Comparative study of Huntington's disease using biochemical, immunocytochemical and molecular genetic methods on the mouse, minipig and human tissues and cells / **HUNTINGTON**

7F14308

Czech-Norwegian Research Programme CZ09

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Prague

Project consortium

- **Promoter**:
- Institute of Animal Physiology and Genetics AS CR, v.v.i., Liběchov, Czech Republic (CZ1)

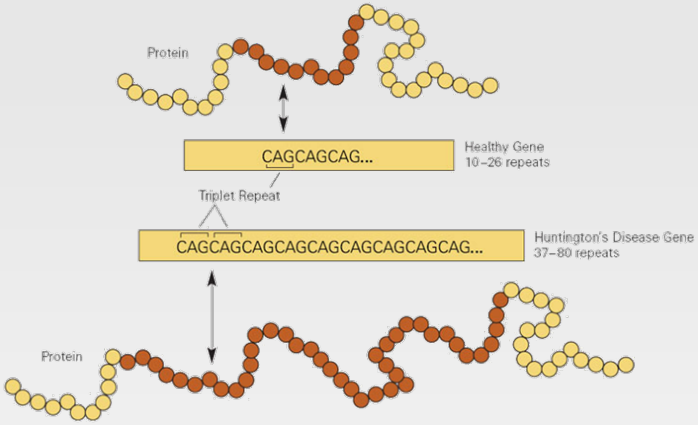
- **Partners**:
- Oslo University Hospital, Oslo, Norway (N1)

- Charles University in Prague, Czech Republic (CZ2)

- University of Oslo, Oslo, Norway (N2)

Why is project needed?

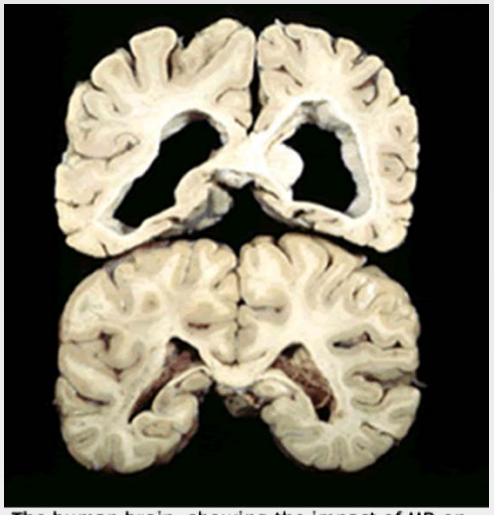
Huntington`s disease



protein Huntingtin

CAG → Q (34/39)

striatum, basal ganglia lesions



The human brain, showing the impact of HD on brain structure in the basal ganglia region of a person with HD (top) and a normal brain (bottom).

http://kobiljak.msu.edu

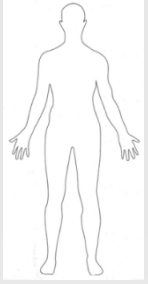
- no effective treatment to halt the progression or prevent the onset of Huntington Disease.
- complex pathophysiology of HD is not yet completely understood.

What are the project‘s objectives?

comparative studies, 3 models

R6/2 mice

Libechov TgHD minipig



HD patients

Different levels: metabolites, proteins, organels, cells, tissues, organs, whole body

WP1 Triplet instability in tissues

WP2 Role of mitochondria in pathophysiology of Huntington’s disease

WP3 Role of Golgi apparatus in pathophysiology of Huntington’s disease

WP4 Formation of huntingtin fibrillar oligomers and aggregates

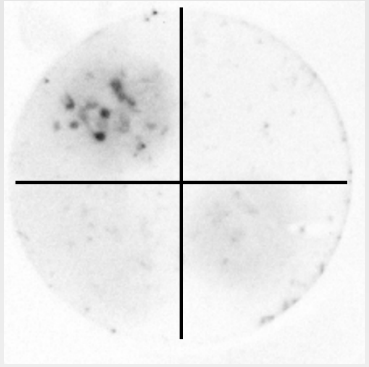
What is the project expected to achieve?

