5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 12

EAN/MDS-ES: Hyperkinetic movement disorders (Level 2)

Ataxia: some order in the disorder?

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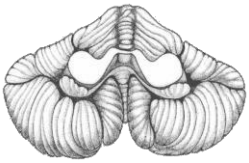
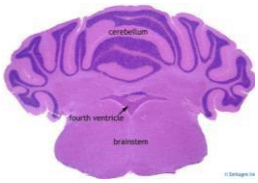
Autosomal Recessive Cerebellar Ataxias: some order in the disorders ?



Mathieu Anheim



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Movement Disorder sessions at the
5th Congress of the European Academy of Neurology
are done in collaboration between MDS-ES and the EAN.

Disclosures

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- Actelion Pharmaceuticals
- Johnson and Johnson
- AbbVie
- Merz
- Aguettant
- LVL
- Orkyn

Cerebellar ataxia

- failure of the conductor
- many causes
- clinical picture:
  - loss of order in the movements
  - difficulties in walking, swerving
  - imbalance, swaying
  - clumsiness, dizziness
  - dysarthria
  - hypotonia
  - slowness

Manto, Handb Clin Neurol, 2012 ; an de Warrenburg et al., Eur J Neurol, 2014

Autosomal recessive cerebellar ataxias (ARCAs)

- rare, heterogeneous and complex
- recessively inherited neurodegeneration
- dominated by cerebellar signs
- ± other neurological and/or extraneurological signs
- onset mostly before the age of 30 years
- major disability after 15 years of disease progression

Anheim et al., NEJM, 2012 ; Beaudin et al., Cerebellum Ataxias, 2017

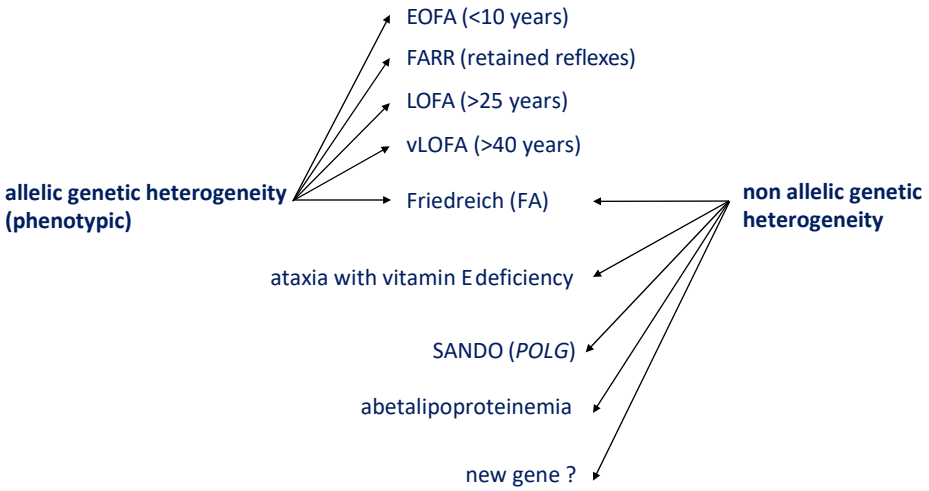
Autosomal recessive cerebellar ataxias (ARCAs)

- next generation sequencing revolution
- explosion of genes (>100)
- difficulties to have an overview
  - rare diseases
  - overlaps
  - variants
  - new genes

- hugh amount of genetic data to be intepreted

Anheim et al., NEJM, 2012 ; Beaudin et al., Cerebellum Ataxias, 2017

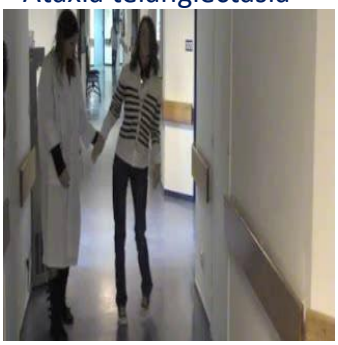
Heterogeneity of ARCAs: difficulties for diagnosis



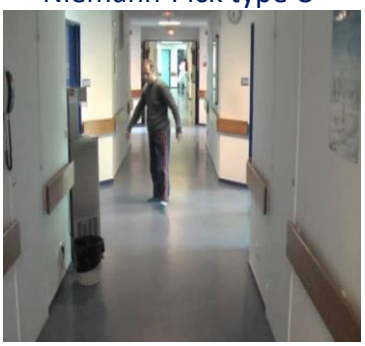
Anheim et al., Arch Neurol, 2012 ; Lecocq et al., Mov Disord, 2016

Ataxia telangiectasia

Niemann-Pick type C



AOA1



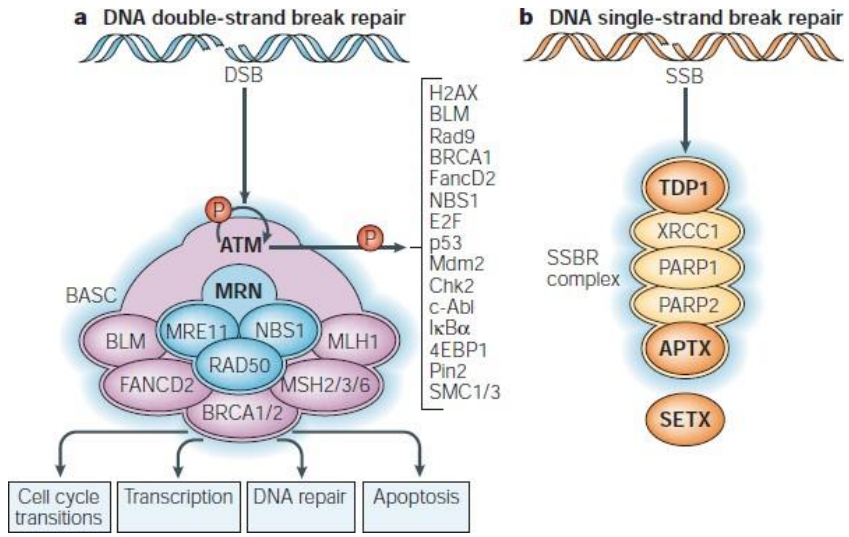
Friedreich's ataxia

Comparing AOA1, AOA2 and ataxia telangiectasia

- share complex, overlapping phenotypes
  - ataxia with cerebellar atrophy
  - movement disorders
    - dystonia, myoclonus, tremor, parkinsonism
  - peripheral neuropathy
  - abnormal ocular movements
    - oculomotor apraxia (saccades of delayed latency)
    - oculocephalic dissociation
    - hypometric/hypermetric saccades
  - elevated AFP serum level

Mariani et al., Sci Rep, 2017

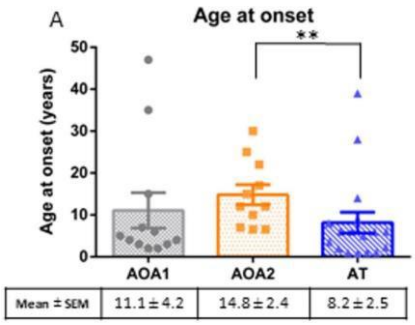
Comparing AOA1, AOA2 and ataxia telangiectasia



Taroni et al., Nat Rev Neurosci, 2004

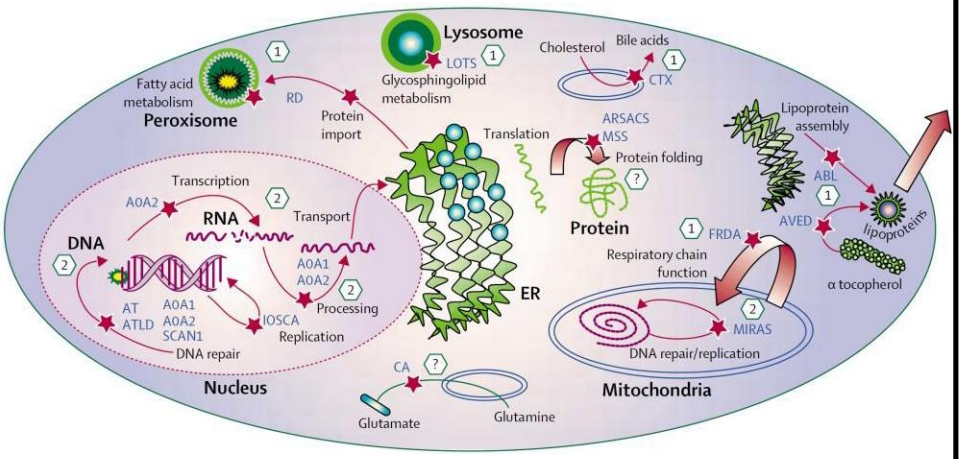
Comparing AOA1, AOA2 and ataxia telangiectasia

