Challenges in Developing precision therapeutics

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Vagelos College of Physicians and Surgeons

IGM Institute for Genomic Medicine

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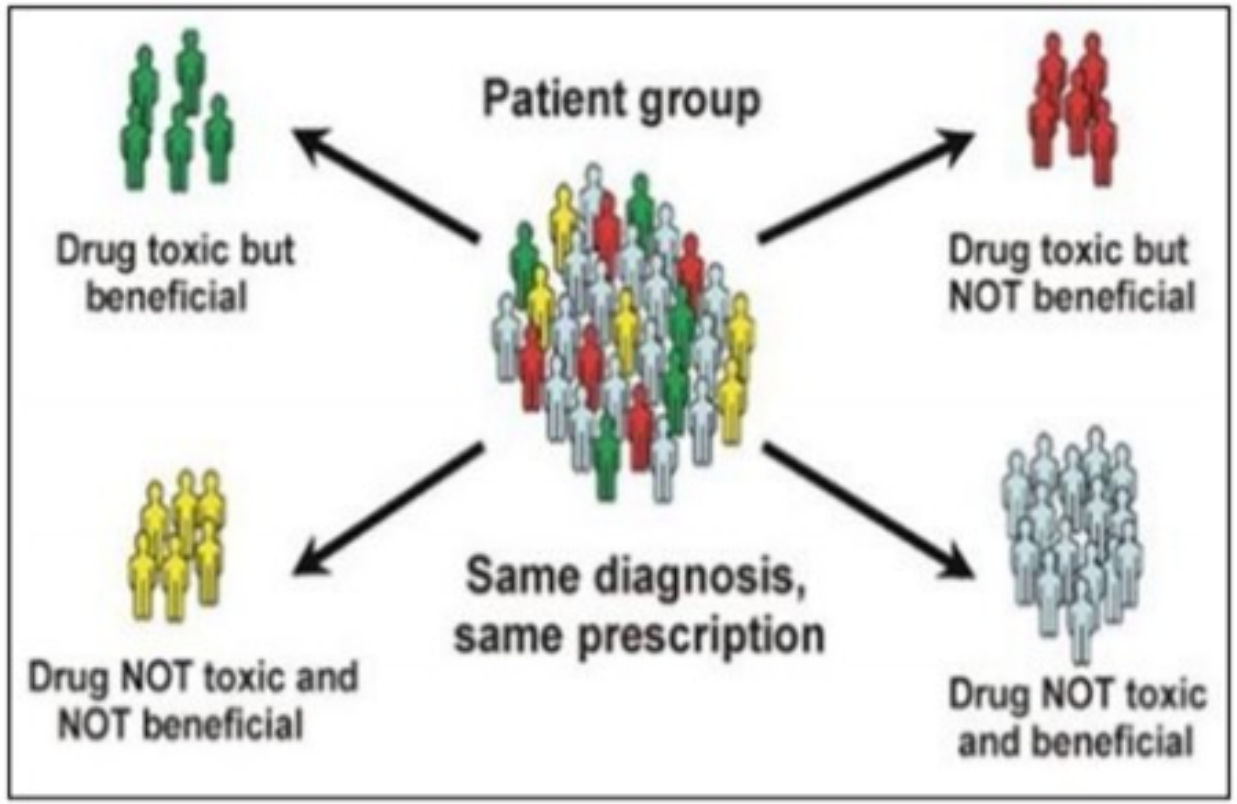
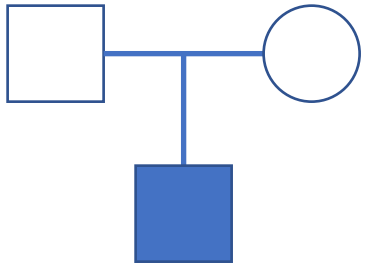
Genetically Stratified Medicine

- Goal is to identify subgroups of patients with similar disease mechanisms and specific responses to medications and treatments
- WES is an important tool in the advancement of genetically stratified medicine
- Relies on widespread sequencing of cohorts of interest and a centralized system for enrollment, sequencing and storage of data



