CTNNB1:
Citizen Natural History
&
Wnt Signaling efforts

Kellan Weston
July 11th, 2025
CTNNB1 Science and Family Conference

CTNNB1 Connect and Cure: Over 430 families strong!

Benefits of Online Registry/Natural History

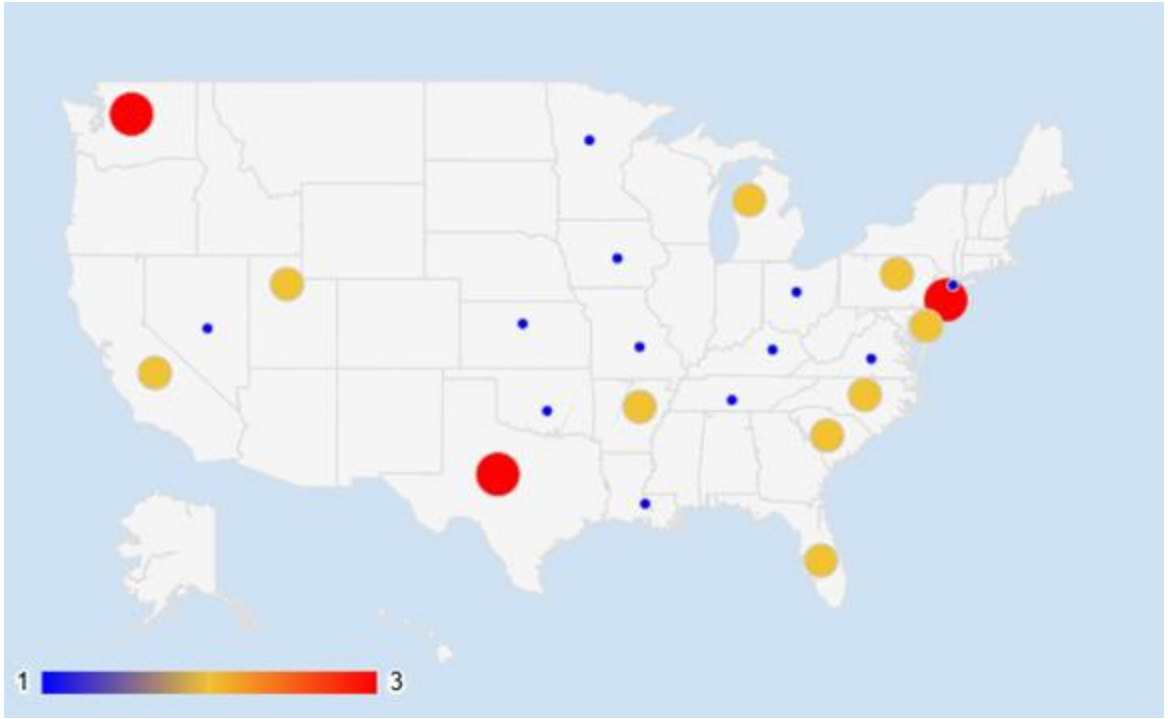
- Less Caregiver burden - no travel required
- An online natural history study can be **global**
    - Available to people from different countries, ethnicities backgrounds
- Can cross-validate an in-person Natural History Study
- Can inform **where we should base future in-person studies and events**

Citizen Natural History Study Demographics

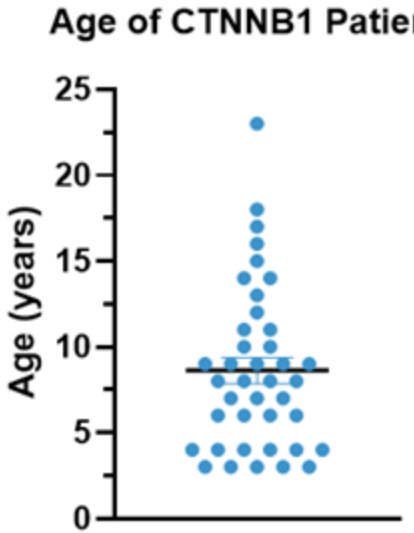
citizen health

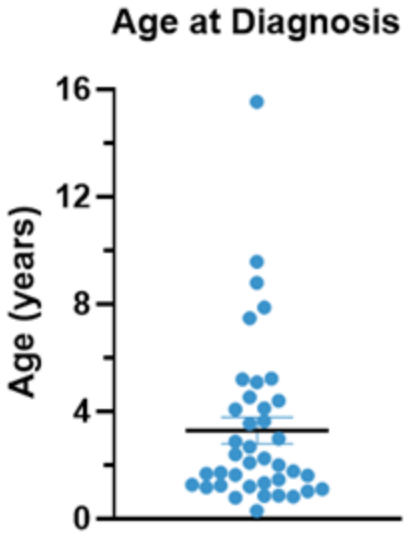
Number of Participants	Number of curated Participants	Age	Average time since last update
>100 patients	40 patients	Average: 8.6 years Range: 3-23 years	2 years

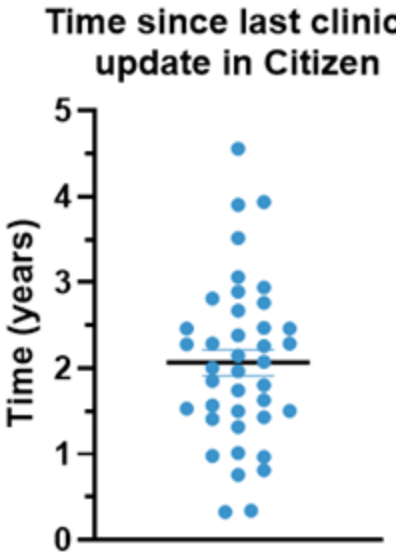
Citizen Natural History Study Demographics



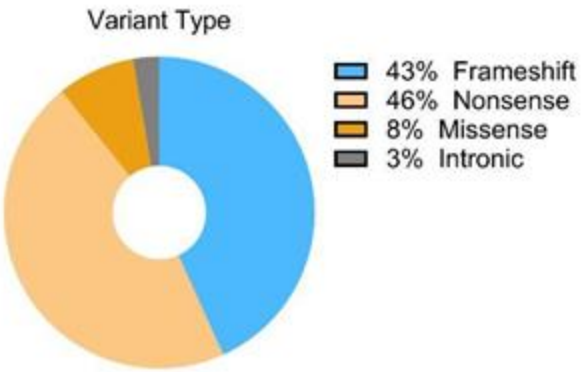
Citizen demographics: Age range

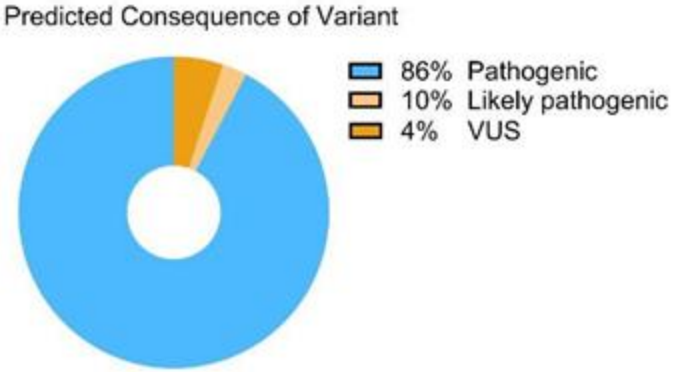




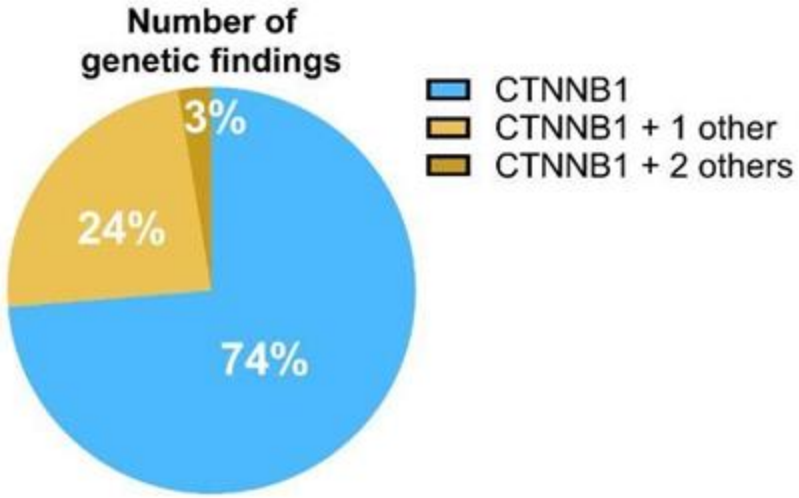


CTNNB1 Genetic Report Findings



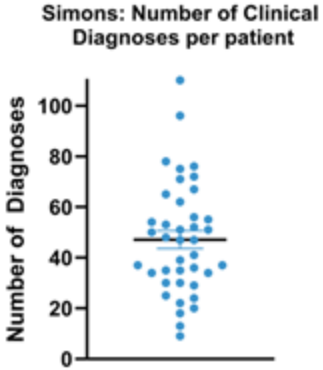


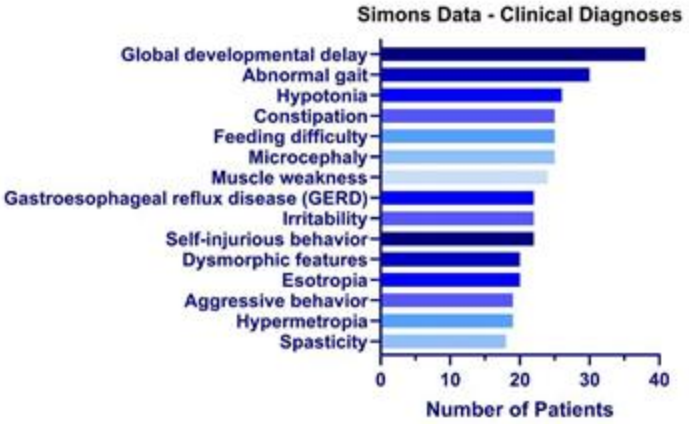
Several patients had mutations in other genes



Secondary Findings: Genes
ATP7B
BRCA1
BRCA2
CERKL
FLG (2 patients)
GLA
MFSD2A
OTOG
PALB2

CTNNB1 Genetic Report Findings





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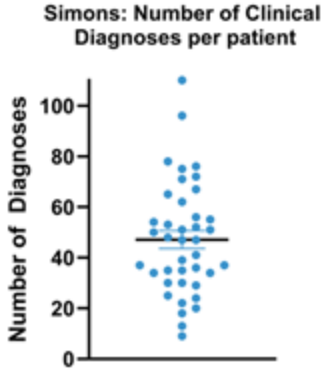
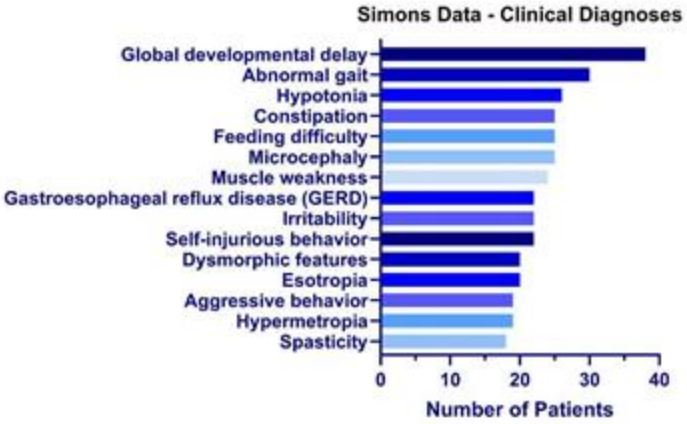
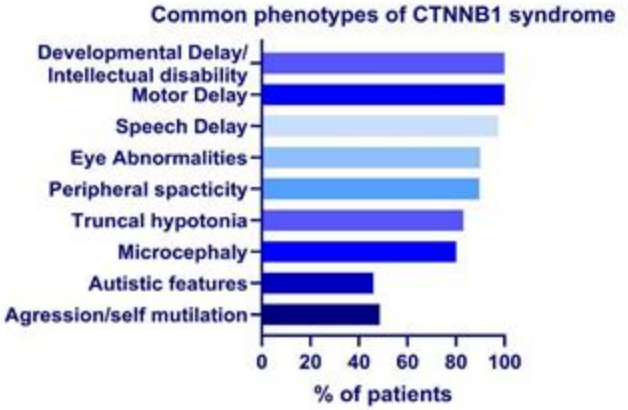




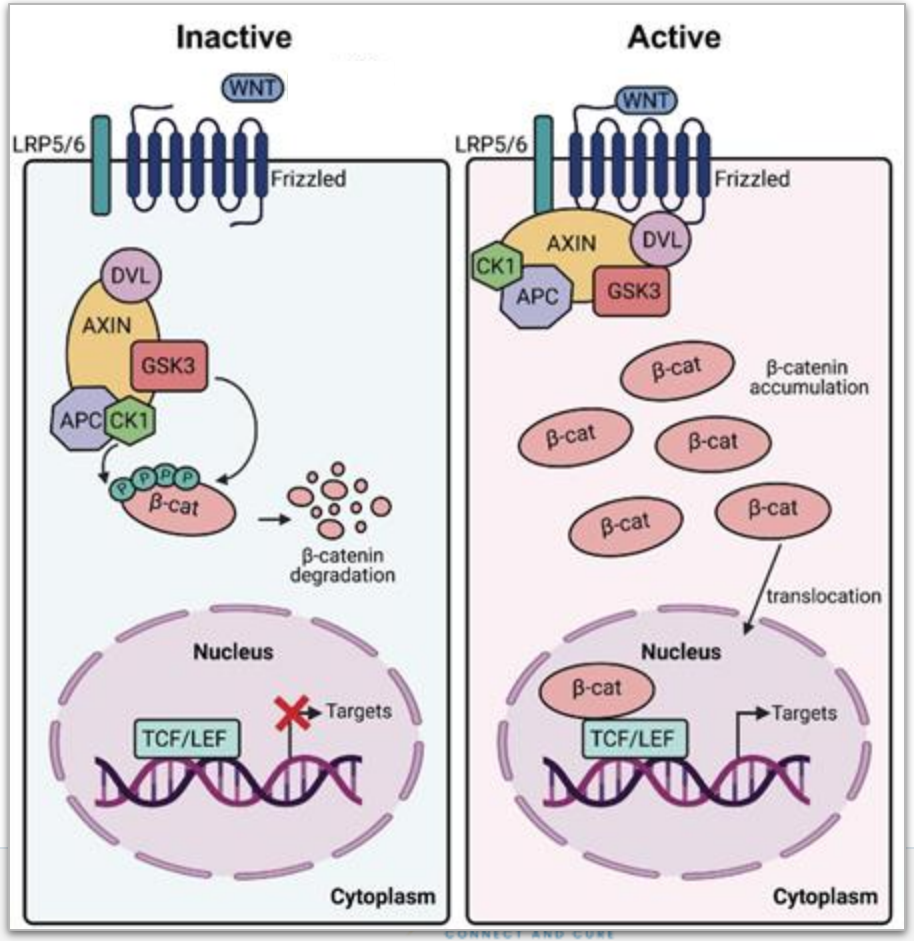


Ho et al, *Genereviews* (2023)

CTNNB1:

Wnt Signaling efforts

What is the canonical Wnt signaling pathway?