- dystonia less frequent in AOA1
- myoclonus more frequent in ataxia telangiectasia
- no difference regarding video-oculography recording



Mariani et al., Sci Rep, 2017

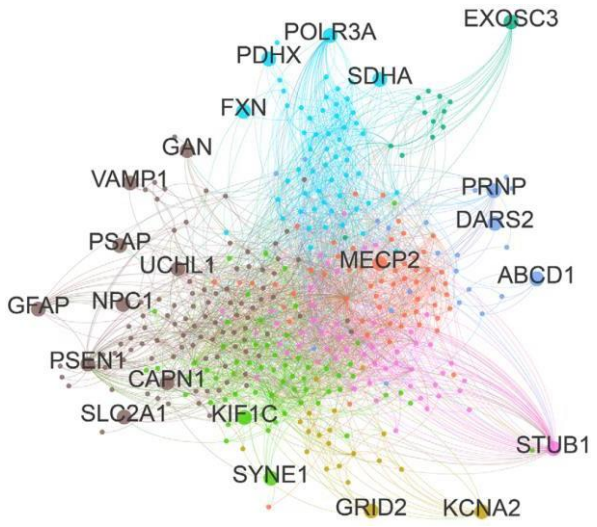
Cellular pathways involved in recessive ataxias



Fogel, Lancet Neurol, 2007

Ataxia to Spastic Paraplegia spectrum

Protein-protein interaction network



Synofzik and Schule, Mov Disord, 2017

REVIEW

The Genetic Nomenclature of Recessive Cerebellar Ataxias

Malco Rossi, MD, PhD,[1] Mathieu Anheim, MD, PhD,[2,3,4] Alexandra Durr, MD, PhD,[5,6] Christine Klein, MD,[7,8] Michel Koenig, MD, PhD,[9] Matthis Synofzik, MD,[10,11] Connie Marras, MD, PhD,[12] and Bart P. van de Warrenburg, MD, PhD,[13]* on behalf of the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders

- enormous clinical and genetic heterogeneity
- new classification according the MDS task force on nomenclature
  - transparent, adaptable, facilitating for diagnosis
- genetically confirmed recessive cerebellar ataxias
- 62 entities with ATX prefix followed by the name of the gene
  - cerebellar ataxia as predominant and/or consistent feature
- 30 entities often combining ataxia and other movement disorders
  - double prefix (e.g. ATX/HSP in case of spastic paraplegia)

Rossi et al., Mov Disord, 2018

REVIEW

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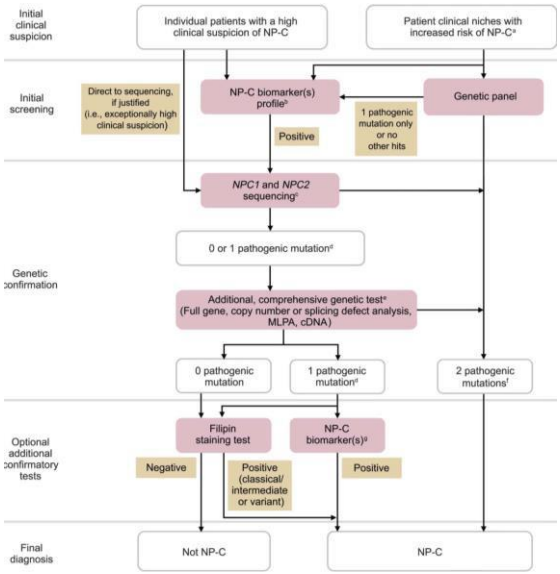
- ATX-ATM
  - ataxia telangiectasia
- ATX-SETX
  - AOA2
- HSP/ATX-SPG7
  - SPG7 (spastic paraparesis and/or ataxia, recessive or dominant !)
- DYT/ATX-ATP7B
  - Wilson's disease

Rossi et al., Mov Disord, 2018

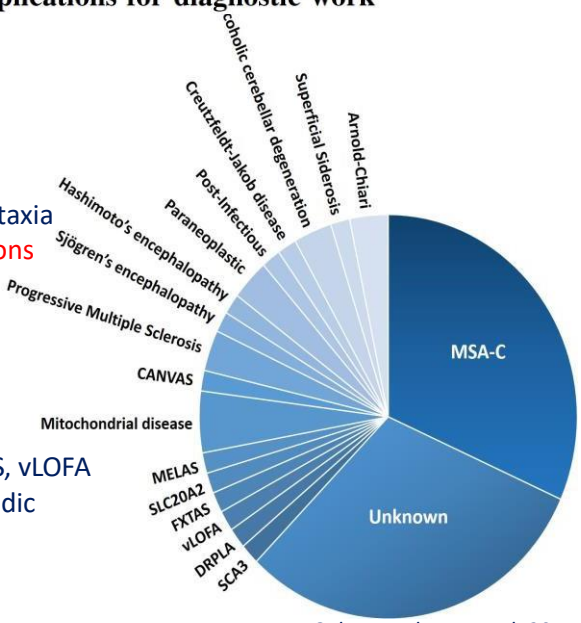
Recommendations for the diagnosis of Niemann-Pick type C



Patterson et al., Neurol Clin Pract, 2017

Deciphering the causes of sporadic late-onset cerebellar ataxias: a prospective study with implications for diagnostic work

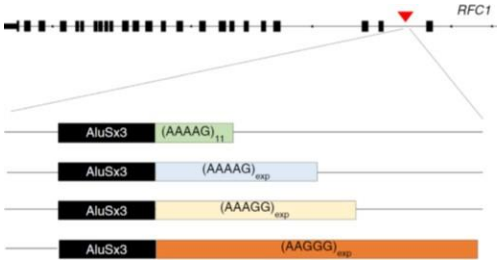
- prospective follow-up of
  - late-onset (>40 yr)
  - sporadic
  - progressive cerebellar ataxia
  - standardized examinations
  - reappraisal
  - genetic analysis
- cohort of 102 patients
  - several genetic diseases including SPG7, CANVAS, vLOFA
  - even dominant in sporadic
  - 30% remains unknown

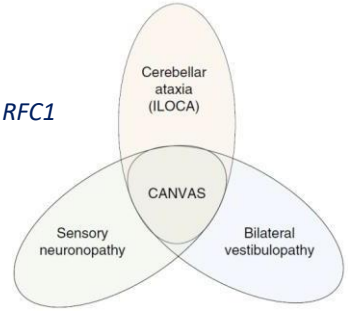


Gebus et al., J Neurol, 2017

Biallelic expansion of an intronic repeat in *RFC1* is a common cause of late-onset ataxia

