Environmental modifiers in Hereditary Spastic Paraplegia

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Question to the audience

Question 1 :

What is your professional background ?

- neurologist,
- neuropediatrician,
- physiatrist,
- researcher,
- resident,
- patient or patient representative,
- nurse,
- physiotherapist,
- occupational therapist,
- speech / language therapist,
- geneticist,
- psychologist,
- other.

Question to the audience

Question 2 :

Have you ever seen patient with hereditary spastic paraplegia ?

- Yes, very often,
- Yes sometimes,
- Just a few,
- No, never

Sommaire

Hereditary spastic paraplegia

Group of rare, inherited, neurological diseases :

- prevalence about : 2.2 to 4.1/100,000
- broad genetic heterogeneity : more than 79 *SPG* genes,
- broad clinical heterogeneity : age-at-onset and symptoms severity.

Ruano, L., Melo, C., Silva, M. C. Coutinho, P. The global epidemiology of hereditary ataxia and spastic paraplegia : a systematic review of prevalence studies. Neuroepidemiology 42, 174 ?183 (2014).

Coutinho, P. et al. Hereditary ataxia and spastic paraplegia in Portugal : a population-based prevalence study. JAMA Neurol. 70, 746 ?755 (2013).

Shribman, S., Reid, E., Crosby, A. H., Houlden, H. Warner, T. T. Hereditary spastic paraplegia : from diagnosis to emerging therapeutic approaches. Lancet Neurol. 18, 1136 ?1146 (2019).

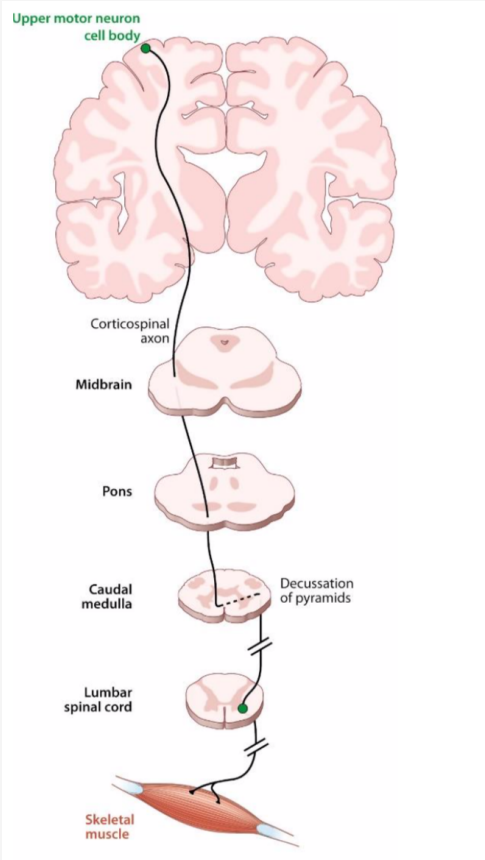
Parodi L et al. (2017). Hereditary spastic paraplegia : more than an upper motor neuron disease. Revue Neurologique.

Pensato, V., Castellotti, B., Gellera, C., Pareyson, D., Ciano, C., Nanetti, L., Moroni, I. (2014). Overlapping phenotypes in complex spastic paraplegias SPG11, SPG15, SPG35 and SPG48. Brain, 137(7), 1907-1920.

Different types of hereditary spastic paraplegia (HSP)

A common symptom

- Lower limbs spasticity :



Blackstone, C. (2012). Cellular pathways of hereditary spastic paraplegia. Annual review of neuroscience, 35, 25-47.

Wide clinical variability

Spastic paraparesis :

- because of the first moto-neuron degeneration,
- but second motoneuron can be involved :

