Studying Neurodevelopmental Disorders Through The Lens of *SYNGAP1*

GBM 24/11/2025
Bernadette Basilico

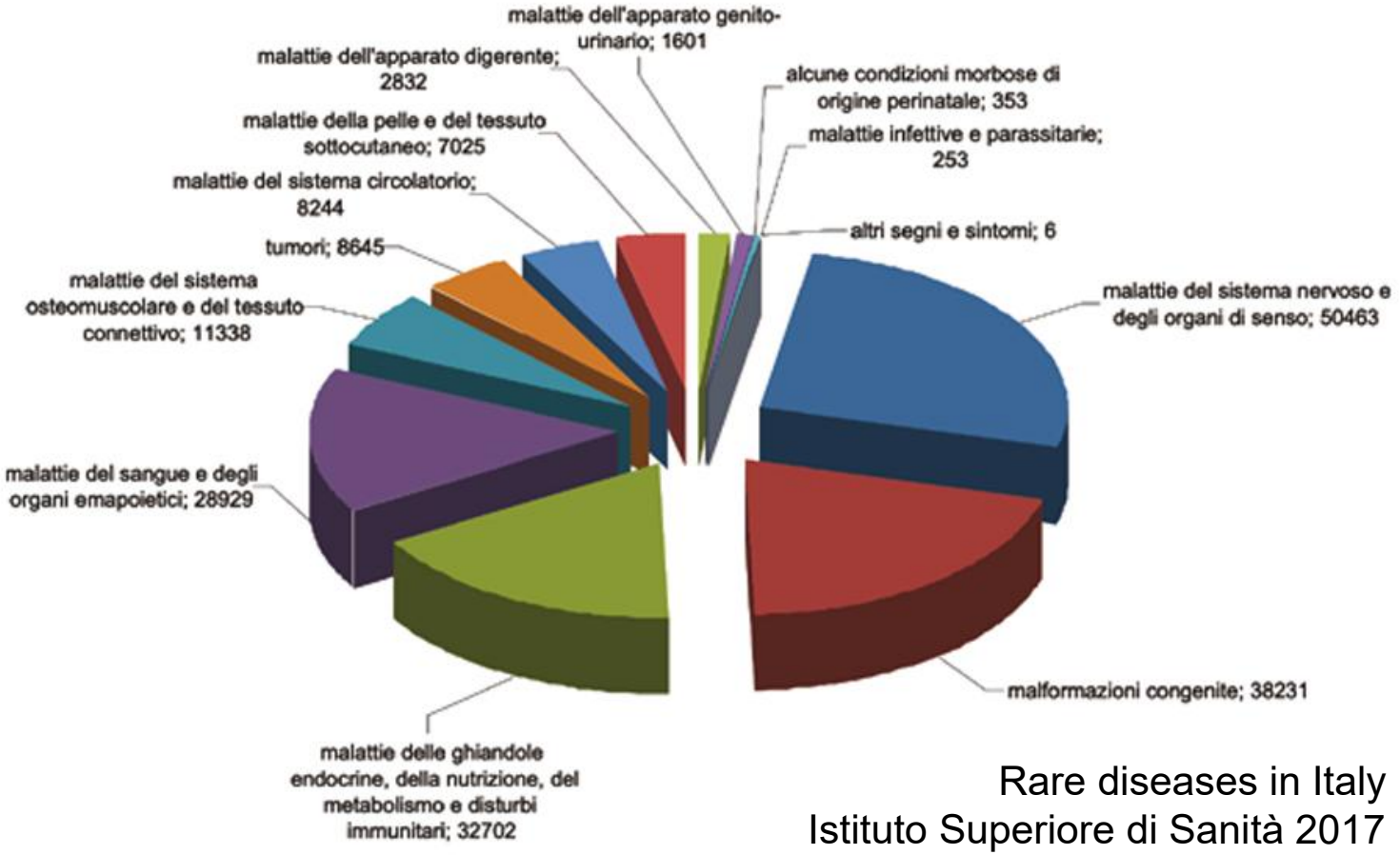
Rare diseases

A rare disease, also called an orphan disease, is a condition that affects a small proportion of the population.
Almost all genetic diseases are rare diseases; however, not all rare diseases have a genetic origin. There are also very rare infectious diseases, as well as rare autoimmune diseases and rare carcinomas (rare cancers).

Clinical and care-related features common to many rare diseases:

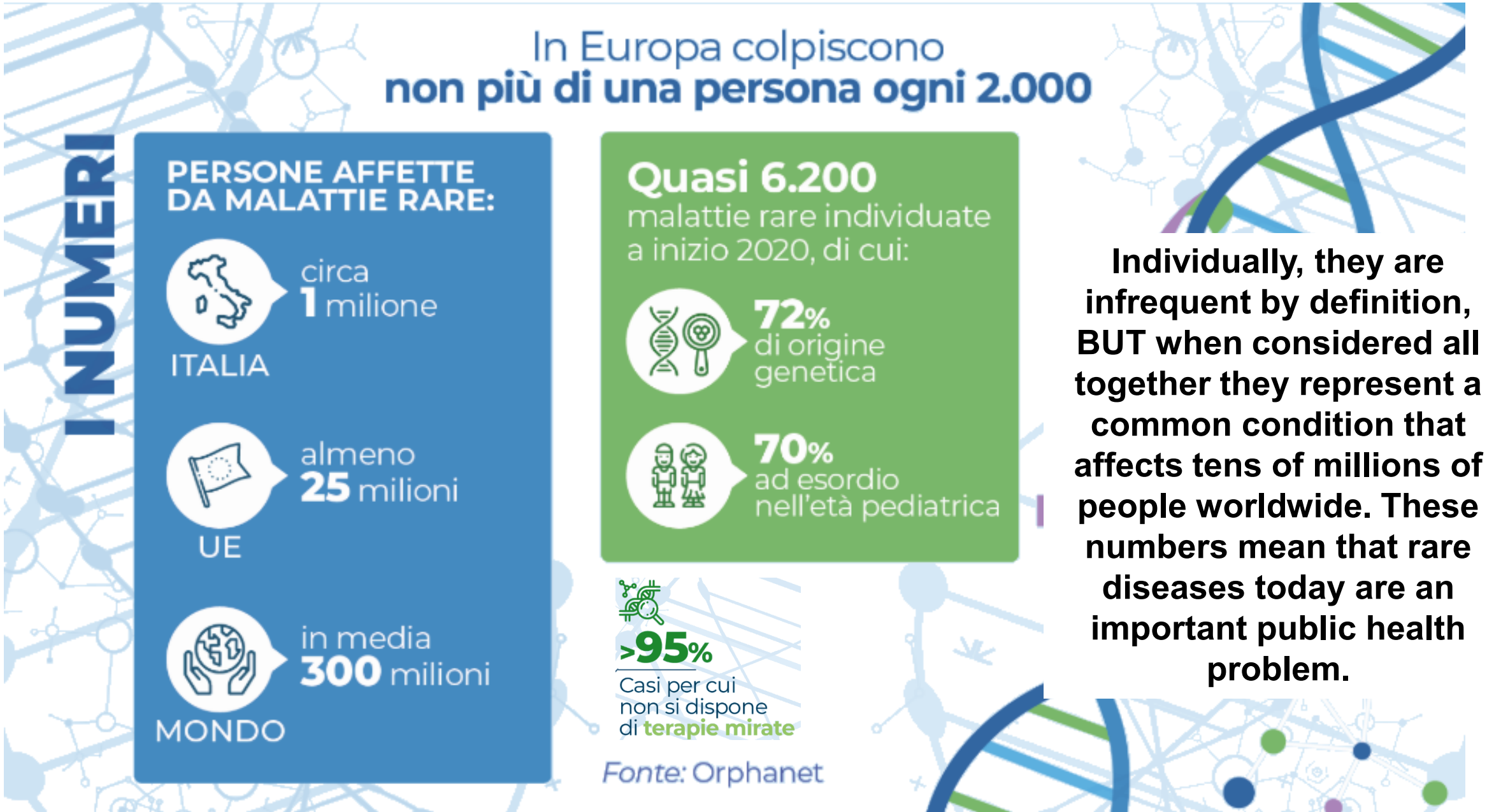
- difficulty in making a diagnosis
- few therapeutic options
- chronic course
- outcomes that are often disabling

(Stoller 2018)



Rare diseases in Italy
Istituto Superiore di Sanità 2017

How rare is a rare disease?



Individually, they are infrequent by definition, BUT when considered all together they represent a common condition that affects tens of millions of people worldwide. These numbers mean that rare diseases today are an important public health problem.

