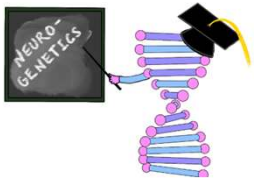


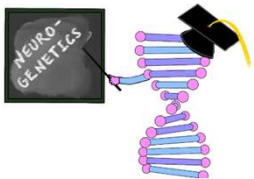
Movement 1: Dystonia

MODULE 5



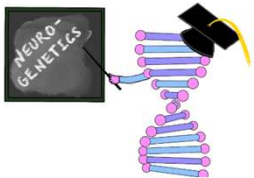
Learning Objectives

- Discuss the differential diagnosis and approach for monogenic causes of dystonia
- Review salient features of autosomal dominant mode of inheritance
- Learn the utility and limitations of exome sequencing in pediatric movement disorders
- Learn the concept of genotype-phenotype correlations using ClinVar and OMIM websites



Chief Complaint

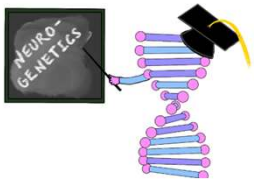
- 11-year-old F with sudden onset of dystonia



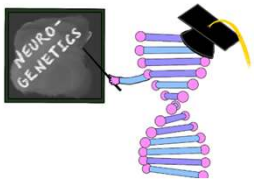
Differential Diagnosis - Interactive



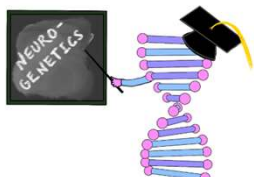
Name of condition	Gene and mode of inheritance	Clinical features and Treatment



Differential Diagnosis



	Gene/ MOI	Loci/ New name	Clinical features
Isolated	<i>TOR1A</i> / AD	DYT1 > DYT-TOR1A	Childhood or adolescent, generalized
	<i>ANO3</i> / AD	DYT24 > DYT-ANO3	Adult, focal or segmental
	<i>KMT2B</i> / AD	DYT28 > DYT-KMT2B	Childhood, generalized, syndromic features
Dystonia+ Parkinsonism	<i>GCH1</i> / AD and AR	DYT5a > DYT-GCH1	Dopa responsive
	<i>TH</i> / AR	DYT5b > DYT-TH	Dopa responsive
	<i>SPR</i> / AR	DYT-SPR	Cognitive impairment, dopa responsive
	<i>PRKRA</i> / AR	DYT16 > DYT-PRKRA	
	<i>ATP1A3</i> / AD	DYT12 > DYT-ATP1A3	Rapid onset
Dystonia + Myoclonus	<i>SGCE</i> / AD	DYT11 > DYT-SGCE	Psychiatric symptoms
Dystonia + Dyskinesia	<i>PRRT2</i> / AD	DYT10	Paroxysmal kinesigenic dyskinesia
	<i>PKND</i> / AD	DYT8	Paroxysmal non-kinesigenic dyskinesia
	<i>SLC2A1</i>	DYT18	Exercise induced dystonia



Red Flags for IEM

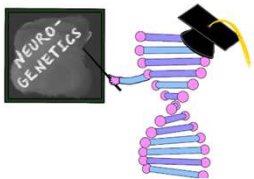
Diffuse clinical picture
with several
neurological and non-
neurological features

Combination of
movement disorders
(ataxia + dystonia,
dystonia +
parkinsonism)

Presence of coma/
encephalopathy
precipitated by illness,
starvation

Distinct MRI findings
(basal ganglia lesions,
hypomyelination,
cerebellar atrophy)

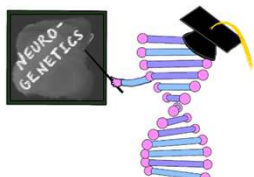
Movement disorder that
is progressively getting
worse and refractory to
standard treatment