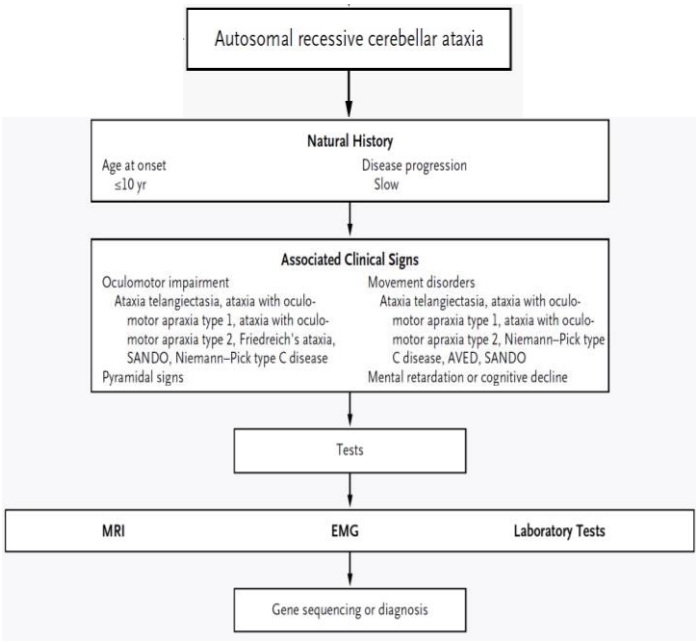
- unlocking CANVAS
  - Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome
    - late-onset ataxia with cerebellar atrophy (≈50 y)
    - sensory neuronopathy (100%)
    - bilateral vestibular areflexia (50%)
    - dysautonomia, and/or cough (20%)
  - genome sequencing
    - biallelic intronic AAGGG repeat expansion in *RFC1*





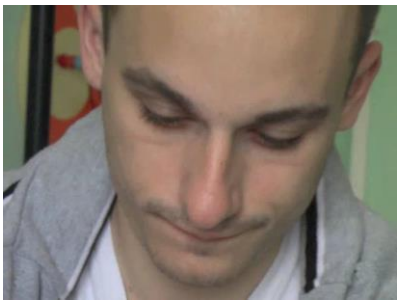
Cortese et al., Nat Genet, 2019

Mancuso et al., J Neurol, 2014

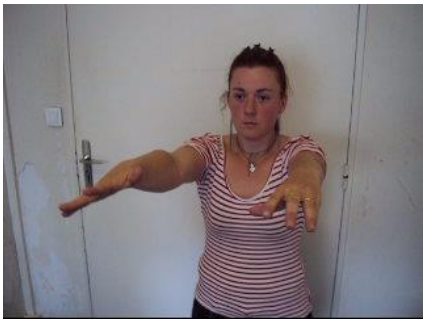


Anheim, Tranchant & Koenig, N Engl J Med, 2012

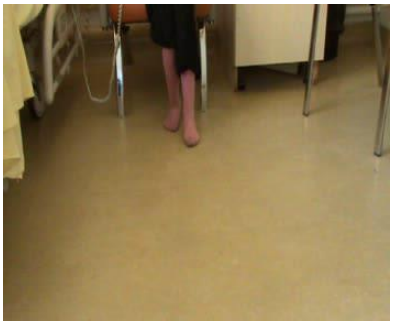
Ataxia with vitamin E deficiency



ARCA2 (*ADCK3*)

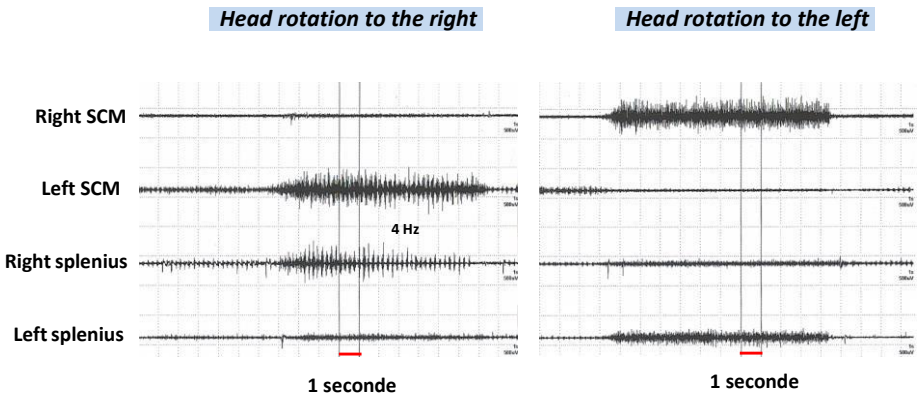


Ataxia Telangiectasia



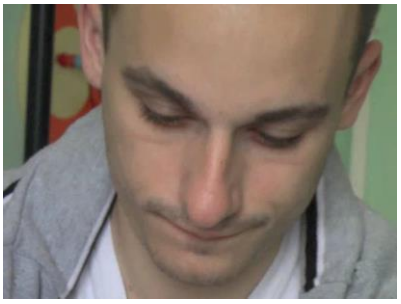
ARSACS

Dystonic cervical tremor in ataxia with vitamin E deficiency



courtesy Pr E. Apartis

Ataxia with vitamin E deficiency



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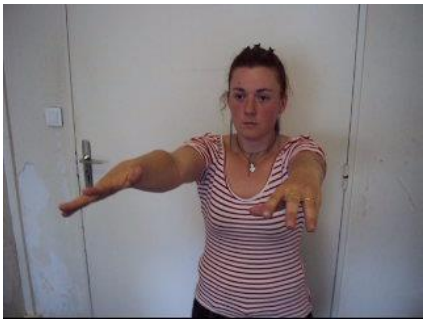
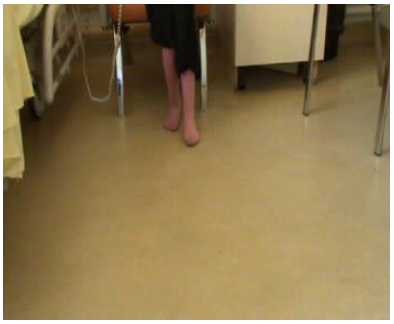
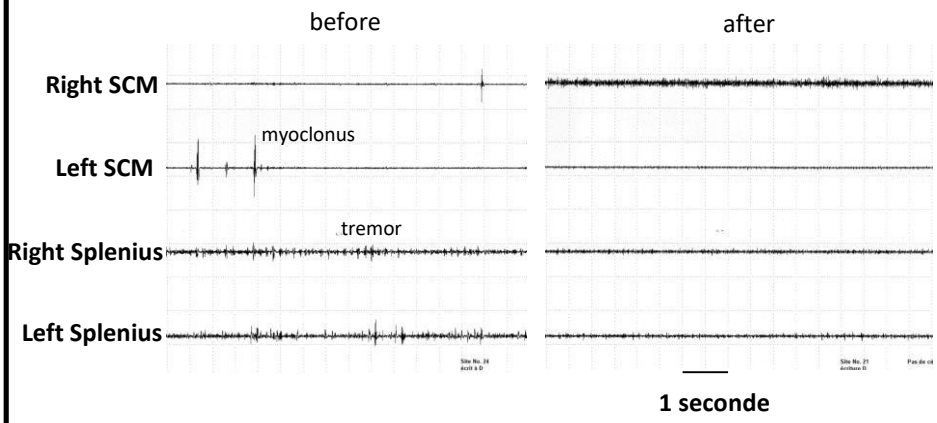


Ataxia Telangiectasia



ARSACS

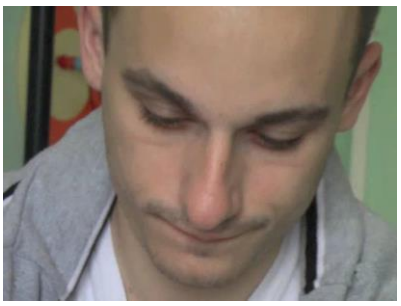
ARCA2 (*ADCK3*) treated with with *CoQ-10*
ubidecarenone 300 mg/d



while writing

Mignot et al. Orphan J Rare Dis, 2013 ; Chang et al., Mov Disord Clin Pract, 2018

Ataxia with vitamin E deficiency



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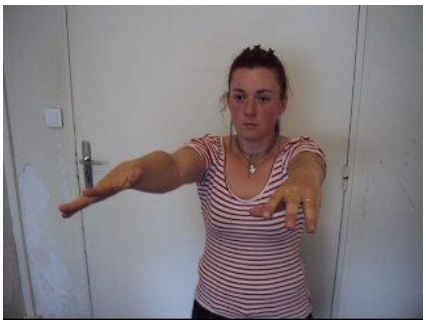
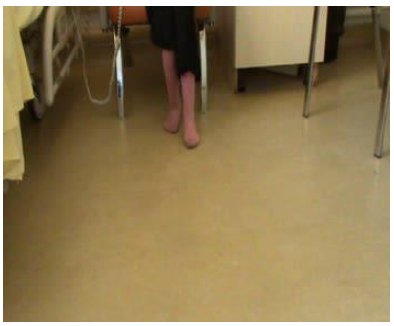


