Studying Neurodevelopmental Disorders Through The Lens of *SYNGAP1*

GBM 08/01/2025
Bernadette Basilico

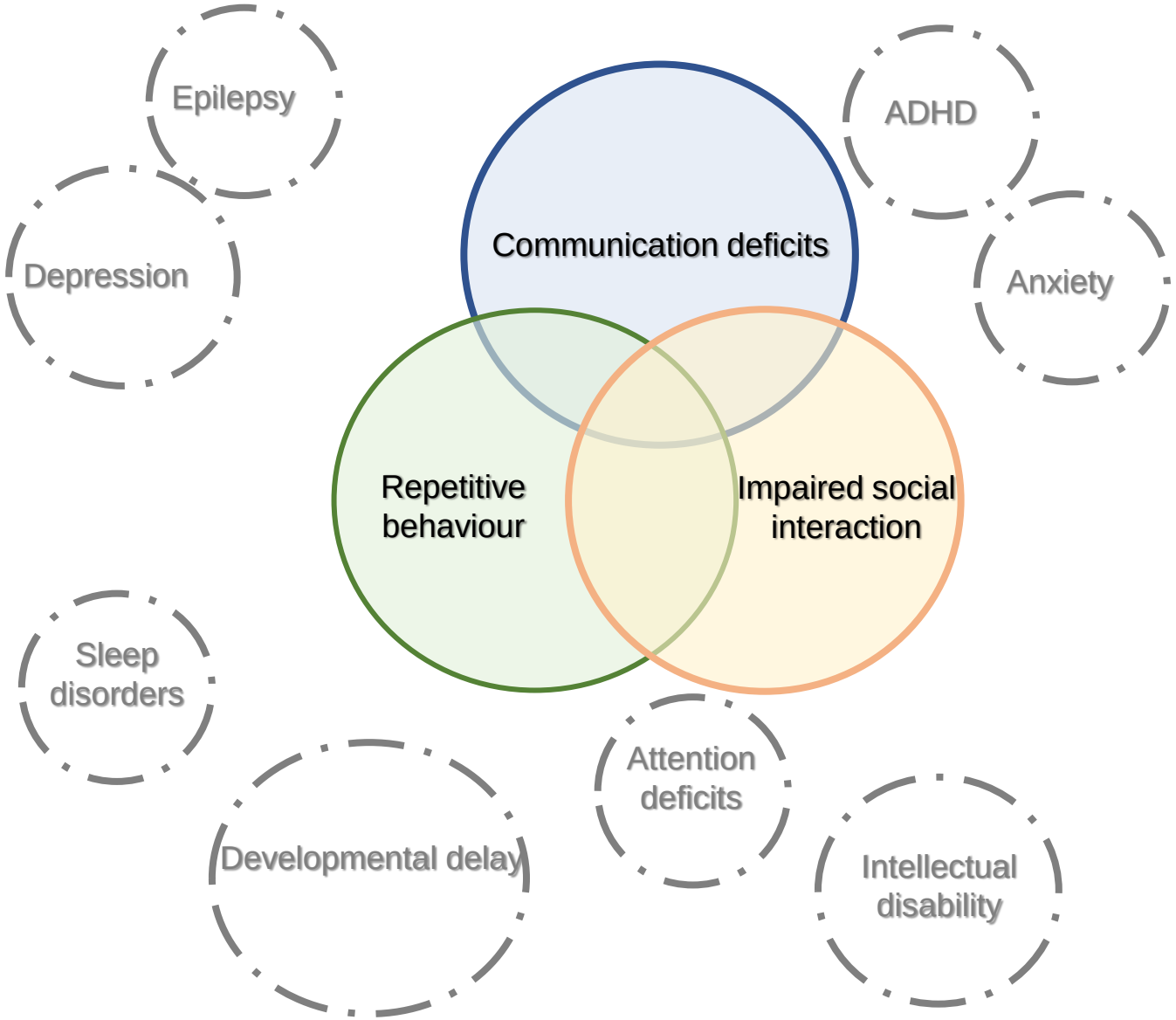
- Neurodevelopmental disorders (NDDs) are a group of conditions that affects the growth and development of the **brain** or the **central nervous system.**

- The term refer to a disorder of brain function that affects emotion, learning ability, self-control and memory and that unfolds as individual grows.

- The term is sometimes erroneously used as an exclusive synonym for autism spectrum disorders.

The diagnosis of NDDs encompasses **a broad spectrum of disorders** with onset in the developmental period (mostly by the age of 2-5 years). Within the specific **diagnostic category** included in **DSM-5,** the following diagnoses are recognized:

- Intellectual disabilities;
- Communication disorders;
- Autism spectrum disorder (ASD);
- Attention deficit/hyperactivity disorder (ADHD);
- Specific Learning Disorders;
- Neurodevelopmental motor disorders.



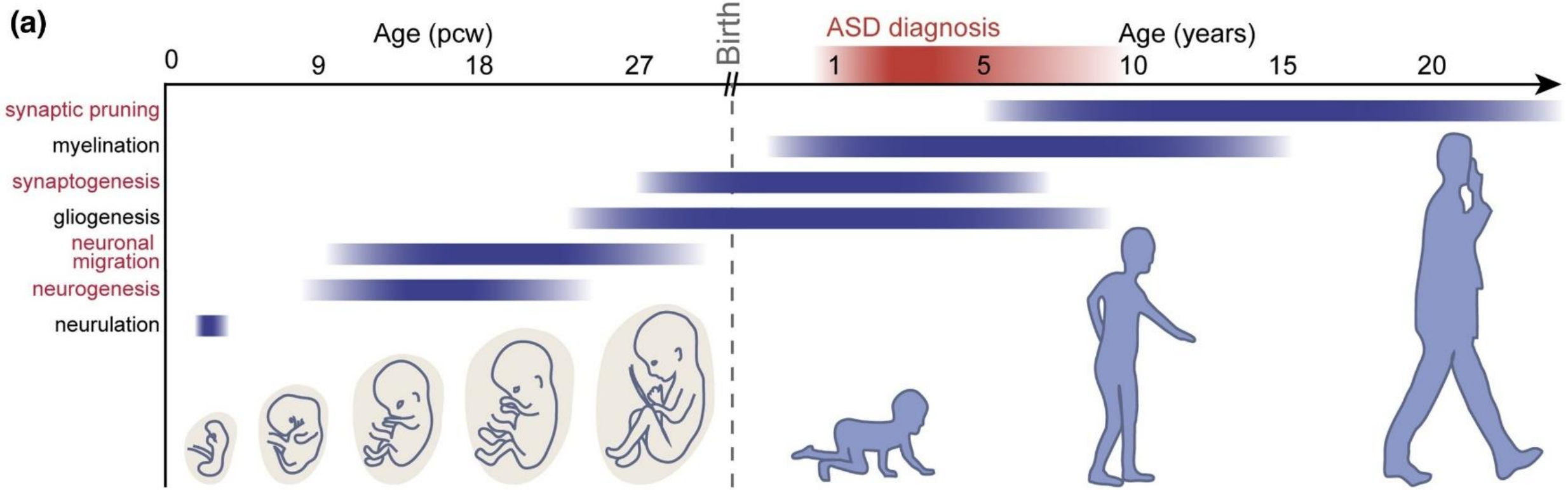
Given the large number of conditions included in this diagnostic category, the symptoms with which they may present vary widely depending on the type and severity of the disorder. **The main domains affected** by Neurodevelopmental Disorders are the following:

- Communication skills
- Social skills
- Repetitive behaviors
- Language
- Learning skills
- Memory
- Motor skills
- Intelligence
- Executive functions

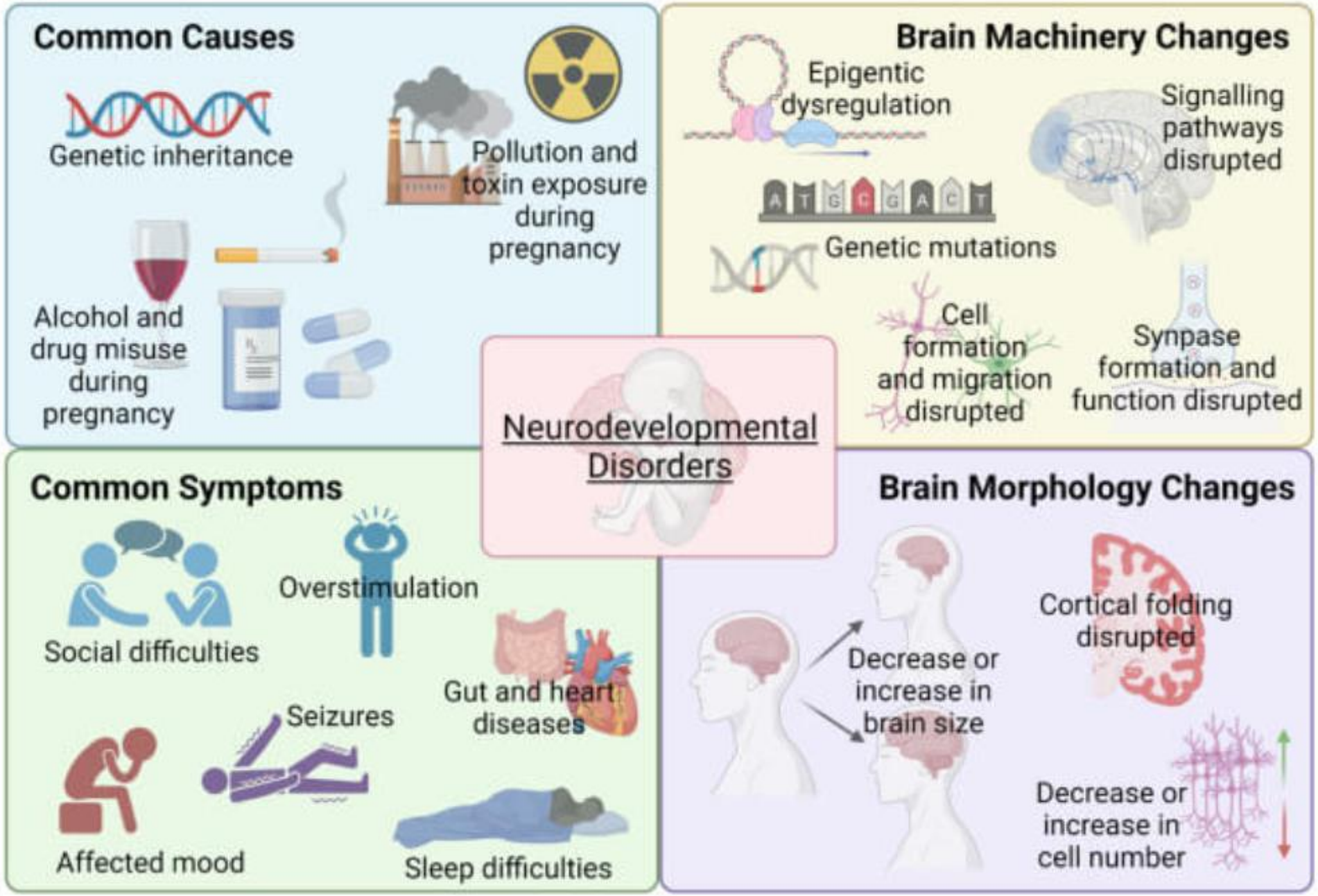
Neurodevelopmental milestones

Human brain development is an orchestrated process of time-limited developmental stages.
Any deviations form these developmental trajectories lead to NDDs.

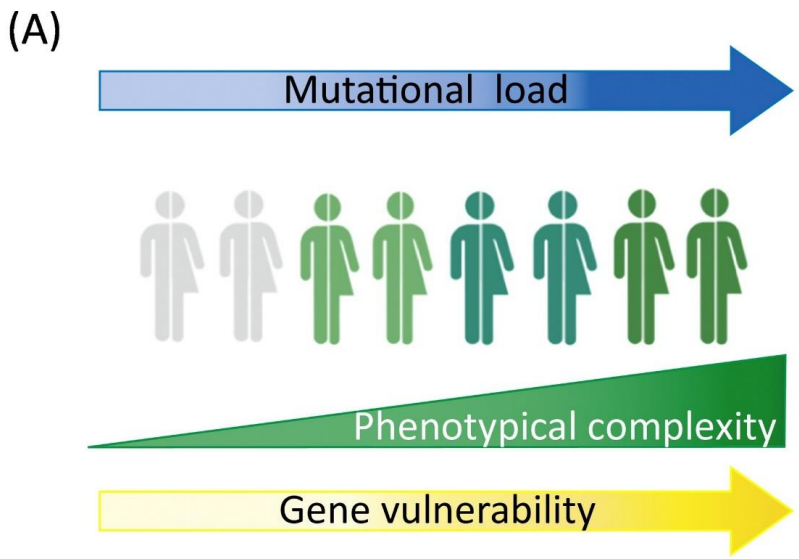
While NDDs-diagnosis typically occurs in childhood, the pathophysiological changes associated may start already during **embryonic development.**



(Basilico et al 2020)

