A New Era in Therapies for Rare Diseases
The Alice Approach: Down the Rabbit Hole and Back Up Again

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Disclosures

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- Alexion
- Reynolds family
- Wilson family
- Burch family
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- Stealth
- PTC Therapeutics
- Synlogic
- Kriya
- Agios
- LogicBio

Consulting

- BioMarin
- BioLogic
- Synlogic
- JNANA
- Sanofi
- Axcella Health
- Homology
- Agios
- Applied Therapeutics

Why study rare diseases?

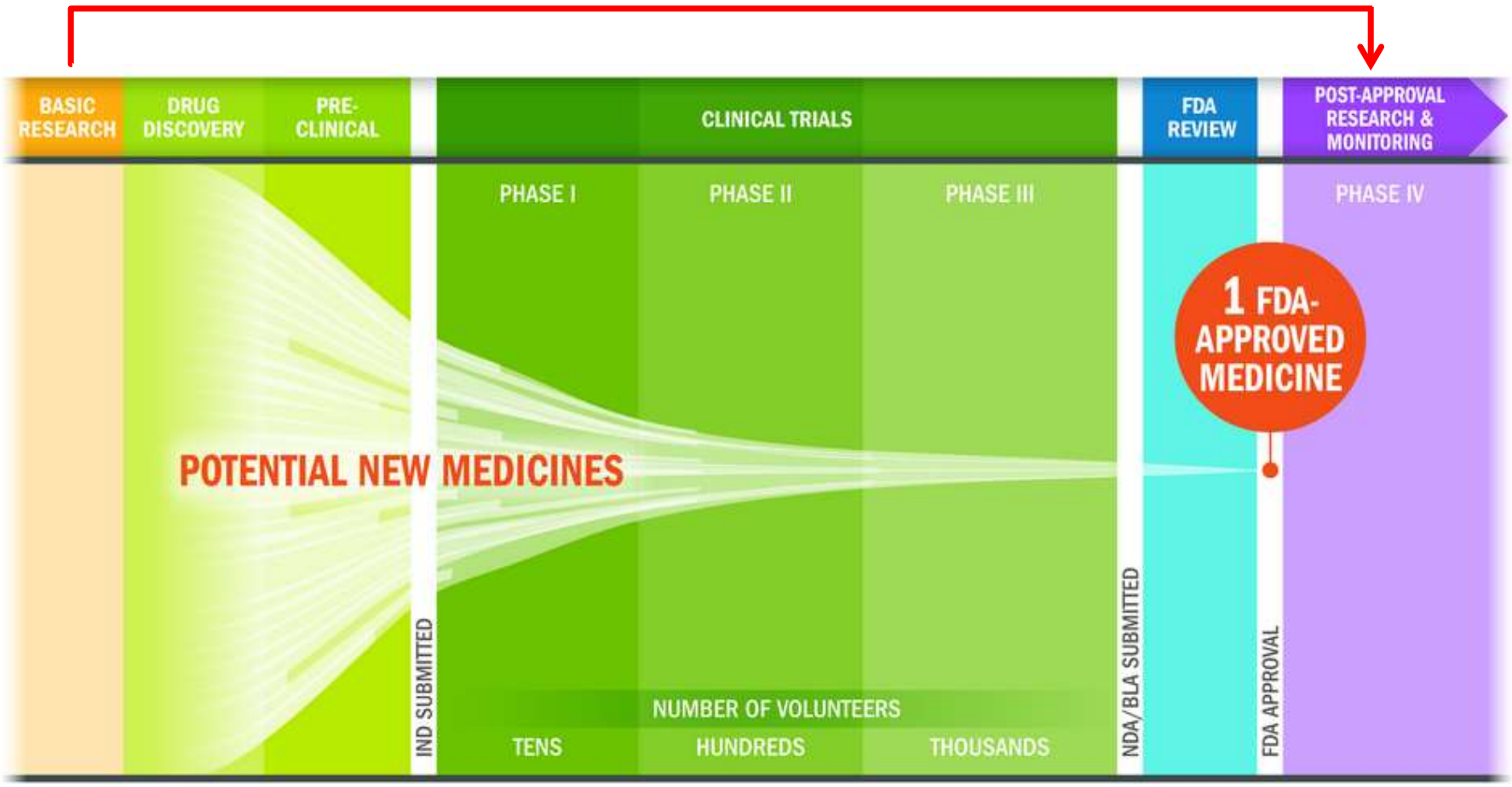
Surprising statistics

- 3% of infants are born with a genetic problem
- 0.5% of babies have an inborn error of metabolism
- 40% of infant and childhood mortality
- 50% of childhood hospital admissions
- 25% of adult hospital admissions

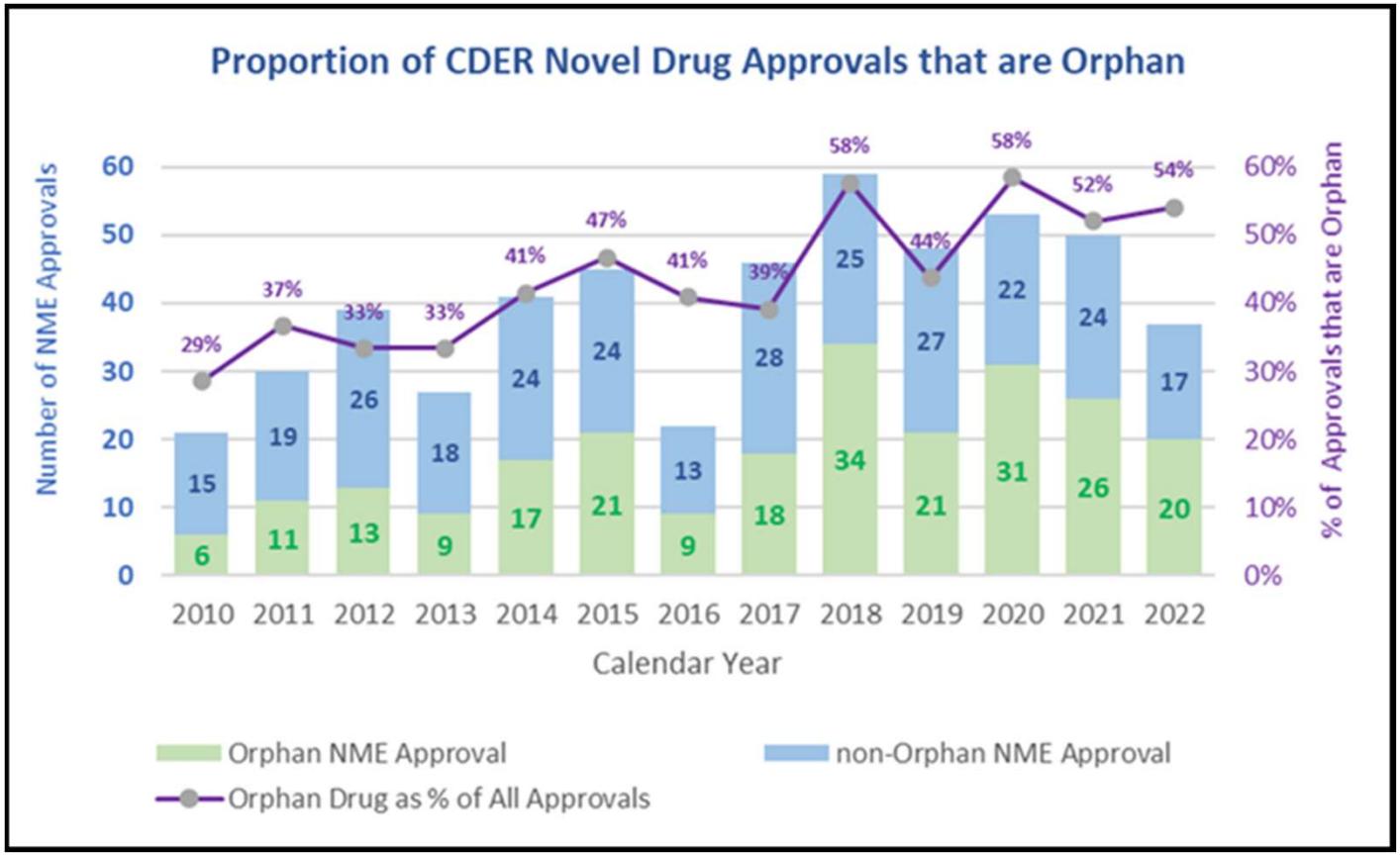
The problem in IEMs

- Metabolites need to proceed to the right place at the right speed at the right time in metabolic pathways
- Blocks have two consequences
  - A deficit of what is supposed to be coming through the pathway
  - Build up of compounds that shouldn't be there behind the block
- Either or both can lead to clinical symptoms

