MED13L Syndrome & CTNNB1 Syndrome: Overview

Kellan Weston, PhD
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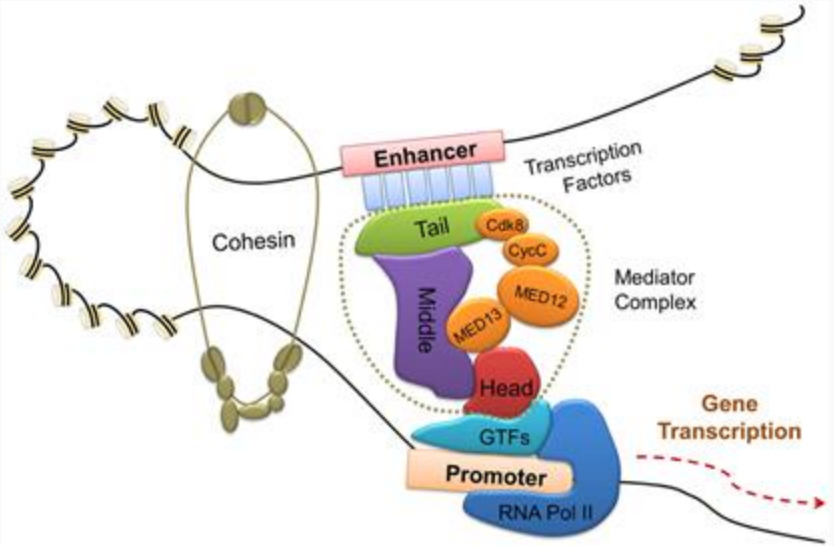
Outline

1. Overview of MED13L Syndrome
2. Overview of CTNNB1 Syndrome
3. Why have a conference together?
    a. Common phenotypes
    b. Potential for common therapeutics

MED13L - Mediator Complex subunit 13L

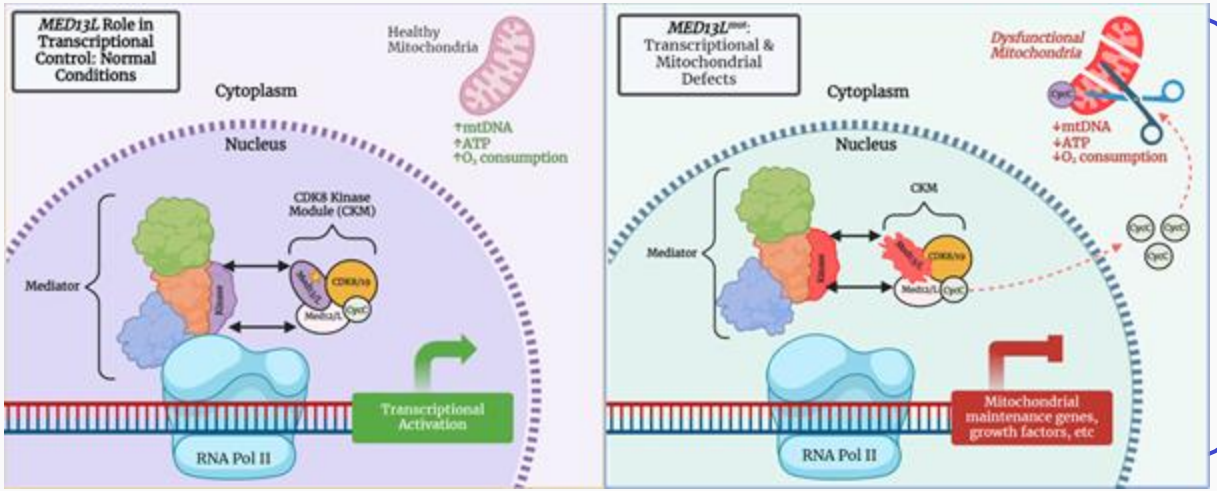
- MED13L Syndrome caused by variants in the *MED13L* gene at 12q24.21
- Mediator is a multiprotein complex that acts as a transcriptional coactivator
- Facilitates interaction between enhancers, promoters, and associated transcription factors
- Required for successful transcription by RNA polymerase II.
- Deletion of MED13L causes disruption to the transcription of genes related to key growth pathways