Ataxia Telangiectasia



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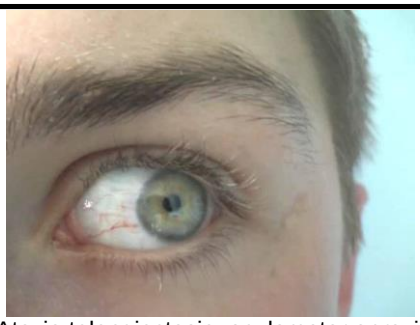
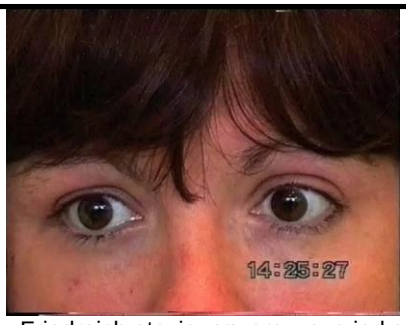
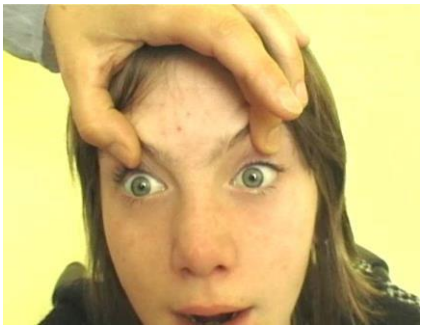


Ataxia telangiectasia: oculomotor apraxia and ocular telangiectasias



Friedreich ataxia: square wave jerks

AOA1: oculocephalic dissociation

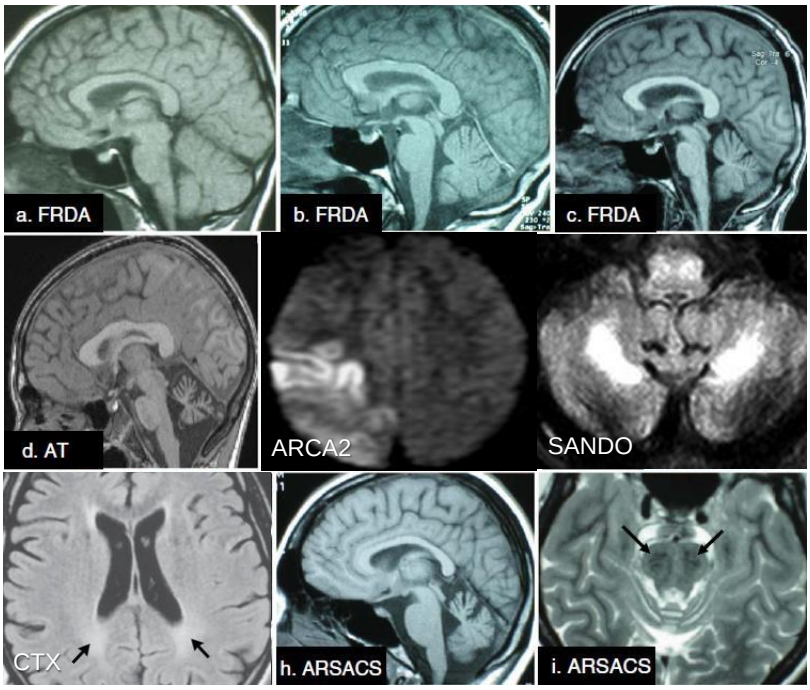


NP-C: vertical supranuclear saccade palsy

Disease	*Gene*	Protein
Ataxia without peripheral neuropathy		
ARCA1	*SYNE1*	SYNE1
ARCA2	*ADCK3*	ADCK3
ARCA3	*ANO10*	Anoctamin
Niemann-Pick C	*NPC1/2*	NPC1/NPC2
Ataxia with pure sensory neuronopathy		
Friedreich ataxia	*FXN*	Frataxin
SANDO	*POLG*	polymerase gamma
Ataxia with vitamin E deficiency	*alpha-TTP*	alpha-TTP
Abetalipoproteinemia	*MTP*	MTP
Ataxia with axonal sensori-motor neuropathy		
Ataxia Telangiectasia	*ATM*	ATM
Ataxia with ocular motor apraxia 1	*APTX*	Aprataxin
Ataxia with ocular motor apraxia 2	*SETX*	Senataxin
Late-onset GM2 gangliosidosis	*HEXA / HEXB*	Hexosaminidase A / B
D ARSACS	*SACS*	Sacsin
D Cerebrotendinous Xanthomatosis	*CYP27*	Sterol 27 hydroxylase
D Refsum Disease	*PhyH / PEX7*	phytanoyl CoA hydroxylase

D: demyelinating

Anheim et al., N Engl J Med, 2012



Laboratory investigations

- GAA expansion: Friedreich
- alpha-fetoprotein: ataxia telangiectasia, AOA2, AOA1, ± ARCA3
- vitamin E: ataxia with vitamin E deficiency, abetalipoproteinemia
- phytanic acid: Refsum
- cholestanol: cerebrotendinous xanthomatosis
- hexosaminidase: late onset Tay-Sachs, Sandhoff
- LDL cholesterol: elevated: AOA1, SCAN1, decreased: abetalipoproteinemia
- albuminemia: decreased: AOA1, SCAN1
- creatine kinase: Marinesco-Sjogren syndrome > AOA2
- lactic acid, muscle CoQ10: ARCA2
- acanthocytosis, lipoproteins: abetalipoproteinemia
- immunoglobulins, karyotype: ataxia telangiectasia
- filipin staining / oxysterols / lysosphingomyelin-509: Niemann-Pick C

RADIAL: an automated version of the algorithm

- Recessive Ataxia ranking differential DIagnosis ALgorithm
- patient suspected with ARCA
  - sporadic/siblings, early onset, ataxia belongs to the phenotype

- knowledgebase:
  - 67 ARCAs described through 124 features
- the phenotype of the patient compared to those of the 67 entities
  - automated analysis
  - score for each ARCA according to the matching
  - the higher the score the more probable the disease

Renaud et al., Ann Neurol, 2018

Validation of algorithm

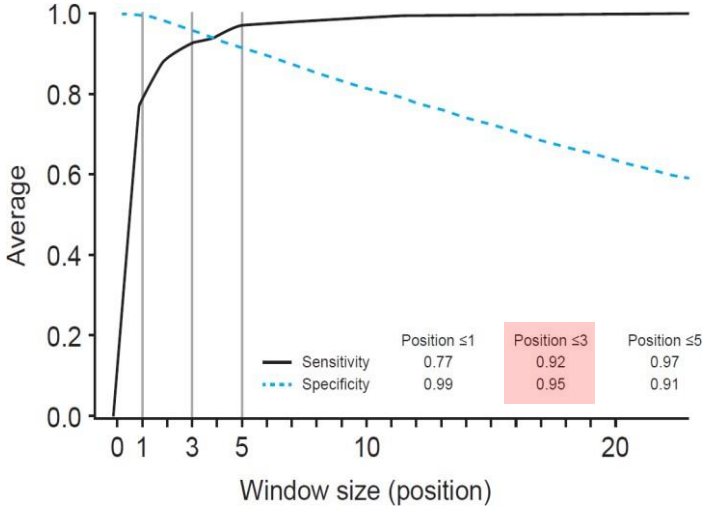
- multinational work
- 47 collaborators from 18 countries
- gathering of 837 patients
- covering 45 entities
- with known clear-cut mutations

→ is RADIAL able to predict the correct genotype based on the phenotype?

