COMBINEDBrain

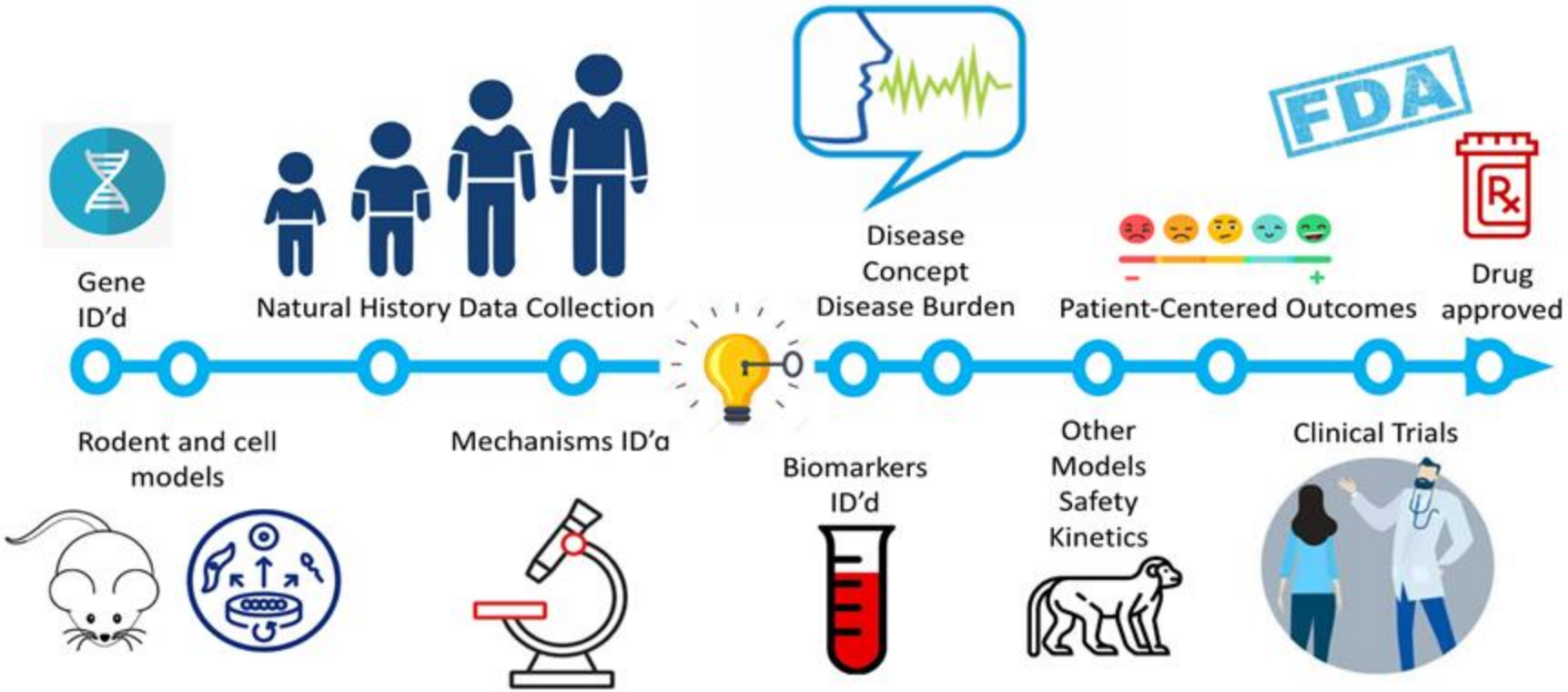
Consortium for Outcome Measures and Biomarkers in Neurodevelopmental Disorders

Plasma Proteomics in Rare, Neurodevelopmental Disorders: A Pilot Biomarker Discovery Project

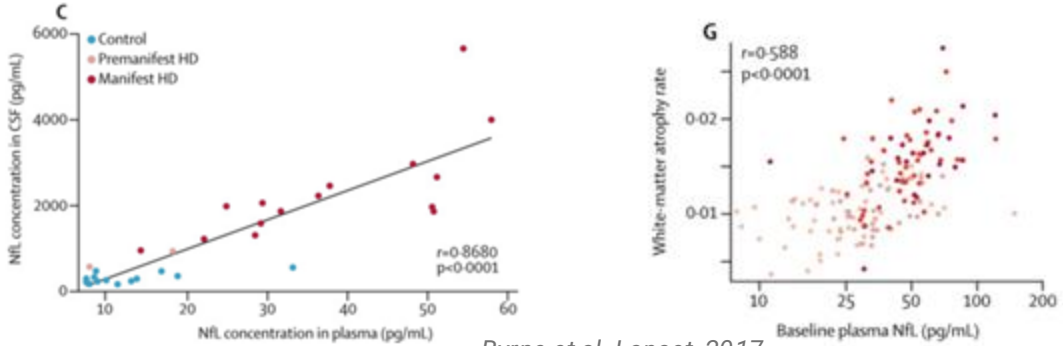
CTNNB1 Connect and Cure
MED13L Foundation
2025 Scientific and Family Summit
July 11th 2025

