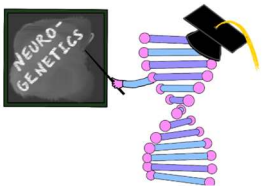


Teaching Guide

Module 5: Movement Disorder/Dystonia

Slide 1: Introduce the phenotype for this module

Slide 2: Objectives, from texts on slide.

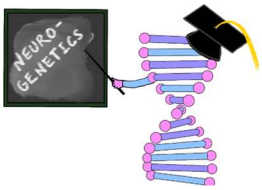
OMIM = Online Mendelian Inheritance in Man.

Slide 3: **Disclose the chief complaint**. Here instead of saying abnormal movements or problems walking, we are already clarifying a phenotype with the goal of eliciting a focused differential for dystonia.

Slide 4: Spend a few minutes having participants **share genetic causes of dystonia** based on their previous knowledge. If they say 'dopa responsive dystonia', encourage them to share what additional information they know about the condition including gene (e.g. GCH1, TH), inheritance pattern, biochemical markers (decreased biopterin/neopterin in GCH1, and normal in TH), treatment (carbidopa/levodopa) etc.

Slide 5-6: This is course material where instructor will be helping participants form some concepts in genetic dystonia. Acknowledge this is a busy slide and clarify *participants are not expected to remember all the genes.* But as they encounter more cases in practice, they will automatically start remembering more about these conditions. **The genetic causes of dystonia can be approached based on (1) If it is focal or generalized, (2) Age of onset, and (3) If it is associated with other neurological manifestations** such as cognitive impairment, myoclonus etc. For example, dystonia plus myoclonus is seen in one specific condition caused by mutation in SGCE gene. Clarify the change in nomenclature. In the past, these conditions were named as DYT1,2… based on the chronology they were described. Then individual genes associated with these respective conditions were discovered over next few decades. Latest nomenclature is using 'DYT' followed by gene name to avoid confusion. The last three disorders included here are paroxysmal dyskinesias which are not actually dystonias. Take note of PRRT2 gene which is an interesting gene that can cause three different neurological conditions including hemiplegic migraine, self-limited seizures and dyskinesias.

Slide 7: **Inborn errors of metabolism** are a unique category of disorders in the sense that diagnostic approach involves both genetic/DNA testing as well as metabolic screening. Discuss the red flags to suspect inborn errors from the slide.



Slide 8: Text from slide. Broad categories of inborn errors that can present **with movement disorders.**

PKAN = Pantothenate kinase-associated neurodegeneration,

CDG = congenital disorder of glycosylation

Slide 9: Here are some classic movement disorders that can present with certain movement disorders. It is important to recognize this is ideal/classic/textbook situation but all **disorders have been recognized to present with atypical symptoms, what we call a 'spectrum'.** This slide can be omitted if time does not permit. PDC = pyruvate dehydrogenase complex,

Slide 10: Text from slide. Emphasize how this case was misdiagnosed as functional disorder due to negative EEG and MRI without genetic investigations being completed.

Slide 11: Given participants a minute to review the pedigree. What is the probable mode of inheritance (Ans: AD)? What are possible explanations of father of proband being unaffected (Ans: Incomplete penetrance and variable expressivity)? Who else is at risk for the condition if gene is identified (Ans: Proband's brother)?

Incomplete penetrance = in a population, when some individuals who carry the pathogenic variant express the associated trait while others do not (present or absent)

Variable expressivity: the range of degree of trait expression among individuals (mild to severe).

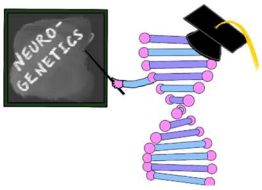
Slide 12/13: Show videos of patient. Have participants describe what they are seeing on exam.

Mother describes her walking pattern as a flapping of the foot, and her left side seems weaker, seems to struggle raising the foot. Tends to wear out the toe of the shoe on the left more. Left toes are always curled, mostly the big toe. Denies diurnal variation or other fluctuation in symptoms from side to side.

Slide 14: **EEG and MRI were negative for this patient.** Ask participants what next step would be. If they say genetic or metabolic testing, ask them what that test would be: multi gene panel for dystonia or exome/ genome would both be appropriate approaches.

Slide 15-18 (Common for several modules. Depending on which module is being done, may or may not repeat all the information)

- Central Dogma developed by Francis Crick is a theory stating that genetic information flows only in one direction, from DNA, to RNA, to protein, or RNA directly to protein.