Rare diseases

Rarity implies:

- limited availability of scientific knowledge
- difficulty in obtaining an appropriate diagnosis
- long delays between the onset of the disease, a correct diagnosis, and adequate treatment (when available)

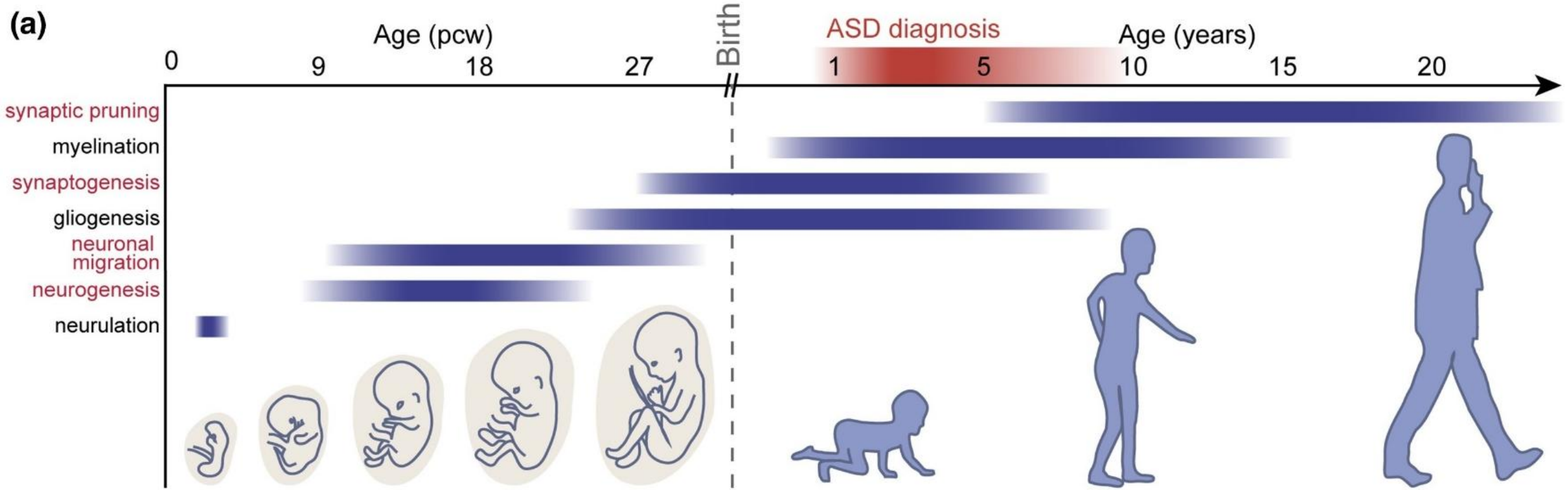
All of this has a negative impact on the prognosis of the condition.

Rare diseases are also characterized by many symptoms that vary not only from one condition to another, but also from one patient to another, even when they have the same disease.
→ To be diagnosed, they require experience with rare conditions and a good understanding of normal variability.

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)

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

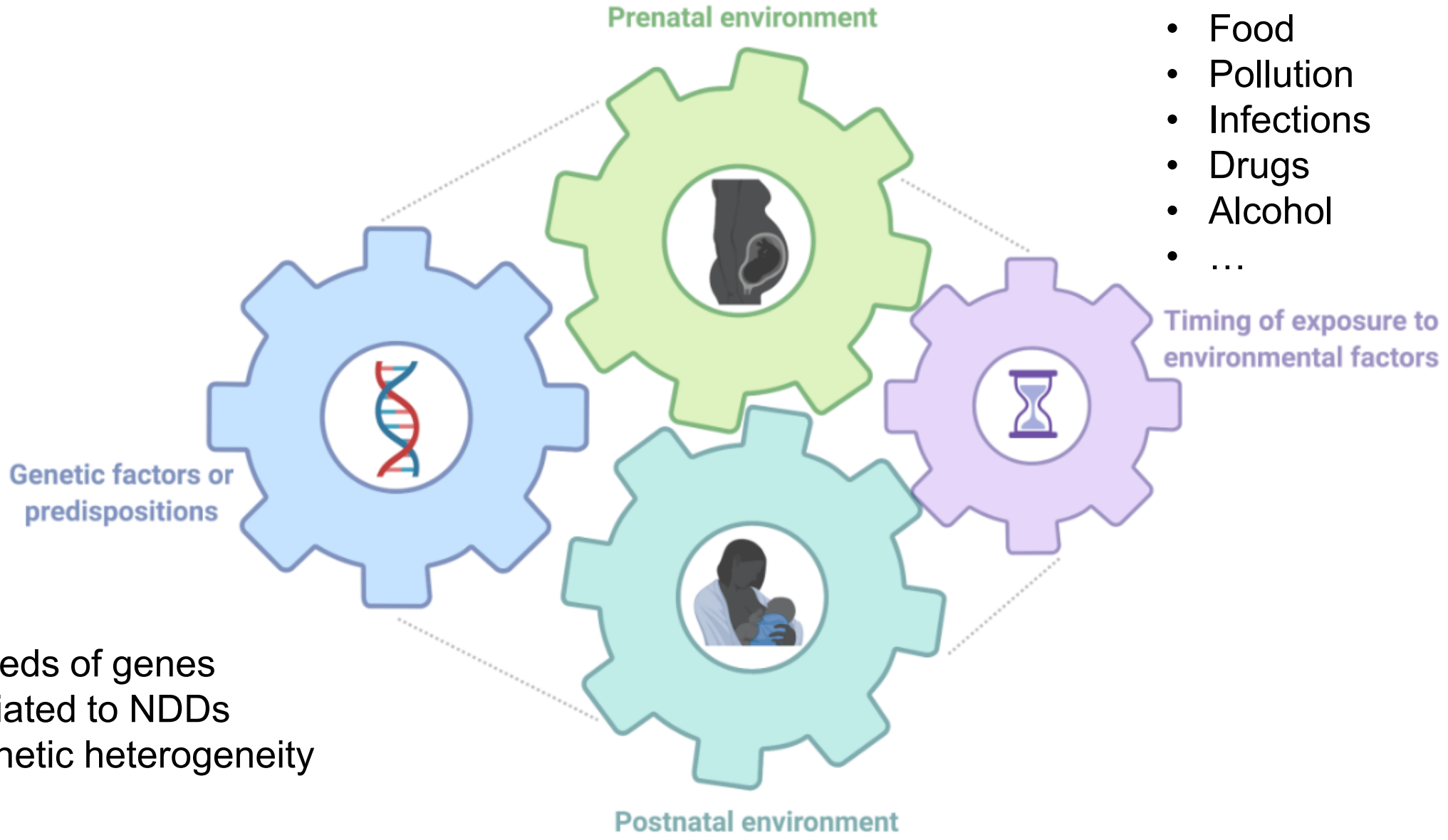
- The term refer to a disorder of brain function that affects emotion, learning ability, self-control and memory and that unfolds as individual grows.

- 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.

NDDs: risk factors



Environmental factors:

- Food
- Pollution
- Infections
- Drugs
- Alcohol
- …

Hundreds of genes associated to NDDs
→ Genetic heterogeneity

Genetic causes: the most common

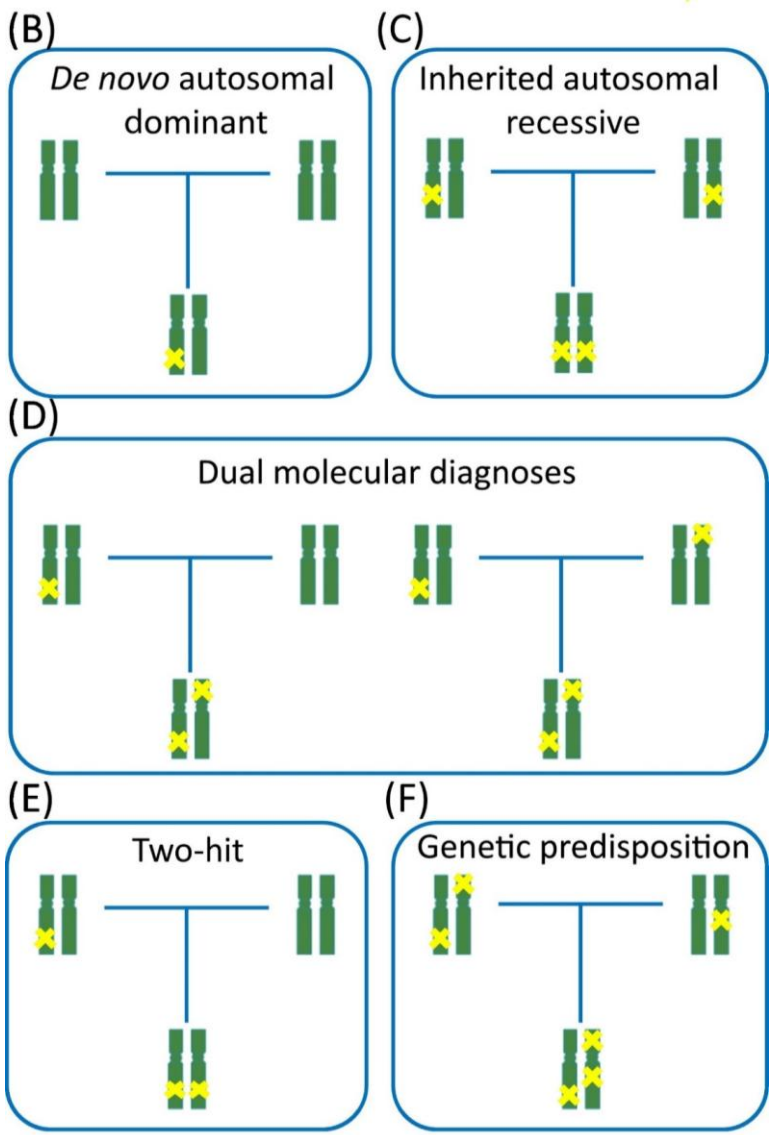
B) *De novo* autosomal dominant: new dominant mutation in children

C) Inherited autosomal recessive: both parents have the same recessive variant → children inherit both copies causing the disease

