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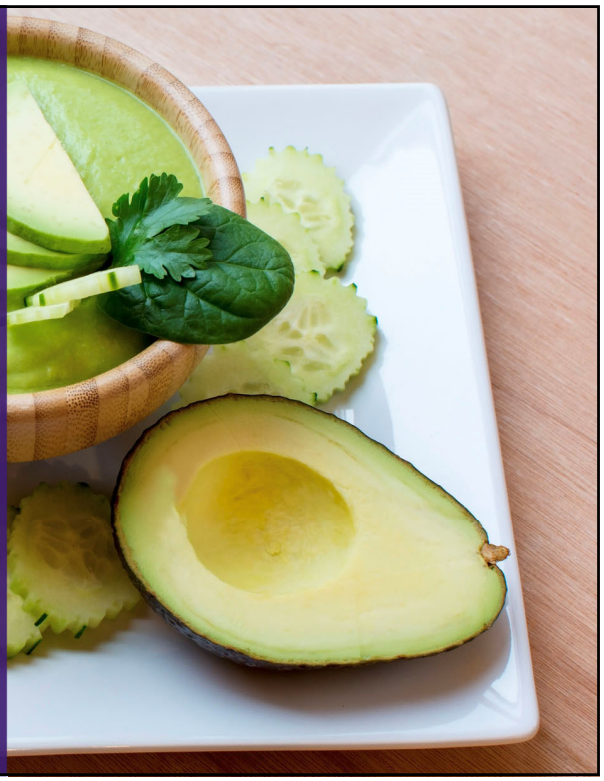
Ketogenic Diet and the Management of Genetic Epilepsy



Ara S. Hall, MD

11/17/22

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Disclosures

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- I served as a local PI for three studies of perampanel in children, sponsored by Eisai®. These studies are now closed.
- I have taught use and programming of Vagal Nerve Stimulators for LivaNova®.
- I may discuss off-label use of several medications in my presentation.
- I received honoraria for this presentation from Nutricia North America.

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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Learning Objectives

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Participants in this activity will:

- Discover which genetic epilepsies may benefit from a medical ketogenic diet.
- Recognize unexpected side effects that may occur in patients with genetic epilepsies and determine if it is related to the medical ketogenic diet or the genetic disorder.
- Determine appropriate candidates and expectations for successful implementation of a medical ketogenic diet in a patient with a genetic disorder.

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What is a genetic disease?

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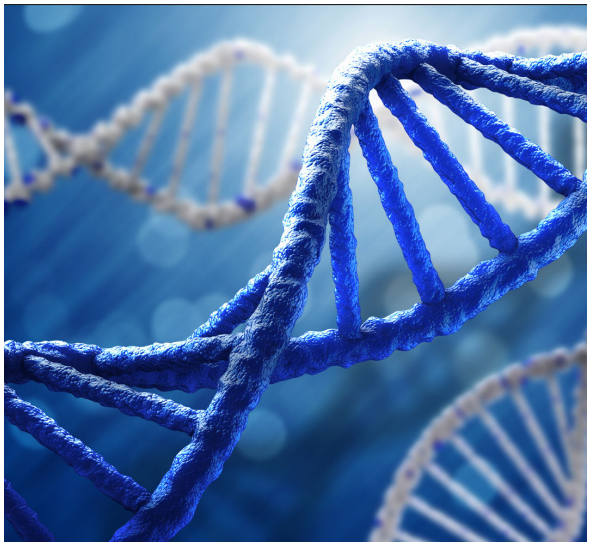
- A genetic disease is caused in whole or in part by a change in the DNA sequence away from the normal sequence.



https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders

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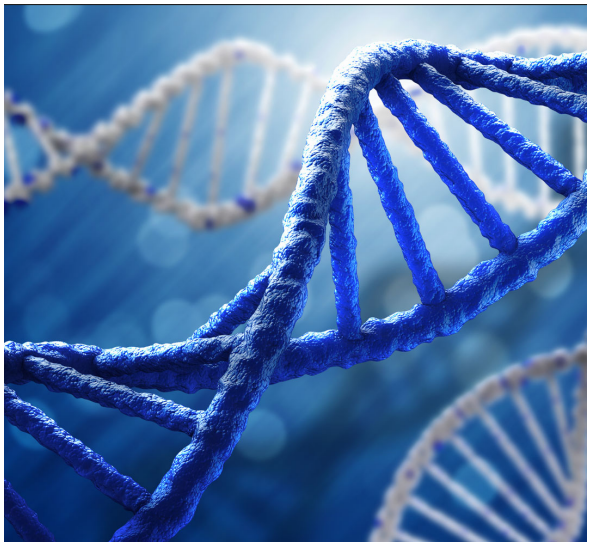
What is a genetic disease?

