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Tom J de Koning, MD PhD, MBA

- **Training:** Pediatrician for Metabolic Diseases
- **Current position:** Principal investigator Movement Disorders Groningen
  Chair department of Pediatrics Lund University
- **Other key activities:** Movement Disorder Clinics in children and adults
  Translational research movement disorders

Movement disorders
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Learning objectives

- **By the end of this webinar:**

- You are not afraid anymore of metabolic diseases
- You will know when to do biochemical testing or genetic testing
- Identify treatable forms of dystonia (limited number of disorders)
- Knowledge of treatment options in dystonia

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What are Metabolic Diseases?

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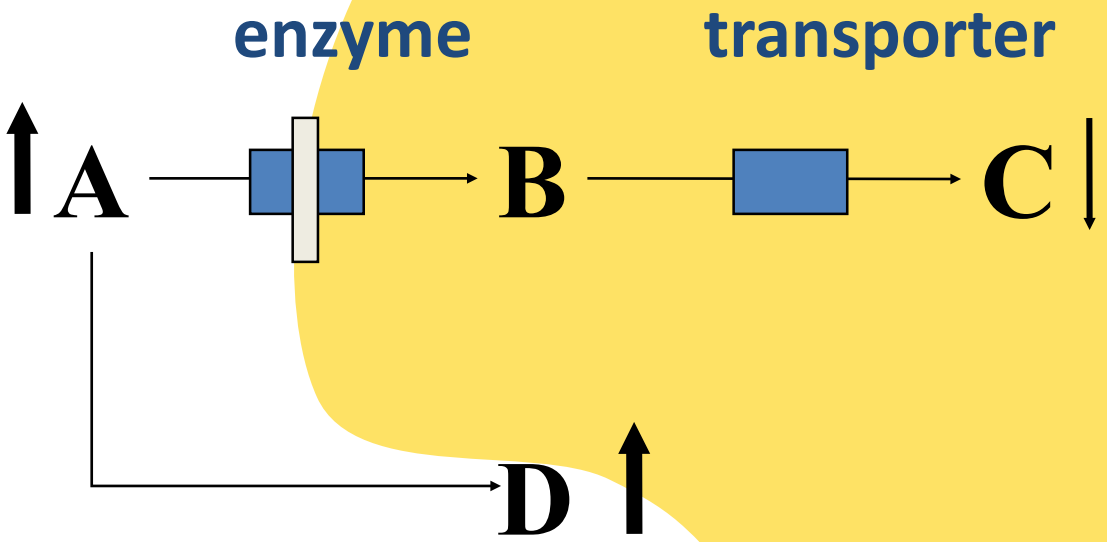

Metabolic Diseases are defects in our biochemistry

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Porphyria

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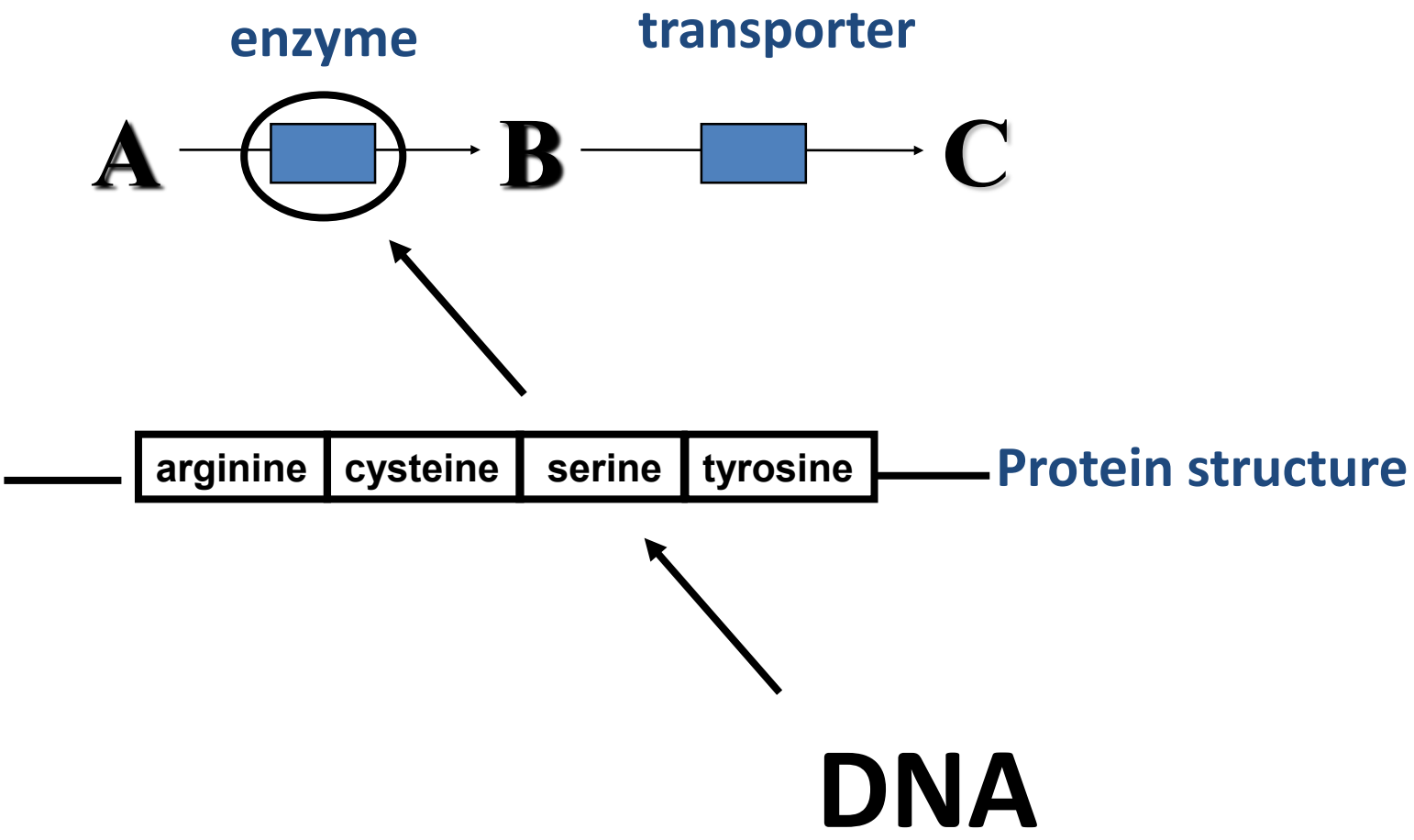

Enzymes are proteins encoded by DNA

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- Metabolic Diseases are genetic disorders
- Making a diagnosis of a metabolic disorder is identical to any other genetic disorder,
- Making the diagnosis of dystonia due to a metabolic disorder is identical to any other forms of dystonia, except in acute onset dystonia

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CLINICAL PRACTICE

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,]*

It is impossible to have knowledge of and have seen all potential dystonia disorders caused by dystonia genes.