Drug development pipeline

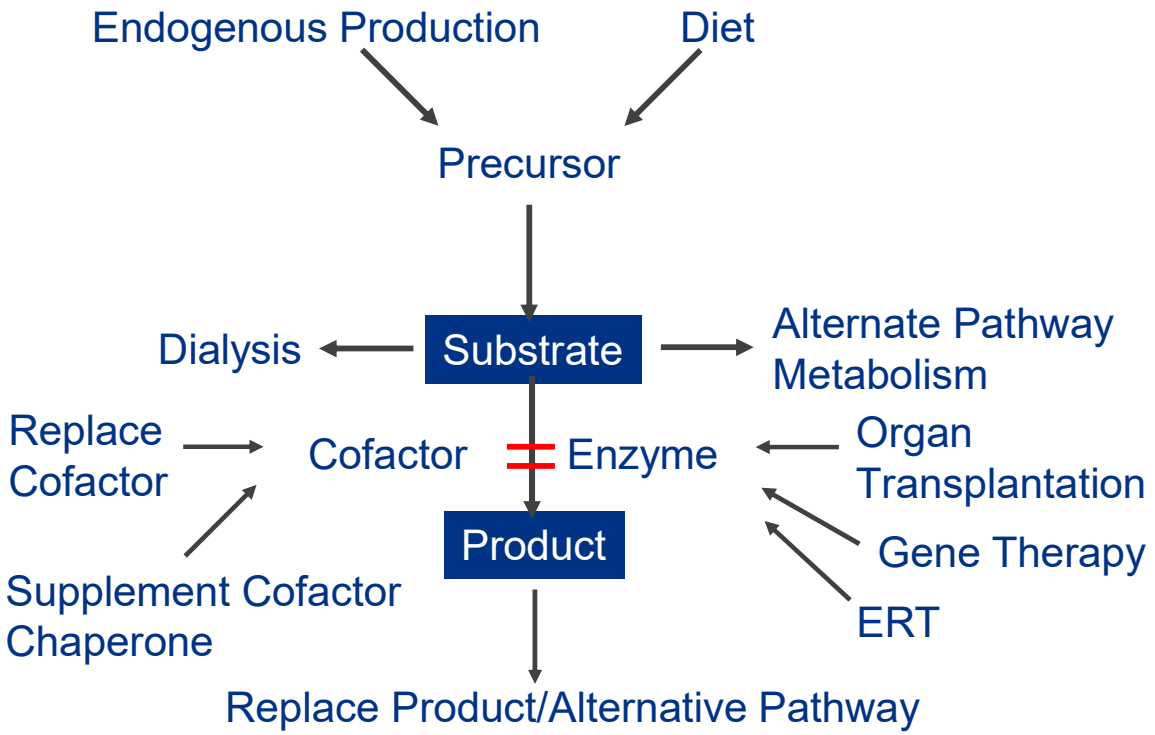


Center for Drug Evaluation and Research



Options for therapy

- Replace/substitute/stabilize enzyme
- Replace product
- Reduce substrate
- Remove toxin
- Supplement cofactor
- Activate alternative pathways for metabolism
- Provide alternative substrates




HOW DO WE
GET THERE FROM HERE?
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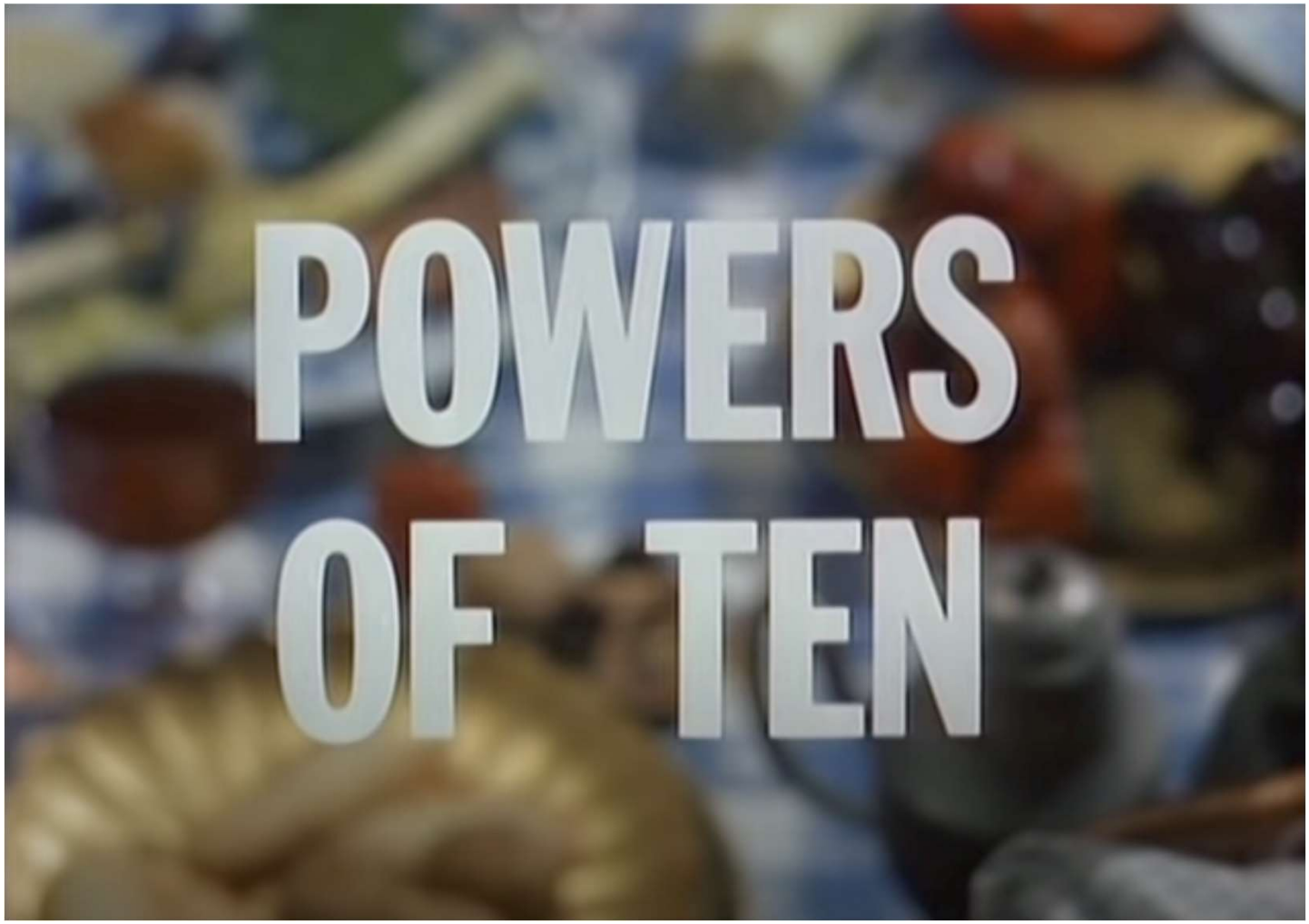
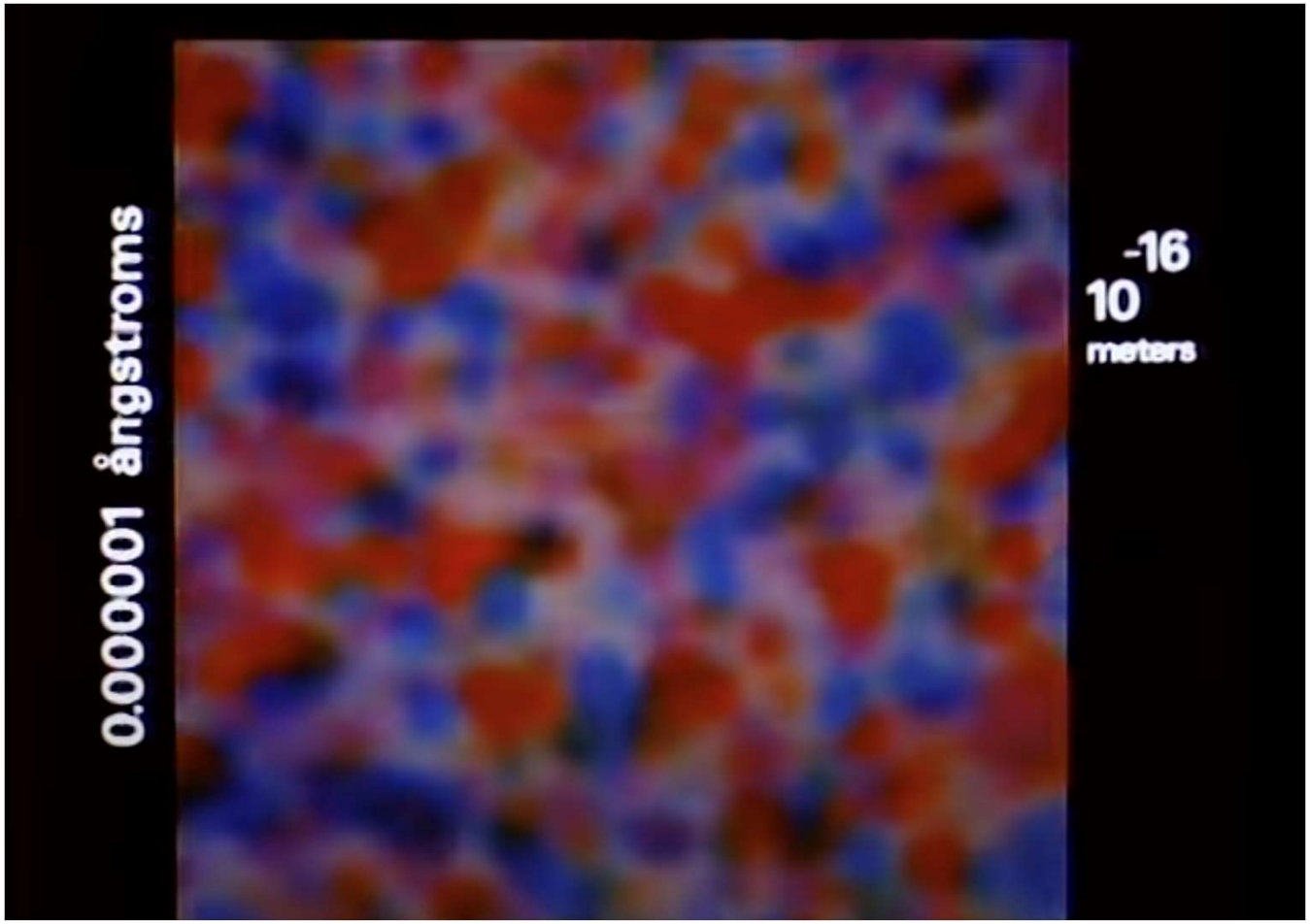
The right way?