- Mutation in one gene
  - Cystic fibrosis
  - Tay-Sachs
  - Sickle cell anemia



https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders

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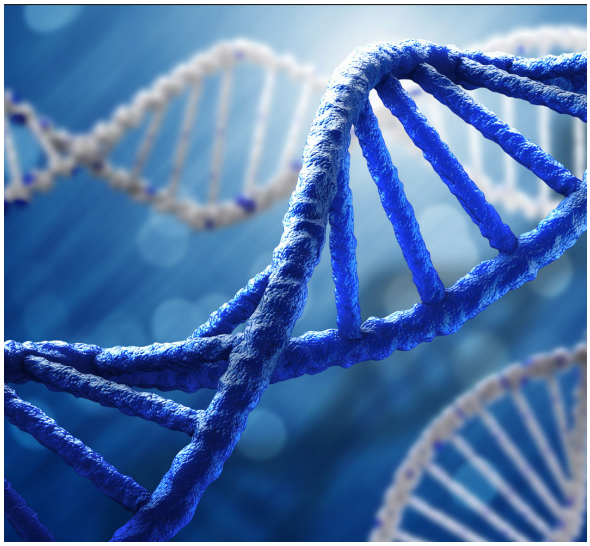
What is a genetic disease?

- Mutation in one gene
- Mutations in multiple genes
- Combination of gene mutations and environment
- Damage to chromosomes



https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders

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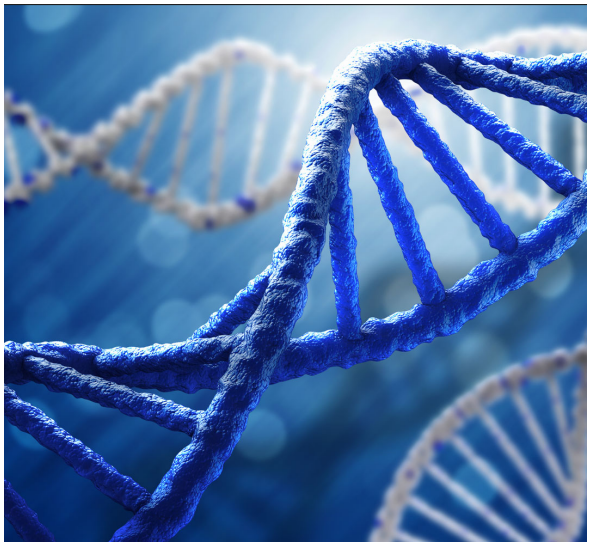
What is a genetic disease?

- Damage to chromosomes
  - Trisomy 21
  - Cri du chat syndrome

Multiple genes are affected.



Plaiasu. Maedica (Bucur). 2017;12:208-13.

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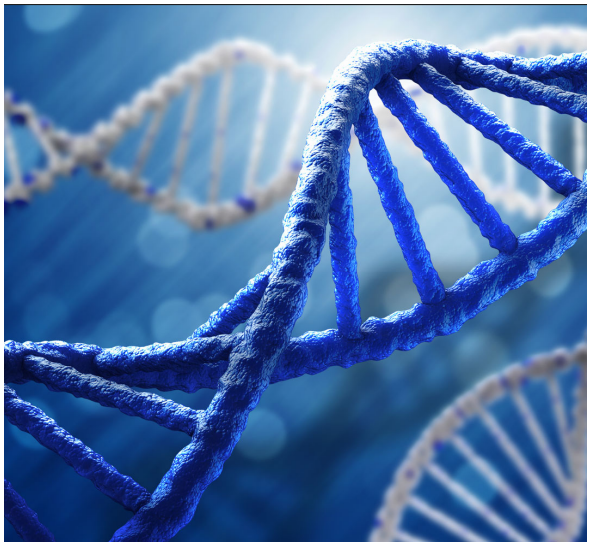
What is a genetic disease?