Zhang et al, *Cancer* (2019)

Normal

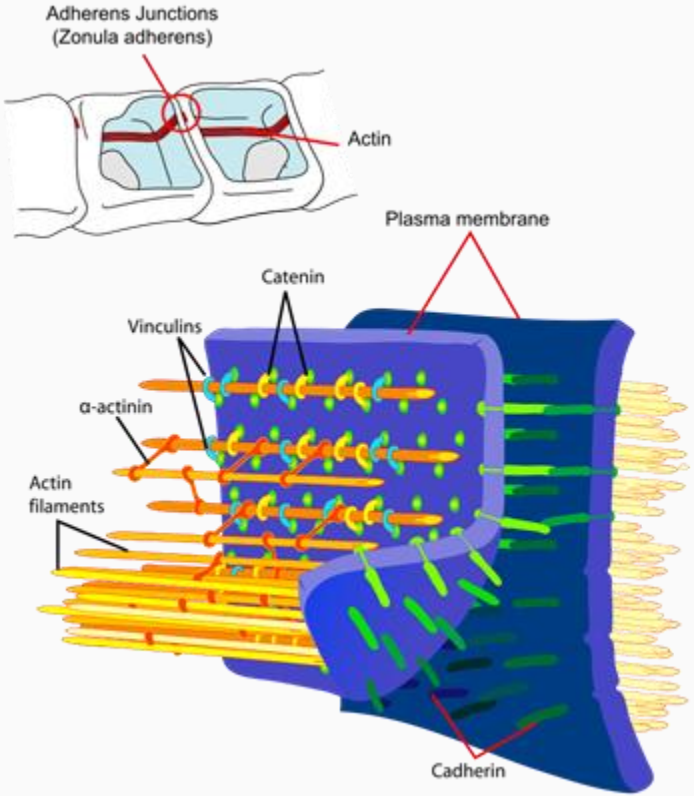
MED13L Syndrome



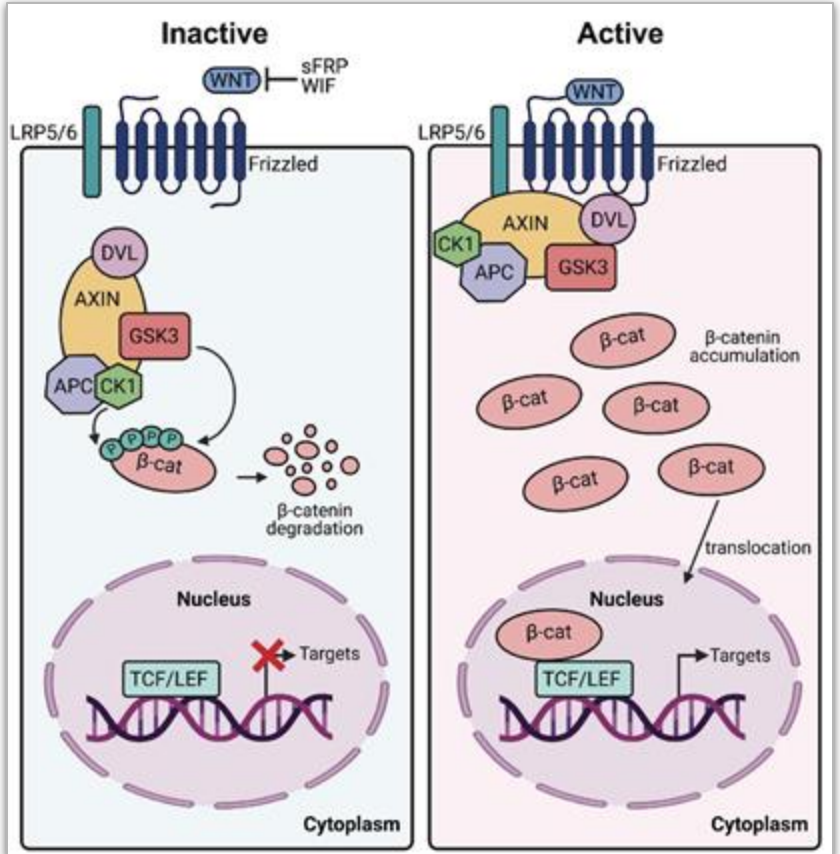
Heilmann et al, *Ther Adv Rare Dis* (2024)