- **When there is variation or mutation or spelling error in the underlying sequence of the gene, that leads to genetic disorders.** These mutations can be inherited or de novo. In some cases, spelling errors are needed in both alleles to produce a defect in the protein, these are known as recessive disorder. Whereas in some cases, one variant in one of the alleles is sufficient to cause a genetic disorder referred to as dominant conditions.
- When analysis of a patient's genes shows a variant, but it is unclear whether the variant is related to the patient's medical condition, it is classified as a variant of uncertain significance (abbreviated as VUS). In many cases, these variants are so rare in the population that little information is available about them. Typically, more information is required to determine if the variant is disease related.
- Such information may include more extensive population data, functional studies, and tracing the variant in other family members who have or do not have the same health condition. Parental testing can be useful to further delineate the variant classification.
    1. Heterozygous: If the variant is found to be inherited from a parent, it would be supportive of benign status. If it is found to be de novo, it could be supportive of pathogenicity in the context of overlapping clinical features.
    2. Compound heterozygous: If the variants are found to be in cis/on same allele, that would be supportive of benign status. If they are found to be in trans/ on different alleles, that could be supportive of pathogenicity in the context of overlapping clinical features. In some cases, we are able to measure an enzyme or transporter activity to evaluate the impact of the genetic variant on the protein, which is called a functional study.

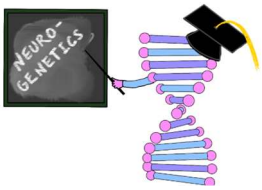
Slide 19- 21: Text from slides

Slide 22-24:

Team A answer: From genecards.org, google, google scholar, PubMed, GeneReviews, Wikipedia. The ATP1A3 gene encodes the alpha-3 catalytic subunit of the Na+/K(+)-ATPase transmembrane ion pump. The ATP1A3 isoform is exclusively expressed in neurons of various brain regions, including the basal ganglia, hippocampus, and cerebellum.

Team B answer: Participants should be able to come up with AHC, RDP and CAPOS using OMIM.

AHC = alternating hemiplegia of childhood,
RDP = Rapid Onset Dystonia Parkinsonism,
CAPOS = cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss



Alternative titles; symbols

SODIUM-POTASSIUM-ATPase, ALPHA-3 POLYPEPTIDE
ATPase, Na+/K+, ALPHA III

HGNC Approved Gene Symbol: ATP1A3

Cytogenetic location: 19q13.2 *Genomic coordinates (GRCh38): 19:41,966,582-41,994,230* (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype View Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
19q13.2	Alternating hemiplegia of childhood 2	614820	AD	3
	CAPOS syndrome	601338	AD	3
	Developmental and epileptic encephalopathy 99	619606	AD	3
	Dystonia-12	128235	AD	3

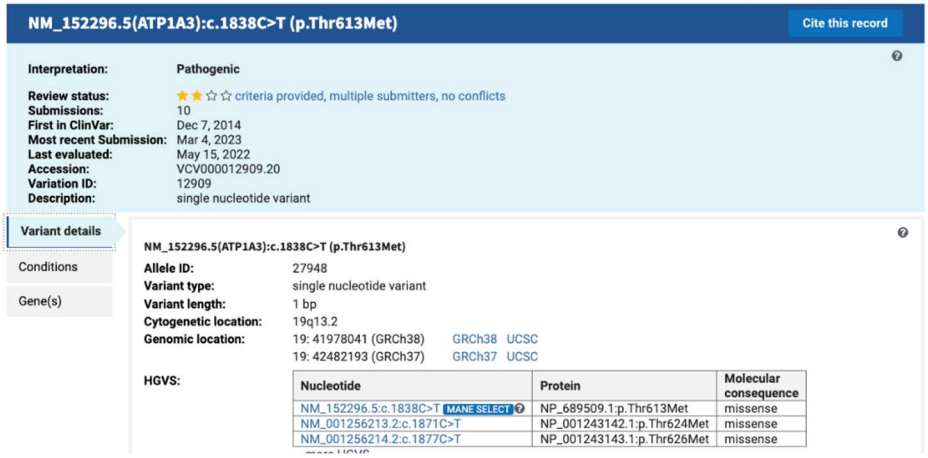
Team C answer: Go to ClinVar, type gene name (ATP1A3) and arrange the variants by location. Or, search for the variant number (12909).

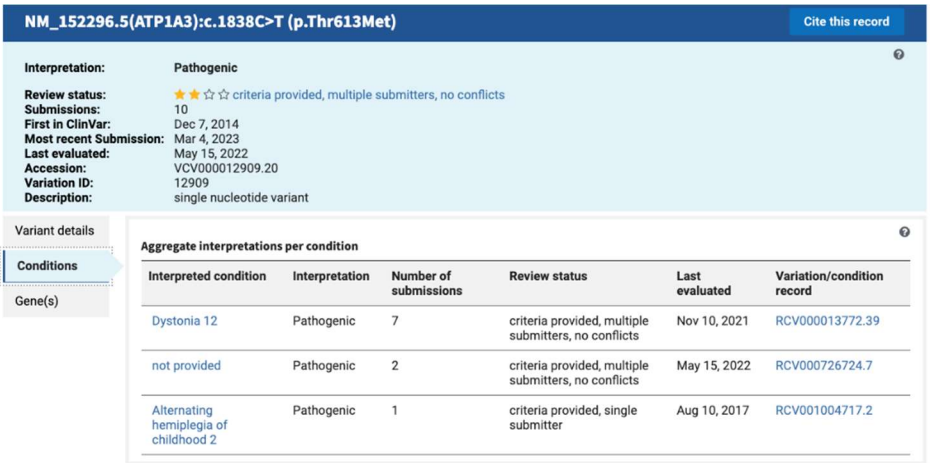
Note that the coordinates given in the genetic testing report are using another transcript variant (NM_001256214.1, c.1877C>T), meaning in this version of the transcript, the change is in base # 1877. And this results in amino acid 626 changing from a threonine to a methionine (p.Thr626Met).

