Clinical and pathophysiological overview of autosomal dominant spinocerebellar ataxias

Franco Taroni

Division of Biochemistry and Genetics
IRCCS Istituto Nazionale Neurologico "Carlo Besta"
Milan, Italy

SCAs

- 27 mapped loci (including DRPLA)
- 15 disease genes (probably) identified
- 7 SCAs (1-2-3-6-7-17 and DRPLA) associated with a CAG triplet repeats (-> polyglutamine diseases)
- 3 SCAs (8-10-12) associated with expansions in non-coding regions
- 5 SCAs (4, 5, 13, 14, 27) associated with missense mutations or nucleotide changes in regulatory regions

Genetic Classification of SCAs

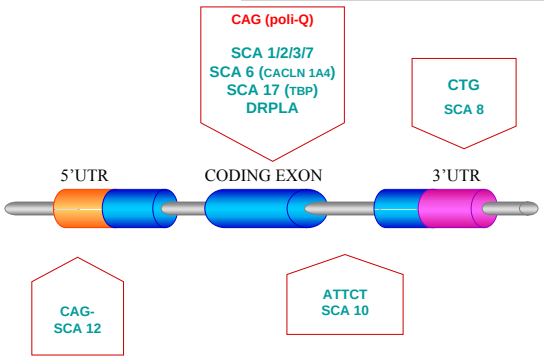
Disease	Locus	Gene – Mutation
SCA1	6p23	Ataxin1-CAG exp.
SCA2	12q24	Ataxin2-CAG exp.
SCA3, MJD	14q24.3-q31	Ataxin3- CAG exp.
SCA4	16q22.1	Puratrophin-1 (5' UTR)
SCA5	11p11-q11	Spectrin
SCA6	19p13	CACNL1A4-CAG exp.
SCA7	3p21.1-p12	Ataxin7-CAG exp.
SCA8	13q21	CTG exp. (3'UTR)
SCA9	Not assigned	
SCA10	22q13	Ataxin10-ATTCTexp.(int 9)
SCA11	15q14-q21.3	1 UK fam.
SCA12	5q31-q33	PPP2R2B-CAG exp.(5'UTR)
SCA13	19q13.3-q13.4	KCNC3
SCA14	19q13.4qter	PRKCG (missense mut.)
SCA15	3p24.2-pter	Australian and Japanese fam.

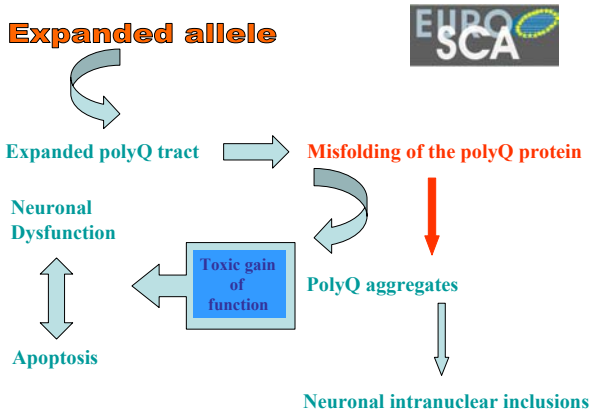
Disease	Locus	Gene – Mutation
SCA16	8q22.1-q24.1	1 Japanese fam.
SCA17	6q27	TBP-CAG exp.
SCA18	7q22-q32	1 Irish fam.
SCA19	1p21-q21	1 Dutch fam.
SCA20	11p13-q11	1 Anglo-Celtic fam.
SCA21	7p21.3-p15.1	1 French fam.
SCA22	1p21-q23	1 Chinese fam.
SCA23	20p13-12.3	1 Dutch fam.
SCA24	reserved	
SCA25	2p15-21	1 French fam.
SCA26	19p13.3	1 Norwegian fam.
SCA27	13q34	FGF14 missense mut.
SCA28	18p11.22-q11.2	
DRPLA	12p13	Atrophin1-CAG exp

Harding's classification of the autosomal dominant cerebellar ataxias
Everett and Wood *Brain* 2004

