evotec

#RESEARCHNEVERSTOPS

HD Proteome Base

FOR FURTHER INFORMATION:

Evotec (Munich) GmbH
Am Klopferspitz 19a
Martinsried, Germany

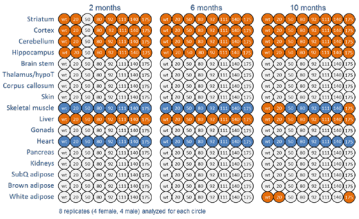
Dr Christoph Schaab
VP Proteomics
christoph.schaab@evotec.com

A Web-Based Data Repository for Time- and Tissue-Resolved Proteome Analysis of Huntington's Disease Mouse Knock-In Allelic Series

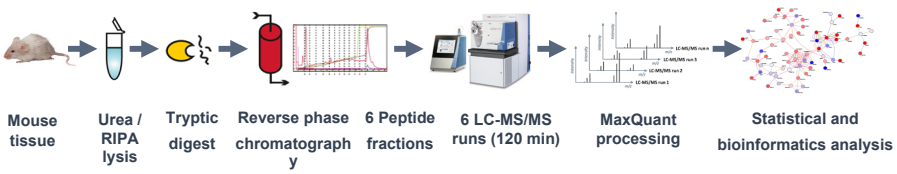
In order to gain a deeper understanding of the pathophysiological mechanisms in Huntington's disease (HD), we compared the proteomes between wild-type and heterozygous Huntingtin knock-in mice with increasing CAG repeat lengths in a number of different brain regions and peripheral tissues at three different ages (2, 6, and 10 months). The analysis of more than 1,200 tissue samples with on average 8,000 quantified proteins comprises one of the largest global, quantitative proteomics studies published so far. More importantly, it allows a systematic analysis of pathways and interaction networks on the protein level, the identi-fication of novel target candidates, and provides a comprehensive resource for training of system biology models.

MICE STRAINS AND COLLECTION OF TISSUES

- Wild-type and heterozygous HTT knock-in mice with increasing CAG repeat lengths.
- Fresh-frozen samples of various brain and peripheral tissues were collected at 2, 6, and 10 months.
- For each node, at least 8 replicates were analyzed. In total, more than 1,200 tissues.
- Allelic series for five tissues were completed so far (marked in orange).
- The same samples were also analyzed by RNAseq (available in HDinHD, https://www.hdinhd.org).

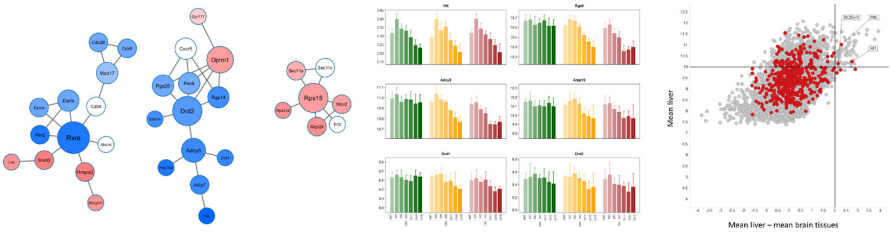


DEEP PROTEOME WORKFLOW



- All tissue samples were measured on Q Exactive or LTQ Orbitrap Velos instruments over three years. This corresponds to a totals of ~700 days measuring time.
- MS raw data was analyzed with the MaxQuant software for peptide and protein identification, as well as label-free quantification (LFQ).
- PLS normalization was applied in order to correct for processing batch effects.
- In total, 17,473 SwissProt mouse proteins were identified.

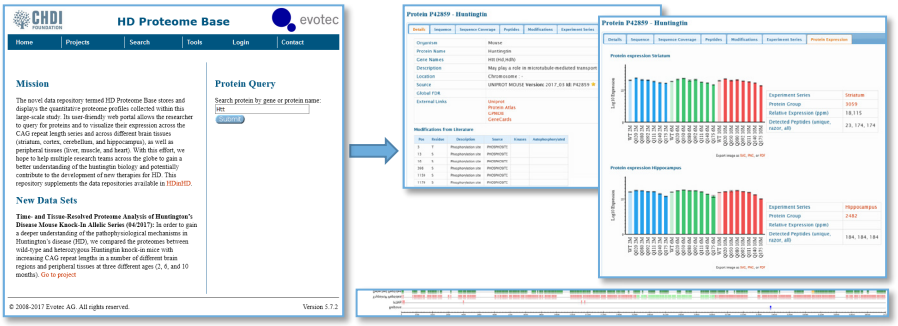
KEY FINDINGS IN BRAIN TISSUES AND LIVER



In brain tissues CAG repeat length dependent proteins are enriched in sub-networks and pathways related to calcium signaling (all), dopamine receptor signaling (striatum), glutamate metabolism (striatum), histidine metabolism (hippocampus), lipoprotein particle receptor binding (hippocampus).

A few liver-specific proteins are CAG repeat length dependent: the eukaryotic translation initiation factor Eif4g1, the peroxisomal coenzyme A diphosphatase Nudt7, and the microsomal triglyceride transfer protein Mttp.

HD PROTEOME BASE



The novel data repository termed HD Proteome Base stores and displays the quantitative proteome profiles collected within this large-scale study. The repository is publicly accessible through a user-friendly web portal that allows the researcher to query for proteins and to visualize their expression across the CAG repeat length series and across different brain tissues (striatum, cortex, cerebellum, and hippocampus), as well as peripheral tissues (liver, muscle, and heart).

With this effort, we hope to help multiple research teams across the globe to gain a better understanding of the huntingtin biology and potentially contribute to the development of new therapies for HD.

https://hdpb.evotec.com