Source: https://www.who.int/medicines/areas/priority_medicines/Ch7_4Stratified.pdf?ua=1

Sequencing for Rare Diseases



Trio exome sequencing

Identify qualifying genotypes

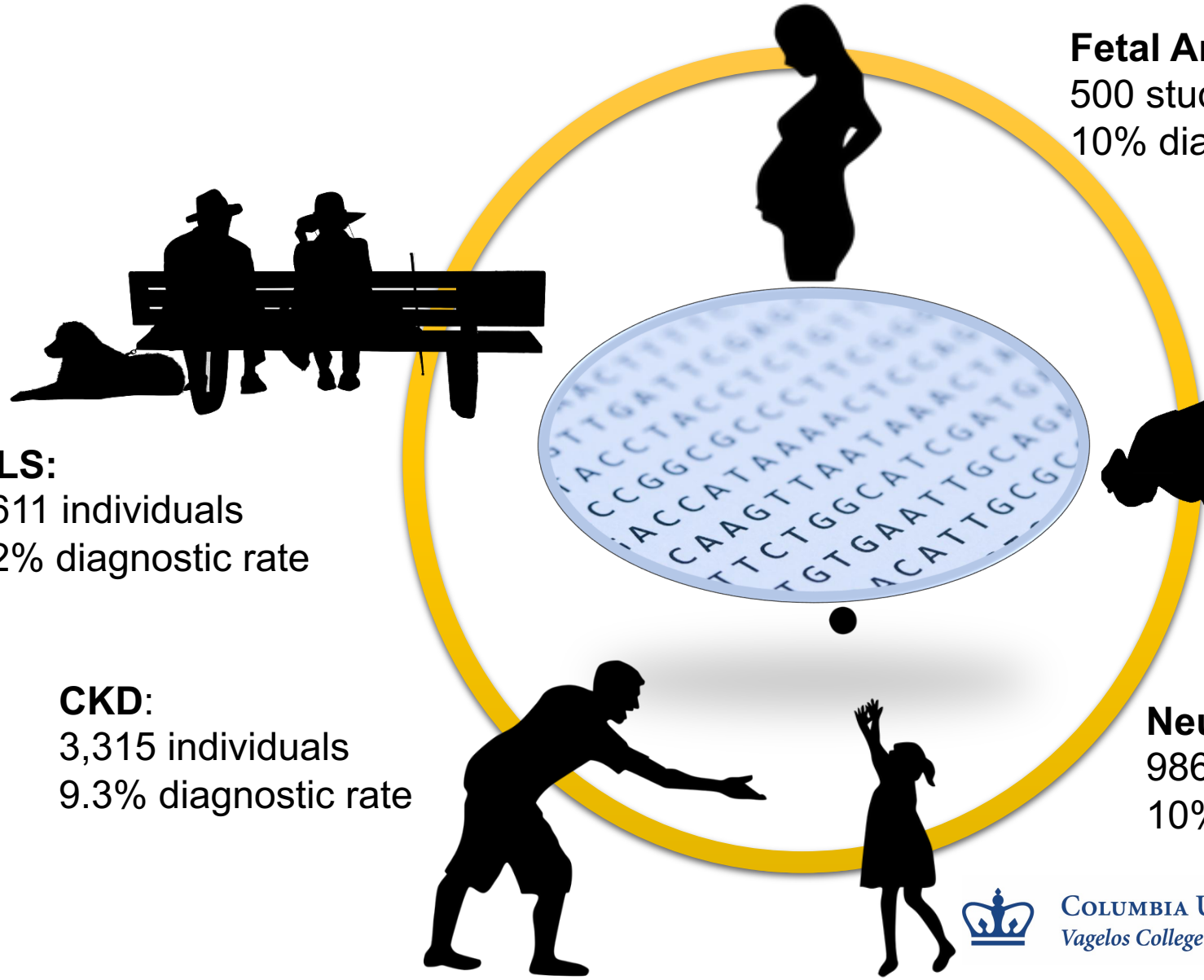
Genetic diagnosis

Genetic candidate

Study	Journal	N	Ascertainment	% resolved
Need 2012	J Med Genet	12	Mixture	50%
Yang 2013	NEJM	250	80% Neuro	25%
Calvo 2012	Sci Transl Med	42	Mitochondrial	24%
DeLigt 2013	NEJM	100	Severe ID	16%
Zhu 2014	Genetics in Medicine	119	Mixture	24%
Srivastava 2014	Annals of Neuro	78	Neuro	41%
Yang 2014	JAMA	2,000	Mixture	25%
Lee 2014	JAMA	814	Mixture	26%