The Alice approach



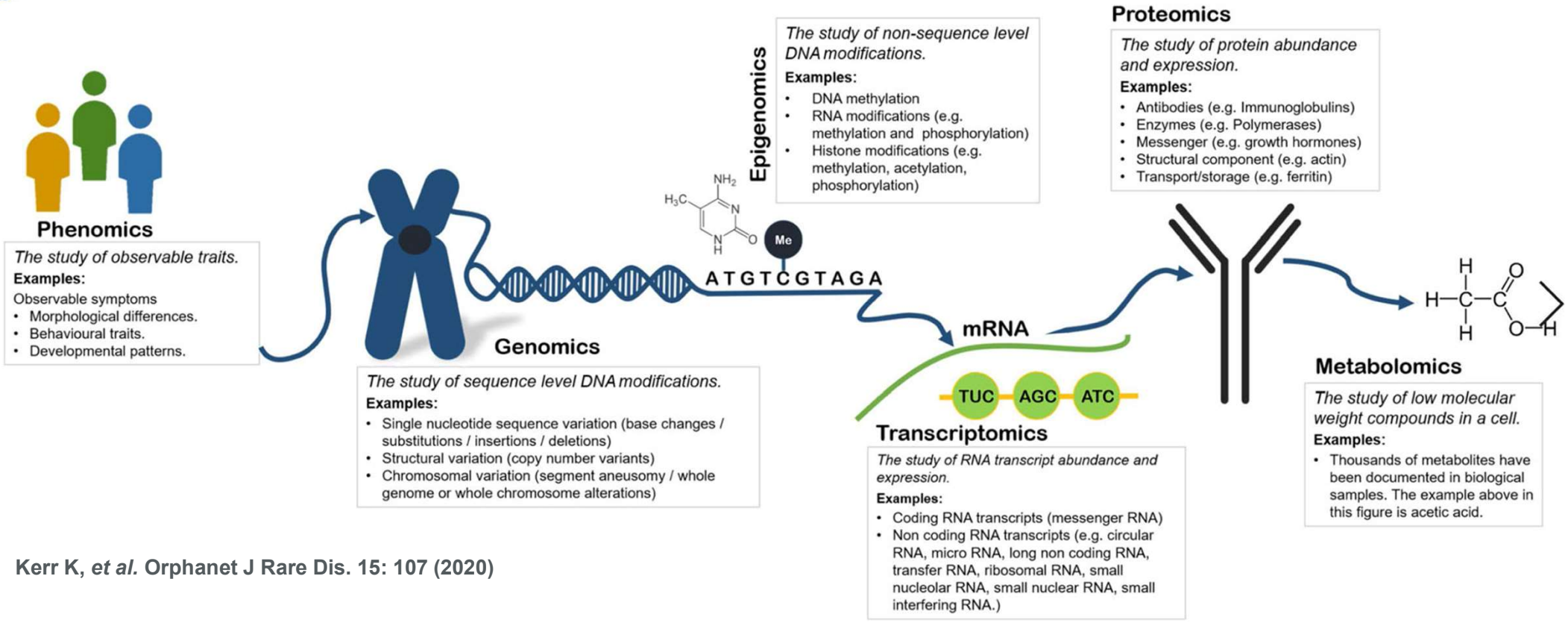
https://www.google.com/search?client=safari&rls=en&q=powers+of+10+video&ie=UTF-8&oe=UTF-8#fpstate=ive&vld=cid:f8c8d350,vid:0fKBhvDjuy0

Down the rabbit hole



Back up again

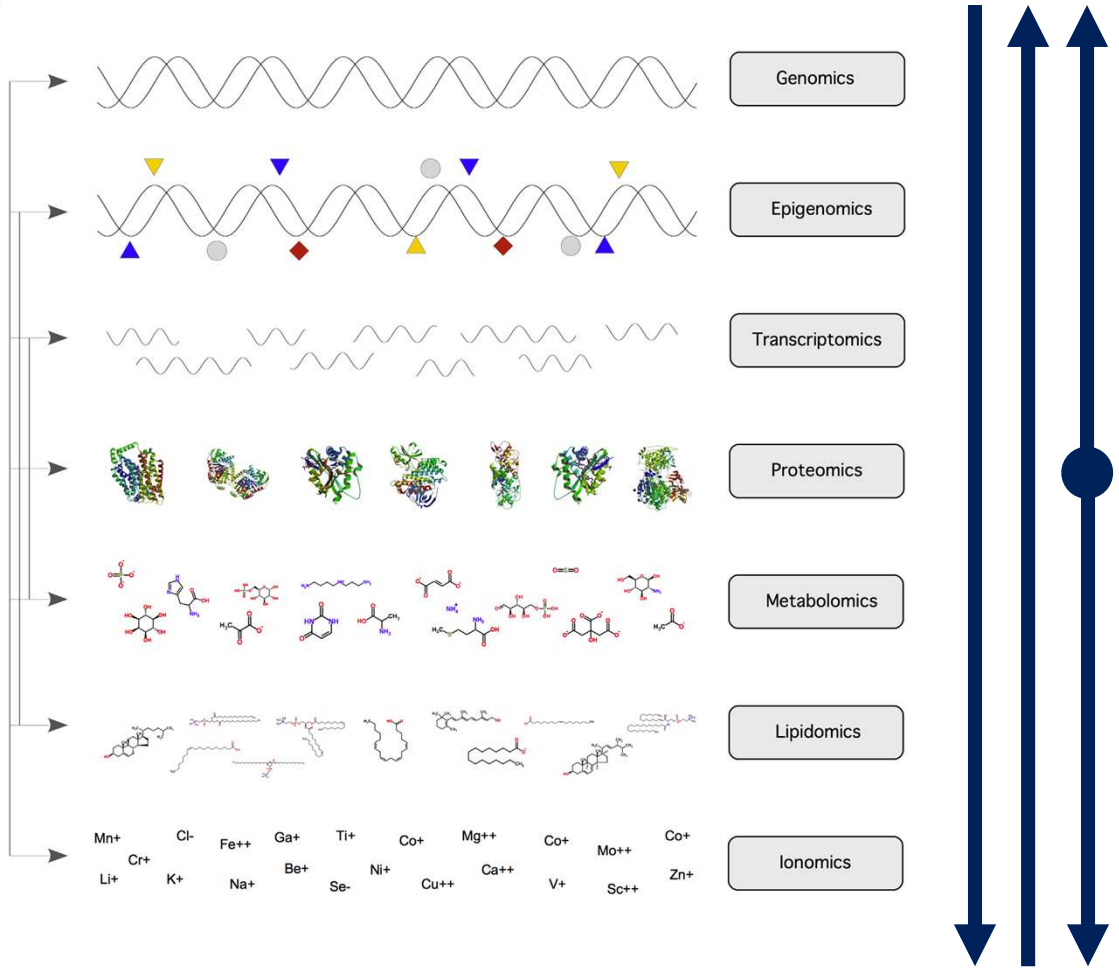
‘Omics



Kerr K, *et al.* Orphanet J Rare Dis. 15: 107 (2020)

The comprehensive study of the roles, relationships, and actions of various types of molecules in cells of an organism

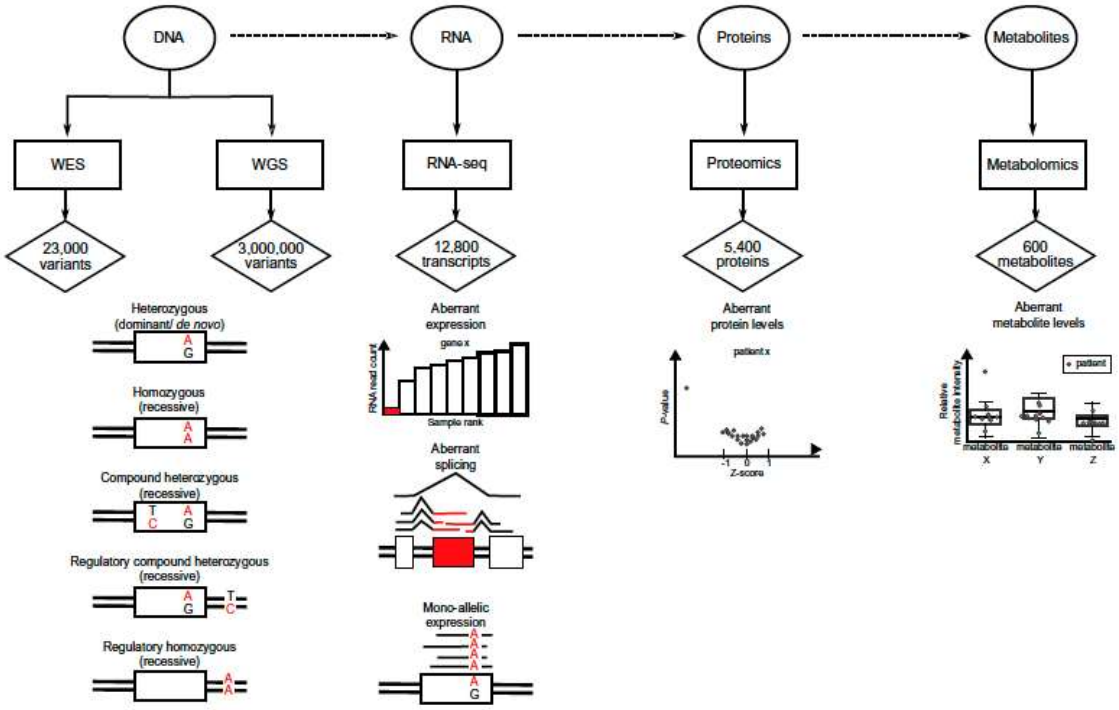
Additional ‘omics



- Technology driven
- Nucleic acid based ‘omics are most robust
- Proteomics and metabolomics remain more limited in spectrum
- Statistical methods of integration are in infancy
- Multivectoral

A numbers game

- Most information, but most variation at DNA level
- RNA sequence is limited to the transcriptome, but can identify splicing variants
- Protein identification is more limited but often the closest biomolecule to a disease
- Metabolomics most limited in scope but reveals patterns that are useful beyond a single diagnostic metabolite



Kremer, *et al.* 2018. *J Inherit Metab Dis*, 41: 525-32.

