Contractions of the FMR1 CGG Repeat in 5,508 Transmissions of Normal, Intermediate, and Premutation Alleles. *Am. J. Med. Genet. A* **2019**, *179*, 1148–1156. [CrossRef]
44. Shin, J.W.; Kim, K.H.; Chao, M.J.; Atwal, R.S.; Gillis, T.; MacDonald, M.E.; Gusella, J.F.; Lee, J.M. Permanent Inactivation of Huntington's Disease Mutation by Personalized Allele-Specific CRISPR/Cas9. *Hum. Mol. Genet.* **2016**, *25*, 4566–4576. [CrossRef]
45. Dabrowska, M.; Juzwa, W.; Krzyzosiak, W.J.; Olejniczak, M. Precise Excision of the CAG Tract from the Huntingtin Gene by Cas9 Nickases. *Front. Neurosci.* **2018**, *12*, 75. [CrossRef]
46. Squitieri, F.; Maffi, S.; Al Harasi, S.; Al Salmi, Q.; D'Alessio, B.; Capelli, G.; Mazza, T. Incidence and Prevalence of Huntington Disease (HD) in the Sultanate of Oman: The First Middle East Post- HTT Service-Based Study. *J. Neurol. Neurosurg. Psychiatry* **2020**, *91*, 1359–1360. [CrossRef]

47. Porro, A.; Berti, M.; Pizzolato, J.; Bologna, S.; Kaden, S.; Saxer, A.; Ma, Y.; Nagasawa, K.; Sartori, A.A.; Jiricny, J. FAN1 Interaction with Ubiquitylated PCNA Alleviates Replication Stress and Preserves Genomic Integrity Independently of BRCA2. *Nat. Commun.* **2017**, *8*, 1073. [CrossRef]
48. Porro, A.; Mohiuddin, M.; Zurfluh, C.; Spegg, V.; Dai, J.; Iehl, F.; Ropars, V.; Collotta, G.; Fishwick, K.M.; Mozaffari, N.L.; et al. FAN1-MLH1 Interaction Affects Repair of DNA Interstrand Cross-Links and Slipped-CAG/CTG Repeats. *Sci. Adv.* **2021**, *7*, eabf7906. [CrossRef]
49. Goold, R.; Flower, M.; Moss, D.H.; Medway, C.; Wood-Kaczmar, A.; Andre, R.; Farshim, P.; Bates, G.P.; Holmans, P.; Jones, L.; et al. FAN1 Modifies Huntington's Disease Progression by Stabilizing the Expanded HTT CAG Repeat. *Hum. Mol. Genet.* **2019**, *28*, 650–661. [CrossRef]
50. Loupe, J.M.; Pinto, R.M.; Kim, K.H.; Gillis, T.; Mysore, J.S.; Andrew, M.A.; Kovalenko, M.; Murtha, R.; Seong, I.; Gusella, J.F.; et al. Promotion of Somatic CAG Repeat Expansion by Fan1 Knock-out in Huntington's Disease Knock-in Mice Is Blocked by Mlh1 Knock-Out. *Hum. Mol. Genet.* **2020**, *29*, 3044–3053. [CrossRef]
51. Goold, R.; Hamilton, J.; Menneteau, T.; Flower, M.; Bunting, E.L.; Aldous, S.G.; Porro, A.; Vicente, J.R.; Allen, N.D.; Wilkinson, H.; et al. FAN1 Controls Mismatch Repair Complex Assembly via MLH1 Retention to Stabilize CAG Repeat Expansion in Huntington's Disease. *Cell Rep.* **2021**, *36*, 109649. [CrossRef]
52. Deshmukh, A.L.; Caron, M.C.; Mohiuddin, M.; Lanni, S.; Panigrahi, G.B.; Khan, M.; Engchuan, W.; Shum, N.; Faruqui, A.; Wang, P.; et al. FAN1 Exo- Not Endo-Nuclease Pausing on Disease-Associated Slipped-DNA Repeats: A Mechanism of Repeat Instability. *Cell Rep.* **2021**, *37*, 110078. [CrossRef]
53. McAllister, B.; Donaldson, J.; Binda, C.S.; Powell, S.; Chughtai, U.; Edwards, G.; Stone, J.; Lobanov, S.; Elliston, L.; Schuhmacher, L.N.; et al. Exome Sequencing of Individuals with Huntington's Disease Implicates FAN1 Nuclease Activity in Slowing CAG Expansion and Disease Onset. *Nat. Neurosci.* **2022**, *25*, 446–457. [CrossRef]
