# Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia

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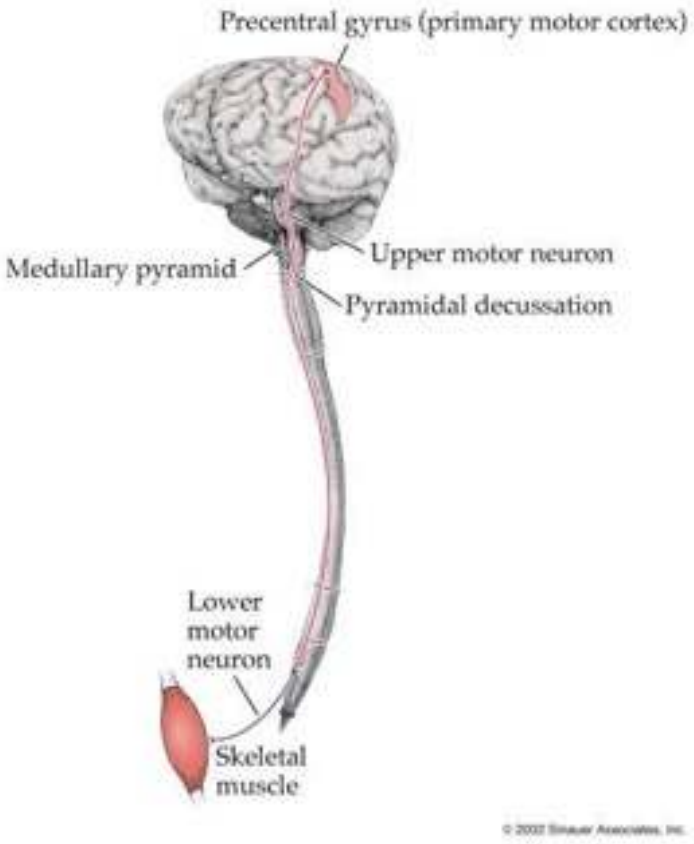
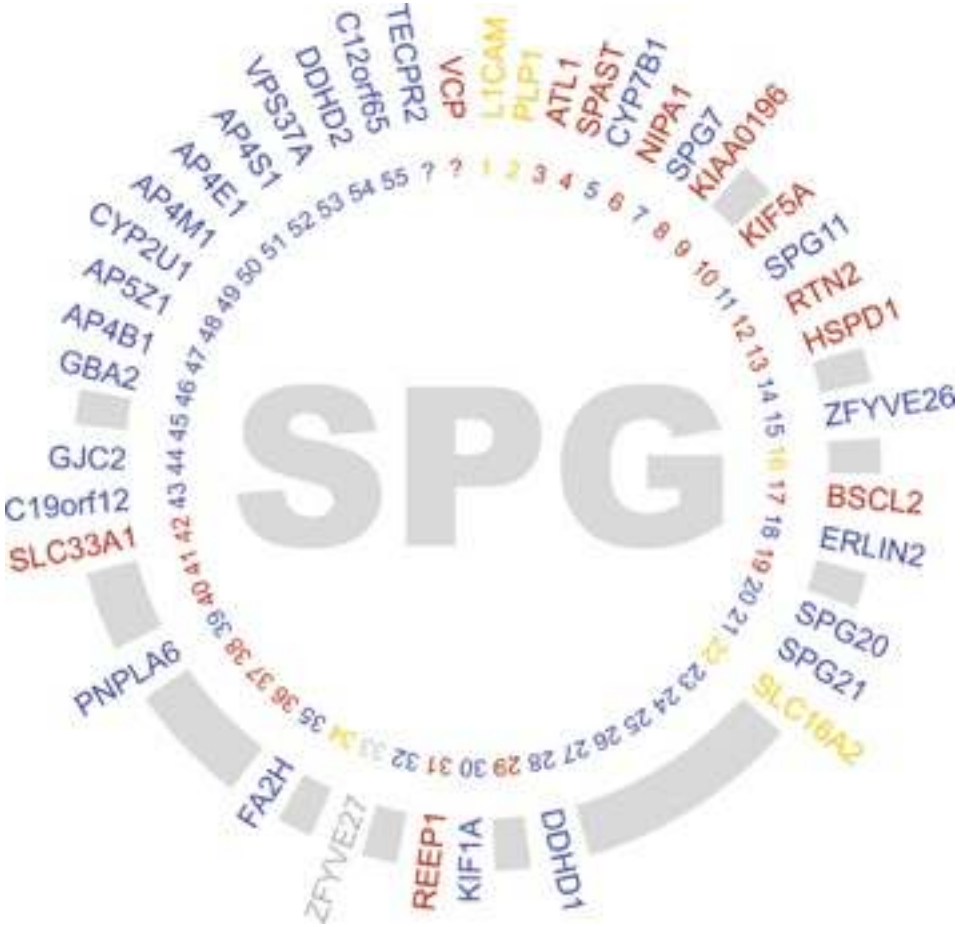
# Complexité des paraparésies spastiques (HSP)