IEMs & Movement Disorders



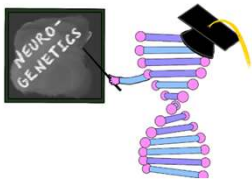
1.	Disorders of Nitrogen containing compounds	Disorders of Creatine metabolism, monoamine neurotransmitters, Glutaric aciduria 1
2.	Disorders of Vitamins, Cofactors, Metals and Minerals	Biotin-thiamine responsive basal ganglia disease, PKAN, Wilson disease,
3.	Disorders of Carbohydrates	GLUT1 transporter deficiency, Pyruvate carboxylase deficiency
4.	Disorders of Mitochondria	Pyruvate dehydrogenase deficiency, <i>SULCA2</i> , Leigh, DJANC19 deficiency
5.	Storage Disorders	Niemann-Pick disease type C, Galactosialidosis
6.	Congenital Disorders of Glycosylation	Phosphomannomutase 2 deficiency, ST3GAL5-CDG



Paroxysmal Movement Disorder Categories in Certain IEMs

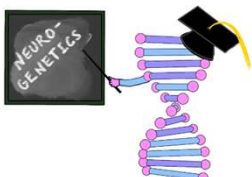


Ataxia	Dystonia	Chorea	Dyskinesia
PDC deficiency Hartnup disease Biotinidase deficiency GLUT1 Glycine encephalopathy (mild)	PDC deficiency GLUT1	Organic acidemias	ABAT- GABA transaminase deficiency Succinic Semialdehyde Dehydrogenase Deficiency

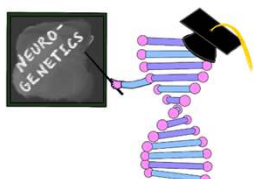
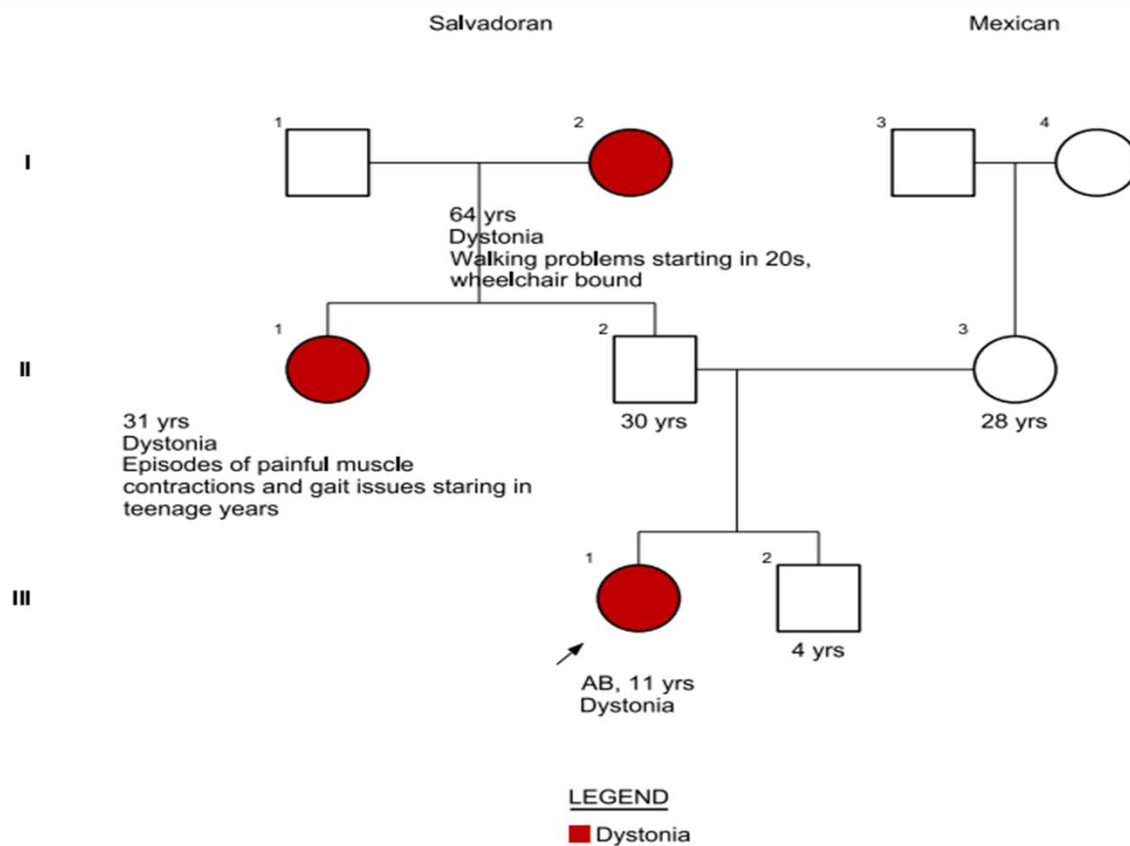


