Paraplégies spastiques

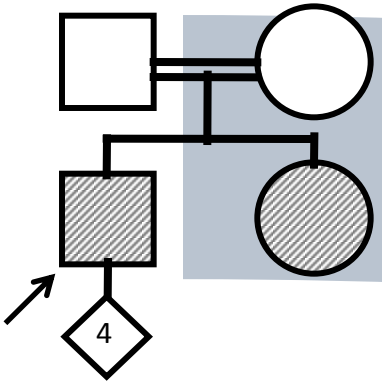
Présentation de trois familles

Pauline MARZIN (interne)

Service de génétique Clinique

10/09/2015

Case 1 : clinical course



40 y

Walking difficulties
Progressive worsening

Normal Brain and spine MRI – visually evoked potential – EMG studies

50 y

Lower limbs :
Babinski – Spasticity
Nocturnal cramps
Hypopallesthesia

55 y

Pyramidal 4 limbs
cerebellar signs
(upper limbs dysmetria – saccadic eye movement)

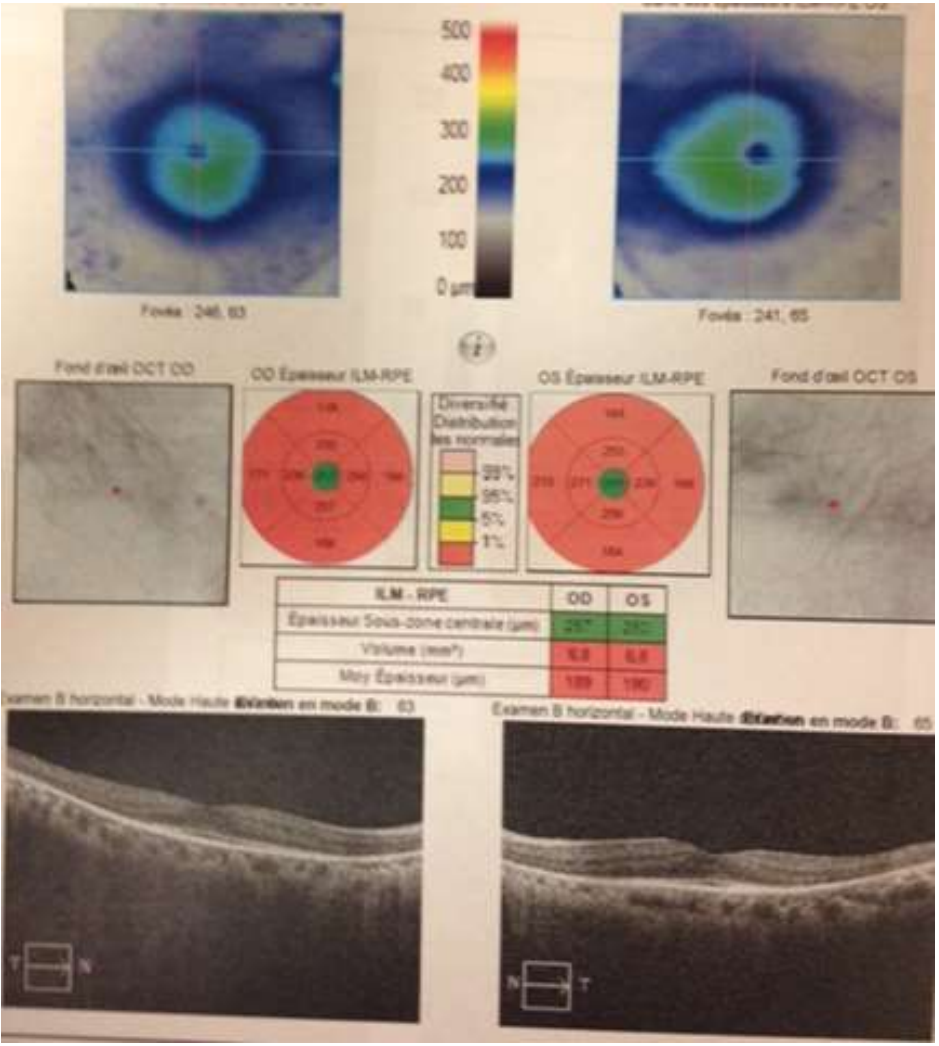
Cognitive impairment
(attentional deficit - memory loss)

Abnormal MRI …

Proximal weakness
Tremor
Psychiatric disturbance
Anosognosia
Nocturnal visual difficulties

Retinis pigmentosa

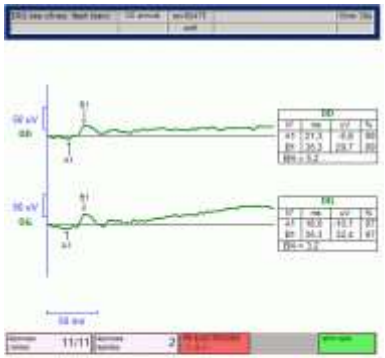
Bilan ophtalmolgique

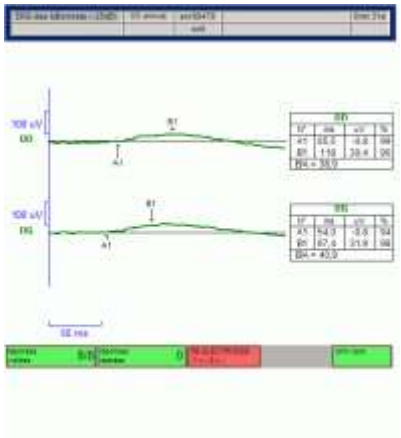


- Champ visuel : déficit annulaire 10 et 30°.
- OCT :
    - Atrophie maculaire en croissant
    - Atrophie couches externes
    - Amincissement couches internes