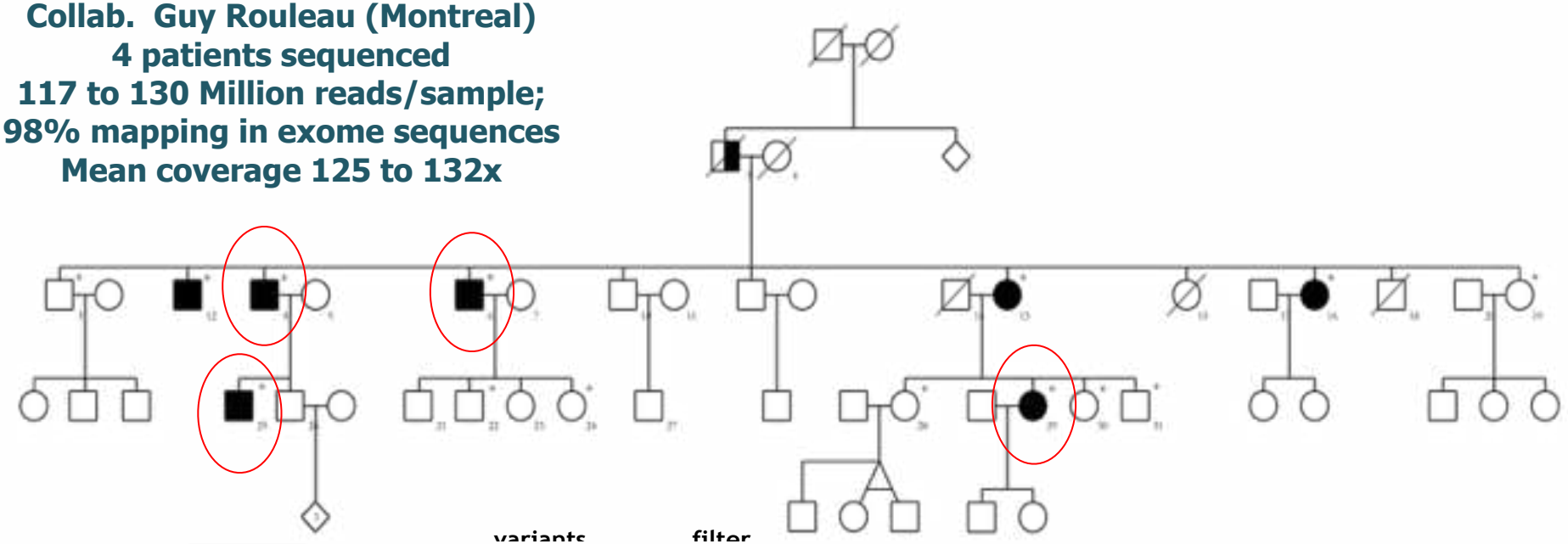
## Dégénérescence du faisceau corticospinal



# Clonage positionnel & séquençage haut débit

**Collab. Guy Rouleau (Montreal)**
**4 patients sequenced**
**117 to 130 Million reads/sample;**
**98% mapping in exome sequences**
**Mean coverage 125 to 132x**

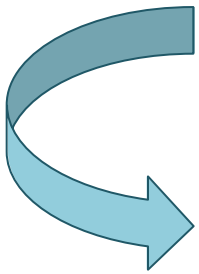


| variants | filter |
|---|---|
| 99 770 | Avg cov >= 10 |
| 90 334 | Excluding "synonymous_SNV" |
| 79 066 | Excluding"intergenic" or"ncRNA" |
| 24 005 | CG frequency <= 0,1% |
| 21 798 | EVS frequency <= 0,1% |
| 18 191 | 1000 Genomes frequency <= 0,1% |
| 5 904 | Non family cases with variants <= 5% |
| 132 | Cosegregation |
| 84 | Regions of linkage |
| 2 | Exac Frequency <=0,1% and excluding frequently mutated genes (MUC |

**2 missense variants segregating in the candidate regions**

# Validation génétique

**PDZD7** : ciliary protein involved in **Usher syndrome** (AR, hearing and visual loss)
**ALDH18A1** : mitochondrial enzyme involved in a neurocutaneous disorder (AR, **P5CS deficiency**)