Anna C Pfalzer, PhD
Chief Scientific Officer, COMBINEDBrain
Assistant Professor, Department of Neurology, VUMC

Drug development for a rare, genetic neurodevelopmental disorder



- A **biomarker** is an objective measure which can be used to predict *disease status*, *progression* and/or *response to treatment*
  - mRNAs, miRNAs, epigenetics, proteins, metabolites, microbiota
  - Biologics
    - Found in biofluids: cerebrospinal fluid, blood, urine, saliva, stool
    - Example: CSF and plasma NfL in HD

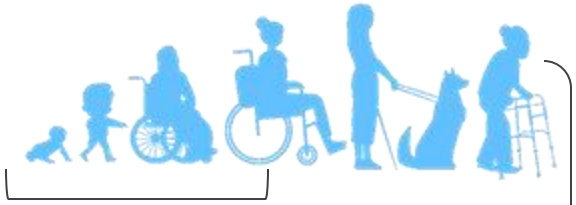


Byrne et al. Lancet, 2017.

- **Limited access to patient samples with rare diseases**

Study Design

Affected (n=20)



<18 yo

Neurotypical (n=40)

<18 yo

Plasma

Proteomics

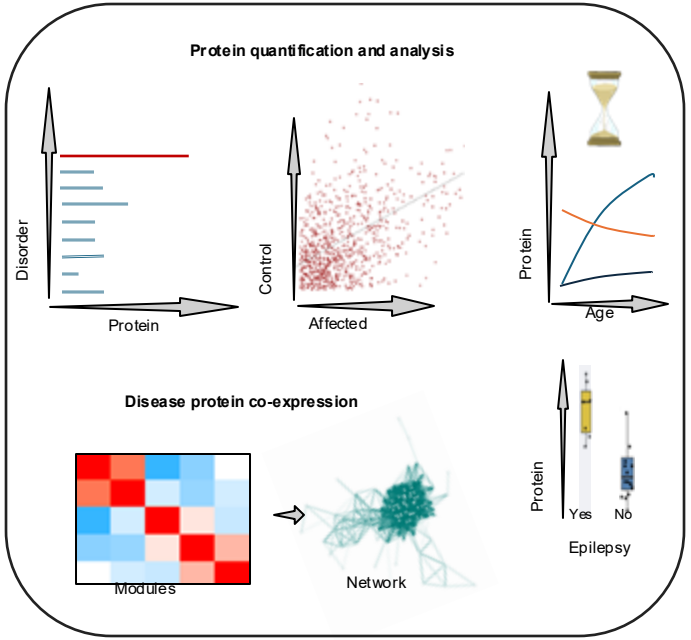
somalogic

~10,000 analytes

Vineland-3

Pediatric epilepsy LHS

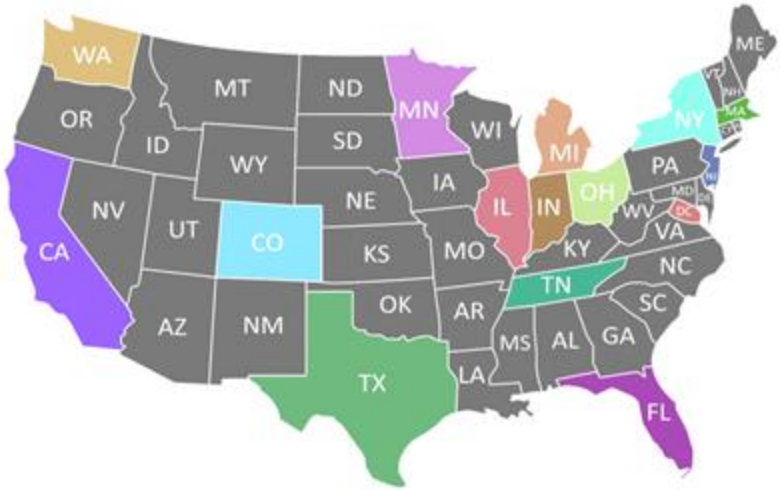
Phenotypic Assessments



Sample Collection

- 19 Family Conferences in 2023
  - Fly research team + pediatric phlebotomists
  - Collect blood -> plasma on-site