54. Phadte, A.S.; Bhatia, M.; Ebert, H.; Abdullah, H.; Elrazaq, E.A.; Komolov, K.E.; Pluciennik, A. FAN1 Removes Triplet Repeat Extrusions via a PCNA- and RFC-Dependent Mechanism. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2302103120. [CrossRef]
55. Bettencourt, C.; Hensman-Moss, D.; Flower, M.; Wiethoff, S.; Brice, A.; Goizet, C.; Stevanin, G.; Koutsis, G.; Karadima, G.; Panas, M.; et al. DNA Repair Pathways Underlie a Common Genetic Mechanism Modulating Onset in Polyglutamine Diseases. *Ann. Neurol.* **2016**, *79*, 983–990. [CrossRef]
56. Mergener, R.; Furtado, G.V.; de Mattos, E.P.; Leotti, V.B.; Jardim, L.B.; Saraiva-Pereira, M.L. Variation in DNA Repair System Gene as an Additional Modifier of Age at Onset in Spinocerebellar Ataxia Type 3/Machado-Joseph Disease. *Neuromol. Med.* **2020**, *22*, 133–138. [CrossRef]
57. Zhao, X.N.; Usdin, K. FAN1 Protects against Repeat Expansions in a Fragile X Mouse Model. *DNA Repair* **2018**, *69*, 1–5. [CrossRef]
58. Deshmukh, A.L.; Porro, A.; Mohiuddin, M.; Lanni, S.; Panigrahi, G.B.; Caron, M.C.; Masson, J.Y.; Sartori, A.A.; Pearson, C.E. FAN1, a DNA Repair Nuclease, as a Modifier of Repeat Expansion Disorders. *J. Huntingt. Dis.* **2021**, *10*, 95–122. [CrossRef]
59. Lee, J.M.; Chao, M.J.; Harold, D.; Elneel, K.A.; Gillis, T.; Holmans, P.; Jones, L.; Orth, M.; Myers, R.H.; Kwak, S.; et al. A Modifier of Huntington's Disease Onset at the MLH1 Locus. *Hum. Mol. Genet.* **2017**, *26*, 3859–3867. [CrossRef]
60. Skarping, K.D.; Petersén, Å.; Gebre-Medhin, S. C09 Huntingtin Gene CAG Repeat Size in Patients with Lynch Syndrome. *J. Neurol. Neurosurg. Psychiatry* **2022**, *93*, A19. [CrossRef]
61. Pinto, R.M.; Dragileva, E.; Kirby, A.; Lloret, A.; Lopez, E.; St. Claire, J.; Panigrahi, G.B.; Hou, C.; Holloway, K.; Gillis, T.; et al. Mismatch Repair Genes Mlh1 and Mlh3 Modify CAG Instability in Huntington's Disease Mice: Genome-Wide and Candidate Approaches. *PLoS Genet.* **2013**, *9*, e1003930. [CrossRef]
62. Tomé, S.; Manley, K.; Simard, J.P.; Clark, G.W.; Slean, M.M.; Swami, M.; Shelbourne, P.F.; Tillier, E.R.M.; Monckton, D.G.; Messer, A.; et al. MSH3 Polymorphisms and Protein Levels Affect CAG Repeat Instability in Huntington's Disease Mice. *PLoS Genet.* **2013**, *9*, e1003280. [CrossRef]
63. Williams, G.M.; Surtees, J.A. MSH3 Promotes Dynamic Behavior of Trinucleotide Repeat Tracts In Vivo. *Genetics* **2015**, *200*, 737–754. [CrossRef]
64. Flower, M.; Lomeikaite, V.; Ciosi, M.; Cumming, S.; Morales, F.; Lo, K.; Hensman Moss, D.; Jones, L.; Holmans, P.; Monckton, D.G.; et al. MSH3 Modifies Somatic Instability and Disease Severity in Huntington's and Myotonic Dystrophy Type 1. *Brain* **2019**, *142*, 1876–1886. [CrossRef]
65. Morales, F.; Vásquez, M.; Santamaría, C.; Cuenca, P.; Corrales, E.; Monckton, D.G. A Polymorphism in the MSH3 Mismatch Repair Gene Is Associated with the Levels of Somatic Instability of the Expanded CTG Repeat in the Blood DNA of Myotonic Dystrophy Type 1 Patients. *DNA Repair* **2016**, *40*, 57–66. [CrossRef]