Soden 2014	Sci Transl Med	119	Neuro	45%
Combined	-	**3,534**	**Mixture**	**26%**

Ten Thousand patients sequenced to date at tertiary care center

Utility of Genomics Throughout the Lifespan



Fetal Anomalies:
500 studied
10% diagnostic rate

Stillbirth:
300 samples
4% diagnostic rate

DiagSeq:
1226 probands
20% diagnostic rate

Neuro:
986 probands
10% diagnostic rate

CKD:
3,315 individuals
9.3% diagnostic rate

ALS:
5611 individuals
12% diagnostic rate

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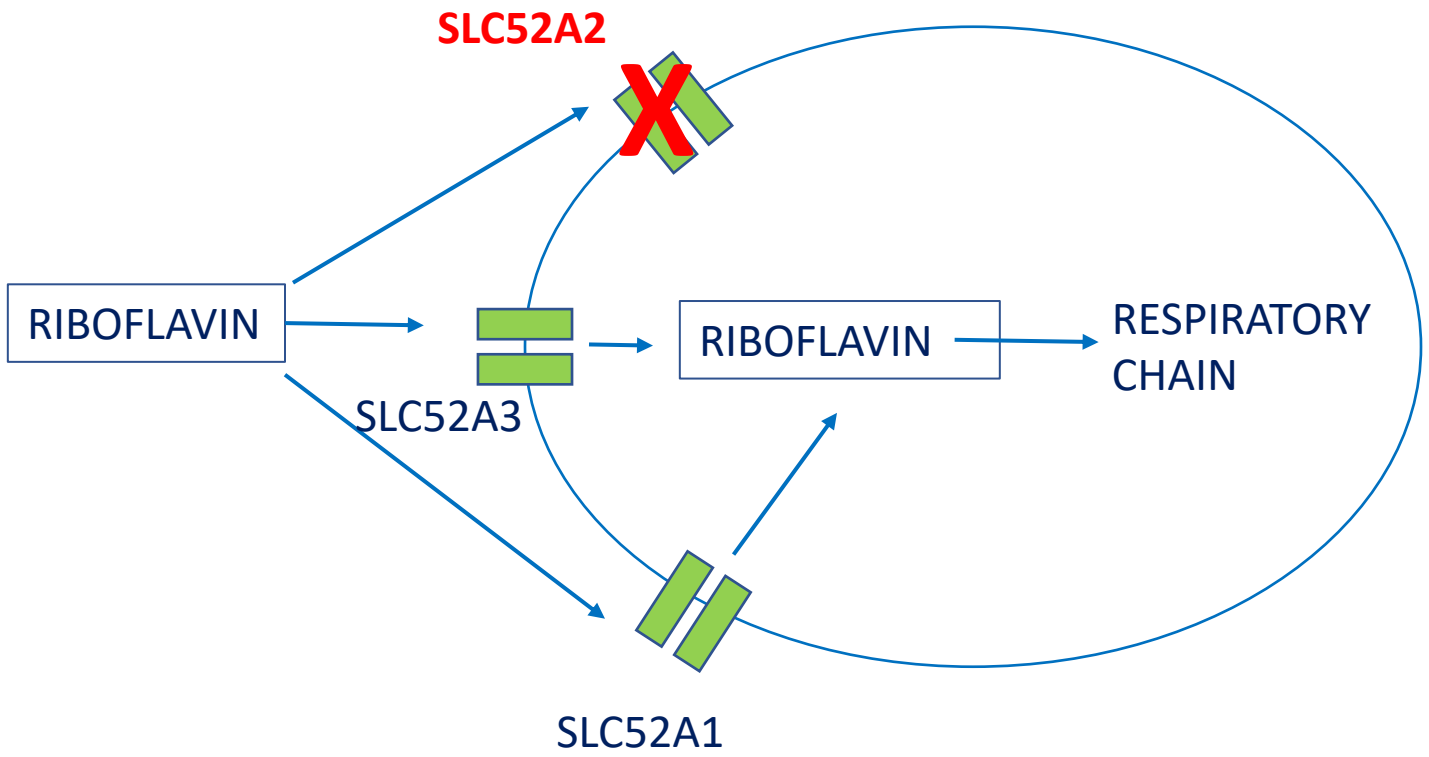
Sequencing Success