- Home visits
  - Contract with mobile phlebotomists
  - Coordinate home visits



- In collaboration with clinical labs

Kennedy Krieger Institute
UNLOCKING POTENTIAL

RUSH UNIVERSITY MEDICAL CENTER

Weill Cornell Medicine

COLUMBIA
COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

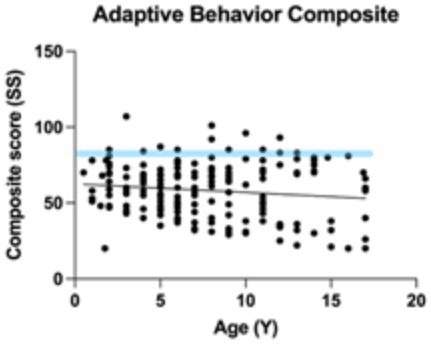
VANDERBILT UNIVERSITY MEDICAL CENTER

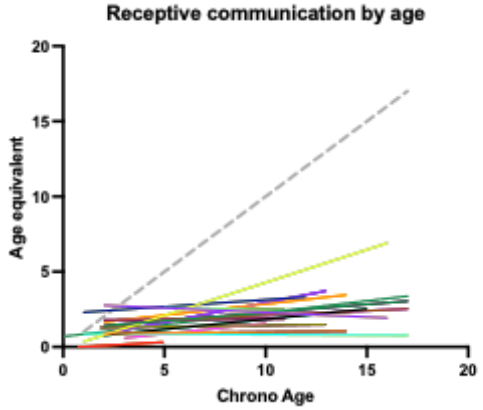
Children's Hospital Colorado

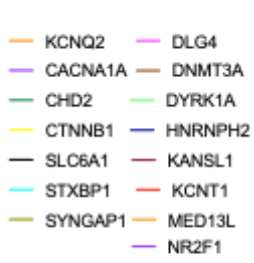
Pediatric participant characteristics

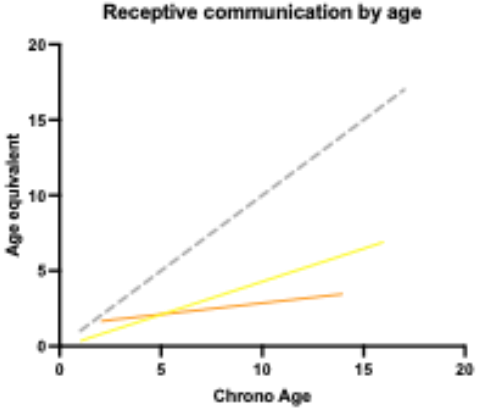
Table 1. Enrollment and Clinical Characteristics Across 28 Neurodevelopmental Disorders							
Disorder	**Sample Size**	**Age± S.D**	**Sex (% Female)**	**Epilepsy (% Yes)**	**ABC**	**CC**	**DLSC**
Controls	127	8.4±4.1	35.3	--	--	--	--
CACNA1A-Related Disorder	16	6.9±3.3	50.0	62.5	66.7	64.8	67.0
Charcot Marie Tooth Disease	1	13±0	100.0	0.0	--	--	--
CHD2-Related Disorder	10	9.8±5.3	60.0	70.0	57.0	52.9	53.6
CTNNB1-Related Disorder	26	7.4±4.1	38.5	3.8	68.5	69.5	66.2
DLG4-Related Synaptopathy	13	7.5±2.7	38.5	30.8	48.9	39.4	49.6
Tatton Brown Rahman Syndrome	14	9.3±3.8	42.9	42.9	64.3	54.3	57.5
DUP15Q Syndrome	15	9.2±5.9	66.7	46.7	62.5	54.0	62.8
DYRK1A Syndrome	15	6.5±3.2	46.7	73.3	54.3	51.7	49.5
FOXG1 Syndrome	11	5.9±4.6	54.5	45.5	35.0	26.5	35.8
Fragile X Syndrome	3	16.2±1.2	0.0	0.0	63.3	64.3	63.7
Glut1 Deficiency Syndrome	7	9.4±4.5	42.9	85.7	75.0	72.0	73.3
HNRNPH2-Related Disorder	16	9.4±4.2	100.0	18.8	53.0	46.3	52.0
Kabuki Syndrome	9	9.3±4.8	77.8	11.1	82.5	84.0	82.5
Koolen-de Vries Syndrome	25	7.3±4.7	28.0	56.0	66.4	62.6	60.8
KCNQ2-Related Epileptic Encephalopathy	23	6.6±3.8	56.5	87.0	50.4	40.5	46.5
KCNT1-Related Epilepsy	10	3.9±2.6	20.0	100.0	50.5	39.5	54.7
Kleefstra Syndrome	11	9.8±4.2	54.5	18.2	47.3	43.3	45.7
MED13L-Related Disorder	18	7.2±4.1	44.4	27.8	61.3	56.3	54.8
NR2F1-Related Disorder	17	9.2±3.7	58.8	64.7	57.1	50.8	54.6
Prader Willi Syndrome	13	8.5±5	38.5	0.0	75.2	77.0	76.0
Phelan McDermid Syndrome	1	17±0	0.0	0.0	--	--	--
SCN2A-Related Epilepsy	2	5±1.4	50.0	50.0	--	--	--
SLC6A1-Related Disorder	13	7±4	23.1	61.5	60.6	50.3	60.9
STXBP1-Related Disorder	20	7.7±5.3	40.0	70.0	45.4	32.0	42.2
SYNGAP1-Related Disorder	39	6.8±3.1	56.4	74.4	58.6	53.0	55.9
Pitt Hopkins Syndrome	10	7.6±4.9	30.0	0.0	33.0	20.0	36.0
Tuberous Sclerosis Complex	1	7±0	0.0	100.0	55.0	59.0	50.0
WWOX-Related Epileptic Encephalopathy	6	4.6±3.8	16.7	83.3	47	30	41

