HSP: Clinical highligts and diagnosis

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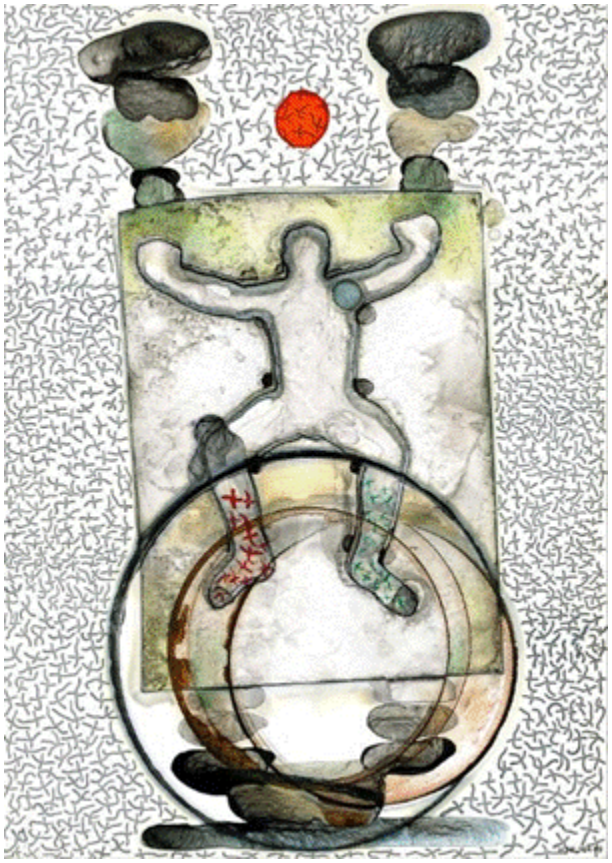
Burgos, May 2011

What is HSP?

- Disease?
- Disorder?
- Pathology?
- Diagnosis
- Doctor?
- Treatment?

- **State?**
- **Anomaly?**
- **Normal variant?**
- **Not necessary?**
- **Other?**
- **Help and support**

Hereditær Spastisk Paraparese i Norge



Disputas 11 desember 2009

Anne Kjersti Erichsen

Neurodegenerative disorder

- Indolent onset following normal development, most often in young adults
- Progression with time
- "Symmetrical" symptoms
- Familial occurrence may be difficult to detect (heterogeneity)
- Selective affection of one or several groups of neurones
- Loss of neurons, dendrites, myelin without inflammatory reaction
- As a rule normal lifespan

Neurodegenerative disorder-1

There are, within recent memory, several examples of diseases that were formally classed as degenerative but are now known to have a metabolic, toxic, or nutritional basis or to be caused by a "slow virus" or a non-viral transmissible agent. It seems reasonable to expect that, with increasing knowledge, more and more diseases whose causes are now unknown will lind their way into these categories. Until such time as the causation of all neurorologic diseases is known, there must be a name and a place for a group of diseases that have no known cause are are united only **by the common attribute of gradually progressive disintegration of part or parts of the nervous system**. In deference to traditional practice, they are collected here under the rubric *degenerative diseases*.

Neurodegenerative disorder

The adjective degenerative has no great appeal to the modern neurologist. For one thing, it has an unpleasant literary connotation, referring as it does to a state of moral turpitude or deviant behaviour as the consequence of a sociopathic tendency. More important, it is not a satisfactory term medically, since it implies an *inexplicable decline from a previous level of normalcy to a lower level of function…..*

In Principles of Neurology, RD Adams, M Victor " AH Ropper, 1997, p1046

Rare neurodegenerative disorder

Rare = prevalence < 75/100 000

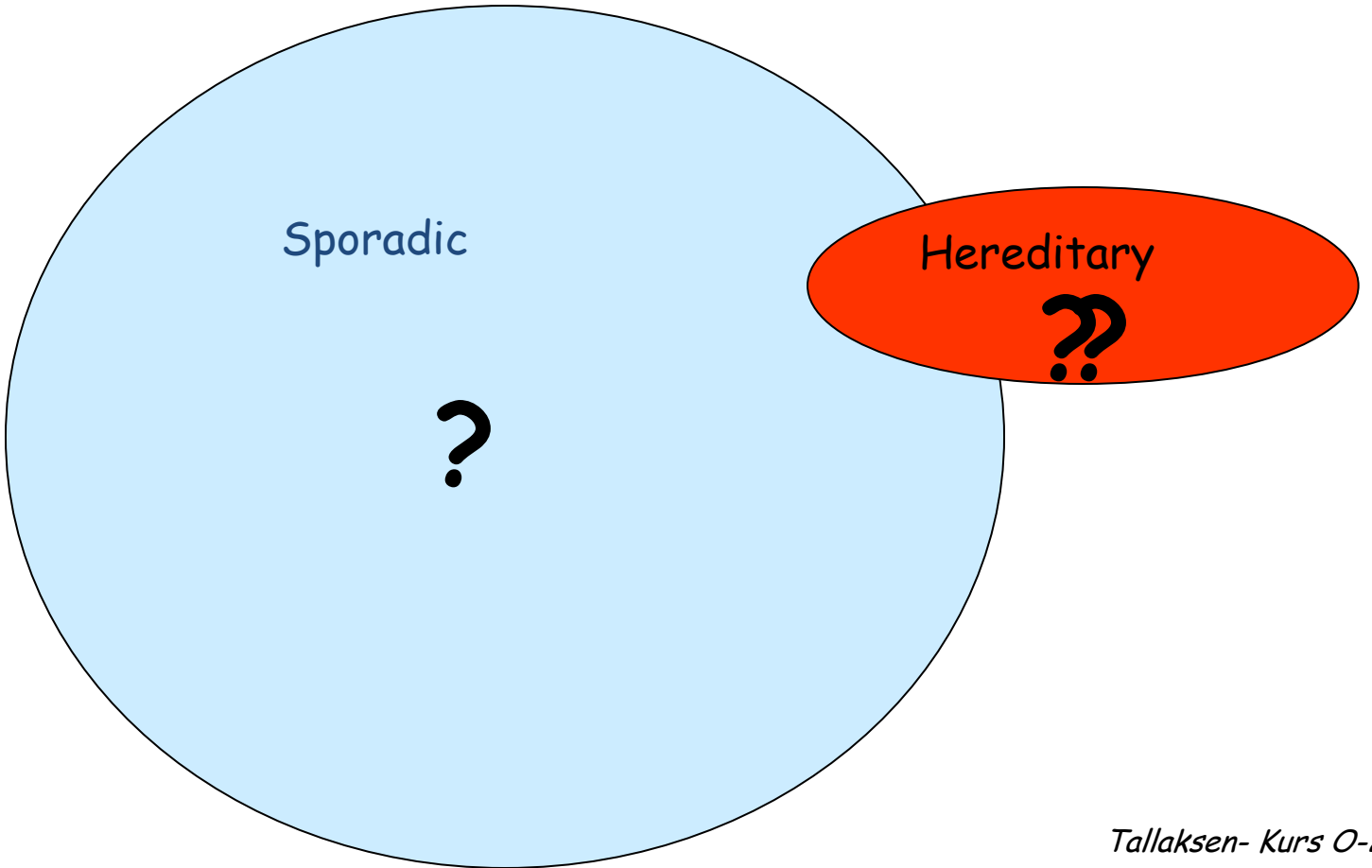
According to literature 0.1-10 / 100 000

In Norway: ca 7.5/100 000 (min. prevalence)

i.e.ca 400 in Norge

Hereditary rare neurodegenerative disorder

It is evident that many of the diseases included in this category depend on genetic factors, or at least they appear in more than one member of the same family and have been, therefore, more properly designated as *heredodegenerative*.



Diagnosis

- **How to make the diagnosis?**
  - *Symptoms*
  - *Family history*
  - *Investigations*

Clinical symptoms

- Gait impairment (cannot run)
- Poor balance
- Stiffness
- Muscular weakness in LL
- Cramps, spasms
- Walk on toes
- Urge

Clinical symptoms

- Pure
- Complicated
  - Associated with other neurological symptoms
- Heredity
- Progressive
- Early/late onset

CLINICAL HETEROGENEITY

Other usual complaints

- Depression
- Fatigue (tretthet, utmattelse)
- Anal sphincter problems
- Sexualfunction problems
- Pain: conspicuously rare, backpain most frequent
- Numbness in feet and legs

Clinical types HSP

"Pure" type

- 1 Gait impairment
- 2 Brisk reflexes
- 3 muscular weakness in LL
- Usually dominant heredity

"Complex" type

- 1+2+3
- + other neurological symptoms
- usually recessive heredity
- Often earlier onset
- Often more severe presentation

Complicated HSP

- Neuropathy
- Cerebellum affection
- Muscle atrophy
- Cognitive impairment (or mental retardation)
- Parkinsonisme-like symptoms, tremor, rigidity, movement disorders
- Psychiatric problems and dementia
- White matter abnormalities
- "thin CC" (thin corpus callosum)

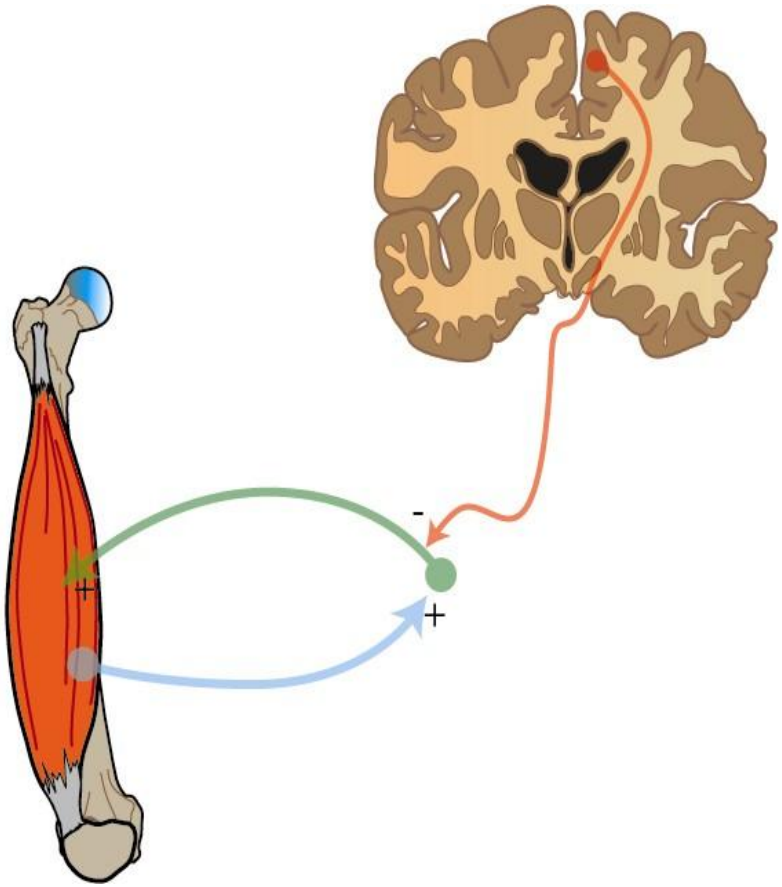
Findings at examination

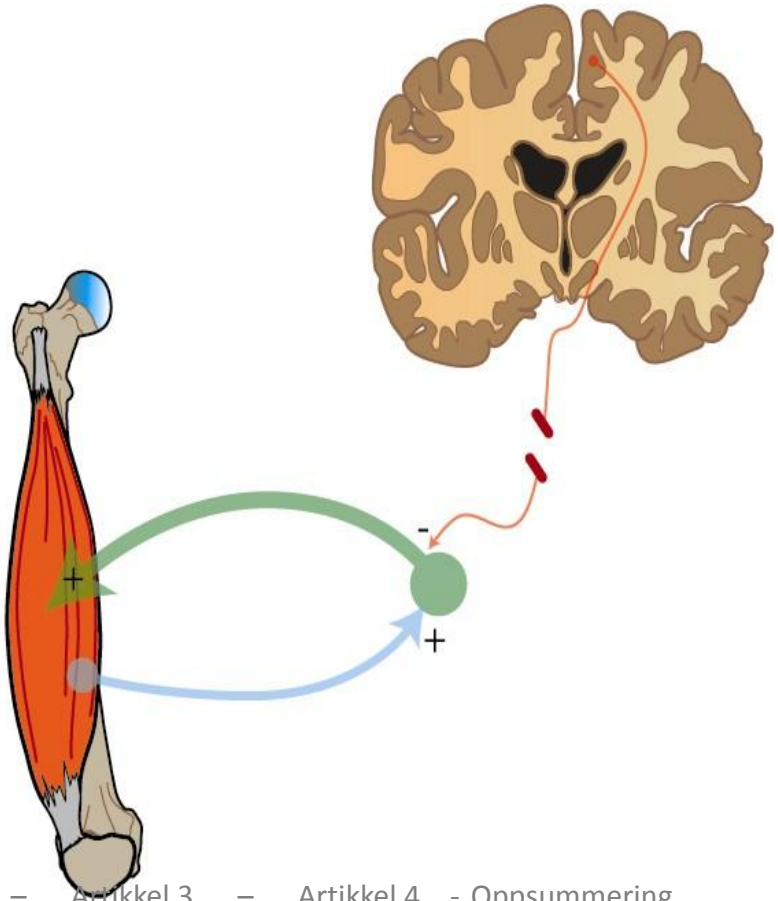
- Spasticity
  - Gait
  - rest
- Brisk reflexes
  - LL
  - UL
  - Extensor plantar reflex
- Muscular weakness(+/-)
- Impaired vibration sense