Goals of multi-omics approach

- Improve diagnosis
- Understand pathophysiology
- Study disease variability
- Identify biomarkers
- Monitor therapies

Combined D,L-2 hydroxyglutaric aciduria

An integrated example

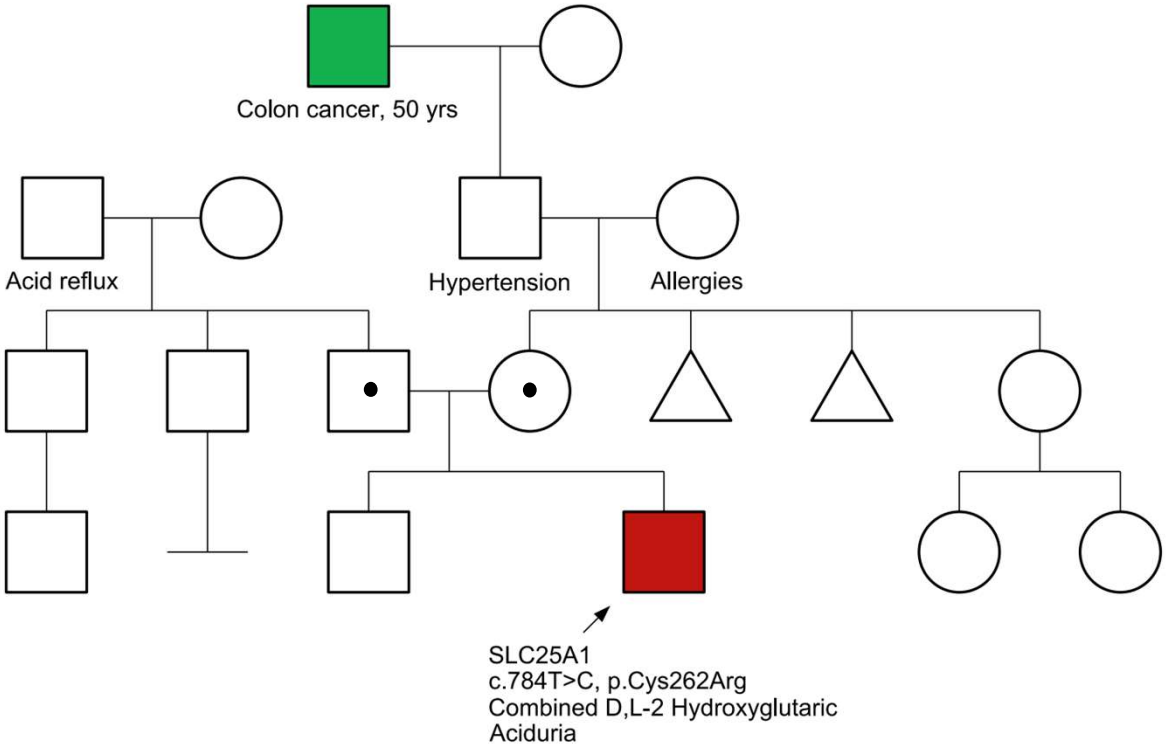
- Chief complaint
  - Hypotonia, apnea, feeding issues
  - Progressive developmental delay, seizures, profound swallowing and aspiration
- Labs
  - Plasma amino acid: Unremarkable
  - Very long chain fatty acid: Reduced C22, C24 and C26
    - Urine organics screen: TCA metabolites and 2-hydroxyglutaric

Metabolites	UOA_1	UOA_2
2-hydroxyglutaric + Artifact	3.24	
2-hydroxyglutaric		1.38
Succinic		1.35
Internal standard	1	1

Bhatia, et al. 2022. In preparation

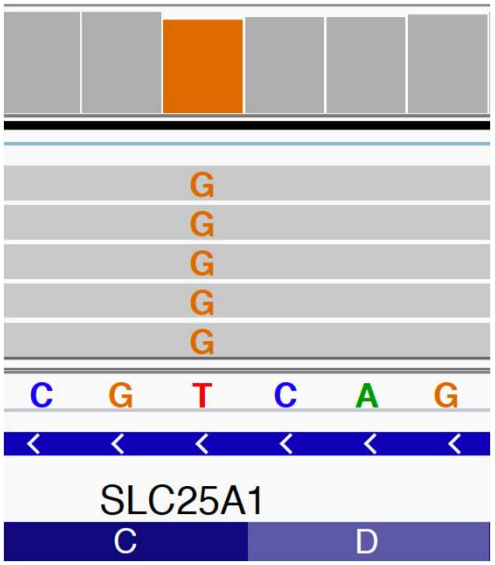
Whole exome sequencing

Homozygous likely pathogenic variant in *SLC25A1*

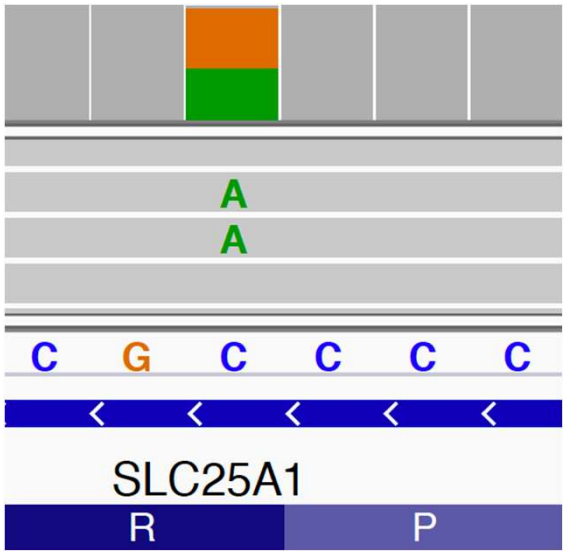


RNA-seq shows abnormal splicing

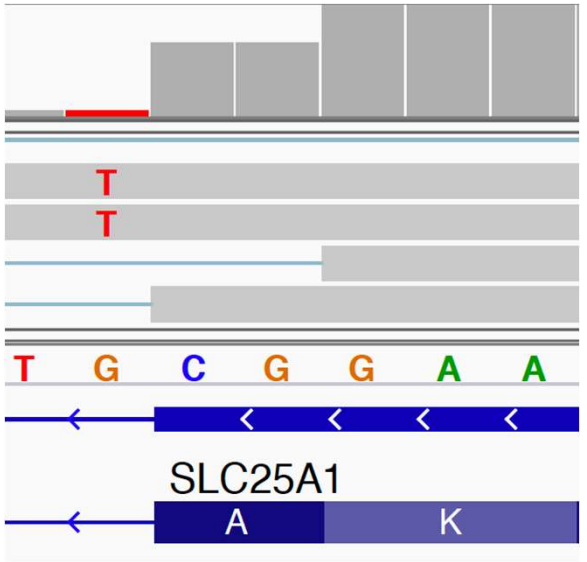
FB893
c.784T>C



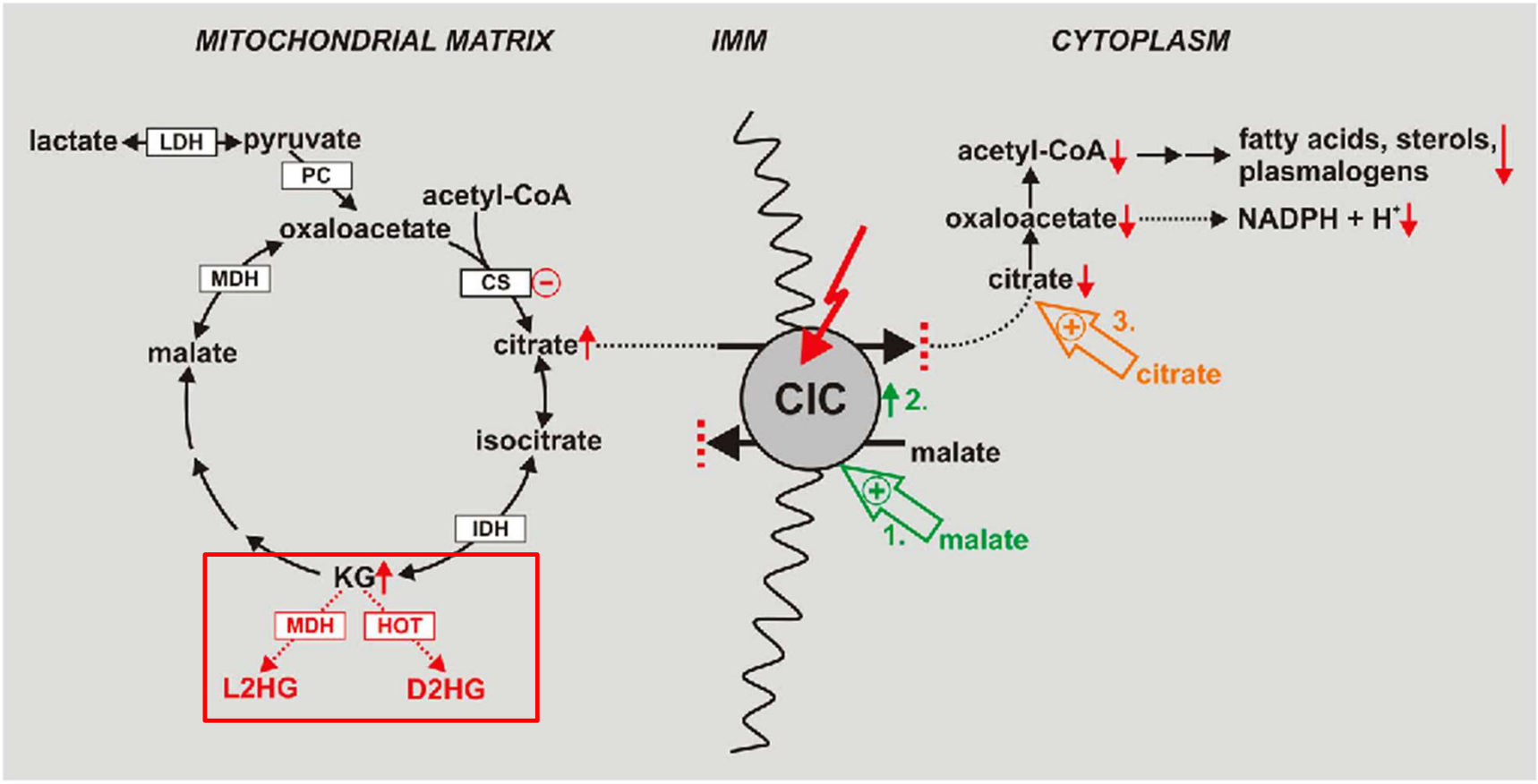
FB897
c.844C>T (p.Arg282Cys)



