# Genetics of movement disorders


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# Movement Disorders

## Hypokinetic disorders (parkinsonism)

- Hypokinesia, bradykinesia, akinesia
- Hypertonia - (cogwheel) rigidity
- Resting tremor
- Postural changes

## Hyperkinetic disorders

- Abnormal movements
  - Tremor
  - Chorea/ballism
  - Dystonia
  - Myoclonus
  - Tics

# Movement disorders are heterogeneous and have a large variety of underlying causes

- Mendelian inheritance
- Genetic risk factors and gene-environment interactions
- “Idiopathic” disorders
- Acquired: vascular, toxic, medication-induced, (para)neoplastic, infectious, inflammatory, auto-immune, traumatic, metabolic,…
- Functional disorders (Functional neurological symptom disorder)

Parkinsonism and Related Disorders 73 (2020) 72–84

Contents lists available at ScienceDirect

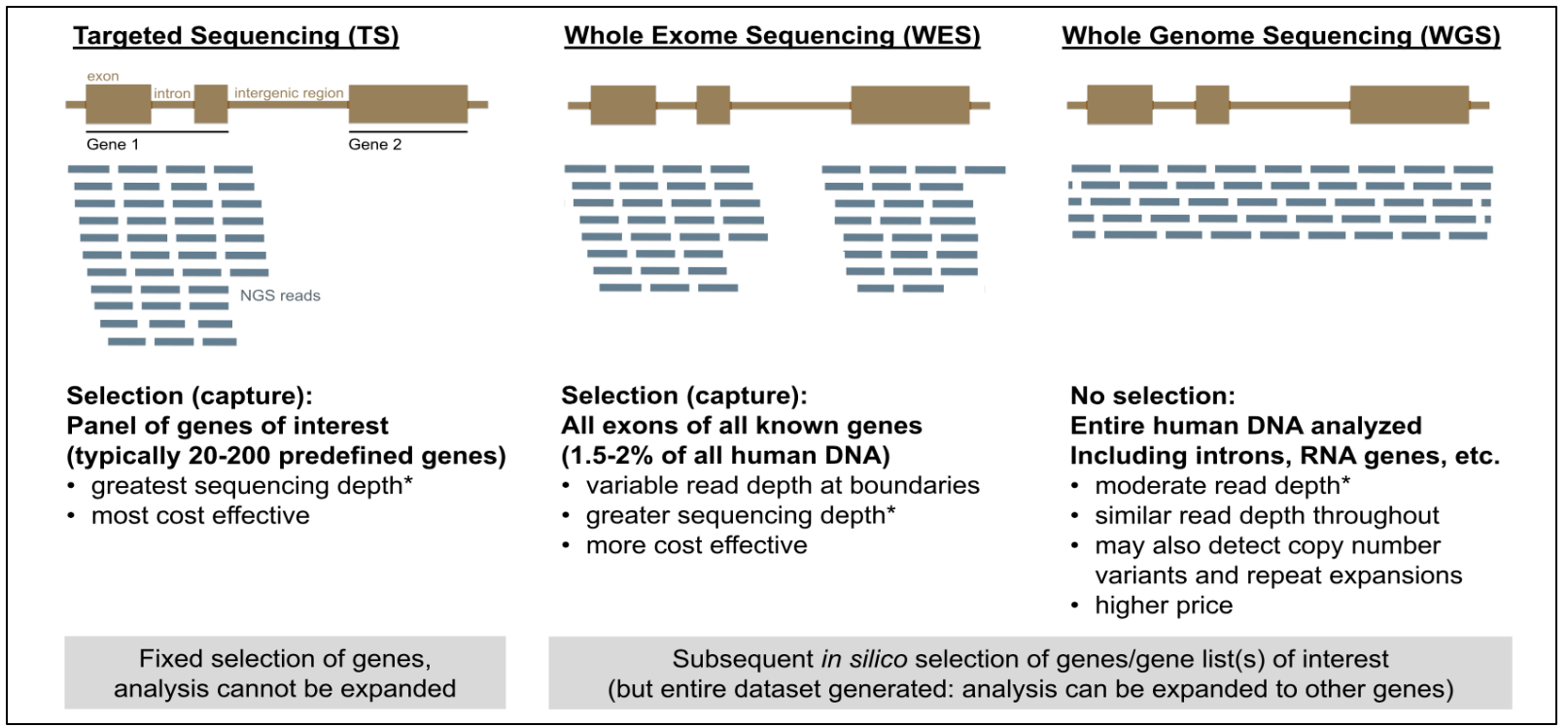
Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

# New generation genetic testing entering the clinic

Sorina Gorcenco[1], Andreea Ilinca[1], Wejdan Almasoudi, Efthymia Kafantari, Arne G. Lindgren, Andreas Puschmann*

*Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Neurology, Lund, Sweden*



RESEARCH ARTICLE OPEN ACCESS

# Exome Sequencing and Multigene Panel Testing in 1,411 Patients With Adult-Onset Neurologic Disorders

Nika Schuermans, MD, Hannah Verdin, PhD, Jody Ghijsels, BSc, Madeleine Hellemans, MD, Elke Debackere, BSc, Elke Bogaert, PhD, Sofie Symoens, PhD, Leslie Naesens, MD, Elien Lecomte, MD, David Crosiers, MD, PhD, Bruno Bergmans, MD, PhD, Kristof Verhoeven, MD, Bruce Poppe, MD, PhD, Guy Laureys, MD, PhD, Sarah Herdewyn, MD, PhD, Tim Van Langenhove, MD, PhD, Patrick Santens, MD, PhD, Jan L. De Bleecker, MD, PhD, Dimitri Hemelsoet, MD, and Bart Dermaut, MD, PhD, for Program for Undiagnosed Rare Diseases (UD-PrOZA)

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*Neurol Genet* 2023;9:e200071. doi:10.1212/NXG.0000000000200071

**Table 1** Description of the Patient Cohort

| | Total patient cohort (%) | Diagnosed patients (%) |
|---|---|---|
| **N** | 1,411 | 144 |
| **Age (y) (mean ± SD)** | 51 ± 20 | 50 ± 19 |
| **Younger than 18** | 97 (7) | 10 (7) |
| **Aged 18 or older** | 1,314 (93) | 134 (93) |
| **Sex** | | |
| **Male** | 669 (47) | 73 (51) |
| **Female** | 742 (53) | 71 (49) |
| **Gene panel** | | |
| **Leukoencephalopathy** | 535 (38) | 44 (30) |
| **Ataxia spasticity** | 365 (26) | 70 (49) |
| **Movement disorders** | 378 (27) | 22 (15) |
| **Paroxysmal episodic disorders** | 99 (7) | 8 (6) |
| **Progressive myoclonic epilepsy (PME)** | 7 (0) | 0 (0) |
| **Neurodegeneration with brain iron accumulation (NBIA)** | 11 (1) | 0 (0) |
| **Amyotrophic lateral sclerosis (ALS)** | 16 (1) | 0 (0) |

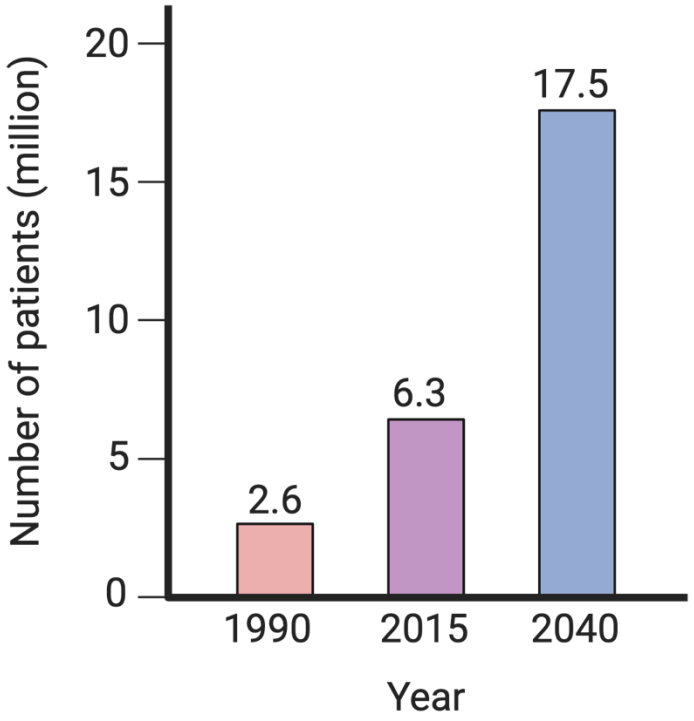
Diagnostic gain (TS/WES) varies between movement disorder types