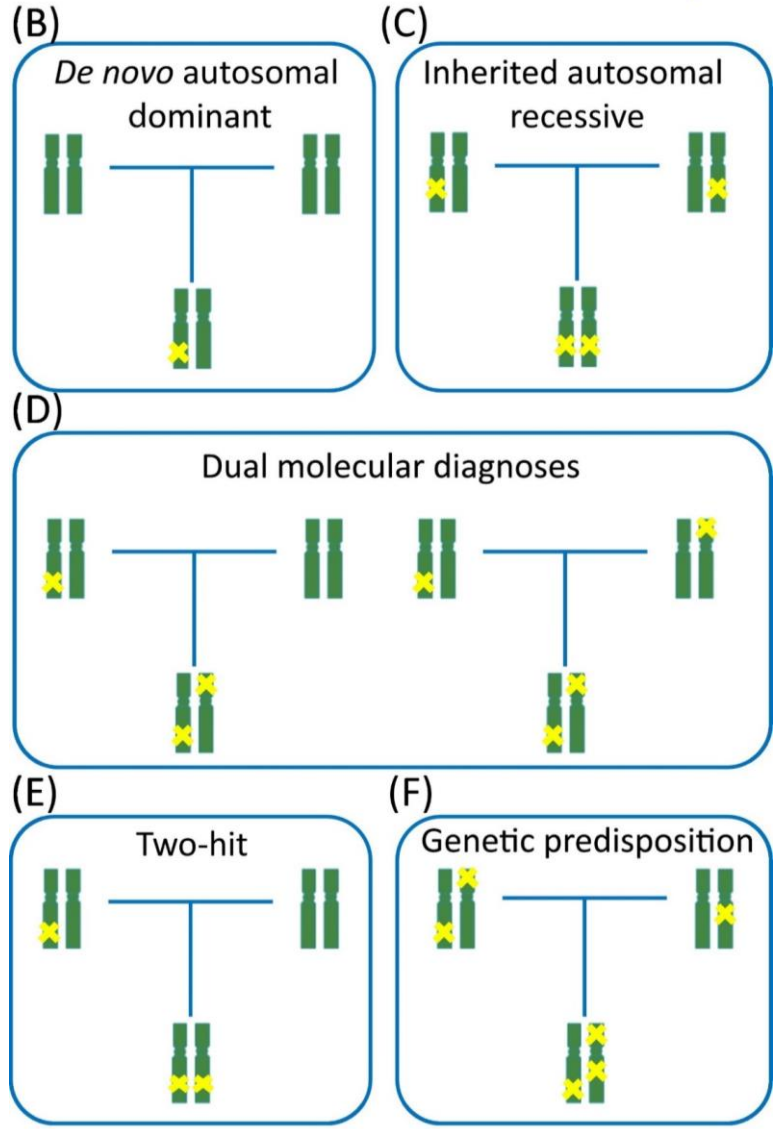

Common Causes
Genetic inheritance
Pollution and toxin exposure during pregnancy
Alcohol and drug misuse during pregnancy
Brain Machinery Changes
Epigentic dysregulation
Signalling pathways disrupted
Genetic mutations
Cell formation and migration disrupted
Synpase formation and function disrupted
Neurodevelopmental Disorders
Common Symptoms
Social difficulties
Overstimulation
Gut and heart diseases
Seizures
Affected mood
Sleep difficulties
Brain Morphology Changes
Decrease or increase in brain size
Cortical folding disrupted
Decrease or increase in cell number

Genetic causes: the most common



Mutational load and degree of vulnerability of the disrupted genes influence the phenotypical outcome.

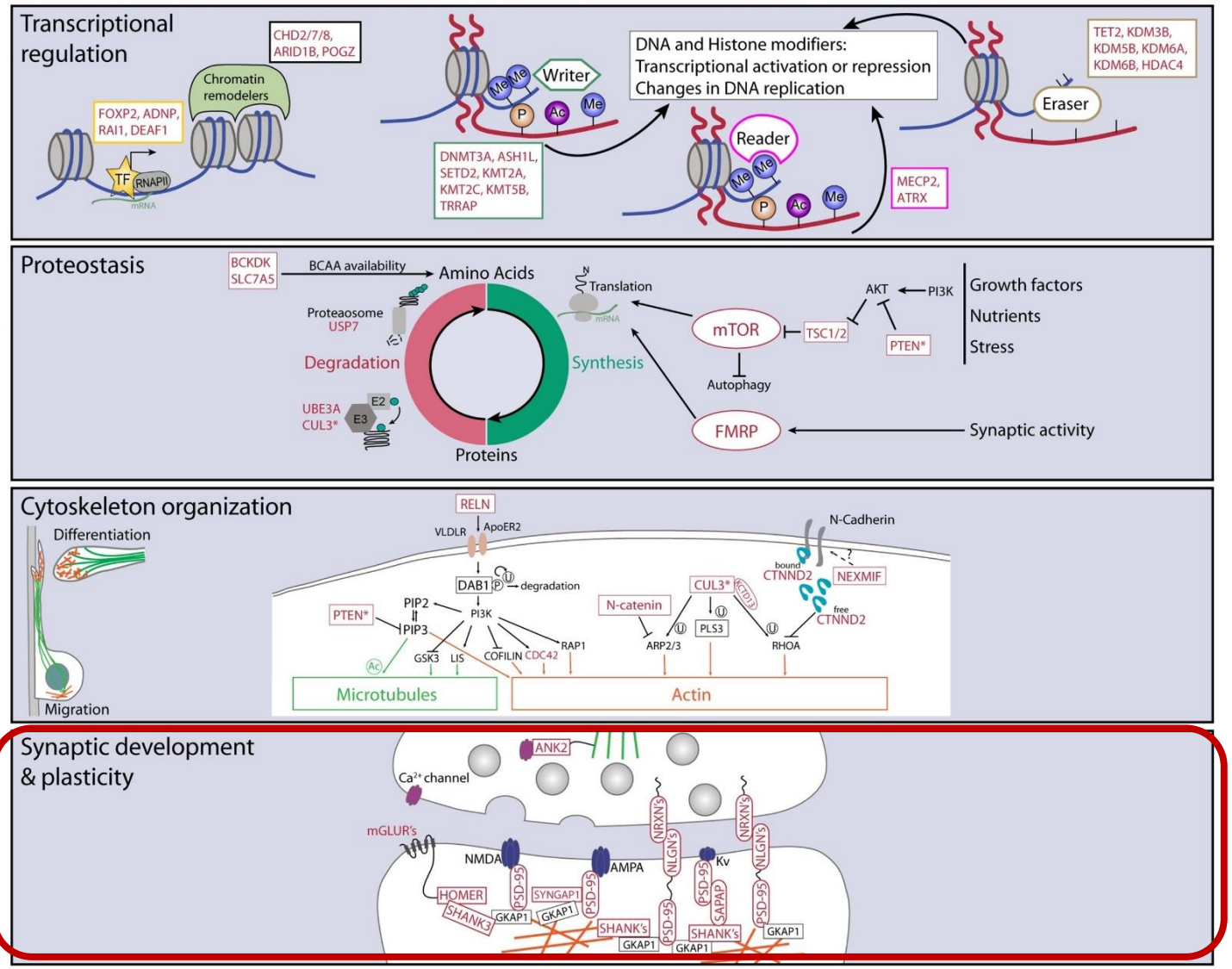
One of the main factors contributing to the development of a Neurodevelopmental Disorder is **genetic predisposition**. In fact, genetics studies conducted in this regard have revealed a significant genetic component underlying these conditions. Many genetic variations and mutations appear to confer an increased **vulnerability toward the development of Neurodevelopmental Disorders**.
<u>These abnormalities may be inherited from parents or may occur spontaneously during fetal development.</u>



(Parenti et al 2020)

Biological subtypes of NDDs

Molecular mechanisms in ASD pathogenesis & drug targets



Genes belonging to this category are transcription factors, chromatin modifiers and genes regulating DNA and histone modifications.

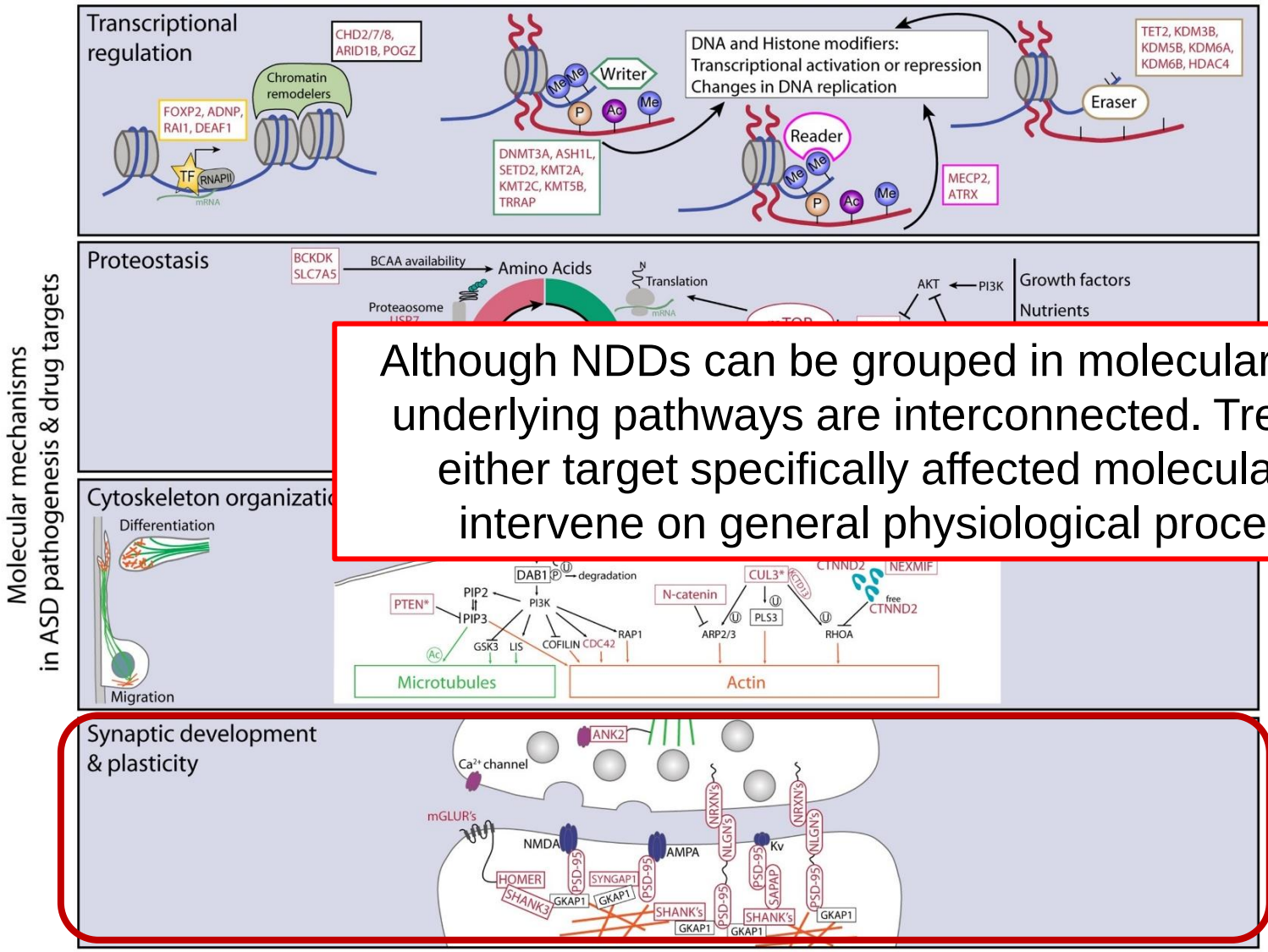
Protein homeostasis is regulated by the interplay of protein synthesis and degradation. Protein abundance is further limited by the availability of amino acids, such as the branched chain amino acids

Cytoskeleton dynamics regulate fundamental brain developmental processes, such as neural migration and differentiation. Several genes converge on the regulation of microtubules and actin organization.

A large number of cell-adhesion and post-synaptic density proteins have been implicated in the aetiology of NDDs. These proteins create an interconnected molecular network stabilizing both inhibitory and excitatory synapses

(Basilico et al 2020)

Biological subtypes of NDDs



Although NDDs can be grouped in molecularly distinct subtypes, the underlying pathways are interconnected. Treatments for ASDs may either target specifically affected molecular hubs (upstream) or intervene on general physiological processes (downstream).

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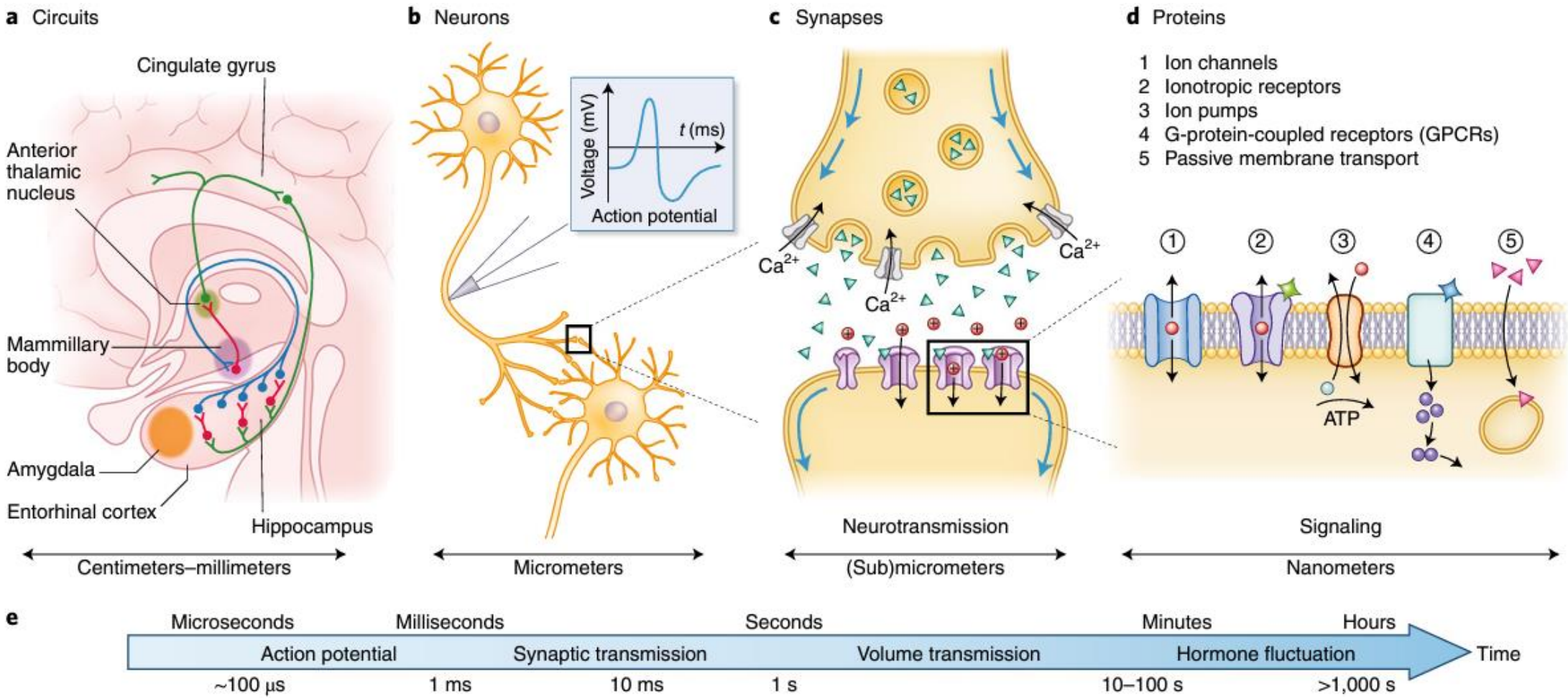
(Basilico et al 2020)