FB897
c.821+1G>A



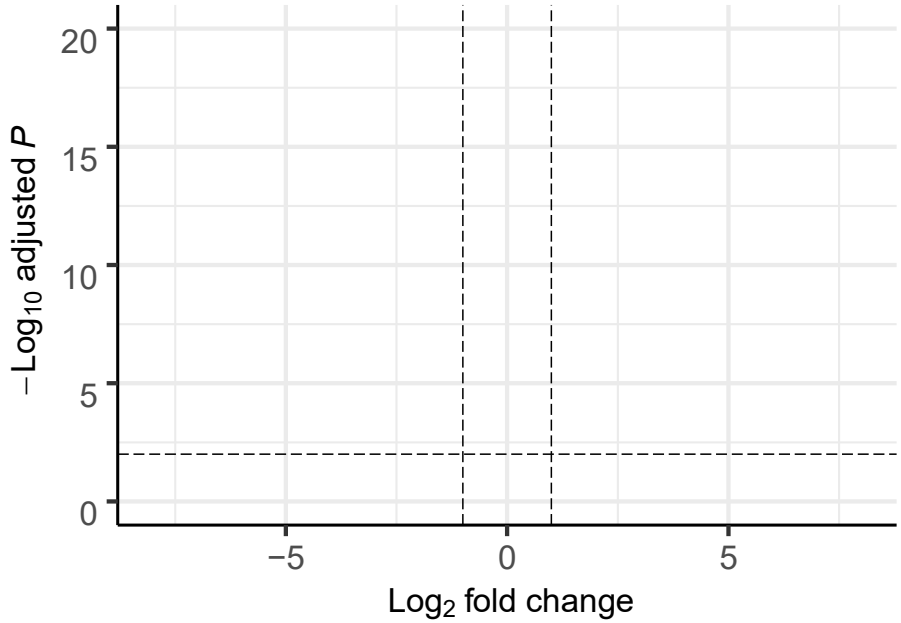
SLC25A1 encodes mitochondrial citrate carrier (CIC)