•Spasticity

•symptom of damage to nerves pathways or medulla spinalis

•Increased tonus due to lost/decreased control of nerve signals from and to muscles





• leads to stiffness, wrong positions in joints, pain and decreased function, can have a positive effect in case of loss of muscle strength

Muscle strength

- May be diminished at any level
- Patient cannot raise his feet
- Patient cannot raise from supine position
- Patient cannot raise from sitting position
- Patient cannot stand without help/with help
- Running difficult, impossible
- Walking distance
- One cane, crutches, wheeling chair

Spastic Paraplegia Rating Scale (SPRS)

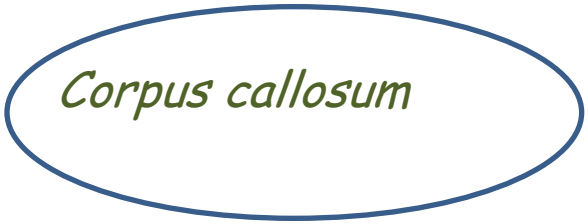
- ☐ **Walking distance without pause**
- ☐ *Due to history, walking aids allowed*
  - ☐ Normal, unlimited
  - ☐ Abnormal exhaustion due to spasticity after more than 500m
  - ☐ Walking distance less than 500m
  - ☐ Walking distance less than 10 m
  - ☐ Unable to walk
- ☐ **Gait quality**
- ☐ *Patient is asked to walk as fast as possible a 10 meter distance including one turn*
  - ☐ Normal
  - ☐ Mild stiffness, running still possible
  - ☐ Clearly spastic gait, interfering with running
  - ☐ Spastic gait requiring use of canes/walker
  - ☐ Unable to walk for a 10 meter distance even with maximal support
- ☐ **Maximum gait speed**
- ☐ **Climbing stairs**
- ■ **Speed of stair climbing**
- ■ **Arising from chair**
- ☐ **Spasticity -knee flexion (Modified Ashworth scale)**
- ☐ **Weakness -hip abduction (Medical Research Council 1976)**
- ☐ **Weakness -foot dorsiflexion (Medical Research Council 1976)**
- ☐ **Contractures of lower limbs**
- ☐ **Pain due to SP related symptoms**
- ☐ **Bladder and bowel function**
- ☐ **+++++**

Investigations

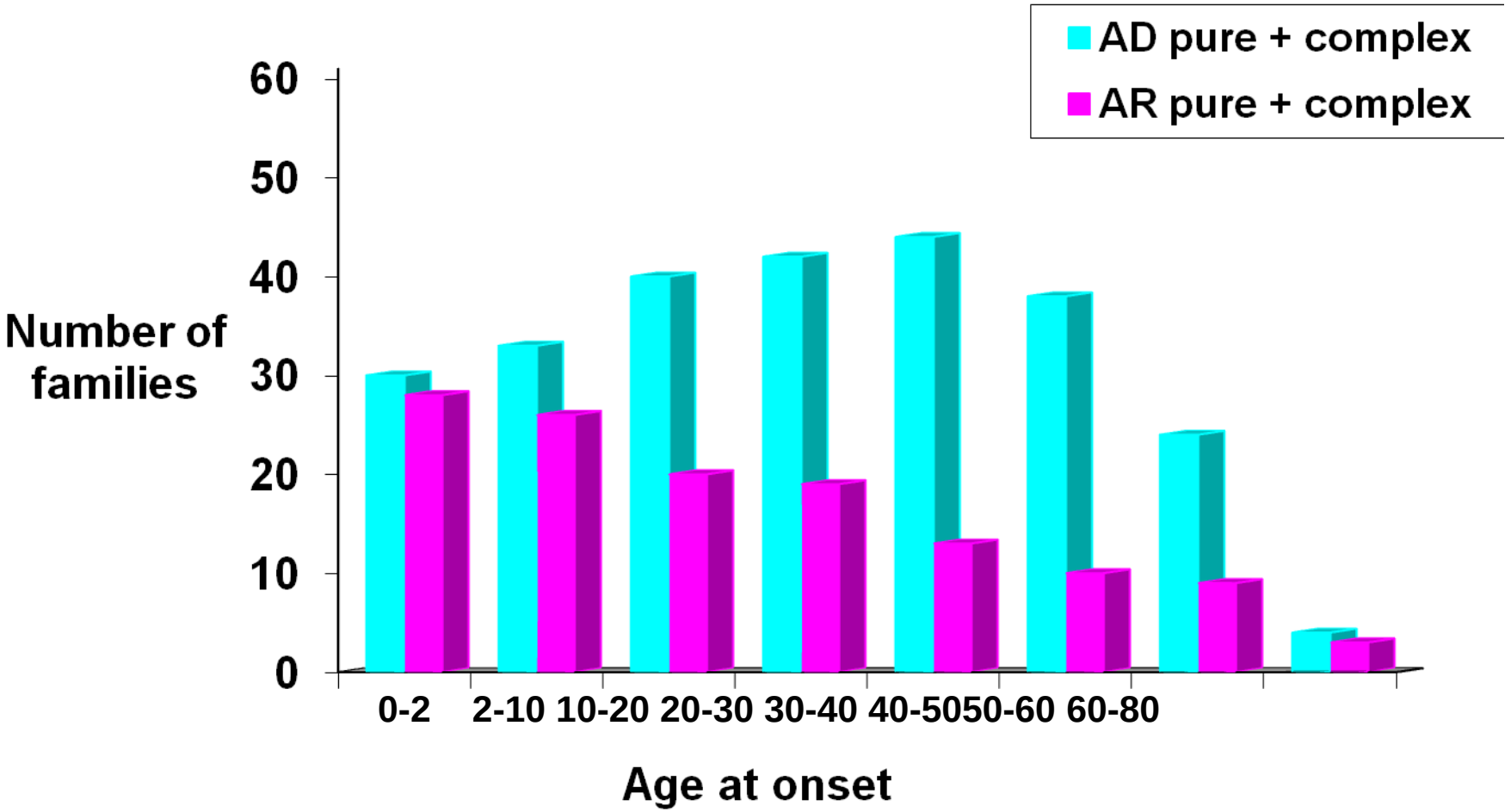
- Mandatory:
  - Radiologic investigation of spine and cerebrum
  - B12
- Eventual:
  - CSF
  - VLCFA
  - Neurography

Markers for HSP?? 2

- Age at onset?
- Clinical symptoms:
  - Type of spasticity?
  - Presence and degree of muscle paresis?
  - Associated symptoms
- Biochemical markers?
- Radiological markers?
  - Spectroskopi
  - MR
  - ++



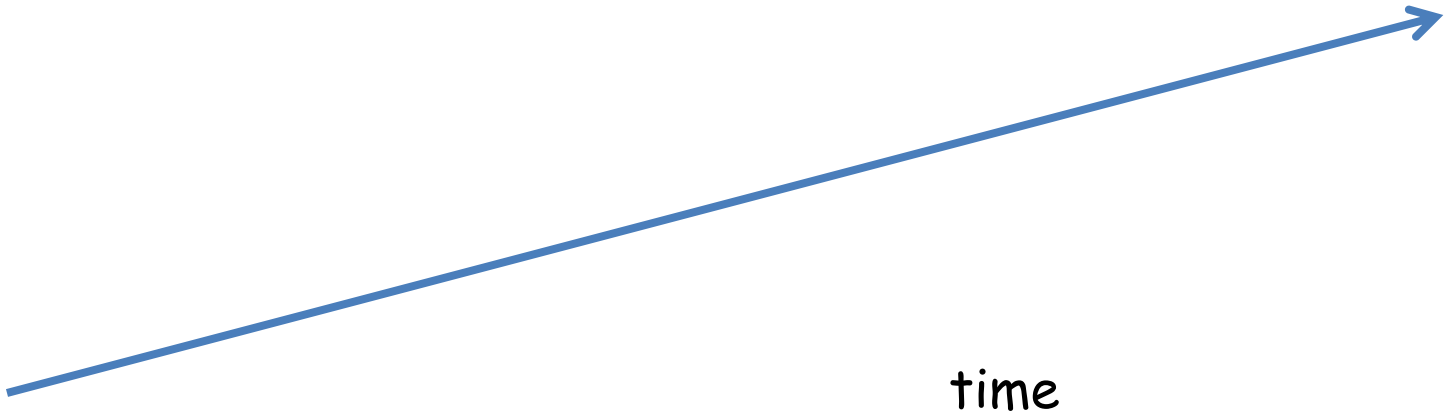
AGE OF ONSET



ENS 2001 Tallaksen

Progression

symptoms



time

Symptoms at onset

For all: prognosis= lineary progression

Diagnosis

Primary spastic paraparesis	Other primary disease with secundary spastic paraparesis
Hereditary disorder	Sporadic disorder

”sporadic” vs “hereditary”

- Sporadic often proves hereditary when:
  - small families
  - family history unknown
  - parents died early
  - “wrong” family!
  - de-novo mutations

Diagnosis- 1

- A. Clinical symptoms
  - 1. Progressive spasticity in lower limbs
  - 2. Brisk reflexes
  - 3. Extensor plantar reflexes
- B. Family history
  - 1. Positive
  - 2. None
  - 3. Unknown

Clinical Diagnosis for HSP

- Definite:
  - Spasticity in lower limbs
  - Brisk reflexes
  - Extensor plantar reflex
  - Family history
- Probable

- Possible

Fink JK et al, Neurology 1996

Definite HSP (certain)	Probable HSP (almost sure)	Possible HSP (cannot be excluded)
1. Other disorders excluded	1. Other disorders excluded+	1. Other disorders excluded
2. Family history of spastic paraparesis	Two of criteria 2-4	2. Family history of spastic paraparesis
3. Progressive gait impairment		Symptoms and findings unconclusive
4. Specific clinical findings		Observation and new examination later

Sporadic: **ASSP** (apparently sporadic spastic paraplegia)

Fink JK. Neurology 2008;71(19):1468-9

- Typically, ASSP is a transitional diagnosis applied for a number of years until
  - 1) a pathogenic mutation in an HSP gene is identified or a family history emerges, and the diagnosis is then changed to HSP;
  - 2) the disorder progresses to involve upper extremities, speech, and swallowing, and the diagnosis is then changed to primary lateral sclerosis;
  - 3) another etiology is identified (e.g., amyotrophic lateral sclerosis).

