

# Ataksi



## Forskningsnyt

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Sektion for Neurogenetik,  
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Panum Institutet,  
Københavns Universitet

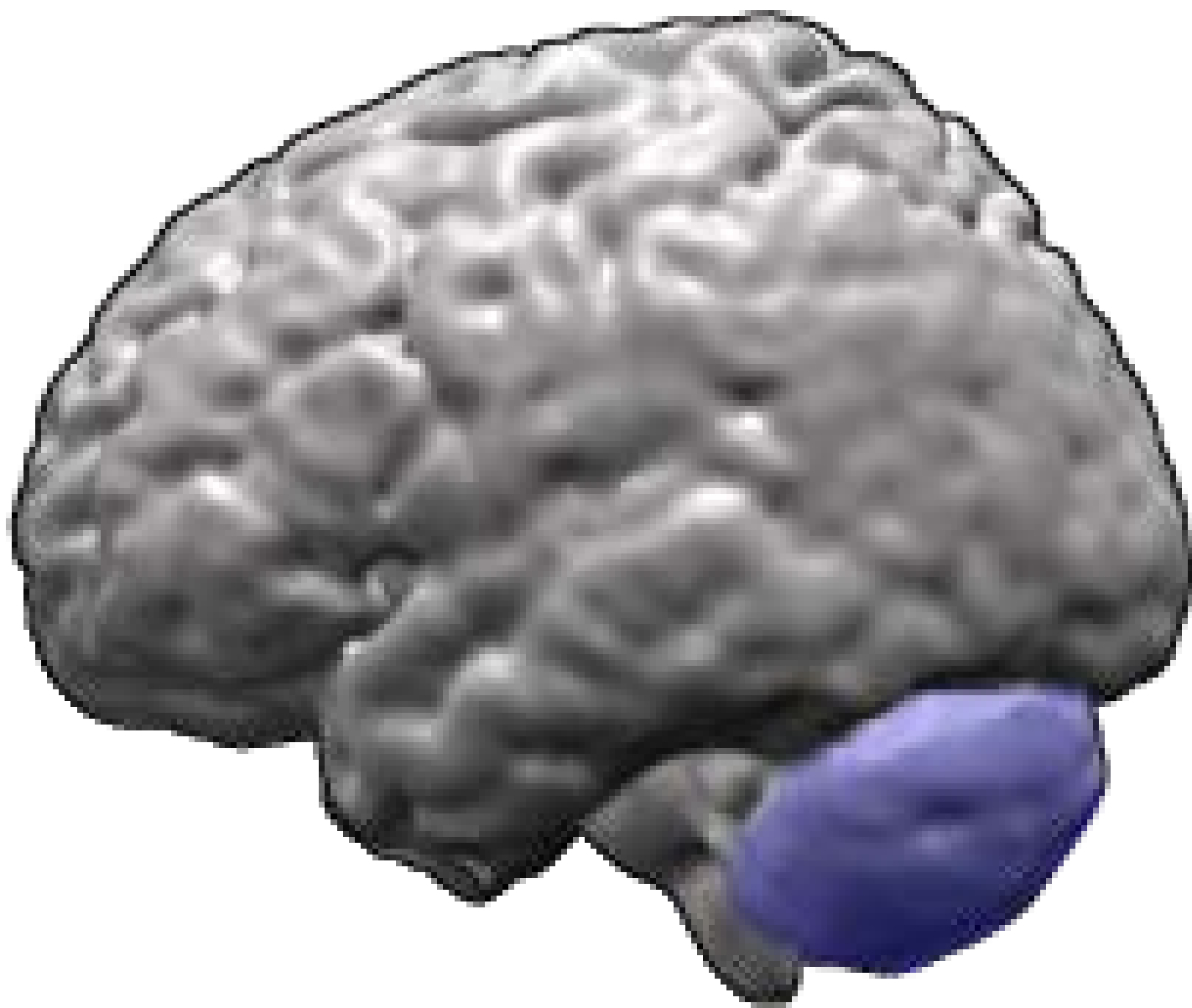


Rigshospitalet



# Disposition

- Ataksi – hvad er det?
- Symptomer
- Hvorfor bliver man syg?
- Behandling
- Forskning med fokus på behandling



# ATAKSI

- Ataxia ~ uorden, mangel på disciplin.
- Klinisk ataxi skyldes:
  1. Lillehjerne lidelse.
  2. Nedsat følesans
  3. Kraftnedsættelse
- Lillehjernen: Kontrol/regulation af muskelspænding og stilling. Fin-tuning og koordinering af bevægelser.

# ATAKSI

- Kan ses isoleret eller som led i anden sygdom f.eks sclerose.
- Debutalder: fra barndom op mod 70 år
- Symptomer: taleproblemer, dobbeltsyn, tygge/synkeproblemer, hoste, rysten, gang/balanceproblemer, føleforstyrrelser i fødder, vandladningsproblemer, problemer med koncentration og overblik.

# ATAKSI

- Typer: Arvelige og ikke-arvelige
- Ikke-arvelige: Alkohol og andre giftstoffer
- Vitaminmangel (B12, E-vitamin)
- Stofskiftesygdom
- Gluten Ataxi
- Multiple System Atrophy (MSA)
-

# ATAKSI

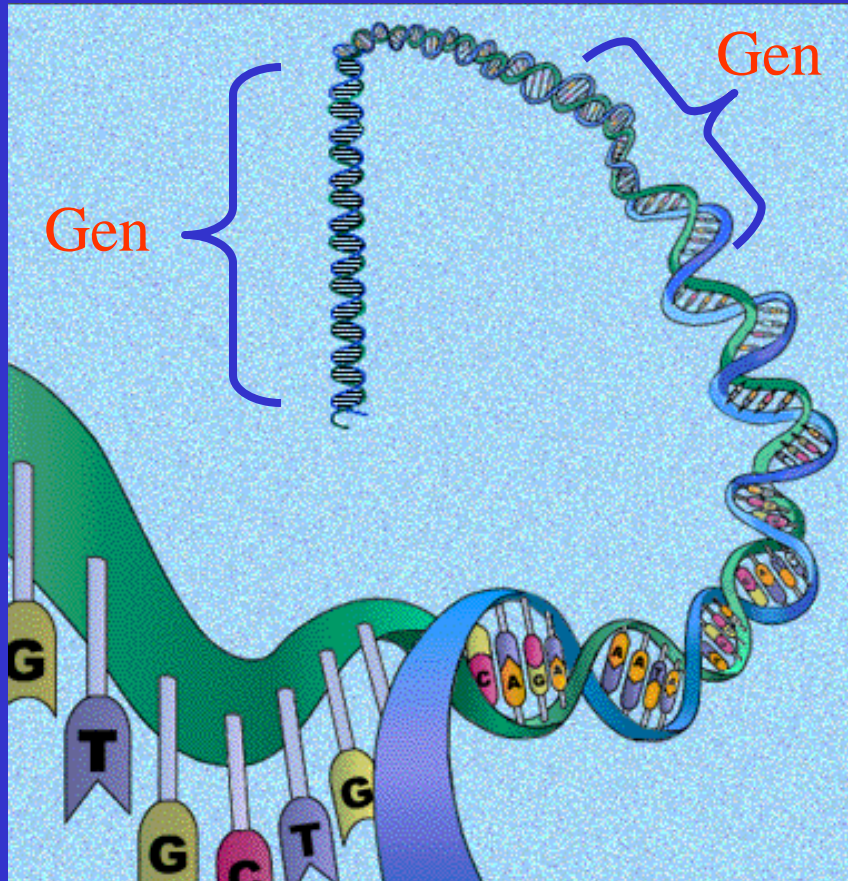
Udredning: Sygehistorie  
Hjernescanning  
Rygmarvsvæske  
Slægtsskema og stamtræ  
Blodprøver  
DNA-analyser  
Neurofysiologi  
Neuropsykologi