66. O'Reilly, D.; Belgrad, J.; Ferguson, C.; Summers, A.; Sapp, E.; McHugh, C.; Mathews, E.; Boudi, A.; Buchwald, J.; Ly, S.; et al. Di-Valent SiRNA-Mediated Silencing of MSH3 Blocks Somatic Repeat Expansion in Mouse Models of Huntington's Disease. *Mol. Ther.* **2023**, *31*, 1661–1674. [CrossRef]
67. Lee, J.M.; Huang, Y.; Orth, M.; Gillis, T.; Siciliano, J.; Hong, E.; Mysore, J.S.; Lucente, D.; Wheeler, V.C.; Seong, I.S.; et al. Genetic Modifiers of Huntington Disease Differentially Influence Motor and Cognitive Domains. *Am. J. Hum. Genet.* **2022**, *109*, 885–899. [CrossRef]
68. McLean, Z.L.; Gao, D.; Correia, K.; Roy, J.C.L.; Shibata, S.; Farnum, I.N.; Valdepenas-Mellor, Z.; Rapuru, M.; Morini, E.; Ruliera, J.; et al. PMS1 as a Target for Splice Modulation to Prevent Somatic CAG Repeat Expansion in Huntington's Disease. *bioRxiv Prepr. Serv. Biol.* **2023**. [CrossRef]

69. Liu, D.; Keijzers, G.; Rasmussen, L.J. DNA Mismatch Repair and Its Many Roles in Eukaryotic Cells. *Mutat. Res. Rev. Mutat. Res.* **2017**, *773*, 174–187. [CrossRef]
70. Iyer, R.R.; Pluciennik, A. DNA Mismatch Repair and Its Role in Huntington's Disease. *J. Huntingt. Dis.* **2021**, *10*, 75–94. [CrossRef]
71. Tabrizi, S.J.; Estevez-Fraga, C.; van Roon-Mom, W.M.C.; Flower, M.D.; Scahill, R.I.; Wild, E.J.; Muñoz-Sanjuan, I.; Sampaio, C.; Rosser, A.E.; Leavitt, B.R. Potential Disease-Modifying Therapies for Huntington's Disease: Lessons Learned and Future Opportunities. *Lancet Neurol.* **2022**, *21*, 645–658. [CrossRef]
72. Keogh, N.; Chan, K.Y.; Li, G.M.; Lahue, R.S. MutSβ Abundance and Msh3 ATP Hydrolysis Activity Are Important Drivers of CTG•CAG Repeat Expansions. *Nucleic Acids Res.* **2017**, *45*, 10068–10078. [CrossRef]
73. Youssoufian, H.; Pyeritz, R.E. Mechanisms and Consequences of Somatic Mosaicism in Humans. *Nat. Rev. Genet.* **2002**, *3*, 748–758. [CrossRef]
74. Biesecker, L.G.; Spinner, N.B. A Genomic View of Mosaicism and Human Disease. *Nat. Rev. Genet.* **2013**, *14*, 307–320. [CrossRef]
75. D'Gama, A.M.; Walsh, C.A. Somatic Mosaicism and Neurodevelopmental Disease. *Nat. Neurosci.* **2018**, *21*, 1504–1514. [CrossRef]
76. Abascal, F.; Harvey, L.M.R.; Mitchell, E.; Lawson, A.R.J.; Lensing, S.V.; Ellis, P.; Russell, A.J.C.; Alcantara, R.E.; Baez-Ortega, A.; Wang, Y.; et al. Somatic Mutation Landscapes at Single-Molecule Resolution. *Nature* **2021**, *593*, 405–410. [CrossRef]
77. Poduri, A.; Evrony, G.D.; Cai, X.; Walsh, C.A. Somatic Mutation, Genomic Variation, and Neurological Disease. *Science* **2013**, *341*, 1237758. [CrossRef]
78. Lodato, M.A.; Rodin, R.E.; Bohrson, C.L.; Coulter, M.E.; Barton, A.R.; Kwon, M.; Sherman, M.A.; Vitzthum, C.M.; Luquette, L.J.; Yandava, C.N.; et al. Aging and Neurodegeneration Are Associated with Increased Mutations in Single Human Neurons. *Science* **2018**, *359*, 555–559. [CrossRef]
79. Proukakis, C. Somatic Mutations in Neurodegeneration: An Update. *Neurobiol. Dis.* **2020**, *144*, 105021. [CrossRef]
80. Analysis of (CAG)n Size Heterogeneity in Somatic and Sperm Cell DNA from Intermediate and Expanded Huntington Disease Gene Carriers—PubMed. Available online: https://pubmed.ncbi.nlm.nih.gov/9401009/ (accessed on 20 April 2024).