Entity	
n	834
FRDA	20
LOFA-VLOF	40
POLG	15
AVED	69
AT	44
AOA1	58
AOA2	60
PMM2	29
SACS	38
PHYH	1
CTX	21
SYNE1	26
ADCK3	13
NPC	57
WD	9
ANO10	14
C10ORF2	24
MRE11	10
ABHD12	9
PNKP	11
STUB1	9
PNPLA6	14
SNX14	7
VWA3B	3
GOSR2	12
SCARB2	15
PEX10	3
WDR73	13
GRM1	10
POLR3A	20
POLR3B	30
KCNJ10	1
OPA1	4
OPA3	10
PEX7	10
VLDLR	15
ZNF592	5
DARS2	8
SPG7	23
GAN	6
GBE1	7
PLA2G6	11
HSD17B4	3
NEU1	26
CP	1

Renaud et al., Ann Neurol, 2018

Results: sensitivity and specificity

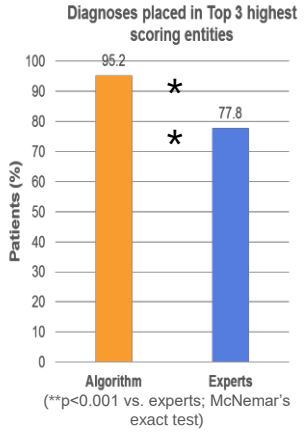


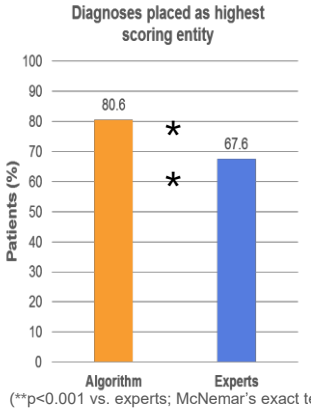
Renaud et al., Ann Neurol, 2018

Man against the machine:
RADIAL outperformed a panel of 5 experts !

Christine Tranchant, Fanny Mochel, Matthis Synofzik, Bart van de Warrenburg, Massimo Pandolfo

Five series of 100 patients were randomly selected from the patient cohort





Renaud et al., Ann Neurol, 2018

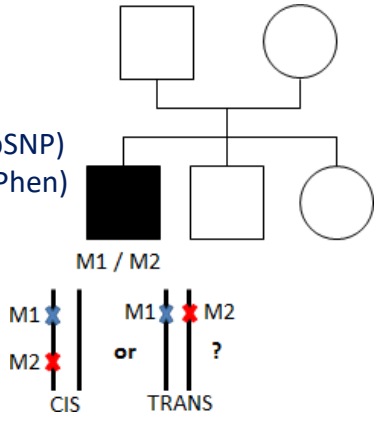
RADIAL was freely online available

However, the RADIAL website has been closed by Johnson and Johnson that bought Actelion Pharmaceuticals

Assessment of a Targeted Gene Panel for Identification of Genes Associated With Movement Disorders

- how to deal with the results provided by NGS ?
- VUS or pathogenic mutation ?

- quality evaluation (depth, coverage)
- database (Exome Variant Server, ExAc, dbSNP)
- pathogenicity prediction tools (SIFT, PolyPhen)
  - amino acid conservation during evolution
  - functional damages due to variation
- segregation analysis in the family



Montaut et al., JAMA Neurol, 2018

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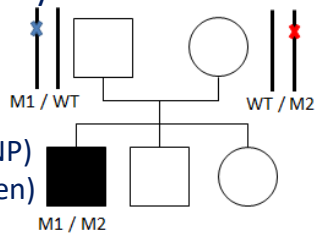

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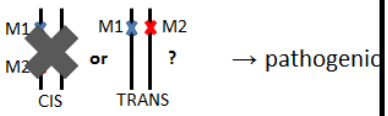

- literature study (PubMed, OMIM)

- close collaboration between neurologists and geneticists
- gene panel / exome / genome: price, time, efficiency

Montaut et al., JAMA Neurol, 2018

Recessive ataxias for which a treatment is available

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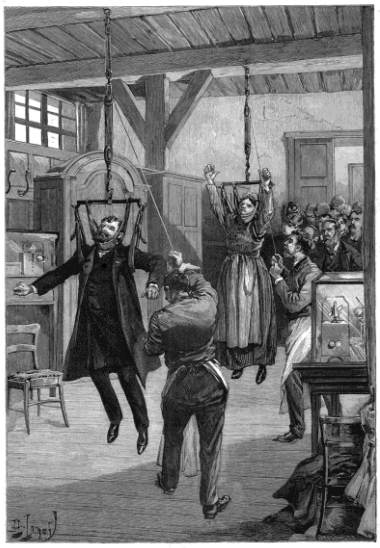


LE NOUVEAU TRAITEMENT DE L'ATAXIE PAR LA SUSPENSION, A LA SALPÊTRIÈRE

TRAITEMENT DE L'ATAXIE LOCOMOTRICE
PAR LA SUSPENSION

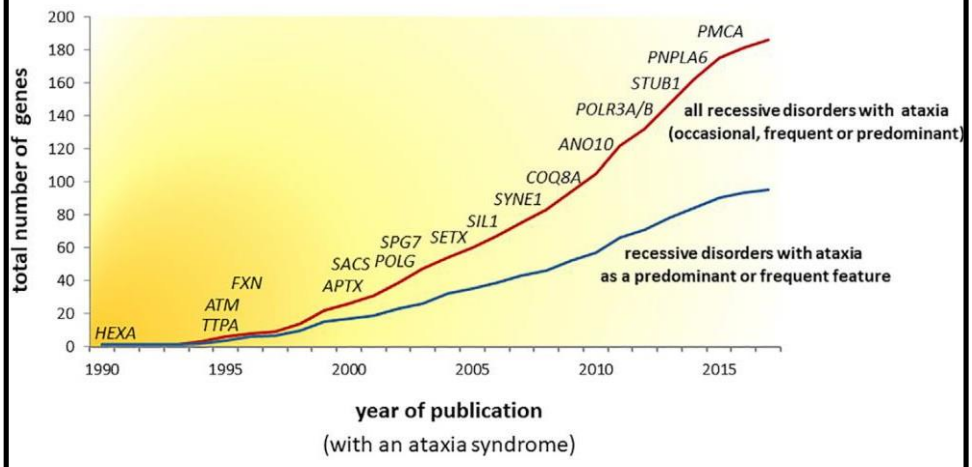
Recessive ataxias for which a treatment is available

- Friedreich ataxia: idebenone, HDACi, pioglitazone, EPO, etravirin ?
- ataxia with vitamin E deficiency: alpha-tocopherol 3 tab/d
- cerebrotendinous xanthomatosis: chenodesoxycholic acid 750mg/d
- Refsum disease: diet low in phytanic acid
- abetalipoproteinemia: low fat diet, vitamins
- Niemann Pick type C: miglustat
- Wilson disease: copper chelator / zinc
- ARCA2: Coenzyme Q 10

Anheim et al., NEJM, 2012 ; Jinnah, Mov Disord, 2018 ; Nilantha de Silva, Pract Neurol, 2019