# Et menneske har 23 kromosom-par

Hvert kromosom-par består af et kromosom fra din mor og et fra din far



# Vores arvemateriale indeholder mange gener

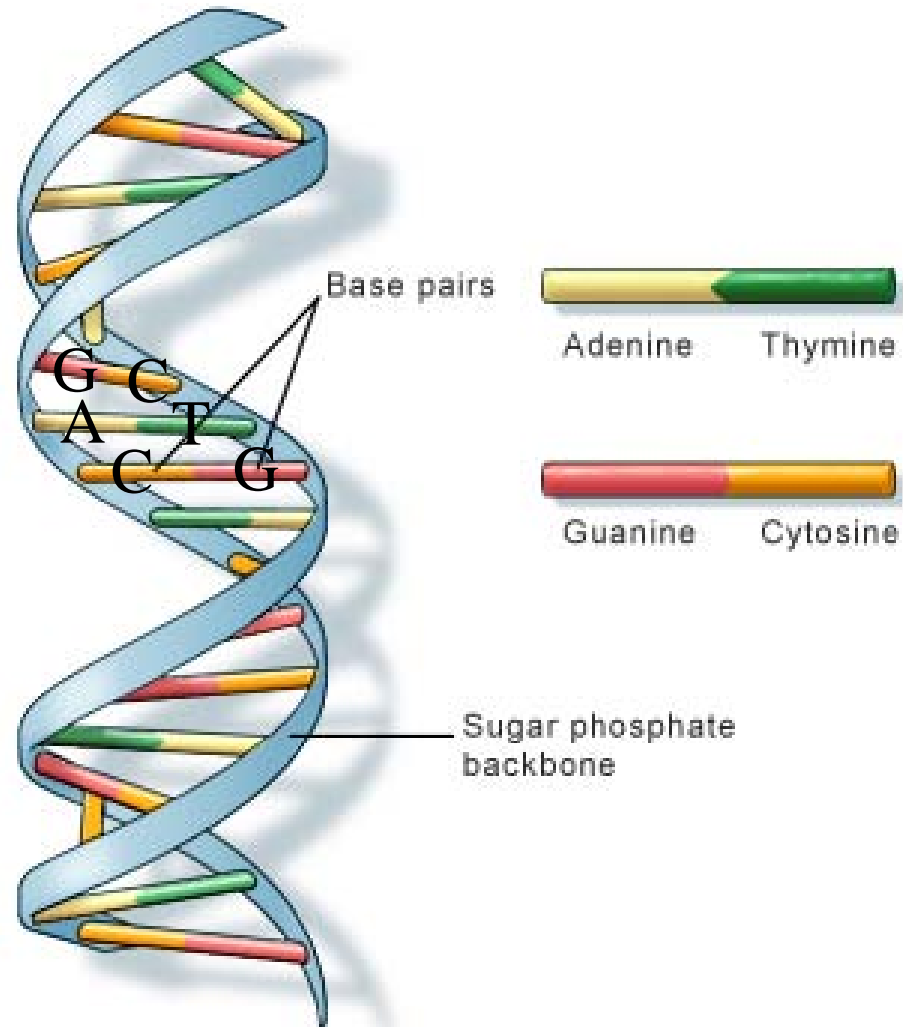


Arvematerialet er lange, trådformede DNA molekyler

Hvert DNA molekyle kaldes et kromosom, og indeholder mange gener = opskrift til mange proteiner

Proteiner er kæder af aminosyrer

# Udsnit af DNA



### Ingredienser:

3 dl let-, mini- eller skummetmælk

4 spsk. sukker

1/4 tsk. safran (stødt eller stilke)

25 g gær

1 spsk. oliemargarine

1/2 tsk. salt

ca. 500 g hvedemel

1 æg til pensling

ca. 1/2 dl rosiner til pynt.

### Tilberedning:

Varm halvdelen af mælken op med sukker og safran. Mælken skal ikke koge, bare være halvvarm så safranen kan opløse sin fine smag. Opløs gæren i resten af mælken i en ælteskål og hæld den varme mælk i. Tilsæt salt, oliemargarine og det meste af melet og ælt dejen godt. Tilsæt mere mel efterhånden, indtil dejen er god og blød og lige akkurat slipper fingrene. Kom et viskestykke eller film over skålen og lad dejen hæve ca. tre kvarter på et lunt sted. Når dejen er hævet rulles den ud i pølser som formes til små boller og snørkler som er typiske for luciabrød, - se billedet. Man kan også sno to pølser til en krans. Læg boller, snørkler eller krans på en bageplade beklædt med bagepapir. Pensl med æg og pynt med en rosin i midten af bollerne, eller i midten af snørklerne og lad dem efterhæve et kvarter. Bag brød og boller ved 225°C i ca. 15 min.

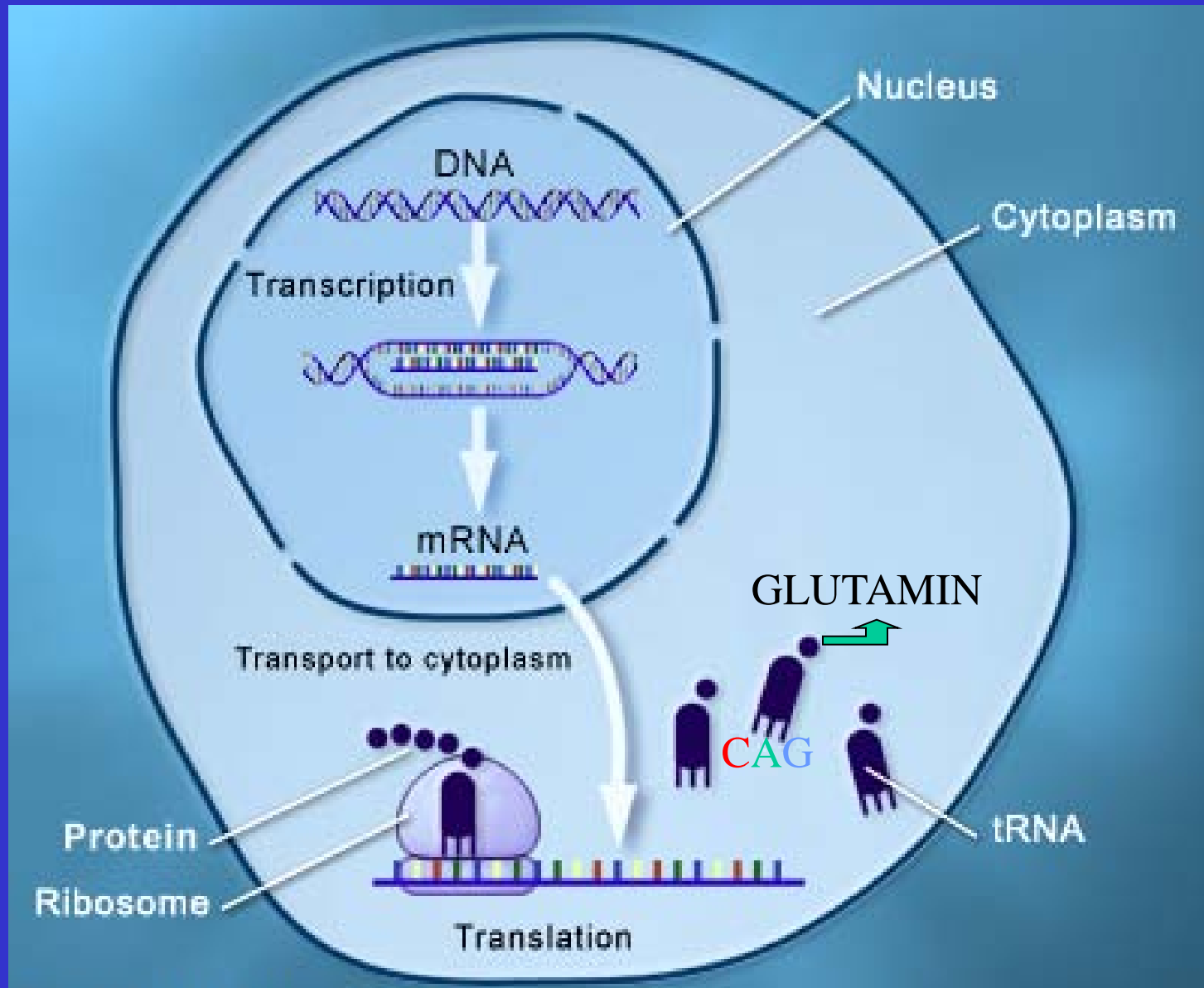
*Tip:* Luciabrød er en af svensk oprindelse. I Sverige er der tradition for at bruge safran i bagværk. Hvis man svært ved at skaffe safran, smager bollerne også fortrinligt med stødt kardemomme i stedet for.

# Lucia-boller






# Fra DNA til protein



# Hvad er en mutation?

En mutation er en ændring i et arveanlæg  
Mutationer vil ofte forårsage sygdom

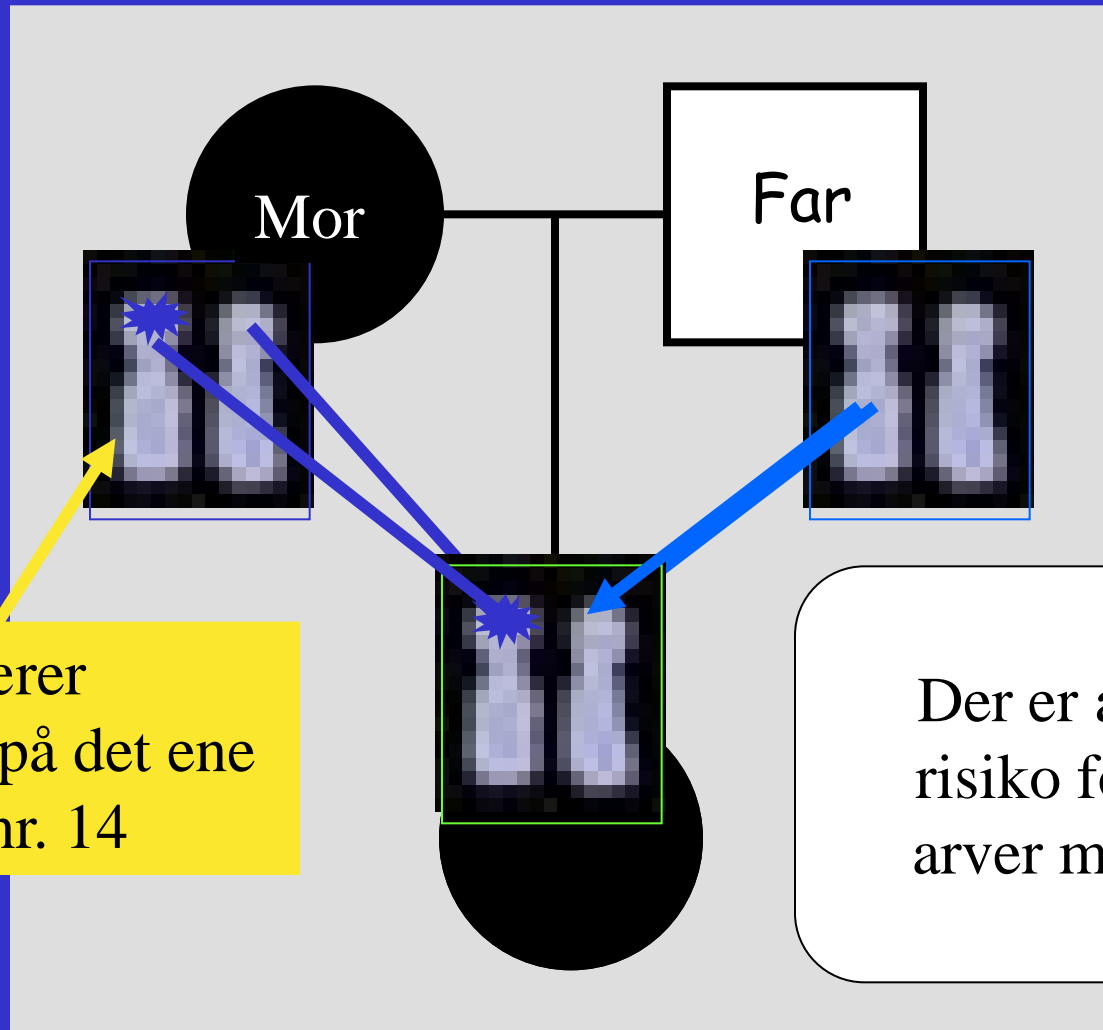
Et arveanlæg - eller et gen - er en "opskrift", der gør kroppen i stand til at lave et bestemt protein.



