European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

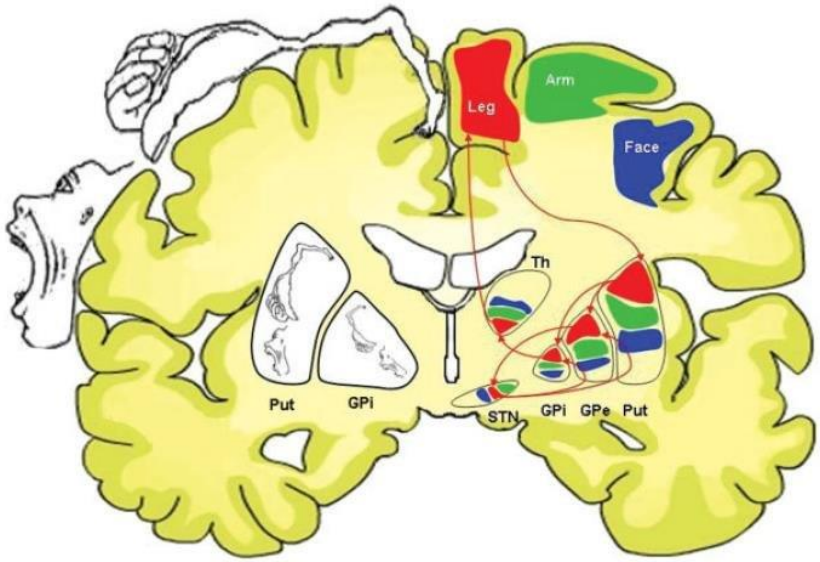
**Webinar – 12. April 2022**

# ‘Basal ganglia diseases in childhood‘

## by Belén Perez Dueñas

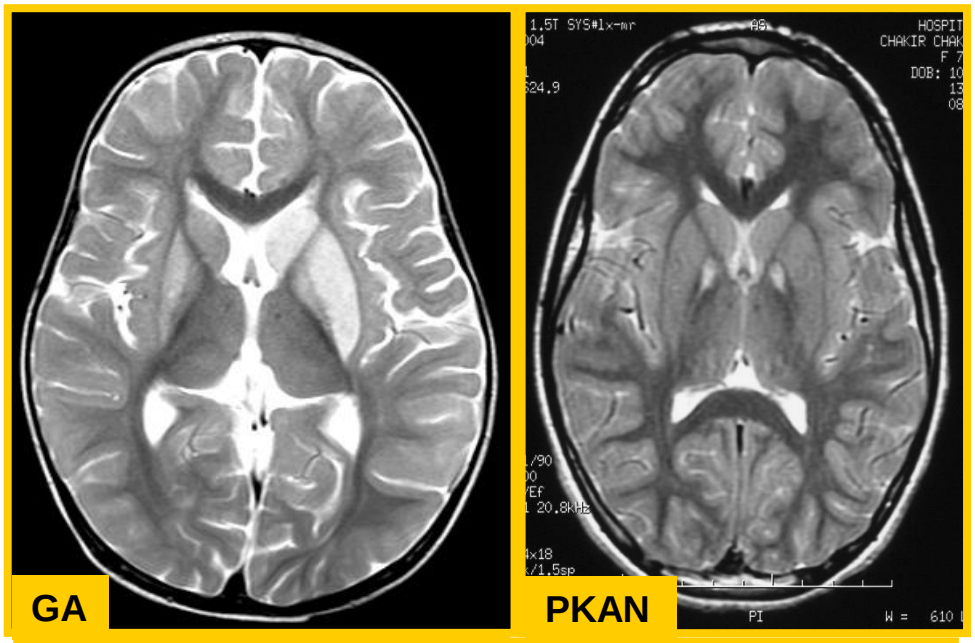
**Hospital Vall d'Hebron, Pediatric Neurology, Movement Disorders , Barcelona, Spain**

# The Basal Ganglia



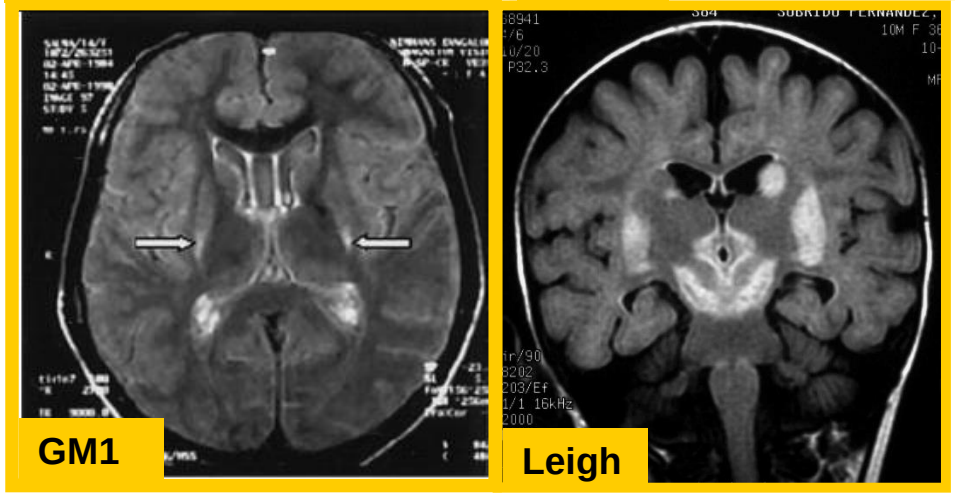

- Deep grey-matter structures involved in the control of posture and voluntary movements, cognition, behavior, and motivational states
- Cortical-basal ganglia-thalamic-cortical loop
- Parallel to the corticospinal pathway (extrapyramidal disorders)
- Implicated in Parkinson D, Huntington D, Tourette S, Dystonia, chorea, tremor.

**INTOXICATION**
*Organic acidurias*
*GAI, PA, MMA*




**METAL DEPOSITION**
*Wilson*
*Manganese homeostasis*
*NBIA*

**LISOSOMAL DISORDERS**
*GM1,GM2,*

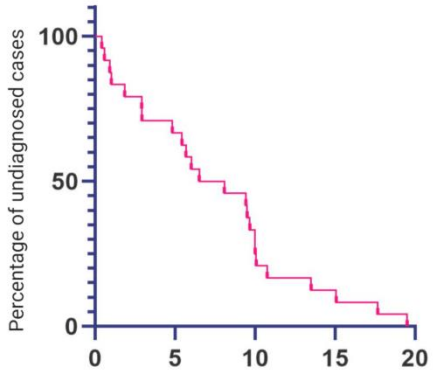


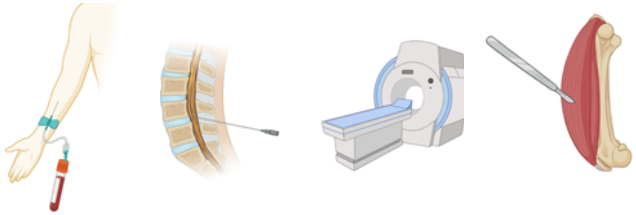

**ENERGY FAILURE**
*Respiratory chain*
*PDH*
*CoQ10*
*Thiamine*
*Creatine (GAMT)*

# Basal Ganglia Diseases

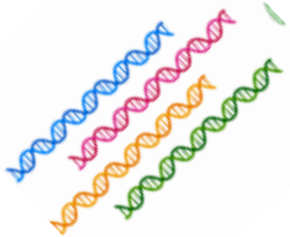
Initial assessment

Invasive Procedures

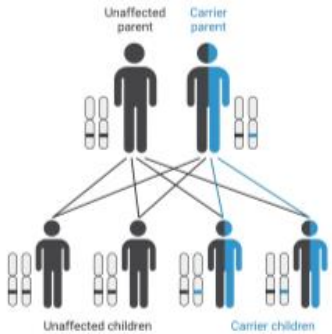


Genetic Diagnosis



Personalized medicine




# Some treatable IEM cause basal ganglia disease in childhood

- Early treatment prevents injury to the nervous system.

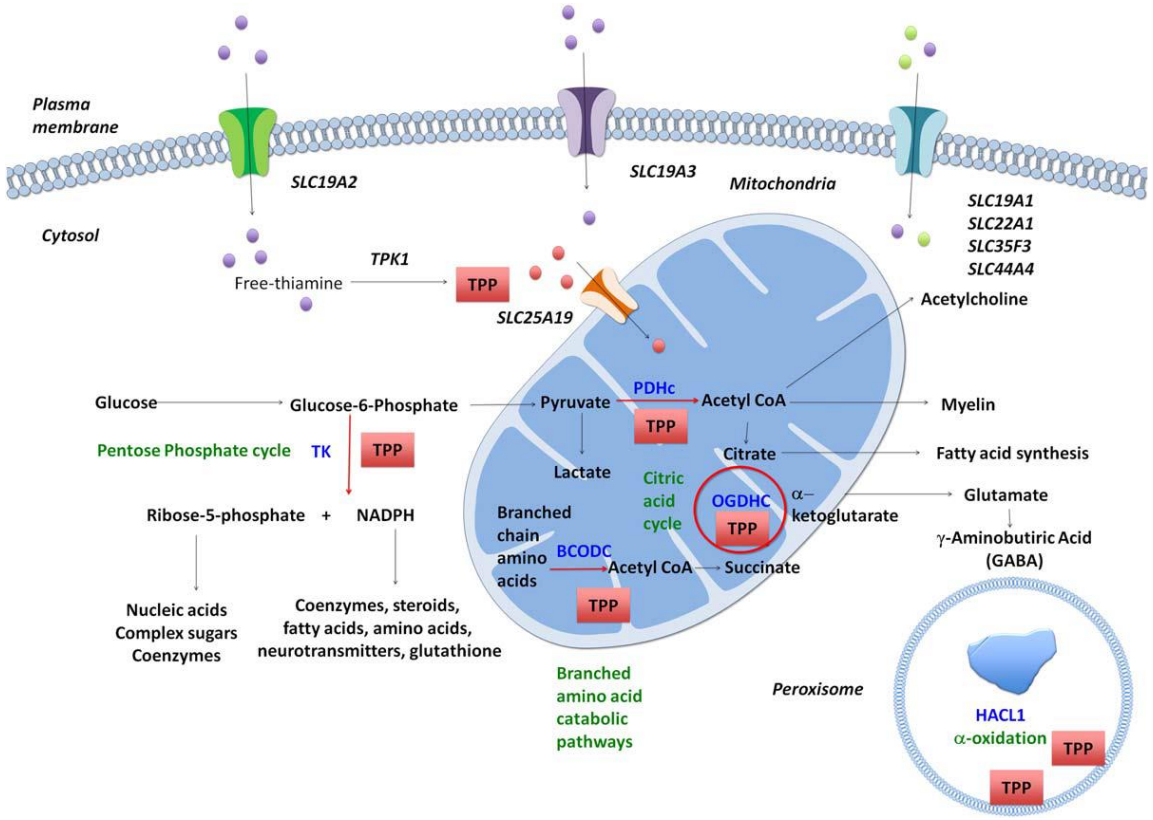
1. Reduction of toxic target molecules
   - Manganese transporter
   - Wilson disease
   - Lysosomal (NPC, GM1…) (Venglustat)

2. Dietary intervention
   - Glutaric Aciduria, propionic academia, methyl malonic academia to prevent basal ganglia necrosis during acute decompensations.
   - Others: MSUD, PDH…

3. Supplements with vitamins
   - Thiamine in PDH (+ketogenic diet), SLC19A3 and ECHS1
   - Biotin (biotinidase def.),
   - Creatin (creatin deficiency síndromes)
   - CoQ10

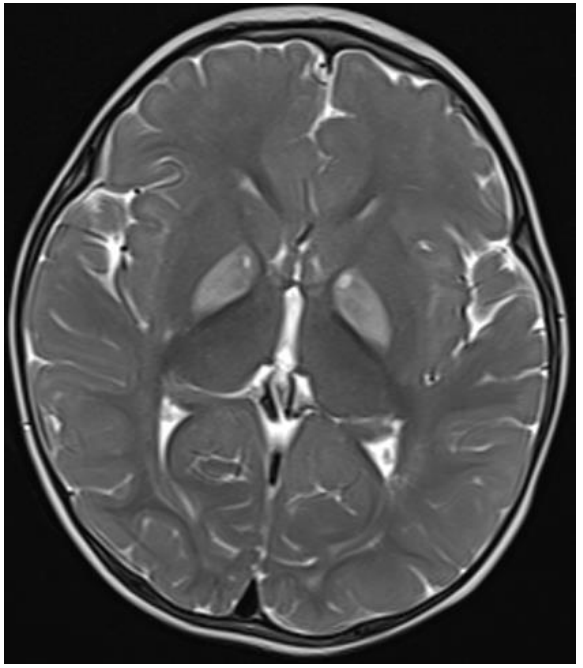
# Don’t forget thiamine

- Thiamine transport and metabolism:
  - SLC19A3
  - TPK1
  - SLC25A19
- Pyruvate dehydrogenase:
  - PDHA1
- MSUD
- Valine metabolism:
  - ECHS1




*Ortigoza-Escobar, Ann Neurol 2017*

# Paroxysmal dystonia

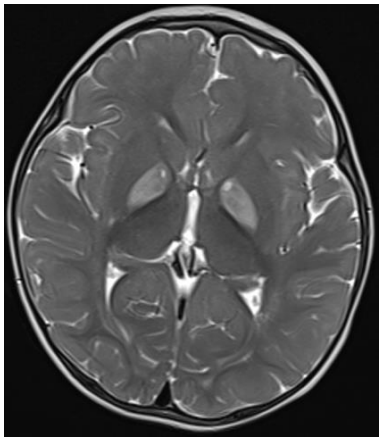


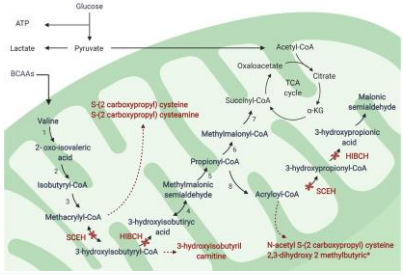
Normal neurodevelopment. Walking at 11 months.
Paroxysmal dystonia of 15-40 minutes at 12 months.
Triggers: fever, infection, exercise
Normal examination between episodes.

# ECHS1 – Paroxysmal dystonia

## BRAIN ENERGY METABOLISM

EXERCISE
FEVER



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# Children with paroxysmal dystonia How to treat?

This child has a Leigh-like phenotype according to MRI but presents with a paroxysmal dystonia phenotype. Both phenotypes are reported in ECHS1 defects. How would you treat his symptoms?

FIND THE WRONG ANSWER

1. I would continue thiamine supplementation at high doses (similar to pyruvate dehydrogenase deficiency)
2. I would also recommend a dietary intervention to reduce substrates and prevent the accumulation of toxic metabolites from the affected pathway.
3. In fact, I would recommend thiamine supplementation in any child with exercise induced paroxysmal dystonia, especially if there are basal ganglia lesions on MRI.
4. The abnormal signal on pallidal nuclei suggests necrosis, and therefore, there is little chance to modify motor symptoms.

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# ECHS1 paroxysmal dystonia

1. Paroxysmal dystonia induced by exercise and infection is a **milder and potentially treatable phenotype** in ECHS1 deficiency.
2. It shows **overlapping features with PDHA1 and SLC19A3** due to basal ganglia lesions and the response to thiamine.
3. **Thiamine is a cofactor for several enzymes involved in mitochondrial energy metabolism** (PDHc, pyruvate dehydrogenase complex), OGDHC (oxoglutarate dehydrogenase complex), and BCODC (branched chain 2-oxo acid dehydrogenase complex).

