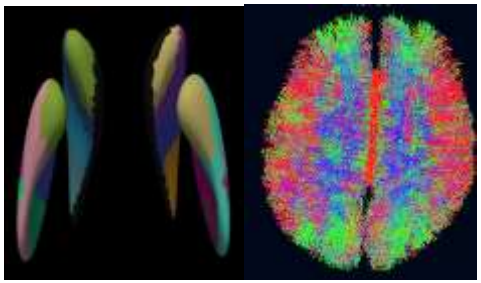
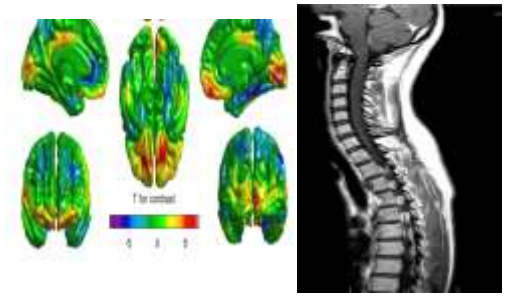


Expert center for
Parkinson's disease



Expert center for
Amyotrophic lateral sclerosis

Centre de compétence maladies
neurogénétiques

Ataxies spinocérébelleuses héréditaires

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Lille Neuroscience & Cognition

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

CHU LILLE

Un syndrome cérébelleux + un arbre généalogique

I – Symptômes : interrogatoire un changement dans l'équilibre +++

Troubles de l'équilibre. Monter sur une chaise ? Chutes parfois
Troubles de la coordination Maladresse dans les mouvements rapides – Dysarthrie

II – Signes cliniques

1.Troubles de l'équilibre lors de la marche : ATAXIE CEREBELLEUSE

Elargissement du polygone de sustentation « danse des tendons » La démarche est pseudo ébrieuse
Dans les formes mineures: **marche en tandem**, lors de l'arrêt brusque de la marche, lors du demi tour décomposé

2. Troubles de l'exécution du mouvement volontaire rapide

Hypermétrie. +++. manœuvres doigt-nez (ou doigt/lobule de l'oreille) et talon/genou, sur le malade allongé. La consigne doit être d'exécuter le mouvement le plus rapide possible
Asynergie. absence de décollement du talon dans la position accroupie.
Le tremblement d'action, ou intentionnel, est inconstant. manœuvre doigt-nez est surtout net au début et à la fin du mouvement volontaire. Il est souvent associé à un tremblement d'attitude.
NB : Les signes cérébelleux sont ipsilatéraux à la lésion

3. Hypotonie

Augmentation de l'amplitude des mouvements imprimés aux membres, réflexes rotuliens pendulaires

4. Troubles de la parole et de l'écriture

Dysarthrie cérébelleuse : la parole est typiquement scandée et explosive

5. Un nystagmus

multidirectionnel et mouvements oculaires saccades

6. Troubles cognitifs et comportementaux

III – Diagnostic différentiel

- Vertige ORL, ataxie proprioceptive - ataxie frontale - ataxie vestibulaire
- Psychiatrique, conditions sociales défavorables

Multiples étiologies des ataxies cérébelleuses : hétérogénéité phénotypique

Causes dégénératives: atrophie multisystématisée

Causes secondaires
Malformations, tumeurs, accidents vasculaires
Maladies démyélinisantes
Causes métaboliques et endocriniennes
Causes médicamenteuses et toxiques
Dégénérescence cérébelleuse paranéoplasique
Causes infectieuses ou transmissibles
Atraxie cérébelleuse GAD+ et dysimmunitaire

Etiologies indéterminées

Etiologies génétiques

Etiologies sporadiques

Ataxies cérébelleuses

Etiologies familiales héréditaires

Formes récessives
Maladie de Friedreich
Ataxie avec déficit en Vitamine E
Ataxie télangiectasie
Ataxie avec apraxie oculomotrice
Ataxie avec neuropathie axonale
Abetalipoproteinemie
Maladie de Refsum
Maladie de Wilson

Formes autosomiques dominantes
Ataxies épisodiques
SCAs
ADRLP

Formes à transmission variable
Epilepsies myocloniques progressives

Formes mitochondriales
Mitochondriopathies

Table 1. Acute Ataxias in Which Symptoms Appear Suddenly or in a Few Days.

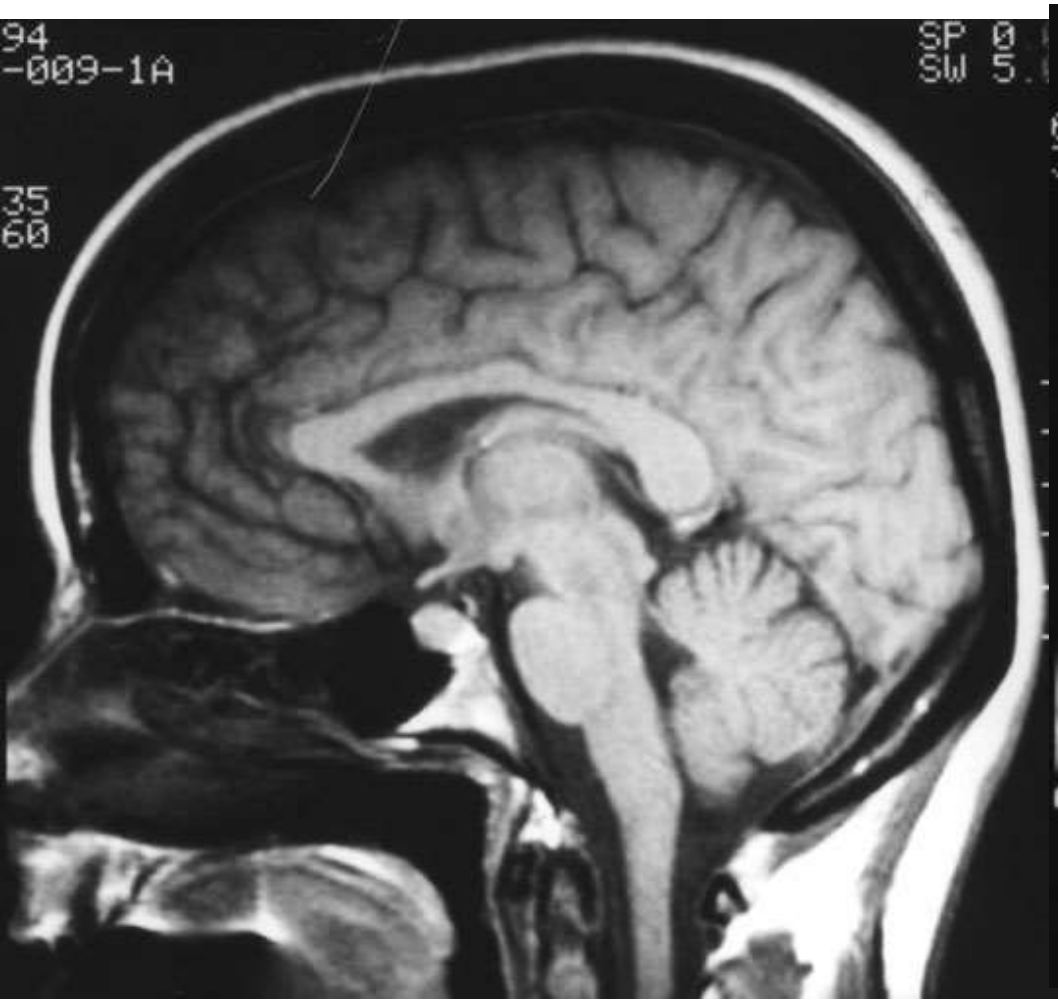
Diagnosis	Evaluation and Findings	Initial Treatment
Alcohol consumption	History of alcohol abuse, increased liver-enzyme levels	Alcohol withdrawal, vitamin B_1 supplementation
Vitamin B_1 deficiency	Serum vitamin B_1 deficiency	Vitamin B_1 supplementation
Drugs (carbamazepine, phenytoin, phenobarbital, lithium, fluorouracil, cytarabine, metronidazole, amiodarone)	History of treatment, abnormally elevated serum level (if applicable)	Drug withdrawal, vitamin B_1 supplementation as therapy or as prevention (if fluorouracil received)
Toxic agents (mercury, thallium, organolead, toluene, solvents, pesticides)	History of intoxication	Immediate cessation of exposure
Ischemic or hemorrhagic cerebellar stroke	Brain MRI	Admission to a stroke unit
Relapse of multiple sclerosis	Brain MRI	Glucocorticoids
Basilar meningitis (due to tuberculosis or listeriosis)	Brain MRI, cerebrospinal fluid examination on direct microscopy	Antibiotics
Cerebellitis (due to varicella–zoster virus infection, rubeola, influenza, JC virus infection, pertussis)	Brain MRI and cerebrospinal fluid examination to detect lymphocytic pleocytosis, serologic tests for viruses	Acyclovir (for varicella–zoster virus)
Cerebellar abscess	Brain MRI	Antibiotics, surgical drainage

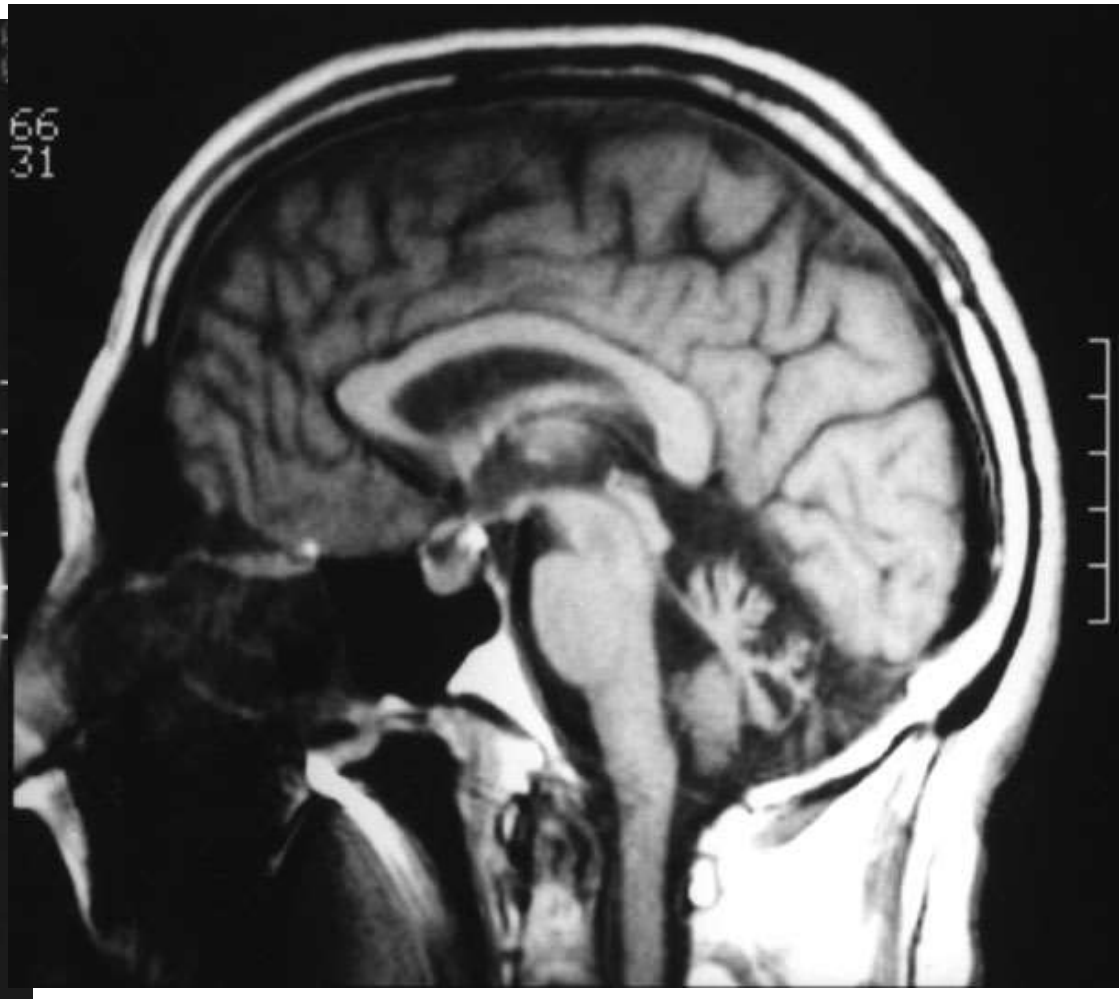
Ataxies dysimmunitaires

- Maladie coeliaque ou enteropathie sensible au gluten
  - Affection dysimmunitaire déclenchée par l'ingestion de gluten, HLA DQ2
  - Manifestations digestives: absentes dans 1/3 cas, Σ malabsorption rare
  - Manifestations neurologiques (10 %) parfois isolées
    - » Ataxie cérébelleuse d'évolution lente avec atrophie cérébelleuse (30%), hypersinaux SB (20%)
    - » Neuropathies axonales (sensitivo-motrice, motrices pures, végétatives, multinévrites)
    - » Démence, Σ frontal, ± troubles psychiatriques, épilepsie avec calcifications occipitales
    - » Myoclonies, myélopathie, myopathie, (rarement: Stiff man Σ, méningite chronique)
    - » LCR normal, TT: régime sans gluten
    - » AC antigliadine, endomysium, transglutaminase, +/- Biopsie duodénale (M. coeliaque)
  - Manifestations systémiques: cutanées, ostéoarticulaires, endocriniennes, hématologiques (lymphome)

- Atrophie cérébelleuse GAD + (Honnorat 1995, série de 15 cas)
  - GAD = glutamic acid decarboxylase décrit dans Stiff man Σ et dans diabète insulinodépendant
  - Action de decarboxylation du glutamate en GABA
  - Femme d'âge moyen, début insidieux
  - Syndrome cérébelleux vermien avec ataxie, dysarthrie constante et nystagmus fréquent (85%)
  - Association fréquente à un diabète et/ou autre maladie auto-immune ? (tx 5 fois supérieur au diabète)
  - Atrophie cérébelleuse pure en IRM
  - Bandes oligoclonales dans LCR
  - anti GAD (Ataxie GAD +)

Examens paracliniques d’atteinte et de diagnostic differentiel





Examens paracliniques d’orientation étiologique:

Neurophtalmologie, EMG, biologie

Ataxie héréditaires: Ordre et chaos

ETAT DES CONNAISSANCES		AVANCEES MAJEURES
XIXè siècle: Description des pionners	→	Reconnaissance des ataxies héréditaires par Friedreich, Marie
Début XX siècle: Chaos diagnostic	→	Observation de variations cliniques, pléthore de catégories cliniques
1980: Simplification nosologique	→	Classification clinique d'Harding
1990: Classification génétique	→	Découverte des étiologies génétiques Gènes: SCA1,2,3,6,7,10,12,14,17,EA1,2,FGF14 Loci: SCA4,5,11,1315,16,18,19,21,22,23,24,25 Mais: ≠ mutations → même phénotype 1 mutation → plusieurs phénotypes Donc intérêt clinique limité
2000: Classification pathogénétique	→	Etude de pathogénie et traitements ?