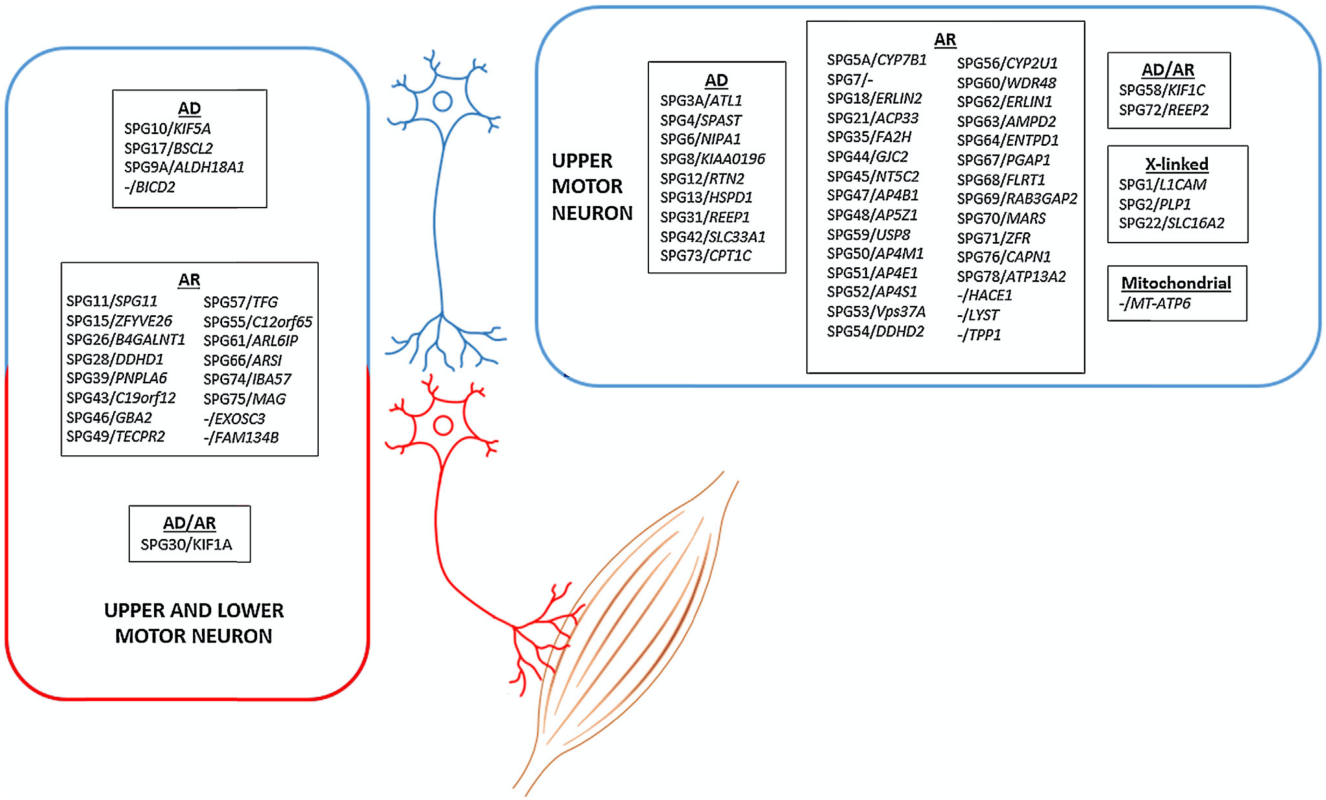
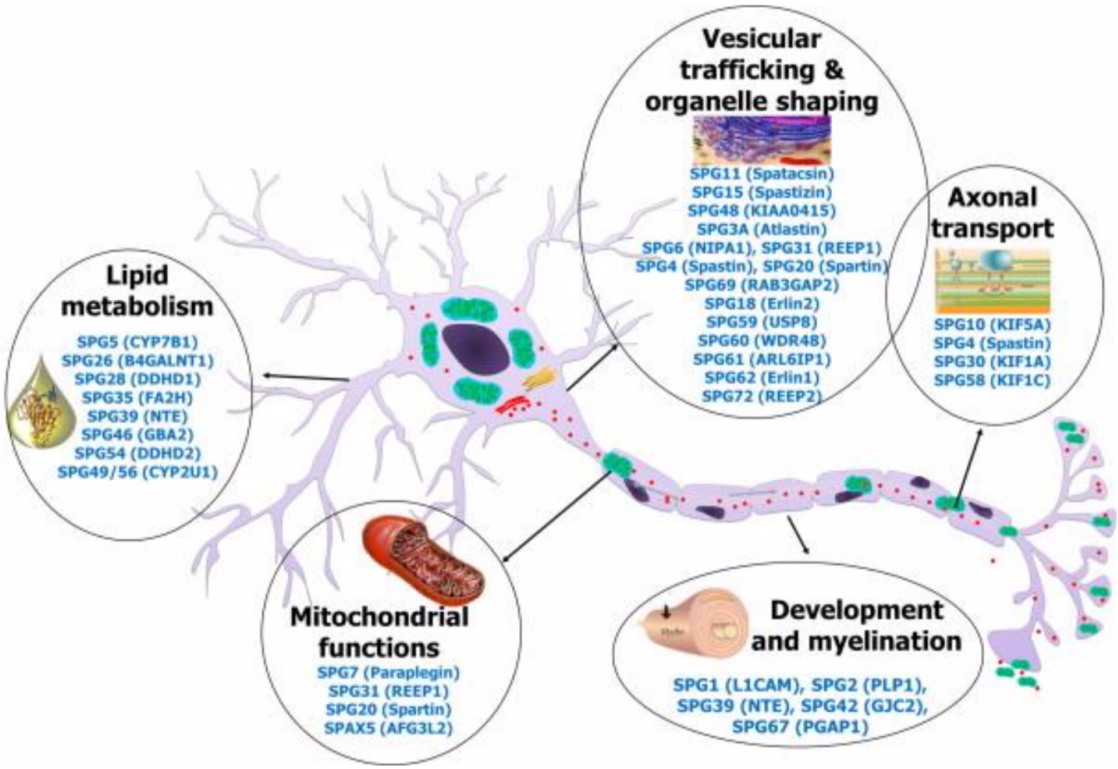


Fig. 1 – Spastic paraplegia genes (SPGs) grouped according to affected motor neurons and mode of inheritance.