⇒ Pathogenicity and function less convincing for PDZD7

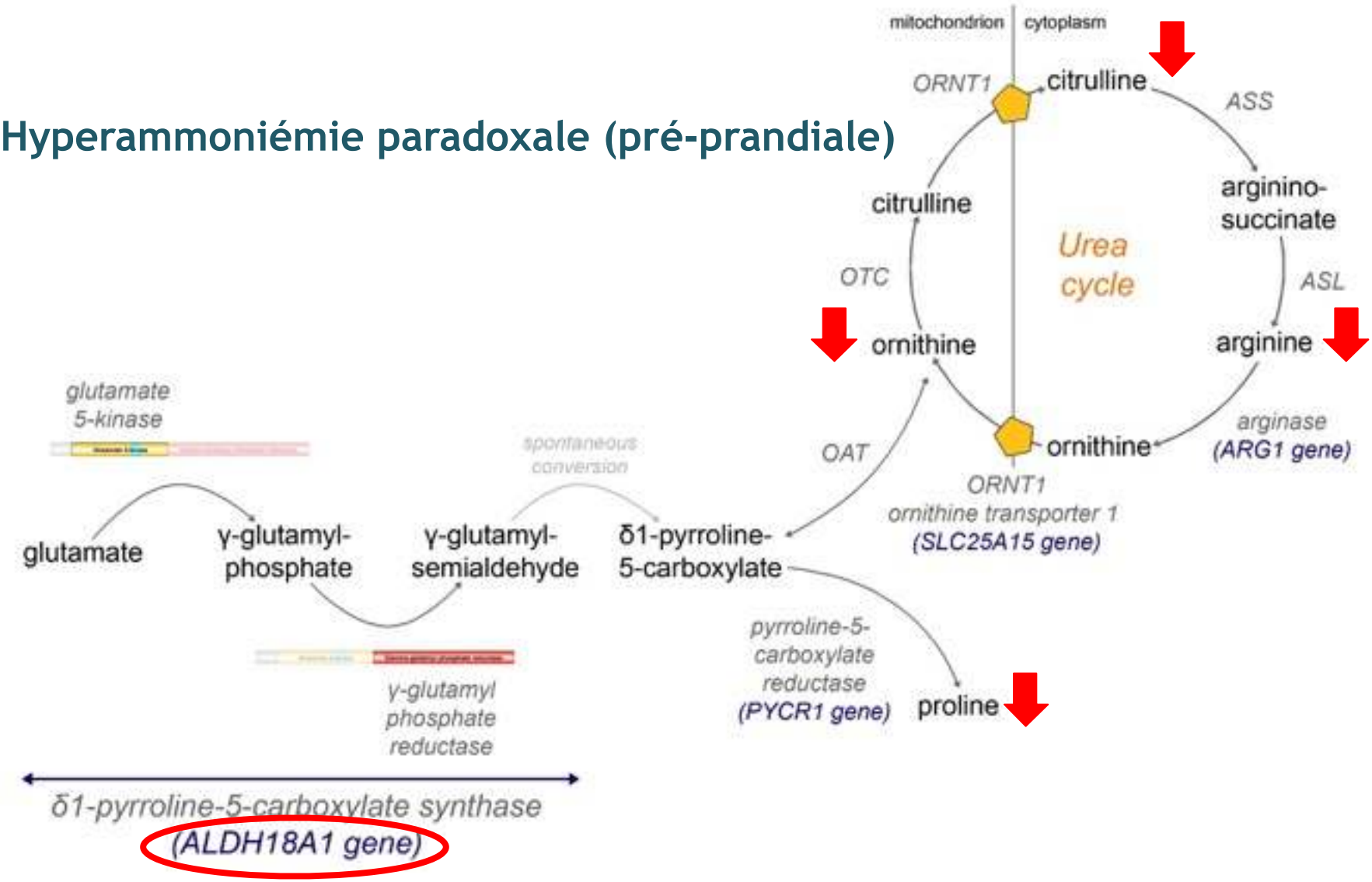
**(A) Genetic screening**
=>Analysis of 435 exomes of HSP families
⇒ Screening of 95 HSP index cases with 48*48 fluidigm microarrays

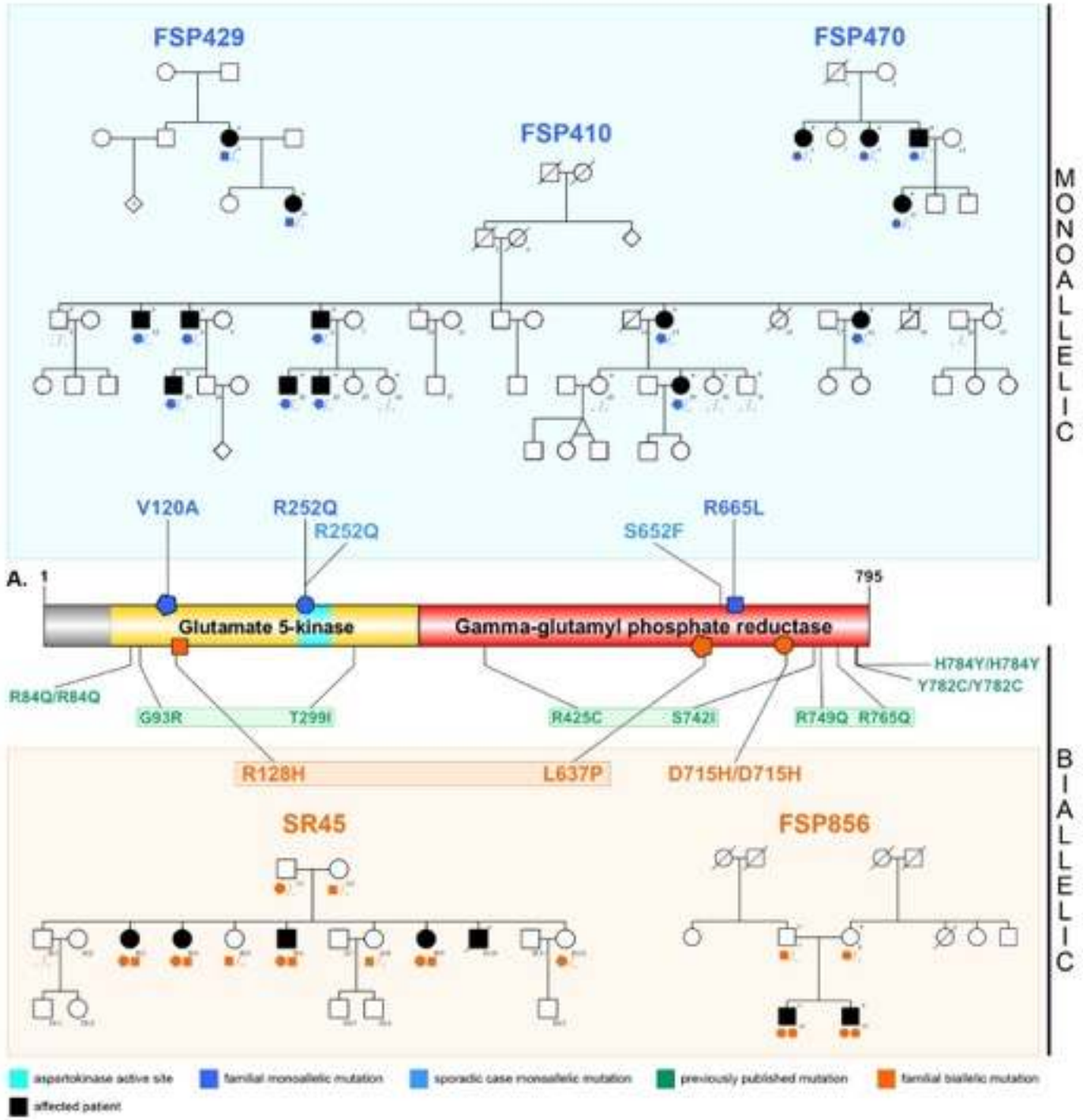
**(B) Functional analyses**
(amino-acid dosages in plasma, in vitro analyses of ALDH18A1 activity)