Familial Parkinson's Disease: 0-10%

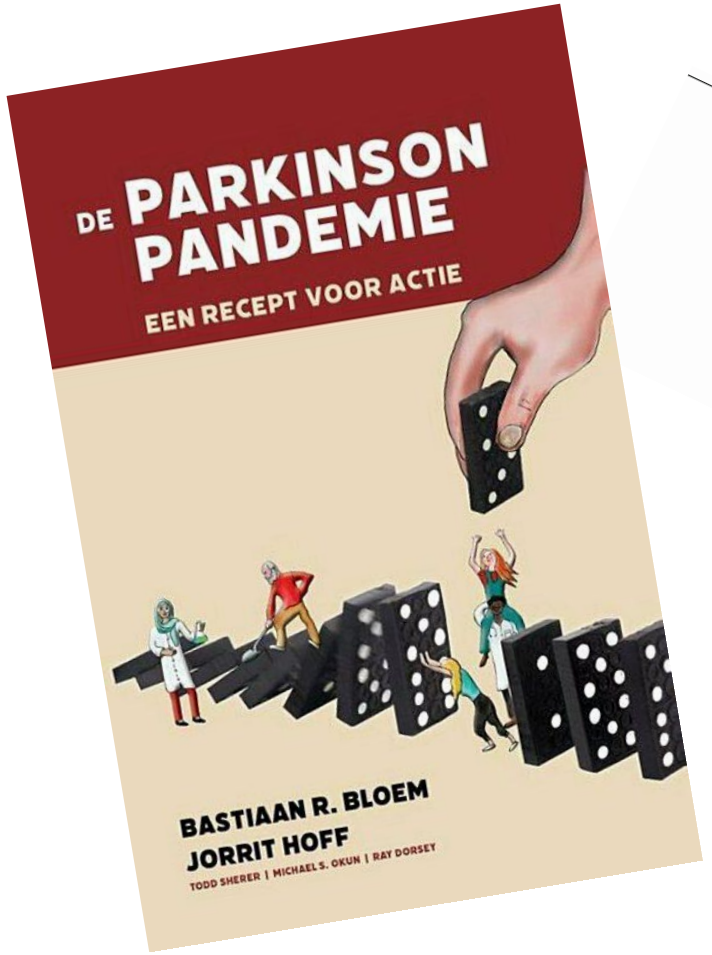
Dystonia: 11-37%

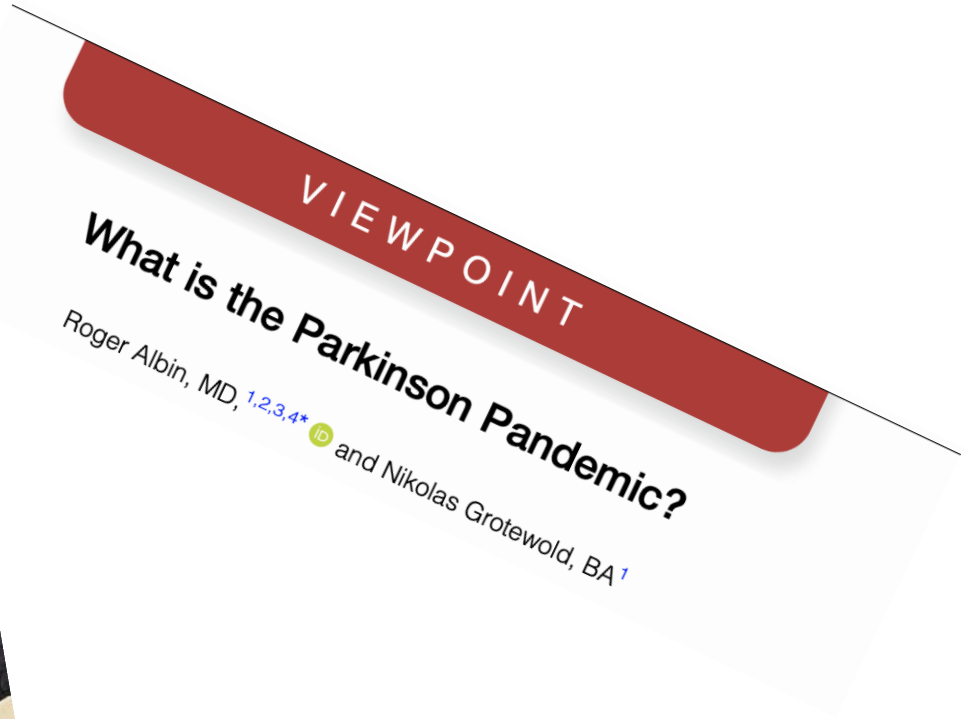
Ataxia/paraplegia: 12-62%

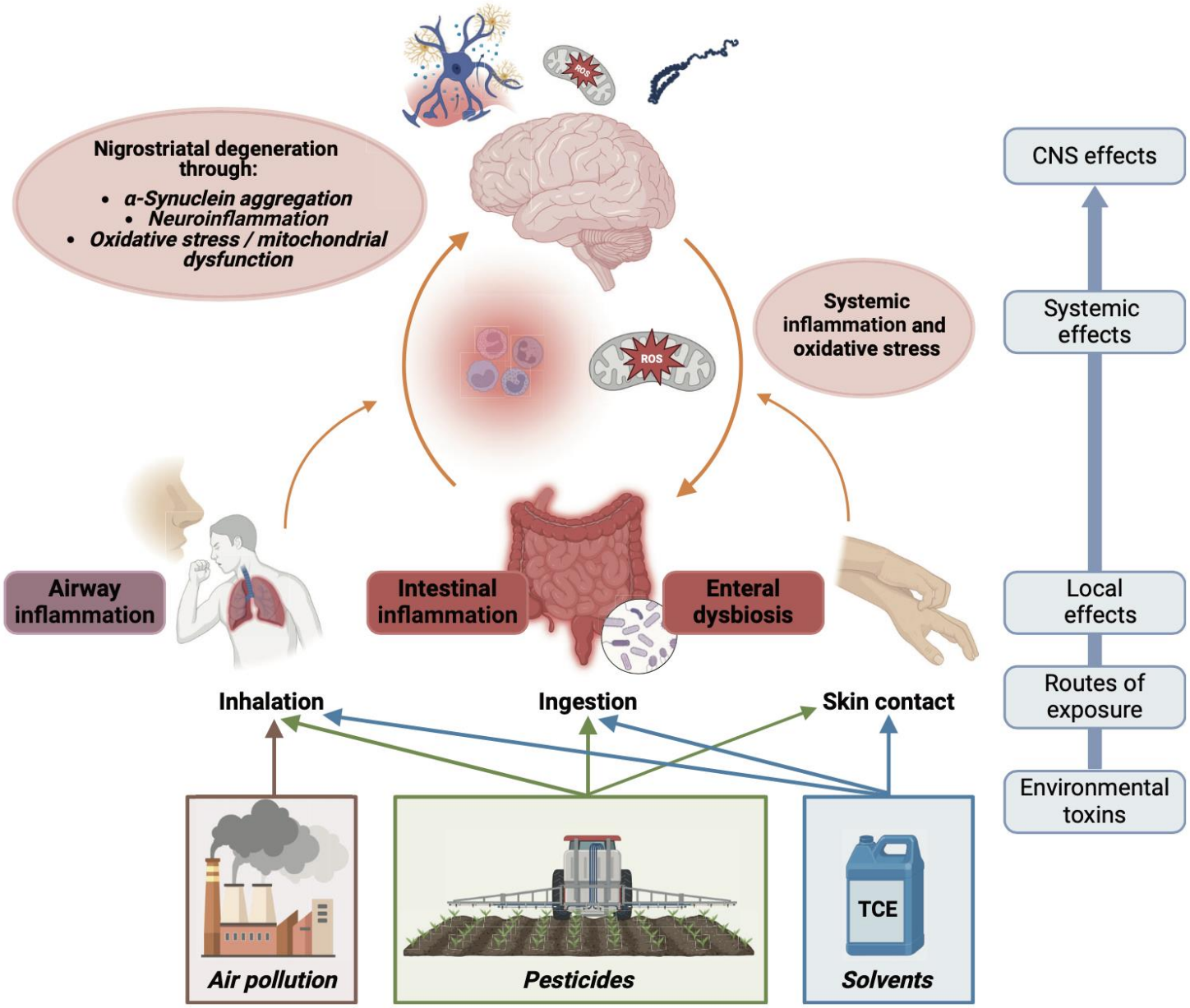
# Parkinson's Disease

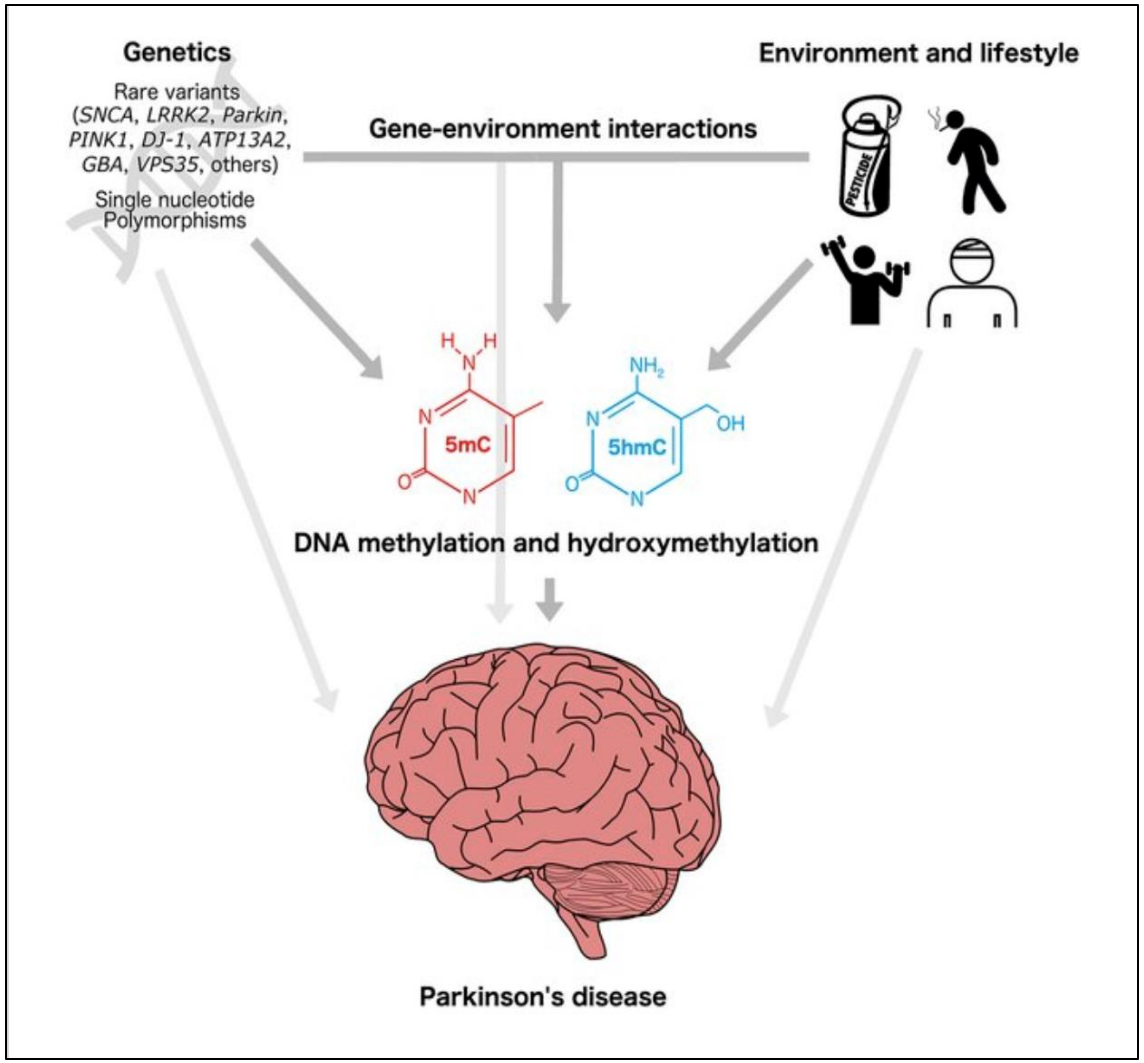


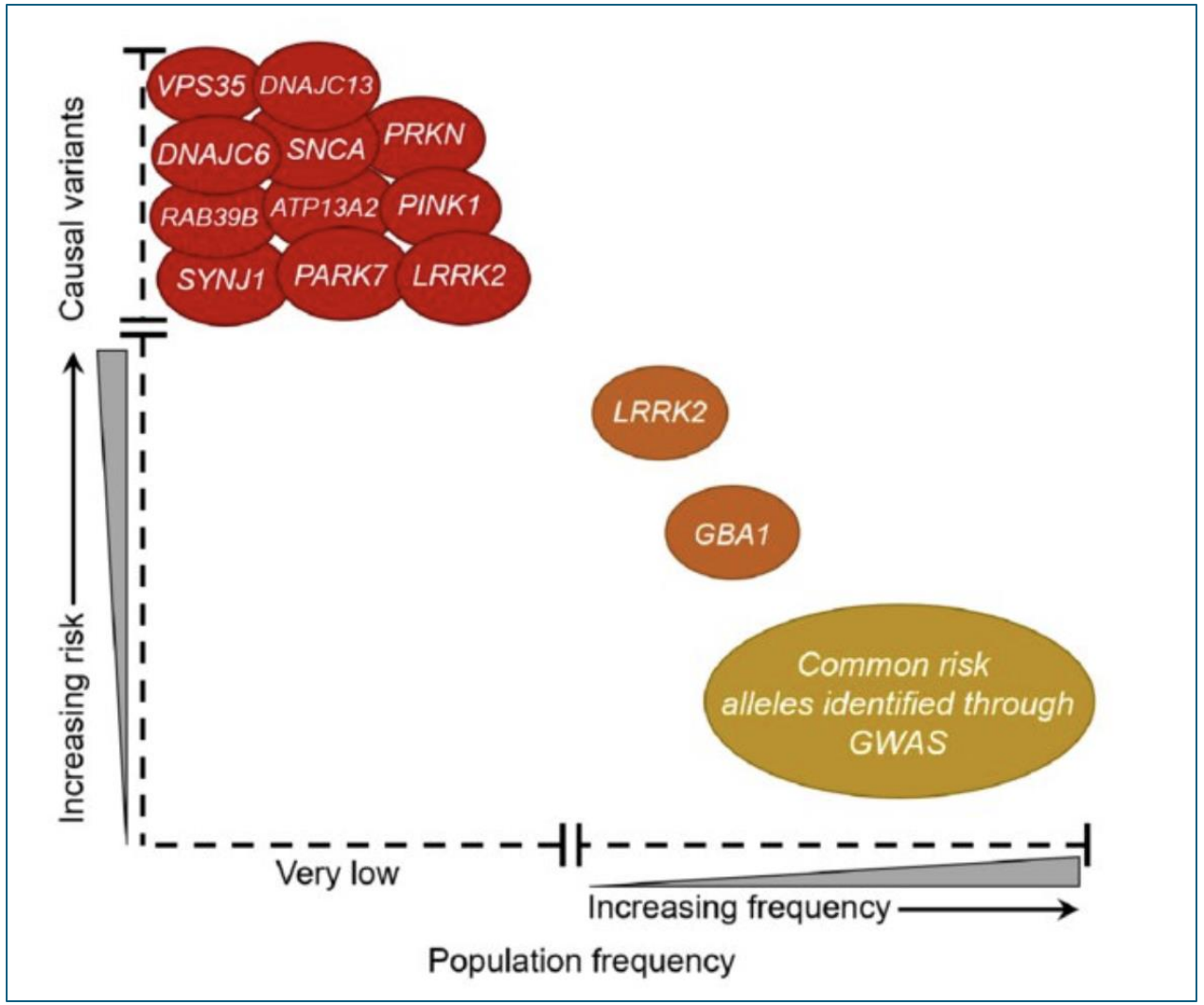

**Lifetime risk: 1 op 15**




Nigrostriatal degeneration through:
α-Synuclein aggregation
Neuroinflammation
Oxidative stress / mitochondrial dysfunction
ROS
ROS
Systemic inflammation and oxidative stress
Airway inflammation
Intestinal inflammation
Enteral dysbiosis
Inhalation
Ingestion
Skin contact
Air pollution
Pesticides
TCE
Solvents
CNS effects
Systemic effects
Local effects
Routes of exposure
Environmental toxins


Genetics
Rare variants
(SNCA, LRRK2, Parkin,
PINK1, DJ-1, ATP13A2,
GBA, VPS35, others)
Single nucleotide
Polymorphisms
Gene-environment interactions
Environment and lifestyle
PESTICIDE
5mC
5hmC
OH
DNA methylation and hydroxymethylation
Parkinson's disease


Causal variants
VPS35
DNAJC13
DNAJC6
SNCA
PRKN
RAB39B
ATP13A2
PINK1
SYNJ1
PARK7
LRRK2
LRRK2
GBA1
Common risk
alleles identified through
GWAS
Increasing risk
Very low
Increasing frequency
Population frequency

| | Mutation | Note | Year of discovery | Proposed disease mechanism | Inheritance | Frequency | Nominated by GWAS | Multiple independent families reported* | Functional evidence† | Negative reports published‡ | Confidence as actual PD gene§ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *SNCA* | Missense or multiplication | Often with dementia | 1997, 2003 | Gain of function or overexpression | Dominant | Very rare | Yes | ++ | ++ | + | Very high |
| *PRKN* | Missense or loss of function | Often early onset | 1998 | Loss of function | Recessive | Rare | No | ++ | ++ | + | Very high |
| *UCHL1* | Missense | .. | 1998 | Loss of function? | Dominant | Unclear | No | – | + | – – | Low |
| *PARK7* | Missense | Often early onset | 2003 | Loss of function | Recessive | Very rare | No | ++ | ++ | + | Very high |
| *LRRK2* | Missense | .. | 2004 | Gain of function | Dominant | Common | Yes | ++ | ++ | + | Very high |
| *PINK1* | Missense or loss of function | Often early onset | 2004 | Loss of function | Recessive | Rare | No | ++ | ++ | + | Very high |
| *POLG* | Missense or loss of function | Atypical PD | 2004 | Loss of function? | Dominant | Rare | No | ++ | + | + | High |
| *HTRA2* | Missense | .. | 2005 | Unclear | Dominant | Unclear | No | – | + | – – | Low |
| *ATP13A2* | Missense or loss of function | Atypical PD | 2006 | Loss of function | Recessive | Very rare | No | ++ | ++ | + | Very high |
| *FBXO7* | Missense | Often early onset | 2008 | Loss of function | Recessive | Very rare | No | ++ | ++ | + | Very high |
| *GIGYF2* | Missense | .. | 2008 | Unclear | Dominant | Unclear | No | + | + | – – | Low |
| *GBA* | Missense or loss of function | .. | 2009 | Likely loss of function | Dominant (incomplete penetrance) | Common | Yes | ++ | ++ | + | Very high |
| *PLA2G6* | Missense or loss of function | Often early onset | 2009 | Loss of function | Recessive | Rare | No | ++ | ++ | + | Very high |
| *EIF4G1* | Missense | .. | 2011 | Unclear | Dominant | Unclear | No | – | + | – – | Low |
| *VPS35* | Missense | .. | 2011 | Loss of function | Dominant | Very rare | No | ++ | + | + | Very high |
| *DNAJC6* | Missense or loss of function | Often early onset | 2012 | Loss of function | Recessive | Very rare | No | ++ | + | + | High |
| *SYNJ1* | Missense or loss of function | Often atypical PD | 2013 | Loss of function | Recessive | Very rare | No | ++ | + | + | High |
| *DNAJC13* | Missense | Same family as *TMEM230* | 2014 | Unclear | Dominant | Unclear | No | + | + | – | Low |
| *TMEM230* | Missense | Same family as *DNAJC13* | 2016 | Loss of function? | Dominant | Unclear | No | – | + | – | Low |
| *VPS13C* | Missense or loss of function | .. | 2016 | Loss of function | Recessive | Rare | Yes | ++ | + | + | High |
| *LRP10* | Missense or loss of function | .. | 2018 | Loss of function? | Dominant | Unclear | No | – | + | – – | Low |

GWAS=genome-wide association study. PD=Parkinson's disease. *In this column, ++ denotes ≥4 families reported; + denotes ≥2 and <4 families reported; – denotes 1 family reported; – – denotes no reported families. †In this column, ++ denotes ≥4 disease-related reports; + denotes ≥1 and <4 disease-related reports; – denotes no disease-related reports. ‡Reports that could not replicate the finding that this gene is a PD gene. In this column, + denotes no negative reports; – denotes ≥1 and <4 negative reports; – – denotes ≥4 negative reports. §Sum of the scores in the three preceding columns, with each + adding 1 and each – subtracting 1; very high denotes a score of ≥5; high denotes a score of 4; medium denotes a score of 2 or 3; low denotes a score of ≤1.

***Table:*** **Mutations that have been reported to cause Parkinson's disease**

Parkinsonism and Related Disorders 98 (2022) 103–113

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journal homepage: www.elsevier.com/locate/parkreldis

Review Article

# Prevalence of ten *LRRK2* variants in Parkinson's disease: A comprehensive review

Christopher Simpson [a], Lisa Vinikoor-Imler [b,1], Feiby L. Nassan [b], Julia Shirvan [b], Cathy Lally [a], Tien Dam [b], Nancy Maserejian [b,*]

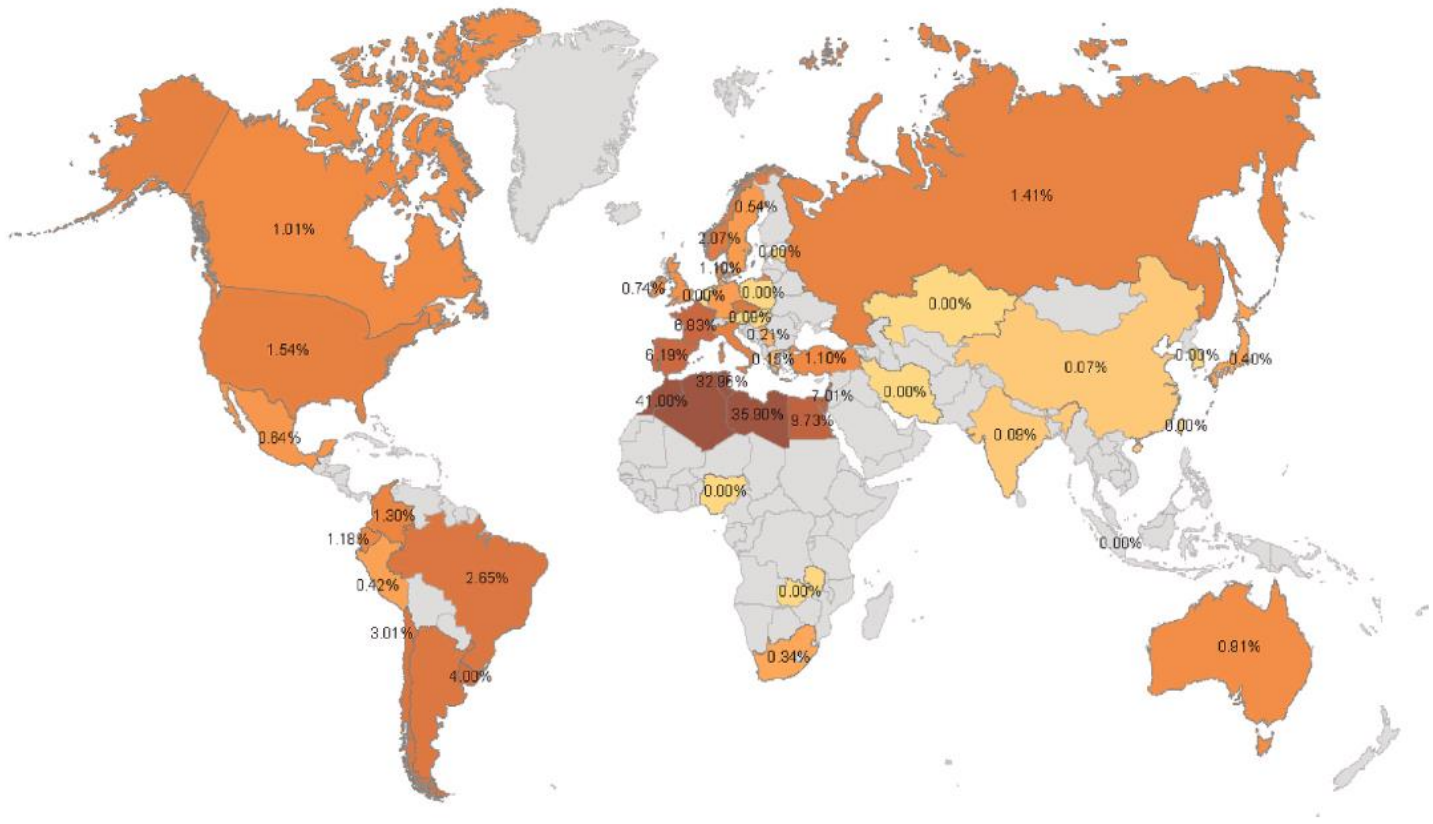


**Fig. 2.** Estimates of G2019S prevalence among patients with Parkinson's disease, adjusted for ethno-racial composition when possible.

nature genetics

Article

https://doi.org/10.1038/s41588-023-01584-8

# Multi-ancestry genome-wide association meta-analysis of Parkinson's disease

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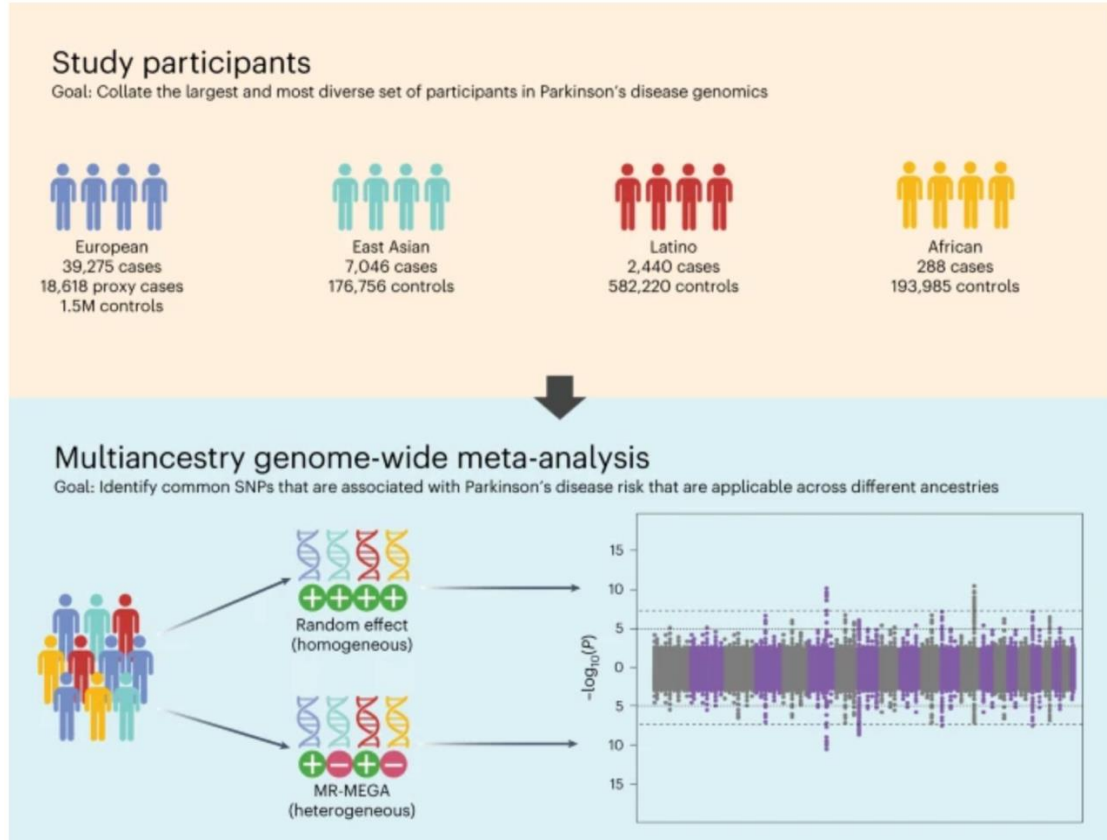
Check for updates