- 18-month-old girl with sudden onset opsoclonus, ataxia, and upper extremity weakness
- Unknown etiology, but treated on suspicion of progressive autoimmune condition
- Submitted whole exome sequencing

Pathogenic mutations identified in *SLC52A2*

Brown-Vialetto-Van Laere Syndrome

Riboflavin transporter deficiency

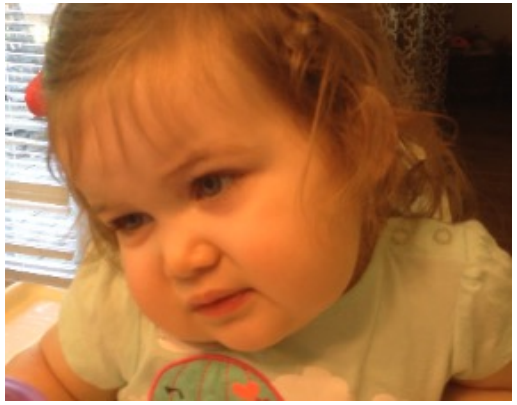


Treat with riboflavin supplementation

Brown-Vialetto-Van Laere Syndrome

3 weeks pre-treatment

2 days of treatment



3 weeks of treatment

4 weeks of treatment

Cara Greene

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Sequencing Changes Medical Management

Example: 30 year old male with life-long history of developmental issues

Compound Heterozygous for variants in
CYP27A1 Cerebrotendinous Xanthomatosis (CTX)

FDA approved medication, CDCA

Sequencing Often Leads to a Road Block

Modeling single gene diseases

Mouse Model
Specific genetic mutation is introduced into the mouse's genome

Cellular Model
Induced Pluripotent Stem Cells (iPSCs) are used to cultivate a "neural network" of cells for continued testing

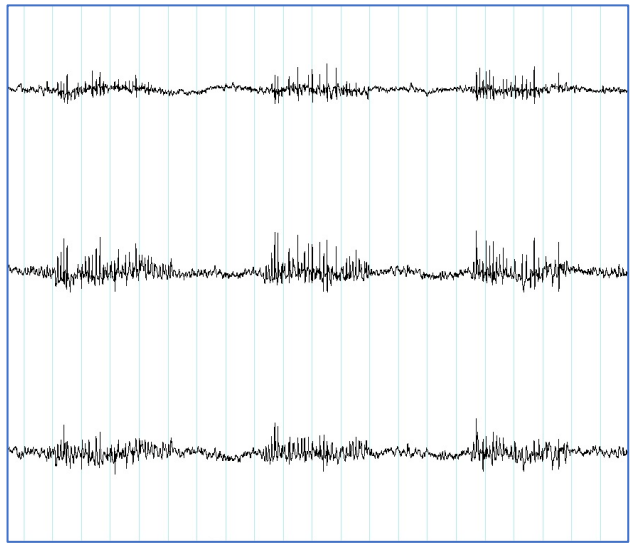
Both models are used to repeatedly test the effect of different drug therapies on the mutated gene

Non-convulsive Seizures in *Gnb1*^{K78R} Mice Corrected By Ethosuximide Treatment