Calling a disease "genetic"

DOES NOT imply inheritance



https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders

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Genetics and Epilepsy

- Seizures are the result of known or presumed genetic defect or problem associated with epilepsy.

https://www.epilepsy.com/causes/genetic

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Genetics and Epilepsy

- Only 1-2% of epilepsies are monogenic.
- Vast majority involve multiple genetic loci.
- 2017 > 750 genes associated with epilepsy
- 2022 OMIM: 3,104 entries for “epilepsy, ictal, or seizure”

Nikkola, et al. Practical Neurology. 2019:56-9.
Online Mendelian Inheritance in Man: https://www.omim.org

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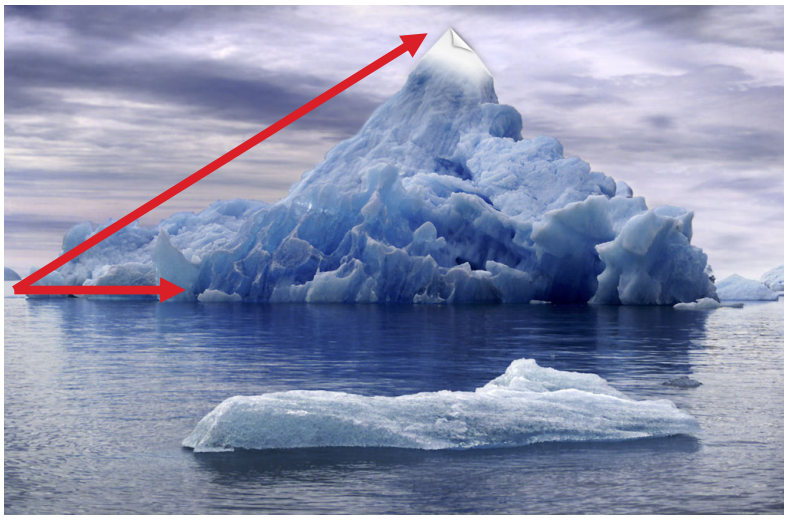
Genetics and Epilepsy



https://www.epilepsy.com/causes/genetic

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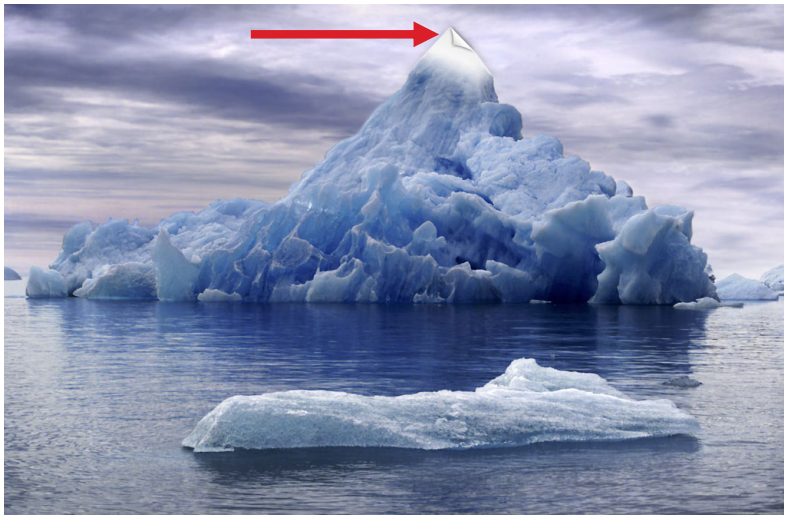
Genetics and Epilepsy



https://www.epilepsy.com/causes/genetic

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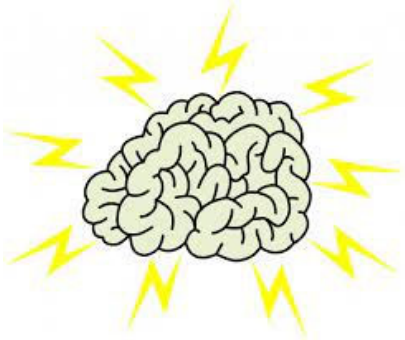
A Brief Word About Epilepsy Syndromes



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Epilepsy Syndromes

There are number of well-defined pediatric epilepsy syndromes:

- Childhood absence epilepsy
- West syndrome
- Dravet syndrome
- Doose syndrome

Scheffer, et al. Epilepsia. 2017;58:512-21.