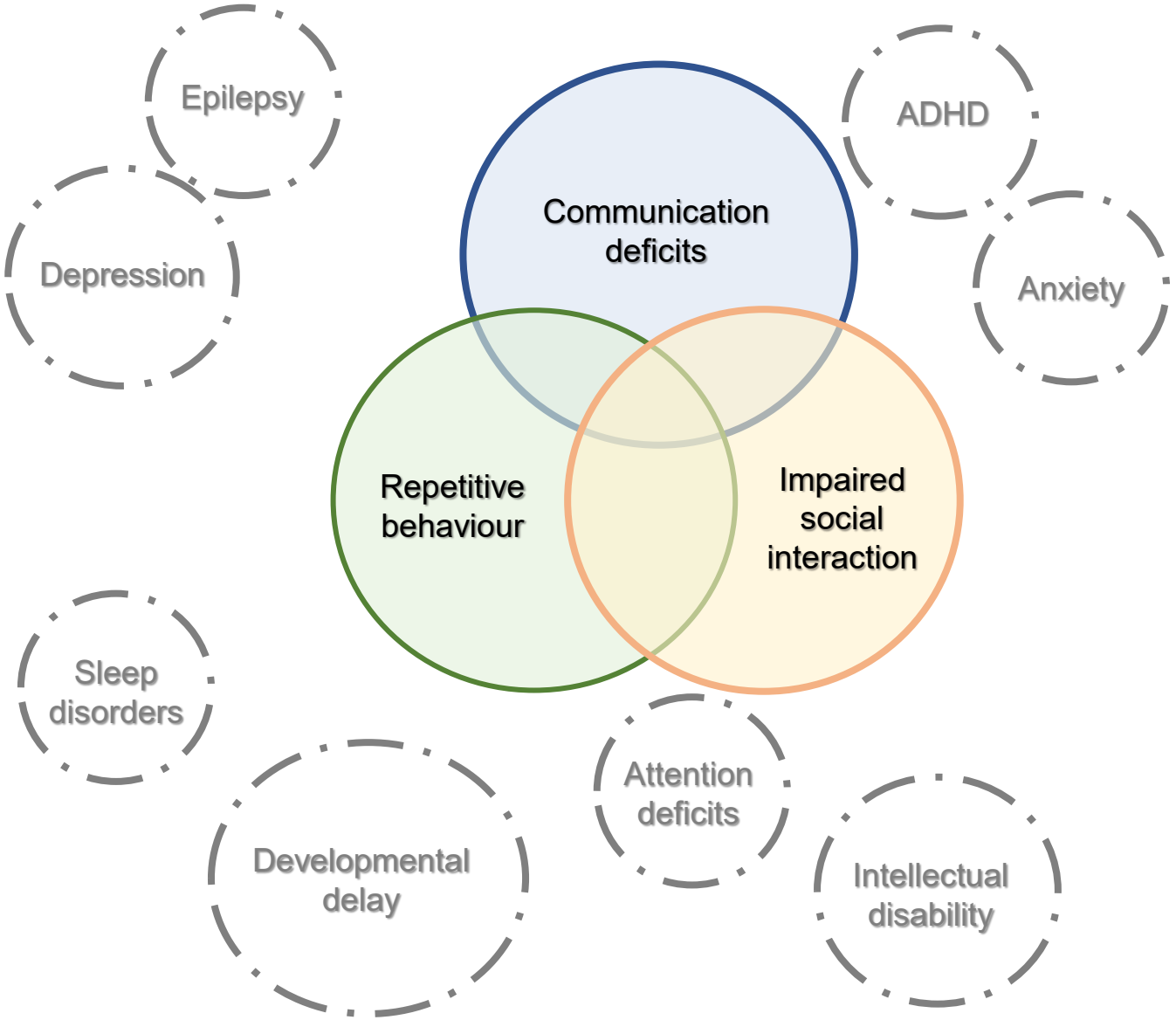
D) Dual molecular diagnoses: two different mutations inherited or inherited plus *de novo* mutations

E) Two-hit: combined effect of an inherited and an acquired variant on the same gene (two hits)

F) Genetic predisposition: children inherit different risk variants. The combination of multiple variants increase the vulnerability for disease appearance



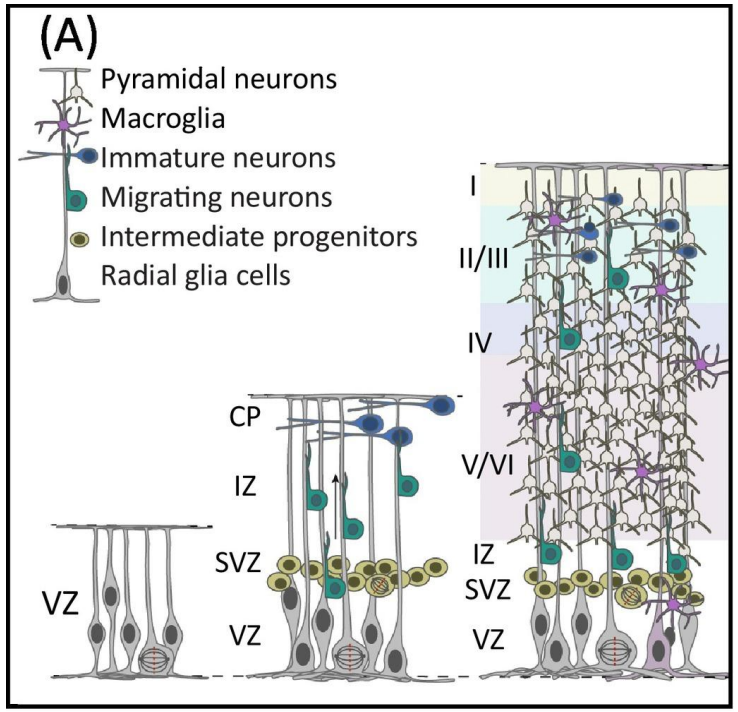
(Parenti et al 2020)



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

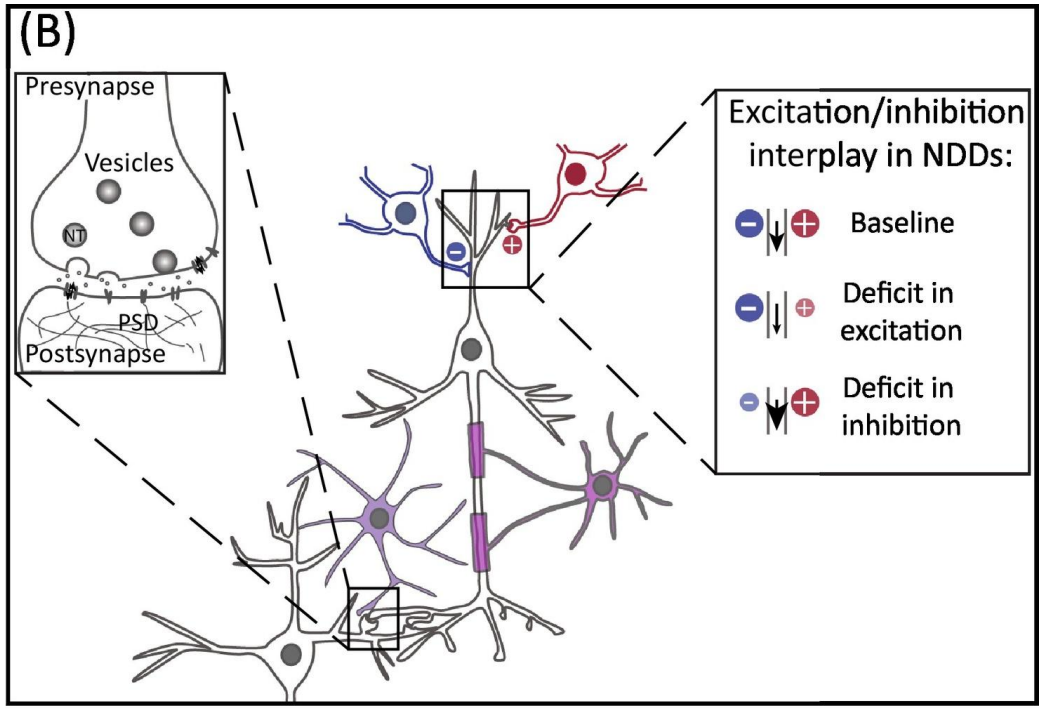
Altered processes in NDDs in the developing and mature brain



Gene mutations associated with NDDs have been identified in genes involved in three biological processes that are critical for development:

(i) regulation of protein synthesis;
(ii) transcriptional and epigenetic regulation;
(iii) synaptic signalling.