Classification pathogénétique des ataxies héréditaires

- **Mitochondrial**
  - **ADN nucléaire : Ataxie de Friedreich**
  - **ADN mitochondrial :**
    - » **MERRF**
    - » **NARP (NP, atax, retino pig)**
    - » **Kearns-Sayre S**
- **Métabolique**
  - **Trouble du cycle de l'urée**
  - **Trouble des acides aminés**
  - **Anomalie du pyruvate**
  - **Anomalie de la vitamine E**
  - **Troubles des lipides**
  - **Maladies de surcharge**
  - **Maladies peroxysomales**
- **Défaut de réparation de l'ADN**
  - **Ataxie télangiectasie**
  - **Ataxie avec apraxie oculomotrice 1 et 2**
  - **Ataxie SCA avec neuropathie axonale 1**
  - **Xeroderma pigmentosum**
  - **Syndrone de Cockayne**
- **Anomalies de conformation et de degradation protéique**
  - **Ataxie spastique autosomale recessive type Charlevoix-Saguenay**
  - **Trouble de la polyglutamine: SCA1,2,3,6,7,17,ADRLP)**
  - **Anomalie de la protéine prion: Gerstmann-Straussler-Sheinker**
- **Channelopathies**
  - **Ataxie épisodique type 1**
  - **Ataxie épisodique type 2**
- **Autres**
  - **SCA à expansion de triplets ou mutations ponctuelles: SCA 8, 10,12,14**
  - **SCA à loci identifiés: SCA 5,11,13,15,16,18,19,21,22,25**
  - **Congénitales: Joubert, CAMOS, syndrome de déficit glycoprotéique-carbohydrate type 1**
  - **SCA à début infantile**
  - **Early onset cerebellar ataxia with retained tendon reflexes (EOCA)**
  - **Ataxie cérébelleuse avec hypogonadisme**
  - **Ataxie myoclonique progressive**
  - **Syndrone de Marinesco-Sjögren**

Ataxies autosomales récessives

Ataxies de Freidreich

- La plus fréquente en Europe
- Gène FRDA 1 (9q13-21.1) code pour une protéine mitochondriale frataxine (FRDA 2)
- Maladie à expansion de trinucléotide GAA
  - » Patients homozygotes (corrélation inverse avec age de début)
  - » Quelques cas hétérozygotes composites (mutation ponctuelle sur l'autre allèle)
- Abandon des critères diagnostiques: âge de début avant 25 ans et aréflexie
- Les lésions médullaires : fx spinocérébelleux > cordonale post > pyramidal
- Diffusion aux nerfs périphériques au tronc cérébral et au cervelet
- Clinique: troubles de la marche
  - » Syndrome cérébelleux, statique et cinétique, dysarthrie
  - » S. radiculocordonal postérieur: aréflexie achilléenne
  - » Neuronopathie sensitive (hypopallesthésie)
  - » Signe de Babinski longtemps seul signe pyramidal
  - » Syndrome dysmorphiques: pieds « creux », scoliose
  - » Intolérance au glucose ou diabète
  - » Variants cliniques: paraparésie spastique, chorée, pas de neuropathie
- Cardiomyopathie
  - » traitement par idebenone Mnesis 5 à 10 mg/Kg/jr soit 2cp/jr (coenzymze Q10) diminue HVG effet neuro ?

Ataxies métaboliques

- Ataxie avec déficit isolé en vitamine E (AVED)
  - Très rare, sauf en Nord afrique
  - Autosomale récessive, gène TTDA
  - Début souvent avant 20 ans, phénotype de FRDA, cardiomyopathie plus rare
  - Dystonies, tremblement céphalique et +/- rétinopathie pigmentaire
  - Administration de vitamine E arrête la progression de la maladie
- Hyperamoniémie
  - Déficit d'une des enzymes du cycle de l'urée
  - Clinique variable : asymptomatique - déficit profond
  - Vomissement, irritabilité, ataxie, dysarthrie, MAI, coma, épilepsie, retard mental
  - Déclenchement par repas riche en protides, acide valproique, infection
  - Traitement : hydratation, repas pauvre en protides, arginine
- Anomalie du métabolisme des acides aminés
  - MB pyruvate, maladie d'Hartnup, déficit en carboxylase, kétoacidurie
- Anomalie du métabolisme lipidique
  - Abetalipoprotéinémie (acanthocytes, stéatorrhée, malabsorption, ↓ß lipoprot), Niemann-Pick C, hexosaminidase, Kufs, Krabbe, cholestanolose, Refsum, adrenomyeloneuropathie

Ataxies avec déficit de réparation de l'ADN

- Ataxie télangiectasie (AT)
  - Très rare, 1/100 000
  - Autosomale récessive, gène ATM
  - ↑ α foeto-protéine,↓ Ig sériques, caryotype anormal (fractures, translocation 7-14)
  - S neurologique sévère et progressif:
    - » S cérébelleux débutant dans l'enfance, fauteuil roulant à la puberté
    - » Dysarthrie, tremblement postural, choreo-athétose, S. park, apraxie oculomotrice
    - » Neuropathie sensitive
  - Télangiectasies stt conjonctivales et plus tardives
  - Déficit immunologique humoral et cellulaire conduit au décés à 20- 30 ans
    - » Infections respiratoires récidivantes: cures d'Ig
    - » Malignité lymphoréticulaire (carcinome et gliome): surveillance et éviter Rx
  - Porteurs hétérozygotes ont un risque plus élevé de cancer notamment du sein
- Ataxie avec apraxie oculomotrice (AOA1: aprataxin, AOA2: senataxin)
  - AOA1: gène APTX, Portugal Japon, phénotype de AT sans atteinte extra neuro, ± AO, ↓ SA, ↑ chol
  - AOA2: gène APTX, 8% des non FRDA en France, phénotype de AT, ↑ α FP
- Ataxie avec neuropathie axonale (SCAN)
  - SCAN1: gène TDP1, 20 ans, ataxie, QI normal, NP axonale sensitive, ↓ SA, ↑ chol
- Xeroderma pigmentosum + signes neuro sévères = S. De Sanctis-Cacchione [Σ de Cockayne]

Ataxies cérébelleuses sporadiques à début tardif

= Idiopathic Late Onset Cerebellar Ataxia (ILOCA)
= Idiopathic Sporadic Cerebellar Ataxia (ISCA)

→ Soit pseudo sporadique: dégénérative familiale
- » Vérification clinique des collatéraux (implications familiales)
- » Forme génétique à révélation tardive (i.e. SCA 6)
- » Formes autosomales récessives

→ Soit atrophie multisystématisée type cérébelleuse (MSA c)
- » 50 % des ataxies cérébelleuses sporadiques à début tardif (Schols et al. 2000)
- » Diagnostic positif:
  - Σ parkinsonien et Σ dysautonomique rapidement évolutif ≤ 9 ans
  - Absence d'ATCD familial
  - Absence de neuropathie, rétinopathie…

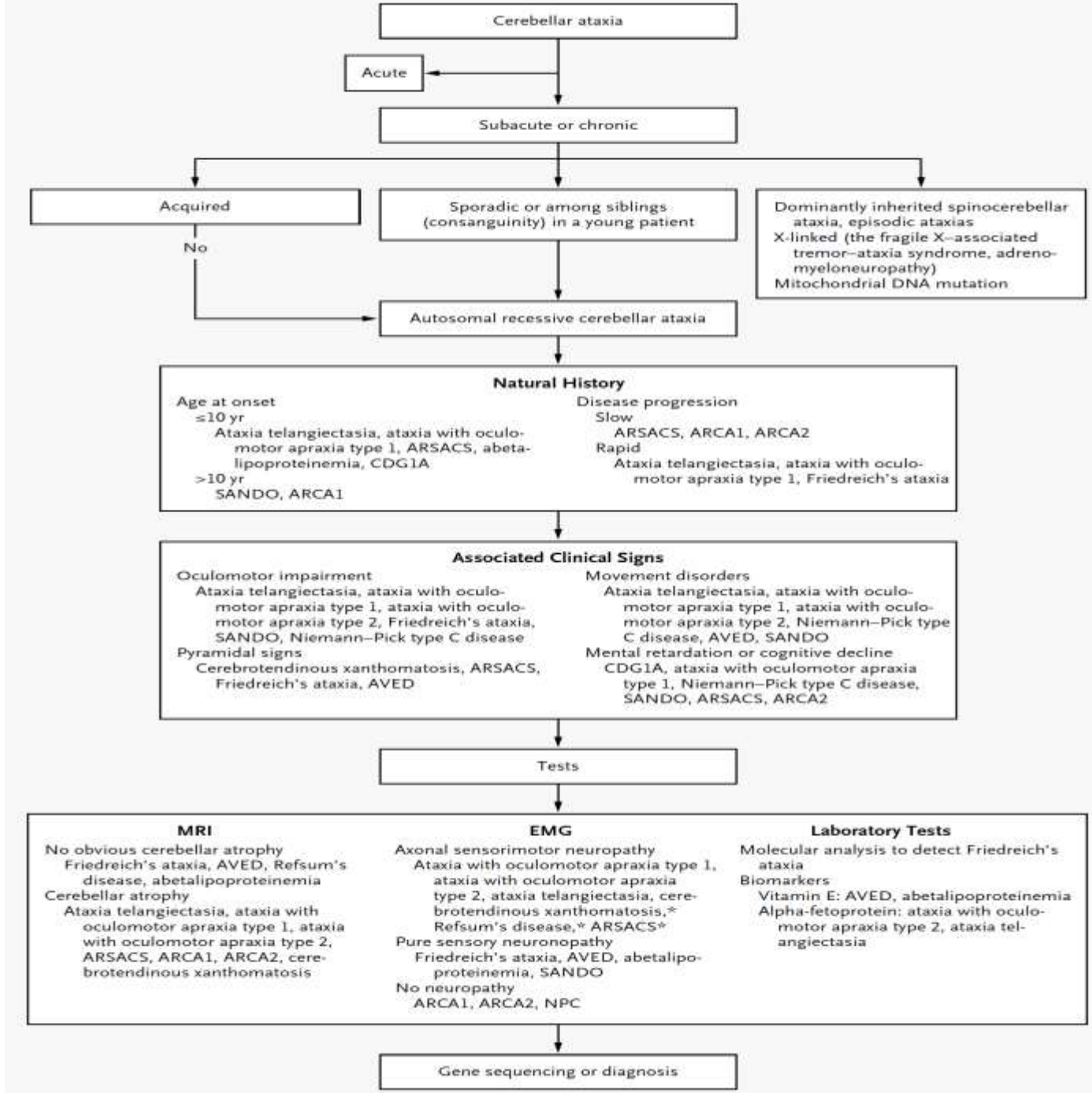
→ Autres pathologies dégénératives? non héréditaires et non AMS
- » Prendre en charge comme AMS
- » Génétique méconnue (ex: mutation de novo)

Table 3. **Clinical Features, Laboratory and Brain MRI Findings, and Molecular Features of the Major Autosomal Recessive Cerebellar Ataxias.***