Sporadic

- How many sporadic HSP?
  - 13% of patients in a population based study (19 possibly affected for 127 definite+probable HSP)
  - 30% in a selected population (32 vs 76)

Sporadic

- Which HSP:
  - 5.5% - 6%-12% SPG4 among sporadic cases?
  - 5% SPG3?
  - SPG7? 7%?? *Brugman F et al.* ***Paraplegin mutations in sporadic adult-onset upper motor neuron syndromes,*** *NEUROLOGY 2008;71:1500-1505.*
- De novo-mutations: unknown frequency

Example

Clinical and genetic findings in a series of Italian children with pure hereditary spastic paraplegia.

Battini R et al, Eur J 2010.

- **Aims**: mutational frequency of SPG4, SPG3A, SPG31 and SPG7 genes
- **Material**: 14 Italian children affected by pure HSP (mean age at diagnosis 5.9 years), 13 apparently sporadic
- **Results**:
  - Three SPG4 mutations
  - One novel large deletion in SPG31
  - No mutations in the SPG7 and SPG3A genes

Differential diagnosis

- 80% multiple sclerosis!!
  - Particularly PPMS

Other disorders with spastic paraparesis

- Myelopathy (cervical spinal stenosis etc)
- Rare infections causing myelitis
  - Herpes, Tbc, syphilis
- Rare myelopathies (HTLV1, HIV)
- Vertebrogene/vascular etiologi
- Cerebral Paresis

cont

- Vitamin deficiency (B12)
- Other hereditary neurodegenerative disorders(spastic ataxia, FRDA, etc)
- Rare metabolic disorders (ALD, AMN)
- Mitochondrial disorders
- Other non hereditary neurodegenerative disorders
  - PLS
  - ALS
- Paraneoplastic disorders
- Vasculitis

- All these can be diagnosed using blodod tests, radiological examinations, spinal fluid analysis

- *But not the following…*

Differentiation of Hereditary Spastic Paraparesis From Primary Lateral Sclerosis in Sporadic Adult-Onset Upper Motor Neuron Syndromes

Frans Brugman et al
Arch Neurol. 2009;66(4):509-514

"In most patients with a sporadic adult-onset upper motor neuron syndrome, differentiation of sporadic presentations of HSP from PLS based on clinical characteristics is unreliable and therefore depends on results of genetic testing."

Disease progression at least 3 yrs 104 patients

Symptoms	SPG4-7(14)	others(90)
Leg involvement only (n=52)		
1 Leg or both legs only	13	39
Arm and leg involvement (n=16)		
Legs→arms	1	5
Legs→right arm		1
Legs→left arm		4
Right leg→right arm→left leg→left arm		1
Right leg→right arm		1
Left leg→left arm		2
Right arm→legs→left arm		1
Bulbar region involvement (36)		
Legs→arms→bulbar region		13
Legs→bulbar region→arms		5
Legs→bulbar region		2
Legs→left arm→bulbar region→ right arm		1
Left leg→left arm→right leg→right arm→bulbar region		1
Right leg→bulbar region→left leg→arms		1
Right leg→bulbar region		1
Right leg→right arm→left leg→bulbar region		1
Arms→bulbar region→legs		1
Arms→bulbar region		1
Left arm→legs→right arm→bulbar region		1
Bulbar region→arms→legs		2
Bulbar region→left arm		1
Bulbar region→legs→arms		1
Bulbar region→legs		1
Bulbar region→right arm and leg→left arm and leg		1
Bulbar region only		2

Treatment

- **NO cure**
- **Symptomatic**
  - ❖ Physiotherapy

✓ Stretching of the spastic muscles

✓ Heat

✓ Balance training

✓ Swimming pool

❖ Drugs

✓ Antispasmodic

✓ Relaxing, anti anxiety, antidepressive

Treatment

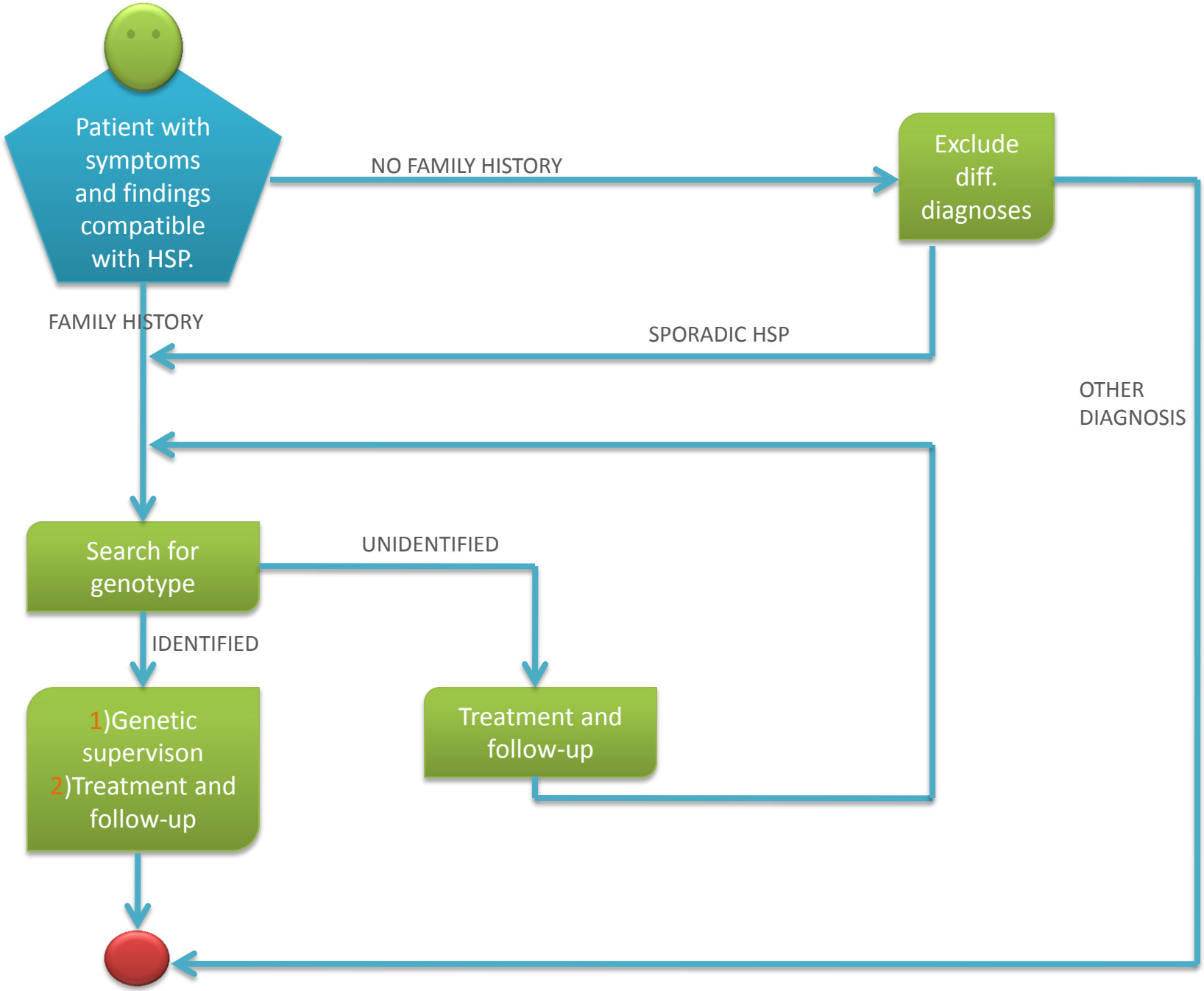
- Gene therapy??
  - Not at the moment
- Alternative therapies?
  - Acupuncture?
  - Specific types of physiotherapy?
  - Diet?
  - Vitamins?
  - Anti oxydants?

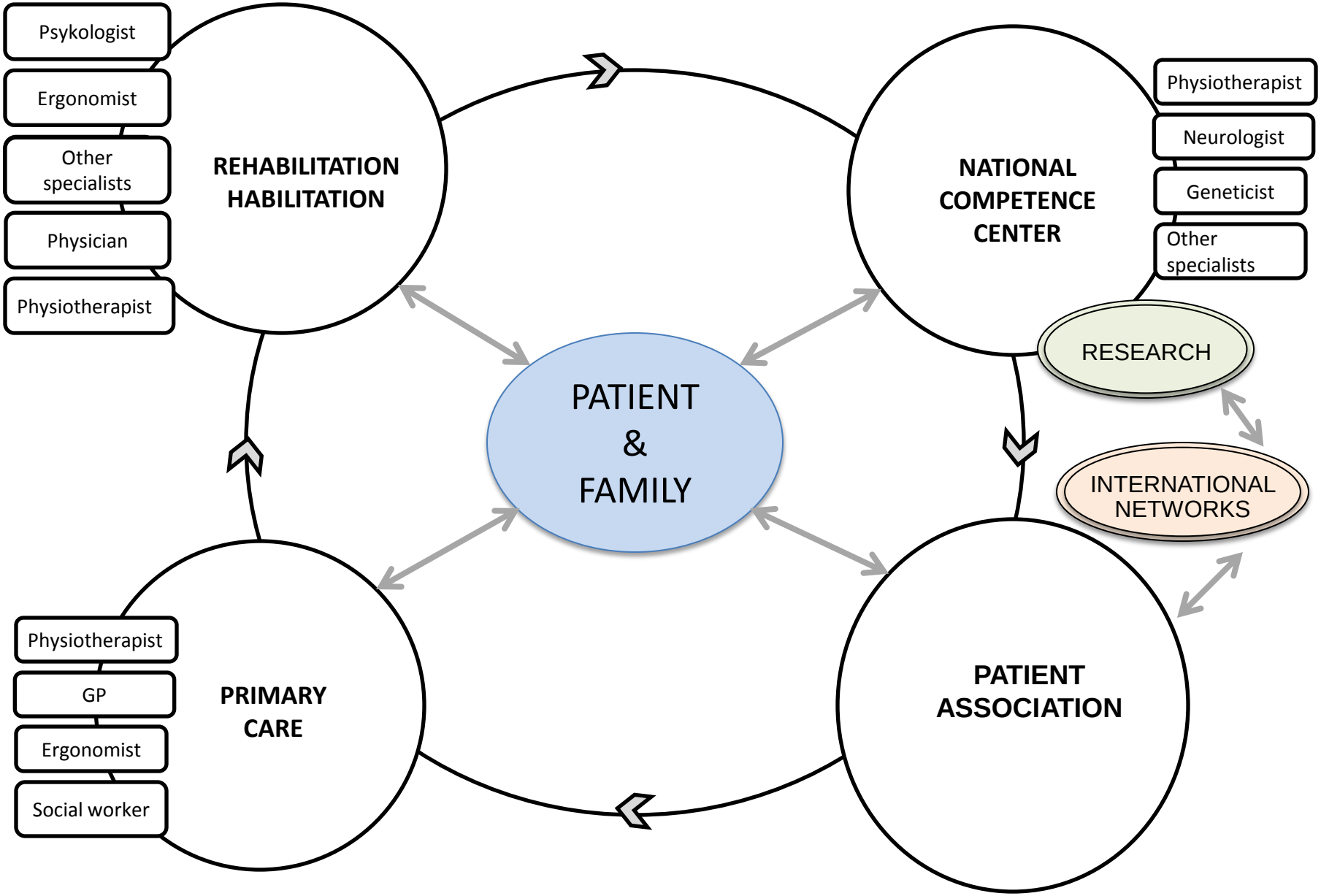
Treatment

- Botulinium toxine
  - For "small" muscles: adductors, ankle muscles
  - Must be tried
  - Maybe best in children?
- Baclofen intrathekal pump
  - For severe spasticity
  - No well established consensus
  - Must be tried, doses needed less than spinal trauma
- Surgery??

