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Vitamins, Variants, Vegemite, and the State of VACTERL/VATER Research

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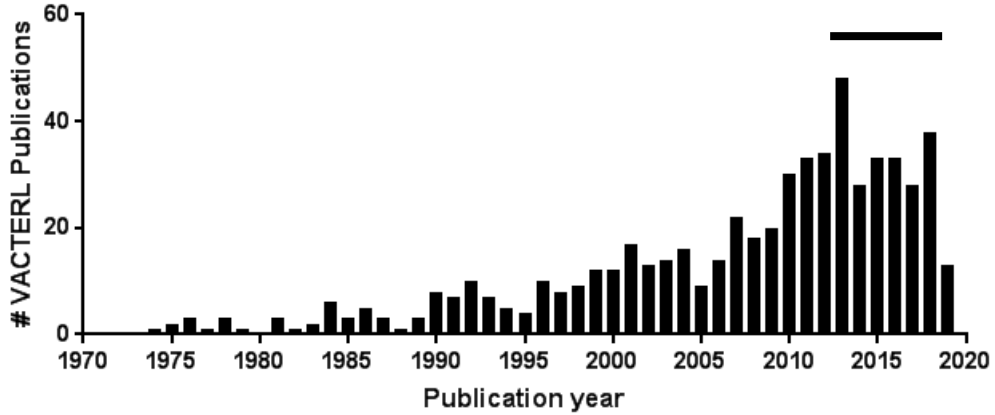
MSP-->PHL or bust! Excited to present my talk 'Vitamins, Variants, Vegemite, and the State of VACTERL/VATER Research' at The #VACTERL Network meeting this weekend. #scicomm #rarediseaseresearch

Agenda

- The state of peer-reviewed literature: What's been published since 2013?
- Tools for identifying funded-research, clinical trials, and scientific literature
- How VACTERL Association became a focus at Mayo Clinic
- On-going studies of VACTERL families at Mayo Clinic

State of VACTERL/VATER Research

- Since 2013, **212** papers published
  - ✓ **26** review articles
  - ✓ **1** meta-analysis
  - ✓ **1** clinical study
  - ✓ **0** clinical trials
  - ✓ **153** humans studies
    - Surgical interventions
    - Diagnostics
    - Case studies
  - ✓ **22** animal studies
    - Embryogenesis
  - ✓ **15** federally-funded
  - ✓ **31** non-federally funded



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1. The **VACTERL** association: mosaic mitotic aneuploidy as a cause and a model.
   Lubinsky M.
   J Assist Reprod Genet. 2019 May 25. doi: 10.1007/s10815-019-01485-y. [Epub ahead of print] Review.
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4. Embryonic hypocellularity, blastogenetic malformations, and fetal growth restriction.
   Lubinsky M.
   Am J Med Genet A. 2017 Jan;173(1):151-156. doi: 10.1002/ajmg.a.37985. Epub 2016 Sep 22. Review.
   PMID: 27717162
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5. Sonic Hedgehog, **VACTERL**, and Fanconi anemia: Pathogenetic connections and therapeutic implications.
   Lubinsky M.
   Am J Med Genet A. 2015 Nov;167A(11):2594-8. doi: 10.1002/ajmg.a.37257. Epub 2015 Jul 21. Review.
   PMID: 26198446
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6. Blastogenetic associations: General considerations.
   Lubinsky M.
   Am J Med Genet A. 2015 Nov;167A(11):2589-93. doi: 10.1002/ajmg.a.37239. Epub 2015 Jul 14.
   PMID: 26174333
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7. The **VACTERL** Association as a disturbance of cell fate determination.
   Lubinsky M.
   Am J Med Genet A. 2015 Nov;167A(11):2582-8. doi: 10.1002/ajmg.a.37238. Epub 2015 Jul 14. Review.
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Spotlight
NIH Categorical Spending (RCDC) for FY2018 now available, highlighting the annual support level for various research, condition, and disease categories based on grants, contracts, and other funding mechanisms used across the National Institutes of Health (NIH), linked to disease burden data published by the National Center for Health Statistics (NCHS) at the Centers for Disease Control & Prevention (CDC).
NIH Inclusion Data by Research and Disease Category Now Available
For over two decades, NIH has required researchers to include women, members of racial and ethnic minority groups, and children in their work absent an acceptable scientific or ethical rationale for their exclusion. Now, for the first time, selected inclusion data on sex/gender and race/ethnicity are publicly available disaggregated for various research, condition, and disease areas. Read announcement
Federal RePORTER allows the public to search for funding information from several research funders, including NIH, USDA, NSF, NASA, EPA, HHS, DOD, VA, and more.
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Organization:
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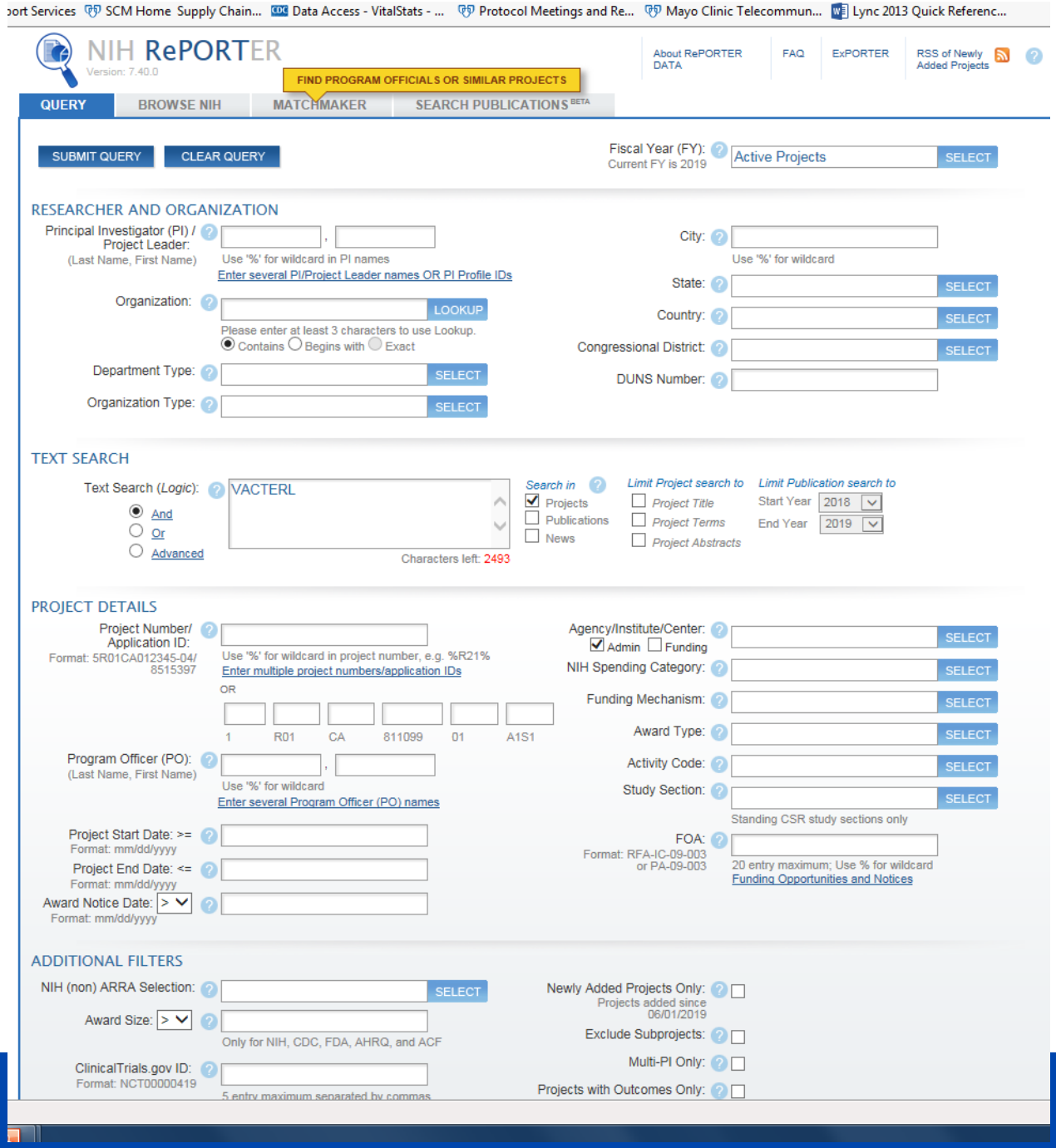
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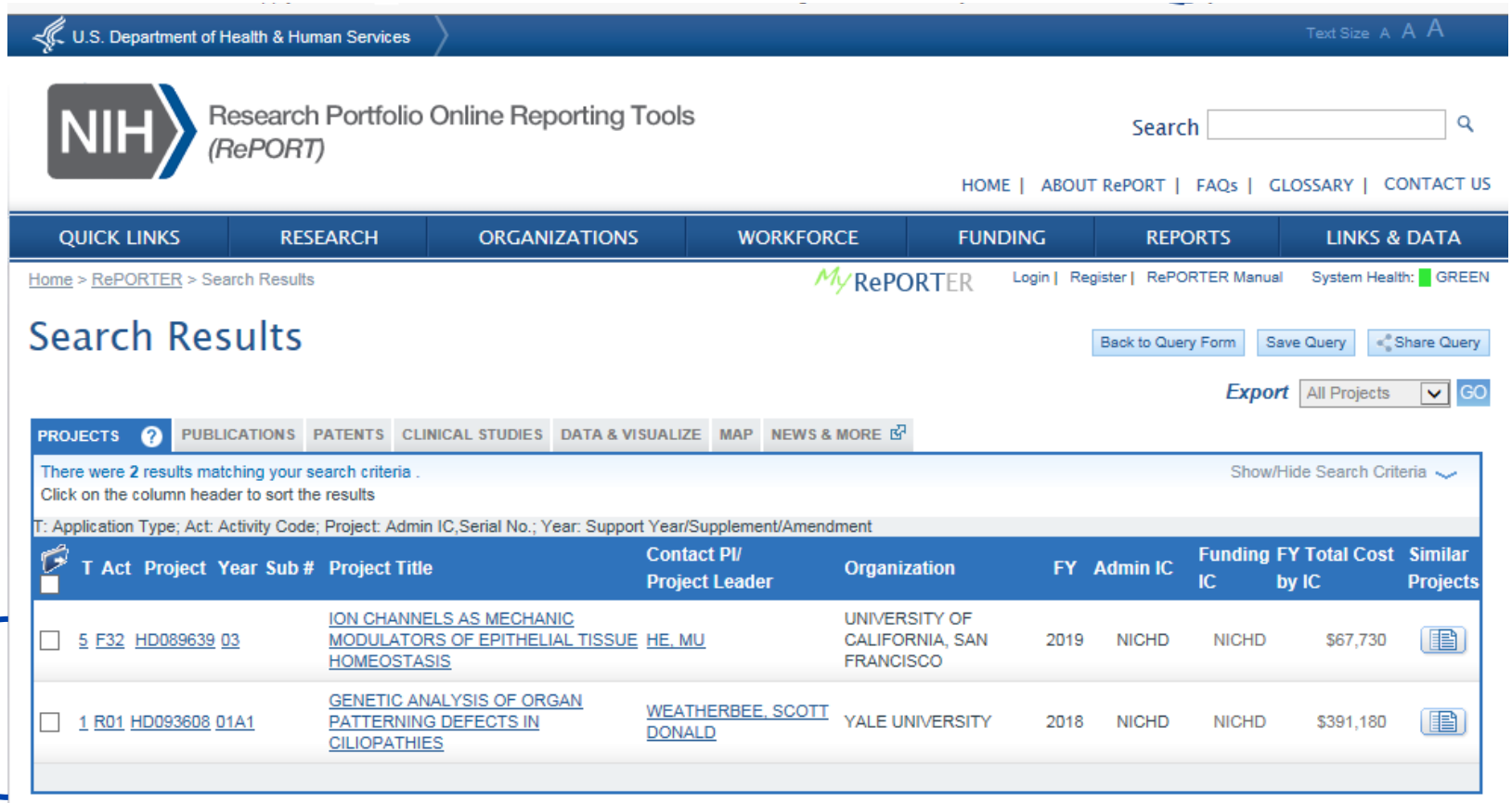
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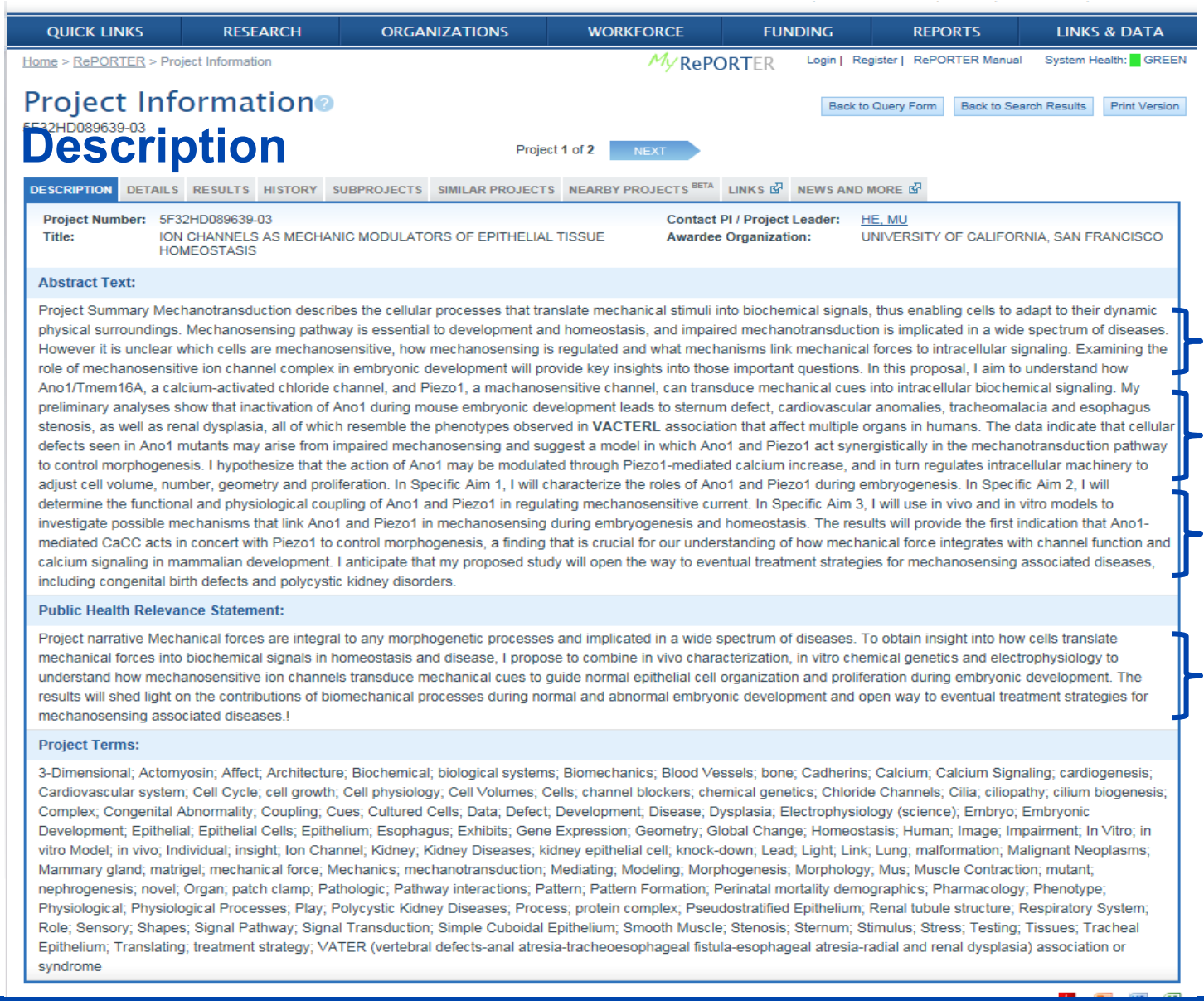
Grants



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Contact PI / Project Leader: HE, MU
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Cytoplasmic Cl- couples membrane remodeling to epithelial morphogenesis.	Proceedings of the National Academy of Sciences of the United States of America. 2017 12 26; 114 (52) :E11161-E11169	He, Mu; Ye, Wenlei; Wang, Won-Jing; Sison, Eirish S; Jan, Yuh Nung; Jan, Lily Yeh		

Patents:

Patent Number	Patent Title	Patent Owner	Primary Agency
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Proc Natl Acad Sci U S A. 2017 Dec 26;114(52):E11161-E11169. doi: 10.1073/pnas.1714448115. Epub 2017 Dec 11.