Disease	Age at Onset	Clinical Features	Laboratory Findings	Brain MRI Findings	Gene and Protein
	yr				
Cerebellar ataxia with pure sensory neuronopathy					
Friedreich's ataxia	Mean, 16; 7–25 in most cases; reported range, 2–60	Most frequent recessive ataxia, bilateral extensor plantar reflexes, scoliosis, square-wave jerks	GAA triplet repeat expansion in intron 1 of the FXN gene	No cerebellar atrophy, spinal cord atrophy	*FXN*, frataxin
Sensory axonal neuropathy with dysarthria and ophthalmoplegia	Range, 20–60	Ophthalmoparesis, dysarthria, ptosis, myoclonus	Variable elevation of serum lactic acid level	Variable cerebellar atrophy, cerebellar white-matter changes, strokelike lesions	*POLG*, polymerase gamma
Ataxia with vitamin E deficiency	Mean, 17; range, 2–50	Similar to Friedreich's ataxia, retinitis pigmentosa, variable head tremor	Significantly decreased serum vitamin E level†	No cerebellar atrophy, spinal cord atrophy	*TTPA*, alpha-tocopherol transfer protein
Abetalipoproteinemia	Birth	Vomiting, diarrhea, neonatal steatorrhea	Decreased serum levels of cholesterol, triglycerides, and vitamins A, D, E, and K; abetalipoproteinemia; acanthocytosis	No cerebellar atrophy	*MTP*, microsomal triglyceride transfer protein
Cerebellar ataxia with sensorimotor axonal neuropathy					
Ataxia telangiectasia	Range, 2–3; <5 in most cases	Telangiectasias; oculocephalic dissociation; susceptibility to infections and cancer; chorea, dystonia, or both	Elevated serum alpha-fetoprotein level, immunoglobulin deficiency, mosaic translocations (specific karyotype)†	Cerebellar atrophy	*ATM*, ataxia telangiectasia mutated
Ataxia with oculomotor apraxia type 1	Mean, 7; range, 1–20	Variable oculocephalic dissociation; chorea, dystonia, or both	Variable elevation of serum LDL cholesterol level and low serum albumin level	Cerebellar atrophy	*APTX*, aprataxin
Ataxia with ocular apraxia type 2	Mean, 15; range, 7–25	Variable oculocephalic dissociation; chorea, dystonia, or both	Elevated serum alpha-fetoprotein level†	Cerebellar atrophy	*SETX*, senataxin

Late-onset GM_2 gangliosidosis	Range, 15–45	Spasticity, weakness, dystonia, epilepsy, cognitive decline, psychosis, anterior horn involvement	Hexosaminidase A deficiency (late-onset Tay–Sachs disease), hexosaminidase A+B deficiency (Sandhoff's disease)	Cerebellar atrophy	*HEXA* (Tay–Sachs variant) or *HEXB* (Sandhoff's disease variant)
Congenital disorder of glycosylation type 1A	Birth	Mental retardation, retinitis pigmentosa, thoracic deformity, epilepsy	Serum transferrin isoelectric focusing	Cerebellar atrophy	*PMM2*, phospho-mannomutase
Autosomal recessive spastic ataxia of Charlevoix–Saguenay	Mean, 2; up to 12	Spastic paraparesis followed by spastic ataxia, demyelinating component of the neuropathy, hypertrophy of the myelinated fibers (of the fundus)		Anterior superior cerebellar atrophy, variable T_2-weighted linear hypointensities in pons	*SACS*, sacsin
Refsum's disease	Range, 10–20	Retinitis pigmentosa, sensorineural deafness, demyelinating neuropathy	Elevated serum phytanic acid level†	No cerebellar atrophy	*PhyH*, phytanoyl-CoA hydroxylase and *PEX7*, PEX7
Cerebrotendinous xanthomatosis	Childhood	Spastic ataxia; mental retardation, dementia, or both; tendon xanthomas; chronic diarrhea; premature cataracts	Elevated serum cholestanol level†	Variable cerebellar atrophy, cerebellar or cerebral leukodystrophy	*CYP27*, sterol 27 hydroxylase
Cerebellar ataxia without neuropathy					
Autosomal recessive cerebellar ataxia type 1	Late onset; mean, 32; range, 17–46	Pure ataxia	Not applicable	Cerebellar atrophy	*SYNE1*, spectrin repeats-nuclear envelope 1
Autosomal recessive cerebellar ataxia type 2	Mean, 4; range, 1–11	Mental retardation, myoclonus, epilepsy, strokelike condition, exercise intolerance	Variable elevation of serum lactic acid level and decreased coenzyme Q10 level	Cerebellar atrophy, variable strokelike cerebral lesions	*ADCK3 (CABC1)*, aarf-domain containing kinase 3
Niemann–Pick type C disease	Range, 2–30	Vertical supranuclear ophthalmoplegia, splenomegaly, dystonia, cognitive disorder	Skin-biopsy findings (filipin staining)	Variable cerebellar or brain atrophy	*NPC1*, NPC1 and *NPC2*, NPC2

* Most congenital and inherited metabolic disorders are excluded. LDL denotes low-density lipoprotein.
† This biomarker is consistently altered (either increased or decreased) in the corresponding autosomal recessive cerebellar ataxia.


Cerebellar ataxia
Acute
Subacute or chronic
Acquired
No
Sporadic or among siblings (consanguinity) in a young patient
Dominantly inherited spinocerebellar ataxia, episodic ataxias
X-linked (the fragile X–associated tremor–ataxia syndrome, adrenomyeloneuropathy)
Mitochondrial DNA mutation
Autosomal recessive cerebellar ataxia
Natural History
Age at onset
≤10 yr
Ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ARSACS, abetalipoproteinemia, CDG1A
>10 yr
SANDO, ARCA1
Disease progression
Slow
ARSACS, ARCA1, ARCA2
Rapid
Ataxia telangiectasia, ataxia with oculomotor apraxia type 1, Friedreich's ataxia
Associated Clinical Signs
Oculomotor impairment
Ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, Friedreich's ataxia, SANDO, Niemann–Pick type C disease
Pyramidal signs
Cerebrotendinous xanthomatosis, ARSACS, Friedreich's ataxia, AVED
Movement disorders
Ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, Niemann–Pick type C disease, AVED, SANDO
Mental retardation or cognitive decline
CDG1A, ataxia with oculomotor apraxia type 1, Niemann–Pick type C disease, SANDO, ARSACS, ARCA2
Tests
MRI
No obvious cerebellar atrophy
Friedreich's ataxia, AVED, Refsum's disease, abetalipoproteinemia
Cerebellar atrophy
Ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ARSACS, ARCA1, ARCA2, cerebrotendinous xanthomatosis
EMG
Axonal sensorimotor neuropathy
Ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ataxia telangiectasia, cerebrotendinous xanthomatosis,* Refsum's disease,* ARSACS*
Pure sensory neuronopathy
Friedreich's ataxia, AVED, abetalipoproteinemia, SANDO
No neuropathy
ARCA1, ARCA2, NPC
Laboratory Tests
Molecular analysis to detect Friedreich's ataxia
Biomarkers
Vitamin E: AVED, abetalipoproteinemia
Alpha-fetoprotein: ataxia with oculomotor apraxia type 2, ataxia telangiectasia
Gene sequencing or diagnosis

Algorithm for recessive cerebellar ataxia

Pr Anheim

Age of onset of ataxia*
Speed of progression*
Ophthalmic signs
Ocular movement disorders
Movement disorders
Cortico-spinal tract
Cognitive & psychiatric
Neurological
Musculo-skeletal
Visceral & gastrointestinal
Skin
Miscellaneous
Neuroimaging data
Electro-myography
Biomarker evidence

Renaud M, et al., A recessive ataxia diagnosis algorithm for the next generation sequencing era. Ann Neurol. 2017.

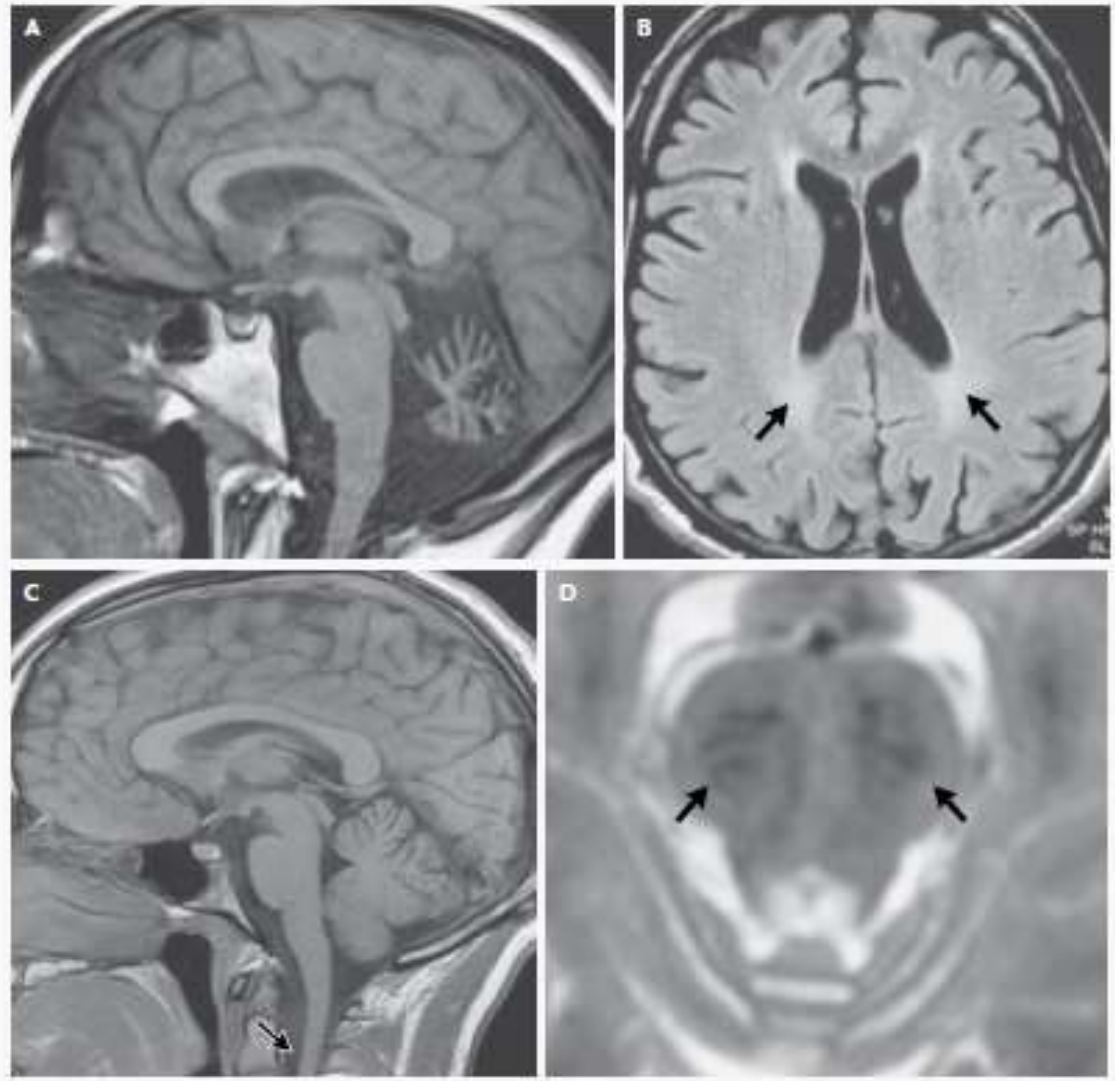


Figure 2. **MRI Scans Showing Four Types of Autosomal Recessive Cerebellar Ataxias.**

Panel A shows marked cerebellar atrophy in a patient with ataxia telangiectasia. Panel B shows moderate periventricular leukoencephalopathy (arrows) in a patient with cerebrotendinous xanthomatosis. Panel C shows no obvious cerebellar atrophy but cervical spinal cord atrophy (arrow) in a patient with Friedreich's ataxia, 10 years after the onset of the disease. Panel D shows T_2-weighted linear hypointensities in the pons (arrows) in a patient with autosomal recessive spastic ataxia of Charlevoix–Saguenay.

