Monthly Mito

EXPERT SERIES

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mito ACTION

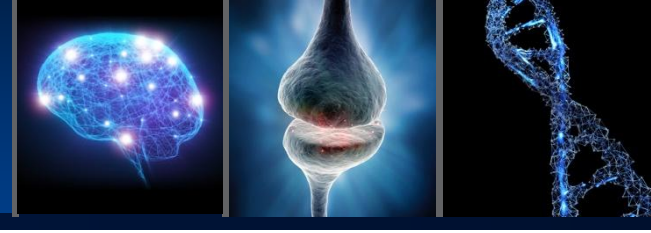
Friday, October 9th
12:00pm EST / 9:00am PST

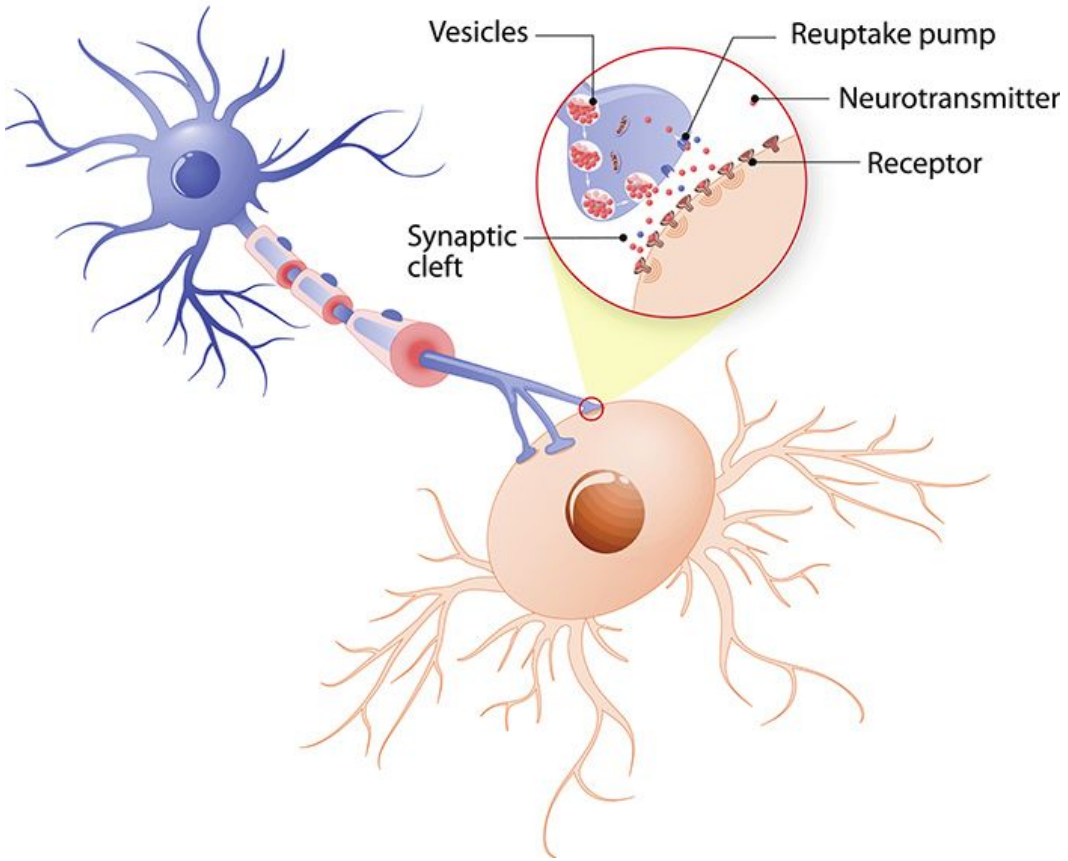
WELCOME

Overlap Between Mitochondrial Disorders and Disorders of Neurotransmitter Metabolism

Dr. Irina Anselm, M.D.
Director of the Mitochondrial Program
Co-Director of the Neurometabolic Program
Boston Children's Hospital

Neurotransmitters: Body's Chemical Messengers

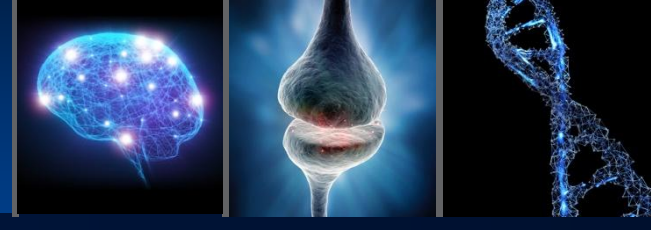


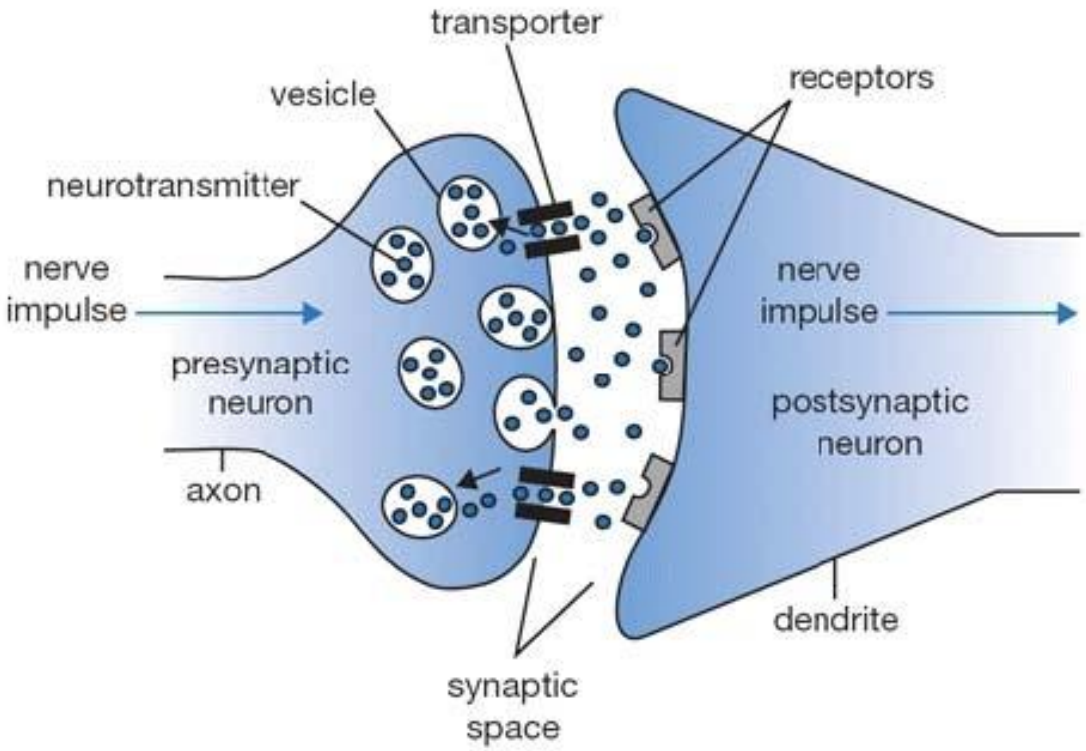


- Molecules used by the nervous system to transmit messages between neurons, or from neurons to muscles
- **Dopamine, serotonin, glutamate, GABA, acetylcholine** convey information from one neuron (message sender) to another "target" neuron (message recipient)

https://qbi.uq.edu.au/brain/brain-physiology/what-are-neurotransmitters

Neurotransmitters: Body's Chemical Messengers

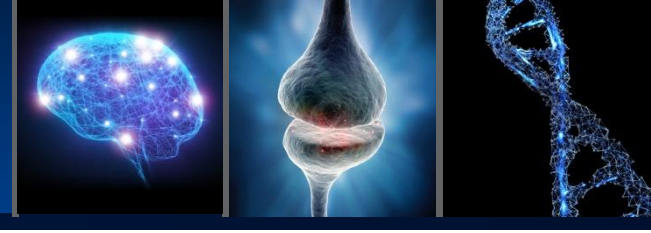


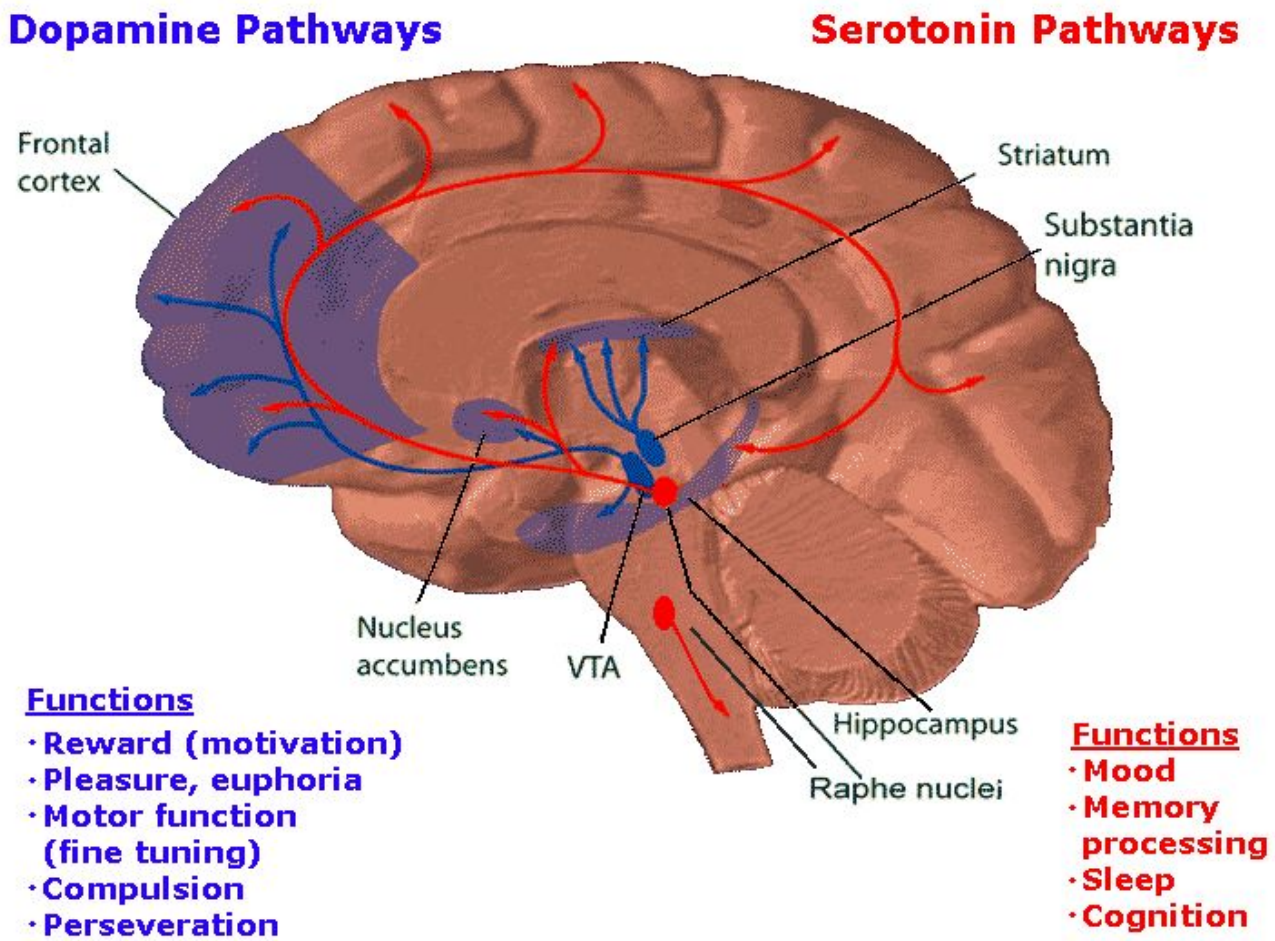


- Molecules used by the nervous system to transmit messages between neurons, or from neurons to muscles
- **Dopamine, serotonin, glutamate, GABA, acetylcholine** convey information from one neuron (message sender) to another "target" neuron (message recipient)
- The small space between the two is called a synapse
- Communication between two neurons happens in the synaptic cleft