Cytoplasmic Cl^- couples membrane remodeling to epithelial morphogenesis.

He M[1], Ye W[1], Wang WJ[2], Sison ES[1,3], Jan YN[1,4,3], Jan LY[5,4,3].

Author information

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2 Institute of Biochemistry and Molecular Biology, College of Life Sciences, National Yang-Ming University, Taipei, 11221, Taiwan.
3 Howard Hughes Medical Institute, University of California, San Francisco, CA 94158.
4 Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94158.
5 Department of Physiology, University of California, San Francisco, CA 94158; Lily.Jan@ucsf.edu.

Abstract

Chloride is the major free anion in the extracellular space (>100 mM) and within the cytoplasm in eukaryotes (10 ~ 20 mM). Cytoplasmic Cl^- level is dynamically regulated by Cl^- channels and transporters. It is well established that movement of Cl^- across the cell membrane is coupled with cell excitability through changes in membrane potential and with water secretion. However, whether cytoplasmic Cl^- plays additional roles in animal development and tissue homeostasis is unknown. Here we use genetics, cell biological and pharmacological tools to demonstrate that TMEM16A, an evolutionarily conserved calcium-activated chloride channel (CaCC), regulates cytoplasmic Cl^- homeostasis and promotes plasma membrane remodeling required for mammalian epithelial morphogenesis. We demonstrate that TMEM16A-mediated control of cytoplasmic Cl^- regulates the organization of the major phosphoinositide species $PtdIns(4,5)P_2$ into microdomains on the plasma membrane, analogous to processes that cluster soluble and membrane proteins into phase-separated droplets. We further show that an adequate cytoplasmic Cl^- level is required for proper endocytic trafficking and membrane supply during early stages of ciliogenesis and adherens junction remodeling. Our study thus uncovers a critical function of CaCC-mediated cytoplasmic Cl^- homeostasis in controlling the organization of $PtdIns(4,5)P_2$ microdomains and membrane remodeling. This newly defined role of cytoplasmic Cl^- may shed light on the mechanisms of intracellular Cl^- signaling events crucial for regulating tissue architecture and organelle biogenesis during animal development.

KEYWORDS: calcium-activated chloride channel; epithelial morphogenesis; membrane remodeling; phosphoinositide; primary cilia

PMID: 29229864 PMCID: PMC5748203 DOI: 10.1073/pnas.1714448115

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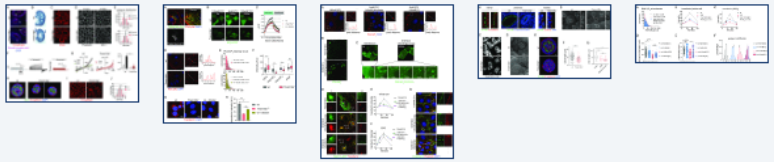

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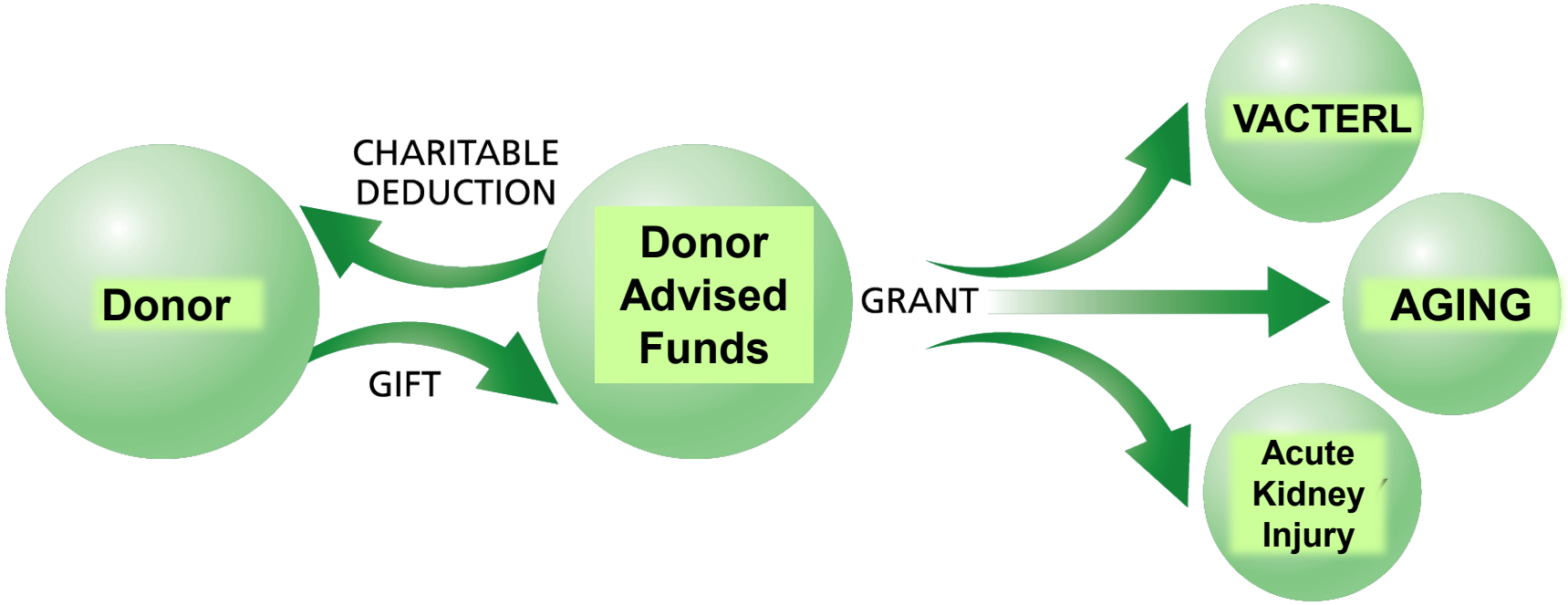
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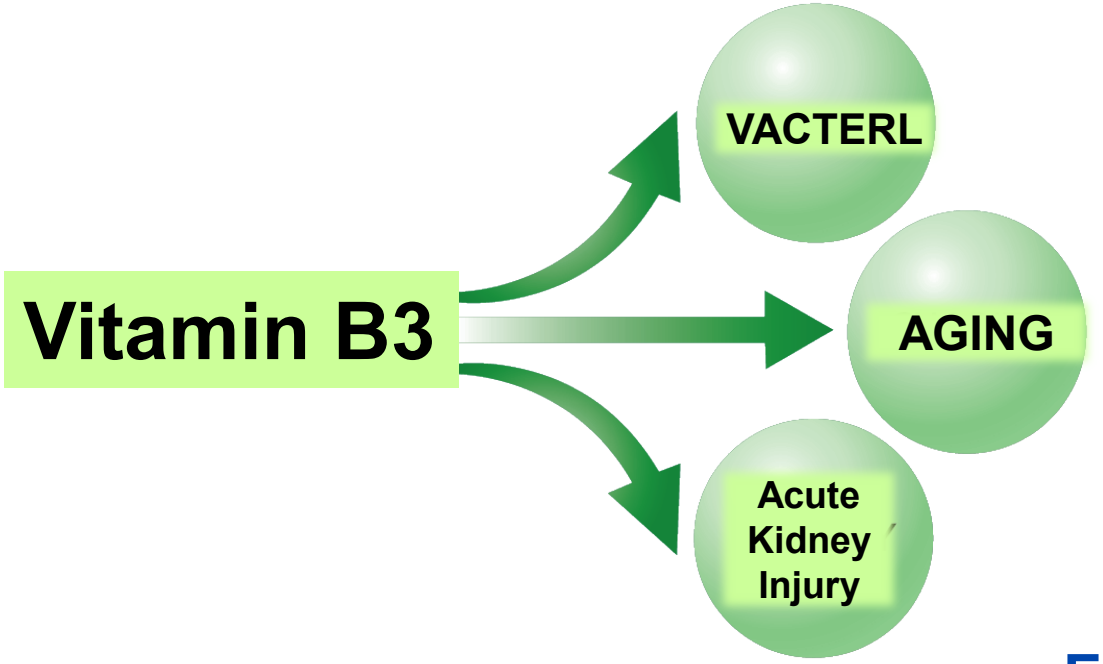

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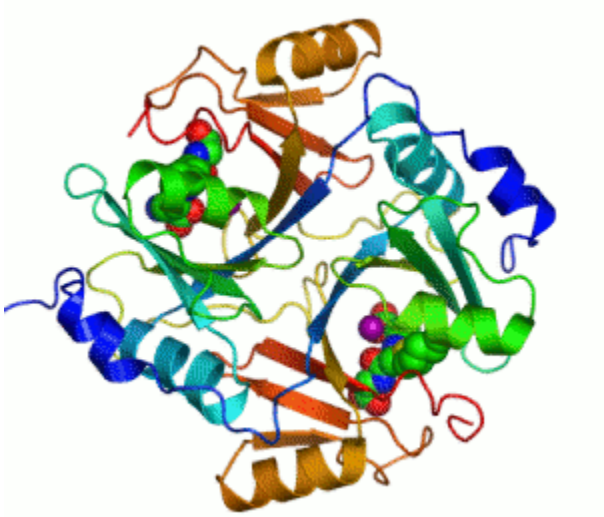
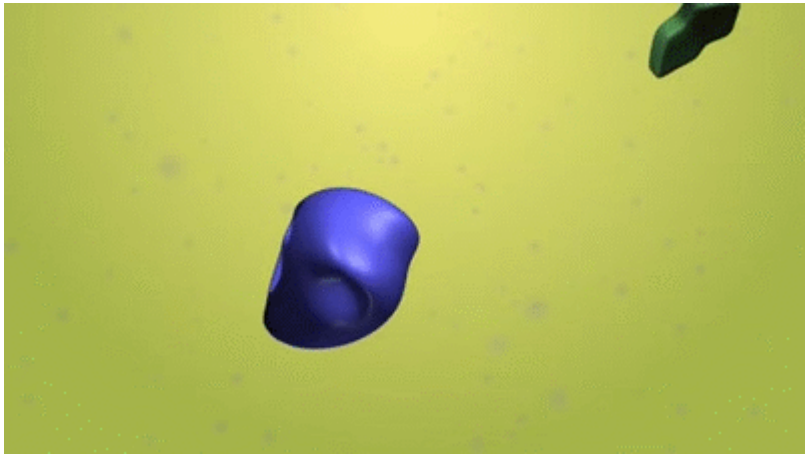
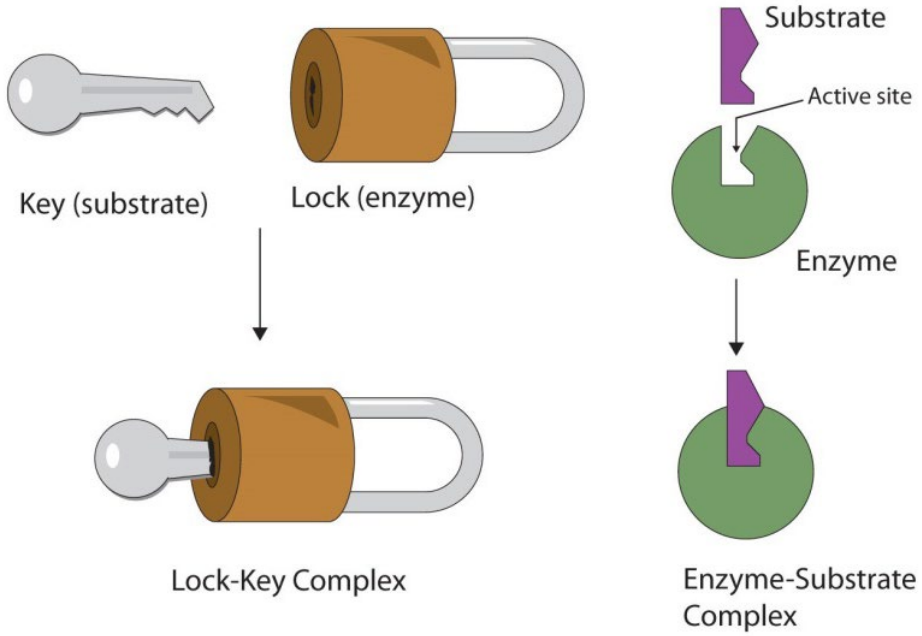
The breakdown of food for energy requires proteins called **enzymes and** biomolecules called **coenzymes (vitamins)**

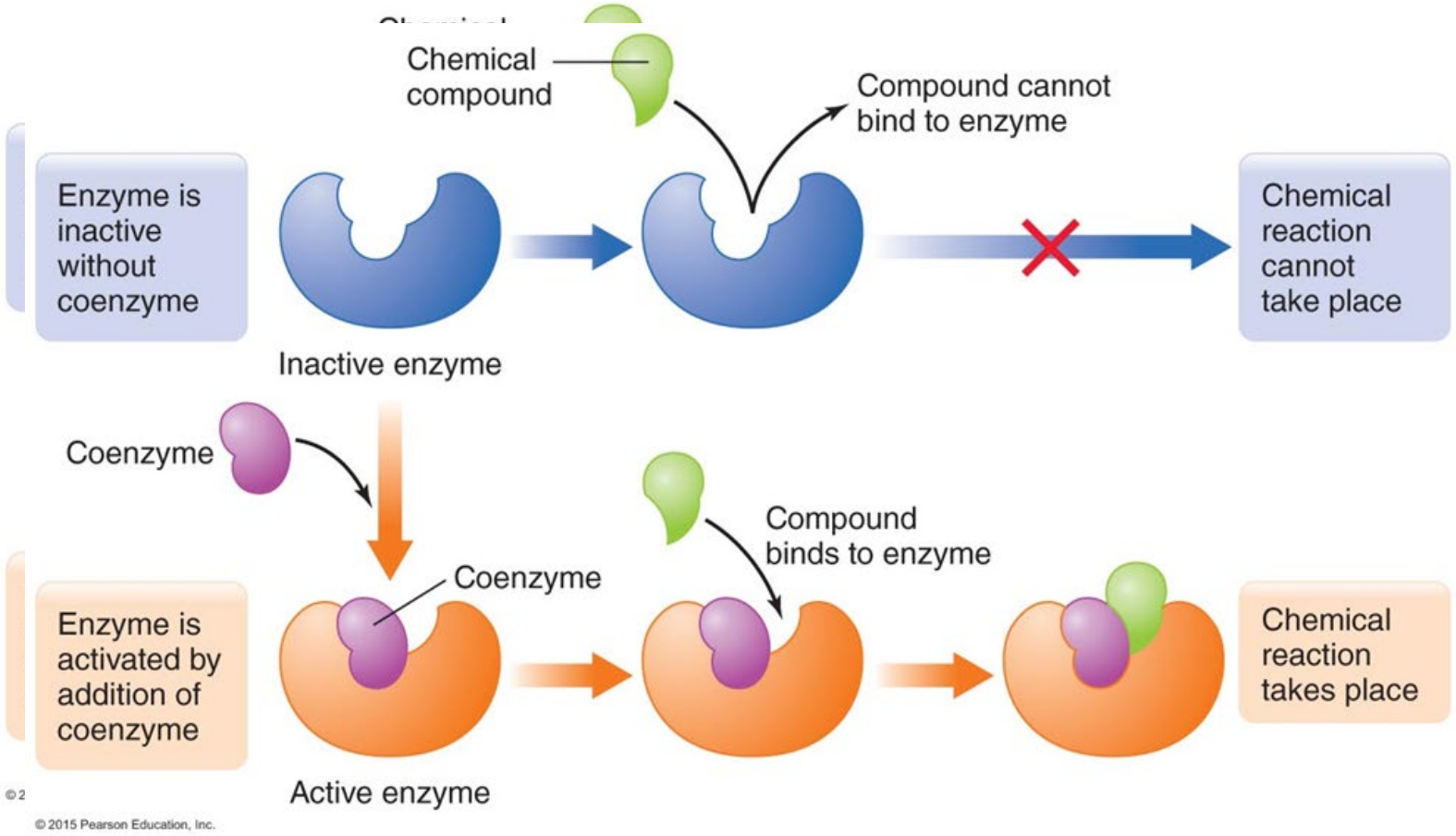




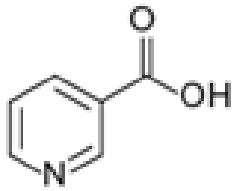
The breakdown of food for energy requires proteins called **enzymes**



