

STXBP1-related disorder

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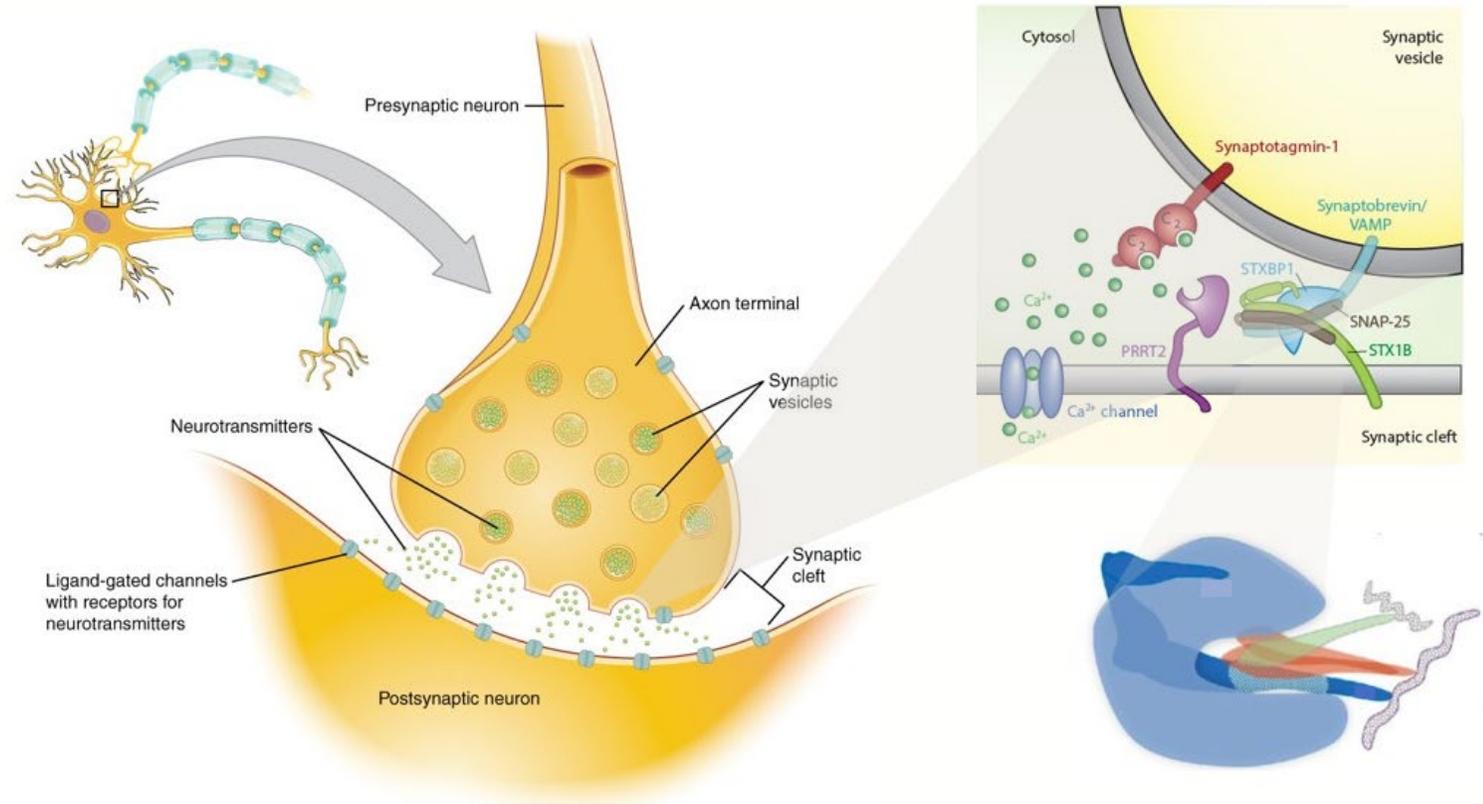
