Title: Disease-Associated Repeat Instability and Mismatch Repair

Author: Monika H.M. Schmidt Christopher E. Pearson

PII: S1568-7864(15)30107-5
DOI: http://dx.doi.org/doi:10.1016/j.dnarep.2015.11.008
Reference: DNAREP 2183

To appear in: *DNA Repair*

Received date: 16-11-2015
Revised date: 23-11-2015
Accepted date: 30-11-2015

Please cite this article as: Monika H.M.Schmidt, Christopher E.Pearson, Disease-Associated Repeat Instability and Mismatch Repair, DNA Repair http://dx.doi.org/10.1016/j.dnarep.2015.11.008

Disease-Associated Repeat Instability and Mismatch Repair

Monika H.M. Schmidt[a,b] & Christopher E. Pearson[a,b*]

[a]Genetics & Genome Biology, The Hospital for Sick Children, Peter Gilgan Centre for Research & Learning, 686 Bay St., Toronto, Ontario, M5G 0A4, *and* [b]Department of Molecular Genetics, University of Toronto, Medical Sciences Bldg., 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada

Abstract

Expanded tandem repeat sequences in DNA are associated with at least 40 human genetic neurological, neurodegenerative, and neuromuscular diseases. Repeat expansion can occur during parent-to-offspring transmission, and arise at variable rates in specific tissues throughout the life of an affected individual. Since the ongoing somatic repeat expansions can affect disease age-of-onset, severity, and progression, targeting somatic expansion holds potential as a therapeutic target. Thus, understanding the factors that regulate this mutation is crucial. DNA repair, in particular mismatch repair (MMR), is the major driving force of disease-associated repeat expansions. In contrast to its anti-mutagenic roles, mammalian MMR curiously drives the expansion mutations of disease-associated (CAG)•(CTG) repeats. Recent advances have broadened our knowledge of both the MMR proteins involved in disease repeat expansions, including: MSH2, MSH3, MLH1, PMS2, and MLH3, as well as the types of repeats affected by MMR, now including; (CAG)•(CTG), (CGG)•(CCG), and (GAA)•(TTC) repeats. Mutagenic slipped-DNA structures have been detected in patient tissues, and the size of the slip-out and their junction conformation can determine the involvement of MMR. Furthermore, the formation of other unusual DNA and R-loop structures is proposed to play a key role in MMR-mediated instability. A complex correlation is emerging between tissues showing varying amounts of repeat instability and MMR expression levels. Notably, naturally occurring polymorphic variants of DNA repair genes can have dramatic effects upon the levels of repeat instability, which may explain the variation in disease age-of-onset, progression and severity. An increasing grasp of these factors holds prognostic and therapeutic potential.

* Corresponding author: Tel: +1-416-813-8256; E-mail: cepearson.sickkids@gmail.com