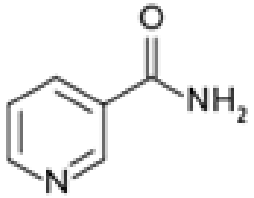
The breakdown of food for energy requires proteins called **enzymes and** (in some cases) biomolecules called **coenzymes (vitamins)**



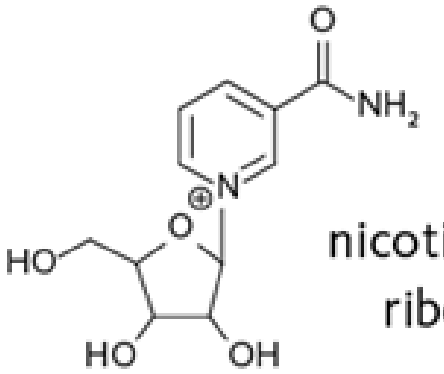
The Vitamin B3 Complex is critical to what is arguably one of the most important metabolic pathways: **NAD+ synthesis**



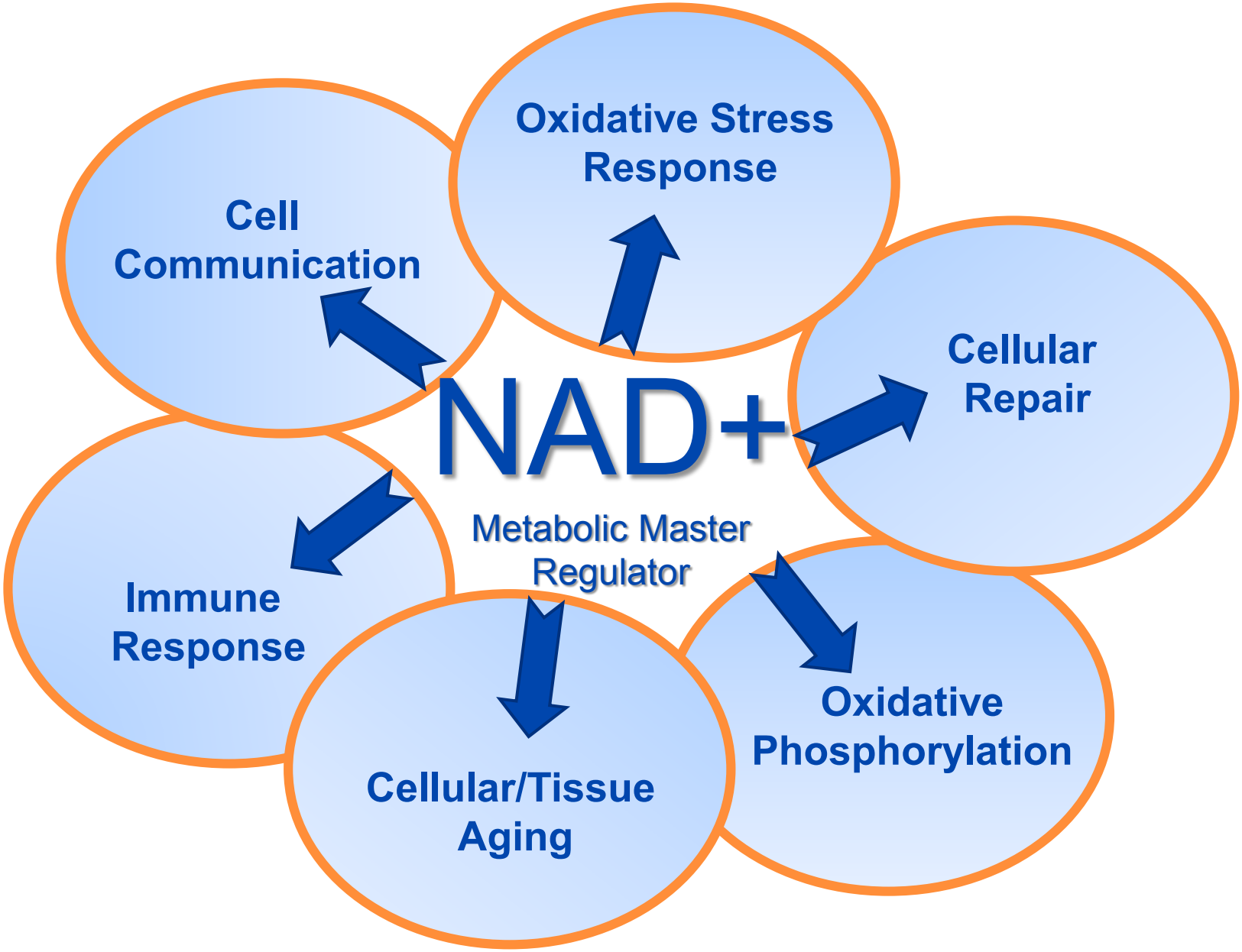
nicotinic acid
(pyridine-3-carboxylic acid;
often referred to as 'niacin')



nicotinamide
(pyridine-3-carboxamide, niacinamide)



nicotinamide
riboside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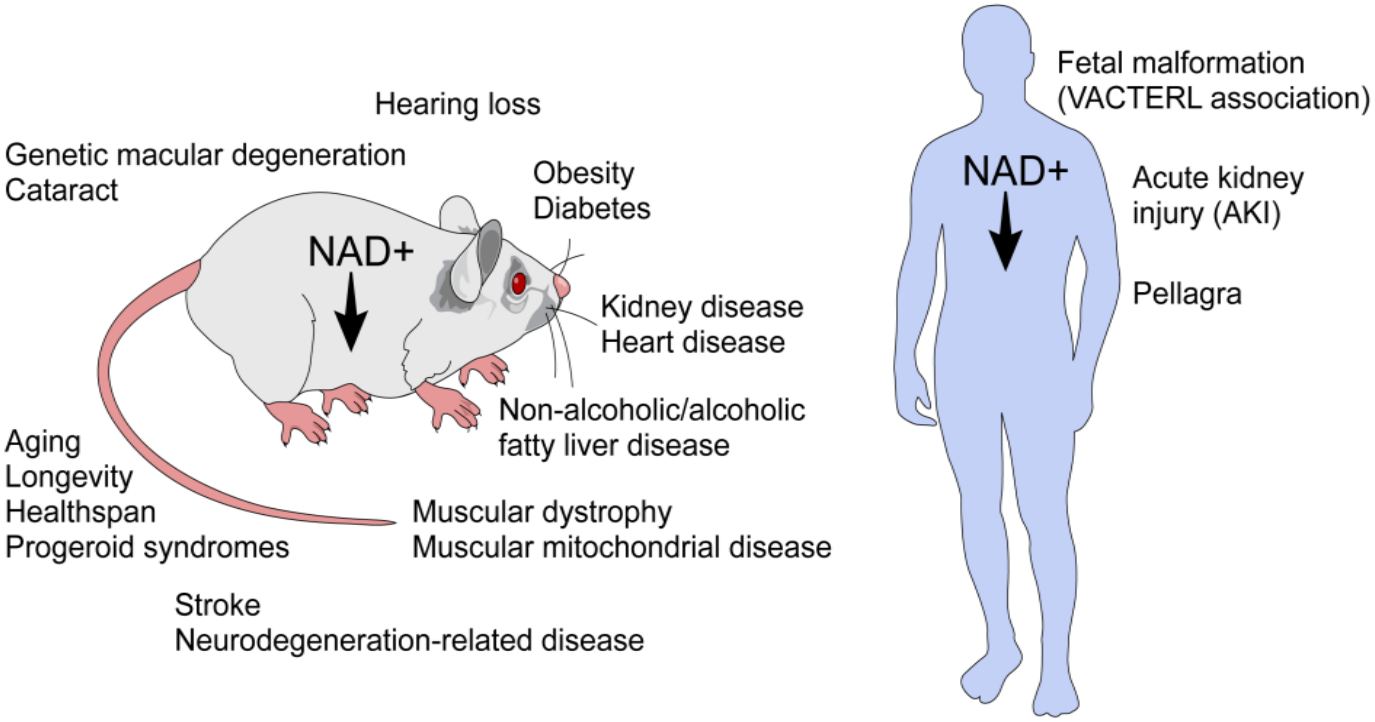
Cellular Repair
NAD+
Metabolic Master Regulator
Immune Response
Oxidative Phosphorylation
Cellular/Tissue Aging

Consequence of low NAD+ levels



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The Connection between Vitamin B3 and VACTERL/VATER Association

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Spread the News: Vitamin B3 in Vegemite Prevents Some Birth Defects

Ownership of salty spread returned home to Australia earlier this year

Jars of Vegemite on a shelf at a grocery store in Melbourne earlier this year. Vitamin B3, which can be found in Vegemite and similar spreads, supplements and other foods, was found to be able to counter a rare genetic cause of birth defects. PHOTO: CARLA GOTTGENS/BLOOMBERG

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NAD Deficiency, Congenital Malformations, and Niacin Supplementation

Hongjun Shi, Ph.D., Annabelle Enriquez, M.B., B.S., Melissa Rapadas, B.Sc., Ella M.M.A. Martin, M.Sc., Roni Wang, B.Sc., Julie Moreau, Ph.D., Chai K. Lim, Ph.D., Justin O. Szot, B.Sc., Eddie Ip, B.App.Sc., James N. Hughes, Ph.D., Kotaro Sugimoto, M.D., Ph.D., David T. Humphreys, Ph.D., et al.

August 10, 2017
N Engl J Med 2017; 377:544-552
DOI: 10.1056/NEJMoa1616361

33 References 32 Citing Articles

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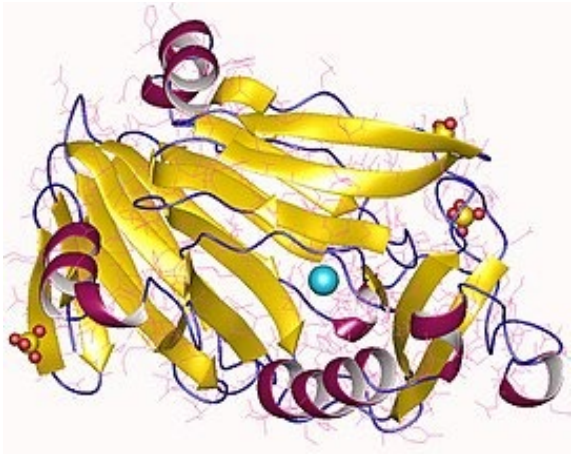

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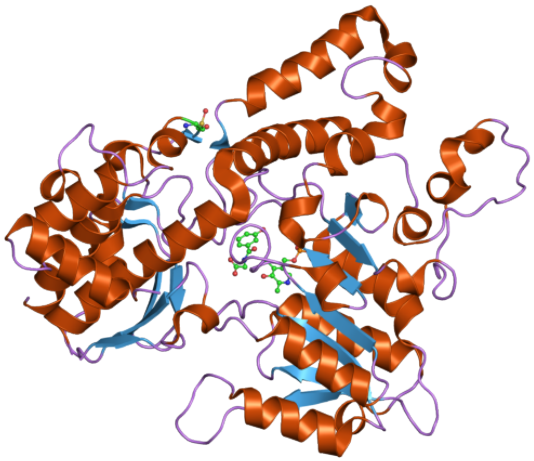

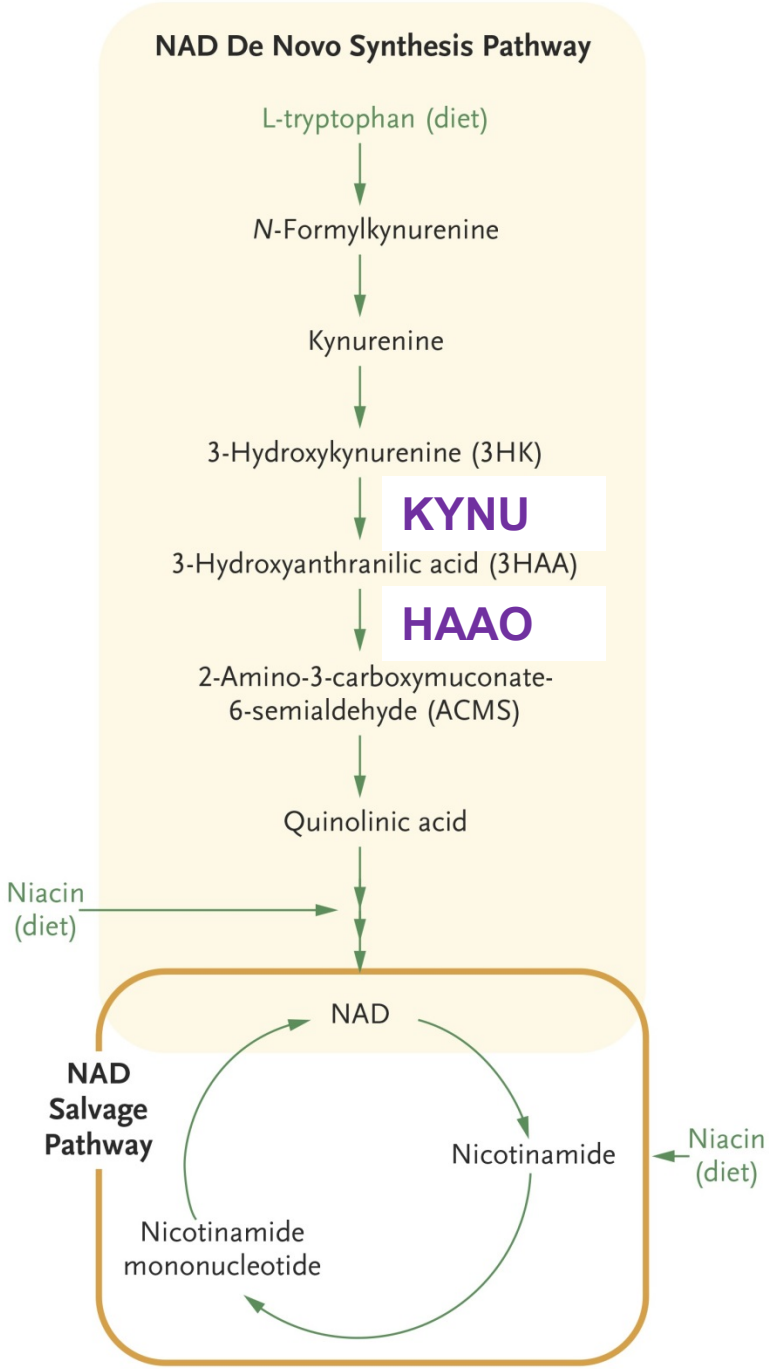

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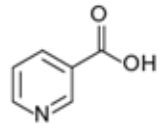
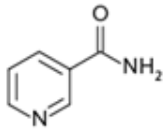
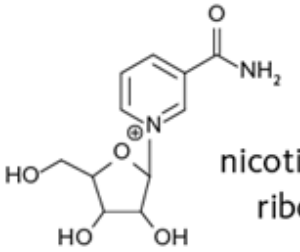