Hvad er et arveanlæg?

Proteinerne sørger for cellens vigtigste funktioner

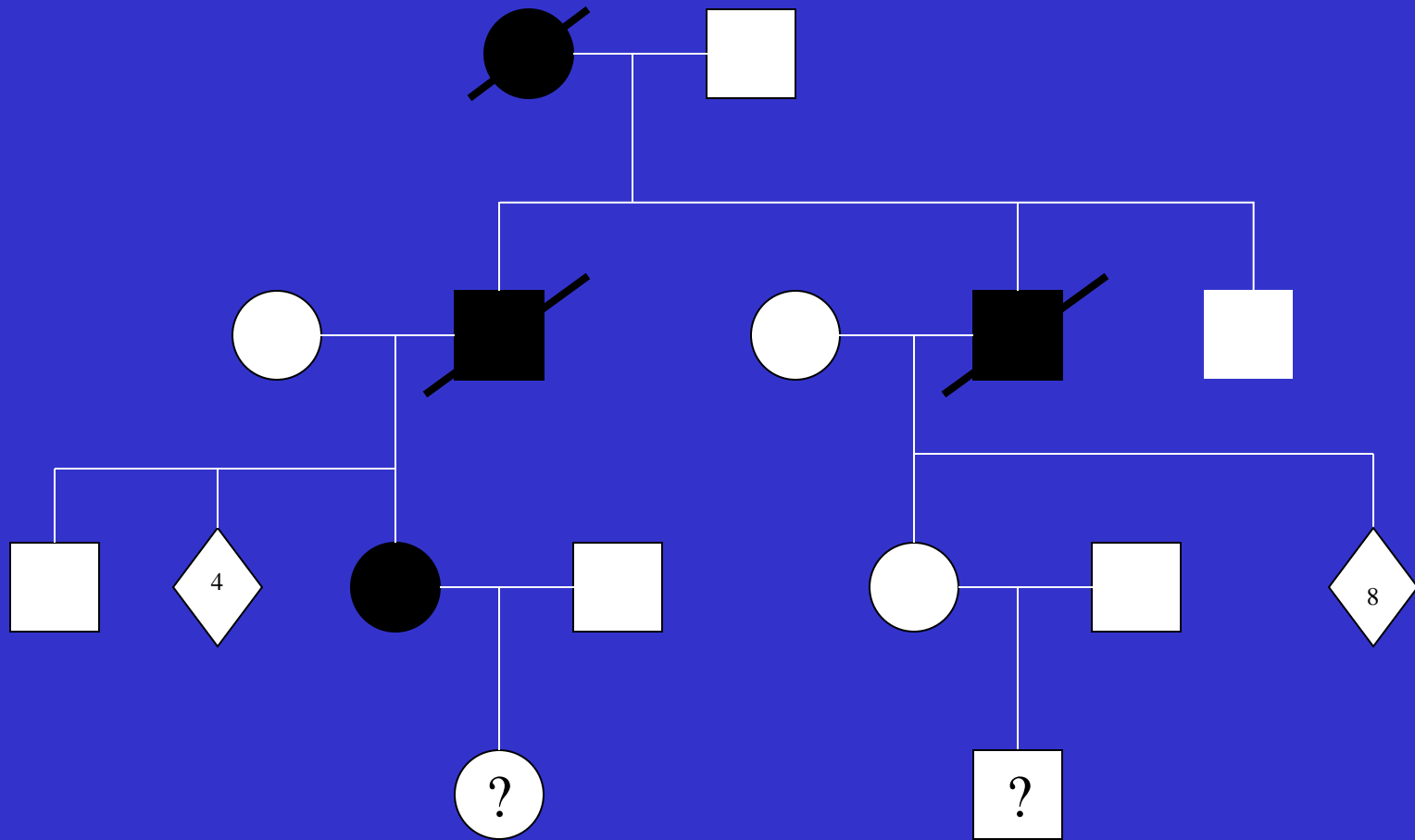
# Dominant arvelig sygdom



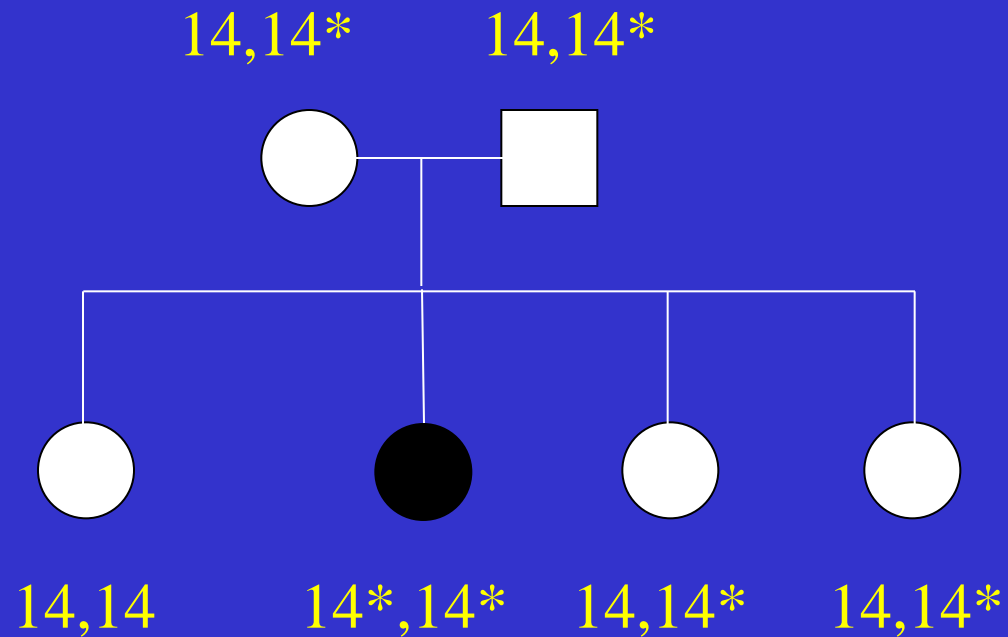
Moderen bærer mutationen på det ene kromosom nr. 14