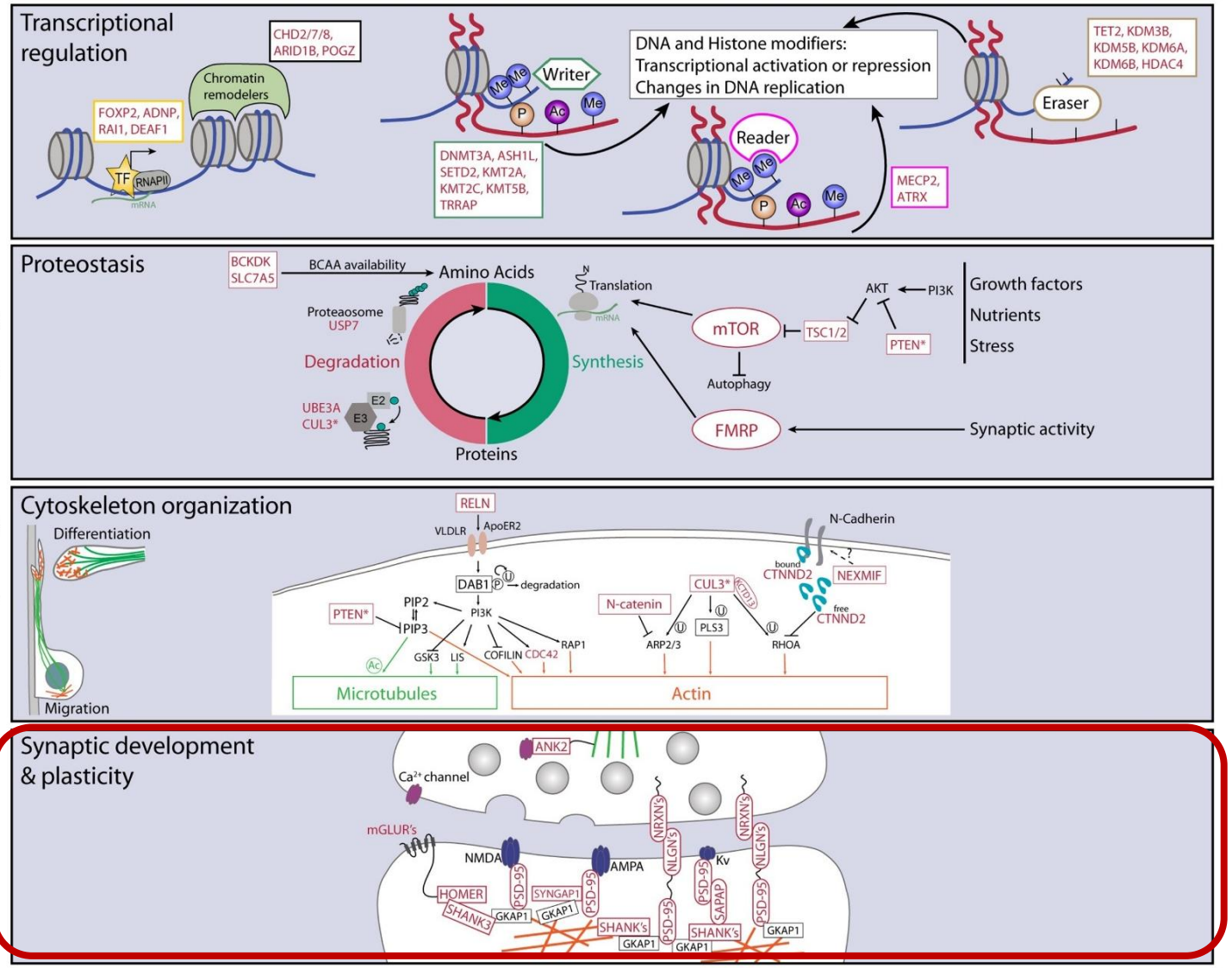
The homeostasis of these processes can be altered during neurogenesis, neuronal migration and differentiation [cf. (A)], which occur in the embryonic brain, or during synaptic maturation and the emergence of excitation/inhibition balance in the postnatal period [cf. (B)].



(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.

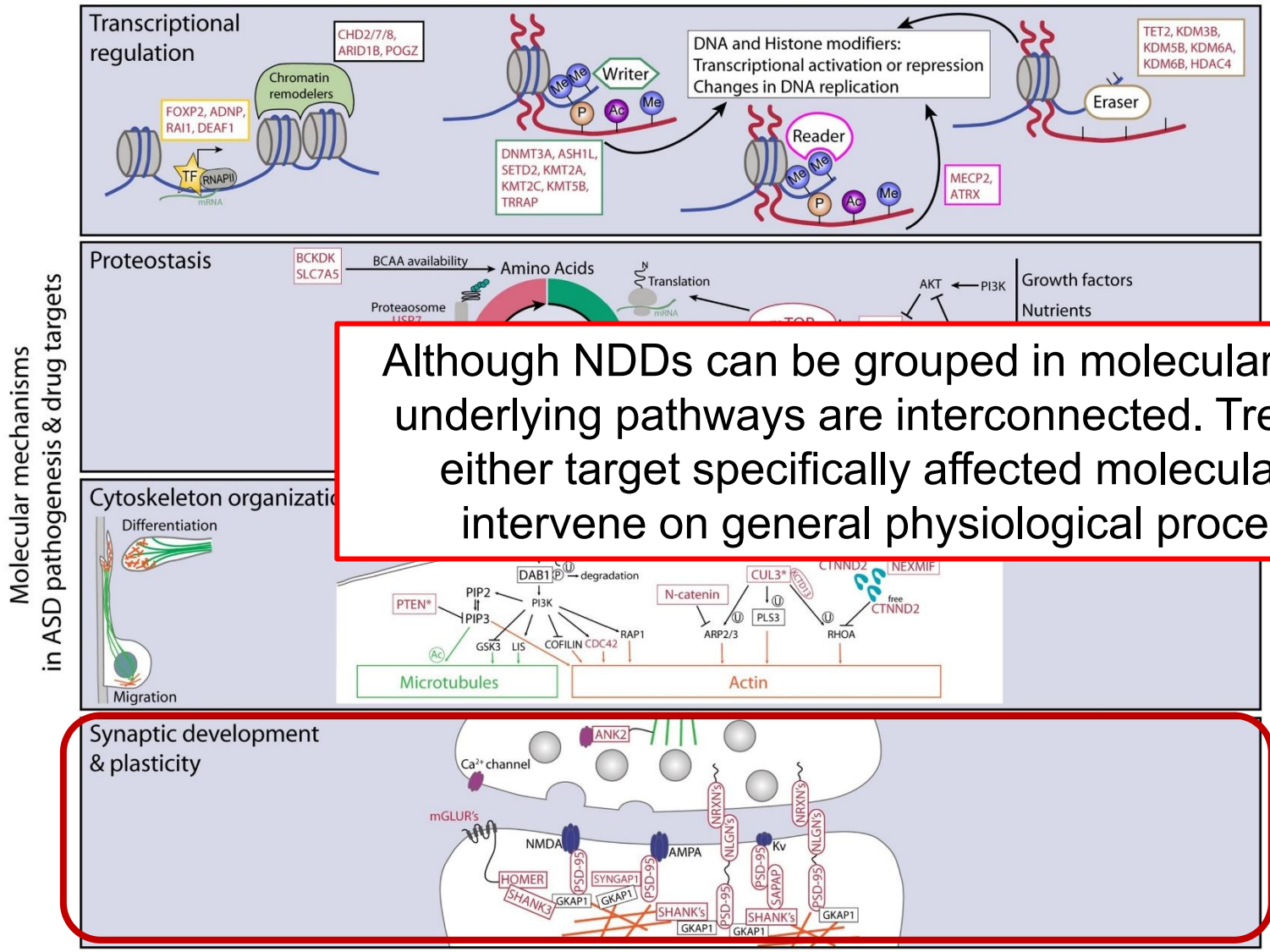
Protein homeostasis is regulated by the interplay of protein synthesis and degradation. Protein abundance is further limited by the availability of amino acids, such as the branched chain amino acids

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).

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 abundance is
mino acids, such as

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

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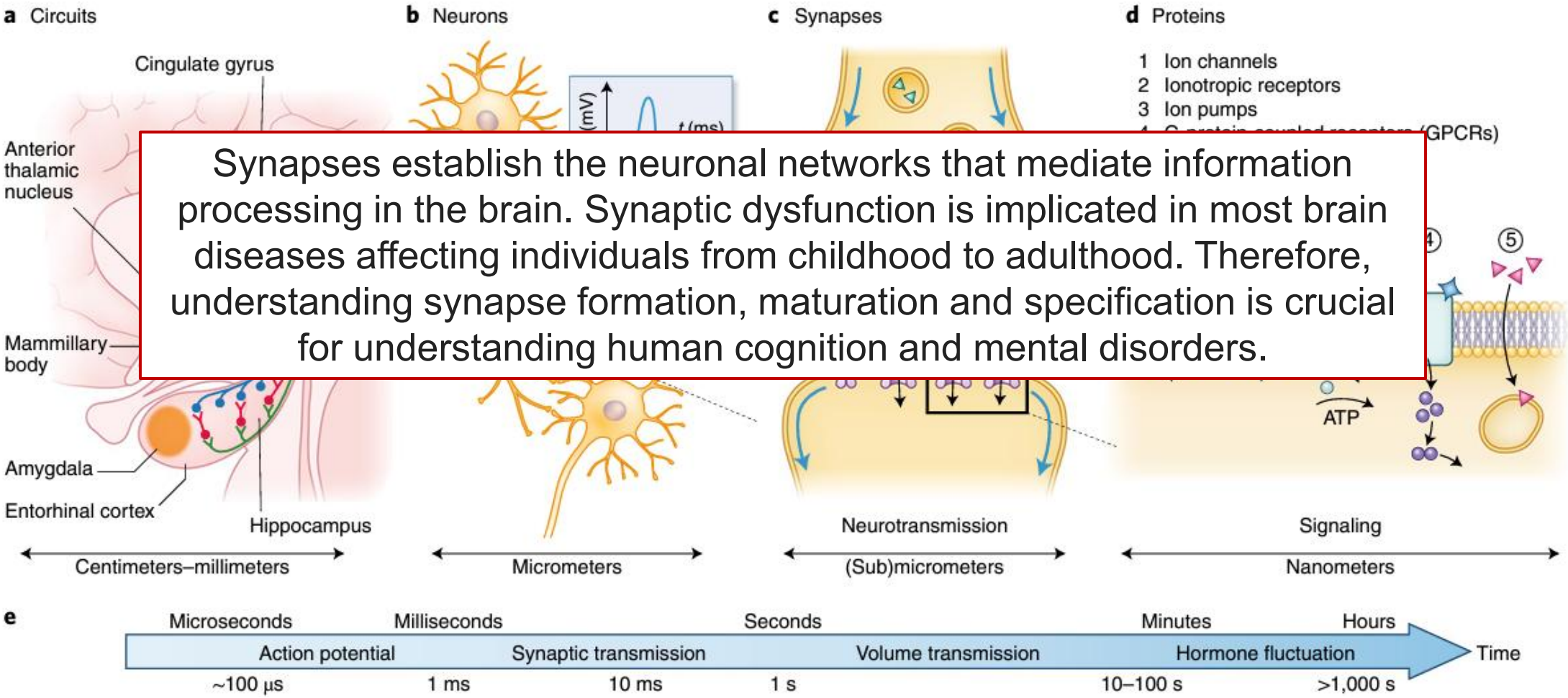
(Basilico et al 2020)