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TABLE 1 Overview of most recently published proposed diagnostic approaches in the field of movement disorders to guide clinicians in the identification of the underlying etiology

Phenotype	Number of Genes Implicated	Reference for Diagnostic Approach
Parkinson's disease	19 risk factors	Payne K, Walls B, Wojcieszek J. Approach to assessment of Parkinson disease with emphasis on genetic testing. Med Clin North Am 2019[15]
Tremor	13 genes	van de Wardt J, van der Stouwe AMM, Dirkx M. Systematic clinical approach for diagnosing upper limb tremor. J Neurol Neurosurg Psychiatry 2020[16]
Dominant cerebellar ataxia	40 genes	de Silva RN, Vallortigara J, Greenfield J, Hunt B, Giunti P, Hadjivassiliou M. Diagnosis and management of progressive ataxia in adults. Pract Neurol 2019[12]
Recessive cerebellar ataxia	117 genes	Beaudin M, Matilla-Dueñas A, Soong BW, et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum 2019[5]
Dystonia	147 genes	van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: A systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry 2015[4]
Myoclonus	116 genes	Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. Nat Rev Neurol 2015[6]
Chorea	20 genes	Termsarasab P. Chorea. Continuum 2019[14]
Myoclonus-dystonia	14 genes	Menozzi E, Balint B, Latorre A, et al. Twenty years on: Myoclonus-dystonia and ε-sarcoglycan—Neurodevelopment, channel, and signaling dysfunction. Mov Disord 2019[1]
Dystonia-ataxia	74 genes	Rossi M, Balint B, Millar Vernetti P, Bhatia KP, Merello M. Genetic dystonia-ataxia syndromes: Clinical Spectrum, diagnostic approach, and treatment options. Mov Disord Clin Pract 2018[18]
Hereditary spastic paraplegia	67 genes	Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: From diagnosis to emerging therapeutic approaches. Lancet Neurol 2019[11]
Paroxysmal movement disorders and episodic ataxia	26 genes	Garone G, Capuano A, Travaglini L. Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias. Int J Mol Sci 2020[13]
Genetic epilepsy-dyskinesia spectrum	73 genes	Papandreou A, Danti FR, Spaull R, Leuzzi V, Mctague A, Kurian MA. The expanding spectrum of movement disorders in genetic epilepsies 2020[8]
Neurodegeneration with brain iron accumulation	10 genes	Salomão RPA, Pedroso JL, Gama MTD, et al. A diagnostic approach for neurodegeneration with brain iron accumulation: Clinical features, genetics and brain imaging. Arq Neuropsiquiatr 2016[9]
Primary familial brain calcification	4 genes	Quintáns B, Oliveira J, Sobrido MJ. Primary familial brain calcifications. *Handbook of Clinical Neurology* 2018[17]

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54/147 dystonia genes are metabolic diseases

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How are you going to tackle this problem?

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REVIEW

Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm

Martje E van Egmond,[1] Anouk Kuiper,[1] Hendriekje Eggink,[1] Richard J Sinke,[2] Oebele F Brouwer,[1] Corien C Verschuuren-Bemelmans,[2] Deborah A Sival,[3] Marina A J Tijssen,[1] Tom J de Koning[2,3]

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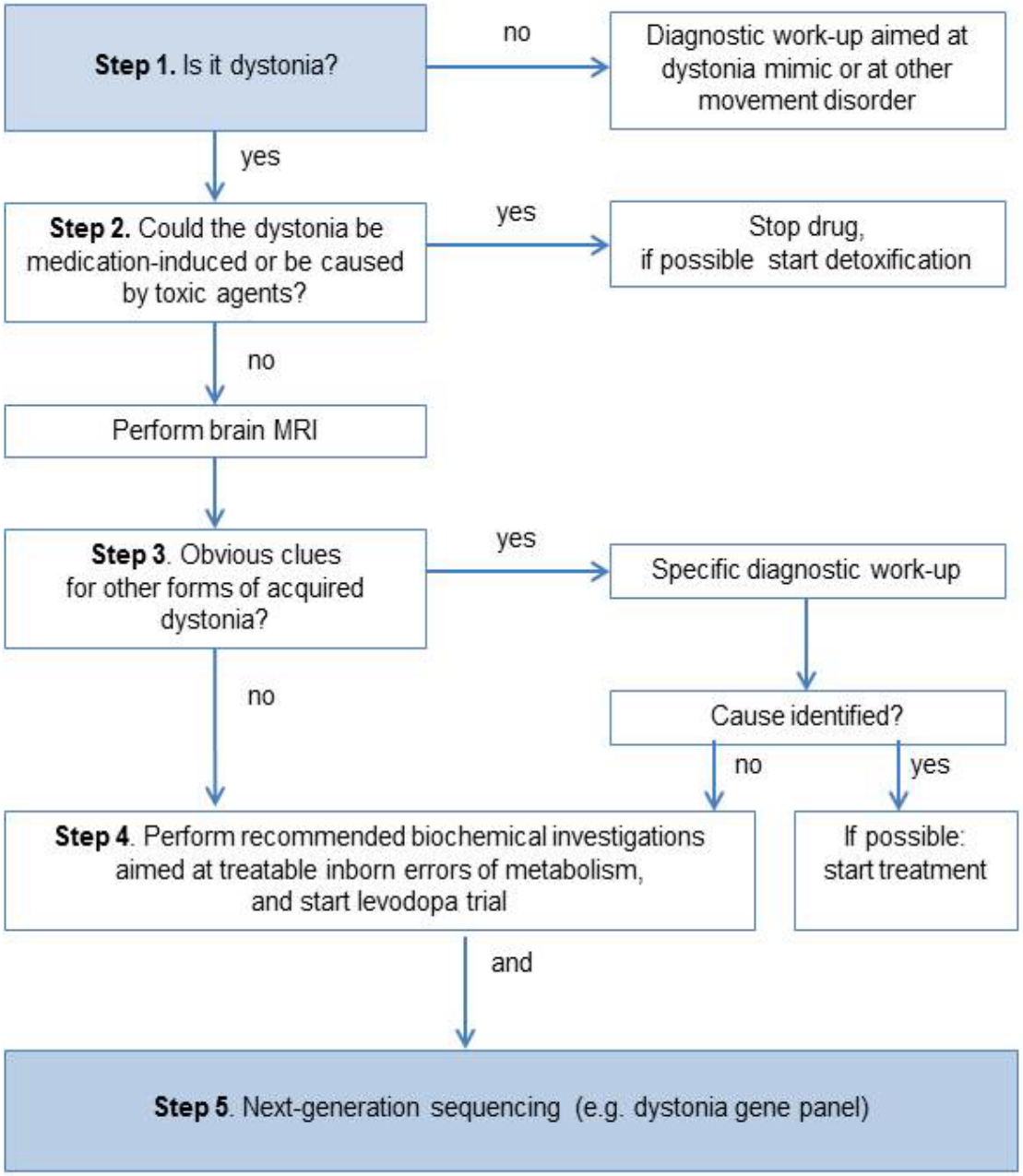
Step 1. Is it dystonia?
no
Diagnostic work-up aimed at dystonia mimic or at other movement disorder
yes
Step 2. Could the dystonia be medication-induced or be caused by toxic agents?
yes
Stop drug, if possible start detoxification
no
Perform brain MRI
Step 3. Obvious clues for other forms of acquired dystonia?
yes
Specific diagnostic work-up
Cause identified?
no
yes
no
Step 4. Perform recommended biochemical investigations aimed at treatable inborn errors of metabolism, and start levodopa trial
If possible: start treatment
and
Step 5. Next-generation sequencing (e.g. dystonia gene panel)