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Epilepsy Syndromes

Syndrome:

- Cluster of features incorporating seizure types, EEG, imaging features
- May have age-dependent features
- May suggest prognosis
- Implications for management
- DOES NOT assign causation in most cases

Scheffer, et al. Epilepsia. 2017;58:512-21

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Epilepsy Syndromes vs Genetics

It's Complicated

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Dravet syndrome

- Onset of seizures in first year of life
- Normal early development
- Fever induced seizures first, often prolonged
- Over time, develop multiple seizure types
- Most children are developmentally delayed

https://www.omim.org/entry/607208?search=Dravet&highlight=dravet

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Dravet syndrome

- Most cases are causes by mutations in the SCN1A gene

https://www.omim.org/entry/607208?search=Dravet&highlight=dravet

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Epilepsy Genetics

SCN1A mutations also cause:

- Developmental and epileptic encephalopathy 6B, non-Dravet
- Familial febrile seizures
- Generalized epilepsy with febrile seizures plus

https://www.omim.org/entry/182389?search=SCN1A&highlight=scn1a

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Doose syndrome

- Myoclonic or myoclonic-atonic seizures
- Prognosis is variable
- ½ of children have normal development or only mild delays
- Other cases have intractable seizures and cognitive regression
- Seizures stop in 54% to 89% of cases

Wirrell. Continuum (Minneap Minn). 2016;22:60-93.

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Doose syndrome

- Mutations in all of the following genes have been identified in Doose syndrome:
  - SCN1A
  - SCN1B
  - SCN2A
  - SLC2A1
  - CHD2
  - SYNGAP1
  - KIAA2022

Hernandez, et al. https://www.epilepsy.com/what-is-epilepsy/syndromes/myoclonic-atonic-epilepsy-doose-syndrome. Accessed October 25, 2022, 2019.

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Doose syndrome

However, most children with this syndrome
DO NOT
have an identified gene mutation.

Hernandez, et al. https://www.epilepsy.com/what-is-epilepsy/syndromes/myoclonic-atonic-epilepsy-doose-syndrome. Accessed October 25, 2022, 2019.

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Epilepsy Syndromes vs Genetics

1 gene ---------->>>>>> multiple disease

1 syndrome--------->>>>>> multiple genetic causes

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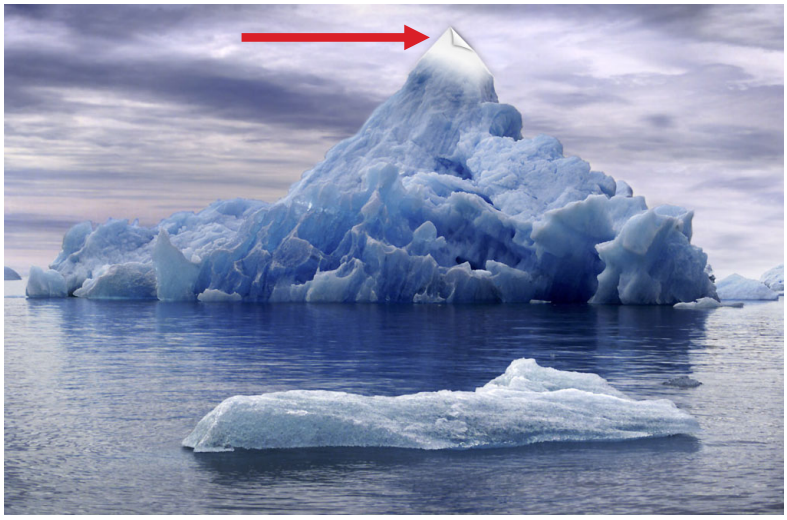
Genetics and Epilepsy



https://www.epilepsy.com/causes/genetic

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Ketogenic Diet and Genetic Epilepsies

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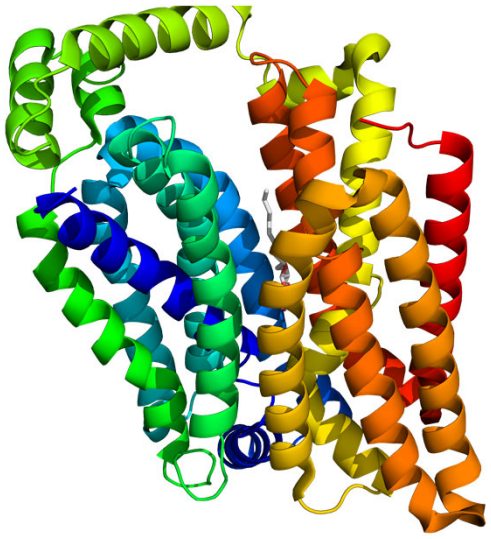
Glut 1 Deficiency

Classic genetic disorder whose most effective treatment remains ketogenic diet

SLC2A1



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Glut 1 Deficiency: Phenotype

- Initially described as
  - Developmental encephalopathy
  - Infantile onset, refractory epilepsy
  - Cognitive impairment - moderate to severe
  - Mixed motor abnormalities including spasticity, ataxia, and dystonia

Pearson, et al. Curr Neurol Neurosci Rep. 2013;13:342.