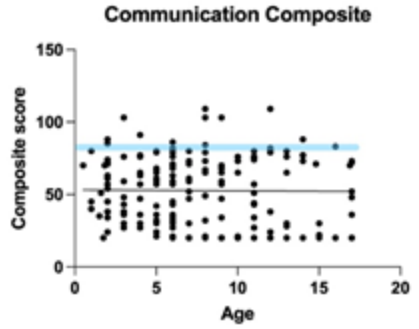
Identifying relevant indicators of disease severity

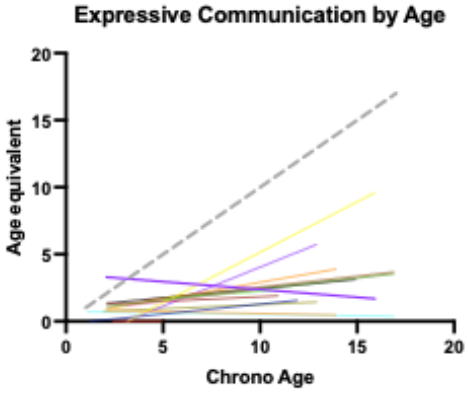


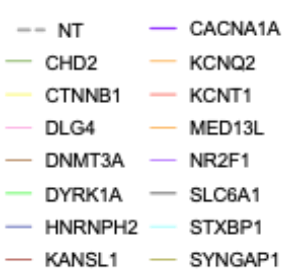


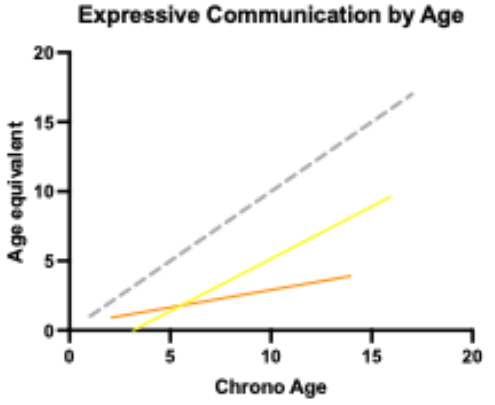




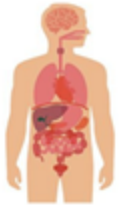


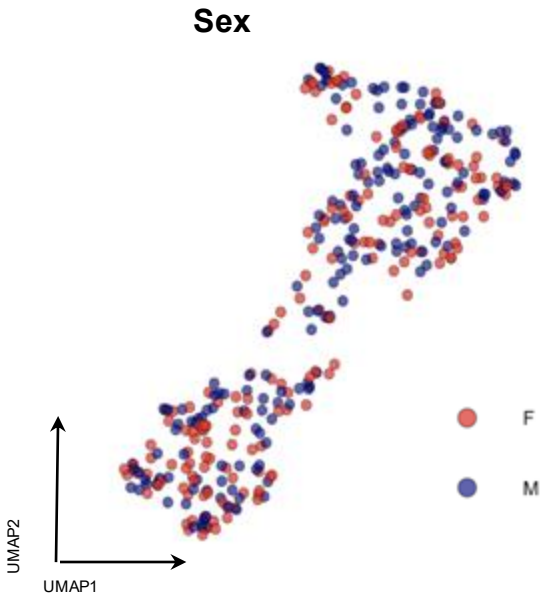


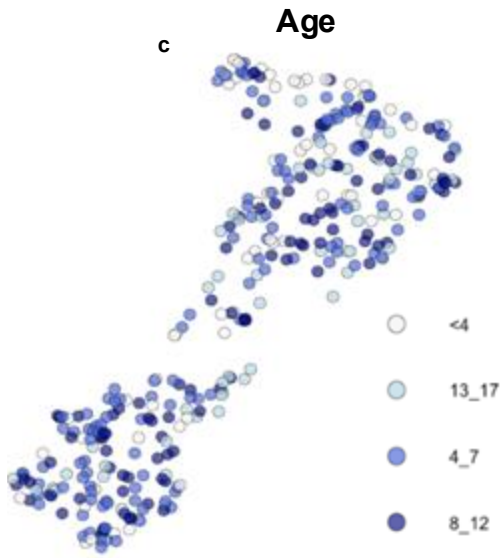




No distinct changes in plasma proteome by sex, age or epilepsy burden

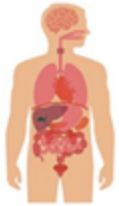


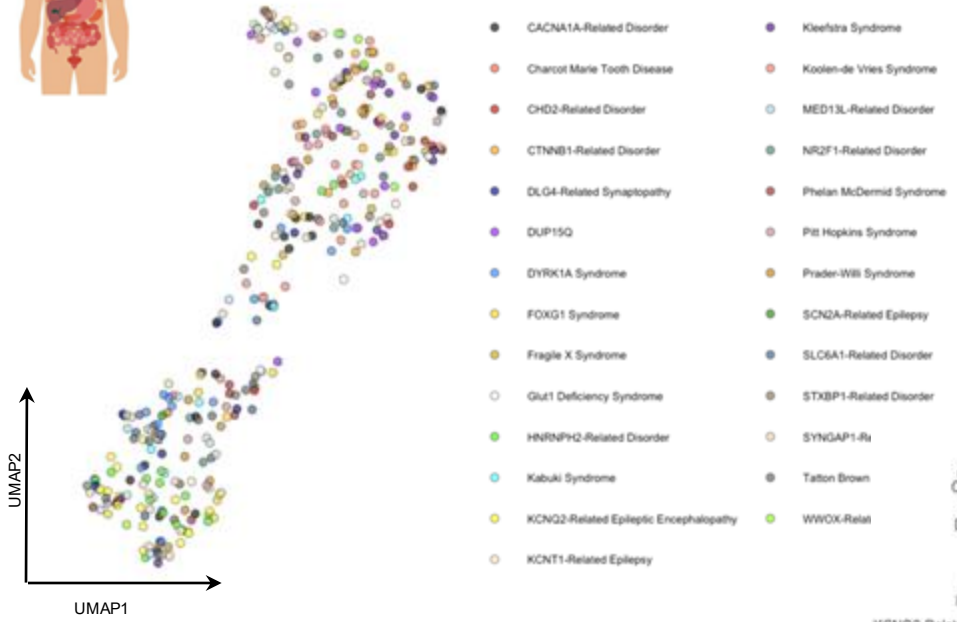


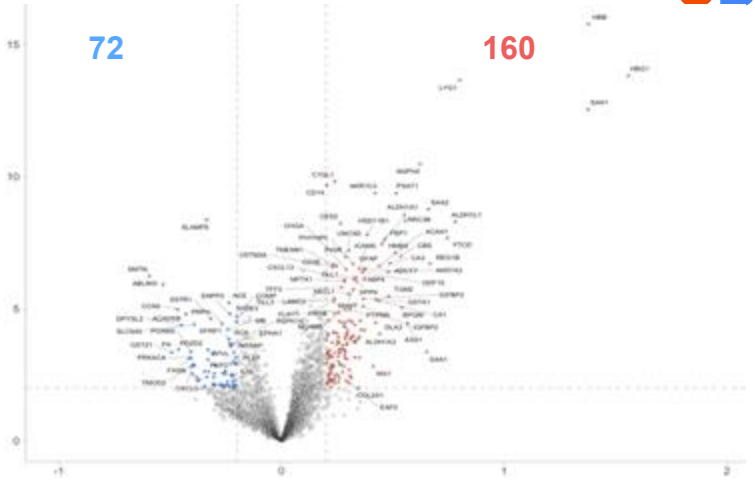