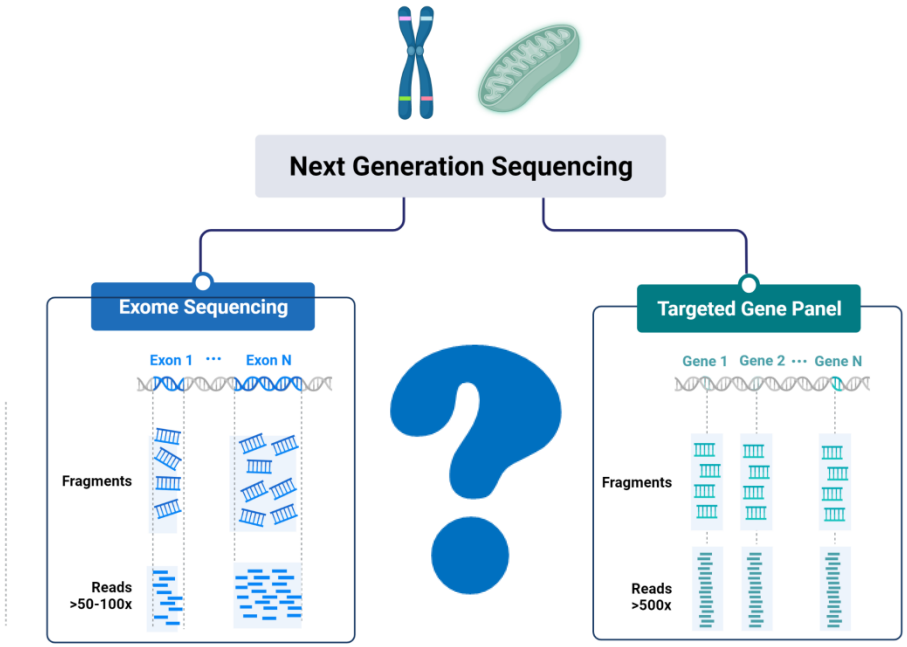
DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

# Genetic diagnosis of basal ganglia disease in childhood

HEIDY BAIDE-MAIRENA[1,2] | LAURA MARTI-SÁNCHEZ[3] | ANNA MARCÉ-GRAU[1] | ANA CAZURRO-GUTIÉRREZ[1] | ANGEL SANCHEZ-MONTANEZ[4] | IGNACIO DELGADO[4] | ANTONIO MORENO-GALDÓ[5,6,7] | ALFONS MACAYA-RUIZ[1,7,8] | ELENA GARCÍA-ARUMÍ[7,9,10] | BELÉN PÉREZ-DUEÑAS[1,7,8] | THE CHILDHOOD BASAL GANGLIA DISEASE GROUP*

*We aimed to identify the genetic aetiology of BBG lesions in childhood. Our diagnostic approach combined clinical and radiological characterization, the use of biomarkers, and NGS studies.*

# Which is the best approach to diagnosis of basal ganglia lesions in childhood?




# Methods

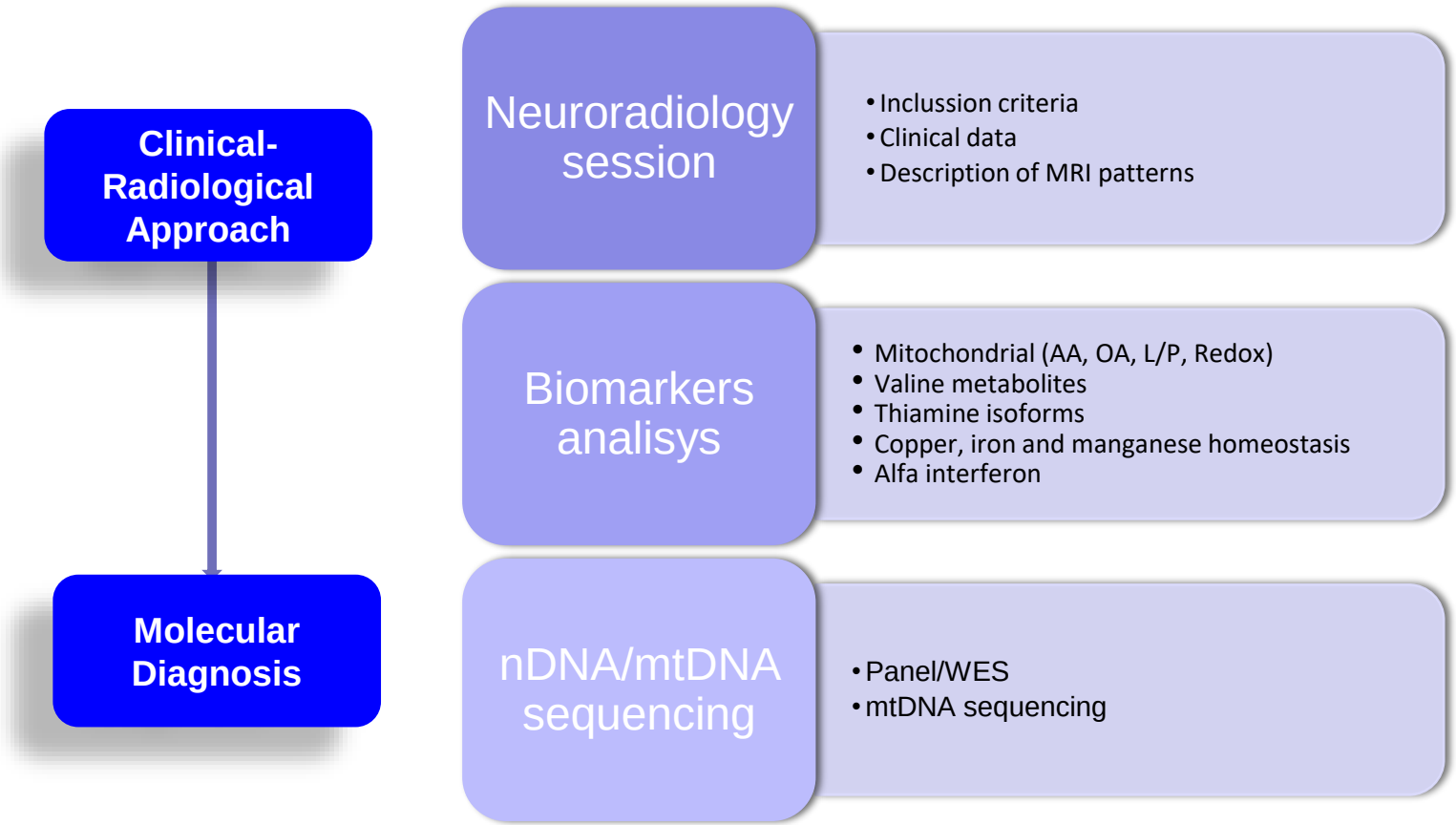
Observational multicentric study

22 Health Care Centres

Children with movement disorders and bilateral BG lesions of unknown etiology.

Genetic testing and biomarker analysis

# Methods


Clinical-Radiological Approach
Molecular Diagnosis
Neuroradiology session
• Inclussion criteria
• Clinical data
• Description of MRI patterns
Biomarkers analisys
• Mitochondrial (AA, OA, L/P, Redox)
• Valine metabolites
• Thiamine isoforms
• Copper, iron and manganese homeostasis
• Alfa interferon
nDNA/mtDNA sequencing
• Panel/WES
• mtDNA sequencing

# Methods

**Clinical-Radiological Approach**

**Molecular Diagnosis**

| | |
|---|---|
| Neuroradiology session | • Inclussion criteria<br>• Clinical data<br>• Description of MRI patterns |
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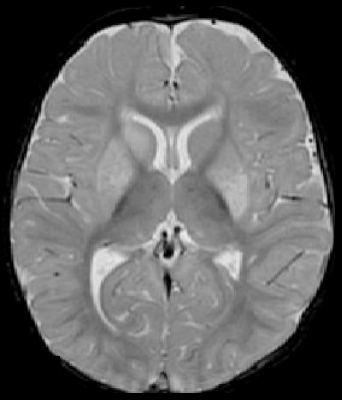
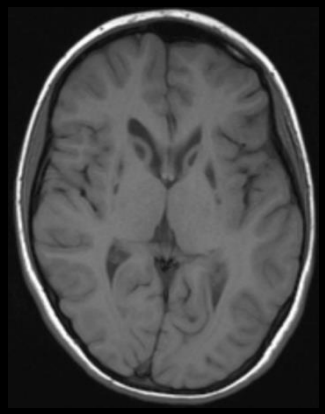
| nDNA/mtDNA sequencing | • WES<br>• WES trio<br>• mtDNA sequencing |

# CLASSIFICATION BASAL GANGLIA LESIONS

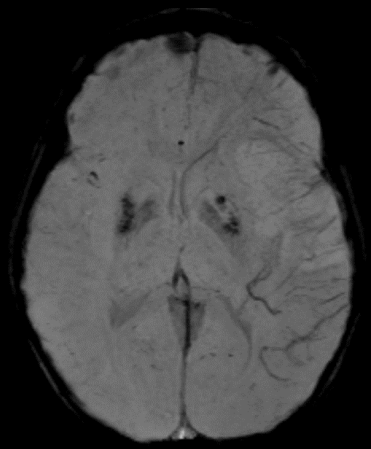
## Striatal necrosis

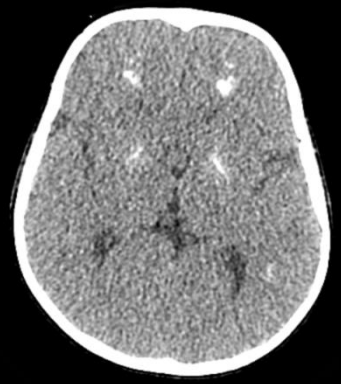




*T2W hyperintensity associated to citotoxicity / atrophy / cavitation of the caudate, putamen or globus pallidus*

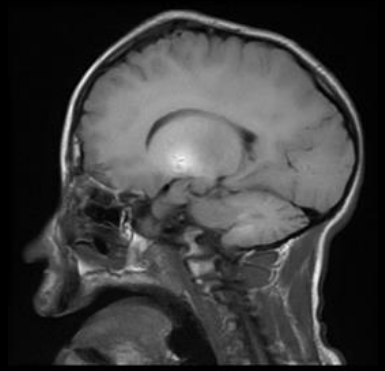
## Calcification

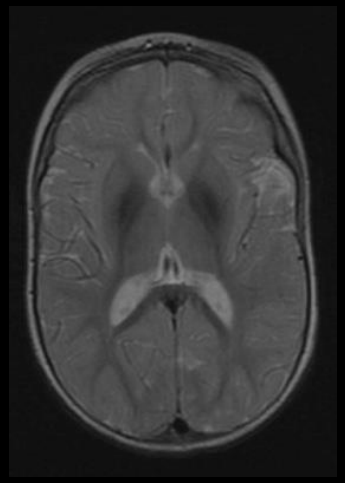




*MRI-GRE (Gradient echo sequences) hypointensity, confirmed by CT*

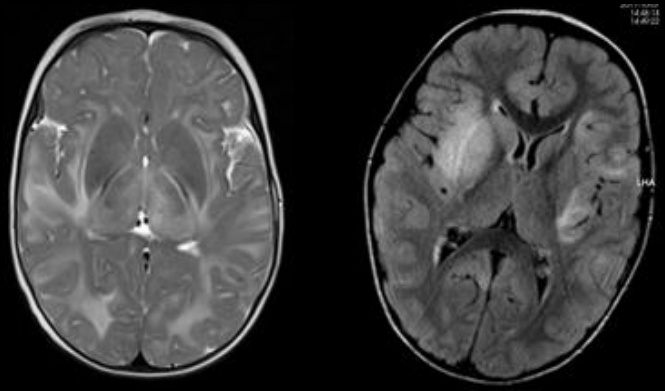
## Brain metal accumulation



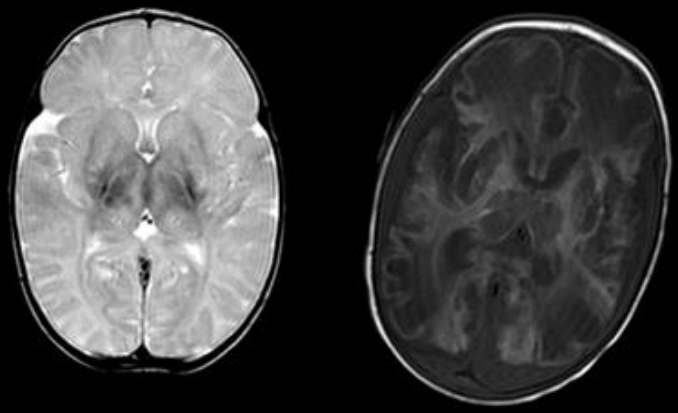


*TW1 hyperintensity / TW2 hypointensity*

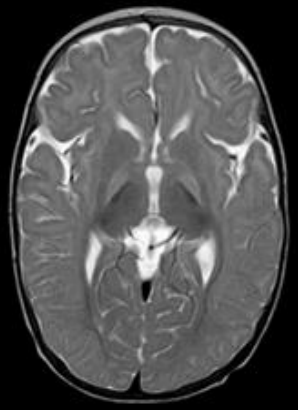
# EXCLUSSION OF ACQUIRED INFLAMATORY/INFECTIOUS LESIONS



PEDIATRIC ADEM



HIPOXIC ISCHEMIC ENCEPHALOPATHY



BILIRUBIN ENCEPHALOPATHY

# Methods

**Clinical-Radiological Approach**

**Molecular Diagnosis**

| | |
|---|---|
| Neuroradiology session | • Inclusion criteria<br>• Brain MRI and clinical data<br>• Classification of the lession to Basal Ganglia |
| Biomarkers analisys | • Mitochondrial (AA, OA, L/P, Redox)<br>• Valine metabolites<br>• Thiamine isoforms<br>• Copper, iron and manganese homeostasis<br>• Alfa interferon |
| nDNA/mtDNA sequencing | • WES<br>• WES trio<br>• mtDNA sequencing |

# Methods


Dr. Garcia Arumí
Mitochondrial Group

Dr. J Montoya
Unizar

**Molecular Diagnosis**

**Neuroradiology session**

- Inclusion criteria
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**Biomarkers analisys**