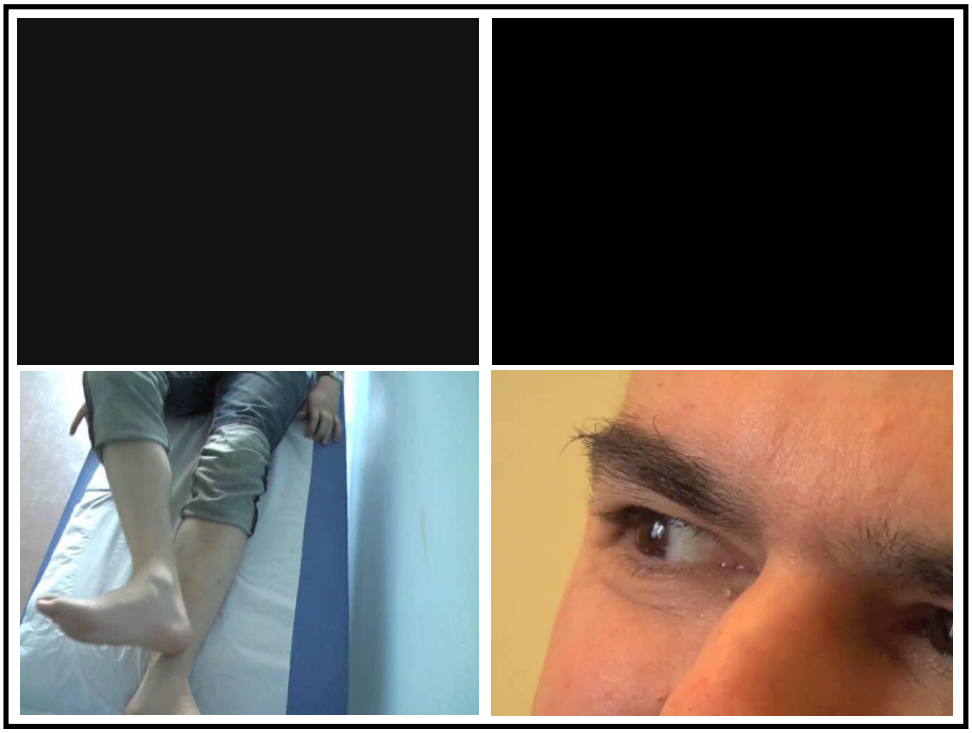
Thank you for your attention

mathieu.anheim@chru-strasbourg.fr

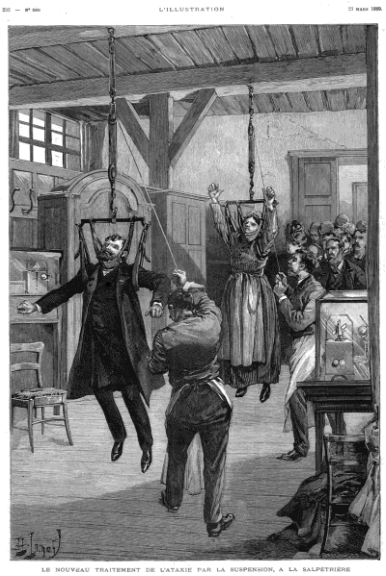


- 12 papers published per month dealing with inherited ataxias
  - new genes
  - new phenotypes/variants

Synofzik et al., Neuron, 2019



Treatment of locomotor ataxia using suspension



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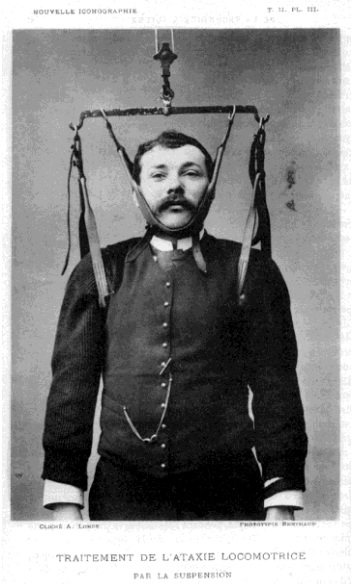

TRAITEMENT DE L'ATAXIE LOCOMOTRICE
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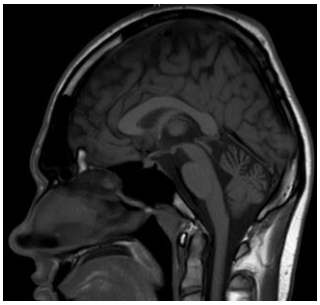
Stand Up with SYNE1 (ARCA1)

Manga with congenital ataxia



Autosomal recessive cerebellar ataxias (ARCAs)

- to provide an automated version of the algorithm to:
  - help diagnostic work in clinical practice
  - guide suitable genetic analysis
  - interpret NGS-induced data
  - provide a knowledgebase on ARCAs

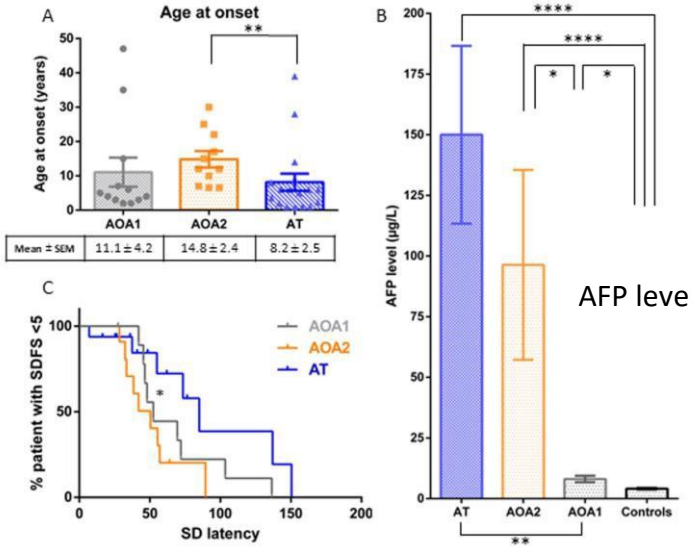
→ **R**ecessive **A**taxia ranking differential **DI**agnosis **AL**gorithm:

"RADIAL"

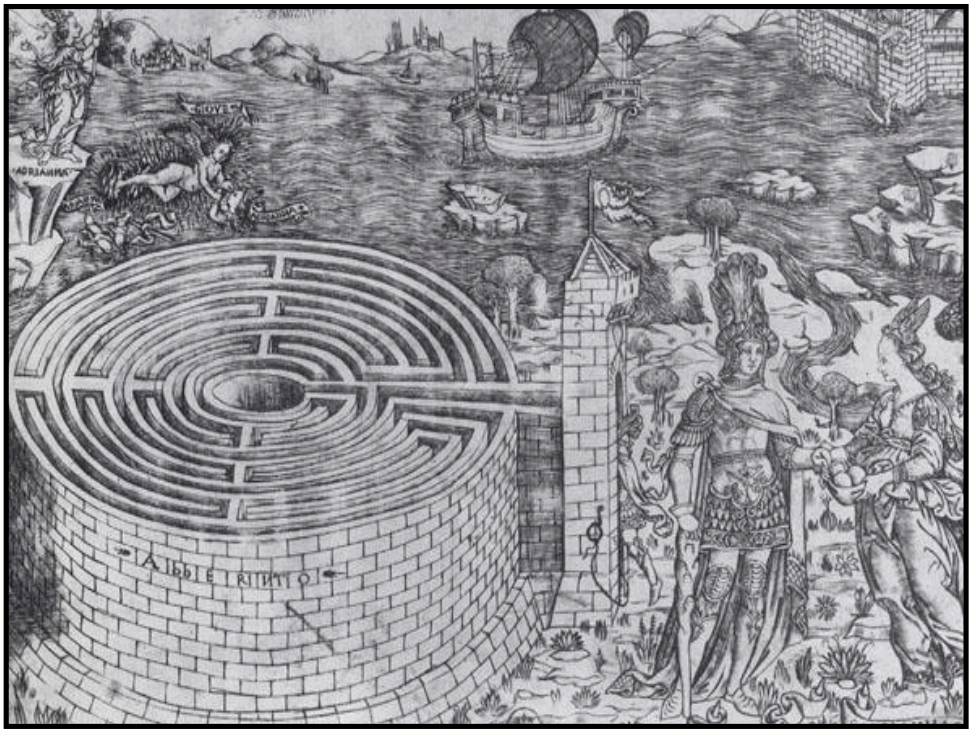
- creation and validation

Renaud et al., Ann Neurol, 2018

Comparing AOA1, AOA2 and ataxia telangiectasia



Mariani et al., Sci Rep, 2017

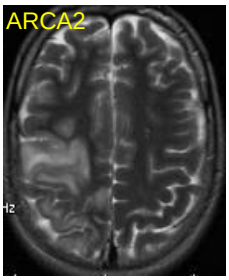


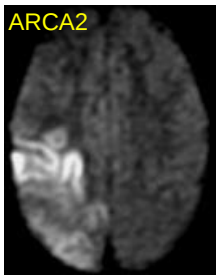
REVIEW

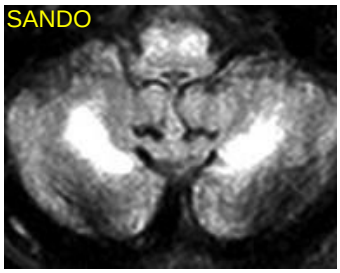
Treatable Inherited Rare Movement Disorders