- Mediator complex's interaction with RNA Polymerase II is disrupted
- Disruption of gene transcription
- Evidence that MED13L variants can be GOF or LOF
- One model: Cyclin C is aberrantly released into the cytoplasm
  - mitochondrial dysfunction
  - Decreased ATP production
  - Increased susceptibility to cell death

β-Catenin facilitates cell adhesion



β-Catenin is a critical component of the Wnt Signaling Pathway

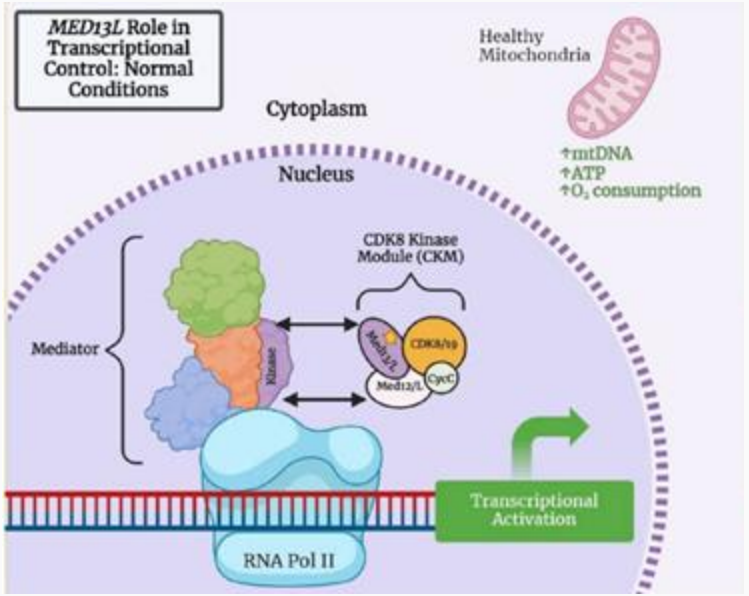


Wnt target genes code for proteins involved in growth and development

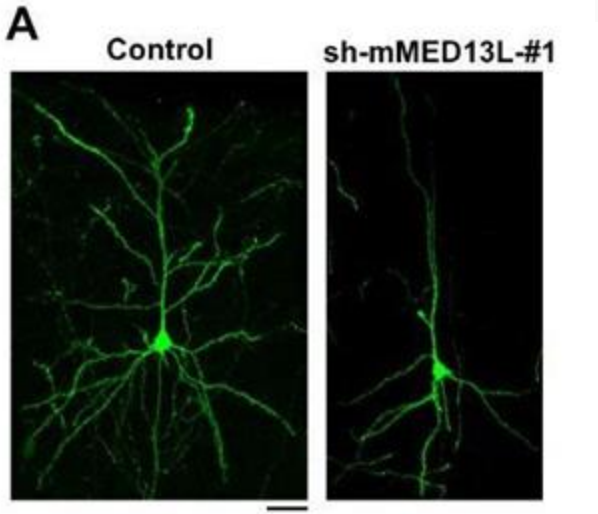
Carraci et al, *Front. Mol. Neurosci.* (2021)