Wnt target genes code for proteins involved in growth and development

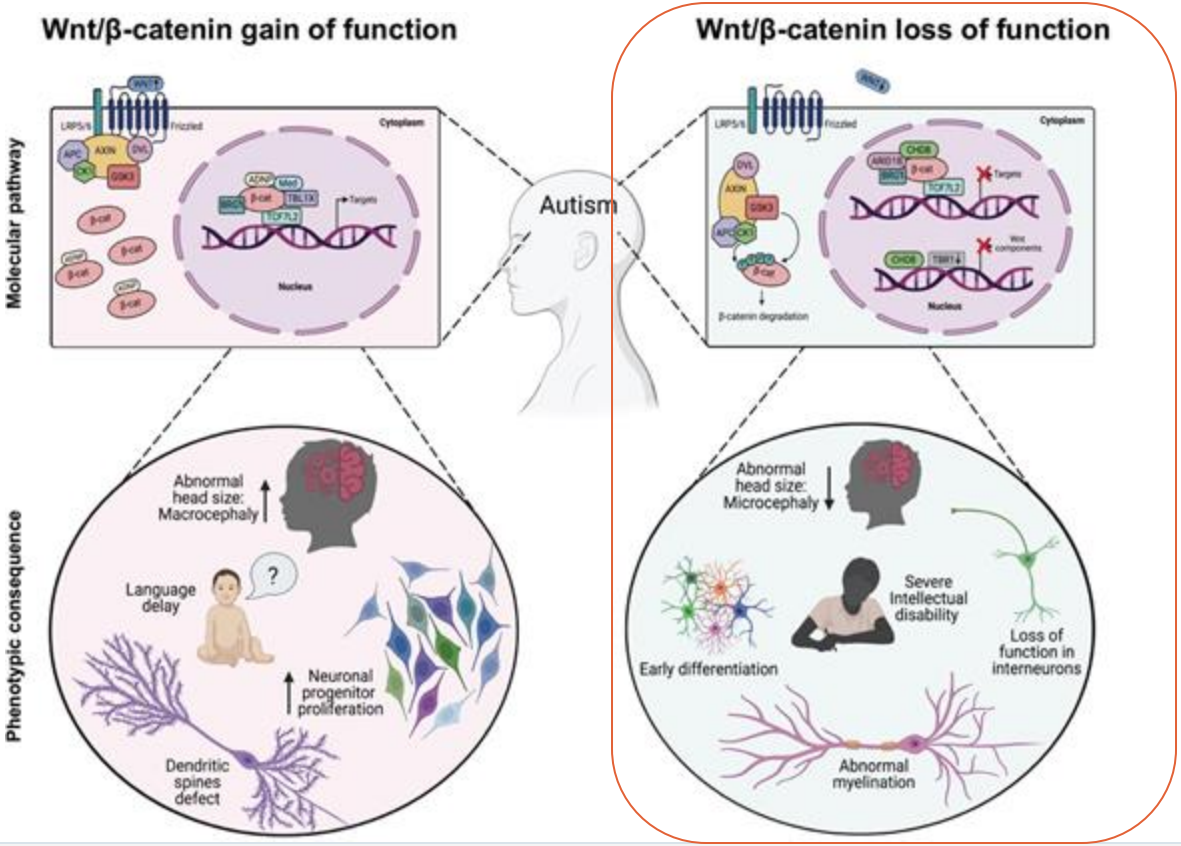
Carraci et al, *Front. Mol. Neurosci.* (2021)

Why is Wnt important?

“Goldilocks” paradigm:

Too much or too little Wnt signaling during development can cause developmental disorders!

Wnt gain of function is also associated with many cancers.



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

Disorders in the working group (so far!)

CTNNB1 Syndrome

Pitt-Hopkins (TCF4)

TCF7L2-Related NDD

MED13L Syndrome

Kabuki Syndrome (KDM6A/KMT2D)

Angelman Syndrome (UBE3A)

DYRK1A Syndrome

CHD8-Related Syndrome

SYNGAP1-Related Disorder

Types of Wnt agonists

Wnt Proteins and Wnt mimics

Recombinant Norrin

Inhibiting Wnt inhibitors

- Sclerostin inhibitors
- DKK1 inhibitors
- SFRP-1 inhibitors
- Recombinant and surrogate R-spondin
- anti-NOTUM small molecules

Disrupting Beta Catenin degradation

- GSK3-β inhibitors
  - Lithium Chloride
  - Small Molecules

Other small molecules and compounds

Goals of the Wnt Working Group

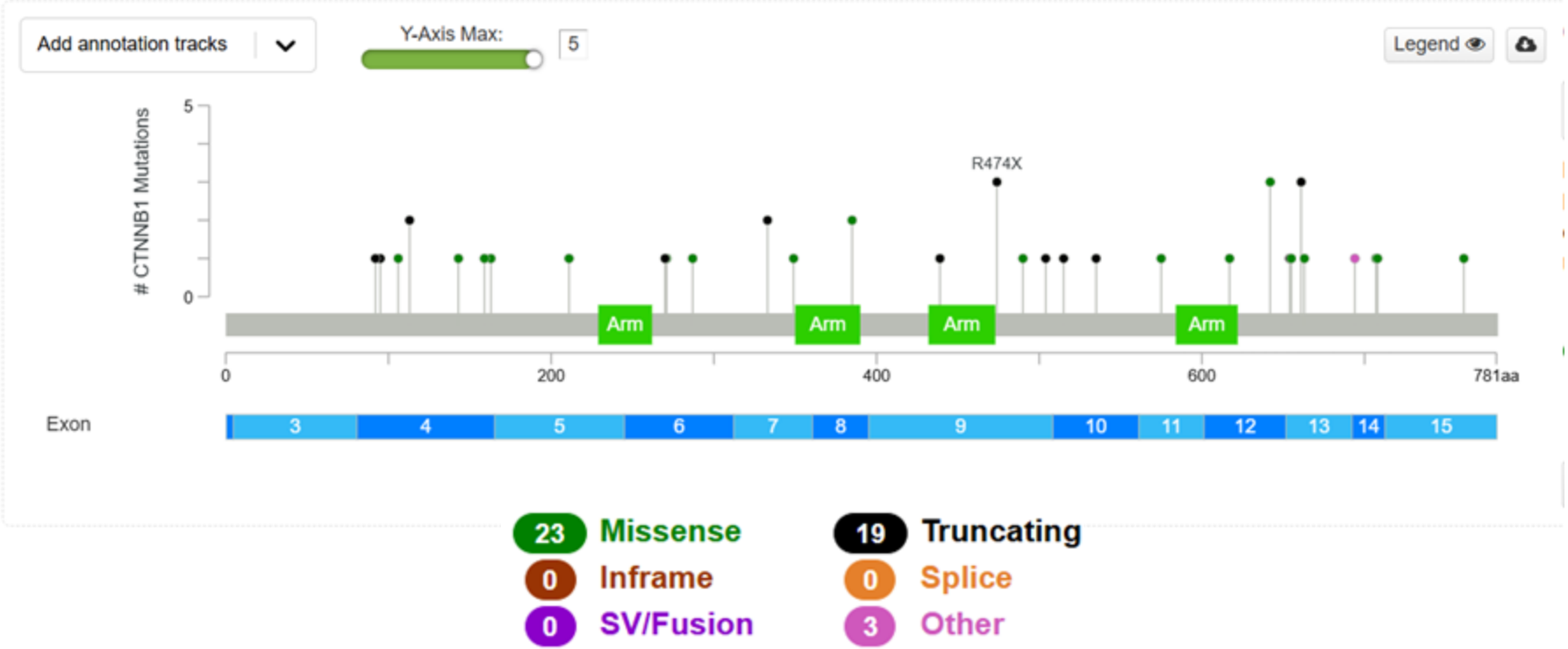
1. Understand the biology of how deficits in the Wnt signaling pathway may be affecting people with each of our rare genetic disorders.
2. Discuss and identify common Wnt pathway targets for therapeutic rescue
3. Identify researchers (academic and industry) in the field and what associations/communities they are already plugged into
4. Bring these research scientists and other experts to the table to discuss the latest research on rescuing Wnt signaling.
5. Discuss possible drug candidates, and bring researchers/expertise to discuss gaps in research
6. (Future) Take steps toward filling those gaps: e.g., funding more basic research, funding research on patient samples, observational studies, preparing for clinical trials.

Please let us know if you are interested in the Wnt working group!

→ We are recruiting basic scientists, clinicians, and foundation leaders who want to contribute to these efforts

Thank you!

Link to the CTNNB1 Research page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Y-Axis Max:
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Legend
CTNNB1 Mutations
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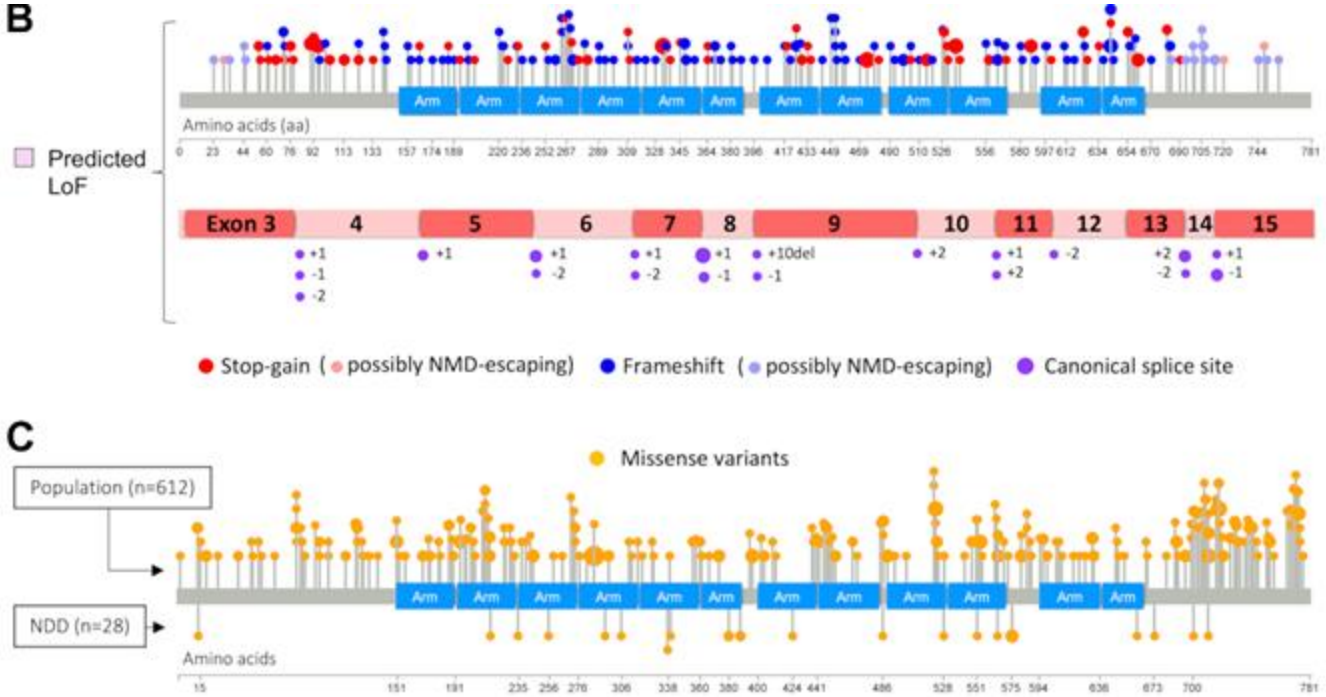
0 SV/Fusion
19 Truncating
0 Splice
3 Other