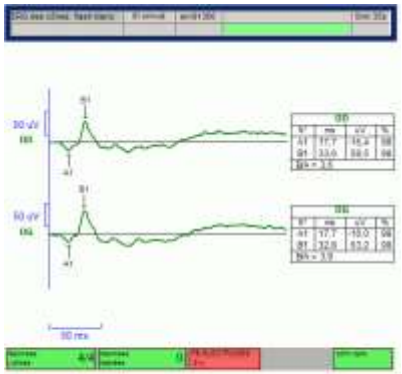
ERG global

Case 1





Normal



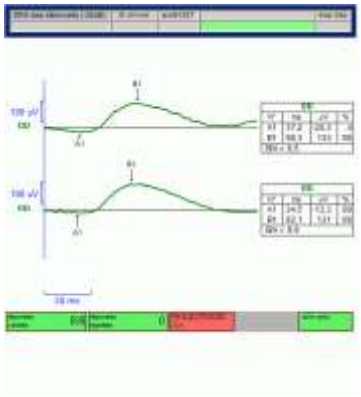
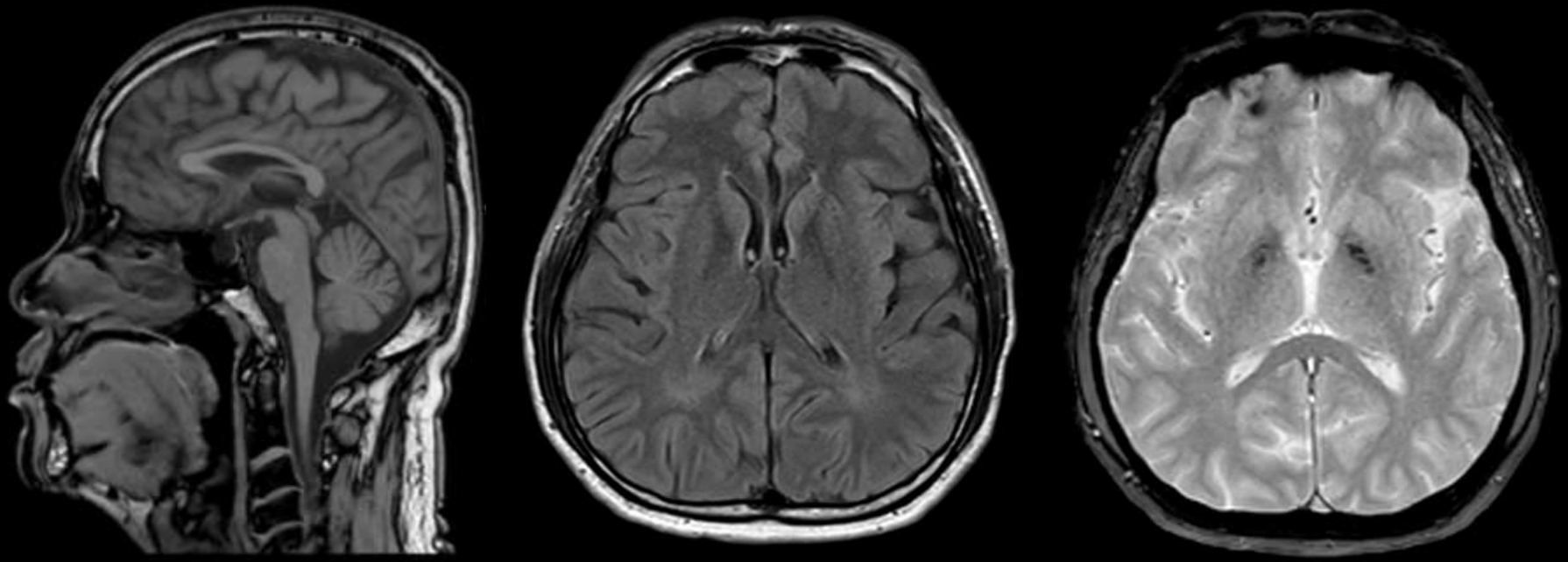
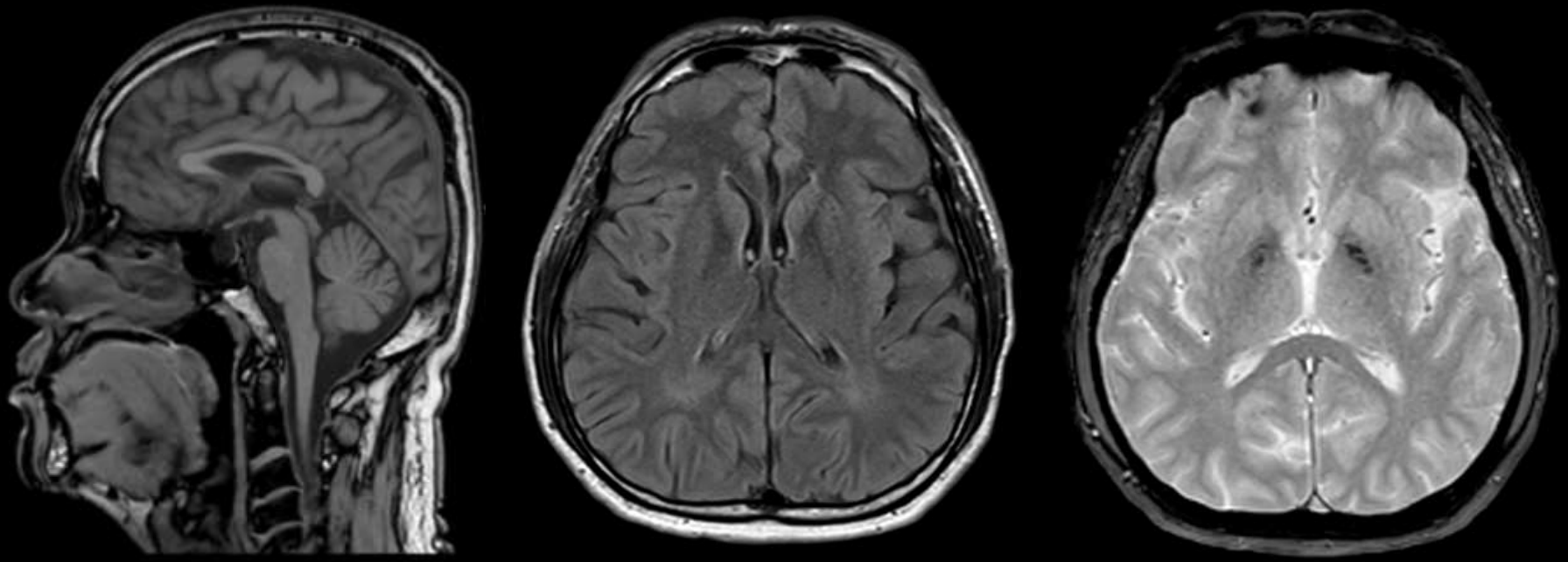
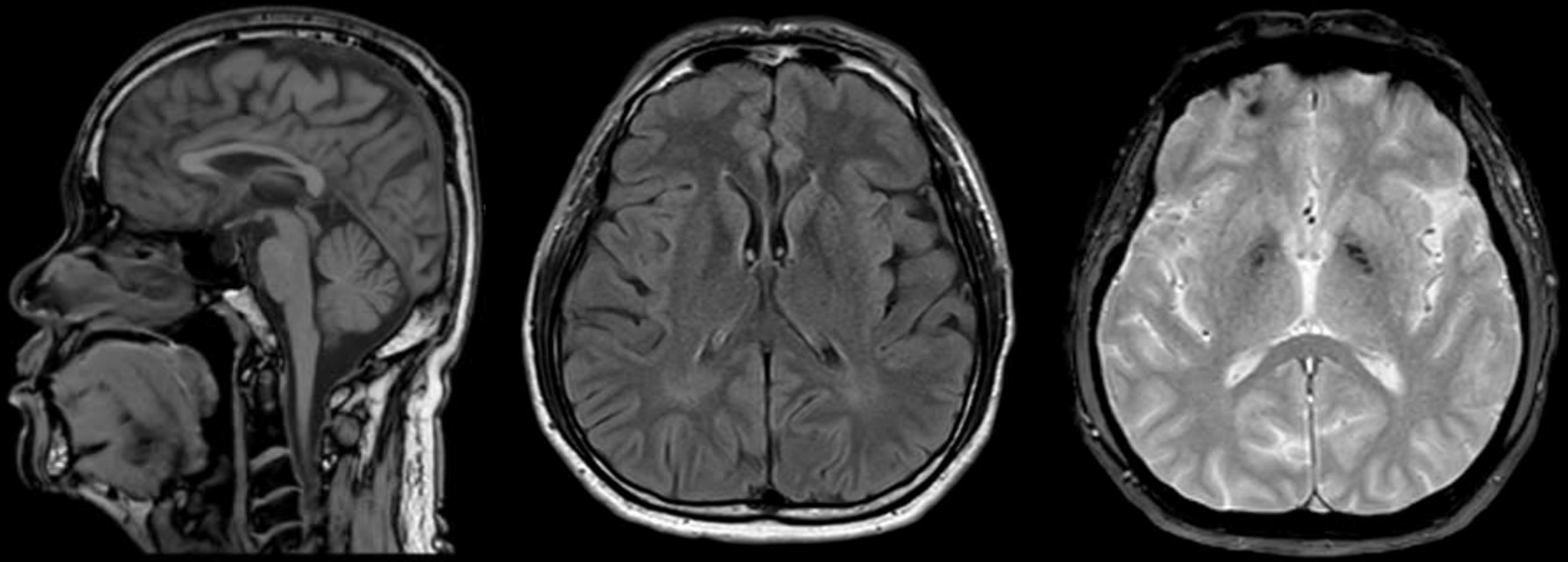