Parodi L et al. (2017). Hereditary spastic paraplegia : more than an upper motor neuron disease. Revue Neurologique.

Cellular mechanisms



Klebe, S., Stevanin, G., Depienne, C. (2015). Clinical and genetic heterogeneity in hereditary spastic paraplegias : from SPG1 to SPG72 and still counting. Revue neurologique, 171(6-7), 505-530.

Variability in SPG4

Age of onset determined by the genetic mutation

- Variation de l'âge de début de la pathologie en fonction de la mutation :

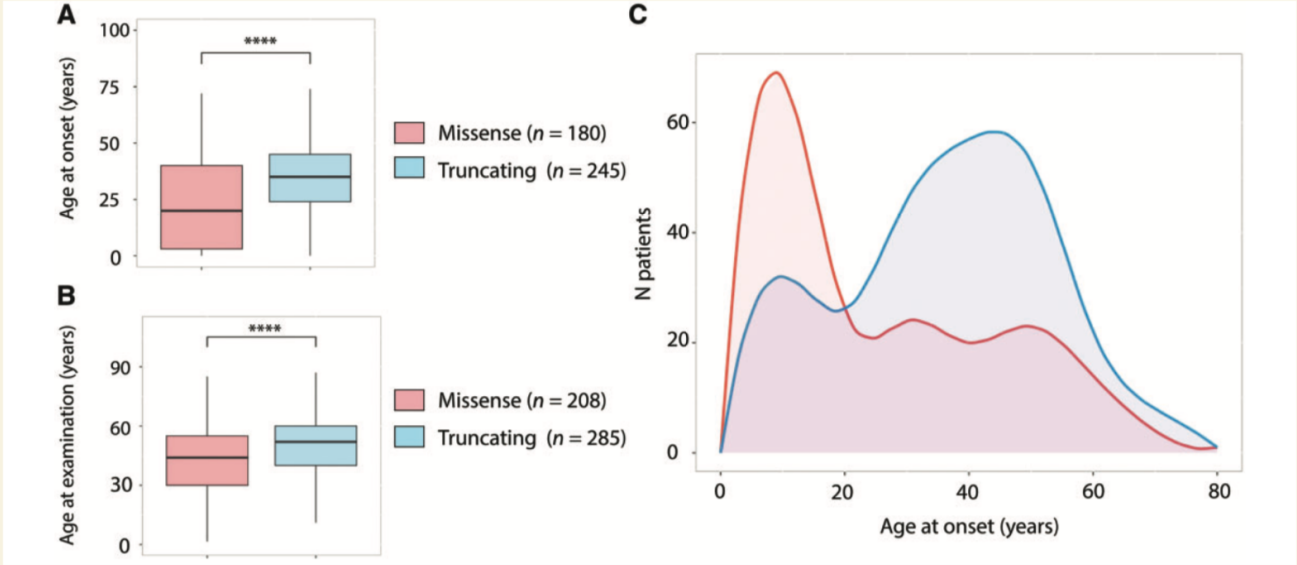


Figure 4 Age at onset distribution and genotype correlations. (**A** and **B**) Boxplots representing the age at examination /at onset for patients carrying missense or truncating mutations (Mann-Whitney test, ****$P < 0.0001$). (**C**) Distribution of the age at onset of missense- and truncating-mutation carriers. The lower age at onset linked to missense mutations is evident, shown by the density curve (red), characterized by a first peak between birth and the first decade of life and a second smaller peak between the third and fifth decades. Truncating-mutation carriers (blue curve) are characterized by a later age at onset, with a small peak between birth and the first decade of life and a major peak between the second and fifth decades.

Parodi, L. et al, (2018). Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. Brain.

Sommaire

Aims of the study

1. To look for environmental modifiers :
   - which could be added to genetic modifiers,
2. To take an overview of the population affected by SPG :
   - disease evolution,
   - management and treatments.

Limits

Rare diseases :

- the number of patients is reduced,
- the genetic heterogeneity is great.

Sommaire

Data collection

Data collection is carried out by means of a self-administered questionnaire.