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**nDNA/mtDNA sequencing**

- Panel / WES
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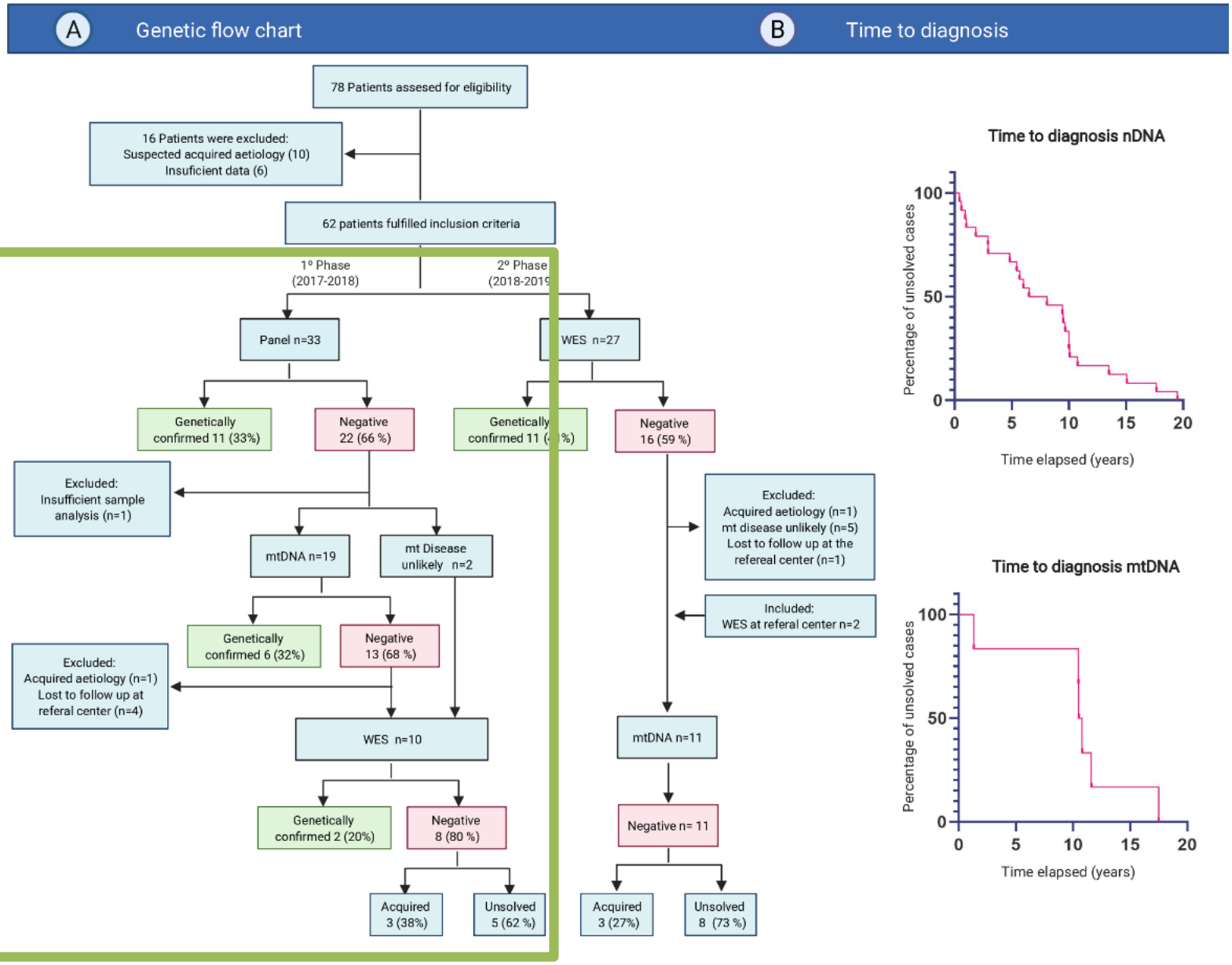
A
Genetic flow chart
B
Time to diagnosis
78 Patients assesed for eligibility
16 Patients were excluded:
Suspected acquired aetiology (10)
Insuficient data (6)
62 patients fulfilled inclusion criteria
1º Phase
(2017-2018)
2º Phase
(2018-2019
Panel n=33
WES n=27
Genetically confirmed 11 (33%)
Negative 22 (66 %)
Genetically confirmed 11 (
%)
Negative 16 (59 %)
Excluded:
Insufficient sample analysis (n=1)
mtDNA n=19
mt Disease unlikely n=2
Genetically confirmed 6 (32%)
Negative 13 (68 %)
Excluded:
Acquired aetiology (n=1)
Lost to follow up at referal center (n=4)
WES n=10
Genetically confirmed 2 (20%)
Negative 8 (80 %)
Acquired 3 (38%)
Unsolved 5 (62 %)
Excluded:
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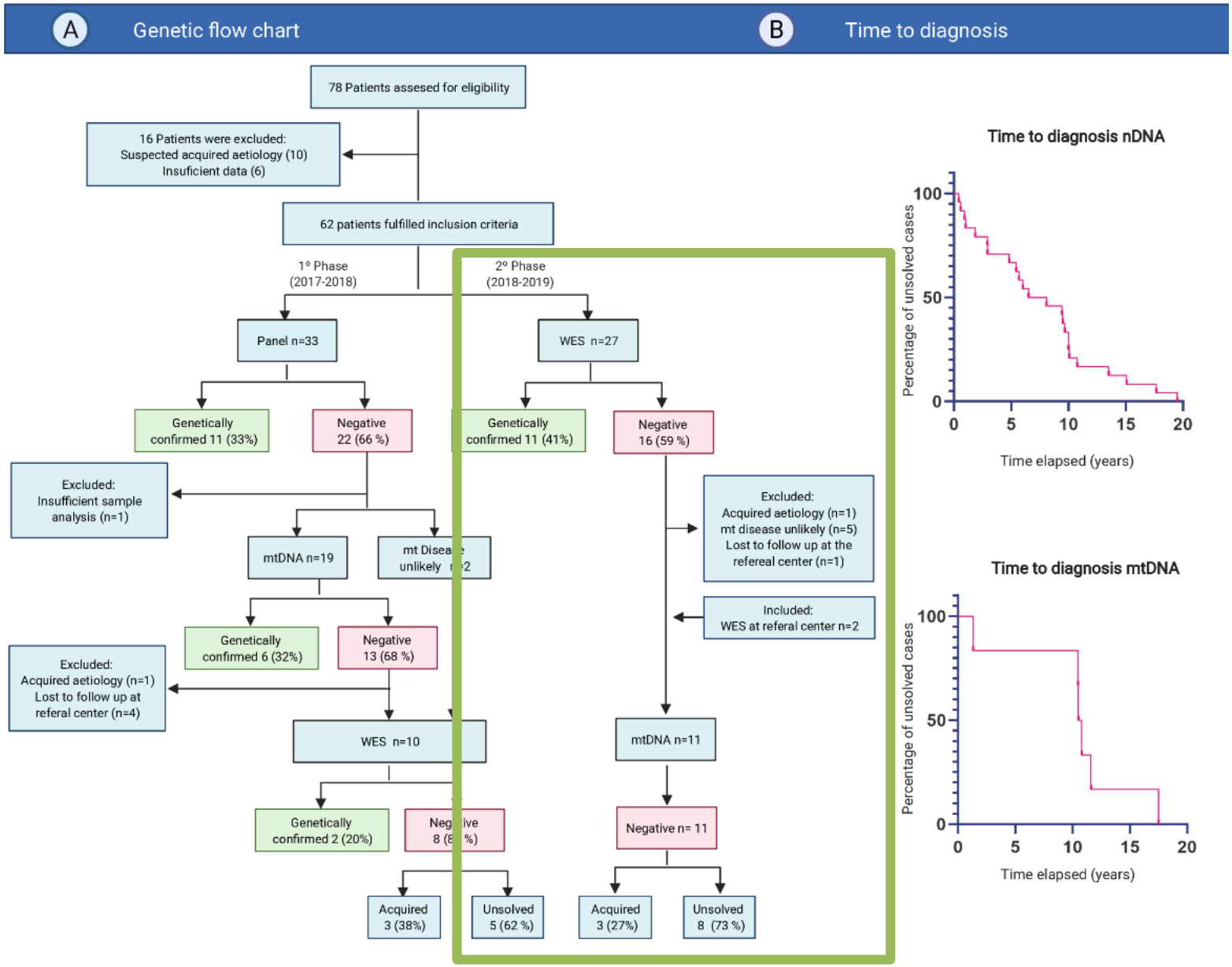
mt disease unlikely (n=5)
Lost to follow up at the refereal center (n=1)
Included:
WES at referal center n=2
mtDNA n=11
Negative n= 11
Acquired 3 (27%)
Unsolved 8 (73 %)
Time to diagnosis nDNA
Percentage of unsolved cases
100
50
0
0
5
10
15
20
Time elapsed (years)
Time to diagnosis mtDNA
Percentage of unsolved cases
100
50
0
0
5
10
15
20
Time elapsed (years)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Time elapsed (years)
Time to diagnosis mtDNA
Percentage of unsolved cases
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20
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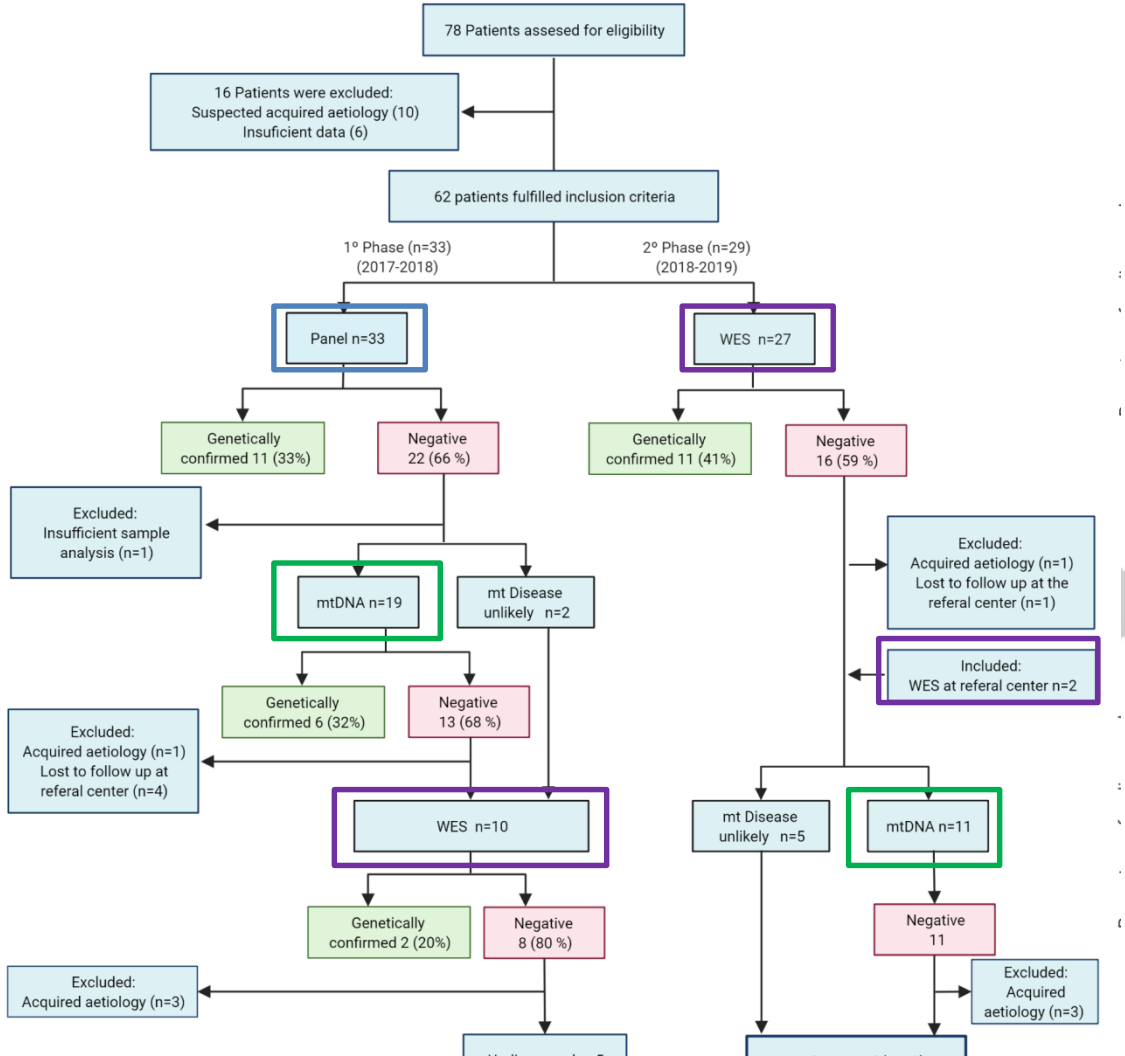
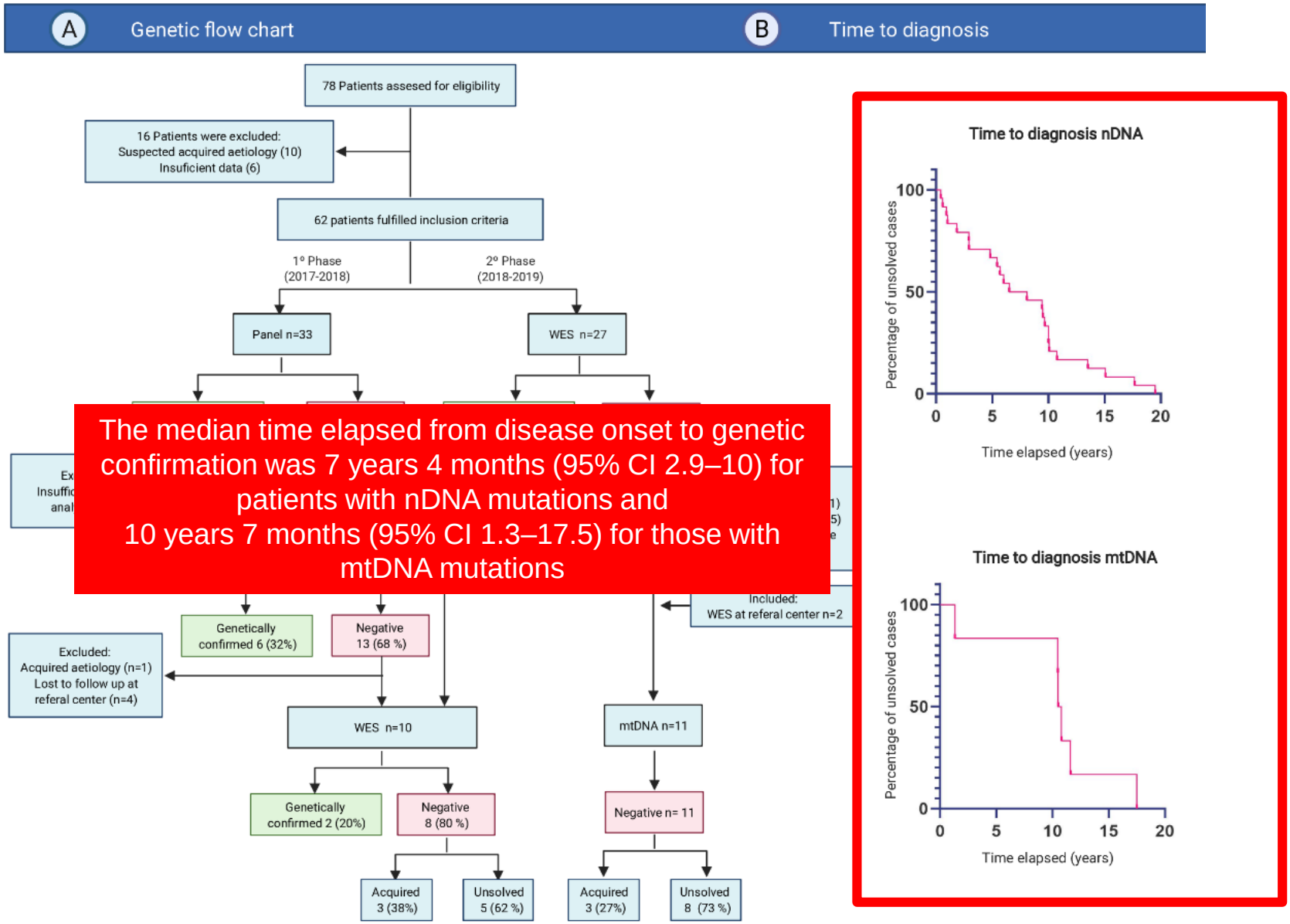
# Results