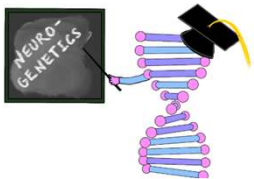
HPI

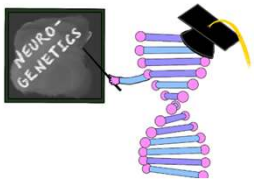
- Birth History: Full term, no complications
- Developmental History: Normal
- 11 years: She had abrupt onset of symptoms. She had decided to go outside and take a walk and suddenly seemed to be moving differently, started to drool. She was not able to talk at the time. She was seen at OSH for evaluation, there was nothing of concern found at that time so was discharged home.
- She got worse at home and could not eat, drink so re-presented to the hospital. She was admitted, had EEG and MRI which were unrevealing, was given a diagnosis of conversion disorder. Family worked with a psychiatrist for a few years and were not seeing an improvement in symptoms.
- In terms of current function, she has difficulty with buttons and zippers, writing, and her hand tends to tense up. Mother assists her with buckling things, but she can put on her shirt without assistance. She has some balance difficulty, walks with a wide based gait, and falls about once a month. Stumbles are more frequent daily, but she can catch herself.



Family History - Interactive

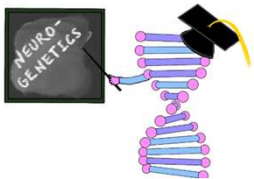




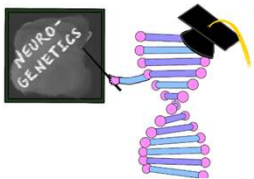
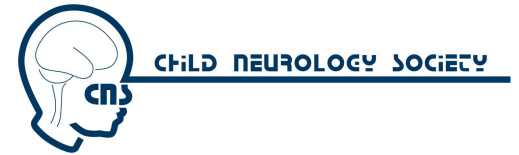
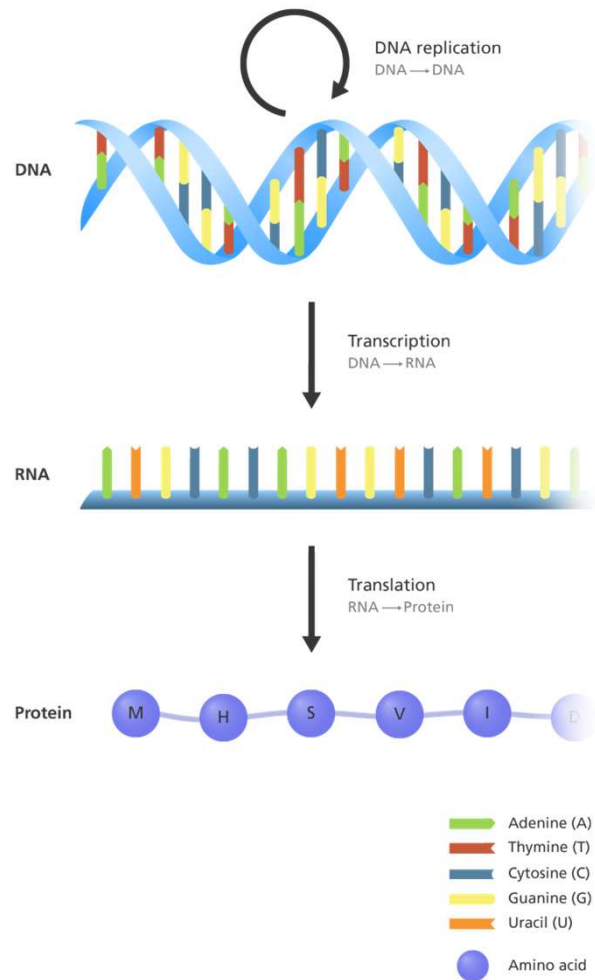


