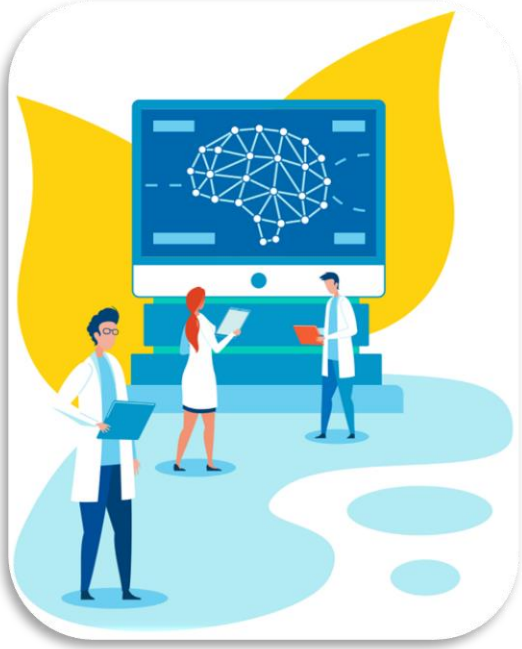
European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Ataxia and HSP'
17 December 2019

Joint webinar series



Non-progressive congenital ataxia

Alfons Macaya
Hospital Universitari Vall d'Hebron
Paediatric Neurology, Barcelona, Spain

Non progressive congenital Ataxia: Webinar Outline

- Introduction and diagnostic algorithm of ataxia in children
- Definition of NPCA
- Clinical features and Examination
- Etiology
- Genetic heterogeneity
- Disease Management
- Conclusions

Learning objectives

- Recognize the presenting signs of NPCA, its co-morbidities and associated outcome
- Identify the main entities in NPCA differential diagnosis
- Assess the role of imaging in diagnosis of very early ataxias
- Identify the more common genetic etiologies of NPCA in order to guide management and genetic counseling

Q1: What is your professional background?

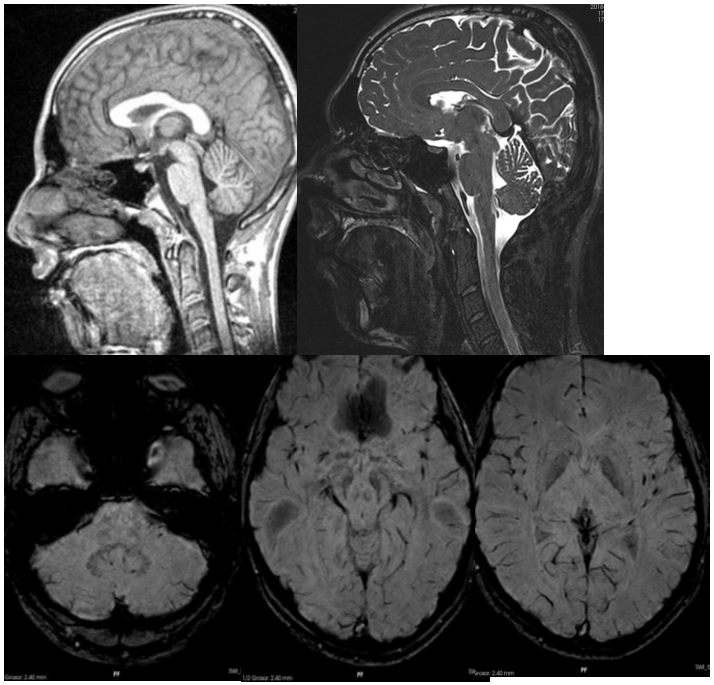
- Neurologist
- Pediatric neurologist
- Basic scientist
- Physiotherapist
- Nurse
- Other

Ataxia in children: classification

- Acute (acquired)
- Recurrent
- Progressive
- **Non-progressive, congenital**

- Cerebellar
- Sensory
- Vestibular

Non-progressive ataxia

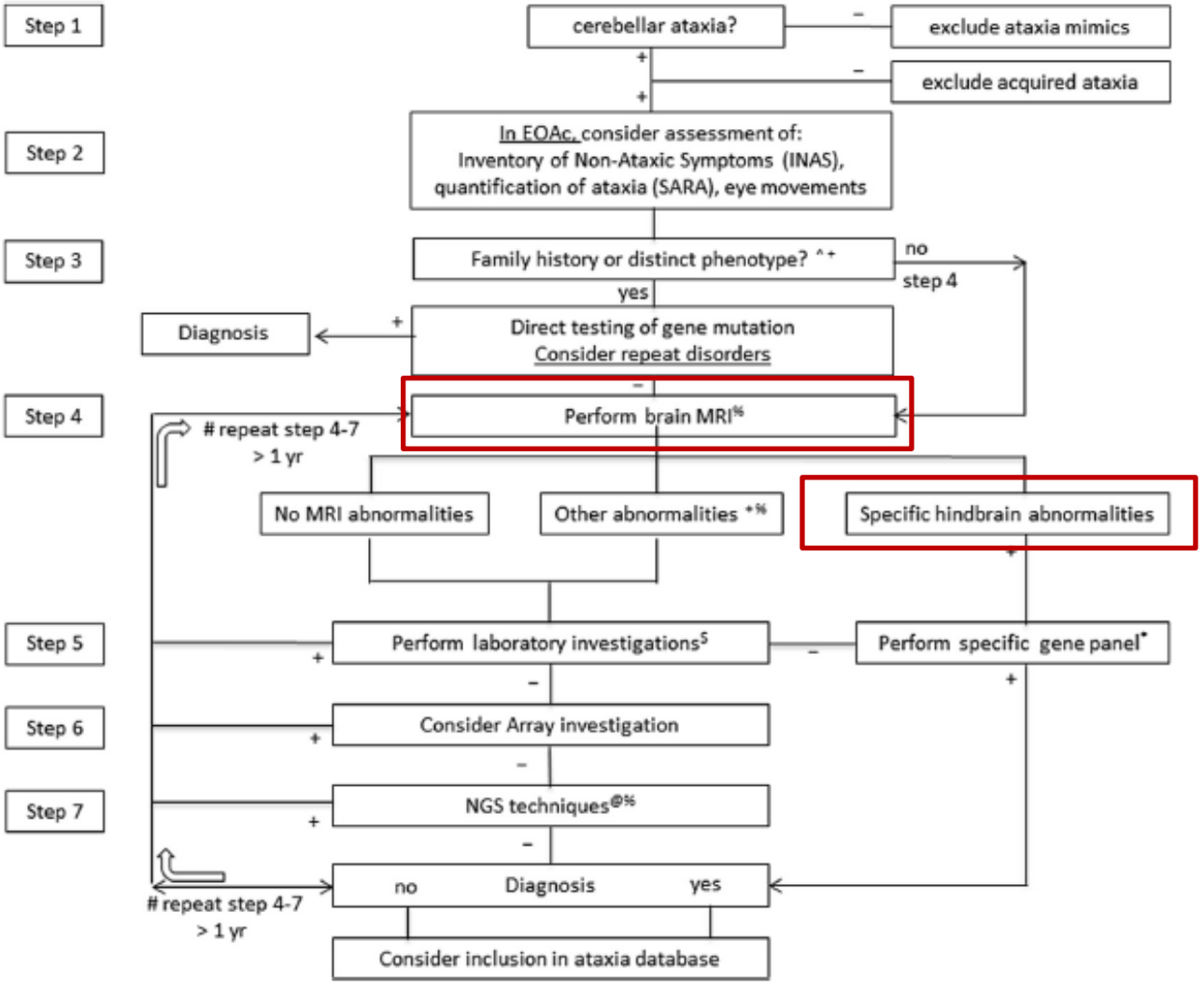


Trio-based WES: candidate gene

No matches on MME

NBIA gene screen: (-)

Clinical diagnostic algorithm in early-onset ataxia

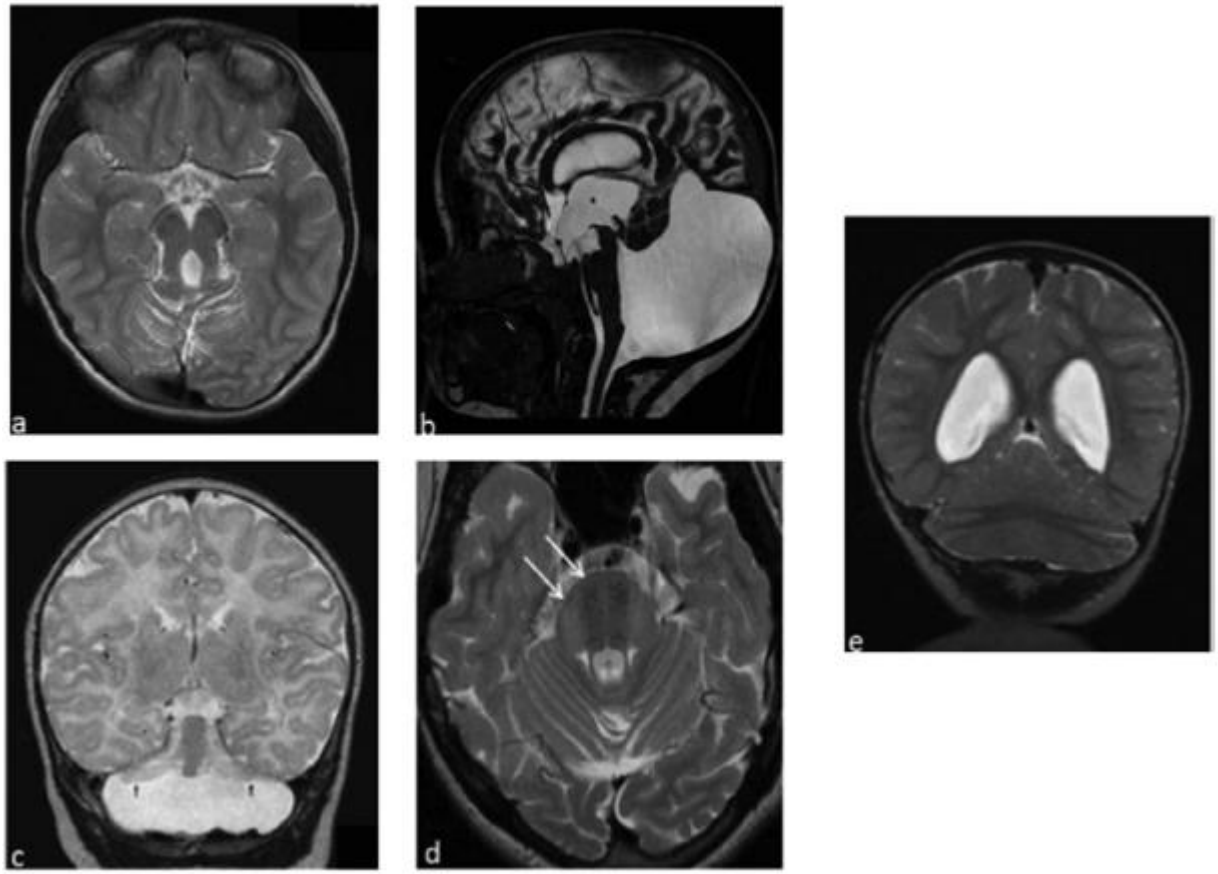


Brandsma R et al., EJPN 2019

Q2: Which among the following is not a hindbrain anomaly associated with early-onset ataxia?