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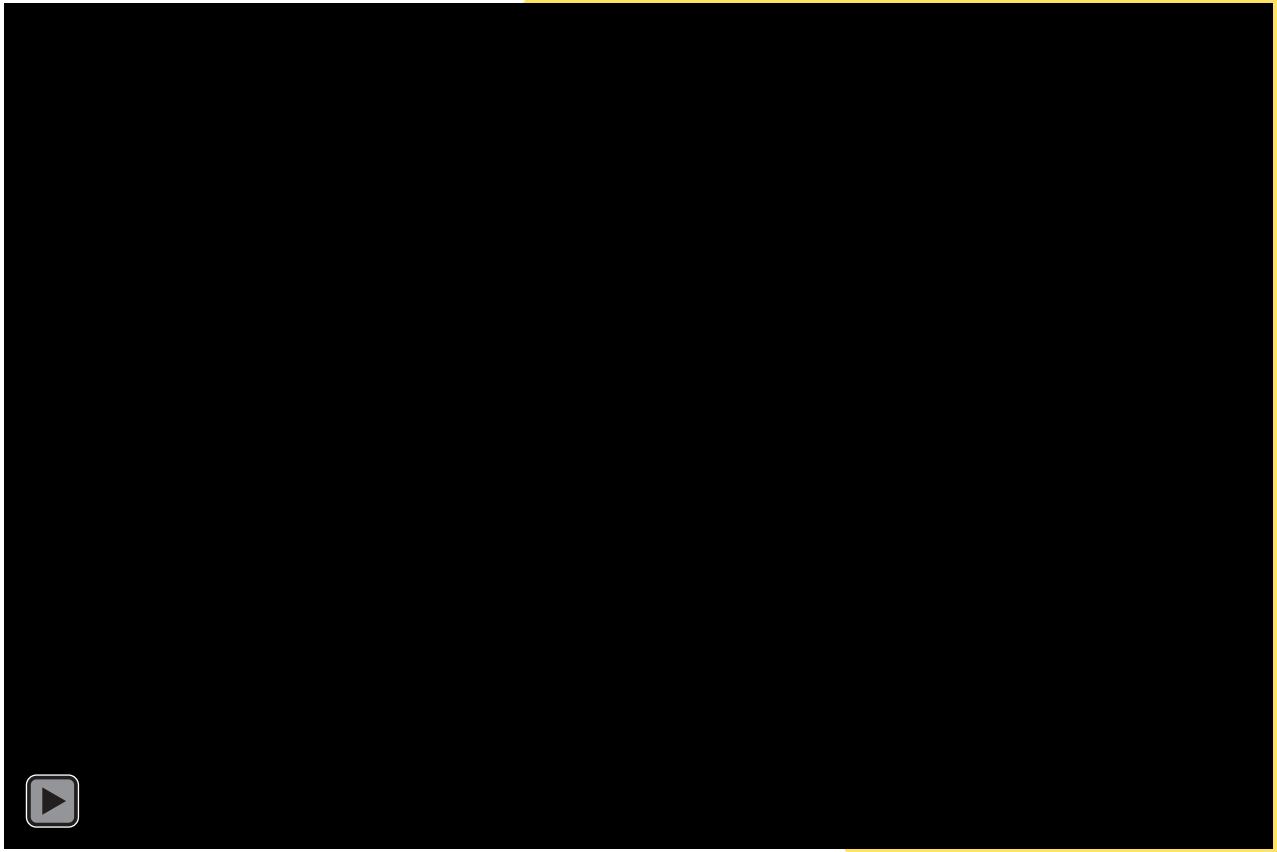

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DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY CLINICAL PRACTICE GUIDE

Diagnostic approach to paediatric movement disorders: a clinical practice guide

RICK BRANDSMA[1] | MARTJE E VAN EGMOND[2] | MARINA A J TIJSSEN[2] | THE GRONINGEN MOVEMENT DISORDER EXPERTISE CENTRE*

1 Department of Pediatric Neurology, University Medical Center Utrecht, Utrecht; **2** Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Correspondence to Marina A J Tijssen at University Medical Center Groningen, 9713 GZ Groningen, the Netherlands. E-mail: m.a.j.de.koning-tijssen@umcg.nl

***Members of the Groningen Movement Disorders Expertise Centre are listed in the Acknowledgements.**

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1	Is it a movement disorder (MD)?	Clinical
2	Classify the MD phenotype and which MD is most prominent?	
3	Could the MD be functional?	
4	Determine the clinical syndrome	
5	Can the movement disorder be caused by an acquired cause?	Diagnostic tests
6	Does the clinical syndrome fit a treatable inborn error of metabolism?	
7	Consider genetic testing	
8	Post next-generation sequencing phenotyping	

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Parkinsonism and Related Disorders 85 (2021) 124–132