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Glut 1 Deficiency: Phenotype

- Now
  - Greater recognition of milder phenotypes.
  - Absence epilepsy and other idiopathic generalized epilepsy syndromes may occur with seizure onset in childhood or adulthood.
  - Movement disorders without epilepsy without any accompanying seizures
  - Intellectual impairment may range from severe to very mild

Pearson, et al. Curr Neurol Neurosci Rep. 2013;13:342.

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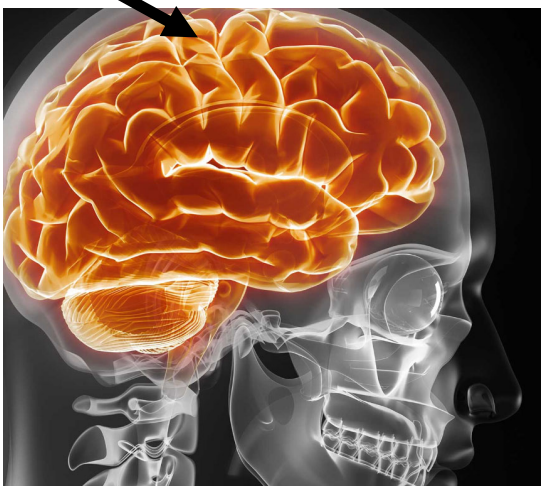
Glut 1 Deficiency

Disorder of energy availability in the brain

Ketogenic diet directly bypasses energy block

Ketones



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Mutation	Disease	Response to Keto	Complications	Citation
STXBP1	STXBP1-realted epileptic encephalopathy	4/12; Sz decrease		Nam et al, 2022
		1/1; Sz decrease		Ünalp et al, 2022
PDHA1	Pyruvate dehydrogenase complex deficiency	2/2; Sz decrease MRI improvement		Inui et al, 2021 Shelkowitz, 2020
DLD	Dihydrolipoamide dehydrogenase deficiency	16,Improved survival		Startetz-Chacham et al, 2021
EIF2S3	MEHMO: MR, sz, hypogonadism, microcephaly and obesity	1/1; Reduced sz, diabetes control	Died of necrotizing pancreatitis	Mori et al, 2021
SCN2A	Early-onset epileptic encephalopathies	1/1: Sz decrease 1/1; Sz control 1/1; Sz control		Tian et al, 2021 Turkdogan et al, 2018 Su et al, 2018
CDKL5	CDKL deficiency disorder	1/29; Sz decrease		Kobayashi et al, 2020
ECHS1	Leigh-like disease, paroxysmal exercise induced dystonia	1/3; Improvement in abnormal movements		Illsinger et al, 2020

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Mutation	Disease	Response to Keto	Complications	Citation
ALG13	Early infantile epileptic encephalopathy, disorder of glycosylation	12/29; improvement in sz 2/2; Seizure control		Ng et al, 2020 Paketci et al,2020
TSC	Tuberous sclerosis	21/31; >50% reduction in seizures		Youn et al, 2020
KCNT1	KCNT-1 related epilepsy	27 patients of whom, 14 tried keto With 57% having improved sz		Borlot et al, 2020
SCN1A	Dravet (in this study)	24 patients in whom, 3 tried keto All three had >50% reduction in sz		Fang et al, 2019
ATP1A3	Alternating hemiplegia of childhood with epileptic encephalopathy	1/1; seizure control		Schirinzi et al, 2018
PGK1	Phosphoglycerate kinase deficiency	1/1; no change	hemolysis	Baba et al, 2017

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Literature Review

- Immediate observations
  - Small numbers of patients
  - Only a handful of gene mutations evaluated
    - 14 total genes

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Literature Review

- Immediate observations
  - Small numbers of patients
  - Only a handful of gene mutations evaluated
  - Response of patients with same affected gene is variable
    - STXBP1 4/12 - 33%
    - CDKL5 1/29 - 3.4% (But had resolution of sz!)
    - ALG13 14/31 - 45%

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Literature Review

Overall response rate in this series:
59.8%

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Literature Review

How does that compare to studies that look at diet response in all pediatric patients with refractory epilepsy?