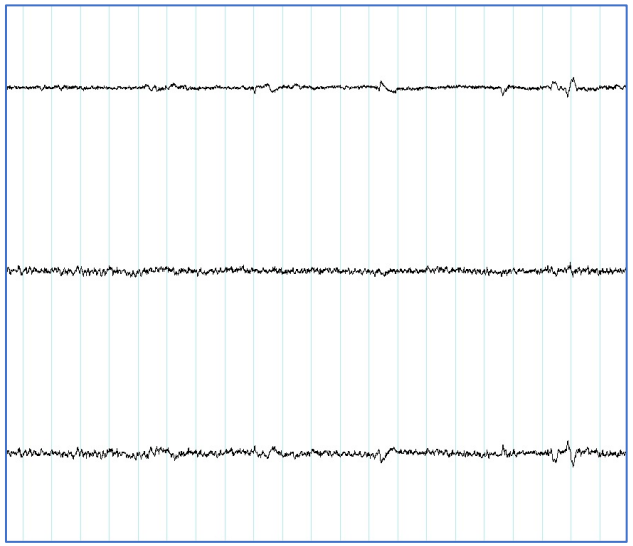
Acute treatment with Ethosuximide stops seizure activity in GNB1 mice

Gnb1$^{K78R/+}$ **mouse EEG**

Before Ethosuximide



After Ethosuximide



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