ADCA I	ADCA II	ADCA III
Cerebellar syndrome "plus" with pyramidal and extrapyramidal signs, neuropathy, ophthalmoplegia and dementia	Cerebellar syndrome "plus" with visual loss and pigmentary retinal degeneration	Pure cerebellar syndrome
SCA 1, 2, 3, 8, 12, 17, 25, 27, 28	SCA 7	SCA 4, 5, 6, 10, 11, 14, 15, 22 , 26

Genetic view of the expansion mutations observed in SCAs

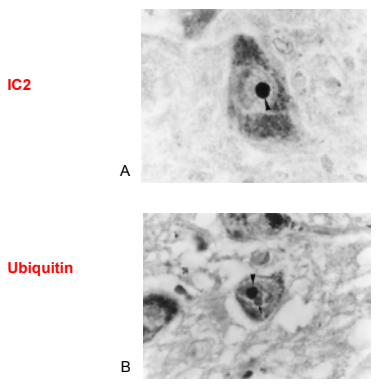




Nuclear inclusions

- Huntington Disease — Nuclear Inclusions
- SBMA — Nuclear Inclusions
- DRPLA — Nuclear Inclusions
- SCA1, 3, 7, 17 — Nuclear Inclusions
- SCA2, SCA6 → Cytoplasmic Inclusions

- → Ubiquitin- and poly-Q-positive NIs in diseased brains are present in specific neuronal subtypes



DiDonato et al. - **Figure 5**

Neurodegeneration and NIs

- neurons with aggregates are not always the most susceptible to death in human diseases
- the correlation between neurodegeneration and NIs is poor in *animal models* overexpressing mutant ataxins

The pathogenic role of NIs is uncertain: NIs cause disease, protect against disease, or are simply incidental?

Sisodia , Science 1998

Neurodegeneration and NIs

Inclusion body formation in neurons by lowering the levels of toxic mutant htt, reduces the risk of neuronal death

- Arrasate et al *Nature* 2004, 431:805-810

?

NIs contain functionally relevant proteins as ubiquitin, chaperones, proteasome components, and transcription factors.

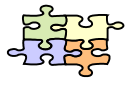
Withdrawal of crucial factors within NIs might lead to the impairment of vital cellular functions

Neurodegeneration : a polyQ-only hypothesis

CAG containing wild-type *and* mutant alleles are both transcribed and translated

Protein domains containing expanded poly-Q are conformationally unstable and switch from α-coils to β-pleated sheets, linked by H-bonds between amide side chains

β-strand domains are sticky and tend to form protein aggregates,
including self-aggregates
in the neuropil and the nucleus



Perutz MF, *Curr Opin Struct Biol* 1996

Neurodegeneration : a polyQ-only hypothesis

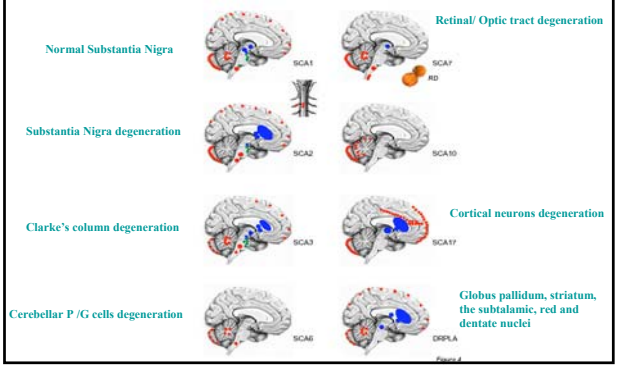
- The timing and the spreading of neurodegeneration in DRPLA, SCA1-3, SCA7, depend on the length of the expanded CAG repeat, Zoghbi 2001
- Cellular and trangenic animal models expressing different long poly-Q domains show neurodegeneration, Rubinsztein 2002
- A large CAG expansion ectopically expressed in *HPRT gene* causes intranuclear inclusions and late-onset neurodegeneration in mice, Ordway 1997

New data cast doubts on the polyQ-only hypothesis

- Wild-type *and* mutant alleles are both abundantly transcribed and translated in many different tissues and organs, yet neuropathology is restricted to specific neural subtypes