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Literature Review

Meta analysis by Sourbron et al, 2020 found response (≥ 50% seizure reduction) rates to ketogenic diet ranged from 35-56%.

Sourbron, et al. Childs Nerv Syst. 2020;36:1099-109.

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Literature Review

Meta analysis by Pizzo et al, 2022 found response (≥ 50% seizure reduction) rates to ketogenic diet ranged from 48.1%.

Pizzo, et al. Expert Rev Neurother. 2022;22:169-77.

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Syndrome analysis provides larger #s

- Yan et al, 2018 reported a response rate of 85% in a series of 20 patients with Dravet syndrome
- Remember that Dravet syndrome tends to be genetically homogeneous, with most patients having SCN1A mutations

Yan, et al. Seizure. 2018;60:144-8.

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Syndrome analysis provides larger #s

- What about Doose syndrome?
  - Wirrell et all, 2016 suggested that in 55% of cases, there is a 50% reduction of seizures with ketogenic diet.
  - Seizure freedom is achieved in 18% of cases when using ketogenic diet to treat myoclonic-atonic epilepsy.

Wirrell. Continuum (Minneap Minn). 2016;22:60-93.

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Syndrome analysis provides larger #s

- What about Doose syndrome?
  - Nickels et al, 2021
  - 57% of patients (95/166) used diet with a 79% response rate

Nickels, et al. Epilepsia. 2021;62:120-7.

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What about metabolic disease?

- Seizures associated with a range of inborn errors of metabolism:
  - Succinic semialdehyde dehydrogenase deficiency
  - Pyruvate dehydrogenase complex deficiency
  - Nonketotic hyperglycinemia
  - ~~Fatty acid oxidation disorders~~
  - Urea cycle disorders

Gavrilovici, et al. J Inherit Metab Dis. 2021;44:42-53.; Scholl-Burgi, et al. J Inherit Metab Dis. 2015;38:765-73.; Shbarou, et al. Neuropediatrics. 2019;50:235-43.; Kava, et al. Eur J Clin Nutr. 2019;73:961-5.

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What about metabolic disease?

- Ketogenic diet has been used successfully, but response is highly variable.
- Contraindicated in fatty acid oxidation disorders
- Avoid catabolism!!

Scholl-Burgi, et al. J Inherit Metab Dis. 2015;38:765-73.; Shbarou, et al. Neuropediatrics. 2019;50:235-43.; Kava, et al. Eur J Clin Nutr. 2019;73:961-5.

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Primary Mitochondrial Disease

- Known or presumed genetic disorders caused by pathogenic variants in genes coding for the mitochondrial respiratory chain and related proteins
- Defect in respiratory chain, the essential final common pathway for aerobic metabolism

Chinnery PF. Primary Mitochondrial Disorders Overview. 2000 Jun 8 [Updated 2021 Jul 29]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1224/

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Primary Mitochondrial Disease

- Mitochondrial malate aspartate shuttle and pyruvate carrier system
  - MDH1, MDH2, GOT2, SLC25A12
    - Neurological/epileptic phenotype
  - SCL25A12
    - Citrine deficiency, complex hepatopathic-neuropsychiatric phenotype

Bölsterli, et al. Nutrients. 2022;14.

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Primary Mitochondrial Disease

- 40 patients with MAS-/-MPC1-defects
  - 13 treated with ketogenic diet
  - 11 significant seizure reduction
  - 6 citrine-deficient had normalization labs and liver enzymes

Bölsterli, et al. Nutrients. 2022;14.

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Primary Mitochondrial Disease

Systematic review on efficacy and safety of ketogenic diet for mitochondrial disease

- **Not enough data for general recommendations**
- May be considered in patients with MD and refractory epilepsy
- Contraindicated in mitochondrial DNA deletion(s) related myopathy
- Relatively high rate of adverse effects

Zweers, et al. Orphanet J Rare Dis. 2021;16:295.

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Why all the variability in response to diet with similar genetic differences?