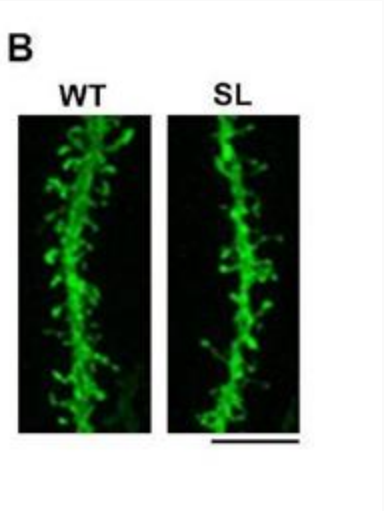
MED13L Interacts with Wnt via an unknown mechanism

- UAB drug screen gave two candidates that modulate Wnt:
  - Verapamil (a Wnt inhibitor). Calcium channel blocker used for hypertension
  - PSE (Plant sterol esters)- a dietary cholesterol-lowering agent shown to affect Wnt
- Wnt was *upregulated* in a MED13L cardiomyocyte knockout mouse
- Plasma Proteomics data points towards possible downregulated Wnt (Anna Pfalzer, PhD)

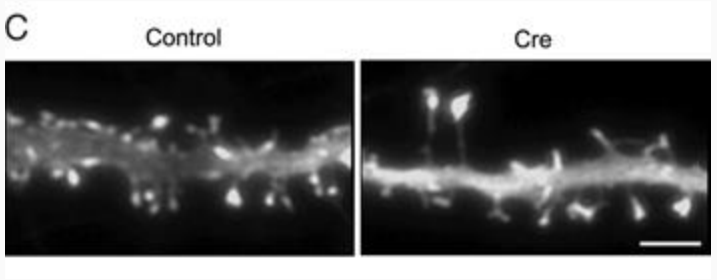


Common neuronal phenotypes caused by MED13L and CTNNB1 disruption





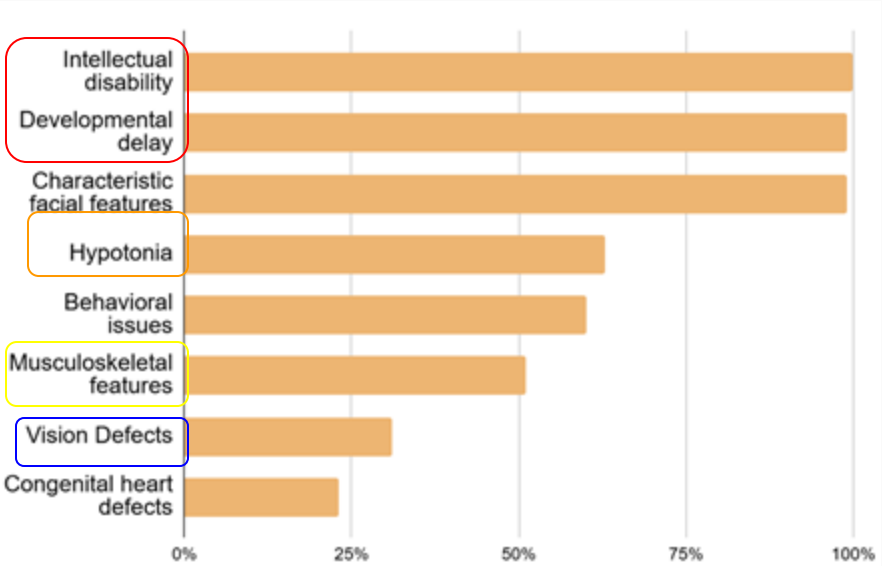
Hamada et al., *Journal of Neurochem* (2023)