Muhlhausen C. et al. (2014) JIMD

TCA gene expression unchanged

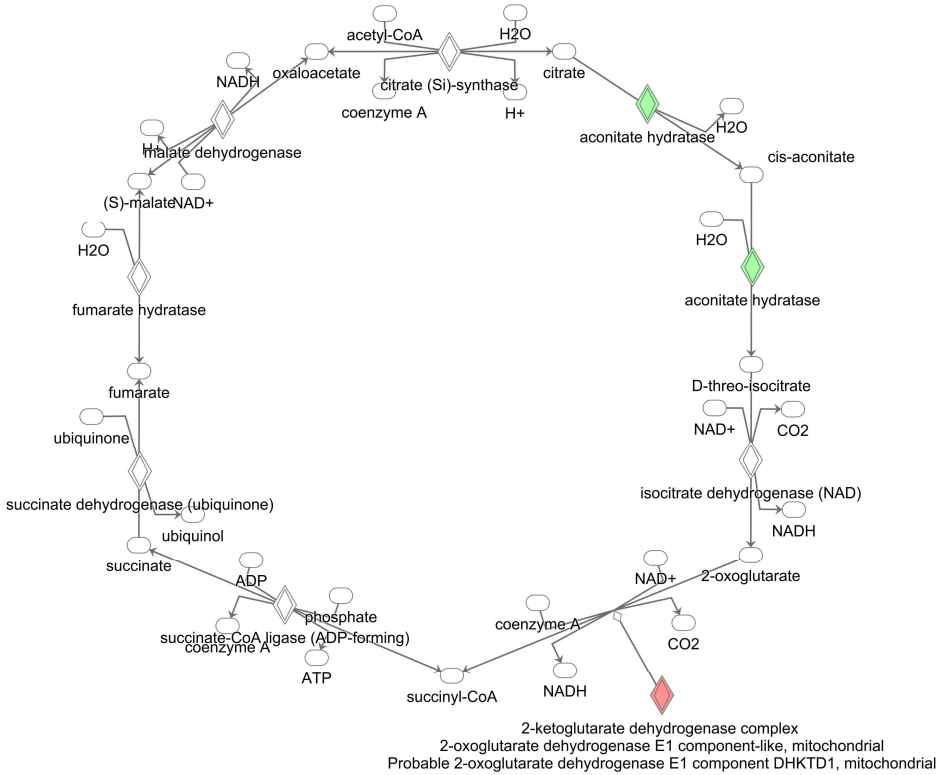
Patients vs. Controls



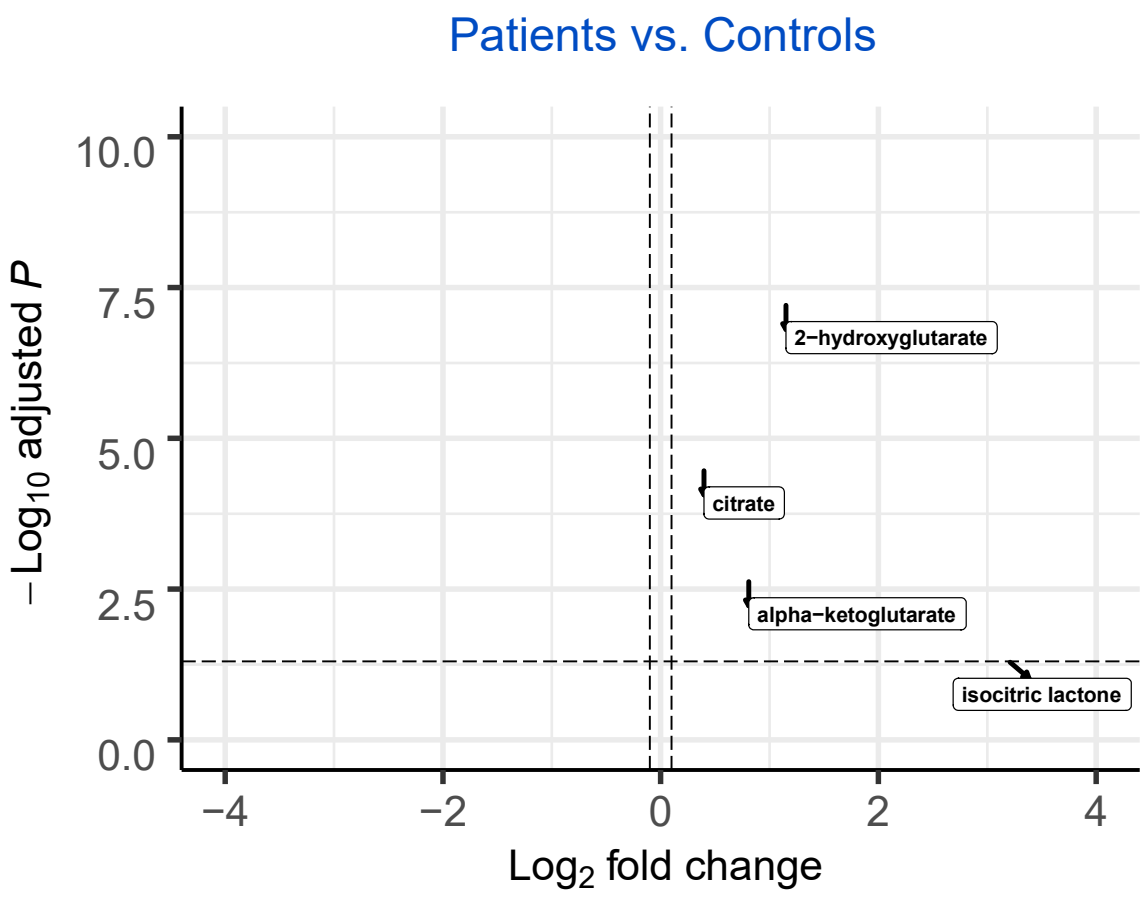
Downregulated
1453

Upregulated
1167

NS Log_2 FC p−value p – value and log_2 FC

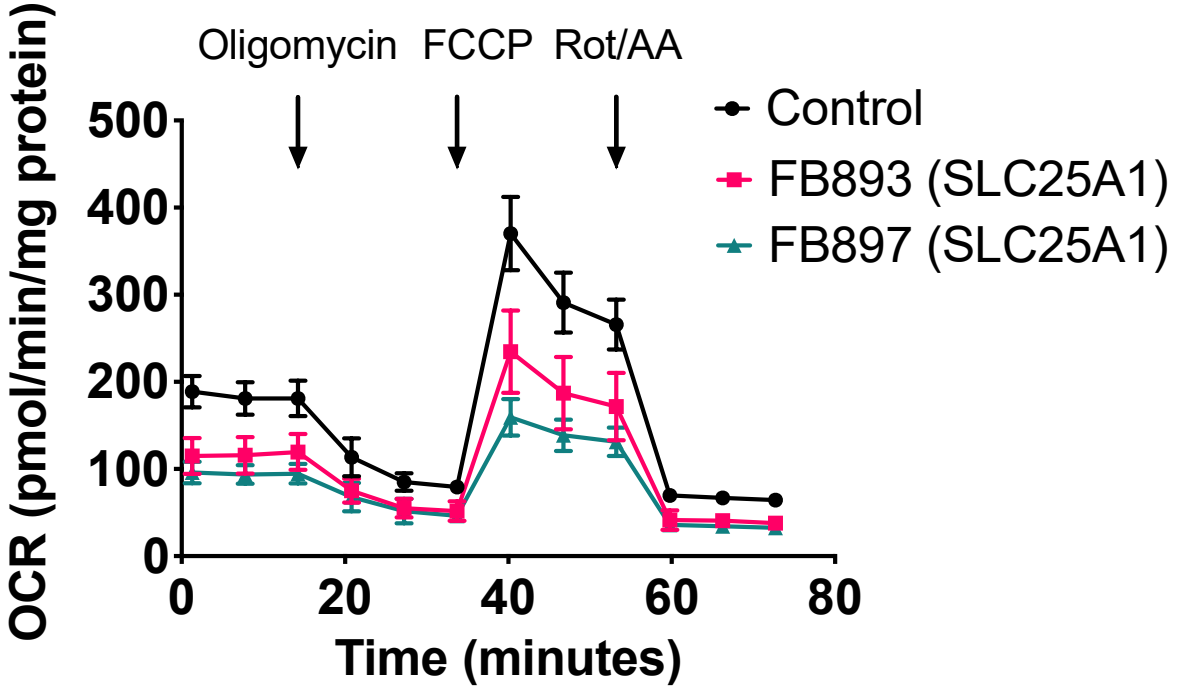


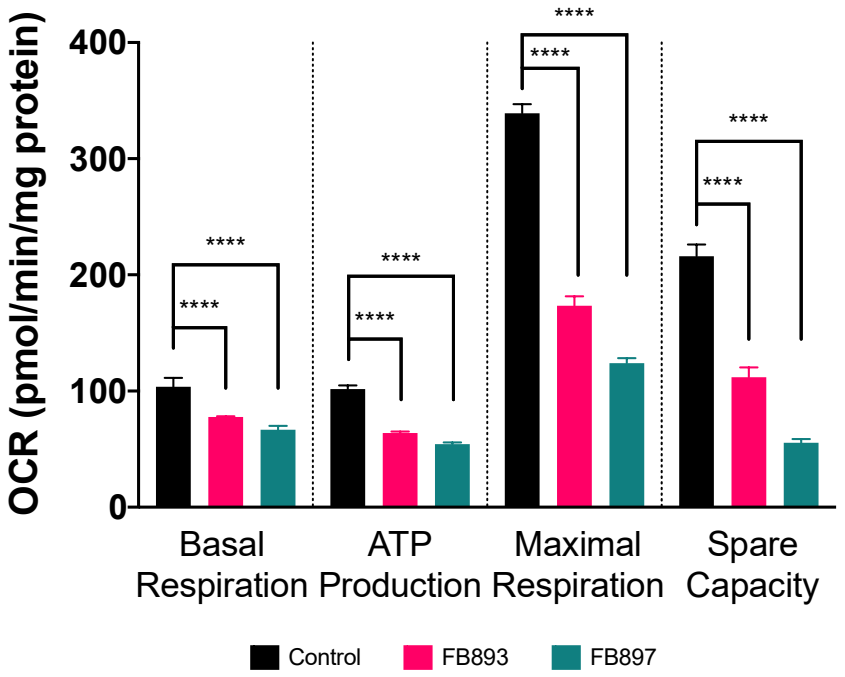
Metabolomics validates biochemical phenotype



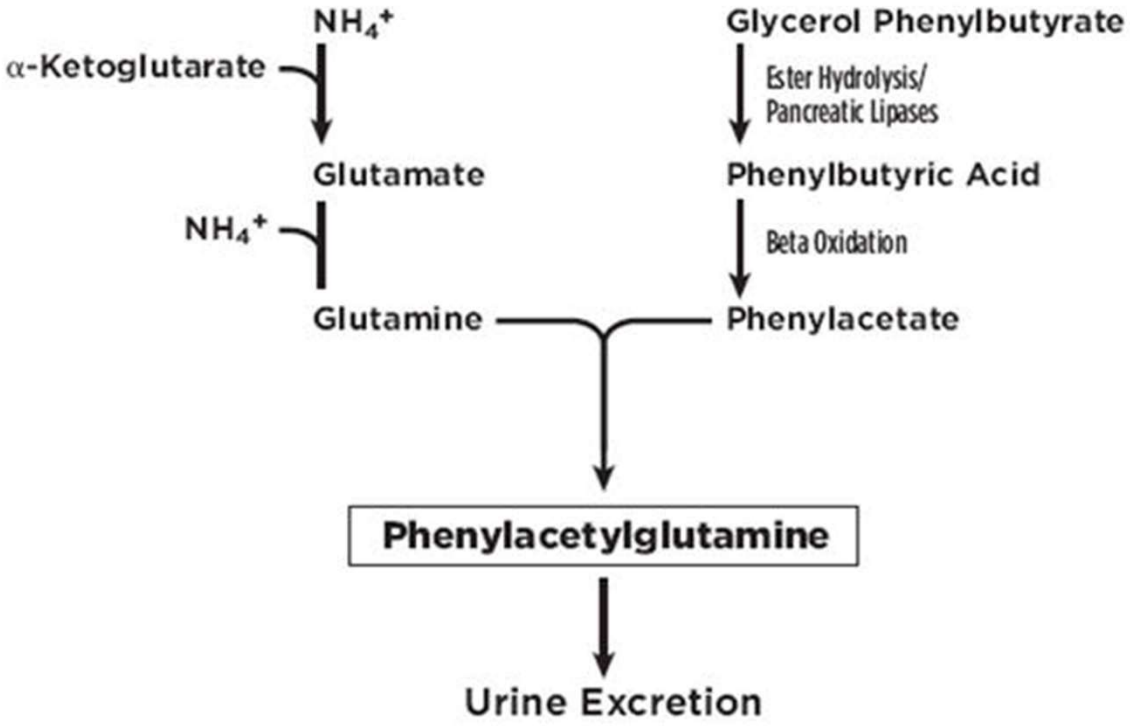
A bioenergetic deficit in patient fibroblasts