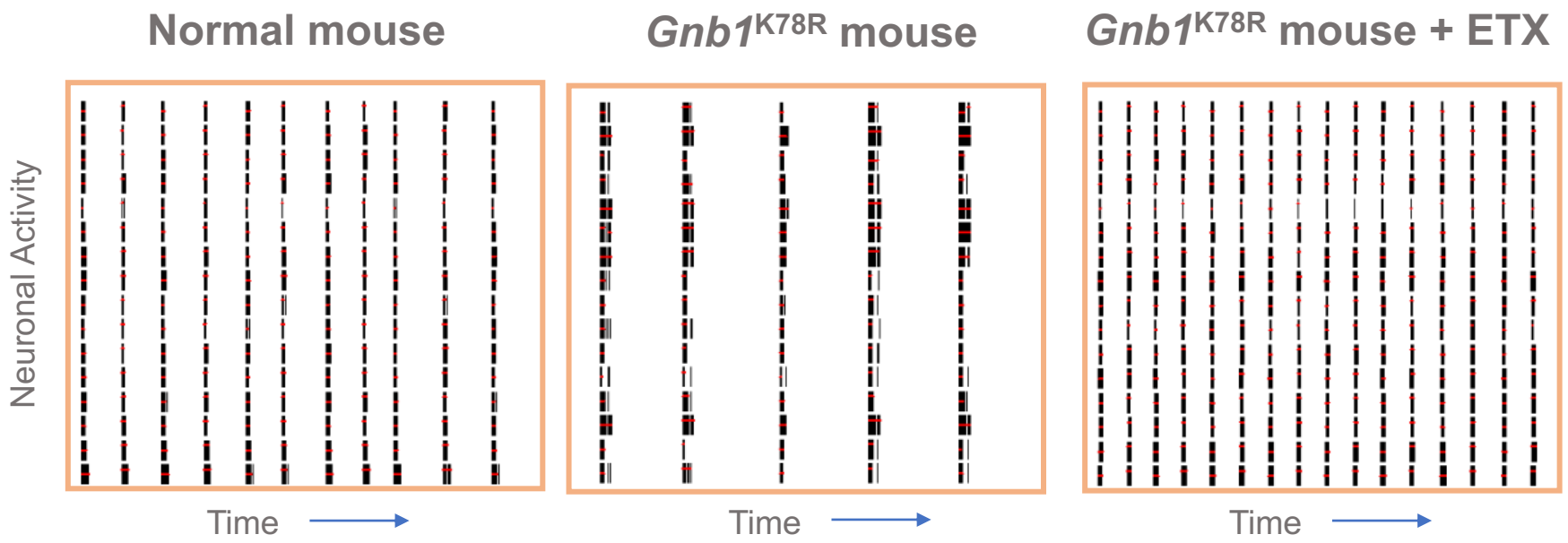
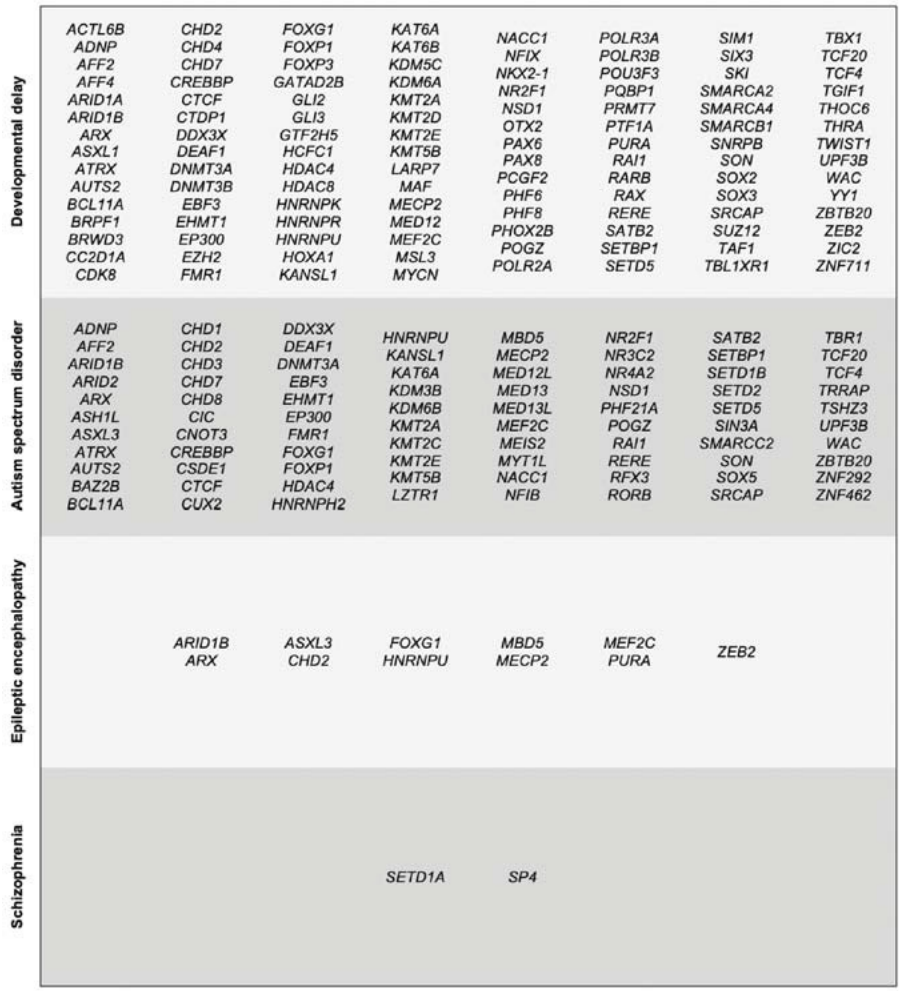
- Ethosuximide did not appear to help conrols seizures in patients
- Repurposing rarely works well enough
  - Consider quinidine