Investigations (Non-Genetic)

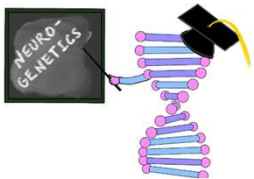
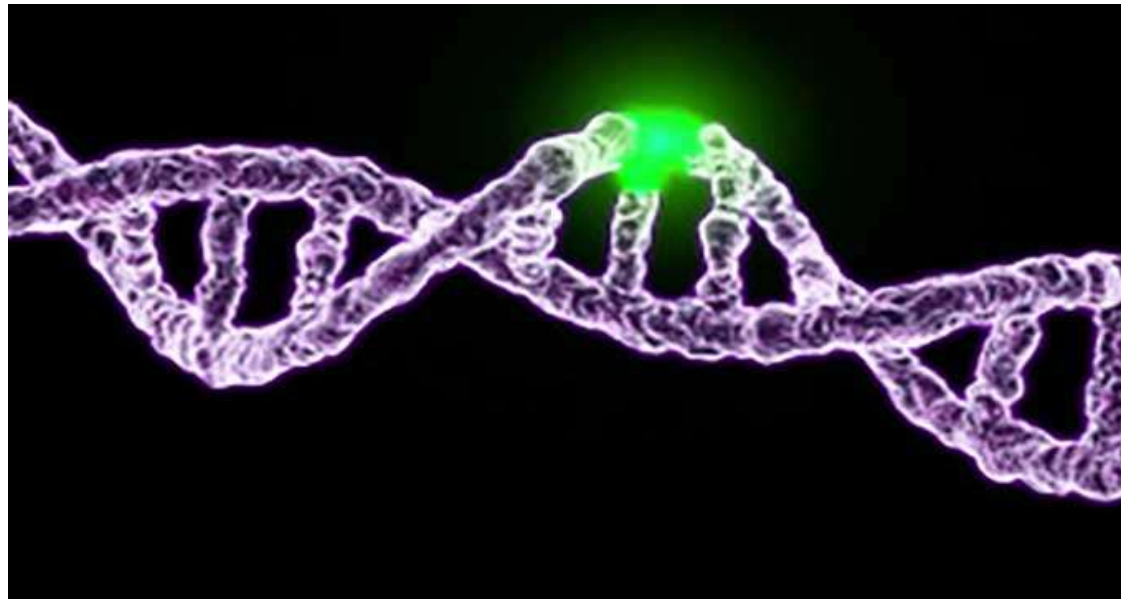
- EEG – WNL
- MRI Brain/ Spine - no abnormalities