Synaptic development and plasticity: how neurons communicate

Progressively zoomed-in view from a brain circuit to a neuron to a synapse to an ion channel



(Frank et al 2019)

Synaptic development and plasticity: how neurons communicate

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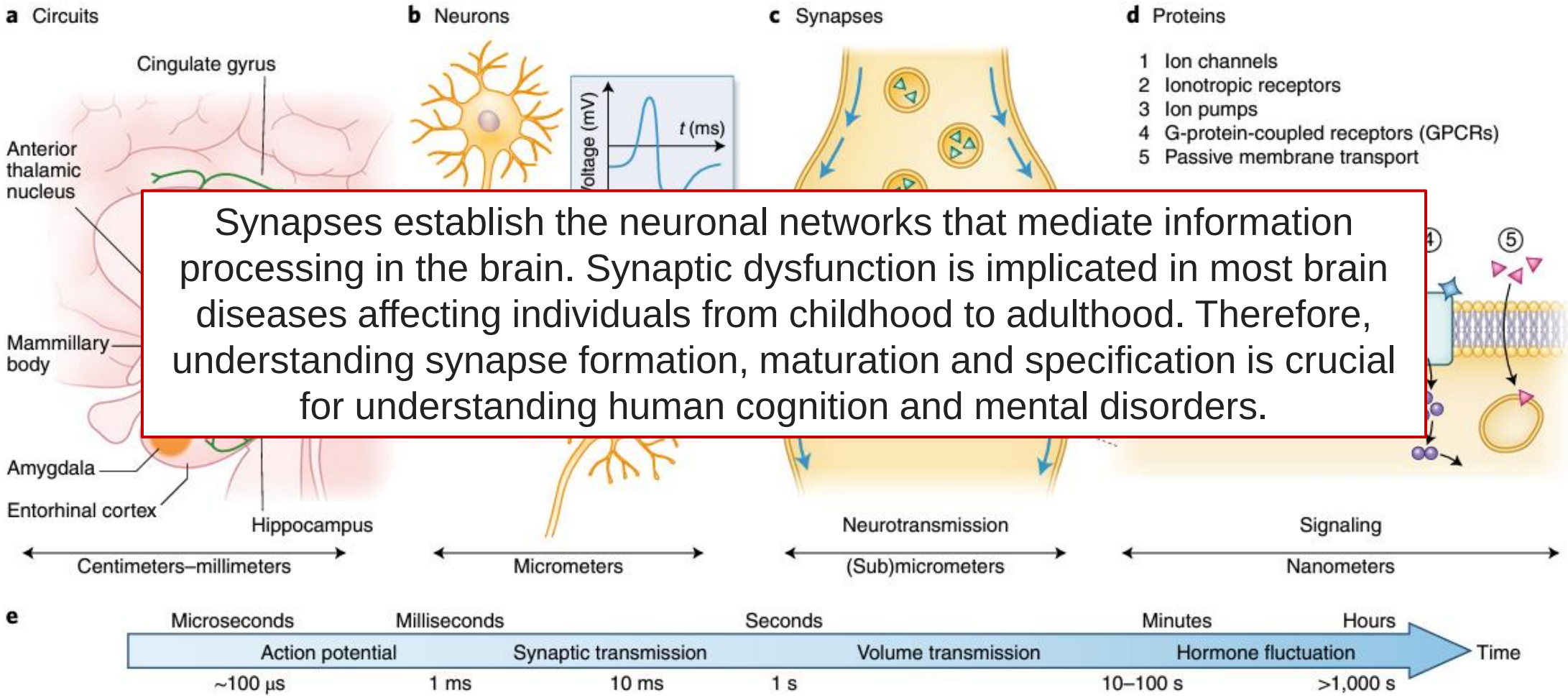


Synapses establish the neuronal networks that mediate information processing in the brain. Synaptic dysfunction is implicated in most brain diseases affecting individuals from childhood to adulthood. Therefore, understanding synapse formation, maturation and specification is crucial for understanding human cognition and mental disorders.

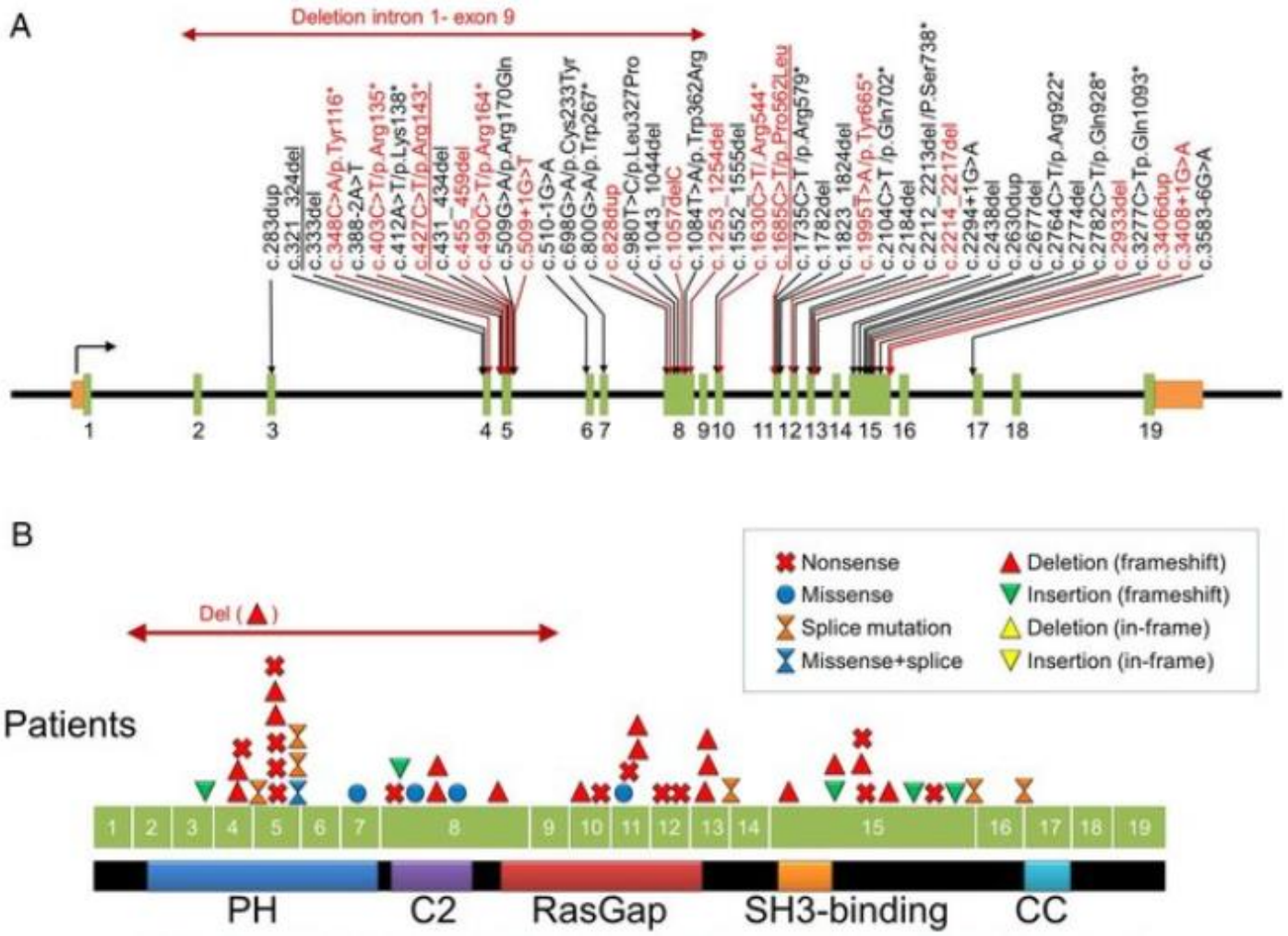
(Frank et al 2019)

SYNGAP1 – Genetics

SFARI GENE SCORE 1S

High Confidence, Syndromic

Criteria 1.1, Syndromic



SYNGAP1-Related Disorders is a rare genetic condition caused by a variant on the *SYNGAP1* gene (6p.21.32)

Mutations in *SYNGAP1*:

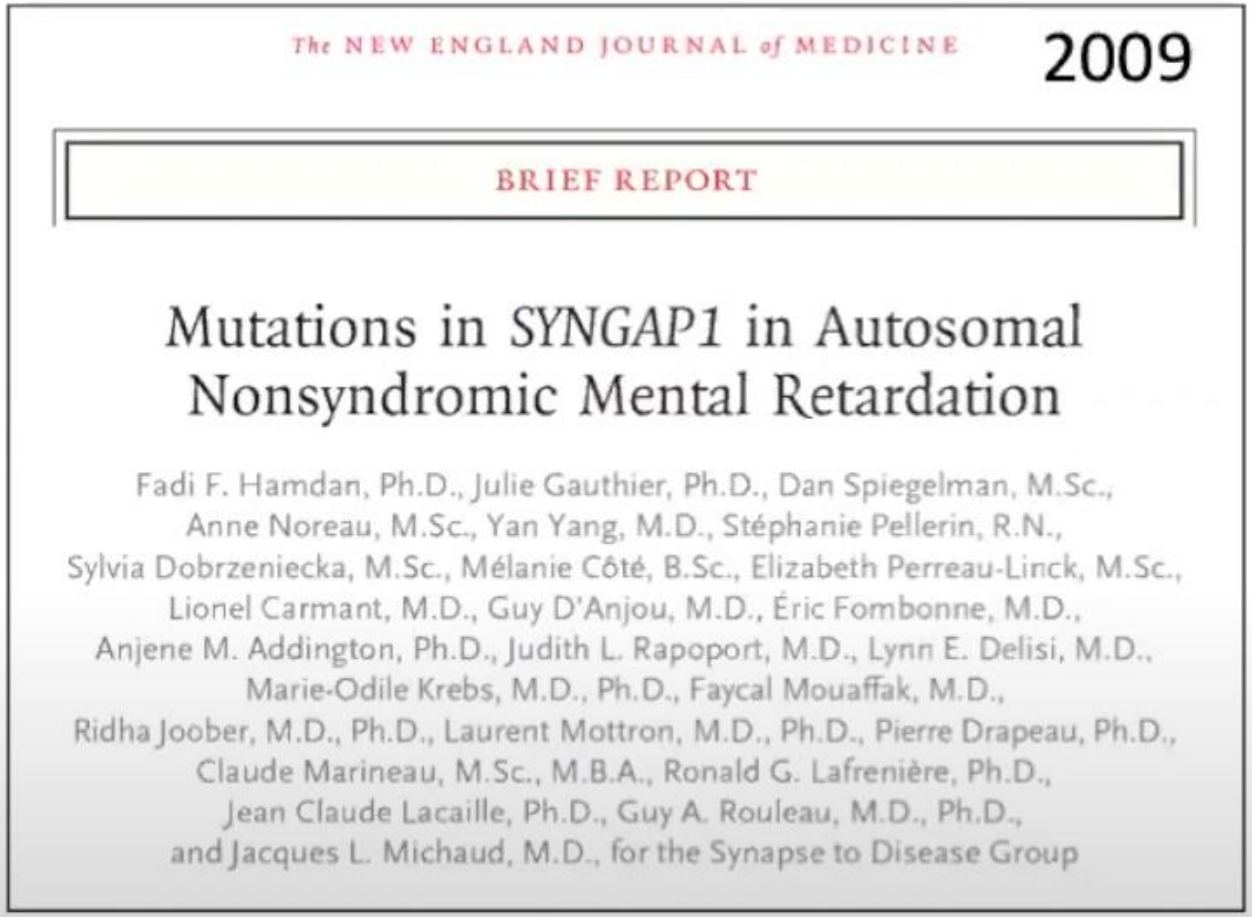
- Nonsense → haploinsufficiency (protein level reduction)
- Missense → changes in protein functions (no truncation)
- Frameshift
- Splice-site

Phenotype heterogeneity:

- Intellectual disability (100 %)
- Epilepsy (>80 %)
- ASD (50 %)
- Other comorbidities

(Mignot et al 2016)