Follow up

- Prevent
  - Contractures
  - Pain (spasms, cramps, feilstilling)
  - Bladder problems ++
  - Problems at work
  - Problems at home
- Diagnosis follow up for not yet specified types
- Information about new therapies
- Genetic counselling


Patient with symptoms and findings compatible with HSP.
NO FAMILY HISTORY
Exclude diff. diagnoses
FAMILY HISTORY
SPORADIC HSP
OTHER DIAGNOSIS
Search for genotype
UNIDENTIFIED
IDENTIFIED
1)Genetic supervison
2)Treatment and follow-up
Treatment and follow-up


Psykologist
Ergonomist
Other specialists
Physician
Physiotherapist
REHABILITATION HABILITATION
NATIONAL COMPETENCE CENTER
Physiotherapist
Neurologist
Geneticist
Other specialists
RESEARCH
INTERNATIONAL NETWORKS
PATIENT & FAMILY
Physiotherapist
GP
Ergonomist
Social worker
PRIMARY CARE
PATIENT ASSOCIATION

Genetic diagnosis in HSP

From the clinician's point of view

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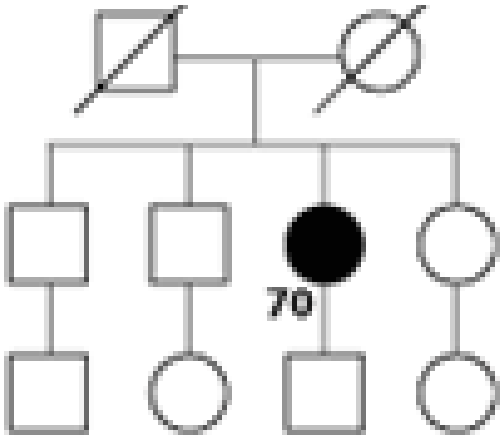
Burgos, May 2011

Types of heredity

- Sporadic
- Autosomal dominant
- Autosomal recessive
- X-linked

Sporadic



”sporadic” vs “hereditary”

- No known family history
- Disease course as typical HSP
- Thorough investigation reveals no other etiology

- Known cases with similar disease in the family
- Disease course as typical HSP
- No other etiology

”sporadic” vs “hereditary”

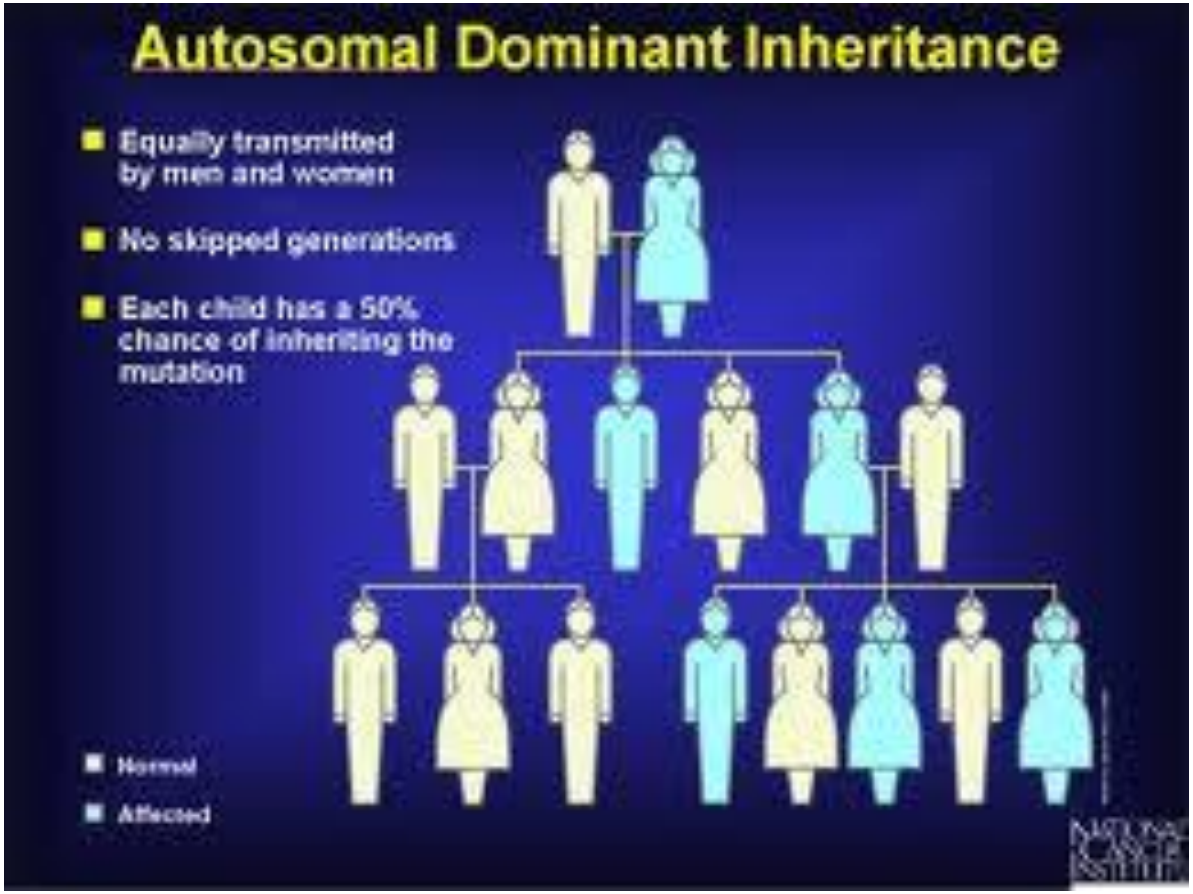
- Sporadic often proves hereditary when:
  - small families
  - family history unknown
  - parents died early
  - “wrong” family!
  - de-novo mutations

Sporadic: ASSP (apparently sporadic spastic paraplegia)

Fink JK. Neurology 2008;71(19):1468-9

- Typically, ASSP is a transitional diagnosis applied for a number of years until 1) a pathogenic mutation in an HSP gene is identified or a family history emerges, and the diagnosis is then changed to HSP; 2) the disorder progresses to involve upper extremities, speech, and swallowing, and the diagnosis is then changed to primary lateral sclerosis; 3) another etiology is identified (e.g., multiple sclerosis).

