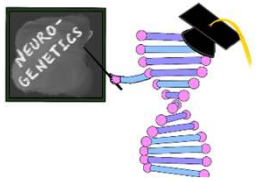
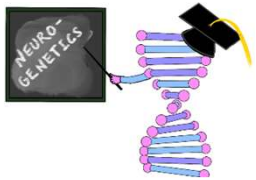
Epilepsy 1

MODULE 1



Learning Objectives

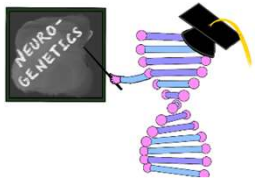
- Develop a genetic differential diagnosis for seizure presenting in the neonatal period
- Review variants of uncertain significance to consider pathogenicity
- Understand the limitations of molecular sequencing and utilize a biochemical study for confirmation of a condition when appropriate
- Review natural history of the particular condition
- Review established treatment and emerging treatment suggestions of the particular condition



CASE

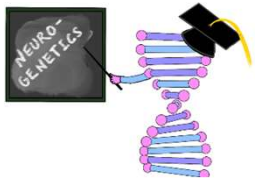
Chief Complaint

- 6-day-old term infant presents with 2 day history of abnormal movements lasting between 30 seconds and 4 minutes



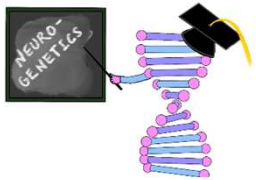
HPI

- Born to 20-year-old woman, adopted at birth
- As far as adoptive parents aware, no pregnancy complications
  - Delivery was at term - vaginal.
  - *No resuscitation required after delivery*
- Reported increased irritability and poor feeding for 1 day
- Family history unknown



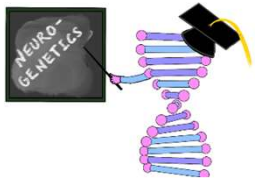
In the ED

- Unremarkable CT Head
- Normal CBC and CMP- specifically normal glucose, normal sodium, calcium, and magnesium
  - Ammonia 55 umol/L
- CSF analysis:
  - WBC 4, RBC 3, Glucose 62, Protein 40 mg/dl
- Started on broad spectrum antibiotics and acyclovir
- Loaded with phenobarbital 20 mg/kg, movements continue



Initial Neurologic Examination

- Head circumference 60%ile, height 40 %ile, weight 45%ile
- Fontanel is soft and flat, no overtly dysmorphic features, no hepatosplenomegaly, no birth marks noted
- Sleeping – awakens with mild stimulation
- Uncoordinated suck
- Mildly hypotonic
- Symmetric moro, normal palmar and plantar grasp

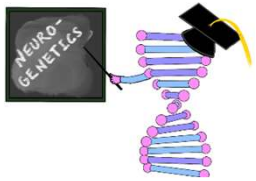


EEG

- Captured abnormal movements, confirmed to be focal seizure
  - Interictal EEG with multifocal epileptiform discharges

Neonatal Seizures Occur in 1-4/1000 Term Births in the US

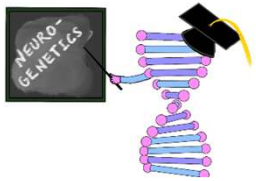
- Seizure etiology
  - HIE 38%
  - Ischemic stroke 18%
  - ICH 12%
  - Epileptic encephalopathy/genetic epilepsy 6%
  - Intracranial infection 4%
  - Brain malformation 4%
  - Transient metabolic (hypoglycemia or electrolyte disturbance) 4%
  - Inborn error of metabolism 3%
  - Benign familial neonatal epilepsy 3%
  - Other/unknown 9%



Glass HC et al. J Pediatric 2016; Nov; 23(4): 321-331

Genetic Differential Diagnosis

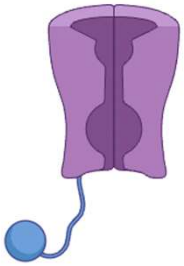
Gene/ Condition	Biochemical Marker	Treatment/ Unique features

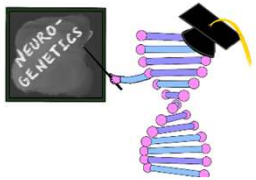


Genetic Differential Diagnosis

Channelopathies - many, among the most commonly seen:

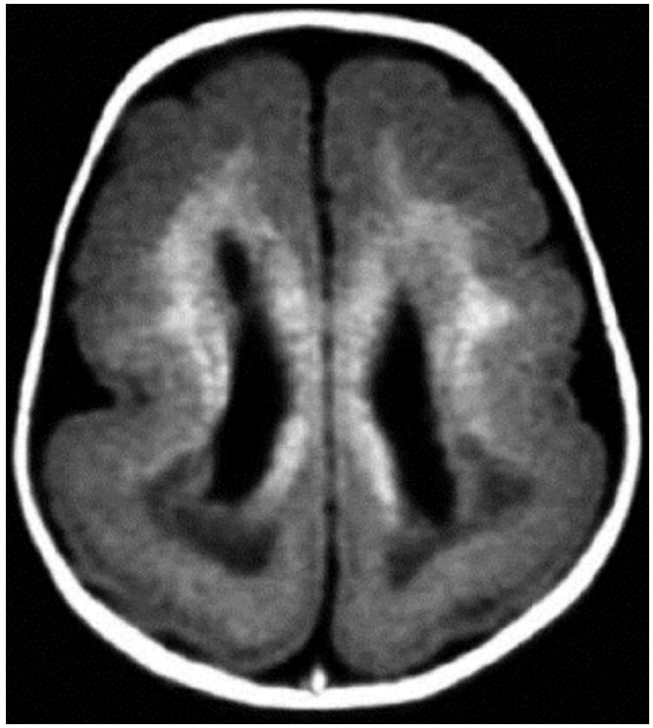
- KCNQ2, KCNQ3
  - Associated with both self-limited (familial) neonatal epilepsy and epileptic encephalopathies
- KCNT1
  - Epilepsy of infancy with migrating focal seizures
- SCN2A
  - Self-limited (familial) neonatal epilepsy and epileptic encephalopathie