Bilan biologique

- Bilan de carence (B1, B6, B12, folates), TSH, T3, T4, marqueurs tumoraux +/- AC anti neuronaux, Ac antinucleaire (diagnostic différentiel)
- Céruléoplasmine, cuprémie, cuprurie (Wilson)
- AC antigliadine, endomysium, transglutaminase, +/- Biopsie duodénale (M. coeliaque)
- anti GAD (Ataxie GAD +)
- Vitamine E (AVED, abétalipoprotéinémie)
- Chol, Igélectrophorèse sérique, α FP (abétalipoprotéinémie, AT, AOA, SCAN, XP)
- Acide phytanique (Refsum)
- ↑ Cholestanol (Cholestanose)
- ↑ Acides gras à très longues chaines (leucodystrophie: adrénomyeloneuropathie)
- ↓ Galactocérébrosidase (leucodystrophie: cellule globoide à début tardif)
- ↓ sulfatase (leucodystrophie métachromatique)
- ↓ Neuraminidase (sialidose)
- ↓ hexosaminidase A et B (gangliosidose GM2)
- Acides aminés, acides organiques (pathologies métaboliques)
- Etude de la glycosilation de la transferrine (Maladie chronique de glycosilation)
- Lactate, pyruvate, épreuve d'effort, ammoniémie (Mitochondriopathie, P. métaboliques)
- +/- ADN mitochondrial, biopsie musculaire (MERRF,KSS, NARP)
- +/- medullogramme: histiocytes bleus (Niemann Pick C)
- +/- Biopsie cutanée, rectale (lipopigment, ceroïde lipofuscinose)

Ataxies autosomales dominantes

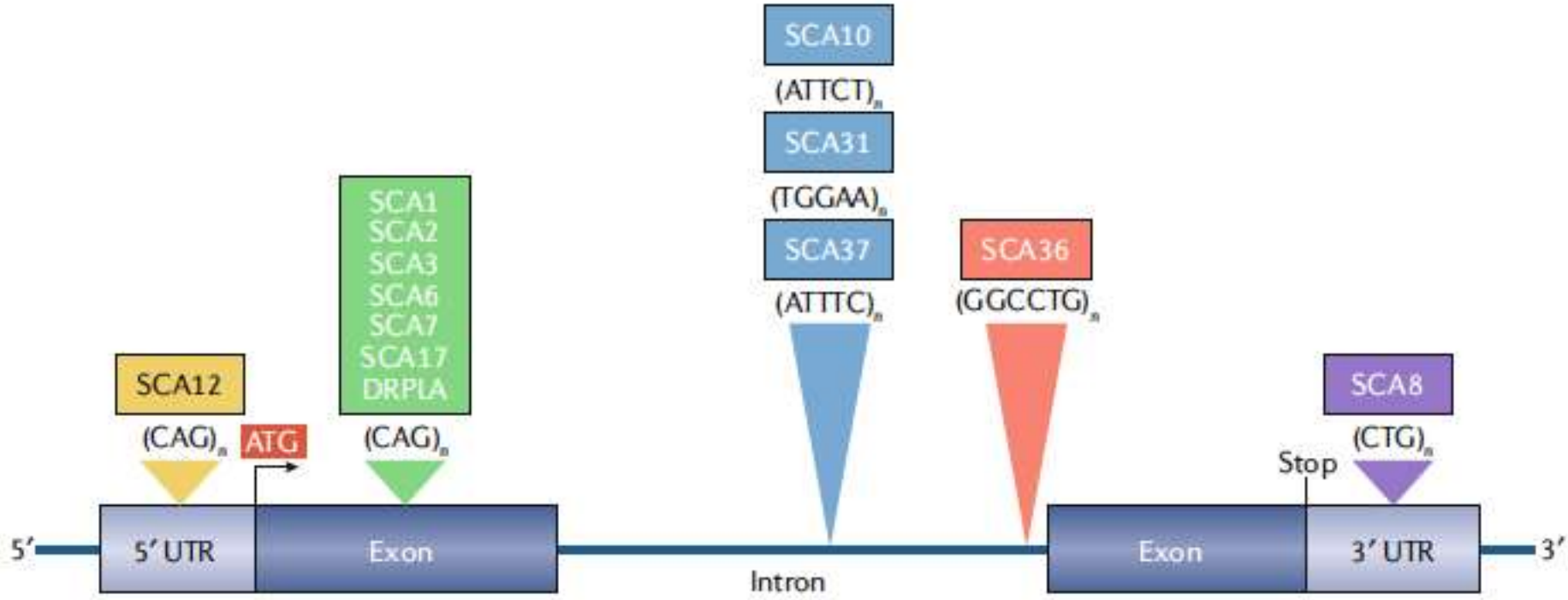
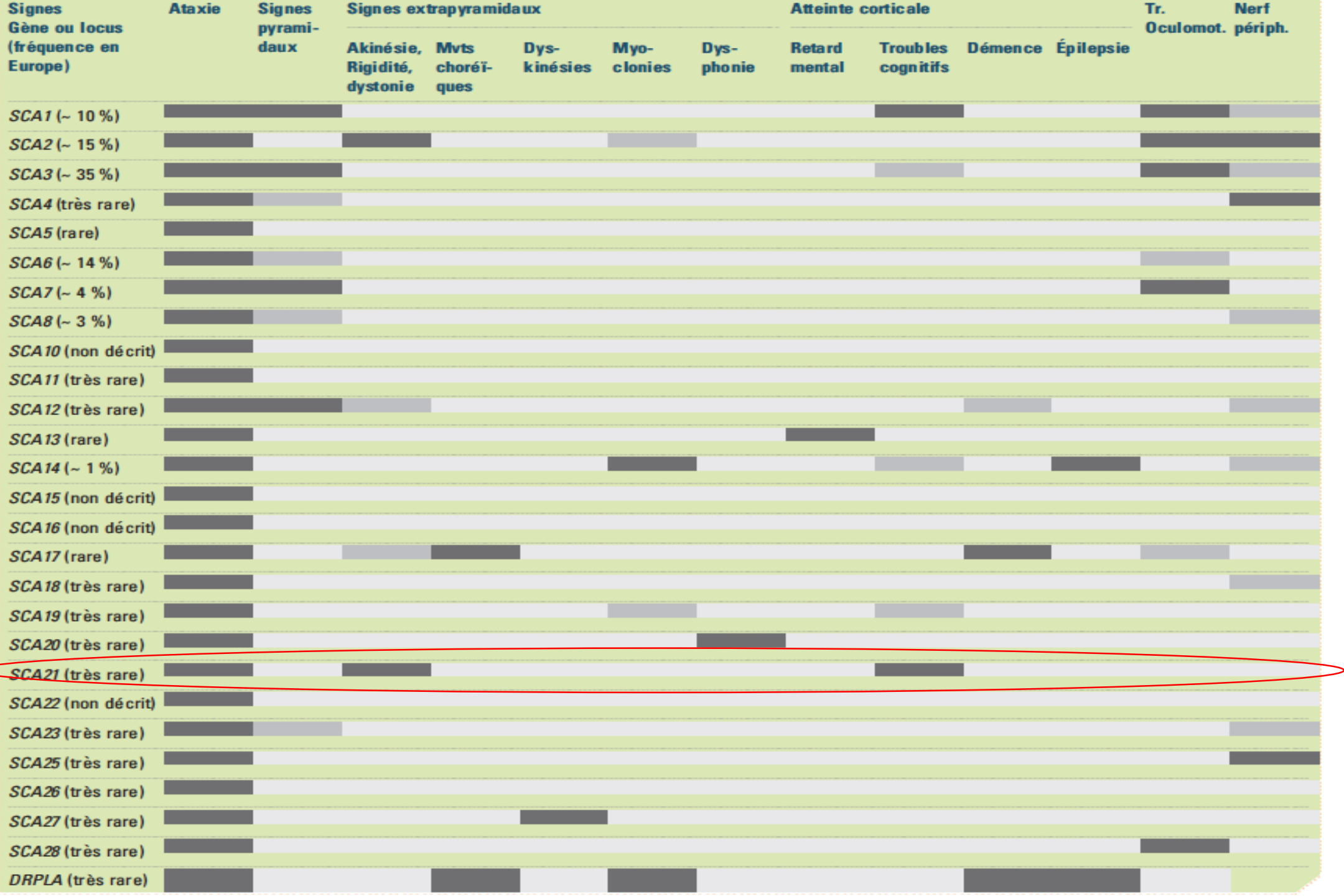


Fig. 1 | **Hereditary degenerative ataxias caused by expanded microsatellite repeats.** A CAG repeat expansion within the open reading frame of the respective genes associated with the spinocerebellar ataxias (SCAs) 1, 2, 3, 6, 7 and 17 and dentatorubral-pallidoluysian atrophy (DRPLA; green) encodes an elongated polyglutamine (polyQ) tract in the protein product. The CAG repeat in SCA12 (yellow), present in *PPP2R2B*, is shown in the 5′ untranslated region (UTR) in this figure but can be intronic depending on the transcription start site. In SCA8 (purple), a CTG repeat is located in the 3′ UTR of *ATXN8OS*. However, the complementary CAG repeat on the opposite strand encodes polyQ in *ATXN8*. Four large intronic microsatellite repeats include three pentanucleotide repeats (blue) in SCAs 10, 31 and 37 and one hexanucleotide repeat (red) in SCA36. In SCA31, a TGGAA repeat is located in *BEAN1*, and a TTCCA repeat is found in *TK2* on the opposite strand, although only the UGGAA-containing transcripts are shown to be pathogenic. Likewise, the large ATTTC repeat, but not the ATTTT repeat, is pathogenic in SCA37. In SCA10, the risk of epilepsy increases sixfold when the ATTCT repeat is interrupted by a stretch of ATCCT repeat. In SCA36, an expanded GGCCTG repeat (with high sequence homology with the GGGGCC repeat in *C9orf72*) is present in *NOP56*.


Signes
Gène ou locus
(fréquence en Europe)
Ataxie
Signes pyrami-daux
Signes extrapyramidaux
Akinésie, Rigidité, dystonie
Mvts choréï-ques
Dys-kinésies
Myo-clonies
Dys-phonie
Atteinte corticale
Retard mental
Troubles cognitifs
Démence
Épilepsie
Tr. Oculomot.
Nerf périph.
SCA1 (~ 10 %)
SCA2 (~ 15 %)
SCA3 (~ 35 %)
SCA4 (très rare)
SCA5 (rare)
SCA6 (~ 14 %)
SCA7 (~ 4 %)
SCA8 (~ 3 %)
SCA10 (non décrit)
SCA11 (très rare)
SCA12 (très rare)
SCA13 (rare)
SCA14 (~ 1 %)
SCA15 (non décrit)
SCA16 (non décrit)
SCA17 (rare)
SCA18 (très rare)
SCA19 (très rare)
SCA20 (très rare)
SCA21 (très rare)
SCA22 (non décrit)
SCA23 (très rare)
SCA25 (très rare)
SCA26 (très rare)
SCA27 (très rare)
SCA28 (très rare)
DRPLA (très rare)

The movement disorder spectrum of SCA21 (ATX-TMEM240): 3 novel families and systematic review of the literature

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ABSTRACT

Spinocerebellar ataxia type 21 (SCA21/ATX-TMEM240) was recently found to be caused by mutations in *TMEM240*, with still limited knowledge on the phenotypic spectrum and disease course. Here we present five subjects from three novel SCA21 families from different parts of the world (including a novel c.196G > A, p.G66R *TMEM240* variant from Colombia), demonstrating that, in addition to cerebellar ataxia, not only hypokinetic features (hypomimia, bradykinesia), but also hyperkinetic movement disorders (poly-mini-myoclonus, proximal myoclonus) are a recurrent part of the phenotypic spectrum of SCA21. Presenting first prospective longitudinal data, our results provide examples of two different disease trajectories: while it was inherently progressive in adult-onset cases, a dramatically improving trajectory was observed in an infantile-onset case. A systematic review of all previously reported SCA21 patients (n = 42) demonstrates that SCA21 is a relatively early-onset SCA (median onset age 18 years; range 1–61 years) with frequent non-cerebellar involvement, including hyporeflexia (69%), bradykinesia (65%), slow saccades (38%) and pyramidal signs (17%). Our results characterize SCA21 as a multisystem disorder with substantial extra-cerebellar involvement, including a wide spectrum of hypo- as well as hyperkinetic movement disorders as well as damage to the midbrain, corticospinal tract and peripheral nerves. However, in contrast to the current perspective on SCA21 disease, cognitive impairment is not an obligatory feature of the disease. The disease course is inherently progressive in adult-onset subjects, but might also be characterized by improvement in infantile-onset cases. These findings have important consequences of the work-up and counseling of SCA21/ATX-TMEM240 patients.

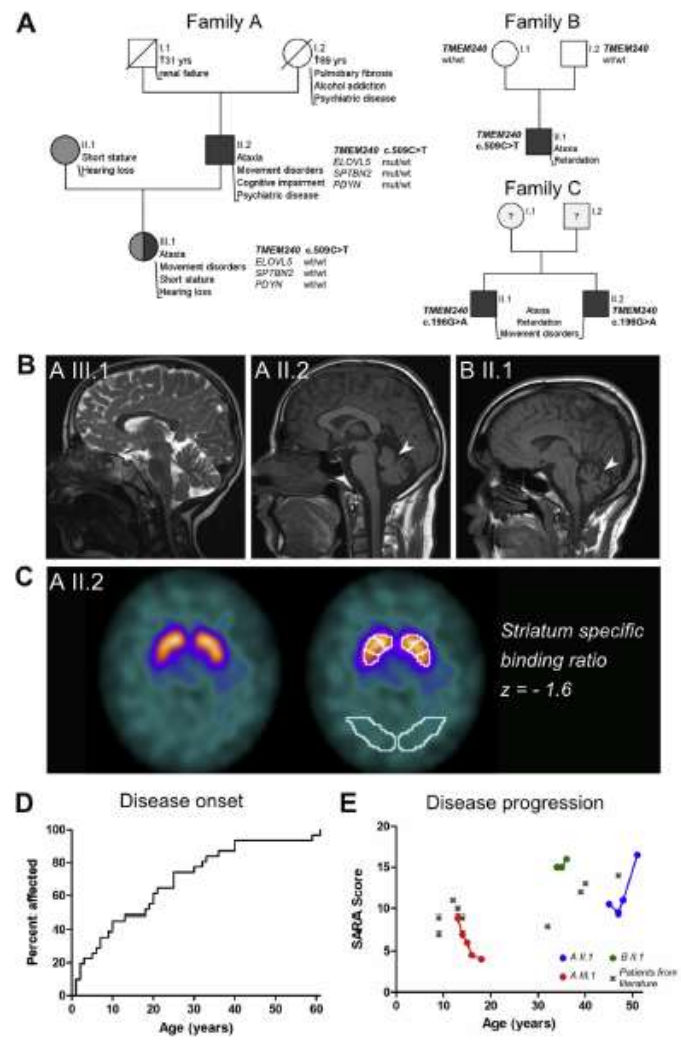


Fig. 1. A) Pedigree of three families with SCA21. The *TMEM240* variant segregated with disease in family A and family C, and occurred de novo in family B. Short stature and hearing loss were present as a second phenotype in family A. Note that II.2 was also carrier of rare variants in three additional SCA genes, which were, however, not found in the likewise affected daughter (subject II.1). **B) Structural MRI of SCA21 patients.** Mild cerebellar atrophy was present in adult patients II.2 of family A and II.1 of family B (arrowheads). MRI was normal in children up to at least 10 years of age, as illustrated by patient III.1 of family A (MRI: mid-sagittal plane; left. T2; middle and right: T1 sequence). **C) Dopamine transporter imaging.** ^{123}I-FP-CIT SPECT in subject A II2 showed a normally configured striatum, but low-normal binding values for all subparts of the striatum (white demarcation lines) (age-corrected). **D)** Cumulative distribution of disease onset across 31 SCA21 patients where disease onset data were available. Disease onset was before age 18 in more than 50%, and before age 40 in more than 90% of cases. **E)** Distribution of cross-sectional (crosses) and longitudinal (dots with lines) SARA scores. Two separate clusters suggest an early improving and a late deteriorating phenotype. Connecting lines indicate prospective longitudinal data, all from subjects of the current study.