PDZD7: no causative variant
**ALDH18A1: 6 additional causative variants in 3 AD families, 2 AR families and 2 sporadic cases**

# Déficit en P5C synthase

## Hyperammoniémie paradoxale (pré-prandiale)

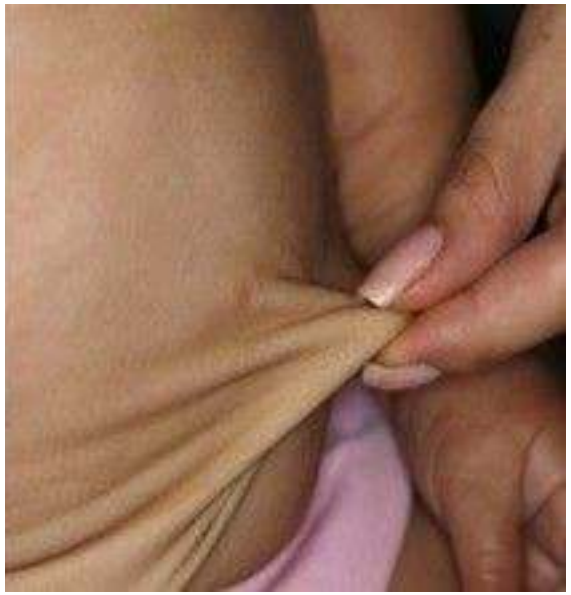



FSP429
FSP470
FSP410
MONOALLELIC
V120A
R252Q
R252Q
S652F
R665L
A.
1
795
Glutamate 5-kinase
Gamma-glutamyl phosphate reductase
H784Y/H784Y
Y782C/Y782C
R84Q/R84Q
G93R
T299I
R425C
S742I
R749Q
R765Q
R128H
L637P
D715H/D715H
BIALLELIC
SR45
FSP856
aspartokinase active site
familial monoallelic mutation
sporadic case monoallelic mutation
previously published mutation
familial biallelic mutation
affected patient

| | N=15 (9 previous studies) |
|---|---|
| *Mutations* | *biallelic* |
| *Neurological signs at onset* | *developmental delay, hypotonia* |
| *Pyramidal signs* | *Yes (12/12), most brisk reflexes* |
| *Other neurologic findings* | *Peripheral axonal neuropathy, seizures in infancy (6/9), distal dystonia* |
| *Cutis laxa (other cutaneous* | *Yes in 15 (sparse hair in 2)* |
| *Skelettal findings* | *Joint hyperlaxity in most, pes planus, coxa valga in some* |
| *Facial dysmorphy* | *Yes in 9* |
| *Growth retardation/ Microcephaly* | *Yes/Yes* |
| *Cataracts (other ocular findings)* | *Yes (7/11) (Corneal clouding, Retinitis* |
| *Gastro-oesophagal* | *3/3* |
| *Inguinal hernia* | *5/9* |
| *MRI* | *TCC >6* |