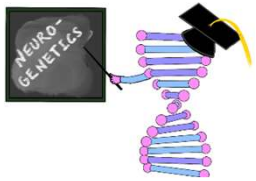


Cortical Malformations

- Neuronal migrational disorders: *LIS1, ARX, DCX,* tubulinopathies, *RELN*

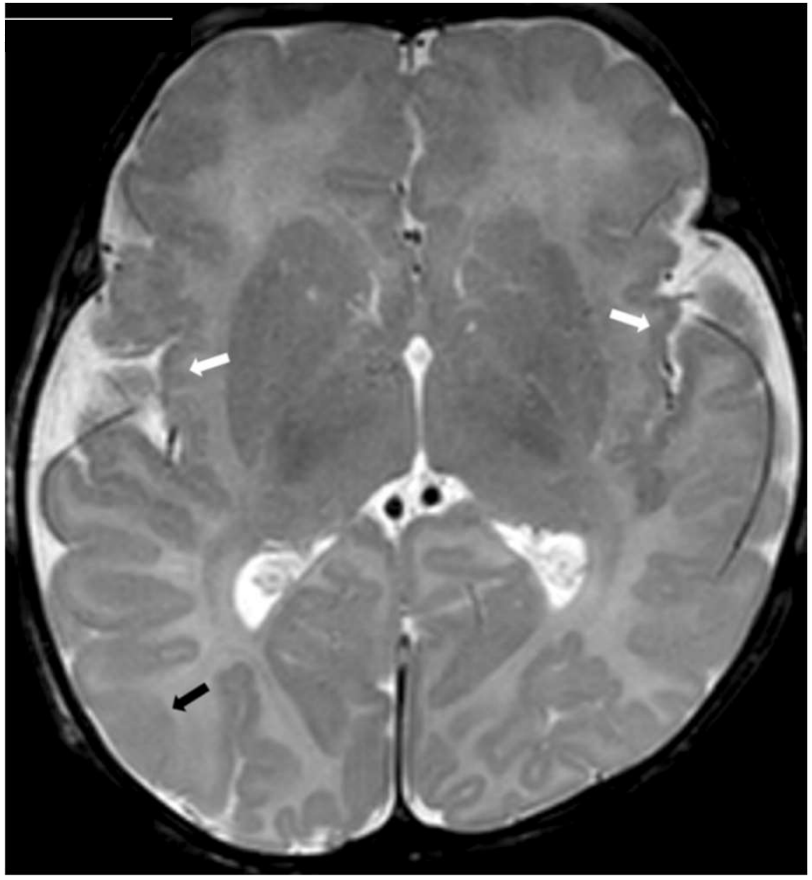


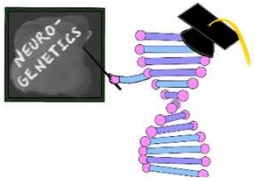
Leventer et al., 2001



Cortical Malformations Cont.

- Peroxisomal biogenesis disorders

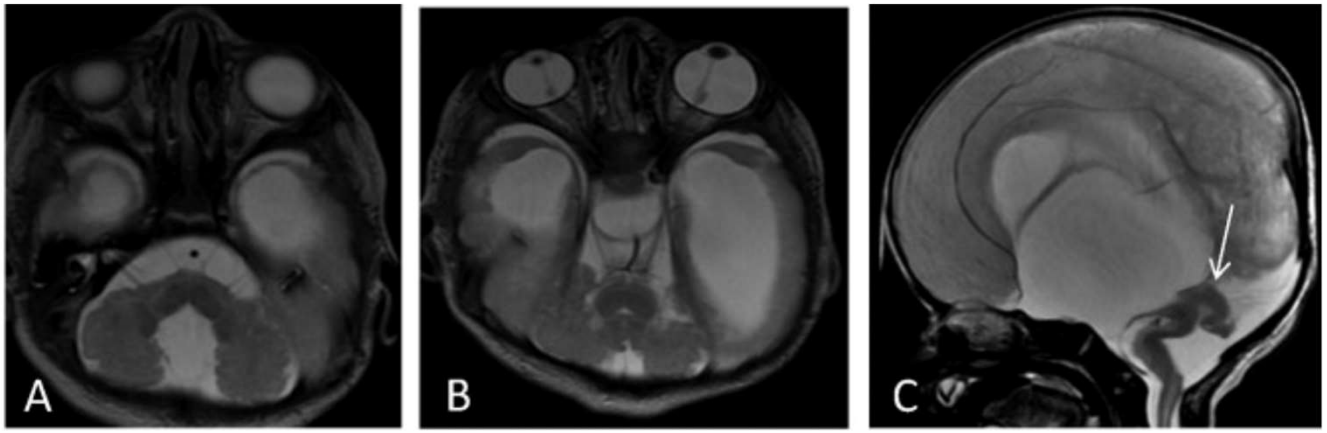


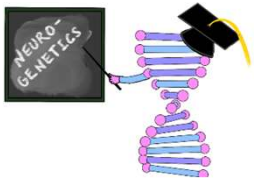


Pfeifer et al. 2017

Cortical Malformations Cont.

- Walker-Warburg syndrome

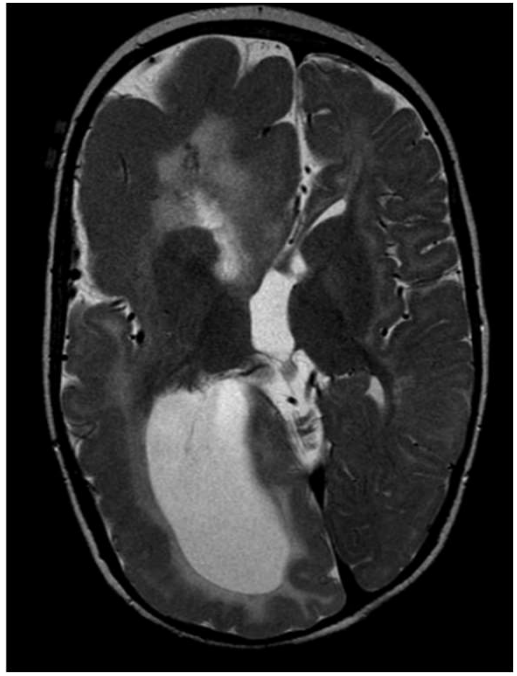




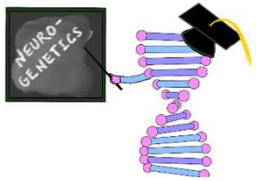
Alharbi et al., 2020.