https://www.google.com/search?q=neurotransmitters

Dopamine and Serotonin

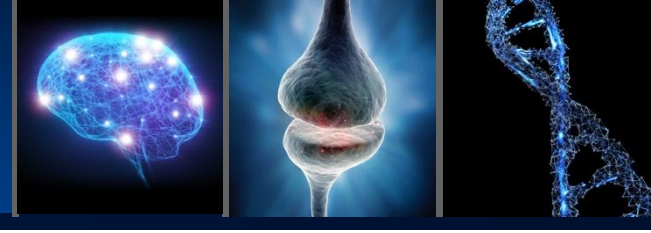


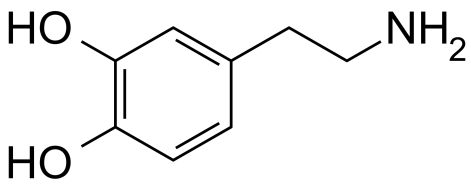


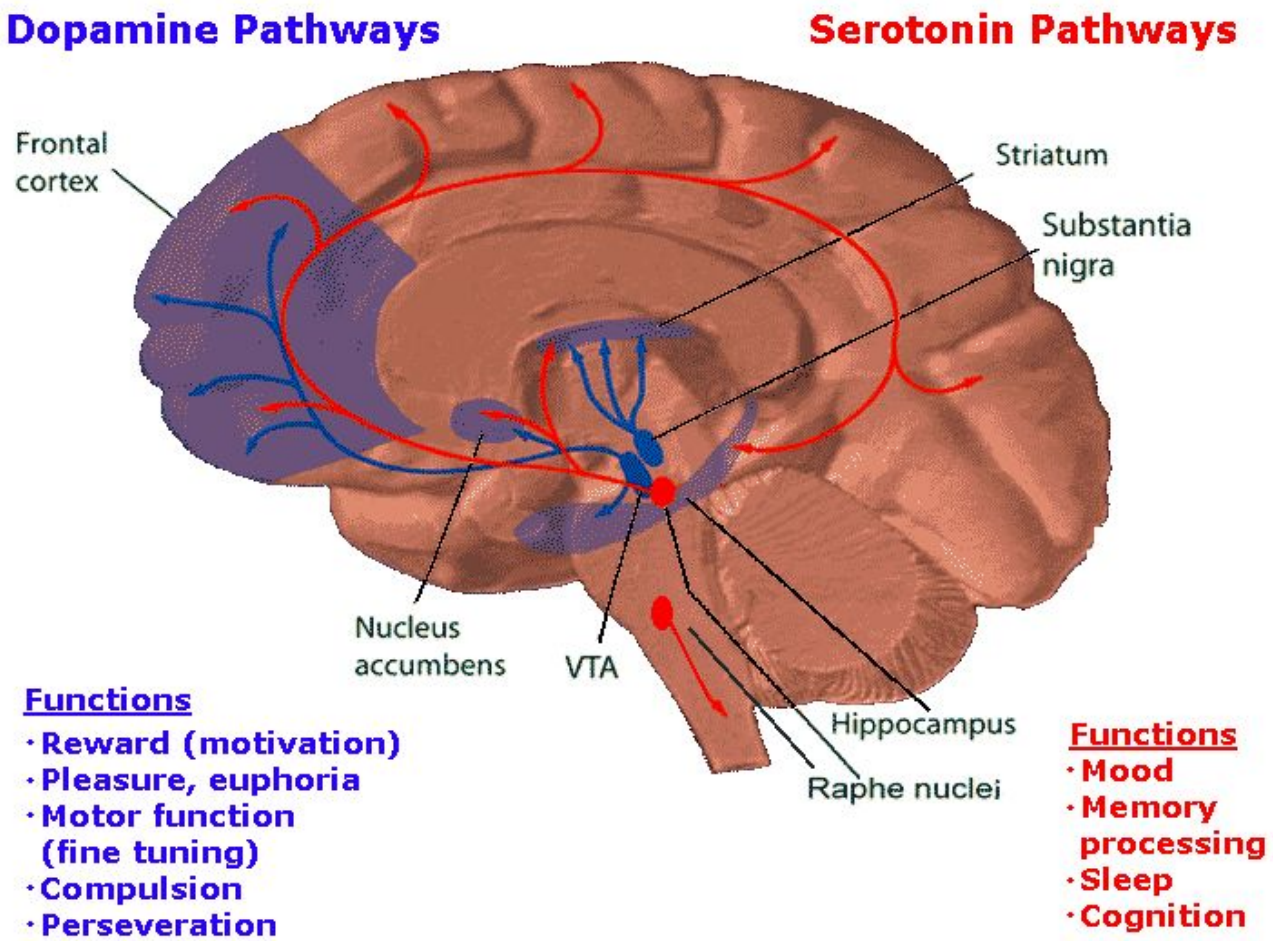
Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

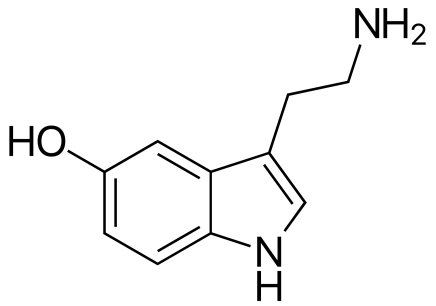
Functions
- Mood
- Memory processing
- Sleep
- Cognition

Dopamine and Serotonin









Functions
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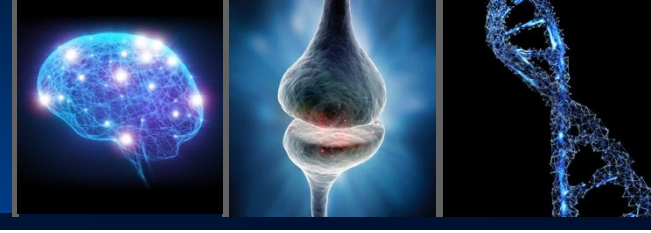
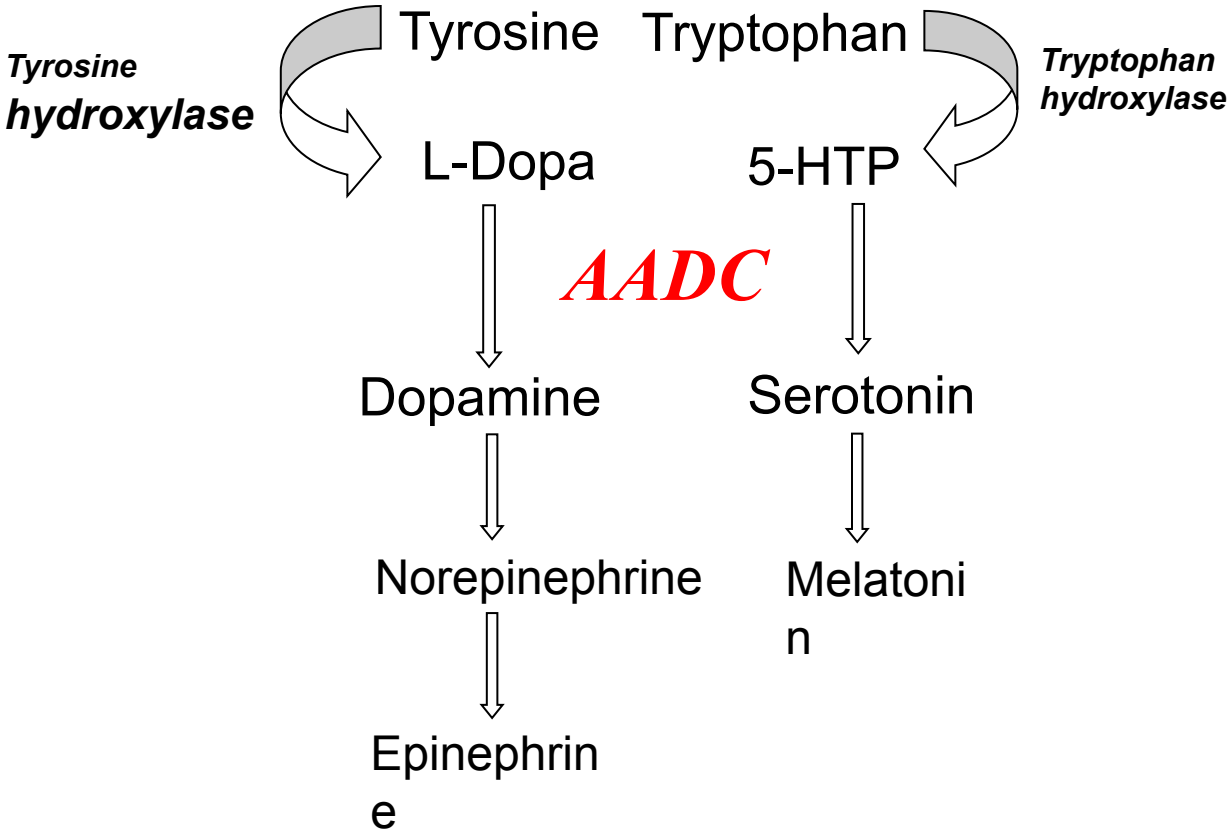
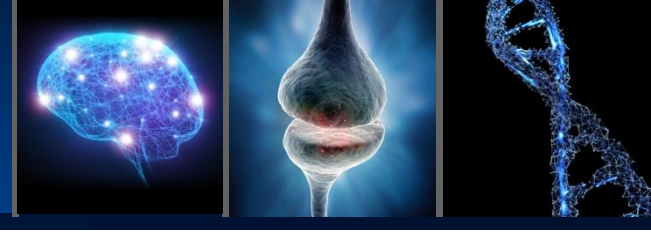
Aromatic Amino Acid Decarboxylase (AADC) Deficiency