Ataxies épisodiques

- EA1
  - TAD, rare, géne KCNA1, sous-unité α d'un canal potassium voltage dépendant
  - Réduction d'amplitude du courant K+ augmente l'excitabilité neuronale
  - Début dans l'enfance et disparaît après 20 ans
  - Crise de qq sec à minutes d'incoordination cérébelleuse déclenchée par stress et mouvement brusque
  - Myokimies per critiques
  - Spectre large allant de l'épilepsie aux neuromyotonies et crampes isolées
- EA2
  - TAD, rare, géne CACNA1A, sous-unité α1A d'un canal calcique voltage dépendant type P/Q
  - Même gène que migraine hémiplégique familiale (mutation faux sens) et SCA 6 (expansion CAG)
  - Canal calcique devient non fonctionnel
  - Début dans l'enfance ou adolescence
  - Crise de qq heures à qq jours d'ataxie, nystagmus, vertige, nausée, déclenchée par stress et exercice, caféine, alcool et phénitoine
  - Σ cérébelleux discret per critiques (caract commune avec SCA6)
  - Traitement par acétazolamine

- EA3, EA4

Diagnostic génétique

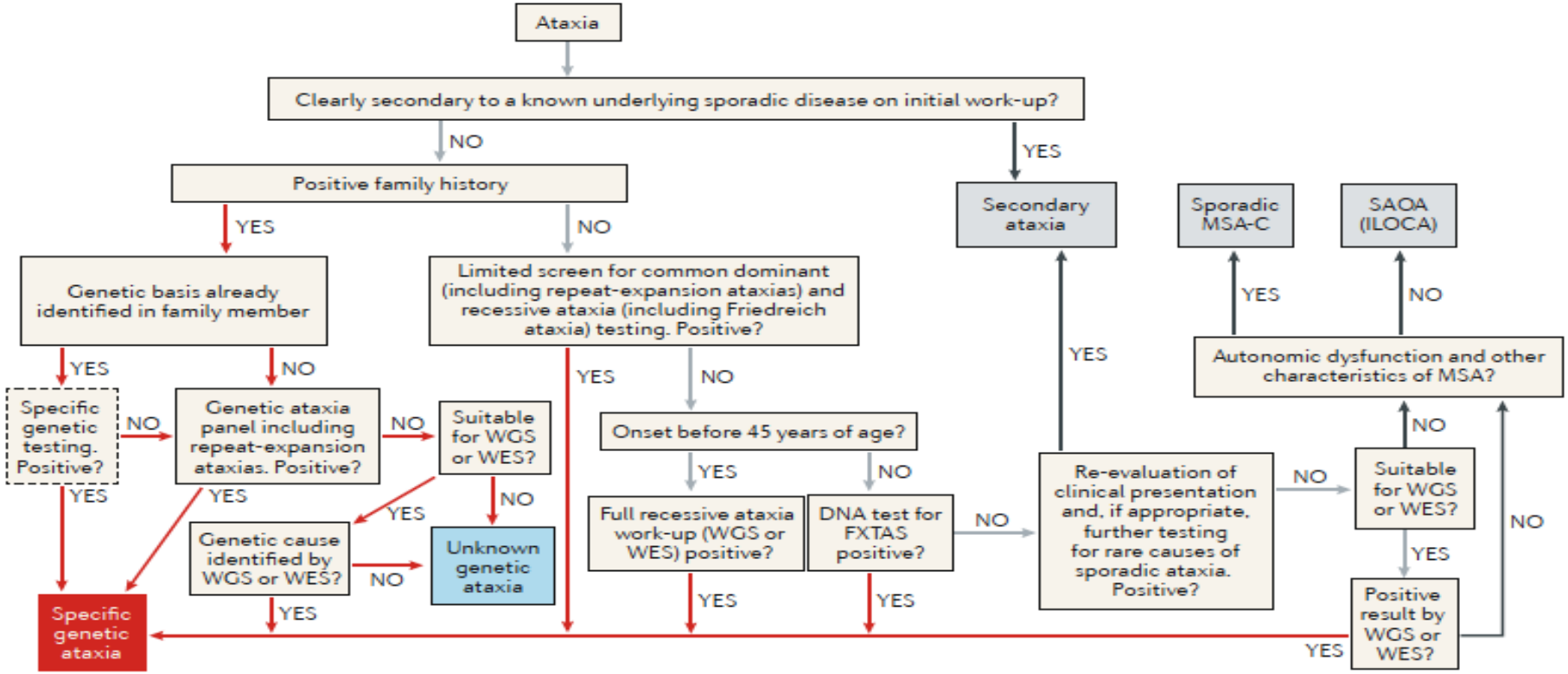
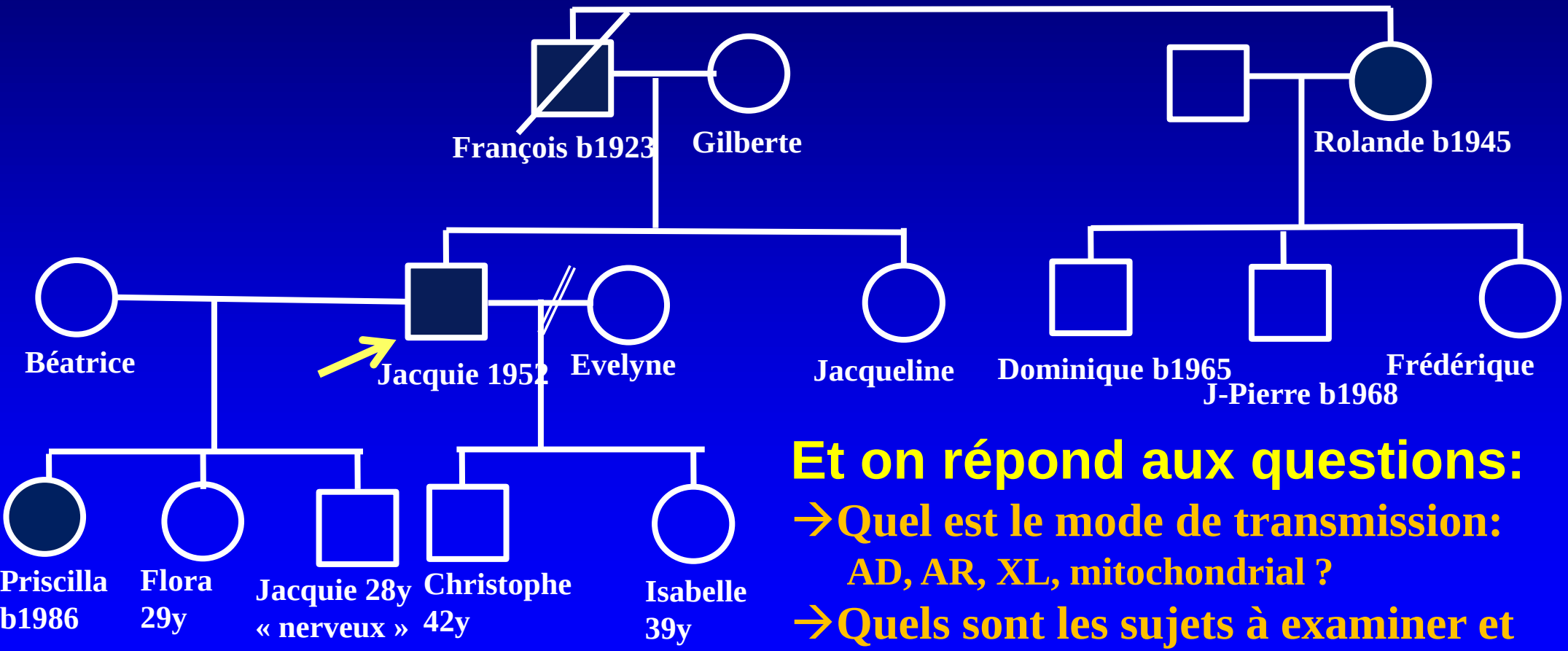


Fig. 2 | **Diagnostic algorithm for progressive ataxias.** Red arrows show steps to the diagnosis of inherited ataxias. Grey arrows indicate processes in which a genetic ataxia is still included in the differential diagnosis. Black arrows are routes to diagnoses of non-genetic ataxias. Obvious secondary ataxia should be excluded before a diagnosis of a spinocerebellar ataxia (SCA) can be made. The next step is to determine whether ataxia is inherited. If genetic diagnosis is already known in the family, optional confirmatory genetic testing is advised. If genetic diagnosis is unknown, panel testing or selective genotyping for dominant and/or recessive ataxias is recommended. If results are negative, whole-exome sequencing (WES), and potentially whole-genome sequencing (WGS), can lead to the specific genetic diagnosis. When no family history is present of a similar ataxic disorder, treatable causes of progressive ataxias should be explored on the basis of the differential diagnosis (for example, immune-mediated ataxias). Once treatable causes are excluded, genetic testing can be considered in patients with apparently sporadic ataxia. After exclusion of secondary ataxias and genetic ataxias, the diagnosis of either probable multiple system atrophy of cerebellar type (MSA-C) or sporadic adult-onset ataxia (SAOA; also known as idiopathic late-onset cerebellar ataxia (ILOCA)) can be established on the basis of the diagnostic criteria. FXTAS, fragile X-associated tremor/ataxia syndrome.

Avant toute chose: on construit l'arbre généalogique



Famille DBS

Et on répond aux questions:

→Quel est le mode de transmission:
AD, AR, XL, mitochondrial ?

→Quels sont les sujets à examiner et prélever ?

Quelle analyse génétique demander?

- **Sur votre seul patient: analyse de triplets**
  - Formes dominantes: SCA1,2,3,6,7,17
    - » +/- en fonction du phénotype: DRPLA, SCA12, SCA36, SCA10 (Mexique)
  - Formes récessives: FRDA
  - lié à l'X: X-Fra
- **Mais si vous voulez étendre l'analyse génétique, on passe en haut débit, il faut une analyse familiale**
  - Qui prélever et analyser ? Les parents ou au moins un autre sujet atteint
- **Et si vous voulez passer à l'exome ou au génome, il faut toute la famille**
  - Sujets atteints et sains. Tous. Au moins 5 personnes, sur 2-3 générations

Panel de gènes connus

Nouveaux gènes possibles

Démarche diagnostique

Localisation anatomique principale: ataxie cérébelleuse ou paraparésie spastique

Eliminer atteinte toxique: (alcool, lithium, dihydan, antimitotique)

Arbre généalogique (3 générations), groupe ethnique et mode de transmission

Age de début et caractéristiques cliniques (signes associés, épisodique vs chronique)

Eliminer atteinte dégénérative acquise AMS

Bilan paraclinique: Bilan biologique métabolique, IRM encéphalique, EMG, ERG

Biologie moléculaire ciblée (Transmission, neuropathie, apraxie OM, rétine, épisodique)

- TAD: ADCA I (SCA 1, 2, 3), ADCA II (SCA 7), ADCA III (SCA 6)
- TAR: FRDA et vitamine E

Démarche thérapeutique

- Pourquoi faire le diagnostic génétique ?
  - Conseil génétique: diagnostic présymptomatique et anténatal
  - EUROSCA: recherche mécanisme physiopathologiques
  - Thérapie génique et essais thérapeutiques
- Traitement spécifique: AVED (vitamine E), AE (acétazolamine)
- Traitement symptomatique
  - Syndrome cérébelleux
    - » IRS à dose moyenne à forte
    - » Levotonine (précurseur de la sérotonine, interaction IMAO et tricyclique) de 600mg à 1,2g/j
    - » Buspar (anxiolytique non sédatif, agoniste 5HT1A pré et post synaptique) 15 à 30 mg/j max 60 mg/j
    - » Mantadix (méca inconnu: Dopa ? GABA?) 100 à 300 mg/j max 400
    - » Neurontin (GABAergique) 1800 à 2400mg/j max 3200
    - » Riluzole 2 cp /j
    - » MPR: charge supplémentaire, kiné, orthophonie
    - » Stimulation du VIM si tremblement cinétique majeur relativement isolé
  - Spasticité
    - » Antispastique et toxine botulique

Table 4 | **Candidate symptomatic drugs for treatment of SCAs**

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA6 and other SCAs	4-Aminopyridine	Restoration of pacemaker activities of Purkinje cells by blocking the voltage-dependent family of potassium channels[87]	Alleviated motor coordination deficits and restored Purkinje cell firing precision in SCA6 mice homozygous for 84 polyQ repeats[87]	Approved by the FDA for symptomatic improvement of walking in multiple sclerosis. A randomized, double-blind, placebo-controlled study showed a decreased number of attacks in patients with episodic ataxia 2 (REF.[213]). A phase I study[214] and a small open-label study[215] have been done in patients with SCAs
SCA2 and other SCAs	Chlorzoxazone	KCNN1 channel activator. Normalization of the Purkinje cell spontaneous firing rate in SCA2 transgenic mice with 58 polyQ repeats[100] and in *Cacna1a*-mutant mice[93]	Not yet done	Chlorzoxazone is approved by the FDA and has been used extensively as a muscle relaxant
SCA44	Nitazoxanide	Negative allosteric modulator of metabotropic glutamate receptor 1 and 5 with potent inhibition of mutant forms of these receptors in transfected cells[214]	Not done in SCA44 models, but similar modulators alleviated ataxia in an SCA1 mouse model[216,217]	Nitazoxanide is approved by the FDA and is used for various helminthic, protozoal and viral infections[218]

KCNN1, small-conductance calcium-activated potassium channel protein 1; polyQ, polyglutamine; SCA, spinocerebellar ataxia.