## A Genetic flow chart




**Molecular Diagnosis**

**30/62 (48 %)**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WES n=10
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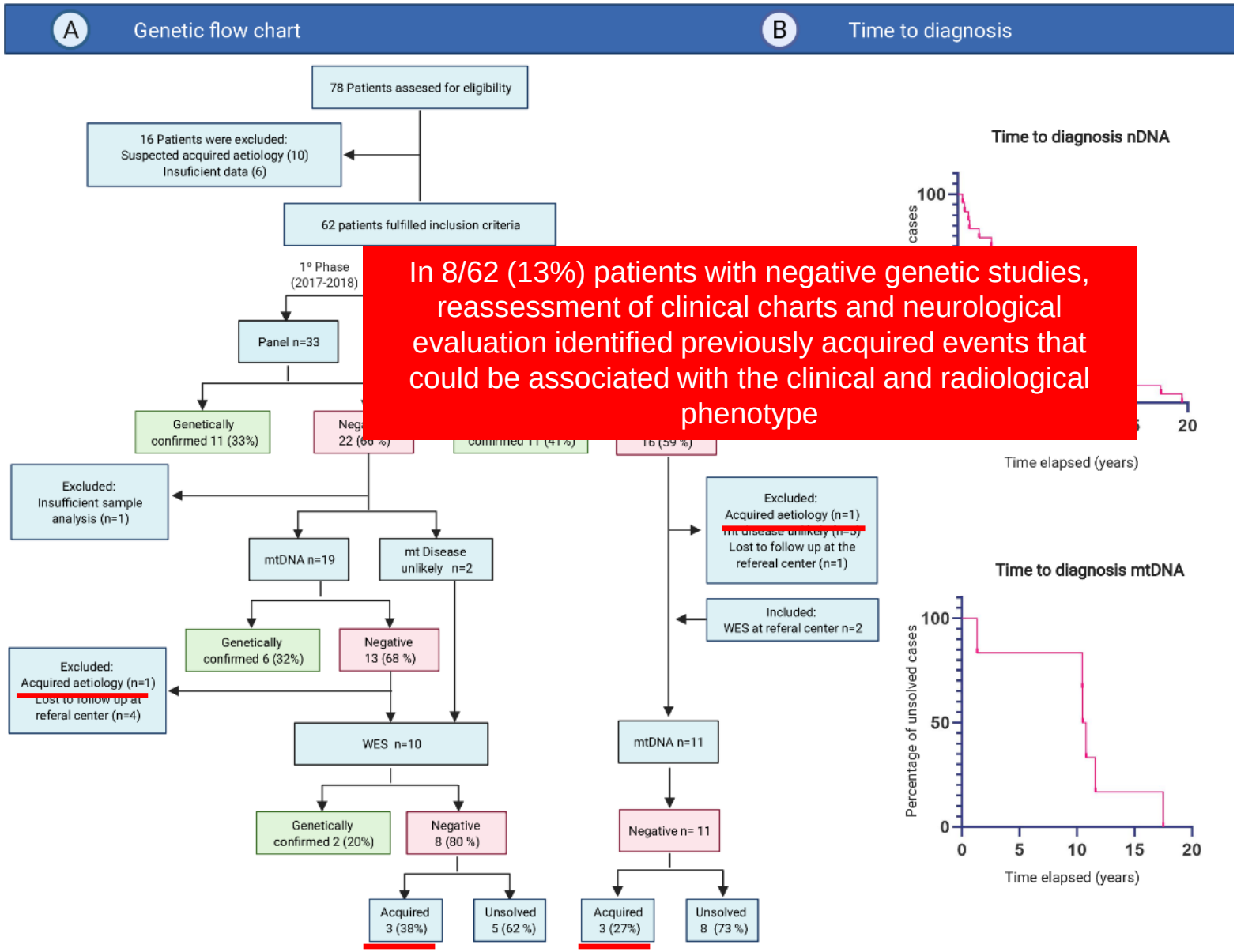
Negative
8 (80 %)
Acquired
3 (38%)
Unsolved
5 (62 %)
Included:
WES at referal center n=2
mtDNA n=11
Negative n= 11
Acquired
3 (27%)
Unsolved
8 (73 %)
The median time elapsed from disease onset to genetic confirmation was 7 years 4 months (95% CI 2.9–10) for patients with nDNA mutations and
10 years 7 months (95% CI 1.3–17.5) for those with mtDNA mutations
Time to diagnosis nDNA
Percentage of unsolved cases
100
50
0
0
5
10
15
20
Time elapsed (years)
Time to diagnosis mtDNA
Percentage of unsolved cases
100
50
0
0
5
10
15
20
Time elapsed (years)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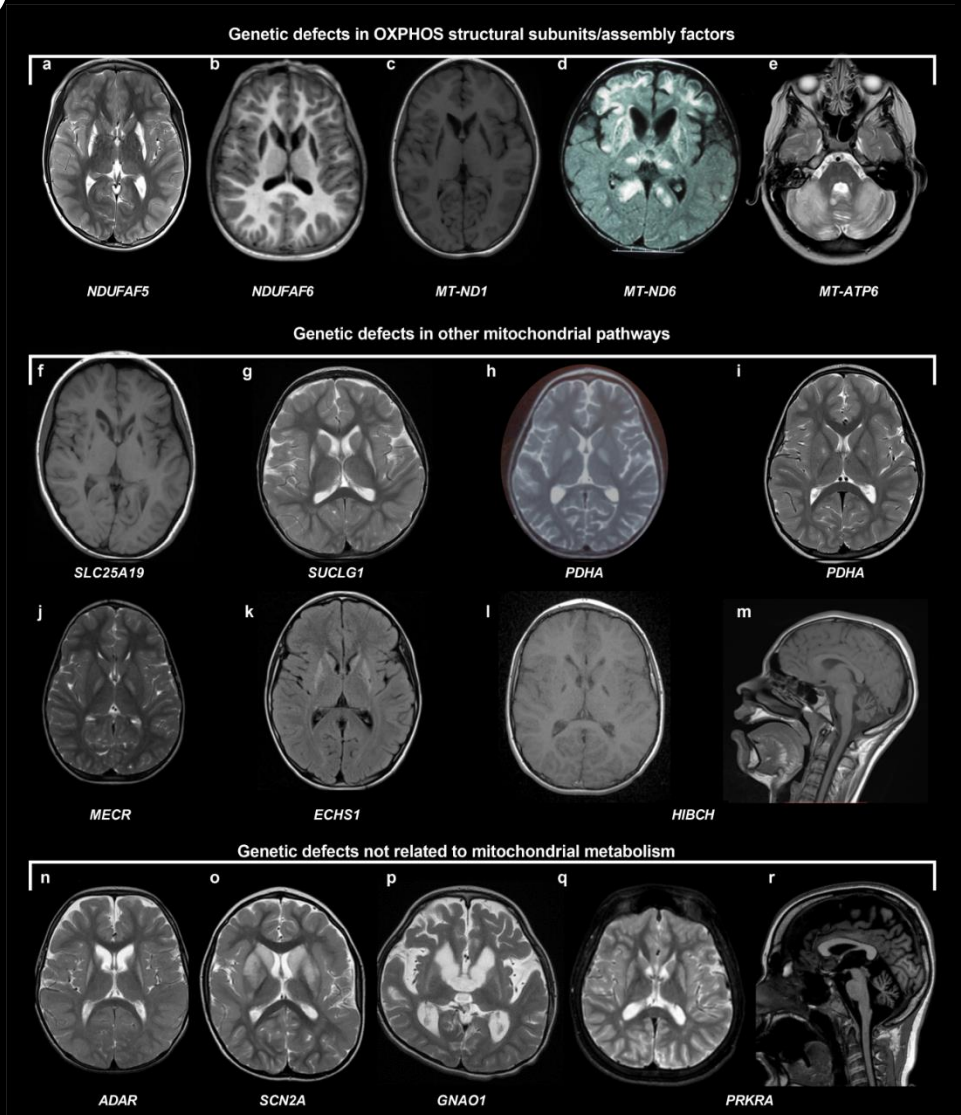
Unsolved 8 (73 %)
In 8/62 (13%) patients with negative genetic studies, reassessment of clinical charts and neurological evaluation identified previously acquired events that could be associated with the clinical and radiological phenotype
Time to diagnosis nDNA
cases
100
20
Time elapsed (years)
Time to diagnosis mtDNA
Percentage of unsolved cases
100
50
0
0
5
10
15
20
Time elapsed (years)

# Basal Ganglia Diseases

## T2-hyperintensity (n=25)

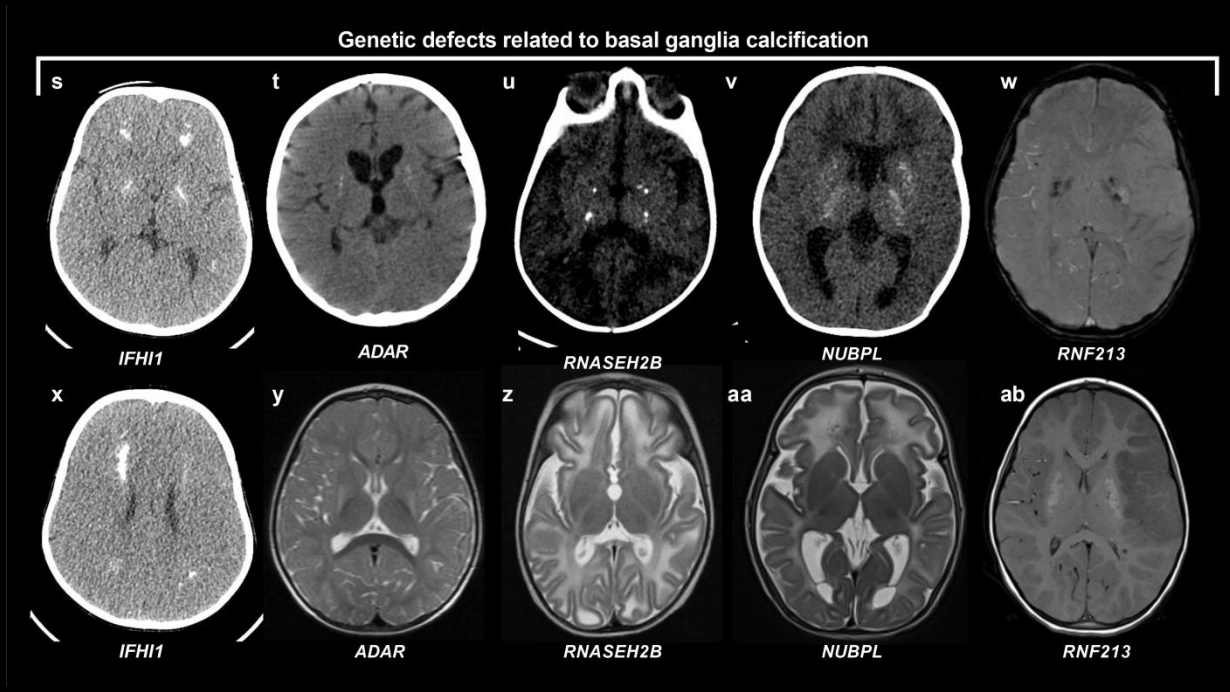
22 genetic defects



# Basal Ganglia Diseases

## Mineralization (calcium n=8; manganese n=1)

22 genetic defects




MRI (T1-, T2-, gradient recalled echo-, SWI) and/or CT

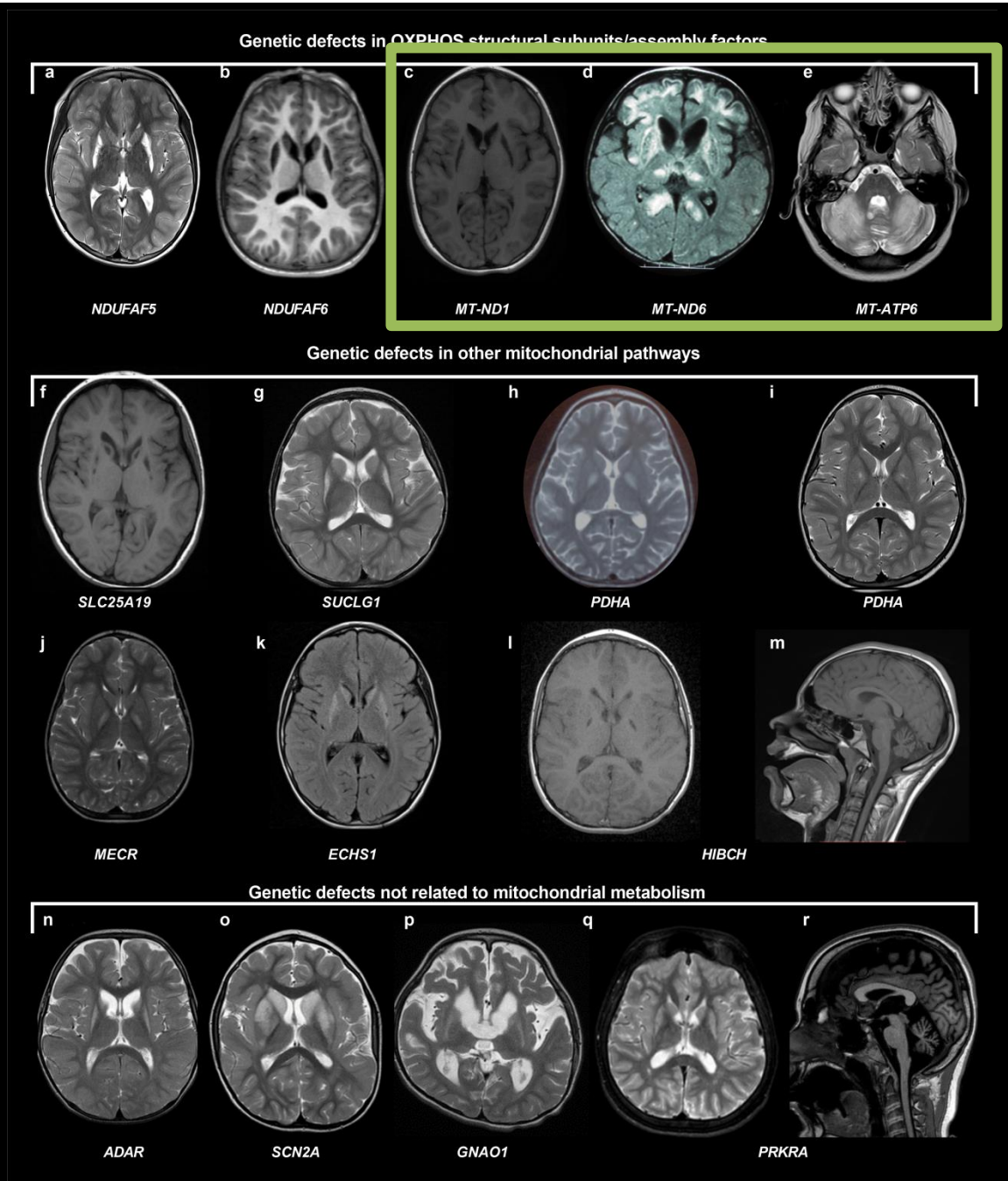
# Basal Ganglia Diseases

**20%**

Mitochondrial encoded

**80%**

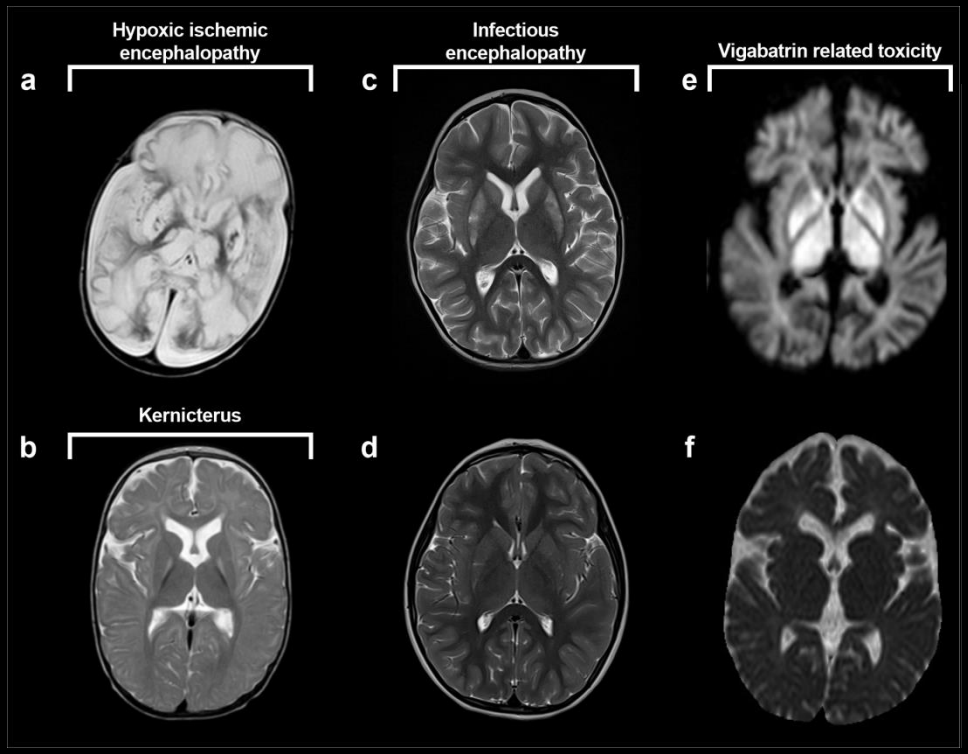
Nuclear encoded

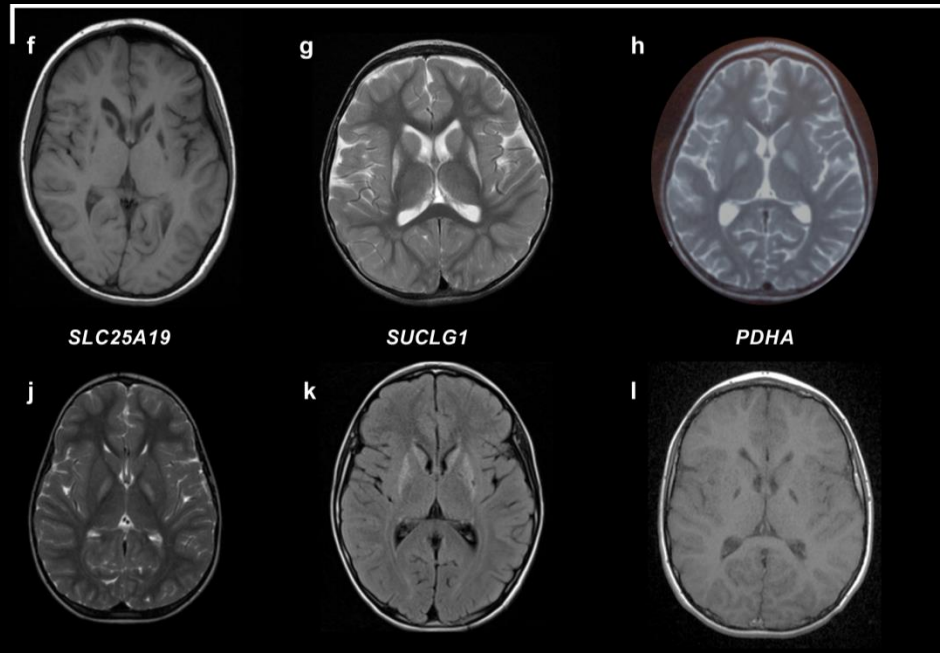


# Basal Ganglia Diseases

## Acquired (13%)

## Genetic (48%)



# Concepts of Leigh syndrome

# Concepts of Leigh syndrome

Select the WRONG ANSWER:

1. Affects 1 in 40,000 live births
2. Onset 0 -12 months of age, in most of the cases
3. Rapid deterioration of cognitive and motor functions, in most cases resulting in death due to respiratory failure
4. Pathogenic variants in more than 200 mitochondrial and nuclear encoded genes have been reported
5. These variants directly or indirectly affect the activity of the mitochondrial respiratory chain (RCC) or pyruvate dehydrogenase complex (PDH)

Gerards, 2015; Sofou, 2014

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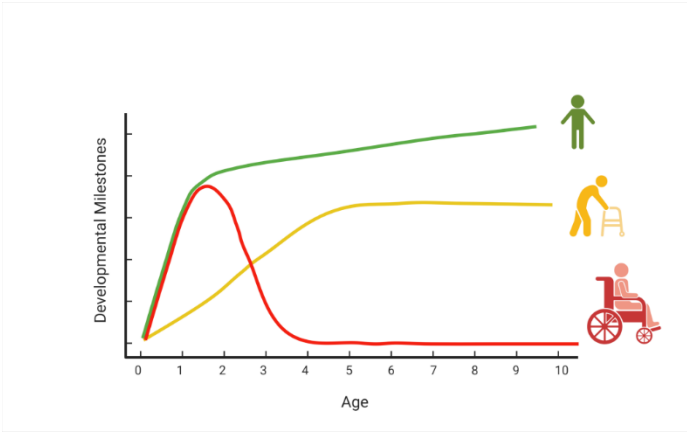
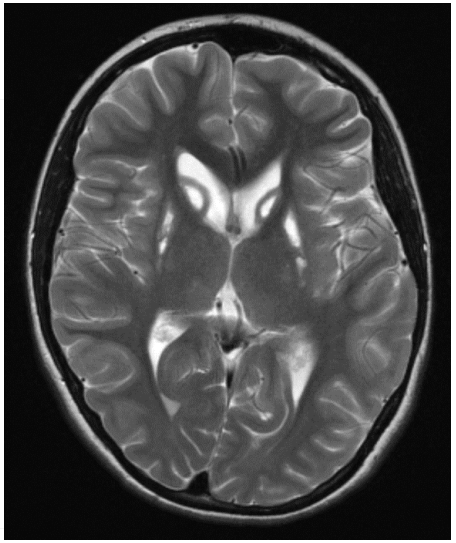
# Leigh Syndrome



Diagnostic criteria:

(1) Characteristic pathology or neuroradiology

(2) Clinical evidence of brainstem and/or basal ganglia dysfunction

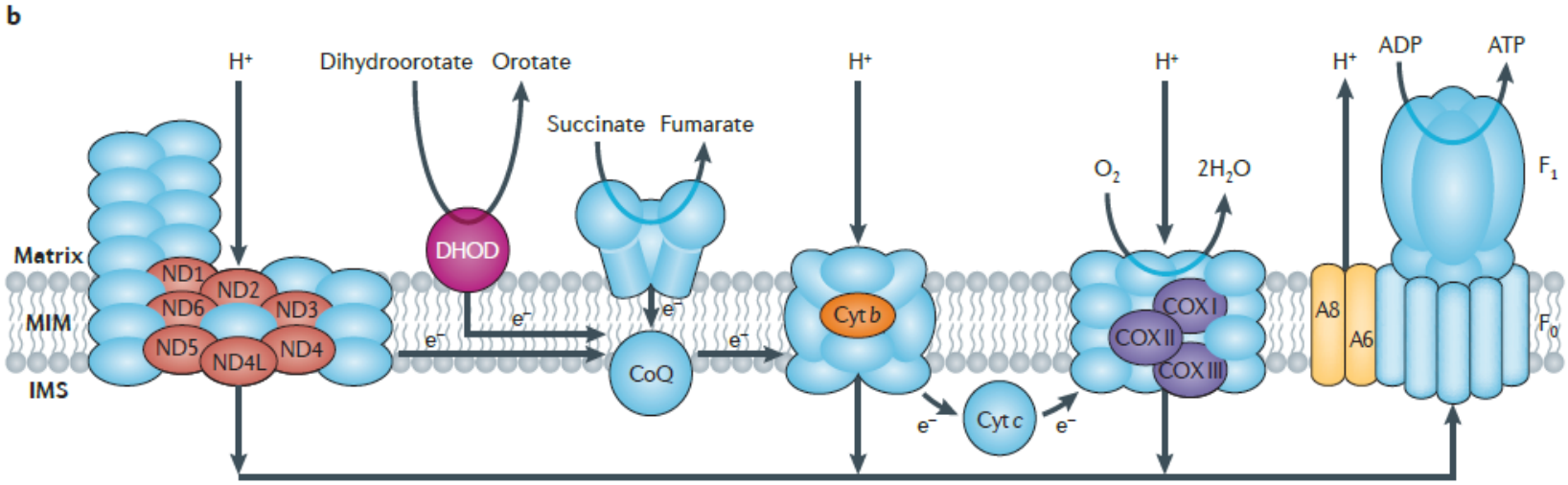
(3) Intellectual and motor developmental delay/regression/arrest

(4) Abnormal energy metabolism indicated by:

- Severe defect in OXPHOS or PDHc activity,
- Elevated serum or CSF lactate
  - Molecular diagnosis in a gene related to mitochondrial energy generation

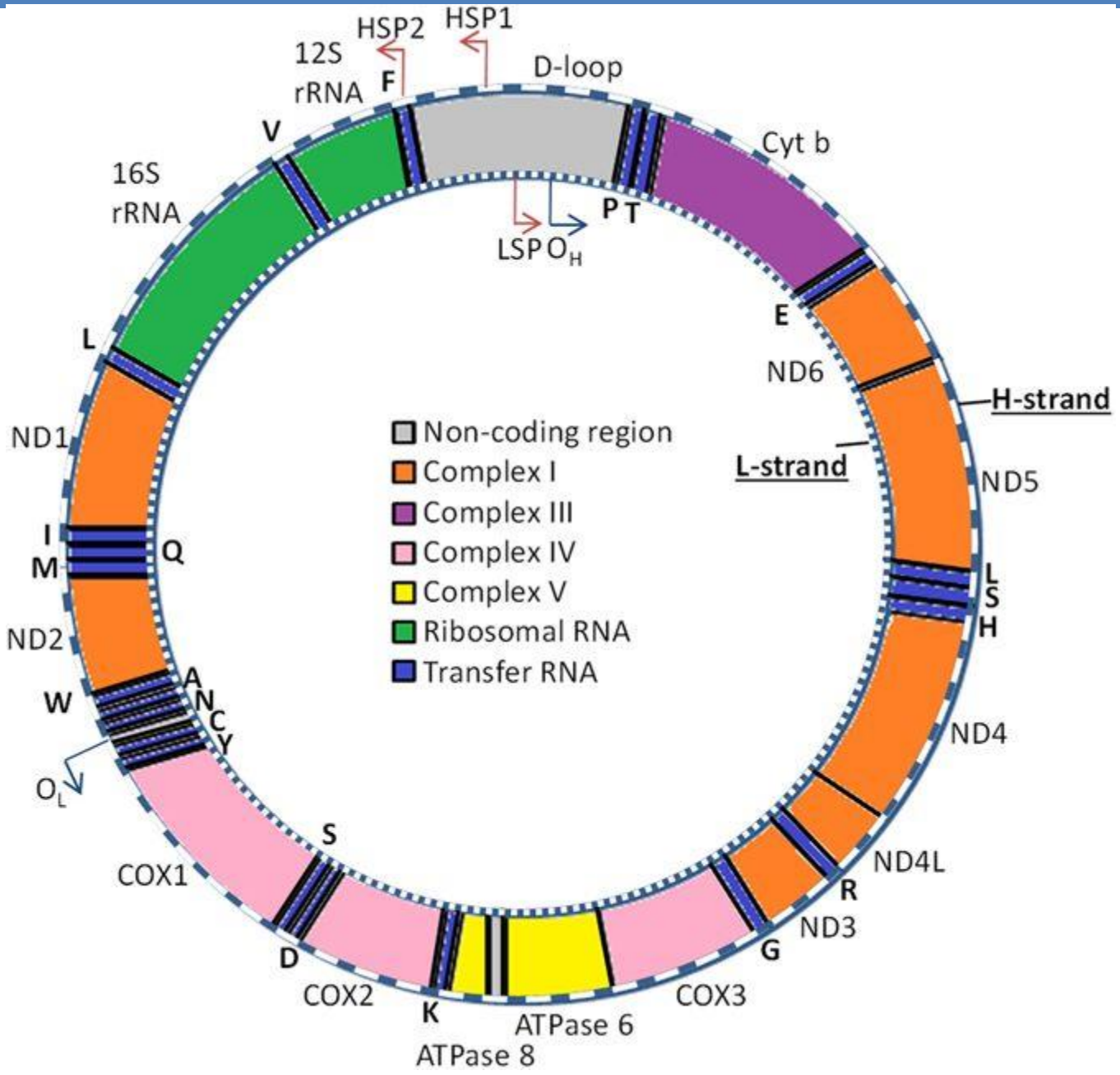
*Rahman 1996*

*Sofou, 2015; Lake NJ, 2016*

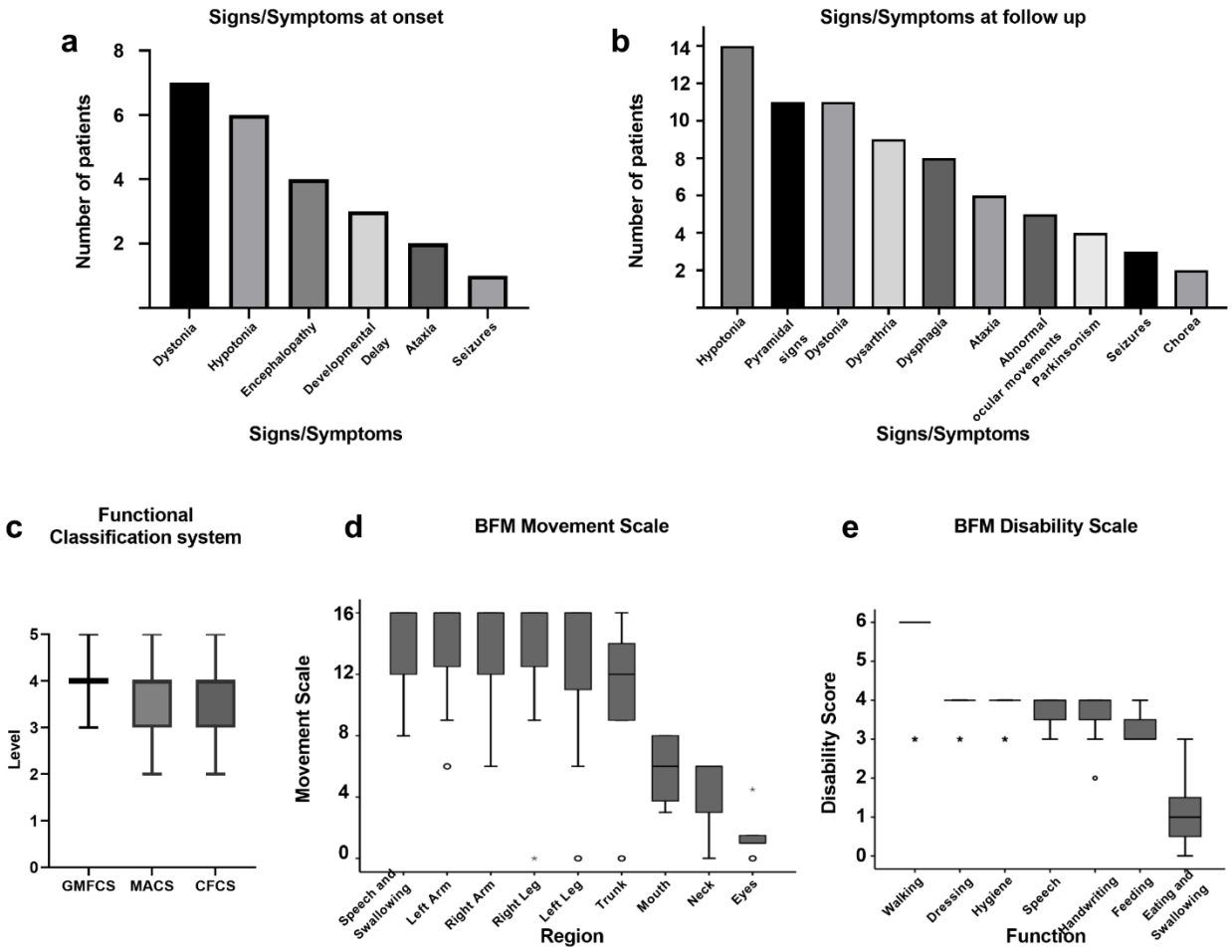



| Polipeptidos | Complejo I | II | III | IV | V |
|---|---|---|---|---|---|
| mtDNA | 7 | 0 | 1 | 3 | 2 |
| nDNA | 44 | 4 | 10 | 10 | 14 |

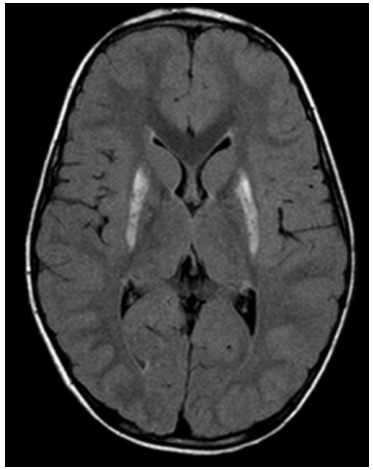
Schon, E. A., DiMauro, S., & Hirano, M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nature Reviews Genetics, 13(12), 878–890. doi:10.1038/nrg3275

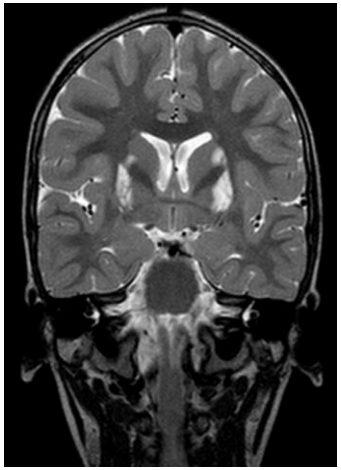

HSP2
HSP1
12S
rRNA
F
D-loop
V
Cyt b
16S
rRNA
P
T
LSP
$O_H$
E
L
ND6
H-strand
ND1
L-strand
ND5
Non-coding region
Complex I
Complex III
Complex IV
Complex V
Ribosomal RNA
Transfer RNA
I
M
Q
L
S
H
ND2
A
W
N
C
Y
ND4
$O_L$
S
ND4L
COX1
R
ND3
D
G
COX2
K
COX3
ATPase 6
ATPase 8

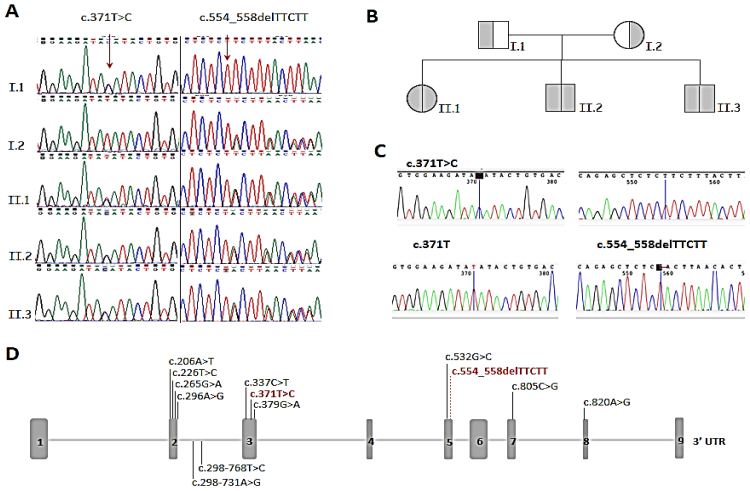
# 16 Leigh syndrome patients showed severe impairment of mobility, manual ability, and communication, as well as severe dystonia.