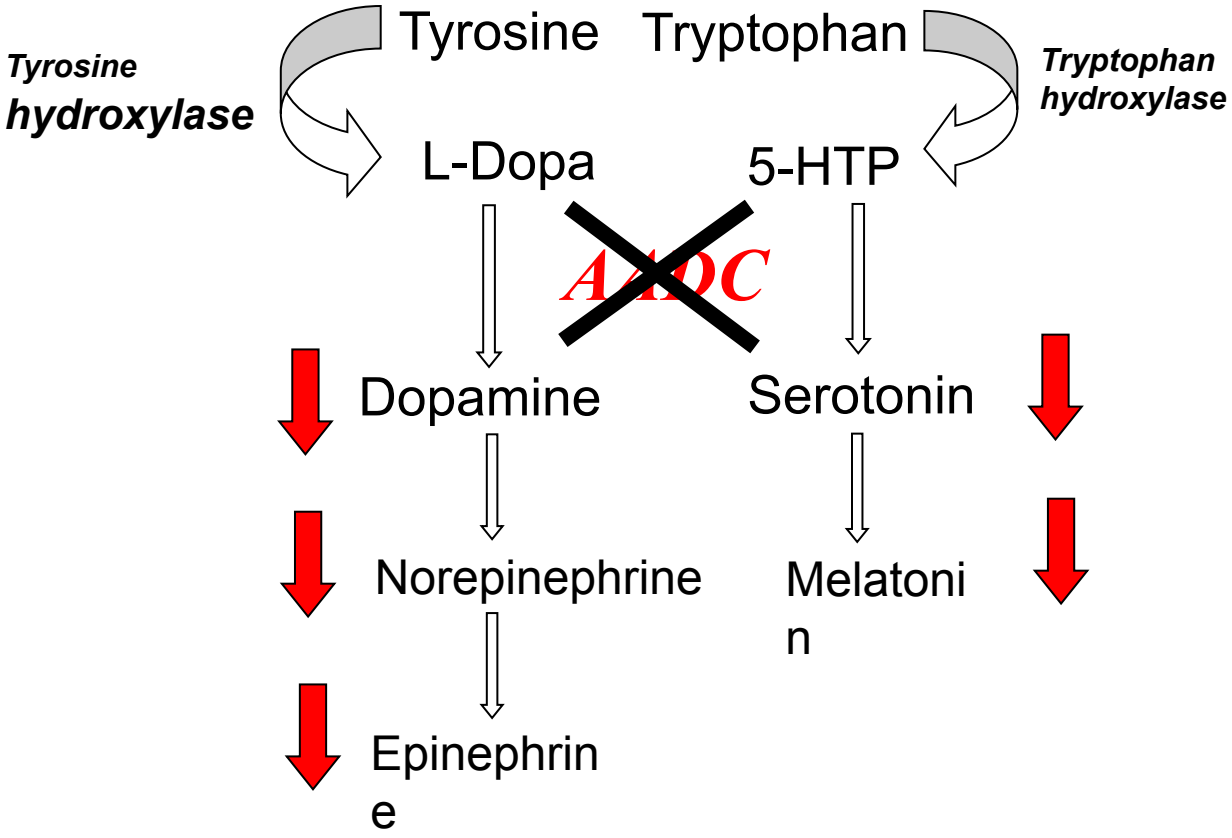




Courtesy of K. Hyland

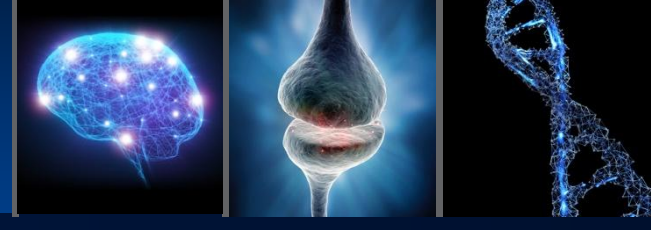
Effect of AADC Deficiency on Dopamine, Serotonin, Epinephrine, and Norepinephrine Metabolism

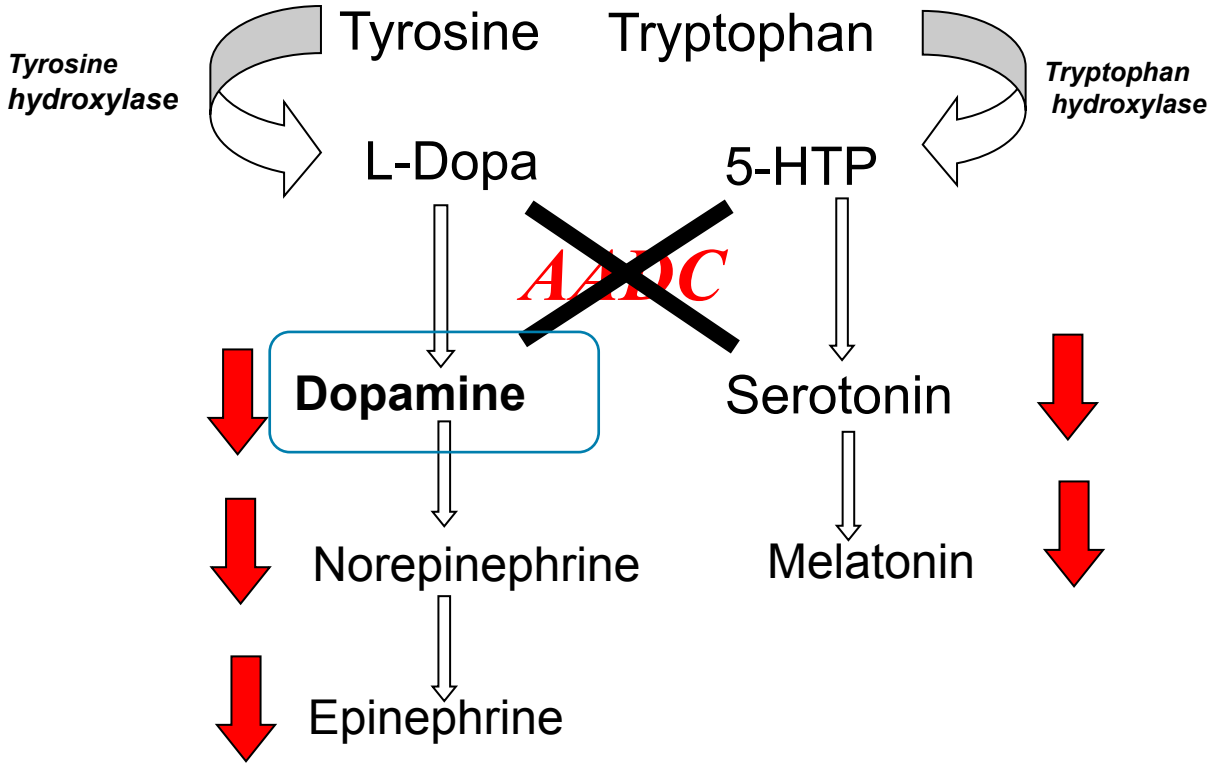




Courtesy of K. Hyland

Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism





Axial hypotonia
Limb hypertonia

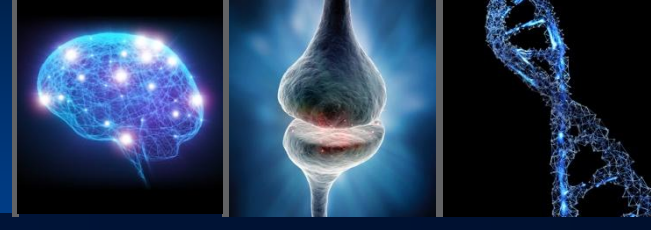
Movement disorders

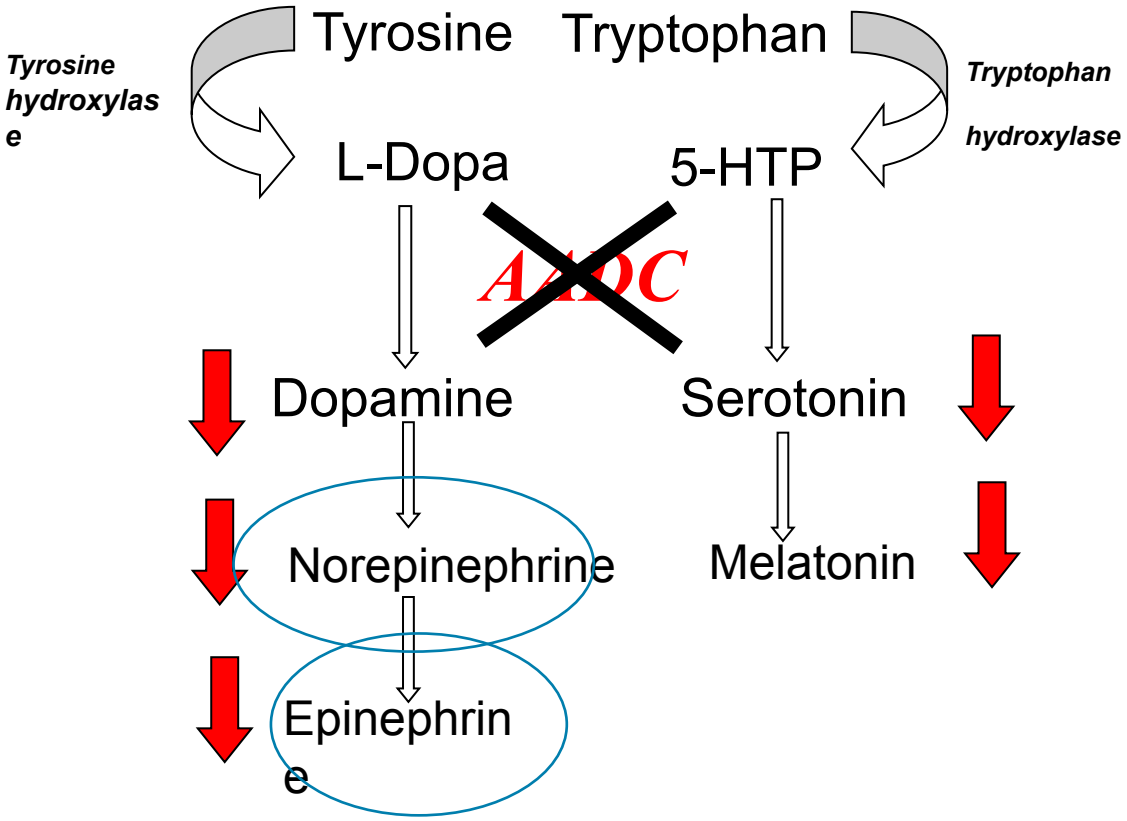
- Dystonia
- Rigidity
- Hypokinesia
- Tremor
- Parkinsonism