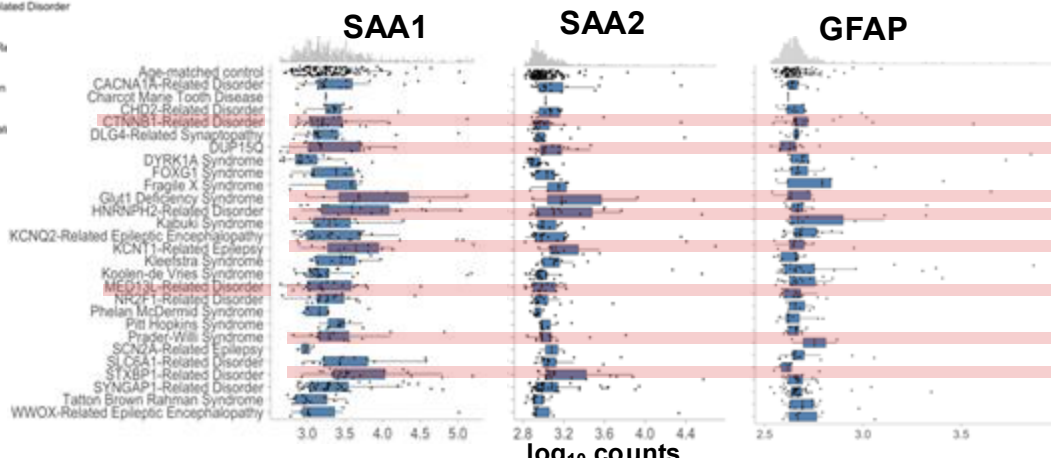
No distinct changes in plasma proteome by genetic etiology

CB









Similarities in plasma proteome in disorders with shared molecular function

Transcription factor (n=8)
HNRNPH2-Related Disorder, MED13L-Related Disorder, FOXG1 Syndrome, NR2F1-Related Disorder, WWOX-Related Epileptic Encephalopathy, CTNNB1-Related Disorder, Smith Magenis Syndrome, Fragile X Syndrome; Pitt Hopkins Syndrome

Channelopathy (n=4)
CACNA1A-Related Disorder, KCNQ2-Related Epilepsy, KCNT1-Related Epilepsy, SCN2A-Related Epilepsy