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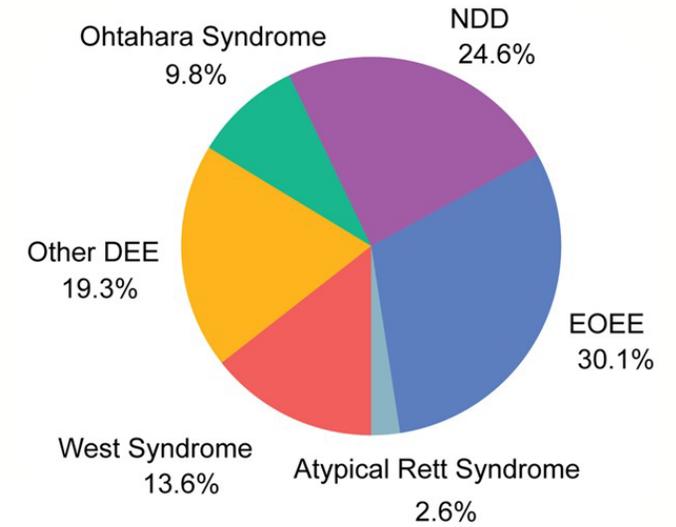
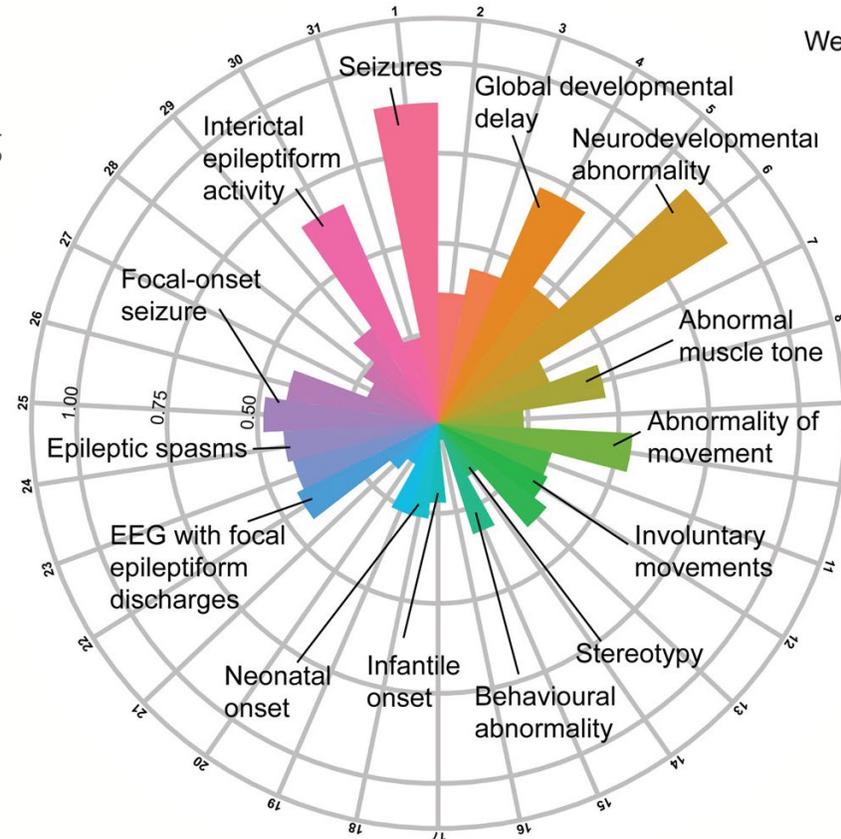
What is *STXBP1*?