Oculogyric crises

Courtesy of K. Hyland

Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism





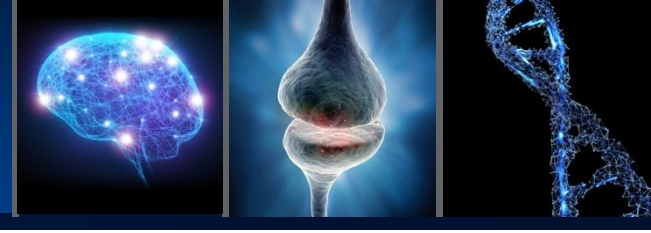
Courtesy of K. Hyland

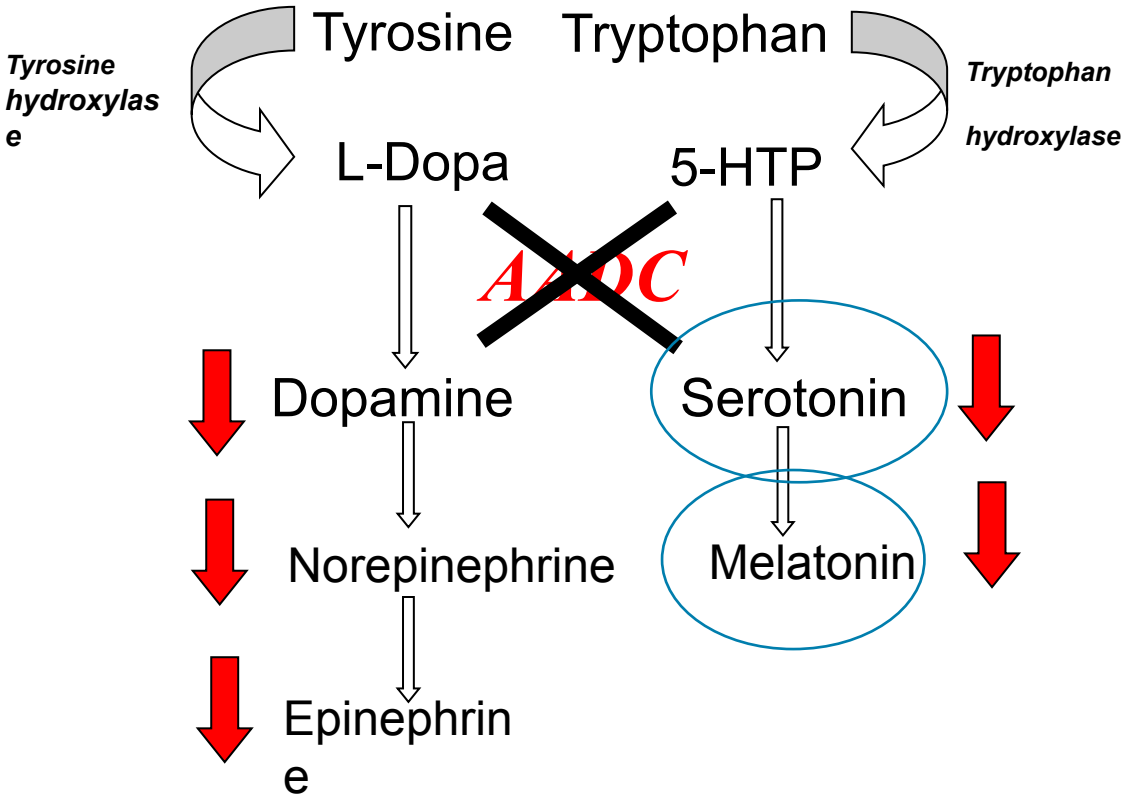
Autonomic instability:

Ptosis, frequently severe
Excessive sweating
Nasal congestion

Arterial hypotension, bradycardia
Temperature instability, especially hypothermia

Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism





Courtesy of K. Hyland

Autonomic instability:

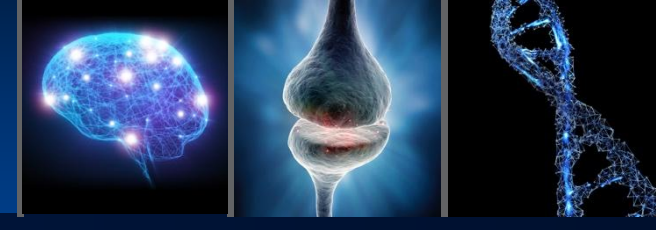
Ptosis, frequently severe
Excessive sweating
Nasal congestion

Arterial hypotension
Temperature instability, especially hypothermia

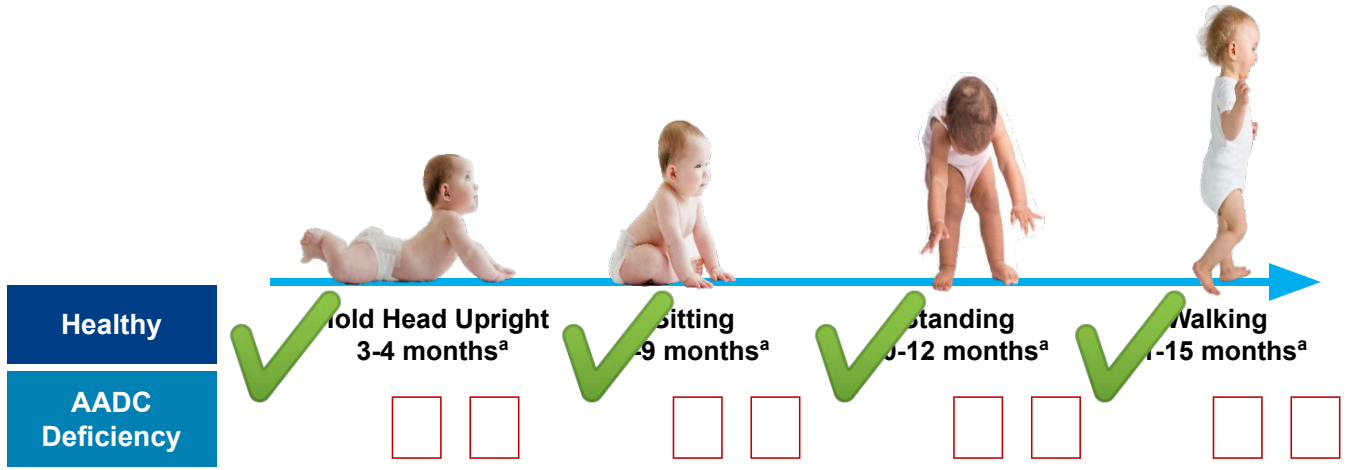
Mood instability, irritability

Sleep problems

Key Symptoms of AADC Deficiency



- Patients with AADC deficiency present very early
- Symptoms start in the first months of life, yet many of them are not diagnosed until much later
- One of the key symptoms of AADC deficiency is developmental delay
- Most children do not reach any motor milestones

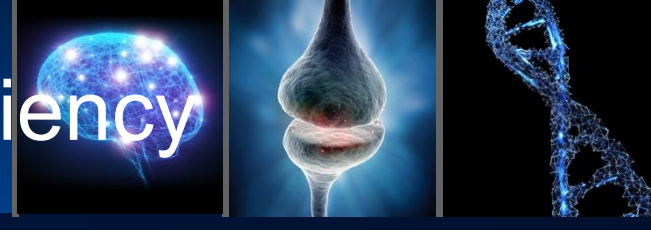


[a]Based on Denver II Developmental Milestone chart.

Wassenberg T, et al. *Orphanet J Rare Dis.* 2017; 12(1):12.

1. Hwu WL, et al. *JIMD Rep.* 2018;40:1-6.
2. Hwu WL, et al. *Sci Transl Med.* 2012;4(134):134ra161.

Diagnostic Odyssey of patients with AADC deficiency

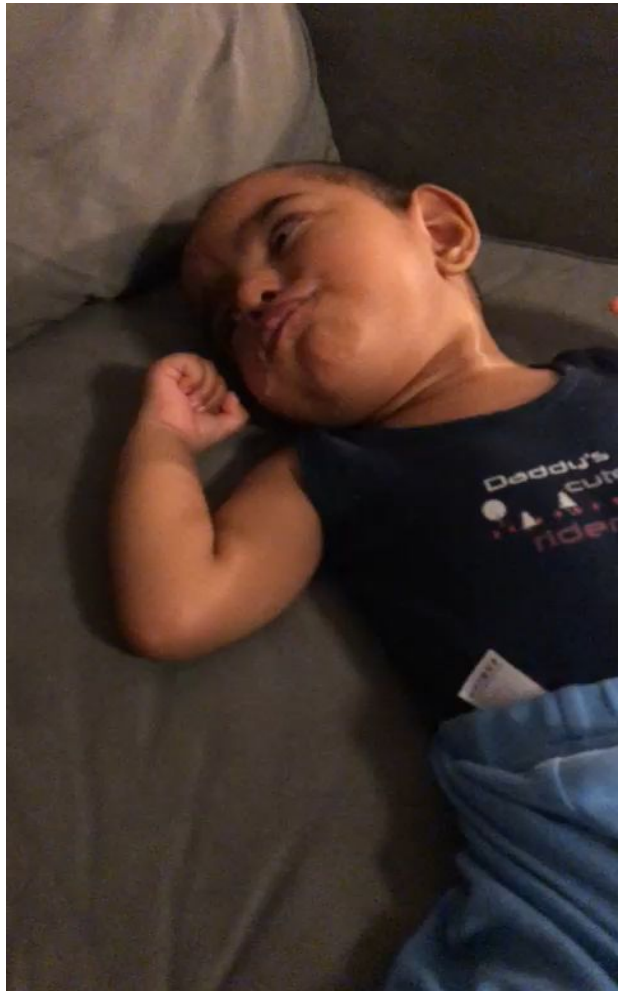


4 old boy from Saudi Arabia

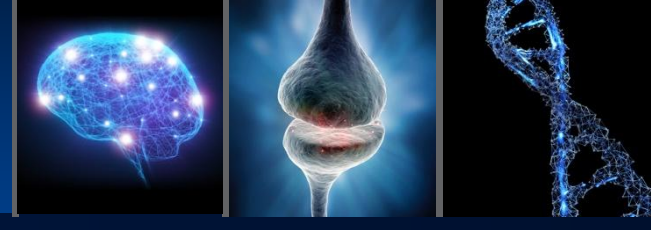
At 6 weeks of age --- episodes suggestive of seizures --- noted to be **hypoglycemic**