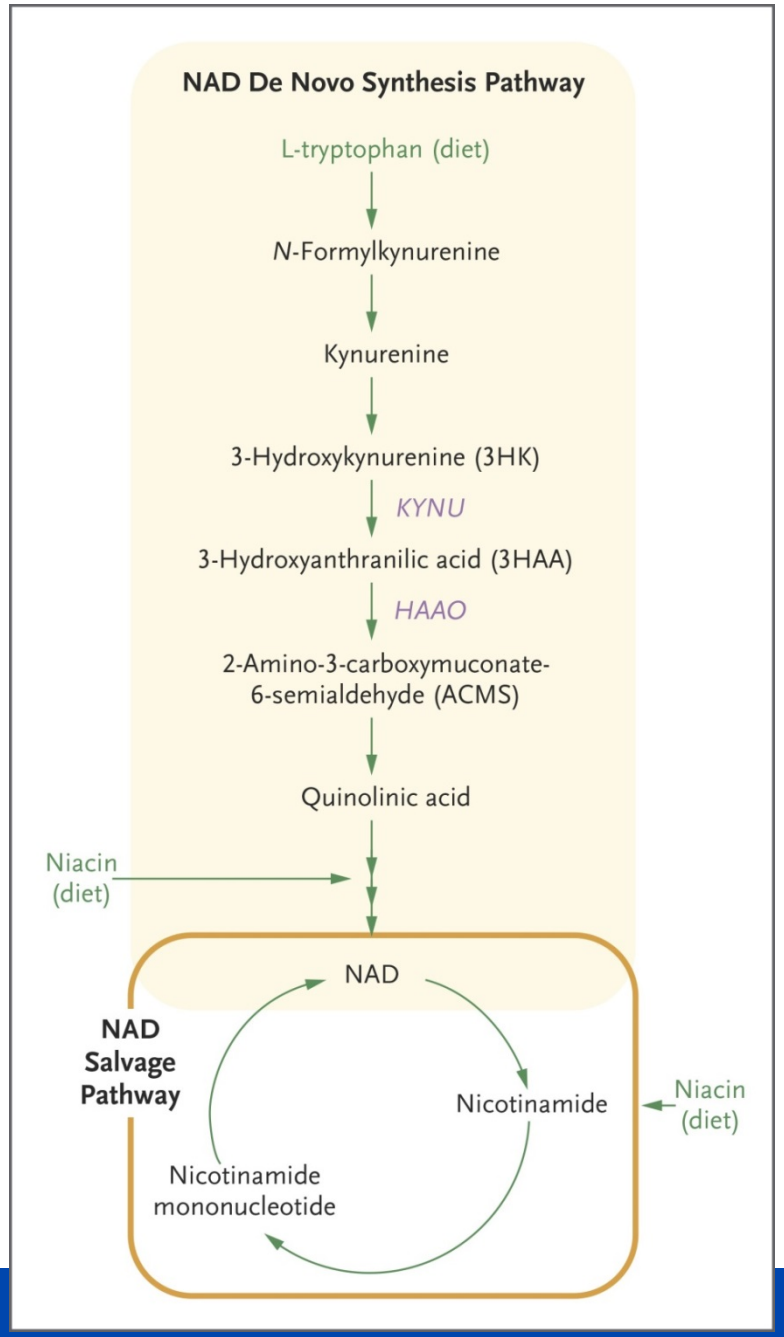
nicotinic acid
(pyridine-3-carboxylic acid;
often referred to as 'niacin')

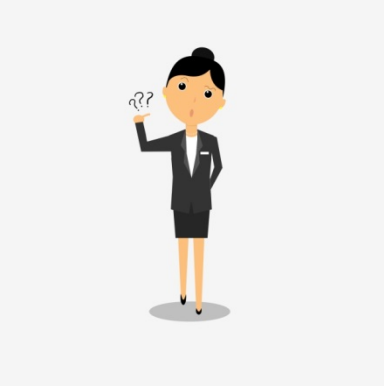


nicotinamide
(pyridine-3-carboxamide, niacinamide)



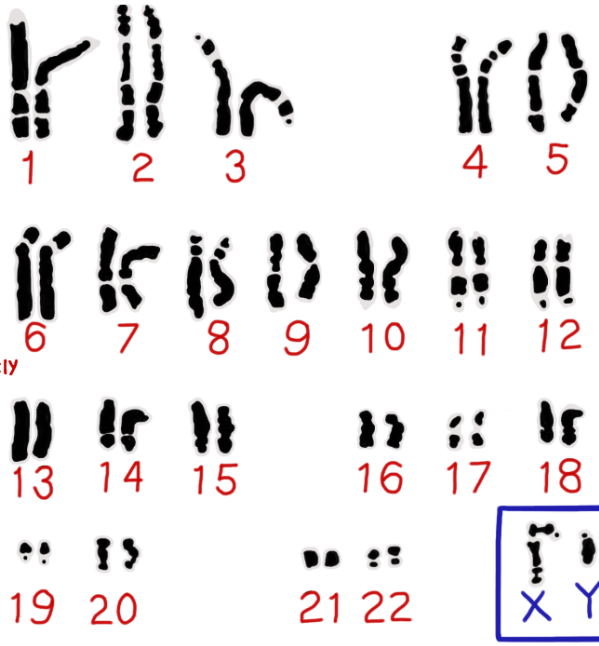
nicotinamide
riboside





Let’s talk about gene variants….

Parents each contribute one chromosome to make 23 pairs

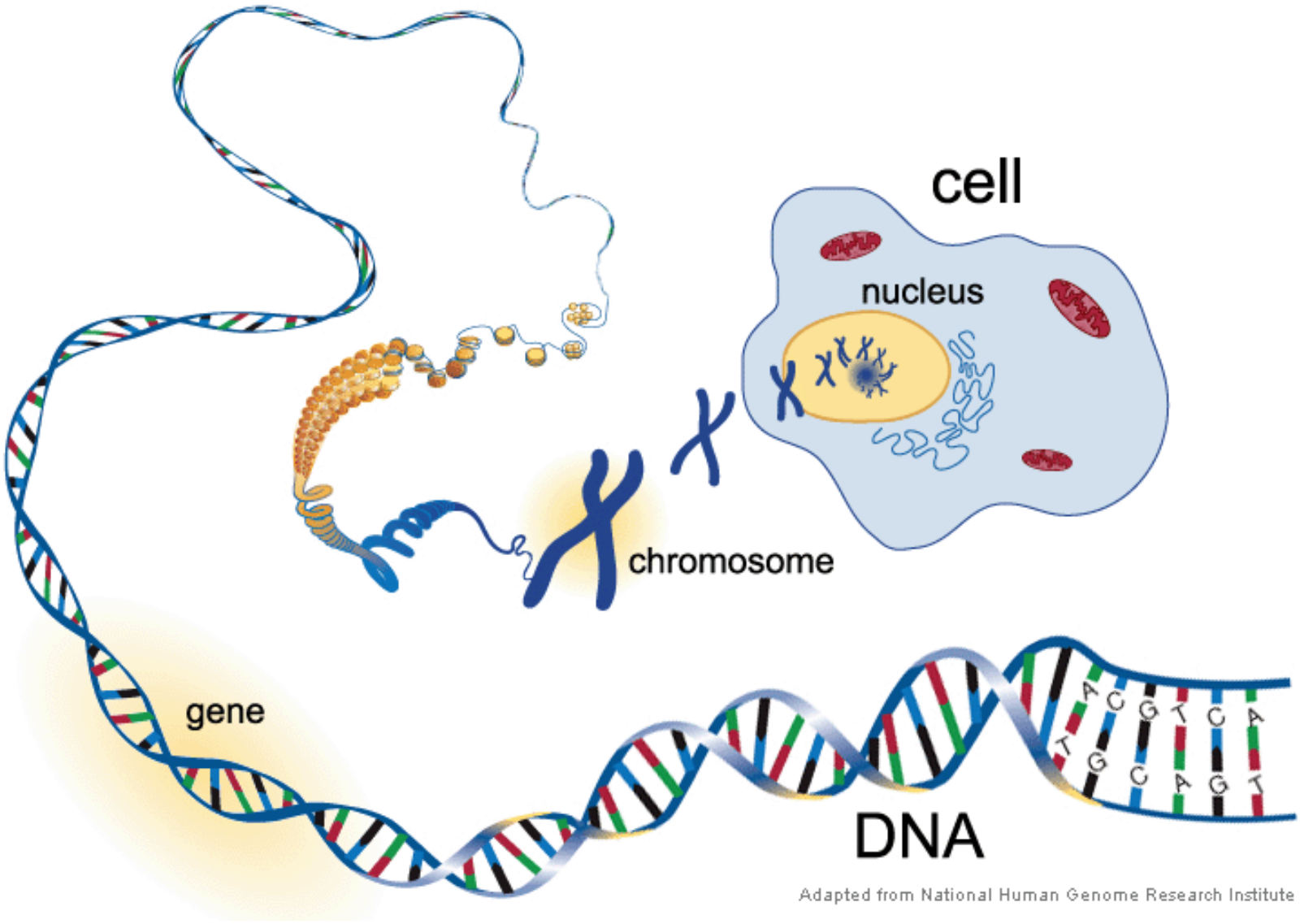


autosome

A chromosome that is not directly involved in determining the sex of an organism.

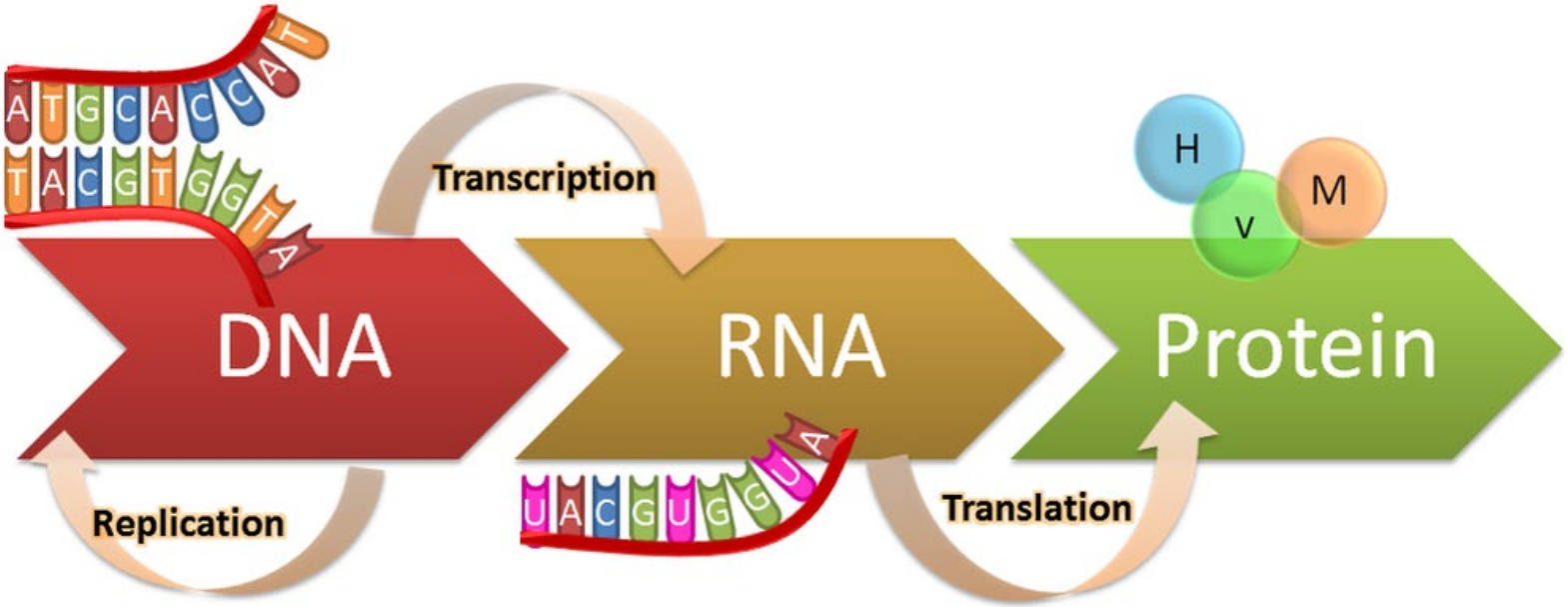
sex chromosome

A chromosome that determines whether an organism is male or female.