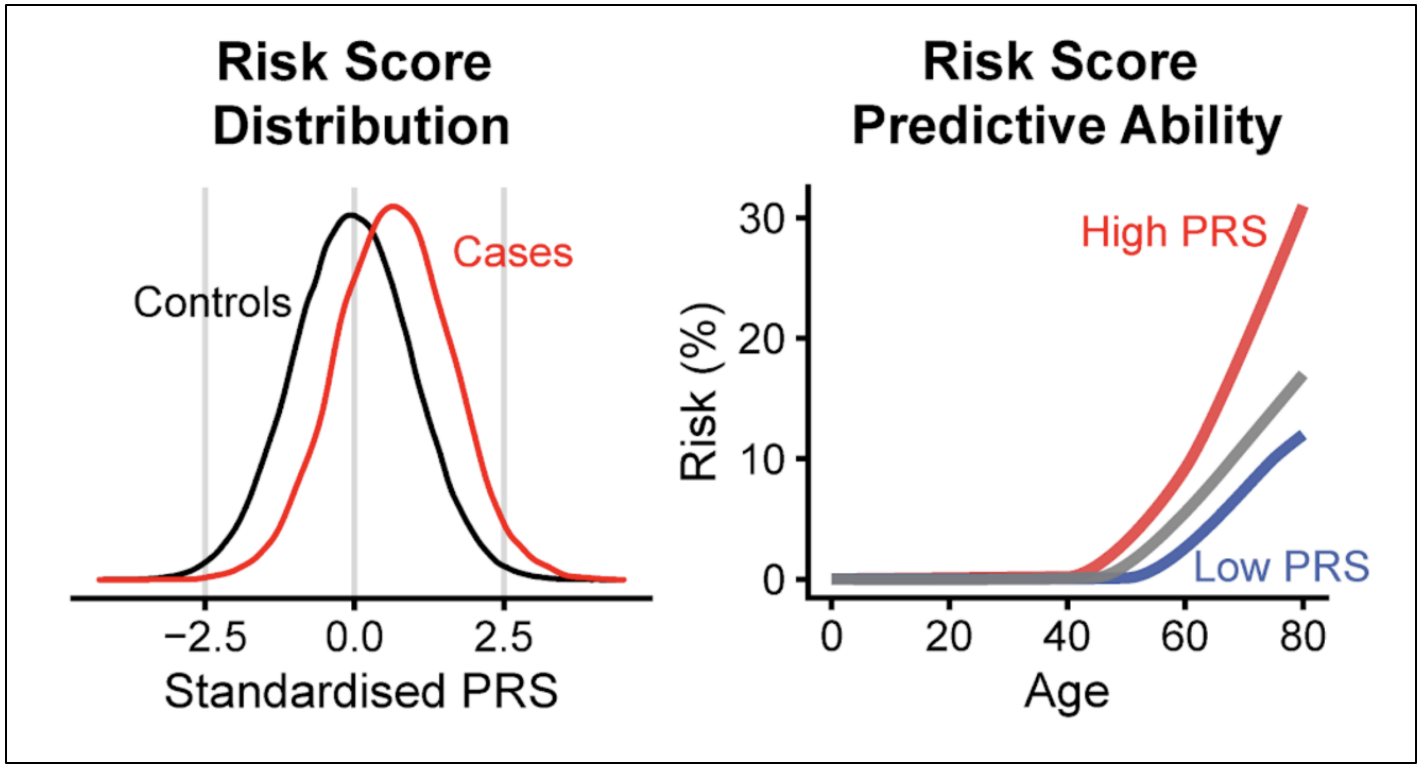
Jonggeol Jeffrey Kim[1,2,167], Dan Vitale[1,3,4,167], Diego Véliz Otani[5,6,167], Michelle Mulan Lian[7,8,167], Karl Heilbron[9], the 23andMe Research Team*, Hirotaka Iwaki[1,3,4], Julie Lake[1], Caroline Warly Solsberg[10,11,12], Hampton Leonard[1,3,4], Mary B. Makarious[1,13,14], Eng-King Tan[15], Andrew B. Singleton[1,4], Sara Bandres-Ciga[1,4], Alastair J. Noyce[2], the Global Parkinson's Genetics Program (GP2)*, Cornelis Blauwendraat[1,4,168] ✉, Mike A. Nalls[1,3,4,168] ✉, Jia Nee Foo[7,8,168] ✉ & Ignacio Mata[16,168] ✉



# Gene–Environment Interactions for Parkinson's Disease

Alexandra Reynoso, MSc [1], Roberta Torricelli, BSc [2], Benjamin Meir Jacobs, MRCP, MSc [2], Jingchunzi Shi, PhD,[1] Stella Aslibekyan, PhD,[1] Lucy Norcliffe-Kaufmann, PhD,[1] Alastair J Noyce, MRCP, PhD [2], and Karl Heilbron, PhD [3,4]

**"Polygenic risk score" (PRS)**



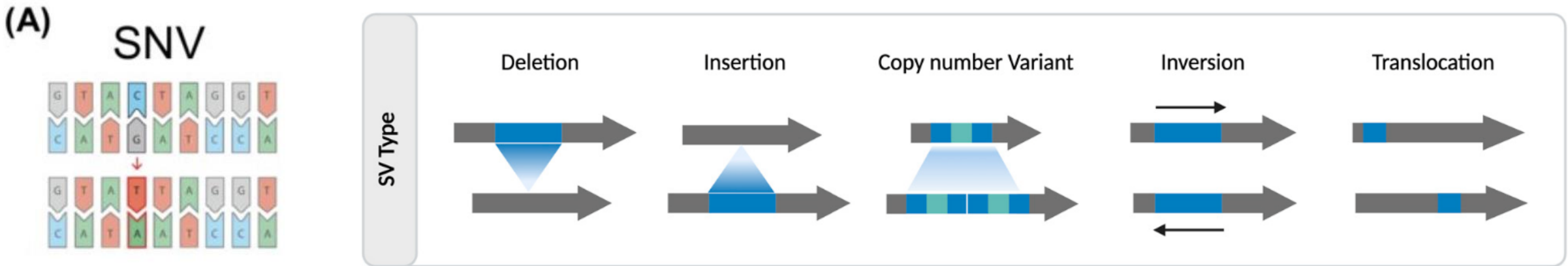
International Journal of
*Molecular Sciences*

MDPI

*Review*

# The Role of Structural Variants in the Genetic Architecture of Parkinson's Disease

**Abigail Miano-Burkhardt [1,2], Pilar Alvarez Jerez [2], Kensuke Daida [1,2], Sara Bandres Ciga [2] and Kimberley J. Billingsley [1,2,*]**



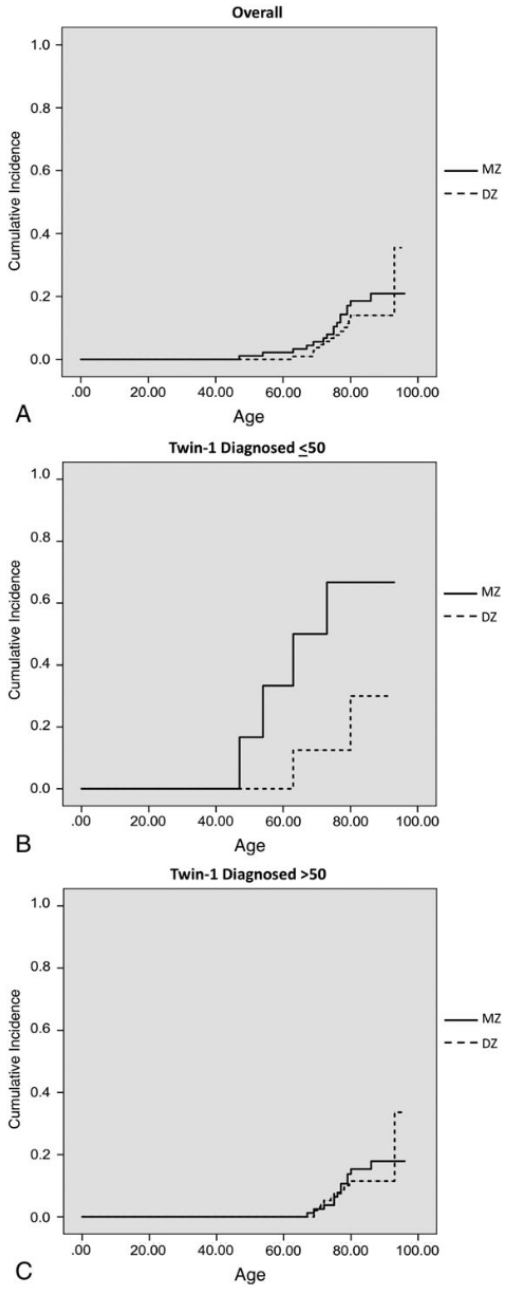



**FIGURE: Cumulative risk of PD in twins with an affected twin, by zygosity. (A) MZ and DZ pairs, overall. (B) MZ and DZ pairs in which PD was diagnosed in twin-1 ≤age 50. (C) MZ and DZ pairs in which PD was diagnosed in twin-1 >age 50. DZ = dizygotic; MZ = monozygotic**

# Concordance for Parkinson's Disease in Twins: A 20-Year Update

Samuel M. Goldman, MD, MPH,[1]
Kenneth Marek, MD,[2] Ruth Ottman, PhD,[3]
Cheryl Meng, MS,[4]
Kathleen Comyns, MPH,[4]
Piu Chan, MD, PhD,[5] Jinghong Ma, MD,[6]
Connie Marras, MD, PhD,[7]
J. William Langston, MD,[8]
G. Webster Ross, MD,[9] and
Caroline M. Tanner, MD, PhD[10]

During the 1990s, we estimated the genetic contribution to Parkinson's disease risk in a large, population-based twin registry. Because many unaffected twins were still alive, previous concordance estimates were based on incomplete information. Ninety-five percent of twins are now deceased. Here, we update concordance and heritability through 2015 using National Death Index data. In total, we identified 30 concordant and 193 discordant pairs. Proband-wise concordance was 0.20 in monozygotic and 0.13 in dizygotic pairs. Heritability was 0.27 overall, 0.83 in pairs diagnosed ≤50, and 0.19 in pairs diagnosed >50. High concordance in dizygotic twins suggests shared effects of early childhood environment.

**ANN NEUROL 2019;85:600–605**

**Total heritability: 25-30%**

“Classical PD”

“Early-onset” PD (29 years)
Motor fluctuations and dystonia
Freezing of gait

PRKN Heterozygous missense
PRKN Heterozygous deletion

# Implications of genetic screening - referrals

- Depending on the context of referral: clinical-scientific
- Clinical genetic issues: support for patients and consent
- Issues:
  - Currently no therapeutic consequences (neuroprotection)
  - Prognosis estimation
  - Selection for specific treatments e.g. deep brain stimulation

genes

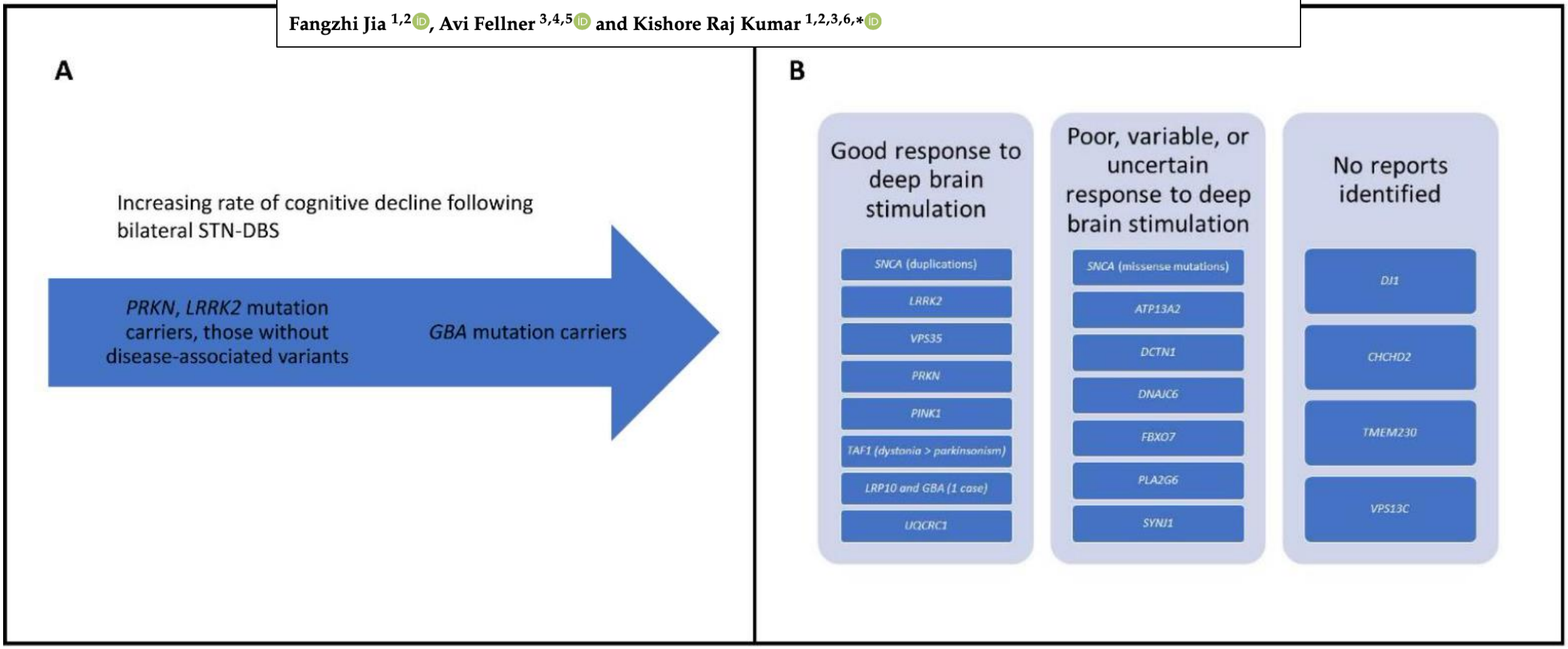
Genes 2022, 13, 471. https://doi.org/10.3390/genes13030471

MDPI

*Review*

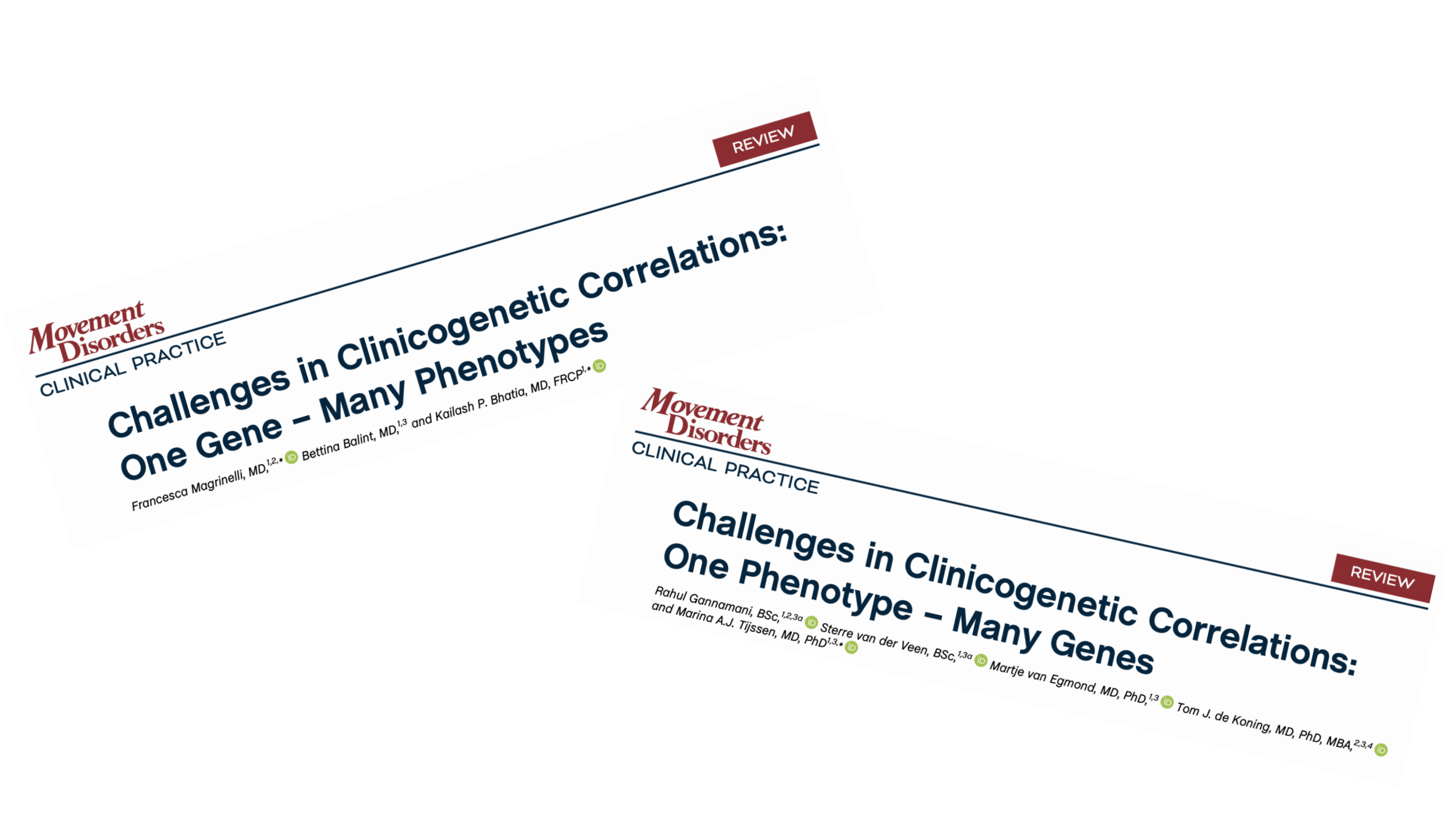
# Monogenic Parkinson's Disease: Genotype, Phenotype, Pathophysiology, and Genetic Testing

**Fangzhi Jia [1,2], Avi Fellner [3,4,5] and Kishore Raj Kumar [1,2,3,6,*]**



# Hyperkinetic disorders
# Abnormal movements: definitions

| Table 1: Five Major Types of Hyperkinetic Movement Disorders | |
|---|---|
| Tremors | Involuntary, alternating movements involving one or more joints occurring at a regular frequency resulting in "rhythmic oscillations" |
| Chorea | Involuntary, non-rhythmic, abrupt movements resulting from continuous flow of muscle contractions from one muscle group to another resulting in jerky or dance like movements |
| Dystonia | Involuntary, slow, sustained contractions of agonist and sometimes also antagonist muscles producing twisting movements and/or abnormal posturing |
| Myoclonus | Involuntary, sudden, brief muscle contractions (positive myoclonus) or inhibition of muscle contractions (negative myoclonus) leading to shock like movements |
| Tics | Simple or complex, repetitive, abnormal movements or sounds usually preceded by an uncomfortable feeling or sensory urge that is relieved by carrying out the behavior. Tics can often be easily mimicked and suppressed by short efforts of will. |