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



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.

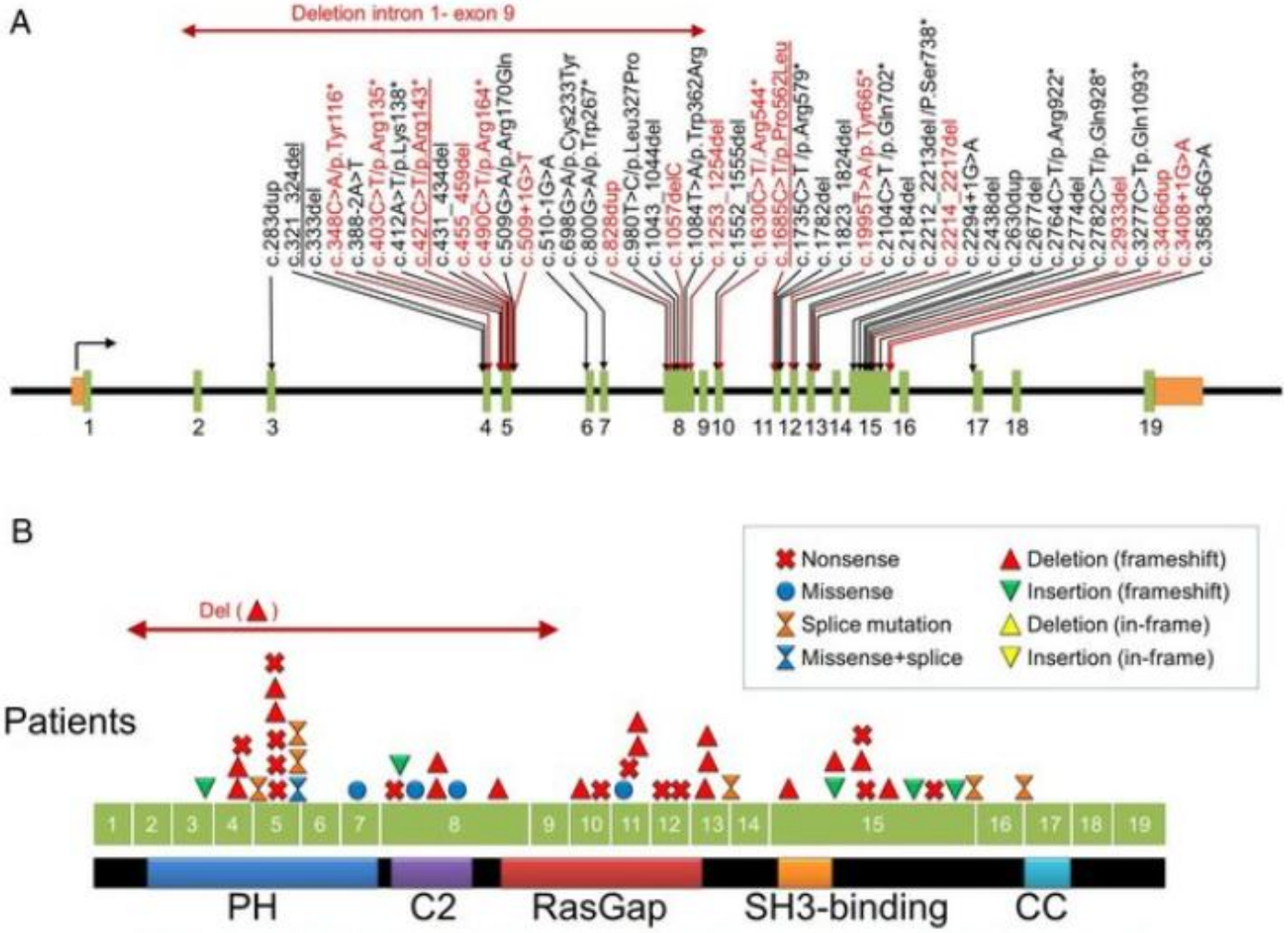
(Frank et al 2019)

SYNGAP1 – Genetics

SFARI GENE SCORE 1S

High Confidence, Syndromic

Criteria 1.1, Syndromic



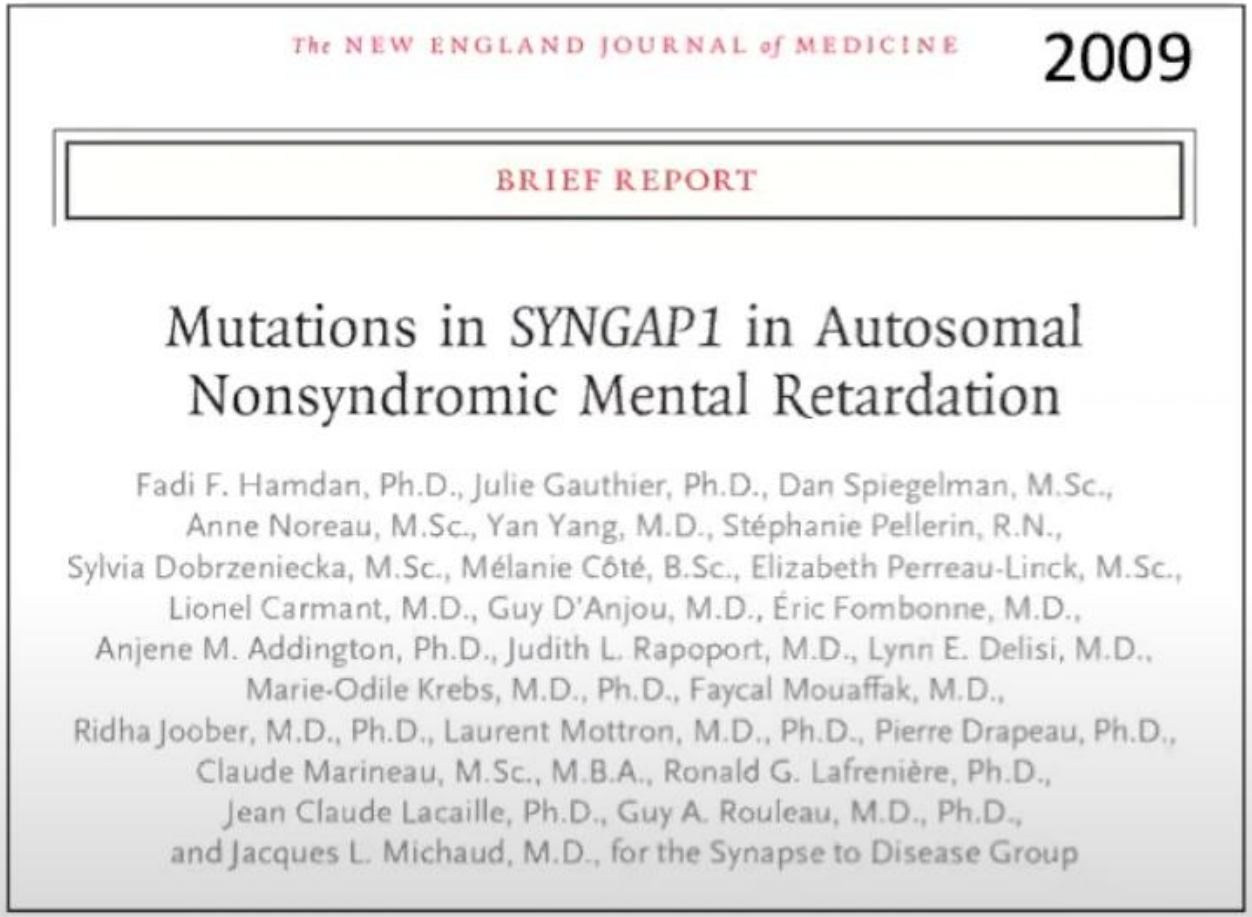
SYNGAP1-Related Disorders is a rare genetic condition caused by a variant on the *SYNGAP1* gene (6p.21.32)

Mutations in *SYNGAP1*:

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

(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

A distinctive generalized developmental and epileptic encephalopathy

Danique R.M. Vlaskamp, MD, Benjamin J. Shaw, MD, Rosemary Burgess, PhD, Davide Mei, MSc, Martino Montomoli, MD, Han Xie, PhD, Candace T. Myers, PhD, Mark F. Bennett, PhD, Wenshu XiangWei, BSc, Danielle Williams, BappSc, Saskia M. Maas, MD, Alice S. Brooks, MD, Grazia M.S. Mancini, MD, PhD, Ingrid M.B.H. van de Laar, MD, Johanna M. van Hagen, MD, PhD, Tyson L. Ware, FRACP, Richard I. Webster, MBBS, MSc, FRACP, Stephen Malone, FRACP, Samuel F. Berkovic, MD, FRS, Renate M. Kalnins, MBBS, Federico Sicca, MD, G. Christoph Korenke, MD, PhD, Conny M.A. van Ravenswaaij-Arts, MD, PhD, Michael S. Hildebrand, PhD, Heather C. Mefford, MD, PhD, Yuwu Jiang, MD, PhD, Renzo Guerrini, MD, FRCP, and Ingrid E. Scheffer, MBBS, PhD, FRACP

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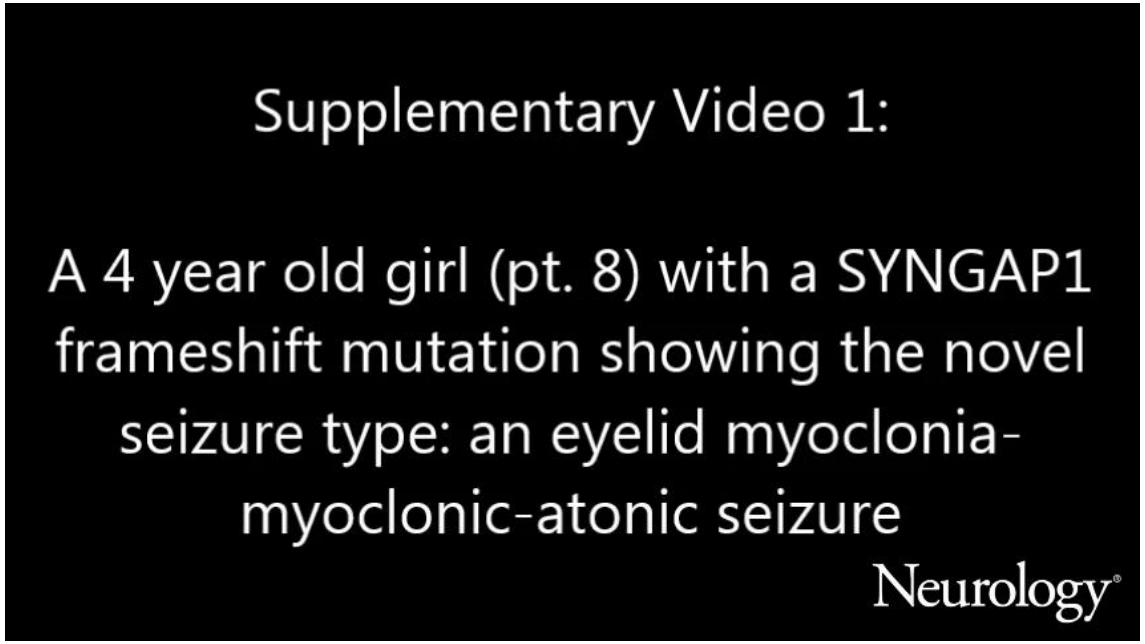
Neurology® 2019;92:e96-e107. doi:10.1212/WNL.0000000000006729

SYNGAP1 mutations cause a **generalized developmental and epileptic encephalopathy (DEE)** with a characteristic syndrome: epilepsy with **eyelid myoclonia with absences** and **myoclonic–atonic seizures**, as well as a tendency to seizures triggered by eating.

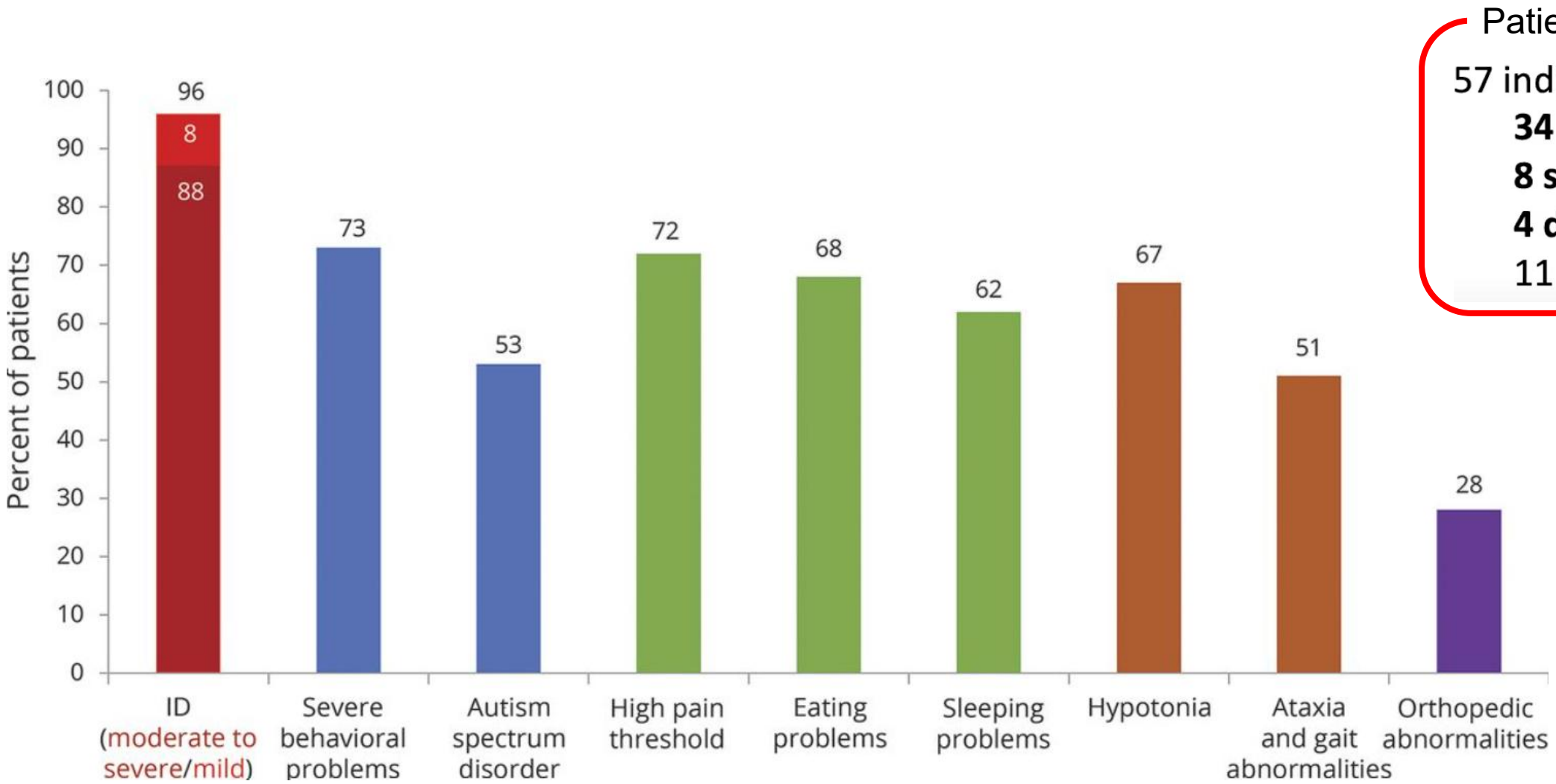
DEE = developmental and epileptic encephalopathies
These are severe epilepsies with seizures that are often drug-resistant, plus encephalopathy (significant developmental delay or loss of skills).

The **developmental impairment** in DEE has **two components**:

- **Developmental encephalopathy:** the delay is due directly to the underlying cause (e.g. genetic).
- **Epileptic encephalopathy:** in some children, very frequent seizures and a markedly abnormal EEG further worsen development.