B
Predicted LoF
Amino acids (aa)
Exon 3
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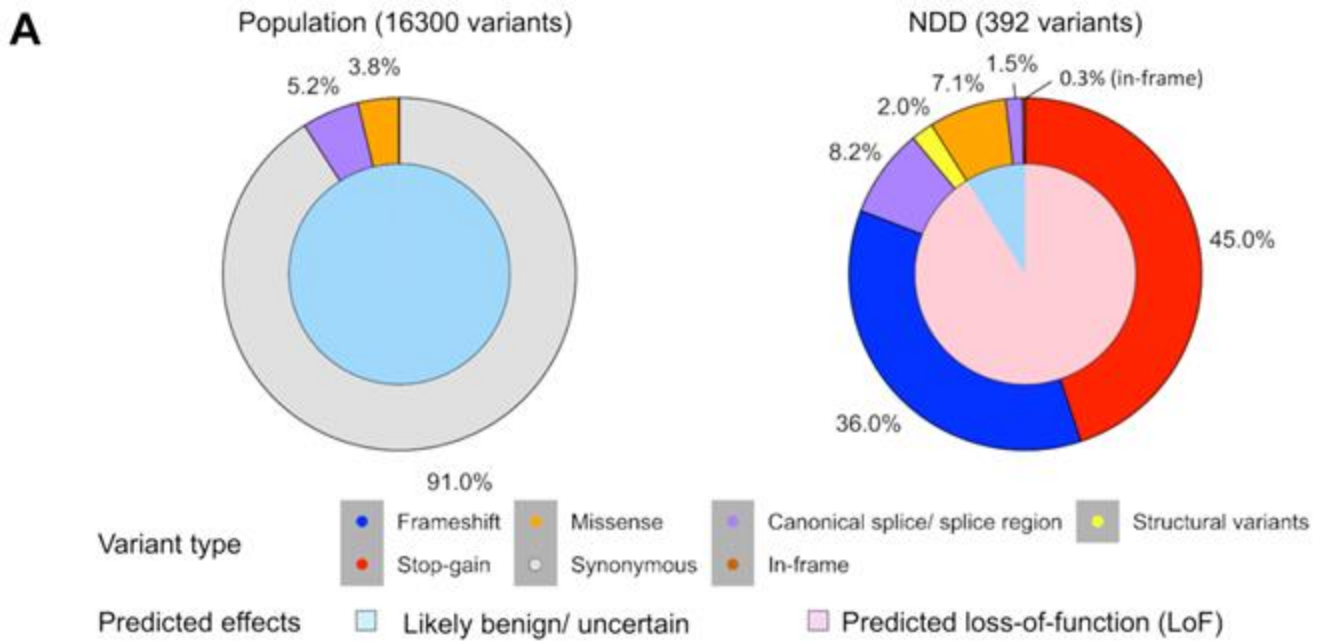
9
10
11
12
13
14
15
Stop-gain (possibly NMD-escaping)
Frameshift (possibly NMD-escaping)
Canonical splice site
C
Missense variants
Population (n=612)
NDD (n=28)
Amino acids


A
Population (16300 variants)
5.2%
3.8%
91.0%
NDD (392 variants)
1.5%
7.1%
0.3% (in-frame)
2.0%
8.2%
45.0%
36.0%
Variant type
Frameshift
Missense
Canonical splice/ splice region
Structural variants
Stop-gain
Synonymous
In-frame
Predicted effects
Likely benign/ uncertain
Predicted loss-of-function (LoF)

Wnt Working Group #2

2/07/2025

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2. Discuss and identify common Wnt pathway targets for therapeutic rescue
3. Identify researchers (academic and industry) in the field and what associations/communities they are already plugged into
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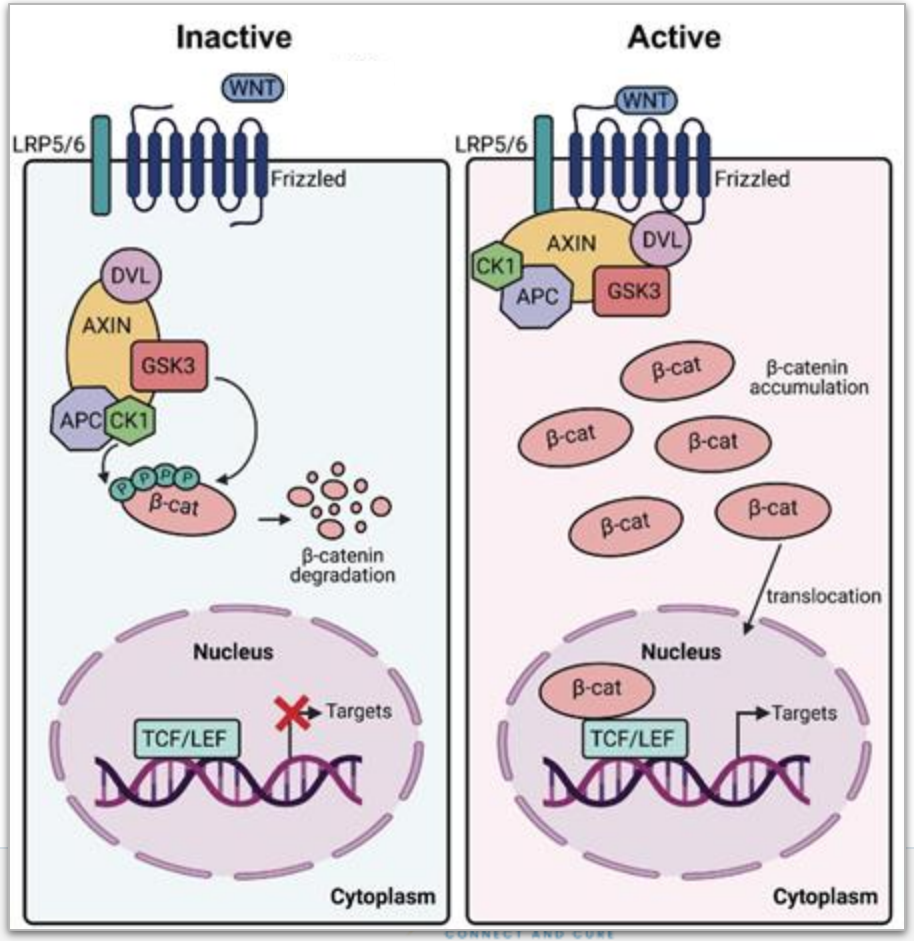
CHD8-Related Syndrome

SYNGAP1-Related Disorder

Recap from last month

- Introduction to the Wnt Pathway
- Introductions of members
- Discussion on the use of lithium as a Wnt activator
- Discussion of sending a representative to the Gordon Conference for Wnt signaling

What is the canonical Wnt signaling pathway?



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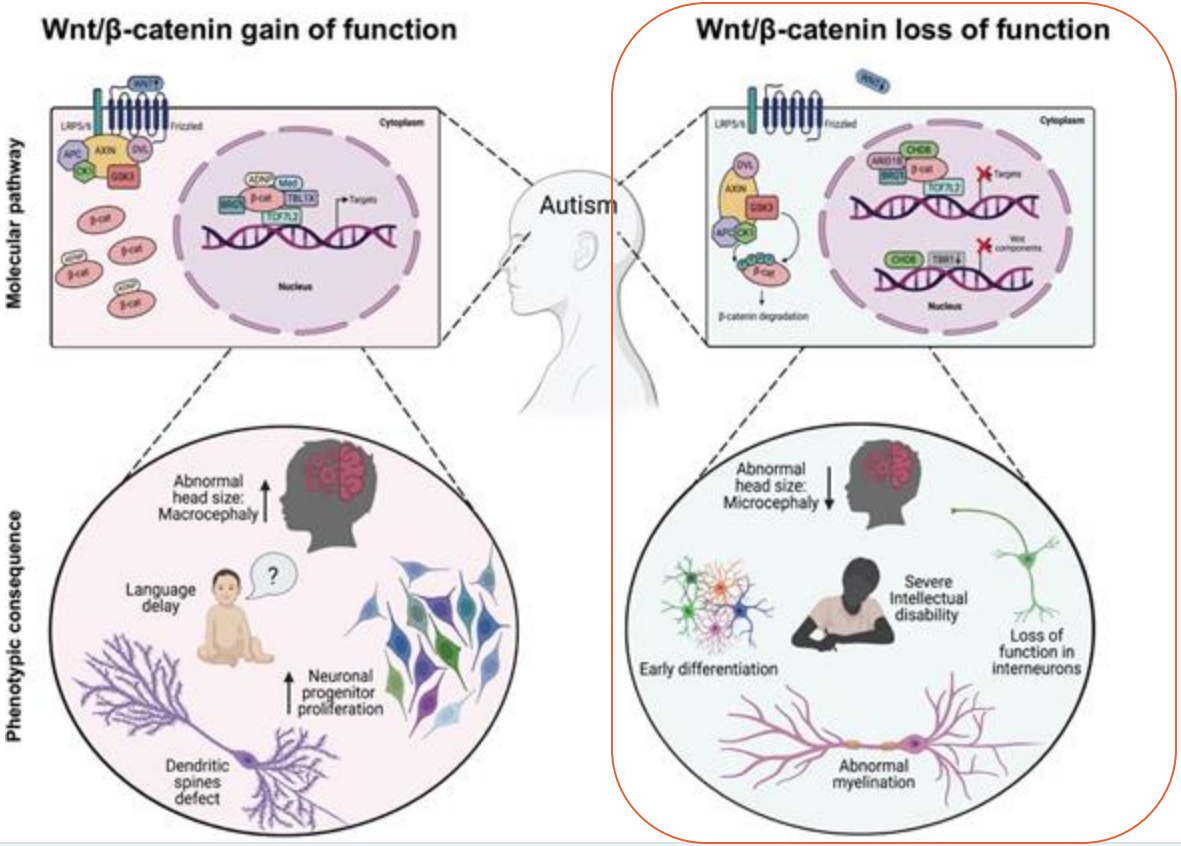
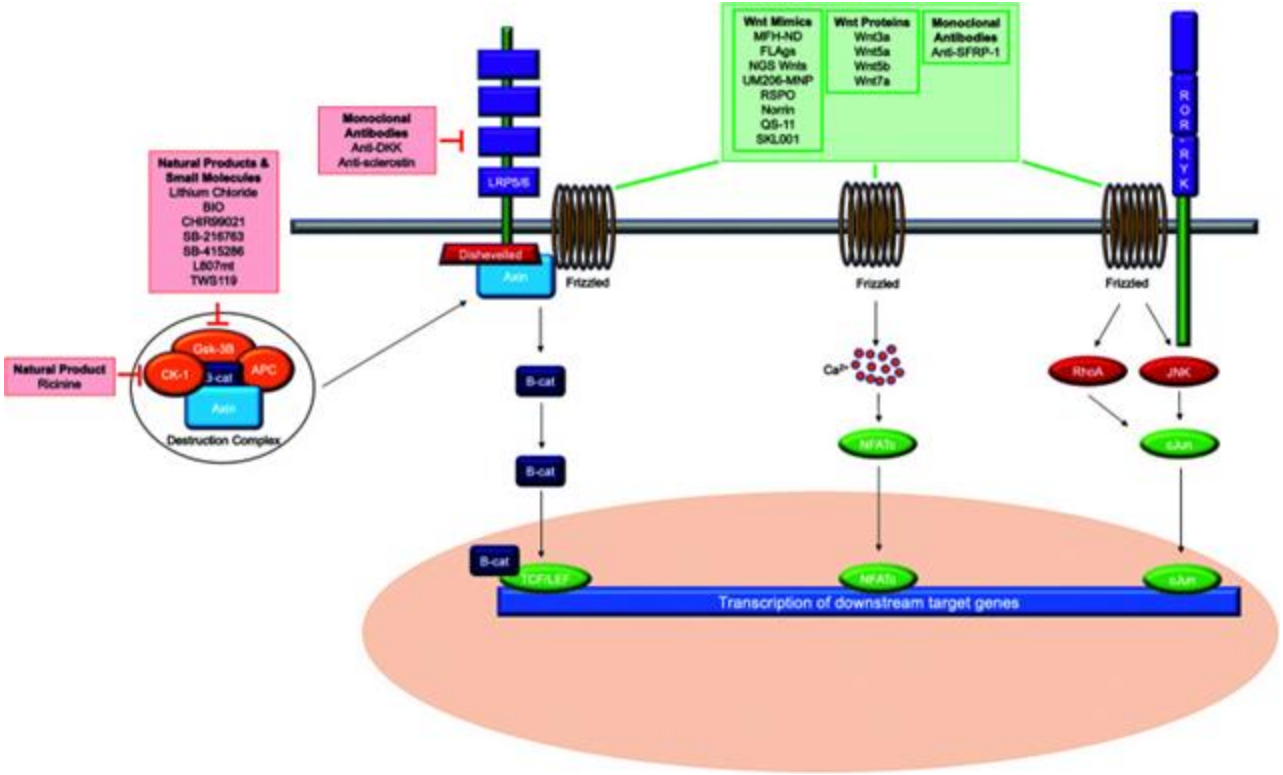


Caracci et al, *Front. Mol. Neurosci.* (2021)

Wnt Agonists: a promising way to rescue loss of Wnt



Bonnet et al, *RSC Chem Biol.* (2021)

Types of Wnt agonists

Wnt Proteins and Wnt mimics

Recombinant Norrin

Inhibiting Wnt inhibitors

Disrupting Beta Catenin degradation

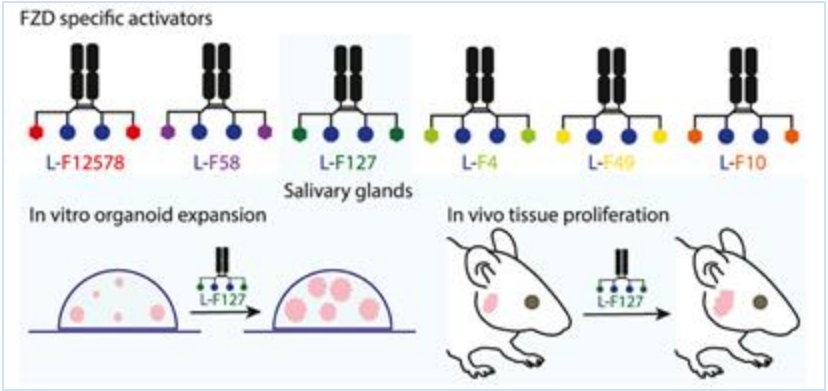
Other small molecules and compounds

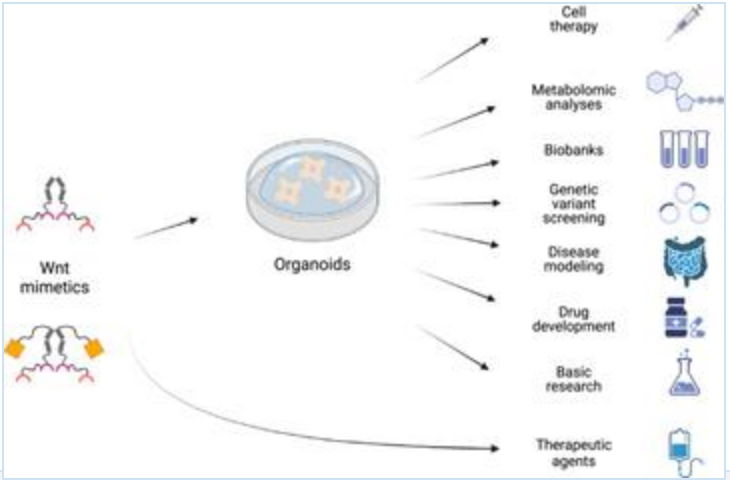
Wnt Proteins and Wnt mimics

Wnt proteins: typically only used in a laboratory setting on cultured cells

Wnt mimics: Still in early stages of development/testing.