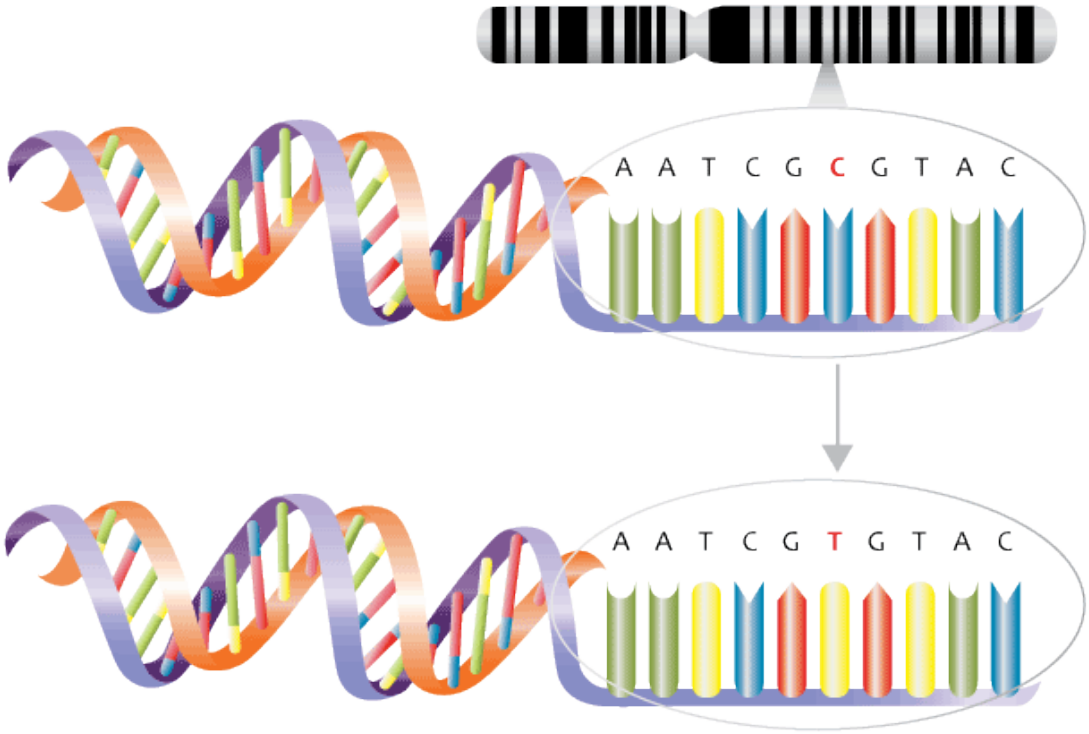


Adapted from National Human Genome Research Institute

Central Dogma of Biology



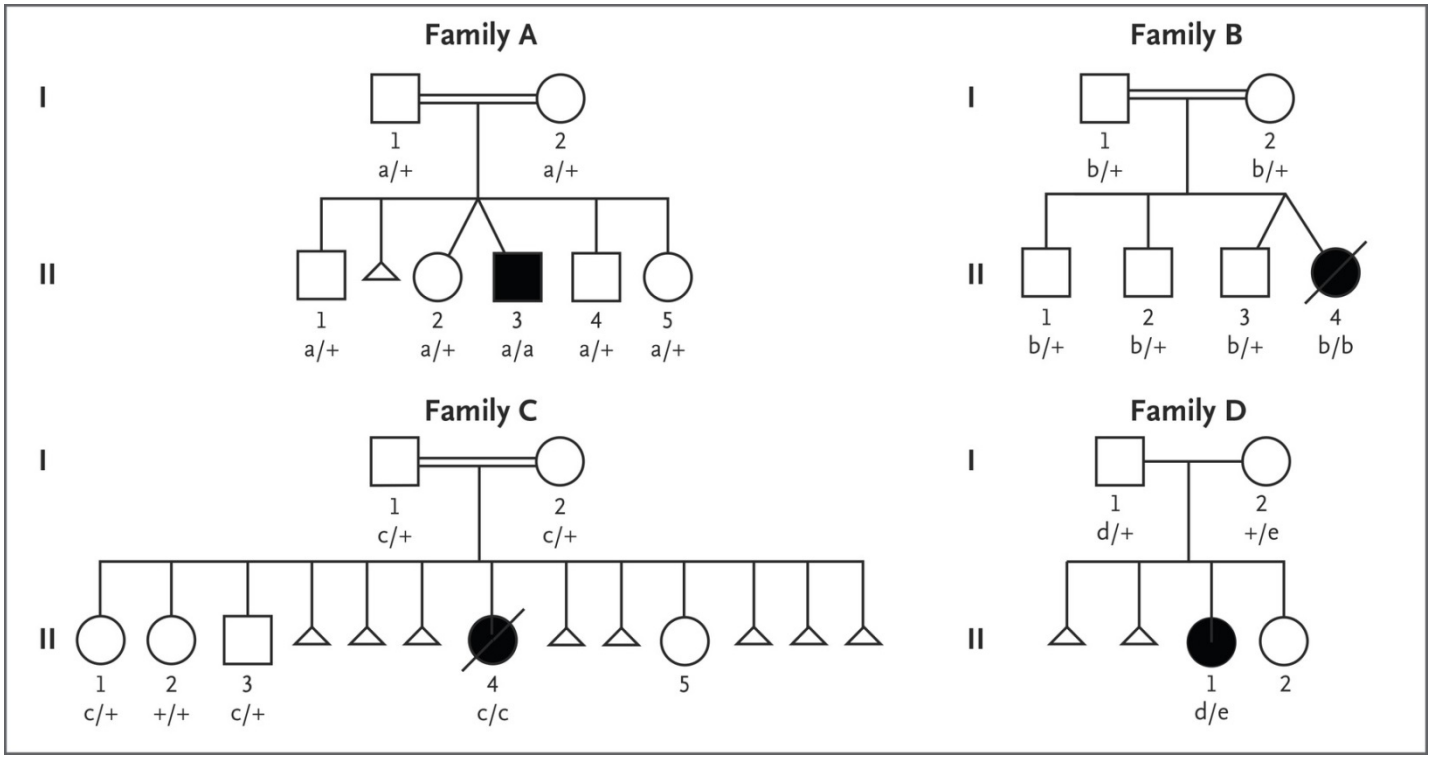
What is a gene variant?

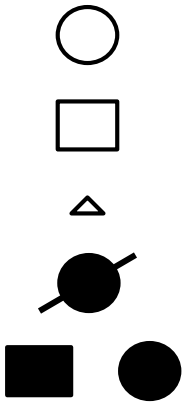


- Pathogenic variant
- Likely pathogenic variant
- Variant of uncertain significance (VUS)
- Likely benign variant
- Benign variant

Patterns of Inheritance of Genes or Gene Variants

- **Mendellian**
  - ✓**Brown eyes (dominant) or Blue eyes (recessive)**
- Incomplete Dominance
  - ✓Green or Hazel Eyes
- Co-dominance
  - ✓Blood Type (A Positive + B Positive = AB Positive)
- Polygenic Inheritance
  - ✓Human Skin Color
- Sex Linked Inheritance
  - ✓Red/Green Color Blindness in Males





Female person

Male person

Miscarriage

Deceased person

Affected person

Marriage among related people

Marriage among non-related people

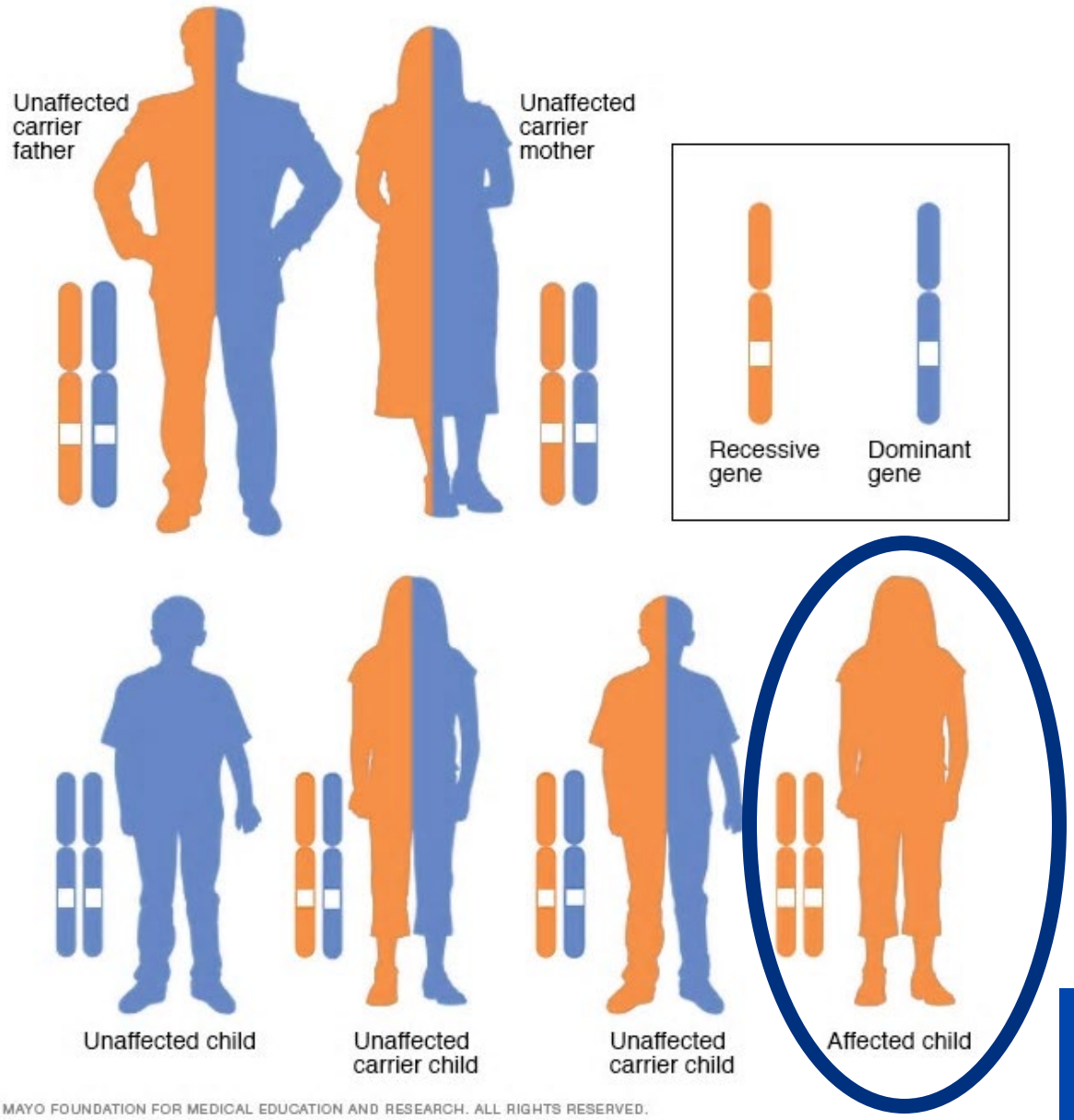
a,b = HAAO variants

c,d,e = KYNU variants

\+ = No variants

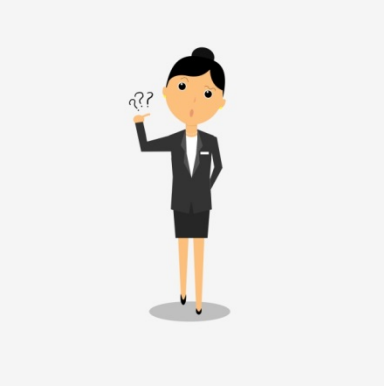
a) How many people in Family C have a gene variant? b) How many people in Family C are affected by a gene variant?

Recessive Pattern of Inheritance



- Malformations similar to those observed in VACTERL Association found in mouse embryos with:
  - ✓gene variants in NAD+ synthesis enzymes (HAAO and KYNU)
  - ✓a diet low in vitamin B3 (niacin)

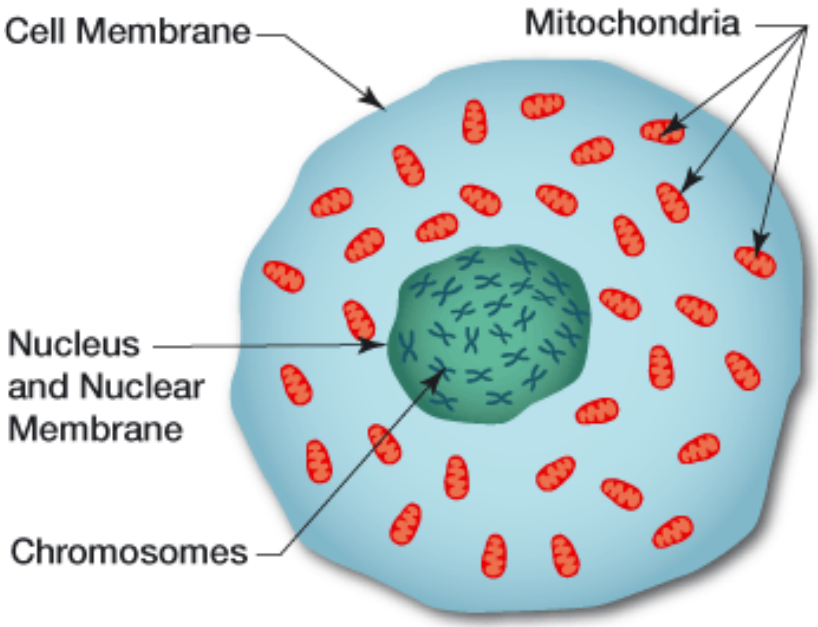
Implications of Identifying **NAD+ Pathway Variants** in Families with VACTERL Association?

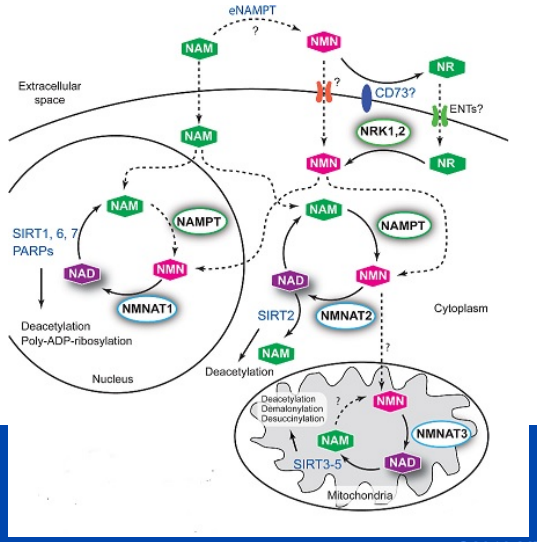


Let’s talk about mitochondria…

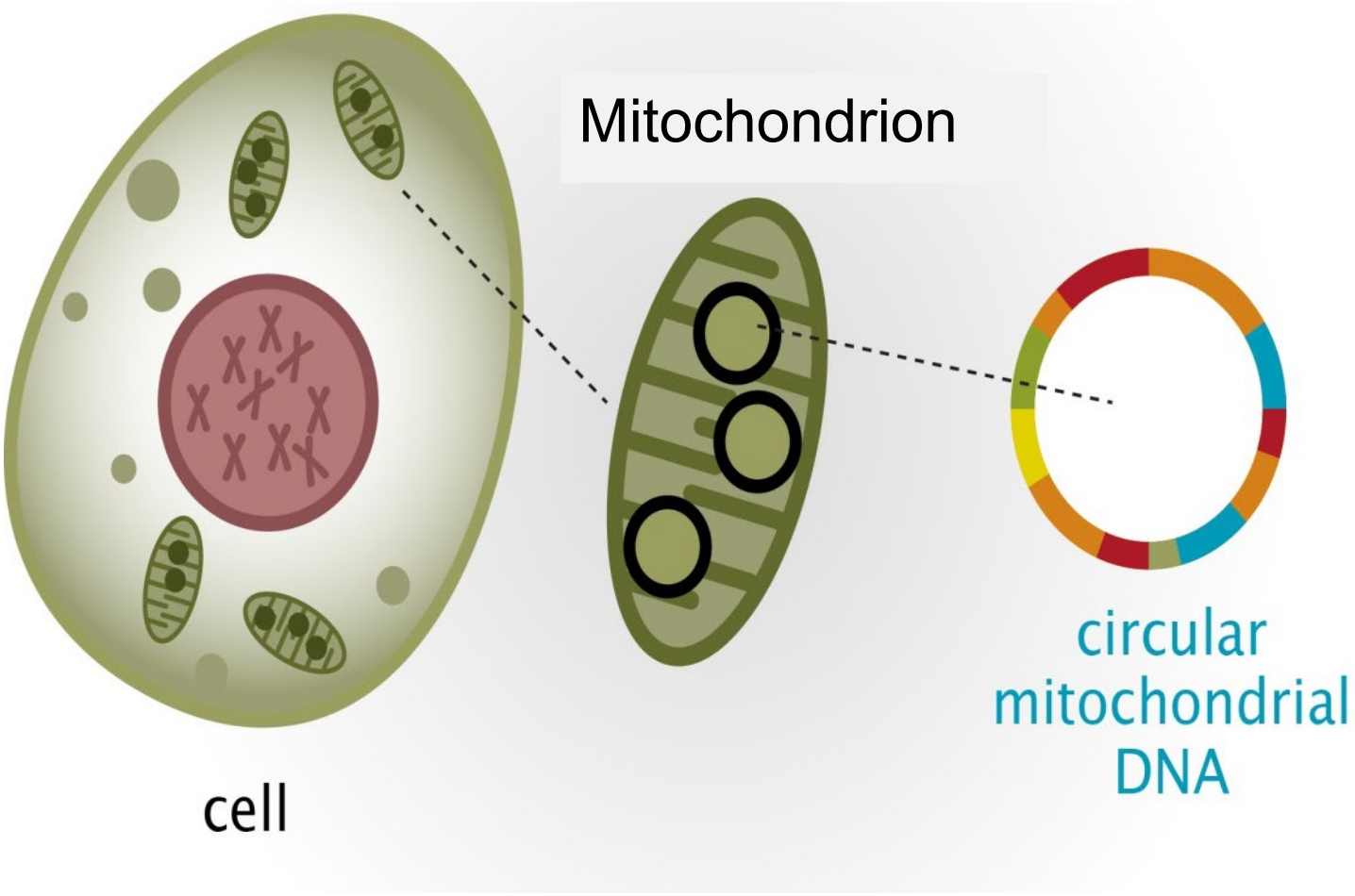
Where is NAD+ synthesized in the cell?