SYNGAP1 encephalopathy is associated with a spectrum of comorbid conditions



Patient cohort

57 individuals

34 truncating

8 splice site

4 deletions

11 missense

(Vlaskamp et al 2019)

Dismorphic features associated with *SYNGAP1* mutations

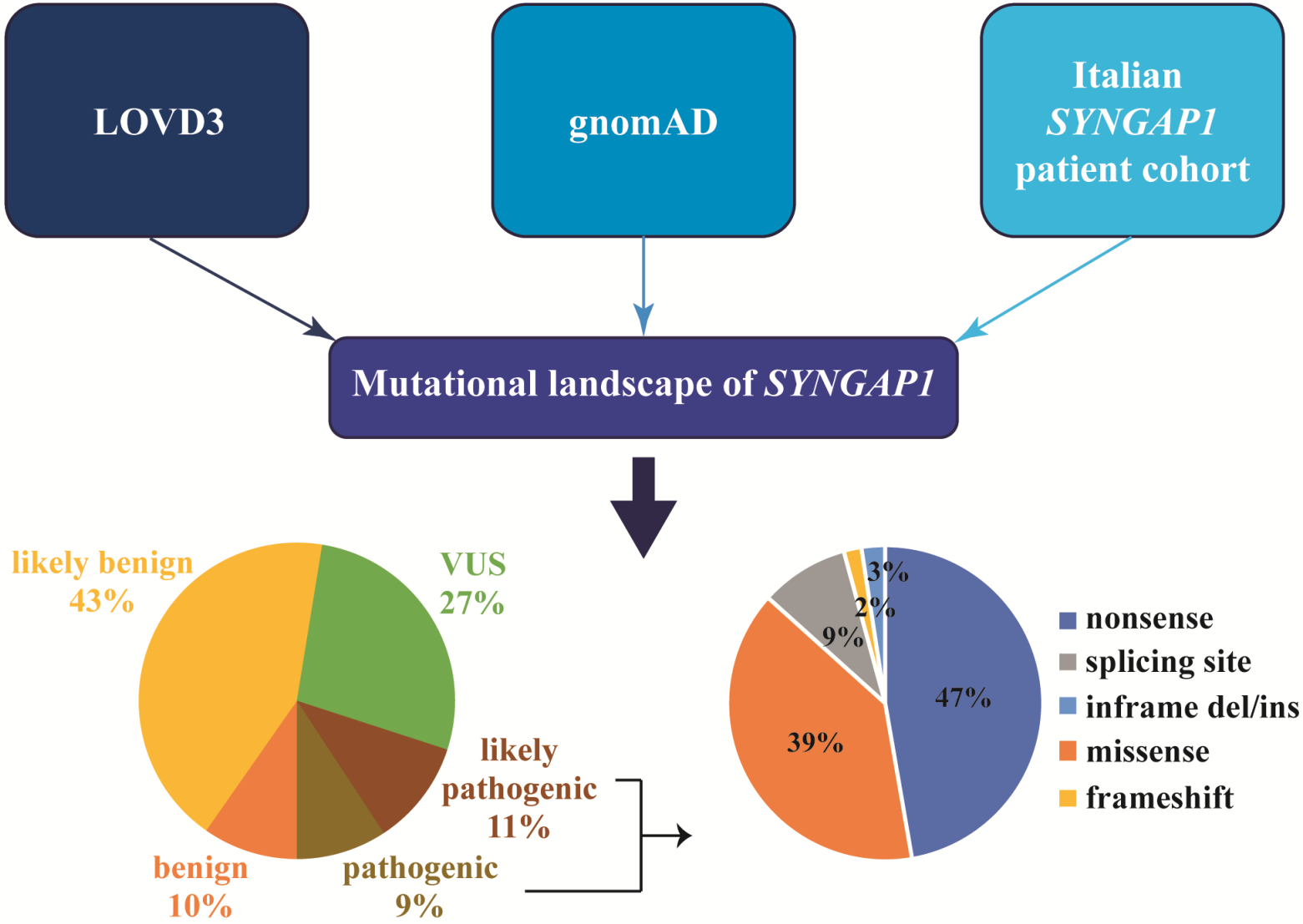
Mild dysmorphic features, not present in all patients.

These include:

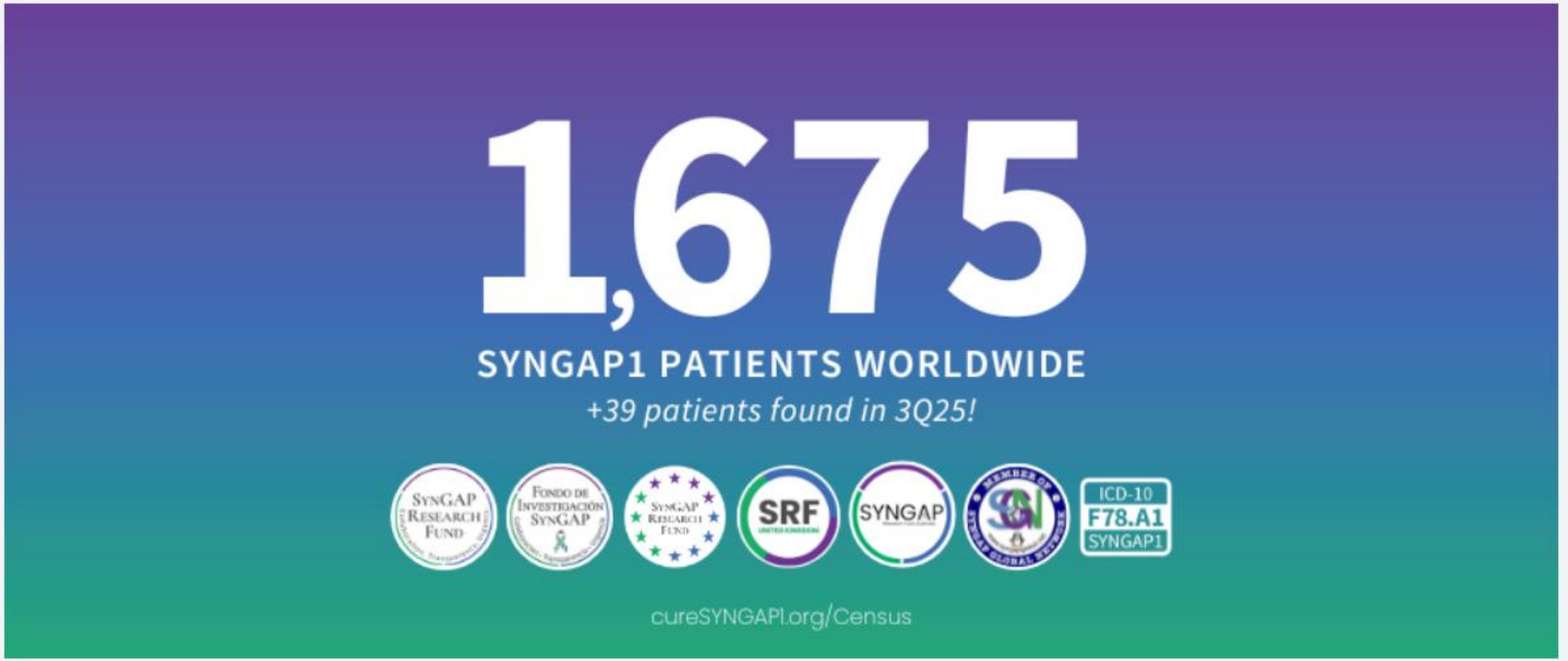
- thick and slightly prominent eyebrows, with a medial curvature in some cases;
- hypertelorism;
- a full nasal tip, slightly upturned in younger children;
- a “heart-shaped” upper lip (Cupid’s bow);
- a wide mouth with gaps (diastema) between the upper incisors;
- a small, pointed chin.

(Vlaskamp et al 2019)

SYNGAP1 – Genetics

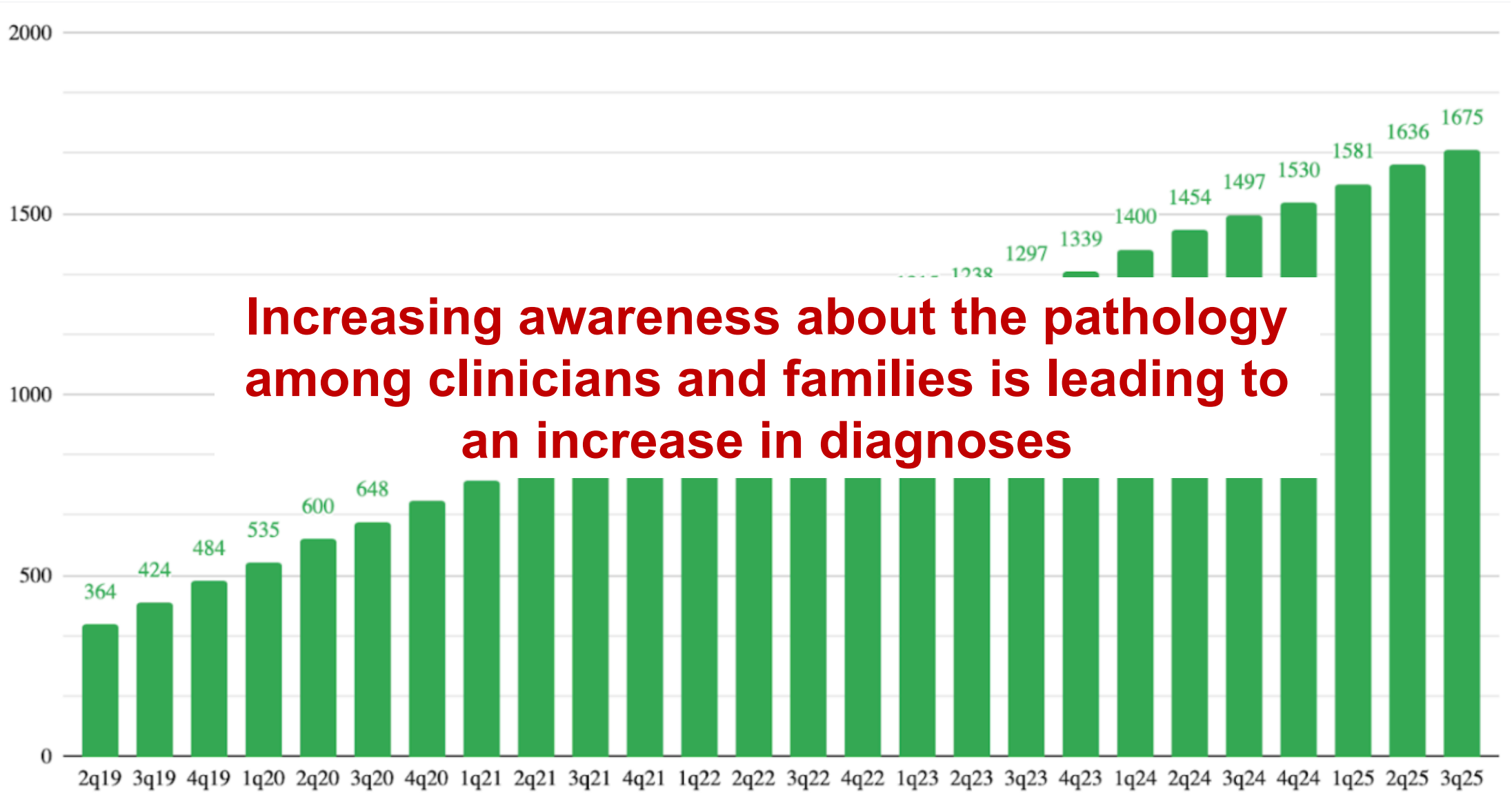


How Many People Have SYNGAP1?