81. Telenius, H.; Kremer, H.P.H.; Thellmann, J.; Andrew, S.E.; Almqvist, E.; Anvret, M.; Greenberg, C.; Greenberg, J.; Lucotte, G.; Squltierl, F.; et al. Molecular Analysis of Juvenile Huntington Disease: The Major Influence on (CAG)n Repeat Length Is the Sex of the Affected Parent. *Hum. Mol. Genet.* **1993**, *2*, 1535–1540. [CrossRef]
82. Fusilli, C.; Migliore, S.; Mazza, T.; Consoli, F.; De Luca, A.; Barbagallo, G.; Ciammola, A.; Gatto, E.M.; Cesarini, M.; Etcheverry, J.L.; et al. Biological and Clinical Manifestations of Juvenile Huntington's Disease: A Retrospective Analysis. *Lancet Neurol.* **2018**, *17*, 986–993. [CrossRef]
83. Squitieri, F.; Jankovic, J. Huntington's Disease: How Intermediate Are Intermediate Repeat Lengths? *Mov. Disord.* **2012**, *27*, 1714–1717. [CrossRef]
84. Mangiarini, L.; Sathasivam, K.; Mahal, A.; Mott, R.; Seller, M.; Bates, G.P. Instability of Highly Expanded CAG Repeats in Mice Transgenic for the Huntington's Disease Mutation. *Nat. Genet.* **1997**, *15*, 197–200. [CrossRef]
85. Telenius, H.; Kremer, B.; Goldberg, Y.P.; Theilmann, J.; Andrew, S.E.; Zeisler, J.; Adam, S.; Greenberg, C.; Ives, E.J.; Clarke, L.A.; et al. Somatic and Gonadal Mosaicism of the Huntington Disease Gene CAG Repeat in Brain and Sperm. *Nat. Genet.* **1994**, *6*, 409–414. [CrossRef]
86. Kennedy, L.; Evans, E.; Chen, C.M.; Craven, L.; Detloff, P.J.; Ennis, M.; Shelbourne, P.F. Dramatic Tissue-Specific Mutation Length Increases Are an Early Molecular Event in Huntington Disease Pathogenesis. *Hum. Mol. Genet.* **2003**, *12*, 3359–3367. [CrossRef]
87. Kennedy, L.; Shelbourne, P.F. Dramatic Mutation Instability in HD Mouse Striatum: Does Polyglutamine Load Contribute to Cell-Specific Vulnerability in Huntington's Disease? *Hum. Mol. Genet.* **2000**, *9*, 2539–2544. [CrossRef]
88. Gonitel, R.; Moffitt, H.; Sathasivam, K.; Woodman, B.; Detloff, P.J.; Faull, R.L.M.; Bates, G.P. DNA Instability in Postmitotic Neurons. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3467–3472. [CrossRef]
89. Larson, E.; Fyfe, I.; Morton, A.J.; Monckton, D.G. Age-, Tissue- and Length-Dependent Bidirectional Somatic CAG•CTG Repeat Instability in an Allelic Series of R6/2 Huntington Disease Mice. *Neurobiol. Dis.* **2015**, *76*, 98–111. [CrossRef]
90. Swami, M.; Hendricks, A.E.; Gillis, T.; Massood, T.; Mysore, J.; Myers, R.H.; Wheeler, V.C. Somatic Expansion of the Huntington's Disease CAG Repeat in the Brain Is Associated with an Earlier Age of Disease Onset. *Hum. Mol. Genet.* **2009**, *18*, 3039–3047. [CrossRef]
91. Dragileva, E.; Hendricks, A.; Teed, A.; Gillis, T.; Lopez, E.T.; Friedberg, E.C.; Kucherlapati, R.; Edelmann, W.; Lunetta, K.L.; MacDonald, M.E.; et al. Intergenerational and Striatal CAG Repeat Instability in Huntington's Disease Knock-in Mice Involve Different DNA Repair Genes. *Neurobiol. Dis.* **2009**, *33*, 37–47. [CrossRef]
92. Kovtun, I.V.; Liu, Y.; Bjoras, M.; Klungland, A.; Wilson, S.H.; McMurray, C.T. OGG1 Initiates Age-Dependent CAG Trinucleotide Expansion in Somatic Cells. *Nature* **2007**, *447*, 447–452. [CrossRef]