Clinvar may refer to a different transcript variant (NM_152296.5), and if you search for variation ID 12909 in ClinVar as the genetic report identifies, this variant is NM_152296.5, c.1838C>T (p.Thr613Met). This is because the two different transcripts have alternate splicing.

The key point is that when referring to a base change in a transcript or amino acid change in a protein, make sure you know which transcript version the coordinates are referring to.


ClinVar
ATP1A3[gene]
Search
Create alert
Advanced
Access
Help
Submit
Statistics
FTP
Graphical view of search results
GRCh37
Gene
Pathogenic
Likely pathogenic
Uncertain significance
Likely benign
Benign
Conflicting
Not provided
other
42472K
42474K
42476K
42478K
42480K
42482K
42484K
42486K
42488K
42490K
42492K
42494K
Search results
Display options
Sort by Location
Download
Items: 1 to 100 of 961
Sort by
Location
Relevance
Gene
Variation
Gene(s)
Protein change
Condition(s)
Clinical significance
See cases
Pathogenic
GRCh37: Chr19:11338618-45129651
GRCh38: Chr19:11227942-44626354
...more


NM_152296.5(ATP1A3):c.1838C>T (p.Thr613Met)
Cite this record
Interpretation: Pathogenic
Review status: criteria provided, multiple submitters, no conflicts
Submissions: 10
First in ClinVar: Dec 7, 2014
Most recent Submission: Mar 4, 2023
Last evaluated: May 15, 2022
Accession: VCV000012909.20
Variation ID: 12909
Description: single nucleotide variant
Variant details
Conditions
Gene(s)
NM_152296.5(ATP1A3):c.1838C>T (p.Thr613Met)
Allele ID: 27948
Variant type: single nucleotide variant
Variant length: 1 bp
Cytogenetic location: 19q13.2
Genomic location: 19: 41978041 (GRCh38) GRCh38 UCSC
19: 42482193 (GRCh37) GRCh37 UCSC
HGVS:
Nucleotide
Protein
Molecular consequence
NM_152296.5:c.1838C>T MANE SELECT
NP_689509.1:p.Thr613Met
missense
NM_001256213.2:c.1871C>T
NP_001243142.1:p.Thr624Met
missense
NM_001256214.2:c.1877C>T
NP_001243143.1:p.Thr626Met
missense


NM_152296.5(ATP1A3):c.1838C>T (p.Thr613Met)
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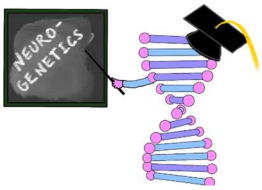
Last evaluated: May 15, 2022
Accession: VCV000012909.20
Variation ID: 12909
Description: single nucleotide variant
Variant details
Conditions
Gene(s)
Aggregate interpretations per condition
Interpreted condition
Interpretation
Number of submissions
Review status
Last evaluated
Variation/condition record
Dystonia 12
Pathogenic
7
criteria provided, multiple submitters, no conflicts
Nov 10, 2021
RCV000013772.39
not provided
Pathogenic
2
criteria provided, multiple submitters, no conflicts
May 15, 2022
RCV000726724.7
Alternating hemiplegia of childhood 2
Pathogenic
1
criteria provided, single submitter
Aug 10, 2017
RCV001004717.2



Team D answer: A genotype-phenotype correlation is the association between specific genetic variants (genotype) and the resulting spectrum of disease expression (phenotype). Phenotype in this patient is RDP, previously known as DYT12.

Slide 25- 28: Texts from slide. Participants should have had some of this information from the exercise. **Point out that ATP1A3 related disorders is on GeneReviews** which is a nice resource to quickly read up regarding well-described genetic conditions.

D-DEMØ=**d**ystonia, **d**ysmorphism of the face, **e**ncephalopathy with developmental delay, brain **M**RI abnormalities always including cerebellar hypoplasia, **no** hemiplegia (Ø), and neonatal onset

RECA = relapsing encephalopathy with cerebellar ataxia
FIPWE= Fever-Induced Paroxysmal Weakness and Encephalopathy
EIEE = Early-onset infantile epileptic encephalopathy

Slide 29: If time permits, point out trivia that toxins to sodium-potassium ATPase pumps (which are made of proteins including ATP1A3) exist in nature.

Wabayo: ouabain is an arrow poison that comes from wabayo tree in Africa
African crested rat chews wabayo tree which contains toxin and then spits toxin into fur
Palytoxin from coral
Digitalis (common foxglove) plant contains digoxin, a cardiac glycoside

Slide 30: Text from slide.

Slide 31: Suggested reading.

Slide 32: Acknowledgments.