Central Dogma



Mutation/ Pathogenic Variant



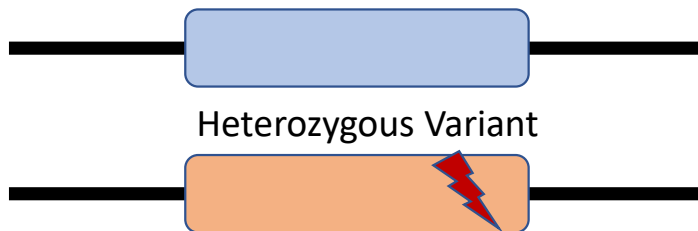


NO DISEASE



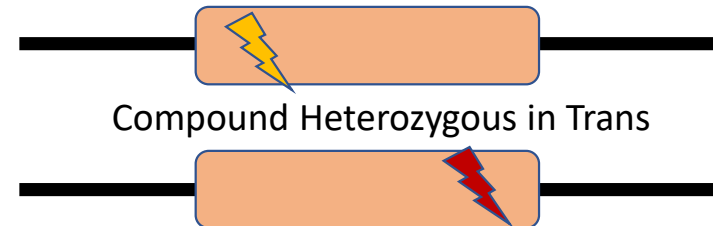
No Variants

Monoallelic/AD





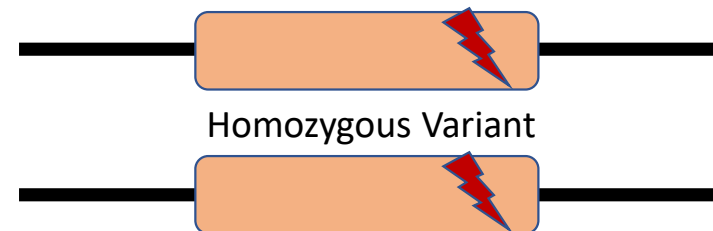
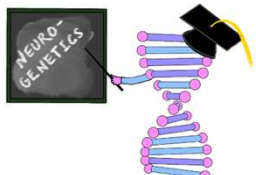
Heterozygous Variant

Biallelic/AR



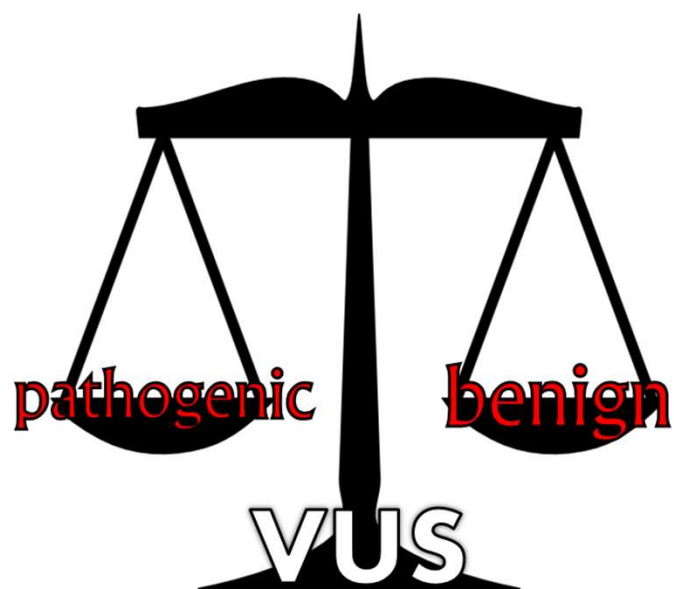
Compound Heterozygous in Trans

-  Unaffected Allele
-  Affected Allele
- AD** Autosomal Dominant
- AR** Autosomal Recessive



Homozygous Variant

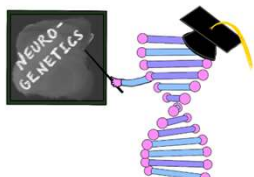
Variant of Uncertain Significance



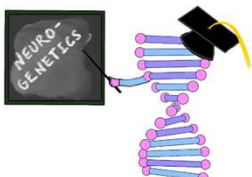
THEATER

THEATRE

THATERE



Approach for VUS Resolution



Look at inheritance pattern

Look at phenotypic match

Look at variant – present in population? Effect on Protein?

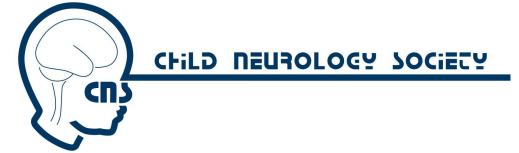
Familial Segregation Studies

Functional studies – measure enzyme or transporter activity



CHILD NEUROLOGY SOCIETY

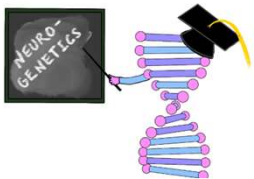
What is Exome Sequencing?