93. Barnat, M.; Capizzi, M.; Aparicio, E.; Boluda, S.; Wennagel, D.; Kacher, R.; Kassem, R.; Lenoir, S.; Agasse, F.; Bra, B.Y.; et al. Huntington's Disease Alters Human Neurodevelopment. *Science* **2020**, *369*, 787–793. [CrossRef]
94. Kaplan, S.; Itzkovitz, S.; Shapiro, E. A Universal Mechanism Ties Genotype to Phenotype in Trinucleotide Diseases. *PLoS Comput. Biol.* **2007**, *3*, 2291–2298. [CrossRef]
95. Hong, E.P.; MacDonald, M.E.; Wheeler, V.C.; Jones, L.; Holmans, P.; Orth, M.; Monckton, D.G.; Long, J.D.; Kwak, S.; Gusella, J.F.; et al. Huntington's Disease Pathogenesis: Two Sequential Components. *J. Huntingt. Dis.* **2021**, *10*, 35–51. [CrossRef]
96. Squitieri, F.; Monti, L.; Graziola, F.; Colafati, G.S.; Sabatini, U. Early Liver Steatosis in Children with Pediatric Huntington Disease and Highly Expanded CAG Mutations. *Park. Relat. Disord.* **2022**, *103*, 102–104. [CrossRef]

97. Khristich, A.N.; Mirkin, S.M. On the Wrong DNA Track: Molecular Mechanisms of Repeat-Mediated Genome Instability. *J. Biol. Chem.* **2020**, *295*, 4134–4170. [CrossRef]
98. Handsaker, R.E.; Kashin, S.; Reed, N.M.; Tan, S.; Lee, W.-S.; McDonald, T.M.; Morris, K.; Kamitaki, N.; Mullally, C.D.; Morakabati, N.; et al. Long Somatic DNA-Repeat Expansion Drives Neurodegeneration in Huntington Disease. *bioRxiv* **2024**. [CrossRef]
99. Lin, B.; Rommens, J.M.; Graham, R.K.; Kalchman, M.; MacDonald, H.; Nasir, J.; Delaney, A.; Goldberg, Y.P.; Hayden, M.R. Differential 3′ Polyadenylation of the Huntington Disease Gene Results in Two MRNA Species with Variable Tissue Expression. *Hum. Mol. Genet.* **1993**, *2*, 1541–1545. [CrossRef]
100. DiFiglia, M.; Sapp, E.; Chase, K.O.; Davies, S.W.; Bates, G.P.; Vonsattel, J.P.; Aronin, N. Aggregation of Huntingtin in Neuronal Intranuclear Inclusions and Dystrophic Neurites in Brain. *Science* **1997**, *277*, 1990–1993. [CrossRef]
101. Lunkes, A.; Lindenberg, K.S.; Ben-Haem, L.; Weber, C.; Devys, D.; Landwehrmeyer, G.B.; Mandel, J.L.; Trottier, Y. Proteases Acting on Mutant Huntingtin Generate Cleaved Products That Differentially Build up Cytoplasmic and Nuclear Inclusions. *Mol. Cell* **2002**, *10*, 259–269. [CrossRef]
102. Sathasivam, K.; Neueder, A.; Gipson, T.A.; Landles, C.; Benjamin, A.C.; Bondulich, M.K.; Smith, D.L.; Faull, R.L.M.; Roos, R.A.C.; Howland, D.; et al. Aberrant Splicing of HTT Generates the Pathogenic Exon 1 Protein in Huntington Disease. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 2366–2370. [CrossRef]
103. Neueder, A.; Dumas, A.A.; Benjamin, A.C.; Bates, G.P. Regulatory Mechanisms of Incomplete Huntingtin MRNA Splicing. *Nat. Commun.* **2018**, *9*, 3955. [CrossRef]
104. Neueder, A.; Landles, C.; Ghosh, R.; Howland, D.; Myers, R.H.; Faull, R.L.M.; Tabrizi, S.J.; Bates, G.P. The Pathogenic Exon 1 HTT Protein Is Produced by Incomplete Splicing in Huntington's Disease Patients. *Sci. Rep.* **2017**, *7*, 1307. [CrossRef]
