# Modifiers of polyglutamine disease pathogenesis

https://neurodegenerationresearch.eu/survey/title-of-pimodifiers-of-polyglutamine-disease-pathogenesis/

**Title of project or programme**

Title of PI Modifiers of polyglutamine disease pathogenesis

**Principal Investigators of project/programme grant**

| Title | Forname | Surname | Institution | Country |
|---|---|---|---|---|
| Professor | David | Rubinsztein | University of Cambridge | UK |

**Address of institution of lead PI**

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|---|---|
| Institution | University of Cambridge |
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**Country**

- United Kingdom

**Total sum awarded (Euro)**

3448417.47

**Start date of award**

01-01-2007

**Total duration of award in months**

48

**The project/programme is most relevant to**

- Huntington's disease

**Research abstract in English**

Huntington's disease (HD) is an incurable, autosomal dominant neurodegenerative disease. It is caused by the abnormal expansion of a CAG trinucleotide repeat close to the N-terminal of the coding part of the gene encoding huntingtin. The CAG repeats encode an expanded polyglutamine (polyQ) repeat tract. About 70% of the variance in the age at onset of HD can be accounted for by CAG repeat number in the disease-causing allele. The residual variance in age at onset unaccounted for by the CAG repeat numbers is likely to be partly due to genetic factors. This proposal aims to characterise genetic pathways that suppress polyglutamine toxicity in vivo. These genes and pathways will be used to prioritise and eventually select druggable targets (e.g. G-protein coupled receptors, ion channels, enzymes and nuclear receptors) for further investigation. We will identify such modifiers using mouse ENU mutagenesis and genome-wide RNAi analysis in fly models

integrated with cell biology studies of modifiers. The logistics and screening systems for the mouse ENU program and the RNAi fly screen have been established in current MRC grants held by the applicants. For the ENU program, we have been identifying dominant enhancer or suppressor mutations of the polyQ phenotype by mating hemizygous female transgenic mice expressing the first 171 residues of huntingtin with 82 repeats on a C3HxC57BL/6 background with BALB/c male mice that have been mutagenised with ENU. To date, the screen has been fruitful, yielding 18 phenodeviants – 11 enhancers and 7 suppressors. In the continuation of the program, we aim to identify the causal modifier mutations and continue with restricted further screening focussing on suppressors. For the fly screen, we have developed a moderate-throughput system using polyQ flies expressing the mutant transgene in the eyes. The polyQ fly eyes show loss of pigmentation and necrotic spots. These flies are crossed to RNAi-bearing flies, to give progeny that express both the mutant polyQ allele and the RNAi in the same cells. After optimising the system, we are now screening ~1000 RNAi lines per month. So far we have screened ~2000 crosses, with a suppressor hit rate of ~2.3% and enhancer hit rate of ~9%. For the new program, we aim to complete the genome-wide screen, focussing on supressors. We will select high priority hits from this screen that are conserved in humans, elucidate their functional roles and confirm that they act in the same way in mouse models.

**In which category does this research fall?**

- Basic research