Figure V-3-1





Midle agged man
Spastic paraplegia +
cerebellar signs
cognitive and psychiatric disturbance
Retinis pigmentosa
T2* Hyposignal of internal pallidum
Consanguinity – sister walking difficulties



Midle agged man
Spastic paraplegia +
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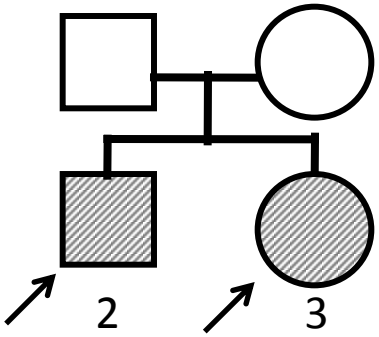
Consanguinity – sister walking difficulties

Hypothesis
-*PANK2*
-*PLA2G6*
-Peroxysome
-mitochondrie

?

Cases 2,3,4,5,6 : clinical courses



Maculopathy

Developmental delay – mild ID -

Normal walking

Spastic paraplegia

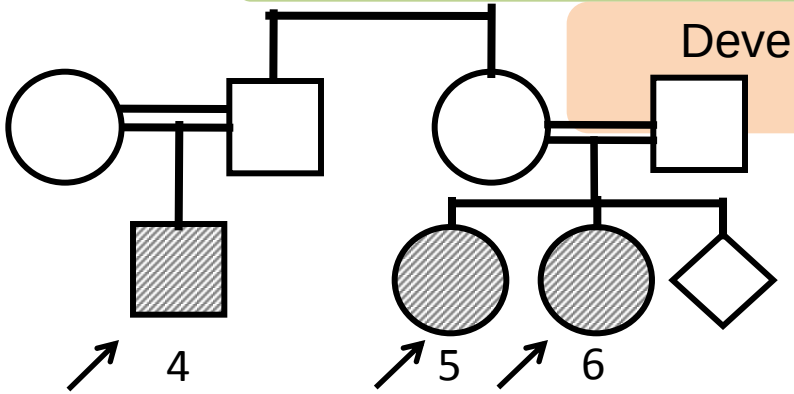
Upper limbs

1 2 10 20

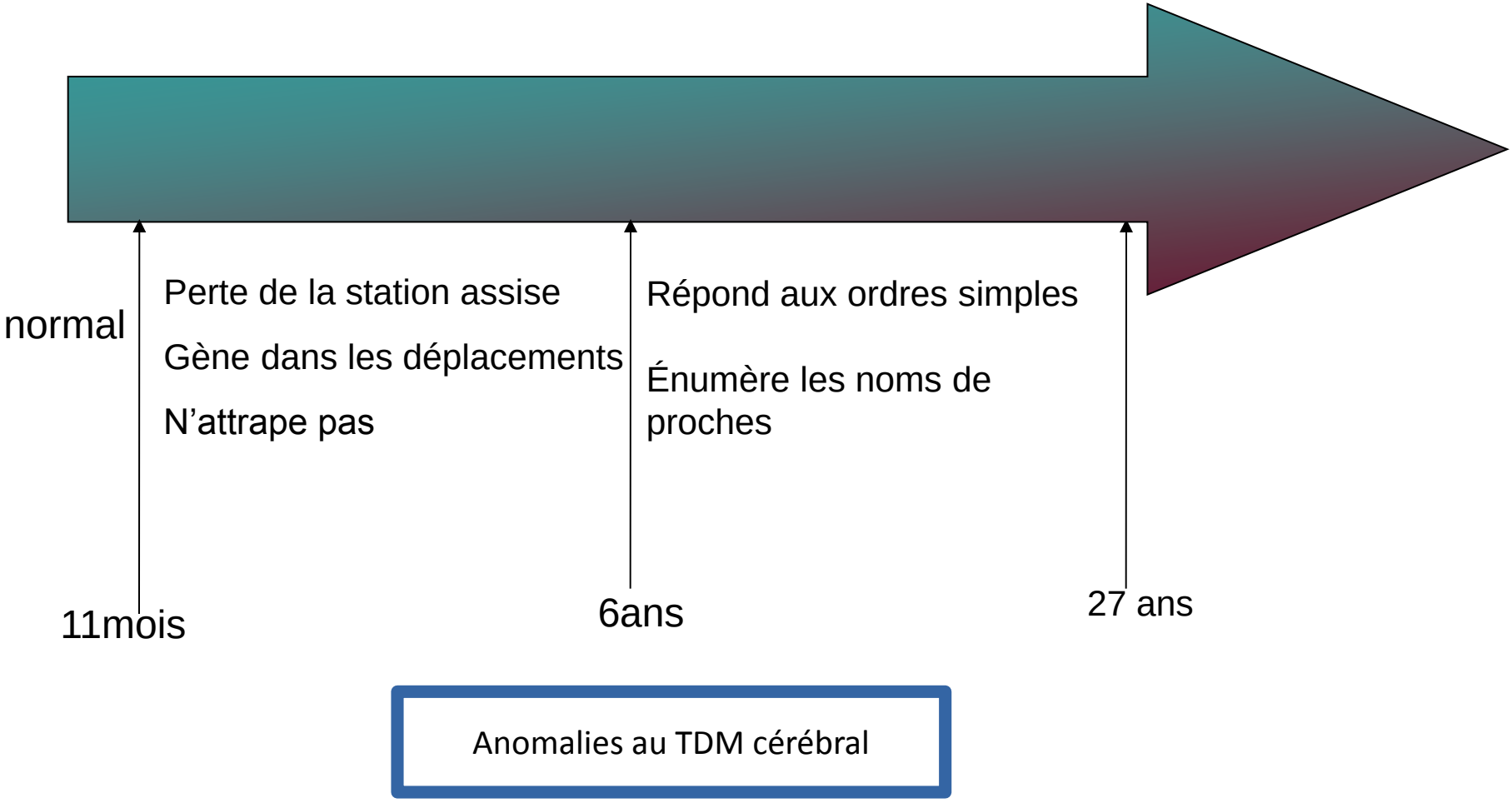
Spastic paraplegia

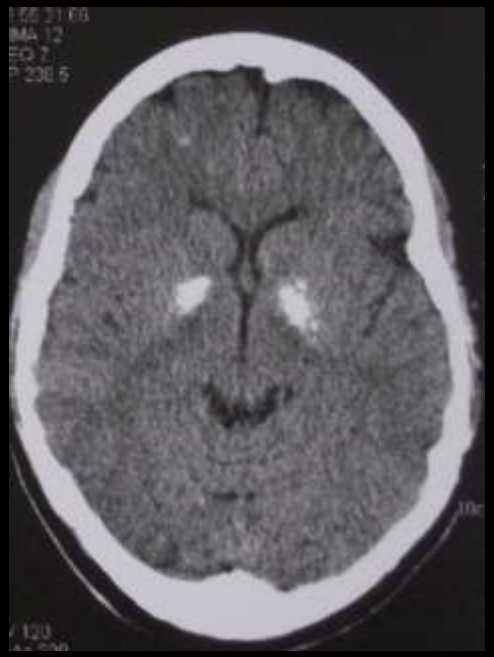
Extrapyramidal signs

Developmental delay – moderate ID – Progressive microcephaly

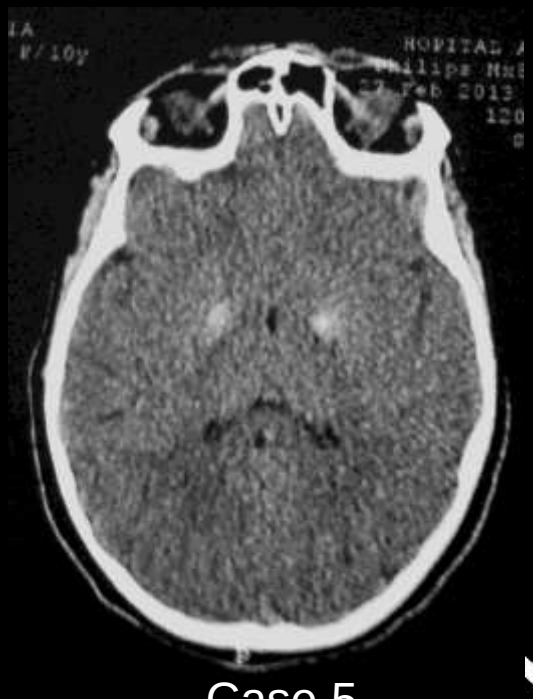


Case 5 : retard de développement psychomoteur

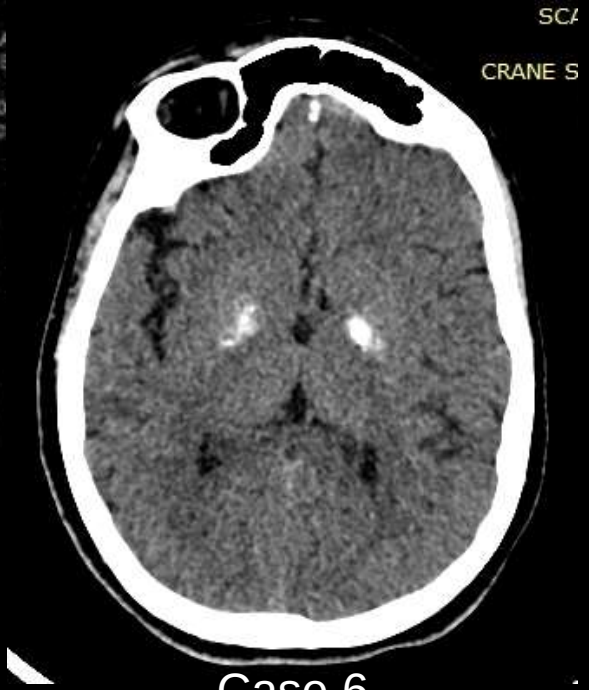




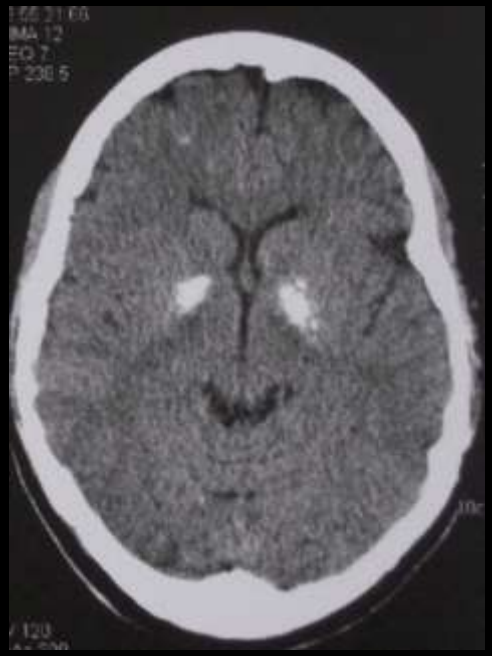
Case 2



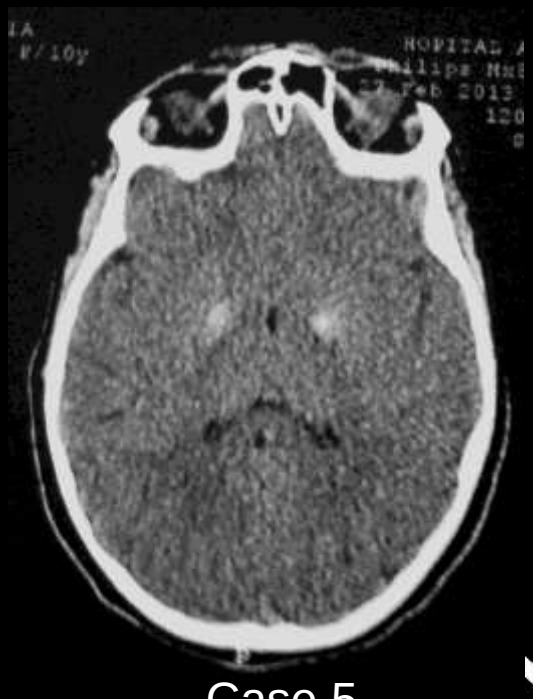
Case 5



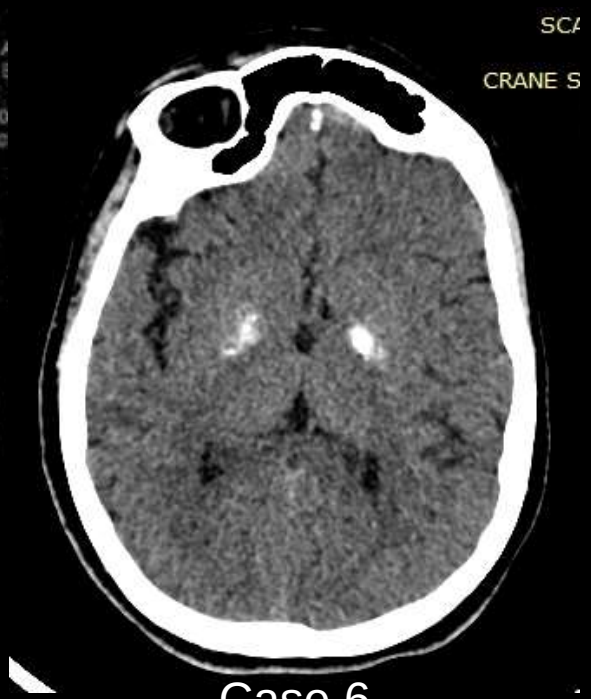