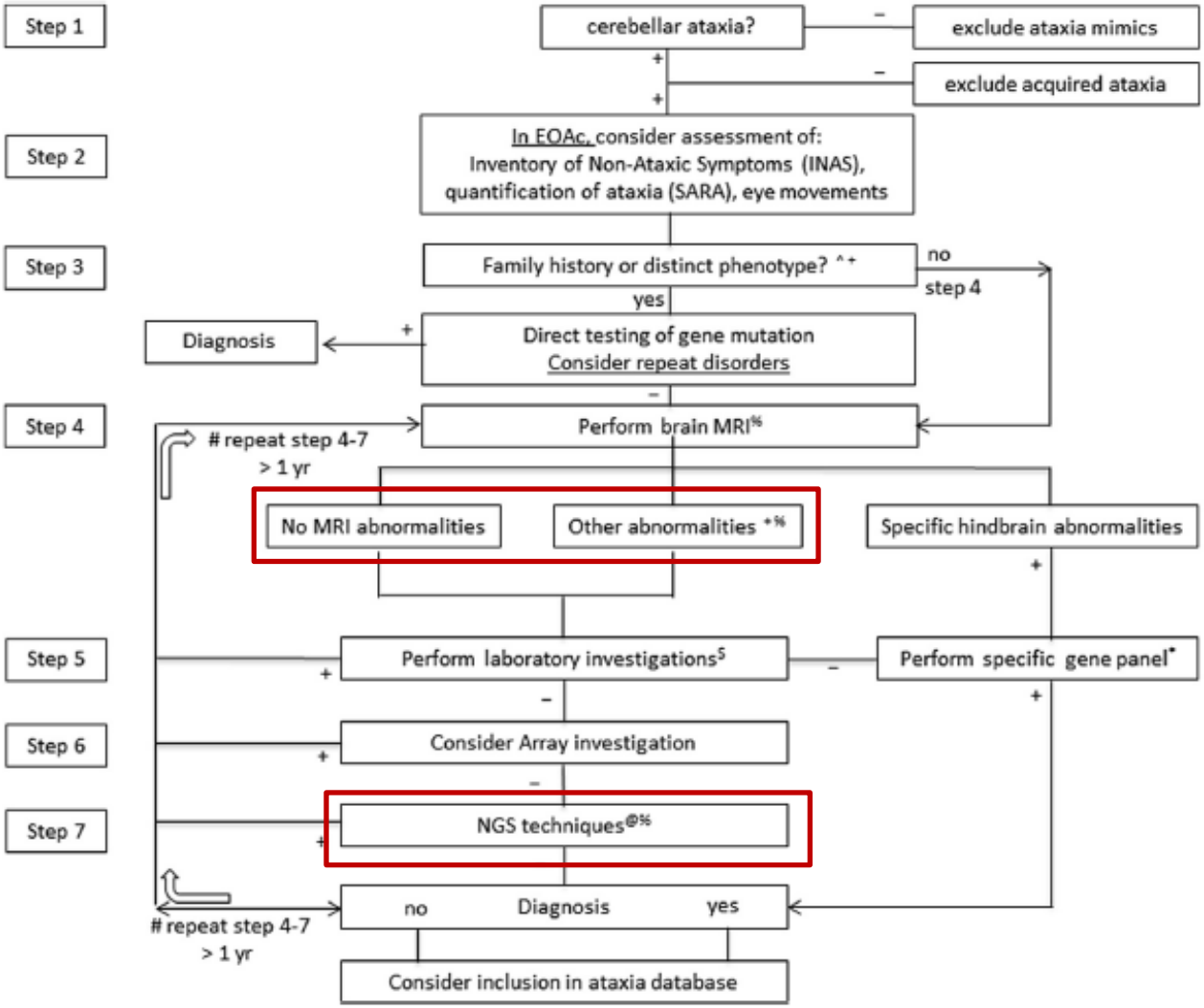
A. Dragonfly pattern
B. Molar tooth sign
C. Hypoplastic vermis + enlarged posterior fossa
D. Blake pouch's cyst

Imaging in childhood Genetic Ataxia: rhombencephalic abnormal patterns



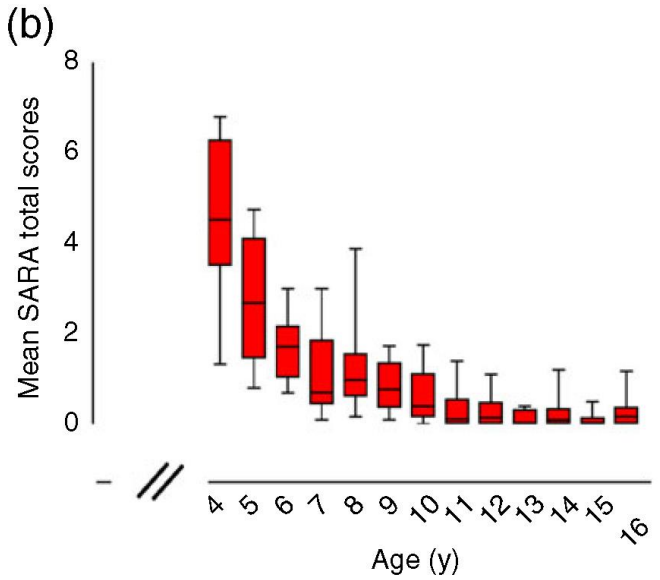
Brandsma R, et al. Eur J Pediatr Neurol 2019

Clinical diagnostic algorithm in early-onset ataxia



Brandsma R et al., EJPN 2019

SARA scale in children



From Lawerman TF et al., Dev Med Child Neurol, 2017

Lawerman TF et al., Front Hum Neurosci ,2017
Brandsma R et al., DMCN 2017
Lawerman TF et al., DMCN 2017
Brandsma R et al., DMCN 2014

Non-Progressive Congenital Ataxia (NPCA)

- Children with early evidence of cerebellar ataxia, without progression on follow-up, and even the tendency to gradual improvement
- Excluded:
    - Lesions following prenatal infection, perinatal illness, supratentorial brain malformations, defined syndromal disorders associated with ataxia, and postnatally acquired neurologic diseases
    - Hindbrain malformations with recognizable neuroradiological pattern

Steinlin , Zangger & Boltshauser, DMCN 1998
Bertini, Zanni & Boltshauser, Hand Clin Neurol 2018

NPCA: History

- Batten FE: “Ataxia in childhood” (Brain, 1905)

- Norman RM: “Primary degeneration of the granular layer of the cerebellum” (Brain, 1940)
- Steinlin , Zangger & Boltshauser: “Non-progressive congenital ataxia” (DMCN, 1998)

➢ NPCA: ARCA subset?

"Congenital cerebellar ataxias are **a relatively small ARCA subset** characterized by infantile onset of motor incoordination, developmental delay, and variable additional manifestations"

Guergueltcheva V et al. Am J Hum Genet, 2012

➢ NPCA or "Ataxic CP"

Early ataxic motor disorder
No regression
Absence of perinatal injury

doi:10.1093/brain/awv117 BRAIN 2015: 138; 1817–1832 | 1817

BRAIN
A JOURNAL OF NEUROLOGY

De novo point mutations in patients diagnosed with ataxic cerebral palsy

Ricardo Parolin Schnekenberg,[1,2] Emma M. Perkins,[3] Jack W. Miller,[4] Wayne I. L. Davies,[4,5,6] Maria Cristina D'Adamo,[6] Mauro Pessia,[6,7] Katherine A. Fawcett,[8] David Sims,[8] Elodie Gillard,[4] Karl Hudspith,[4] Paul Skehel,[3] Jonathan Williams,[9] Mary O'Regan,[10] Sandeep Jayawant,[11] Rosalind Jefferson,[12] Sarah Hughes,[12] Andrea Lustenberger,[13] Jiannis Ragoussis,[1,†] Mandy Jackson,[3] Stephen J. Tucker[14,15] and Andrea H. Németh[4,16]

Q3: Which of the following is true about NPCA clinical features

A. Seizures are rare in NPCA
B. Most patients walk unassisted before age 10
C. Oculomotor anomalies are a late clinical sign
D. Normal cognition occurs in more than 50%

NPCA: early signs

- Infantile hypotonia
- Motor delay
- Speech delay
- Ocular dyspraxia / nystagmus