This questionnaire is completed by patients with spastic paraparesis and is proposed :

- during medical consultations,
- thanks to patients' organisations (APL, APSHE).

Data collected

Among the data collected, there are :

- Anthropometric data :
  - sex,
  - age,
  - BMI,
- Medical information :
  - early post-natal history,
  - other history (cancer, cardiovascular disease, diabetes),
  - age-at-onset,
  - symptomatic treatments and their effectiveness,
  - factors that influence spasticity,
- Life habits, social habits... :
  - toxic consumption,
  - environment (place, work, food).

ICM
Institut du Cerveau et de la Moelle épinière

QUESTIONNAIRE

Dans le cadre d'une enquête menée par le Dr Alexandra Durr et le Dr Christel Depienne (Institut du Cerveau et de la Moelle Epinière) portant sur l'étude des liens éventuels entre les paraparésies spastiques héréditaires (PSH) et les facteurs environnementaux, nous souhaiterions recueillir des renseignements complémentaires vous concernant. Ces informations, qui resteront anonymes, pourraient nous permettre d'avancer dans la compréhension de la maladie.

Date du jour (Jour/Mois/Année): I_I_I/I_I_I/I_I_I_I_I

DDN (Mois/Année): I_I_I/I_I_I_I_I Département du lieu de résidence : I_I_I

Sexe : 1❑ Masculin 2❑ Féminin

Poids I_I_I_I kg
Taille I_I_I_I cm

1) Où avez-vous vécu la majeure partie de votre vie?

1❑A la campagne 2❑A la ville 3❑A la mer 4❑A la montagne

2) Dans votre enfance :

A la naissance ; avez-vous été réanimé ? 1❑OUI 0❑NON

Votre mère vous a-t-elle allaitée? 1❑Oui 0❑Non
Si oui, indiquez pendant combien de temps vous avez pris le sein exclusivement :

I_I_I 1❑jours 2❑semaines 3❑mois 4❑années

3) MALADIE

Type de maladie
1❑Paraparésie spastique ou Maladie de Strümpell Lorrain
2❑Autre : précisez……

Age de début de la maladie I_I_I ou année de début I_I_I_I_I

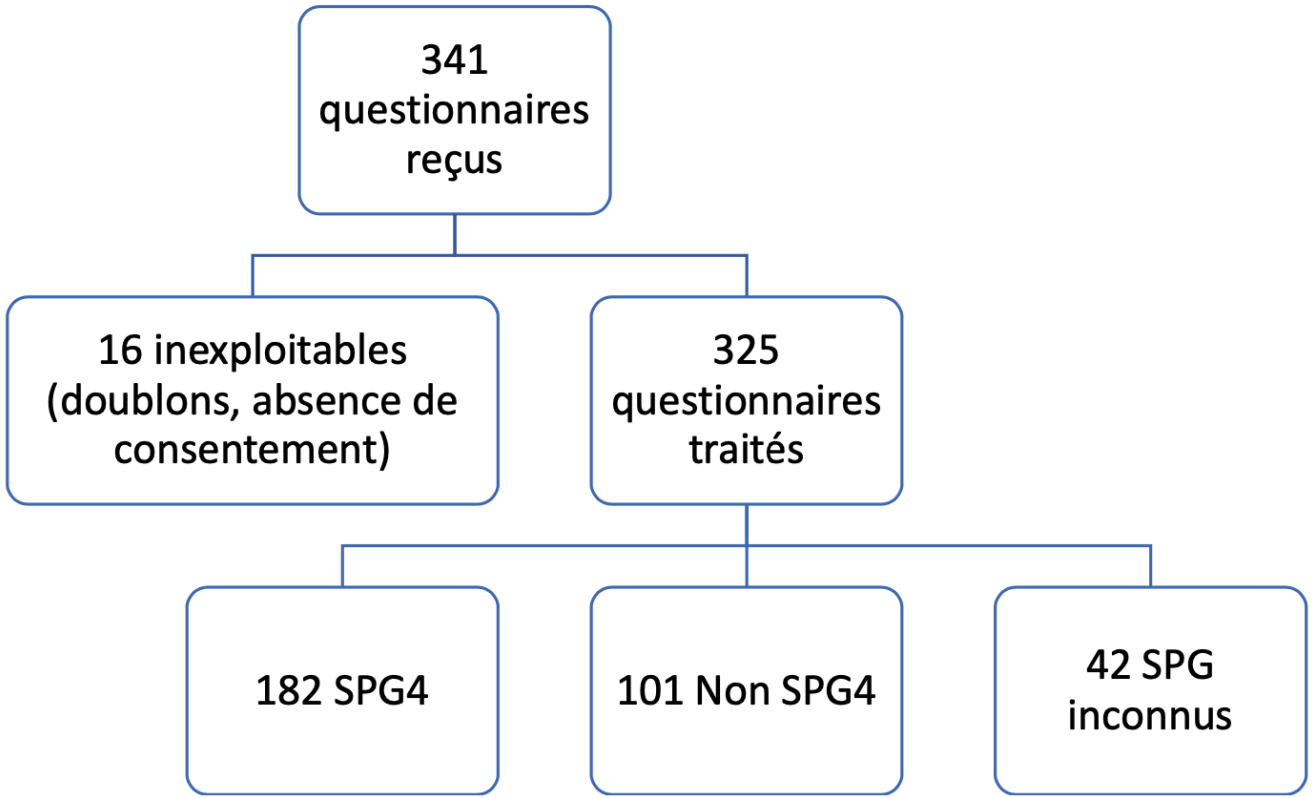
Depuis quand êtes-vous suivi ? :
Age au début du suivi I_I_I ou année du début de suivi I_I_I_I_I