SYNGAP1 in intellectual disability: first clinical association in 2009



The NEW ENGLAND JOURNAL of MEDICINE 2009

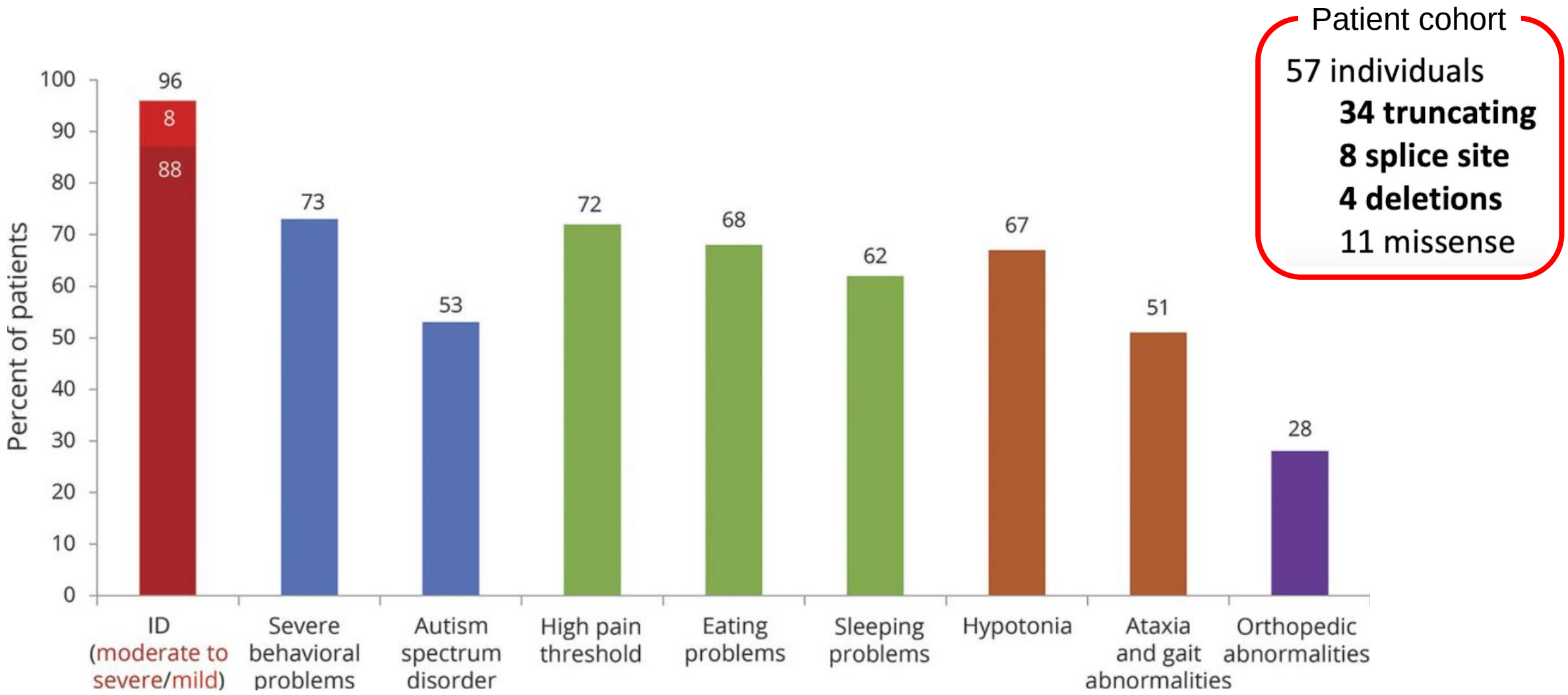
BRIEF REPORT

Mutations in *SYNGAP1* in Autosomal Nonsyndromic Mental Retardation

Fadi F. Hamdan, Ph.D., Julie Gauthier, Ph.D., Dan Spiegelman, M.Sc., Anne Noreau, M.Sc., Yan Yang, M.D., Stéphanie Pellerin, R.N., Sylvia Dobrzeniecka, M.Sc., Mélanie Côté, B.Sc., Elizabeth Perreau-Linck, M.Sc., Lionel Carmant, M.D., Guy D'Anjou, M.D., Éric Fombonne, M.D., Anjene M. Addington, Ph.D., Judith L. Rapoport, M.D., Lynn E. Delisi, M.D., Marie-Odile Krebs, M.D., Ph.D., Faycal Mouaffak, M.D., Ridha Joober, M.D., Ph.D., Laurent Mottron, M.D., Ph.D., Pierre Drapeau, Ph.D., Claude Marineau, M.Sc., M.B.A., Ronald G. Lafrenière, Ph.D., Jean Claude Lacaille, Ph.D., Guy A. Rouleau, M.D., Ph.D., and Jacques L. Michaud, M.D., for the Synapse to Disease Group

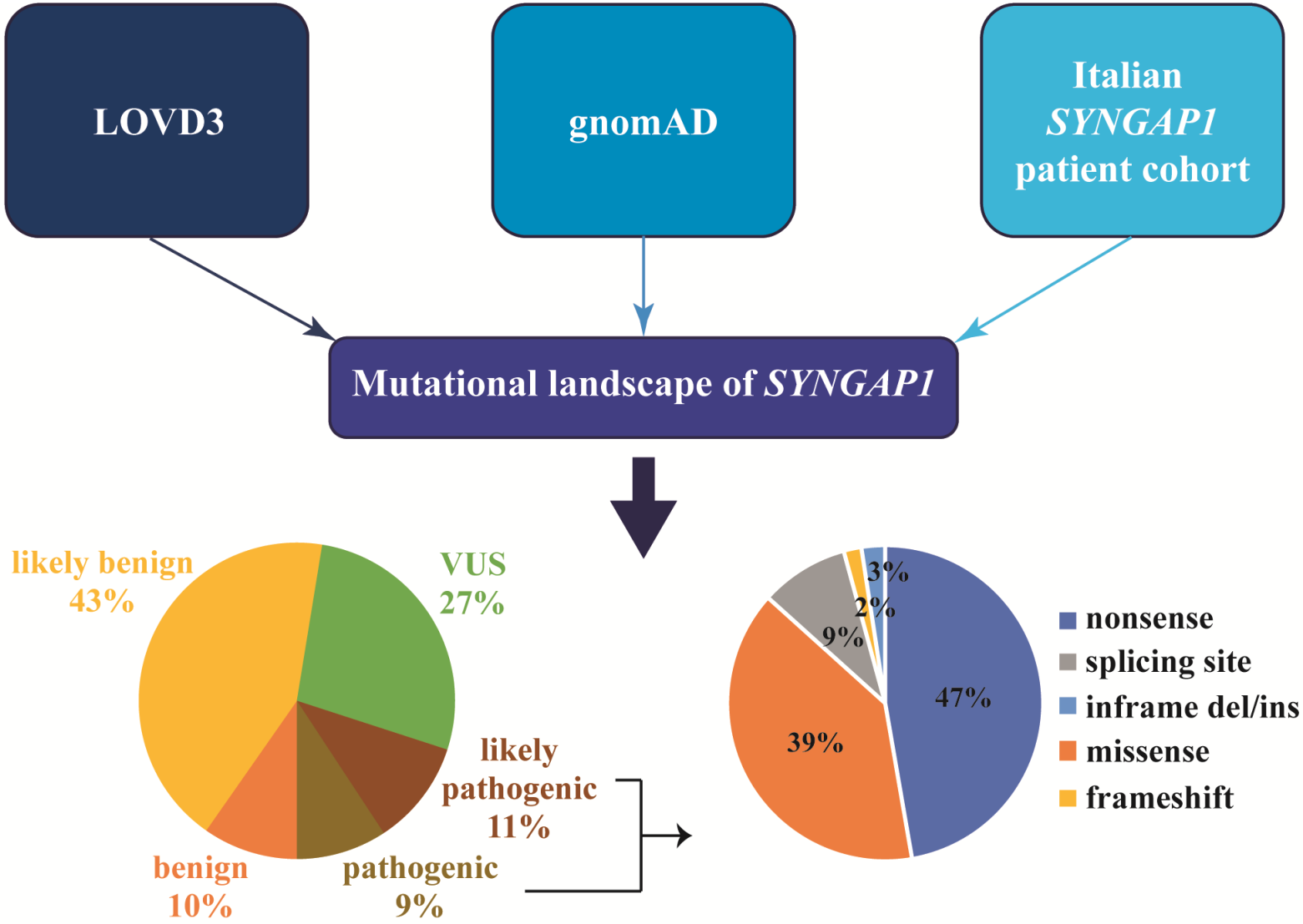
- 3/94 patients with ID had *de novo* truncating variant
- 0/142 autism
- 0/143 schizophrenia
- 0/190 unaffected
- Several additional studies
  - 18 patients
  - At least 12 w/seizures

SYNGAP1 encephalopathy is associated with a spectrum of comorbid conditions



(Vlaskamp et al 2019)

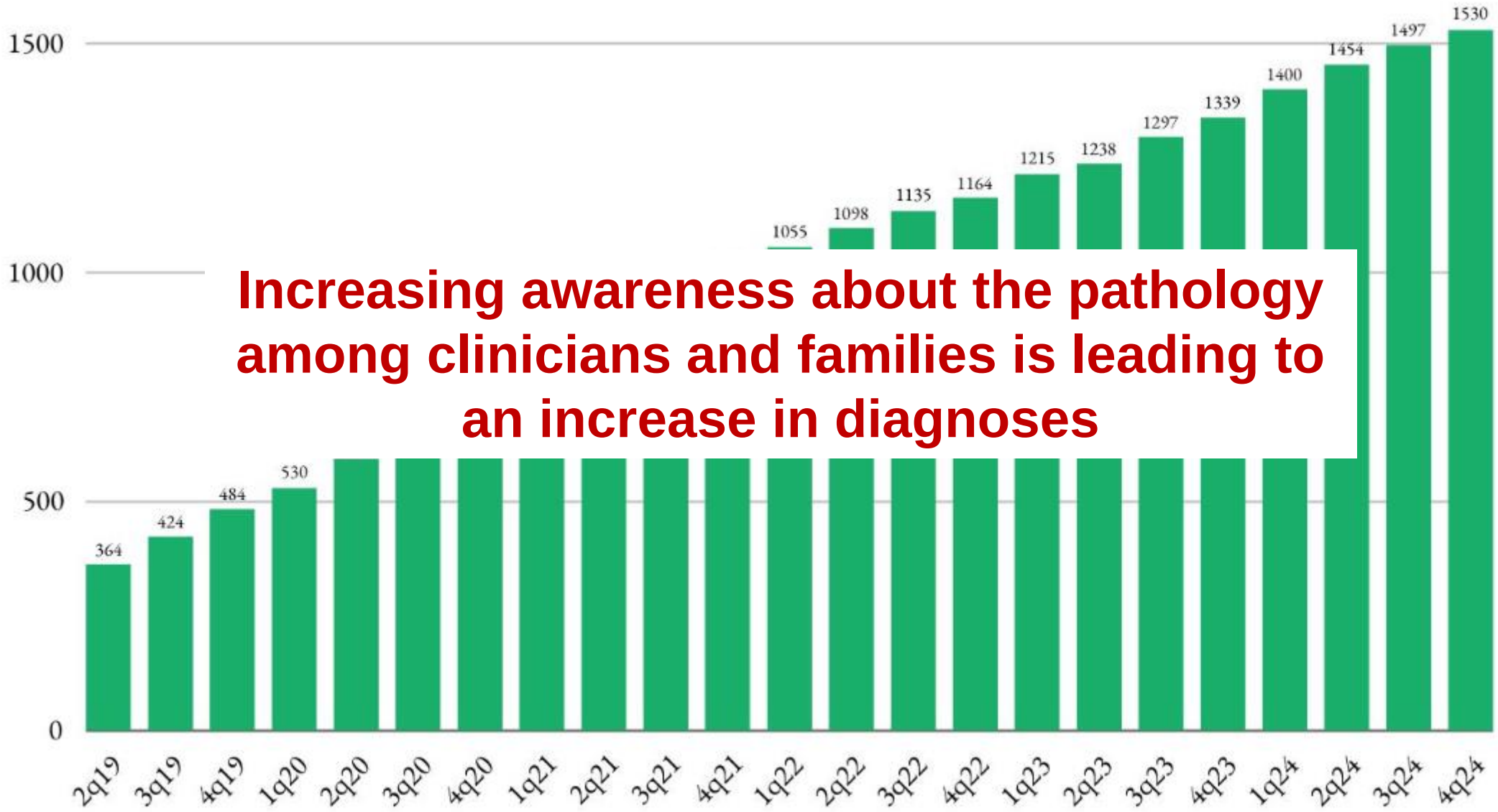
SYNGAP1 – Genetics



How Many People Have SYNGAP1?

Source: SYNGAP1 Census 2024

Known *SYNGAP1* patients worldwide



Increasing awareness about the pathology among clinicians and families is leading to an increase in diagnoses

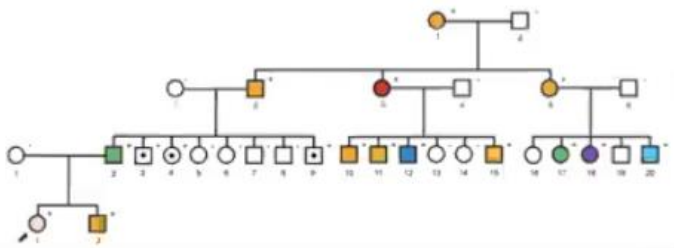
Source: SYNGAP1 Census 2024

Why genetics is important?

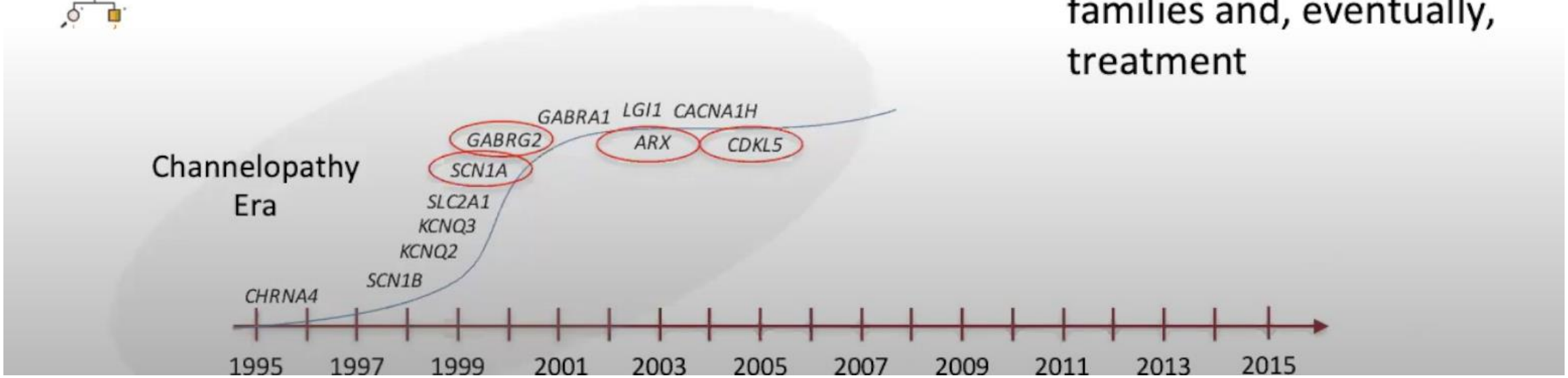
Knowing the genetic diagnosis....