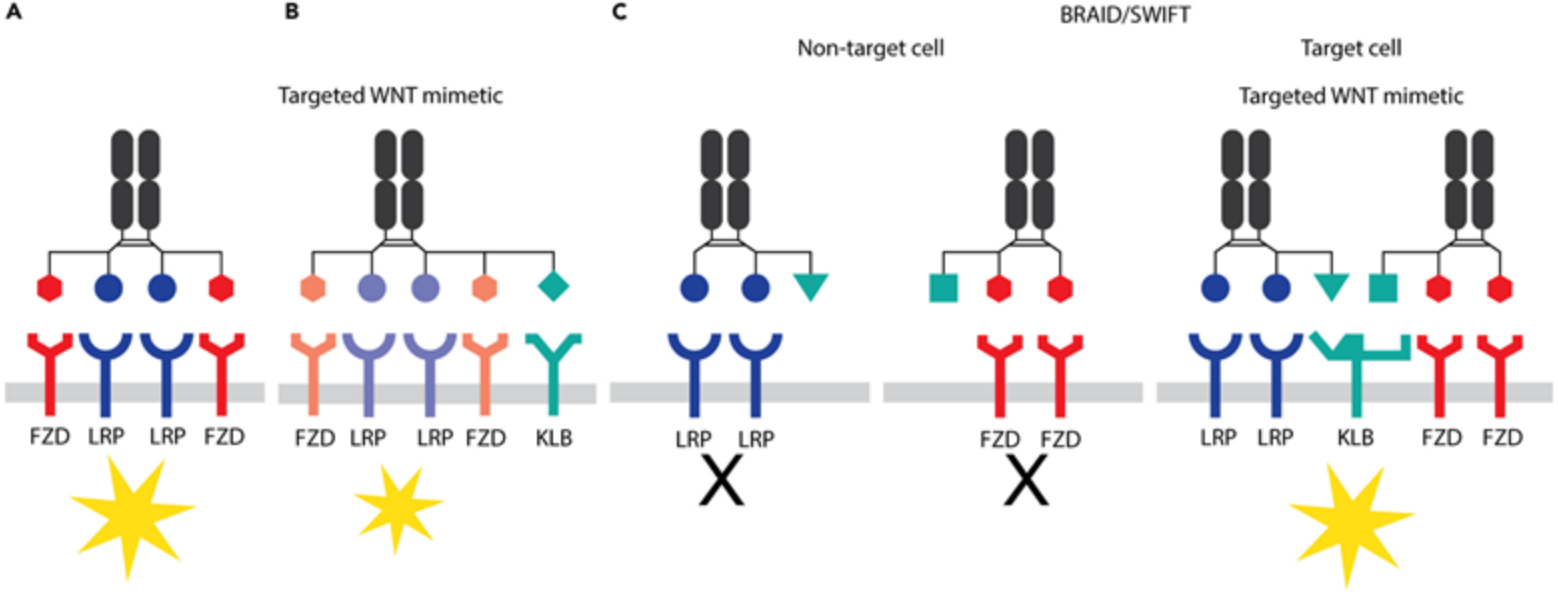
- Need to be soluble, potent, and selective
- First characterized in 2017
  - (Stanford - Calvin Kuo and K Christopher Garcia)
- Antibody-based mimetics are being tested in models of tissue regeneration
  - Stimulated intestine and liver growth
  - *In vitro* organoid expansion (salivary gland and alveolar organoids)
  - *In vivo* salivary gland growth





Maimets, *Cell Chem Biol.* 2023
Post et al, *Cell Chem Biol.* (2023)

Potential advantage of Wnt mimetics: ability to target cells



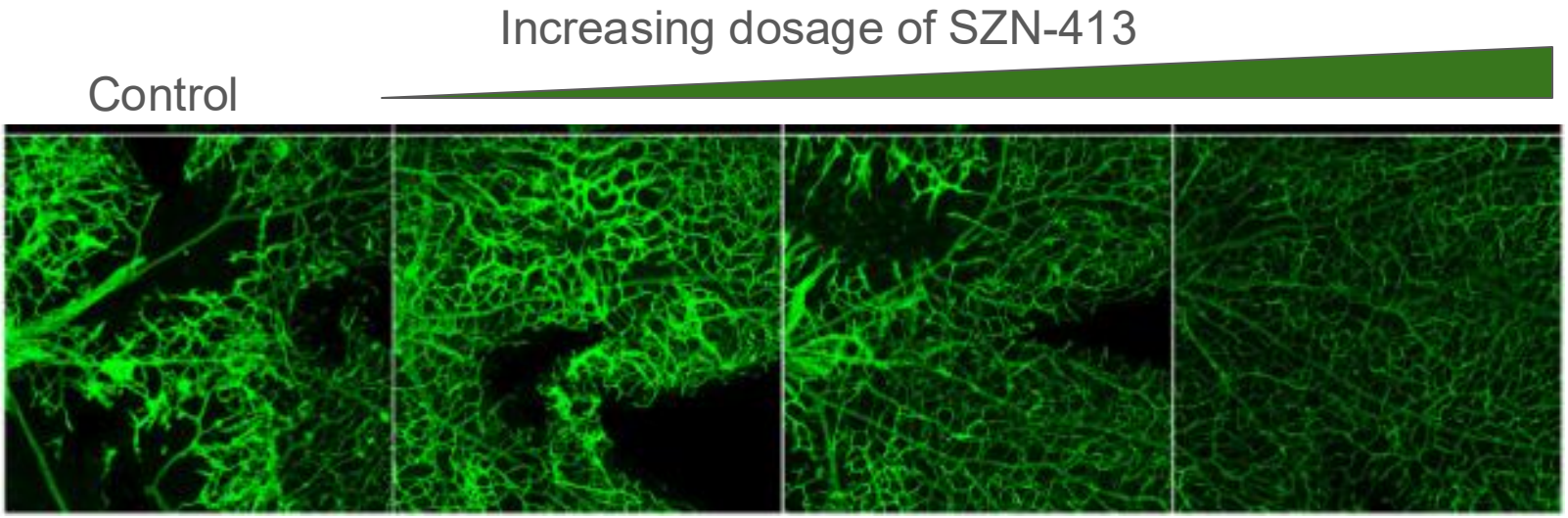
Cell-targeted WNT mimetics can be generated by fusing a binding domain to a cell-targeting receptor to a WNT mimetic.

Post et al, *iScience* (2024)

Wnt Mimetics as a potential therapeutic

- Founded out of Stanford in 2017 specifically to activate Wnt
- Founders:
  - K. Christopher Garcia, Ph.D.
  - Roeland Nusse, Ph.D.
  - Calvin Kuo, M.D., Ph.D.
  - Claudia Janda, Ph.D.
- **SZN-043** is in phase I clinical trials for Liver Cirrhosis
- **SZN-413** is specifically for retinopathies - still in pre-clinical stages
  - First publication: tested on retinal and brain endothelial cells, and in mouse **retinopathy** model
  - Most recent publication was published in an *in vitro* model of **pulmonary fibrosis**

Surrozen's SZN-413



Retina vascularization in a mouse model of oxygen-induced retinopathy (OIR)

Nguyen et al, *Transl Vis Sci Technol* (2022)

venbio

Types of Wnt agonists

Wnt Proteins and Wnt mimics

Recombinant Norrin

Inhibiting Wnt inhibitors

Disrupting Beta Catenin degradation

Other small molecules and compounds

Recombinant Norrin

Norrin: (Gene: *NDP*) (130 amino acid length)

- A secreted signaling molecule expressed in the CNS, particularly in the eye
- Binds with high affinity and specificity to FZD-44 and LRP5/6 to activate B-catenin
- Mutations of *NDP* → **Norrie disease** and f**amilial exudative vitreoretinopathy (FEVR)**
- Has been used to study Wnt/β-catenin pathway activation in the context of retinopathies
    - FEVER, Norrie, and diabetic retinopathy
    - Dearth of research on non-retinopathy models

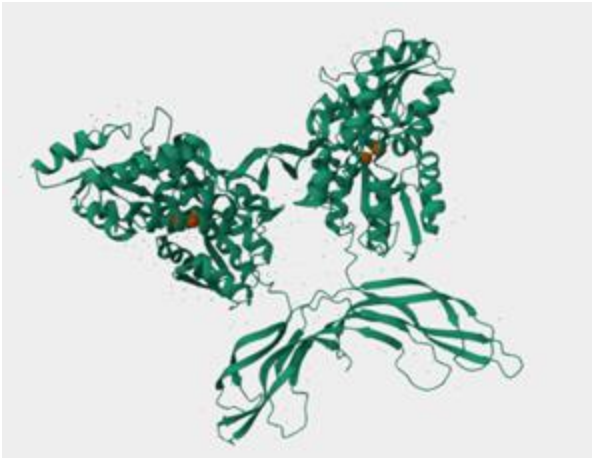


Image source: UniProt.org

Norrin as a therapeutic for FEVR

In 2022, the FDA granted Orphan Drug Designation for **Noregen (CTR-107)**

- A synthetic protein modeled after Norrin
- Being developed by Caeregen - they partnered with Oakland University for the basic science
- Wacker Biotech will produce the drug and complete clinical trial drug product production at its site in Amsterdam, the Netherlands, to support Phase I/II clinical study initiation in 2024
- I cannot find any more information on whether the clinical trials have begun

Caeregen® therapeutics

Noregen™

Regenerative Therapy to Heal Diseases of the Retina

Types of Wnt agonists

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Recombinant Norrin

Inhibiting Wnt inhibitors

- Sclerostin inhibitors
- DKK1 inhibitors
- SFRP-1 inhibitors
- Recombinant and surrogate R-spondin
- anti-NOTUM small molecules

Disrupting Beta Catenin degradation

Other small molecules and compounds

Sclerostin inhibitors

Sclerostin (gene: *SOST):* highly and selectively expressed in **osteoblasts and osteocytes**. Inhibits Wnt by binding to the LRP5/6 co-receptor, preventing association with the Fz receptor.

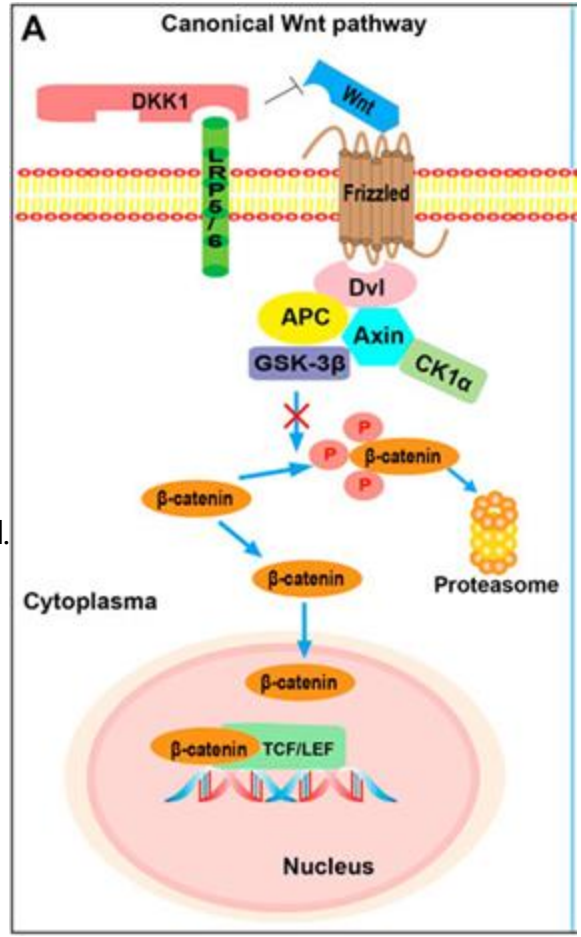
Romosozumab (EVENITY™): FDA-approved anti-sclerostin monoclonal antibody

- Approved for postmenopausal osteoporosis (https://www.evenity.com/)
  - Effectiveness has been debated (see Nelson 2022 review)

DKK inhibitors

Dickkopf-1 binds to LRP5/6 to inhibit Wnt signaling

- PF-04840082 - monoclonal antibody
- RH2-18 - monoclonal antibody
- BHQ880 (investigational drug - Novartis)
  - Phage-delivered monoclonal antibody
  - B-catenin levels were upregulated in mouse models
  - Used for multiple myeloma. Phase II clinical trials were not very successful.
- DKN-01 (Sirexatamab - Leap Therapeutics)
  - IgG4 monoclonal antibody
  - Tested in Phase I and Phase II trials for Lung and gynecologic cancers
  - Tested in cancer patients with CTNNB1 *activating* mutations (!)
- Gallocyanine derivitaves (NCI8642) - small molecule inhibitor. Only tested in cell culture so far.



Jiang et al., *Frontiers in Pharmacology* (2022)

SFRP-1 inhibitors

SFRP is a family of secreted Wnt inhibitors (5 members in humans).

Loss of SFRP-1 can impact bone mass.