Cortical Malformations Cont.

- Hemimegalencephaly
- Focal cortical dysplasias

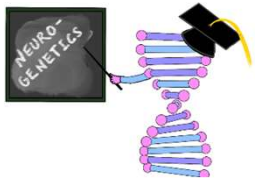


Radiopedia.org Hemimegalencephaly



Inborn Errors of Metabolism

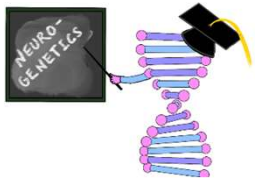
- Disorders of amino acid metabolism and transport
  - MSUD, glycine encephalopathy, disorders of serine synthesis and transport; molybdenum cofactor deficiency, isolate sulfite oxidase deficiency
- Organic acidemias
  - Methylmalonic academia, propionic academia, isovaleric acidemia
- Urea cycle disorders
  - OTC, ASS-1, CPS1, ASL, HHH, NAGS
- Vitamin responsive epilepsy
  - Pyridoxine dependent epilepsy, PNPO deficiency, biotinidase deficiency, holocarboxylase synthetase deficiency
- Disorders of membrane transport
  - Glut1
- Disorders of mineral metabolism
  - Menkes
- Mitochondrial encephalopathy



Back to the Case:

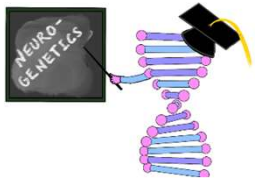
Over the course of the next 2 days:

- Ongoing work up:
  - MRI brain unremarkable
  - Serum lactate: 2
  - Pending testing: Plasma amino acids, urine organic acids, CSF amino acids, acylcarnitine profile, Genetic epilepsy panel
- Ongoing clonic seizures, now sometimes lasting 10-15 minutes, several a day
  - Stepwise treatment over the next 2 days
    - Loaded with 60 mg/kg/levetiracetam
    - 20 mg/kg fosphenytoin
    - Started on enteral pyridoxine at 30 mg/kg/day divided BID
    - Additional 20 mg/kg of phenobarbital
- No further seizures after hospital day 3



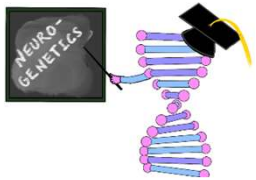
Discharge

- Patient is discharged to home on hospital day 7
- Enteral medication regimen: Phenobarbital 5 mg/kg/day; Levetiracetam 60 mg/kg/day; enteral pyridoxine 30 mg/kg/day
- Remained seizure free
- Passed swallow evaluation, has fed well since hospital day 4



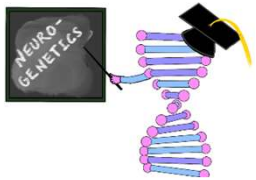
Hospital Follow Up 5 Weeks Later

- No ongoing seizures
- Feeding well
- No developmental concerns: regards faces, startles appropriately to sounds
- Examination is normal

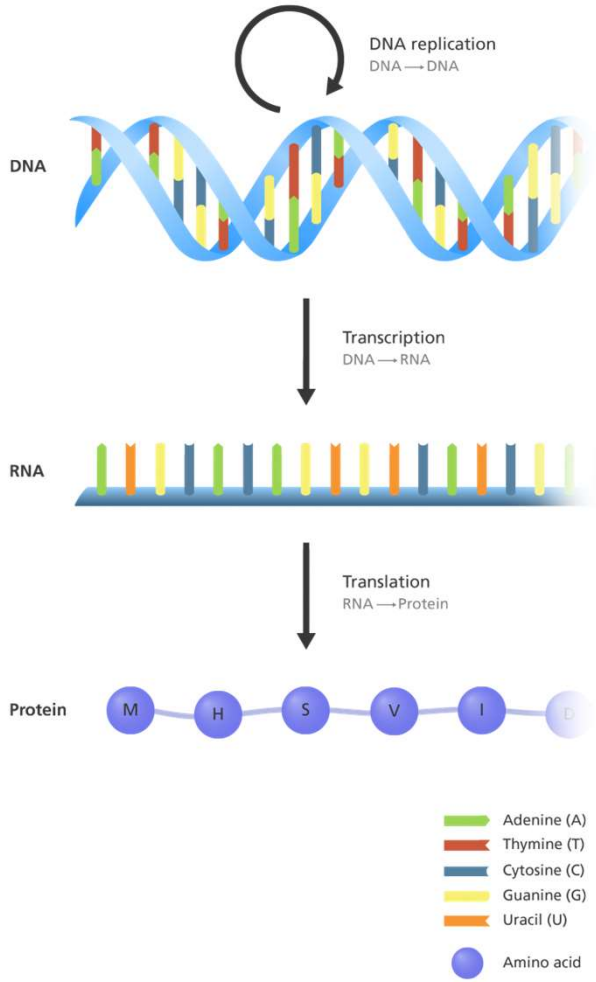


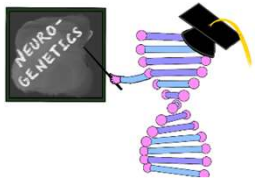
Results From Initial Hospitalization

- Plasma amino acids - no significant abnormalities
- Urine organic acids - nonspecific elevations in several metabolites
- CSF amino acids - normal
- Acylcarnitine profile - normal
- Genetic epilepsy panel
  - ALDH7A1 c.187G>T (p.Gly63Ter) heterozygous
  - ALDH7A1 c.1556G>A (p.Arg519Lys) heterozygous
  - DOCK7: c.818+1G>T heterozygous