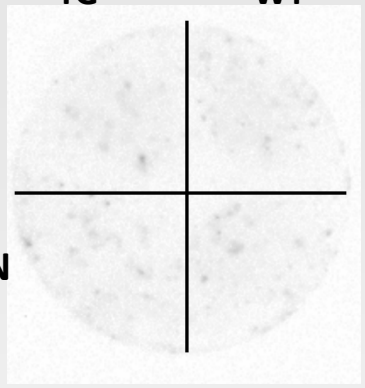
- **Expected results**:
- Improved knowledge about the pathophysiological mechanisms of HD
- Perfectly characterized model in presymptomatic stages of the disease
- To find potentional biomarkers of disease
- To provide a model for preclinical safety testing
- Application of non-invasive approach
- ----------
- **Outputs till 09/2016**:
- International conferences 2x
- Workshops 4x
- Posters 23x
- Publications 14x
- Diploma/bacchelor thesis 3x

3rd Conference on Large Animal Models of Neurodegenerative Diseases, Liblice, 9.-10.November 2015

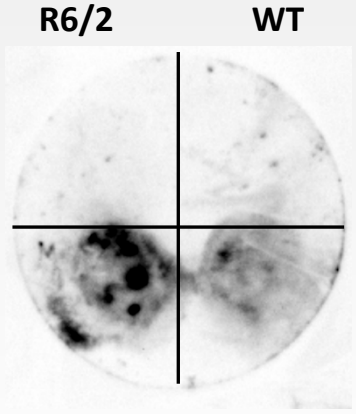
Filter retardation assay for detecting aggregates of huntingtin

MINIPIG





MICE



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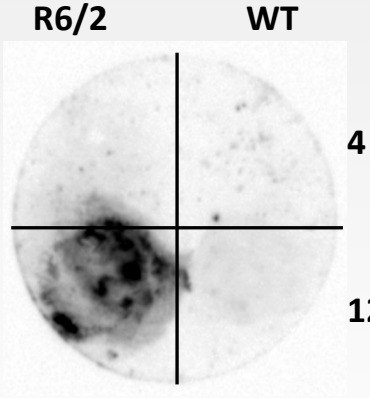