105. Scherzinger, E.; Sittler, A.; Schweiger, K.; Heiser, V.; Lurz, R.; Hasenbank, R.; Bates, G.P.; Lehrach, H.; Wanker, E.E. Self-Assembly of Polyglutamine-Containing Huntingtin Fragments into Amyloid-like Fibrils: Implications for Huntington's Disease Pathology. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4604–4609. [CrossRef]
106. Fienko, S.; Landles, C.; Sathasivam, K.; McAteer, S.J.; Milton, R.E.; Osborne, G.F.; Smith, E.J.; Jones, S.T.; Bondulich, M.K.; Danby, E.C.E.; et al. Alternative Processing of Human HTT MRNA with Implications for Huntington's Disease Therapeutics. *Brain* **2022**, *145*, 4409–4424. [CrossRef]
107. Cleary, J.D.; Ranum, L.P.W. Repeat Associated Non-ATG (RAN) Translation: New Starts in Microsatellite Expansion Disorders. *Curr. Opin. Genet. Dev.* **2014**, *26*, 6–15. [CrossRef]
108. Bañez-Coronel, M.; Ayhan, F.; Tarabochia, A.D.; Zu, T.; Perez, B.A.; Tusi, S.K.; Pletnikova, O.; Borchelt, D.R.; Ross, C.A.; Margolis, R.L.; et al. RAN Translation in Huntington Disease. *Neuron* **2015**, *88*, 667–677. [CrossRef]
109. Grima, J.C.; Daigle, J.G.; Arbez, N.; Cunningham, K.C.; Zhang, K.; Ochaba, J.; Geater, C.; Morozko, E.; Stocksdale, J.; Glatzer, J.C.; et al. Mutant Huntingtin Disrupts the Nuclear Pore Complex. *Neuron* **2017**, *94*, 93–107.e6. [CrossRef]
110. Das, M.R.; Chang, Y.; Anderson, R.; Saunders, R.A.; Zhang, N.; Tomberlin, C.P.; Vale, R.D.; Jain, A. Repeat-Associated Non-AUG Translation Induces Cytoplasmic Aggregation of CAG Repeat-Containing RNAs. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2215071120. [CrossRef]
111. Yang, S.; Yang, H.; Huang, L.; Chen, L.; Qin, Z.; Li, S.; Li, X.J. Lack of RAN-Mediated Toxicity in Huntington's Disease Knock-in Mice. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 4411–4417. [CrossRef]
112. Alvarez-Mora, M.I.; Podlesniy, P.; Gelpi, E.; Hukema, R.; Madrigal, I.; Pagonabarraga, J.; Trullas, R.; Mila, M.; Rodriguez-Revenga, L. Fragile X-Associated Tremor/Ataxia Syndrome: Regional Decrease of Mitochondrial DNA Copy Number Relates to Clinical Manifestations. *Genes. Brain. Behav.* **2019**, *18*, e12565. [CrossRef]
113. Stanga, S.; Caretto, A.; Boido, M.; Vercelli, A. Mitochondrial Dysfunctions: A Red Thread across Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 3719. [CrossRef]
114. Kalra, J. Crosslink between Mutations in Mitochondrial Genes and Brain Disorders: Implications for Mitochondrial-Targeted Therapeutic Interventions. *Neural Regen. Res.* **2023**, *18*, 94–101. [CrossRef]
115. Fontana, G.A.; Gahlon, H.L. Mechanisms of Replication and Repair in Mitochondrial DNA Deletion Formation. *Nucleic Acids Res.* **2020**, *48*, 11244–11258. [CrossRef]
116. Dai, Y.; Wang, H.; Lian, A.; Li, J.; Zhao, G.; Hu, S.; Li, B. A Comprehensive Perspective of Huntington's Disease and Mitochondrial Dysfunction. *Mitochondrion* **2023**, *70*, 8–19. [CrossRef]
117. Sawa, A.; Wiegand, G.W.; Cooper, J.; Margolis, R.L.; Sharp, A.H.; Lawler, J.F.; Greenamyre, J.T.; Snyder, S.H.; Ross, C.A. Increased Apoptosis of Huntington Disease Lymphoblasts Associated with Repeat Length-Dependent Mitochondrial Depolarization. *Nat. Med.* **1999**, *5*, 1194–1198. [CrossRef]