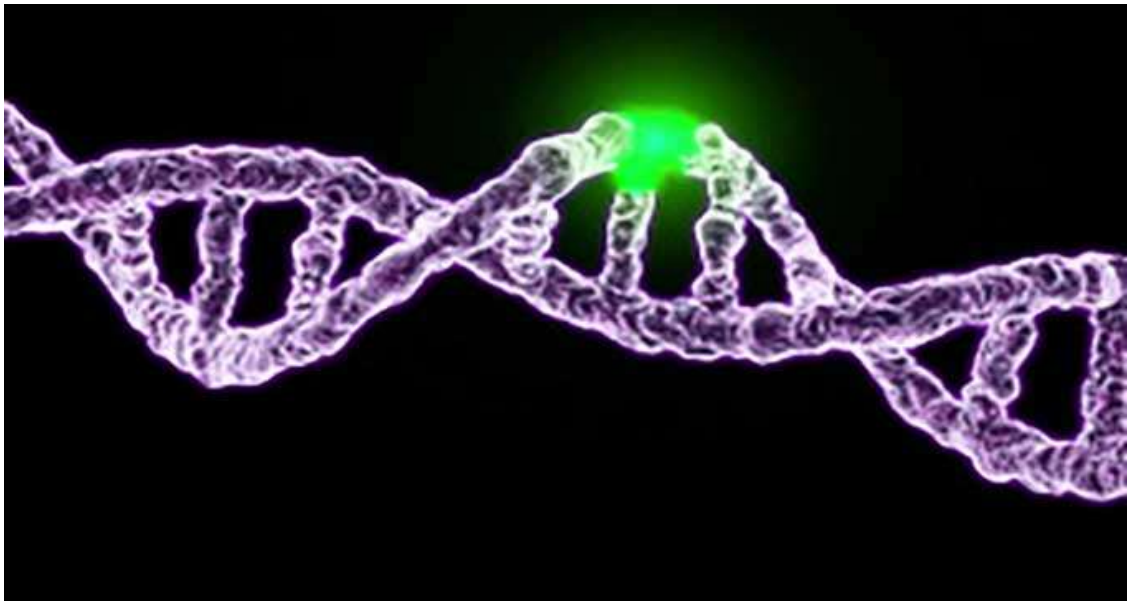


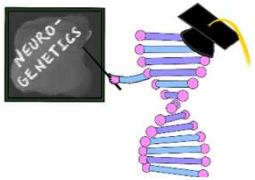
Central Dogma



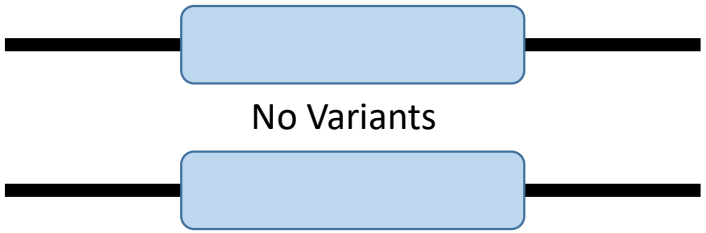


Mutation/Pathogenic Variant



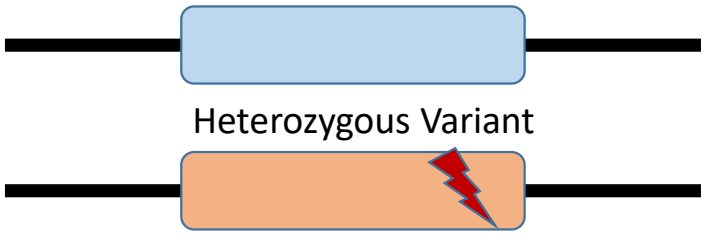


NO DISEASE



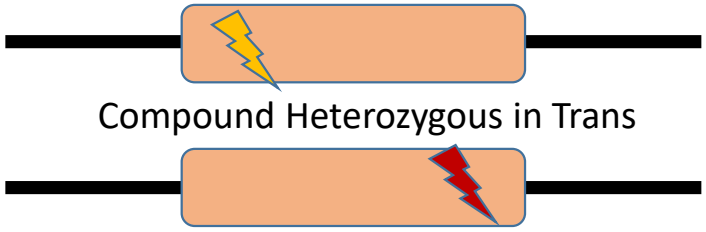
No Variants

Monoallelic/AD



Heterozygous Variant

Biallelic/AR



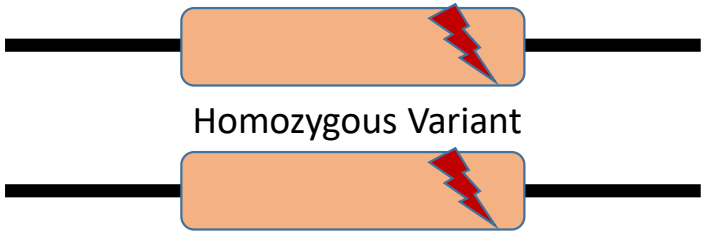
Compound Heterozygous in Trans

Unaffected Allele

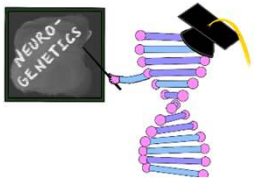
Affected Allele

AD Autosomal Dominant

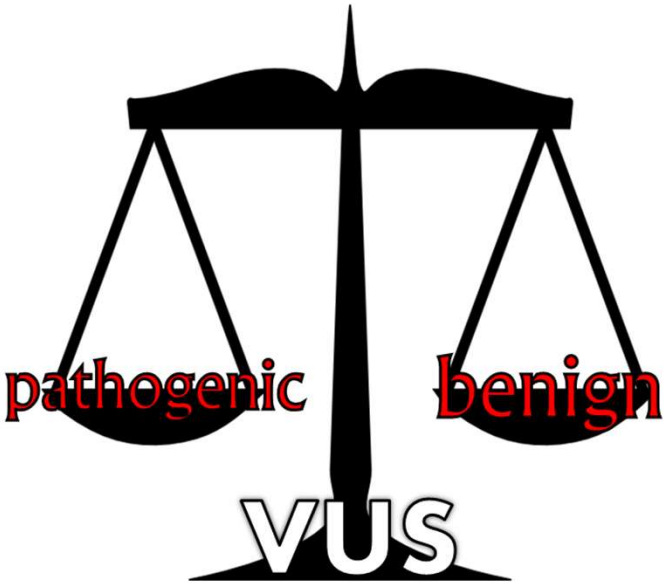
AR Autosomal Recessive



Homozygous Variant



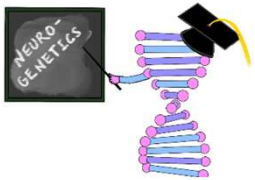
Variant of Uncertain Significance



THEATER

THEATRE

THATERE



Tools for VUS Resolution

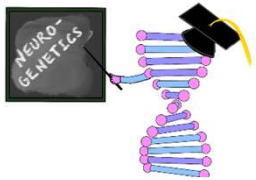
Look at inheritance pattern

Look at phenotypic match

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

Familial Segregation Studies

Functional studies – measure enzyme or transporter activity

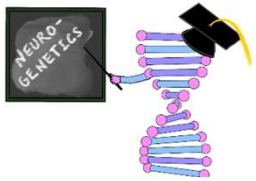


Interpretation

Review actual test results

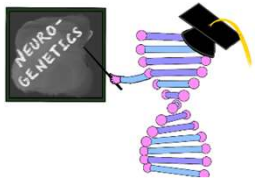
Look at disorders and modes of inheritance; discuss if they fit patient's phenotype

Use following resources: OMIM, ClinVar, GeneReviews, PubMed



Interactive Exercise

- *What is the name of the condition caused by this gene?*
- *What is the mode of inheritance?*
- *Does the variant seem damaging, benign or uncertain?*
- *What is the typical age of presentation?*
- *Does it have a serum biomarker?*
- *Is it treatable?*
- *Do you think this gene is the cause of your patient's symptoms?*



Group 1: ALDH7A1 c.187G>T (p.Gly63Ter)
Group 2: ALDH7A1 c.1556G>A (p.Arg519Lys)
Group 3: DOCK7: c.818+1G>T

Group 1: ALDH7A1 c.187G>T (p.Gly63Ter)

- *What is the name of the condition caused by this gene?*