- Genetic disorder first identified in 2008 in people with severe neonatal epilepsy
- Caused by disease-causing variants in the *STXBP1* gene
- Now known to cause diverse array of neurodevelopmental and epilepsy disorders
- *STXBP1* is a critical protein in the SNARE complex
- Mediates synaptic vesicle docking and fusion in the central nervous system



What is *STXBP1*-related disorder?

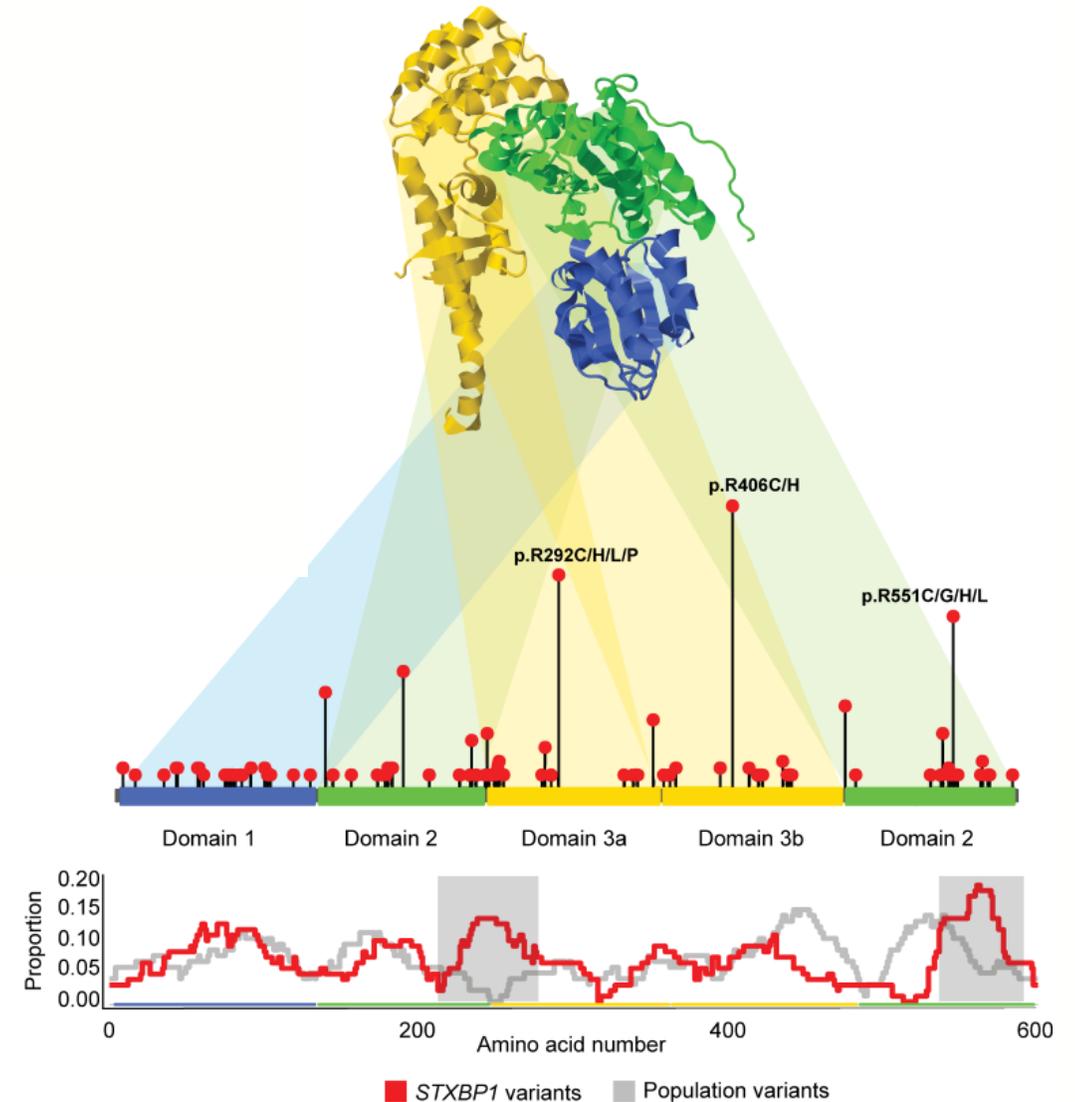
- ***STXBP1* is a complex, congenital neurodevelopmental disorder**
- **Consistent symptoms (up to 100%)**
 - Global developmental delay
 - Hypotonia
 - Speech impairment, often non-speaking
- **Frequent symptoms**
 - Variable cognitive impairment
 - Most often severe
 - Variable seizure disorders
 - Epilepsy intractable in ~ 20%
 - Epileptic spasms
 - Spasticity in addition to hypotonia
 - Movement disorders and tremor
 - Ataxia/ gait instability
 - Autism and behavior abnormalities
 - GI dysregulation



Xian et al., 2021

Estimated Prevalence of *STXBP1*

- Estimated incidence 1:30,000
 - Lopez-Rivera et al., *Brain* 2020
- *STXBP1* 5th most common diagnosis in patients with epilepsy genetic testing
 - Symonds and McTague, *EJ Paediatric Neurology* 2019
- >120 individuals seen at Children's Hospital of Philadelphia
- >220 individuals diagnosed at only one US genetic testing lab
- 238 US individuals with *STXBP1*-related disorder connected to advocacy organization
- 534 individuals described in recent *Brain* publication