Une mutation a-t-elle été identifiée chez vous ou dans votre famille?
1❑OUI 0❑NON
Si oui, quel centre a réalisé l'analyse : ……
Gène/Mutation :……

1

Sommaire

Flow-chart


341 questionnaires reçus
16 inexploitables (doublons, absence de consentement)
325 questionnaires traités
182 SPG4
101 Non SPG4
42 SPG inconnus

Description of the population

Mutations	n (%)	Sex ratio F/M		Median age (min-max)	Where patients collected the survey: Consultation	Patients' associations*
SPG4	**182 (56%)**	**79/103**	**0.77**	**57.8 (23.6-89.6)**	**119 (65%)**	**63 (35%)**
Non SPG4	**101 (31.1%)**	**52/49**	**1.06**	**55.1 (14.1 -78.7)**	**61 (60%)**	**40 (39.6%)**
SPG7	16 (4.9%)	8/8	1.00	63.4 (38.1-72.1)	9 (56%)	7 (44%)
SPG3A	12 (3.7%)	9/3	3.00	43.0 (14.1-64.8)	11 (92%)	1 (8%)
SPG5	6 (1.8%)	3/3	1.00	59.3 (29.4-67.4)	5 (83%)	1 (17%)
SPG31	5 (1.5%)	2/3	0.67	49.9 (29.8-67.8)	5 (100%)	0 (0%)
SPG10	4 (1.2%)	2/2	1.00	48.1 (37.6-58.0)	4 (100%)	0 (0%)
SPG30	4 (1.2%)	3/1	3.00	40.8 (29.1-42.9)	4 (100%)	0 (0%)
SPG8	3 (0.9%)	1/2	0.50	70.1 (55.0-78.4)	2 (67%)	1 (33%)
SPG9	3 (0.9%)	2/1	2.00	40.7 (35.1-62.0)	2 (67%)	1 (33%)
SPG15	2 (0.6%)	1/1	1.00	34 (29.8-38.2)	0 (0%)	2 (100%)
SPG6	1 (0.3%)	0/1		29.1	0 (0%)	1 (100%)
SPG11	1 (0.3%)	0/1		35.2	0 (0%)	1 (100%)
SPG12	1 (0.3%)	1/0		61.7	1 (100%)	0 (0%)
SPG48	1 (0.3%)	0/1		71.6	1 (100%)	0 (0%)
SPG4 excluded	32 (9.8%)	15/17	0.88	56.1 (28.0-78.7)	15 (47%)	17 (53%)
SPG3 4 6 8 31 42 excluded	3 (0.9%)	2/1	0.50	53.0 (52.6-56.5)	0 (0%)	3 (100%)
SPG4 7 excluded	1 (0.3%)	1/0			1 (100%)	0 (0%)
SPG3 4 7 10 31 et 64 excluded	1 (0.3%)	0/1		68.9	0 (0%)	1 (100%)
SPG4 7 8 17 31 42 excluded	1 (0.3%)	0/1		66.7	0 (0%)	1 (100%)
SPG4 42 excluded	1 (0.3%)	0/1		62.2	0 (0%)	1 (100%)
SPG4 8 31 42 excluded	1 (0.3%)	0/1		66.8	0 (0%)	1 (100%)
Unknown	**42 (12.9%)**	**14/28**	**0.50**	**62.6 (22.7-88.5)**	**12 (29%)**	**30 (71%)**
Total	**325**	**145/180**	**0.81**	**56.9 (14.1-89.6)**	**192 (59.1%)**	**133 (40.9%)**

* 29 from the ASL association and 1 from APSHE.