NPCA: clinical features in children and adults

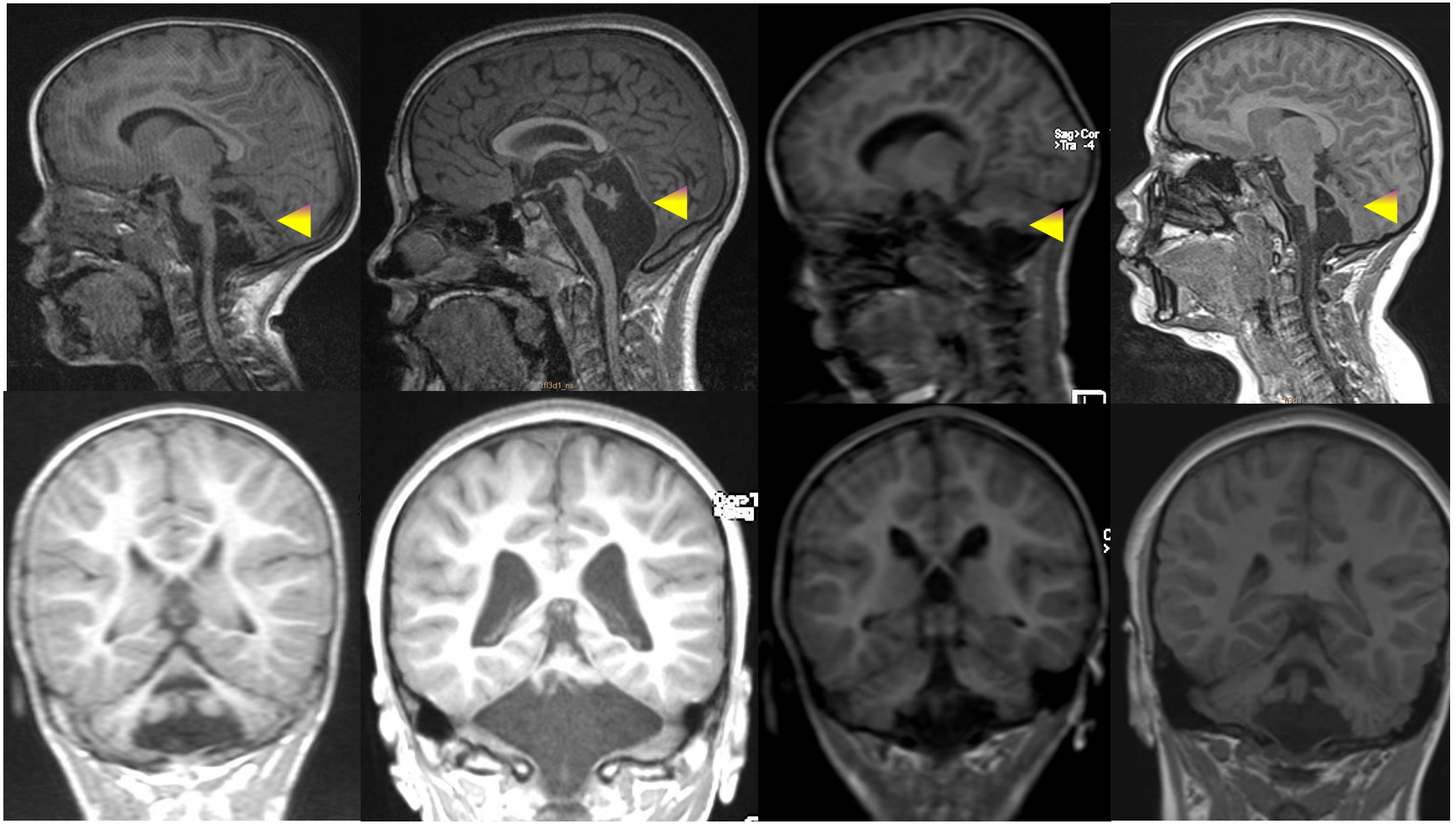
- High prevalence of cognitive and language impairments
- Increased occurrence of seizures
- Ocular signs (nystagmus, strabismus)
- Behavioral disorders
- Microcephaly
- Spasticity
- Dystonia

NPCA: Differential diagnosis

Other congenital ataxic syndromes

- Cerebellar – destructive lesions
- Progressive cerebellar with onset in infancy
- Sensory ataxia
- Leukoencephalopathy

Congenital ataxia: genetic vs. acquired



A.J. - PT 27wk, ID

J.S.- PT 24wk, ID, ASD, ocular dysp.

E.C.- PT 24wk, mild ID

I.R.- PT 26 wk, mild ID, ataxia

Some progressive ataxias with infantile onset

• Ataxia-telangiectasia	AR	*ATM*
• Ataxia-telangiectasia–like disorder 2	AR	*PCNA*
• Spastic Ataxia 6	AR	*SACS*
• SCAR 12	AR	*WWOX*
• SCAR 13	AR	*GRM1*
• SCAR 15	AR	*KIAA0226*
• SCAR 20	AR	*SNX14*
• Succinyl semialdehyde DH deficiency	AR	*ALDH5A1*
• Marinesco-Sjögren syndrome	AR	*SIL1*
• SCA 13	AD	*KCNC3*

Difficult distinction among NPCA and very early-onset slowly progressive ataxia in young children

(VEOPA term proposed: Valence S, Burglen L, et al. Genet Med 2019)

Congenital Sensory Ataxia:

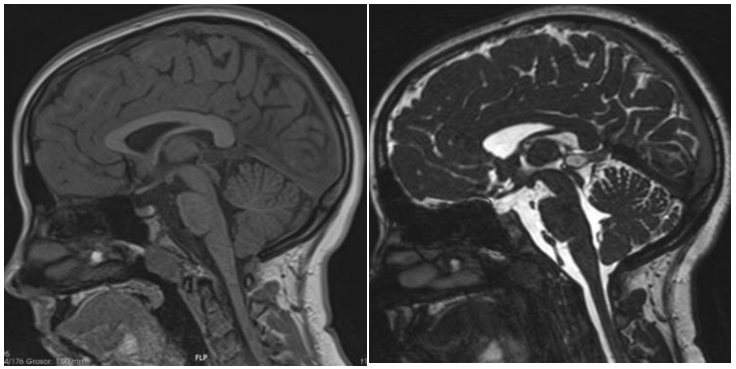
PIEZO 2 biallelic mutations:

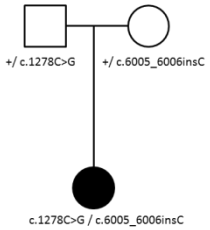
Non-selective cation channel

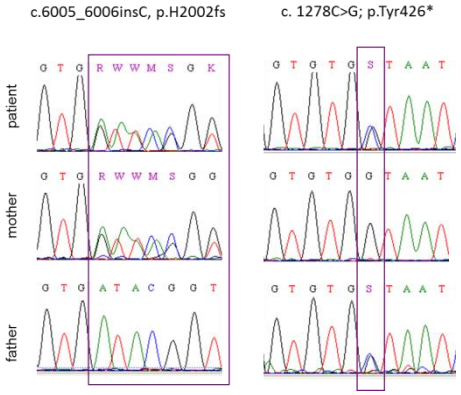
Mechanically activated –currents in somatosensory neurons

Loss of proprioception and discriminative touch

Ataxia, dysmetria, scoliosis







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Role of *PIEZO2* in Human Mechanosensation

Chesler AT et al, 2016

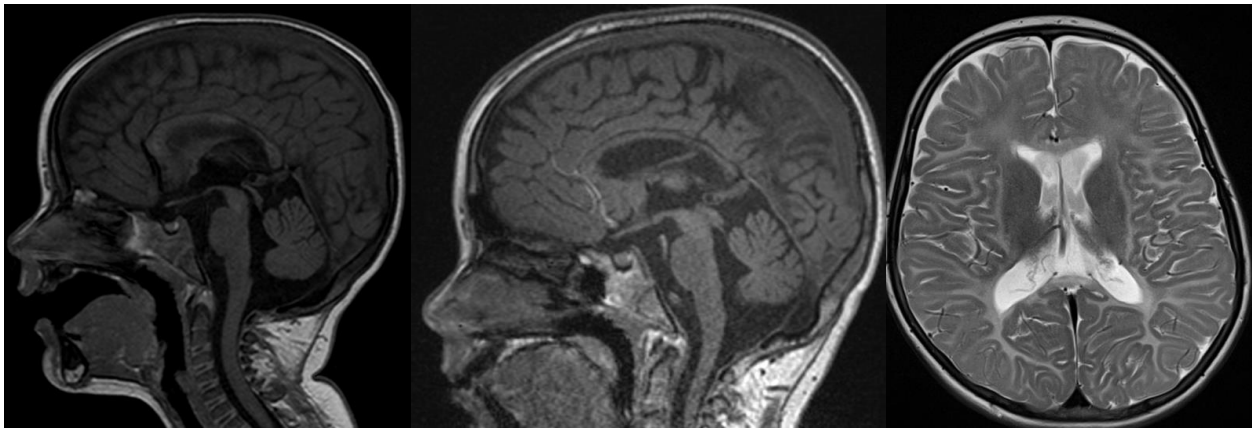
Congenital ataxia: Leukoencephalopathy

GJC2 biallelic variants

GAP junction protein (Connexin 47)
Hypomyelinating leukoencephalopathy -2

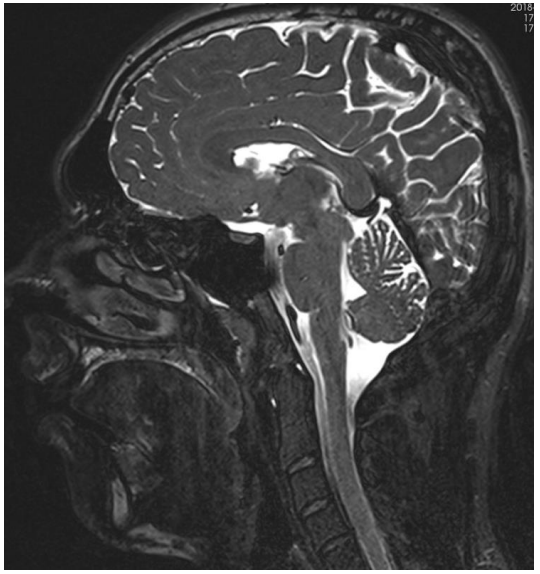
Occasional, mild cerebellar atrophy

Ataxia may precede and overshadow spasticity



Non-Progressive Congenital Ataxia (NPCA): Imaging

- Normal findings
- Cerebellar hypoplasia - vermis/hemispheres
- Prominent interfolial spaces (atrophy vs. underdevelopment)



Q4: What is the most common genetic cause of congenital ataxia?