# Formes décrites initialement (AR)

Retard mental, microcéphalie, cataracte, cutis laxa, syndrome pyramidal réflexe

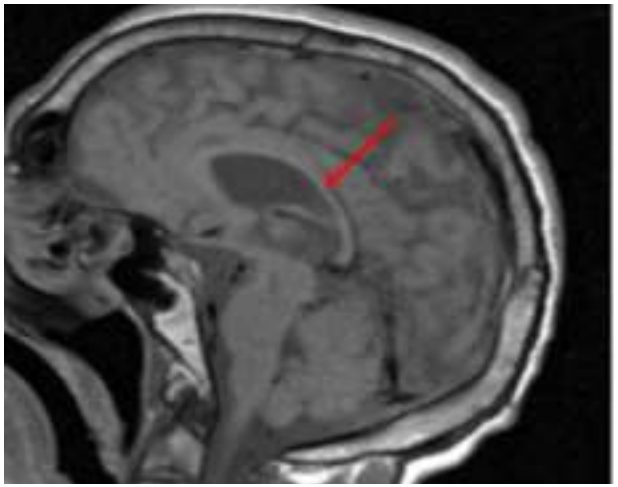


Anomalies CAA très inconstantes

| | N=15 (9 previous studies) | This study (FSP856) | This study (SR45) |
|---|---|---|---|
| *Mutations* | *biallelic* | *D715H/D715H* | *R128H/L637P* |
| *Neurological signs at onset* | *developmental delay, hypotonia* | *Intellectual deficiency* | *Global delay, growth* |
| *Pyramidal signs* | *Yes (12/12), most brisk reflexes* | *Moderate to severe* | *Severe, tetraplegia (2/4) or tetraparesis* |
| *Other neurologic findings* | *Peripheral axonal neuropathy, seizures in infancy (6/9), distal dystonia* | *No* | *No* |
| *Cutis laxa (other cutaneous* | *Yes in 15 (sparse hair in 2)* | *No* | *No* |
| *Skelettal findings* | *Joint hyperlaxity in most, pes planus, coxa valga in some* | | |
| *Facial dysmorphy* | *Yes in 9* | *Yes* | *Yes* |
| *Growth retardation/ Microcephaly* | *Yes/Yes* | *No/Yes* | *Yes/Yes* |
| *Cataracts (other ocular findings)* | *Yes (7/11) (Corneal clouding, Retinitis* | *NA* | *Yes 1/4* |
| *Gastro-oesophagal reflux* | *3/3* | *NA* | *NA* |
| *Inguinal hernia* | *5/9* | *NA* | *NA* |
| *MRI* | *TCC >6* | *Normal* | *Thin CC, mild cerebellar atrophy, WM anomalies* |

# Formes d'HSP récessives

Retard mental, microcéphalie ±cataracte
Paraparésie spastique début précoce



CAA normales

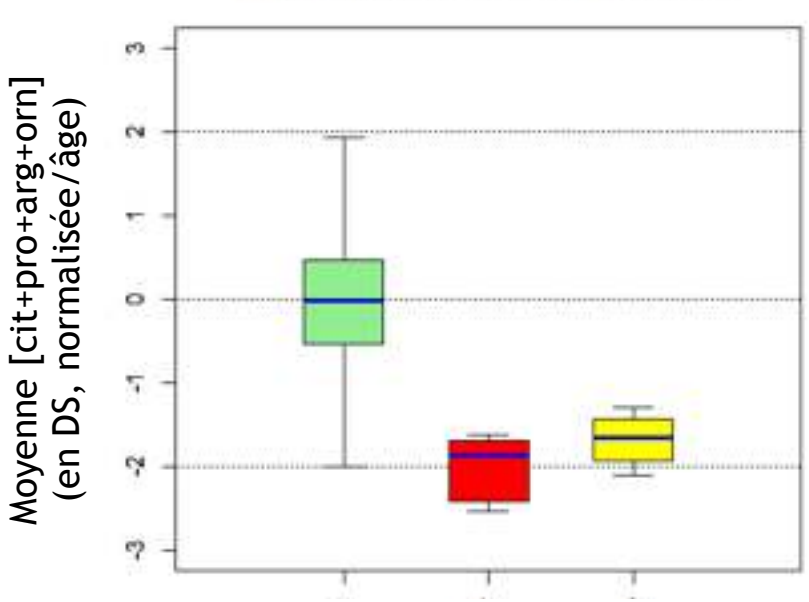
# Formes d'HSP dominantes

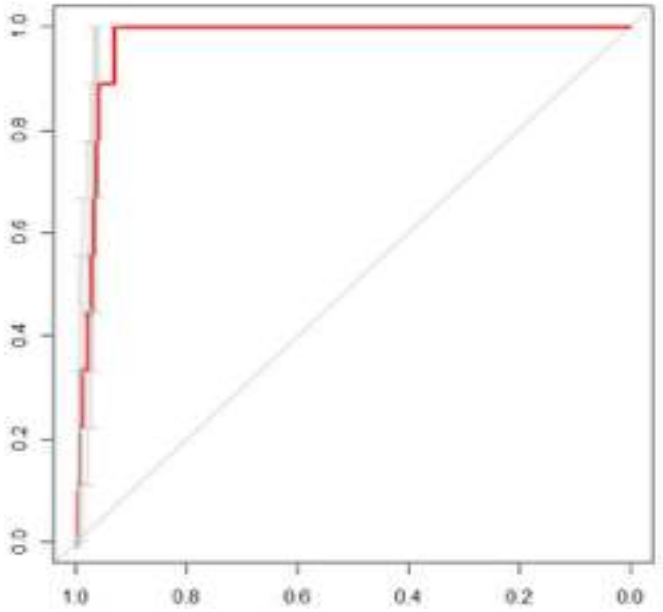
Paraparésie spastique début tardif
± cataracte