Table 3 | **Candidate disease-modifying drugs for treatment of SCAs**

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA1	MSK1 inhibitor	Inhibitors of the RAS–MAPK–MSK1 pathway decrease levels of ATXN1 and alleviate neurodegeneration in cellular and animal models of SCA1 (REFS[68,69])	Further screening and optimization is ongoing	Strong scientific premise. Rigorous preclinical studies are planned. No relevant human clinical observations
SCA1	Stereotactic AAV-mediated delivery of miRNA-like RNAi	RNAi suppresses polyglutamine-induced neurodegeneration in an SCA1 mouse model[196]. Therapeutic benefits after RNAi expression vector delivery to deep cerebellar nuclei[197]	RNAi prevents and reverses phenotypes induced by mutant human ATXN1 (REF.[198])	Preclinical study is ongoing in B. Davidson's laboratory under the NIH CREATE BIO[199] grant support, which mandates rigorous preclinical study designs and go/no-go milestones[200]
SCA2	Dantrolene	Inhibits intracellular Ca^{2+} release and protects Purkinje cells from cell death in the SCA2-58Q mouse model[201]	Feeding SCA2-58Q mice with dantrolene alleviated age-dependent motor deficits (beam-walk and rotarod assays)[201]	Modest scientific premise. Needs rigorous preclinical studies. No relevant human clinical observations
SCA3	Dantrolene	Inhibits intracellular Ca^{2+} release and protects neuronal cells in pontine nuclei and substantia nigra regions from cell death in SCA3-YAC-84Q transgenic mice[202]	Feeding SCA3-YAC-84Q transgenic mice with dantrolene improved their motor performance[202]	Modest scientific premise. Needs rigorous preclinical studies. No relevant human clinical observations
SCA3	Citalopram	Identified in an unbiased screening for inhibition of mutant ATXN3 aggregation and reduction of ATXN3 neurotoxicity through neuronal serotonin pathways in cell and animal models[70]	Efficacy of citalopram was verified in multiple SCA3 transgenic animal models, with chronic treatment leading to decreased neuronal ATXN3 aggregates, astrogliosis, weight loss and motor dysfunction[70]	Strong scientific premise. Good preclinical studies in two independent laboratories. No relevant human clinical observations
SCA3	Aripiprazole	Identified in an unbiased screen of FDA-approved drugs for reduction of the level of mutant ATXN3 in a cell-based assay[71]	Not yet done	Unknown mechanism(s) of the effect on the mutant ATXN3. Needs rigorous preclinical studies in SCA3 animal model(s). No relevant human clinical trials or observations
SCA3	Lentiviral delivery of allele-specific[203] and allele-nonspecific[204,205] siRNA against *Atxn3* in a rat model	Silencing of *Atxn3* mitigates degeneration in rat. Suppression of wild-type *Atxn3* has no adverse effects and allele-nonspecific silencing might be beneficial in rat[203–205]	Further preclinical studies are needed	Strong scientific premise for targeting the mRNA of the mutant ATXN3. Therapeutic efficacy shown in the rat model needs to be replicated in mouse models. Needs rigorous preclinical studies in SCA3 animal models. No relevant human clinical trials or observations
SCA3	Stereotactic AAV delivery of miRNA	RNAi suppresses ATXN3 levels and alleviates molecular phenotype in SCA3 mouse models[206,207]	RNAi has induced no behavioural changes	Strong scientific premise for targeting the mRNA of the mutant ATXN3. Needs rigorous preclinical studies in SCA3 animal models. No relevant human clinical trials or observations
SCA1, SCA2 and SCA3	ASO against *ATXN1*, *ATXN2* or *ATXN3*	In these SCAs, toxic gain-of-function mechanisms are well established. Targeting the mRNA containing toxic polyglutamine expansion is supported by a strong rationale[2]	Reduction of mutant ATXN2 (REF.[208]) and ATXN3 (REF.[209]) mRNA by ASO treatment, and skipping of CAG-repeat-containing exon 10 of ATXN3 (REF.[210]), are promising therapeutic approaches	Strong scientific premise for targeting the mRNA of the mutant ATXNs. Needs rigorous preclinical studies in animal models of SCA. No relevant human clinical trials or observations
SCA6	miR-3191-5p	In SCA6, the CAG expansion is found in the second cistron (α1ACT) of *CACNA1A*. miR-3139 attenuates IRES-driven translation of toxic α1ACT[66]	AAV9–miR-3191-5p protected α1ACT-Q33 mice from ataxia, motor deficits and Purkinje cell degeneration[66]	Toxic mutant mRNA is the target. Needs rigorous preclinical studies in SCA6 animal models. No relevant human clinical trials or observations

Table 3 (cont.) | **Candidate disease-modifying drugs for treatment of SCAs**

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA7	Direct delivery of AAV or miRNA to retina in an SCA7 mouse model[211]	In SCA7, toxic gain-of-function mechanisms are well established[2,3]. Targeting of the mRNA containing a toxic polyglutamine expansion is supported by a strong rationale. Eyes are severely affected in SCA7 and are readily accessible for delivery of miRNA[211]	Non-allele-specific suppression of ATXN7 levels was accompanied by preservation of retinal function in SCA7 mice	Both wild-type and mutant *ATXN7* mRNA are targeted. Needs rigorous preclinical studies in SCA7 animal models. No relevant human clinical trials or observations
SCA7	Direct delivery of AAV or miRNA to cerebellum of a mouse model of SCA7 (REF.[212])	In SCA7, toxic gain-of-function mechanisms are well established. Targeting of the mRNA containing a toxic polyglutamine expansion is supported by a strong rationale	Non-allele-specific suppression of ATXN7 levels was accompanied by improvement of ataxic phenotype in SCA7 mice	Both wild-type and mutant *ATXN7* mRNA are targeted. Needs rigorous preclinical studies in SCA7 animal models. No relevant human clinical trials or observations

α1ACT, α1A carboxyl terminus; AAV, adeno-associated virus; ASO, antisense oligonucleotide; ATXN, ataxin; CREATE BIO, Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics; IRES, internal ribosome entry site; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MSK1, nuclear mitogen and stress-activated protein kinase 1; RNAi, RNA interference; SCA, spinocerebellar ataxia; siRNA, small interfering RNA.

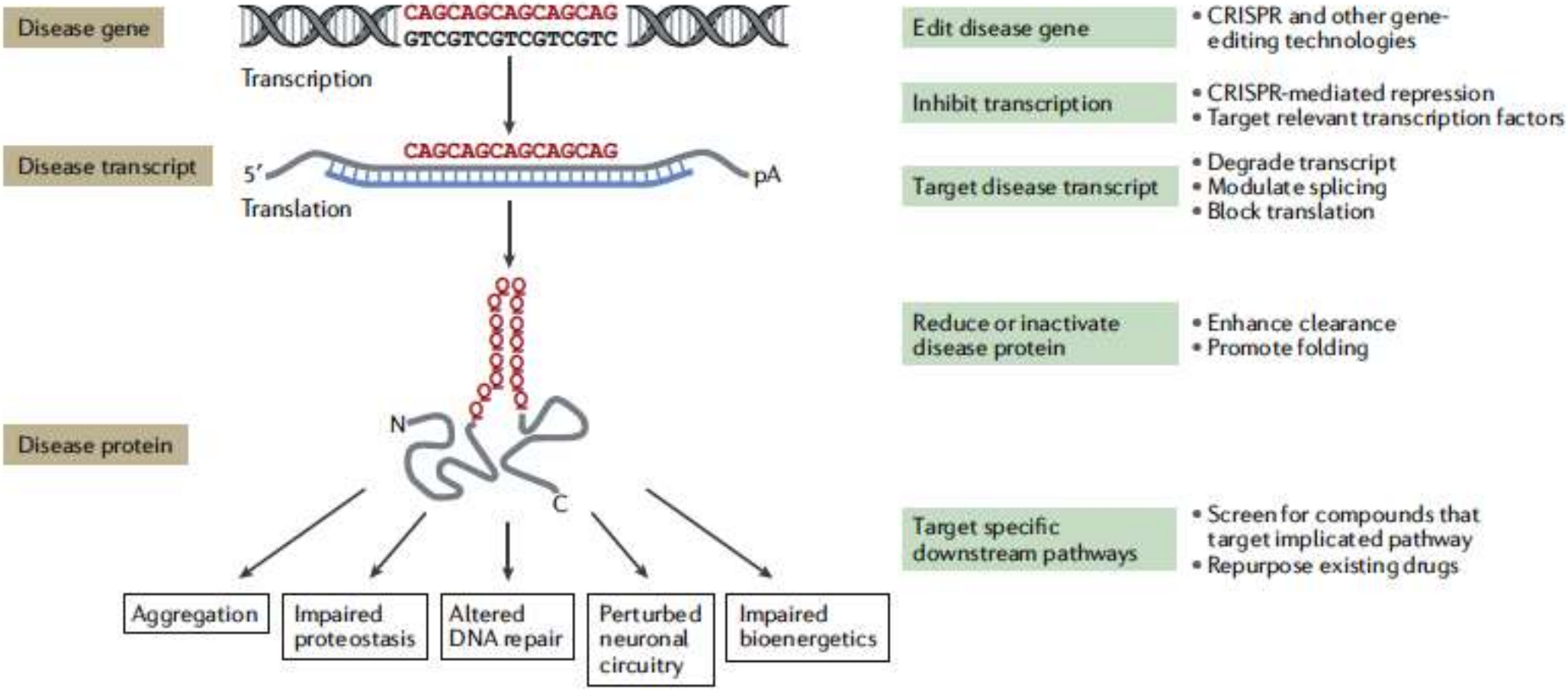


Fig. 3 | **Therapeutic strategies for the SCAs.** A generic CAG repeat polyglutamine disease gene is used to illustrate positions along the pathogenic cascade for which disease-modifying therapeutic approaches are being developed. Examples of specific strategies at each point are shown on the right. Five representative downstream consequences of the spinocerebellar ataxia (SCA) disease protein are shown that represent potentially targetable pathways shared across multiple SCAs; this list is not intended to be comprehensive. C, carboxyl terminus; N, amino terminus; pA, polyadenosine tail.

MERCI !