Movement Disorders
CLINICAL PRACTICE
REVIEW
Challenges in Clinicogenetic Correlations: One Gene – Many Phenotypes
Francesca Magrinelli, MD,[1,2,*] Bettina Balint, MD,[1,3] and Kailash P. Bhatia, MD, FRCP[1,*]
Movement Disorders
CLINICAL PRACTICE
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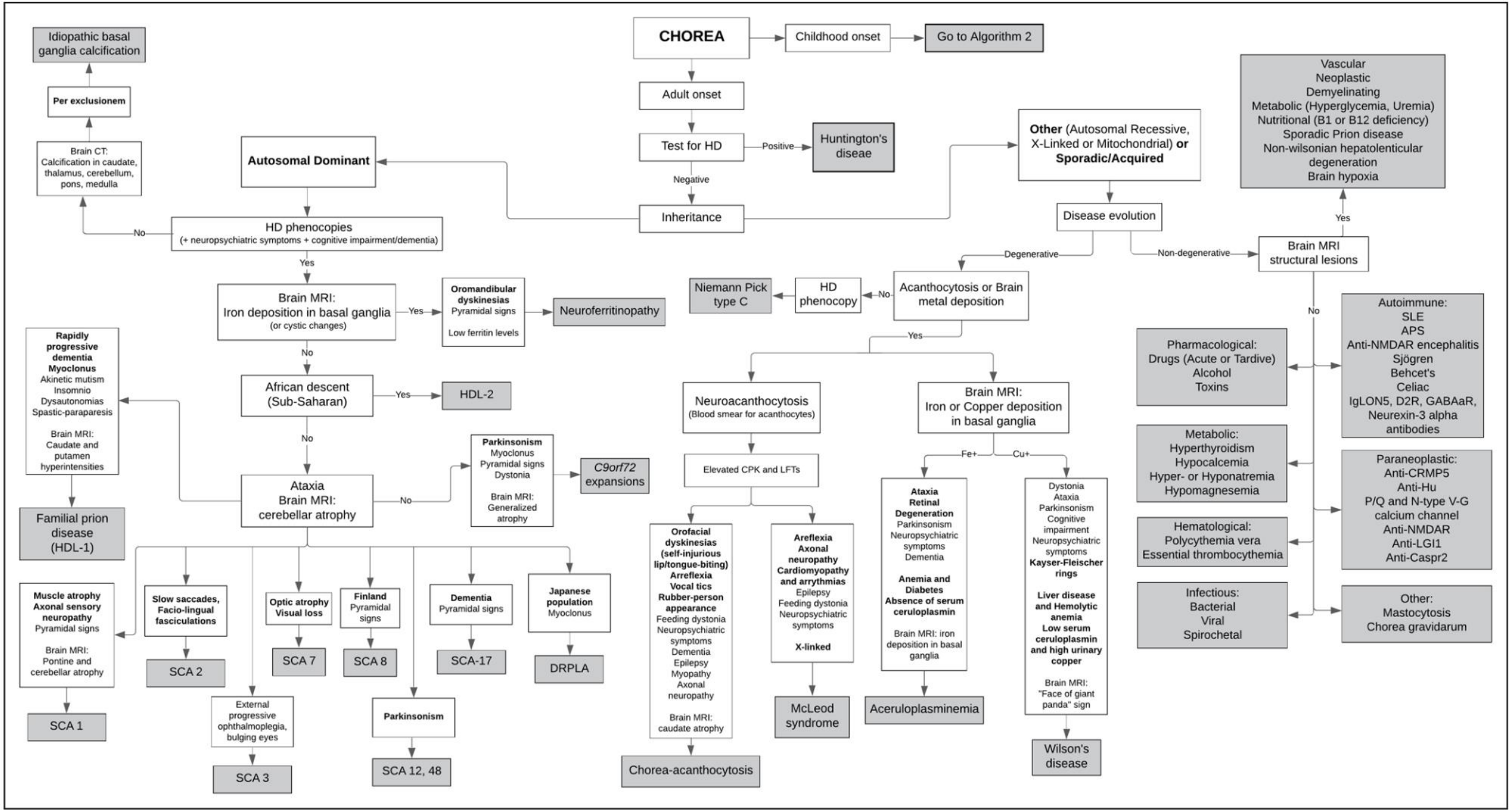
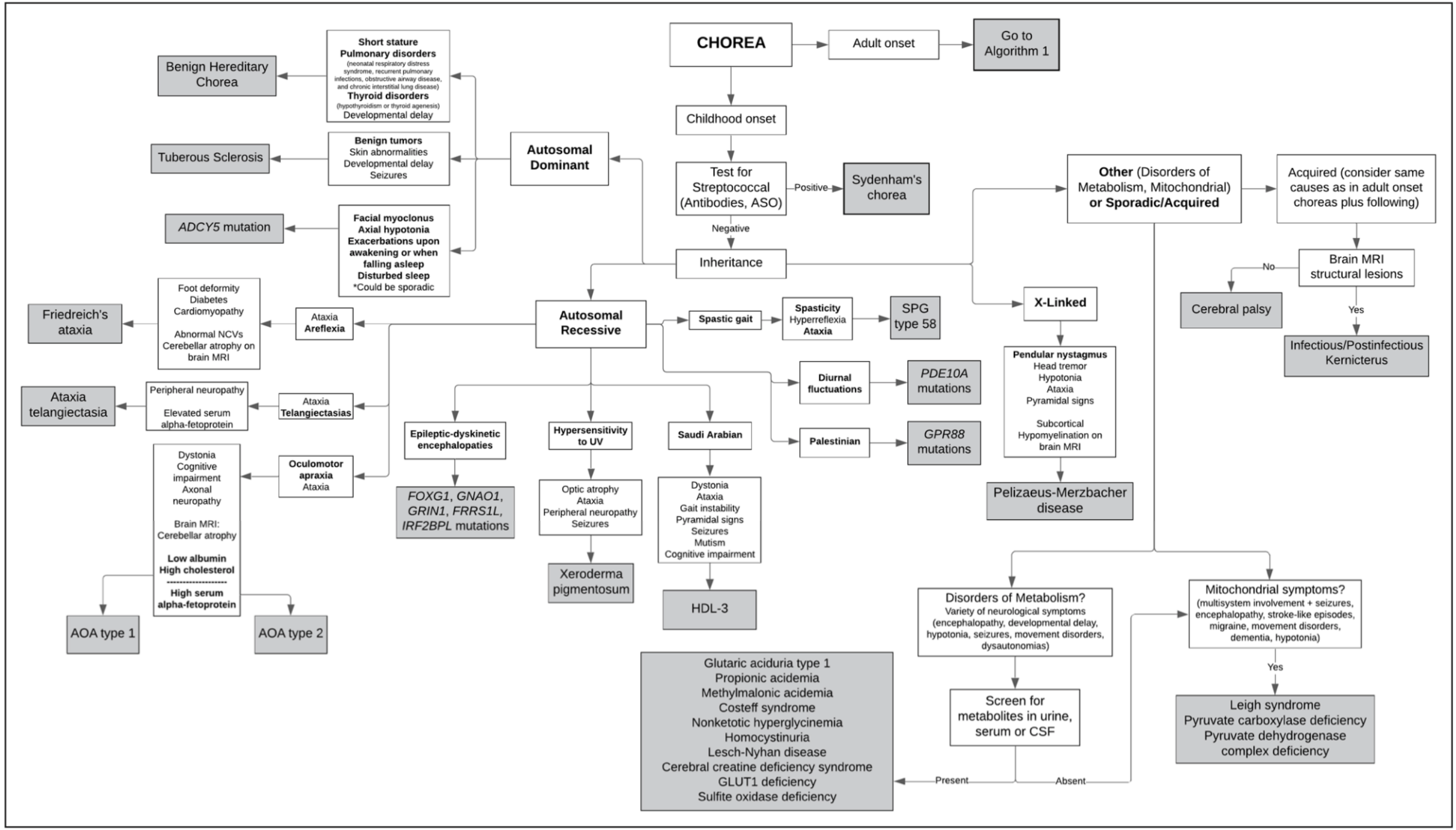
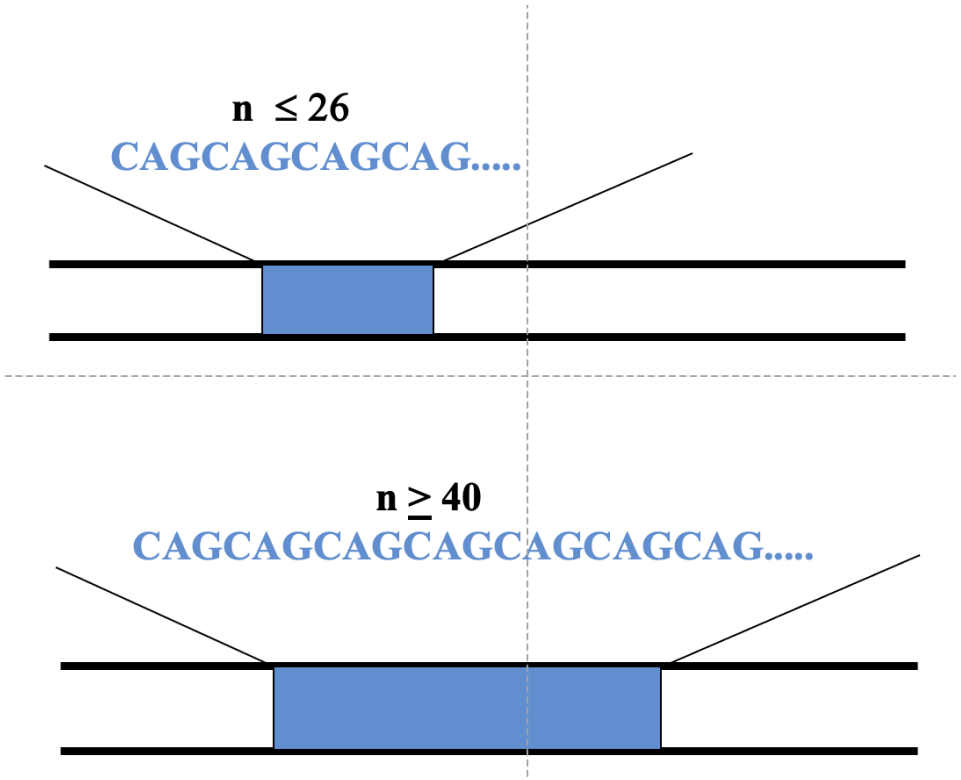
Challenges in Clinicogenetic Correlations: One Phenotype – Many Genes
Rahul Gannamani, BSc,[1,2,3a] Sterre van der Veen, BSc,[1,3a] Martje van Egmond, MD, PhD,[1,3] Tom J. de Koning, MD, PhD, MBA,[2,3,4]
and Marina A.J. Tijssen, MD, PhD[1,3,*]


CHOREA
Childhood onset
Go to Algorithm 2
Adult onset
Test for HD
Positive
Huntington's diseae
Negative
Inheritance
Autosomal Dominant
Other (Autosomal Recessive, X-Linked or Mitochondrial) or Sporadic/Acquired
Disease evolution
Degenerative
Non-degenerative
Vascular
Neoplastic
Demyelinating
Metabolic (Hyperglycemia, Uremia)
Nutritional (B1 or B12 deficiency)
Sporadic Prion disease
Non-wilsonian hepatolenticular degeneration
Brain hypoxia
Yes
Brain MRI structural lesions
No
Idiopathic basal ganglia calcification
Per exclusionem
Brain CT: Calcification in caudate, thalamus, cerebellum, pons, medulla
No
HD phenocopies
(+ neuropsychiatric symptoms + cognitive impairment/dementia)
Yes
Brain MRI: Iron deposition in basal ganglia
(or cystic changes)
Yes
Oromandibular dyskinesias
Pyramidal signs
Low ferritin levels
Neuroferritinopathy
No
African descent (Sub-Saharan)
Yes
HDL-2
No
Ataxia
Brain MRI: cerebellar atrophy
No
Parkinsonism
Myoclonus
Pyramidal signs
Dystonia
Brain MRI: Generalized atrophy
C9orf72 expansions
Rapidly progressive dementia
Myoclonus
Akinetic mutism
Insomnio
Dysautonomias
Spastic-paraparesis
Brain MRI: Caudate and putamen hyperintensities
Familial prion disease (HDL-1)
Muscle atrophy
Axonal sensory neuropathy
Pyramidal signs
Brain MRI: Pontine and cerebellar atrophy
SCA 1
Slow saccades, Facio-lingual fasciculations
SCA 2
External progressive ophthalmoplegia, bulging eyes
SCA 3
Optic atrophy
Visual loss
SCA 7
Finland
Pyramidal signs
SCA 8
Parkinsonism
SCA 12, 48
Dementia
Pyramidal signs
SCA-17
Japanese population
Myoclonus
DRPLA
Niemann Pick type C
HD phenocopy
No
Acanthocytosis or Brain metal deposition
Yes
Neuroacanthocytosis
(Blood smear for acanthocytes)
Elevated CPK and LFTs
Orofacial dyskinesias (self-injurious lip/tongue-biting)
Arreflexia
Vocal tics
Rubber-person appearance
Feeding dystonia
Neuropsychiatric symptoms
Dementia
Epilepsy
Myopathy
Axonal neuropathy
Brain MRI: caudate atrophy
Chorea-acanthocytosis
Areflexia
Axonal neuropathy
Cardiomyopathy and arrythmias
Epilepsy
Feeding dystonia
Neuropsychiatric symptoms
X-linked
McLeod syndrome
Brain MRI: Iron or Copper deposition in basal ganglia
Fe+
Cu+
Ataxia
Retinal Degeneration
Parkinsonism
Neuropsychiatric symptoms
Dementia
Anemia and Diabetes
Absence of serum ceruloplasmin
Brain MRI: iron deposition in basal ganglia
Aceruloplasminemia
Dystonia
Ataxia
Parkinsonism
Cognitive impairment
Neuropsychiatric symptoms
Kayser-Fleischer rings
Liver disease and Hemolytic anemia
Low serum ceruloplasmin and high urinary copper
Brain MRI: "Face of giant panda" sign
Wilson's disease
Pharmacological:
Drugs (Acute or Tardive)
Alcohol
Toxins
Metabolic:
Hyperthyroidism
Hypocalcemia
Hyper- or Hyponatremia
Hypomagnesemia
Hematological:
Polycythemia vera
Essential thrombocythemia
Infectious:
Bacterial
Viral
Spirochetal
Autoimmune:
SLE
APS
Anti-NMDAR encephalitis
Sjögren
Behcet's
Celiac
IgLON5, D2R, GABAaR, Neurexin-3 alpha antibodies
Paraneoplastic:
Anti-CRMP5
Anti-Hu
P/Q and N-type V-G calcium channel
Anti-NMDAR
Anti-LGI1
Anti-Caspr2
Other:
Mastocytosis
Chorea gravidarum


CHOREA
Adult onset
Go to Algorithm 1
Childhood onset
Test for Streptococcal (Antibodies, ASO)
Positive
Sydenham's chorea
Negative
Inheritance
Autosomal Dominant
Short stature
Pulmonary disorders
(neonatal respiratory distress syndrome, recurrent pulmonary infections, obstructive airway disease, and chronic interstitial lung disease)
Thyroid disorders
(hypothyroidism or thyroid agenesis)
Developmental delay
Benign Hereditary Chorea
Benign tumors
Skin abnormalities
Developmental delay
Seizures
Tuberous Sclerosis
ADCY5 mutation
Facial myoclonus
Axial hypotonia
Exacerbations upon awakening or when falling asleep
Disturbed sleep
*Could be sporadic
Autosomal Recessive
Spastic gait
Spasticity
Hyperreflexia
Ataxia
SPG type 58
Ataxia
Areflexia
Foot deformity
Diabetes
Cardiomyopathy
Abnormal NCVs
Cerebellar atrophy on brain MRI
Friedreich's ataxia
Ataxia
Telangiectasias
Peripheral neuropathy
Elevated serum alpha-fetoprotein
Ataxia telangiectasia
Oculomotor apraxia
Ataxia
Dystonia
Cognitive impairment
Axonal neuropathy
Brain MRI:
Cerebellar atrophy
Low albumin
High cholesterol
---
High serum alpha-fetoprotein
AOA type 1
AOA type 2
Epileptic-dyskinetic encephalopaties
FOXG1, GNAO1, GRIN1, FRRS1L, IRF2BPL mutations
Hypersensitivity to UV
Optic atrophy
Ataxia
Peripheral neuropathy
Seizures
Xeroderma pigmentosum
Saudi Arabian
Dystonia
Ataxia
Gait instability
Pyramidal signs
Seizures
Mutism
Cognitive impairment
HDL-3
Diurnal fluctuations
PDE10A mutations
Palestinian
GPR88 mutations
Other (Disorders of Metabolism, Mitochondrial) or Sporadic/Acquired
Acquired (consider same causes as in adult onset choreas plus following)
Brain MRI structural lesions
No
Cerebral palsy
Yes
Infectious/Postinfectious Kernicterus
X-Linked
Pendular nystagmus
Head tremor
Hypotonia
Ataxia
Pyramidal signs
Subcortical Hypomyelination on brain MRI
Pelizaeus-Merzbacher disease
Disorders of Metabolism?
Variety of neurological symptoms (encephalopathy, developmental delay, hypotonia, seizures, movement disorders, dysautonomias)
Screen for metabolites in urine, serum or CSF
Present
Absent
Glutaric aciduria type 1
Propionic acidemia
Methylmalonic acidemia
Costeff syndrome
Nonketotic hyperglycinemia
Homocystinuria
Lesch-Nyhan disease
Cerebral creatine deficiency syndrome
GLUT1 deficiency
Sulfite oxidase deficiency
Mitochondrial symptoms?
(multisystem involvement + seizures, encephalopathy, stroke-like episodes, migraine, movement disorders, dementia, hypotonia)
Yes
Leigh syndrome
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase complex deficiency

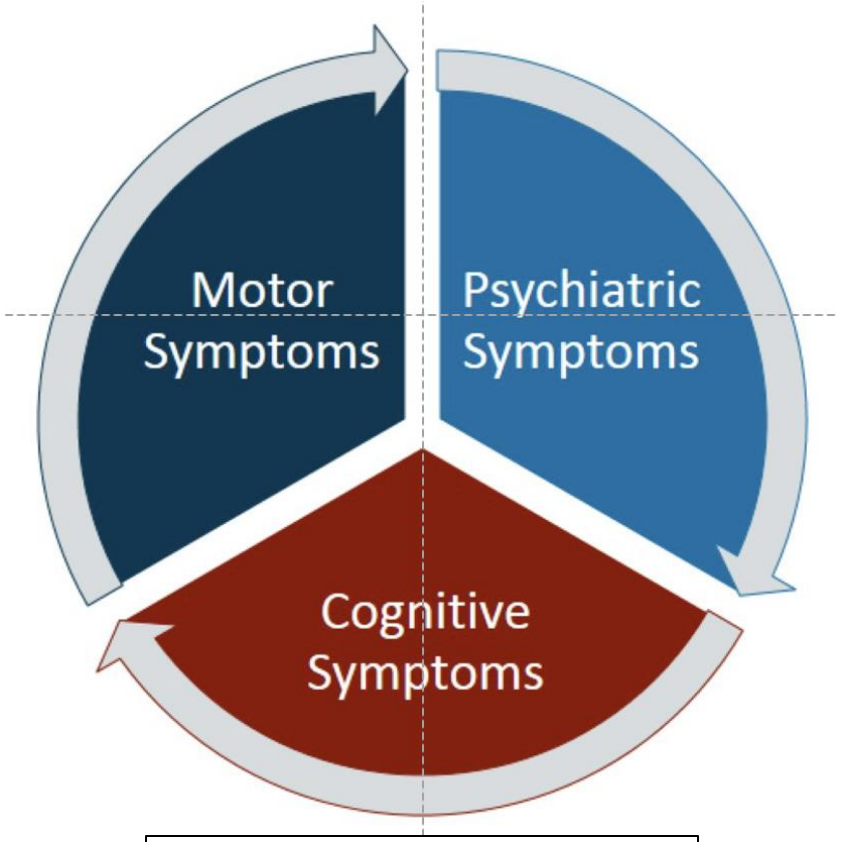
# Huntington’s Disease
# A trinucleotide repeat disorder




| Huntington's status | | CAG repeat length |
|---|---|---|
| Unaffected | Normal | 10-26 |
| | Intermediate allele | 27-35 |
| Affected | Reduced penetrance | 36-39 |
| | Full penetrance | 40+ |