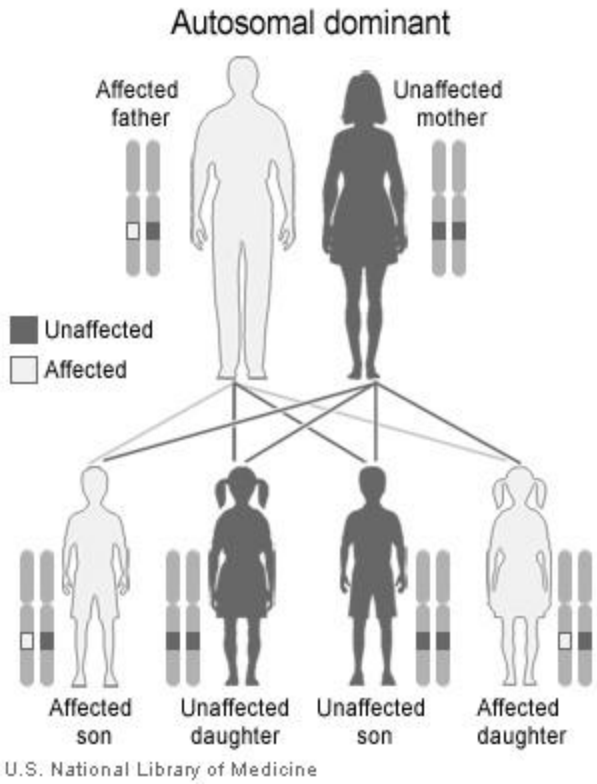
Autosomal dominant inheritance

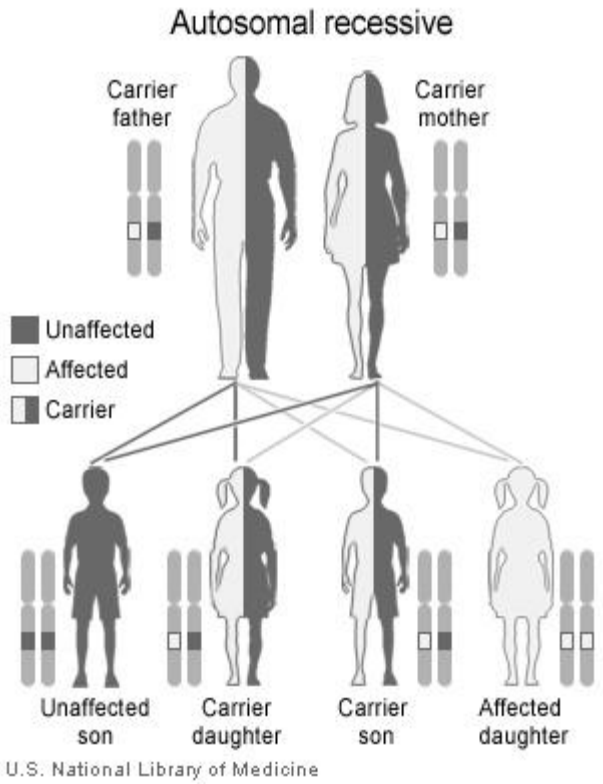


Heredity

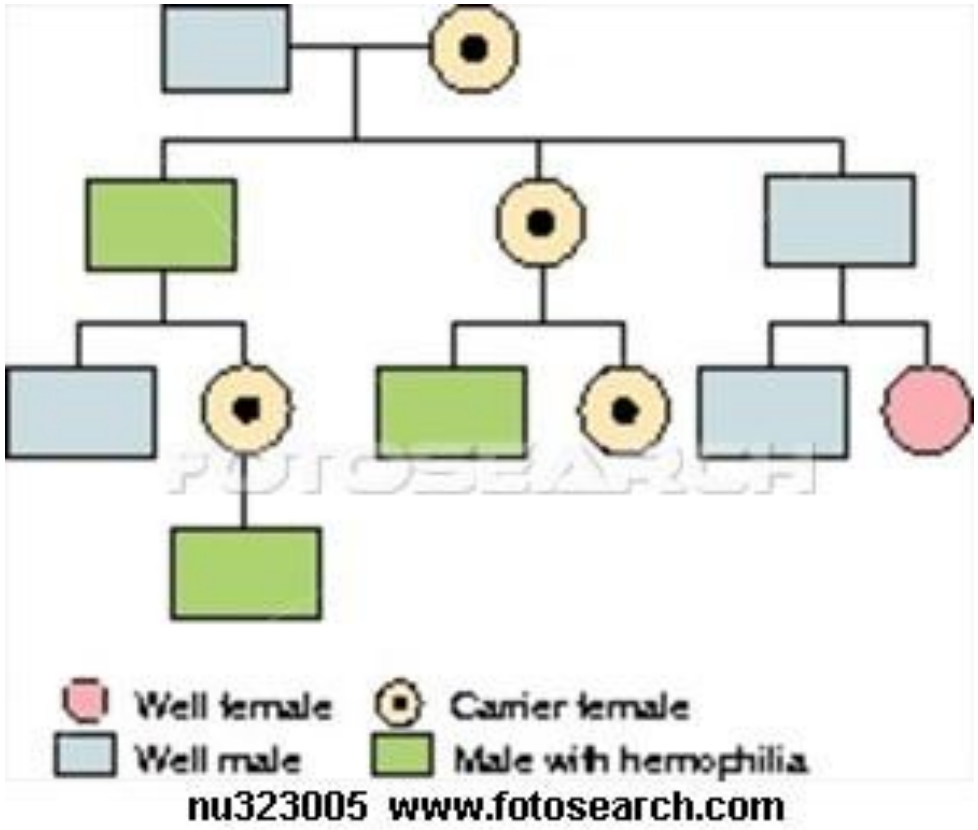
AD= autosomal dominant

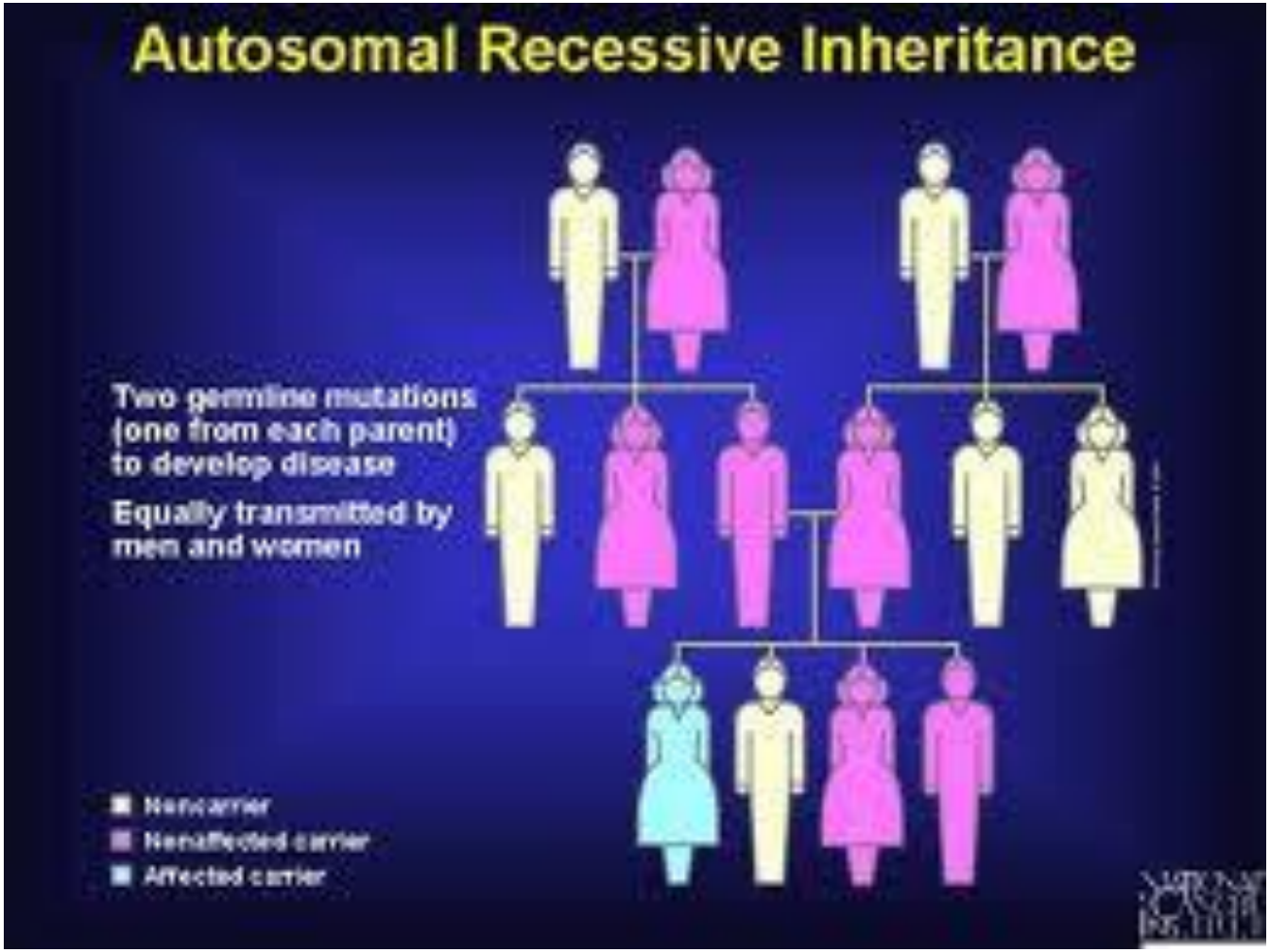
AR= autosomal r
recessiv



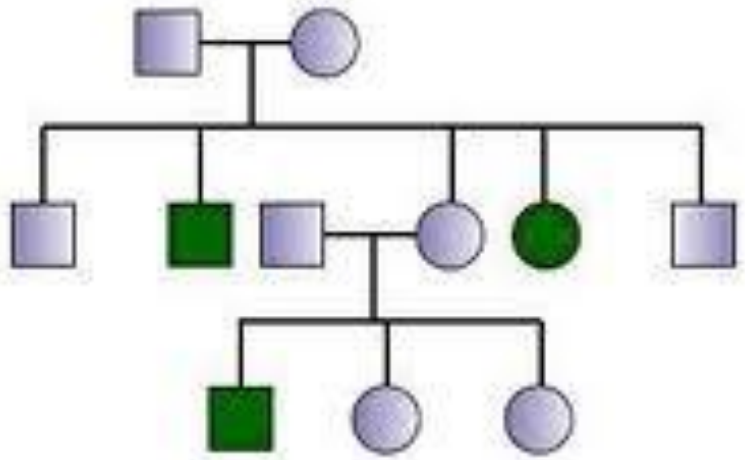


X-linked inheritance




Autosomal Recessive Inheritance
Two germline mutations (one from each parent) to develop disease
Equally transmitted by men and women
Noncarrier
Nonaffected carrier
Affected carrier

Autosomal recessive inheritance



Pedigree showing
autosomal recessive inheritance
of sickle cell anaemia

Genetic HSP

- > 48 forms described, most only in a few families, many with their own phenotype
- SPG4 = ca 40% of all dominant
- Nr 2= SPG3 (10-15%), nr 3=SPG31
- *SPG11, 15,21 most frequent recessive forms*
- *Possibly SPG7??*
- 43% genetic diagnosis in our material

GENETIC CLASSIFICATION OF DOMINANT HSP

Dominant HSP

- Most "pure " forms
- But associated signs and symptoms may be present (bladder-sexual dysfunction, orthopedic problems, UL symptoms)
- Some associated neurological symptoms not unfrequent: neuropathy
- Some associated symptoms often mentionned (fatigue, cramps)

name	Locus/gene/protein	Onset (yrs)	P/C, occurrence
SPG3	**14q-SPG3A-**atlastin	1-7(63)	P-Early onset, many families: **10-15%**
SPG4	**2p-SPAST-spastin**	**1-74**	**P-Most frequent: 50%**
SPG6	15q-***CYPB1***	12-35	**P**-A few families
SPG8	8q-***KIAA0196-*** strumpellin	18-60	**P**-A few families
SPG9	10q23.3-q24.1	1-40	**C**-< 5 families
SPG10	**12q- KIF5A**	**2-51**	**P/C-3%**
SPG12	19q-13	1-22	**P**-<5 families
SPG13	***2q24-HSP60***	17-68	**P-**1 family
SPG19	9q33-q34	36-55	**P**

name	Locus/gene/protein	Onset (yrs	P/C, occurrence
SPG27	10q22.1-10q24.1	25-45	P-
SPG29	1p31.1-21.1	11-30	C-?
SPG31	**2p- *REEP1***	**1-60**	**P-8%**
SPG33	*10q24.2-**ZFYVE27***		
SPG36	12q23-24	14-33	C
SPG37	8p21.1	8-60	P
SPG38	4p15-p15	12-20	C
SPG37	8p21.1-1q13.3	8-60	P
SPG42	3q- ***SLC33A***	4-42	P-1 family, mild
SAX1	12p13	10-20	C

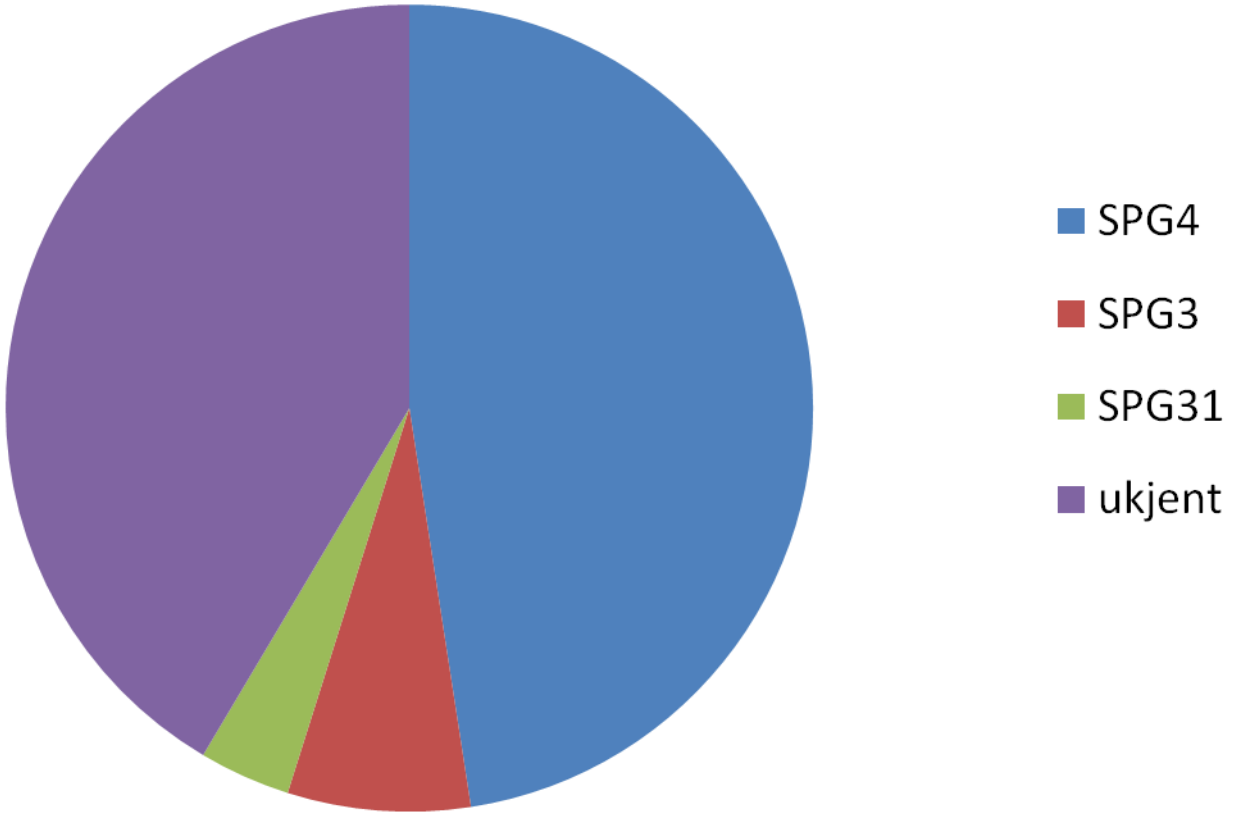
Which type of dominant HSP?

name	Locus/gene/protein	Onset (yrs)	Occurrence
SPG3	**14q-*SPG3A*-atlastin**	**1-7(63)**	**Early onset, many families: 10-15%**
SPG4	**2p-*SPAST*-spastin**	**1-74**	**Most frequent: 50%**
SPG6	15q-CYPB1	12-35	A few families
SPG8	8q-KIAA0196-strumpellin	18-60	A few families
SPG10	**12q- *KIF5A***	**2-51**	**3%**
SPG13	2q-HSP60	17-68	1 family
SPG31	**2p- *REEP1***	**1-60**	**8%**
SPG42	3q- SLC33A	4-42	1 family, mild

Which type dominant HSP?

navn	Locus/gen/protein	Start (år)	Særtrekk/forekomst
SPG3	14q-SPG3A-atlastin	1-7(63)	Early onset, many families: 10-15%
SPG4	2p-SPAST-spastin	1-74	Most frequent: 50%
SPG10	12q- KIF5A	2-51	3%
SPG31	2p- REEP1	1-60	8%

Typer dominant HSP, Norge 2010



SPG3

MIM 182600

- Insidious onset, mostly early (<20 yrs)
- Highly variable severity
- Variable progression
- Reduced penetrance
- Reported: scoliosis, axonal neuropathy

Additional Clinical Features of SPG3A Probands and Affected Family Members

Ivanova, N. et al. Arch Neurol 2007;64:706-713.