Der er altså 50% risiko for at børn arver mutationen

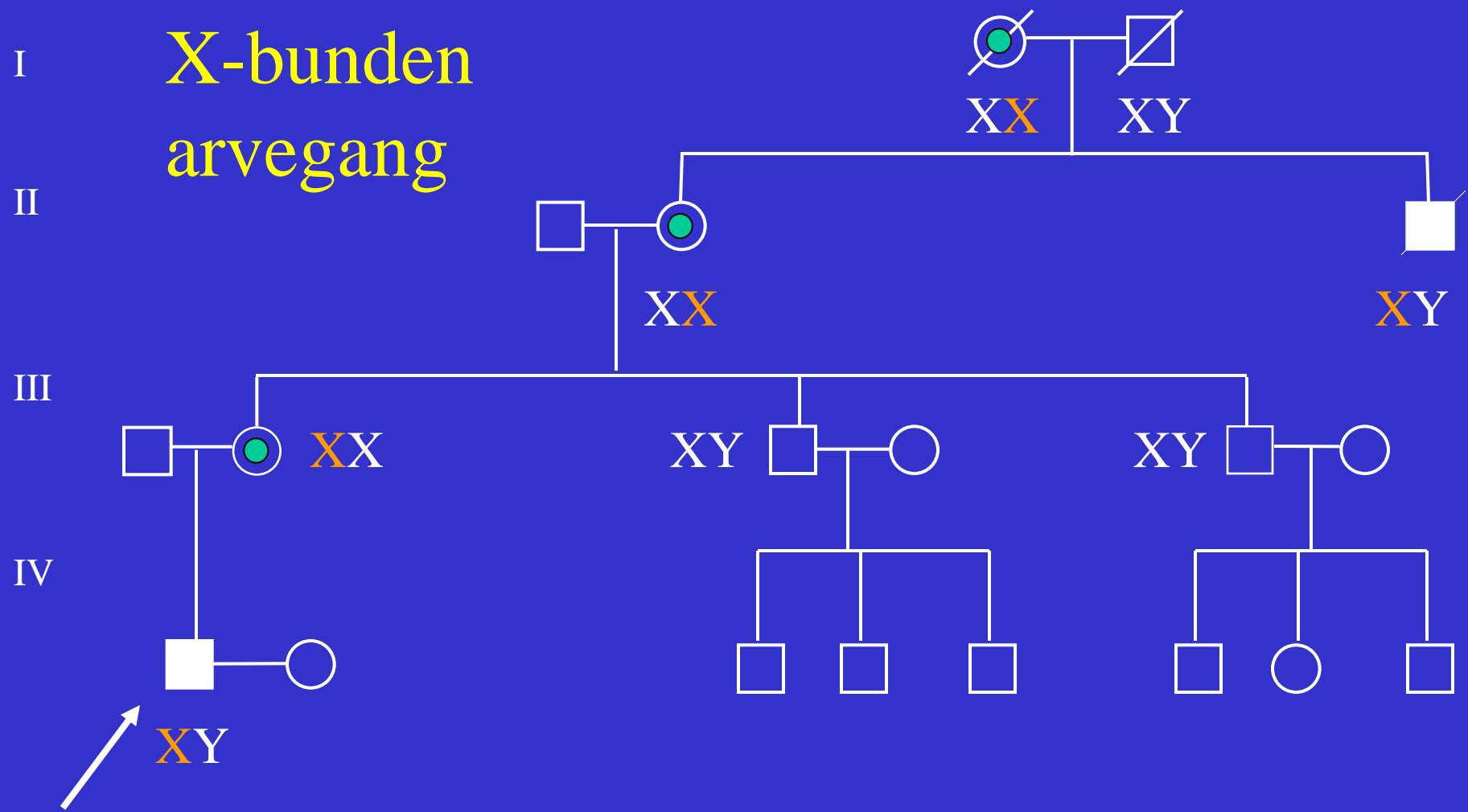
# Autosomal dominant arvegang



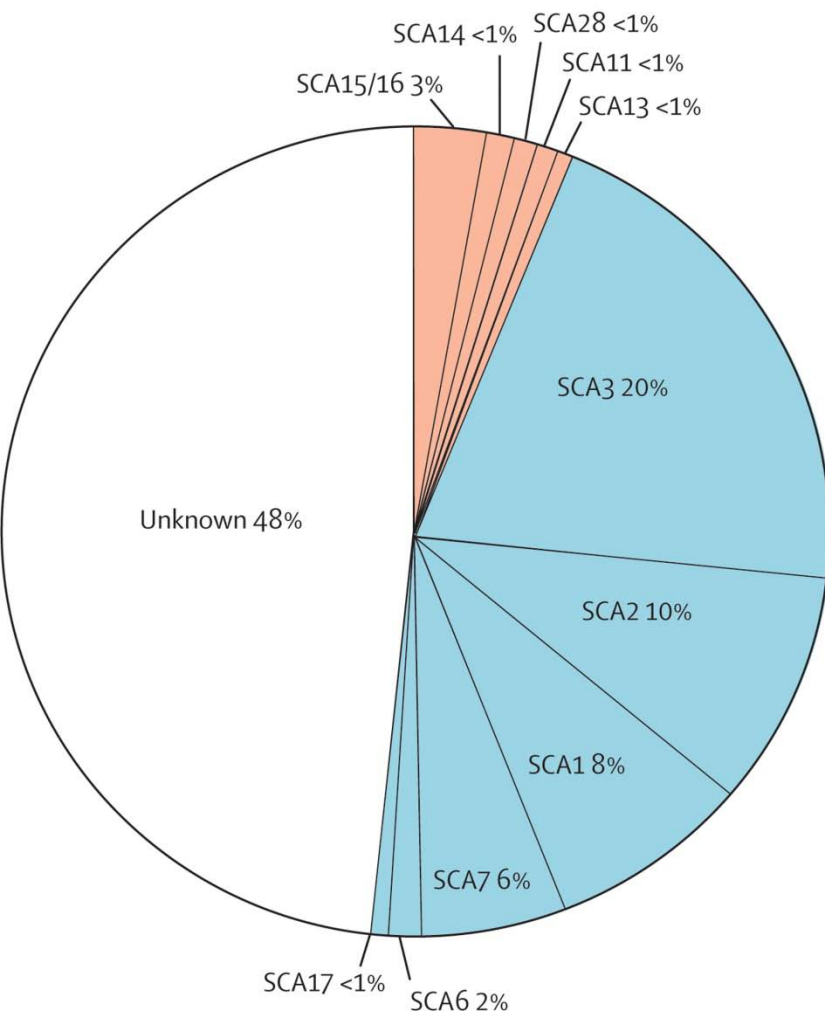
# Autosomal recessiv arvegang



# X-bunden arvegang



Conventional mutations 6%  
Polyglutamine expansions 45%



Dürr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *The Lancet Neurology*. Volume 9, Issue 9, September 2010, Pages 885-94.

Gene	Mutations	Key symptom in addition to cerebellar ataxia	
<b>Polyglutamine expansions SCAs</b>			
SCA1	ATXN1	CAG repeat	Early swallowing and respiratory signs
SCA2	ATXN2	CAG repeat	Slow eye movements
SCA3	ATXN3	CAG repeat	..
SCA6	CACNA1A	CAG repeat	..
SCA7	ATXN7	CAG repeat	Visual loss
SCA17	TBP	CAG repeat	Dementia
DRPLA	ATN1	CAG repeat	Epilepsy
<b>Non-coding expansion SCAs</b>			
SCA8	ATXN8 and ATXN8OS	CTG repeat	..
SCA10	ATXN10	ATTCT	..
SCA12	PPP2R2B	CAG repeat	..
SCA31=16qlinked	BEAN-TK2	TGGAA repeat	..
<b>Conventional mutations SCAs</b>			
SCA5	SPTBN2	Missense, in-frame deletion	..
SCA11	TTBK2	Frameshift	..
SCA13	KCNC3	Missense	Mental retardation
SCA14	PRKCG	Missense	Myoclonus
SCA15/16	ITPR1	Missense, deletion	..
SCA20	..	Duplication	Dysphonia
SCA27	FGF14	Missense, frameshift	..
SCA28	AFG3L2	Missense	Ptosis
<b>Loci (test unavailable)</b>			
SCA4	..	..	Sensory neuropathy
SCA18	..	..	Sensory neuropathy
SCA19	..	..	..
SCA21	..	..	Mental retardation
SCA22	Allelic to SCA19?	..	Mental retardation
SCA23	..	..	..
SCA25	..	..	Sensory neuropathy
SCA26	..	..	..
SCA30	..	..	..

CAG - REPEAT  
SYGDOMME

# CAG Repeat mutationen

Normalt allel:

5' .....ATCGAAATGCCGATATATGCATTAA  
GTCCAGCAGCAGCAGCAGCAGCAGCAGATGCC.....3'

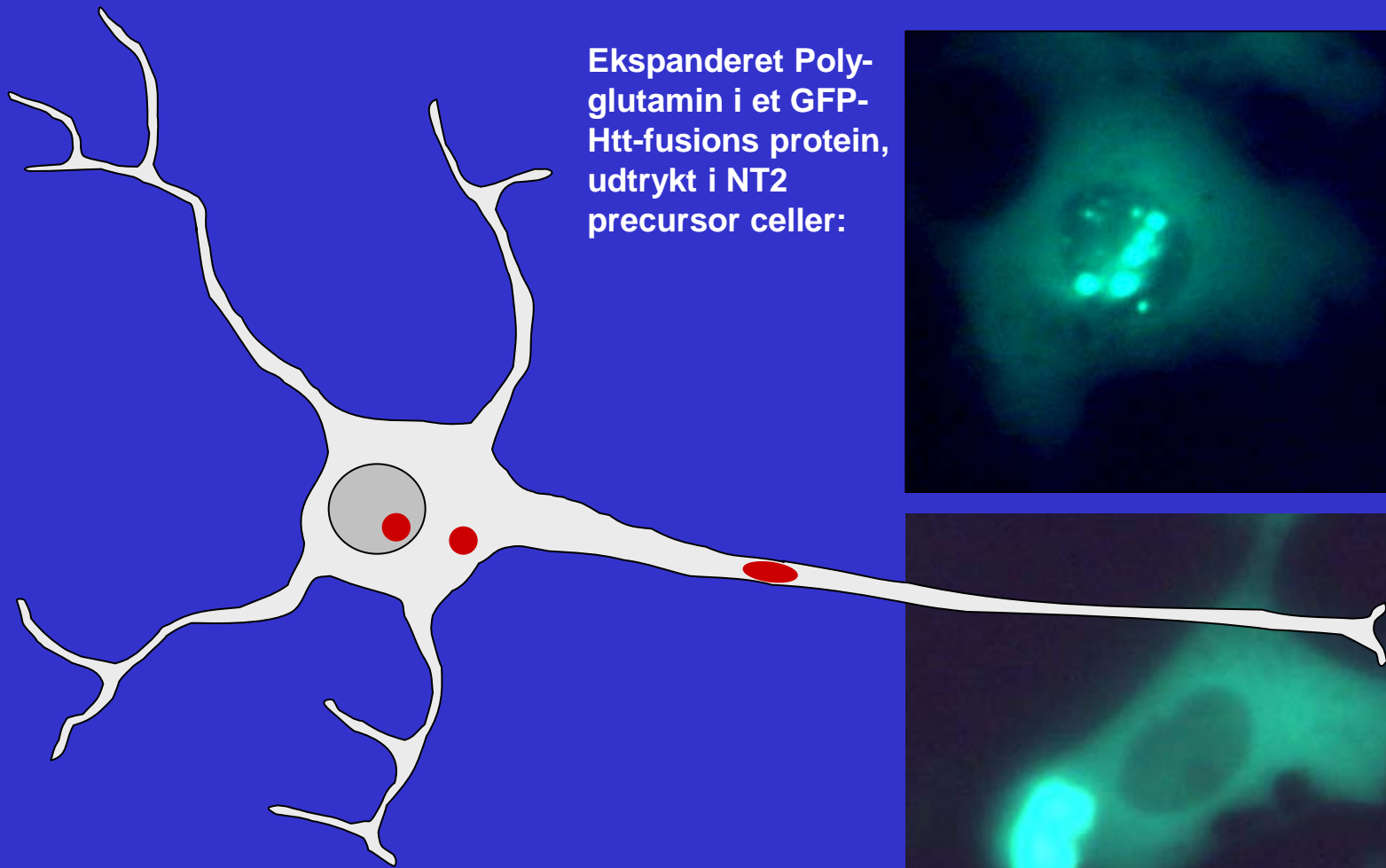
Expanderet allel:

5' .....ATCGAAATGCCGATATATGCATTAA  
GTCCAGCAGCAGCAGCAGCAGCAGCAG  
CAGCAGCAGCAGCAGCAGCAGCAGCAG  
CAGCAGCAG.....CAGCAGCAGATGCC.....3'

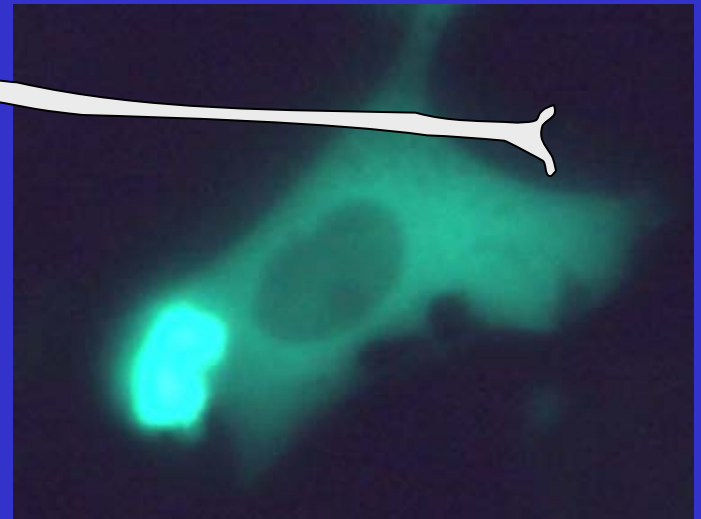
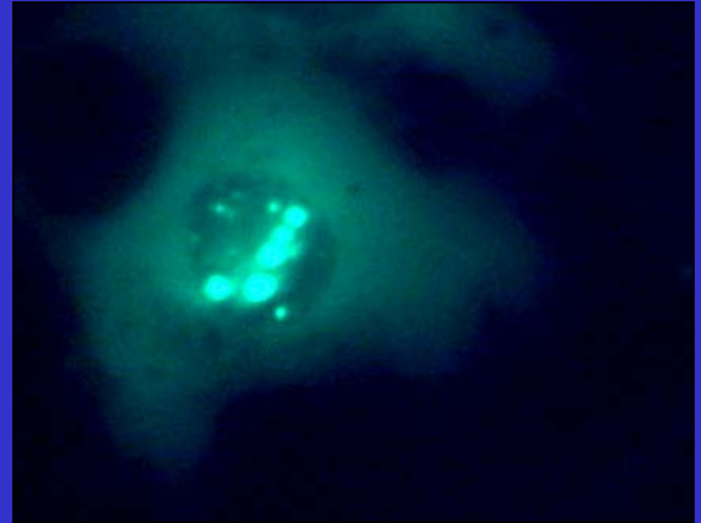
# CAG repeat sygdomme

<u>Sygdom</u>	<u>Locus</u>	<u>Protein</u>	<u>Normal område</u>	<u>Sygdoms område</u>
SBMA	Xq11-q12	Androgen recep.	9-33	38-75
HD	4p16.3	Huntingtin	9-39	36-121
DRPLA	12pter-p12	Atrophin	3-36	49-88
SCA1	6p22-p23	Ataxin-1	6-39	39-81
SCA2	12q23-q24.1	Ataxin-2	14-34	34-59
MJD/SCA3	14q32.1	MJD1/Ataxin-3	12-40	61-84
SCA6	19p13	CACNLA1A4	4-18	20-30
SCA7	3p12-p13	Ataxin-7	7-17	38-130
SCA17	6q27	TBP	29-42	47-55

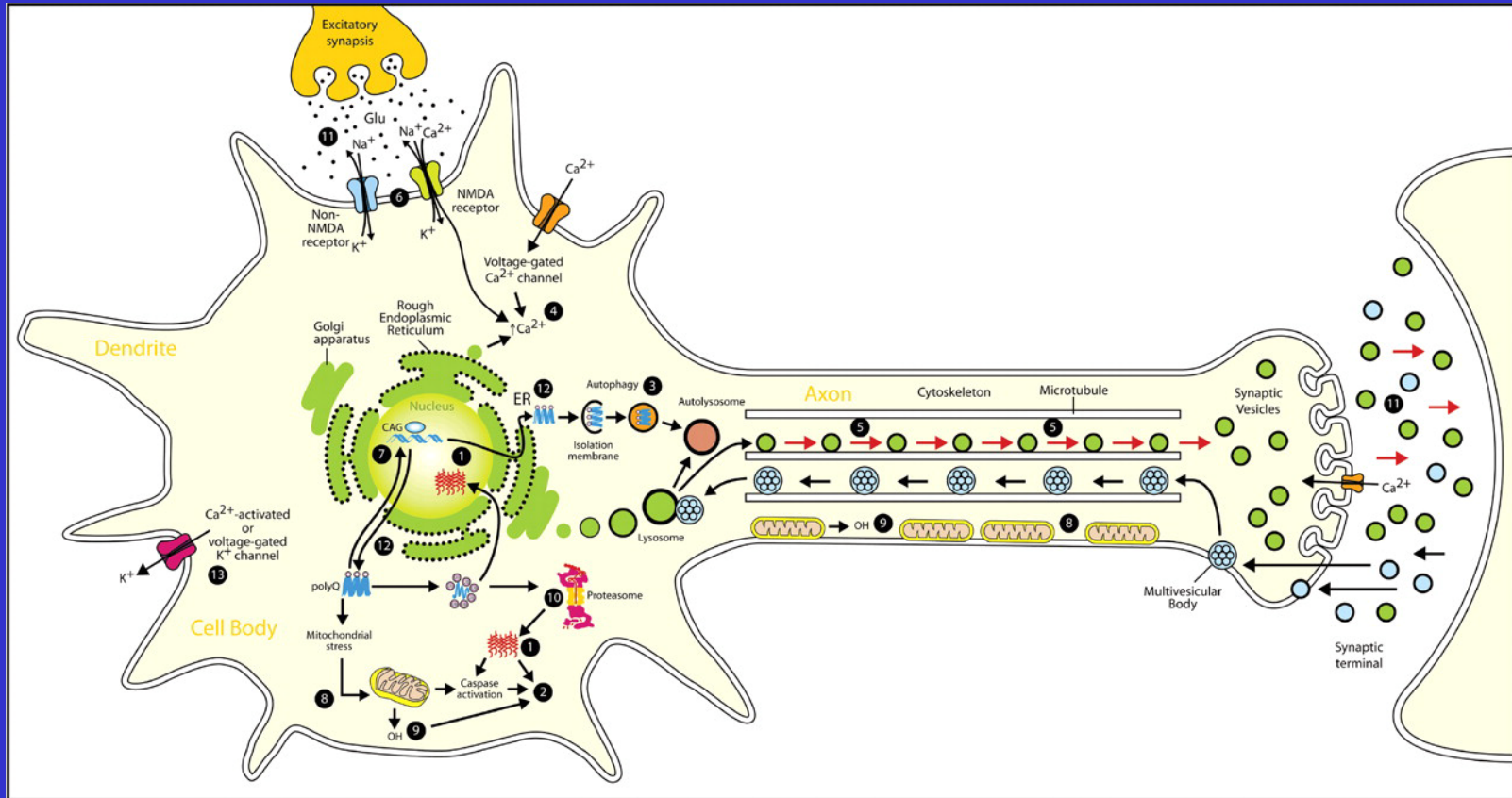
# Nukleære, perinukleære og neuropil inclusioner



Ekspanderet Polyglutamin i et GFP-Htt-fusions protein, udtrykt i NT2 precursor celler:



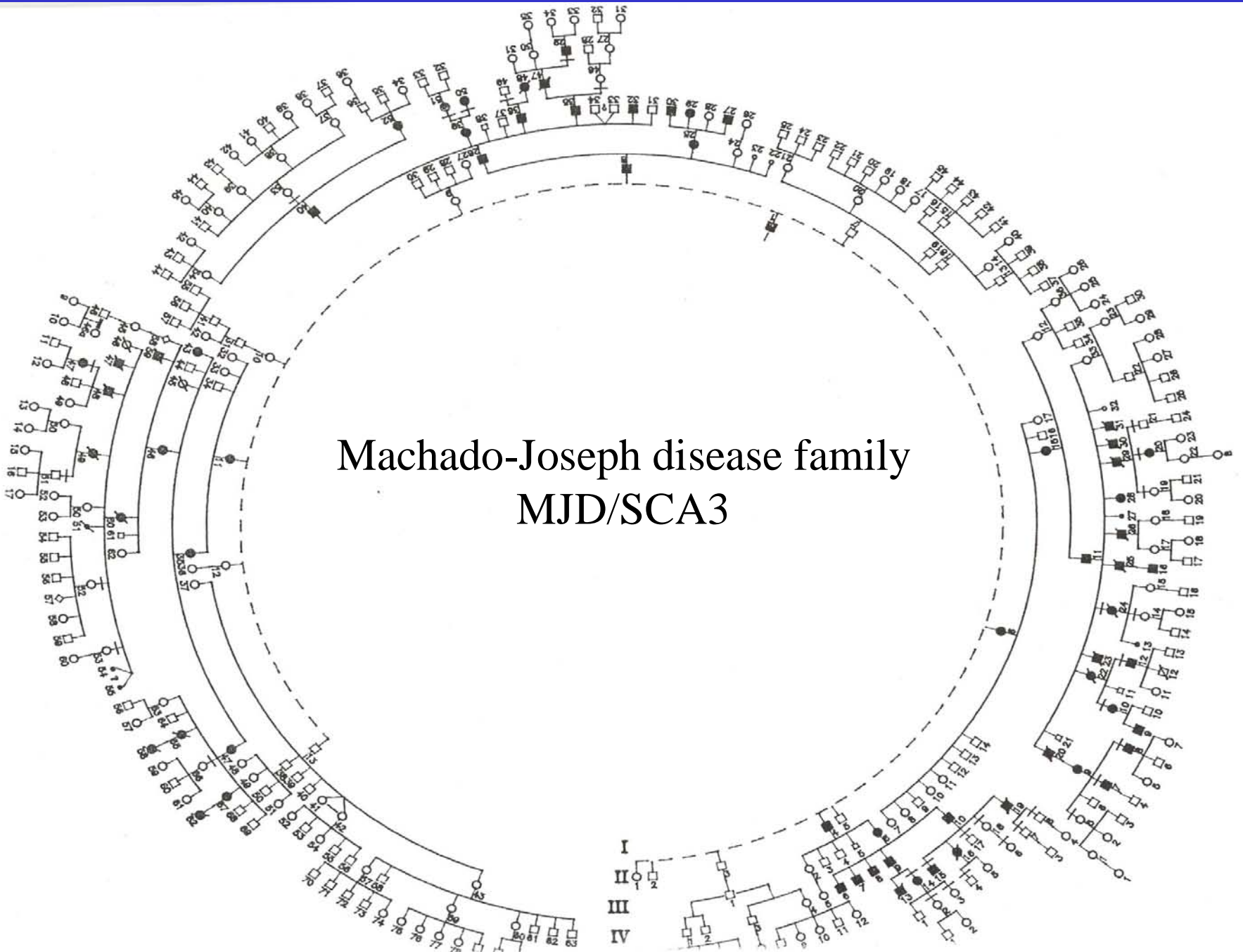
# Molekylære mekanismer til neurodegeneration ved SCA



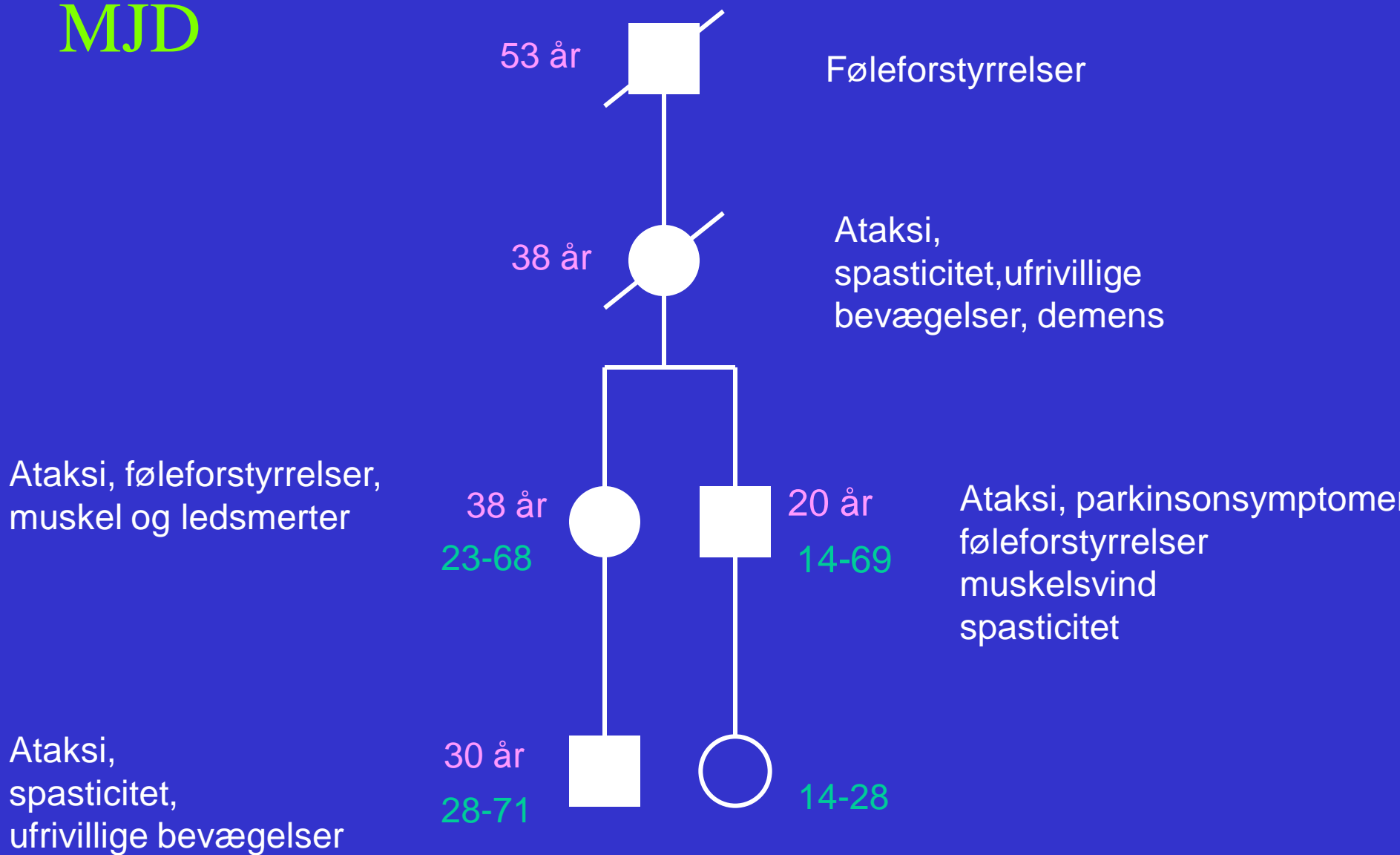
Duenas, A. M. et al. Brain 2006 129:1357-1370

Molecular mechanisms of neurodegeneration in spinocerebellar ataxias. 1, aggregation; 2, apoptosis; 3, autophagy; 4, Ca<sup>2+</sup> homeostasis alterations; 5, disruption of axonal transport and vesicle trafficking; 6, excitotoxicity; 7, interference with gene transcription; 8, mitochondrial impairment; 9, oxidative stress; 10, alterations of proteasome degradation; 11, synaptic dysfunction; 12, unfolded protein response (UPR); 13, potassium channel dysfunction; Ca<sup>2+</sup>, calcium ions; ER, endoplasmic reticulum; Glu, glutamate; K<sup>+</sup>, potassium ions; Na<sup>+</sup>, sodium ions; Q, glutamine; Ub, ubiquitin.

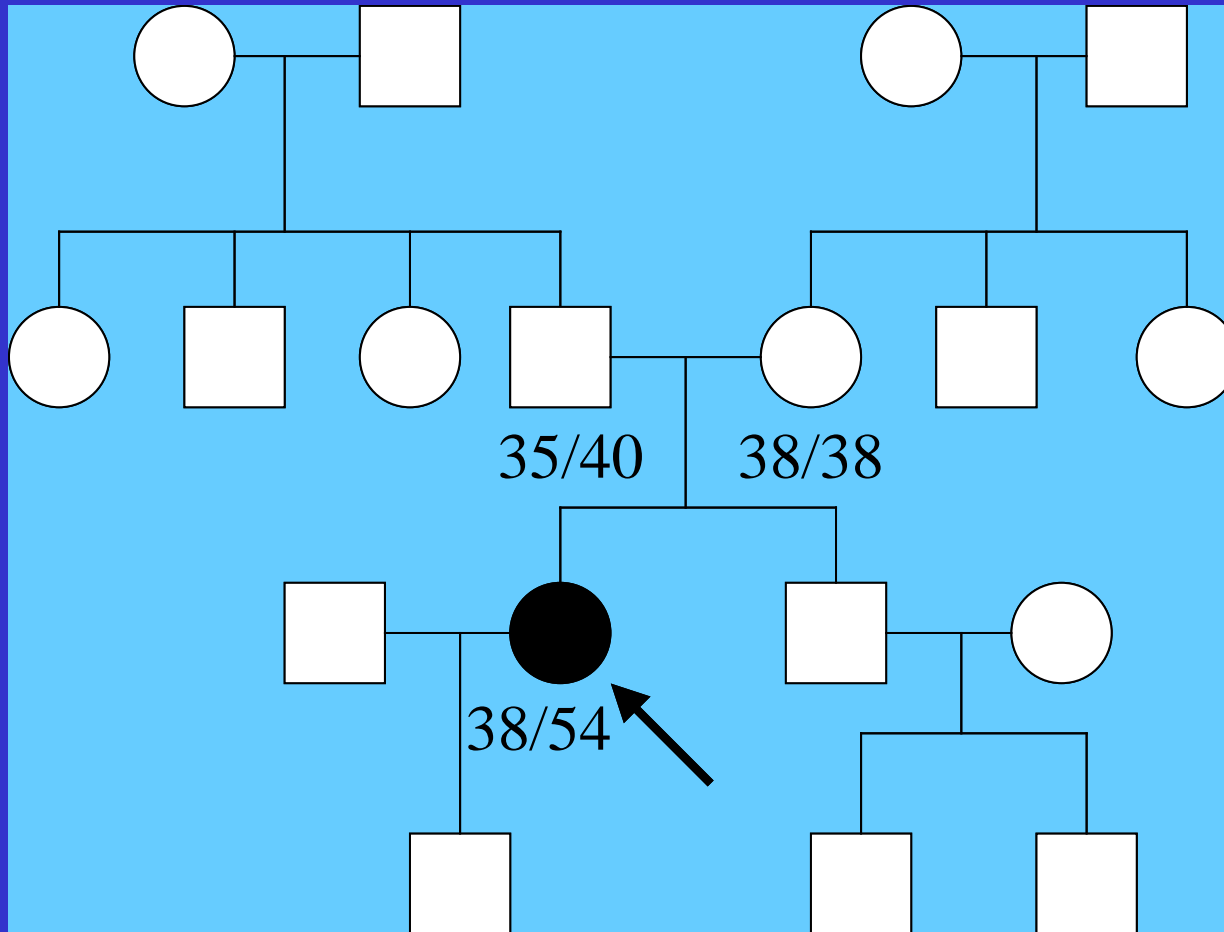
Machado-Joseph disease family  
MJD/SCA3