Les Programmes Hospitaliers de Recherche Clinique (PHRC)

Table 1 | **SCAs caused by microsatellite repeat expansions**

Disease	Gene (repeat location)	Repeats, principal repeat unit			Notable characteristic clinical signs	Anticipation
		Normal	Intermediate	Disease		
SCAs caused by polyglutamine-coding CAG repeat expansions						
SCA1	*ATXN1*	6–39[a]	40	41–83	Hypermetric saccades and pyramidal signs	+
SCA2	*ATXN2*	<31	31–33	34–200	Slow saccades and areflexia	+[b]
SCA3	*ATXN3*	12–44	45–55	56–86	Bulged eyes and motor neuron signs	+
SCA6	*CACNA1A*	<18	19	20–33	Downbeat nystagmus	–
SCA7	*ATXN7*	4–19	28–33	34 to >460	Visual loss	+
SCA17	*TBP*	25–40	–	41–66	Huntington disease-like	–[b]
DRPLA	*ATN1*	6–35	36–48	49–88	Huntington disease-like	+
SCAs caused by non-coding microsatellite repeat expansions						
SCA8[c]	*OSATXN8* (3′ UTR)	15–34, CTG or CAG	34–89, CTG or CAG	89–250, CTG or CAG	Reduced penetrance	–
SCA10[d]	*ATXN10* (intron)	8–32, ATTCT	33–799, ATTCT	800–4,500, ATTCT, ATTCC, ATCCT or ATCCC	Some families with epilepsy	+ (in some families)
SCA12	*PPP2R2B* (5′ UTR)	7–28, CAG	29–66, CAG	67–78, CAG	Tremor	–
SCA31[e]	*BEAN* (intron)	<400, ATTTT	Unknown	500–760 TGGAA	Pure cerebellar ataxia	+
SCA36	*NOP56* (intron)	3–14, GGCCTG	Unknown	650–2,500	Motor neuron disease	–
SCA37[f]	*DAB1* (5′ UTR; intron)	<400, ATTTT	Unknown	31–75, ATTTC repeats within ATTTT repeats	Pure cerebellar ataxia	–

Table 2 | **SCAs caused by point mutations**

Disease	Gene	Mutation	Notable characteristic clinical signs
SCA5	*SPTBN2*	Missense	Downbeat nystagmus and some patients with spasticity, anticipation
SCA11	*TTBK2*	Missense	Some patients with pyramidal signs
SCA13	*KCNC3*	Missense	Variable between families
SCA14	*PRKCG*	Missense	Tremor or myoclonus, facial myokymia
SCA15 and 16	*ITPR1*	Deletion	Pure cerebellar ataxia with tremor
SCA18	*IFRD1*	Missense	Sensorimotor neuropathy
SCA19 and 22	*KCND3*	Missense, in-frame 3 bp deletion	Extracerebellar features variable between families
SCA20	Multiple (*DAGLA*)*	260 kb duplication	Pure cerebellar ataxia with spasmodic dysphonia, palatal tremor
SCA21	*TMEM240*	Missense	Cognitive impairment, extrapyramidal signs
SCA23	*PDYN*	Missense	Extracerebellar features variable between families
SCA26	*EEF2*	Missense	Pure cerebellar ataxia
SCA27	*FGF14*	Missense	Mental retardation, tremor
SCA28	*AFG3L2*	Missense	Spastic ataxia
SCA29	*ITPR1*	Missense	Pure cerebellar ataxia, congenital non-progressive
SCA34	*ELOVL4*	Missense	Hyperkeratosis, MSA-C-like
SCA35	*TGM6*	Missense	Hyperreflexia and variable other extracerebellar features
SCA38	*ELOVL5*	Missense	Pure cerebellar ataxia, some patients have sensory neuropathy
SCA40	*CCDC88C*	Missense	Spastic ataxia
SCA41	*TRPC3*	Missense	Pure cerebellar ataxia
SCA42	*CACNA1G*	Missense	Dementia
SCA43	*MME*	Missense	Peripheral neuropathy
SCA44	*GRM1*	Missense, +1bp frameshift	Spasticity
SCA45	*FAT2*	Missense	Pure cerebellar ataxia (single family)
SCA46	*PLD3*	Missense	Sensory neuropathy

MSA-C, multiple system atrophy of cerebellar type. Data were extracted from Online Mendelian Inheritance of Men (OMIM) and GeneReviews of corresponding SCAs. *The duplicated region in direct orientation contains 12 or more genes, including *DAGLA*.

Ataxies à expansion tri ou penta nucléotides

9 gènes qui rendent comptent de 40 à 60¨% des patients

- Triplets CAG codent pour la polyglutamine
  - SCA 1, 2, 3, 6, 7, 17, ADRLP (TAD)
    - » Début à l'âge adulte, qq cas dans l'enfance quand transmission paternelle
    - » Evolution progressive, sans rémission et souvent fatale après 10 à 30 ans
    - » Les signes cliniques à partir d'un seuil de répétitions (20 pour SCA6 et 54 pour SCA3)
    - » Corrélation négative entre le nombre de répétitions et l'âge de début
    - » Répétions instables, augmentation pendant la transmission: anticipation (sauf SCA6)
    - » Cas sporadiques provenant d'allèles intermédiaires
    - » Le gène est exprimé ubiquitairement
    - » La protéine pathologique s'accumule dans les inclusions intranucléaires neuronales ubiquitaires (sauf SCA2 et
    - » Ces agrégats résultent d'anomalie de conformation et de dégradation protéique et ont des propriétés toxiques anormales
  - Maladie de Huntington, atrophie musculaire spinobulbaire liée à l'X (Kennedy)
  - Triplets CAG non polyglutamine: SCA 12
- Triplets GAA: ataxie de Friedreich Triplets CGG: syndromes X fragile (FraXA et Fra XE)
- Triplets CTG: SCA 8 Quintuplet ATTCT: SCA 10

Signes cliniques évocateurs d'un génotype SCA spécifique

Signe Clinique	Génotype SCA
Age de début	Enfance: SCA7, 13, DRPLA / Adulte jeune: SCA 1,2,3 / âgé: SCA6
Anticipation	La plupart des SCA; majeure dans SCA7 et DRPLA
Espérance de vie normale	SCA6, SCA11
Signes pyramidaux	SCA1,3,7,12; certaines SCA6,8 ; rarement SCA2
Saccades lentes	Précoces et prédominantes: SCA2,7; tardives: SCA1, 3 (+/- SCA6)
Nystagmus	SCA6 et EA2
Akinésie, rigidité, dystonie	SCA2, 3, 9; SCA12 (akinésie); SCA21
Chorée	Précoce et majeure: DRPLA; SCA 17 ; rarement :SCA2;
Aréflexie généralisée	SCA2, 4; formes à début tardif de SCA3
Maculopathie	SCA7
Epilepsie	SCA10; formes de DRPLA et SCA7 débutant dans l'enfance
Démence	DRPLA; formes à début précoce de SCA2,7; SCA17
Myoclonies	SCA 14,2; SCA19
Tremblement tête et main	SCA12,16
Neuropathie	SCA4, SCA18 (SMNA)
Retard mental	SCA 13

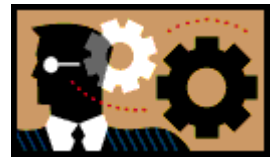
(Subramony et al., 2001)

Ataxies autosomales récessives

Locus	Chro.	Gène/prot	Caractétristiques
FRDA	9q13	Frataxin	Neuropathie sensitive, aréflexie, cardiomy.
AVED	8q13	TTPA	~FRDA, ↓ Vitamine E
AT	11q22	ATM	A, télangiectasies, deficit immuno, ↑αFP
ATLD	11q21	MRE11	~ AT, évolution plus lente
AOA-1	9p13	aprataxin	précoce, apraxie OM, chorée, neuropathie, ↓ QI
AOA-2	9q34	senataxin	id, QI N, ↑αFP
SCAN-1	14q31	TDP1	Neuropathie, hypoesthésie, chol, SA
EOCA	13q12		Ataxie début précoce, avec réflexes N
EPM-1	21q22	cystatin B	Ataxie, epilepsie myoclonique
AR SACS	13q12	sacsin	Ataxie, neuropathie, Σ pyramidal
Cayman Ataxia	19p13	caytaxin	Hypotonie précoce, Σ cérébel. non évolutif, ↓ QI
Abetalipoprotein	4q24	MTP	A, NP, retinopathie, acantho, stéatorrhée

Ataxie héréditaires: Ordre et chaos

ETAT DES CONNAISSANCES



XIXè siècle: Description des pionners

Début XX siècle: Chaos diagnostic

AVANCEES MAJEURES

Reconnaissance des ataxies héréditaires par Friedreich, Marie

Observation de variations cliniques, pléthore de catégories cliniques

Ataxie héréditaires: Ordre et chaos

I) → **Forme cérébelleuse (TAD)**
→ **Forme spinocérébelleuse (TAR)**

II) → **Atrophie corticale** → **Localisée: atrophie olivocérébelleuse Holms**
→ **Diffuse**
→ **Atrophie des voies cérébelleuses**
→ **Atrophie olivo-ponto-cérébelleuse (cérébellipède)**
→ **Atrophie des noyaux dentelet (cérébellifuge)**

III) En fonction de la clinique

→ **Friedreich**
→ **Strumpell Lorain**
→ **Pierre Marie**

Classification clinique d'Harding (1993)

- **ADCA type I : Syndrome cérébelleux et autres signes**
  - » **Ophtalmoplégie, atrophie optique, saccades oculaires lentes**
  - » **Syndromes pyramidal et extrapyramidal**
  - » **Neuropathie**
- **ADCA type II : Syndrome cérébelleux et maculopathie**
  - » **Les signes de l'ADCA I peuvent être présents**
- **ADCA type III : Syndrome cérébelleux sans atteinte multisystèmique**
  - » **Demeure relativement isolé après 10 ans (possible association de signes discrets)**
- **ADRLP: Atrophie dentato-rubro-pallido-luysienne**
  - » **Association variable de chorée, myoclonie, ataxie, parkinson et démence**

Correspondance entre classification clinique type ADCA et génétique type SCA (Harding, 1993)

ADCA type I (début 35-40 ans)

- SCA1 (Jackson 1977)
- SCA2 (Gispert 1993)
- SCA3/MJD (Takiyama 1993; Stevanin 1994)
- Certaines SCA 4 (Flanigan 1996)
- SCA12 (Holmes 1999)
- SCA13 (Herman-Bert 2000)
- SCA17 (Nakamura 2001)
- SCA18 (Brkanac 2002)
- SCA19 (Schelhaas 2001; Verbeek 2002)
- SCA21 (Devos 2001)

ADCA type III (Evolution lente et début > 45 ans)

- SCA4 (Nagaoka 2000)
- SCA5 (Ranum 1994)
- SCA6 (Zhuchenko 1997)
- SCA8 (Koob 1999)
- SCA10 (Zu 1999)
- SCA11 (Worth 1999)
- SCA14 (Yamashita 2000; Brkanac 2002)
- SCA15 (Storey 2001)
- SCA16 (Miyoshi 2001)
- SCA22 (Chung 2003)

ADCA type II (début 30 ans)

- SCA7 (Benomar 1995; Gouw 1995; Holmberg 1995)

ADCA I et II

Gene	Locus	Mutation (patho)	Caractéristiques cliniques ± associées au Σ cérébelleux
SCA 1	6p22-23	CAG (39-83)	± ophtalmoplégie, atrophie optique, pyramidal, parkinson., démence,
SCA 2	12q23-24.1	CAG (32-77)	± idem SCA 1 mais ophtalmoplégie et hyporéflexie plus fréquentes
SCA3/MJD	14q32.1	CAG (54-89)	± idem SCA 1 mais signes extrapyramidaux plus fréquents
SCA 4	16q22.1		Certaines familles SCA 1 mais neuropathie sensitive et hyporéflexie
SCA9			± idem SCA 3
SCA12	5q31-33	CAG (66-80)	idem SCA 1, tremor, démence tardive, neuropathie
SCA13	19q13.3-13.4		Retard psychomoteur, nystagmus, syndrome pyramidal
SCA17	6q27	CAG (43-54)	Démence, Huntington-like ou DRLPA-like
SCA18	7q22-q32		Neuropathie axonale sensitive-motrice, signes pyramidaux
SCA19	1p21-q21		Troubles cognitifs, tremblements, myoclonies
SCA21	7p21.3-p15.1		Parkinsonism, hyporéflexie, troubles cognitifs, évolution lente

ADCA III et

Gene	Locus	Mutation (patho)	Caractéristiques cliniques ± associées au Σ cérébelleux
SCA 4	16q22.1		Certaines familles ataxie relativement pure
SCA 5	11		Début 14-40 ans, ataxie # pure, lentement progressive
SCA 6	19p13.1	CAG (21-33)	Début # 45ans, nystagmus, extrapyramidal modéré, hypopallesthésie
SCA 8	13q21	CTG (107-250)	+/- spasticité, bulbaire, oculomoteur, neuropathie, tremblement, cognitif
SCA10	22q13	ATTCT (63)	ataxie # pure, nystagmus, épilepsie (20%)
SCA11	15q14-21.3		ataxie # pure, hyperréflexie modérée
SCA14	19q13.4-qter	Mut. ponctuelle	ataxie # pure, début > 39 ans, cas juvéniles avec myoclonies
SCA15	3p24.2-3pter		ataxie # pure +/- tremblement et myoclonies, troubles oculomoteurs
SCA16	8q22.1-q24.13		ataxie # pure, tremblement du chef, nystagmus
SCA22	1p21q23		ataxie # pure hyporéflexie, dysphagie, nystagmus
SCA25	2p15-p21		Neuropathie sensitive +/- phénotype Friedreich

ADCA III et

Harding [2]	Gene	Fréquence	Harding [2]	Gene	Fréquence
ADCA I	SCA 1	5-40 %			
ADCA I	SCA 2	10-40 %			
ADCA I	SCA3/MJD	11-84 %	**ADCA III**	SCA 6	1-16 %
ADCA II	SCA 7	5-8 %			

Ataxies associées à une anomalie de conformation et de dégradation protéique

- **Autosomale dominante :** SCA 1, 2, 3, 6, 7, 17 et ADRLP
- **Ataxie spastique autosomale récessive type Charlevoix Saguenay (SACS)**
  - Nord Est du Québec
  - Striation rétinienne, ataxie précoce, dysarthrie, nystagmus, spasticité, amyotropie distale, NP sensitivo motrice

