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Introduction

Special Issue: DNA Repair and Somatic Repeat Expansion in Huntington's Disease

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The CAG repeat mutation in the *HTT* gene that causes Huntington's disease (HD) was discovered in 1993 [1]. Although our understanding of the underlying biology and our ability to model many aspects of the disease have improved substantially, no treatment that alters the course of this devastating disorder has been found. Why do we think this special issue is timely now? The wealth of detail available in HD research, and the knowledge of DNA repair and somatic repeat expansion in HD, make an issue of JHD focusing on the mechanisms that may underlie these events highly topical. Over the past five years, novel genetics has transformed our understanding of the factors that are critical in the pathogenesis of HD, and is beginning to provide similar insight into other repeat expansion disorders [2, 3]. A characteristic feature shared by these diseases is the instability of the repeat tracts in the germline, and in somatic cells where the repeat expands over time. This has long been recognized, historically stimulating much research into these phenomena. The history of this research, indicating the insights and barriers to acceptance of ideas around repeat expansion, its mechanisms and influence on the presentation of human disease, is outlined by Darren Monckton in this issue [4].

Since 2015, genome-wide association studies (GWAS), enabled both by large systematic observational studies and technical advances in genetic analyses, have revealed that HD is modified by genes in DNA repair pathways. One of the most striking findings in the GWAS was the observation of variant glutamine-encoding repeat sequences at the 3' end of the *HTT* CAG repeat tract, providing the opportunity to distinguish the contribution to HD onset made by the pure repeat tract and the encoded glutamine repeat. The current genetic findings are outlined by Hong et al. in their article [5]. They also explore the implications of these data for mechanisms underlying disease pathophysiology. They propose that two steps are required for pathogenesis in HD: first an expansion of the *HTT* CAG repeat in

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somatic cells, followed by downstream pathogenic events occurring in response to those CAG repeats in cells that are expanded from the inherited length. They provide details of their website that allows users to explore these recent genetic data interactively to support their own research [3].

The presence of variant *HTT* repeat sequences revealed a need for accurate sequencing of the CAG tract. Ciosi et al. [6] explore the potential methods for performing this and for quantifying somatic CAG instability. These include high throughput sequencing techniques such as MiSeq - short-read Illumina-based next generation sequencing where up to 300 bp of sequence can be read confidently and longer reads are possible. Very long reads through repeats of the lengths seen in many HD mouse models are not amenable to this robust and well-established technology. Thus, other long read – sometimes referred to as 3rd generation sequencing - has been explored to solve this issue [7].

We have two reviews that explore the biology of the most significant HD-modifier genes and pathways that have emerged from GWAS and their potential roles in HD and other repeat disorders [8, 9]. Iyer and Pluciennik [9] examine the mechanism of the mismatch repair proteins, strongly implicated in modulating age at onset and progression of HD. In a complementary review, Deshmukh et al. [8] outline the biology of FAN1 DNA repair nuclease, the most significant gene in the HD age at onset modifier studies with multiple genetic signals that both delay and hasten onset. They consider what is known about the functions of FAN1, its roles in other diseases, and survey the evidence that underpins its potential role in somatic expansion of the *HTT* CAG repeat. Both reviews consider how the mismatch repair pathway and FAN1 might act together to modify HD though a concerted mechanism, whether that mechanism involves somatic expansion of the CAG repeat locus, and what opportunities these mechanisms might provide for therapeutic interventions.

Wheeler and Dion [10] provide a comprehensive compendium of the model systems used to explore CAG repeat instability, with a focus on mammalian systems, and the genetic modifiers of instability uncovered using these systems. Their review surveys these models and their specific experimental paradigms, discussing their relative advantages and disadvantages. The significance of the observations from these systems is discussed in the context of human data. They also outline a network of connections between modifiers gleaned from the various models that might indicate DNA repair pathway crosstalk in the context of repeat instability, complementing the reviews on mismatch repair [9] and FAN1 [8] in this issue.

Over 50 human genetic disorders are caused by an expanded tandem repeat tract, in a variety of repeats in both coding and non-coding sequences across the genome [11]. New methods are demonstrating that there are likely to be many more repeat expansion loci that have clinical associations [12, 13]. Available evidence points to the involvement of DNA repair proteins, whose activities underlie repeat length alterations for at least some of these diseases [14–16]. To provide a wider perspective on the potential operation of these mechanisms across the repeat expansion disorders, Zhao et al. [17] consider the evidence from mouse models of Friedreich's ataxia and Fragile X-related disorders, caused by expansions in (GAA)n and (CGG)n expansions, respectively. They discuss the mechanisms operating in HD that are also likely to operate in other non-CAG expansion disorders, despite differences in genomic location, repeat motif sequence and pathogenic length of the repeats.

Potential molecular mechanisms underlying disease modification that arise from human genetic data are explored by Maiuri et al. [18]. These include somatic repeat expansions but also indicate other mechanisms that might be operating prior to, in parallel with, or downstream of somatic repeat expansion: processes that may lead to a vicious cycle of DNA damage inducing somatic expansion, inducing more DNA damage [19]. Critically, we do not know what level of somatic *HTT* CAG expansion is required to render cells dysfunctional or to cause cell death. This is important for a full understanding of the pathogenic process and has implications for potential therapeutic approaches in HD. Donaldson et al. [20] set out to explore the threshold of the CAG expansion that elicits intracellular toxicity in HD and how that could be better understood and measured in the future.

Finally, Benn et al. [21], viewing the available biological evidence regarding somatic repeat instability in HD, propose the steps that will be necessary to generate new therapeutics for HD, or potentially repurpose existing therapeutics to target DNA repair mechanisms and somatic repeat expansion. They discuss drugs currently available, some in clinical use, that target the DNA damage response and repair pathways in oncology, showing that targeting these pathways therapeutically can be done. They detail the steps in the therapeutic pipeline, outline what information we possess, and focus on key considerations

with respect to drug discovery and development using DNA damage and repair mechanisms as a target for repeat expansion diseases, including HD.

This is the first time much of this information has been brought together and synthesised with a focus on HD. We hope that readers find this special issue educational and stimulating and that it serves to speed discovery and treatments. We learnt a lot – we hope our readers do likewise!

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