Table 3. Additional Clinical Features of *SPG3A* Probands and Affected Family Members

Patient	AA Change	Age at Examination, y	Pes Cavus	LL Sensory Problems	UL Hyperreflexia	UL Distal Weakness	UL Distal Atrophy	Bladder Disturbances	Additional Features	Severity*	Progression
SL-41, II.1	F151S	49	+	Decreased vibration, hypesthesia, hypalgesia	–	–	–	–	Neuropathy	3	R
SL-53, II.1	L157W	41	–	–	+	+	–	–	–	3	S
SL-53, III.1	L157W	3	?	–	?	?	?	–	–	3	R
SL-258, III.3	Q191R	39	–	Decreased vibration	–	–	–	–	Neuropathy	3	S
SL-121, II.2	R239C	61	–	–	–	–	–	–	–	2	S
SL-121, III.2	R239C	36	–	–	–	–	–	–	–	1	S
SL-121, III.3	R239C	33	–	–	–	–	–	–	–	2	S
SL-121, IV.2	R239C	8.5	–	–	–	–	–	–	–	2	S
SL-121, IV.3	R239C	4.5	–	–	–	–	–	–	–	2	S
HSP-5, II.3	L250P	69	–	–	–	–	–	–	–	3	R
HSP-5, III.1	L250P	37	–	–	–	–	–	–	–	3	R
HSP-5, III.3	L250P	39	–	–	–	–	–	–	–	2	S
HSP-5, IV.1	L250P	15	–	–	+	–	–	–	–	4	R
HSP-5, IV.3	L250P	12	–	–	–	+	–	–	–	3	R
HSP-5, IV.4	L250P	10	–	–	–	–	–	–	–	3	R
SL-6, II.2	H258R	49	–	–	–	–	–	–	–	4	S
SL-6, III.1	H258R	25	–	–	–	–	–	–	–	2	S
SL-6, III.3	H258R	22	–	–	–	–	–	–	–	2	S
SL-239, I.2	Y336H	63	–	Decreased vibration	+	–	–	–	–	3	S
SL-239, II.1	Y336H	34	–	–	–	–	–	–	–	3	S
SL-166, II.1	M408T	4.5	–	?	+	+	+	–	Neuropathy, dysarthria, bradykinesia, growth retardation	4	R
SL-109, I.2	G469A	63	+	–	–	–	–	–	–	1	S
SL-109, II.3	G469A	40	+	Decreased vibration	–	–	–	–	Neuropathy	2	S
SL-109, II.5	G469A	29	+	–	–	–	–	–	Neuropathy	2	S
SL-109, III.1	G469A	10	–	–	–	–	–	–	–	2	S
HSP-6, II.3	G482V	63	–	–	–	–	–	–	–	0	NA
HSP-6, II.5	G482V	61	–	–	+	+	–	–	–	2	S
HSP-6, III.4	G482V	32	–	–	–	+	–	–	–	3	R
HSP-6, III.5	G482V	34	–	–	–	+	–	–	[Epilepsy]	3	R
HSP-6, IV.2	G482V	12	–	–	–	+	–	–	–	3	R
SL-291, II.1	A492fsX522	36	–	–	–	–	–	–	–	2	S
SL-108, II.3	R495W	57	–	–	–	–	–	–	–	2	S
SL-108, III.2	R495W	42	–	?	–	–	–	–	–	2	S
SL-108, III.7	R495W	34	+	Hyperesthesia	–	–	–	–	Neuropathy	2	S
SL-108, IV.1	R495W	20	–	–	–	–	–	–	–	1	S
SL-108, IV.3	R495W	12	–	–	–	–	–	–	–	1	S
Overall, %			14	15	14	20	3	0	17 Complex HSP	2-3 (78)	

Abbreviations: AA, amino acid; LL, lower limbs; NA, not applicable; R, rapid; S, slow; UL, upper limbs; +, present; –, absent; ?, unknown; [epilepsy], brackets indicate not related to hereditary spastic paraplegia.

*Refer to the severity scale in the "Methods" section.

Ivanova, N. et al. Arch Neurol 2007;64:706-713.

- **Results** In 12 probands (6.6%), we identified 12 different *SPG3A* mutations (11 missense and 1 insertion/frameshift) of which 7 were novel and 3 were de novo. We found **incomplete penetrance in 1 family** (G482V). In most cases, *SPG3A* mutations were associated with an early age at onset (mean, 3 y); however, in 1 family (R495W mutation), symptoms started later (mean, 14 y) with clear intrafamilial variability (8-28 y). Six patients with an *SPG3A* mutation (F151S, Q191R, M408T, G469A, R495W) originating from 5 unrelated families presented with a complex form of hereditary spastic paraplegia associated with a neuropathy (17%). Our electrophysiological and pathological findings confirmed an axonal sensory-motor neuropathy. There was no correlation between the genotype and the presence of a neuropathy.

SPG3A is the most frequent cause of hereditary spastic paraplegia with onset before age 10 years

M. Namekawa et al, NEUROLOGY 2006;66 :112-114

- *SPG3A* mutations were found in 13.5% (7/52) of AD-HSP families with onset before age 20 years and 31.8% (7/22) in families with onset before age 10 years.

SPG4

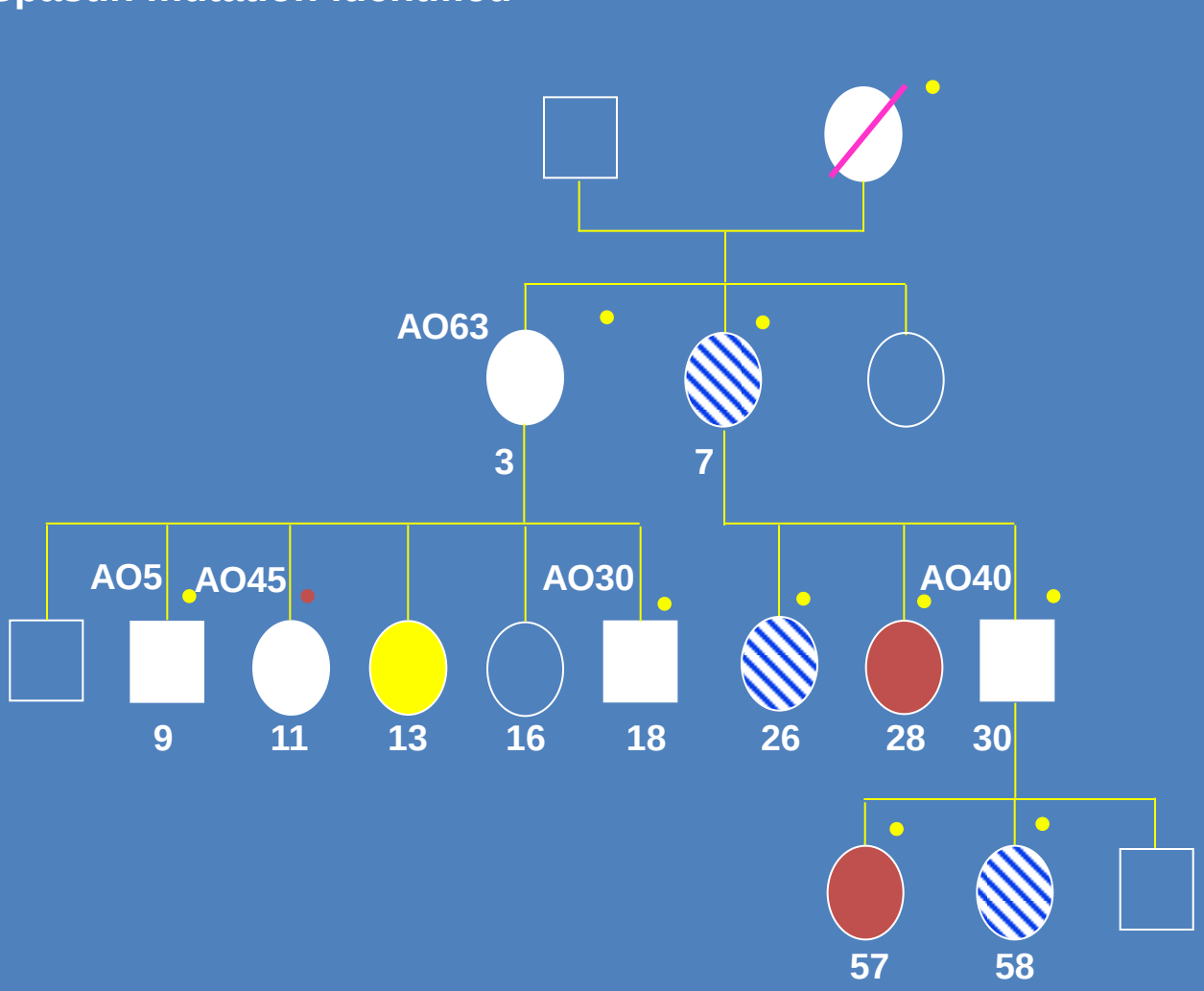
- Most frequent, most reported, best known
- "Pure" form
- No phenotype-genotype correlations
- Great intra/inter-familial variability
- Same for men and women
- Faster progression at older onset
- Modifying factors?

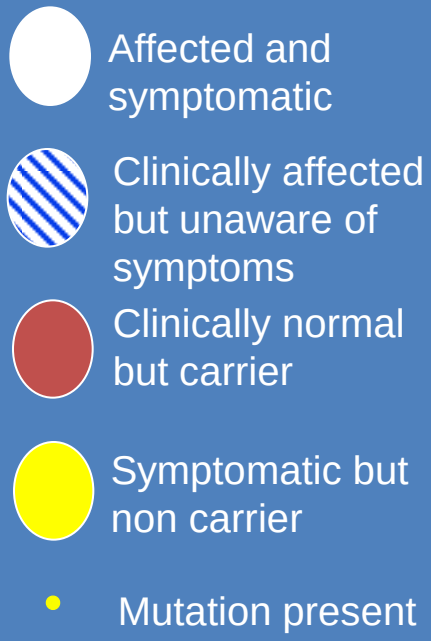
SPG4

- How frequent are de novo-mutations?
- Penetrance:
  - Age-dependent
  - Incomplete– ca 85% at 45 yrs
  - 20% asymptomatic
- *NB: therefore difficult to give a precise onset of disease*
- No antecipation