Case 6



Case 2

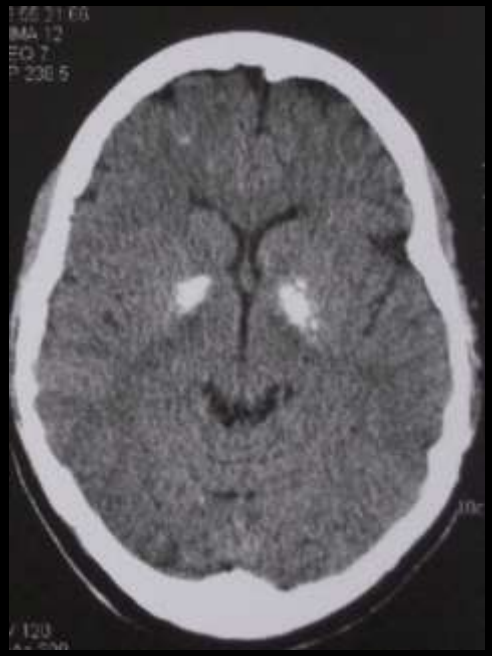


Case 5

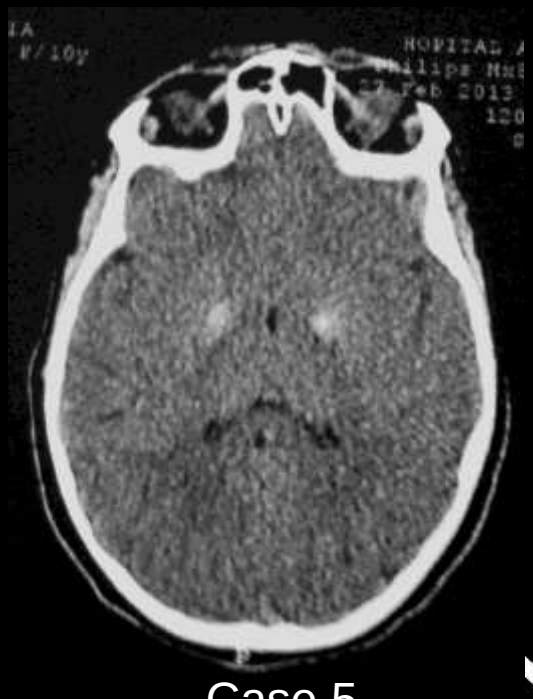


Case 6

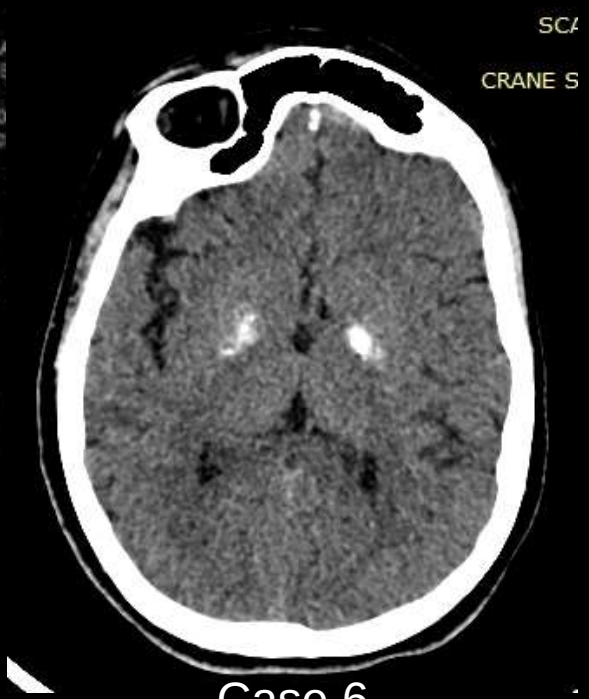
Early onset
Spastic paraplegia +
Developmental delay
Maculopathy
Basal ganglia calcifications
Consanguinity



Case 2



Case 5

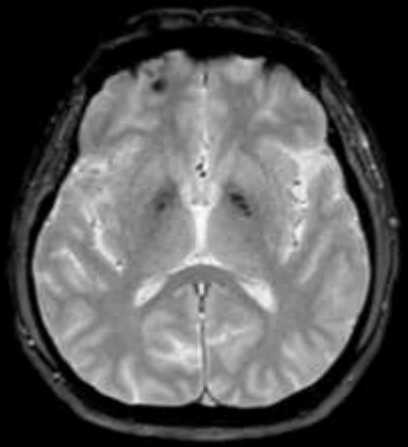


Case 6

Early onset
Spastic paraplegia +
Developmental delay
Maculopathy
Basal ganglia calcifications
Consanguinity

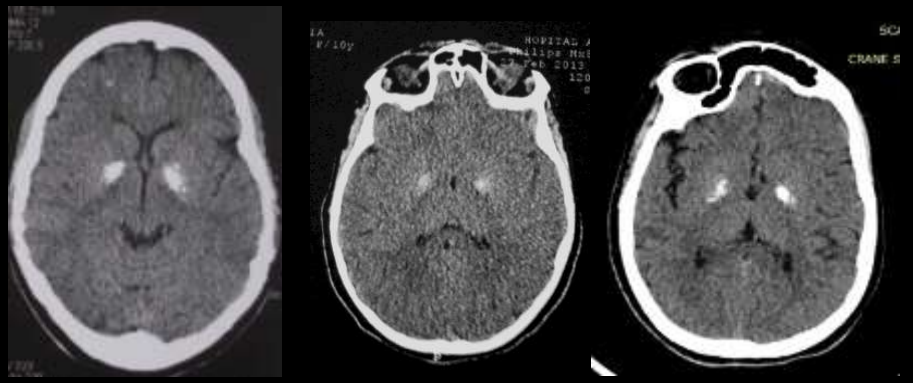
- Sd d'aicardi goutieres
- Mitochondrie

?