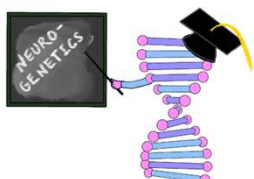
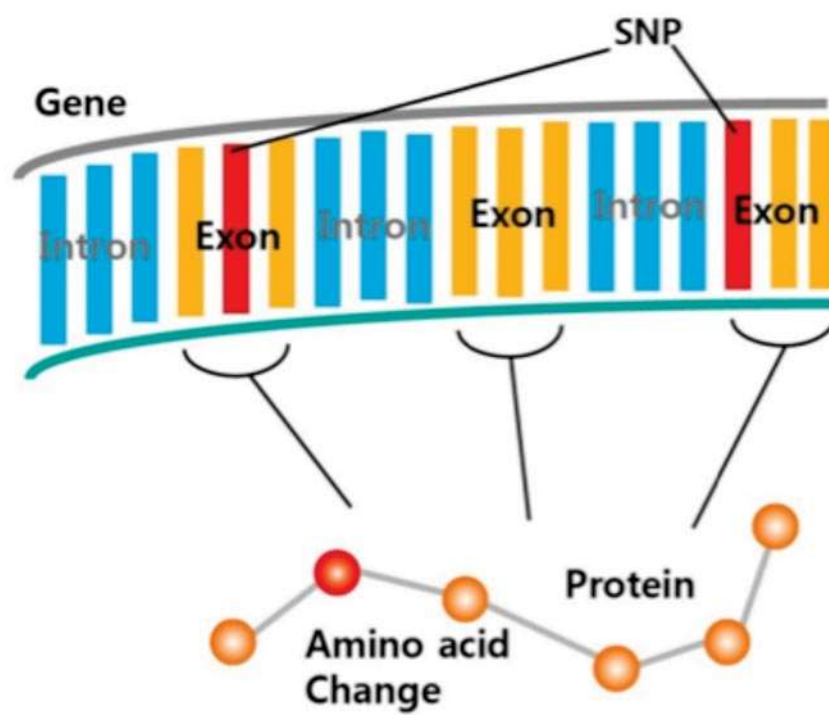
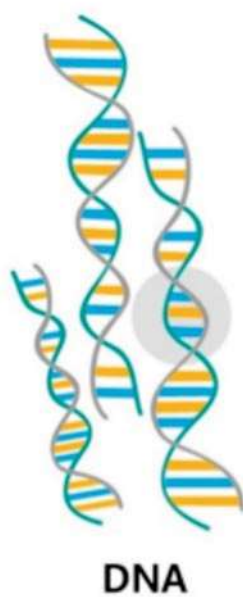


Exome sequencing is a widely used next-generation sequencing (NGS) method that involves sequencing the protein-coding regions of the genome.



The human exome represents less than 2% of the genome but contains ~85% of known disease-related variants.





Limitations of Exome Sequencing



- Clinical laboratories who provide exome sequencing filter variants based on phenotypic information provided by the ordering clinicians. This can lead to difficulties in reporting results that a laboratory does not believe are relevant to the testing indication
- Depth of coverage for each gene (10x, 20x)
- Intronic variants (vs genome sequencing)
- Chromosomal microdeletion/duplication syndromes
- Trinucleotide disorders
- Methylation disorders
- Disorders of mitochondrial DNA



RESULT SUMMARY

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
ATP1A3	NM_001256214.1:c.1877C>T	p.(Thr626Met)	rs80356534	heterozygous	PolyPhen: Probably damaging Align-GVGD: C0 SIFT: - MutationTaster: Disease causing Conservation_nt: high Conservation_aa: high	gnomAD: - ESP: - 1000 G: 0.000076 CentoMD: 0.000085	Missense Pathogenic (class 1)

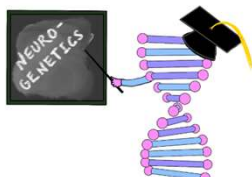
Variant annotation based on OTFA (using VEP v83). * AlignGVGD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

VARIANT INTERPRETATION

ATP1A3, c.1877C>T p.(Thr626Met)