At 7 months --- tonic episodes with eye deviation that were felt to be **seizures**. Treated with antiepileptics

At 9 months, evaluation for **disorders of glucose metabolism**



Diagnostic Odyssey



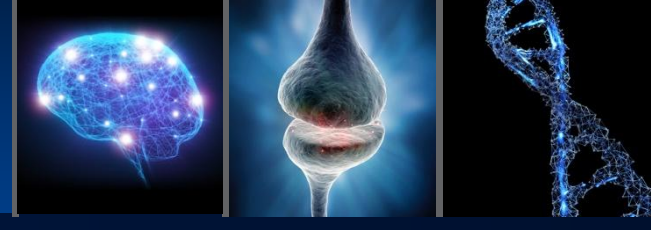
Several admissions with video EEG telemetry: episodes are not seizures

Episodes appear to represent dystonia in combination with oculogyric crises

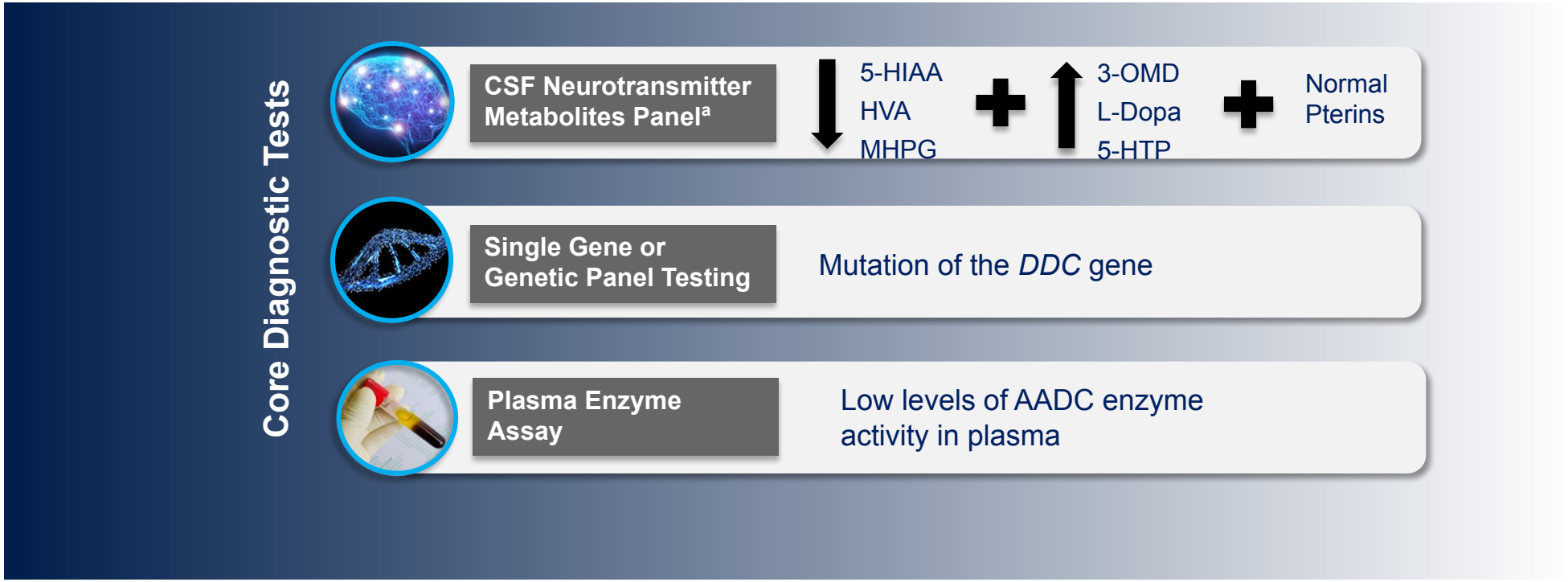
Exome sequencing revealed homozygous mutation in *DDC* gene

Neurotransmitter metabolite testing on CSF consistent with AADC deficiency

Consensus Guidelines Recommendation: Core Diagnostic Test to Confirm AADC Deficiency



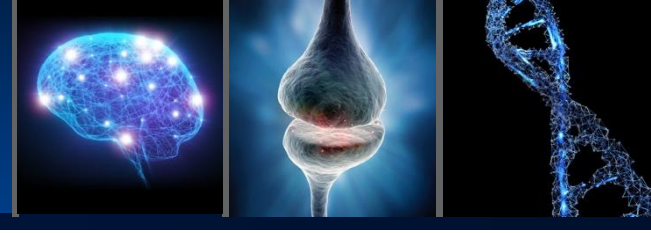
2 out of 3 core diagnostic tests should be positive to confirm AADC deficiency:

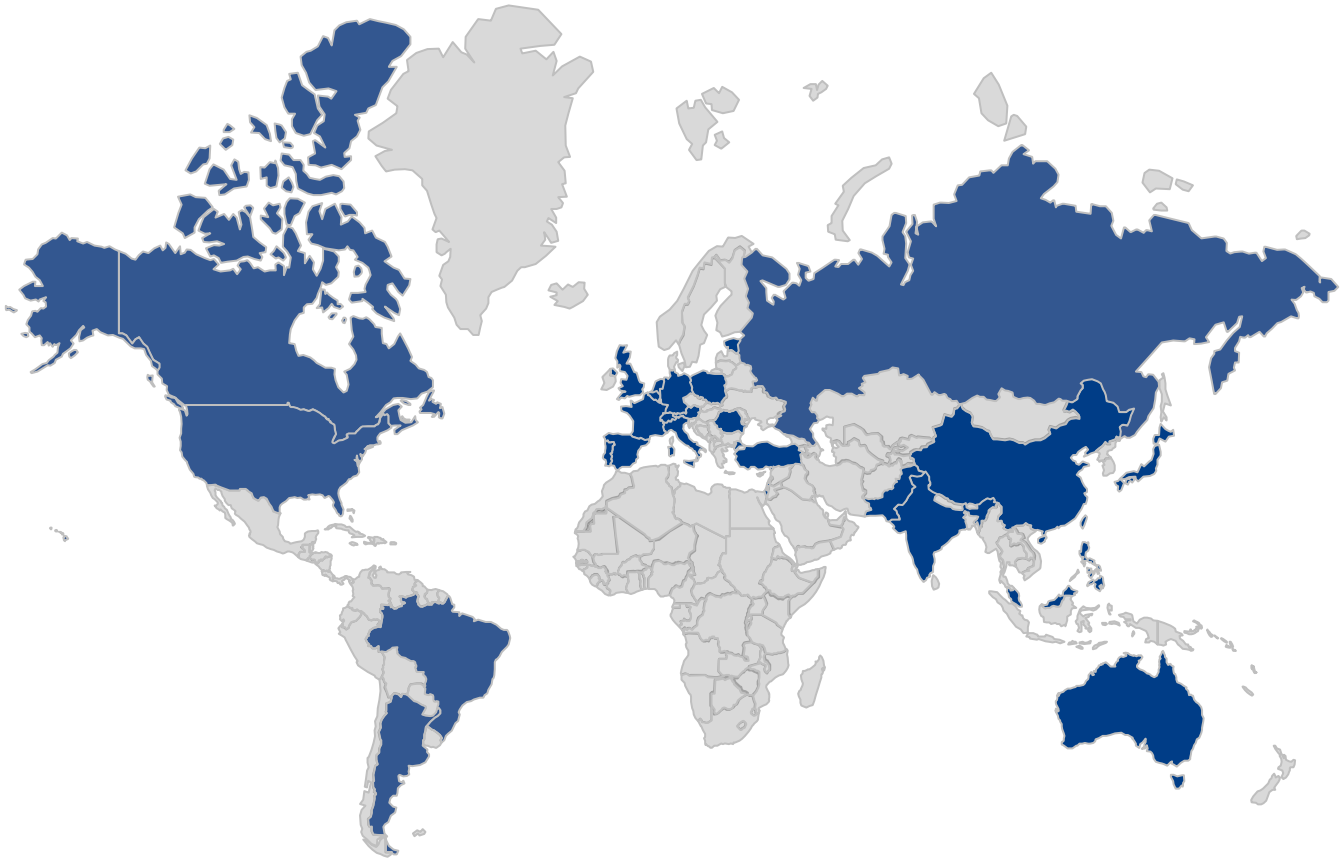


MHPG, 3-methoxy-4-hydroxyphenylglycol.
[a]The appendix includes the pathway for production and metabolism for serotonin, dopamine, and other catecholamines.

Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12.

AADC Deficiency Has Been Documented Worldwide





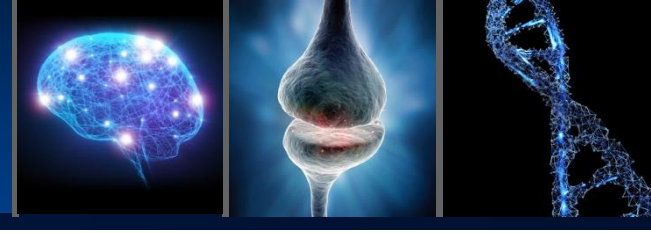
AADC deficiency can affect patients of varying populations[3]:

- Asian
- Caucasian
- Arabic
- Iranian
- Jewish

Disease first described in 1990
More prevalent in Asian population

1. JAKEdb website. http://www.biopku.org/jake/jake_start.asp. Accessed January 31, 2018.
2. Data on File. Agilis Biotherapeutics. 2018.
3. Wassenberg T, et al. *Orphanet J Rare Dis*. 2017;12(1):12.

Prevalence of AADC deficiency



- **Predicted birth rates**
  - US 1/42,000 - 1/90,000
  - EU 1/118,000
  - Japan 1/182,000
- **Prevalence**
  - Worldwide ~ 1800
  - US 840
  - EU 853
  - Japan 125

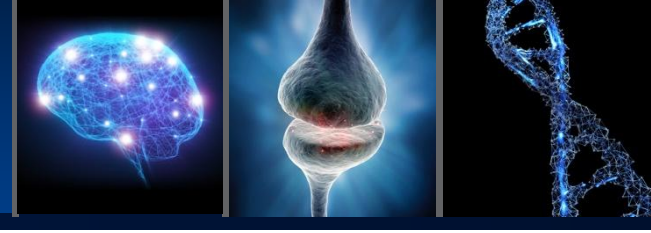
Mean age of symptom onset **2.7 months**

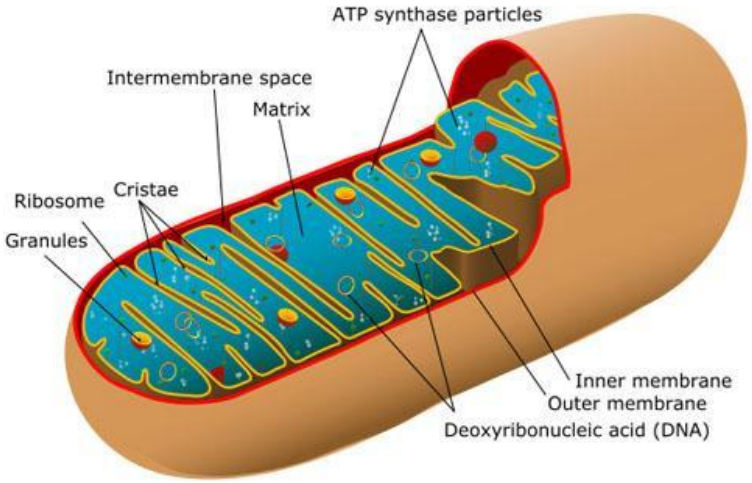
Mean age at diagnosis **3.5 years**

(median 13 months; range: 2 months–23 years)

Himmelreich N, et al. *Mol Genet Metab.* 2019 May;127(1):12-22.