Check for updates

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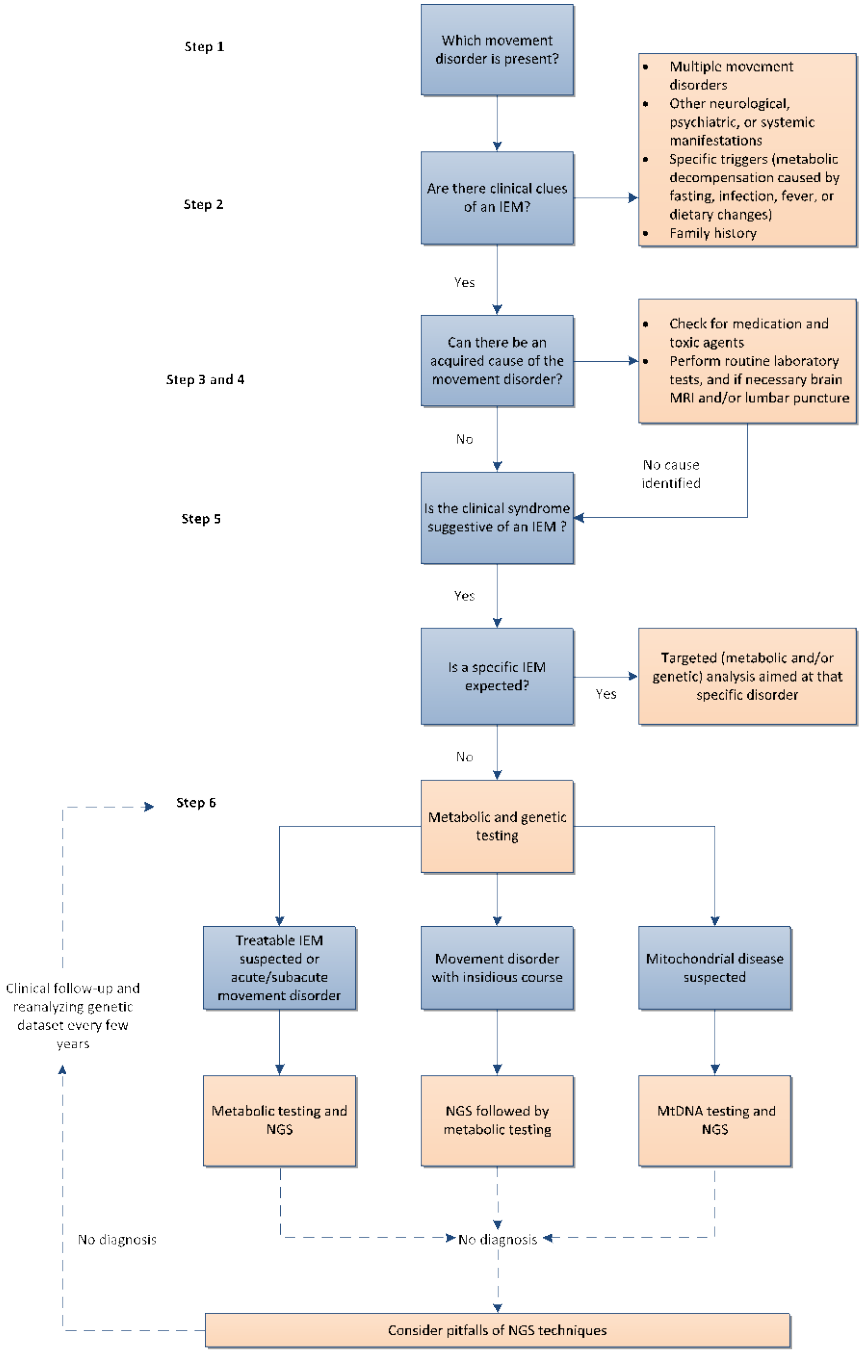

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- When seeing a patient with dystonia you need to decide first is it likely an acquired disorder or not.
- Acquired:
  - Side effect of medication?
  - Infection / postinfectious?
  - Auto antibody / autoimmune
  - Functional disorder

Next do you think of a (treatable) metabolic disease?

- Do you think of a specific disorder
  - Aim your diagnostics at this specific disorder

- Acute onset or intermittend movement disorder
- Insidious onset movement disorder

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Clinical presentations of metabolic diseases

4 big groups of clinical presentations:

- Acute or intermittent encephalopathy
- Chronic progressive brain dysfunction
- Myopathy and rhabdomyolysis
- Liver failure

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Acute or intermittent encephalopathy

- Toxic metabolite / intoxication type
  - Amino acids
  - Urea cycle
  - Organic acid disorders
  - Porphyria
- Cellular energy failure
  - Mitochondrial disease
- Onset often related to infections

  or drugs, ie valproate or change in diet

Ataxia
Myoclonus
Dystonia
Chorea
Tremor

Plus
Seizures
Confusion
Psychosis
Anxiety
Coma

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Chronic progressive brain dysfunction

- Usually starts with very mild symptoms
- Focal onset, later generalised movement disorders
- Slowly progressive
- Over time multiple movement disorders and or other neurological abnormalities (eye movement disorders, seizures, neuropathy, cognitive dysfunction, myopathy)

Table 2 – Overview of the most important neurometabolic causes of dystonia.

Group of IEM	Examples
Neurotransmitter disorders (mono-amine and pterines metabolism)	GTP-cyclohydrolase 1 deficiency, Tyrosine hydroxylase deficiency, Sepiapterin reductase deficiency, AADC deficiency, PTPS deficiency, DHRP deficiency
Organic acidurias and amino acidopathies	Glutaric aciduria type 1, Methylmalonic aciduria, Propionic aciduria, Maple syrup urine disease, Hartnup disease
Mitochondrial syndromes	MELAS, Leigh syndrome, POLG mutations, Thiamine transporter defect
Lysosomal storage disorders	Niemann-Pick type C, GM1 gangliosidosis type 3, Fucosidosis
Metal storage disorders	Wilson's disease, NBIAs (including PKAN), Dystonia with brain manganese accumulation
Disorders in carbohydrate metabolism	Classical galactosemia, Glut1 deficiency
Vitamin and cofactor deficiencies	Vitamin E deficiency, Biotinidase deficiency, Cerebral folate deficiency
Other	GAMT deficiency, Cerebrotendinous xanthomatosis

Please note that this is not a complete, exhaustive list of all IEM that can present with dystonia.

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How to recognise treatable forms of dystonia?