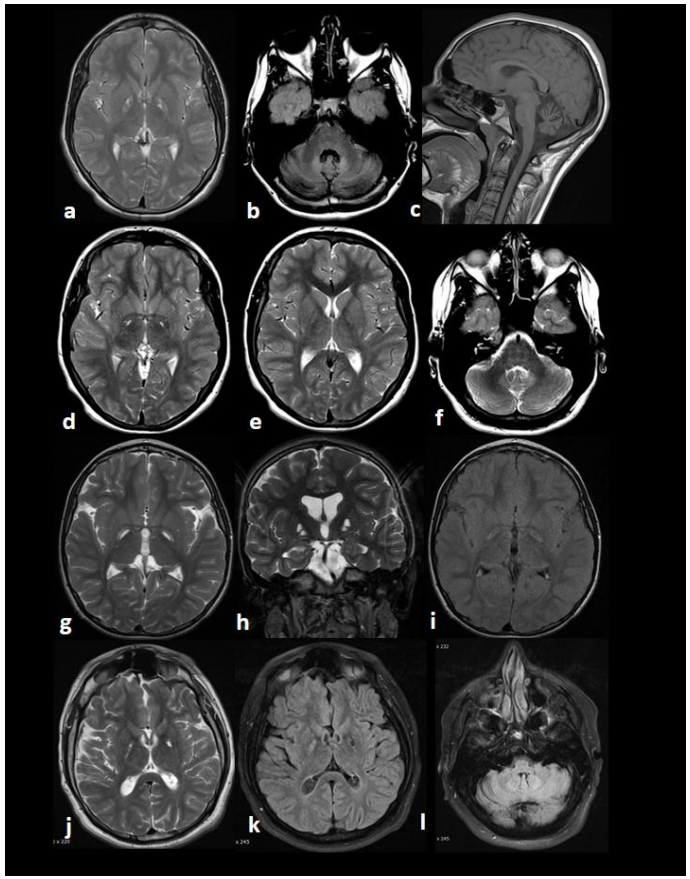
# *NDUFAF6*: Complex I deficiency



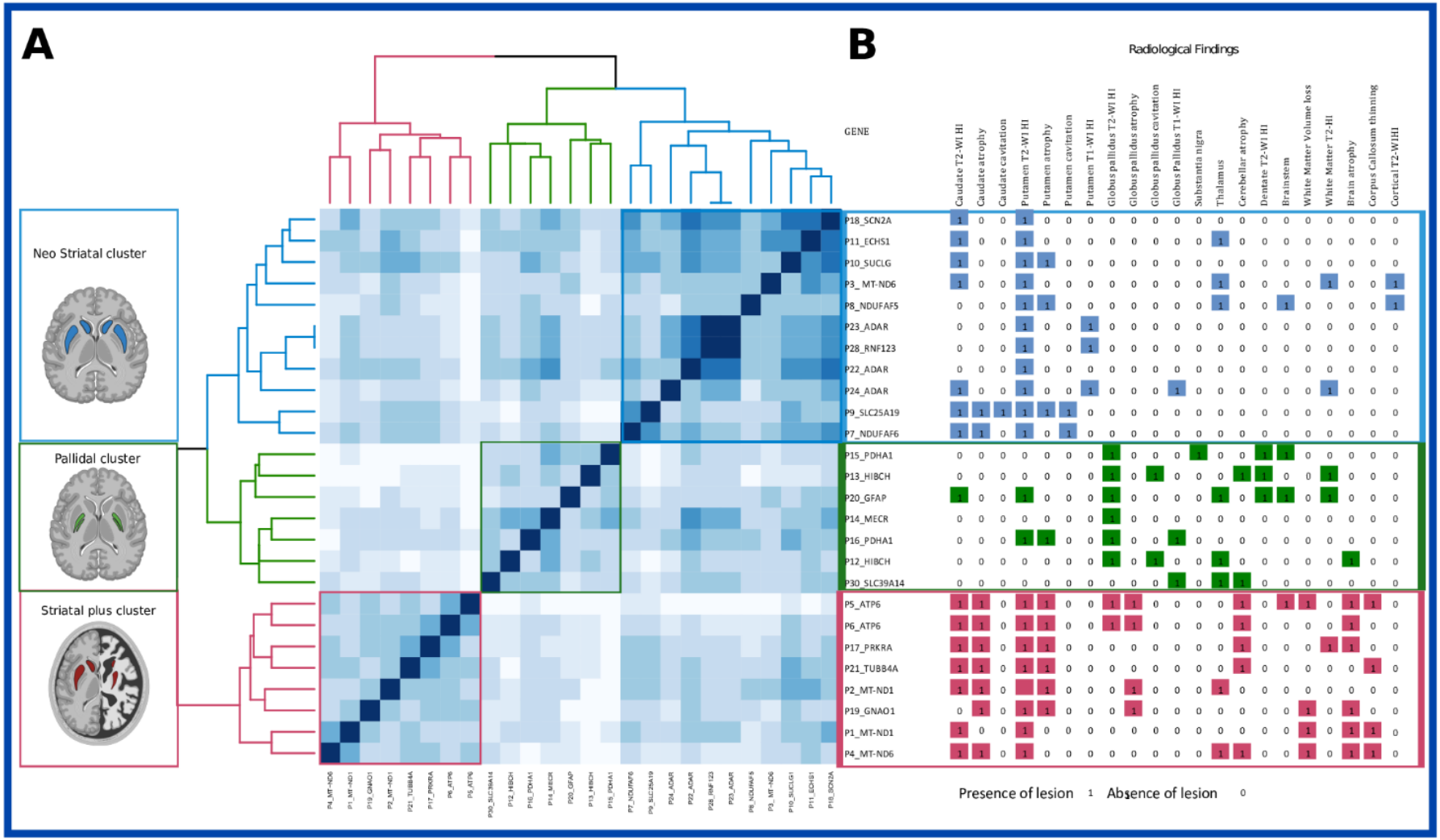




## *ECHS1 and HIBCH*: Valine metabolism

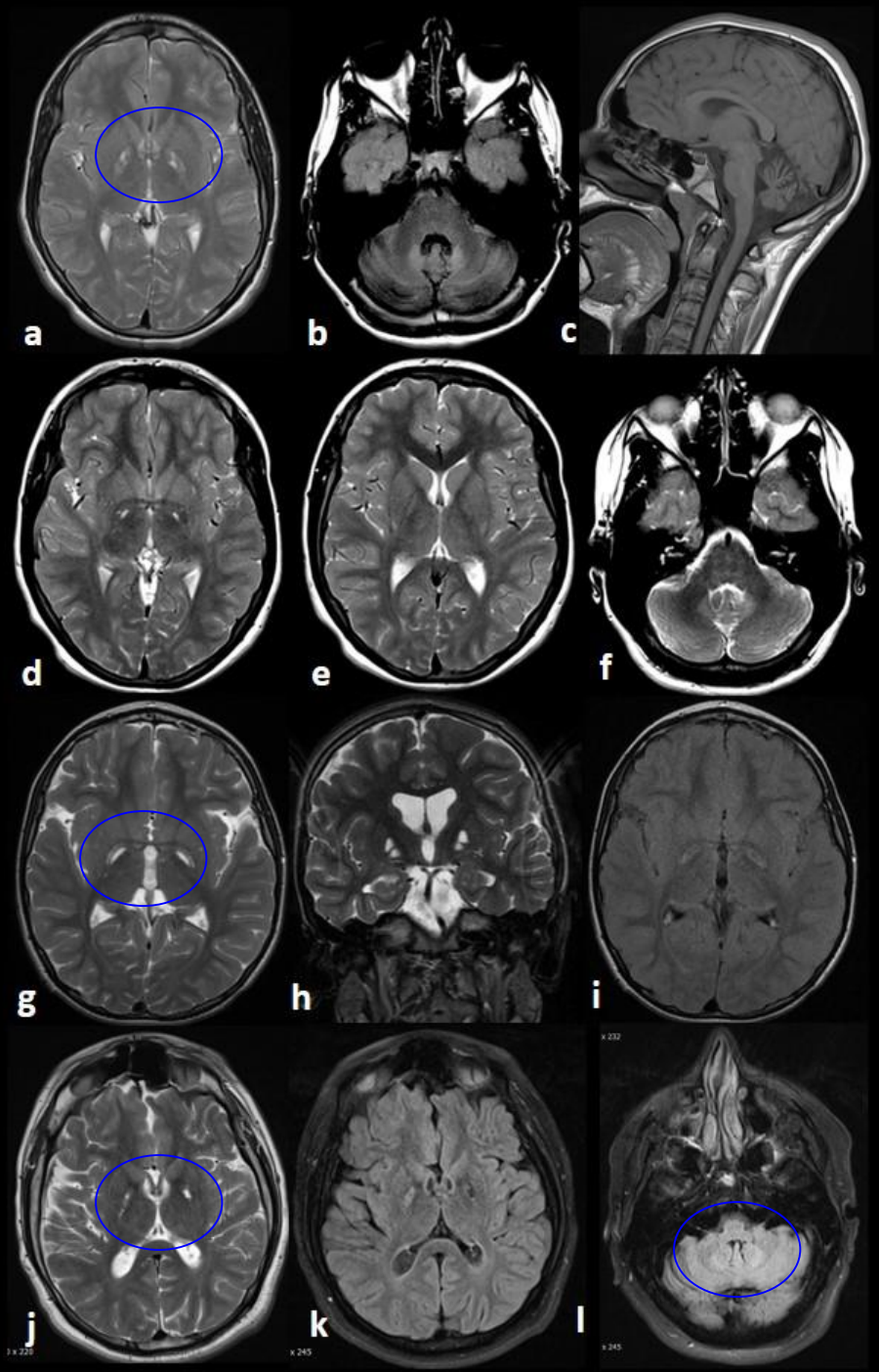


In 26 patients with MRI BBG lesions and genetic confirmation, hierarchical clustering analysis, an agglomerative approach for combining groups, was performed to search for phenotype–genotype associations.



# HIBCH

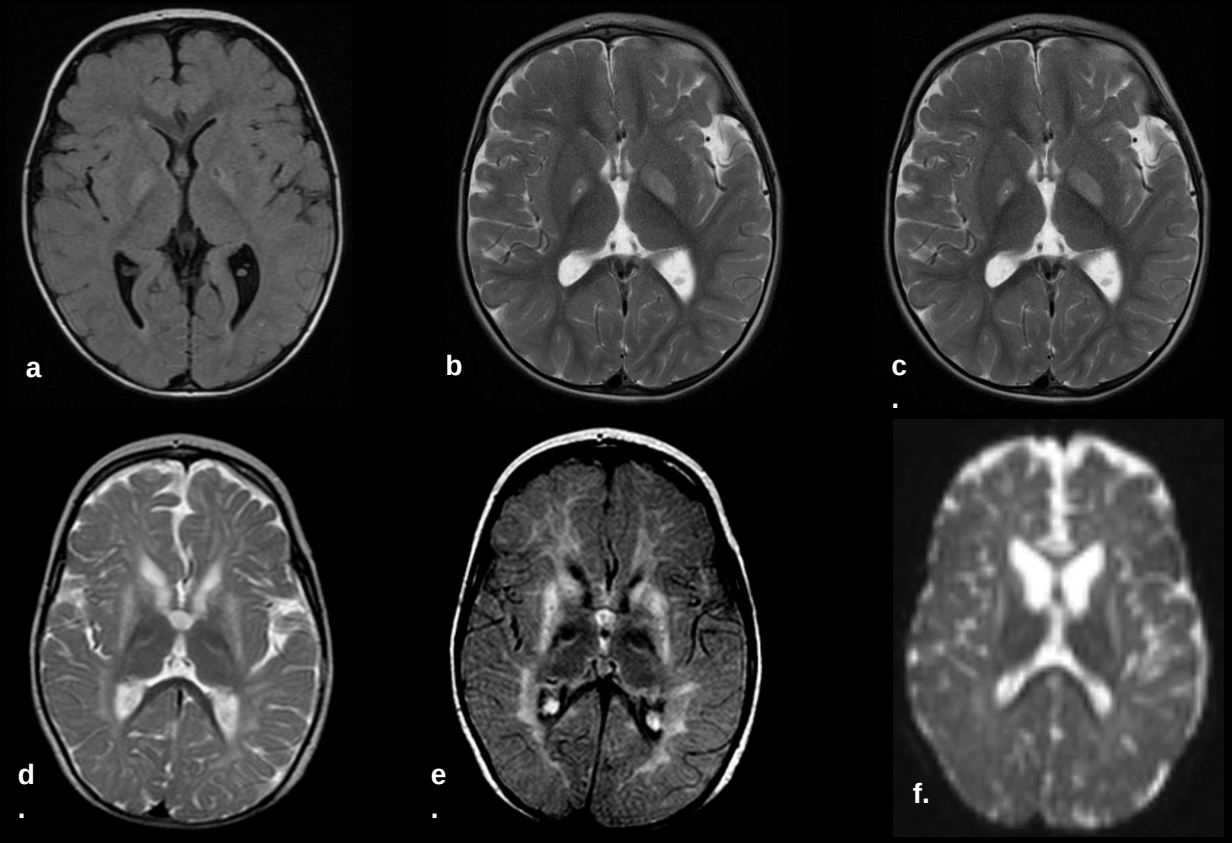
Caudate lesion: 1 / 5
Putamen 3 / 5
Pallidum 5 /5  (GP cavitation: 3 / 5)
Dentate T2 hyperintensities 3/5