# Huntington's disease: symptoms

Chorea and other MD
Gait and stability
Swallowing
Oculomotor dysfunction

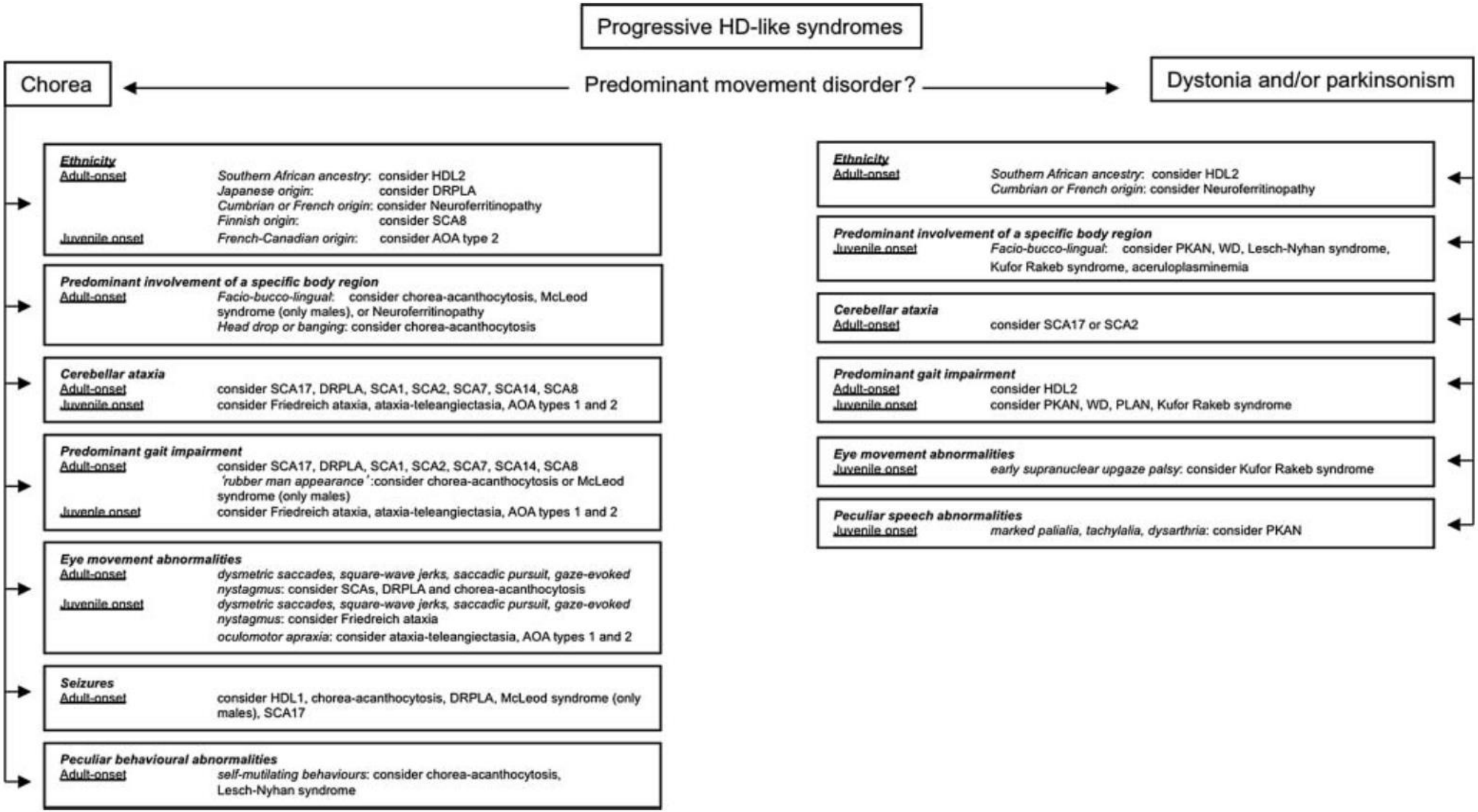



Impulsivity
Depression/apathy
Irritability
Personality change

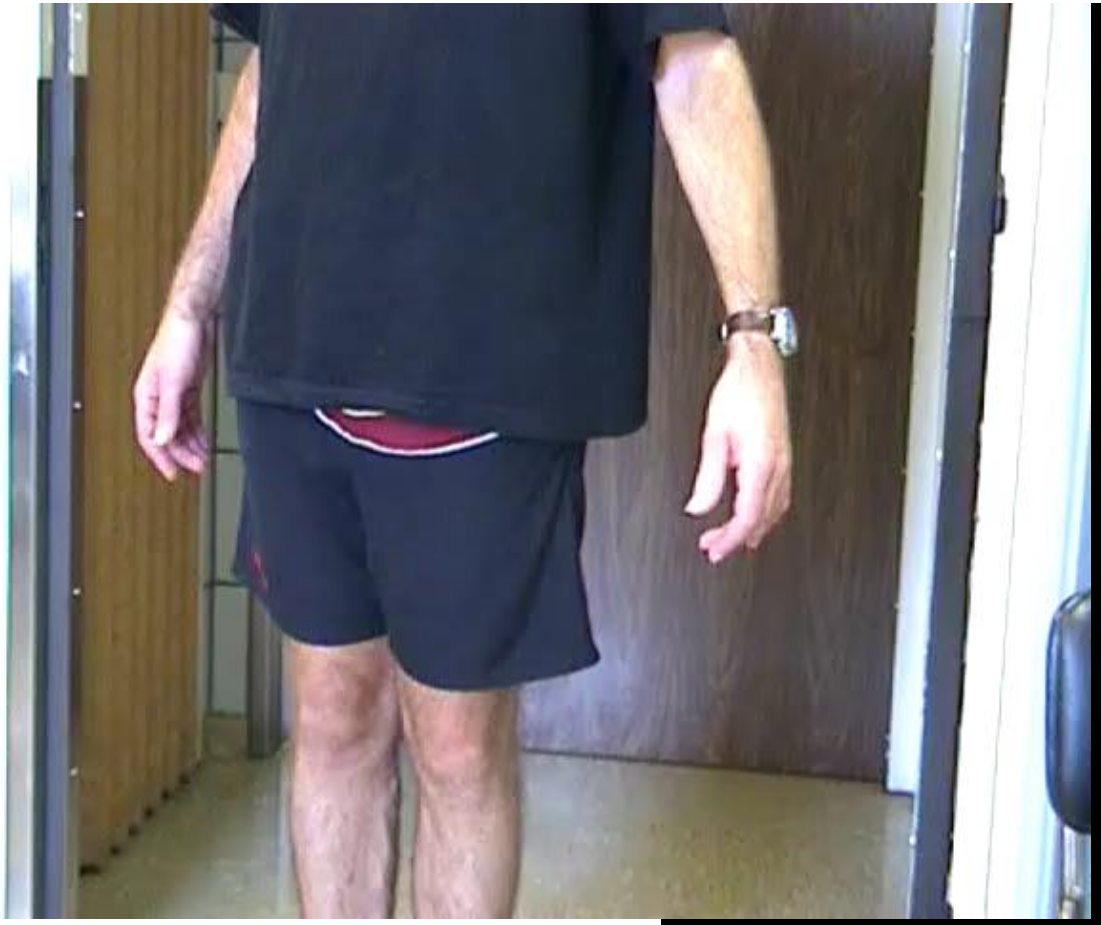
Attention
Executive function
Memory
Dementia

# Huntington’s disease: clinical genetics

- Symptomatic testing
- Presymptomatic testing
- Pre-implantation diagnosis


Progressive HD-like syndromes
Predominant movement disorder?
Chorea
Dystonia and/or parkinsonism
Ethnicity
Adult-onset
Southern African ancestry: consider HDL2
Japanese origin: consider DRPLA
Cumbrian or French origin: consider Neuroferritinopathy
Finnish origin: consider SCA8
Juvenile onset
French-Canadian origin: consider AOA type 2
Predominant involvement of a specific body region
Adult-onset
Facio-bucco-lingual: consider chorea-acanthocytosis, McLeod syndrome (only males), or Neuroferritinopathy
Head drop or banging: consider chorea-acanthocytosis
Cerebellar ataxia
Adult-onset
consider SCA17, DRPLA, SCA1, SCA2, SCA7, SCA14, SCA8
Juvenile onset
consider Friedreich ataxia, ataxia-teleangiectasia, AOA types 1 and 2
Predominant gait impairment
Adult-onset
consider SCA17, DRPLA, SCA1, SCA2, SCA7, SCA14, SCA8
'rubber man appearance':consider chorea-acanthocytosis or McLeod syndrome (only males)
Juvenile onset
consider Friedreich ataxia, ataxia-teleangiectasia, AOA types 1 and 2
Eye movement abnormalities
Adult-onset
dysmetric saccades, square-wave jerks, saccadic pursuit, gaze-evoked nystagmus: consider SCAs, DRPLA and chorea-acanthocytosis
Juvenile onset
dysmetric saccades, square-wave jerks, saccadic pursuit, gaze-evoked nystagmus: consider Friedreich ataxia
oculomotor apraxia: consider ataxia-teleangiectasia, AOA types 1 and 2
Seizures
Adult-onset
consider HDL1, chorea-acanthocytosis, DRPLA, McLeod syndrome (only males), SCA17
Peculiar behavioural abnormalities
Adult-onset
self-mutilating behaviours: consider chorea-acanthocytosis, Lesch-Nyhan syndrome
Ethnicity
Adult-onset
Southern African ancestry: consider HDL2
Cumbrian or French origin: consider Neuroferritinopathy
Predominant involvement of a specific body region
Juvenile onset
Facio-bucco-lingual: consider PKAN, WD, Lesch-Nyhan syndrome, Kufor Rakeb syndrome, aceruloplasminemia
Cerebellar ataxia
Adult-onset
consider SCA17 or SCA2
Predominant gait impairment
Adult-onset
consider HDL2
Juvenile onset
consider PKAN, WD, PLAN, Kufor Rakeb syndrome
Eye movement abnormalities
Juvenile onset
early supranuclear upgaze palsy: consider Kufor Rakeb syndrome
Peculiar speech abnormalities
Juvenile onset
marked palialia, tachylalia, dysarthria: consider PKAN

# Huntington’s Disease



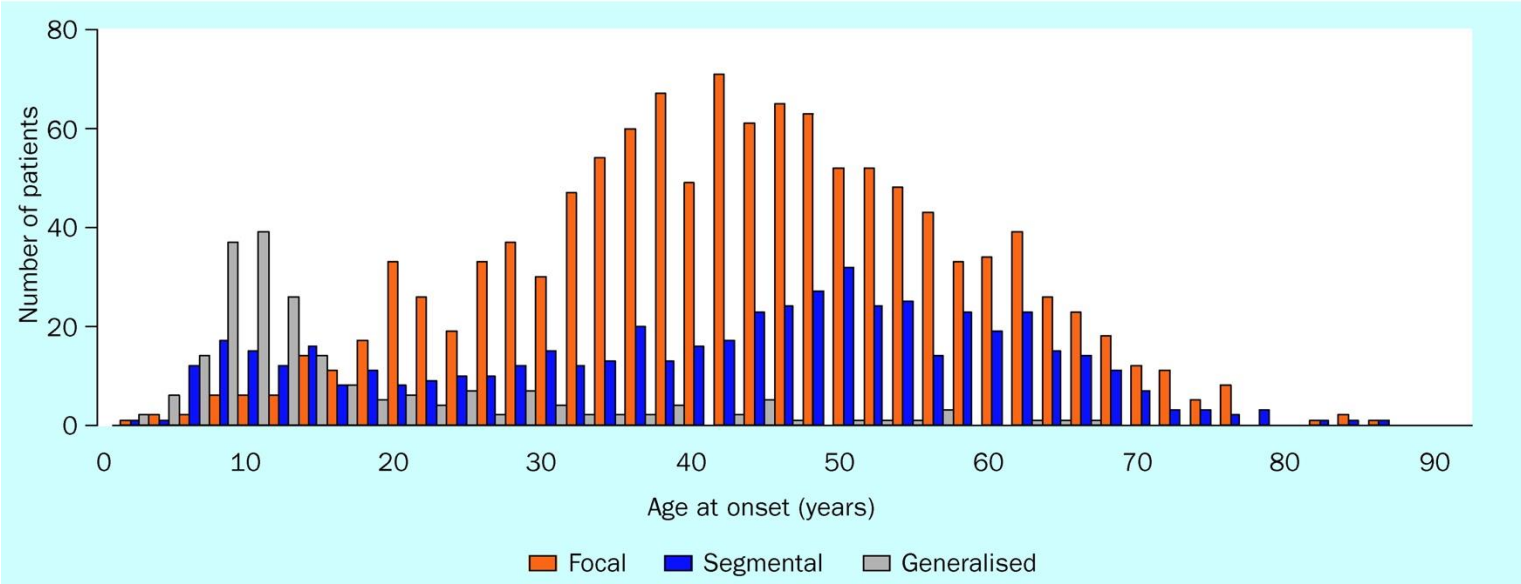
# Spinocerebellar ataxia type 17

AAO 32y

Involuntary movements
Gait problems
Cognitive deterioration

Cerebellar atrophy

# Dystonia




Early-onset dystonia: May begin focally but more often generalized
More often genetic origin

Late-onset dystonia: More often remaining focal or segmental
More often sporadic

# Dystonia Genes

| Form of Dystonia | | Gene | Locus Name | New Designation & Phenotypic Subgroup | Additional Distinguishing Features | MOI |
|---|---|---|---|---|---|---|
| **Isolated** | | *TOR1A* | DYT1 | DYT-TOR1A | Childhood or adolescent-onset, generalized | AD |
| | | *THAP1* | DYT6 | DYT-THAP1 | Adolescent-onset, cranial or generalized | AD |
| | | *ANO3* | DYT24 | DYT-ANO3 | Adult-onset, focal or segmental | AD |
| | | *GNAL* | DYT25 | DYT-GNAL | Mostly adult-onset, focal or segmental | AD |
| | | *KMT2B* | DYT28 | DYT-KMT2B | Early-onset, generalized, mild syndromic features | AD |
| **Combined** | **Dystonia + parkinsonism** | *GCH1* | DYT5a | DYT-GCH1 | Dopa-responsive | AD, AR |
| | | *TH* | DYT5b | DYT-TH | Dopa-responsive | AR |
| | | *SPR* | Not assigned | DYT-SPR | Dopa-responsive, cognitive impairment | AR |
| | | *TAF1* [1] | DYT3 | DYT-TAF1 | Neurodegeneration | XL |
| | | *PRKRA* | DYT16 | DYT-PRKRA | Dystonia w/mild parkinsonism | AR |
| | | *ATP1A3* | DYT12 | DYT-ATP1A3 | Rapid-onset | AD |
| | **Dystonia + myoclonus** | *SGCE* | DYT11 | DYT-SGCE | Psychiatric disease | AD |
| | **Paroxysmal dystonia + other dyskinesia** | *PNKD* [2] | DYT8 | PxMD-PNKD | Paroxysmal nonkinesigenic dyskinesia | AD |
| | | *PRRT2* | DYT10 | PxMD-PRRT2 | Paroxysmal kinesigenic dyskinesia | AD |
| | | *SLC2A1* | DYT18 | PxMD-SLC2A1 | Paroxysmal exertion-induced dyskinesia | AD |

# Dystonia Genes

| Form of Dystonia | | Gene | Locus Name | New Designation & Phenotypic Subgroup | Additional Distinguishing Features | MOI |
|---|---|---|---|---|---|---|
| **Isolated** | | *TOR1A* | DYT1 | DYT-TOR1A | Childhood or adolescent-onset, generalized | AD |
| | | *THAP1* | DYT6 | DYT-THAP1 | Adolescent-onset, cranial or generalized | AD |
| | | *ANO3* | DYT24 | DYT-ANO3 | Adult-onset, focal or segmental | AD |
| | | *GNAL* | DYT25 | DYT-GNAL | Mostly adult-onset, focal or segmental | AD |
| | | *KMT2B* | DYT28 | DYT-KMT2B | Early-onset, generalized, mild syndromic features | AD |
| **Combined** | **Dystonia + parkinsonism** | *GCH1* | DYT5a | DYT-GCH1 | Dopa-responsive | AD, AR |
| | | *TH* | DYT5b | DYT-TH | Dopa-responsive | AR |
| | | *SPR* | Not assigned | DYT-SPR | Dopa-responsive, cognitive impairment | AR |
| | | *TAF1* [1] | DYT3 | DYT-TAF1 | Neurodegeneration | XL |
| | | *PRKRA* | DYT16 | DYT-PRKRA | Dystonia w/mild parkinsonism | AR |
| | | *ATP1A3* | DYT12 | DYT-ATP1A3 | Rapid-onset | AD |
| | **Dystonia + myoclonus** | *SGCE* | DYT11 | DYT-SGCE | Psychiatric disease | AD |
| | **Paroxysmal dystonia + other dyskinesia** | *PNKD* [2] | DYT8 | PxMD-PNKD | Paroxysmal nonkinesigenic dyskinesia | AD |
| | | *PRRT2* | DYT10 | PxMD-PRRT2 | Paroxysmal kinesigenic dyskinesia | AD |
| | | *SLC2A1* | DYT18 | PxMD-SLC2A1 | Paroxysmal exertion-induced dyskinesia | AD |

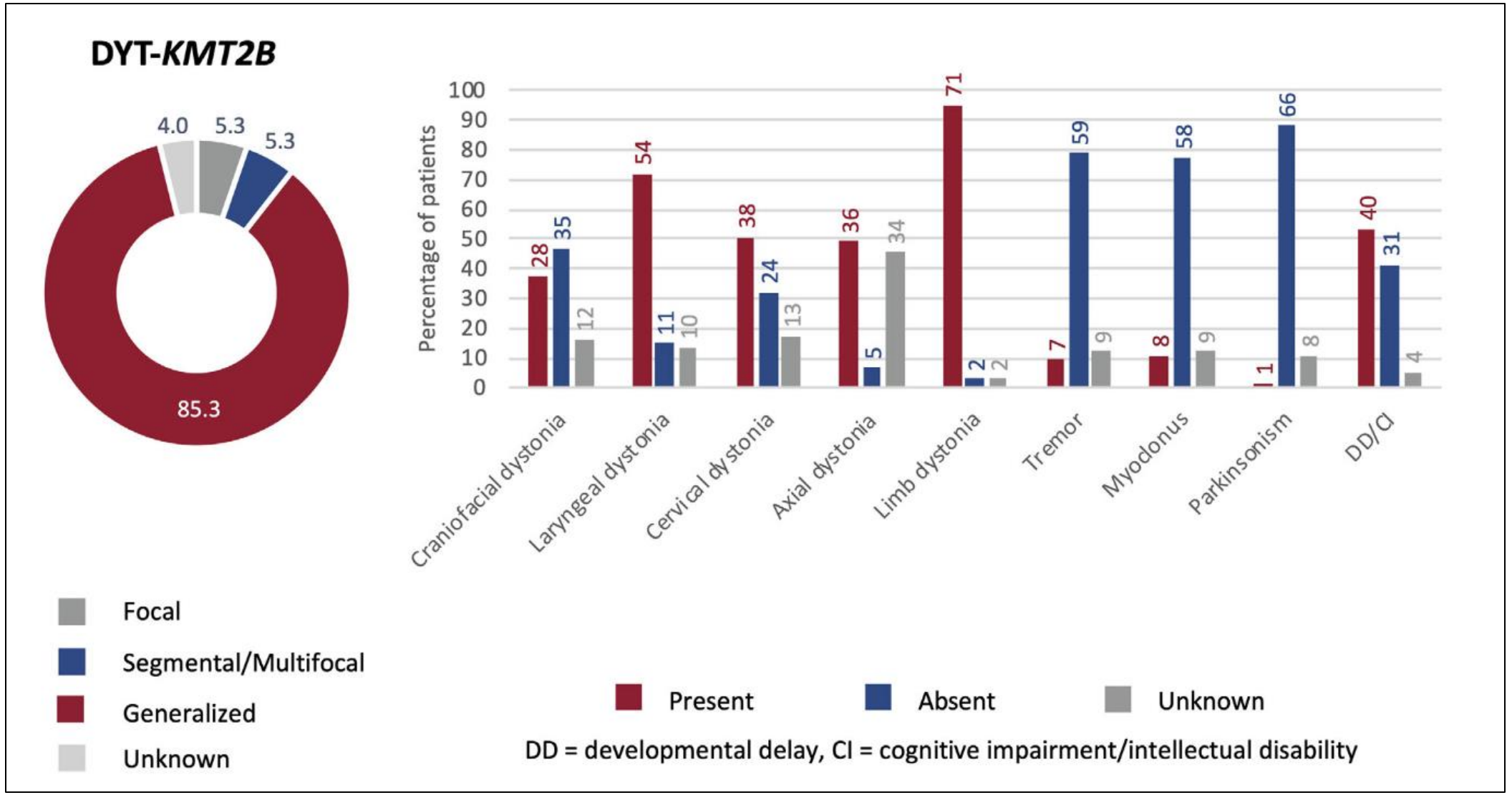
# DYT28 – KMT2B mutations (de novo!)