Treatable dystonias:

- Treatment dystonia is treament of metabolic disease
  - Neurotransmitter disorders (DRD, SR, TH; L-dopa)
  - Glucose transporter deficiency (Glut 1 deficiency; ketogenic diet)

- Paroxysmal dyskinesias
  - Paroxysmal kinesiogenic dyskinesia (PRRT2;carbamazepine)
  - Excercise induced dyskinesia (glucose transporter, pyruvate dehydrogenase deficiency, DRD; ketogenic diet or L-dopa)

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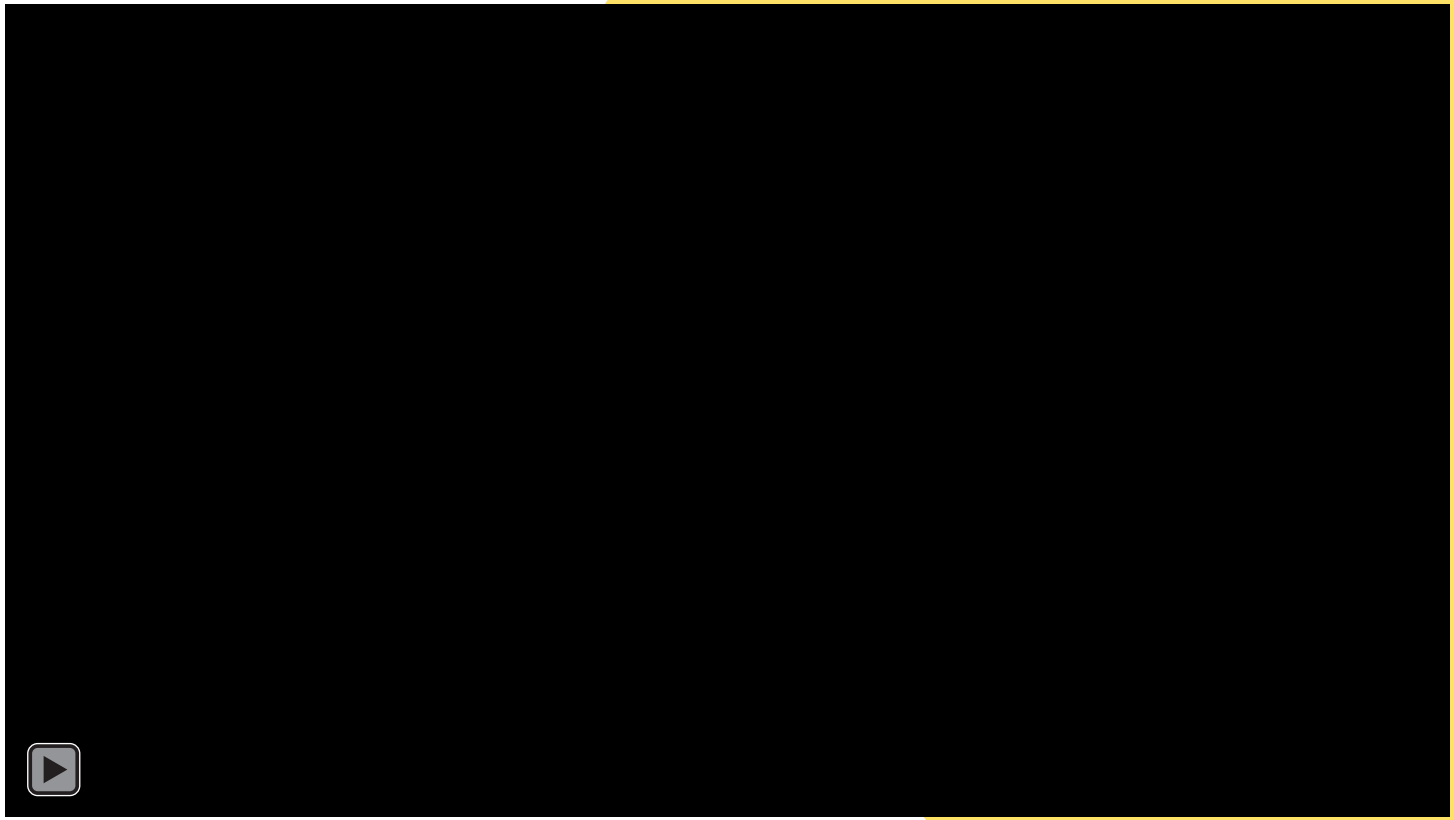

The Phenotypic and Genetic Spectrum of Paroxysmal Kinesigenic Dyskinesia in China

Xiao-Jun Huang, MD,[1,2†] Shi-Ge Wang, MD,[1,2†] Xin-Nan Gao, PhD,[3,4,5,6†] Wei-Fan Xiao, MM,[1,2†] Fei-Xia Zhan, MM,[1,2†] Za-Yu Zhu, MM,[1,2†] Xiao-Meng Yu, MD,[1,2†] Qing Liu, MM,[1,2†] Kun-Li Yin, PhD,[3,7,8†] Xiao-Rong Liu, MD, PhD,[9,10†] Yu Zhang, MD, PhD,[1,2†] Zhao-Guo Liu, MD, PhD,[1,2†] Xiao-Li Liu, MM,[1,2†] Lan Zhang, MM,[1,2†] Xun Wang, MD,[1,2†] Li Wu, MD, PhD,[11,12†] Tian-Yi Feng, MM,[11,12†] Yue Wang, MM,[11,12†] Min Zhang, MD,[11,12†] Cong-Hui Ji, MD,[11,12†] Wei-Guo Tang, MD,[13,14†] Chao Zhang, MM,[11,12†] Peng Zheng, MD,[11,12†] Chun-Xia Wang, MD, PhD,[17,18†] Jian-Guang Tong, MD, PhD,[17,18†] Wei Lu, MD, PhD,[17,18†] Fu-Xin Zheng, MD, PhD,[11,12†] Gao-Jun Zhao, MD,[19,20†] Xun-Hua Li, MD, PhD,[21,22†] Hua Li, MD,[17,18†] Tao Chen, MD, PhD,[11,12†] Hai-Yan Li, MD, PhD,[11,12†] Xiao-Guang Luo, MD, PhD,[23,24†] Yun-Yun Song, PhD,[1†] Hui-Dong Tang, MD, PhD,[1,2†] Xing-Hua Luan, MD, PhD,[1,2†] Hai-Yan Zhou, MD, PhD,[1,2†] Bin-Shu Tang, MD, PhD,[1,2†,*] Sheng-Di Chen, MD, PhD,[1,2†,*] and Li Cao, MD, PhD[1,2†,*]

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REVIEW

Unravelling of the paroxysmal dyskinesias

Roberto Erro,[1] Kailash P Bhatia[2]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2018-318932).

BMJ

Erro R, Bhatia KP. *J Neurol Neurosurg Psychiatry* 2019;**90**:227–234. doi:10.1136/jnnp-2018-318932

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- Supplementing missing substrate
  - Vitamin E deficiency
  - Thiamine transporter deficiency
  - Folate transporter deficiency
- Getting rid of accumulated compound
  - Wilson's disease
  - Brain Manganese accumulation

- Good treatment results will be obtained in:
  - Dopa responsive dystonias
  - Paroxysmal dyskenesias
- All other secundairy dystonias, when dystonia is already present, treatment is aimed at stopping progression of disease
- Disease specific treatment can give some improvement of movement disorders, but in general limited effect
  - Dietary treatment in metabolic diseases
  - Supplementing missing substrate
  - Chelation therapy

Majority of patients require symptomatic treatment of their dystonia

- Trihexyphenidyl (artane)
- Gabapentin
- (Baclofen)
- Benzodiazepines
- Botulinum toxin
- Deep brain stimulation (DBS)

How to diagnose a metabolic movement disorder?