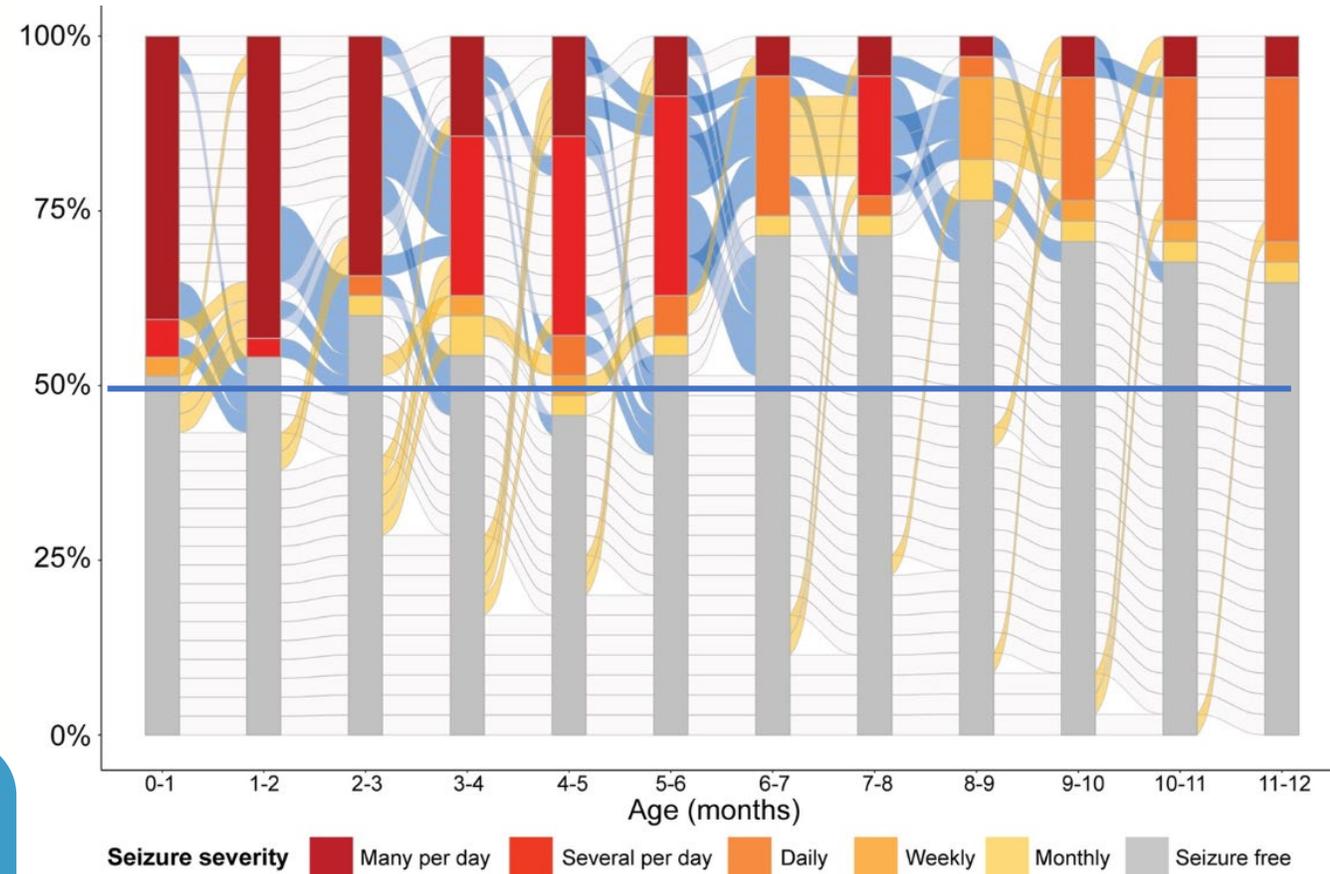


Xian et al., 2021

What makes *STXBP1* unique?

- Variable, dynamic seizure course
- Very early onset epilepsy
 - 90% onset within first year
- Subcortical myoclonus
- Marked expressive language delay
- Prominent variability in presentation across individuals
- Emerging subgroups

At no point in the first year do more than 50% of children with *STXBP1* have seizures



Xian et al., 2021

Subgroups in *STXBP1*

- *STXBP1*-related disorder is a diagnosis that contains multiple diseases
- Certain variant types can explain some phenotypic variability
 - **Protein truncating variants (nonsense, frameshift, deletion, splice):**
 - Epileptic spasms, ataxia, hypotonia
 - **p.Arg406His/Cys**
 - Hypertonia, burst-suppression EEG
 - **p.Arg292Cys/His/Leu/Pro**
 - Focal seizures, markers for intractable epilepsy
 - **p.Arg551Cys/Gly/His/Leu**
 - Generalized onset-seizure, EEG with abnormally slow frequencies

How is *STXBP1* currently coded?