| This study (FSP410) | This study (FSP429) | This study (FSP470) | This study (GSHSP44) | This study (25014) |
|---|---|---|---|---|
| *V120A* | *R665L* | *R252Q* | *S652F* | *R252Q* |
| *Pyramidal signs* | *Pyramidal signs* | *Pyramidal signs* | *Pyramidal signs* | *Pyramidal signs* |
| *Moderate to severe* | *Severe* | *Moderate to severe* | *Mild* | *Moderate to severe* |
| *Mild cerebellar signs (2/6), motor neuropathy (2/6), dementia* | *Cerebellar signs (1/2)* | *No* | *No* | *No* |
| *No* | *No* | *No* | *No* | *Chronic cellulitis* |
| *Pes cavus (3/6)* | *Pes cavus (1/2)* | *Pes cavus (2/4)* | *Pes cavus, hip replacement* | |
| *No* | *No* | *No* | *No* | *No* |
| *No/No* | *No/No* | *No/No* | *No/No* | *No* |
| *Yes 1/6* | *NA* | *Yes 1/4* | *NA* | *No* |
| *NA* | *NA* | *1/4* | *NA* | *NA* |
| *NA* | *NA* | *NA* | *NA* | *NA* |
| *Mild CC atrophy (1/3)* | *WM anomalies, thin dorsal cord, pons hypersignal (1/2)* | *Left arachnoidien cyst (1/4)* | *Spinal cord atrophy* | *Cortical atrophy (frontoparietal predominance)* |

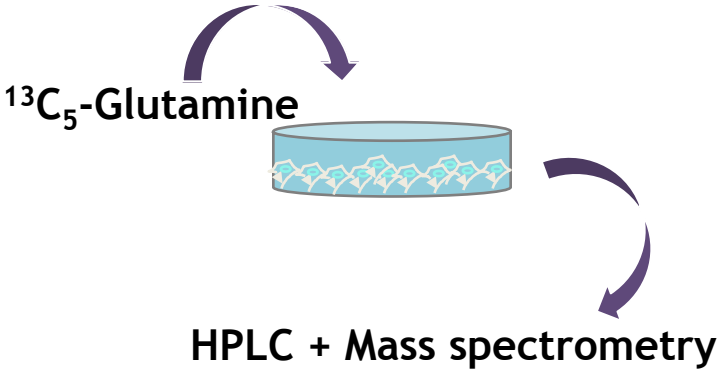
# CAA plasmatiques / formes dominantes

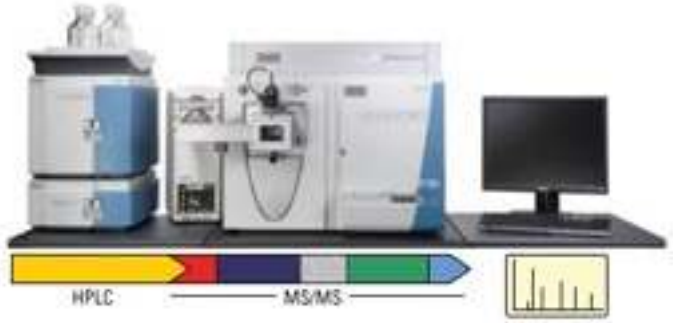
| Patient | Age | Proline | Ornithine | Citrulline | Arginine | Valine | Leucine | Isoleucine | Threonine | Glutamine | Alanine | Methionin | Lysine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *FSP410-032* | *43* | *163* | *35* | *12* | *58* | *190* | *116* | *51* | *69* | *517* | *237* | *22* | *146* |
| *FSP410-029* | *45* | *117* | *83* | *8* | *63* | *215* | *110* | *61* | *208* | *740* | *400* | *23* | *201* |
| *FSP410-013* | *70* | *73* | *46* | *8* | *54* | *178* | *108* | *51* | *91* | *632* | *277* | *18* | *178* |
| *FSP429-021* | *40* | *209* | *54* | *1* | *28* | *267* | *119* | *52* | *114* | *470* | *304* | *19* | *175* |
| *Normal* | | *150-220* | *50-100* | *20-35* | *60-100* | *210-280* | *100-150* | *50-80* | *95-195* | *430-670* | *285-415* | *20-35* | *155-230* |