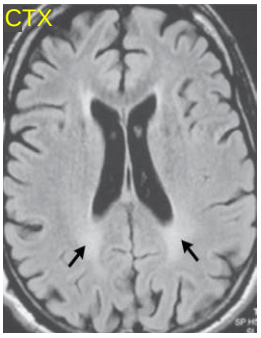
Disorder	Cause (gene)	Movement disorder	Other clinical features[2]	Treatment
Cerebrotendinous xanthomatosis	Sterol-27 hydroxylase (*CYP27A*)	**Ataxia**, spastic paresis, dystonia, parkinsonism, myoclonus	Tendon xanthomas, cataracts, neuropathy, seizures, cognitive impairment	Chenodeoxycholic acid
Dystonia/parkinsonism with manganese accumulation	Manganese transport (*SLC39A14, SLC30A10*)	**Dystonia, parkinsonism**	Liver disease, polycythemia	EDTA chelation therapy
Gaucher disease (neurologic subtype 3)	Glucocerebrosidase (*GBA*)	**Parkinsonism**, **ataxia**, spasticity	Developmental delay, epilepsy, organomegaly, cytopenia	Enzyme replacement therapy, N-butyl-deoxynojirimycin (Miglustat)
Niemann Pick type C[1]	Cholesterol trafficking (*NPC1* or *NPC2*)	**Ataxia**, dystonia, myoclonus, spasticity	Dementia, seizures, supranuclear gaze palsy	N-butyl-deoxynojirimycin (Miglustat)
Wilson disease	Copper transporter (*ATP7B*)	**Dystonia, parkinsonism**, tremor, chorea, myoclonus	Liver disease, Kayser-Fleischer rings, cognitive or psychiatric impairment	Penicillamine, trientine, zinc

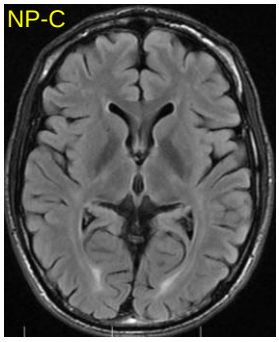
Jinnah et al., Mov Disord, 2018

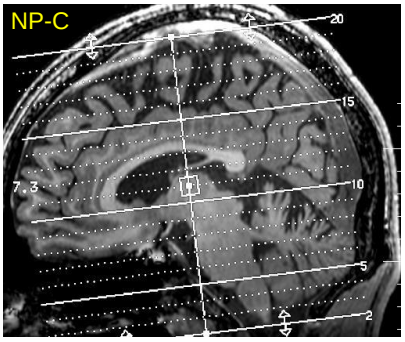












Biallelic expansion of an intronic repeat in *RFC1* is a common cause of late-onset ataxia

	Familial cases ($n=23$)	Sporadic cases ($n=33$)	All cases ($n=56$)	*P*
Male	12 (52%)	15 (45%)	27 (48%)	NS
Age at onset	53 ± 8	54 ± 10	54 ± 9	NS
Disease duration at examination	13 ± 9	10 ± 6	11 ± 7	NS
Sensory neuropathy	23 (100%)	33 (100%)	56 (100%)	NS
Cerebellar syndrome	18 (78%)	27 (82%)	45 (80%)	NS
Bilateral vestibular impairment	17 (74%)	13 (39%)	30 (53%)	0.01
Dysautonomia	4 (17%)	9 (27%)	13 (23%)	NS
Cough	7 (30%)	14 (42%)	21 (37%)	NS
SAP upper limbs				
Reduced	6/21 (29%)	4/31 (13%)	10/52 (19%)	NS
Absent	15/21 (71%)	27/31 (87%)	42/52 (81%)	NS
SAP lower limbs				
Reduced	2/21 (10%)	1/31 (3%)	3/52 (6%)	NS
Absent	19/21 (90%)	30/31 (97%)	49/52 (94%)	NS
Normal motor conduction	19/21 (90%)	26/31 (84%)	45/52 (87%)	NS
Cerebellar atrophy at CT/MRI scan	14/17 (82%)	21/25 (84%)	35/42 (83%)	NS
Full-blown CANVAS syndrome	15 (65%)	11 (33%)	26 (46%)	0.02

Cortese et al., Nat Genet, 2019

Thank you for your attention

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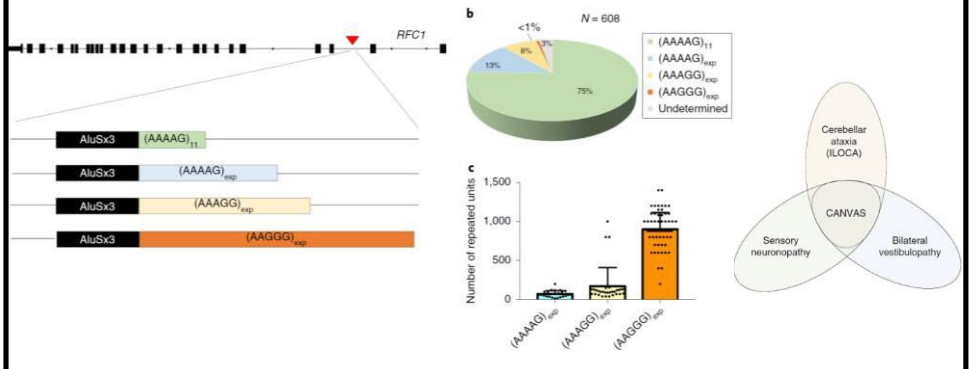

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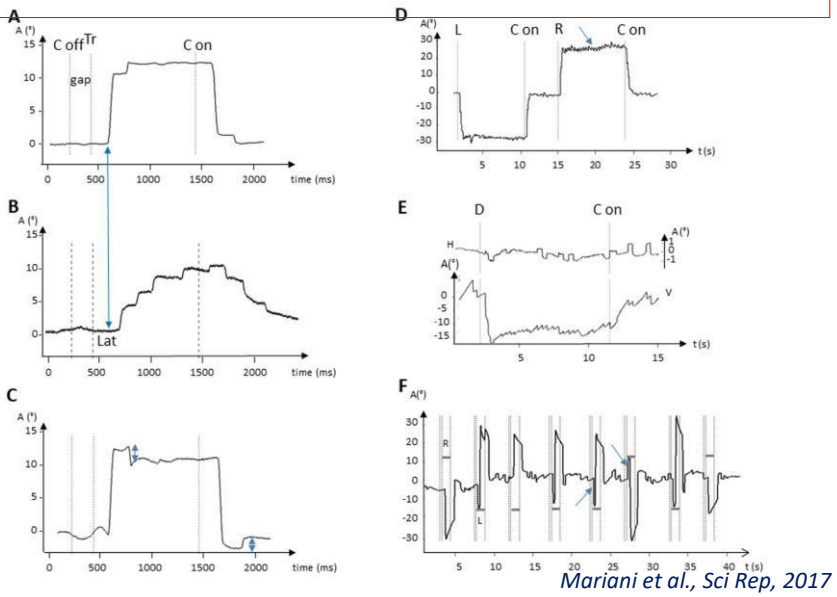