Chromatin modifiers (n=5)
Tatton Brown Rahman Syndrome, Kleefstra Syndrome, Kabuki Syndrome, Koolen-de Vries Syndrome, CHD2-Related Disorder

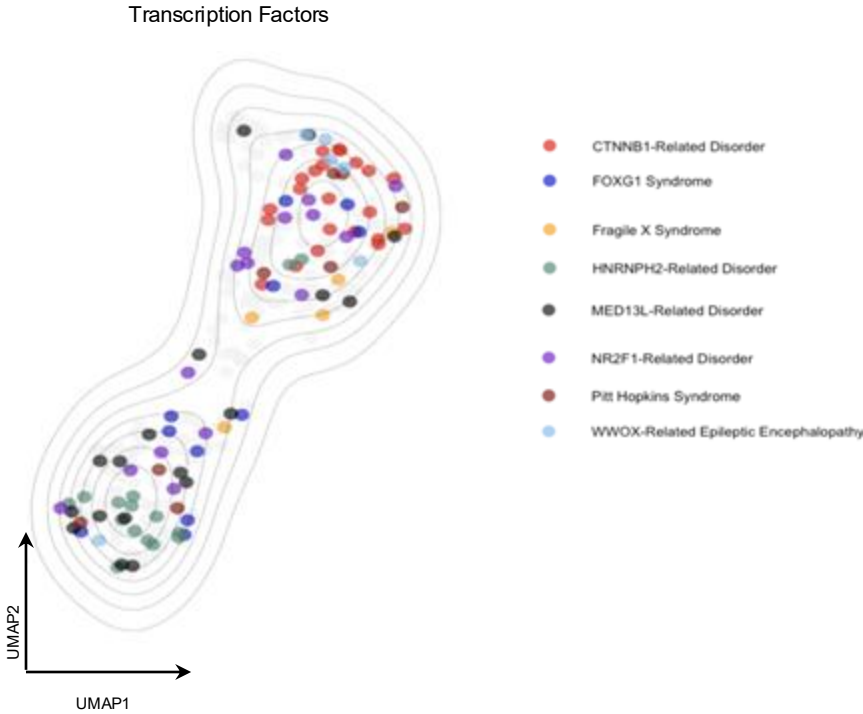
Copy number variant (n=2)
Prader-Willi Syndrome, DUP15Q Syndrome

Synaptopathy (n=5)
DLG4-Related Synaptopathy, Phelan McDermid Syndrome, STXBP1-Related Disorder, SYNGAP1-Related Disorder, SLC6A1-Related Disorder

Transporter (n=1)
Glut1 Deficiency Syndrome

Kinase (n=1)
DYRK1A Syndrome

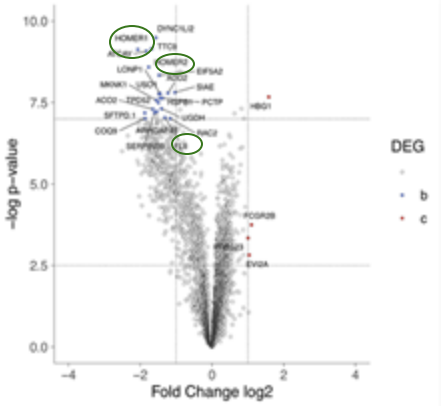
Demyelination (n=1)
Charcot Marie Tooth Syndrome