Whole exome sequencing

Mutation dans le gène DDHD1



Whole exome sequencing

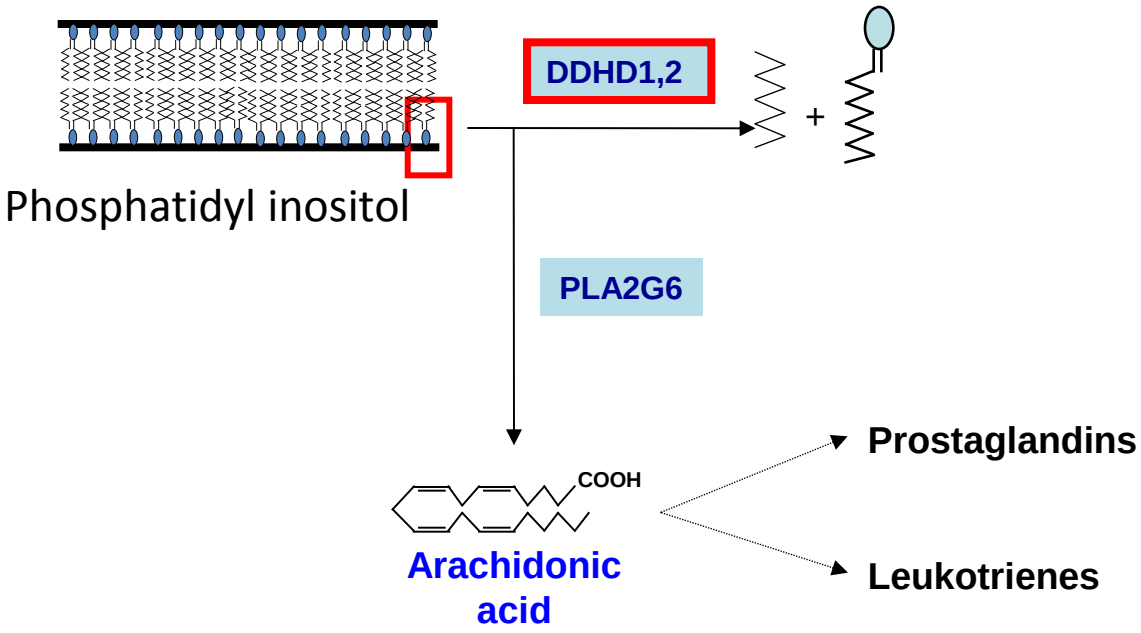
↓

Mutation dans le gène CYP2U1

PS liées au métabolisme lipidique

Exemple de DDHD1 et CYP2U1

Phospholipids remodeling : phospholipases



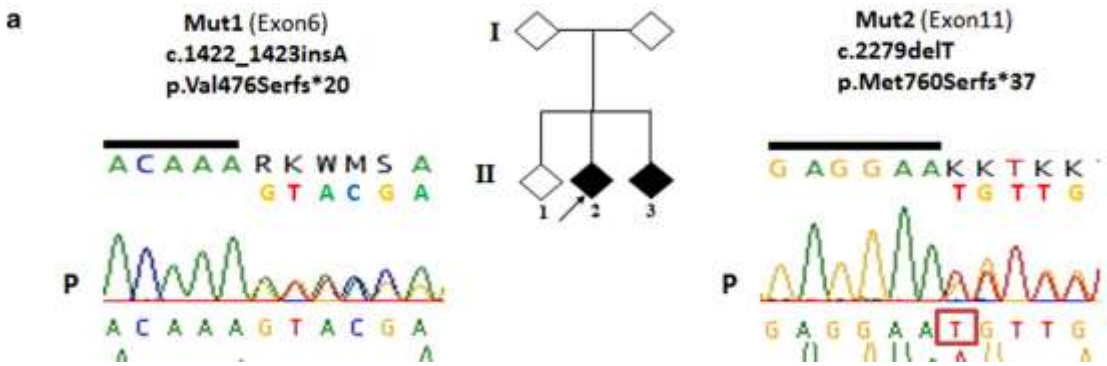
DDHD1 (SPG28) mutations

DDHD1 mutations: rather pure HSP

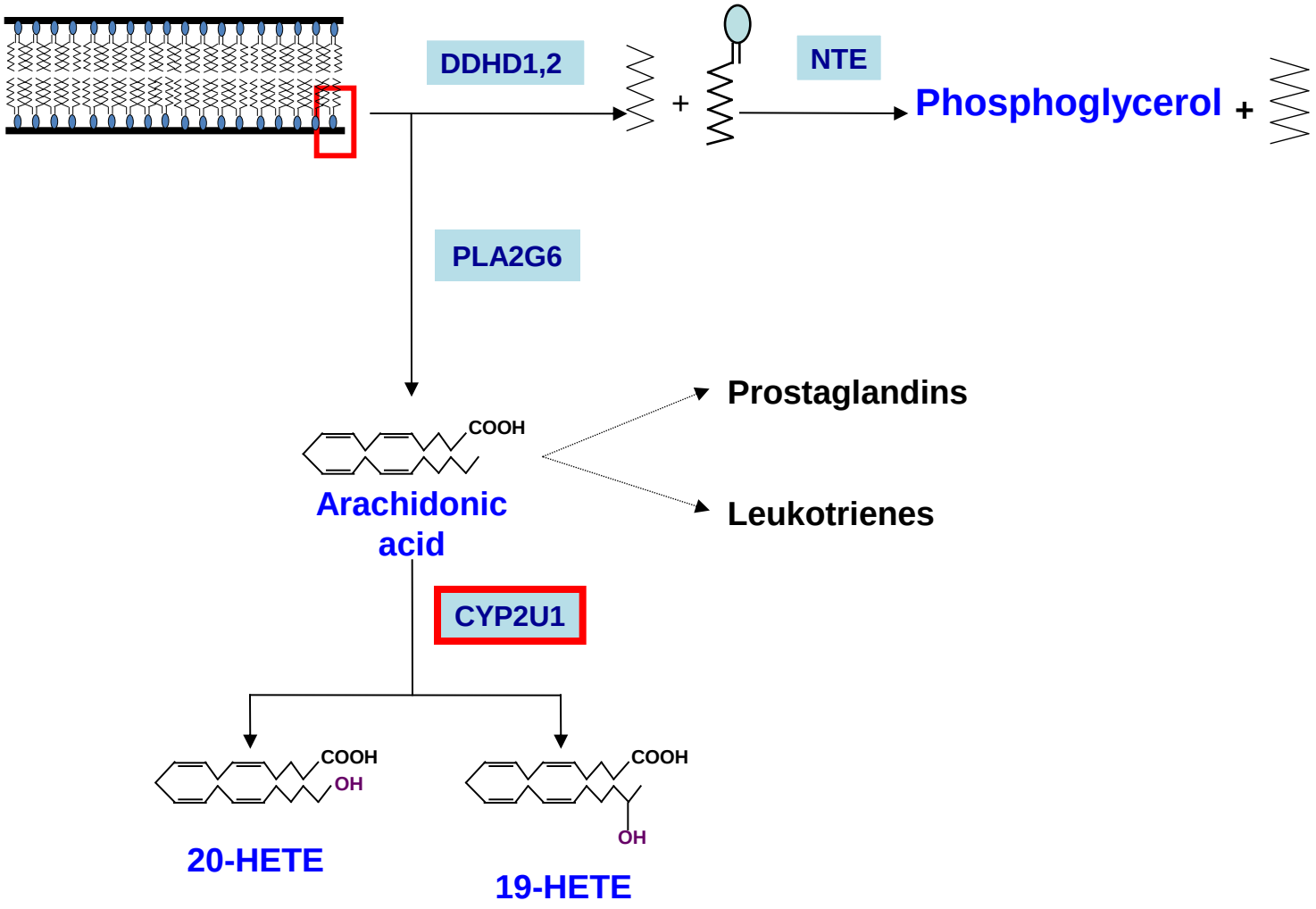
- Onset in childhood or adolescence
- Slowly progressive till adulthood
- cerebellar eye movement disturbances