118. Panov, A.V.; Gutekunst, C.A.; Leavitt, B.R.; Hayden, M.R.; Burke, J.R.; Strittmatter, W.J.; Greenamyre, J.T. Early Mitochondrial Calcium Defects in Huntington's Disease Are a Direct Effect of Polyglutamines. *Nat. Neurosci.* **2002**, *5*, 731–736. [CrossRef]
119. Siddiqui, A.; Rivera-Sánchez, S.; Castro, M.D.R.; Acevedo-Torres, K.; Rane, A.; Torres-Ramos, C.A.; Nicholls, D.G.; Andersen, J.K.; Ayala-Torres, S. Mitochondrial DNA Damage Is Associated with Reduced Mitochondrial Bioenergetics in Huntington's Disease. *Free Radic. Biol. Med.* **2012**, *53*, 1478–1488. [CrossRef]
120. Hering, T.; Birth, N.; Taanman, J.W.; Orth, M. Selective Striatal MtDNA Depletion in End-Stage Huntington's Disease R6/2 Mice. *Exp. Neurol.* **2015**, *266*, 22–29. [CrossRef]

121. Acevedo-Torres, K.; Berríos, L.; Rosario, N.; Dufault, V.; Skatchkov, S.; Eaton, M.J.; Torres-Ramos, C.A.; Ayala-Torres, S. Mitochondrial DNA Damage Is a Hallmark of Chemically Induced and the R6/2 Transgenic Model of Huntington's Disease. *DNA Repair* **2009**, *8*, 126–136. [CrossRef]
122. Horton, T.M.; Graham, B.H.; Corral-Debrinski, M.; Shoffner, J.M.; Kaufman, A.E.; Beal, M.F.; Wallace, D.C. Marked Increase in Mitochondrial DNA Deletion Levels in the Cerebral Cortex of Huntington's Disease Patients. *Neurology* **1995**, *45*, 1879–1883. [CrossRef]
123. Gu, M.; Gash, M.T.; Mann, V.M.; Javoy-Agid, F.; Cooper, J.M.; Schapira, A.H.V. Mitochondrial Defect in Huntington's Disease Caudate Nucleus. *Ann. Neurol.* **1996**, *39*, 385–389. [CrossRef]
124. Tramutola, A.; Bakels, H.S.; Perrone, F.; Di Nottia, M.; Mazza, T.; Abruzzese, M.P.; Zoccola, M.; Pagnotta, S.; Carrozzo, R.; de Bot, S.T.; et al. GLUT-1 Changes in Paediatric Huntington Disease Brain Cortex and Fibroblasts: An Observational Case-Control Study. *EBioMedicine* **2023**, *97*, 104849. [CrossRef]
125. Banoei, M.M.; Houshmand, M.; Panahi, M.S.S.; Shariati, P.; Rostami, M.; Manshadi, M.D.; Majidizadeh, T. Huntington's Disease and Mitochondrial DNA Deletions: Event or Regular Mechanism for Mutant Huntingtin Protein and CAG Repeats Expansion?! *Cell. Mol. Neurobiol.* **2007**, *27*, 867–875. [CrossRef]
126. Chen, C.M.; Wu, Y.R.; Cheng, M.L.; Liu, J.L.; Lee, Y.M.; Lee, P.W.; Soong, B.W.; Chiu, D.T.Y. Increased Oxidative Damage and Mitochondrial Abnormalities in the Peripheral Blood of Huntington's Disease Patients. *Biochem. Biophys. Res. Commun.* **2007**, *359*, 335–340. [CrossRef]
127. Liu, C.S.; Cheng, W.L.; Kuo, S.J.; Li, J.Y.; Soong, B.W.; Wei, Y.H. Depletion of Mitochondrial DNA in Leukocytes of Patients with Poly-Q Diseases. *J. Neurol. Sci.* **2008**, *264*, 18–21. [CrossRef]
128. Petersen, M.H.; Budtz-Jørgensen, E.; Sørensen, S.A.; Nielsen, J.E.; Hjermind, L.E.; Vinther-Jensen, T.; Nielsen, S.M.B.; Nørremølle, A. Reduction in Mitochondrial DNA Copy Number in Peripheral Leukocytes after Onset of Huntington's Disease. *Mitochondrion* **2014**, *17*, 14–21. [CrossRef]