Mariani et al., Sci Rep, 2017

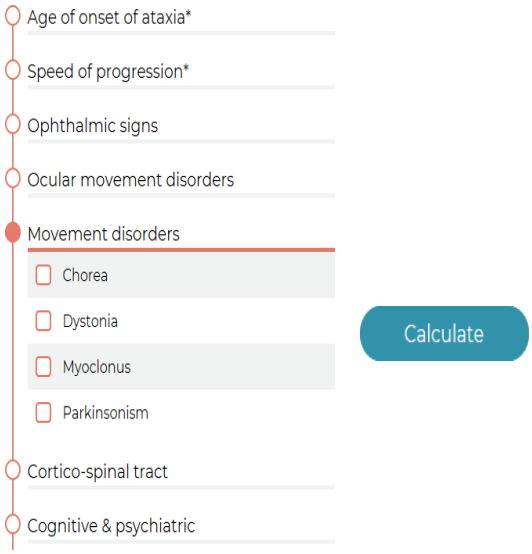
RADIAL is freely online available

http://radial-ataxia-algorithm.com/

You may share your feeling
You may let your email address for further studies

More than 3,000 users and 5,000 sessions in 12 months
20 visits per day

RADIAL Algorithm



RADIAL Algorithm

Symptoms selected:

- Age of onset of ataxia >= 10 years
- Gaze evoked nystagmus
- Hypometric saccades
- Oculomotor apraxia/Oculocephalic dissociation
- Chorea
- Absence of tendon reflexes
- Obvious cerebellar atrophy
- Pure sensory neuropathy
- Elevated serum alpha-fetoprotein level

Rank			Score
1	Ataxia-oculomotor apraxia 2 (AOA2)	Refine	37
2	Ataxia-telangiectasia (AT)	Refine	33
	Ataxia-oculomotor apraxia 3 (AOA3)	Refine	33
3	Ataxia-oculomotor apraxia 1 (AOA1)	Refine	29
4	Ataxia-oculomotor apraxia 4 (AOA4)	Refine	24
5	Spinocerebellar ataxia, autosomal recessive 10 (SCAR10) / ARCA3	Refine	22

*Note: Scores below 20 might be less reliable. We strongly suggest to refine your algorithm.

Conclusion – Perspectives

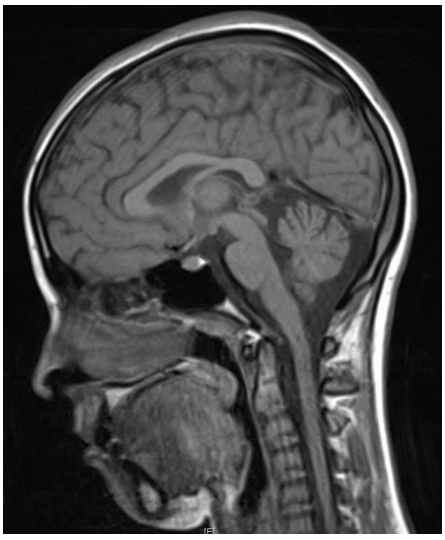
- powerful and innovative tool

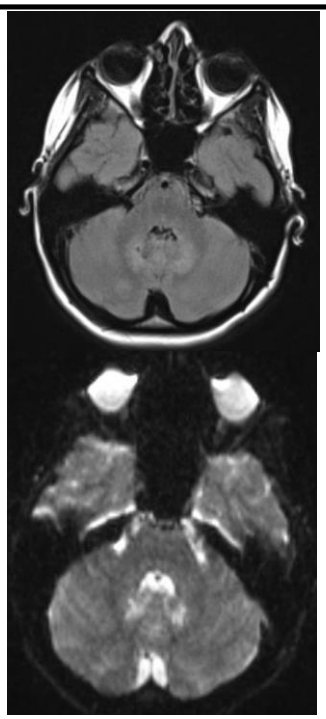
⇒ very good sensitivity and specificity to diagnose ARCA

- provides guidance for diagnostic work of ARCA in clinical practice
- may be helpful for interpretation of NGS results
- must be confirmed by further studies

Une expérience douloureuse

- patiente de 13 ans
  3ème, très bons résultats scolaires
- adressée par neuropédiatre pour avis neurogénétique
- troubles de la marche liés à une ataxie cérébelleuse
  - depuis presque un an (octobre 2014)
  - installation insidieuse
  - aggravation progressive
- IRM, biologie standard, PES, EEG, EMG normaux





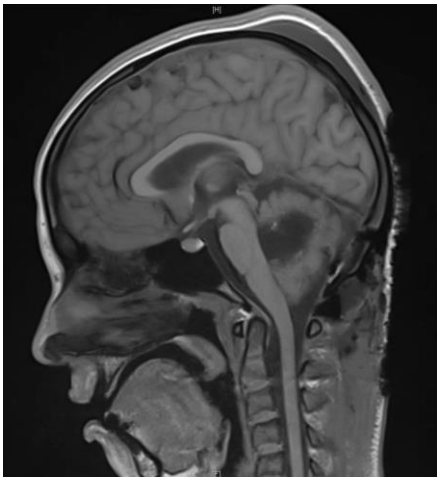
- examen clinique (septembre 2015)
  - ataxie cérébelleuse
  - discrètes myoclonies d'allure sous-corticales
  - évolution chronique
  - cas sporadique chez une patiente jeune
- suspicion d'ataxie cérébelleuse récessive
  - bilan auto-immun et paranéoplasique: négatif
  - biomarqueurs: négatifs
  - mini-exome de 4000 gènes: négatif
- revue en octobre 2015 (stable) et mars 2016 (aggravation)

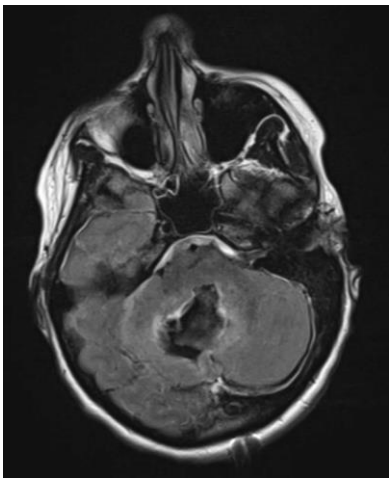
Le 1 mai 2016 à 15:35, | a écrit :

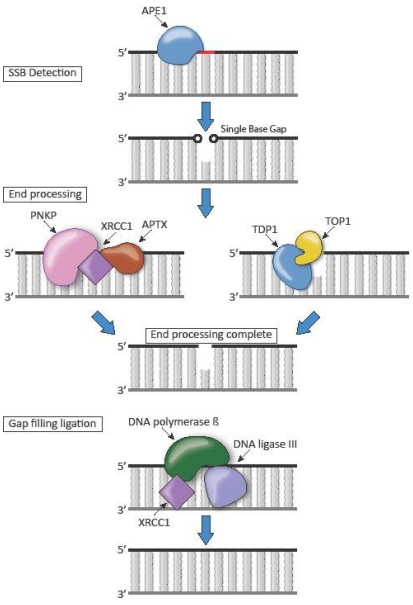
Bonjour docteur
Ma fille vomie depuis 2 jours et se plaint de mots de Tete depuis 2 semaines Elle a mal au cou quand elle se tourne vers la droite Elle dit voir flou et trouble quand elle marche J ai L impression que sa ma démarche à empirée Puis je vous voir demain?
Merci
Bonne journée
Ilana Perez
0662834745

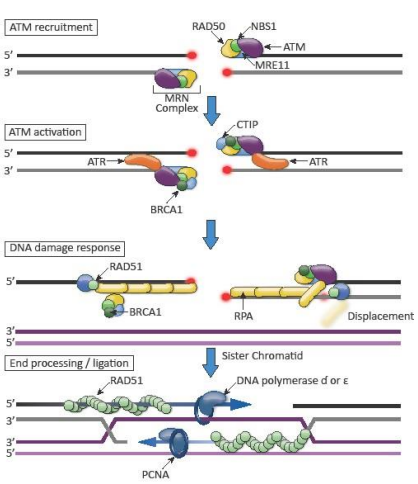
- examen clinique:
  - diplopie binoculaire dans le regard vers la gauche
  - aggravation de l'ataxie cérébelleuse
  - tableau d'HTIC
- IRM cérébrale en urgence

Not that rare, not inherited but treatable !









Renaud et al., in preparation