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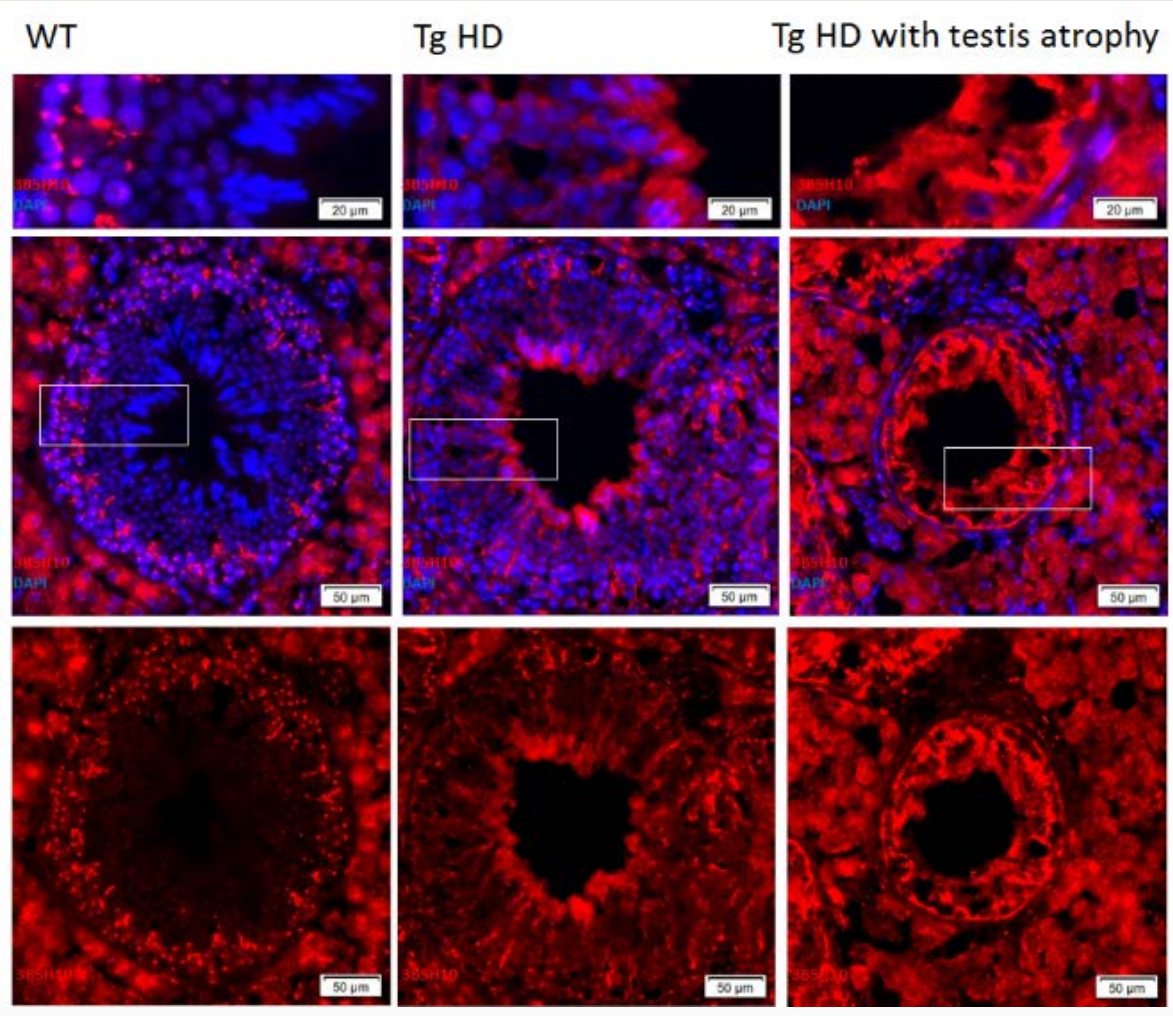
Localization of mutated huntingtin in the transgenic boar testis



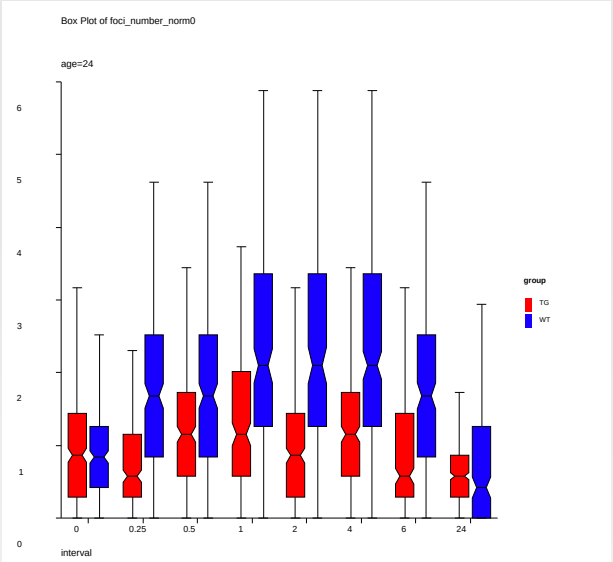
Immunofluorescence for 3B5H10antibody show localization of mtHtt in apical part of Sertoli cells of Tg HD boars