N-Substituted Piperidinyl Diphenylsulfonyl Sulfonamide **(WAY-316606):**

- selectively binds to SFRP-1, thereby activating the Wnt/β-catenin pathway
- Rescues osteoporosis in a mouse model (intraperitoneal injection)
- Studied in hair loss models
  - Seems to have undergone phase I trials, but safety was a concern
  - I'm still looking for good information on trials
- Easily available from major chemical suppliers

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Inhibiting Wnt inhibitors

Disrupting Beta Catenin degradation

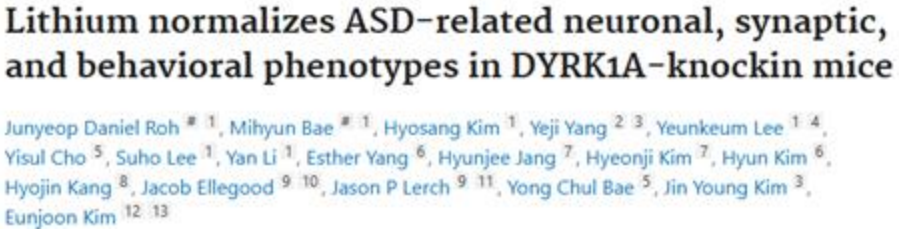
- GSK3-β inhibitors
  - Lithium Chloride
  - Small Molecules

Other small molecules and compounds

Lithium Chloride

- Directly inhibits GSK-3α and GSK-3β → activates Wnt
- Used as a mood stabilizer for bipolar disorder, schizophrenia, depression, and other illnesses
  - Little is known about its mechanism of action in the brain
  - Crosses the BBB
  - Stimulates neuronal activity
- Cons:
  - Toxicity is a concern
  - Nonspecific - will likely have off-target effects

Research that Lithium may broadly help NDDs



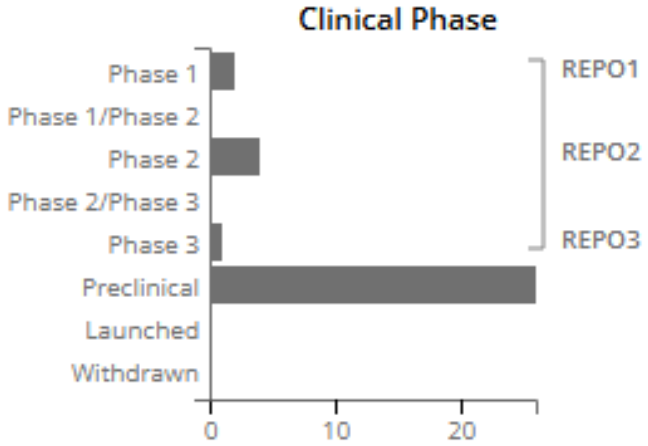
- Lithium has been reported as being used for behavior management in individuals with neurodevelopmental disorders
  - Angelman
  - CTNNB1 - anecdotal reports
  - Phelan-McDermid (SHANK3)

GSK3β inhibitors: Promising but require development

GSK3β inhibitors have been long used in laboratory setting

Requirements for human use:

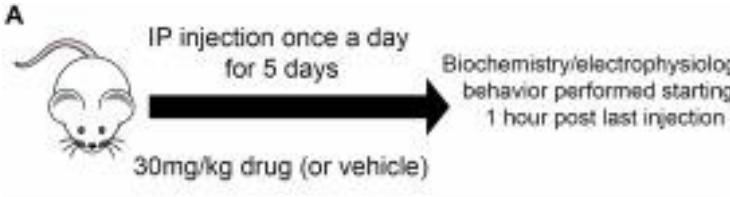
- Safety profile
- Specificity
- Crosses the blood brain barrier



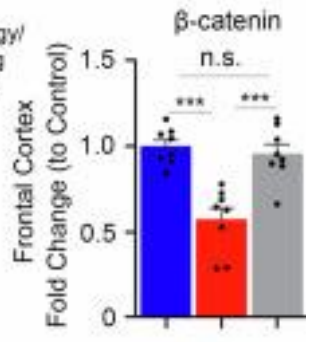
GSK3B inhibitors (Spreadsheet link)

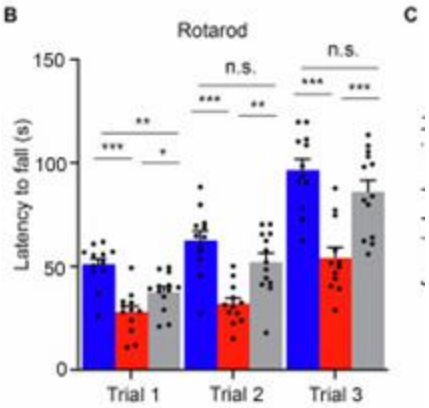
Compound	Notes
Riluzole	FDA-approved for ALS, in clinical trials for AD. May up- or down-regulate Wnt - studies conflict
AMO-02 (Tideglusib)	Phase II. Noscira. Alzheimer's. Discontinued.
LY2090314	Phase II. Eli Lilly. Leukemia. Discontinued. Shown *in vivo* to increase Axin2 expression.
BRD0320, BRD0705, BRD3731	Broad Institute. They have a number of GSK3a/B inhibitors
CHIR99021	Commonly used in labs; has crosstalk with other pathways (incl. Notch)
TWS119	Used in mice
IQ-1	targets PP2A, a phosphatase of the destruction complex that inhibits GSK-3β
Arylindolemaleimide (SB-216763), anilinomaleimide (SB-415286)	Shown to rescue neurodegenerative phenotypes in rat brain cultures
L807mts	highly specific GSK-3β inhibitor. Used in Mouse model of AD.
SB-216763	Reagent.
SB-415286	Reagent.
BAY 36-7620	Reagent.
4MT2001, 4MT1060	4M Therapeutics is characterizing, with a grant from SynGAP.

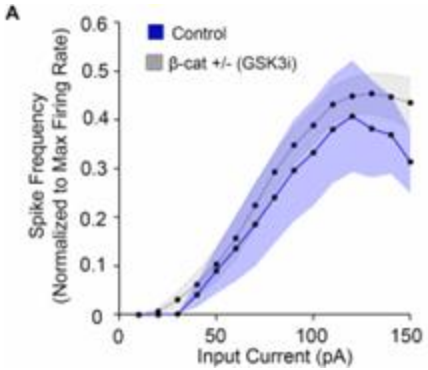
Michele Jacob: GSK3B inhibitor in a CTNNB1 mouse

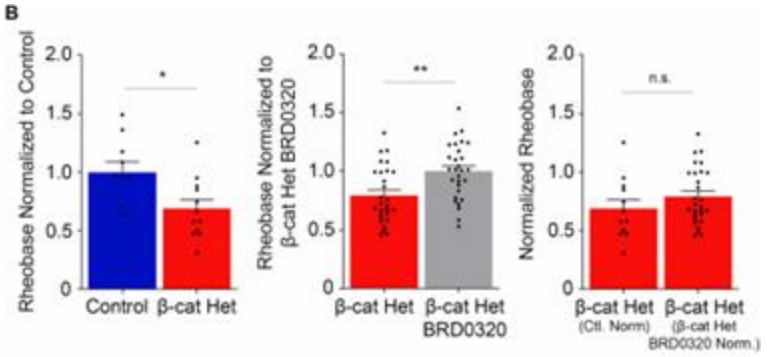


BRD0320 (both α and β paralogs)
BRD0705 (α selective)
BRD3731 (β selective)









Ideas for next steps for the Wnt working group

Drug Discovery and Repurposing for modulating Wnt in our disorders:

- Leverage previous drug screens to understand which Wnt modulators may be best for each disorder
  - AI drug screening (NCATs)
  - Broad institute
- Do a cross-Wnt disorder screen
  - COMBINEDBrain plasma proteomics
  - **Unravel: AI drug repurposing based on nose mRNA**
  - Future: fund a cross-disorder Wnt-focused drug screen (*in vitro* or *in vivo)*
- Engage expertise of Wnt researchers
  - Invite to present at working group
  - Meet with researchers one-on-one - academic and industry
  - Gordon Wnt conference (Summer 2025)
- FDA-approved drugs: off-label or OTC
  - Observational trial model
  - Find Clinicians willing to do case studies

Action Items

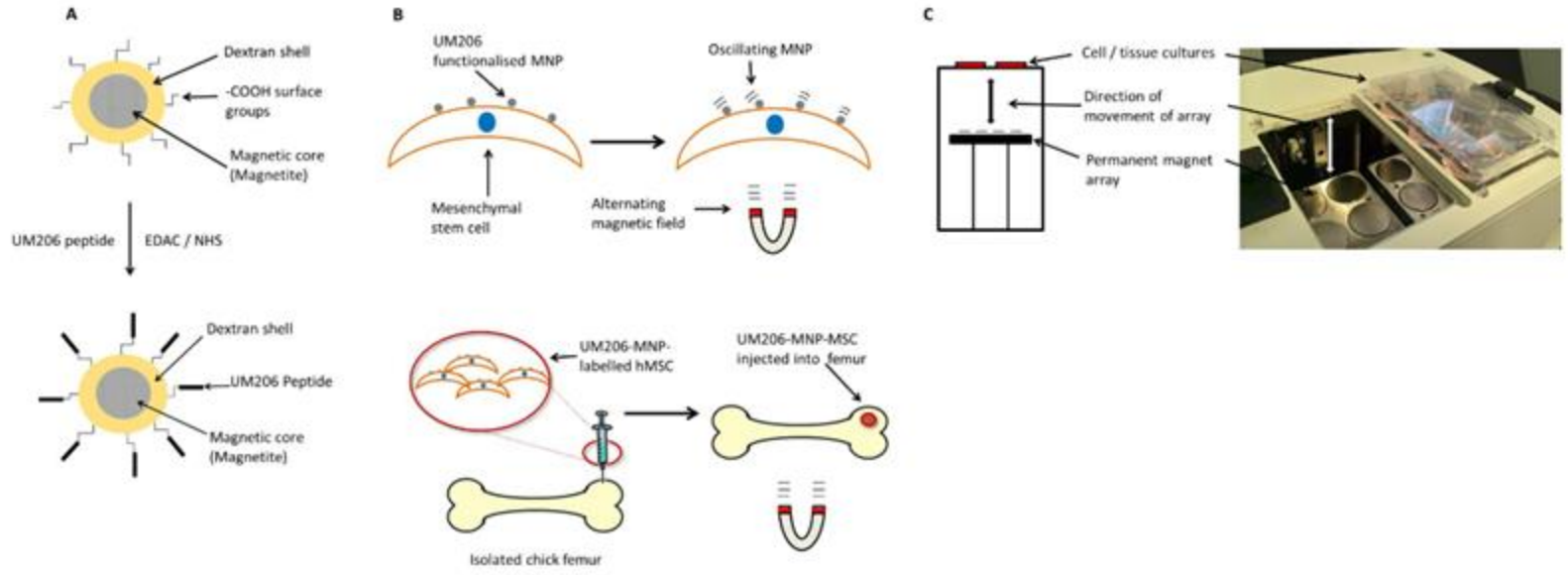
- Please ask your scientific advisory board members to join us!
- Please look at this spreadsheet and add info on Wnt agonists you know of
- Please fill out this Form to tell us what drug candidates your community may be interested in for observational studies
- Please set up a chat with Kellan if you have any resources/history with modulating the Wnt signaling pathway in your group
    - Scientific researchers
    - Industry and Academic contacts
    - History with using a Wnt-modulating therapy

Thank you!

UM206 - a synthetic peptide ligand for FZD1 and FZD2

- A peptide activator of canonical Wnt. Binds to Frizzled.
- Used in combination with a **magnetic nanoparticle** to stimulate Wnt TCF/LEF activity
- Characterized by Alicia El Haj in the UK (Keele University)
- Has never been used *in vivo* - onlv *in vitro* in HEK cells and *ex vivo* in chick femurs and rat brains.

Figure 1.



R-Spondin and anti-NOTUM

R-Spondin:

https://pubmed.ncbi.nlm.nih.gov/37406727/

All pre-clinical research.

Anti-NOTUM

“They are interesting compounds to study *in vitro* models of Alzheimer's disease, but to date, these compounds are not metabolically stable.”

Alyson axtman wnt actvates the aa1 kinase to promote….

Wnt Working Group #3

5/23/2025

Goals of the Wnt Working Group

1. Understand the biology of how deficits in the Wnt signaling pathway may be affecting people with each of our rare genetic disorders.
2. Discuss and identify common Wnt pathway targets for therapeutic rescue
3. Identify researchers (academic and industry) in the field and what associations/communities they are already plugged into
4. Bring these research scientists and other experts to the table to discuss the latest research on rescuing Wnt signaling.
5. Discuss possible drug candidates, and bring researchers/expertise to discuss gaps in research
6. (Future) Take steps toward filling those gaps: e.g., funding more basic research, funding research on patient samples, observational studies, preparing for clinical trials.

Disorders in the working group (so far!)

CTNNB1 Syndrome

Pitt-Hopkins (TCF4)

TCF7L2-Related NDD

MED13L Syndrome

Kabuki Syndrome (KDM6A/KMT2D)

Angelman Syndrome (UBE3A)

DYRK1A Syndrome

CHD8-Related Syndrome

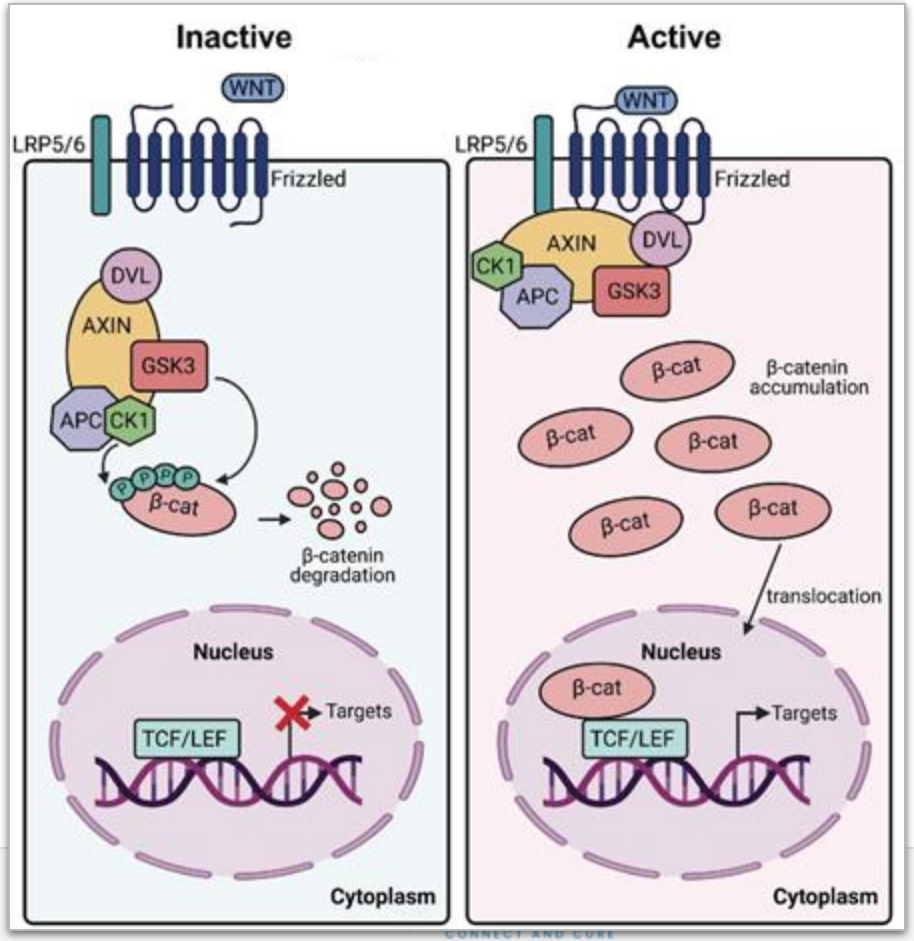
SYNGAP1-Related Disorder

May 23rd Agenda

- Round of introductions
- Recap of previous meetings
  - Overview of Wnt Signaling
  - Overview of therapeutic approaches
  - Progress toward our working group goals

- Presentation: how Wnt signaling is relevant to each of our gene disorders
- Discussion: How do we want to proceed as a group?
  - Types of projects
  - Establishing collaborations

What is the canonical Wnt signaling pathway?