- Improves prognosis counseling
- Facilitates discussion of recurrence risk
- May affect choice of medications
- Provides research opportunities
- Connects families with the same genetic diagnosis

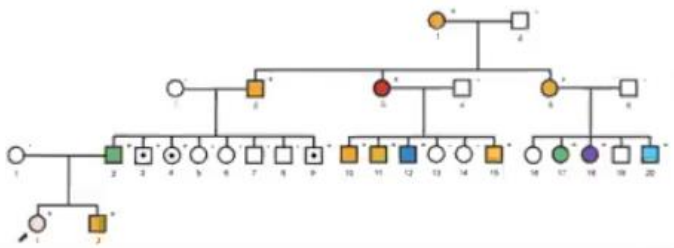
Genetic diagnosis (Epilepsy genes)



GOAL: Identify additional genetic causes of DEE in order to improve diagnosis, genetic counseling for families and, eventually, treatment



Genetic diagnosis (Epilepsy genes)



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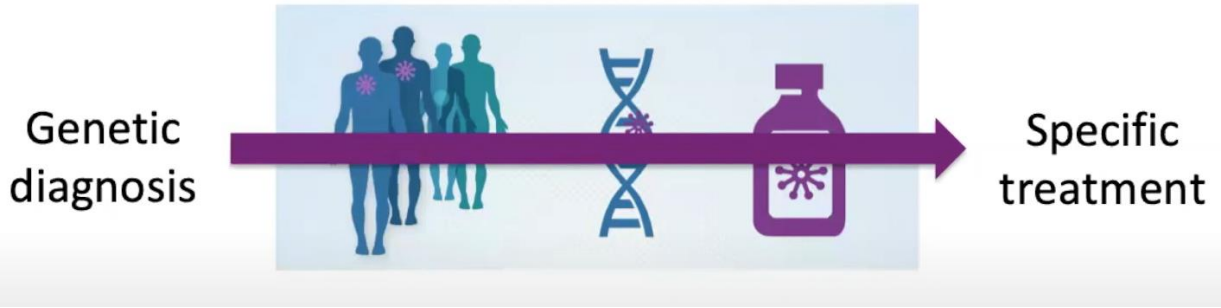
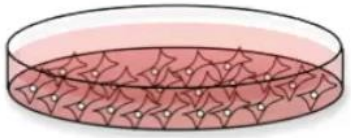
Why genetics is important?
From diagnosis to treatment

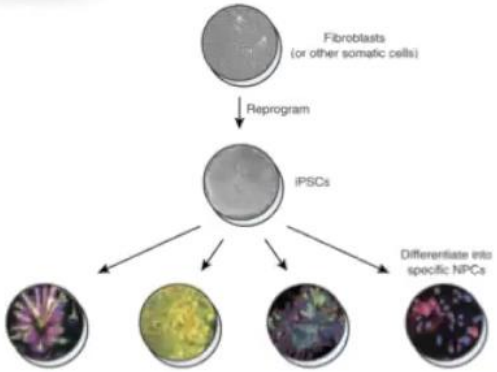


- Studies in cells



- Model organism experiments

- Patient cells: “stem cell” studies



SYNGAP1 discovery in 1998

Neuron

Volume 20, Issue 5, May 1998, Pages 895-904

Article

A Synaptic Ras-GTPase Activating Protein (p135 SynGAP) Inhibited by CaM Kinase II

Hong-Jung Chen [1], Michelle Rojas-Soto [1], Asako Oguni [1], Mary B Kennedy [1] *

Neuron

Volume 20, Issue 4, April 1998, Pages 683-691

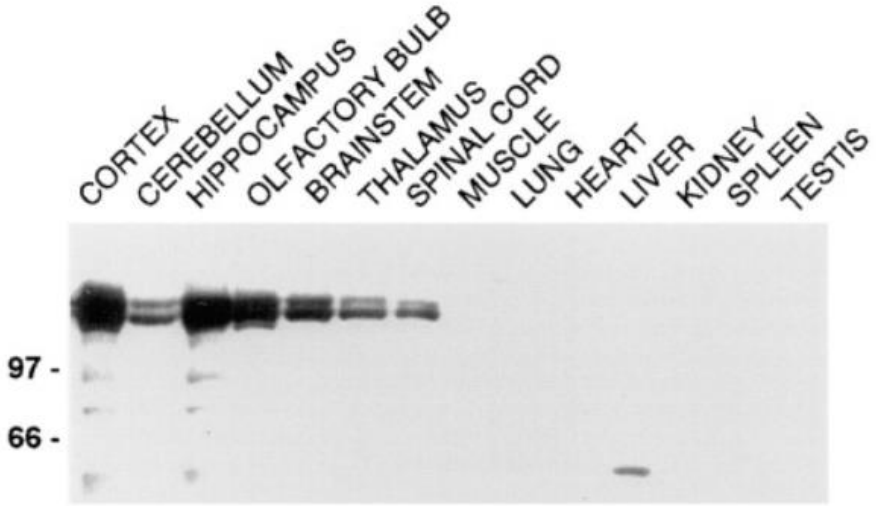
Article

SynGAP: a Synaptic RasGAP that Associates with the PSD-95/SAP90 Protein Family

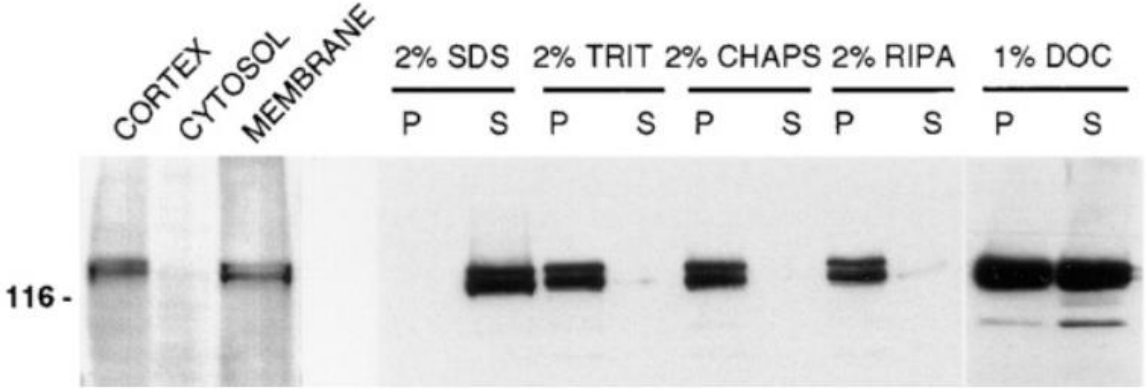
Jee Hae Kim [1], Dezhi Liao [1], Lit-Fui Lau [1], Richard L Huganir [1] *

SYNGAP1 discovery – Huganir lab

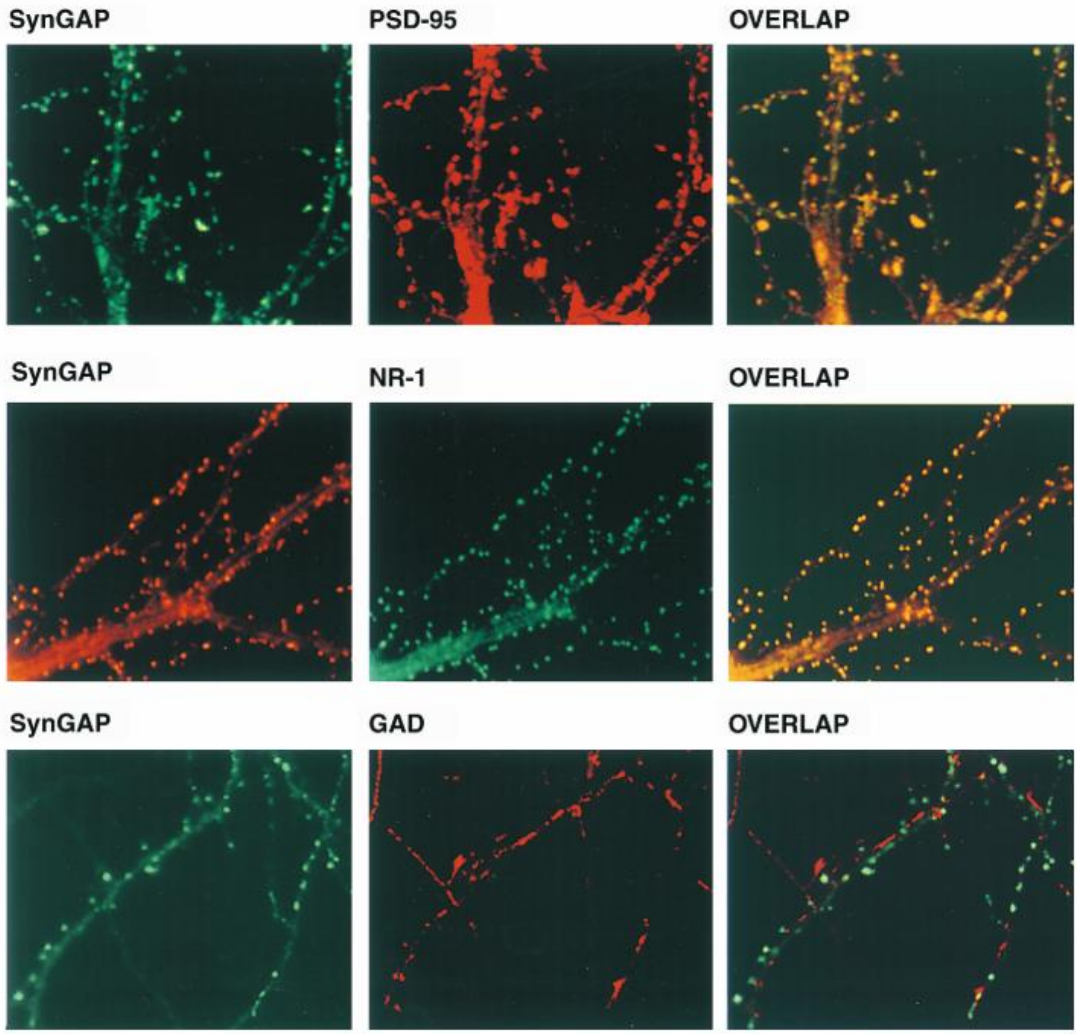
Brain-Specific Expression of SynGAP



SynGAP is localized to membrane fractions



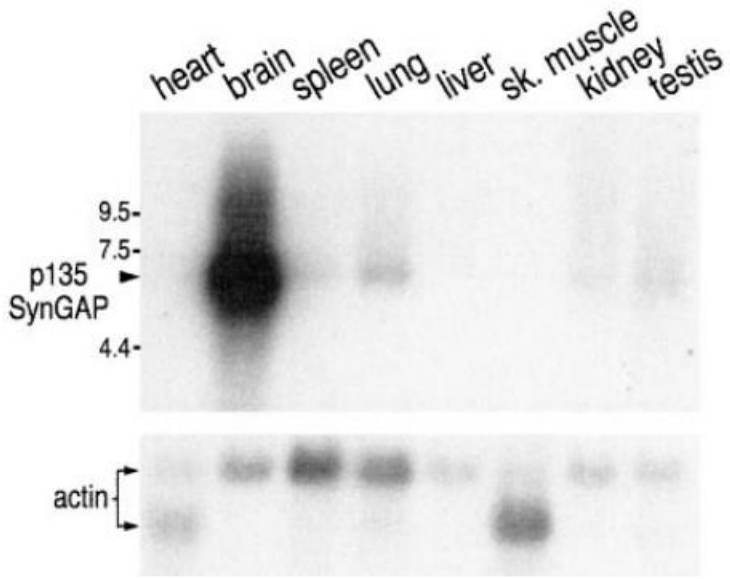
SynGAP is specifically localized at excitatory synapses



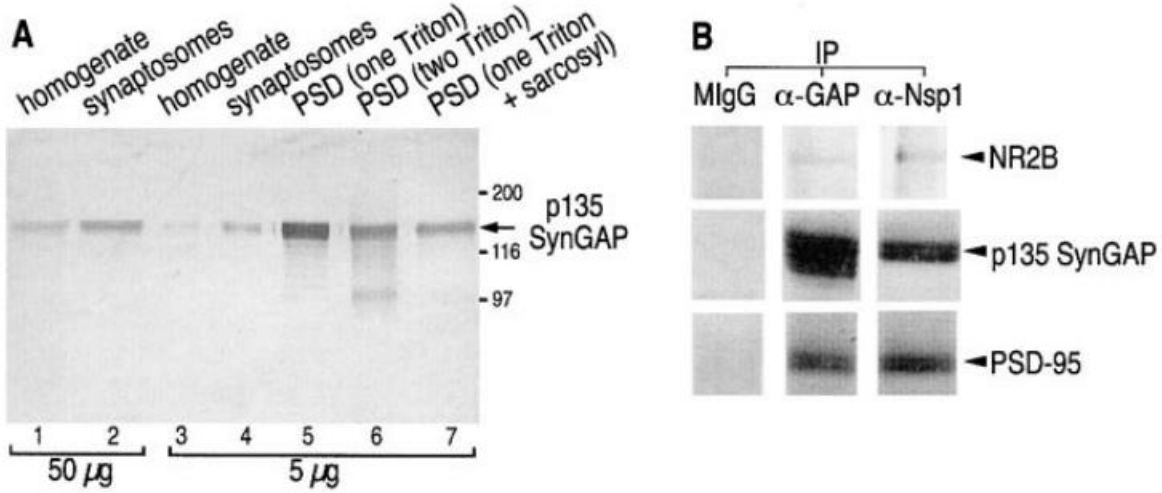
(Kim et al 1998)

SYNGAP1 discovery – Kennedy lab

SynGAP is expressed primarily in brain and is localized to synapses containing NMDA receptors.