# MJD



# SCA17



# ILOCA (ideopatisk late onset cerebellar ataxia)

- Abele M et al., Brain, maj 2002
- 112 patienter.
- Debut efter 20 års alderen.
- Informativ og negativ familiær historie. (- lign hos 1. og 2. grads slægtninge)
- Alle undersøgelser negative

# Multipel System Atrofi

- Sporadisk, sent debuterende
- Degeneration af forskellige hjerneområder: basale ganglier, hjernestamme, cerebellum og pyramidebaner
- Symptomer fra 4 områder:
  - Autonom dysfkt./vandladningsgener
  - Parkinson
  - Ataxi
  - HSP-symptomer

# Mistanke om arvelig SCA/HSP

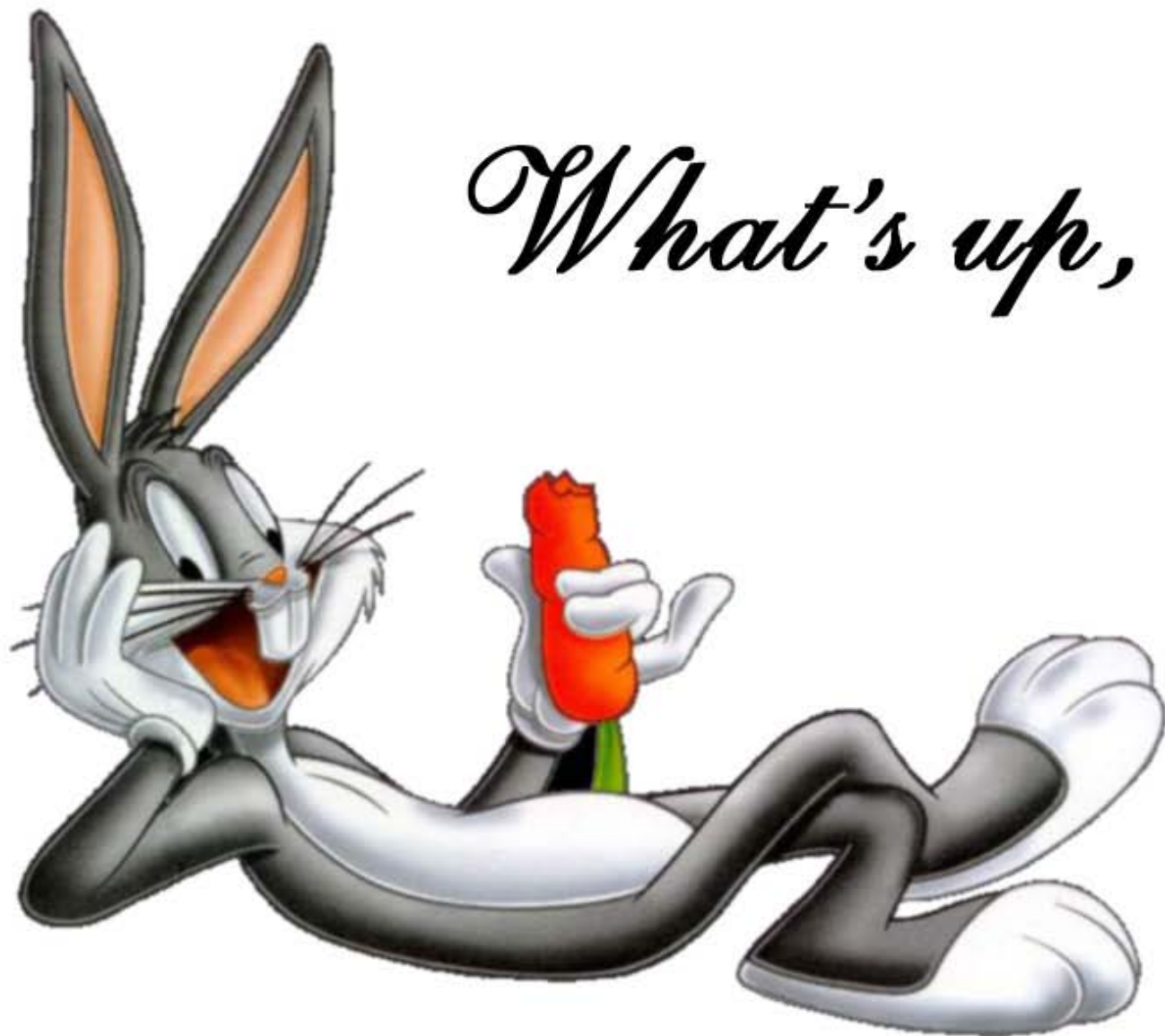
- 2-3 eller flere syge 1. grads slægtninge i mere end én generation
- Udredning. Er det en samme sygdom hos de ramte i familien ?
- Blodprøve fra en sygdomsramt.
- Molekylær-genetisk diagnose ?

Sygdomsmodificerende behandling

INGEN

# Symptomatisk behandling

- Spasticitetsdæmpende
- Mod vandladningsgener
- Antidepressiva
- Ikke-medikamentelt



*What's up, Doc ?*



# Tiantan Puhua Stem Cell Center

A- A+ RESET

\*First name:

\*Last name:

\*Email address:

\*Confirm your email address:

If you are seeking treatment for a family member or a friend and would like them to receive the information too, please insert their NAME and EMAIL address:

\*The country I live in:

Phone number:  
(optional)

Fax:  
(optional)

\*The medical condition of which I am interested to receive information about:

If you choose the "Other" in the medical condition field, please fill the name of the disease:

\*Patient's age:

\*How long does the patient suffer from the disease:

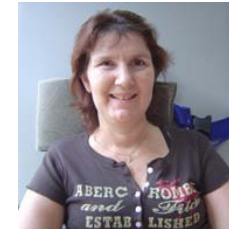
Comments:



Penny Thomas  
Parkinson's disease  
U.S.A  
[read more...](#)



Gabor Bocskai  
Cerebral Palsy  
Hungary  
[read more...](#)



Karen Brooks  
ALS  
Australia  
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One of our international staff members will contact you within 48 hours  
For more information please visit our website: [www.stemcellspuhua.com](http://www.stemcellspuhua.com)



## Quote of the Day

" It just all adds up to make me feel more confident in walking abilities and stuff like that. Walking in crowds, and before you start to panic when you get in a crowd cause like kids would cross in front of you, and I couldn't stop and would crash into them and stuff like that. I feel like I can at least stop or walk around them and stuff like that so. "

P. F., Ataxia

StemCellsChina.com

## Beike - Kymberly Graf



Ataxia

Saturday, 08 July 2006 02:20

Contact a Specialist

## Contact a Specialist

Patient Name \*

Email \*

Phone Number (include co

Patient's City and Country

Primary Diagnosis

## Featured News

- Closer to Miracle of Sight
- New Hope
- Sierra Returns Home Today
- Girl Receives Help in China
- Sight in Sight for London
- Girl Prepares Trip to China
- Blind Women Seeking Treatment

## PATIENT EXPERIENCE - ATAXIA

NAME: Kymberly Graf

COUNTRY: Canada

AGE: 19

DIAGNOSIS: Spinocerebellar Ataxia 2

**REASON FOR COMING FOR TREATMENT:** The patient's family had a history of hereditary ataxia. She had suffered from the symptoms for around 6 years. Her condition had worsened to the extent that it was starting to affect her studies.

**START OF TREATMENT:** April 4, 2006 Umbilical Cord Stem Cell and Nerve Growth Factor Injections with Rehabilitation Therapy

## BEFORE THE TREATMENT:

Video: [Before](#)

Physical symptoms included a lack of motor ability, specifically in walking, limb control and coordination. For example, the patient's parents described in detail her need to compose herself before and during walking, specifically when going down stairs, during which she would need to compose herself approximately "Every three steps." Lack of control in her hands had resulted in an inability to operate her computer, much less write with a pen. When catching a basketball in therapy, she would drop around 50% of the throws. In addition, her speech was deteriorating, she coughed excessively and would tire easily. Her father said her symptoms would increase in severity when she was tired.

