Investigation of the pathogenic agent in a *Drosophila* model of polyglutamine disease

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Declaration

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Catherine McLeod

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Abstract

A substantial body of evidence supports the identity of polyglutamine as the pathogenic agent in a variety of human neurodegenerative diseases (some of which are clinically indistinguishable from the polyglutamine diseases) that are due to expanded repeats that cannot encode polyglutamine. As polyglutamine cannot be the pathogenic agent in these diseases, either the different disorders have distinct pathogenic pathways or some other common agent is toxic in all of the expanded repeat diseases. Recently, evidence has been presented in support of RNA as the pathogenic agent in Fragile X- associated tremor/ataxia syndrome (FXTAS), caused by expanded CGG repeats at the *FRAXA* locus. A *Drosophila* model of FXTAS, in which 90 copies of the CGG repeat are expressed in an untranslated region of RNA, exhibits both neurodegeneration and similar molecular pathology to the polyglutamine diseases. Therefore the identity of the pathogenic agent in a *Drosophila* model of the polyglutamine diseases was explored. This included examining the possibility that RNA mediates the disease phenotype by expression of repeat constructs including expanded CAA and CAG repeats and an untranslated CAG repeat. Alternative putative pathogenic mechanisms including polyalanine toxicity, DNA damage and axonal blockage were also examined. The results obtained support the identity of polyglutamine as the pathogenic agent in this *Drosophila* model of polyglutamine disease. However, additional preliminary results were obtained suggesting that repeat-containing RNA expressed at a sufficiently high level can exert a toxic effect. The phenotype induced by repeat-containing RNA in *Drosophila* is milder than the polyglutamine phenotype, characterised by degeneration and shows cell type-specificity. Thus, although in this *Drosophila* model, polyglutamine toxicity appears to occur in the absence of a contribution by RNA, the possibility that it contributes towards pathogenesis in the human diseases cannot be ruled out.