- **Mitochondria**
- Cytoplasm
- Nucleus

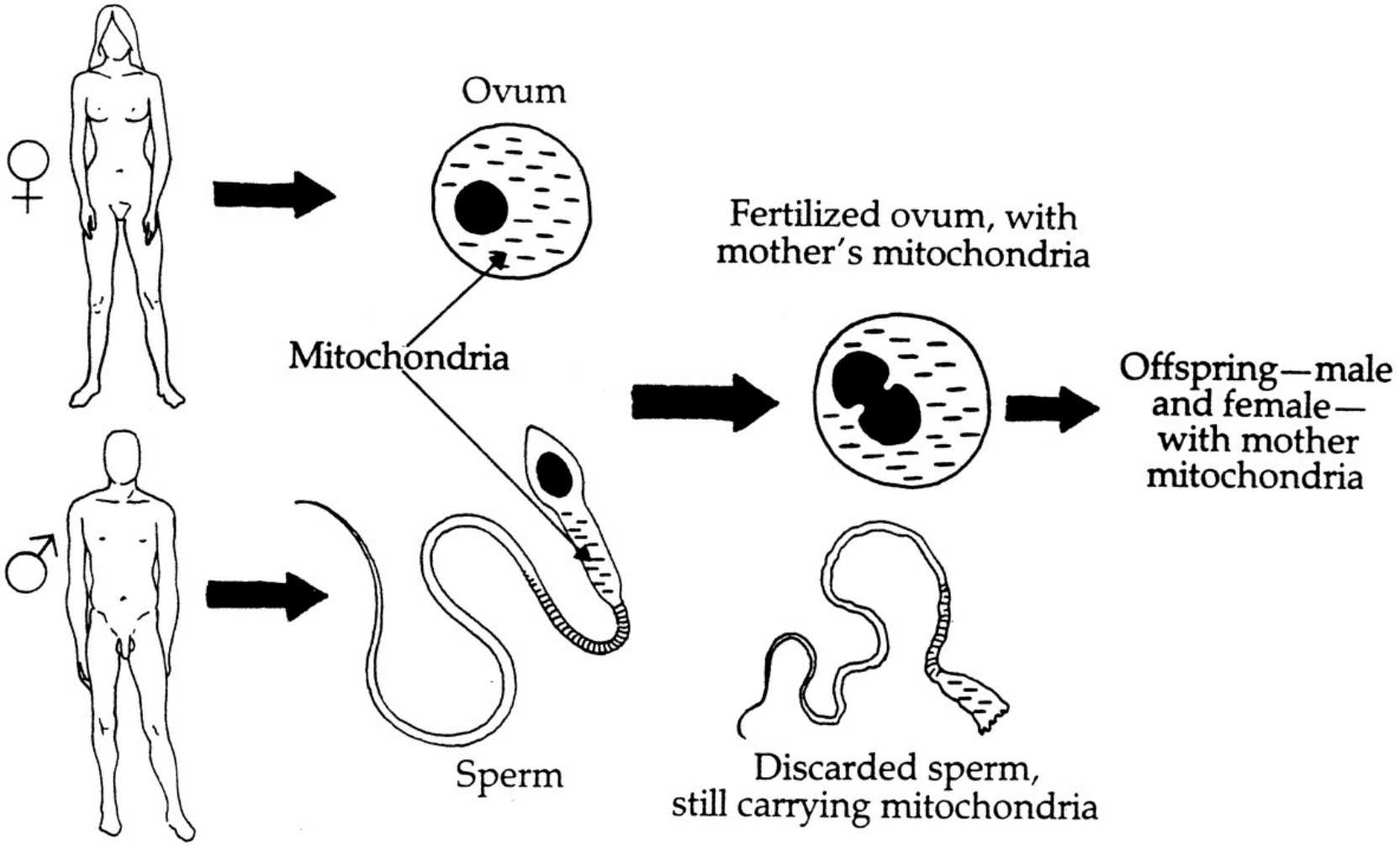




Curious properties of mitochondria



Curious properties of mitochondria

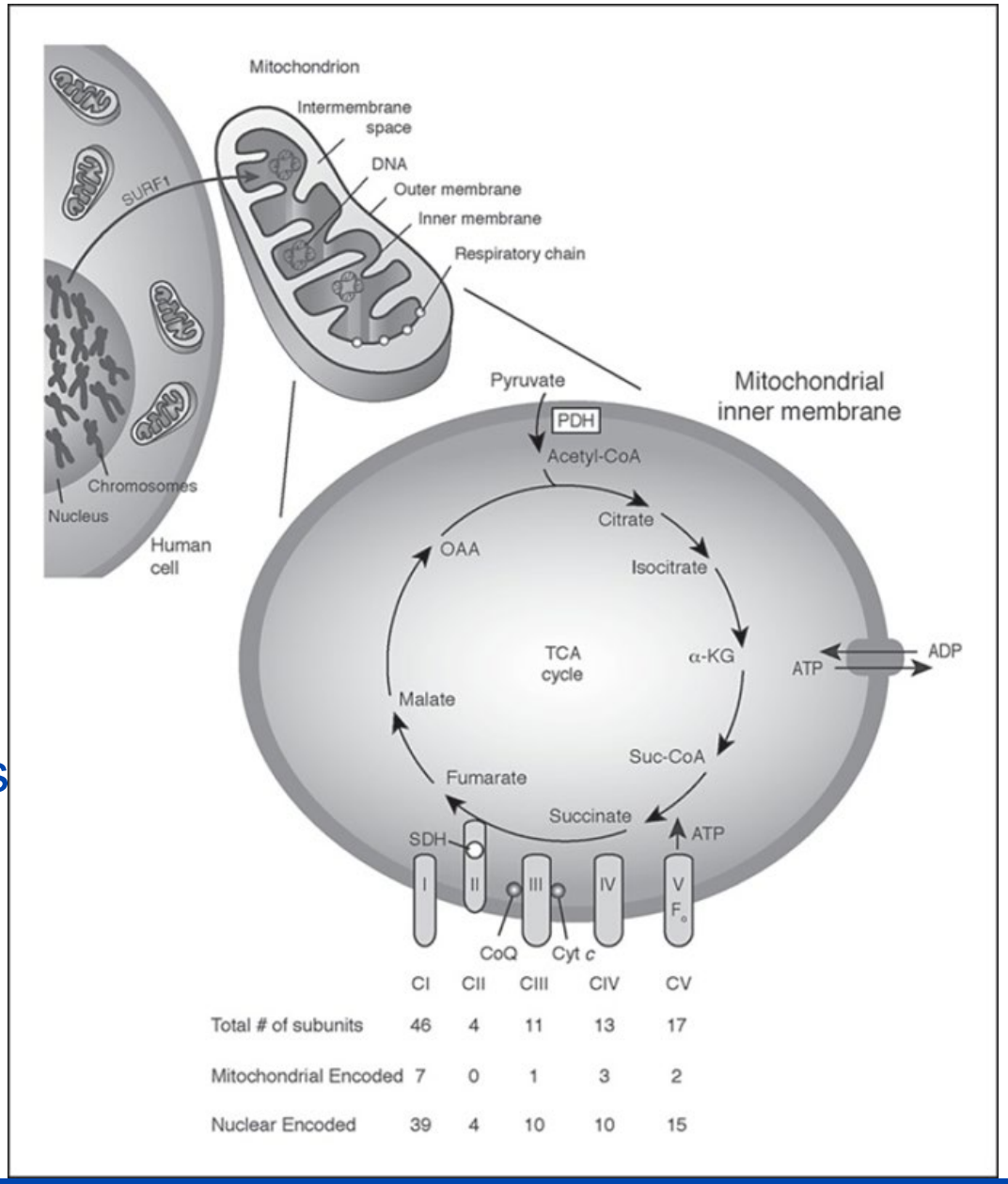


Genet Med. 2019 Jun 7. doi: 10.1038/s41436-019-0568-0. [Epub ahead of print]

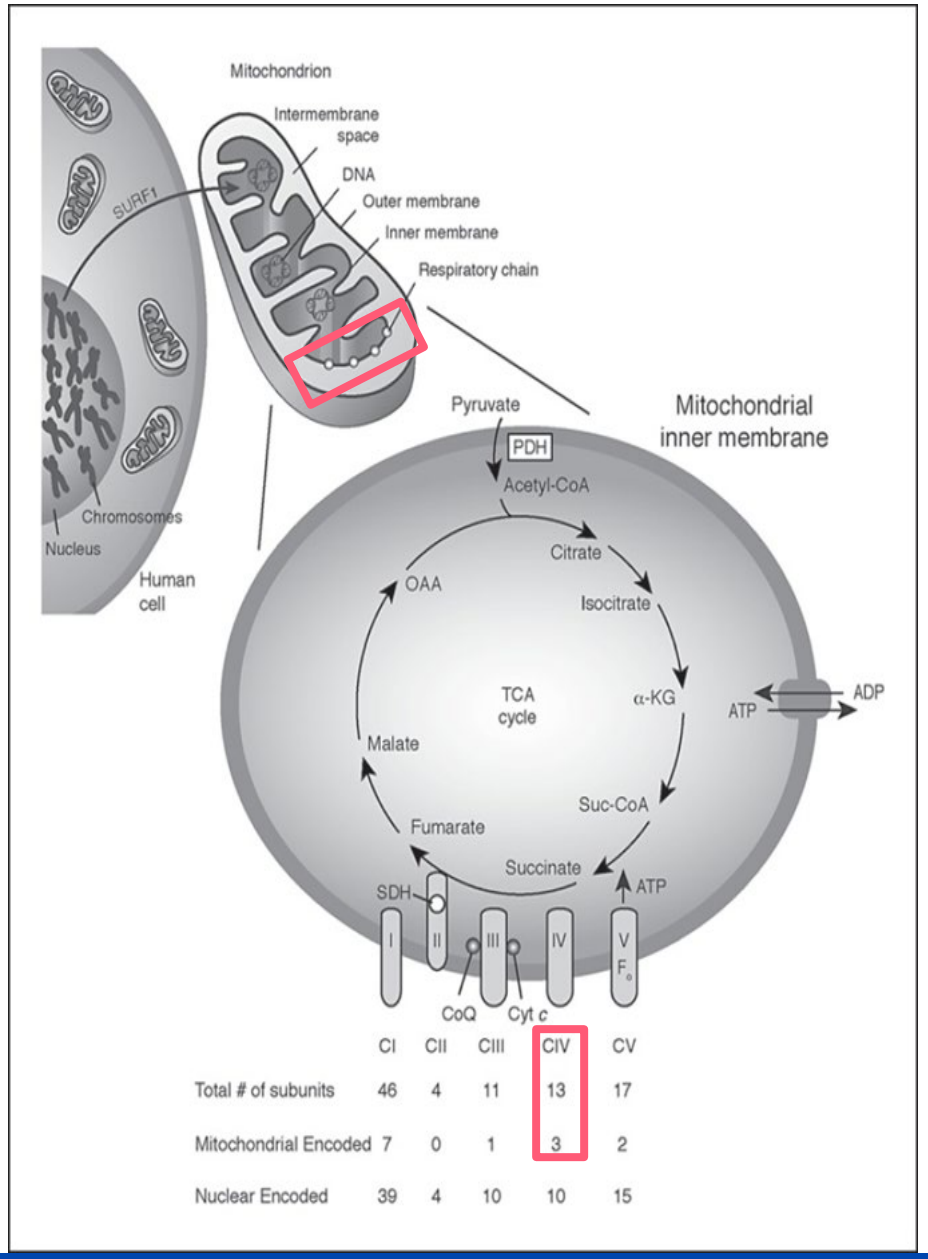
Biparental inheritance of mitochondrial DNA in humans is not a common phenomenon.

Rius R[1,2], Cowley MJ[3,4,5], Riley L[6,7], Puttick C[3,8], Thorburn DR[1,2,9], Christodoulou J[10,11,12,13].

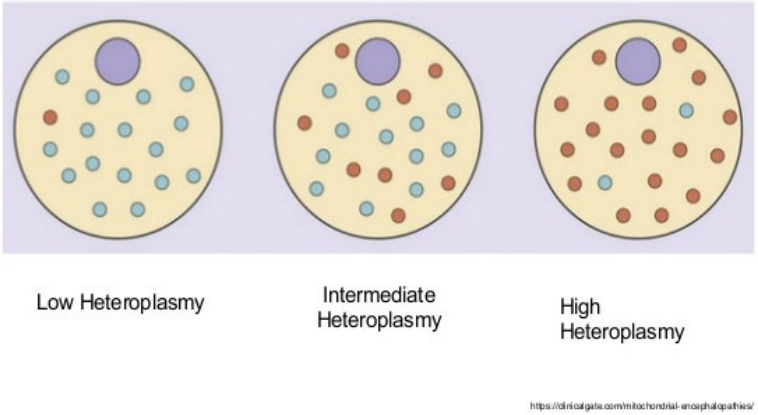
- Mitochondria convert the energy from food into a form that cells can use
- Mitochondria have their own DNA and contain **37 genes**
- **Thirteen (13)** of these genes provide instructions for making **enzymes** involved in energy (ATP) production.



- Over **250 mtDNA variants** have been reported in humans
- 6 cases of proven mitochondrial dysfunction in patients with VACTERL association
- 5 of the 6 affected individuals demonstrated **Complex IV** deficiencies



- Not all cells receive an equal amount of variant mitochondria DNA (non-Mendellian inheritance)
  - ✓ **Heteroplasmy**



- **Tissues with higher energy demands** are more vulnerable to mitochondrial defects:
  - ✓ *central nervous system*
  - ✓ *skeletal and cardiac muscle*
  - ✓ *pancreas*
  - ✓ *liver*
  - ✓ *kidney*

- Overlaps between **VACTERL** association and **mitochondrial disorders**

Open Questions in VACTERL Research

- Do variants in NAD+ metabolism occur in US families with the same **frequency** as reported previously?
- How do variants in the **NAD+ synthesis** pathway impact NAD+ levels in VACTERL families?
- With what frequency will we identify **mitochondrial DNA variants** in VACTERL families?

MAYO CLINIC

Genetic Variants in Nicotinamide Adenine Dinucleotide (NAD) Synthesis Pathway

An On-Going Clinical Study at the Mayo Clinic

Principal Investigator (PI): Dr. Eduardo Chini
Co-Investigator (Co-I): Dr. Kelly Hogan

Tests to be performed

- **DNA** and **mitochondrial sequencing** in collaboration with GeneDx
  - ✓Health survey will be used to interpret results
  - ✓All samples will be de-identified to protect identity of participants
  - ✓Only study staff will have access to participant protected health information (PHI)
  - ✓No PHI will leave Mayo Clinic or be shared outside of the study team
- **Targeted metabolomics** to measure NAD levels will be performed at the Mayo Clinic

- **This study will collect health information and blood and urine samples <u>at Mayo Clinic or a lab convenient to your family</u>.**

- **Eligible participants:**

✓Consented **individuals** with a history of VACTERL Association;

✓Consented first degree **family members** of individuals with VACTERL Association;

✓Consented **women** with a history of recurrent miscarriage and a family history of VACTERL Association;

- **Recent inclusion of children under 13:**

Acta Paediatr. 2017 Oct;106(10):1694-1701. doi: 10.1111/apa.13973. Epub 2017 Aug 3.