Description of the population

	SPG4 (n=182)	Non SPG4 (n=101)	
Sex M : n (%) Sex F : n (%)	103 (57%) 79 (43%)	49 (49%) 52 (51%)	p=0.192
BMI: mean (STD) min - max n	25.3 (4.0) 18.4 - 38.5 175	24.3 (4.2) 17.1 - 38.1 100	p=0.067
Sedentarity Index: mean (STD) min - max n	4.29 (2.63) 0 - 9 182	4.14 (2.69) 0 - 9 101	p=0.643

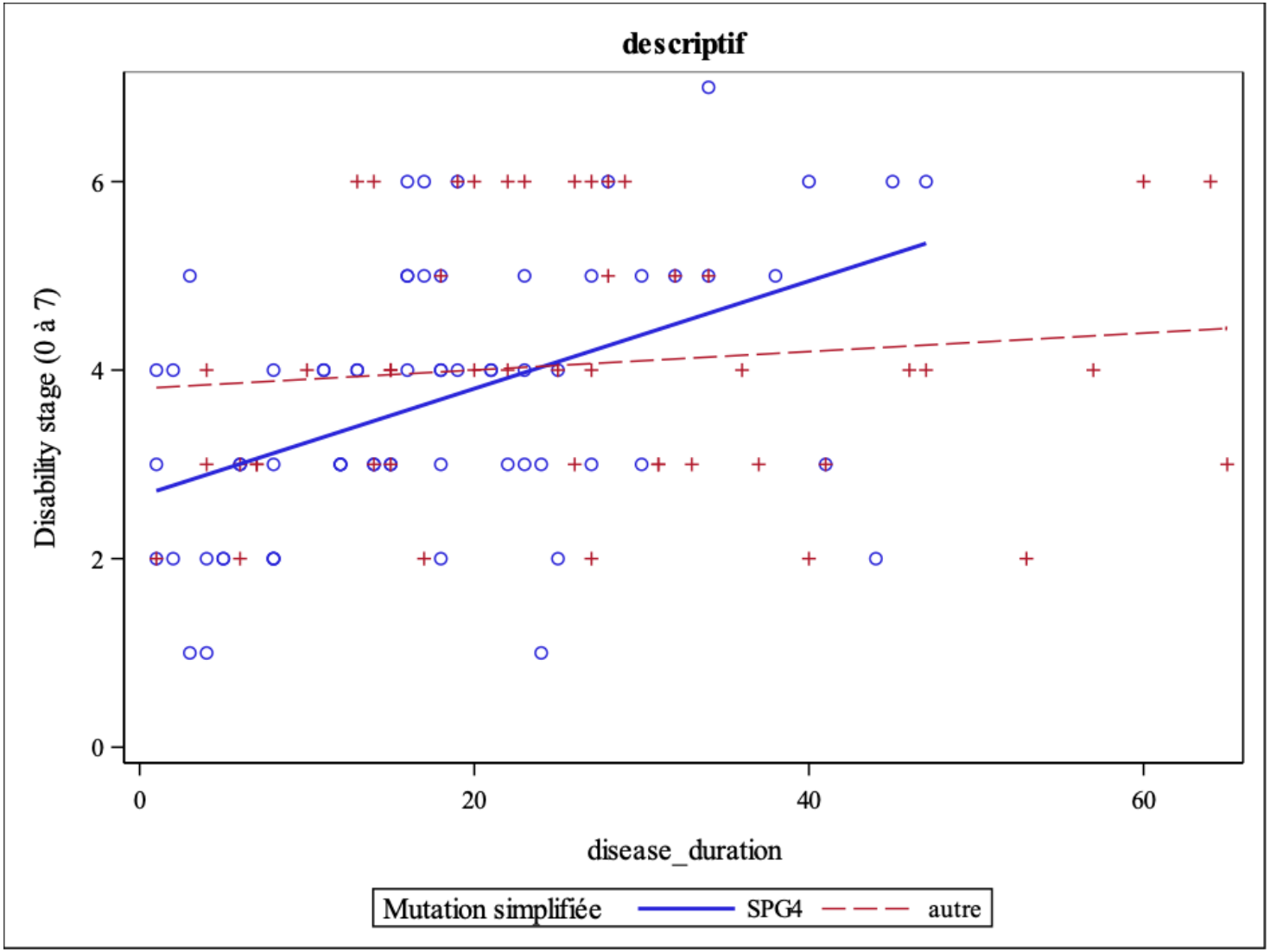
Description of the population

	SPG4 (n=182)	Non SPG4 (101)	
Age: mean (STD)	56.21 (13.78)	52.49 (13.98)	p=0.0343*
min - max	23 - 89	14 - 79	
n	178	97	
Age at onset: mean (STD)	36.1 (15.19)	24.53 (15.64)	p<0.0001*
min - max	0 - 70	0 - 65	
n	126	76	
Age at the beginning of the follow-up: mean (STD)	39.0 (16.25)	28.40 (16.60)	p<0.0001*
min - max	0 - 73	0 - 69	
n	147	87	
Duration disease: mean (STD)	20.42 (12.20)	27.36 (14.95)	p=0.0011*
min - max	1 - 73	1 - 65	
n	122	72	
Disability stage: mean (STD)	3.6 (1.5)	3.9 (1.4)	p=0.282
min - max	0 - 7	1 - 6	
n	103	67	