- *What is the mode of inheritance?*
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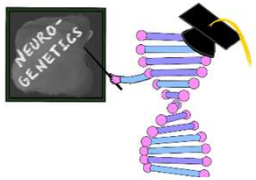
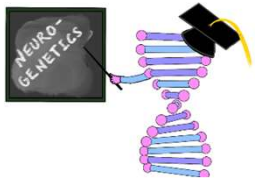


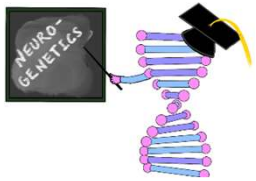
Group 2: ALDH7A1 c.1556G>A (p.Arg519Lys)

- *What is the name of the condition caused by this gene?*
- *What is the mode of inheritance?*
- *Does the variant seem damaging, benign or uncertain?*
- *What is the typical age of presentation?*
- *Does it have a serum biomarker?*
- *Is it treatable?*
- *Do you think this gene is the cause of your patient's symptoms?*



Group 3: DOCK7: c.818+1G>T

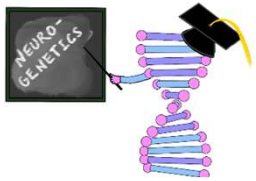
- *What is the name of the condition caused by this gene?*
- *What is the mode of inheritance?*
- *Does the variant seem damaging, benign or uncertain?*
- *What is the typical age of presentation?*
- *Does it have a serum biomarker?*
- *Is it treatable?*
- *Do you think this gene is the cause of your patient's symptoms?*



Phenotypes

- ALDH7A1: Autosomal recessive pyridoxine dependent epilepsy

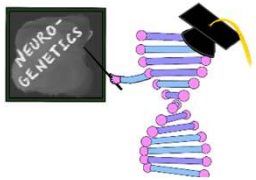
- DOCK7: Autosomal recessive epileptic encephalopathy
  - Dysmorphic features, intractable epilepsy, cortical blindness



Determining the Significance of the Testing

- ALDH7A1: two variants - one likely path, one VUS in a recessive condition
  - Need to determine phase - if both variants are on the same allele, patient is at most a carrier
  - Parental testing is done for this
  - *What do we do when biological parents are unavailable?*

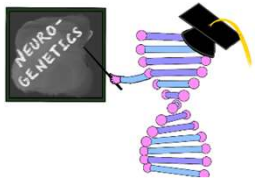
- DOCK7: one pathogenic variant in a recessive condition
  - *Is it possible there is a pathogenic variant on the other allele that was missed through sequencing techniques?*
  - If phenotype fit descriptions, could consider del/dup testing