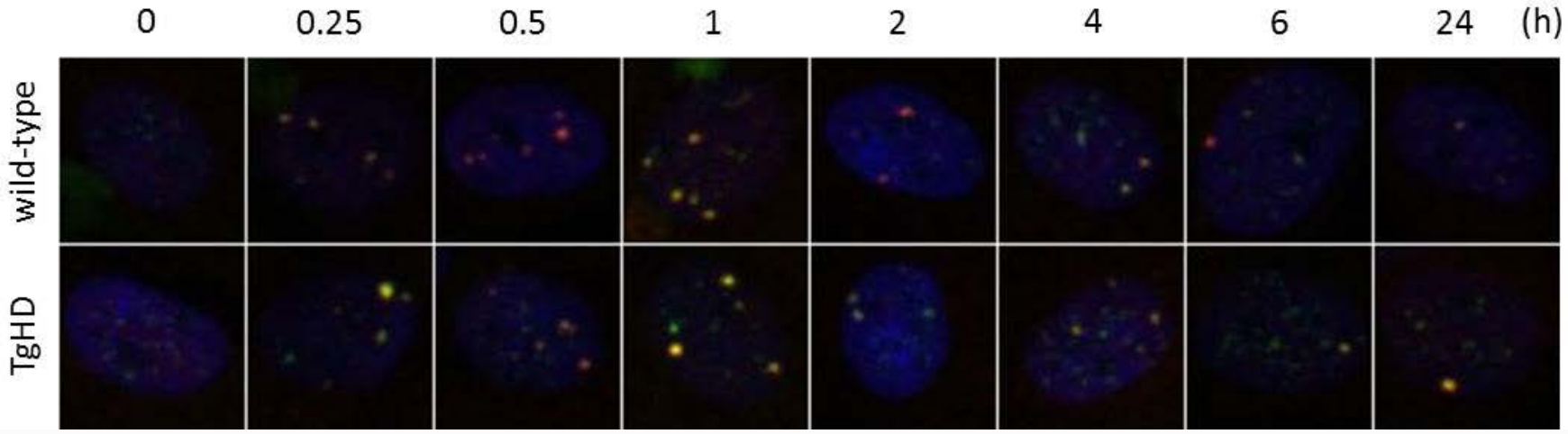
and cytoplasm of Sertoli cells in case of progresive apoptosis germ cells in seminiferous tubules of TgHD boar

Quantitative confocal microscopy to detect DNA damage defects

Compromised recognition of double strand breaks (DBS) in 24 and 48 months old TgHD fibroblasts

lower relative increase of γH2AX in TgHD in 24 and 48 month





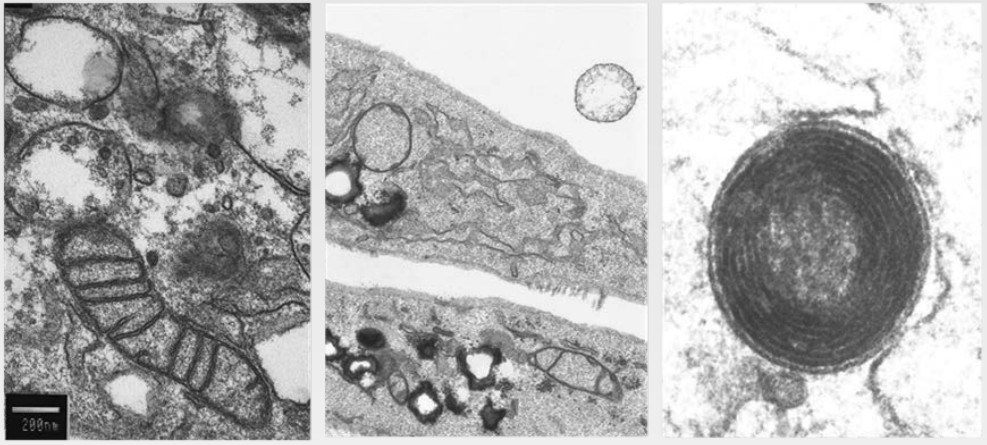
Mitochondrial impairment in patients with Huntington disease