A. De novo heterozygous mutations
B. Microdeletions
C. Autosomal dominant inheritance
D. Autosomal recessive inheritance

Genetic basis of NPCA

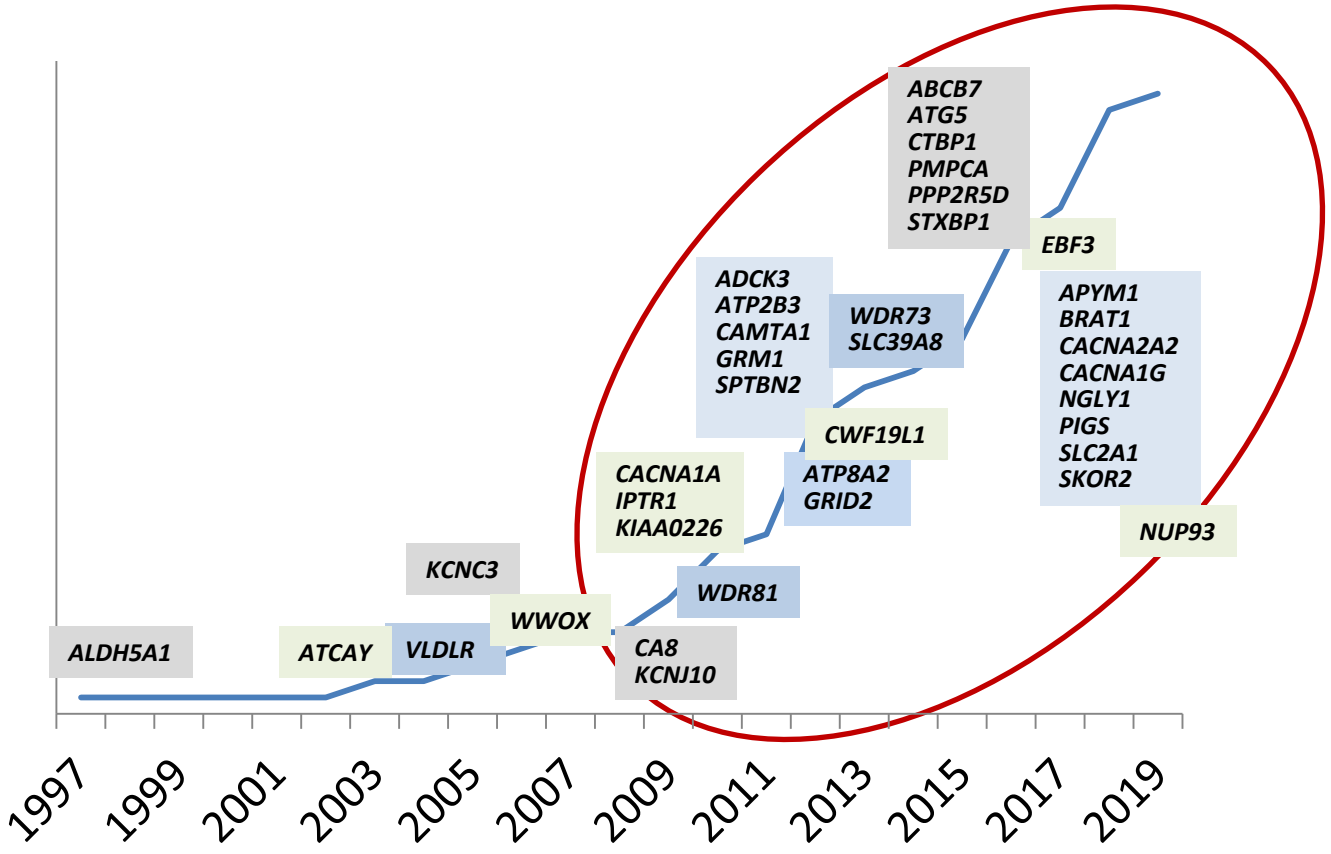
Summary of autosomal genes associated with nonprogressive congenital ataxia

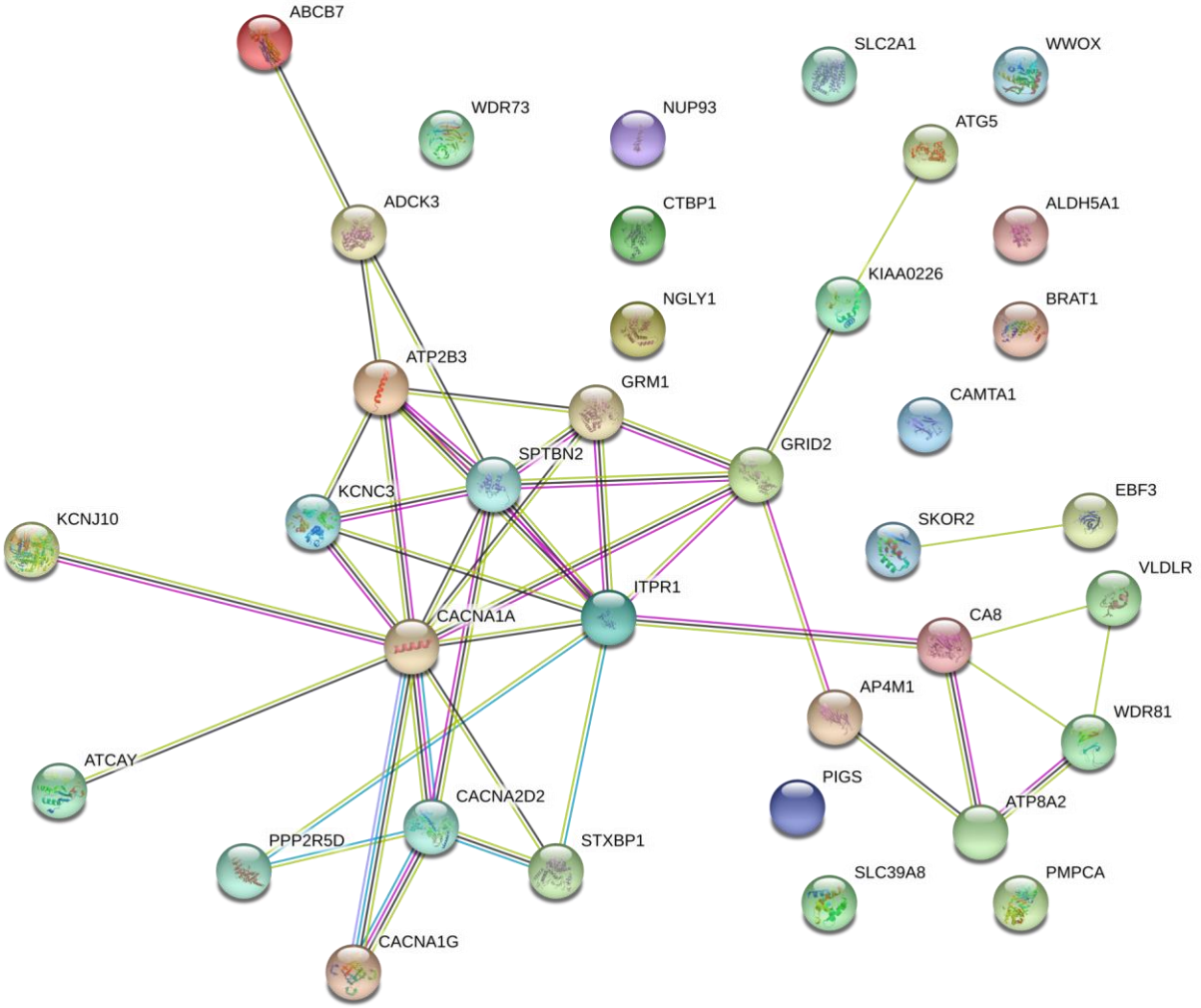
Gene	Phenotype	Cytogenetic band	References
CACNA1A	Congenital or early-onset ataxia ± hemiplegic migraine, ± seizures	19p13.13	Blumkin et al. (2010) Travaglini et al. (2017)
KCNC3	Ataxia, ID, seizures, short stature	19q13.33	Figueroa et al. (2010)
ITPR1	Ataxia, ± ID, ± aniridia (Gillespie syndrome)	3p26.1	Huang et al. (2012) McEntagart et al. (2016)
VLDLR	Ataxia, ID, ± short stature, ± pachygyria	9p24.2	Boycott et al. (2005)
WDR81	Ataxia, ID, pyramidal signs, cerebral atrophy	17p13.3	Gulsuner et al. (2011)
CA8	Ataxia, mild ID	8q12.1	Turkmen et al. (2009)
ATP8A2	Ataxia, severe ID, cortical atrophy	13q12.13	Onat et al. (2013)
PMPCA	Ataxia, ID, short stature	9q34.3,	Choquet et al. (2016)
WWOX	Ataxia, ID, seizures, limb spasticity	16q23.1	Gribaa et al. (2007)
GRM1	Ataxia, ID, pyramidal signs, seizures, short stature	6q24.3	Guergueltcheva et al. (2012)
SPTBN2	Ataxia, ID, eye movement abnormalities	11q13.2	Lise et al. (2012)
KCNJ10	EAST syndrome Nonsyndromic early-onset ataxia	1q23.2	Scholl et al. (2009) Nicita et al. (2017)
KIAA0226		3q29	Assoum et al. (2010)
GRID2	Early-onset ataxia, ID, eye movement abnormalities	4q22.1	Hills et al. (2013)
WDR73	Ataxia, microcephaly, ID, short stature, optic atrophy	15q25.2	Vodopiutz et al. (2015) Vodopiutz et al. (2015)
CAMTA1	Early-onset ataxia, mild ID, ± seizures	1p36.31	Thevenon et al. (2012)
ATCAY	Ataxia, ID, tremor	19p13.3	Nystuen et al. (1996) Bomar et al. (2003)
ATG5	Ataxia, ID	6q21	Yapici and Eraksoy (2005) Kim et al. (2016)

EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; ID, intellectual disability.