VARIABLE EXPRESSION AND REDUCED PENETRANCE IN SPG4

Spastin mutation identified





With permission- Alexandra Dürr

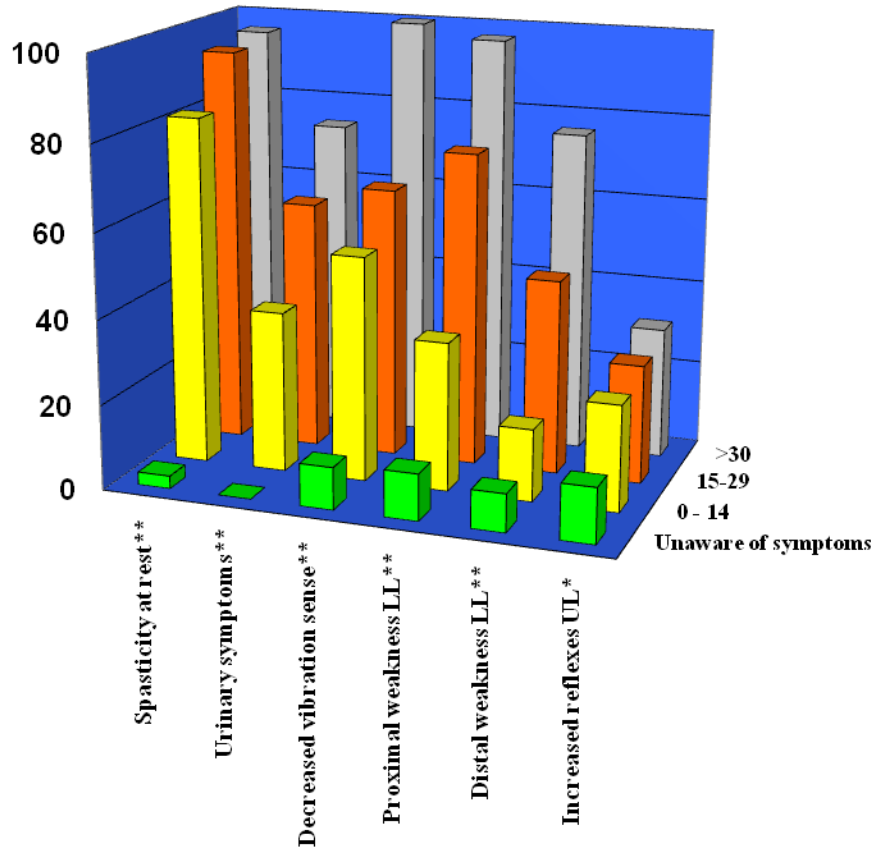
Clinical features of 224 SPG4 patients

- Age at onset: 29±17 (0-74) yrs
- Disease duration: 21±15 (0-73) yrs
- Mean age when walking impossible: 48±17 (22-79)
- Severe spasticity at gait/at rest: 34%/19%
- Increased reflexes LL: 91%
- Increased reflexes UL: 27%
- Extensor plantar reflex: 81%
- Proximal muscle weakness LL: 54%
- Distal muscle weakness LL: 36%
- distal muscle wasting: 9%
- Decreased/abolished vibration sense at ankles: 58%/11%
- Urinary urgency / incontinence: 38%/2%
- Pes cavus/scoliosis: 21%/5%

FREQUENCY OF CLINICAL SIGNS IN SPG4

As a function of disease duration

tients
(%)



Disease duration
(years)

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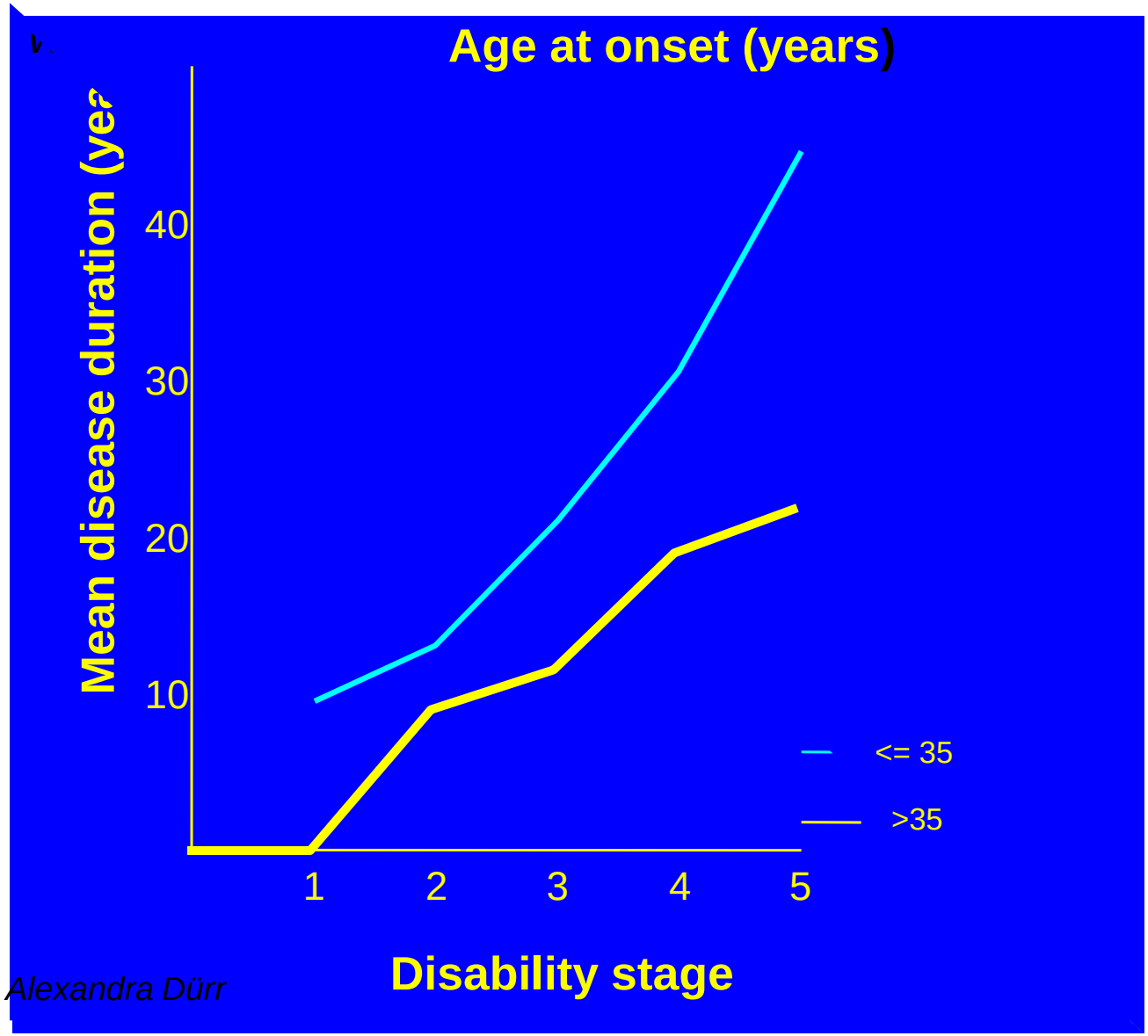
Disability, disease duration and age at onset in SPG4



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Additional symptoms

- Cognitive impairment
- Psychiatric disorder
- Cerebellar ataxia
- Dysarthria
- Mental retardation
- Silver phenotype
- Corpus callosum atrophy
- Epilepsy?
- Posterior fossa abnormalities

SPG4: conclusions

- Large inter and intra-heterogeneity
- No sex difference
- Milder form when early onset
- Average onset: young adults (30 yrs)
- No impact on life duration
- Ca 20% affected but asymptomatic (unaware of symptoms)
- Ca 6% clinically asymptomatic

SPG6

MIM 600363

- Few families
- Onset 12-35 yrs
- Insidious onset
- Progressive disorder
- Variable severity
- NIPA1 gene

SPG8

MIM 603563

- Adult onset (18 to 60 years)
- Insidious onset
- Severe phenotype
- Calves atrophy, pes cavus
- Unknown occurrence, few families
- Unpublished own data: not found in 28 AD-HSP index cases, non SPG4- non SPG3
- KIAAO196 gene
- Must be rare

SPG8

MIM 603563

- Unknown occurrence, few families
- Unpublished own data: not found in 28 AD-HSP index cases, non SPG4- non SPG3
- KIAAO196 gene
- Must be rare

SPG10

MIM 604187

- Onset 8-40 yrs
- Few families
- Upper limb weakness may occur later
- Upper limb sensory loss may occur later
- Axonal neuropathy
- Scoliosis
- *KIF5A* gene

SPG10 is a rare cause of spastic paraplegia in European families.

Schüle R et al, *J Neurol Neurosurg psychiatry 2008;79(5):584-7.*

- CONCLUSIONS: SPG10 accounts for approximately 3% of European autosomal dominant HSP families. All mutations affect the motor domain of kinesin and thus most likely impair axonal transport. Clinically, SPG10 is characterised by spastic paraplegia with mostly subclinical peripheral neuropathy.

SPG31

MIM 610250

- 3-6% in cases with autosomal dominant inheritance.
- Dysphagia (less common)
- Muscle wasting due to chronic denervation
- Amyotrophy
- Distal sensory loss
- Variable severity
- Pure or complicated

SPG42

MIM 612539

- **A total of 220 patients with autosomal dominant spastic paraplegia do not display mutations in the SLC33A1 gene (SPG42).**

  Schlipf NA et al , Europ Hum Gen 2010

Conclusion:

We consider SLC33A1 gene mutations as being very rare in a European ADHSP cohort, if present at all.

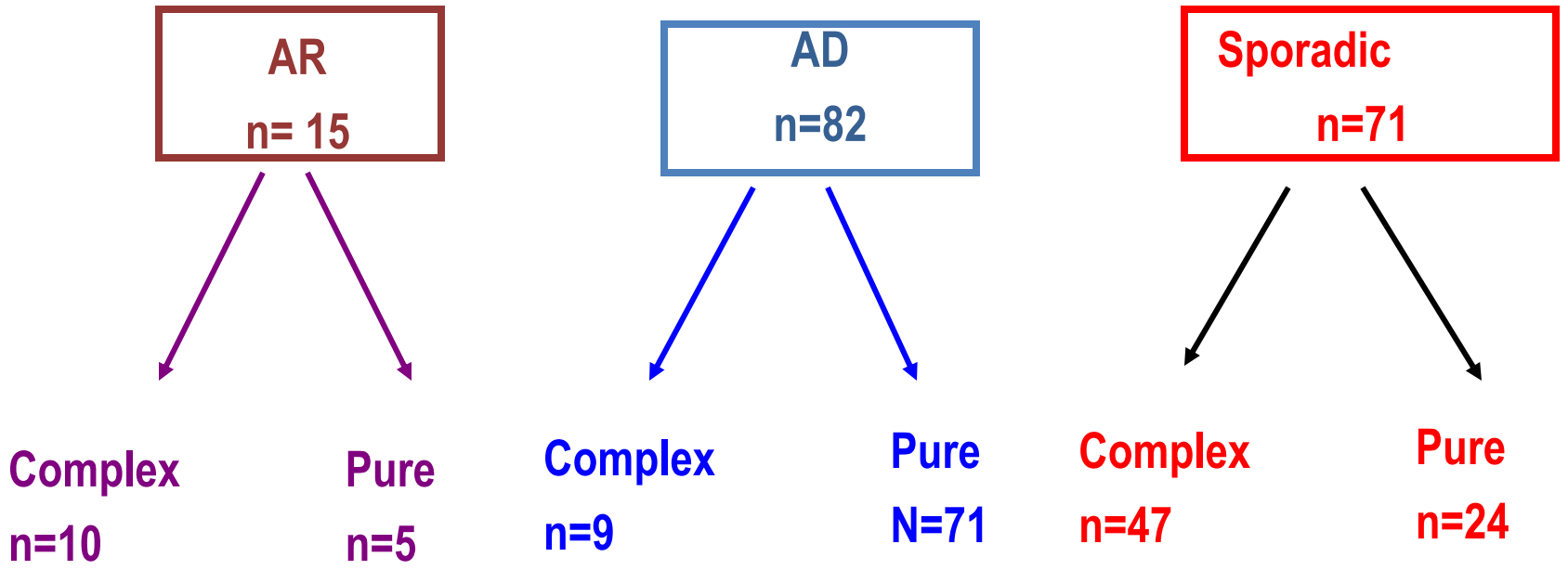
Which type of dominant HSP?

name	Locus/gene/protein	Start (yrs)	Characteristics/occurrence
SPG3	14q-SPG3A-atlastin	1-7(63)	Early onset, many families: 10-15%
SPG4	2p-SPAST-spastin	1-74	Most frequent: 50%
SPG10	12q- KIF5A	2-51	3%
SPG31	2p- REEP1	1-60	8%