Gnb1^{K78R} Neurons Corrected By Ethosuximide Treatment

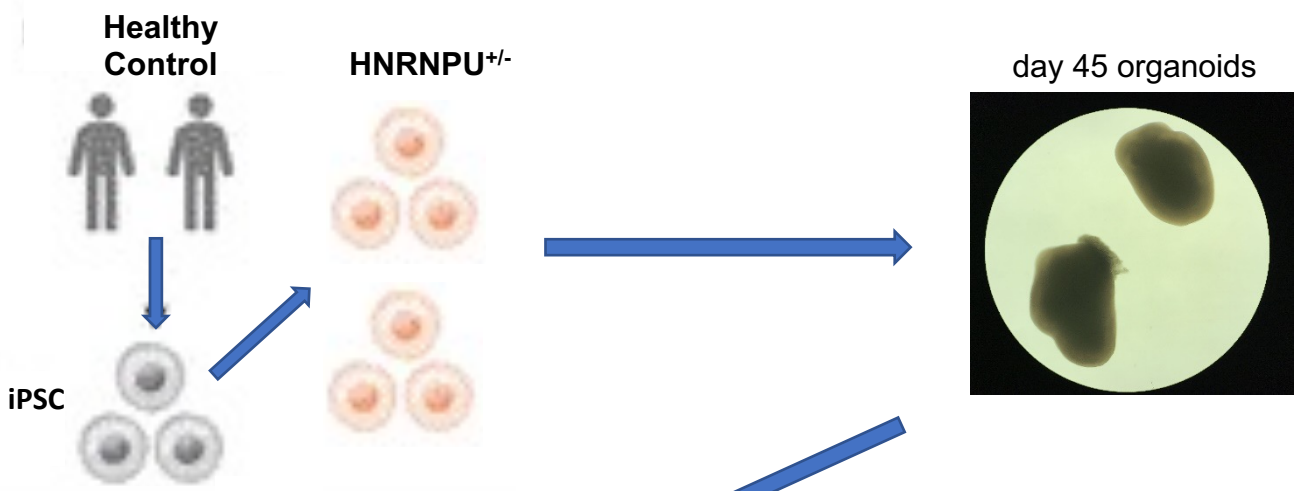
Ethosuximide corrects the abnormal neuronal activity in the neuronal cell models



Expression dysregulation in NDD



Modelling Human HNRNPU Dysregulation in Cortical Organoids



scRNA sequencing

Upregulated genes

Downregulated genes

Pseudobulk cross-species comparison of disease signature

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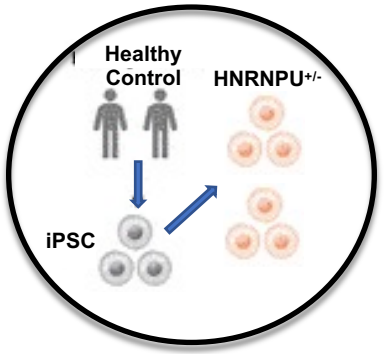
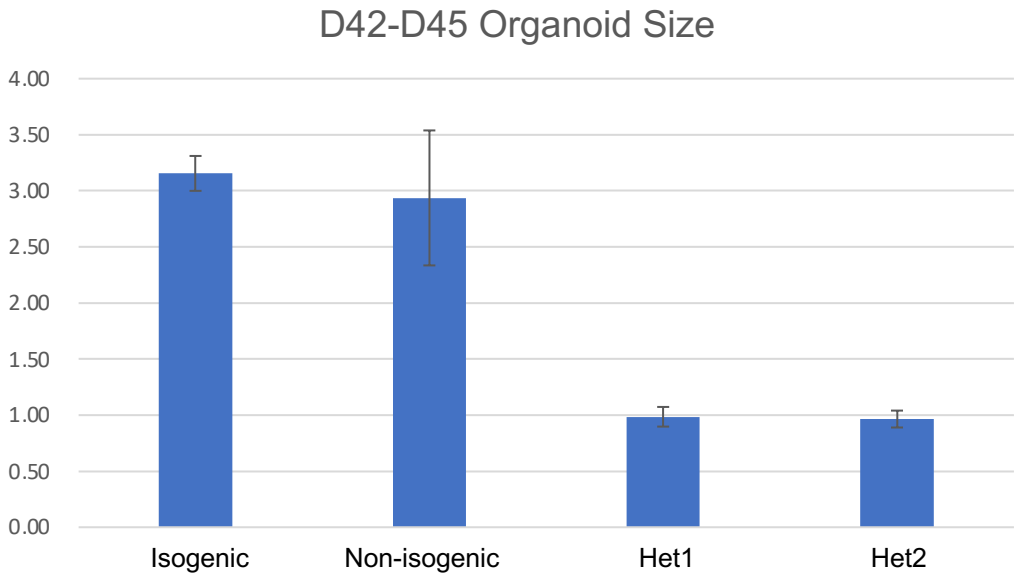
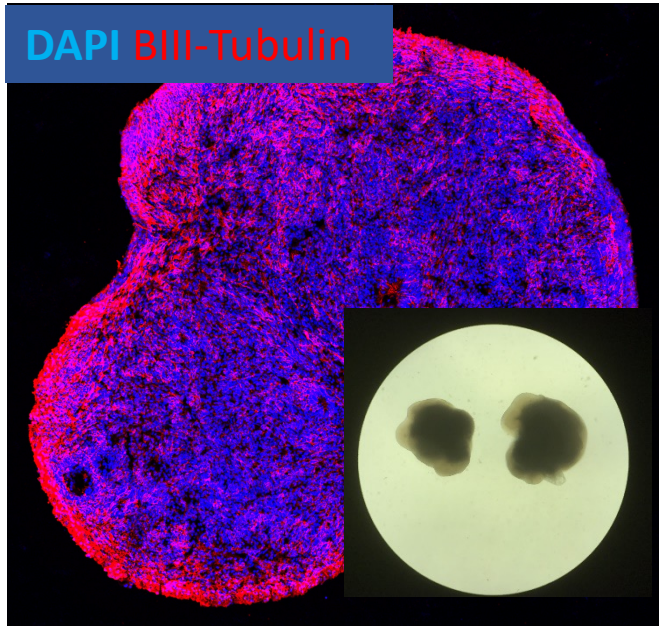
Impaired Growth in HNRNPU Cortical Organoids



