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A CAG repeat threshold for therapeutics targeting somatic instability in Huntington's disease

Sarah G Aldous[1], Edward J Smith[1], Christian Landles[1], Georgina F Osborne[1], Maria Cañibano-Pico[1], Iulia M Nita[1], Jemima Phillips[1], Yongwei Zhang[2], Bo Jin[2], Marissa B Hirst[3], Caroline L Benn[4], Brian C Bond[5], Winfried Edelmann[2], Jonathan R Greene[3], Gillian P Bates[1]
Affiliations expand

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Abstract

The Huntington's disease mutation is a CAG repeat expansion in the huntingtin gene that results in an expanded polyglutamine tract in the huntingtin protein. The CAG repeat is unstable, and expansions of hundreds of CAGs have been detected in Huntington's disease post-mortem brains. The age of disease onset can be predicted partially from the length of the CAG repeat as measured in blood. Onset age is also determined by genetic modifiers, which in six cases involve variation in DNA mismatch repair pathways genes. Knocking-out specific mismatch repair genes in mouse models of Huntington's disease prevents somatic CAG repeat expansion. Taken together, these results have led to the hypothesis that somatic CAG repeat expansion in Huntington's disease brains is required for pathogenesis. Therefore, the pathogenic repeat threshold in brain is longer than (CAG)40, as measured in blood, and is currently unknown. The mismatch repair gene MSH3 has become a major focus for therapeutic development, as unlike other mismatch repair genes, nullizygosity for MSH3 does not cause malignancies associated with mismatch repair deficiency. Potential treatments targeting MSH3 currently under development include gene therapy, biologics and small molecules, which will be assessed for efficacy in mouse models of Huntington's disease. The zQ175 knock-in model carries a mutation of approximately (CAG)185 and develops early molecular and pathological phenotypes that have been extensively characterised. Therefore, we crossed the mutant huntingtin allele onto heterozygous and homozygous Msh3 knock-out backgrounds to determine the maximum benefit of targeting Msh3 in this model. Ablation of Msh3 prevented somatic expansion throughout the brain and periphery, and reduction of Msh3 by 50% decreased the rate of expansion. This had no effect on the deposition of huntingtin aggregation in the nuclei of striatal neurons, nor

on the dysregulated striatal transcriptional profile. This contrasts with ablating Msh3 in knock-in models with shorter CAG repeat expansions. Therefore, further expansion of a (CAG)185 repeat in striatal neurons does not accelerate the onset of molecular and neuropathological phenotypes. It is striking that highly expanded CAG repeats of a similar size in humans cause disease onset before 2 years of age, indicating that somatic CAG repeat expansion in the brain is not required for pathogenesis. Given that the trajectory for somatic CAG expansion in the brains of Huntington's disease mutation carriers is unknown, our study underlines the importance of administering treatments targeting somatic instability as early as possible.

Keywords: Huntington’s disease; MSH3; genetic modifiers; pathogenic CAG repeat length; somatic CAG repeat instability.