MODIFSPA

Pauline Lallemant-Dudek

Description of the population



Description of the population

Conclusion :

- The SPG4 have a higher age at onset,
- the follow-up begins later,
- but the disability stage of the 2 populations is not significantly different,
- **the SPG4 evolution is faster and more severe than the Non SPG4.**

Professional activities

	SPG4 (n=182)	Non SPG4 (n=101)	
Farmer: n (%)	1 (0.6%)	3 (3.1%)	
Agricultural employee: n (%)	1 (0.6%)	0	
Boss industry / trade: n (%)	3 (1.8%)	1 (1.0%)	
Liberal profession / Senior executive: n (%)	11 (6.7%)	10 (10.4%)	
Middle manager: n (%)	31 (18.8%)	16 (16.7%)	
Employee: n (%)	**75 (45.5%)**	**38 (39.6%)**	p= 0.0091*
Worker: n (%)	**26 (15.8%)**	**5 (5.2%)**	
Staff service: n (%)	4 (2.4%)	1 (1.0%)	
Other: n (%)	9 (5.5%)	13 (13.5%)	
Non-working: n (%)	4 (2.4%)	9 (9.4%)	

Professional activities

Physical activity at work :

	SPG4 (n=182)	Non SPG4 (n=101)	
Seated and small displacement: n (%)	95 (57.2%)	68 (73.1%)	p=0.0111*
Intense physical work: n (%)	71 (42.8%)	25 (26.9%)	

Conclusion :

- The Non SPG4 have more qualified jobs than the SPG4,
- the SPG4 have jobs with more physical work.

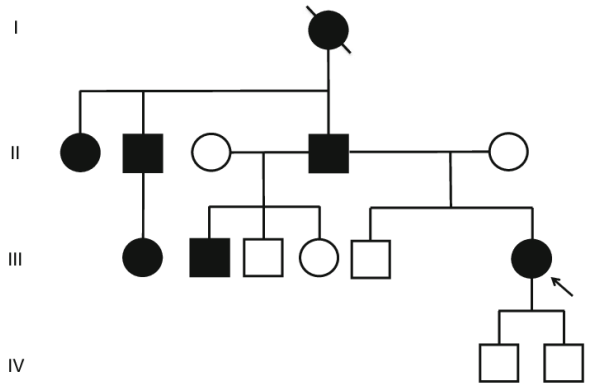
Trigger of the disease

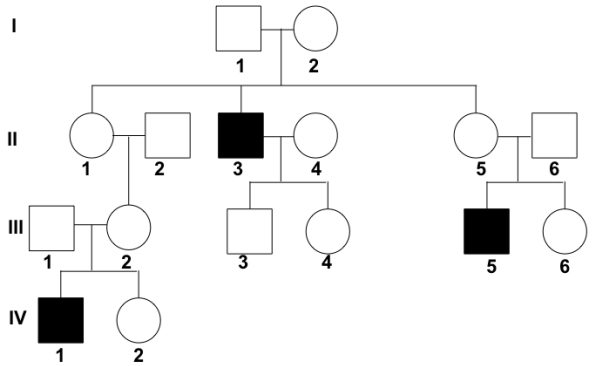
	SPG4 (n=182)	Non SPG4 (n=101)	
Existence of a trigger factor: n (%)	**30 (16.95%)**	**31 (31.31%)**	**p=0.006***
Accident / physical injury: n (%)	*6 (20%)*	*9 (29.03%)*	*p=0.4128*
Emotional upset: n (%)	*5 (16.67%)*	*7 (22.58%)*	*p=0.5613*
Iatrogeny: n (%)	*6 (20.0%)*	*5 (16.13%)*	*p=0.6942*
Death of a relative: n (%)	*5 (16.67%)*	*4 (12.90%)*	*p=0.7315*
Stress / anxiety: n (%)	*3 (10%)*	*3 (9.68%)*	*p=0.9663*
Depression : n (%)	***3 (10%)***	***0 (0%)***	***p=0.0710***
Pregnancy / birth: n (%)	*2 (6.67%)*	*1 (3.23%)*	*p=0.6124*
Physical work: n (%)	*1 (3.33%)*	*2 (6.45%)*	*p=0.5734*

Trigger of the disease

Conclusion :

- The Non SPG4 believe more often that a trigger factor is responsible of the beginning of their disease,
- the patients'experience could depend of the transmission type (autosomal dominant versus recessive).