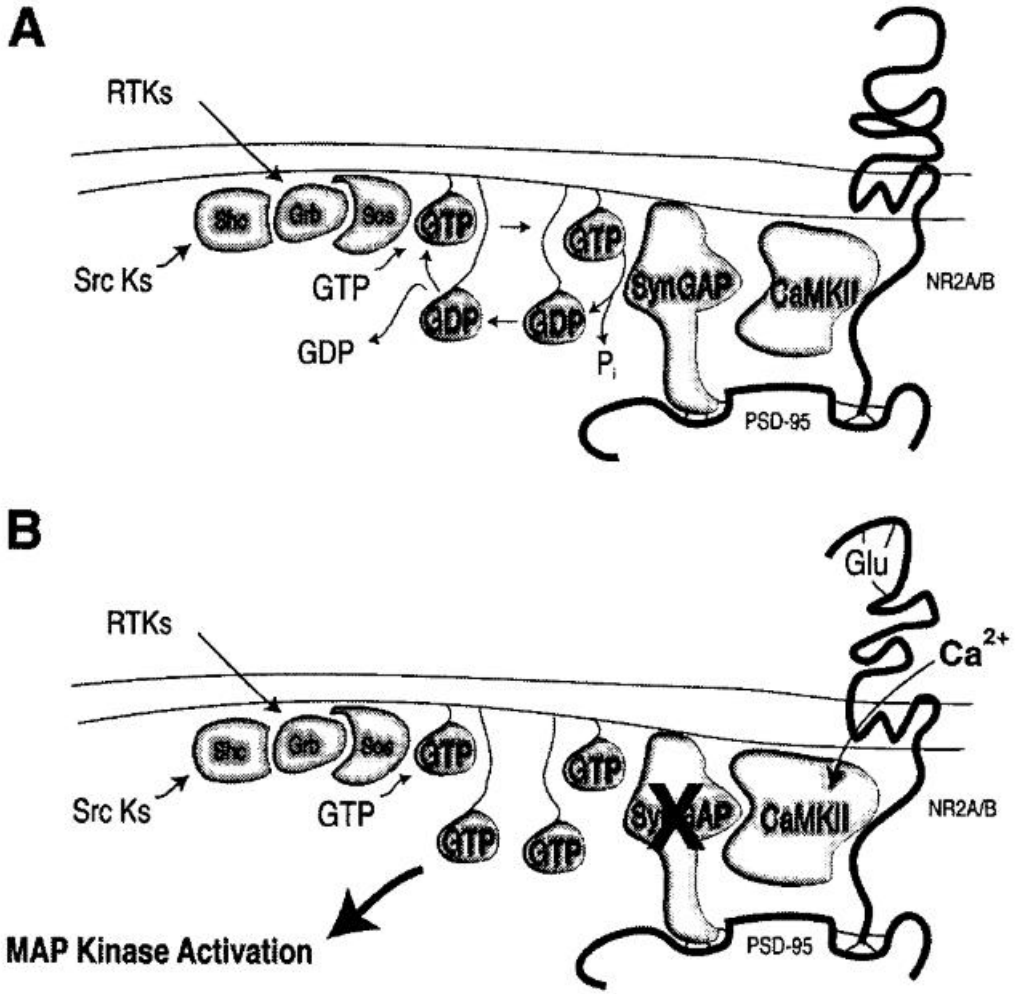


It constitutes 1%–2% of total protein in isolated PSDs and is rapidly phosphorylated upon activation of CaMKII in the PSD.



(Chen et al 1998)

SYNGAP1 discovery – Kennedy lab



<u>Hypothesized Effects of Regulation of p135 SynGAP by NMDA-Receptor Activation at Glutamatergic Synapses</u>.

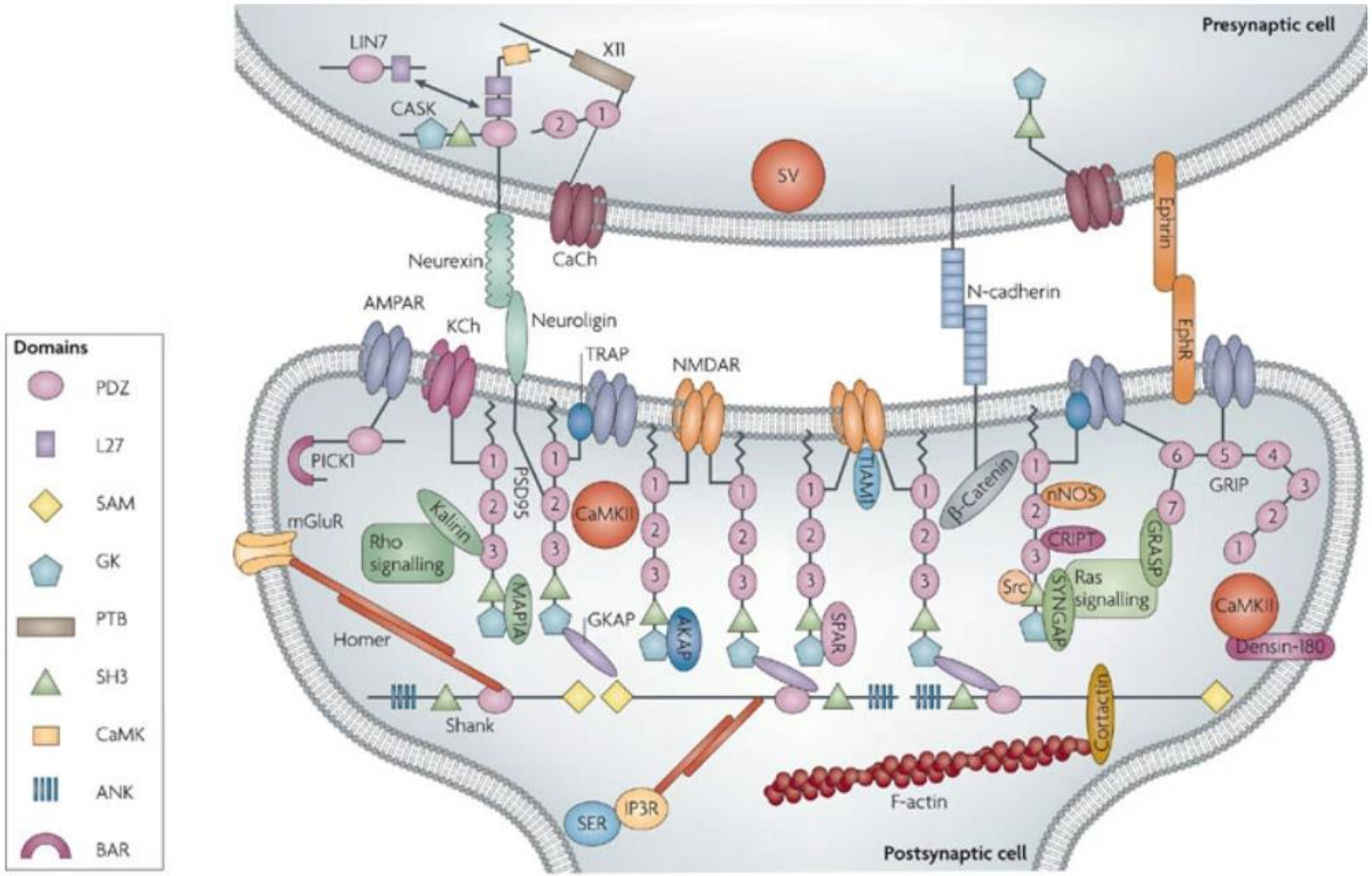
Active p135 SynGAP at postsynaptic densities will keep the steady-state level of active Ras low near the synapse by catalyzing rapid hydrolysis of Ras-GTP to Ras-GDP.

Activation of NMDA receptors produces an influx of Ca2+ that activates CaMKII at the postsynaptic density. CaMKII then phosphorylates and inactivates p135 SynGAP, releasing the brake on the accumulation of active Ras-GTP and leading to increased activation of the MAP kinase cascade.

(Chen et al 1998)

SYNGAP1 – Molecular function

SynGAP as a “molecular hub” for the regulation of synaptic strength at baseline (limiting the number of AMPAR) and following neuronal activity



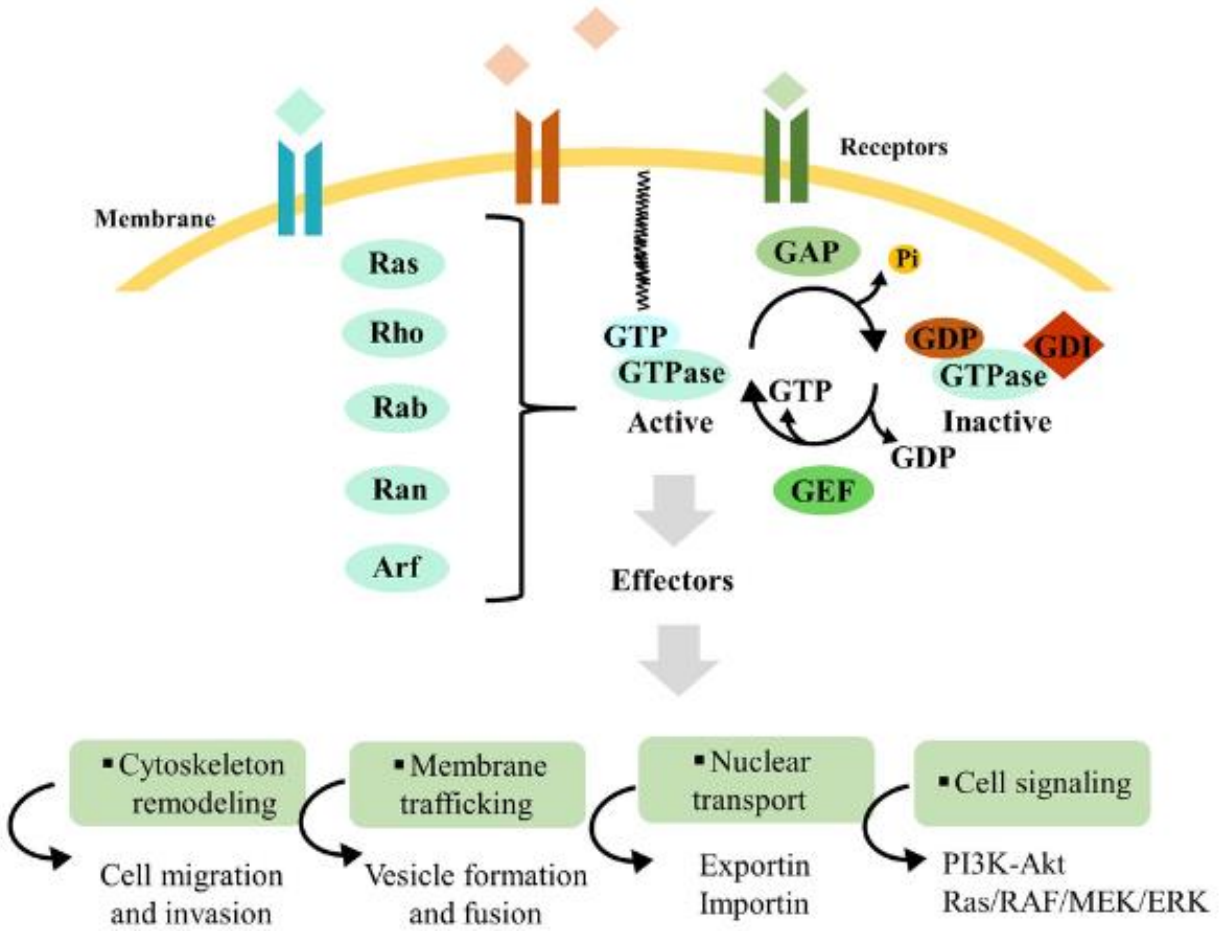
The postsynaptic density is comprised of membrane receptors and ion channels, scaffold and adaptor proteins, signaling proteins, cell-adhesion molecules and components of the cytoskeleton.

The presynaptic and postsynaptic membranes are connected by cell-adhesion molecules.

(Feng and Zhang 2009)

SYNGAP1 – Molecular function

"Classic role": GAP protein that mediates the transition from the active (GTP) to the inactive (GDP) form of small GTPase (e.g. Ras)



As result of the loss of the GTPase activity, small GTP proteins (e.g., Ras, Rap) are inappropriately bound to GTP at too high proportion and for too long

→ SynGAP as an enhancer of GTPase activity

→ Ras signaling overactivation if SynGAP is missing

(Weldon et al 2018; Brito et al 2020)