Bertini E, Zani G, Boltshauser E, Hand Clin Neurol 2018)

Genetic basis of NPCA





GO biological process	Fold	pvalue	Genes
Rhythmic synaptic transmission	> 100	6.29E-05	*CACNA2D2, CACNA1A*
Negative regulation of histone H4 acetylation	> 100	6.29E-05	*ATG5, CTBP1*
Aggrephagy	> 100	8.38E-05	*ATG5, WDR81*
Cerebellar Purkinje cell layer morphogenesis	> 100	4.76E-06	*SPTBN2, CACNA1A, SKOR2*
Cell differentiation in hindbrain	77.38	1.12E-05	*GRID2, CACNA1A, SKOR2*
Cerebellar cortex formation	70.93	1.42E-05	*GRID2, CACNA1A, SKOR2*

Patient sample

- 21 subjects evaluated for suspected cerebellar syndrome in infancy, evolving into overt ataxia on follow-up
- 2 excluded after diagnosis of non-cerebellar conditions
- Negative family history
- Normal or unspecific findings on neuroimaging at presentation (MTM, PF cysts, RES, PCH pattern excluded)
- Negative "standard" work-up (CDG, other metabolic screen, lactate, vit E, Ig's)
- Non-progressive course

- All cases underwent WES analysis: Trio (14) or Singleton (7) between 2012 and 2018

Patients: clinical presentation

	Gene	Sex	Age (y)	Initial symptoms	Initial MRI (age)	Independent gait (age)
1	*Candidate*	M	19	Motor developmental delay	Normal (22 mo)	5 y
2	-	F	24	Motor and speech delay	Vermian hypoplasia (19 mo)	9 y
3	***ITPR1***	M	17	Hypotonia, head lag, “mydriasis”	Global CA (23 mo)	3 y
4	***CACNA1A***	M	9	Hypotonia, abn.ocular movements	Normal (13 mo)	Non-ambulatory
5	***SLC39A8***	F	19	Hypotonia, GDD, ocular dyspraxia	Global CA (9 mo)	Few steps unsupported
6	***STXBP1***	M	10	Hypotonia, titubation	Mild vermian atrophy (2y)	2 y
7	***CA8***	M	7	Hypotonia, motor delay	Mild vermian atrophy (2y)	6 y
8	***CTBP1***	M	11	Motor and language delay	Mild CA (22 mo)	Non-ambulatory
9	-	M	10	Hypotonia, motor delay	Normal (4y)	2 y
10	*Candidate*	M	14	Hypotonia, motor delay	Normal (3y)	3,5 y
11	***ITPR1***	M	6	Hypotonia, poor visual tracking	Normal (5 mo)	Non-ambulatory
12	***ALDH5A1***	M	12	Hypotonia, motor delay, absent speech	Normal (1 mo)	4 y
13	-	F	6	Motor delay	Normal (23 mo)	2 y
14	***SLC2A1***	M	5	Motor delay	Normal (19 mo)	2 y
15	***Candidate***	F	13	GDD	Normal (8 y)	2 y
16	***EBF3***	M	17	Motor delay, ocular dyspraxia	Vermian hypoplasia (18 mo)	NA
17	***PPP2R5D***	F	5	Hypotonia, GDD, ocular dyspraxia	Normal (2 y)	3 y
18	-	F	13	Hypotonia , GDD	Normal (2 y)	2 y
19	-	F	7	Hypotonia, GDD, ocular apraxia,apnea	Normal (1 mo)	4 y

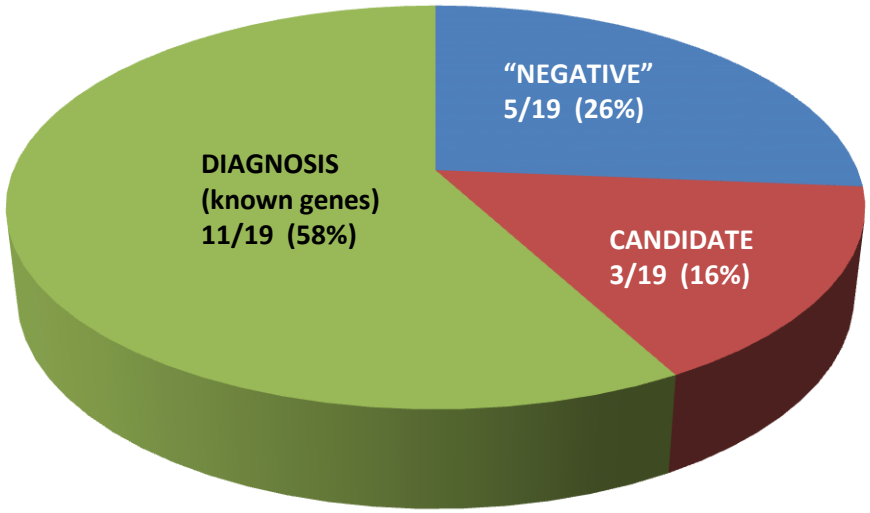
Patients clinical and imaging findings; outcome

Pt	Gene	Cognitive dysfunction	Seizures	Spasticity	Oculomotor	Other	Cerebellar MRI pattern	Current status
1	*Candidate*	**No**	No	↑DTRs	nystagmus	Dystonia	Mild vermian atrophy NBIA¿	ICARS 38
2	-	Mild	No	No	-		Progressive atrophy	SARA 16
3	***ITPR1***	Moderate	No	↑DTRs	OMA, hypometric saccades	Iris hypoplasia	Global CA, stability	
4	***CACNA1A***	Severe	Yes	↑DTRs	OMA, Nystagmus, hypometric sacc.	Scoliosis; seizures upon mild head Trauma	Stable vermian atrophy	
5	***SLC39A8***	Moderate	No	↑DTRs	Nystagmus, dyspraxia	IDDM	Global CA, stability	SARA 16
6	***STXBP1***	Severe	Yes	↑DTRs	Dyspraxia, hypermetric sacc.		Mildly progression CA	
7	***CA8***	Mild	No	↑DTRs	Saccadization	Consanguinity	Stable vermian atrophy	SARA 18
8	***CTBP1***	Moderate	No	No	Square jerks	Scoliosis, vitiligo	Severe, progressive CA	SARA >20
9	-	Mild	No	↑DTRs	Dyspraxia		NA	
10	*Candidate*	Mild	No	No	Dyspraxia		NA	
11	***ITPR1***	Mild	No	↑DTRs	Nystagmus	“Arreactive mydriasis“	Mild vermian atrophy	
12	***ALDH5A1***	Moderate	No	No		Hypomimia	Mild atrophy	
13	-	Moderate	Yes?	Brisk DTRs	-		Normal	
14	***SLC2A1***	Mild	No	↑DTRs	-	Hypoglycorrhachia	Normal	
15	***Candidate***	Learning dis.	Yes	Yes	-	ADHD	Mild CA	
16	***EBF3***	Mild	No	No	Nystagmus, dyspraxia	Childhood periodic syndrome	Vermian hypoplasia	
17	***PPP2R5D***	Moderate	No	No	-	Macrocephaly Enamel dysplasia	(rep.) Normal	
18	-	Moderate	Yes	No		Scoliosis, vertebral fusion	Mild CA, stable	SARA 14
19	**-**	Severe	No	No	apraxia	Hypomimia, ASD	Normal	

Trio-based WES in Developmental Encephalopathies
NPCA -- Ataxia/ID/ASD/Epilepsy

WES 21 cases

2 excluded
Non-NPCA



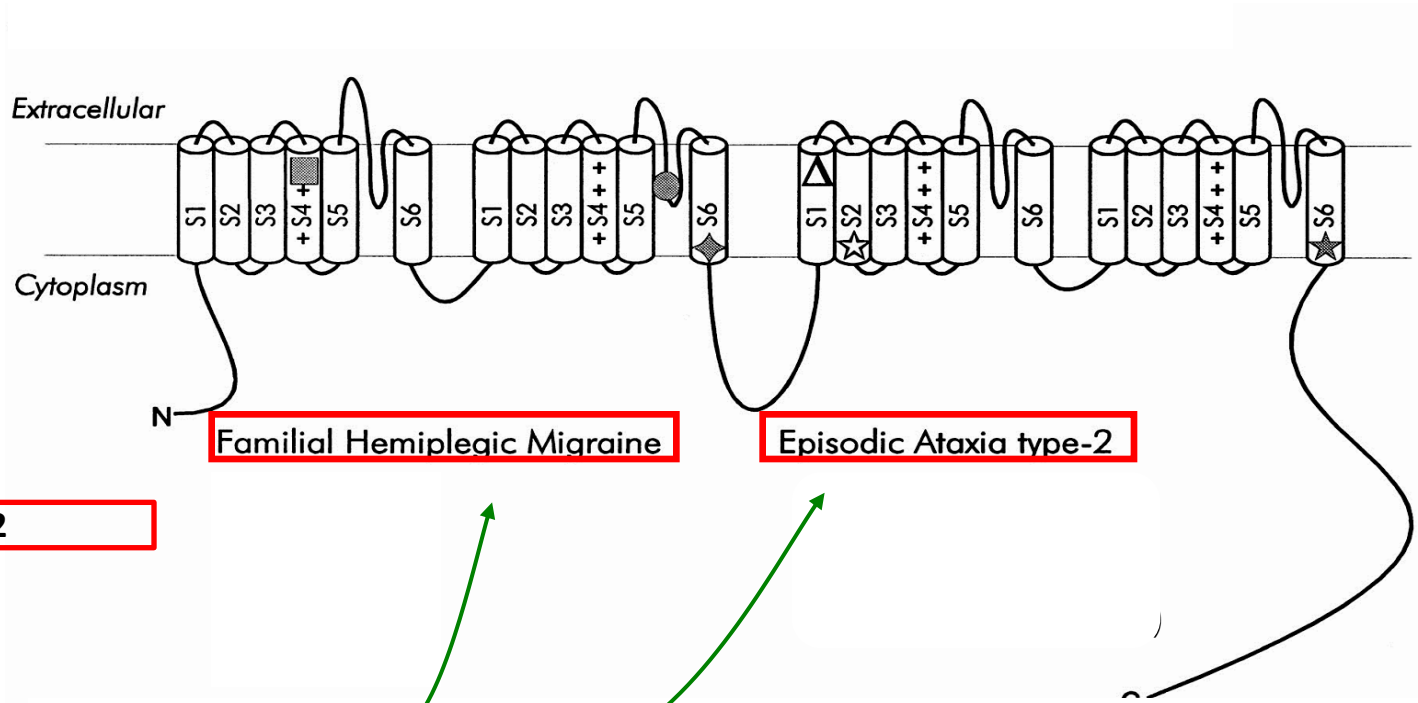
3 AR

8 AD

Developmental disorders with NPCA as leading clinical sign

CACNA1A: One gene, many phenotypes

α1 subunit of voltage-gated neuronal calcium P/Q channel



EIEE 42

GoF
LoF

Biallelic

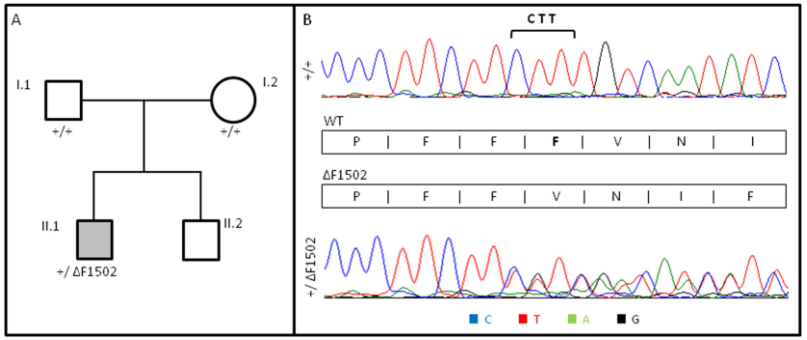
Spinocerebellar ataxia (SCA6)