Wnt target genes code for proteins involved in growth and development

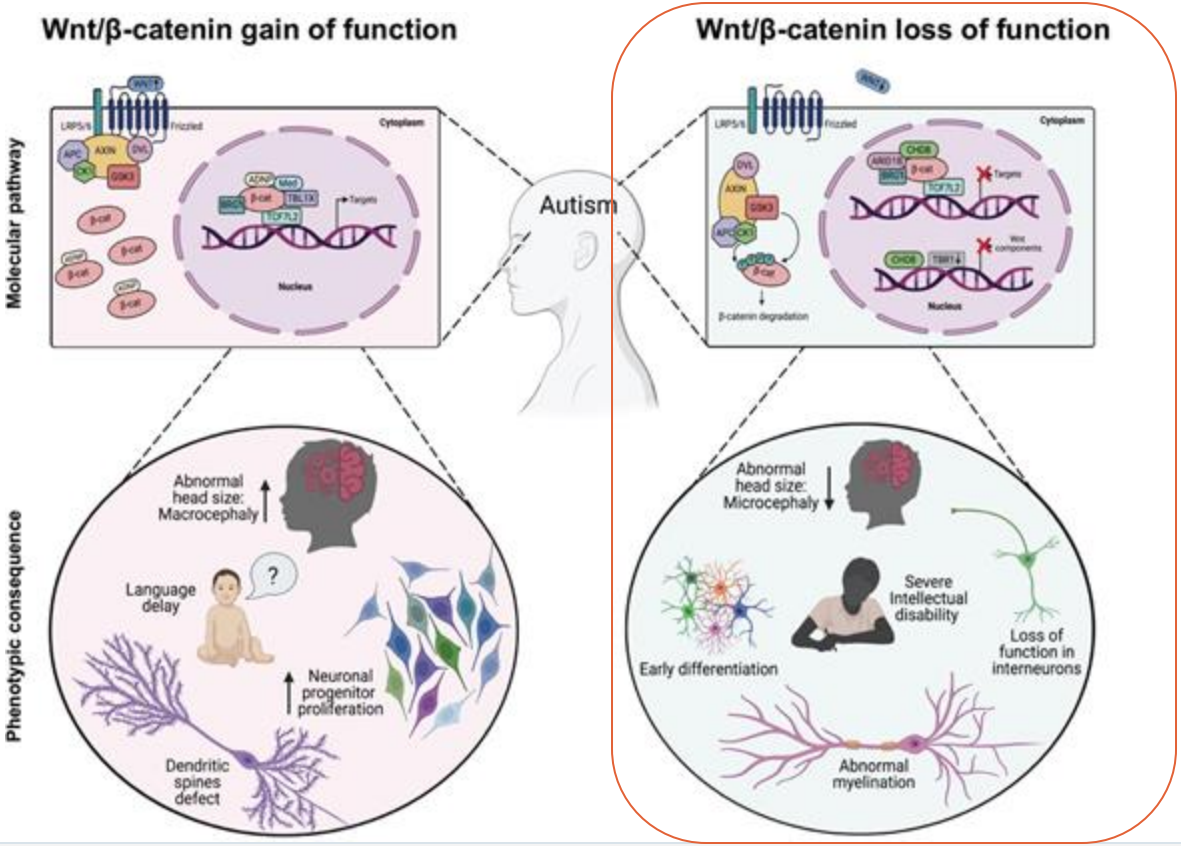
Carraci et al, *Front. Mol. Neurosci.* (2021)

Why is Wnt important?

“Goldilocks” paradigm:

Too much or too little Wnt signaling during development can cause developmental disorders!

Wnt gain of function is also associated with many cancers.



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

Wnt Working Group #2: Types of Wnt agonists

Wnt Proteins and Wnt mimics

Recombinant Norrin

Inhibiting Wnt inhibitors

- Sclerostin inhibitors
- DKK1 inhibitors
- SFRP-1 inhibitors
- Recombinant and surrogate R-spondin
- anti-NOTUM small molecules

Disrupting Beta Catenin degradation

- GSK3-β inhibitors
  - Lithium Chloride
  - Small Molecules

Other small molecules and compounds

Link to slides here

Wnt Working Group #3: NDDs and Wnt

Genes that are:

Part of the Wnt Signaling Pathway

- CTNNB1 Syndrome
- TCF7L2-related NDDs
- Kabuki Syndrome (KDM6A/KMT2D)

Known Wnt Signaling Pathway interactors

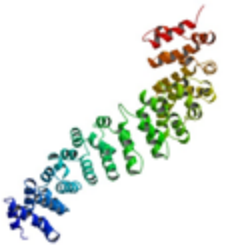
- Angelman Syndrome (UBE3A)
- Pitt-Hopkins (TCF4)
- DYRK1A Syndrome

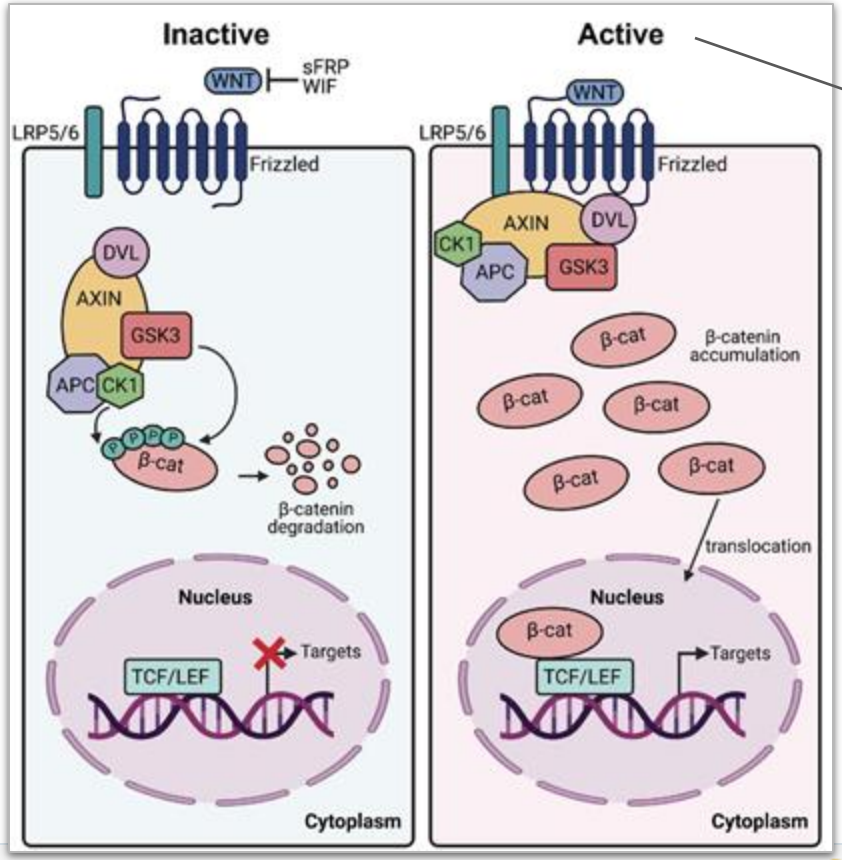
Affect Wnt in an unknown manner

- MED13L Syndrome
- CHD8-Related Syndrome
- SYNGAP1-Related Disorder

Link to document with literature review details

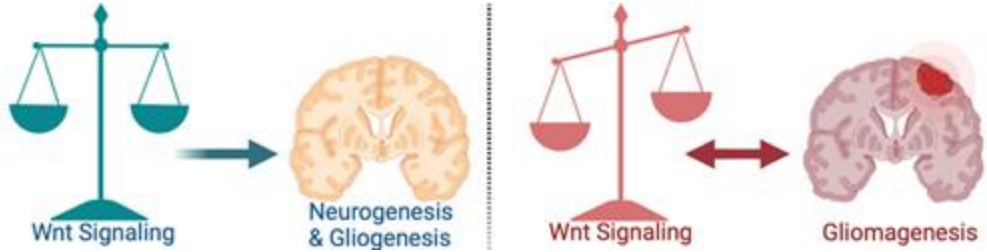
CTNNB1/Beta-Catenin: the heart of the Wnt Pathwa





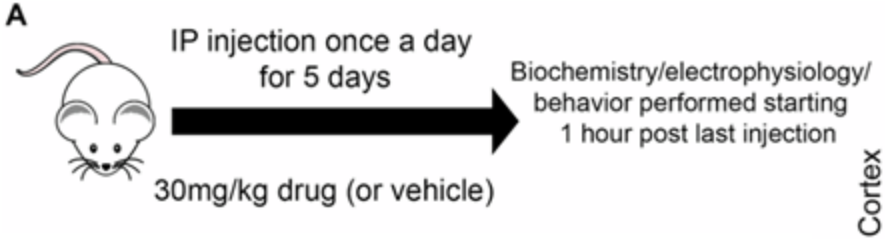
Wnt target genes code for proteins involved in growth and development

https://wnt.stanford.edu/target_genes

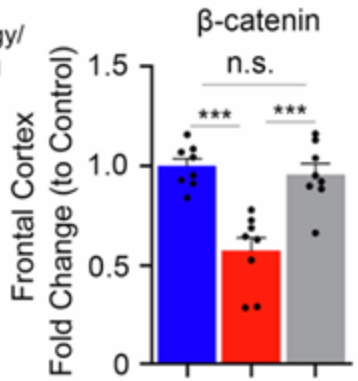


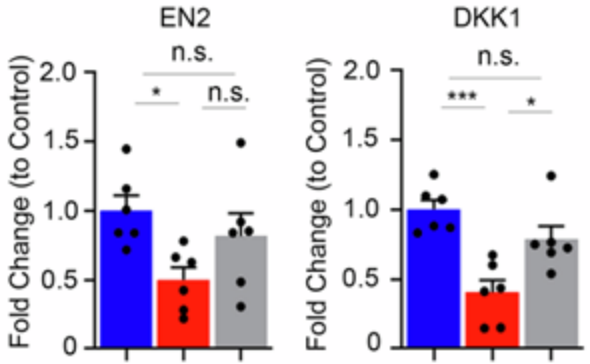
Carraci et al, *Front. Mol. Neurosci.* (2021)
Alkailani et al, *Front Mol Neurosci* (2022)

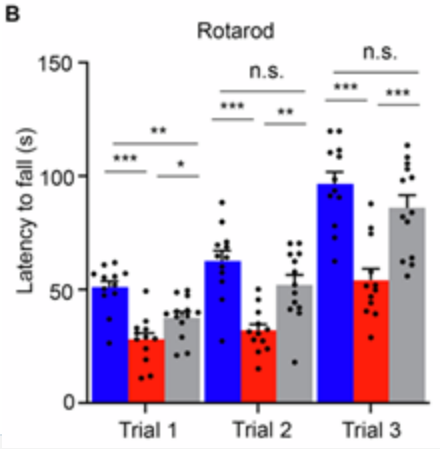
Dr. Michele Jacob: GSK3B inhibitor in a CTNNB1 mouse

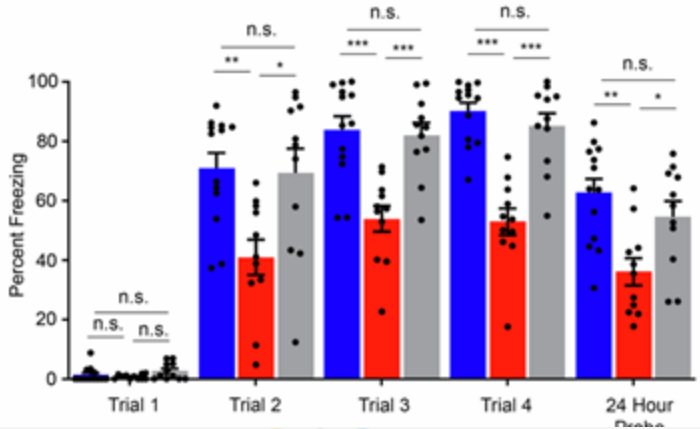


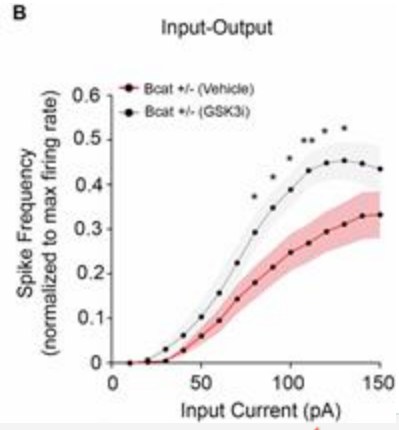
BRD0320 (both α and β paralogs)
BRD0705 (α selective)
BRD3731 (β selective)











CTNNB1 CONNECT AND CURE

Alexander et al, *EMBO Mol Med* (2024)

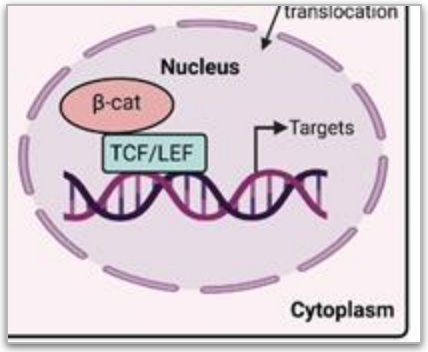
COMBINED

TCF7L2 = the transcription factor for Wnt target genes

TRND
TCF7L2-Related Neurodevelopmental Disorder

- Transcription Factor 7-Like 2
  - **Can also be known by T-Cell Factor 4 (TCF4)!*
  - ENTREZ gene ID 6934, OMIM 602228
  - Chromosome 10q25.2-q25.3

- B-catenin binds to TCF7L2 and LEF to upregulate expression of Wnt genes. Together, they form the on/off switch for Wnt signaling
- TCF4L7 is in a positive feedback loop - it itself is a canonical Wnt signaling target.
- Has been implicated in other diseases, including Type 2 diabetes mellitus, colon cancer, and schizophrenia.