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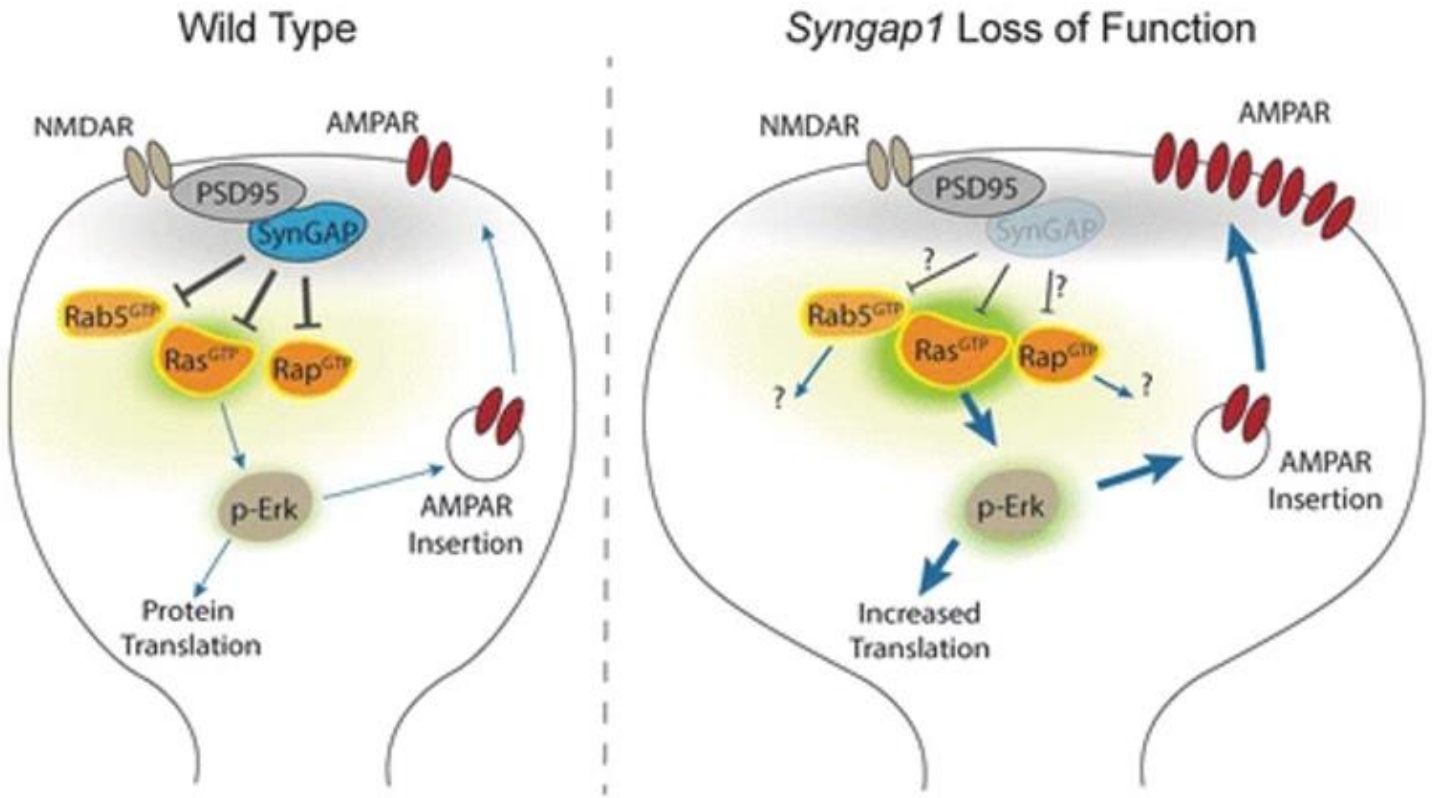
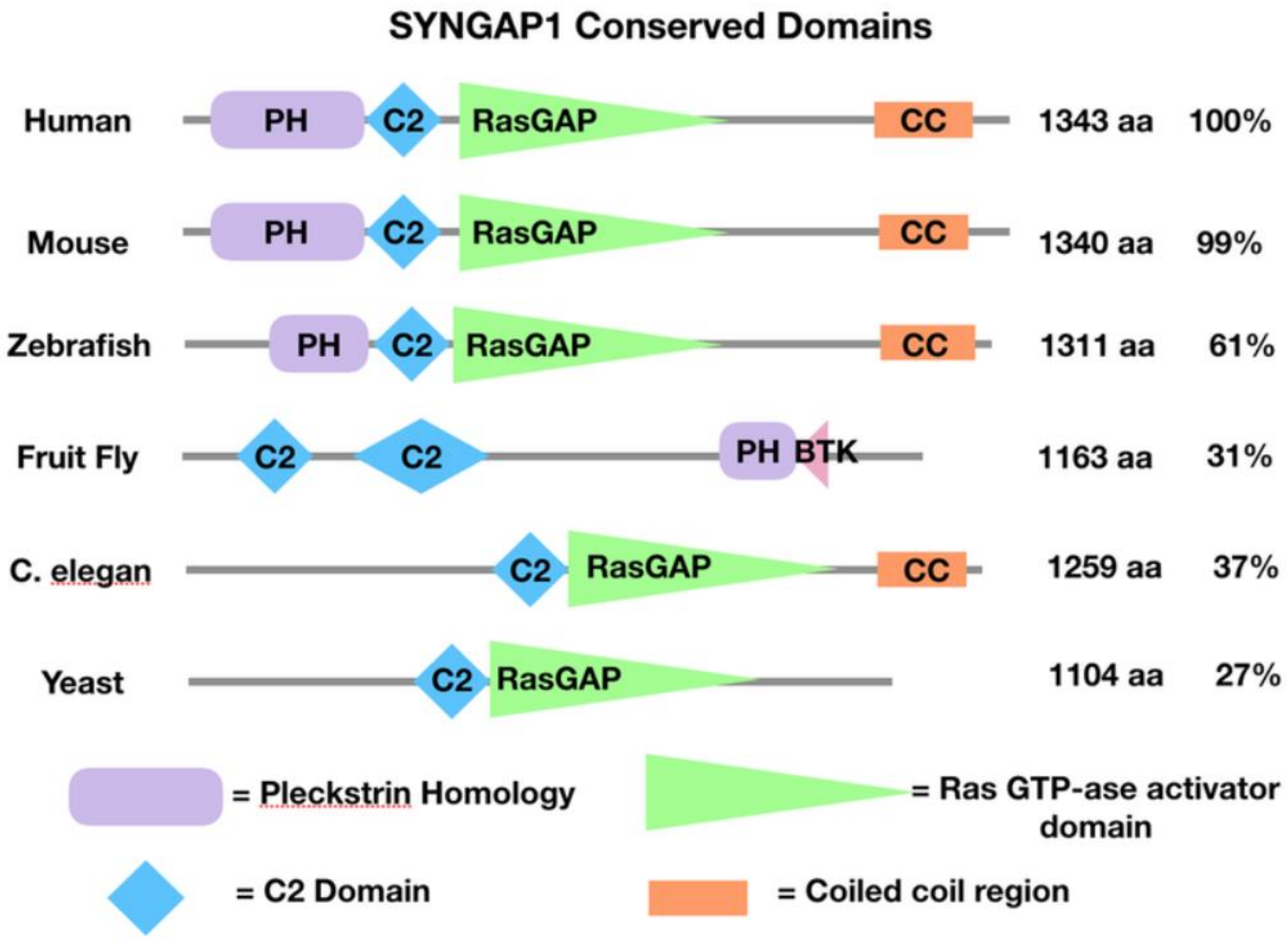


- Influence on PSD composition
- Negative regulator of AMPAR trafficking
- Premature maturation of dendritic spines
- Negative regulator of synaptic plasticity
- Excitation/inhibition imbalance
- Cognitive deficits

(Weldon et al 2018; Brito et al 2020)

The SynGAP protein: today



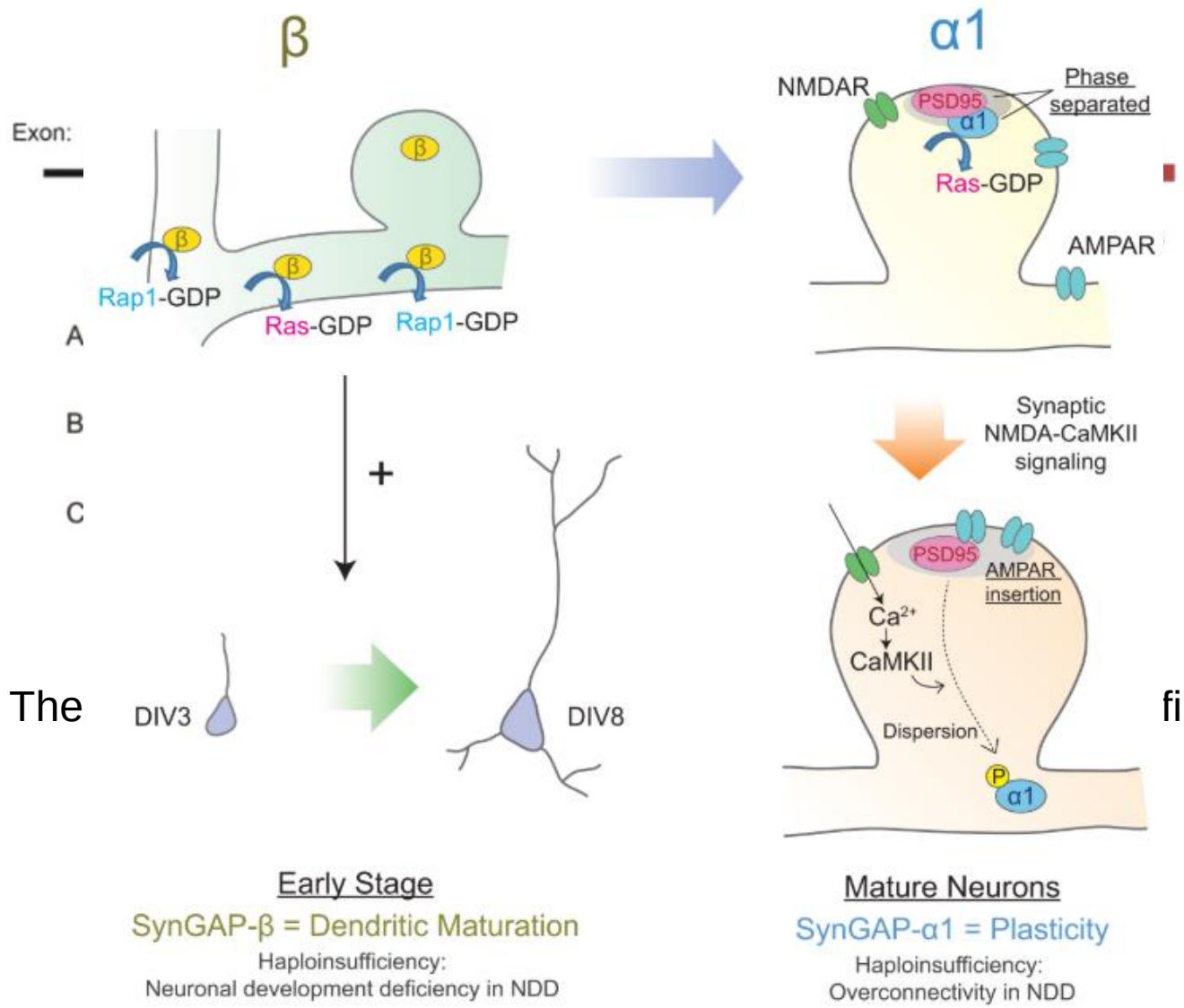
PH → recruiting proteins to different membranes/compartments; binding of inositol phosphates, and various proteins

C2 → targeting proteins to cell membranes; binding of phospholipids, inositol polyphosphates, and intracellular proteins

RasGAP → catalytic domain; acceleration of the GTPase activity of Ras, thereby "switching" it into an "off" position

Coiled Coil (CC) → protein clustering/oligomerization

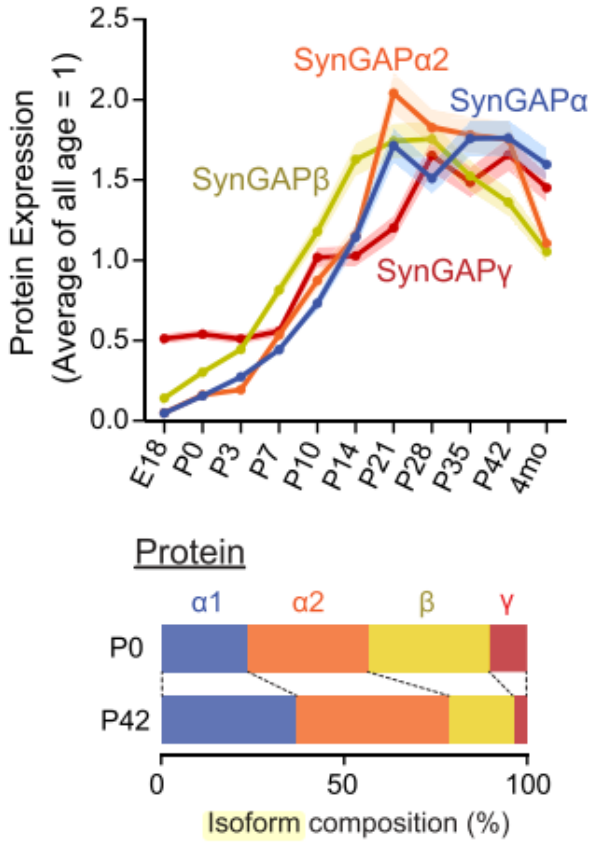
SYNGAP1 alternative splicing and resulting isoforms



The files

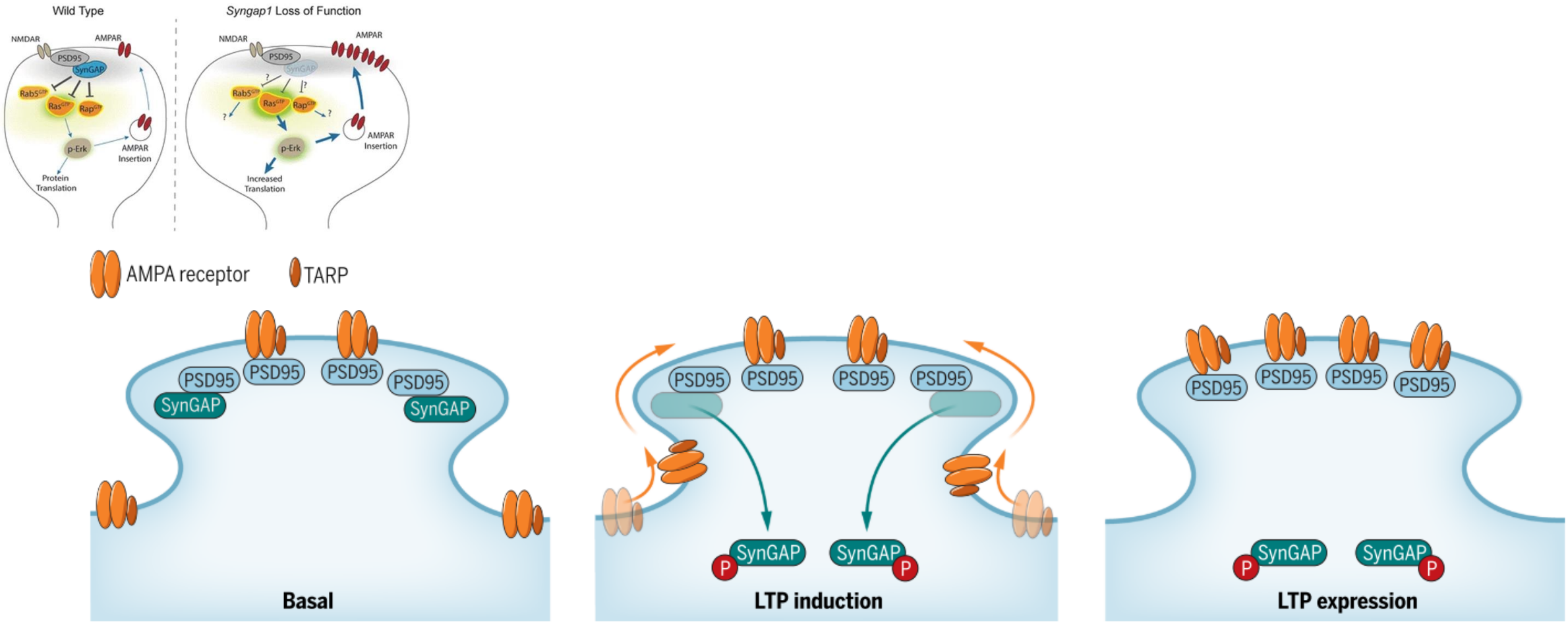
Fine control of Ras and Rap1 activation during early development – when SYNGAP1 is missing their overactivation could lead to an abnormal development