Question to the audience

Question 3 :

What treatment do you or would you prescribe against spasticity for HSP patients ?

- Oral treatment (baclofene for example),
- Physiotherapy,
- Botulinium toxin injection.

Spasticity management

What patients are consuming :

	SPG4 (n=182)	Non SPG4 (n=101)	
Therapeutic management against spasticity: n (%)	146 (84.4%)	82 (83.7%)	p=0.8762
Oral treatment: n (%)	82 (47.7%)	36 (37.1%)	p=0.0937
Physiotherapy: n (%)	**118 (68.6%)**	**71 (73.2%)**	**p=0.4289**
Botulinum toxin injection : n (%)	47 (27.3%)	22 (22.7%)	p=0.4022

Spasticity management

What patients find effective :

	SPG4 (n=182)	Non SPG4 (n=101)	
Oral treatment : n (%)	49 (30.4%)	23 (25.6%)	p=0.4124
Physiotherapy : n (%)	**102 (63.8%)**	**68 (77.3%)**	**p=0.0295***
Botulinum toxin injection : n (%)	32 (19.8%)	16 (18.2%)	p=0.7632

Conclusion :

- Physiotherapy is the most consumed treatment.
- Physiotherapy is the only treatment estimated to be effective for more than 50% patients.

Question to the audience

Question 4 :

Do you find these results astonishing ?

- Yes, absolutely
- With no opinion
- No, these were expected.

Spasticity management

Presentation of patients with efficient physiotherapy (n=170) :

	Odds Ration	95% Wald Confidence Limits	p
Mutation: SPG4 vs Non SPG4	**0.413**	**0.195-0.877**	**0.0213***
Physiotherapy frequency	**1.568**	**1.304-1.886**	**<0.0001***
Disability stage	1.071	0.853-1.346	0.5537

Conclusion :

- The more physiotherapy sessions patients have, the more effective they find them.

Factors affecting spasticity

	SPG4 (n=182)	Non SPG4 (n=101)	
Worsening of symptoms			
Stress: n (%)	**133 (74.7%)**	**78 (78.8%)**	**p=0.4462**
Cold: n (%)	**117 (65.4%)**	**61 (62.2%)**	**p= 0.5540**
Tiredness: n (%)	***42 (41.6%)***	***40 (59.7%)***	***p=0.0218****
Infection: n (%)	52 (29.4%)	44 (44.9%)	p=0.0097*
Emotion: n (%)	*23 (22.8%)*	*7 (10.5%)*	*p=0.0411**
Long-lasting position: n (%)	*14 (13.9%)*	*11 (16.4%)*	*p=0.6485*
Physical trouble : n (%)	*13 (12.9%)*	*8 (11.9%)*	*p=0.8582*
Heat: n (%)	11 (6.2%)	3 (3.1%)	p= 0.5540
Humidity: n (%)	*9 (8.9%)*	*5 (7.5%)*	*p=0.7395*
Improvement of symptoms			
Heat: n (%)	**95 (55.23%)**	**56 (58.33%)**	**p=0.5771**
Physical work: n (%)	***37 (50.68%)***	***18 (40.61%)***	***p=0.3048***
Relaxation: n (%)	*24 (32.88%)*	*20 (45.45%)*	*p=0.1737*
Emotion : n (%)	*13 (17.81%)*	*7 (15.91%)*	*p=0.7915*
Bath: n (%)	*7 (9.59%)*	*4 (9.09%)*	*p=0.9287*
Cold: n (%)	12 (6.98%)	3 (3.13%)	p=0.5771
Stress: n (%)	4 (2.35%)	3 (3.16%)	p=0.6952
Infection: n (%)	5 (2.96%)	1 (1.06%)	p=0.3240

Factors affecting spasticity

Conclusion :

To improve spasticity, advice that may be given :

- to avoid stress and cold,
- to privilege warm environments,

To improve spasticity, medical team sould :

- help to manage fatigue,
- prescribe physiotherapy,
- insist on and facilitate adapted physical activities.

Servelhere, K. R. et al. Non-motor symptoms in patients with hereditary spastic paraplegia caused by SPG4 mutations. Eur. J. Neurol. 23, 408 ?411 (2016).

Sartori, R. D. G., Marelli, M., D ?Angelo, M. G. and Delle Fave, A. Autonomy level and quality of everyday experience of people with Hereditary Spastic Paraplegia. Health Soc. Care Community 27, e850 ?e860 (2019).

Thank you for your attention

I want to thank

- the 'BTN' team in the Paris Brain Institute,
- clinical research associates,
- the patients and the associations.