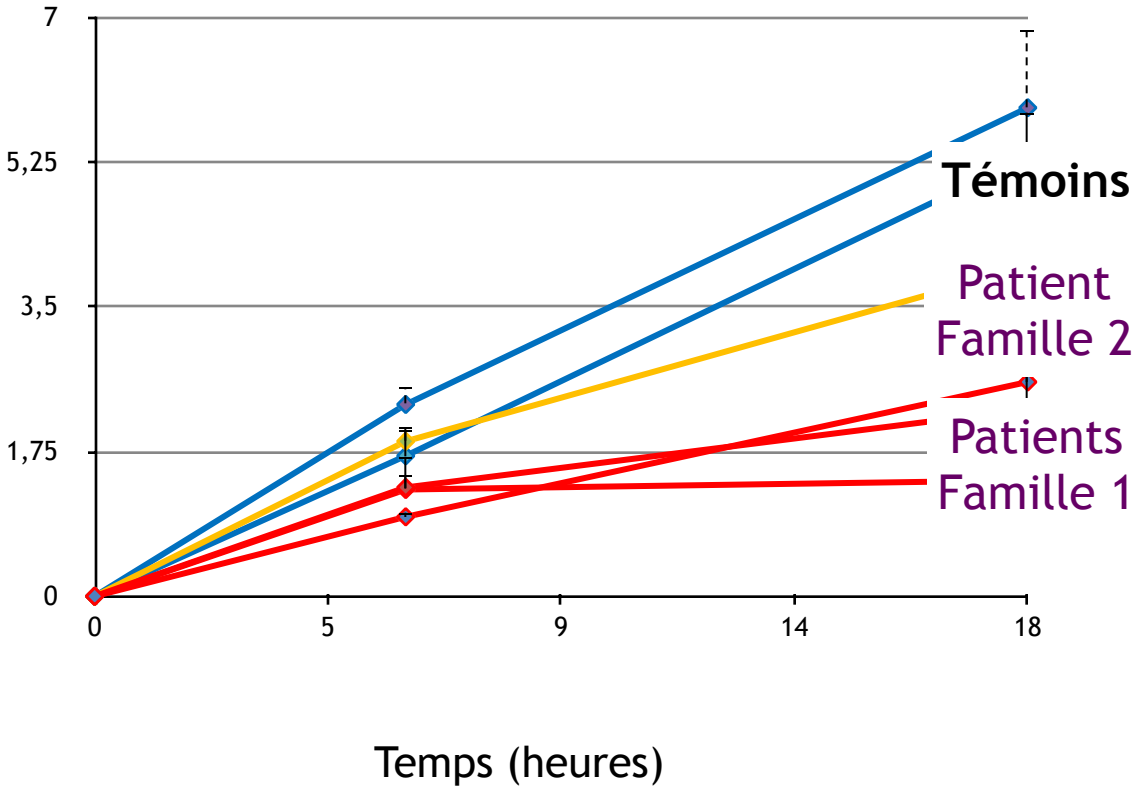



# Etude de synthèse de proline: charge en glutamine $^{13}C_5$

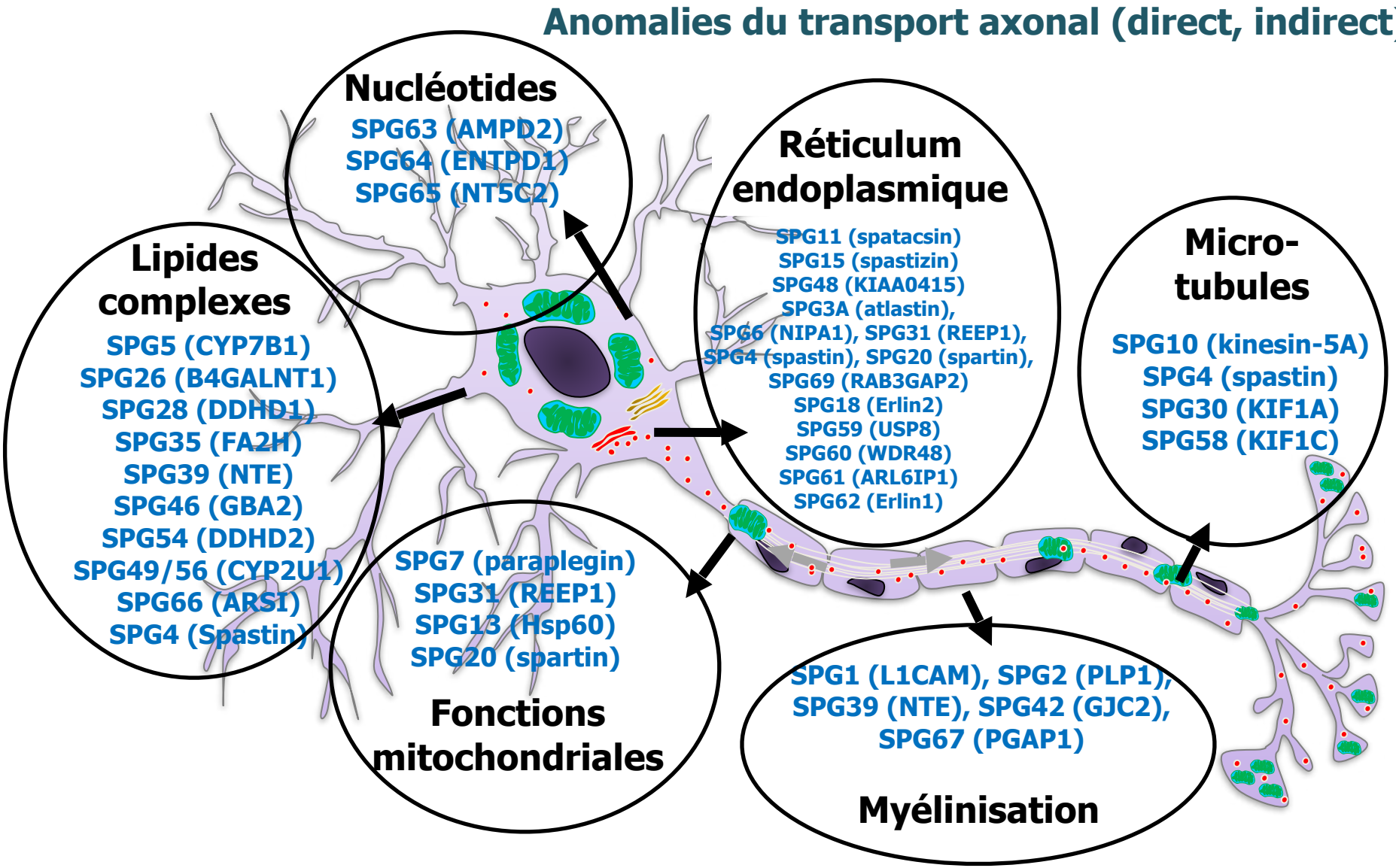


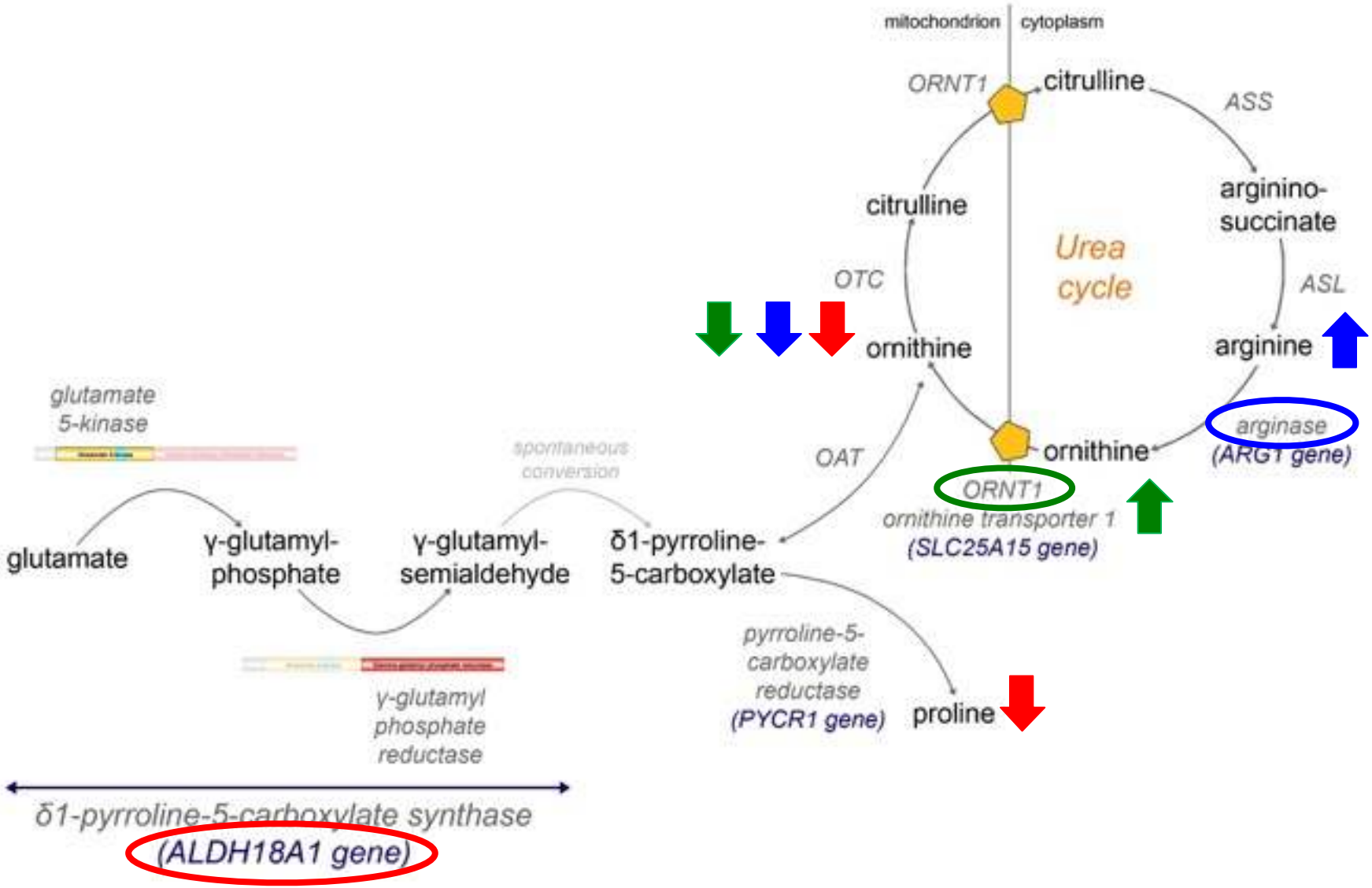

## Proline/fumarate



# Physiopathologie dans les HSP?



# Physiopathologie dans les HSP?



# Conclusions

- **Intérêt de la CAA plasmatique dans les HSP?** Citrullinémie
  Autres biomarqueurs HSP: AGTLC, 25 et 27-hydroxycholestérol, homocystéine

- **Rôle de déplétion mitochondriale en ornithine dans les HSP?**
  Lien avec créatine intracérébrale?

- **Perspectives thérapeutiques: supplémentation en citrulline?**

- **Maladies métaboliques avec transmission AR et AD**
  ELOVL4 : AR HSP, retard, ichtyose / AD Stargardt ou ataxie & érythrokératodermie

*Coutelier et al, Brain 20*

# Remerciements

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