- Acute or intermittend onset dystonia / movement disorders
  - Need for speed
    - Routine biochemical testing (lactate, ammonia, bloodgas, uric acid, ketones)
    - Acylcarnitines, amino acids, or organic acids in urine
    - Start emergency treatment
- Insidious onset disorders
  - Next generation sequencing
  - (targeted biochemical/metabolic testing)

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RESEARCH ARTICLE

A Post Hoc Study on Gene Panel Analysis for the Diagnosis of Dystonia

Martje E. van Egmond, MD,[1,2*] Coen H.A. Lugtenberg, MD,[1] Oebele F. Brouwer, MD, PhD,[1]
Maria Fiorella Contarino, MD, PhD,[3,4] Victor S.C. Fung, PhD, FRACP,[5] M. Rebecca Heiner-Fokkema, PhD,[6]
Jacobus J. van Hilten, MD, PhD,[3] Annemarie H. van der Hout, PhD,[7] Kathryn J. Peall, MD, PhD,[8] Richard J. Sinke, PhD,[7]
Emmanuel Roze, MD, PhD,[9] Corien C. Verschuuren-Bemelmans, MD,[7] Michel A. Willemsen, MD, PhD,[10]
Nicole I. Wolf, MD, PhD,[11] Marina A. Tijssen, MD, PhD,[1] and Tom J. de Koning, MD, PhD[1,7,12]

- Next Generation Sequencing (NGS) approach is cost effective
- Superior for detecting unusual or late onset phenotypes

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Clinical application of next-generation sequencing to the practice of neurology

Jessica Rexach, Hane Lee, Julian A Martinez-Agosto, Andrea H Németh, Brent L Fogel

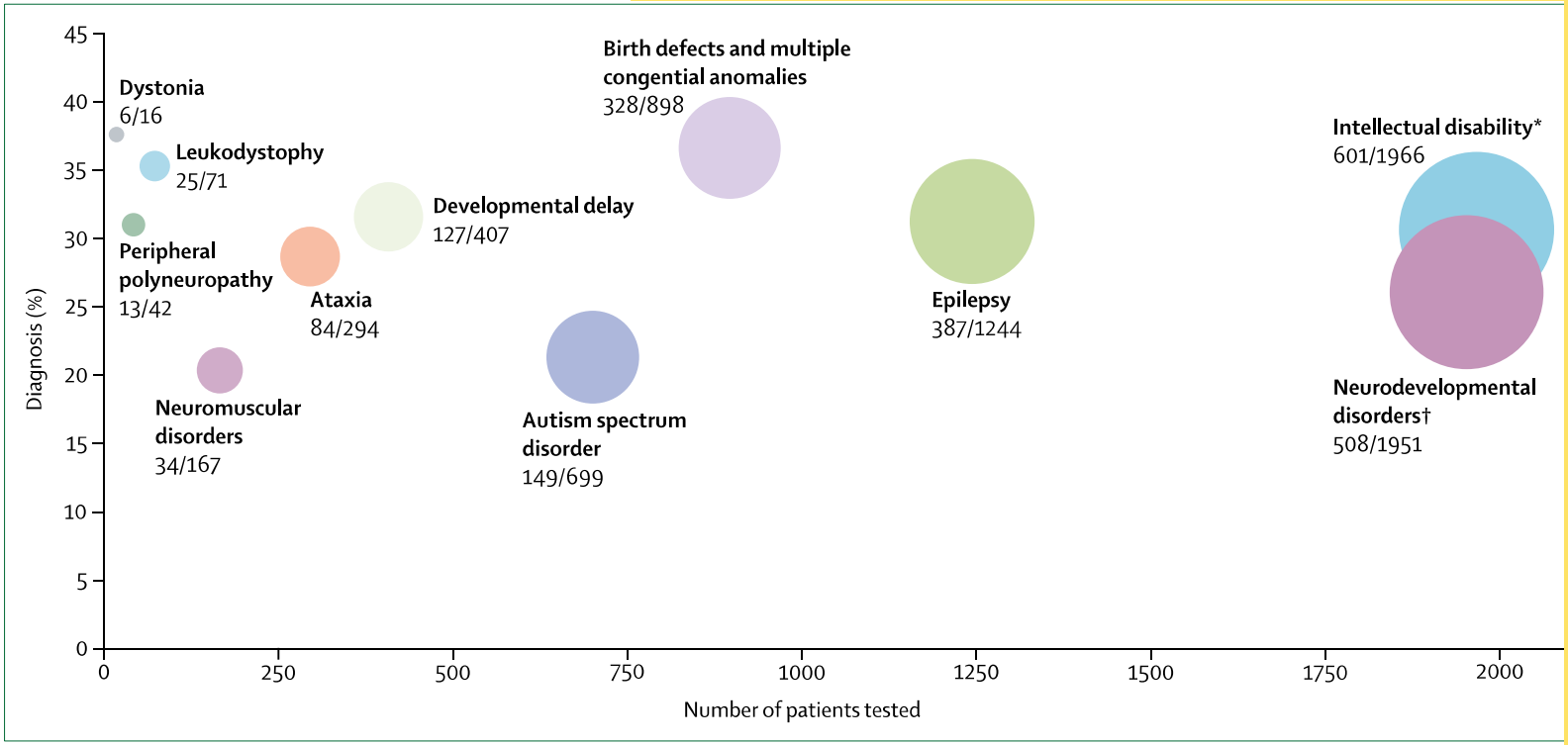

Figure 1: Proportion of patients molecularly diagnosed with various neurological diseases by whole exome sequencing

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How to diagnose a metabolic movement disorder?

- As a clinician you decide what the diagnosis is for the complaints with which the patient comes to you
- The result on the lab form is not the same as the diagnosis
- You need to have an opinion on the results of genetic testing
- Identical to the report of a MRI scan, you likely look at the scan yourself to see whether this actually explains the symptoms of your patient
- So deciding yourself is needed when looking at genetic (or biochemical) test results

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How to diagnose a metabolic movement disorder?