STRIATAL NECROSIS
Related to mitocondrial metabolism

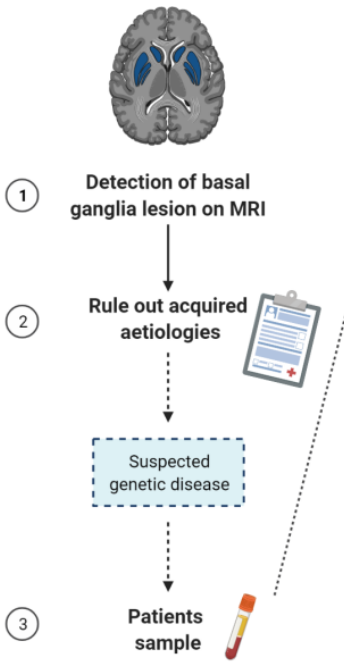
# ECHS1

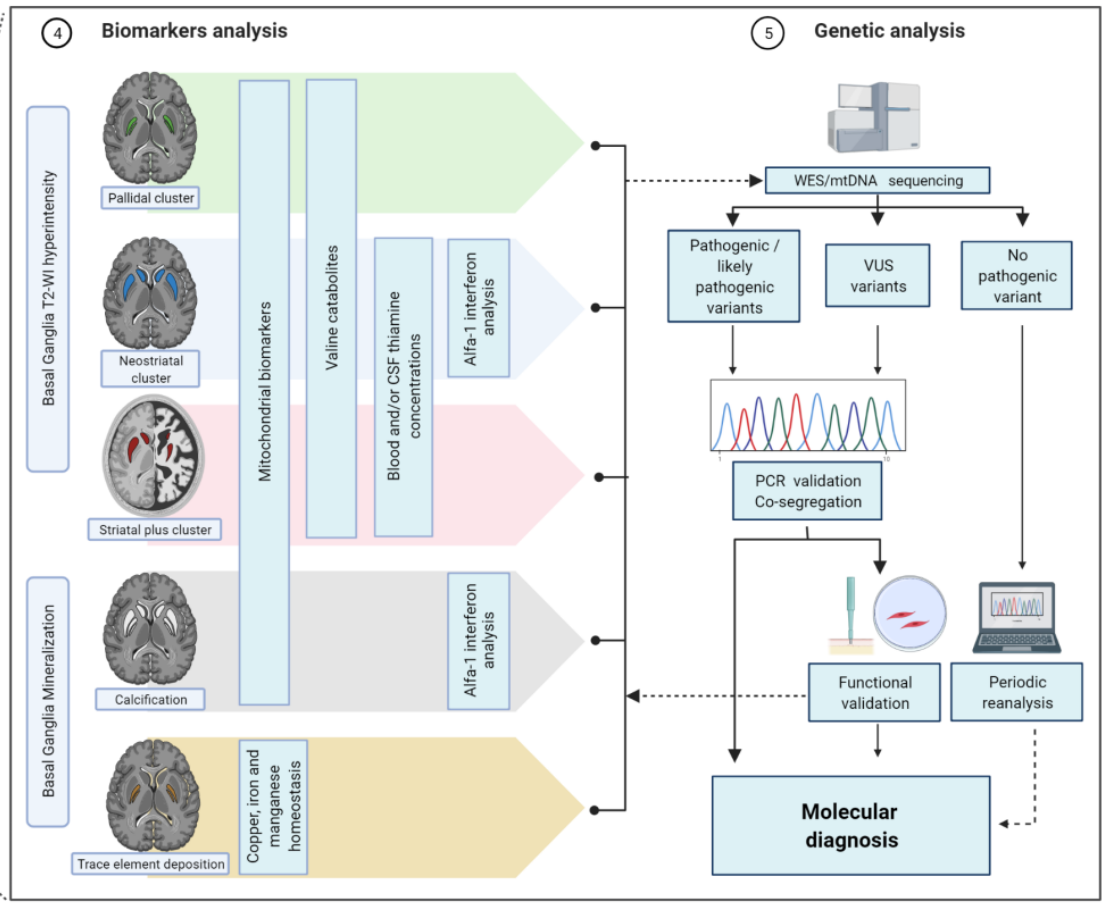
Caudate 6/9
Putamen 6/9
GP 3/9



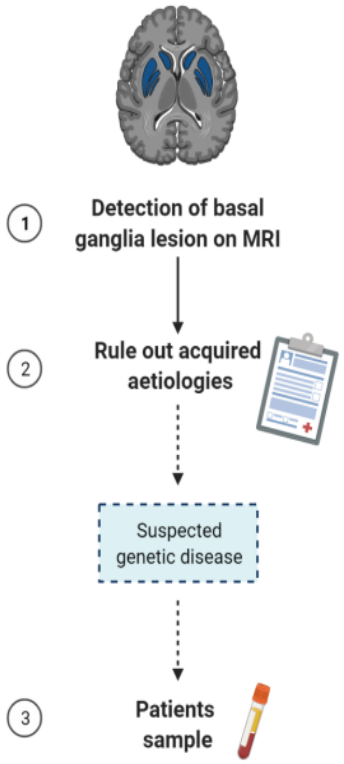

STRIATAL NECROSIS
Related to mitocondrial metabolism

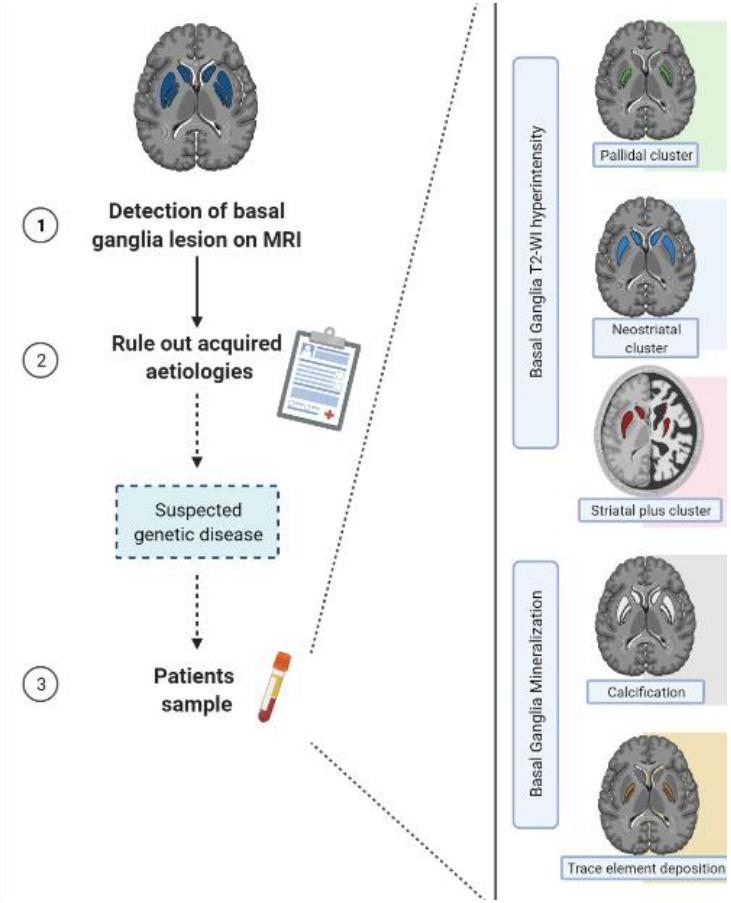
# Which is the best approach to diagnosis of basal ganglia lesions in childhood?

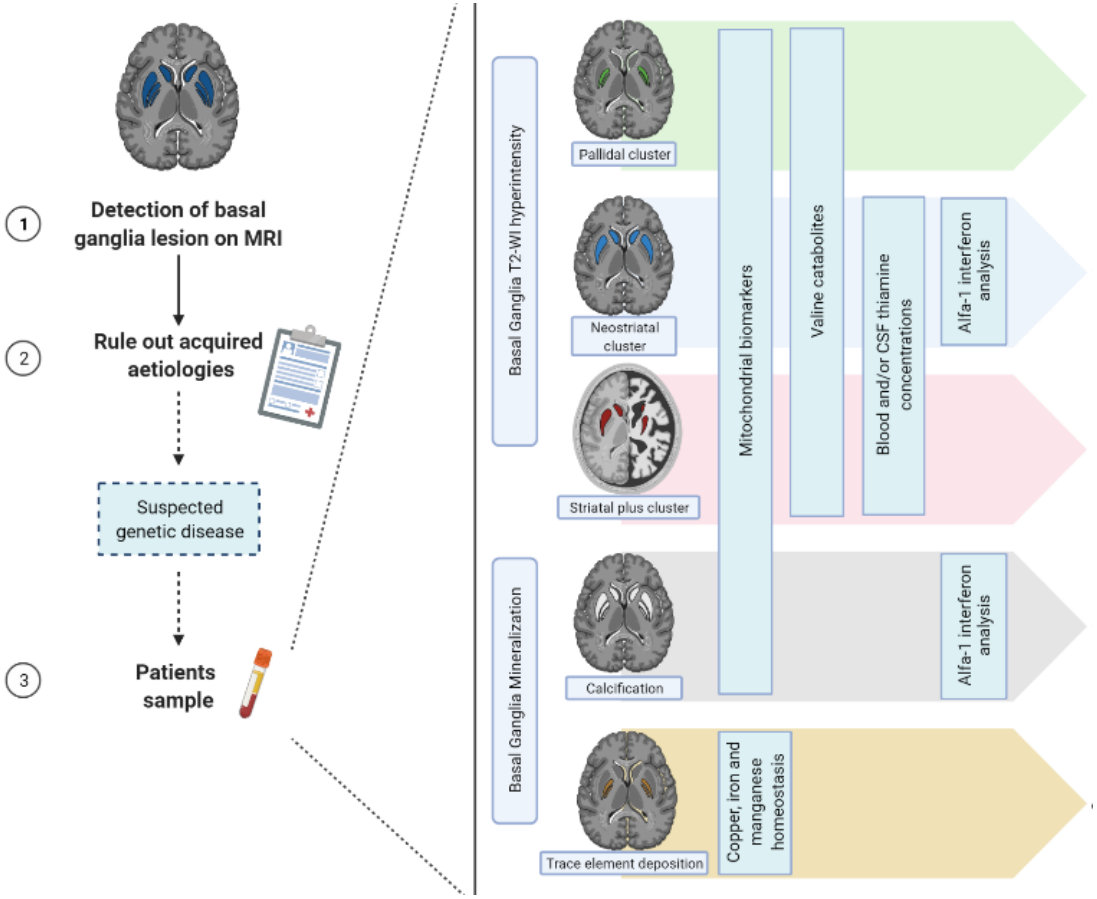


# Diagnosis approach to basal ganglia lesions in childhood




1
Detection of basal ganglia lesion on MRI
2
Rule out acquired aetiologies
Suspected genetic disease
3
Patients sample
Basal Ganglia T2-WI hyperintensity
Pallidal cluster
Neostriatal cluster
Striatal plus cluster
Basal Ganglia Mineralization
Calcification
Trace element deposition




## Low sensitivity and specificity for mitochondrial biomarkers:

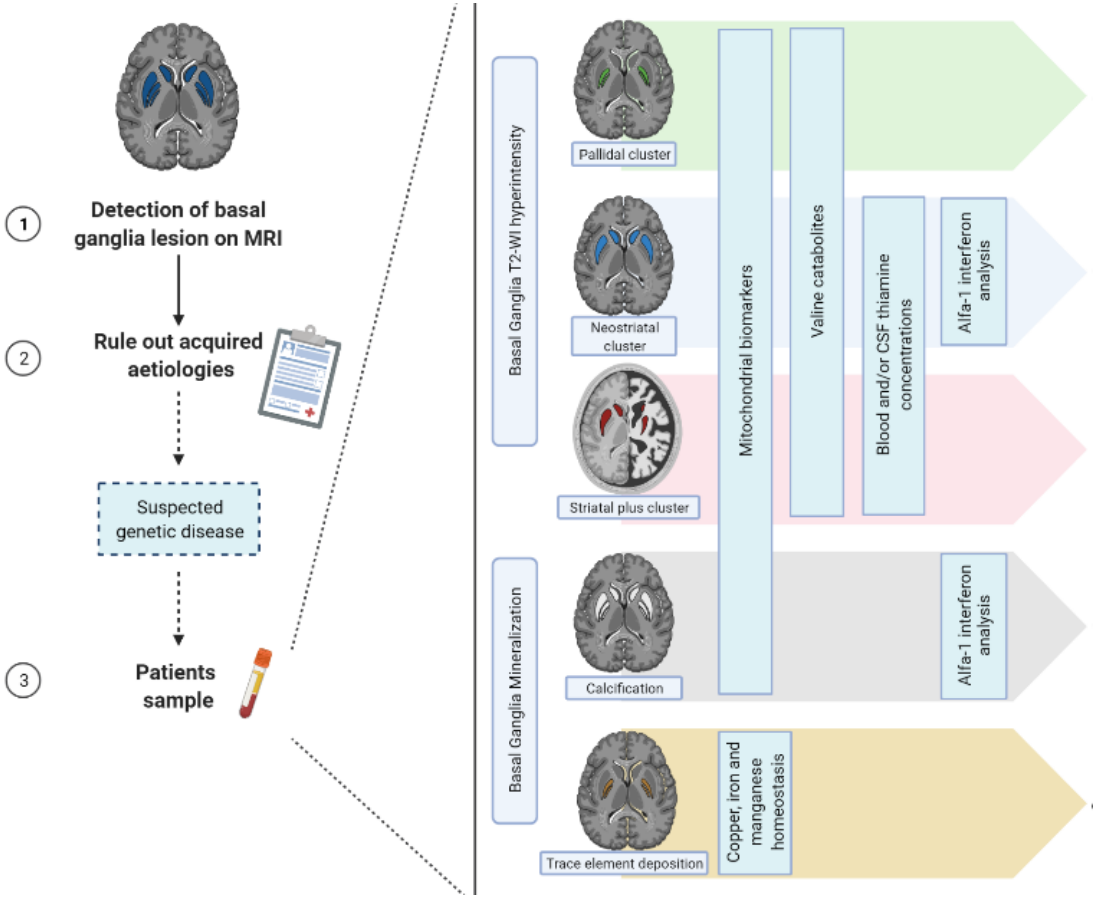
- High lactate in patients with mitochondrial (9/16) and non-mitochondrial (6/16) diseases

- Complex I deficiency decreased in 3 patients with NDUFAF6, MT-ND1, MT-ND6 but normal in 3 more (MT-ND1, MT-ND6,NDUFAF5).

- Combined RCC deficiencies in 5/12 patients with mitochondrial defects, and other genetic (ADAR-related AGS) or acquired aetiologies (EIEE).

# RESPIRATORY CHAIN DEFICIENCIES

| mutation | | | Clinical characteristics | MRI | MCD | RCC analysis (muscle) | |
|---|---|---|---|---|---|---|---|
| NDUFAF6 | LS | 2,5y | Dystonia | ↑T2: Putamen & caudate | 5 | ↓CI muscle | Normal |
| 3697G>A 90% ***MT-ND1*** | LS | 3 years | Dystonia | Striatal Necrosis | 6 | NORMAL | ↑Lactate MRS |
| m.3700G>A 99% ***MT-ND1*** | LS | 30 M | Dystonia | Striatal Necrosis | 5 | ↓CI muscle | Normal |
| 14459G>A 93% ***MT-ND6*** | LS | Neonatal | IUGR, epilepsy, MELAS | Striatal Necrosis, Stroke like frontal white matter lesions | 5 | NORMAL | Normal |
| 14487T>C 72% ***MT-ND6*** | LS | 7 years | Dystonia-parkinsonism, myoclonic epilepsy, optic neuropathy | Striatal Necrosis, brain atrophy | 8 | ↓CI muscle | Normal |
| 9176T>C 98% ***MT-ATP6*** | LS | 8 months | Intermittent ptosis, developmental delay, epilepsy, ataxia | Striatal Necrosis, cerebellar atrophy | 10 | NORMAL | ↑ Lactate and alanine |
| 9191T>C 98% ***MT-ATP6*** | LS | 4 months | Hypotonia and bradikinesia | Striatal Necrosis | 5 | NORMAL | Normal |

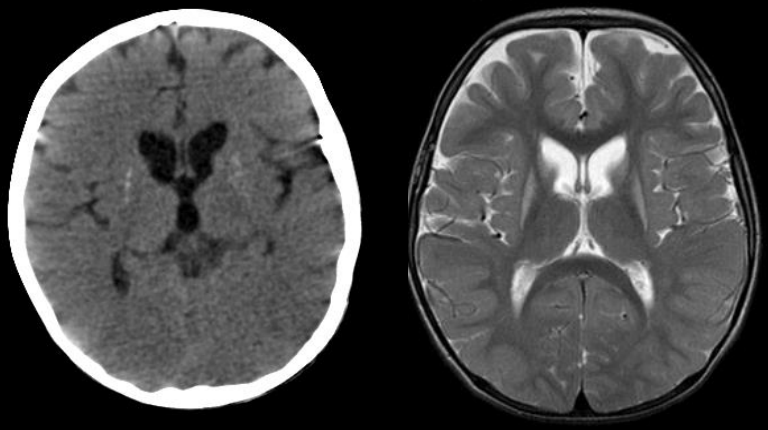



## Basal Ganglia calcifications:

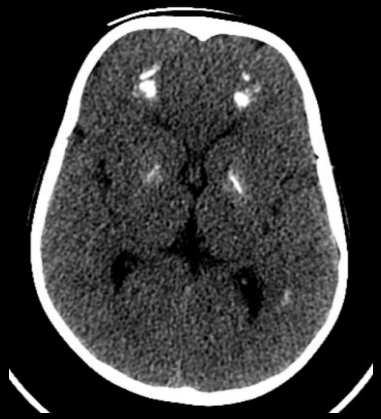
- Patients with IFIH1, ADAR, and RNASEHB-related AGS showed elevated CSF pterins (3/3) and an abnormal interferon signature (4/4).