Liguori et al, 2014

Tesson et al, 2012



Phospholipids remodeling : phospholipases



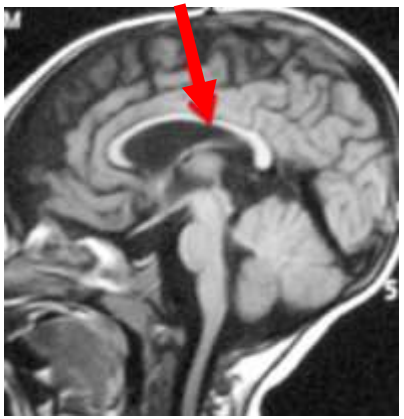
CYP2U1 mutations (SPG56)

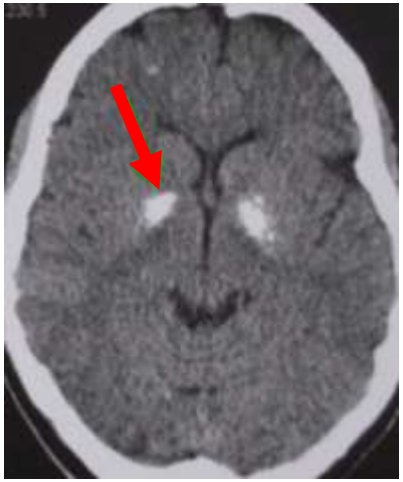
Early onset HSP (<8 years old)

From pure to complex HSP (frequently involving the upper limbs)