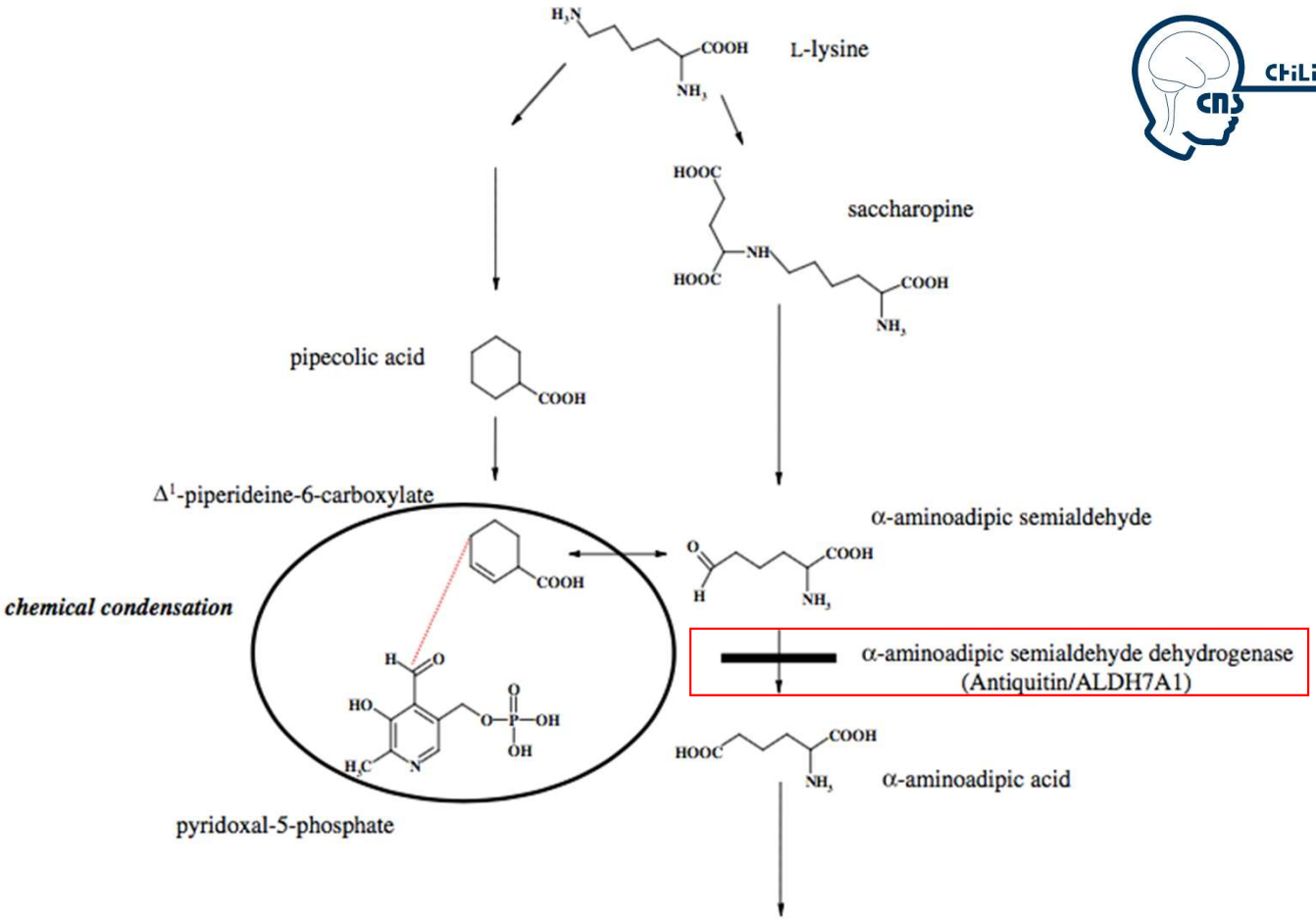


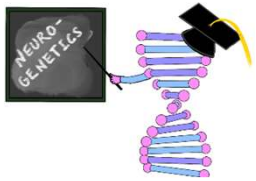
Is There a Biochemical Marker for the Phenotype?

- Patient is currently not seizing: *is this because of the pyridoxine?*

- Could consider holding pyridoxine to see if seizures reoccur but this is not ideal





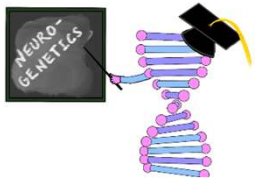


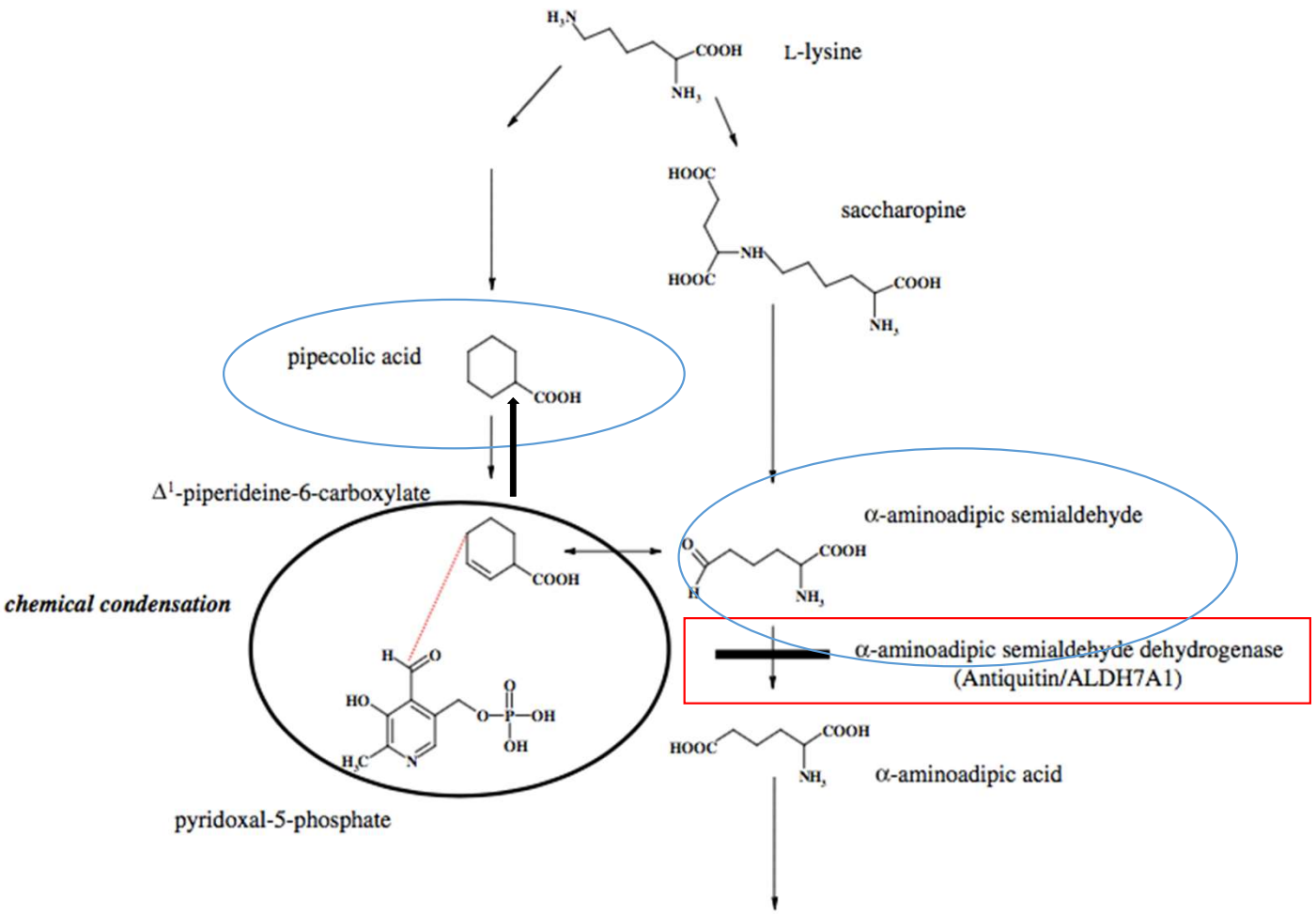
Defect in pyridoxine-dependent epilepsy is in lysine metabolism