Isoforms expression in mice over time



(Kilinc et al 2018; Araki et al 2020)

Role of SynGAP in determining slot availability for the AMPAR-TARP complex independently of its GAP activity



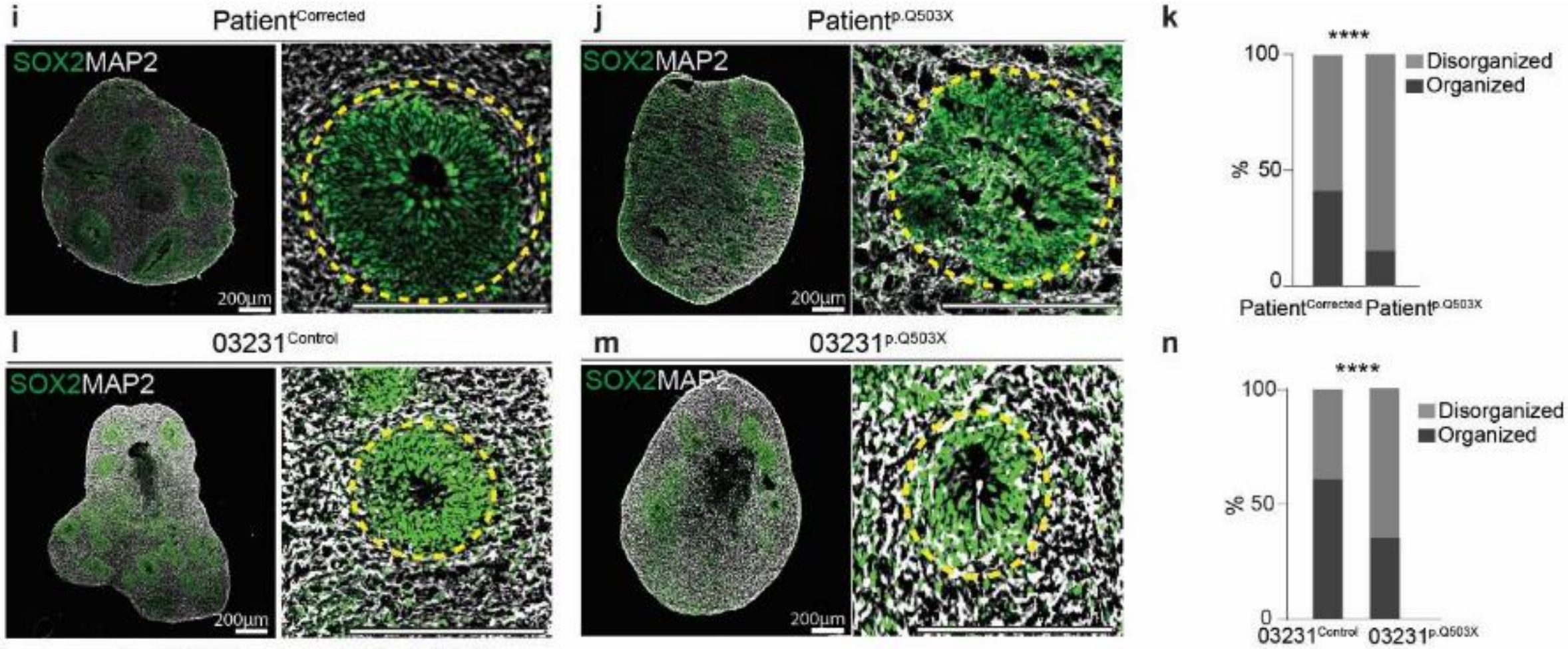
Model of SynGAP regulation of synaptic plasticity. SynGAP regulates synapses by competing with AMPAR-TARP complexes to form LLPS condensates with PSD95. During LTP induction, phosphorylation of SynGAP promotes the dispersal of SynGAP from the synapse and is replaced with AMPAR-TARP complexes, resulting in the potentiation of synaptic transmission.

(Araki et al 2024)

SYNGAP1 – Non-canonical role in brain development

New finding : SYNGAP1 is expressed already in radial glia progenitors

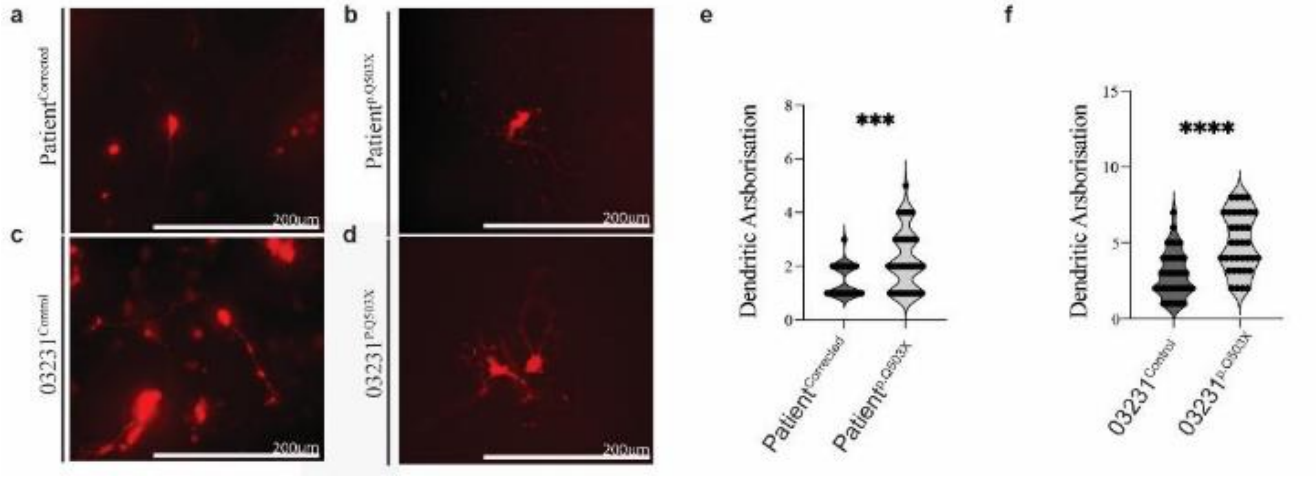
Cortical plate disorganization during development affecting cell division mode

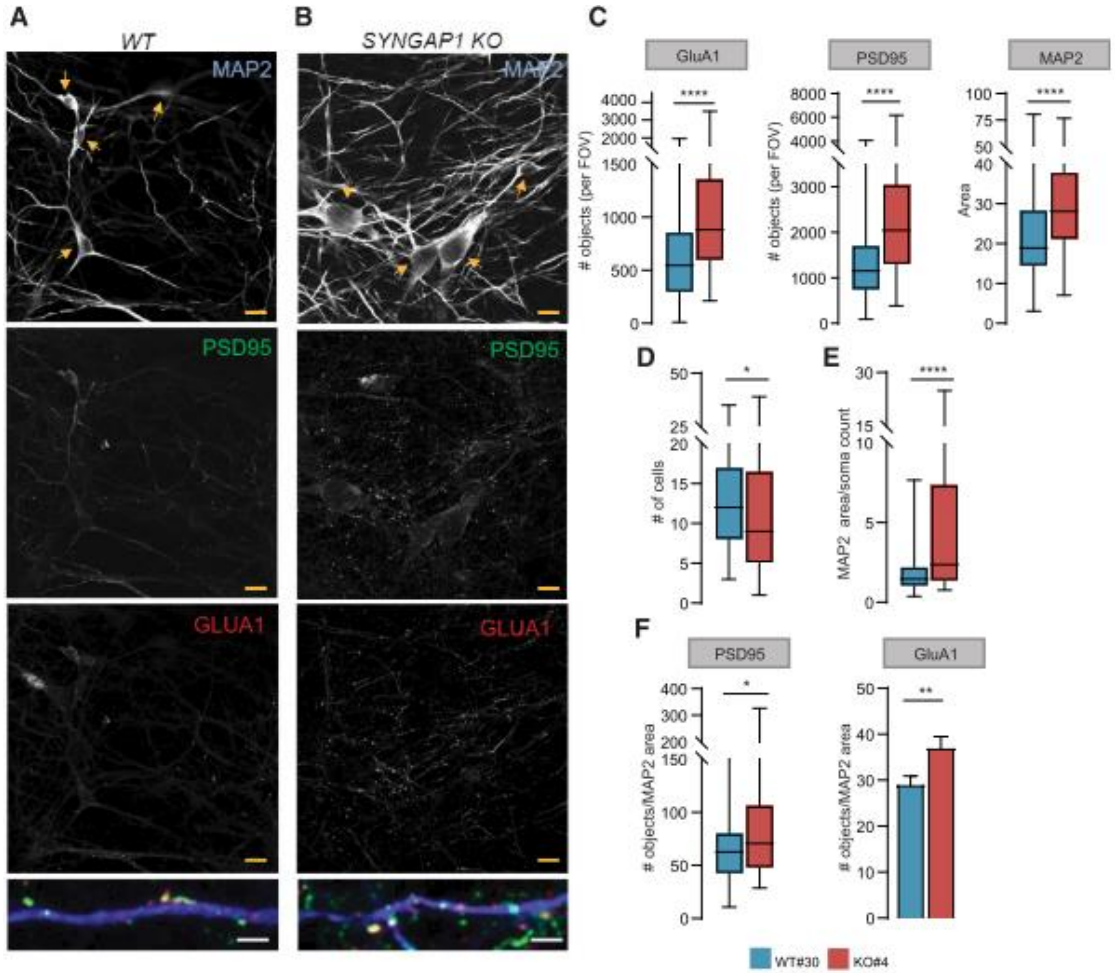


(Birtele et al 2023)

SYNGAP1 – Non-canonical role in brain development

Accelerated maturation of cortical projection neurons and iNeurons





(Birtele et al 2023)

(Llamosas et al 2020)

SYNGAP1 – Non-canonical role in brain development

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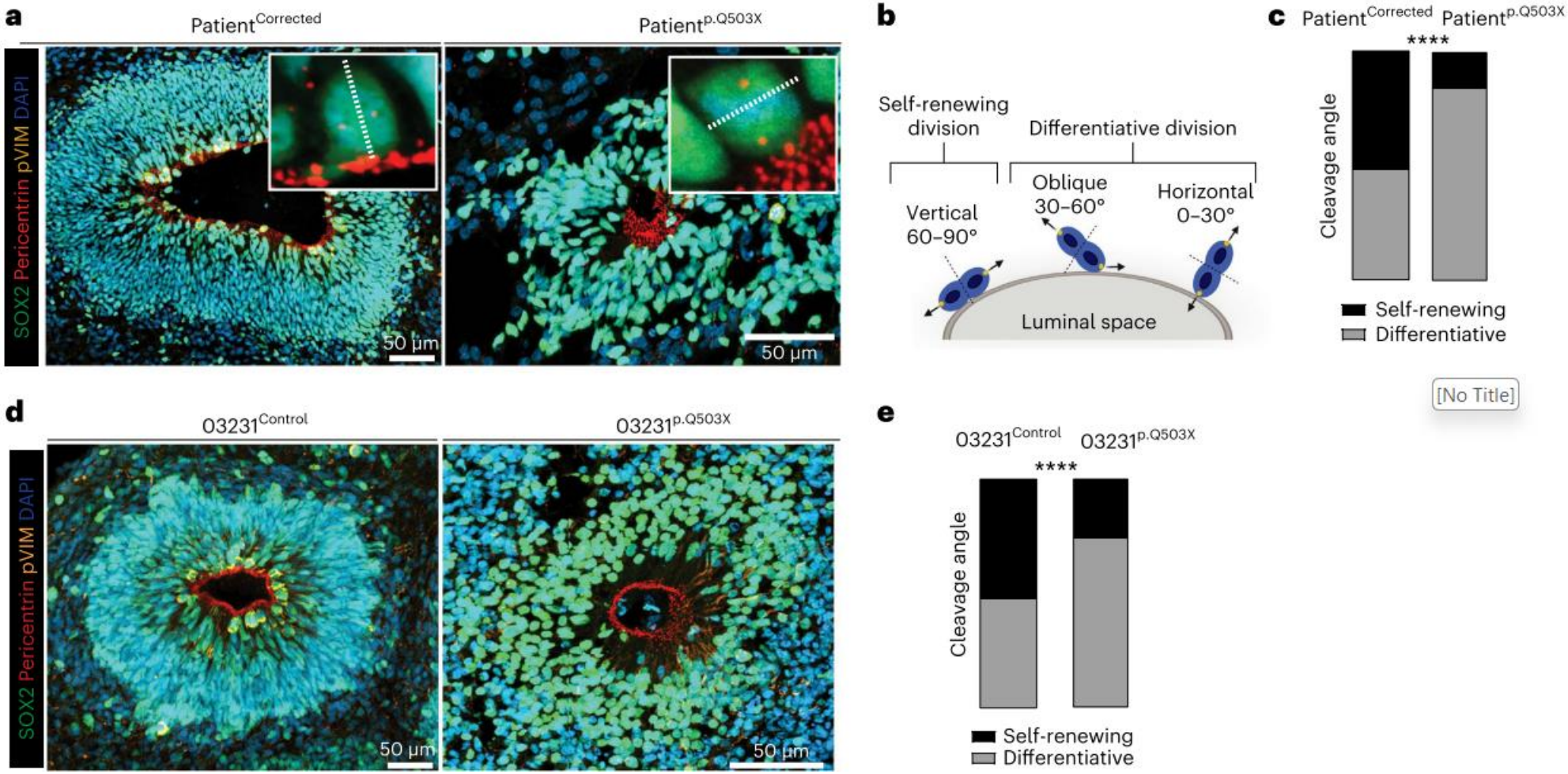

(Birtele et al 2023)

SYNGAP1 research at Sapienza University