Clinical Review & Education

JAMA Insights

Distinguishing Variant Pathogenicity From Genetic Diagnosis
How to Know Whether a Variant Causes a Condition

Leslie G. Biesecker, MD; Robert L. Nussbaum, MD; Heidi L. Rehm, PhD

JAMA November 13, 2018 Volume 320, Number 18 **1929**

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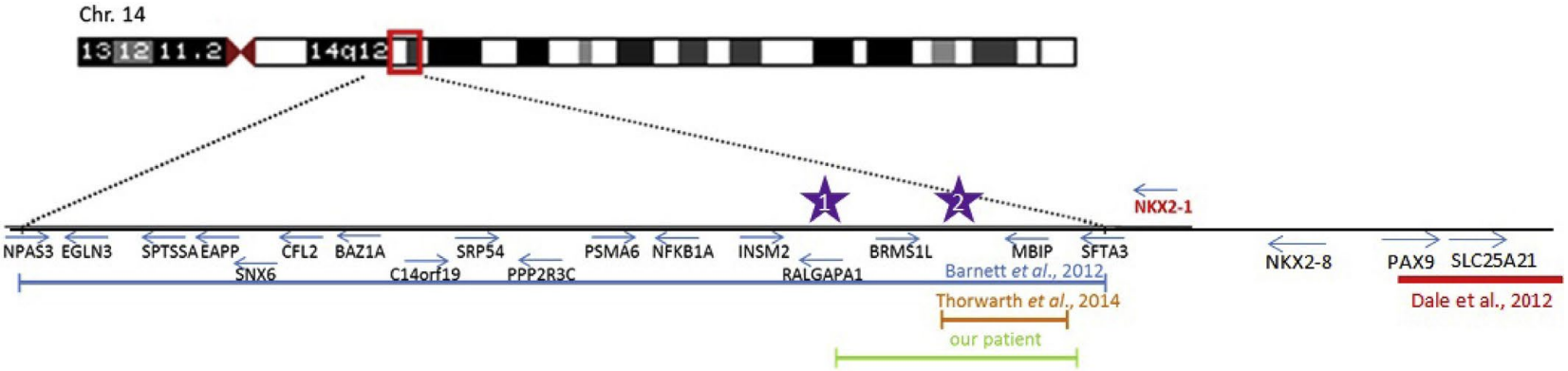
Pitfalls in exome sequencing

- Coverage is not always 100% (GC rich areas are less well represented affects frequently exon 1)
- Large structural rearrangements (deletions of whole exons) are difficult to detect and not reported (also in Sanger, you need MLPA)
- Genomic deletions can give defects in transcription of nearby genes (Benign Hereditary Chorea) or include your gene of interest
- Intronic mutations and mutations in promotor regions are not picked up (because introns are not captured), except in Whole Genome Sequencing
- Nucleotide repeats (Huntingtons, SCA's, myotonic dystrophy, FRA-X) are not reported
- Intronic nucleotide repeats are a new class of mutations
- mtDNA is usually not reported in exome sequencing
- A single mutation in a recessive gene (in particular in metabolic diseases) can give a clinical phenotype

Pitfalls in exome sequencing

- Genomic deletions can give defects in transcription of nearby genes (Benign Hereditary Chorea) or include your gene of interest



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Pitfalls in exome sequencing

- Intronic mutations and mutations in promotor regions are not picked up (because promotor regions and introns are not captured), except in Whole Genome Sequencing

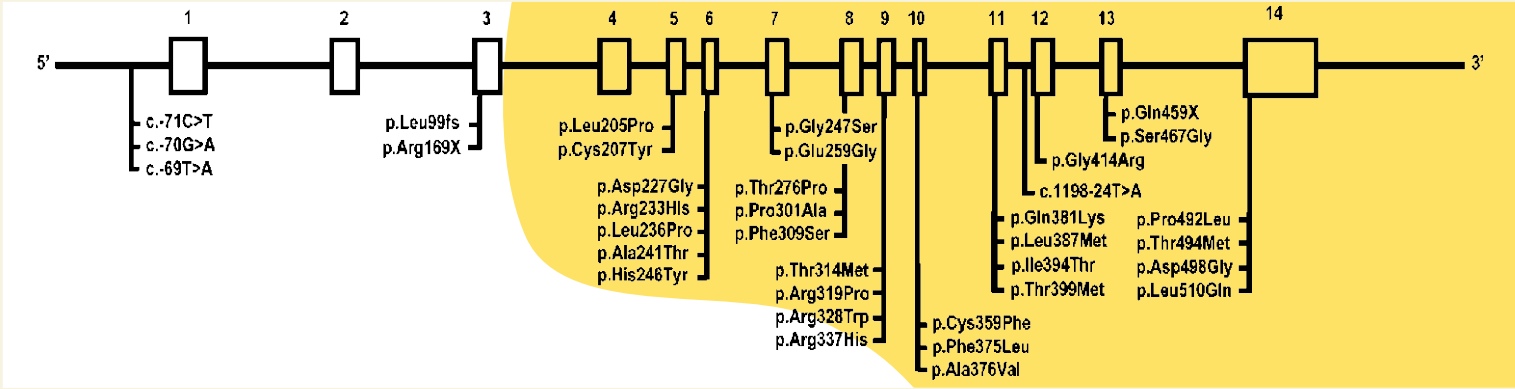

Figure 4 Overview of all known pathogenic mutations in the TH gene. The cyclic adenosine monophosphate response element of the TH promotor resides between residues −67 and −74 upstream of the ATG initiation codon.

Tyrosine hydroxylase gene (*TH*)

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Pitfalls in exome sequencing

- Specific pentanucleotide and trinucleotide intronic repeats give rise to myoclonus and familial cortical tremor and glutaminase deficiency.
- Intronic mutations that affect methylation can give rise to autosomal recessive disorders

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Pitfalls in exome sequencing

doi:10.1093/brain/awy160 BRAIN 2018: 141; 2280–2288 | 2280

BRAIN
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REPORT

Intronic pentanucleotide TTTCA repeat insertion in the *SAMD12* gene causes familial cortical myoclonic tremor with epilepsy type 1

Zhidong Cen,[1,*] Zhengwen Jiang,[2,*] You Chen,[1] Xiaosheng Zheng,[1,3] Fei Xie,[1,4] Xiaodong Yang,[1,5] Xingjiao Lu,[1,6] Zhiyuan Ouyang,[1] Hongwei Wu,[1,7] Si Chen,[1,8] Houmin Yin,[1] Xia Qiu,[1] Shuang Wang,[1] Meiping Ding,[1] Yelei Tang,[1] Feng Yu,[2] Caihua Li,[9] Tao Wang,[9] Hiroyuki Ishiura,[10] Shoji Tsuji,[11,12] Chuan Jiao,[13] Chunyu Liu,[14] Jianfeng Xiao[15] and Wei Luo[1]

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BRAIN 2018: 141; 2232–2244 | 2232