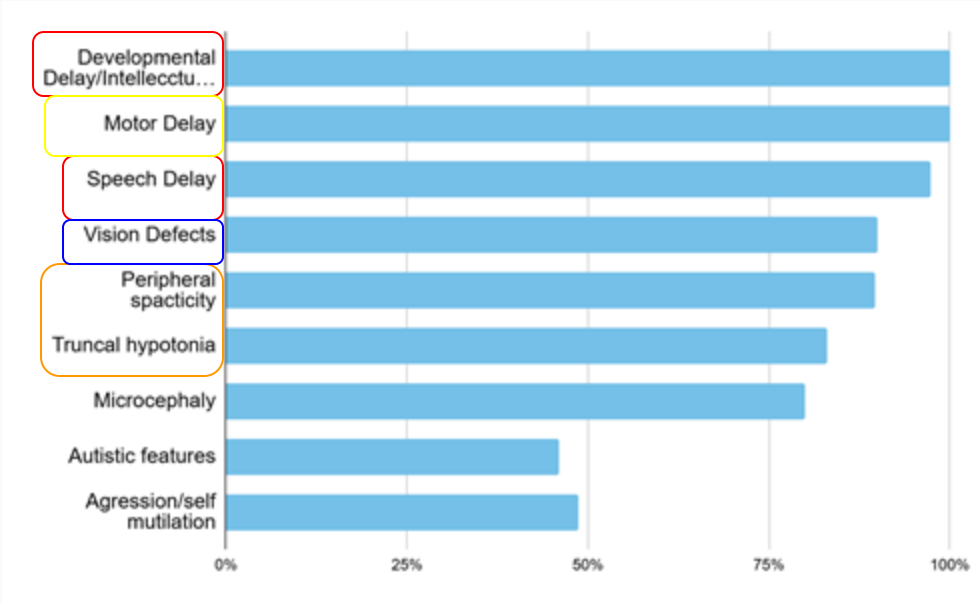
Okuda et al., *PNAS* (2007)

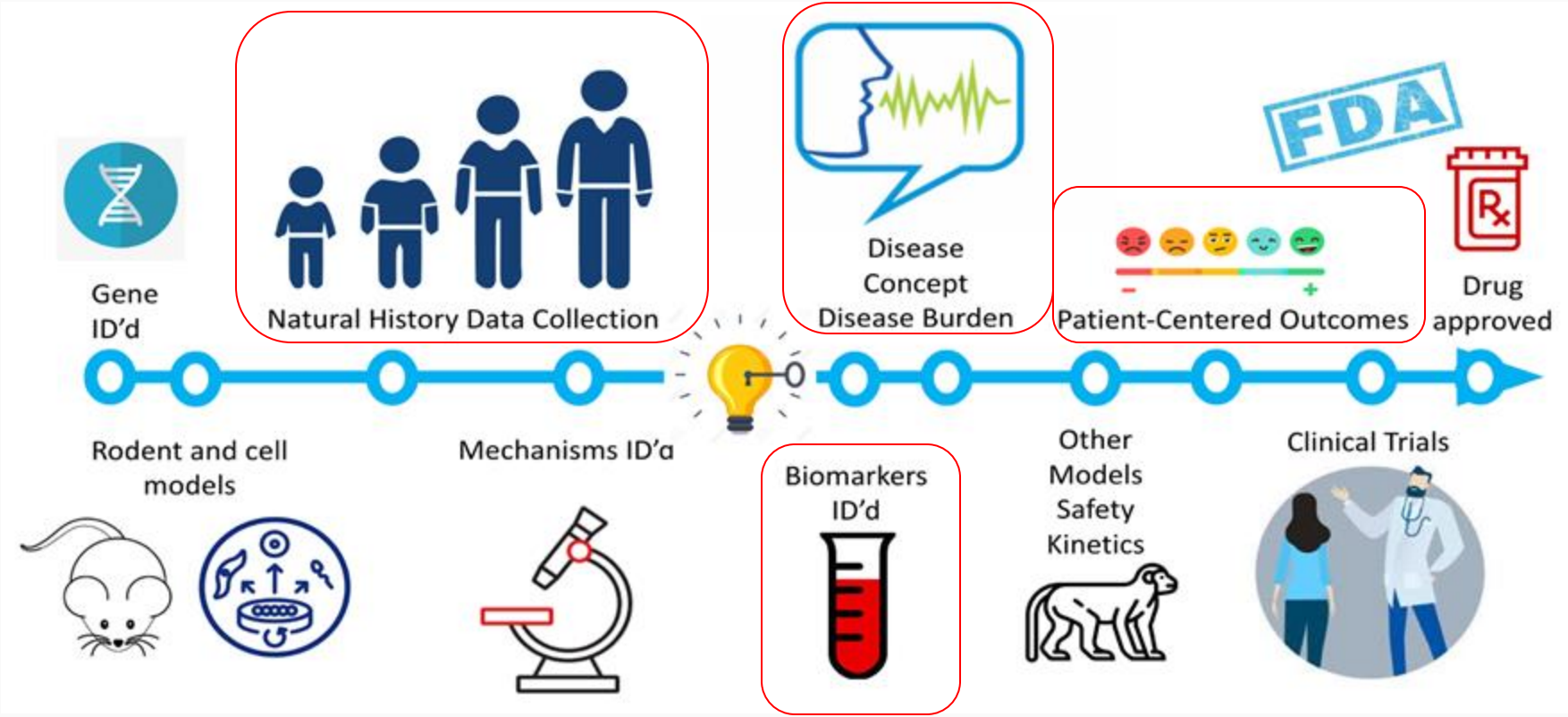
Strong overlap in clinical phenotypes between MED13L and CTNNB1 Syndromes