Stockler et al. Pyridoxine dependent epilepsy and antiquitin deficiency clinical and molecular characteristics and recommendations for diagnosis, treatment and follow up. Molecular Genetics and Metabolism. 104 (2011) 48-60

Diagnostic Markers

- Elevated alpha amino adipic semialdehyde
  - Urine, plasma, CSF
  - Should be informative even if already on pyridoxine therapy
- Elevated Pipecolic acid
  - Urine, plasma, and CSF
  - Levels may decrease with treatment



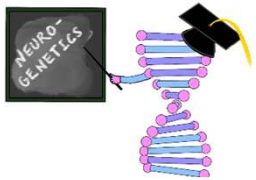


Stockler et al. Pyridoxine dependent epilepsy and antiquitin deficiency clinical and molecular characteristics and recommendations for diagnosis, treatment and follow up. Molecular Genetics and Metabolism. 104 (2011) 48-60

Urine Alpha Amino Adipic Semialdehyde was Sent

- 28.07 mmol/mol creatinine (normal <0.5 mmol/mol creatinine)

- This biochemical result confirms a diagnosis of pyridoxine-dependent epilepsy (PDE-ALDH7A1)

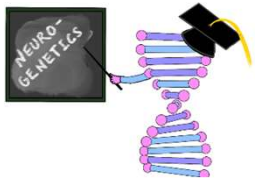


PYRIDOXINE DEPENDENCY: REPORT OF A CASE OF INTRACTABLE CONVULSIONS IN AN INFANT CONTROLLED BY PYRIDOXINE

By Andrew D. Hunt, Jr., M.D.,* Joseph Stokes, Jr., M.D., Wallace W. McCrory, M.D., and H. H. Stroud, M.D.
Philadelphia

CHILD NEUROLOGY SOCIETY

- Term neonate with seizure onset at 3 hours of life - refractory to treatment
- Had several admissions during which she was made NPO, given IV fluids, and an IM multivitamin cocktail containing pyridoxine
  - Noticed that she would be seizure-free during this period
- Pyridoxine determined to treat seizures completely



Hunt AD Jr, Stokes J Jr, McCrory WW, Stroud HH. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics. 1954; 13: 140-5

Pyridoxine

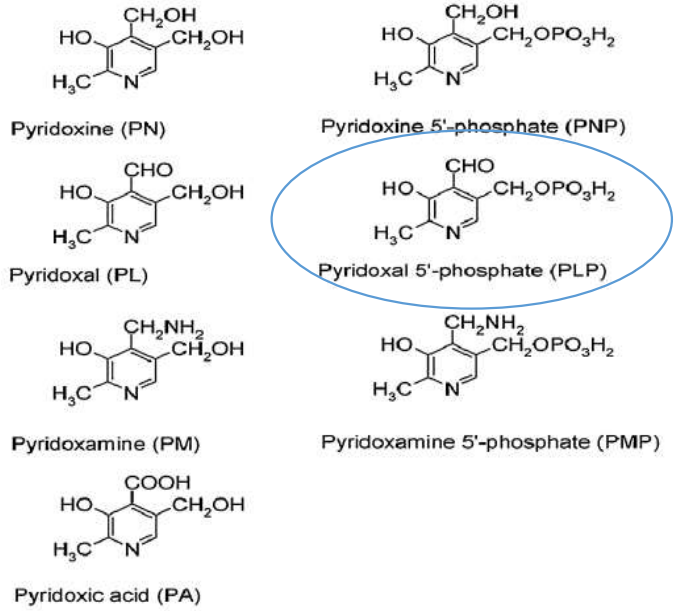
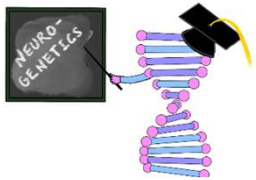


Fig. 1. Structural forms of the 7 B_6 vitamers (adapted from Harper [10]).

PLP is essential cofactor in enzymatic reactions involving neurotransmitter metabolism.



Bowling FG. Pyridoxine supply in human development. *Seminars in Cell and Developmental Biology*. 22 (2011): 611-618.

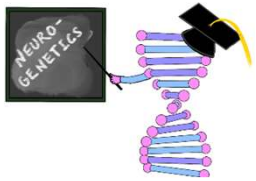
CHILD NEUROLOGY SOCIETY

nature medicine

March 2006

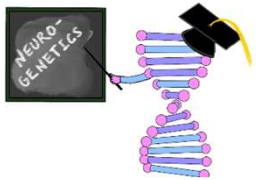
Mutations in antiquitin in individuals with pyridoxine-dependent seizures

Philippa B Mills[1], Eduard Struys[2], Cornelis Jakobs[2], Barbara Plecko[3], Peter Baxter[4], Matthias Baumgartner[5], Michèl A A P Willemsen[6], Heymut Omran[7], Uta Tacke[7], Birgit Uhlenberg[8], Bernhard Weschke[8] & Peter T Clayton[1]



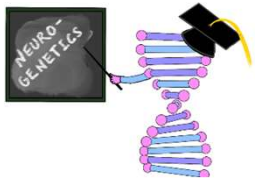
Clinical Characteristics

- Infants with unexplained, early onset epilepsy and poorly responsive to pharmacologic treatment
  - Multiple seizure types
  - Long lasting focal or unilateral seizures
- Signs of encephalopathy (irritability, restlessness, crying, vomiting) preceding seizures
  - Some infants have clinical similarities of infants with HIE



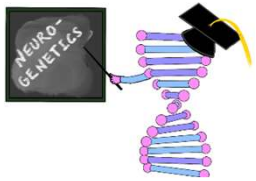
Atypical Cases Have Also Been Reported

- Later onset seizures
- Seizures that initially respond to anti-seizure medications



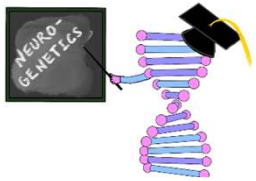
Diagnostic Markers (again)