Young children with severe congenital malformations (VACTERL) expressed mixed feelings about their condition and worries about needles and anaesthesia.

Kassa AM[1,2], Engvall G[1], Engstrand Lilja H[1,2].

✓Permission from parent

✓Child's assent

✓Buccal (cheek) swab performed by parent

✓Urine collection from toilet-trained children by parent

Requires abstinence from certain foods 24 hours prior to study:

- Red meat and meat products

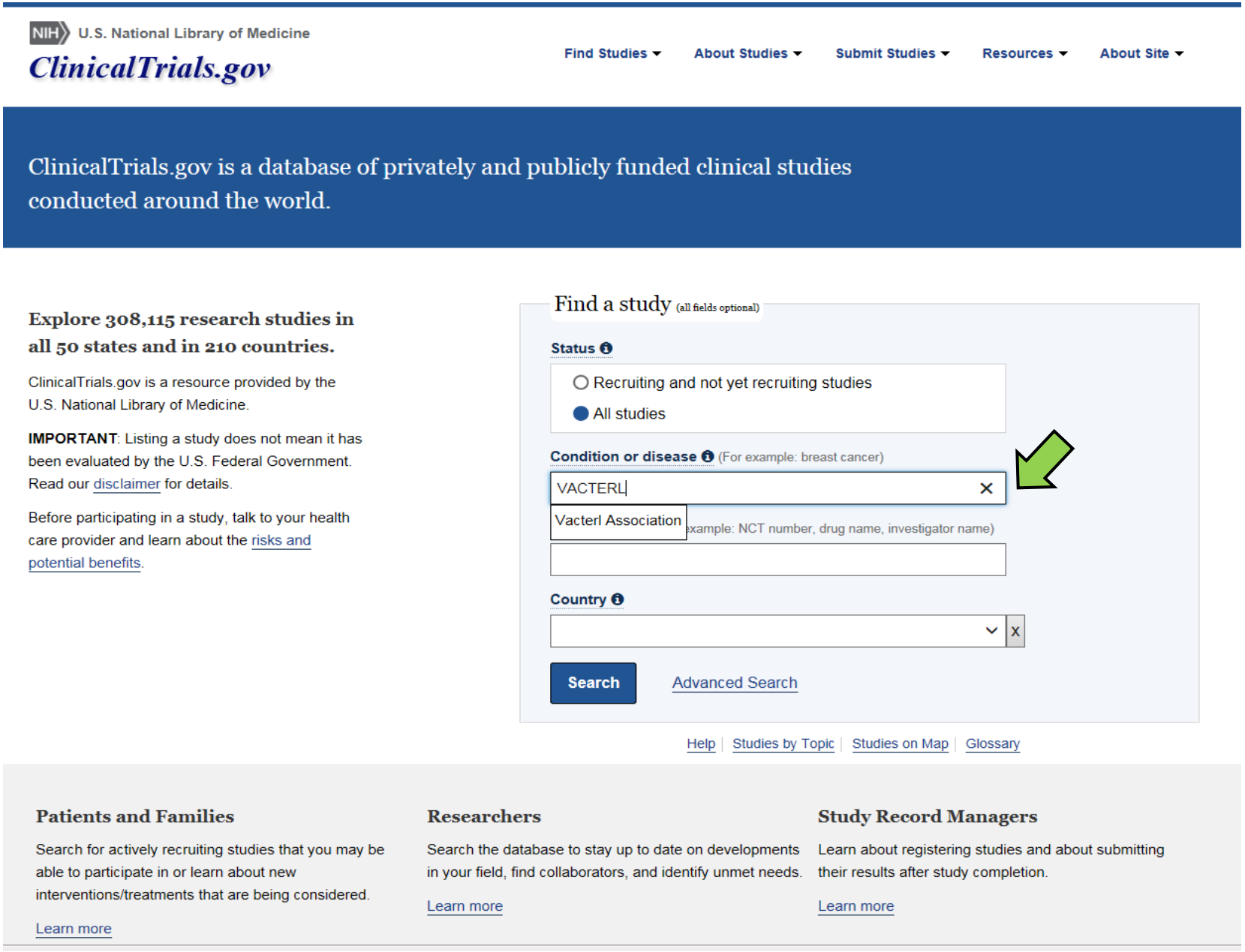
- Fowl

- Peanuts

- Products containing brewer's yeast (eg beer, vegemite)

MAYO CLINIC

Tools for finding privately and federally funded clinical studies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IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.
Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.
Find a study (all fields optional)
Status
Recruiting and not yet recruiting studies
All studies
Condition or disease (For example: breast cancer)
VACTERL
Vacterl Association
example: NCT number, drug name, investigator name)
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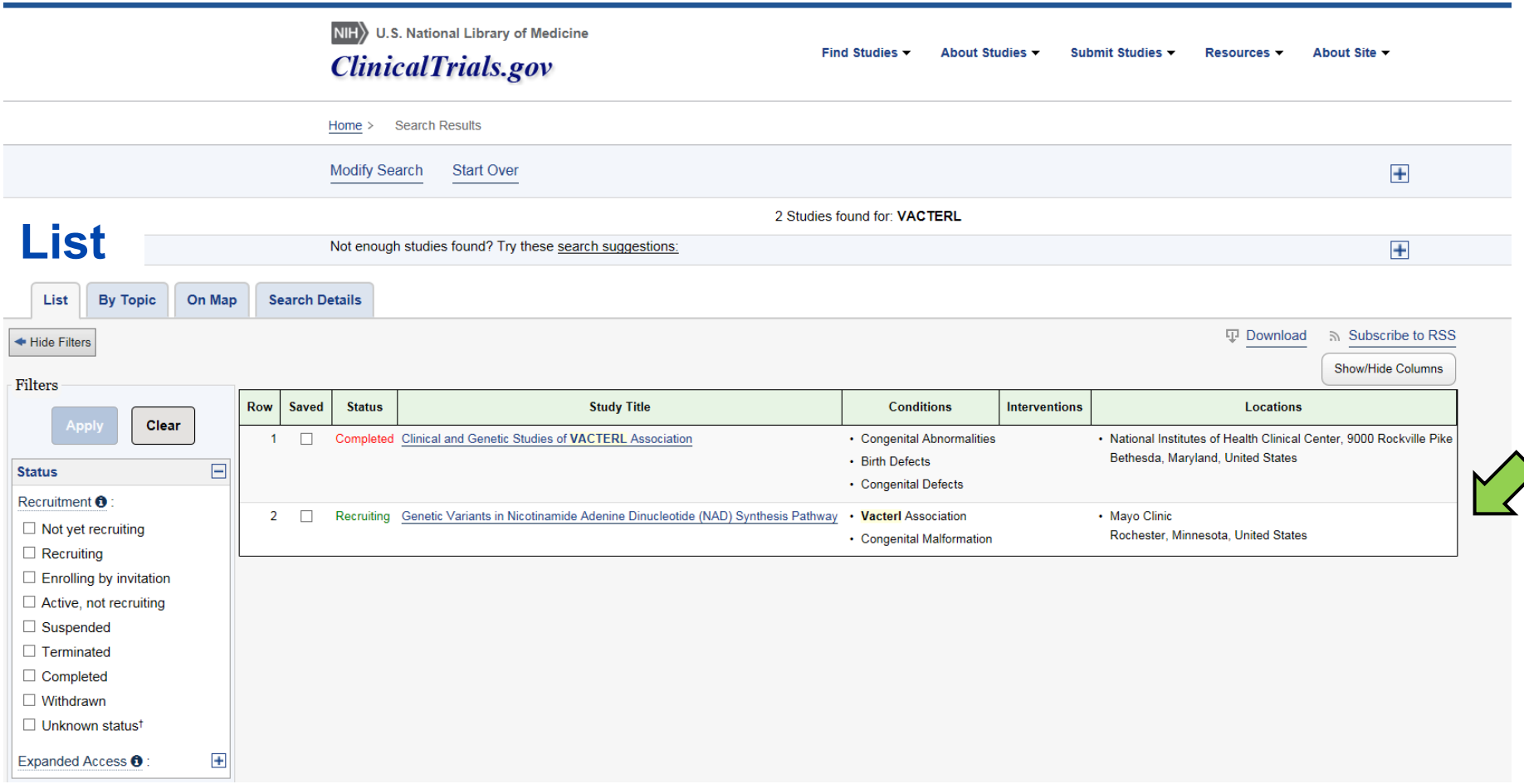
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2 Studies found for: VACTERL
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Clear
Status
Recruitment :
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Recruiting
Enrolling by invitation
Active, not recruiting
Suspended
Terminated
Completed
Withdrawn
Unknown status†
Expanded Access :
Row
Saved
Status
Study Title
Conditions
Interventions
Locations
1
Completed
Clinical and Genetic Studies of VACTERL Association
Congenital Abnormalities
Birth Defects
Congenital Defects
National Institutes of Health Clinical Center, 9000 Rockville Pike Bethesda, Maryland, United States
2
Recruiting
Genetic Variants in Nicotinamide Adenine Dinucleotide (NAD) Synthesis Pathway
Vacterl Association
Congenital Malformation
Mayo Clinic Rochester, Minnesota, United States

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Trial record **2 of 2** for: VACTERL

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Genetic Variants in Nicotinamide Adenine Dinucleotide (NAD) Synthesis Pathway

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03799705

Recruitment Status : Recruiting
First Posted : January 10, 2019
Last Update Posted : April 26, 2019
See Contacts and Locations

Sponsor:
Mayo Clinic

Study Details

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
Researchers are trying to identify versions of genes as well as factors in subjects blood associated with certain types of congenital malformations(CMs). This study will help the researchers to better understand family traits that contribute to CMs.

Condition or disease
Vacterl Association
Congenital Malformation

Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	13 Years and older (Child, Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Sampling Method:	Non-Probability Sample

Study Population

A US population consisting of adults with VACTERL, adults and offspring with a family history of VACTERL, and women with a history of miscarriage and/or congenital malformations.

Criteria

Inclusion Criteria:

1. Adults with confirmed or putative diagnosis of VACTERL association;
2. Families (mother, father, offspring 13 and over) with a history of VACTERL-associated malformations
3. Gravid or non-gravid women with a history of miscarriage and/or offspring with non-VACTERL-associated malformations
4. Willingness to abstain from red meat, meat products, chicken, peanuts, or brewer's yeast (including beer) at least 24 hours prior to blood and urine collection

Exclusion Criteria:

1. Parents of non-biological children
2. Children under 13 years of age
3. Children (13 and over) with congenital malformations associated with an identifiable environmental or lifestyle exposure
4. Children (13 and over) with congenital malformations associated with confirmed chromosomal disorders
5. Failure to abstain from red meat, meat products, chicken, peanuts, or brewer's yeast (including beer) at least 24 hours prior to blood and urine collection.

Contacts and Locations

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03799705***

Contacts

Contact: Heather LaBrec, BA 507-293-3446 LaBrec.Heather@mayo.edu

Contact: Kelly A Hogan, Ph.D. 507-284-0746 hogan.kelly@mayo.edu

Locations

United States, Minnesota

Mayo Clinic **Recruiting**

Rochester, Minnesota, United States, 55905

Contact: Heather LaBrec, BA 507-293-3446 LaBrec.Heather@mayo.edu

Contact: Kelly A Hogan, Ph.D. 507-284-0746 hogan.kelly@mayo.edu

Principal Investigator: Eduardo Chini, MD PhD

Sponsors and Collaborators

Mayo Clinic

Investigators

Principal Investigator: Eduardo Chini, MD PhD Mayo Clinic

More Information

Additional Information:

Mayo Clinic Clinical Trials

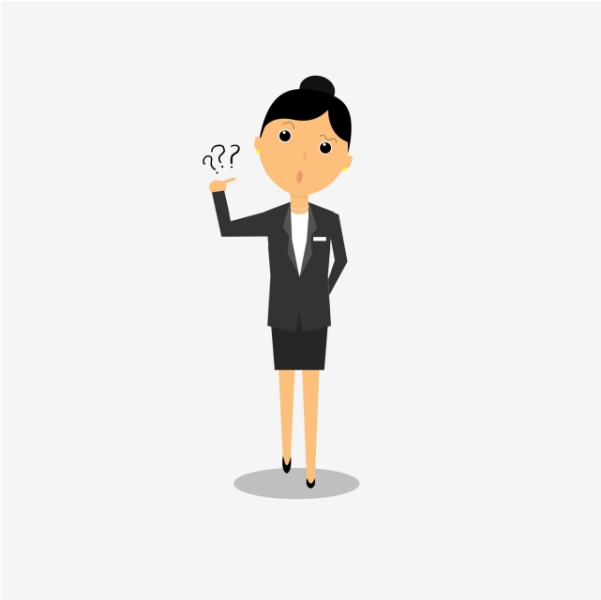
Responsible Party:	Eduardo N. Chini, Principal Investigator, Mayo Clinic
ClinicalTrials.gov Identifier:	NCT03799705 History of Changes
Other Study ID Numbers:	18-001135
First Posted:	January 10, 2019 Key Record Dates
Last Update Posted:	April 26, 2019
Last Verified:	April 2019

MAYO CLINIC

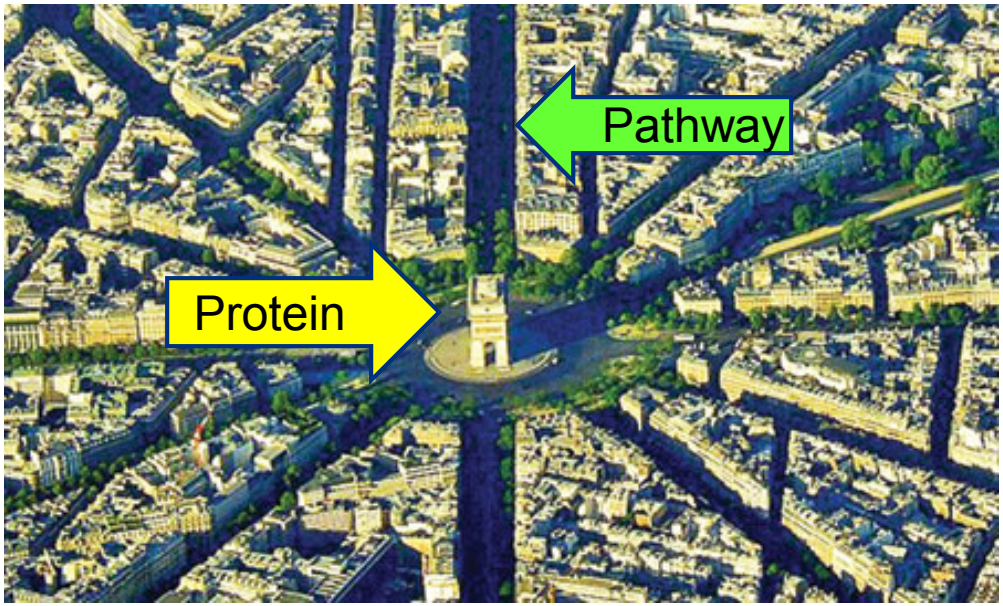
Preliminary Findings from a Group of GeneDx patients with VACTERL Diagnoses

In collaboration with Dr. Ben Solomon, GeneDx, Bethesda, MD

- How do we analyze a list of gene variants identified in people with VACTERL Association?



