

Title: Humanized SCA3 knock-in mouse: progress in identification of new deregulated molecules
by high throughput NGS and proteomic studies

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Humanized SCA3 knock-in ataxin-3 mouse model (Ki91) contains the following hallmarks of the disease: instability of the CAG mutation, ataxin-3 positive inclusions, astrogliosis, purkinje cell degeneration and early transcriptional changes. To provide a more holistic view of the neurodegenerative process in SCA3 Ki91 knock-in model we proposed to identify the deregulated molecules using transcriptome, proteome, phosphoproteome and ubiquitome profiling by NGS and mass spectrometry. The homozygous k300 knock-in animals containing the CAG repeats without Ataxin-3 protein were also included in NGS transcriptome studies.

The NGS of cerebellum and cortex of pre-symptomatic Ki91 (mut/mut) 8-week old animals has shown deregulation of several genes on mouse chromosome 12 and 19. Serpina3n which is located at chromosome 12 was deregulated in both Ki91 and K300 mouse. The induction of Serpina3n in both models increased when both alleles contained CAG repeat tract. Moreover the increased expression of Serpina3n was identified in astrocytes but not in granular cell neurons in the cerebellum.

The enrichment and profiling of phosphoproteins was performed in pre-symptomatic Ki91 (mut/mut) 8-week old animals and identified number of deregulated phosphoproteins. Among deregulated proteins the GO analysis identified RNA binding, axon and dendrite development, regulation of synaptic transmission, learning, regulation of cytoskeleton organization.

Summarizing young presymptomatic homozygous Ki91 animals reveal limited number of transcriptional changes predominantly clustering on mouse chromosome 12 and 19 and show greater scale of phosphoproteins deregulation in cerebellum and cerebral cortex.

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