- Coding for *STXBP1* variable and unspecific across medical centers
 - Z15.89 – “Susceptibility to disease, genetic”
 - G40.802 – “Other epilepsy, not intractable, without status epilepticus”
 - F78.A9 – “Other genetic related intellectual disability”
 - G40.## - By other epilepsy phenotype only
- *STXBP1* cannot be neatly categorized into existing codes
 - Extremely variable epilepsy presentations
 - Cognitive impairment
 - Movement disorders
 - Hypotonia
 - Complex GI dysfunction
- Patients coded differently depending on medical specialty
- Current codes used include disorders very different from *STXBP1*

Unique treatment implications

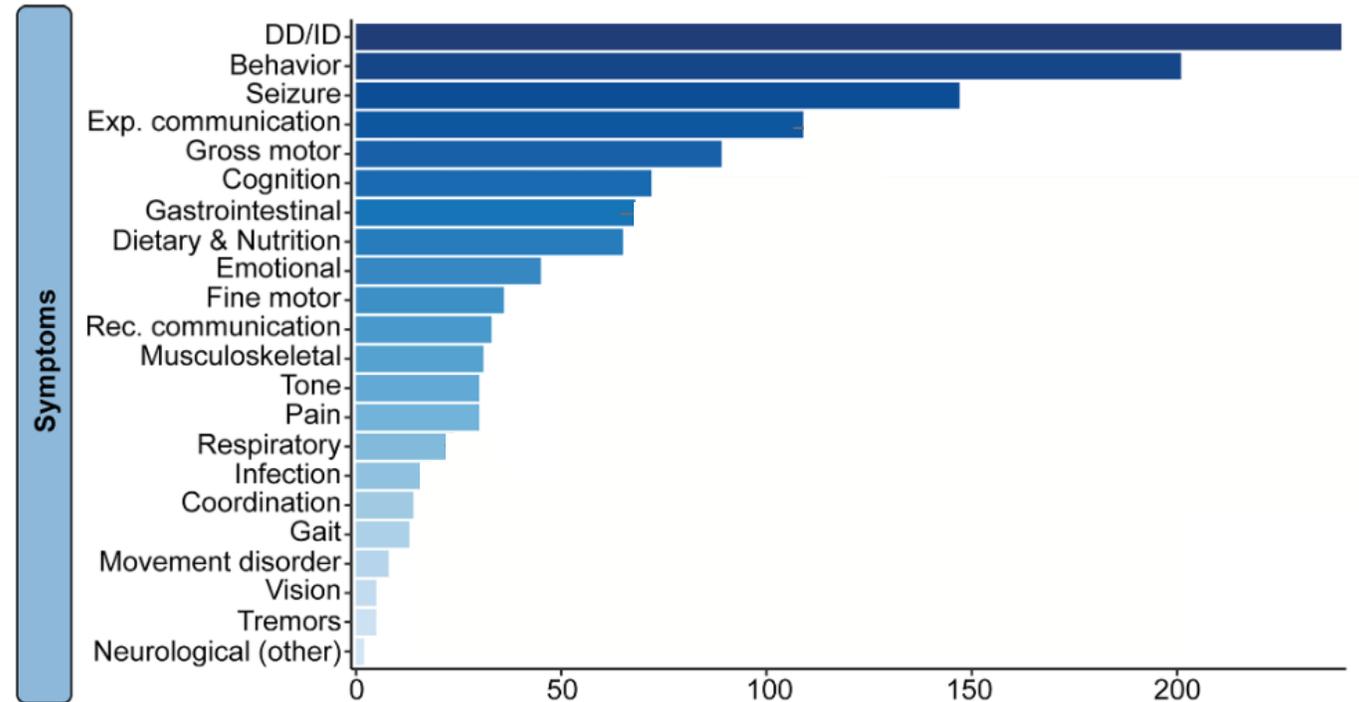
- *STXBP1* diagnosis effects choice of ASDs and seizure monitoring
 - Screening for infantile spasms
 - Preferential use of ketogenic diet
- Monitor for spasticity
 - Initiate bracing and rehab treatment
- Intensive physical and occupational therapy
- Behavioral therapy
- Assistive devices
- Feeding therapies and G-tube interventions
- Early introduction of alternative communication strategies