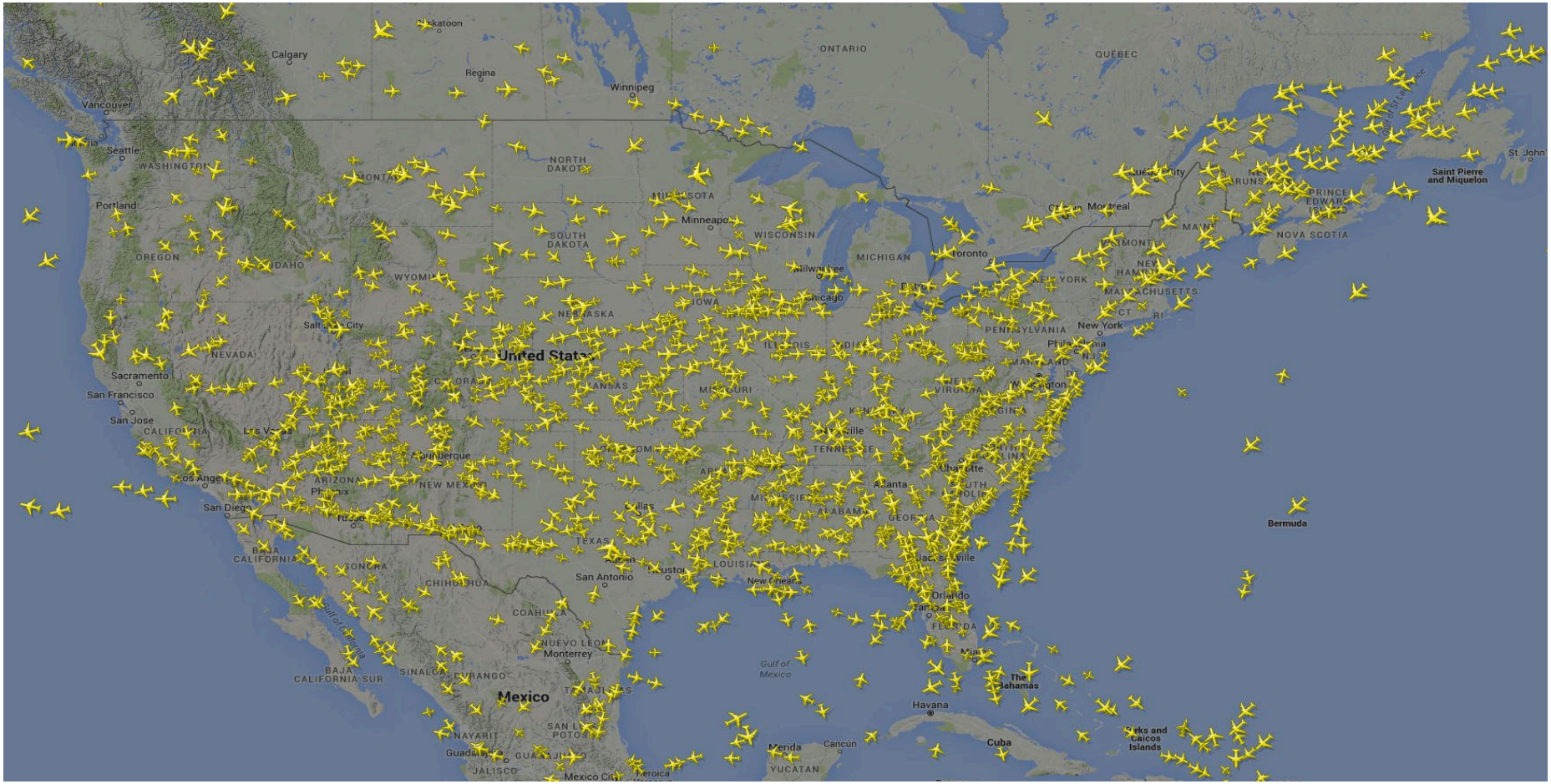
- We relate them to one another by performing ‘pathway’ or ‘network’ analysis.



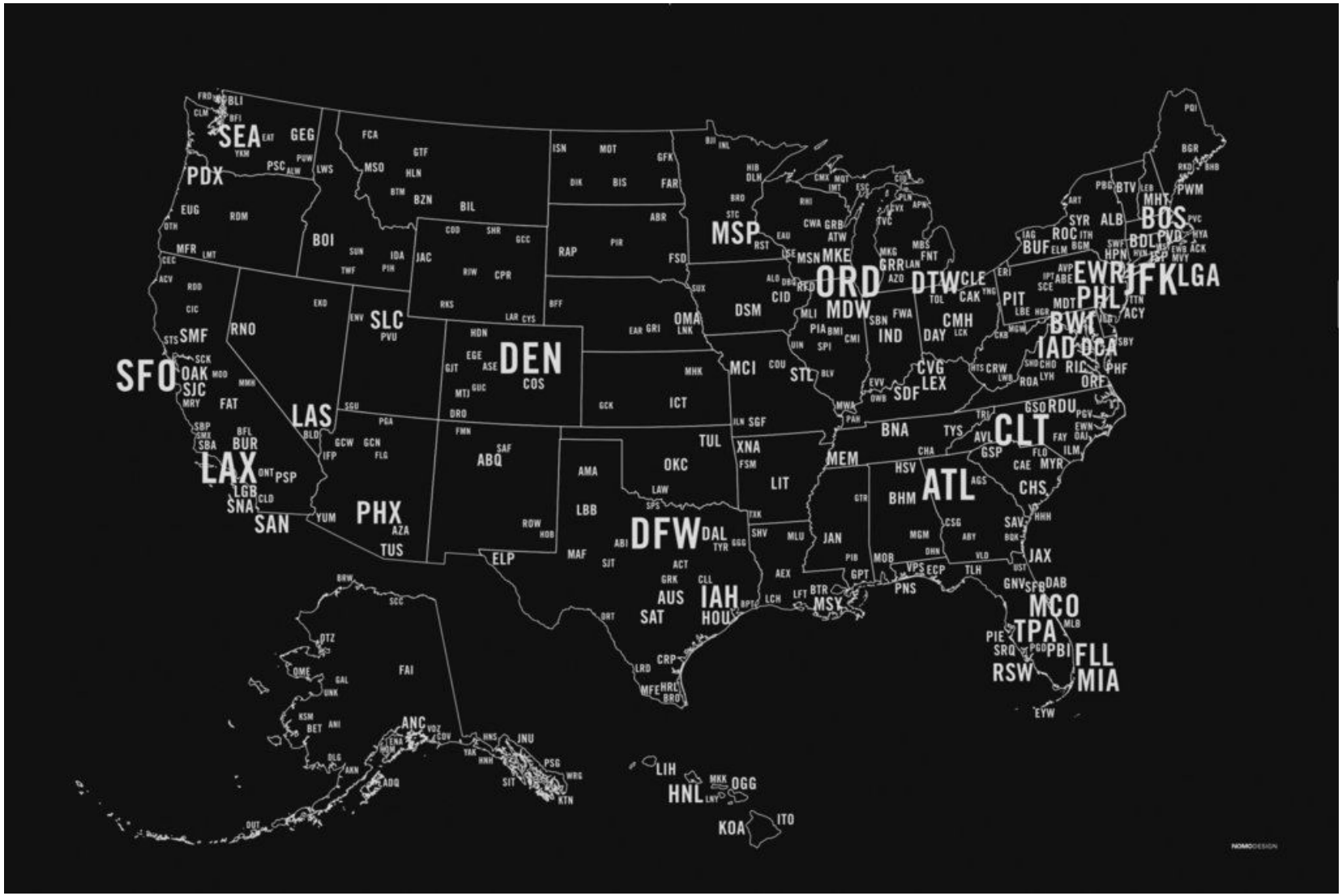
Examples of Real World Networks

- Information Networks
  - World Wide Web
  - Library catalog
- Social Media Networks
  - Facebook
  - Instagram
- Communication Networks
  - Telecommunications
  - Power Grids
  - **Transportation**

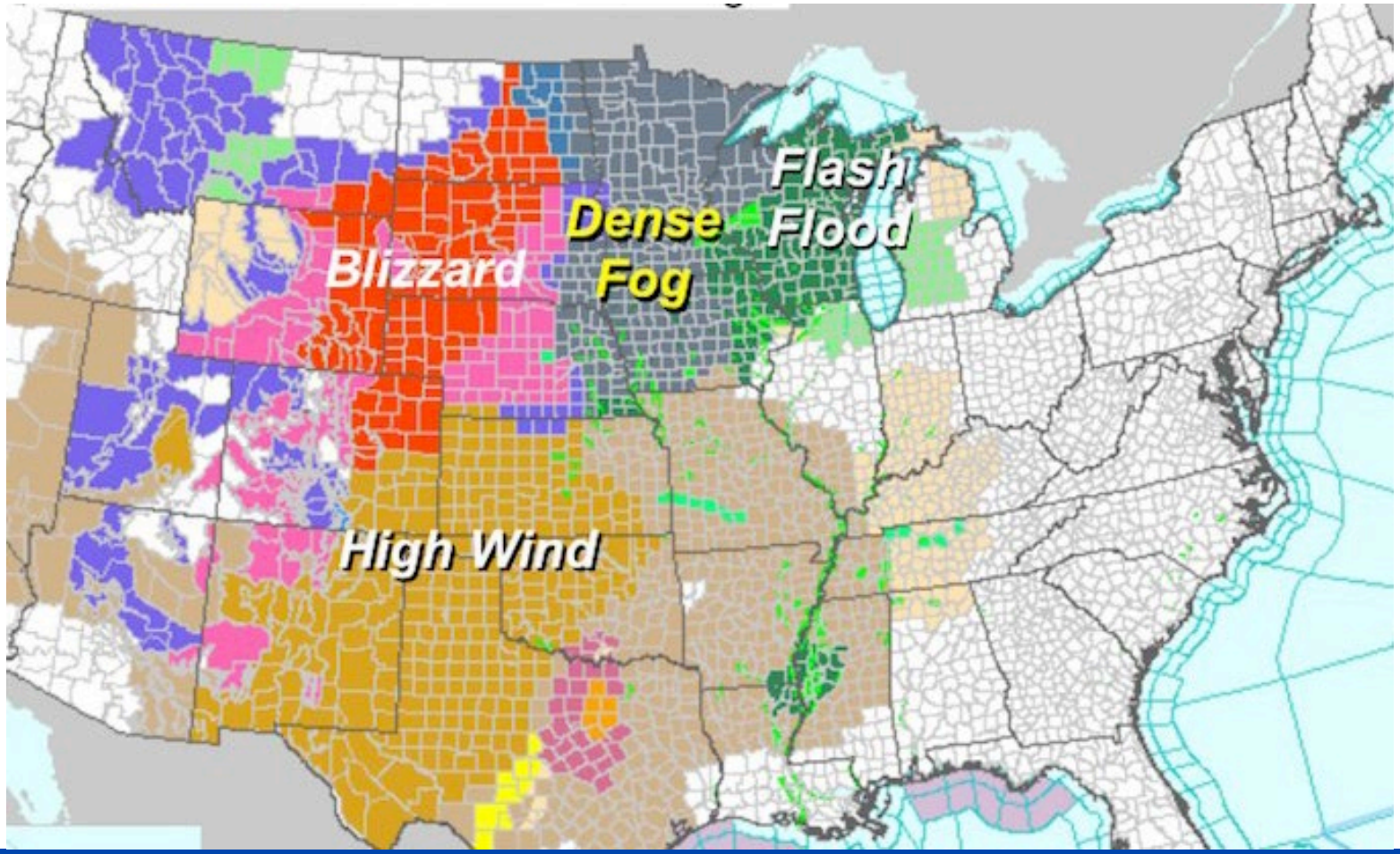
Flight Paths = Communication Pathways in and between Cells



Airport Destinations = Proteins



Factors affecting airline travel network



- **Weather** (can) result in changes to **flight paths** and arrival or departure from **airports**

- **Gene variants** (can) alter **communication** within and between cells by affecting **proteins** that drive **cellular processes**

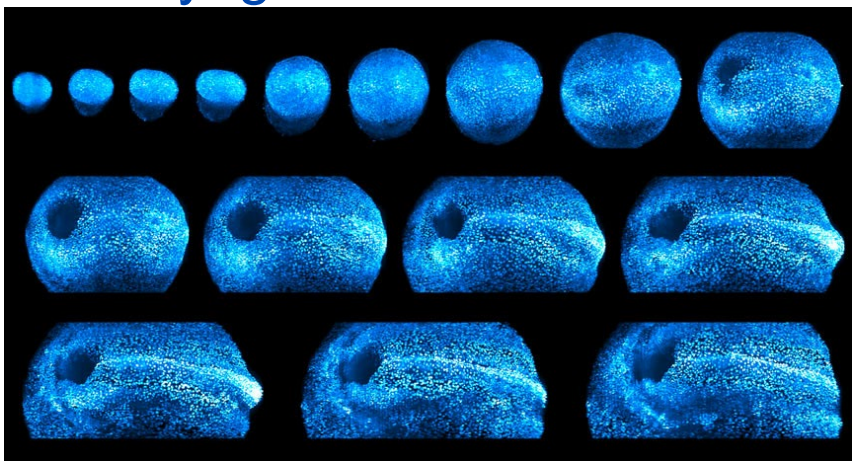
Examples of ‘cellular processes’

- Communication between the cellular environment and the nucleus
- Breakdown of our food into high energy molecules like ATP, which is made in the mitochondria
- Growth, repair and regeneration of cellular components
- Response to stress and maintenance of homeostasis (stability or equilibrium)

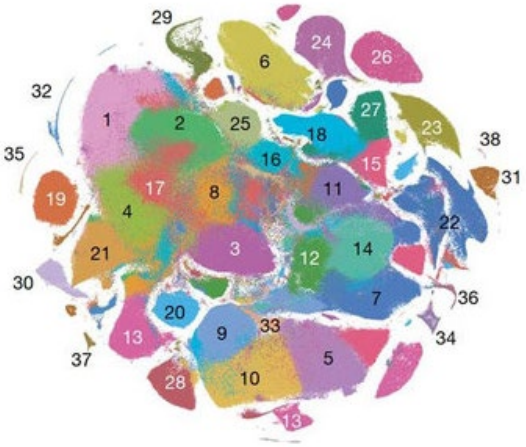
What do we learn from identifying cellular pathways altered by gene variants?

- Using web-based software:
  - ✓We identify **pathways** affected by gene variants
  - ✓We identify **periods of development** affected by affected pathways

- Embryogenesis



- Organogenesis



What we hope to learn by studying gene variants in VACTERL Association?

- **Pathway** alterations that impact early development
- **Interactions** between the mitochondrial and nuclear genomes
- **Frequency** of variants among populations
- **Hypothesis generation** for further studies in the lab

Food for Thought:
Does this study resonate for you?

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

From crisis to self-confidence and adaptation; Experiences of being a parent of a child with VACTERL association – A complex congenital malformation

Ann-Marie Kassa, Helene Engstrand Lilja, Gunn Engvall

Published: April 19, 2019 • https://doi.org/10.1371/journal.pone.0215751

- **Study Aim**
  - ✓To describe experiences of being a parent of a child with VACTERL Association

- **Method**
  - ✓Interviews with 10 mothers and 9 fathers

- **Results/Conclusions**
  - ✓'Crisis Reaction' upon diagnosis of child
  - ✓ *Participation* in care → *Shared responsibility* for care → *Adaptation* to daily care once medical support was established
  - ✓Discrepancies in knowledge and experience among healthcare professionals
  - ✓Importance of meeting other families

Questions?

- VACTERL research is benefactor-funded through the Department of Development, Mayo Clinic, Rochester, Minnesota

- On-going clinical study: **Identifying Genetic Variants in Nicotinamide Adenine Dinucleotide (NAD+) Synthesis Pathway in Patients With Congenital Malformations**
  - https://clinicaltrials.gov/ct2/show/NCT03799705
  - Contact LaBrec.Heather@mayo.edu

- Follow @Loose_Lab_Rat on Twitter