129. Jędrak, P.; Krygier, M.; Tońska, K.; Drozd, M.; Kaliszewska, M.; Bartnik, E.; Sołtan, W.; Sitek, E.J.; Stanisławska-Sachadyn, A.; Limon, J.; et al. Mitochondrial DNA Levels in Huntington Disease Leukocytes and Dermal Fibroblasts. *Metab. Brain Dis.* **2017**, *32*, 1237–1247. [CrossRef]
130. Askeland, G.; Dosoudilova, Z.; Rodinova, M.; Klempir, J.; Liskova, I.; Kuśnierczyk, A.; Bjørås, M.; Nesse, G.; Klungland, A.; Hansikova, H.; et al. Increased Nuclear DNA Damage Precedes Mitochondrial Dysfunction in Peripheral Blood Mononuclear Cells from Huntington's Disease Patients. *Sci. Rep.* **2018**, *8*, 9817. [CrossRef]
131. Younesian, S.; Yousefi, A.M.; Momeny, M.; Ghaffari, S.H.; Bashash, D. The DNA Methylation in Neurological Diseases. *Cells* **2022**, *11*, 3439. [CrossRef]
132. De Souza, R.A.G.; Islam, S.A.; McEwen, L.M.; Mathelier, A.; Hill, A.; Mah, S.M.; Wasserman, W.W.; Kobor, M.S.; Leavitt, B.R. DNA Methylation Profiling in Human Huntington's Disease Brain. *Hum. Mol. Genet.* **2016**, *25*, 2013–2030. [CrossRef]
133. Sugars, K.L.; Rubinsztein, D.C. Transcriptional Abnormalities in Huntington Disease. *Trends Genet.* **2003**, *19*, 233–238. [CrossRef]
134. Ng, C.W.; Yildirim, F.; Yap, Y.S.; Dalin, S.; Matthews, B.J.; Velez, P.J.; Labadorf, A.; Housman, D.E.; Fraenkel, E. Extensive Changes in DNA Methylation Are Associated with Expression of Mutant Huntingtin. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 2354–2359. [CrossRef]
135. McFarland, K.N.; Huizenga, M.N.; Darnell, S.B.; Sangrey, G.R.; Berezovska, O.; Cha, J.H.J.; Outeiro, T.F.; Sadri-Vakili, G. MeCP2: A Novel Huntingtin Interactor. *Hum. Mol. Genet.* **2014**, *23*, 1036–1044. [CrossRef]
136. Benn, C.L.; Sun, T.; Sadri-Vakili, G.; McFarland, K.N.; DiRocco, D.P.; Yohrling, G.J.; Clark, T.W.; Bouzou, B.; Cha, J.H.J. Huntingtin Modulates Transcription, Occupies Gene Promoters In Vivo, and Binds Directly to DNA in a Polyglutamine-Dependent Manner. *J. Neurosci.* **2008**, *28*, 10720. [CrossRef]
137. Pan, Y.; Daito, T.; Sasaki, Y.; Chung, Y.H.; Xing, X.; Pondugula, S.; Swamidass, S.J.; Wang, T.; Kim, A.H.; Yano, H. Inhibition of DNA Methyltransferases Blocks Mutant Huntingtin-Induced Neurotoxicity. *Sci. Rep.* **2016**, *6*, 31022. [CrossRef]
138. Horvath, S.; Langfelder, P.; Kwak, S.; Aaronson, J.; Rosinski, J.; Vogt, T.F.; Eszes, M.; Faull, R.L.M.; Curtis, M.A.; Waldvogel, H.J.; et al. Huntington's Disease Accelerates Epigenetic Aging of Human Brain and Disrupts DNA Methylation Levels. *Aging* **2016**, *8*, 1485–1512. [CrossRef]
139. Pellegrini, M.; Bergonzoni, G.; Perrone, F.; Squitieri, F.; Biagioli, M. Current Diagnostic Methods and Non-Coding RNAs as Possible Biomarkers in Huntington's Disease. *Genes* **2022**, *13*, 2017. [CrossRef]
140. Ruffo, P.; De Amicis, F.; Giardina, E.; Conforti, F.L. Long-Noncoding RNAs as Epigenetic Regulators in Neurodegenerative Diseases. *Neural Regen. Res.* **2023**, *18*, 1243–1248. [CrossRef]