- Elevated alpha amino adipic semialdehyde
  - Urine, plasma, CSF
  - Should be informative even if already on pyridoxine therapy
  - Elevations have been reported in molybdenum cofactor deficiency and sulfite oxidase deficiency
- Elevated Pipecolic acid
  - Urine, plasma, and CSF
  - Levels may decrease with treatment;
  - Very high pipecolic acid - consider peroxisomal disorders



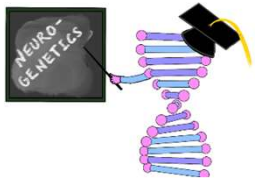
Treatment Should not be Delayed

- IV pyridoxine challenge
  - 100 mg IV pyridoxine while monitoring EEG
  - Cardiorespiratory support should be available-risk of apnea and comatose states after initial IV pyridoxine.
- Oral pyridoxine trial 30 mg/kg/day pyridoxine
  - Should be continued until biochemical screening tests are resulted



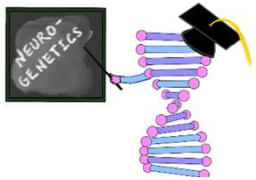
Treatment

- Lifelong pharmacologic supplements of pyridoxine
- Daily dosages of 15-30 mg/kg/day - not to exceed 500 mg/day
- Doses may be doubled in times of illness
- Additional anti-seizure medications typically not needed



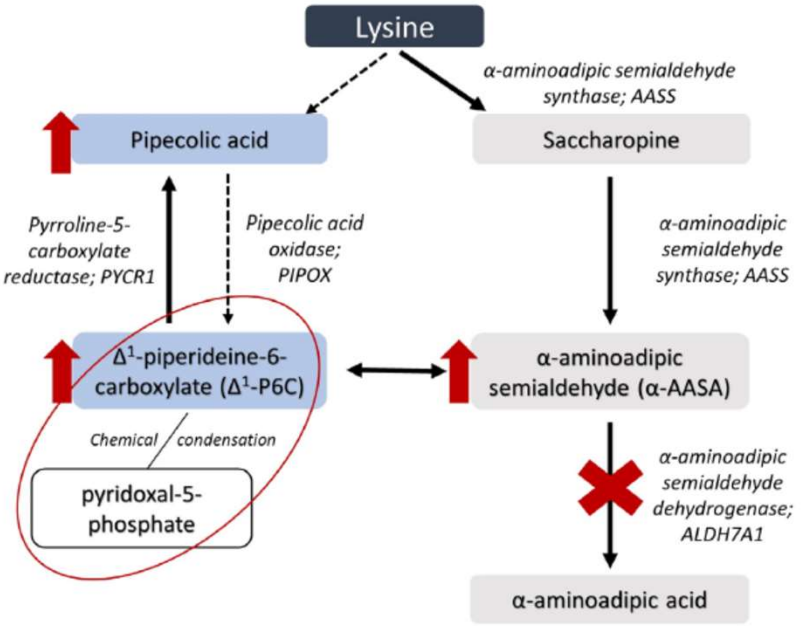
Neurodevelopment

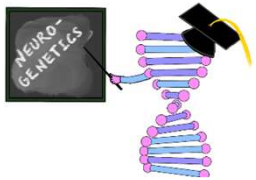
- Epileptic encephalopathy
- Intellectual disability is common (up to 75% of patients)
  - Normal IQ has been reported
- At least one report from a patient where pyridoxine was started prenatally
  - Did not prevent neurodevelopmental challenges



"Triple Therapy" Has Been Proposed in the Literature

- Pyridoxine
- Lysine-restricted diet
- Arginine supplementation 150-200 mg/kg/day
  - Lysine and arginine use the same intracellular transporter system
  - Supplementing arginine can decrease uptake of dietary lysine

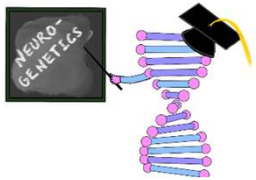




Coughlin CR et al. Consensus guidelines for the diagnosis and management of pyridoxine dependent epilepsy due to alpha aminoadipic semialdehyde dehydrogenase deficiency. JIMD 2021; 44:178-192.

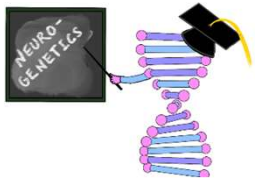
Lysine Reduction Therapies

- Commercially available lysine-free amino acid formulas are typically formulated for glutaric aciduria type I and low in tryptophan.
  - This will need to be supplemented.
- If the formula is not well tolerated, can decrease protein to low end of RDA for age.
- If arginine is used without a low lysine diet - a higher level of 400 mg/kg/day may be needed.
- These expert consensus treatment recommendations are largely based on case reports and case series



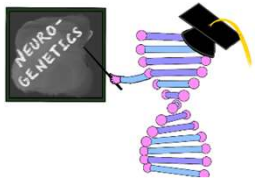
Other Conditions with Pyridoxine Responsiveness

- Pyridoxamine 5’-phosphate oxidase deficiency (PNPO)
- Tissue non-specific alkaline phosphatase (TNSALP) deficiency (congenital hypophosphatasia)
- Hyperprolinemia type II



Take Home Points

- There is a genetic differential for neonatal onset seizures.
- IEMs are individually rare but overall can be a significant cause of neonatal seizures/encephalopathy when hypoxic injury is ruled out.
- These conditions must be suspected as they are amenable to treatment and early treatment can improve outcomes.
- Biochemical testing continues to have an important role in the evaluation of patients, particularly understanding the pathogenicity of VUSs
- While pyridoxine can treat seizures related to ALDH7A1 pathogenic variants, many children continue to have developmental delays and ID
- Emerging consideration for lysine reduction therapies - longitudinal studies in registries will be needed to understand optimal treatment regimens



Suggested Reading

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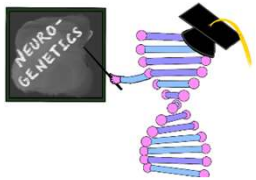
- Myers CT, Mefford HC. Genetic investigations of the epileptic encephalopathies: Recent advances. Prog Brain Res. 2016;226:35-60.
- Axeen EJT, Olson HE. Neonatal epilepsy genetics. Semin Fetal Neonatal Med. 2018 Jun;23(3):197-203.



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