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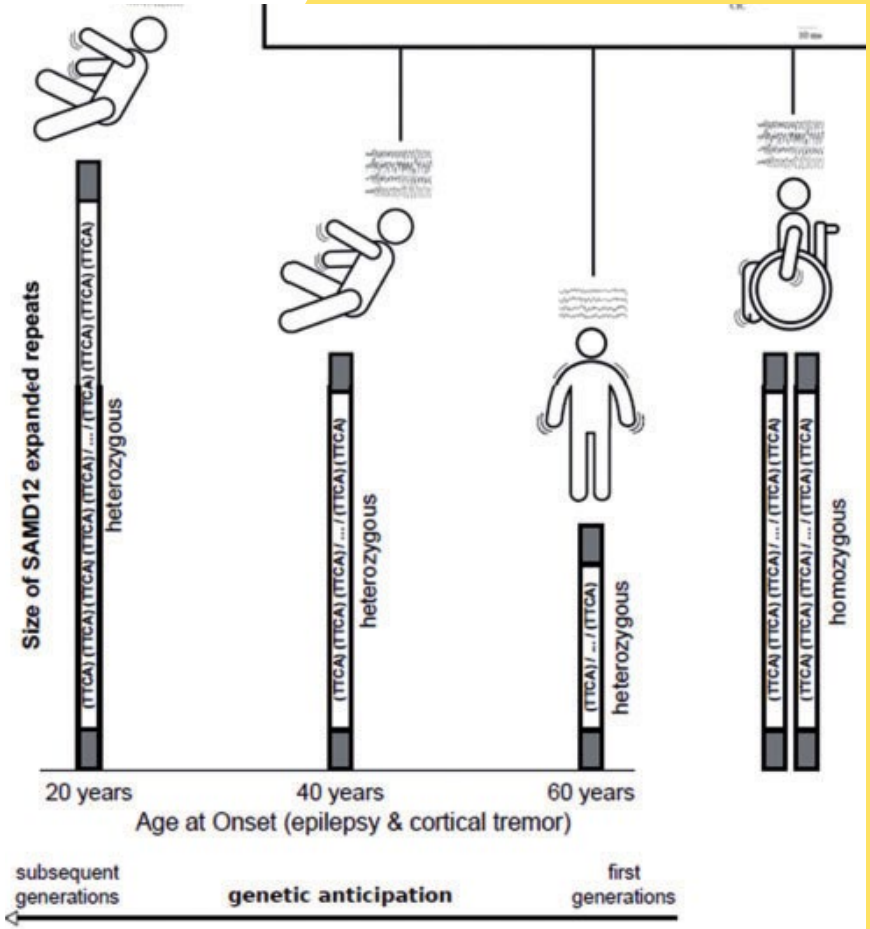
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

Unstable non-coding pentanucleotide repeats destabilize cortical excitability



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Pitfalls in exome sequencing

- Heterozygote mutations can give rise to autosomal recessive disease (affect dimerization of enzyme complex or affect allelic expression)
- Heterozygote mutations can give gain of function and hence metabolic disease
- Mitochondria have their own DNA, mutations in mtDNA are not reported in WES

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Dominant negative mutations

doi:10.1093/brain/awv143 BRAIN 2015: 138; 2191–2205 | 2191

BRAIN
A JOURNAL OF NEUROLOGY

Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia

Marie Coutelier,[1,2,3,4,5,6] Cyril Goizet,[7,8] Alexandra Durr,[1,2,3,4,9] Florence Habarou,[10] Sara Morais,[1,2,3,4,6,11,12,13] Alexandre Dionne-Laporte,[14] Feifei Tao,[15] Juliette Konop,[1,2,3,4,6] Marion Stoll,[16] Perrine Charles,[9] Maxime Jacoupy,[1,2,3,4] Raphaël Matusiak,[1,2,3,4] Isabel Alonso,[11,12,13] Chantal Tallaksen,[1,2,3,4,#] Mathilde Mairey,[1,2,3,4,6] Marina Kennerson,[16] Marion Gaussen,[1,2,3,4,6] Rebecca Schule,[15,17,18] Maxime Janin,[10] Fanny Morice-Picard,[7,8] Christelle M. Durand,[7] Christel Depienne,[1,2,3,4,9] Patrick Calvas,[19] Paula Coutinho,[11,12,20] Jean-Marie Saudubray,[9] Guy Rouleau,[14,21] Alexis Brice,[1,2,3,4,9] Garth Nicholson,[16] Frédéric Darios,[1,2,3,4] José L. Loureiro,[11,20] Stephan Zuchner,[15] Chris Ottolenghi,[10] Fanny Mochel[1,2,3,4,9] and Giovanni Stevanin[1,2,3,4,6,9]

Mutations in Δ1-pyrroline-5-carboxylate synthase, P5CS (*ALDH18A1*)

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Diagnostic Strategy

- Is there need for speed?
  - Biochemical testing and metabolic testing
- Do you suspect a specific disorder?
  - Aim your diagnostics at this specific disorder!
- When not a single disorder is suspected, start NGS diagnostics including metabolic diseases.
- When there are LP or VUS variants reported in a gene that really could explain the phenotype, you should pursue this potential diagnosis. Also, when only 1 mutation is found
  - Is there a biochemical or enzymatic test that could make this diagnosis more likely, MLPA, array-CGH or perhaps imaging studies?

- Keep in mind that in some cases one mutations in a recessive gene can explain the phenotype so could a dominant negative effect or allelic expression imbalance explains the phenotype.
- Consider sending material to a laboratory of which the disorder is a research focus.

- When NGS diagnostics did not result in a molecular diagnosis, but a genetic cause is highly suspected, consider whether a diagnosis can be missed due to any of the pitfalls of NGS diagnostics.
  - Large structural rearrangements, genomic deletions or could a repeat disorder perhaps be the cause? Was mtDNA tested? Could dedicated biochemical testing be beneficial for the diagnostic process?
- When all of this this still does not result in a molecular diagnosis, follow-up on the clinical evolution of the phenotype is the best thing to do and share these clinical phenotypes within your network.
  - Repeat diagnostic testing after 1-2 year, depending on progression of the symptoms

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Key conclusions

- Metabolic Diseases are genetic disorders
- Making a diagnosis of a metabolic disorder is identical to any other genetic disorder, except in acute onset movement disorders
- Treatable metabolic movement disorders are rare, in most cases treatment is aimed at stopping progression of the disorder
- Make use of diagnostic algorithms and determine what works best in your clinic

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NEXT Webinar

‘Adult leukodystrophies - early symptoms of late-onset leukodystrophies’

by Fanny Mochel,
Institute of Brain and Spine, Paris, France

5. October 2021