

P034 Toxic effects of expanded polyalanine repeats in *Drosophila*
Zdenek Berger, Janet E. Davies, Cahir J. O'Kane,
David C. Rubinsztein

*Departments of Medical Genetics, University of Cambridge,
Cambridge Institute for Medical Research, Wellcome Trust/MRC
Building, Addenbrooke's Hospital, Hills Road, Cambridge, CB2
2XY, UK. Department of Genetics, University of Cambridge, CB2
3EH, UK*

The expansion or duplication of polyalanine repeats is the primary mutation causing at least nine diseases. In one of these diseases, oculopharyngeal muscular dystrophy, polyalanine expansions in the polyadenine binding protein 2 (PABP2) lead to the formation of intranuclear aggregates similar to those seen in polyglutamine diseases.

Expression of polyalanine expansions has been previously shown to form aggregates and cause toxicity in mammalian cells. In order to study the effects of polyalanine expansion mutations *in vivo*, we have generated a *Drosophila* model expressing nuclear-targeted green fluorescent protein tagged with short and long polyalanine tracts.

Expanded alanines form aggregates *in vivo* and cause toxic effects when expressed in a variety of different tissues in *Drosophila*. The pathogenic effects are alleviated by aggregation inhibitor Congo red. These data suggest that toxicity of polyalanine expansions is at least partially associated with their tendency to aggregate. In addition, toxicity of polyalanines is attenuated by rapamycin, which induces degradation of the mutant protein by autophagy. This suggests that induction of autophagy might be a valid therapeutic approach for other diseases caused by aggregate-prone proteins.