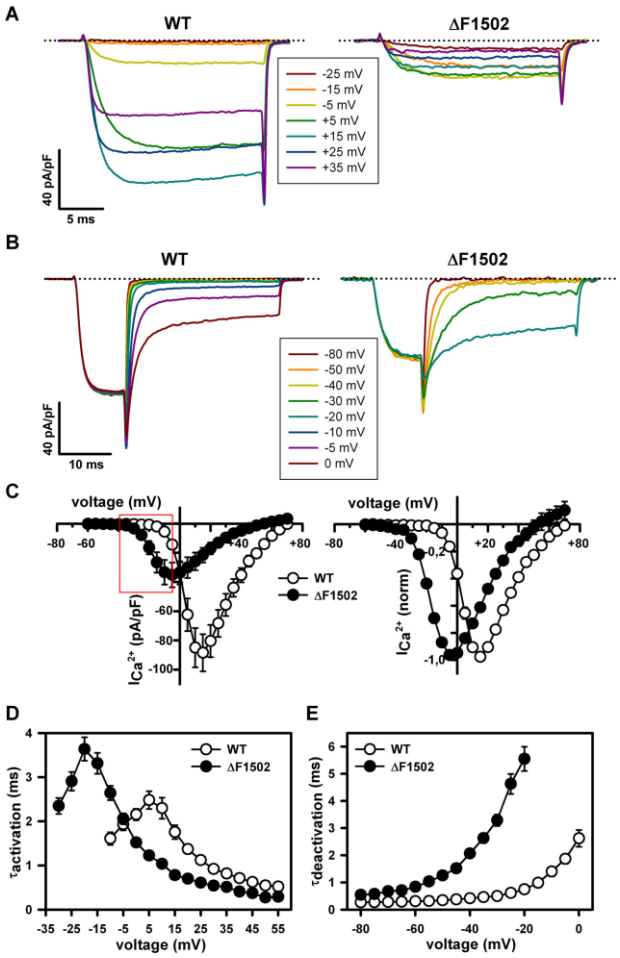
Normal: $(CAG)_{4-18}$
Mutant: $(CAG)_{21-33}$
(polyglutamine tract)

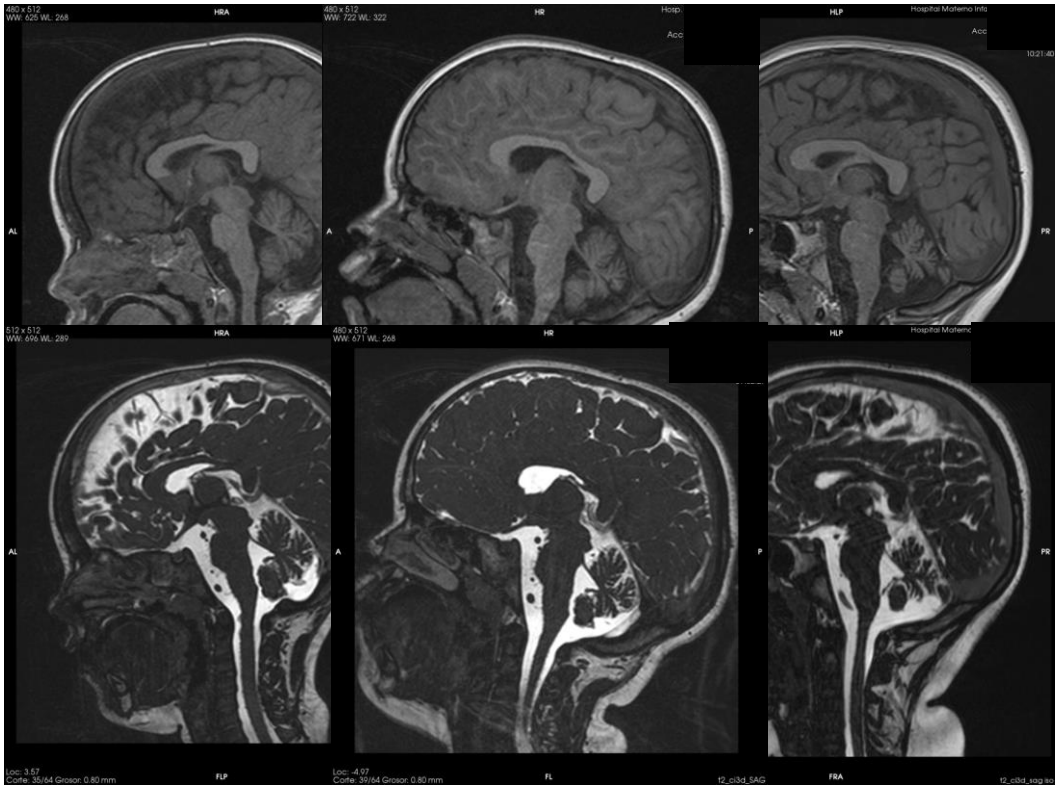
Congenital ataxia: *CACNA1A* encephalopathy

Upgaze tonic deviation

Congenital ataxia: *CACNA1A* encephalopathy







2011 2013 2017

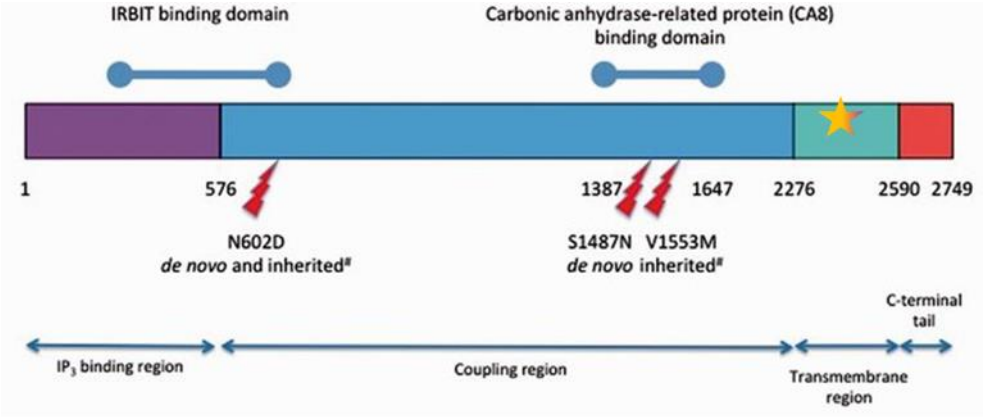
Non-progressive ataxia despite increasing CA

