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Repeat-Associated Diseases, Mutagenesis, Pathogenesis,
and Therapeutic Avenues

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At least 40 neurological, neurodegenerative and neuromuscular diseases are associated with unstable repeating DNA sequences. Diseases include fragile X mental retardation, myotonic dystrophy, Huntington's disease, and a series of spinocerebellar ataxias. Repeat instability often involves expansions of simple repeats like trinucleotides CAG/CTG but also includes tetra-, penta-, hexa-, and dodecanucleotide repeats. The list of diseases caused by unstable repeats is continuing to grow with the recent discoveries of spinocerebellar ataxia type 36, amyotrophic lateral sclerosis and frontotemporal dementia being caused by unstable hexanucleotide repeats. In many diseases the repeats continue to expand through generations leading to increased disease severity and decreasing age-of-onset through generations—a phenomenon known as genetic anticipation. Moreover, the repeats continue to expand through the course of an individ-

ual's life, with expansions being largest in affected tissues. Such somatic expansions are likely sources for the progressive nature of the diseases as well as their tissue selectivity. Pathogenic mechanisms involve loss-of-function, toxic-RNA-gain-of-function, toxic-protein gain-of-function, toxic overexpression of non-mutant proteins, aberrant splicing, aberrant transcriptome expression, and possibly aberrant translation of polyamino acid repeats. There are many downstream effects with numerous clinical presentations. Both the processes of repeat expansion and pathogenesis are potential targets for therapeutic intervention for affected individuals. Recent advances in our understanding of the avenues will be covered.

※The authors declare there is no conflict of interest relevant to this article.