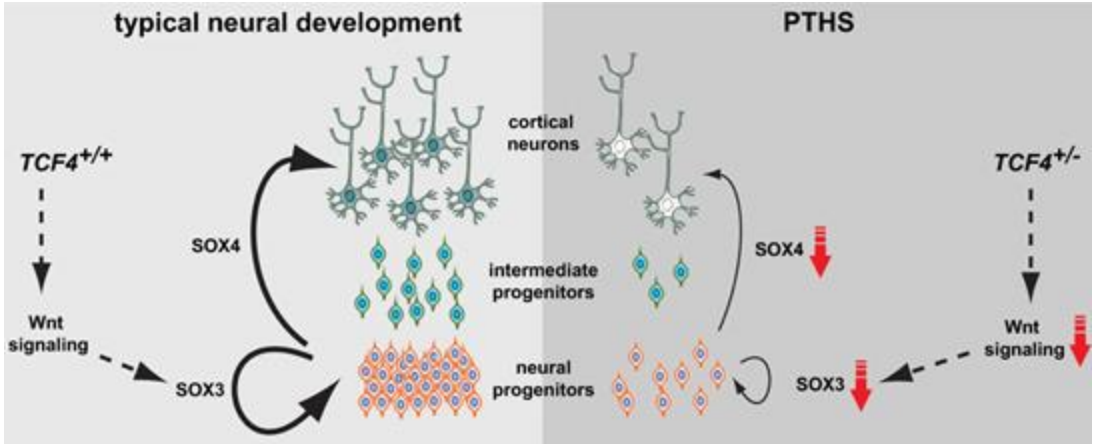
Pitt Hopkins Syndrome (TCF4)

PITT HOPKINS RESEARCH FOUNDATION

TCF4 - Transcription Factor 4

- Also known as: Ephrussi-box binding E2-2 and Immunoglobulin Transcription Factor 2 (ITF2)
- On chromosome 18
- *(not to be confused with another gene with the same name! - **TCF7L2 (T-Cell Factor 4)**
- HUGO Standard Nomenclature=TCF4; Entrez Gene ID 6925; Ensembl ENSG00000196628

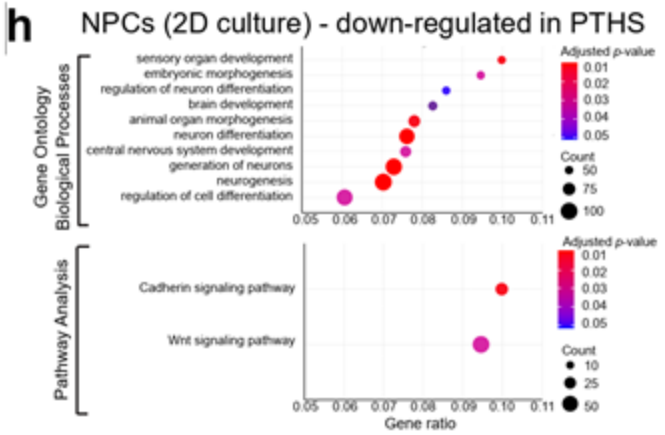
TCF4 is bound by Beta-Catenin to activate



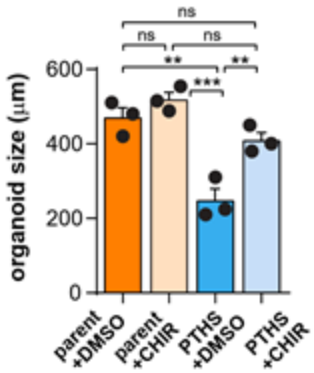
Papes et al., *Nat Comm,* (2022)

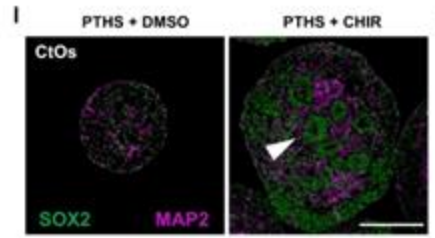
Activating Wnt rescues Pitt Hopkins Phenotypes

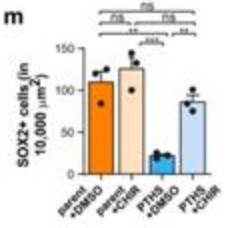
RNA-seq in patient-derived neural progenitor cells: decrease in Wnt pathway gene expression



Treated with CHIR99021:
Decreased cell death
Increased oranoid size
Rescued Sox2

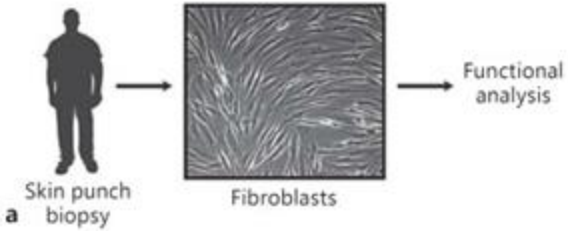


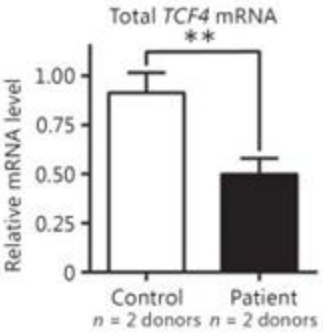


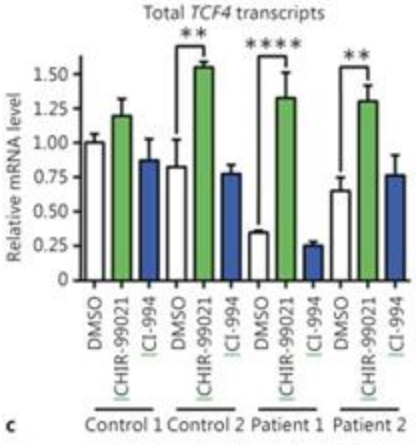


Papes et al., *Nat Comm,* (2022)

Activating Wnt rescues TCF4 transcript levels





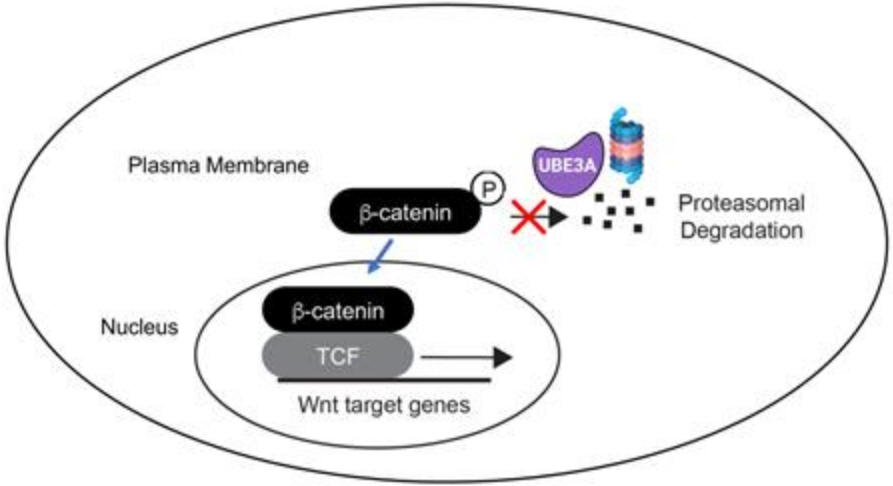


*CHIR-99021 and CI-994 each upregulated different transcripts of TCF4

Hennig et al., *Mol Neuropsych,* (2017)

Angelman Syndrome: UBE3A activity directly affects Wnt

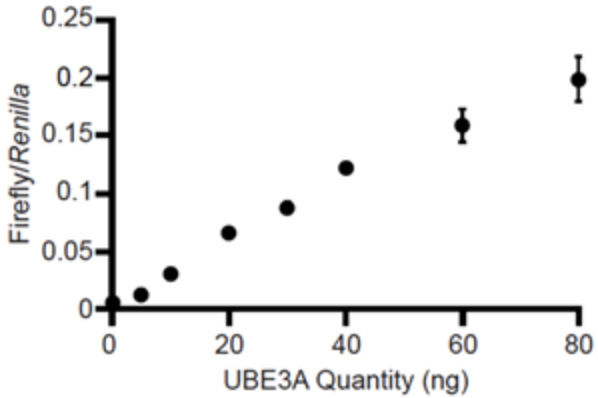
UBE3A stabilizes β-Catenin, which upregulates Wnt signaling



Yi, JJ et al. J Biol Chem (2017)

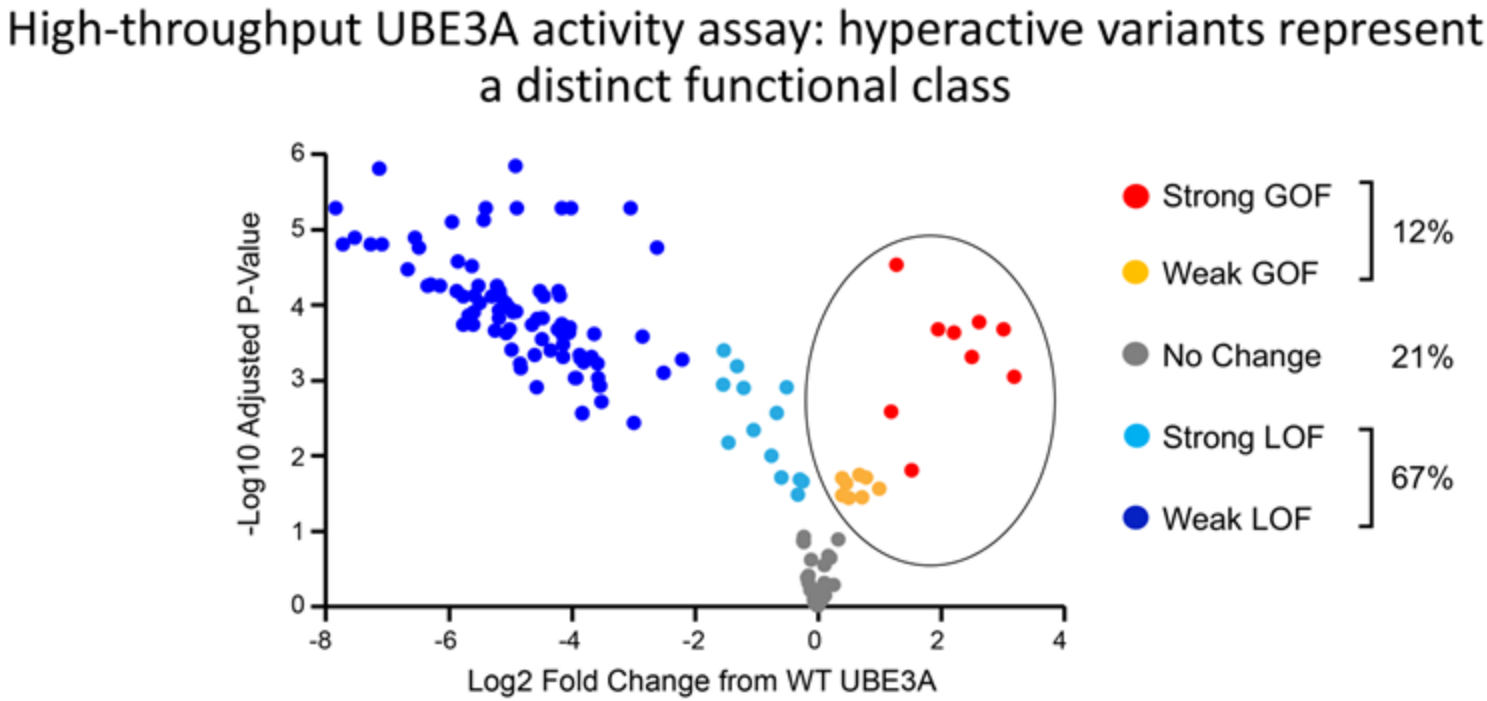
Angelman Syndrome: UBE3A activity directly affects Wnt

Wnt is an accurate reporter of UBE3A activity



Yi et al, *J Biol Chem* (2017)
Kuhnle S et al., *J Biological Chem*, (2018)

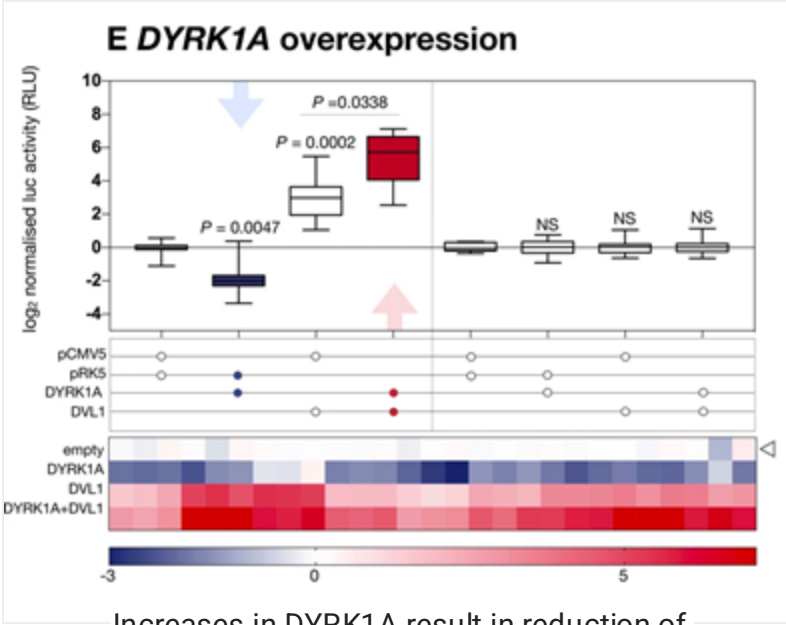
Angelman Syndrome: UBE3A activity directly affects Wnt