Seizures and coma episodes after minor head trauma

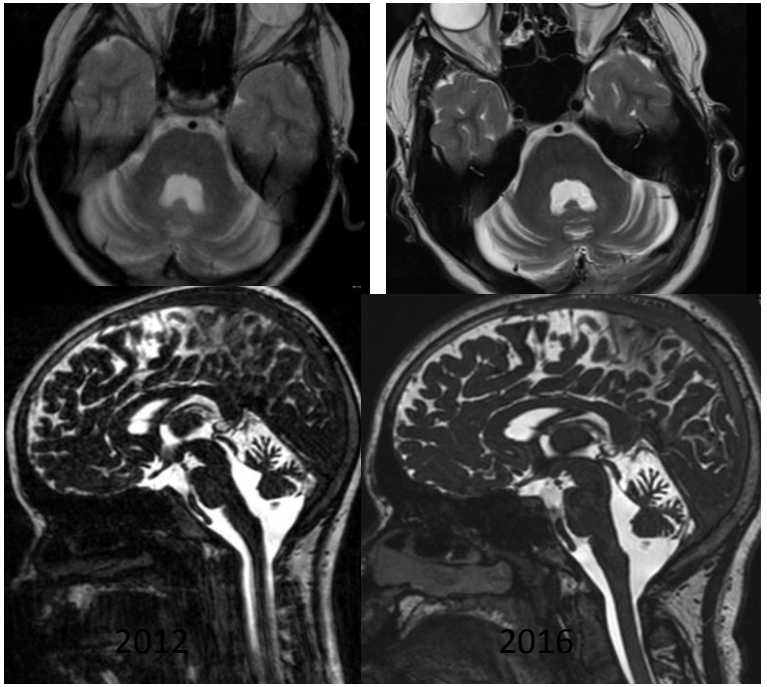
No improvement on acetazolamide

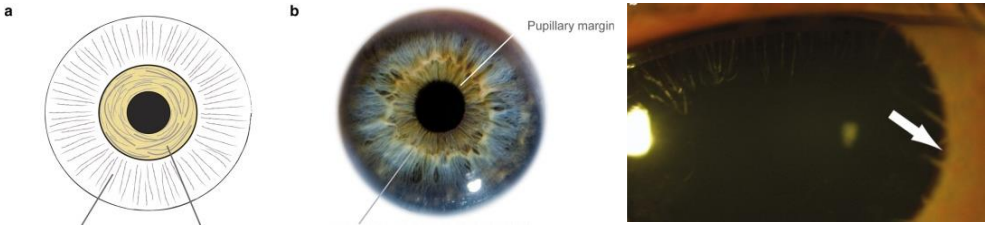
Bahamonde MI et al., 2015

Congenital ataxia: *ITPR1*



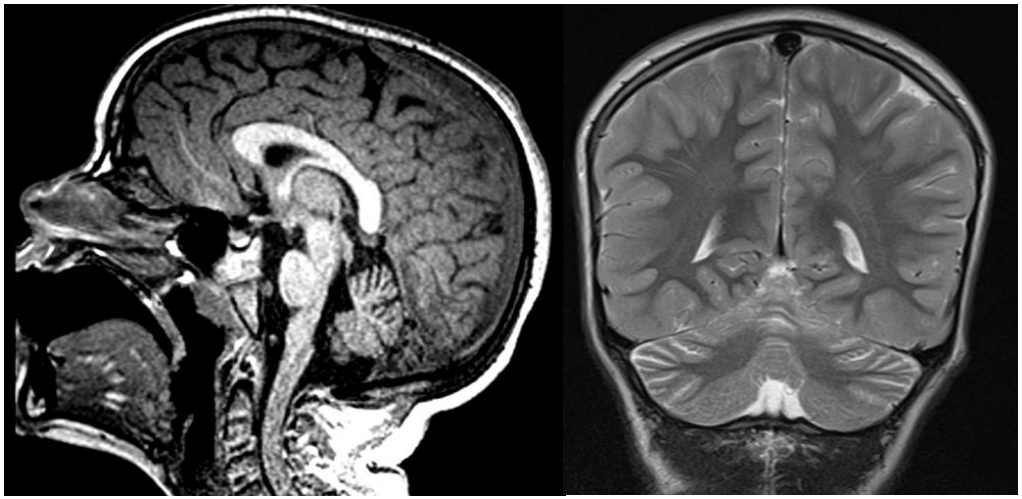
Schnekenberg et al. Brain 2015





Hall HN et al., Human Genetics (2019)

Cerebellar ataxia, mental retardation and dysequilibrium syndromes (CAMRQs)



Congenital ataxia, ID, slight cerebellar atrophy/hypoplasia
«Negative» trio-based WES

WES reanalysis: RoH

NM_004056 chr8: 61144941; ***CA8*** c.418-3C>G Hom pLI = 0.78

Trio analysis of new candidate genes:
Rule out homozygous even if non-consanguineous (RoH)
Consider low/moderate effect variants

Dysequilibrium (CAMRQ) syndromes:

Type 1: *VLDLR*
Type 2: *WDR81*
Type 3: *CA8*

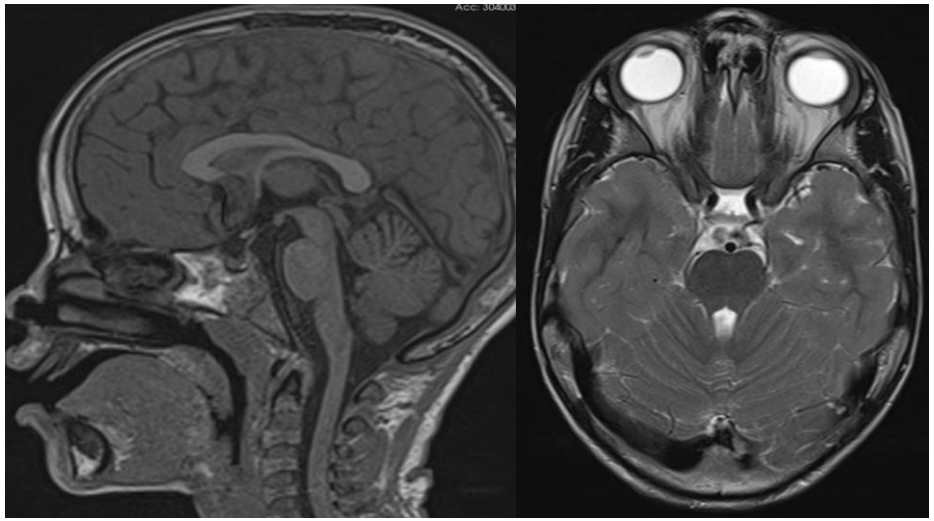
OPEN ACCESS Freely available online PLOS GENETICS

CA8 Mutations Cause a Novel Syndrome Characterized by Ataxia and Mild Mental Retardation with Predisposition to Quadrupedal Gait

Seval Türkmen[1☯], Gao Guo[1☯], Masoud Garshasbi[2,3], Katrin Hoffmann[1], Amjad J. Alshalah[4], Claudia Mischung[1], Andreas Kuss[2], Nicholas Humphrey[5], Stefan Mundlos[1,2,6], Peter N. Robinson[1,6*]

NPCA as part of complex neurodevelopmental disorders

Congenital ataxia: STXBP1



NPCA; Seizure onset : age 4 y

The STXBP1-related phenotypes:

- **EIEE (Ohtahara's)**
- **ID, ASD**
- **«Tremor-ataxia-retardation» phenotype** (Gburek-Augustat J et al. Eur J Paediatr Neurol. 2016)

Congenital ataxia: *de novo EBF3* variant

COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

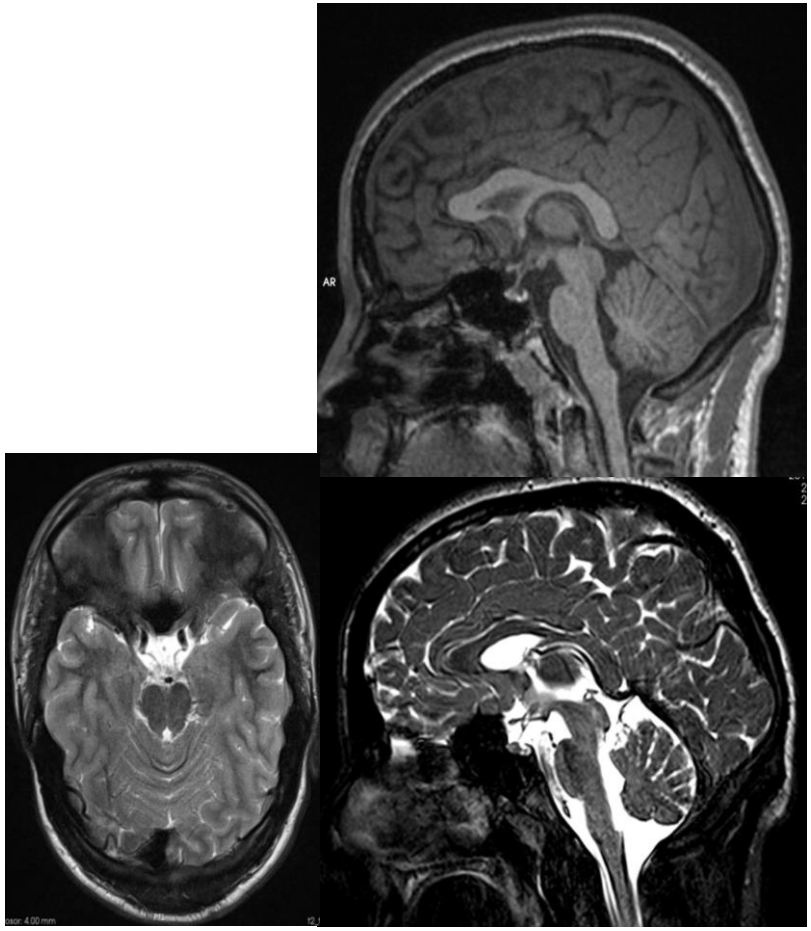
De novo variants in *EBF3* are associated with hypotonia, developmental delay, intellectual disability, and autism

Tanaka AJ et al., 2017

***EFBN1* haploinsufficiency:**

Hypotonia
Developmental delay
ID, autism
Facial dysmorphism
*** Ataxia 6/7**

-Oculomotor apraxia



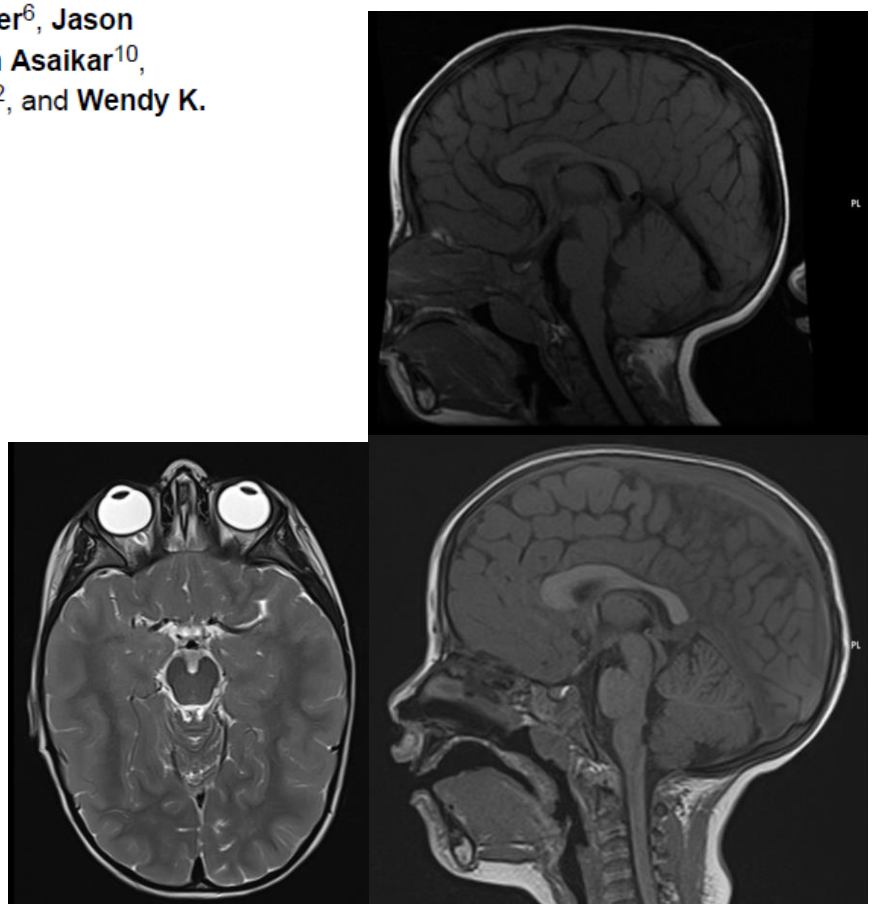
Congenital ataxia: *PPP2R5D*

Neurogenetics. 2016 January ; 17(1): 43–49. doi:10.1007/s10048-015-0466-9.