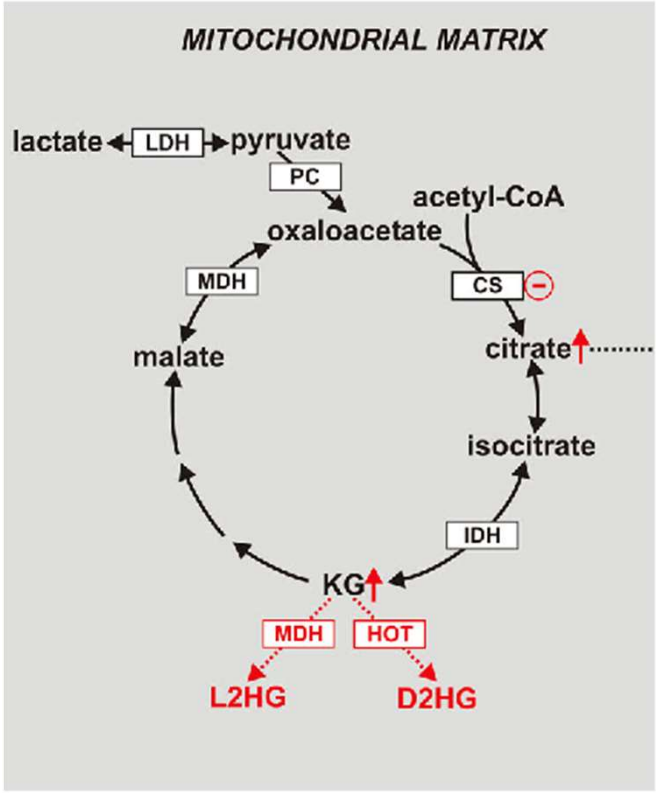
Seahorse Bioanalyzer studies



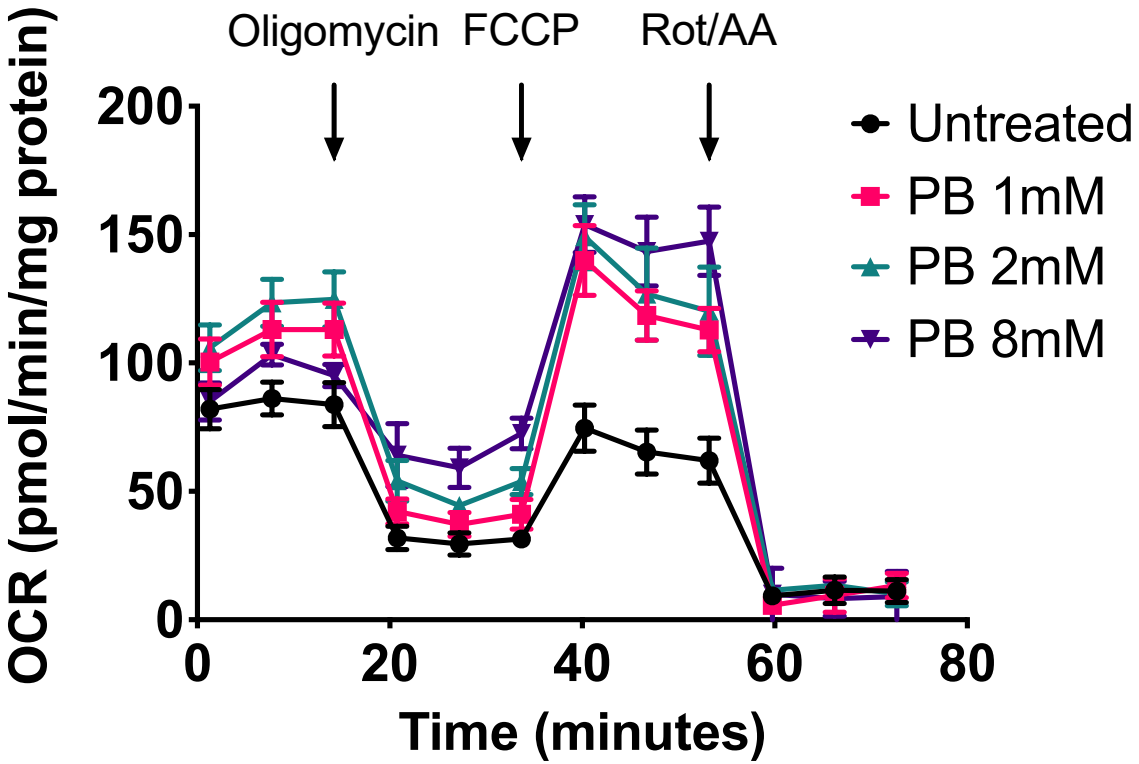


Phenylbutyrate depletes mitochondrial 2KGA

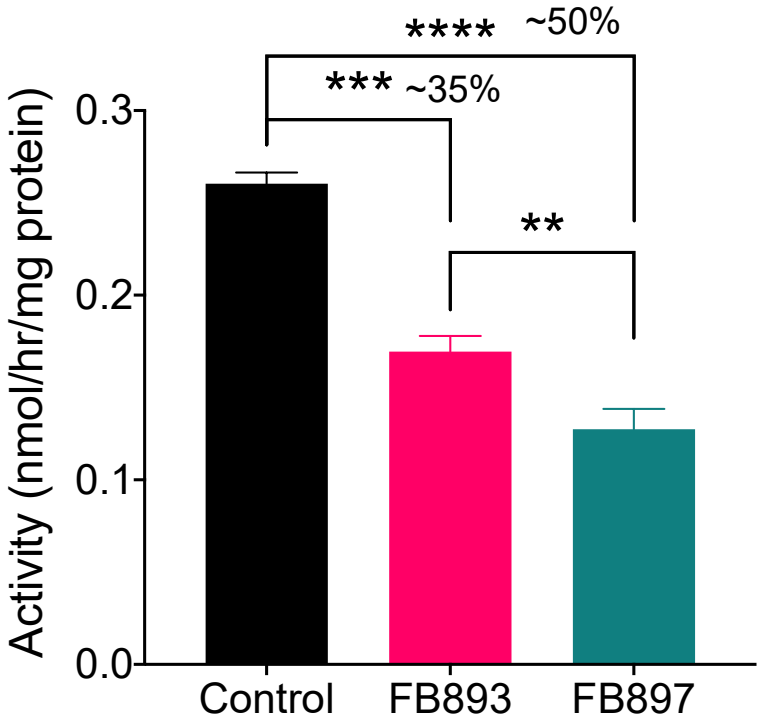


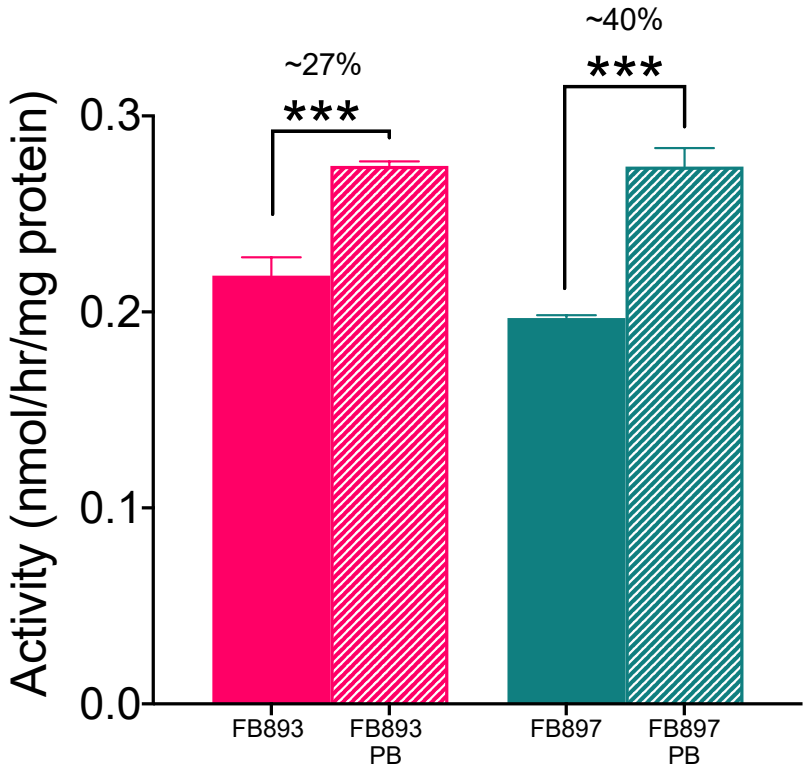


PB improves patient fibroblast bioenergetics



PB improves fibroblast fatty acid oxidation

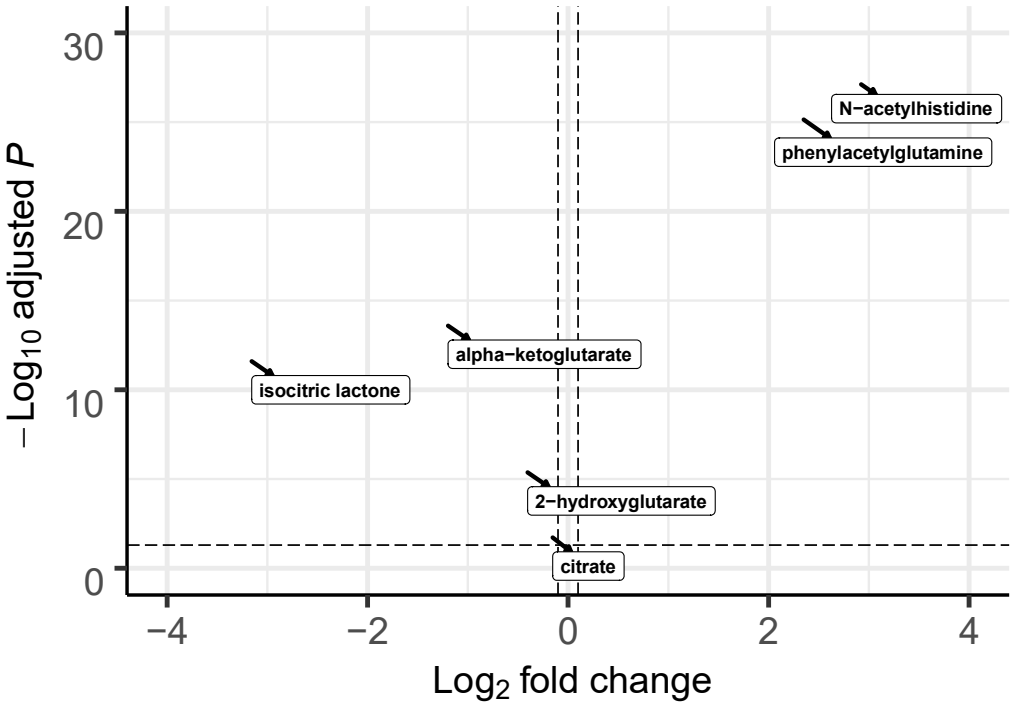


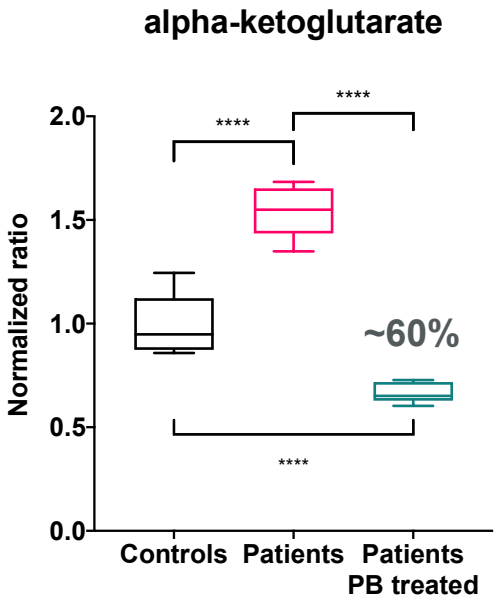


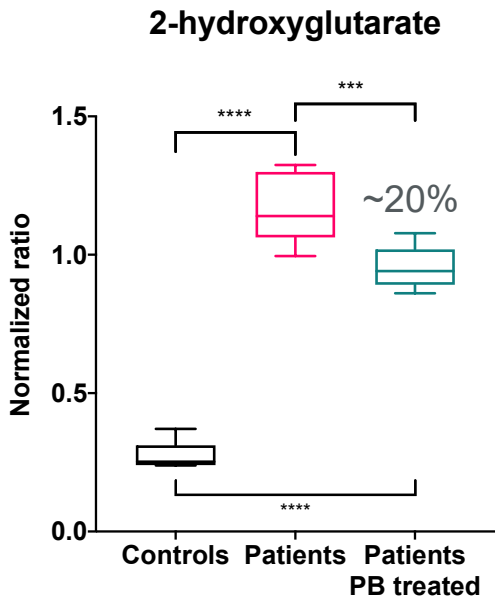
Olivia D'annibale

PB reduces 2-KG and 2-HG

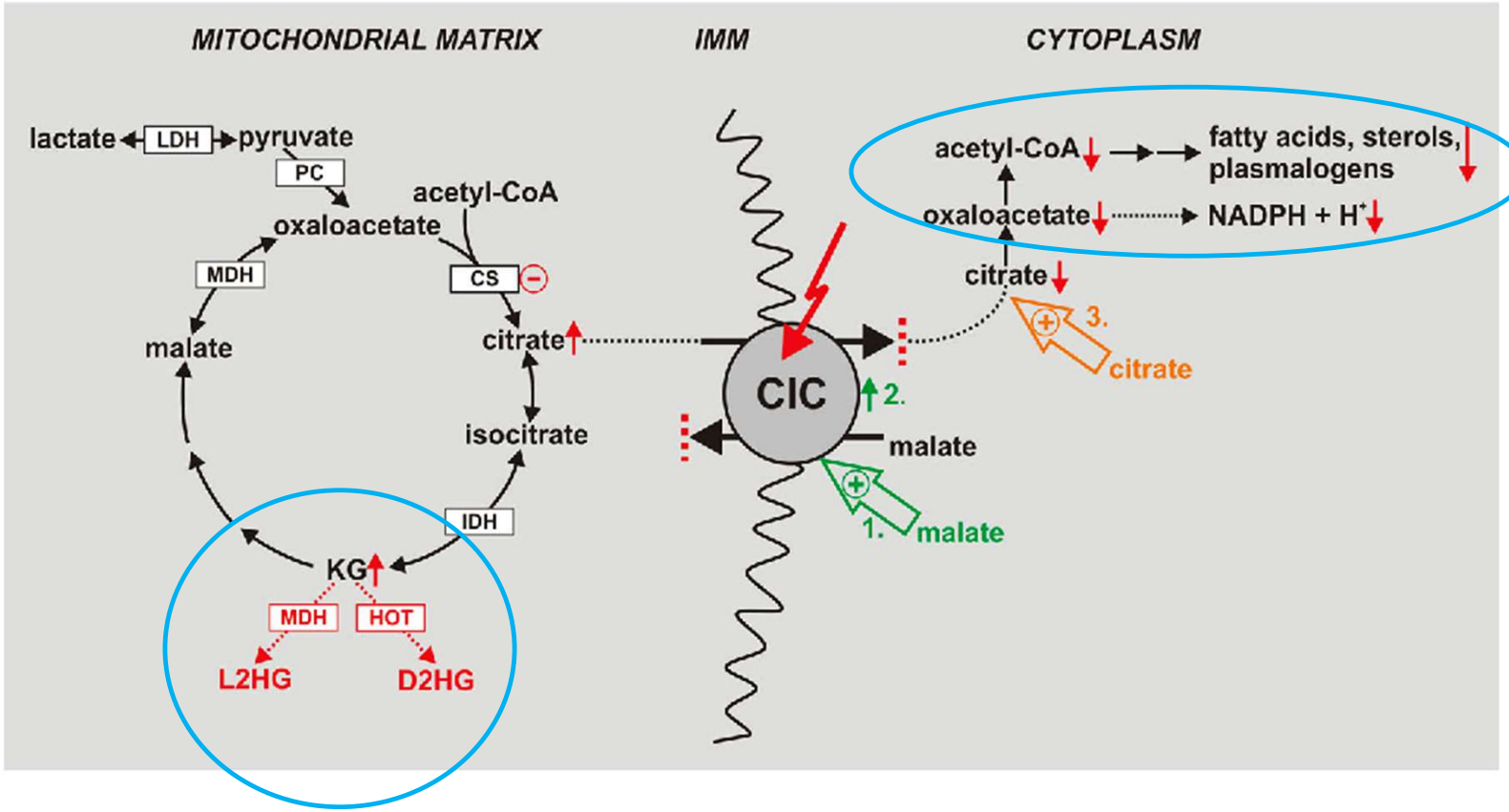
Patients-PB treated vs. Patients-Untreated







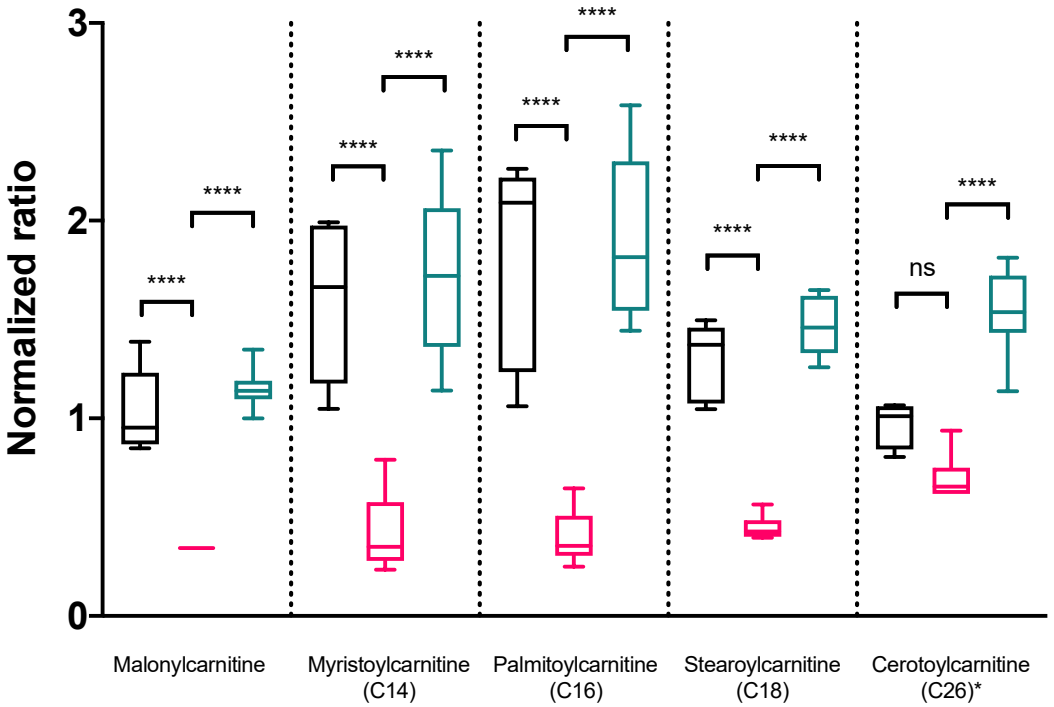
Potential complex lipid synthesis defect in DL2HG