## AFTER THE TREATMENT:

See Videos: [After 1](#), [After 2](#), [After 3](#), [After 4](#), [After 5](#), [After 6](#), [After 7](#), [After 8](#)

Improvements in the patient's mobility and coordination were most pronounced. In physiotherapy video 'After 5', the patient's mother describes her ability to turn around as vastly improved, noting that she no longer has to spend as much time 'organizing herself'.



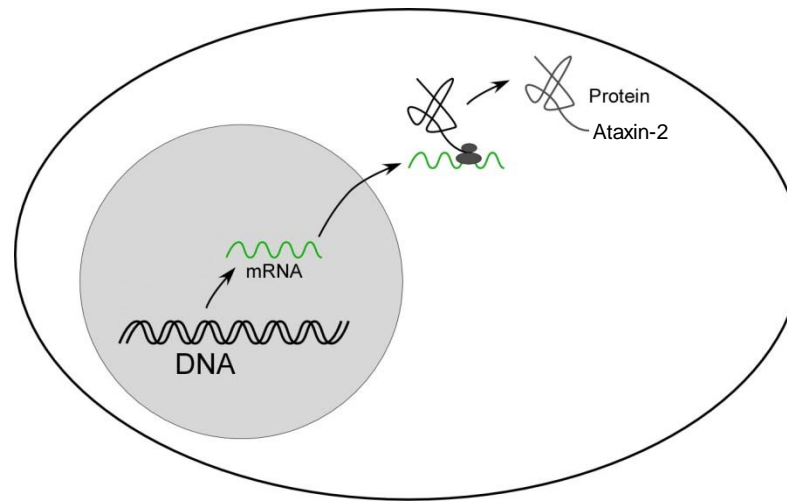
## Site Search

## Patient Experiences

- ALS - Mr. Reynolds
- ALS - Ms. Brooks
- Ataxia - Mr. Arruda
- Ataxia - Mr. Blair
- Ataxia - Ms. Crowter
- Ataxia - Ms. Graf
- Ataxia - Ms. Gray
- Ataxia - Ms. Jones
- Ataxia - Mr. K. Graf
- Ataxia - Mr. Knoblauch
- Ataxia - Mr. Martin
- Ataxia - Mr. Nate
- Ataxia - Mr. P. Flynn
- Ataxia - Mr. R. Flynn
- Ataxia - Mr. T. Graf
- Ataxia - Mr. Wallace
- Autism - Mr. Lachlan
- Autism - Ms. Maria
- Autism - Mr. Pacis
- Autism - Mr. Wang
- Autism - Mr. Yu
- Batten Disease - Mr. Dell'Aringa
- Brain Injury - Mr. Anduha
- Brain Injury - Mr. Ashton
- Brain Injury - Mr. Blazevic
- Brain Injury - Mr. Cui
- Brain injury - Mr. Hayward
- Brain Injury - Ms. McAfee
- Brain Injury - Mr. Nguyen
- Cerebral Palsy - Mr Andrew Ricci

# Idéen

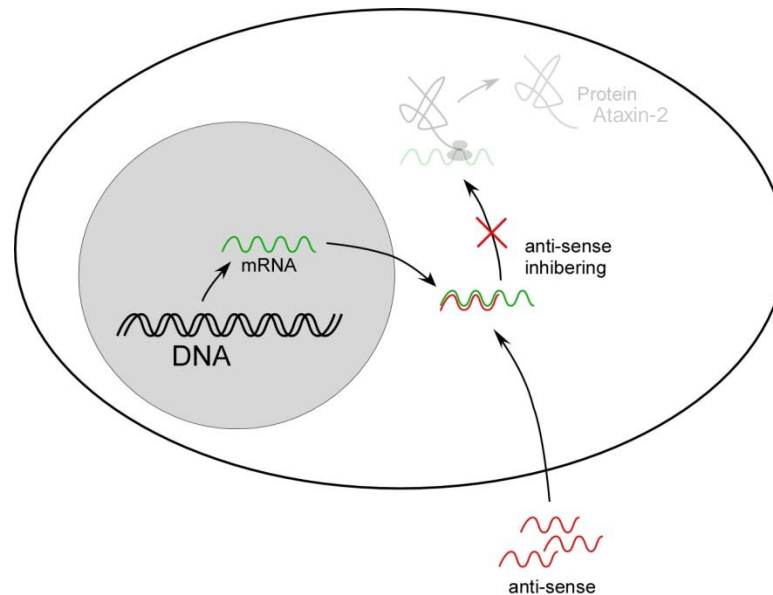
- Anti-sense tanken



- Anti-sense idéén og SCA (eller andre sygdomme med sygdomsfremkaldende genmutationer)
  - Enkelt princip

# Idéen

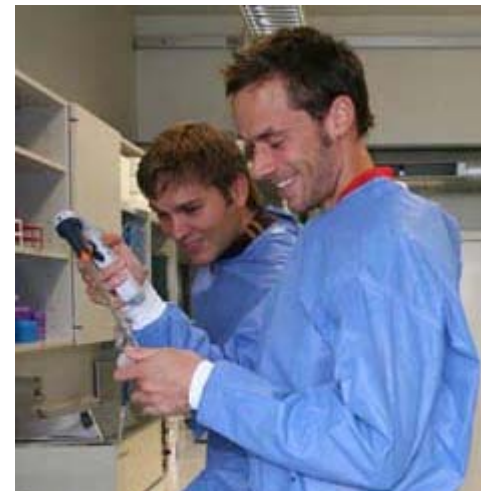
- Anti-sense tanken



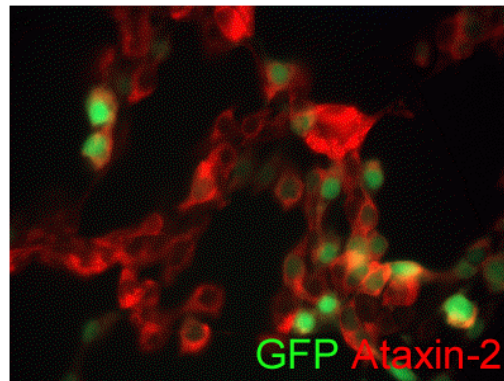
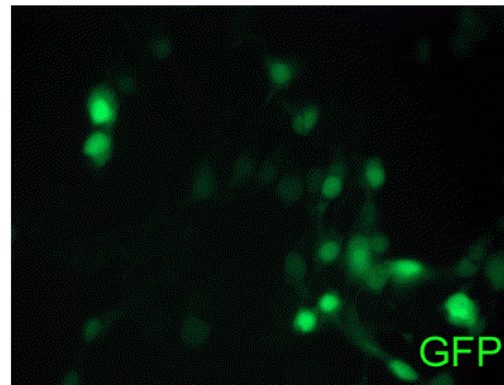
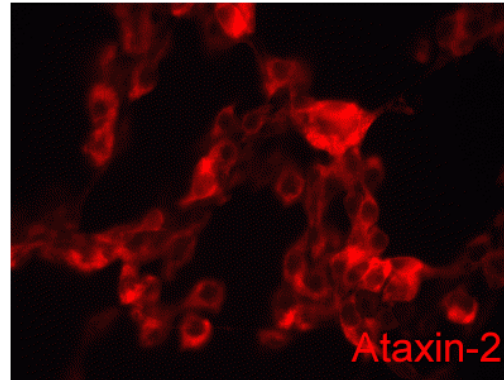
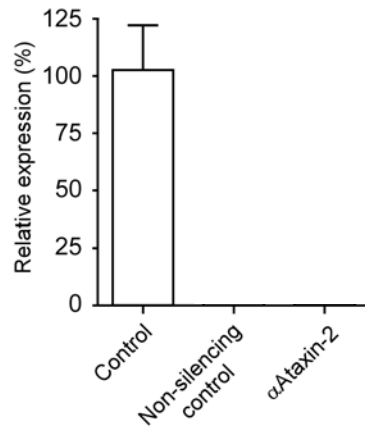
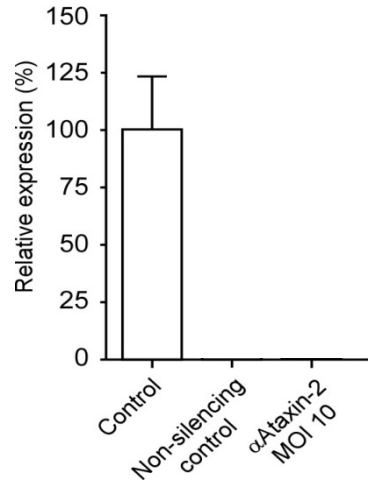
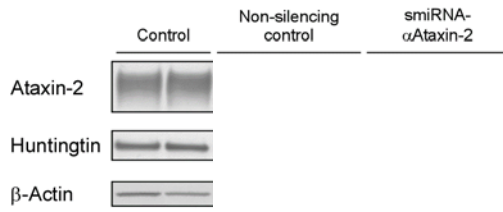
- Anti-sense idéén og SCA (eller andre sygdomme med sygdomsfremkaldende genmutationer)
  - Enkelt princip

# Problemer

- I behandlingsstrategien skal der tages højde for:
  - At nedreguleringen af det sygdomsfremkaldende protein skal være effektiv
  - At hjernen er svært tilgængelig og uhyre kompleks
  - At virkningen skal være livslang
  - At behandlingen skal være effektiv i et udbredt område og i et enormt antal celler
  - At ikke alle typer celler i hjernen skal påvirkes



# Vores resulater på SCA2 i celler



Hvornår har vi så behandlingen?