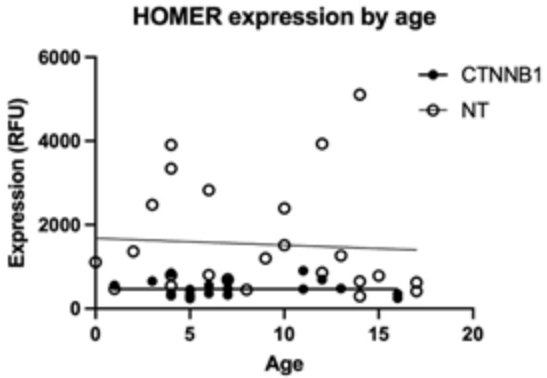


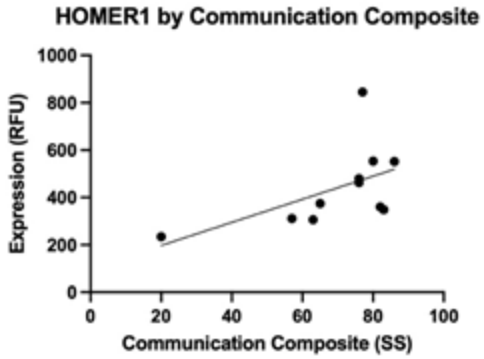
Differential expression by disorder

CB

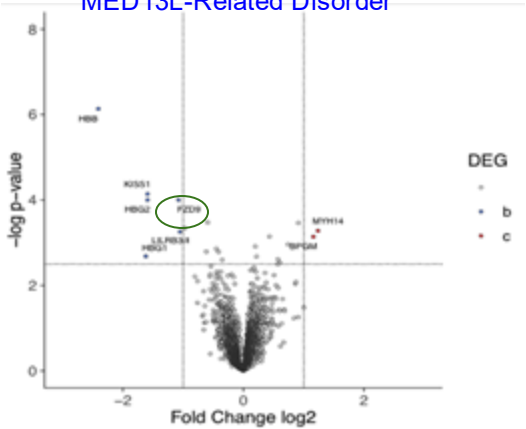
CTNNB1-Related Disorder

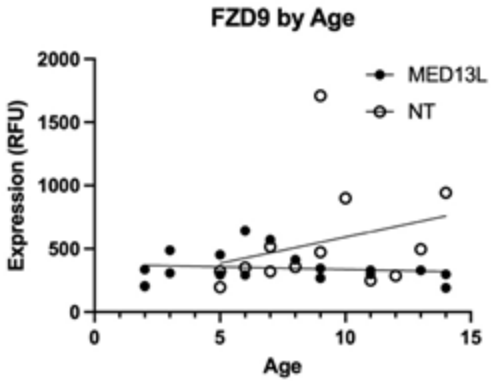


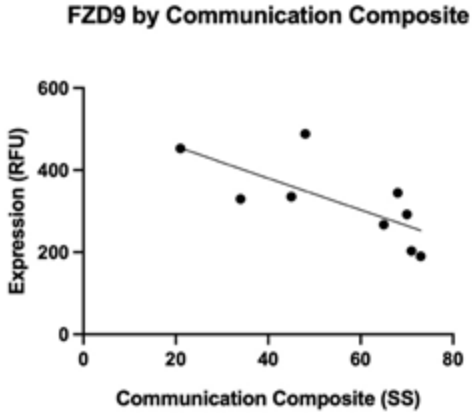




MED13L-Related Disorder



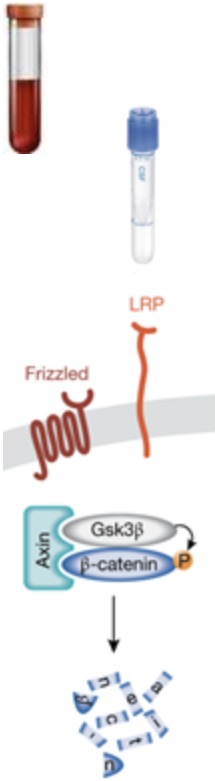




Current "Conclusions" / Next Steps

- Several proteins enriched across *several disease groups*
- Identify appropriate phenotypic measures to use for clinical severity
- More cross-sectional plasma samples to validate initial findings (GFAP, SAA1/2)
- Longitudinal samples
- Validate plasma findings in cerebrospinal fluid

- **MED13L/ CTNNB1:** preliminary findings suggest altered expression of Wnt signaling in plasma -> validate in additional cross-sectional samples