Mitochondrial Disorders





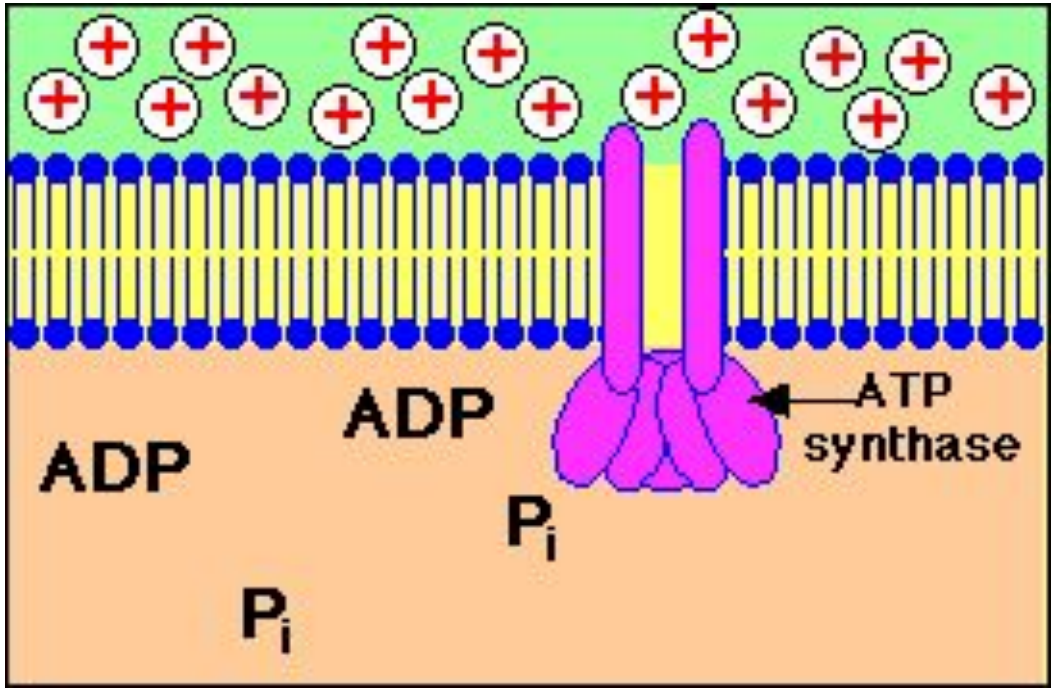
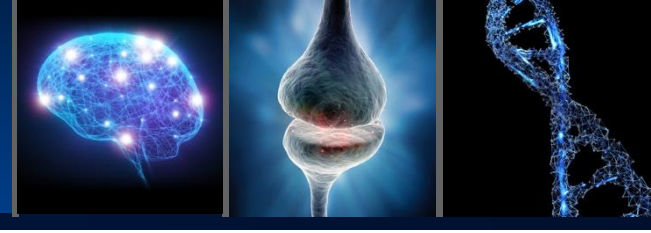


Image by Mariana Ruiz Villarreal

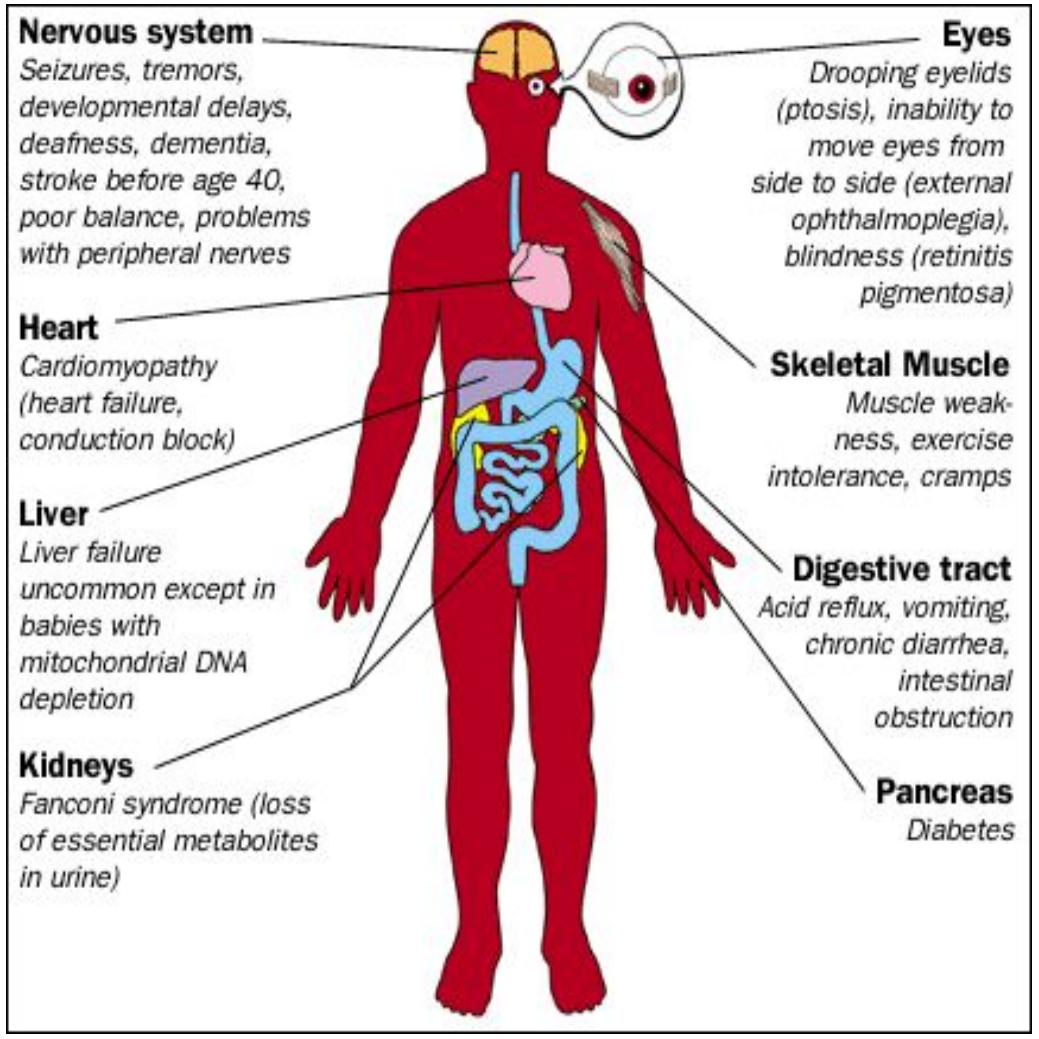
http://cmapspublic.ihmc.us/rid=1102536487930_333741980_4083/ATPanim.gif

http://www.mammag.uci.edu/foswiki/bin/view/MAMMAG/PhilosophicalPremiseOfMAMMAG

Mitochondrial Disorders

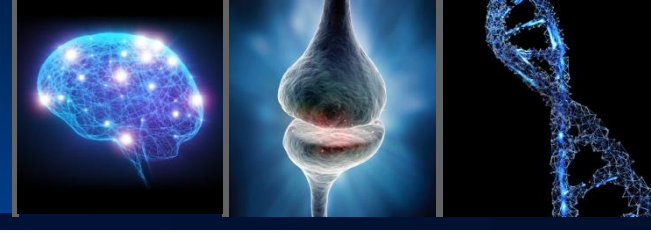


- Arise as a result of dysfunction of the mitochondrial respiratory chain
- Disorders impacting the structure or function of the mitochondria
- Tissues and organs that are highly dependent on aerobic metabolism are affected the most



Source: Mitochondria Research Society

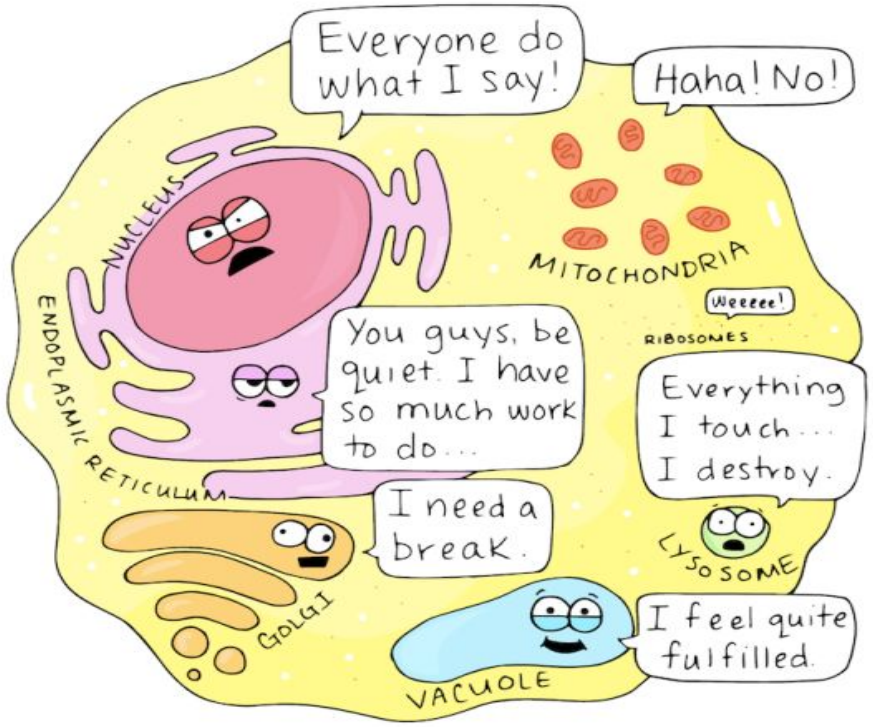
Mitochondrial Disorders



"Any symptom, any organ, any age, any mode of inheritance"

- Munnich & Rustin (Am.J.Med.Genet. 2001, 106:4-17)