AAO 10y

Speech disorder
Segmental

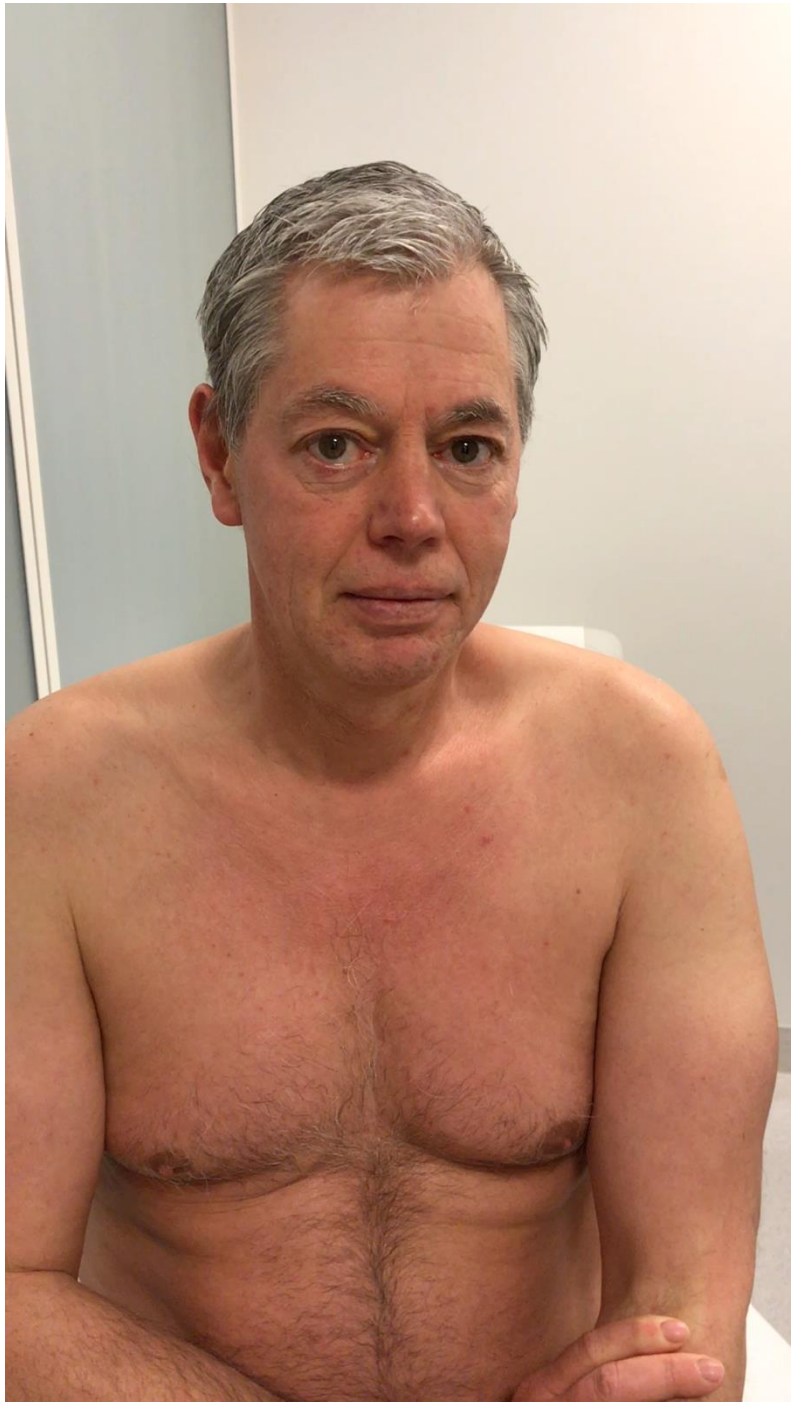
AAO 8y

Generalized dystonia


DYT-*KMT2B*
4.0
5.3
5.3
85.3
Focal
Segmental/Multifocal
Generalized
Unknown
Percentage of patients
100
90
80
70
60
50
40
30
20
10
0
28
35
12
54
11
10
38
24
13
36
5
34
71
2
2
7
59
9
8
58
9
1
66
8
40
31
4
Craniofacial dystonia
Laryngeal dystonia
Cervical dystonia
Axial dystonia
Limb dystonia
Tremor
Myodonus
Parkinsonism
DD/CI
Present
Absent
Unknown
DD = developmental delay, CI = cognitive impairment/intellectual disability

# DYT11: Myoclonus Dystonia with SCGE mutations

Myoclonus-dystonia in KCTD17 mutation



# Paroxysmal dystonia: PRRT2 mutation

The Cerebellum (2024) 23:2152–2168
https://doi.org/10.1007/s12311-024-01703-z

REVIEW

# An Update on the Adult-Onset Hereditary Cerebellar Ataxias: Novel Genetic Causes and New Diagnostic Approaches

Laura Ivete Rudaks[1,2,3,4] · Dennis Yeow[1,2,3,5,6] · Karl Ng[2,7] · Ira W. Deveson[3,8] · Marina L. Kennerson[1,2,9] · Kishore Raj Kumar[1,2,3,8,10]

**Hereditary ataxia**

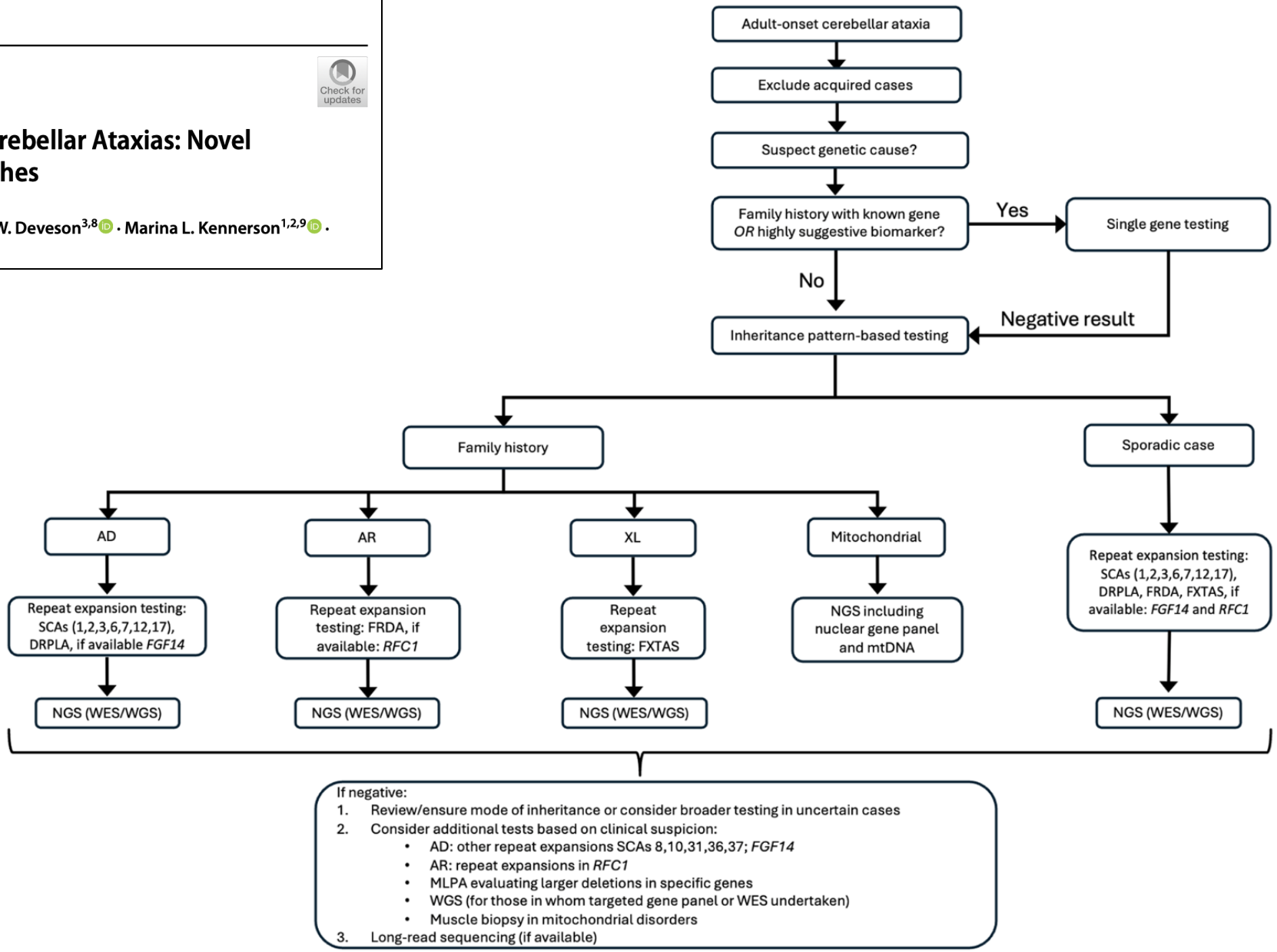


**Table 1** Autosomal dominant spinocerebellar ataxias

| Phenotype | Gene | Variant type | Locus | Phenotype MIM |
|---|---|---|---|---|
| SCA1 | *ATXN1* | $(CAG)_n$ repeat | 6p22.3 | 164400 |
| SCA2 | *ATXN2* | $(CAG)_n$ repeat | 12q24.12 | 183090 |
| SCA3 (Machado-Joseph disease) | *ATXN3* | $(CAG)_n$ repeat | 14q32.12 | 109150 |
| SCA4 | *ZFHX3* | $(GGC)_n$ repeat | 16q22.2-q22.3 | 600223 |
| SCA5 | *SPTBN2* | Missense, deletion | 11q13.2 | 600224 |
| SCA6 | *CACNA1A* | $(CAG)_n$ repeat<br>*Allelic disorders EA2 and FHM occur with point mutations/ deletions* [63, 64] | 19p13.13 | 183086 |
| SCA7 | *ATXN7* | $(CAG)_n$ repeat | 3p14.1 | 164500 |
| SCA8 | *ATXN8/ ATXN8OS* | $(CAG)_n/(CTG)_n$ repeat | 13q21/ 13q21.33 | 608768 |
| SCA9 | Unknown | Unknown | Not mapped | 612876 |
| SCA10 | *ATXN10* | Non-coding $(ATTCT)_n$ repeat | 22q13.31 | 603516 |
| SCA11 | *TTBK2* | Insertion, deletion | 15q15.2 | 604432 |
| SCA12 | *PPP2R2B* | Non-coding $(CAG)_n$ repeat | 5q32 | 604326 |
| SCA13 | *KCNC3* | Missense | 19q13.33 | 605259 |
| SCA14 | *PRKCG* | Missense, deletion | 19q13.42 | 605361 |
| SCA15/16 | *ITPR1* | Missense, deletion<br>*Allelic disorder SCA29 caused by missense variants* | 3p26.1 | 606658 |
| SCA17 | *TBP* | $(CAG)_n$ repeat | 6q27 | 607136 |
| SCA18 | Unknown – *IFRD1* candidate gene | Missense variant in candidate gene *IFRD1* identified in one family [109] | 7q22-q32 | 607458 |
| SCA19/22 | *KCND3* | Missense, deletion | 1p13.2 | 607346 |
| SCA20 | 12 genes | 260-kb duplication identified in one reported family [110] | 11q12 | 608687 |
| SCA21 | *TMEM240* | Missense, nonsense | 1p36.33 | 607454 |
| SCA23 | *PDYN* | Missense | 20p13 | 610245 |
| SCA24 – reassigned SCAR4 | - | - | - | - |
| SCA25 | *PNPT1* | Splice site | 2p16.1 | 608703 |
| SCA26 | *EEF2* | Missense | 19p13.3 | 609306 |
| SCA27A | *FGF14* | Missense, nonsense, insertion, deletion | 13q33.1 | 193003 |
| SCA27B | *FGF14* | Non-coding $(GAA)_n$ repeat | 13q33.1 | 620174 |
| SCA28 | *AFG3L2* | Missense, duplication | 18p11.21 | 610246 |
| SCA29 | *ITPR1* | Missense<br>*Allelic disorder SCA15 caused by missense variants or deletions* | 3p26.1 | 117360 |
| SCA30 | Unknown | | 4q34.3-q35.1 | 613371 |
| SCA31 | *BEAN1* | Non-coding $(TGGAA)_n$ repeat | 16q21 | 117210 |
| SCA32 | Unknown | - | 7q32-q33 | 613909 |
| SCA33* – not assigned | - | - | - | - |
| SCA34 | *ELOVL4* | Missense | 6q14.1 | 133190 |
| SCA35 | *TGM6* | Missense, deletion | 20p13 | 613908 |
| SCA36 | *NOP56* | Non-coding $(GGCCTG)_n$ repeat | 20p13 | 614153 |
| SCA37 | *DAB1* | Non-coding $(ATTTC)_n$ repeat | 1p32.2-p32.1 | 615945 |
| SCA38 | *ELOVL5* | Missense | 6p12.1 | 615957 |
| SCA39* | 44 genes | 7.5 Mb duplication identified in one family [111] | 11q21-q22.3 | - |
| SCA40 | *CCDC88C* | Missense | 14q32.11-q32.12 | 616053 |
| SCA41 | *TRPC3* | Missense | 4q27 | 616410 |
| SCA42 | *CACNA1G* | Missense | 17q21.33 | 616795 |
| SCA43 | *MME* | Missense | 3q25.2 | 617018 |
| SCA44 | *GRMR1* | Missense, duplication | 6q24.3 | 617691 |

# AD SCA

**Table 1** (continued)

| Phenotype | Gene | Variant type | Locus | Phenotype MIM |
|---|---|---|---|---|
| SCA45 | *FAT2* | Missense | 5q33.1 | 617769 |
| SCA46 | *PLD3* | Missense | 19q13.2 | 617770 |
| SCA47 | *PUM1* | Missense | 1p35.2 | 617931 |
| SCA48 | *STUB1* | Missense, nonsense, insertion, deletion, duplication | 16p13.3 | 618093 |
| SCA49 | *SAMD9L* | Missense | 7q21.2 | 619806 |
| SCA50 | *NPTX1* | Missense | 17q25.3 | 620158 |
| SCA51* | *THAP11* | $(CAG)_n$ repeat | 16q22.1 | - |
| DRPLA | *ATN1* | $(CAG)_n$ repeat | 12p13.31 | 125370 |
| **Other autosomal dominant complex ataxias** | | | | |
| ADCADN | *DNMT1* | Missense | 19p13.2 | 604121 |
| ATXPC | *SAMD9L* | Missense | 7q21.2 | 159550 |
| SPAX-1 | *VAMP1* | Splice site | 12p13.31 | 108600 |

ADCADN: autosomal dominant cerebellar ataxia, deafness, and narcolepsy; ATXPC: ataxia-pancytopenia syndrome; DRPLA: dentatorubral-pallidoluysian atrophy; EA2: episodic ataxia type 2; FHM: familial hemiplegic migraine; SCAR4: autosomal recessive spinocerebellar ataxia-4; SPAX-1: autosomal dominant spastic ataxia-1

*Not yet assigned on Online Mendelian Inheritance in Man® (OMIM®)

**Table 1** Autosomal dominant spinocerebellar ataxias

| Phenotype | Gene | Variant type | Locus | Phenotype MIM |
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| SCA2 | *ATXN2* | $(CAG)_n$ repeat | 12q24.12 | 183090 |
| SCA3 (Machado-Joseph disease) | *ATXN3* | $(CAG)_n$ repeat | 14q32.12 | 109150 |
| SCA4 | *ZFHX3* | $(GGC)_n$ repeat | 16q22.2-q22.3 | 600223 |
| SCA5 | *SPTBN2* | Missense, deletion | 11q13.2 | 600224 |
| SCA6 | *CACNA1A* | $(CAG)_n$ repeat<br>*Allelic disorders EA2 and FHM occur with point mutations/ deletions* [63, 64] | 19p13.13 | 183086 |
| SCA7 | *ATXN7* | $(CAG)_n$ repeat | 3p14.1 | 164500 |
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| SCA9 | Unknown | Unknown | Not mapped | 612876 |
| SCA10 | *ATXN10* | Non-coding $(ATTCT)_n$ repeat | 22q13.31 | 603516 |
| SCA11 | *TTBK2* | Insertion, deletion | 15q15.2 | 604432 |
| SCA12 | *PPP2R2B* | Non-coding $(CAG)_n$ repeat | 5q32 | 604326 |
| SCA13 | *KCNC3* | Missense | 19q13.33 | 605259 |
| SCA14 | *PRKCG* | Missense, deletion | 19q13.42 | 605361 |
| SCA15/16 | *ITPR1* | Missense, deletion<br>*Allelic disorder SCA29 caused by missense variants* | 3p26.1 | 606658 |
| SCA17 | *TBP* | $(CAG)_n$ repeat | 6q27 | 607136 |
| SCA18 | Unknown – *IFRD1* candidate gene | Missense variant in candidate gene *IFRD1* identified in one family [109] | 7q22-q32 | 607458 |
| SCA19/22 | *KCND3* | Missense, deletion | 1p13.2 | 607346 |
| SCA20 | 12 genes | 260-kb duplication identified in one reported family [110] | 11q12 | 608687 |
| SCA21 | *TMEM240* | Missense, nonsense | 1p36.33 | 607454 |
| SCA23 | *PDYN* | Missense | 20p13 | 610245 |
| SCA24 – reassigned SCAR4 | - | - | - | - |
| SCA25 | *PNPT1* | Splice site | 2p16.1 | 608703 |
| SCA26 | *EEF2* | Missense | 19p13.3 | 609306 |
| SCA27A | *FGF14* | Missense, nonsense, insertion, deletion | 13q33.1 | 193003 |
| SCA27B | *FGF14* | Non-coding $(GAA)_n$ repeat | 13q33.1 | 620174 |
| SCA28 | *AFG3L2* | Missense, duplication | 18p11.21 | 610246 |
| SCA29 | *ITPR1* | Missense<br>*Allelic disorder SCA15 caused by missense variants or deletions* | 3p26.1 | 117360 |
| SCA30 | Unknown | | 4q34.3-q35.1 | 613371 |
| SCA31 | *BEAN1* | Non-coding $(TGGAA)_n$ repeat | 16q21 | 117210 |
| SCA32 | Unknown | - | 7q32-q33 | 613909 |
| SCA33* – not assigned | - | - | - | - |
| SCA34 | *ELOVL4* | Missense | 6q14.1 | 133190 |
| SCA35 | *TGM6* | Missense, deletion | 20p13 | 613908 |
| SCA36 | *NOP56* | Non-coding $(GGCCTG)_n$ repeat | 20p13 | 614153 |
| SCA37 | *DAB1* | Non-coding $(ATTTC)_n$ repeat | 1p32.2-p32.1 | 615945 |
| SCA38 | *ELOVL5* | Missense | 6p12.1 | 615957 |
| SCA39* | 44 genes | 7.5 Mb duplication identified in one family [111] | 11q21-q22.3 | - |
| SCA40 | *CCDC88C* | Missense | 14q32.11-q32.12 | 616053 |
| SCA41 | *TRPC3* | Missense | 4q27 | 616410 |
| SCA42 | *CACNA1G* | Missense | 17q21.33 | 616795 |
| SCA43 | *MME* | Missense | 3q25.2 | 617018 |
| SCA44 | *GRMR1* | Missense, duplication | 6q24.3 | 617691 |