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The Importance of Background

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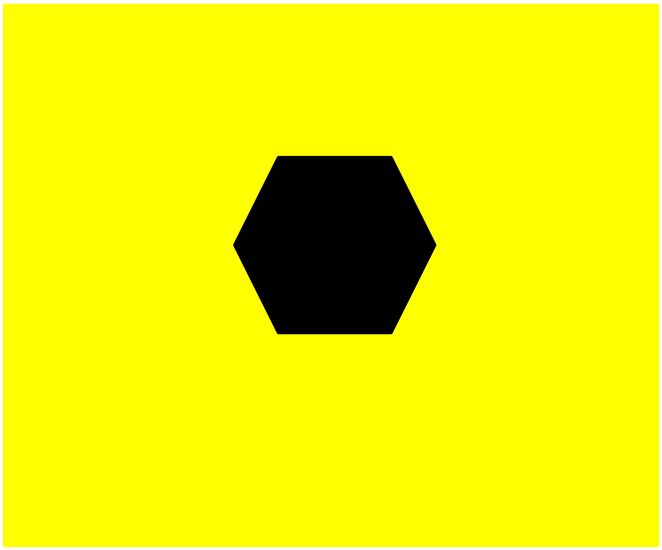
The Importance of Background



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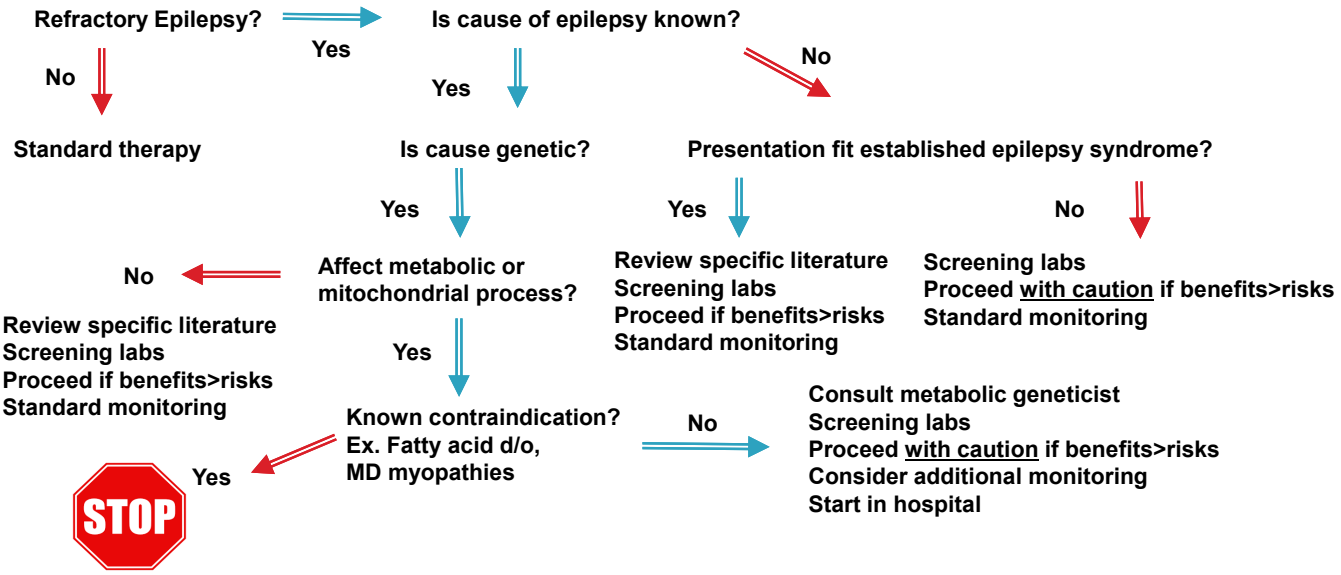
When to use Ketogenic Diet for Genetic Epilepsy



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Summary

1. Literature currently suggests specific benefits for PDH, STXBP1, ALG13, TSC, KCNT1, SCN2A, SCN1A – this will likely change rapidly as genetic understanding expands.
2. Outcomes related to seizure control are likely to be highly variable.
3. Unexpected side effects (hemolysis, necrotizing pancreatitis, rhabdomyolysis, death) may occur but are generally rare.
4. Close monitoring is crucial, especially in disorders involving mitochondrial dysfunction or other metabolic derangement, as these patients are more likely exhibit unusual effects.
5. Pre-start screening labs are always recommended.
6. Ketogenic diet is likely to be safe and well tolerated in most patients with genetic epilepsies.

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Questions?

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