X-linked HSP

name	Locus/gene/protein	onset (yrs)	Characteristics, ocurrence
SPG1	Xq28- *L1CAM*	1-5	C- CC agenesis, Mental retardation, Aphasia, Shuffling gait, Adducted thumbs, Hydrocephalus (CRASH). >100 mutations
SPG2	Xq21- *PLP2*	1-18	C-From light HSP to Pelizeus Merzbacher phenotype >100 mutations
SPG16	Xq11.2	1-5	P-severe. 2 families
SPG22	Xq13.2- *SLC13A2/MCT8*	1	C-Mental retardation, dysmorphia, hypotonia, dystonia, low S-thyroxin, Allan-Herndon-Dudley syndrome. Several families.
SPG34	Xq24-q25	10-25	P- 1 large Brazilian family

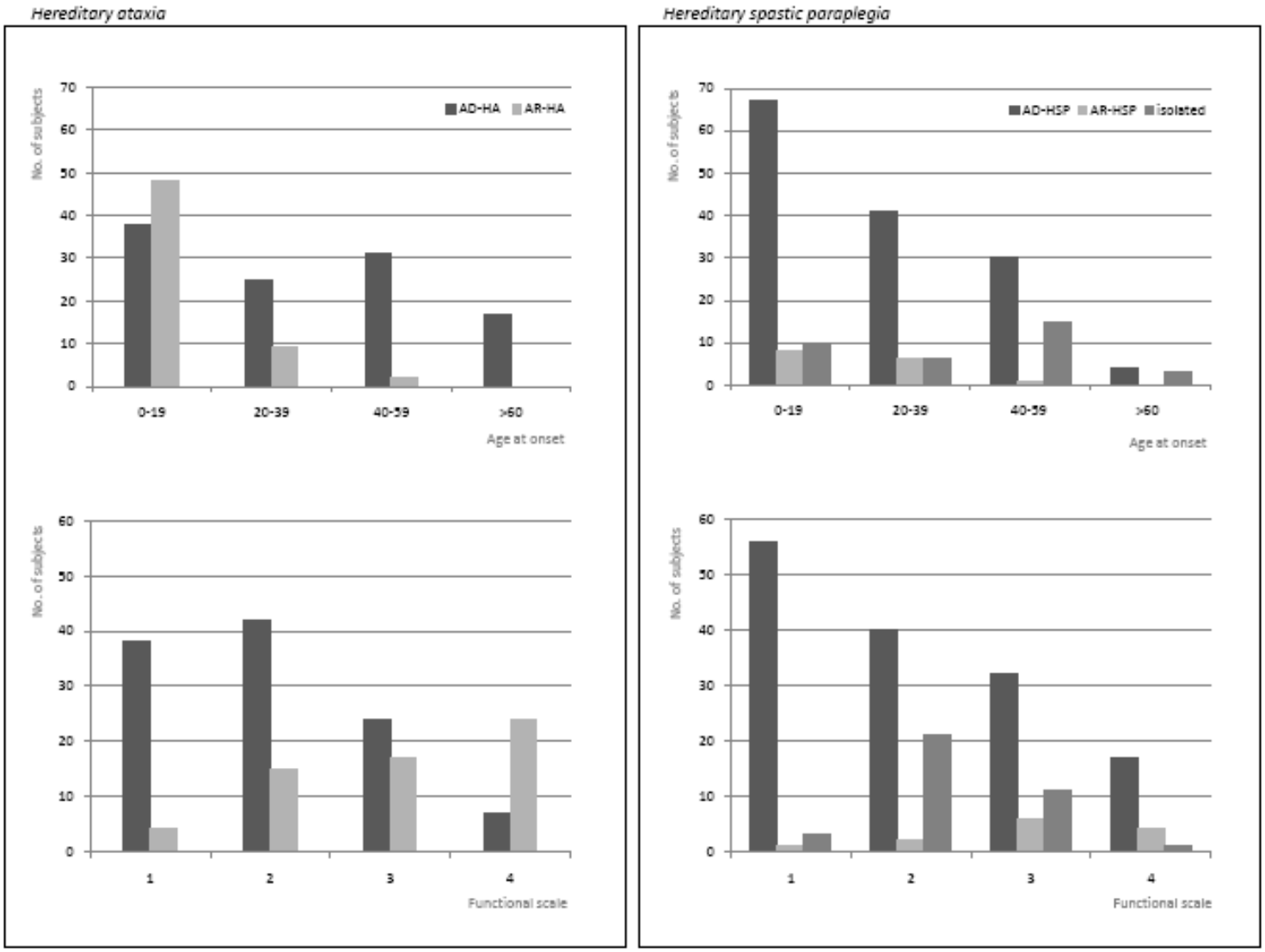
HSP- 99 families, 286 individuals oct. 2010



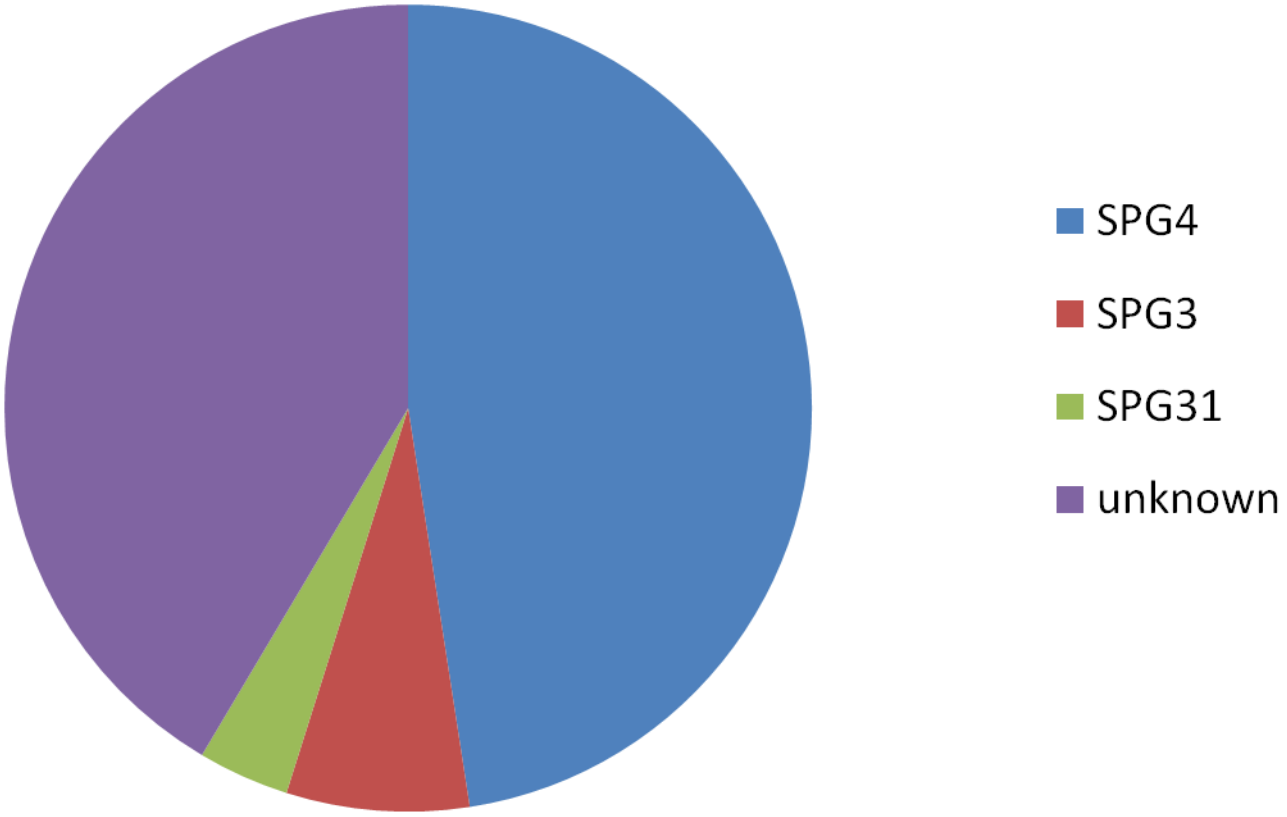
HSP in Norway
281010

Number of individuals: 286
136 men, 130 women
Pure form HSP: 103
Complicated form: 68

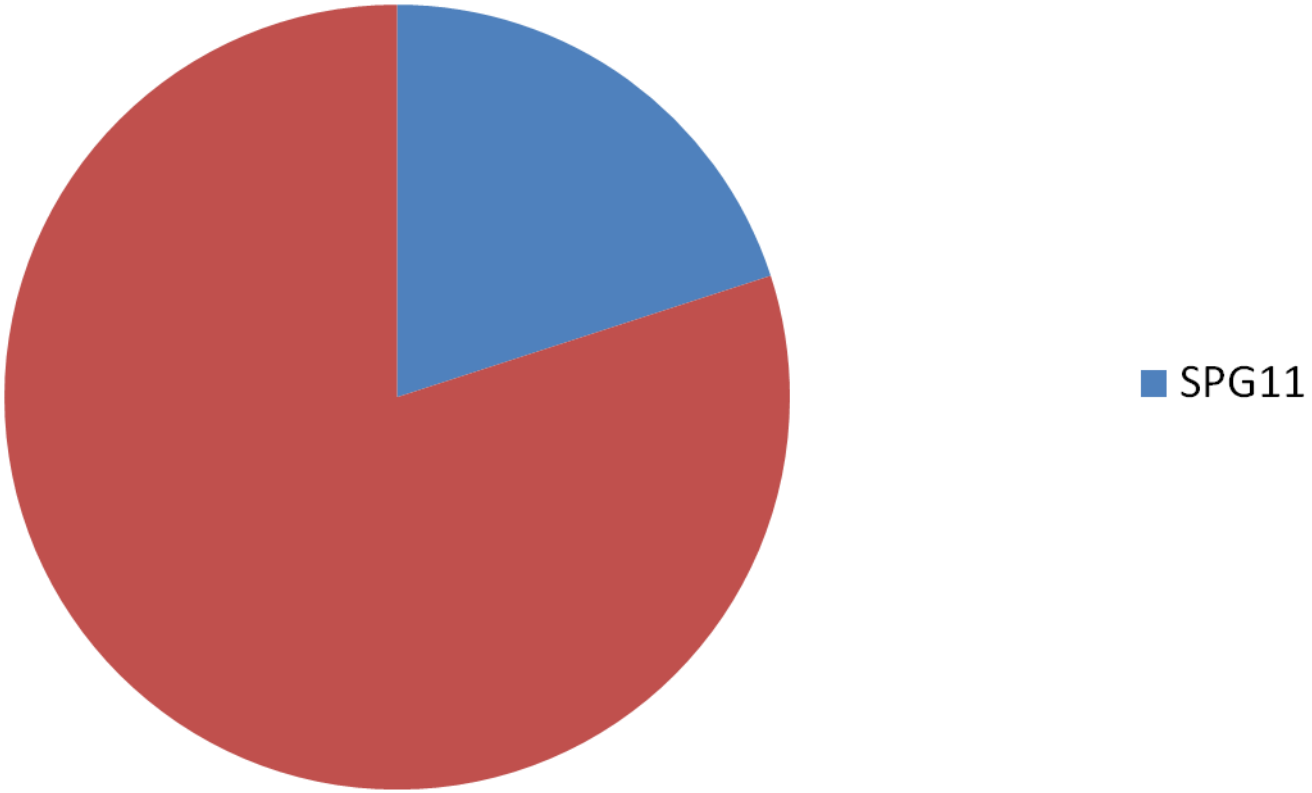
Heredity	AD	AR	X-linked	sporadic
Antall families	82	15	3	71
Pure/comp	71/9	5/10	3/0	24/47


Hereditary ataxia
AD-HA
AR-HA
No. of subjects
0-19
20-39
40-59
>60
Age at onset
No. of subjects
1
2
3
4
Functional scale
Hereditary spastic paraplegia
AD-HSP
AR-HSP
Isolated
No. of subjects
0-19
20-39
40-59
>60
Age at onset
No. of subjects
1
2
3
4
Functional scale

Dominant HSP, Norway 2010



Recessive HSP, Norway 2010



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RESTAURANT