The ATP1A3 variant c.1877C>T p.(Thr626Met) causes an amino acid change from Thr to Met at position 626. According to HGMD Professional 2019.1, this variant has previously been described as disease causing for Dystonia-parkinsonism, rapid-onset by de Carvalho Aguiar et al., 2004 (PMID: 15260953) and others. ClinVar lists this variant as pathogenic (clinical testing, Variation ID: 12909). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic variants in ATP1A3 gene are associated with dystonia 12, an autosomal dominant disorder. Dystonia 12 or rapid-onset dystonia-parkinsonism (RDP) is a very rare movement disorder, characterized by the abrupt onset of parkinsonism and dystonia, often triggered by physical or psychological stress. Rapid-onset dystonia parkinsonism causes movement abnormalities that can make it difficult to walk, talk, and carry out other activities of daily life. In this disorder, dystonia affects the arms and legs, causing muscle cramping and spasms. Facial muscles are often affected, resulting in problems with speech and swallowing. The movement abnormalities associated with rapid-onset dystonia parkinsonism tend to begin near the top of the body and move downward, first affecting the facial muscles, then the arms, and finally the legs. ATP1A3 is important for maintaining the electrochemical gradients of potassium and sodium across the plasma membrane. These mutations are thought to lead to neuronal dysfunction. Other genes, which have not yet been identified, may also be involved (OMIM®: 182350).



Question for each Team:

Team A: What does the gene code for and where is it expressed?

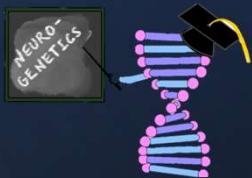
Team B: What disorder (s) does the gene cause?

Team C: Look at the details of the particular variant on test report and ClinVar?

Team D: What is the definition of genotype-phenotype correlation? What phenotype do you think our patient has?



Rapid Dystonia Parkinsonism (RDP)

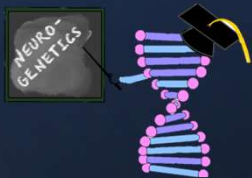


- RDP has been characterized by abrupt onset of dystonia over days to weeks with parkinsonism (primarily bradykinesia and postural instability); common bulbar involvement; and absence or minimal response to an adequate trial of L-dopa therapy, with few exceptions.
- Often fever, physiologic stress, or alcoholic binges trigger the onset of symptoms.
- After their initial appearance, symptoms often stabilize with little improvement; occasionally second episodes occur with abrupt worsening of symptoms.
- Age of onset ranges from four to 55 years, although a childhood variation of RDP with onset between ages nine and 14 months has been reported.

Alternating Hemiplegia of Childhood (AHC)



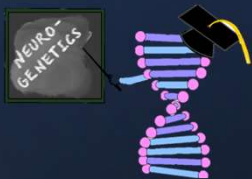
- Onset before 18 mo of age
- Repeated attacks of hemiplegia involving either side of the body
 - Asymmetry is characteristic
- Episodes of bilateral hemiplegia or quadriplegia
 - Generalization or from bilateral from the start
- Other paroxysmal disturbances, during attacks and/or in isolation
 - Tonic or dystonic spells, oculomotor, autonomic
- Immediate disappearance of symptoms in sleep
 - Symptoms may resume after waking
- Developmental and non-paroxysmal neurologic abnormalities
 - Choreoathetosis, dystonia, or ataxia



Genetics of AHC/RDP



- *ATP1A3*-RDP is a disorder of the sodium-potassium ATPase (Na^+/K^+ -pump)
 - Classic prevalence estimate: 1/million
 - Underestimate
- Heterozygous *ATP1A3* pathogenic variants explain most “classic” AHC (>75-90%)
 - Few cases: *ATP1A2*, *SCN1A*, *CACNA1A*
- *ATP1A3*-AHC is autosomal dominant
 - Variable expressivity
 - Usually *de novo*
 - Occasional inheritance from less severely affected parent





Polymicrogyria

Cardiac failure
Progressive cerebral + cerebellar atrophy
EIEE/neonatal seizure onset
Encephalopathy, ID