MED13L



CTNNB1

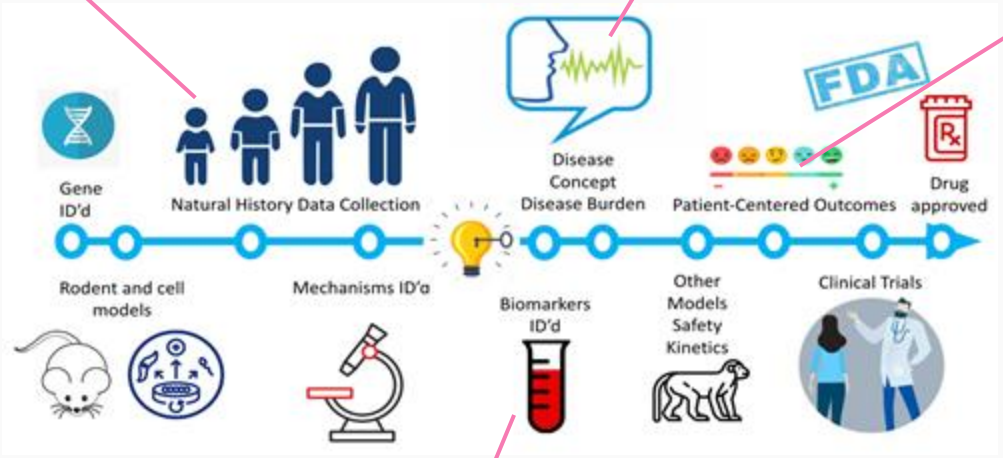



Gene ID'd
Natural History Data Collection
Disease Concept Disease Burden
FDA
Patient-Centered Outcomes
Drug approved
Rodent and cell models
Mechanisms ID'd
Biomarkers ID'd
Other Models Safety Kinetics
Clinical Trials

CTNNB1: Boston Children's, Citizen, Simons
MED13L: Boston Children's Rare-X, Simons

Disease Concept Models with COMBINEDBrain

ORTAS Toileting Study
Surveys that are on Rare-X, Citizen, and Simons



*There are QR codes to these studies and more at the tables!

Donating blood, stool, urine, nasal swabs

- Plasma Proteomics study
- Transcriptomics study and drug repurposing screen
- Gut Microbiome study
- EEG study

Thank You!

1. **Natural History Studies**
    a. CTNNB1: Boston Childrens', Citizen, Simons
    b. MED13L: Rare-X, Simons
2. **Disease Concept Models** (COMBINEDBrain)
3. **Biomarkers:**
    a. Blood plasma proteomics study (COMBINEDBrain)
    b. EEG readings
4. **Outcome Measures:**
    a. ORTAS Toileting survey (COMBINEDBrain)
    b. Observational studies