# AD SCA

**Table 1** (continued)

| Phenotype | Gene | Variant type | Locus | Phenotype MIM |
|---|---|---|---|---|
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| SCA46 | *PLD3* | Missense | 19q13.2 | 617770 |
| SCA47 | *PUM1* | Missense | 1p35.2 | 617931 |
| SCA48 | *STUB1* | Missense, nonsense, insertion, deletion, duplication | 16p13.3 | 618093 |
| SCA49 | *SAMD9L* | Missense | 7q21.2 | 619806 |
| SCA50 | *NPTX1* | Missense | 17q25.3 | 620158 |
| SCA51* | *THAP11* | $(CAG)_n$ repeat | 16q22.1 | - |
| DRPLA | *ATN1* | $(CAG)_n$ repeat | 12p13.31 | 125370 |
| **Other autosomal dominant complex ataxias** | | | | |
| ADCADN | *DNMT1* | Missense | 19p13.2 | 604121 |
| ATXPC | *SAMD9L* | Missense | 7q21.2 | 159550 |
| SPAX-1 | *VAMP1* | Splice site | 12p13.31 | 108600 |

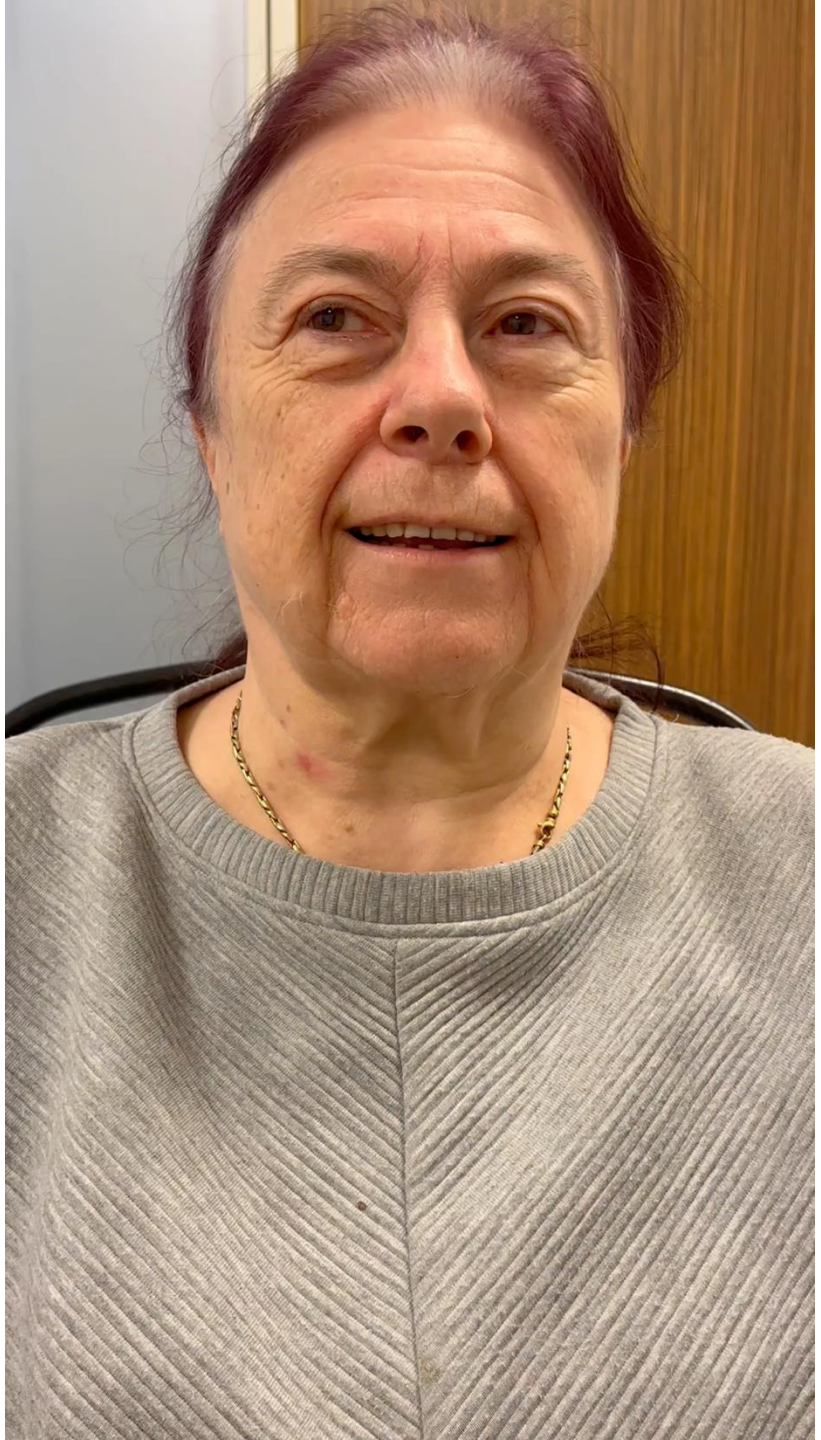
ADCADN: autosomal dominant cerebellar ataxia, deafness, and narcolepsy; ATXPC: ataxia-pancytopenia syndrome; DRPLA: dentatorubral-pallidoluysian atrophy; EA2: episodic ataxia type 2; FHM: familial hemiplegic migraine; SCAR4: autosomal recessive spinocerebellar ataxia-4; SPAX-1: autosomal dominant spastic ataxia-1

*Not yet assigned on Online Mendelian Inheritance in Man® (OMIM®)

**SCA2**

AAO 53y
Currently 68 y

Ataxia
Chorea
Myokymia



# AR ataxia

**Table 3** Adult-onset autosomal recessive hereditary cerebellar ataxias

| Condition | Other names | Gene | Locus | Phenotype MIM |
|---|---|---|---|---|
| ATX-*ABHB12* | Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) | *ABHD12* | 20p11.21 | 612674 |
| ATX-*ADCK3* | ARCA2; SCAR9; Primary coenzyme Q10 deficiency-4 (COQ10D4) | *ADCK3* | 1q42.13 | 612016 |
| ATX-*ANO10* | ARCA3; SCAR10 | *ANO10* | 3p22.1–21.33 | 613728 |
| ATX-*APTX* | AOA1 | *APTX* | 9p21.1 | 208920 |
| ATX-*ATM* | Ataxia-telangiectasia (AT) | *ATM* | 11q22.3 | 208900 |
| ATX-*C10orf2* | Mitochondrial DNA depletion syndrome-7 (MTDPS7) | *TWNK* | 10q24.31 | 271245 |
| ATX-*CWF19L1* | SCAR17 | *CWF19L1* | 10q24.31 | 616127 |
| ATX-*CYP27A1* | Cerebrotendinous xanthomatosis (CTX) | *CYP27A1* | 2q35 | 213700 |
| ATX-*FXN* | Friedreich ataxia (FRDA) | *FXN* | 9q21.11 | 229300 |
| ATX-*GDAP2* | SCAR27 | *GDAP2* | 1p12 | 618369 |
| ATX-*GRID2* | SCAR18 | *GRID2* | 4q22.1–22.2 | 616204 |
| ATX-*GRN* | Neuronal ceroid lipofuscinosis-11 (CLN11) | *GRN* | 17q21.31 | 614706 |
| ATX-*L2HGDH* | L-2-hydroxyglutaric aciduria (L2HGA) | *L2HGDH* | 14q21.3 | 236792 |
| ATX-*MAN2B1* | Alpha-mannosidosis | *MAN2B1* | 19p13.13 | 248500 |
| ATX-*NPC1* | Niemann-Pick disease type C1 (NPC1) | *NPC1* | 18q11.2 | 257220 |
| ATX-*NPC2* | Niemann-Pick disease type C2 (NPC2) | *NPC2* | 14q24.3 | 607625 |
| ATX-*PEX7* | Refsum disease | *PEX7* | 6q23.3 | 614879 |
| ATX-*PHYH* | Refsum disease | *PHYH* | 10p13 | 266500 |
| ATX-*PIK3R5* | AOA3 | *PIK3R5* | 17p13.1 | 615217 |
| ATX-*RFC1* | Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) | *RFC1* | 4p14 | 614575 |
| ATX-*RNF216* | Cerebellar ataxia and hypogonadotrophic hypogonadism; Gordon Holmes syndrome | *RNF216* | 7p22.1 | 212840 |
| ATX-*SETX* | AOA2; SCAR1; SCAN2 | *SETX* | 9q34.13 | 606002 |
| ATX-*STUB1* | SCAR16 | *STUB1* | 16p13.3 | 615768 |
| ATX-*SYNE1* | ARCA1; SCAR8; recessive ataxia of Beauce | *SYNE1* | 6q25.2 | 610743 |
| ATX-*TTPA* | Ataxia with vitamin E deficiency (AVED) | *TTPA* | 8q12.3 | 277460 |
| ATX-*TTC19* | Mitochondrial complex III deficiency nuclear type 2 (MC3DN2) | *TTC19* | 17p12 | 615157 |
| ATX-*XRCC1* | SCAR26 | *XRCC1* | 19q13.31 | 617633 |
| ATX/HSP-*DARS2* | Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) | *DARS2* | 1q25.1 | 611105 |
| ATX/HSP-*HEXA* | Tay-Sachs disease | *HEXA* | 15q23 | 272800 |
| ATX/HSP-*HEXB* | Sandhoff disease | *HEXB* | 5q13.3 | 268800 |
| ATX/HSP-*PNPLA6* | Boucher-Neuhauser syndrome | *PNPLA6* | 19p13.2 | 215470 |
| ATX/HSP-*SACS* | Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS); SPAX6 | *SACS* | 13q12.12 | 270550 |
| ATX/HSP-*VPS13D* | SCAR4 | *VPS13D* | 1p36.22–36.21 | 607317 |
| HSP/ATX-*CAPN1* | SPG76 | *CAPN1* | 11q13.1 | 616907 |
| HSP/ATX-*CLCN2* | Leukoencephalopathy with ataxia (LKPAT) | *CLCN2* | 3q27.1 | 615651 |
| HSP/ATX-*CYP7B1* | SPG5 | *CYP7B1* | 8q12.3 | 270800 |
| HSP/ATX-*KIF1C* | SPAX2 | *KIF1C* | 17p13.2 | 611302 |
| HSP/ATX-SPG7 | SPG7 | *PGN* | 16q24.3 | 607259 |
| ATX/MYC-*TPP1* | SCAR7 | *TPP1* | 11p15.4 | 609270 |
| MYC/ATX-*NEU1* | Sialidosis type I | *NEU1* | 6p21.33 | 256550 |
| DYT/ATX-*ATP7B* | Wilson disease | *ATP7B* | 13q14.3 | 277900 |
| *MTTP* | Abetalipoproteinemia | *MTTP* | 4q23 | 200100 |
| *POLG* | Mitochondrial recessive ataxia syndrome (MIRAS); sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO); spinocerebellar ataxia with epilepsy (SCAE) | *POLG* | 15q26.1 | 607459 |
| SPAX2 | Autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL) | *MARS2* | 2q33.1 | 611390 |
| SPAX10 | - | *COQ4* | 9q34.11 | 620666 |

AOA: ataxia-oculomotor apraxia; ARCA: autosomal recessive cerebellar ataxia; SCAR: autosomal recessive spinocerebellar ataxia; SCAN: spinocerebellar ataxia with axonal neuropathy; SPAX: spastic ataxia; SPG: spastic paraplegia

# AR ataxia

**Table 3** Adult-onset autosomal recessive hereditary cerebellar ataxias

| Condition | Other names | Gene | Locus | Phenotype MIM |
|---|---|---|---|---|
| ATX-*ABHB12* | Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) | *ABHD12* | 20p11.21 | 612674 |
| ATX-*ADCK3* | ARCA2; SCAR9; Primary coenzyme Q10 deficiency-4 (COQ10D4) | *ADCK3* | 1q42.13 | 612016 |
| ATX-*ANO10* | ARCA3; SCAR10 | *ANO10* | 3p22.1–21.33 | 613728 |
| ATX-*APTX* | AOA1 | *APTX* | 9p21.1 | 208920 |
| ATX-*ATM* | Ataxia-telangiectasia (AT) | *ATM* | 11q22.3 | 208900 |
| ATX-*C10orf2* | Mitochondrial DNA depletion syndrome-7 (MTDPS7) | *TWNK* | 10q24.31 | 271245 |
| ATX-*CWF19L1* | SCAR17 | *CWF19L1* | 10q24.31 | 616127 |
| ATX-*CYP27A1* | Cerebrotendinous xanthomatosis (CTX) | *CYP27A1* | 2q35 | 213700 |
| ATX-*FXN* | Friedreich ataxia (FRDA) | *FXN* | 9q21.11 | 229300 |
| ATX-*GDAP2* | SCAR27 | *GDAP2* | 1p12 | 618369 |
| ATX-*GRID2* | SCAR18 | *GRID2* | 4q22.1–22.2 | 616204 |
| ATX-*GRN* | Neuronal ceroid lipofuscinosis-11 (CLN11) | *GRN* | 17q21.31 | 614706 |
| ATX-*L2HGDH* | L-2-hydroxyglutaric aciduria (L2HGA) | *L2HGDH* | 14q21.3 | 236792 |
| ATX-*MAN2B1* | Alpha-mannosidosis | *MAN2B1* | 19p13.13 | 248500 |
| ATX-*NPC1* | Niemann-Pick disease type C1 (NPC1) | *NPC1* | 18q11.2 | 257220 |
| ATX-*NPC2* | Niemann-Pick disease type C2 (NPC2) | *NPC2* | 14q24.3 | 607625 |
| ATX-*PEX7* | Refsum disease | *PEX7* | 6q23.3 | 614879 |
| ATX-*PHYH* | Refsum disease | *PHYH* | 10p13 | 266500 |
| ATX-*PIK3R5* | AOA3 | *PIK3R5* | 17p13.1 | 615217 |
| ATX-*RFC1* | Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) | *RFC1* | 4p14 | 614575 |
| ATX-*RNF216* | Cerebellar ataxia and hypogonadotrophic hypogonadism; Gordon Holmes syndrome | *RNF216* | 7p22.1 | 212840 |
| ATX-*SETX* | AOA2; SCAR1; SCAN2 | *SETX* | 9q34.13 | 606002 |
| ATX-*STUB1* | SCAR16 | *STUB1* | 16p13.3 | 615768 |
| ATX-*SYNE1* | ARCA1; SCAR8; recessive ataxia of Beauce | *SYNE1* | 6q25.2 | 610743 |
| ATX-*TTPA* | Ataxia with vitamin E deficiency (AVED) | *TTPA* | 8q12.3 | 277460 |
| ATX-*TTC19* | Mitochondrial complex III deficiency nuclear type 2 (MC3DN2) | *TTC19* | 17p12 | 615157 |
| ATX-*XRCC1* | SCAR26 | *XRCC1* | 19q13.31 | 617633 |
| ATX/HSP-*DARS2* | Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) | *DARS2* | 1q25.1 | 611105 |
| ATX/HSP-*HEXA* | Tay-Sachs disease | *HEXA* | 15q23 | 272800 |
| ATX/HSP-*HEXB* | Sandhoff disease | *HEXB* | 5q13.3 | 268800 |
| ATX/HSP-*PNPLA6* | Boucher-Neuhauser syndrome | *PNPLA6* | 19p13.2 | 215470 |
| ATX/HSP-*SACS* | Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS); SPAX6 | *SACS* | 13q12.12 | 270550 |
| ATX/HSP-*VPS13D* | SCAR4 | *VPS13D* | 1p36.22–36.21 | 607317 |
| HSP/ATX-*CAPN1* | SPG76 | *CAPN1* | 11q13.1 | 616907 |
| HSP/ATX-*CLCN2* | Leukoencephalopathy with ataxia (LKPAT) | *CLCN2* | 3q27.1 | 615651 |
| HSP/ATX-*CYP7B1* | SPG5 | *CYP7B1* | 8q12.3 | 270800 |
| HSP/ATX-*KIF1C* | SPAX2 | *KIF1C* | 17p13.2 | 611302 |
| HSP/ATX-SPG7 | SPG7 | *PGN* | 16q24.3 | 607259 |
| ATX/MYC-*TPP1* | SCAR7 | *TPP1* | 11p15.4 | 609270 |
| MYC/ATX-*NEU1* | Sialidosis type I | *NEU1* | 6p21.33 | 256550 |
| DYT/ATX-*ATP7B* | Wilson disease | *ATP7B* | 13q14.3 | 277900 |
| *MTTP* | Abetalipoproteinemia | *MTTP* | 4q23 | 200100 |
| *POLG* | Mitochondrial recessive ataxia syndrome (MIRAS); sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO); spinocerebellar ataxia with epilepsy (SCAE) | *POLG* | 15q26.1 | 607459 |
| SPAX2 | Autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL) | *MARS2* | 2q33.1 | 611390 |
| SPAX10 | - | *COQ4* | 9q34.11 | 620666 |

AOA: ataxia-oculomotor apraxia; ARCA: autosomal recessive cerebellar ataxia; SCAR: autosomal recessive spinocerebellar ataxia; SCAN: spinocerebellar ataxia with axonal neuropathy; SPAX: spastic ataxia; SPG: spastic paraplegia

# Movement disorders in spastic paraplegia

**Table 1** Movement disorders associated to hereditary spastic paraplegia (SPG)

| Movement disorder | HSP | Gene | Inheritance |
|---|---|---|---|
| **Ataxia** | SPG4 | *SPAST* | AD |
| | SPG6 | *NIPA1* | AD |
| | SPG7 | *SPG7* | AD |
| | SPG10 | *KIF5A* | AD |
| | SPG11 | *KIAA1840* | AR |
| | SPG27 | *10q22.1-q24.1* | AR |
| | SPG30 | *KIF1A* | AR |
| | SPG31 | *REEP1* | AD |
| **Dystonia** | SPG7 | *SPG7* | AD |
| | SPG11 | *SPG11* | AR |
| | SPG22 | *SLC16A2* | XLR |
| | SPG26 | *B4GALNT1* | AR |
| | SPG35 | *FA2H* | AR |
| | SPG48 | *AP5Z1* | AR |
| | SPG49 | *TECPR2* | AR |
| | SPG58 | *KIF1C* | AR |
| | SPG64 | *ENTPD1* | AR |
| | SPG76 | *CAPN1* | AR |
| **Myoclonus** | SPG4 | *SPAST* | AD |
| | SPG7 | *SPG7* | AD |
| | SPG35 | *FA2H* | AR |
| | SPG48 | *AP5Z1* | AR |
| **Parkinsonism** | SPG7 | *SPG7* | AD |
| | SPG4 | *SPAST* | AD |
| | SPG11 | *KIAA1840* | AR |
| | SPG15 | *ZFYVE26* | AR |
| | SPG48 | *AP5Z1* | AR |
| **Tremor** | SPG7 | *SPG7* | AD |
| | SPG9 | *ALDH18A1* | AR |
| | SPG11 | *SPG11* | AR |
| | SPG15 | *ZFYVE26* | AR |
| | SPG76 | *CAPN1* | AR |

Abbreviations: AD, Autossomal dominant; AR, Autossomal recessive; XLR, X-linked recessive.