Dystonia, cognitive impairment, infraclinical axonal neuropathy

MRI: thin corpus callosum, basal ganglia calcifications





Citterio et al, 2014

Tesson et al, 2012

Paraplégies Spastiques Héréditaires

Forme Pure

- Spasticité membres inférieurs
- Hypopallesthésie
- Troubles sphinstériens

- IRM normal

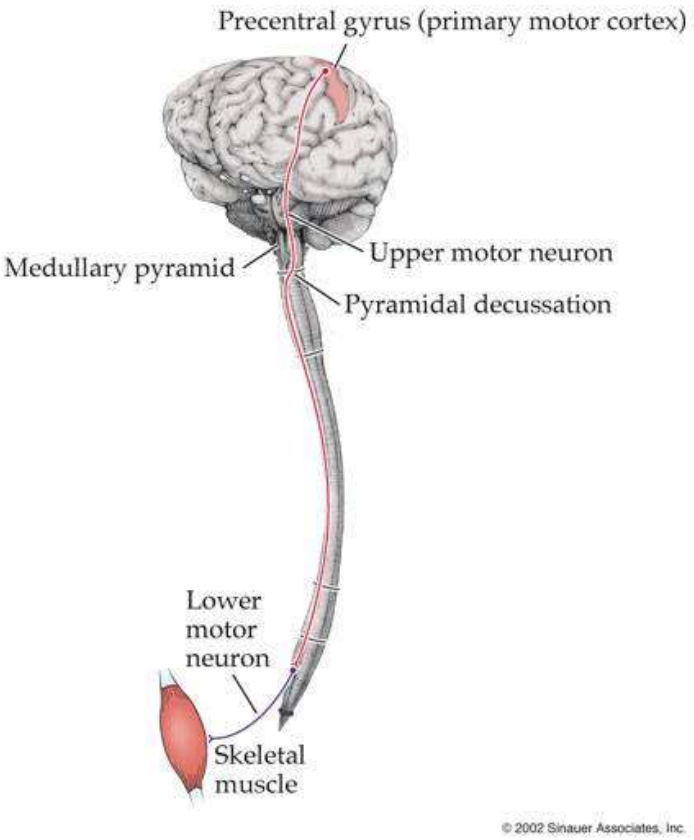
Forme Complexe

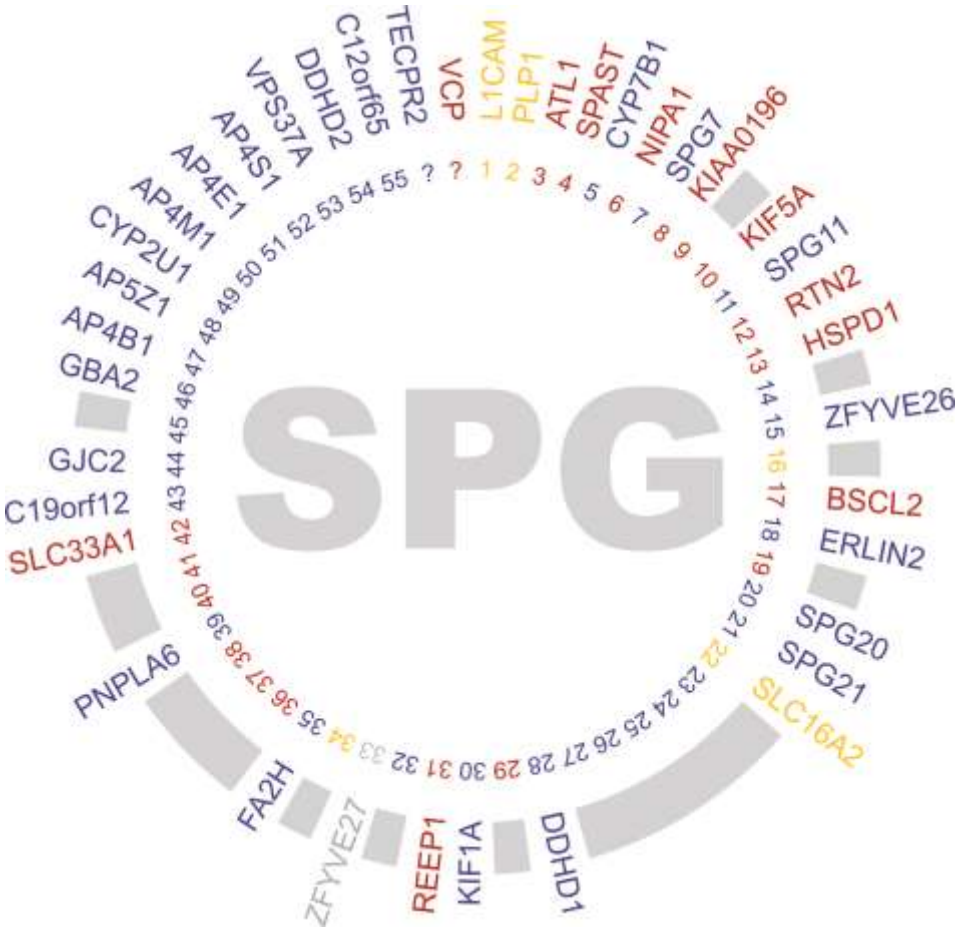
Spasticité membres inférieurs

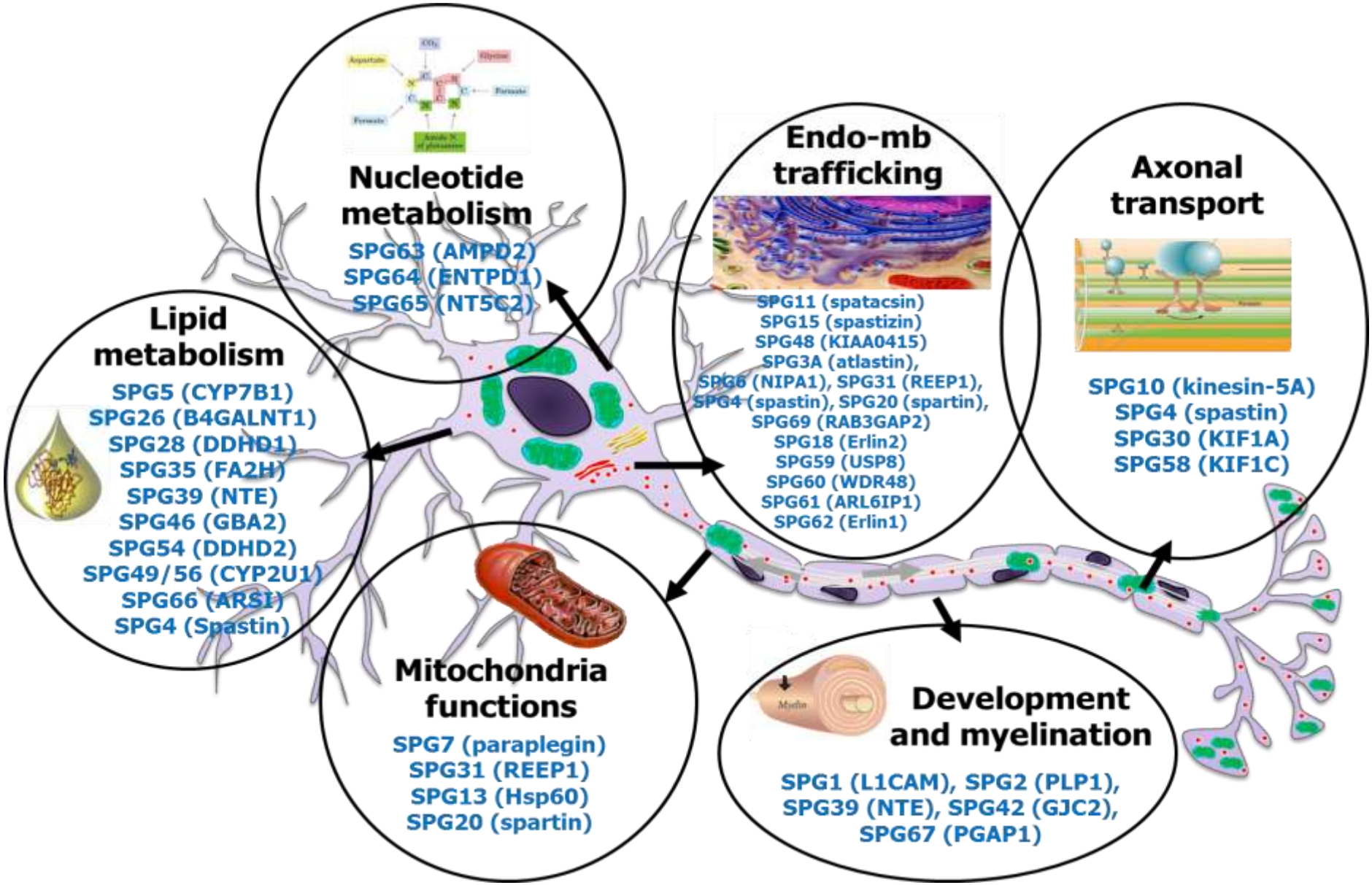
Signes neuro et/ou extra neurologiques:

- Déficience intellectuelle
- Ataxie cérébelleuse
- Neuropathie
- Atrophie optique
- Épilepsie …
- IRM cérébrale : anomalies fréquentes

HSP and lipid metabolism : few diseases inside the myriad of HSP






Nucleotide metabolism
SPG63 (AMPD2)
SPG64 (ENTPD1)
SPG65 (NT5C2)
Endo-mb trafficking
SPG11 (spatacsin)
SPG15 (spastizin)
SPG48 (KIAA0415)
SPG3A (atlastin),
SPG6 (NIPA1), SPG31 (REEP1),
SPG4 (spastin), SPG20 (spartin),
SPG69 (RAB3GAP2)
SPG18 (Erlin2)
SPG59 (USP8)
SPG60 (WDR48)
SPG61 (ARL6IP1)
SPG62 (Erlin1)
Axonal transport
SPG10 (kinesin-5A)
SPG4 (spastin)
SPG30 (KIF1A)
SPG58 (KIF1C)
Lipid metabolism
SPG5 (CYP7B1)
SPG26 (B4GALNT1)
SPG28 (DDHD1)
SPG35 (FA2H)
SPG39 (NTE)
SPG46 (GBA2)
SPG54 (DDHD2)
SPG49/56 (CYP2U1)
SPG66 (ARSI)
SPG4 (Spastin)
Mitochondria functions
SPG7 (paraplegin)
SPG31 (REEP1)
SPG13 (Hsp60)
SPG20 (spartin)
Development and myelination
SPG1 (L1CAM), SPG2 (PLP1),
SPG39 (NTE), SPG42 (GJC2),
SPG67 (PGAP1)

METABOLIC SPASTIC PARAPLEGIA

CLINICAL

INAD – PLA2G6
(regression neuropathy optic atrophy)

Ichthyosis
FALDH, ELOVL4

Hypogonadism
NTE

Fundoscopy
Optic atrophy: PLA2G6
Retinitis: FALDH, NTE, DDHD1
Maculopathy: CYP2U1
Cataract : GBA2

BIOMARKERS

NH3, AAP, OAU
Hcy, B12, folates
VLCFA
oxysterols
cholestanol
Lipidomic?

Candidate gene
HSP panel, exome?

EMG

CT / MRI / MRS

Leucodystrophy

NBIA
PLA2G6, FA2H

BG calcifications
CYP2U1, DDHD1

Thin CC +/- abnormal WM
DDHD1/2, CYP2U1
FA2H, GBA2
GPI-anchor synthesis

MRS
FALDH, DDHD2

Remerciements

Service de génétique clinique :

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Giovanni Stevanin

Mathilde Mairey

Laure Raymond

Guillaume Banneau

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Sylvie Forlani

Christelle Dussert

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