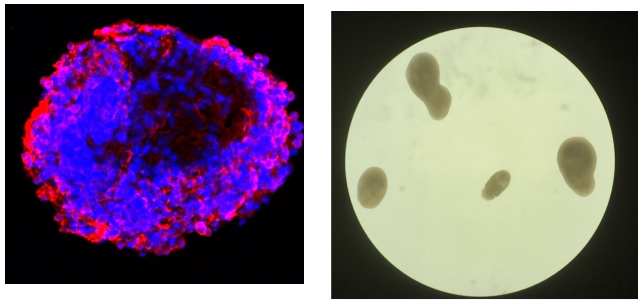
Wild-type and Mutant organoids generate significant neuronal populations in ~1.5 months



Isogenic Control (PGP1) – Day 42



HNRNPU$^{+/-}$ Clone 1 (D11) – Day 42



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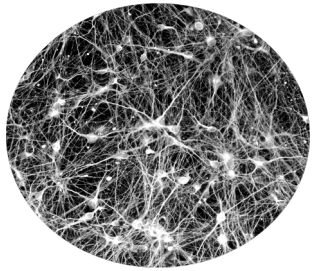
HNRNPU Drug Discovery Using Gene Expression Profiling

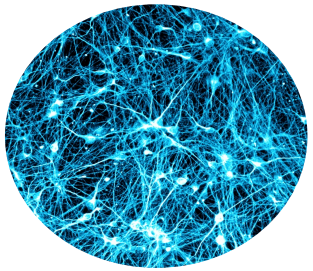


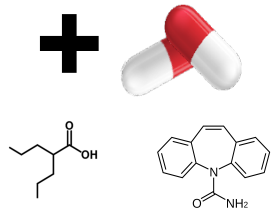
Upregulated genes

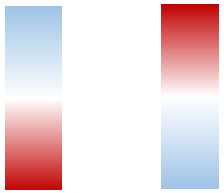
Downregulated genes

***Hnrnpu* disease signature**

Neurons from <u>normal</u> mouse



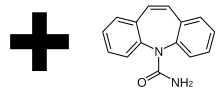




Neuronal drug response signature

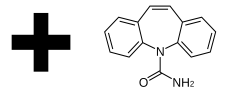
Drug Validation

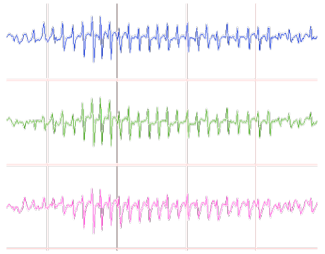
In neurons



Correction of *Hnrnpu* disease signature

In *Hnrnpu* mice





Seizure threshold testing

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Drug devopment for rare diseases requires significant industry effort