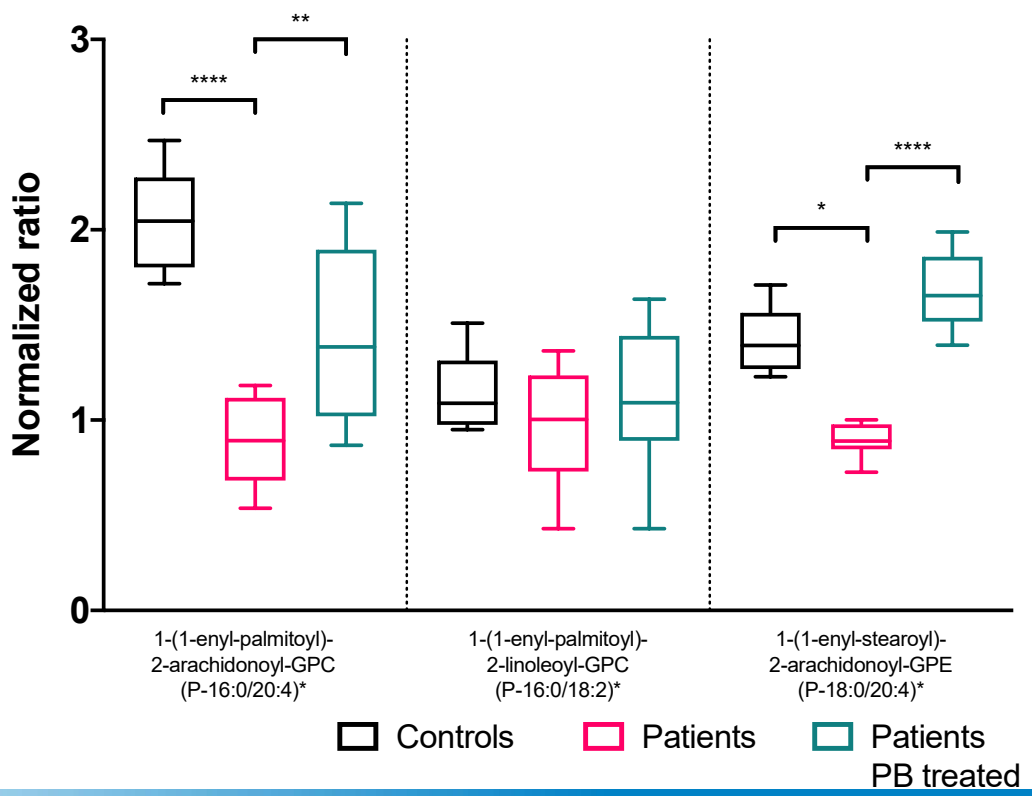


Phenylbutyrate

Muhlhausen C. et al. (2014) JIMD

Dysregulated ACNs and complex lipids

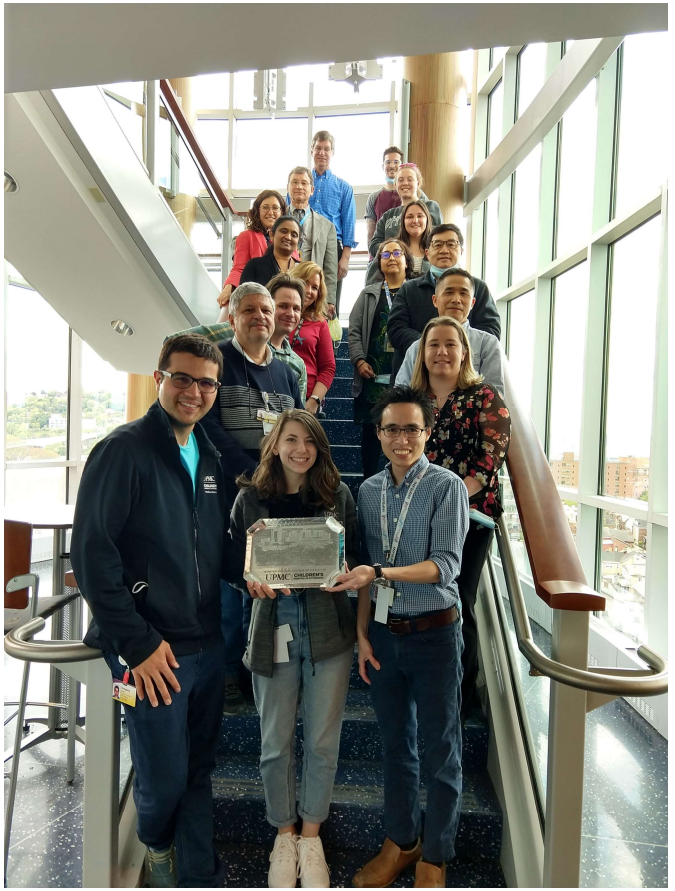




Summary

- Traditional drug development pipelines don’t work for rare diseases
- Extensive understanding of pathophysiology of IEMs provides insight into target and options for designing drugs
- Multiomics provides unique insights into IEMs
- New technologies make screening candidate drugs easier
- Still need FDA/EMA recognition of novel trial design for approval of drugs for rare diseases

Thanks to my lab and collaborators



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Thank you