⇨ a role for the cellular enviroment

SCA Neuropathology
Taroni and Di Donato 2004



the protein context

Distinct phenotypes depend on the intrinsic properties of each mutant protein leading to specific protein-protein interactions in different cellular compartments which drive the neuropathology and the clinical phenotype

the protein context

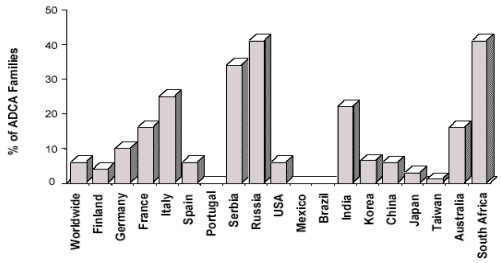
- When expressed in axoplasm Q78 ataxin-3 blocks fast axonal transport in *Drosophila* larvae inducing the formation of aggregates (axonal blockages)
- When expressed in the nucleus Q78 ataxin-3 induces apoptotic neuronal death
- Gunawardena et al, Neuron 2003; 40:25-40

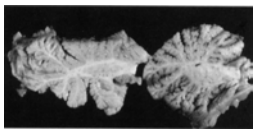
Seven SCAs with a CAG-polyQ expansion

Disease	Gene product	Main clinical features
SCA1	ataxin-1	Ataxia, spasticity, ophthalmoparesis, slow saccades, axonal polyneuropathy, cognitive impairment
SCA2	ataxin-2	Ataxia, extrapyramidal symptoms, spasticity, ophthalmoparesis, slow saccades, axonal polyneuropathy
SCA3	ataxin-3	Ataxia, parkinsonism, extrapyramidal features, spasticity (severe), ophthalmoparesis, axonal polyneuropathy
SCA6	CACNA1A	Prominent cerebellar features (ataxia, dysarthria, nystagmus, tremor)
SCA7	ataxin-7	Ataxia, retinal degeneration, ophthalmoplegia, large anticipation
SCA17	TATA-binding protein	Ataxia, psychosis and behavioural changes, dystonia, parkinsonism, mental deterioration
DRPLA	atrophin-1	Myoclonus epilepsy, ataxia, chorea, dementia, rigidity

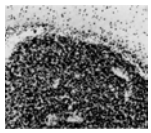
Nat Rev Neurosci 2004;5: 641-655

SCA1 Frequency wordlwide

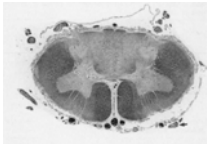




A



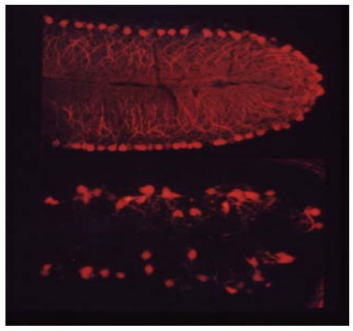
B

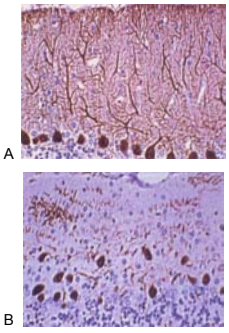


C

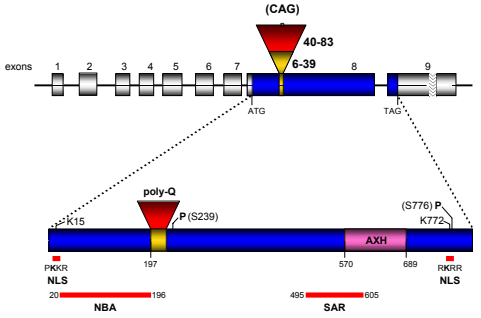
DiDonato et al. - ***Figure 4***

SCA1 trangenic mouse Burright., Cell 1995





DiDonato et al. - **Figure 7**



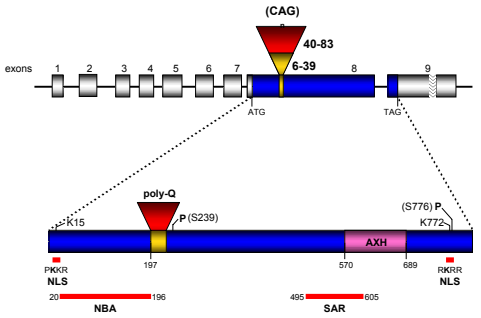
DiDonato et al. - **Figure 1**

EUROSCA

the protein context

In the presence of NLS, Ser-776 phosphorylation of ataxin-1 by Akt kinase drives its nuclear localization, interaction with 14-3-3 proteins , and generation of pathology in SCA1 mice
…a crucial pathogenic event