Signes parkinsoniens dans les ataxies

- **Présents dans tous les SCA**
- **Plus fréquemment dystonies chez jeunes et Σ Parkinson chez sujets âgés**
- **Orientent de manière non spécifiques le diagnostic génétiques des SCA**
  - **SCA où atteinte des GGB a été prouvée à l'autopsie: SCA 2, 3**
  - **Fréquents: SCA 2, 3, 9, 12, 21, ADRLP**
  - **Variables: SCA 1**
  - **Rares: SCA 6 et ataxie de Friedreich**
  - **Caractéristiques: SCA 2, 3, 12 et 21**
    - **Tremblement postural → SCA 2**
    - **Dystonies ou Σ Parkinson → SCA 3, ADRLP**
    - **Tableau de pseudo parkinson → SCA 3**
    - **Akinésie → SCA 12**
    - **Akinésie et rigidité très modérées ± tremblement → SCA 21**
- **Parfois dopasensibles → Traitement**
- **Si prédominants et sporadiques → suspicion d'AMS type c**
  - **50 % des ataxies cérébelleuses sporadiques à début tardif (Schols et al. 2000)**
  - **Diagnostic positif:**
    - **Σ parkinsonien et Σ dysautonomique rapidement évolutif ≤ 9 ans**
    - **Absence d'ATCD familial**
    - **Absence de neuropathie, rétinopathie…**
- **Mauvais pronostic des signes parkinsoniens dans une ataxie idiopathique**
  - **Bradykinésie, instabilité posturale, dysarthrie, tremblement posturale et cinétique**

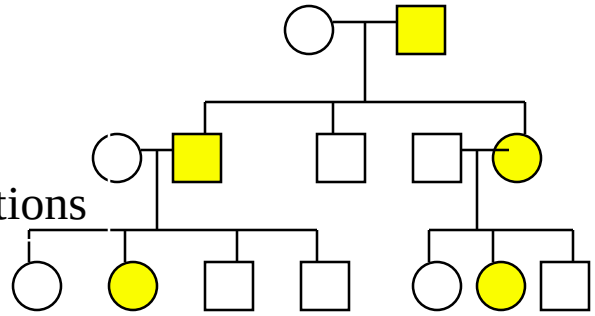
Diagnostic génétique des ADCAs

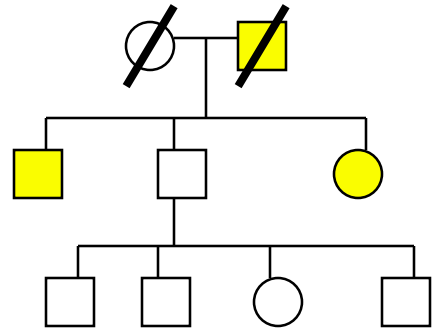
- **1 seul patient prélevable -> étude des seules mutations connues**
  - **SCA 1,2,3,6,7 (selon clinique)**
  - **possible mais plus rare: SCA8,(10),12,17, ADRLP**
- **Prélèvement possible de toute la famille**

10 méioses

Sains et malades

plusieurs générations



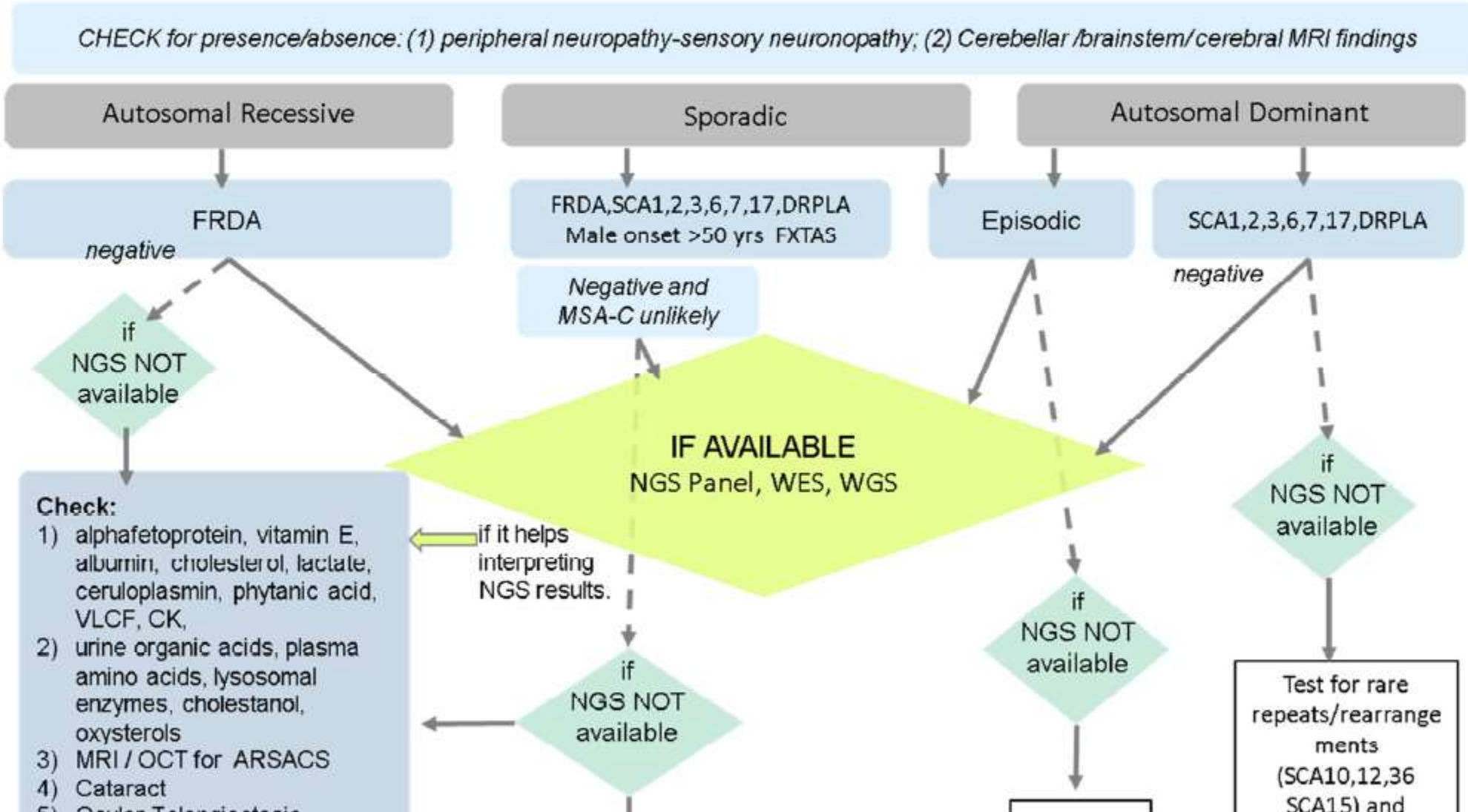


- Etude des autres loci connus:
  SCA 4,5,11,13,14,15,16,18,19,21,22,25
- Etude de nouveaux loci

Pas d'analyse de liaison possible

Diagnostic flowcharts –Ataxias

Exclusion of acquired causes*** in case of negative family history, (sub)acute onset, specific medical history, etc.
***Common Acquired Causes: auto immune diseases (MS, sarcoidosis, celiac disease, etc), toxic reaction, head trauma, cerebral palsy, tumor, stroke, infections, vitamine deficiency, paraneoplastic syndromes



Typical signs and symptoms of cerebellar ataxia

Clumsiness, swerving

Difficulty in walking

Balance problems, swaying, falling (leading to or manifested as trauma)

Difficulty in dressing, handling utensils, and writing

Slurred speech

Hypotonia, slowness

Delayed motor development (onset of walking after 18 mo)

Intentional hand tremor

Dizziness (patient is sometimes referred to otorhinolaryngologist)

Visual disturbances (patient is sometimes referred to ophthalmologist)

Incidental finding of cerebellar atrophy on magnetic resonance imaging

Mistakes to avoid if diagnosis of cerebellar ataxia is uncertain

Neglecting the disorder

Considering a psychiatric origin

Suspecting an otorhinolaryngologic, ophthalmologic, orthopedic, or a rheumatologic cause

Not requesting a second examination several weeks or months later

Not referring patient to a neurologist or a pediatrician who specializes in neurology

Not urgently investigating an acute cerebellar ataxia

Notre panel de gènes Ataxie : 366 gènes

AAAS	ATCAY	CC2D2A	CUL4B	ERCC8	GLRX5	KIF26B	NEU1	PHYH	RPGRIP1L	SPG7	TRAPPC11	YME1L1
AARS2	ATG5	CCDC88C	CWF19L1	ERLIN1	GM2A	KIF5C	NHLRC1	PIBF1	RPIA	SPR	TRPC3	ZIC1
ABCB7	ATM	CEP104	CYP27A1	ETFA	GOSR2	KIF7	NKX6-2	PIK3R5	RRM2B	SPTAN1	TSEN15	ZIC4
ABCD1	ATP13A2	CEP120	DAB1	ETFB	GRID2	L1CAM	NOL3	PITRM1	RUBCN	SPTBN2	TSEN2	ZNF423
ABHD12	ATP1A2	CEP290	DARS2	ETFDH	GRM1	L2HGDH	NOP56	PLA2G6	SACS	SQSTM1	TSEN34	ZNF592
ACO2	ATP1A3	CEP41	DBT	EXOSC3	GSN	LAGE3	NOTCH3	PLD3	SAMD9L	STUB1	TSEN54	
ADCK3	ATP2B3	CEP55	DDB2	EXOSC8	HEXA	LAMA1	NPC1	PLEKHG4	SARS	SUFU	TTBK2	
ADCK4	ATP7B	CFAP52	DKC1	FA2H	HEXB	LITAF	NPC2	PLP1	SCARB2	SYNE1	TTC19	
ADGRG1	ATP8A2	CHMP1A	DLAT	FAT2	HIBCH	LMNB1	NPHP1	PMM2	SCN1A	SYT14	TTC21B	
AFG3L2	ATXN10	CHP1	DNAJC19	FGF12	HPRT1	LMNB2	NUBPL	PMPCA	SCN2A	TBC1D23	TTPA	
AHI1	B9D1	CLCN2	DNAJC5	FGF14	HSD17B4	LRPPRC	OFD1	PNKP	SCN8A	TCF4	TUBB4A	
AIMP1	B9D2	CLN5	DNMT1	FGFR3	HSPD1	LYST	OPA1	PNPLA6	SCYL1	TCTN1	UBA5	
ALAS2	BCKDK	CLP1	EBF3	FLVCR1	HTRA1	MAG	OPA3	POLG	SEPSECS	TCTN2	UBR4	
ALG6	BEAN1	COA7	EEF2	FMR1	IFRD1	MARS2	OPHN1	POLH	SETX	TCTN3	UBTF	
AMACR	BOLA3	COL18A1	EIF2B1	FOLR1	INPP5E	MECP2	OSGEP	POLR3A	SIL1	TDP1	UCHL1	
AMPD2	BRAF	COQ2	EIF2B3	FOXC1	ITM2B	MKS1	OTC	POLR3B	SLC17A5	TDP2	VAMP1	
AMT	BRF1	COQ4	EIF2B4	FRMD4A	ITPR1	MLC1	PAX6	POMGNT1	SLC1A3	TGM6	VHL	
ANO10	BTD	COQ6	EIF2B5	FXN	KCNA1	MMACHC	PCLO	PRICKLE1	SLC25A1	THG1L	VLDLR	
AP5Z1	C10ORF2	COQ7	ELOVL4	GALC	KCNA2	MMADHC	PCNA	PRKCG	SLC25A15	TMEM107	VPS13A	
APOA1BP	C12ORF65	COQ9	ELOVL5	GBA	KCNC1	MME	PDE6D	PRNP	SLC25A26	TMEM138	VPS13D	
APOB	C19ORF12	COX10	EMC1	GBA2	KCNC2	MPV17	PDHA1	PRPS1	SLC25A46	TMEM216	VPS53	
APTX	C2CD3	COX20	EOMES	GBE1	KCNC3	MRE11A	PDHX	PRRT2	SLC2A1	TMEM231	VRK1	
ARHGAP42	C5ORF42	CP	EPM2A	GCDH	KCND3	MTPAP	PDSS1	PTEN	SLC30A9	TMEM237	VWA3B	
ARL13B	CA8	CPS1	EPRS	GCLC	KCNJ10	MTTP	PDSS2	PTF1A	SLC52A2	TMEM240	WDR73	
ARMC9	CACNA1A	CRAT	ERCC1	GCSH	KCNMA1	NALCN	PDYN	RARS	SLC6A19	TMEM67	WDR81	
ARSA	CACNA1G	CSPP1	ERCC2	GFAP	KCTD7	NBN	PEX10	RARS2	SLC9A1	TOE1	WFS1	
ARX	CACNB4	CSTB	ERCC3	GJB1	KIAA0556	NDUFAF2	PEX16	RBM10	SLC9A6	TP53RK	WWOX	
ASL	CAMTA1	CTDP1	ERCC4	GJC2	KIAA0586	NDUFB3	PEX2	RELN	SMG9	TPK1	XPA	
ASS1	CAPN1	CTSA	ERCC5	GLB1	KIF1A	NDUFS2	PEX6	REPS1	SNAP25	TPP1	XPC	
ATAD3A	CASK	CTSD	ERCC6	GLDC	KIF1C	NEFL	PEX7	RNF216	SNX14	TPRKB	XRCC1	

Principe général du Next-Generation Sequencing