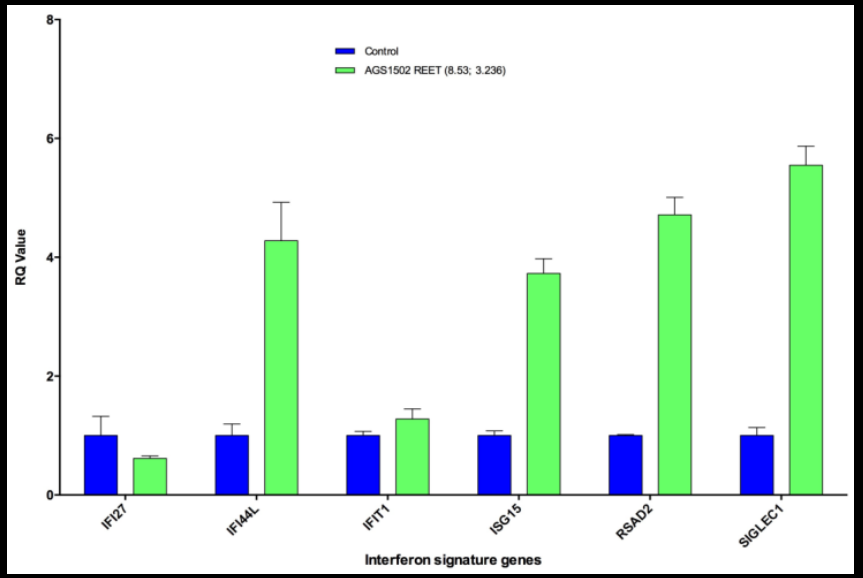
## Aicardi- Goutières Syndrome (AGS)

### ADAR1



### IFHI1

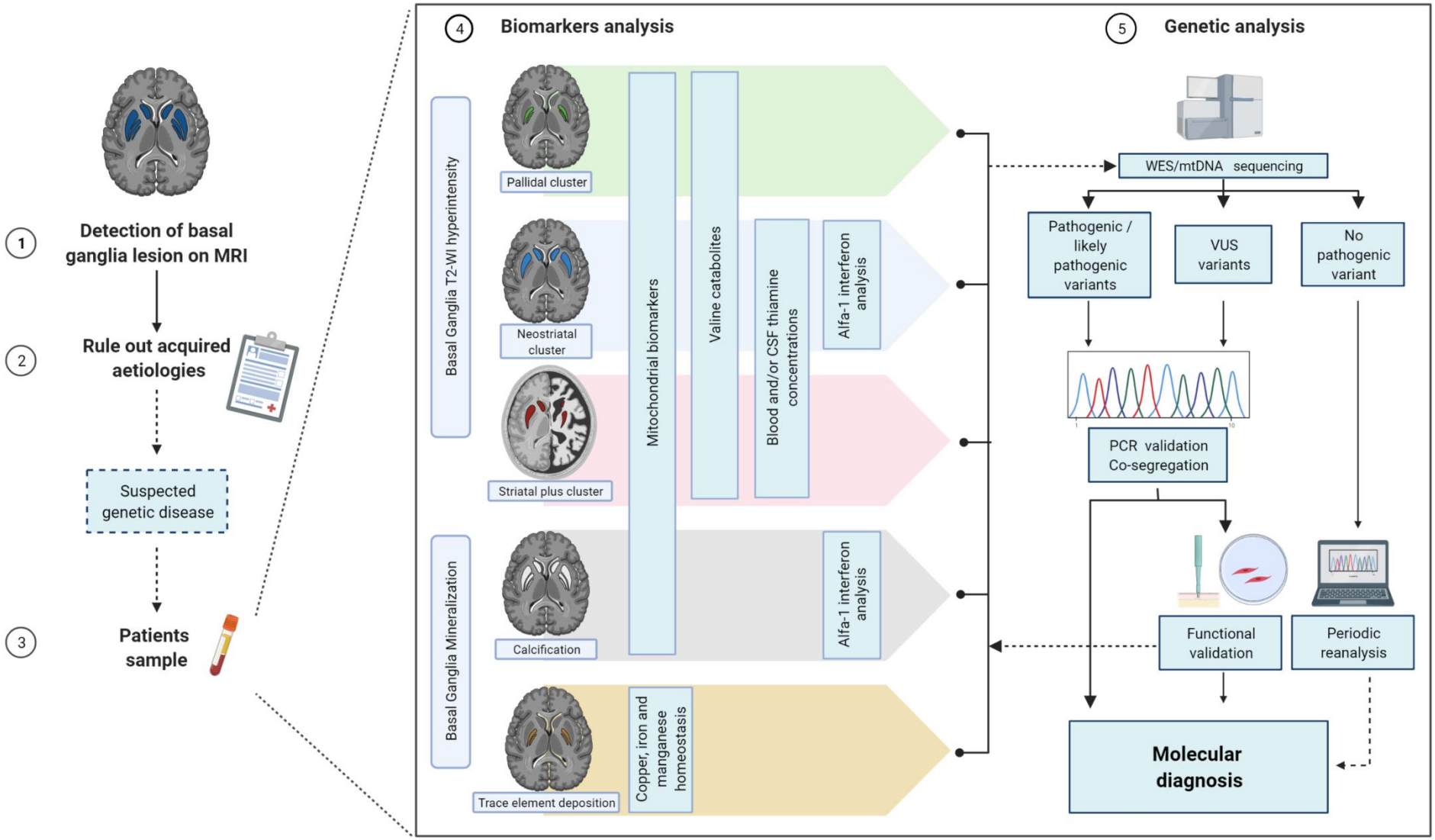





INTERFERON SIGNATURE IS A RELIABE BIOMARKER FOR AICARDI GOUTIERES PATIENTS

BASAL GANGLIA CALCIFICATION

# Diagnosis approach to basal ganglia lesions in childhood



# What this paper adds?

01 Combined exome-mitochondrial DNA sequencing achieved a higher rate of diagnosis in childhood basal ganglia diseases than panel tests.

02 Mitochondrial diseases and Aicardi–Goutières syndrome were the most frequent aetiologies.

03 Division of radiological findings into clusters could guide biomarker and genetic investigations.

04 The interferon signature was a good biomarker for children with basal ganglia calcifications of unknown cause.

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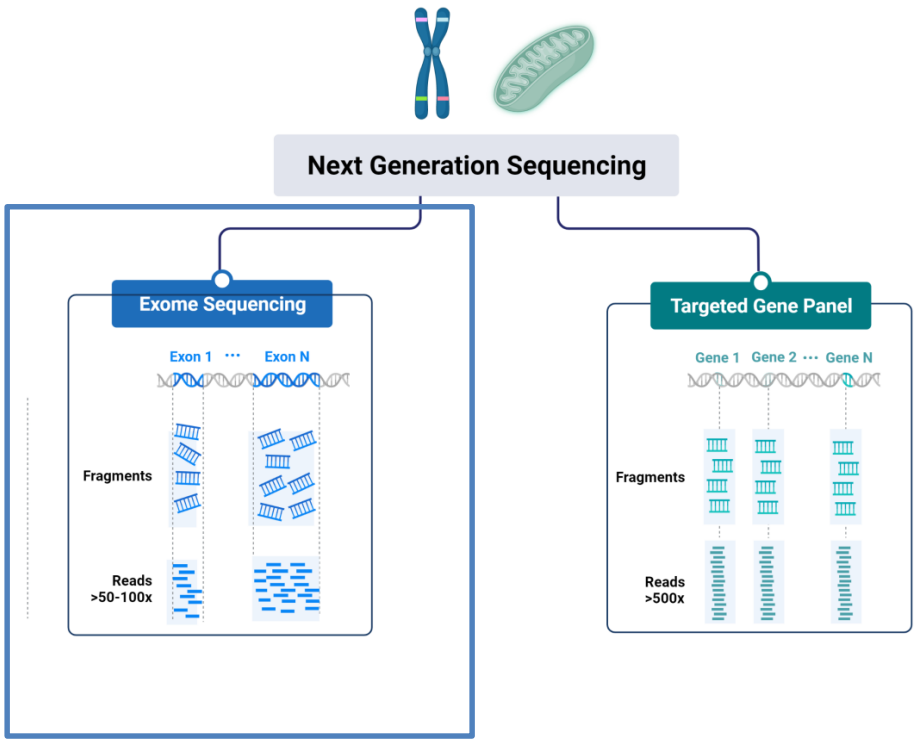
The molecular diagnosis rate was increased from panels (33%) toith custom panels to 41% with WES.




Diagnosis Rate:

Panels 33% → WES 41% → mtDNA 48%

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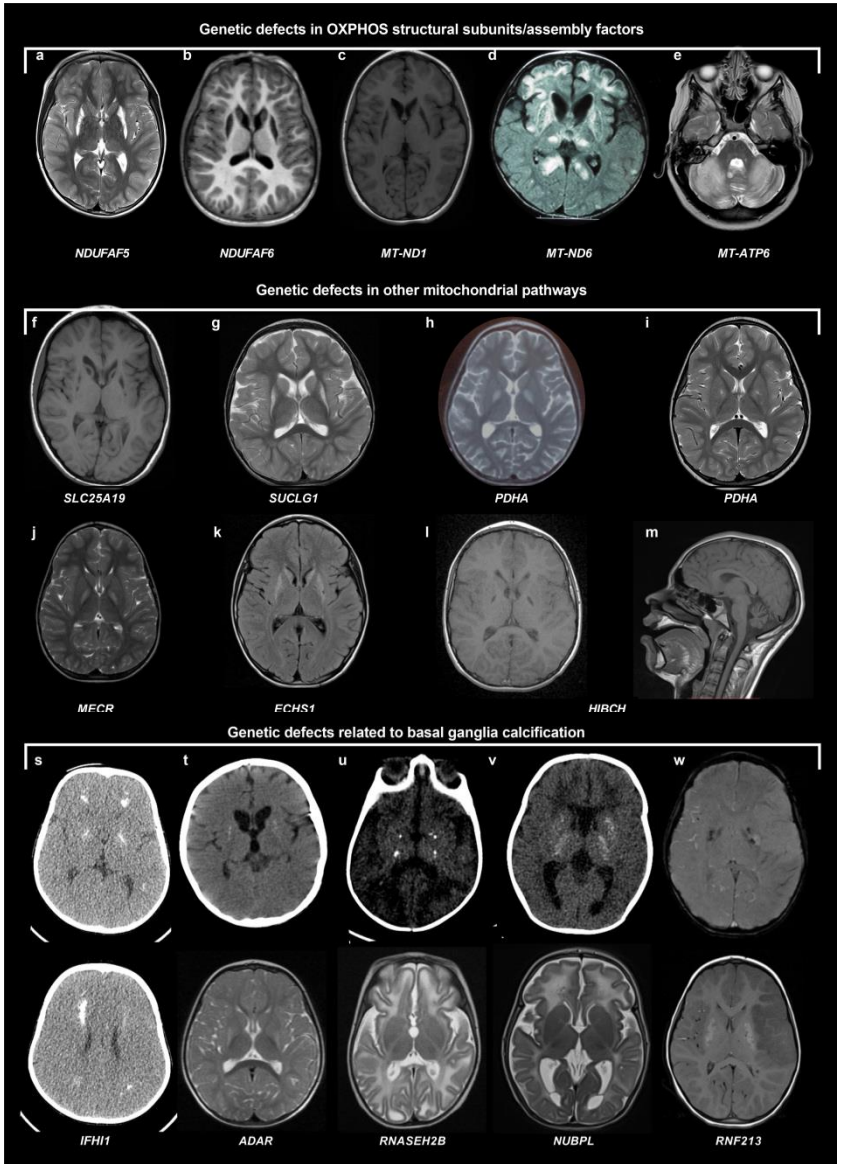

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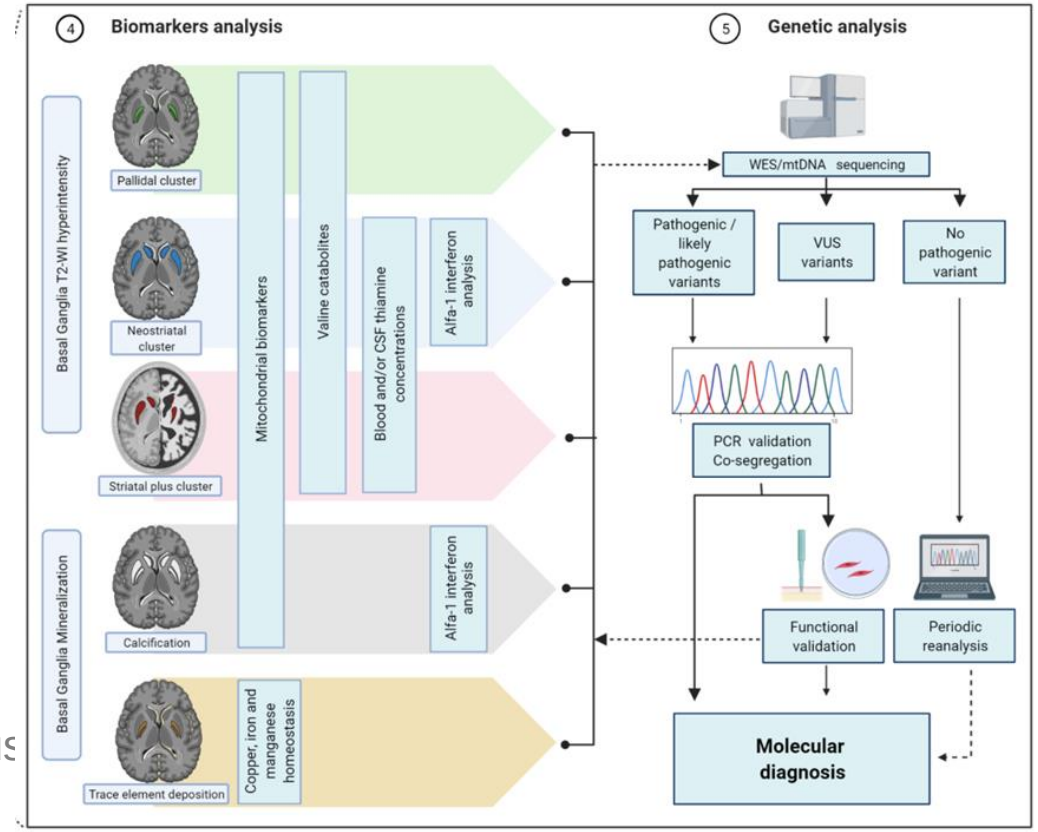

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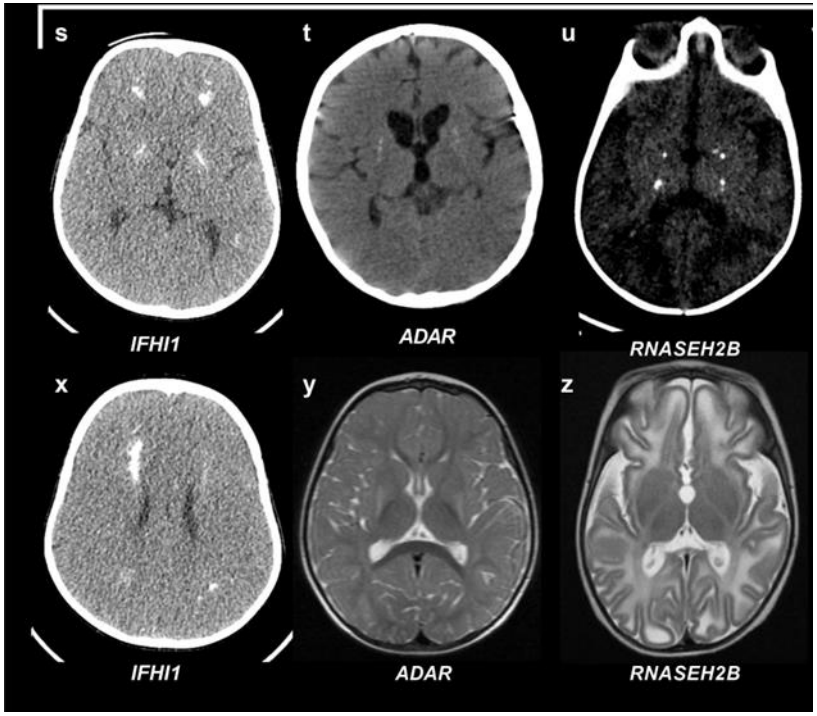

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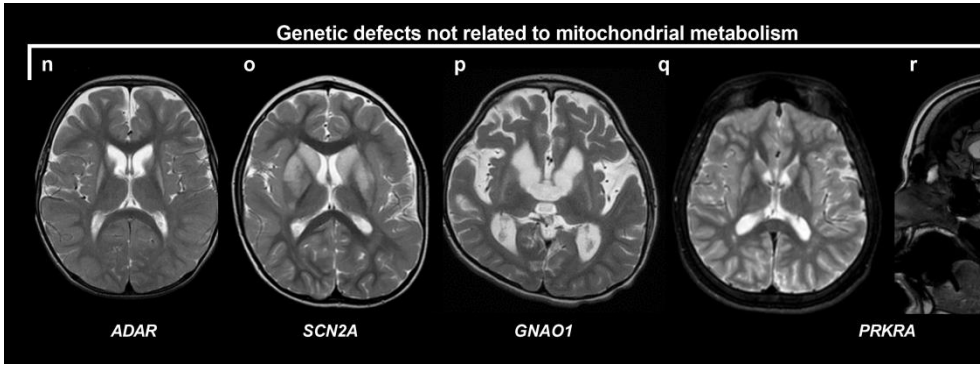


05

Mitochondrial biomarkers such as lactate and respiratory chain complex activities showed poor sensitivity and specificity for mitochondrial disease.

# Network and funding

H Baide
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