Weston et al., *Nat Comms* (2021)

DYRK1A: modulates Wnt in a context-dependent manner

- Dual-specificity tyrosine phosphorylation-regulated kinase 1A
- On Chromosome 21. One of the top two primary genes thought to be responsible for Down Syndrome symptoms in Trisomy 21
- Haploinsufficiency causes **DYRK1A Syndrome.**
- DYRK1A phosphorylates p-120 Catenin
    - Elimination of p120-catenin inhibits early responses to Wnt, such as LRP5/6 and Dvl-2 phosphorylation and axin recruitment to the signalosome, as well as later effects, such as β-catenin stabilization



Increases in DYRK1A result in reduction of *basal* Wnt signalling activity but further increases *active* Wnt signalling substantially

Lithium normalizes ASD-related neuronal, synaptic, and behavioral phenotypes in DYRK1A-knockin mice

Junyeop Daniel Roh [#1], Mihyun Bae [#1], Hyosang Kim [1], Yeji Yang [2,3], Yeunkeum Lee [1,4], Yisul Cho [5], Suho Lee [1], Yan Li [1], Esther Yang [6], Hyunjee Jang [7], Hyeonji Kim [7], Hyun Kim [6], Hyojin Kang [8], Jacob Ellegood [9,10], Jason P Lerch [9,11], Yong Chul Bae [5], Jin Young Kim [3], Eunjoon Kim [12,13]

Roh et al., *Mol Psychiatry* (2024)

Granno et al., *Sci Reports* (2019)

Kabuki Syndrome (KDM6A/KMT2D)

- Kabuki Syndrome Type 1 (~80% of patients): KMT2D (formerly MLL2)
- Kabuki Syndrome Type 2 (~20% of patients): KDM6A (X-linked inheritance!)

- The Wnt pathway is a **downstream target of KMT2D**
  - Kabuki syndrome patients have been found to have Pilomatricoma—a benign hair cell tumor characterized by lobules of epithelial cells.
  - KS may predispose patients to pilomatricoma formation because CTNNB1 plays a role in the WNT pathway, which is regulated by KMT2D

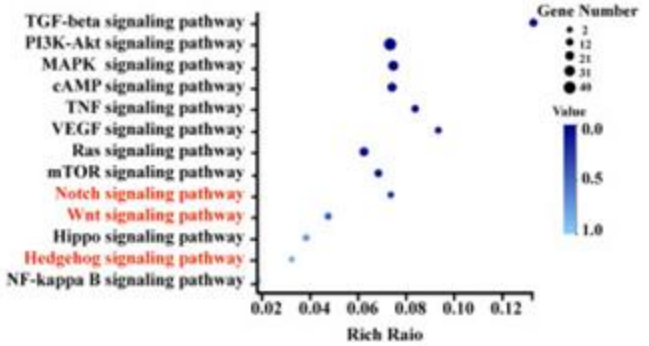
- Experiments with Wnt have yielded mixed results:
  - Some show KMT2D upregulates Wnt, while others show evidence that it may downregulate Wnt
  - Likely cell type and developmentally specific!

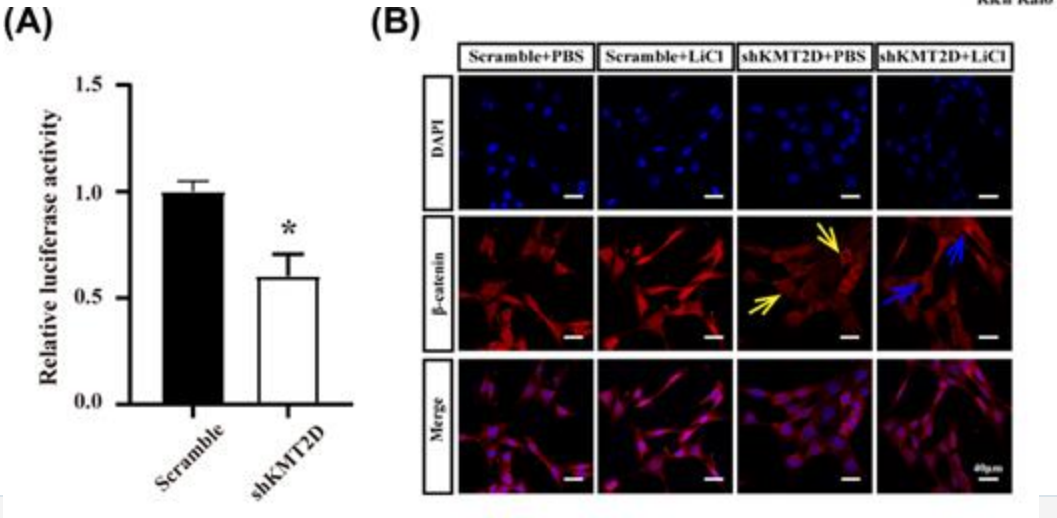
- KMT2D and KDM6A are likely indirect regulators of Wnt via modulating H3K4me3 - methylation levels.

Kabuki Syndrome (KDM6A/KMT2D)

Knockdown of KMT2D in epithelial dental cells:

- Decreased Wnt signaling pathway genes (RNAseq)
- Decreases nuclear B-catenin
  - Partially rescued by LiCl

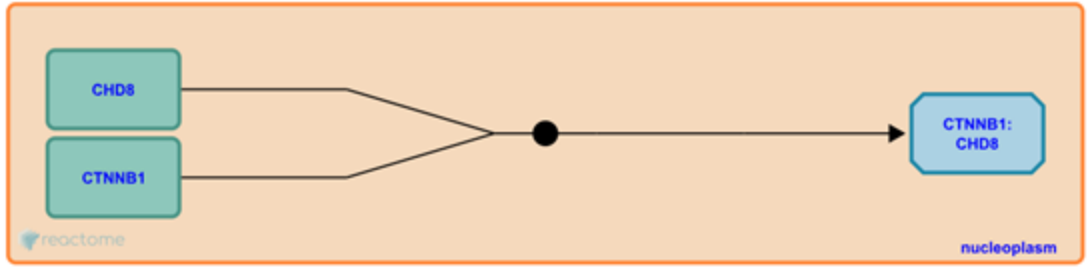


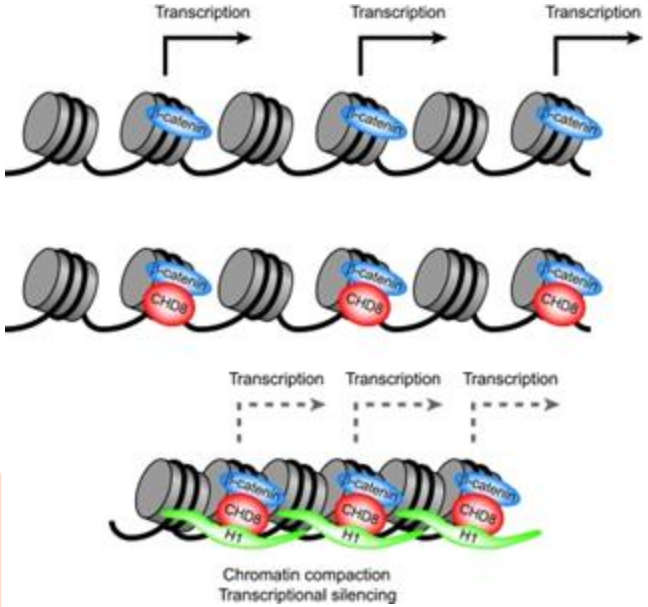


Pang et al., *BioSci* Reports (2021)

CHD8: a negative regulator of Wnt

- Cadherin 8
- CHD8 is a negative regulator of the Wnt-β-catenin signaling pathway that binds directly to β-catenin and suppresses its transactivation activity
- CHD8 promotes the association of β-catenin and histone H1 → chromatin compaction and transcriptional silencing → inhibition of β-catenin-dependent transactivation.

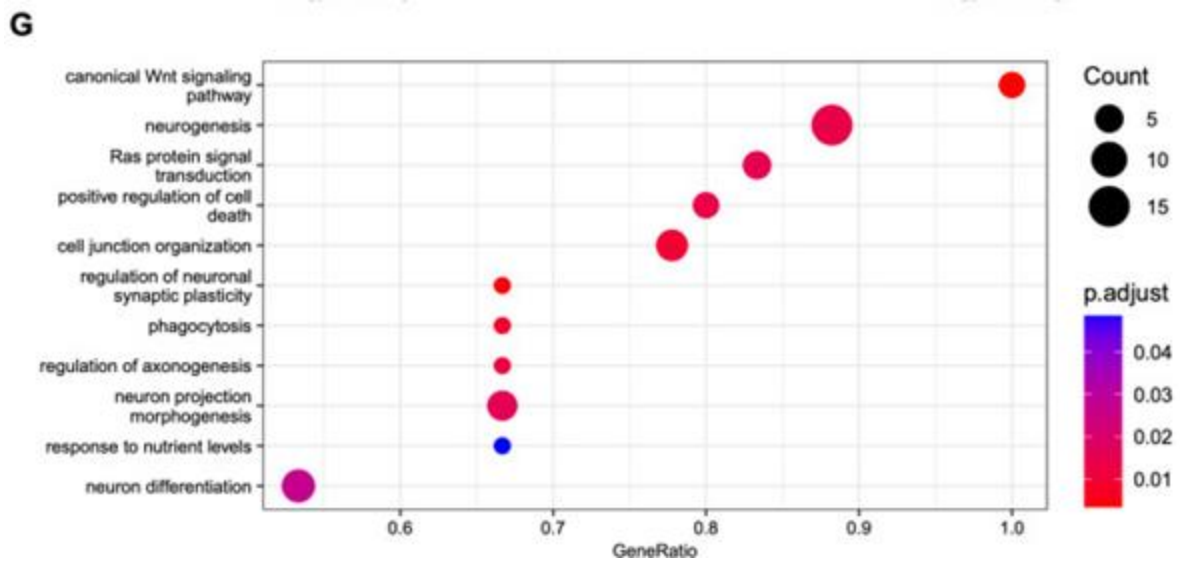




Chenn et al 2023

SYNGAP1: Relationship with Wnt unclear

- SYNGAP1: synaptic Ras GTPase activating protein 1
- SYNGAP1 knockdown mouse produced upregulation of Wnt target genes



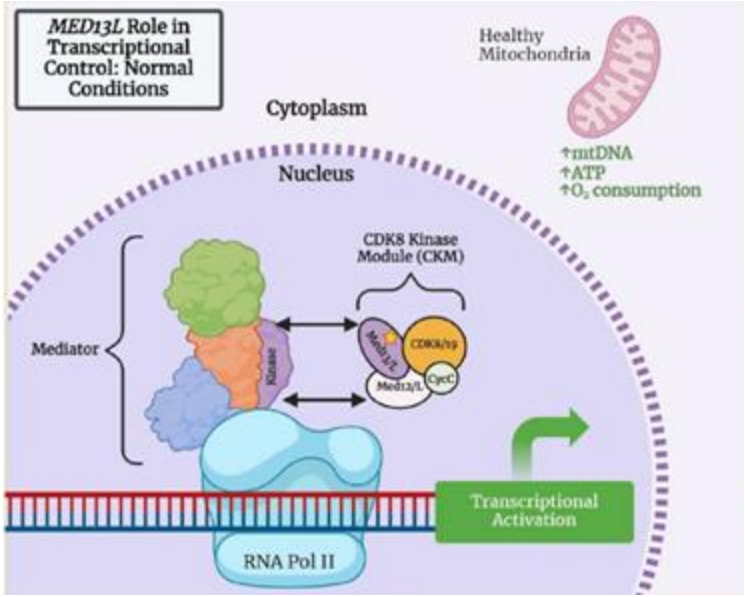
Araki et al., *BioRxiv* (2023)

MED13L: Interacts via an unknown mechanism

- Mediator Complex Subunit 13L
  - Subunit of the Mediator Kinase Module, which is itself a subunit of Mediator, which mediates associations between RNAPII and TFs

- UAB drug screen gave two candidates that modulate Wnt:
  - Verapamil (Wnt inhibitor)
  - PSE - a dietary cholesterol-lowering agent shown to affect Wnt

- Wnt was *upregulated* in a MED13L cardiomyocyte knockout mouse



Ideas for next steps for the Wnt working group

Drug Discovery and Repurposing for modulating Wnt in our disorders:

- Leverage **previous drug screens** to understand which Wnt modulators may be best for each disorder
  - AI drug screening (NCATs)
  - Broad institute
- Do a **cross-Wnt disorder screen**
  - COMBINEDBrain plasma proteomics
  - **Unravel: AI drug repurposing based on nose mRNA**
  - **Fund a cross-disorder Wnt-focused drug screen (*in vitro* or *in vivo*)**
    - We have the cell lines - could we design an *in vitro* screen?
- Engage expertise of Wnt researchers
  - Invite to present at working group
  - Meet with researchers one-on-one - academic and industry
  - Gordon Wnt conference (Summer 2025)
- FDA-approved drugs: off-label or OTC
  - Observational trial model
  - Find Clinicians willing to do case studies

Action Items

- Please ask your scientific advisory board members to join us!
- Please look at this spreadsheet and add info on Wnt agonists you know of
- Please fill out this Form to tell us what drug candidates your community may be interested in for observational studies
- Please set up a chat with Kellan if you have any resources/history with modulating the Wnt signaling pathway in your group
  - Scientific researchers
  - Industry and Academic contacts
  - History with using a Wnt-modulating therapy

In-Meeting discussion points

- Let’s compile a list of number of patients per disorder, so that we can show pharma the number of patients that would benefit from a basket study
- The information given in these last few Wnt Working Groups could potentially become the foundation for a published review
- What about a CZI-type grant for the future?
- Let’s reach out to the industry groups that have worked on Wnt agonists

Thank you!