A specific code will benefit medical care for *STXBP1*

STXBP1 is a unique disease

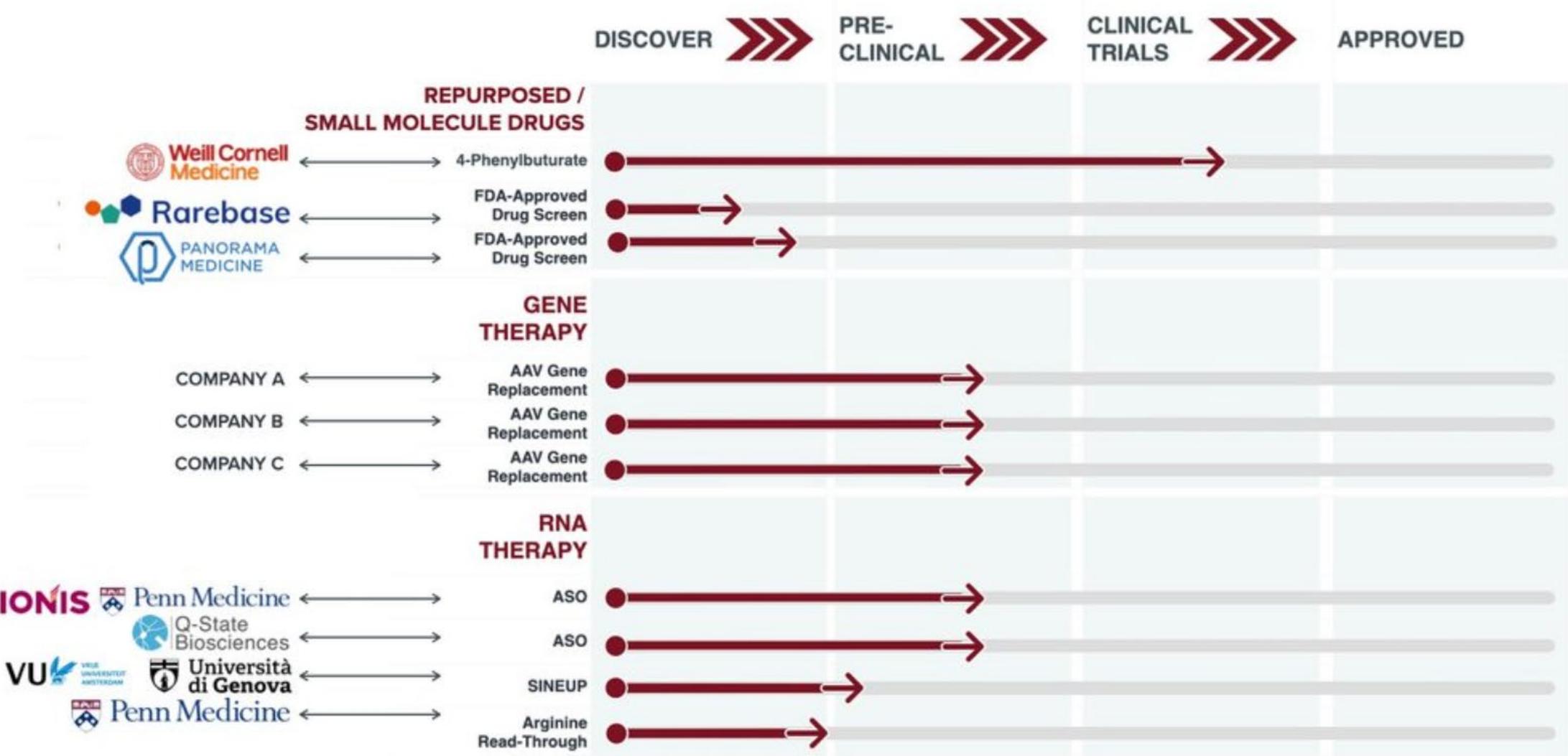
Unique code would allow for:

- Multisystem effects to be adequately captured
- Consistent codes to be used across patients, rather than many different codes
- Automatic flagging of care recommendations in the electronic medical record
- Estimates of disease incidence
- Tracking of outcomes over time



Sullivan et al., 2022

Research progress in STXBP1



Summary

- *STXBP1* is common
 - A child with *STXBP1* is born in the US every third day
 - Prevalence estimated at 1/30,000
- *STXBP1* is a complex neurodevelopmental disorder
 - Current ICD-10-CM code does not capture full picture of disorder
- Giving *STXBP1* a unique ICD-10-CM code would impact medical care in people with a severe disorder