# Molecular Genetic Characterization of SCA8

https://neurodegenerationresearch.eu/survey/molecular-genetic-characterization-of-sca8-2/

**Principal Investigators**

RANUM, LAURA P W

**Institution**

UNIVERSITY OF FLORIDA

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

Molecular Genetic Characterization of SCA8

**Source of funding information**

NIH (NINDS)

**Total sum awarded (Euro)**

€ 2,311,196.33

**Start date of award**

16/06/2000

**Total duration of award in years**

3

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

Spinocerebellar ataxia (SCA)

**Keywords**

Spinocerebellar Ataxias, Molecular Genetics, gain of function, Tremor,

**Research Abstract**

? DESCRIPTION (provided by applicant): Research on spinocerebellar ataxia type 8 (SCA8) supported by this application has led to two discoveries that fundamentally change our understanding of how a broad category of microsatellite expansion mutations are expressed. First, we demonstrated that the SCA8 CTG•CAG expansion is bidirectionally transcribed1. This was the first demonstration that a single expansion mutation could lead to the expression and

accumulation of toxic CUG and CAG expansion RNAs and a CAG-encoded polyGln expansion protein1. Second, we discovered that the canonical rules of translation do not apply for CTG•CAG repeats and that CAG and CUG expansion transcripts can express homopolymeric expansion proteins in all three frames without an AUG start codon2. We showed this repeat associated non-ATG (RAN) translation is hairpin-dependent, occurs without frameshifting or RNA editing and is observed in cell culture and SCA8 patient tissues2. RAN translation also occurs in myotonic dystrophy type 1 (DM1)2, C9ORF72 amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD9)3-5, and fragile X tremor ataxia syndrome (FXTAS)6. The discoveries of bidirectional transcription and RAN translation change our understanding of how genes are expressed and highlight the need for therapies that target both sense and antisense transcripts as well as RAN proteins. Our central hypothesis is that both RNA and RAN gain of function (GOF) contribute to SCA8 and can be mitigated by therapies based on MBNL1 overexpression or RNA knockdown. Our specific aims will test the following hypotheses: 1) RNA gain of function and RAN translation contribute to SCA8; 2) RAN translation can be modulated by MBNL proteins and stress pathways; 3) antisense oligo (ASO) knockdown of ATXN8 and ATXN8OS will block RNA and RAN effects and reverse disease in an SCA8 mouse model.

**Lay Summary**
PUBLIC HEALTH RELEVANCE: We have discovered a new translational mechanism that directs expression of an unexpected category of proteins lacking the normal regulatory signals. The project goals are to understand how RNA and these novel proteins contribute to SCA8 and to develop therapeutic strategies.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Spinocerebellar ataxia (SCA)

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
N/A