AHC

ID, epilepsy
Cardiac
Other triggers

RDP

Later onset
+parkinsonism
Deficits persist

Asymmetry

D-DEMØ

Episodic dystonia Ø hemiplegia
Facial dysmorphism

Paroxysmal movement disorders + other deficits

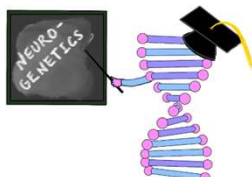
ATP1A3
phenotypes

SNHL
Optic atrophy

CAPOS
(p.E818K)

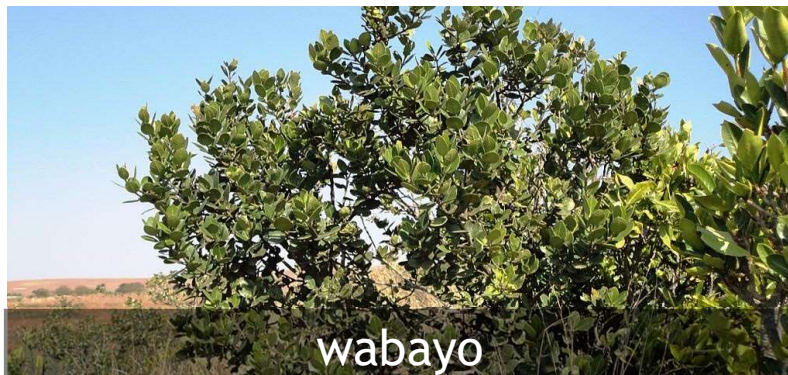
Febrile illness trigger
Symmetric
Encephalopathy, cerebellar ataxia, weakness

atypical RDP/RECA/FIPWE





Neuronal Na^+/K^+ -ATPase is the key enzyme involved in AHC



wabayo



Palythoa zoanthid coral

[Ned Tijdschr Geneeskd. 2019 Aug 29;163. pii: D4064.](#)

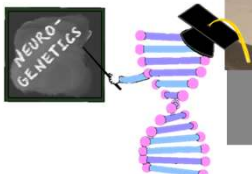
[Corneal melting after moving a tropical aquarium].



African crested rat



Digitalis



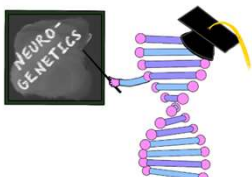
Take Home Points

AD inheritance is characterized by members of multiple generations and both sexes involved. Incomplete penetrance and variable expressivity are key features.

Exome sequencing is a widely used next-generation sequencing (NGS) method that involves sequencing the protein-coding regions of the genome. There are several limitations.

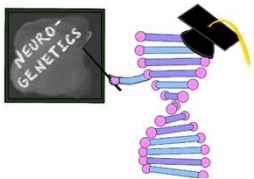
Different variants in same gene can lead to different severities and presentations based on affect of mutation on the protein.

ATP1A3 variants lead to several neurological disorders including AHC, RDP and CAPOS



Suggested Reading

- Wijemanne S, Jankovic J. Dopa-responsive dystonia--clinical and genetic heterogeneity. *Nat Rev Neurol*. 2015 Jul;11(7):414-24.
- Brashear A, Sweadner KJ, Cook JF, Swoboda KJ, Ozelius L. *ATP1A3*-Related Neurologic Disorders.
- Keller Sarmiento IJ, Mencacci NE. Genetic Dystonias: Update on Classification and New Genetic Discoveries. *Curr Neurol Neurosci Rep*. 2021 Feb 9;21(3):8.
- Sen K, Gropman AL, Disorders of Monoamine Metabolism. *Rudolph's Pediatrics*.



Acknowledgements

Leads:

- Kuntal Sen (CNMC)
- Louis Dang (UM)

Core members:

- Amitha Ananth (UAB)
- Andrea Gropman (CNMC)
- Education
 - Rachel Gottlieb-Smith (UM)
 - Jeff Strelzik (CNMC)

Committee members:

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- Divakar Mithal (Northwestern)
- Christa Habela (Hopkins)
- Kristin Baranano (Hopkins)
- Lisa Emrick (Baylor)
- Margie Ream (Nationwide)
- Julie Ziobro (UM)

Additional Members:

- Alexa Taylor (CNMC)