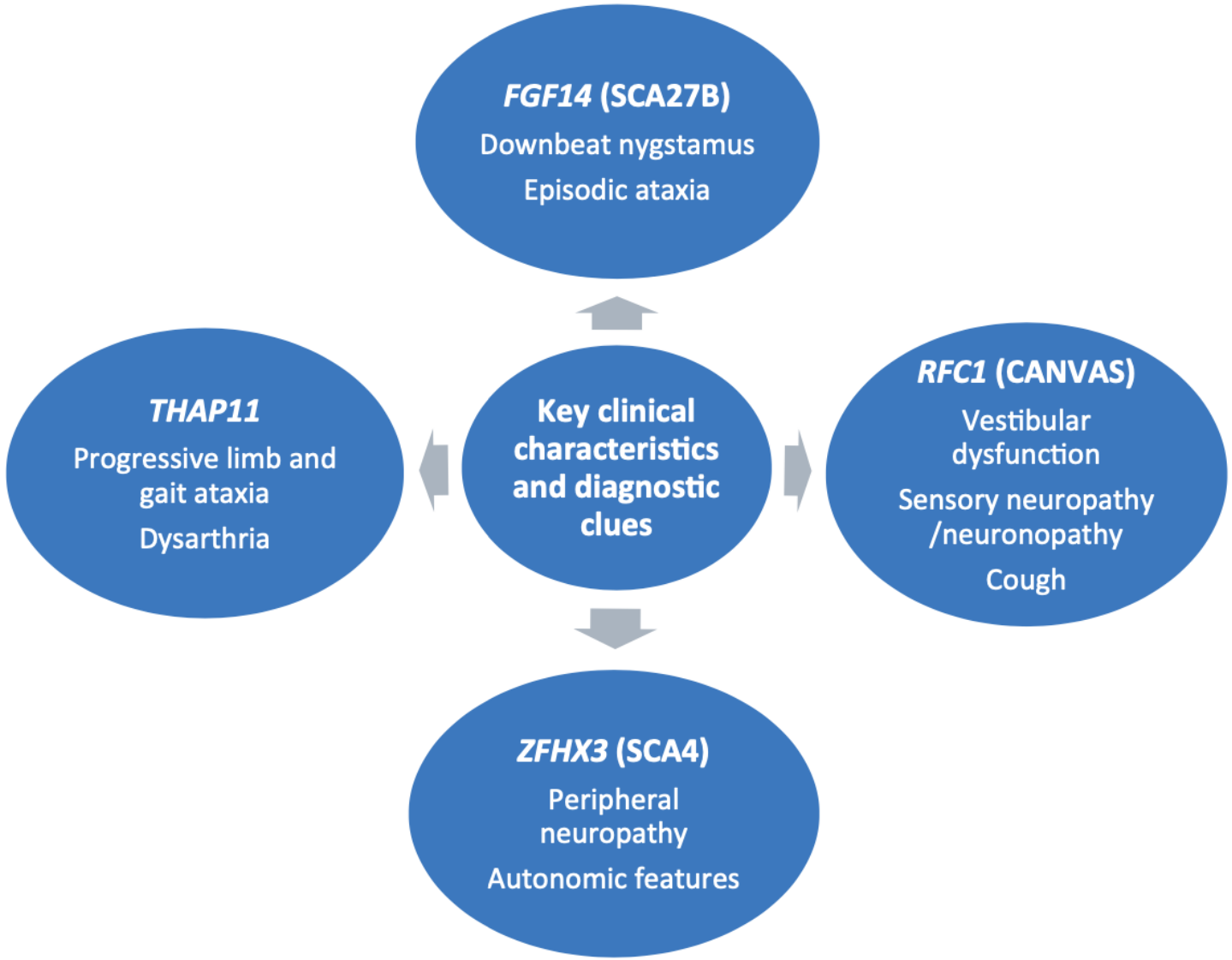
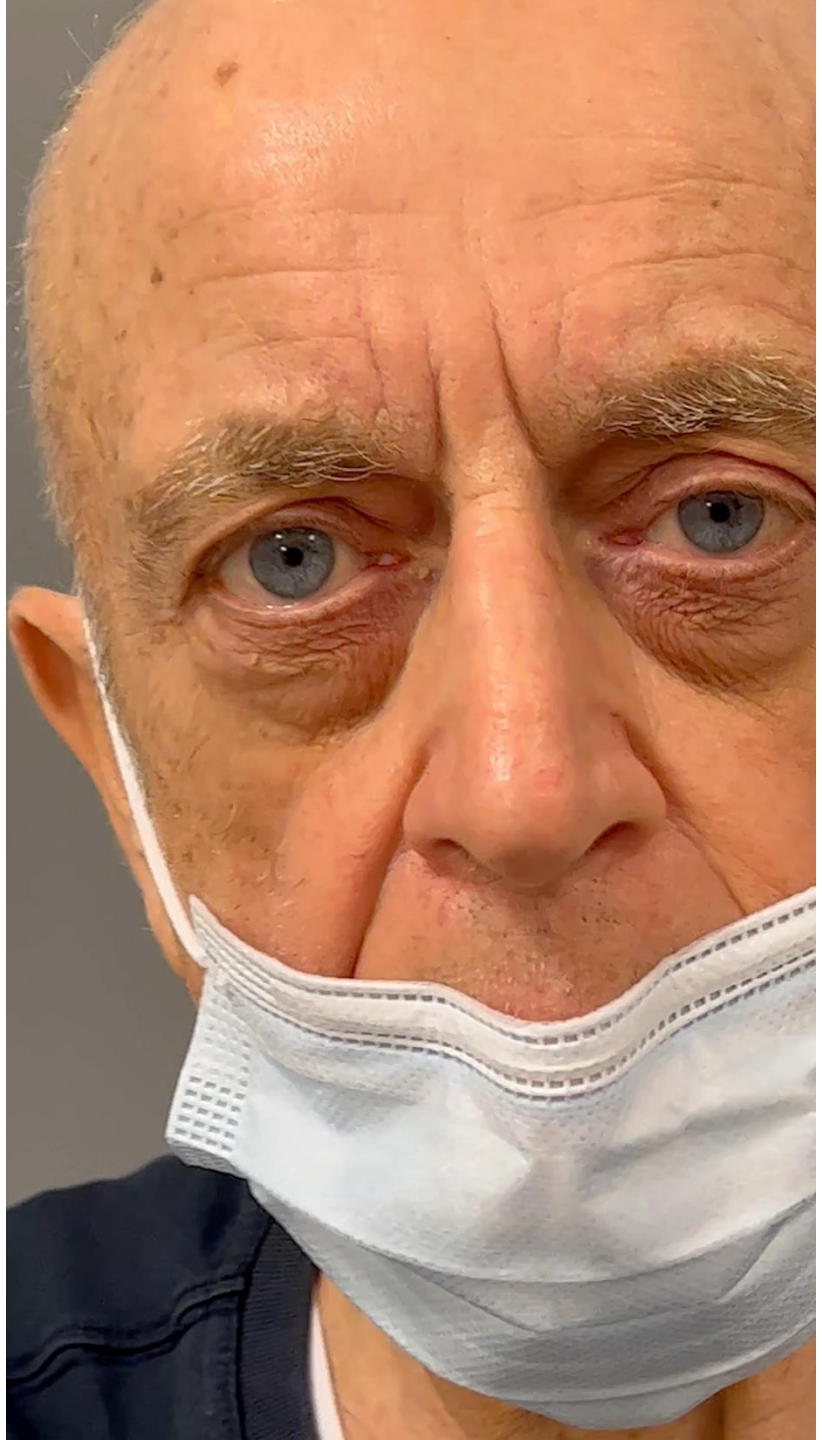


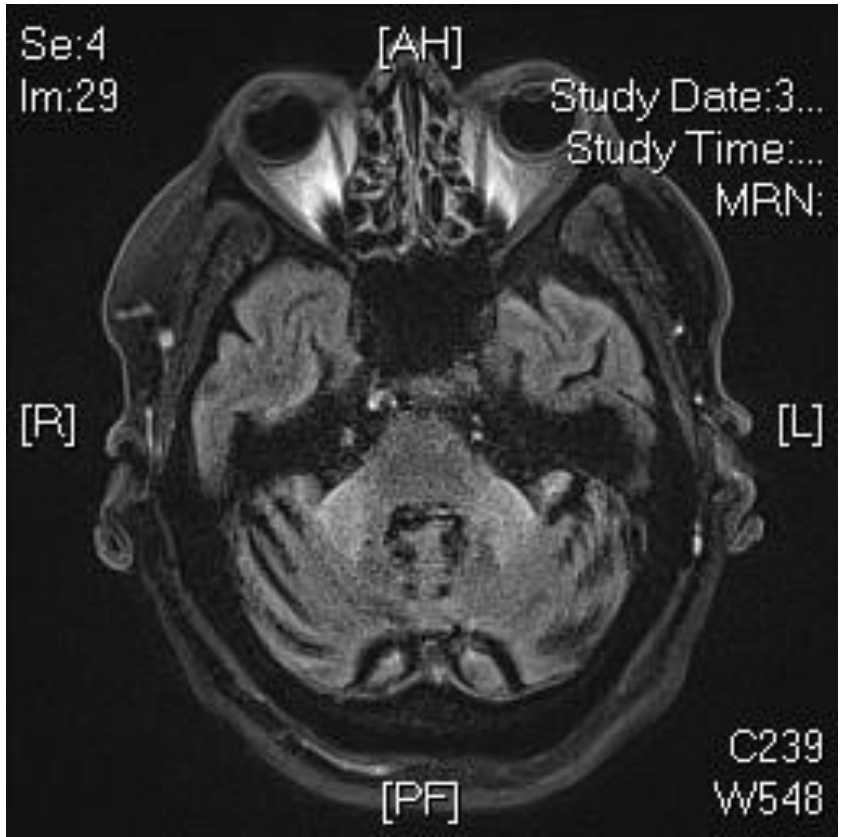

**Fig. 1** Recently described short tandem repeat expansions causing cerebellar ataxia with key diagnostic clues

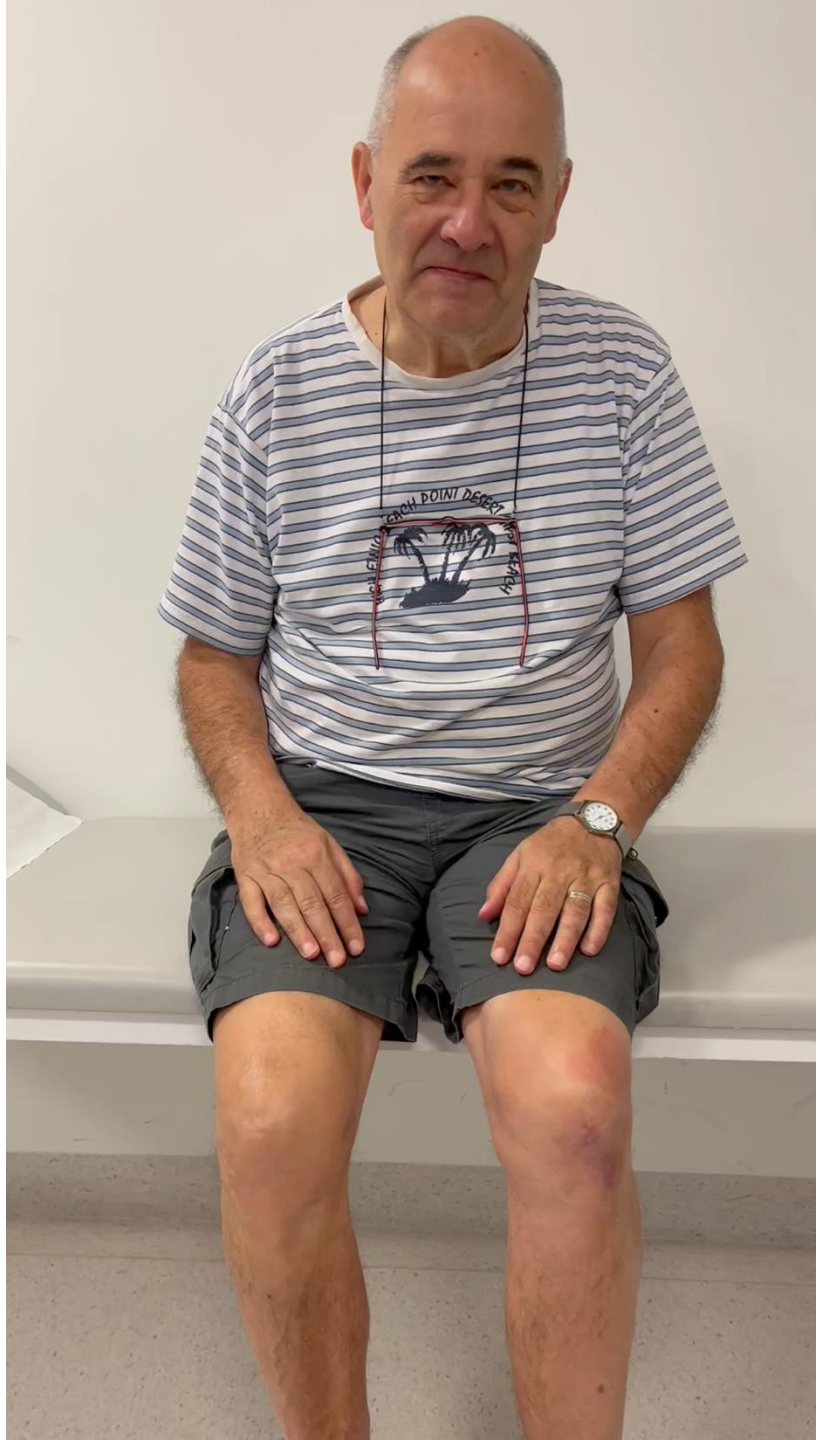
**CANVAS**

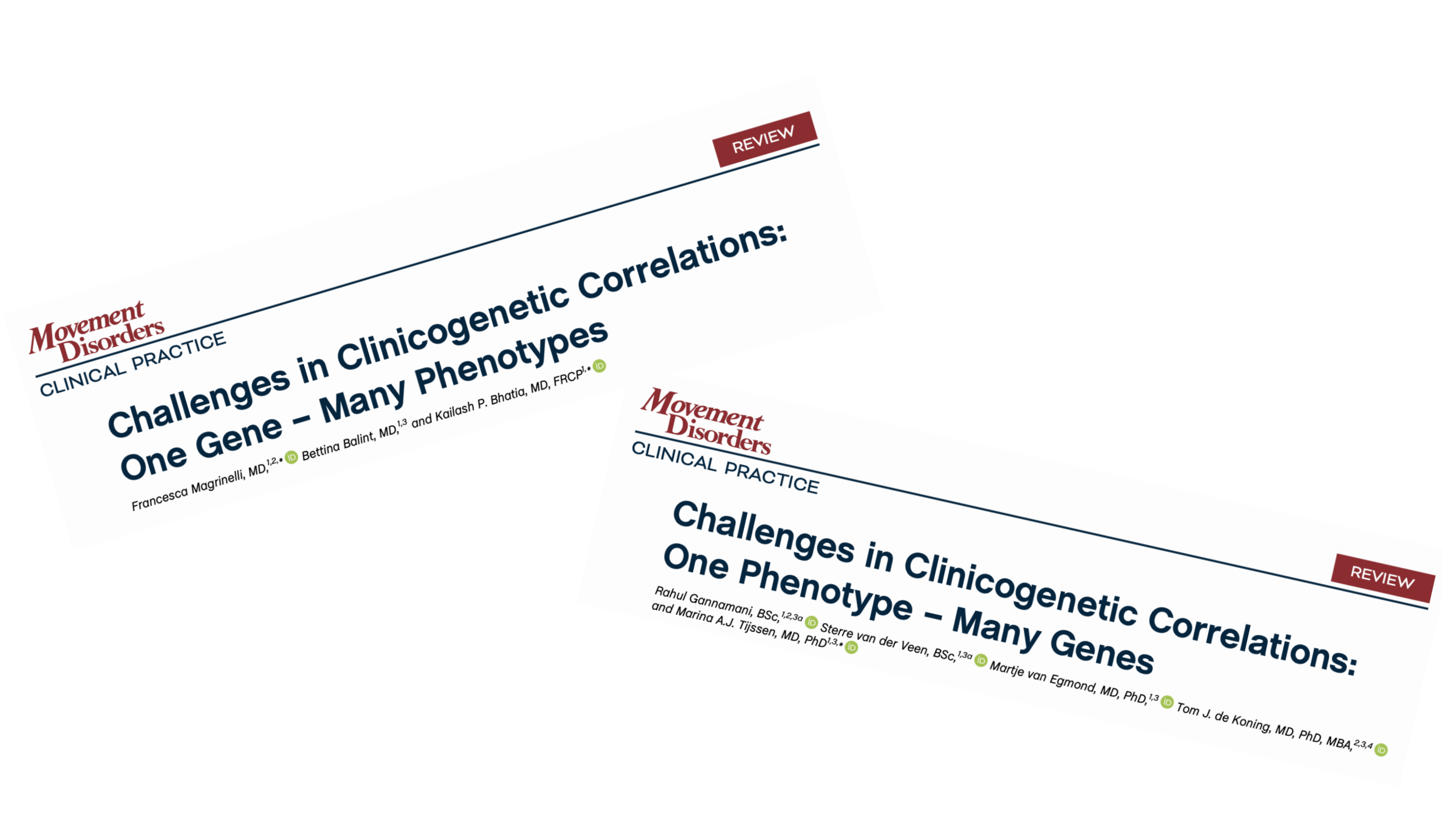
Vestibular areflexia
(Head impulse test)
Cough



# FXTAS

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