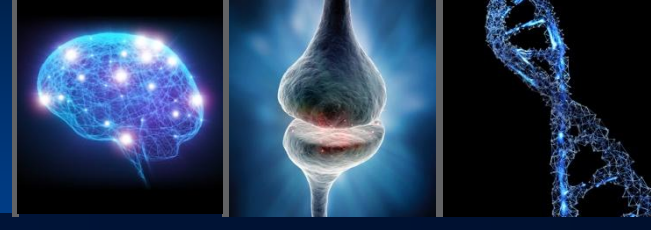
- Hundreds of different diseases
- Different combination of symptoms
- Many genes causing the same disease
- The same gene can cause many different types of MDs
- Neurological symptoms are very common, especially in children with MDs

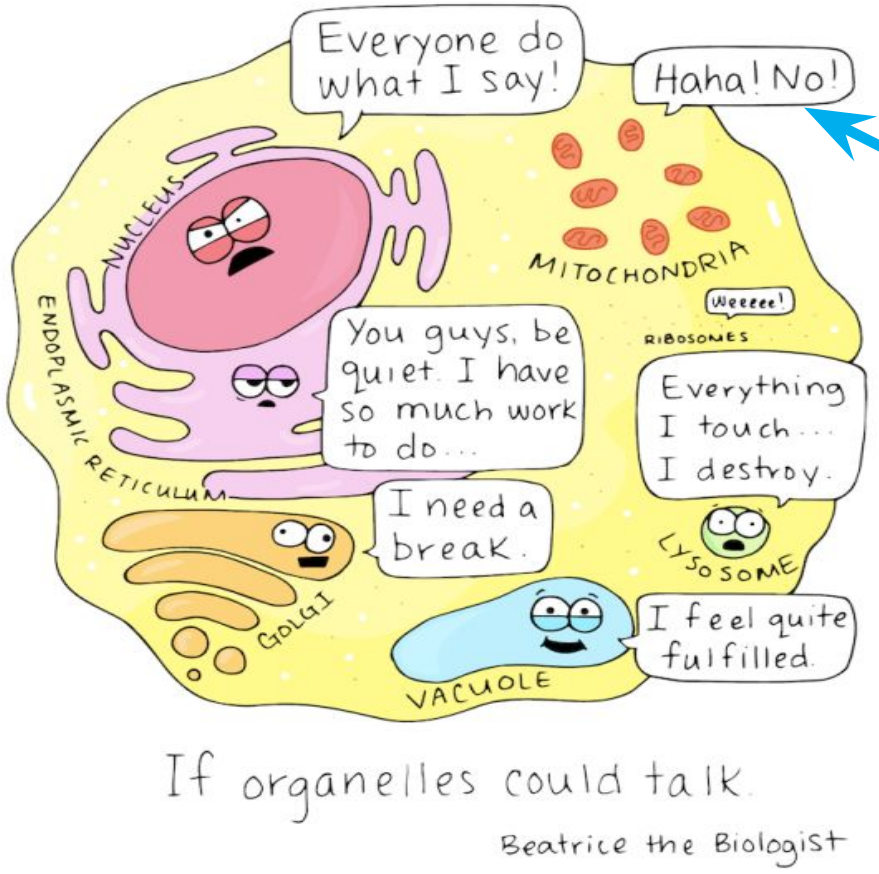


If organelles could talk.

Beatrice the Biologist

"If organelles could talk," available at: www.beatricebiologist.com





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Incorrect!

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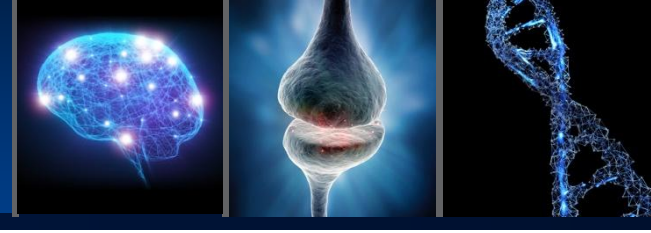
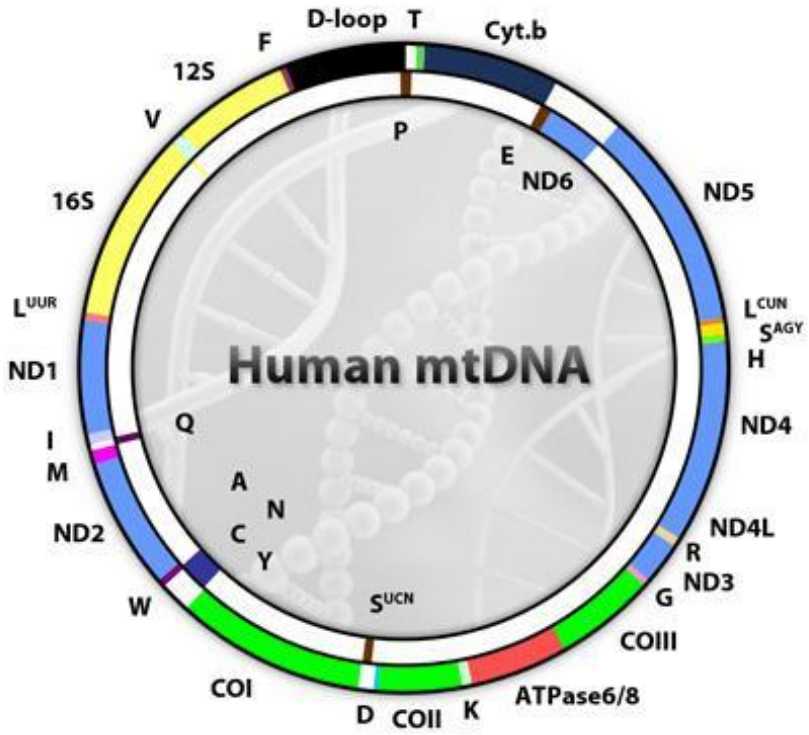
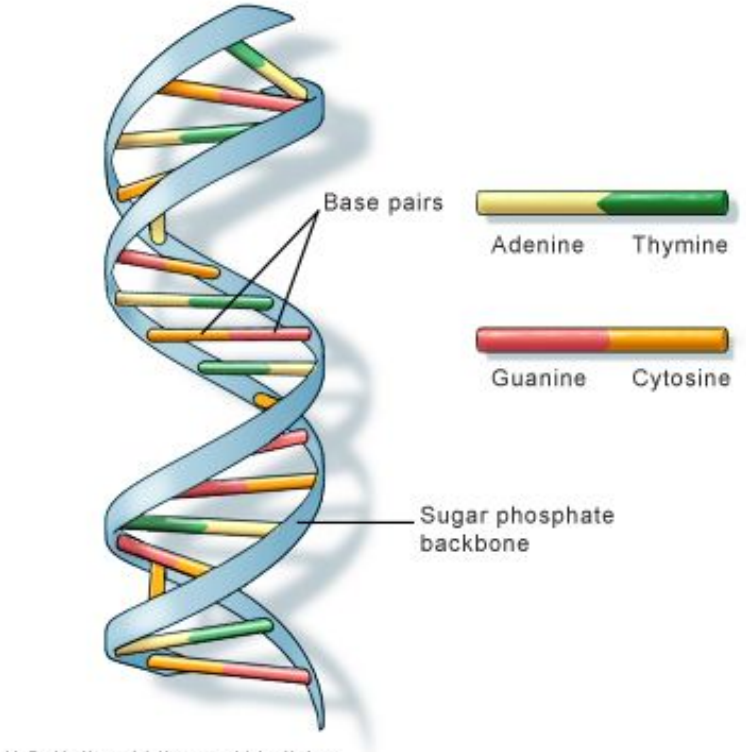
Prevalence of Mitochondrial Disorders



- At least 1 in 4,300 of adults will develop mitochondrial disease

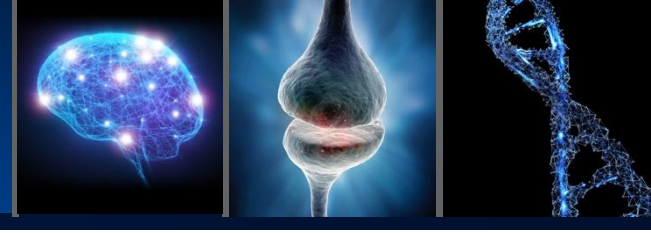


Source: The Mariani Foundation Center for the Study of Pediatric Mitochondrial Diseases, hosted by the Molecular Neurogenetics Unit of the IRCCS Foundation Neurological Institute "C. Besta" at Bicocca http://www.mitopedia.org/eng/img/mitocondri2_z.jpg



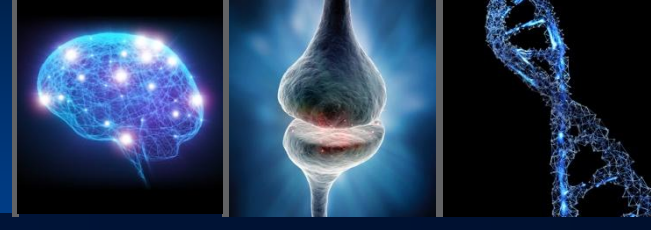
Source: U.S. National Library of Medicine

Why are patients with disorders of NT metabolism diagnosed with MDs?



- Many common features
- Lack of awareness
- Problems with obtaining genetic testing

Common Features



Disorders of NT metabolism

- developmental delay
- abnormal muscle tone
- dysautonomia
- oculogyric crises can look like seizures
- difficult to diagnose

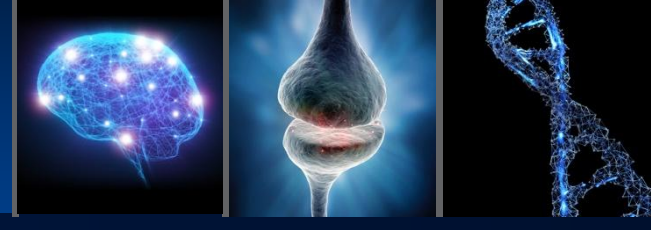
- Present early
- No newborn screening at the moment, but it is possible

Mitochondrial Disorders

- developmental delay
- abnormal muscle tone
- dysautonomia
- seizures
- difficult to diagnose

- Can present early
- No newborn screening, hardly possible

Differences



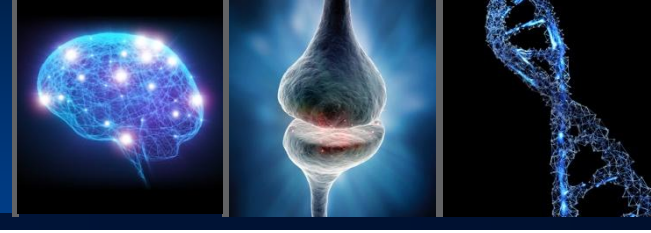
Disorders of NT metabolism

- Affect primarily CNS
- Diagnosis can be made by metabolic CSF analysis
- Brain MRI normal or nonspecific
- Metabolically stable
- Can be diagnosed by gene panels

Mitochondrial disorders

- Affect multiple organs
- Metabolic screening can suggest, but is never fully diagnostic of a MD
- Brain MRI frequently abnormal, esp. in children, but can be normal
- Metabolically unstable
- Can be diagnosed by gene panels, but frequently requires whole exome sequencing and mtDNA sequencing

PTC PINPOINT:
No-Charge Neurotransmitter Disorders Gene Panel



PTC PINPOINT™

Invitae and PTC Therapeutics have partnered to offer the PTC Pinpoint sponsored testing program, which provides no-charge genetic testing and counseling for individuals in the US suspected of having a neurotransmitter disorder such as AADC deficiency.