Emamian et al, *Neuron* 2003; 38:375



DiDonato et al. - **Figure 1**

the protein context

AXH domain in ataxin-1 causes protein dimerization and interactions with GF1-Senseless proteins…. thus decreasing GF1-Senseless-dependent **transcription**….. a pathogenic event independent from the poly-Q stretch

Tsuda et al, Cell 2005

State of the Art ?

The poly-Q stretch and its protein context drive distinct multifaceted pathological processes which induce preferential pathology in specific neural subsets according to unique protein-protein interactions

gain-of-function mechanisms drive the start of pathology, yet **loss of cellular** pathways, i.e. transcriptional regulation, proteasome function, mitochondrial function, axonal transport might play a role in disease

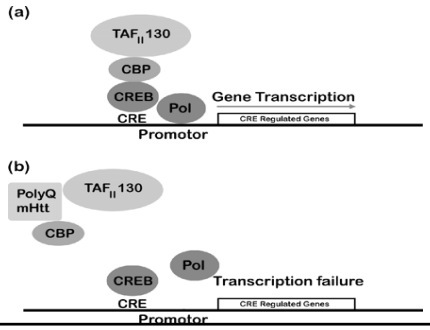
Nat Rev Neurosci 2004; 5: 641-655

transcriptional activity

TBP , Androgen Receptor, huntingtin, ataxin-1, ataxin-3, ataxin-7, atrophin-1,
are directly or indirectly involved in transcriptional regulation

Defective/deranged transcription might act as the final effector of the dominant "toxic gain of function", or it might contribute to cell death throughout "loss of function" mechanisms

CREB/CBP-mediated gene transcription and mutant polyQ Htt
Everett and Wood , *Brain* 2004



What ultimate effects of mutant proteins?

The regional specificity of neuropathology might not be a function of where polyQ proteins are found but rather of the total set of genes whose transcription is altered by mutant protein(s)

doi:10.1093/brain/awh651 *Brain* (2006), **129**, 235–242

SCA28, a novel form of autosomal dominant cerebellar ataxia on chromosome 18p11.22–q11.2

Claudia Cagnoli,[1,*] Caterina Mariotti,[2,*] Franco Taroni,[2] Marco Seri,[4] Alessandro Brussino,[1] Chiara Michielotto,[1] Marina Grisoli,[3] Daniela Di Bella,[2] Nicola Migone,[1] Cinzia Gellera,[2] Stefano Di Donato[2,*] and Alfredo Brusco[1,*]

[1]Dipartimento di Genetica Biologia e Biochimica, Università degli Studi di Torino and S.C. Genetica Medica, Ospedale San Giovanni Battista di Torino, Torino, [2]UO Biochimica e Genetica and [3]UO Neuroradiologia, Istituto Nazionale Neurologico Carlo Besta, Milano and [4]UO Genetica Medica, Università degli Studi di Bologna, Bologna, Italy

Correspondence to: Stefano Di Donato, MD, UO Biochimica e Genetica, Istituto Nazionale Neurologico Carlo Besta, via Celoria, 11-20133 Milano, Italy

Clinical Features

- Juvenile onset: mean 19.5 years (range 12-36)
- No anticipation
- Slow progression
- Onset: Gait ataxia and unsteadiness, plus dysartria
- Gaze-evoked nistagmus, slow saccades
- 6/11 patiens had ophtalmoparesis, ptosis was present in 5
- Brisk DTR and Babinski sign
- No sensory impairment

Multipoint analysis of 16 markers on chromosome 18