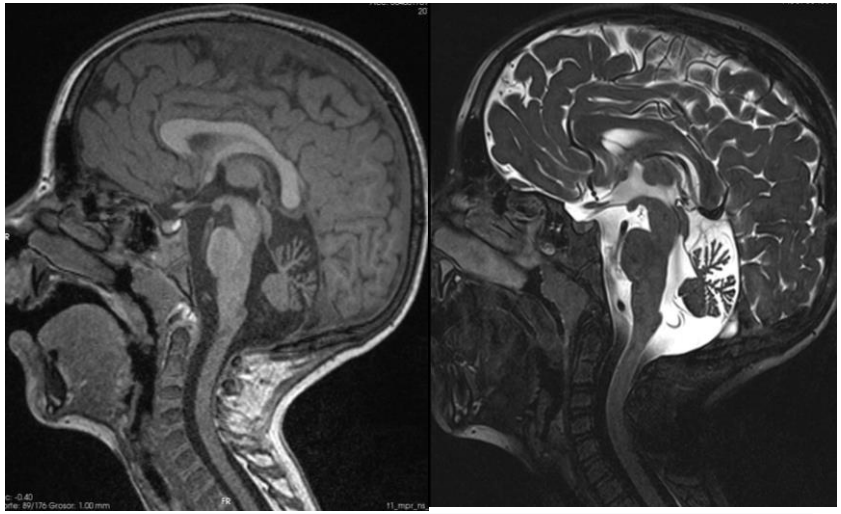
De Novo Missense Variants in *PPP2R5D* Are Associated with Intellectual Disability, Macrocephaly, Hypotonia, and Autism

Linshan Shang[1], Lindsay B. Henderson[2], Megan T. Cho[2], Donald S. Petrey[3], Chin-To Fong[4], Katrina M. Haude[4], Natasha Shur[5], Julie Lundberg[5], Natalie Hauser[6], Jason Carmichael[6], Jeffrey Innis[7,8], Jane Schuette[7,8], Yvonne W. Wu[9], Shailesh Asaikar[10], Margaret Pearson[11], Leandra Folk[2], Kyle Retterer[2], Kristin G. Monaghan[2], and Wendy K. Chung[1,12,*]

- -ASD, ID gene
- -Regulates PI3K/AKT and tau phosphorylation
- -2/7 Ataxia



Congenital ataxia: *CTBP1*



CTBP1 (MIM [617915](#))

Neurogenetics
DOI 10.1007/s10048-016-0482-4

ORIGINAL ARTICLE

A recurrent de novo *CTBP1* mutation is associated with developmental delay, hypotonia, ataxia, and tooth enamel defects

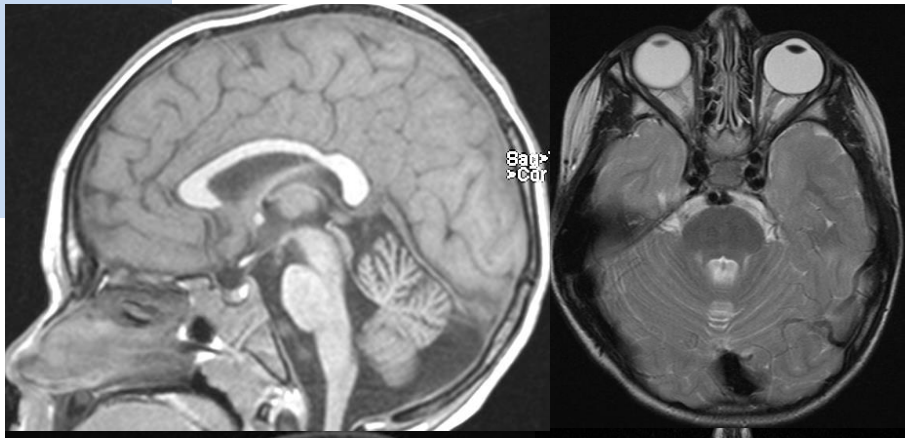
David B. Beck[1] · Megan T. Cho[2] · Francisca Millan[2] · Carin Yates[2] · Mark Hannibal[3] · Bridget O'Connor[3] · Marwan Shinawi[4] · Anne M. Connolly[5] · Darrel Waggoner[6] · Sara Halbach[6] · Brad Angle[7] · Victoria Sanders[7] · Yufeng Shen[8] · Kyle Retterer[2] · Amber Begtrup[2] · Renkui Bai[2] · Wendy K. Chung[1]

Metabolic disorders presenting as NPCA

Congenital ataxia: *ALDH5A1*

- **Succinic Semialdehyde Dehydrogenase Deficiency**
- Static encephalopathy characterized by:
  - Cognitive deficiency
  - Prominent expressive language deficit
  - Hypotonia
  - Epilepsy
  - Hyporeflexia
  - Ataxia
- Increased urine gamma OH butyrate

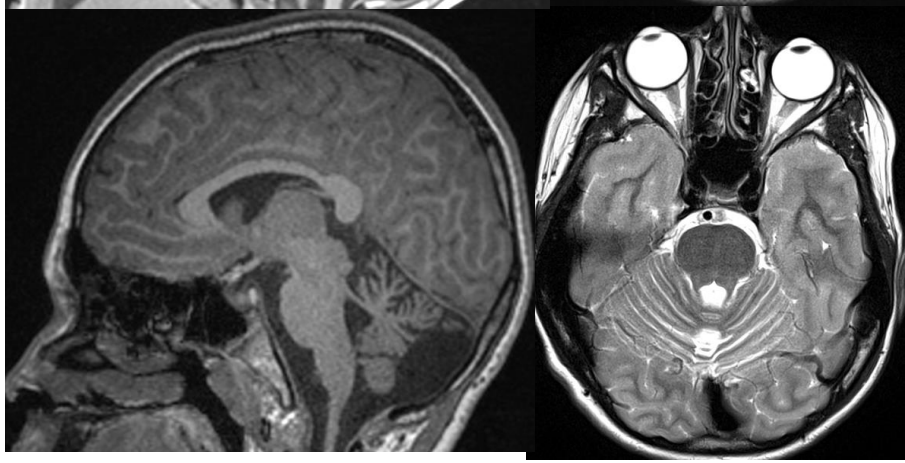
3 y



At age 2 y: “dyesquilibrium”, global delay

Complete ataxic syndrome
Severe dysphasia
Upbeat nystagmus on vertical gaze

11y



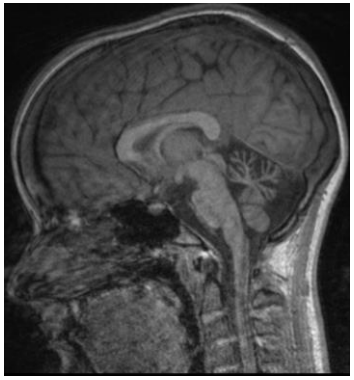
Congenital ataxia: *SLC39A8*

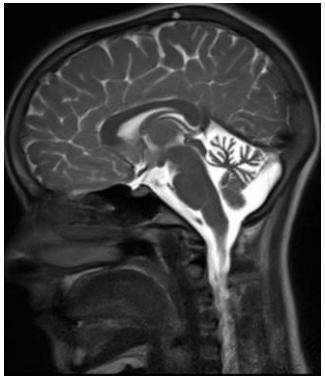
REPORT AJHG, 2015

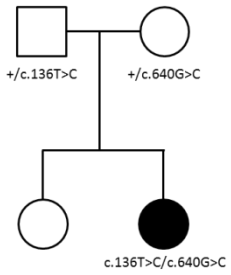
Autosomal-Recessive Intellectual Disability with Cerebellar Atrophy Syndrome Caused by Mutation of the Manganese and Zinc Transporter Gene *SLC39A8*

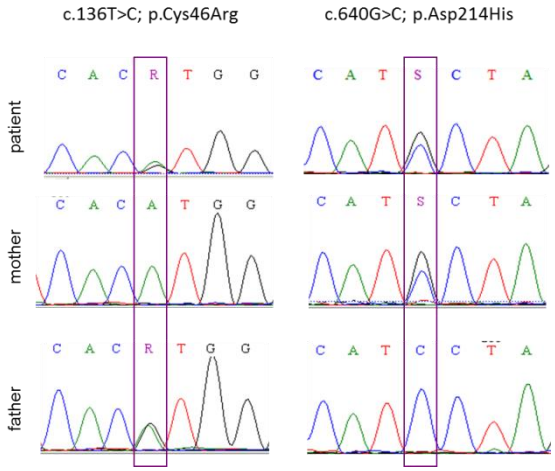
Kym M. Boycott,[1,15,*] Chandree L. Beaulieu,[1,15] Kristin D. Kernohan,[1] Ola H. Gebril,[2] Aziz Mhanni,[3]

Mn, Zn, other cofactors deficiency
Hutterite, Egyptian population
Hypotonia – squint - ID – short stature
Cerebellar atrophy
Type IIn CDG
Leigh-like syndrome









Therapy in NPCA

- Physical – occupational therapy
- *CACNA1A*:
  - Combined corticosteroid pulses and hypertonic solution in acute decompensations (Camia F et al Cephalalgia 2017)
  - Acetazolamide
- SSADH deficiency:
  - Vigabatrin

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

Institutional Logo,
‚Speakers' picture or disease related picture

Key Points /Conclusions

- Early-onset of clinical signs (1st year), more often **hypotonia** and **motor delay**
- **Global developmental delay** and **abnormal ocular movements** common
- Ataxia is essentially **non-progressive,** but seizures, cognitive and behavioural impairment common (overlap with other developmental encephalopathies)
- Imaging ranges from normal to isolated cerebellar atrophy/hypoplasia
- Over 35 associated genes, increasing heterogeneity
- Previously considered to fall into AR-**IOSCA** category, but distinct genetic counseling and prognosis