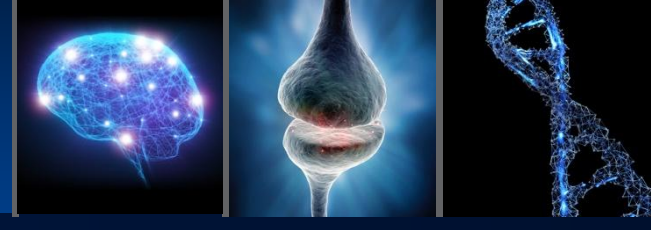
The panel analyzes up to 37 genes that are associated with disorders of monoamine metabolism, GABA metabolism, and neurotransmitter receptors and transporters utilizing either blood or saliva samples.

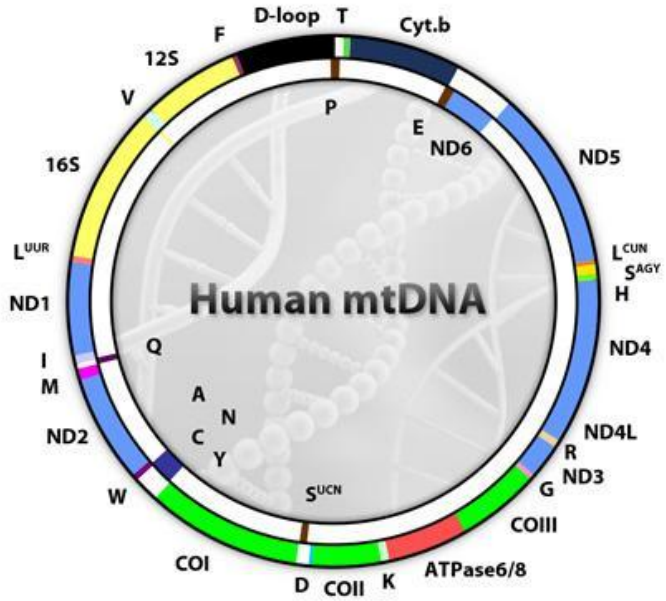
Individuals tested through the PTC Pinpoint Program are eligible for no charge post-test genetic counseling to help interpret their test results.

No age limit as to whom can be tested.

www.invitae.com/PTC-pinpoint

Diagnosis of Mitochondrial Disorders

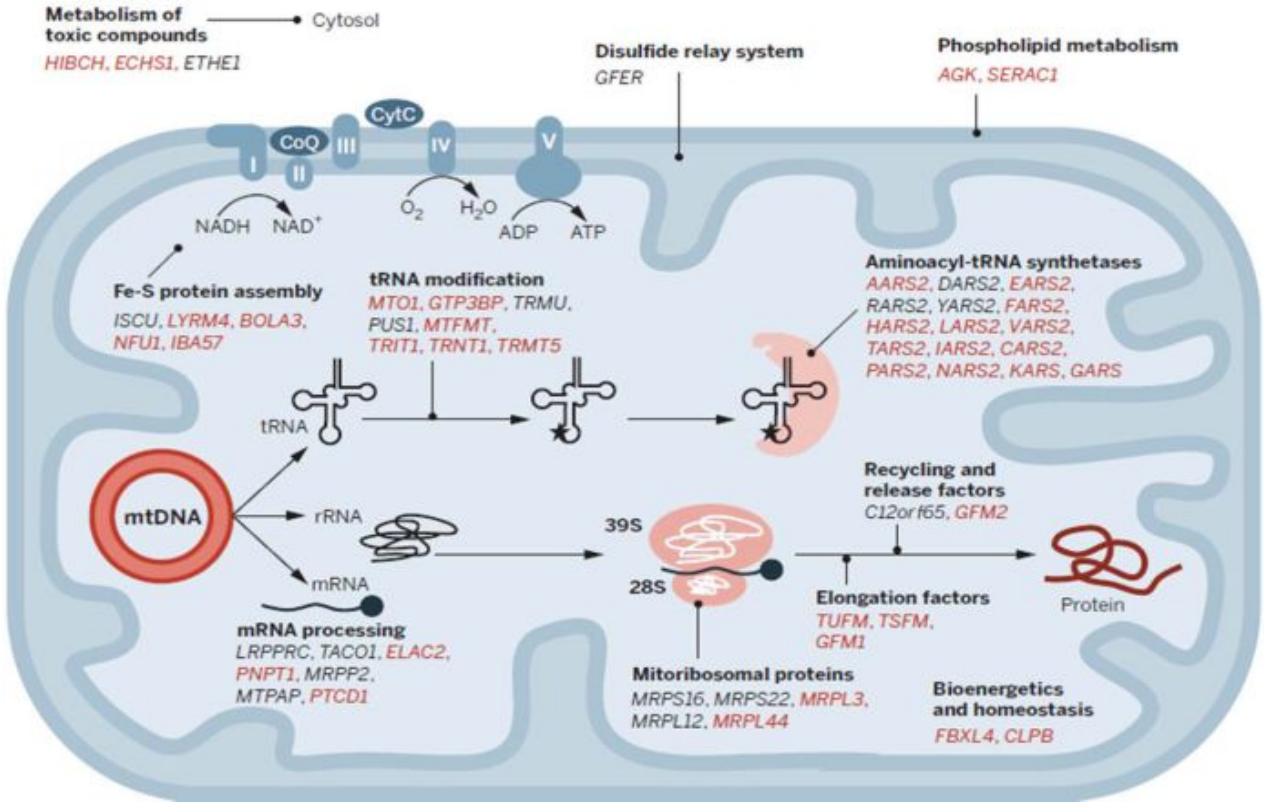




Sequence analysis of the entire mitochondrial genome with quantification of heteroplasmy levels

Detection of deletions with breakpoints and heteroplasmy

Around 1400+ nuclear genes are involved in proper mitochondrial function

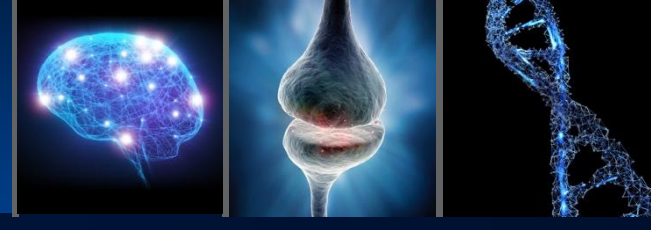


Next generation (NGS) panels (up to 1100 genes)

Whole genome (exome) sequencing

Science, VOL 349 ISSUE 6255

Therapies



Disorders of NT metabolism

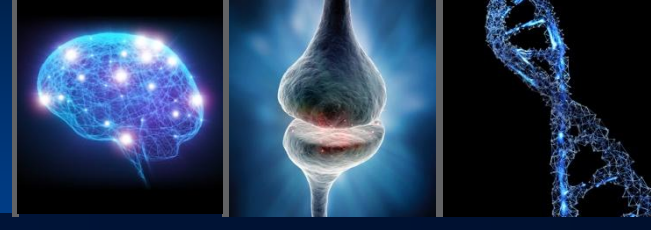
- Specific treatments: Dopamine and serotonin agonists, Melatonin
- Gene therapy for AADC is available

Mitochondrial disorders

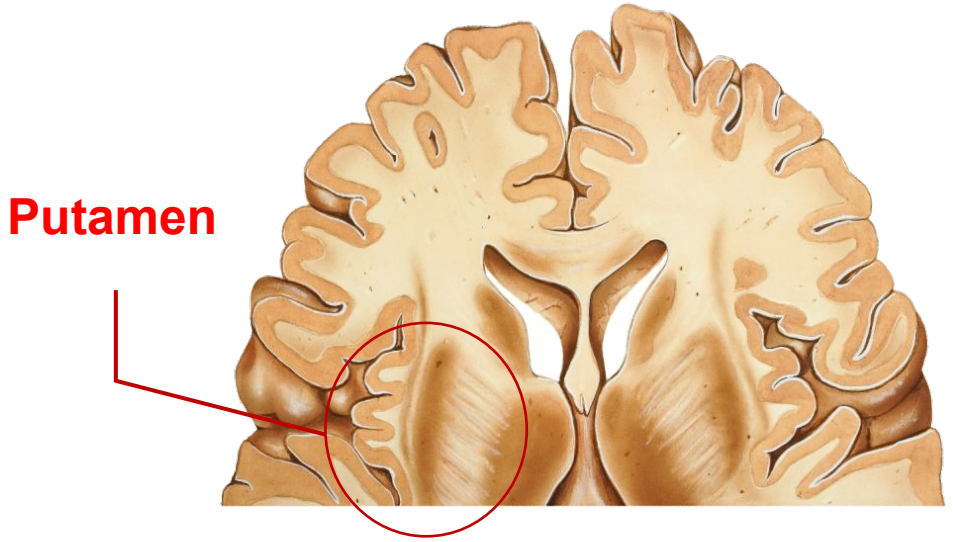
- No specific therapies with rare exceptions
- Gene therapies not available

Treatment of AADC Deficiency

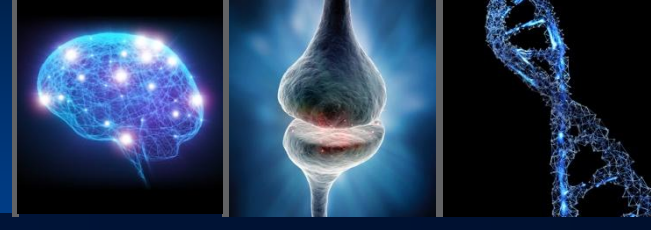
There is hope for AADC deficiency!



Several companies around the world developed gene therapy in which virus carrying the deficient enzyme (aromatic amino acid decarboxylase) is injected directly in the brain



Summary



- Disorders of Neurotransmitter Metabolism and Mitochondrial Disorders are underdiagnosed, but diagnosis of NTs is less complicated.

- In spite of being very different conditions, they may have similar clinical presentations.

- Gene therapy is on the horizon for NTs, but not yet for MDs.

Thank you for your attention