COMBINEDBrain

Biorepository Team

- **Sasha Elmizadeh, BS**
- **Grace Viggiano, BS**
- **Danielle Moberg, BS**
- Taylor Morris, BS
- Zollie Yavarow, PhD
- Rachel Heilmann, PharmD
- Donnielle Rome-Martin, PhD
- Rithika Tummala, BS
- Insung Kim, BS
- Martina Hannaalla, BS
- Ananya Terala, BS
- Sarah Poliquin, PhD
- Kellan Weston, PhD
- Nick Aguilar, BS
- William Kleener, BS

Data Collection Team

- Simons Searchlight
  - **Wendy Chung, MD, PhD**
  - Jennifer Tjernagel, MS
  - Kaitlyn Singer, MS
- Matrix
  - **Jason Colquitt, MS**
  - Andrea Rogers, MS

Computational Team

- **Ricardo Ramirez, PhD**
- Megan Aumann, PhD
- Darryl Perry, MS

Neuropsych Team

- Natasha Ludwig, PhD


ultragenyx


actio
BIOSCIENCES


MAHZI
therapeutics


NOVARTIS


IONIS


Bial

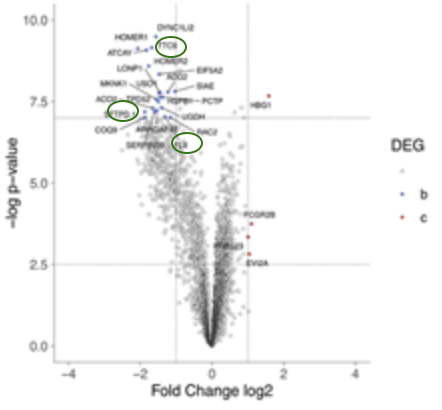

Biogen


SERVIER

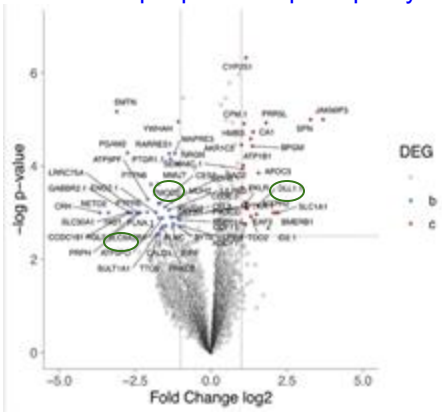

Roche

SPECIAL THANKS

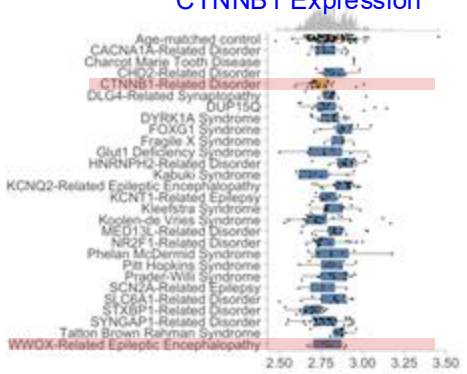
CTNNB1-Related Disorder



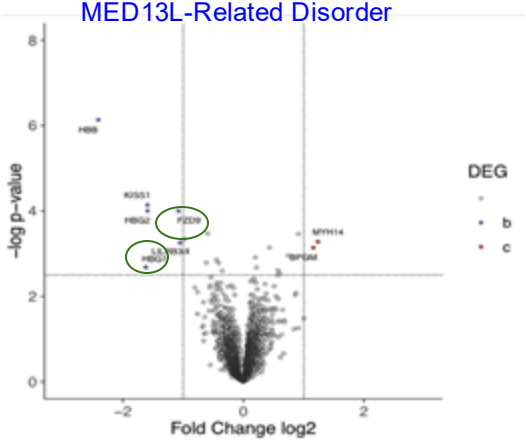
WWOX-Epileptic Encephalopathy



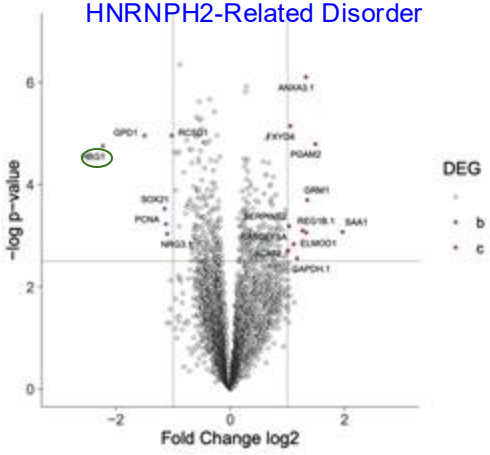
CTNNB1 Expression



MED13L-Related Disorder



HNRNPH2-Related Disorder



FOXG1 Syndrome