Control

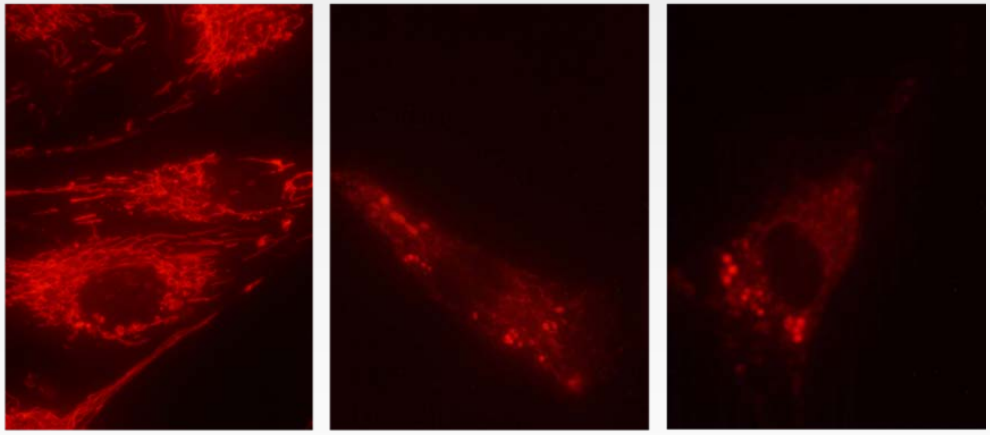
Patient

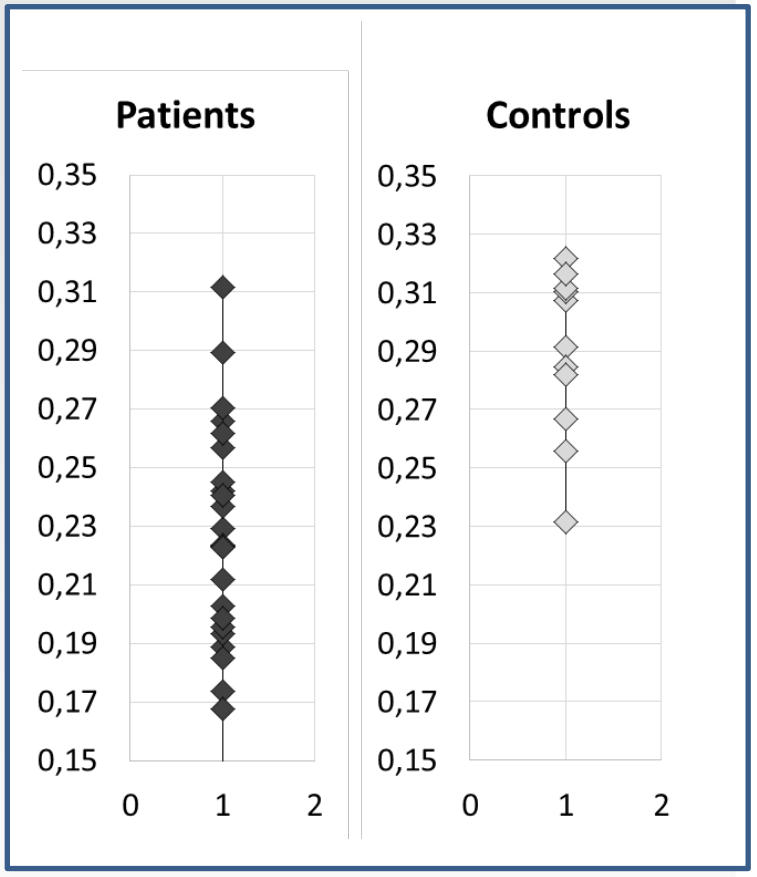
Mitochondrial density

Mitochondrial Ultrastructure



Mitochondrial Network





Myoblasts

Fibroblasts

Who is going to benefit from the project?

Global - *Patients and affected famillies*

Quality of life of affected individuals

Social and economical impact on families and *society*

International research community– improving knowledge, information availability

Local - *Scientific teams*

Exchange of know-how,

Increasing scientific potential

Education of PhD students

Exchange of students

Women's employment

Parental leave returnees

Thank you very much! Tusen takk!

Speakers :

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http://pigmod.avcr.cz/norske-fondy/