Source: SYNGAP1 Census 2025

Known *SYNGAP1* patients worldwide



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

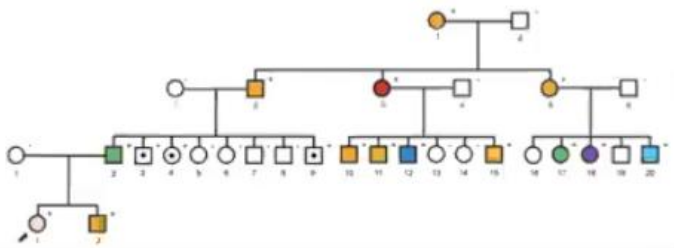
Source: SYNGAP1 Census 2025

Why genetics is important?

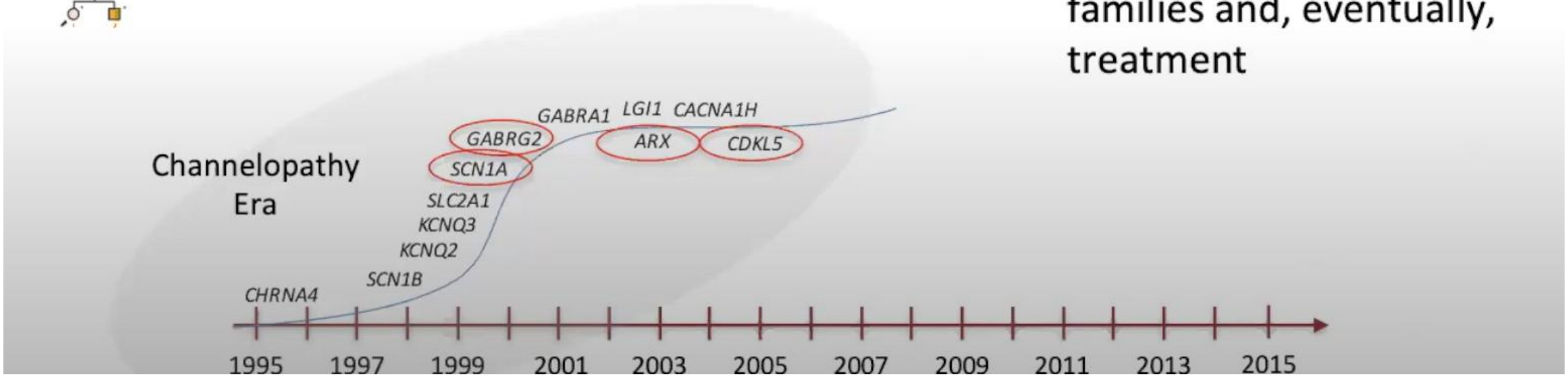
Knowing the genetic diagnosis….

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

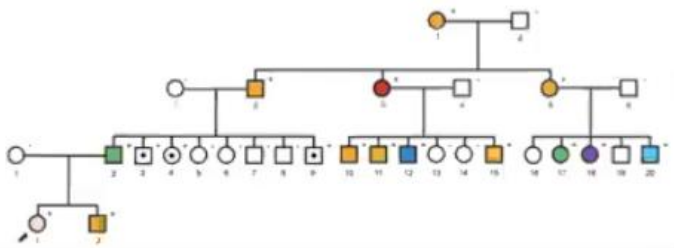
Genetic diagnosis (Epilepsy genes)



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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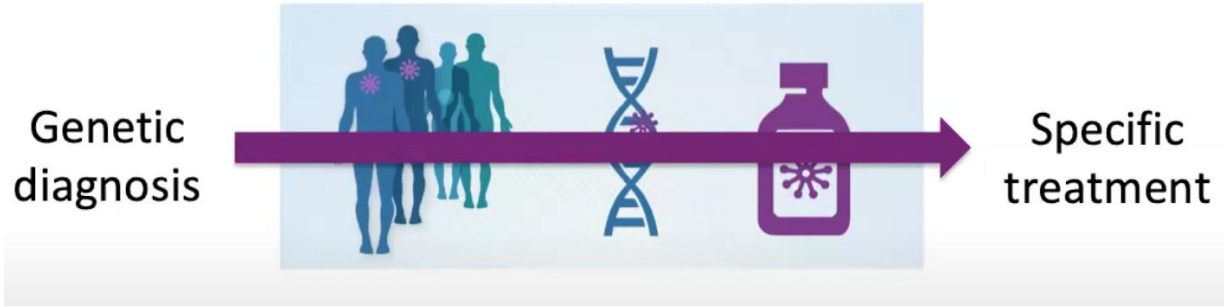
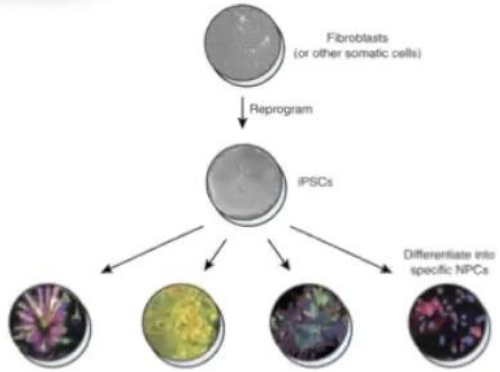
Why genetics is important?
From diagnosis to treatment



- 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

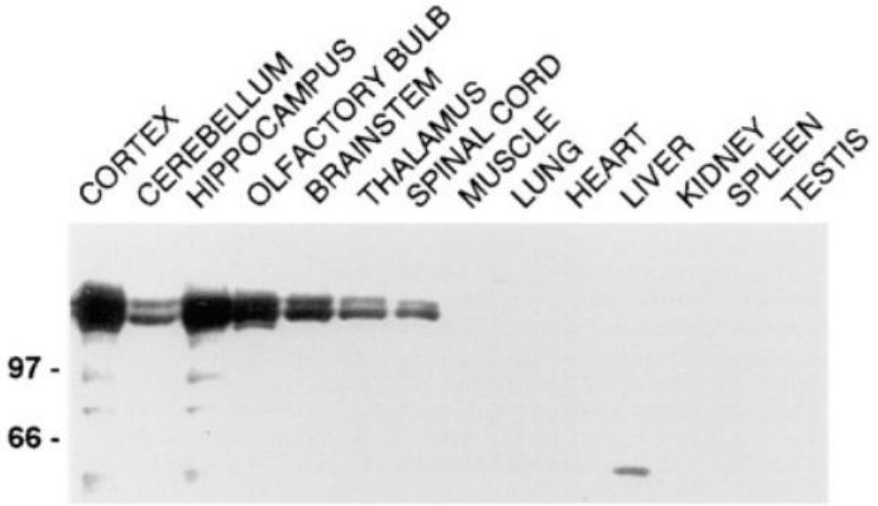
Article

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

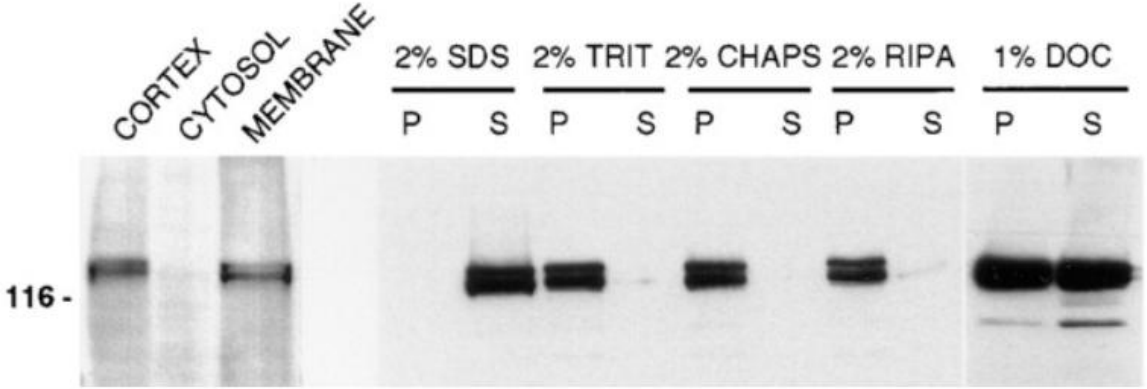
Jee Hae Kim [1], Dezhi Liao [1], Lit-Fui Lau [1], Richard L Huganir [1] *

SYNGAP1 discovery – Huganir lab

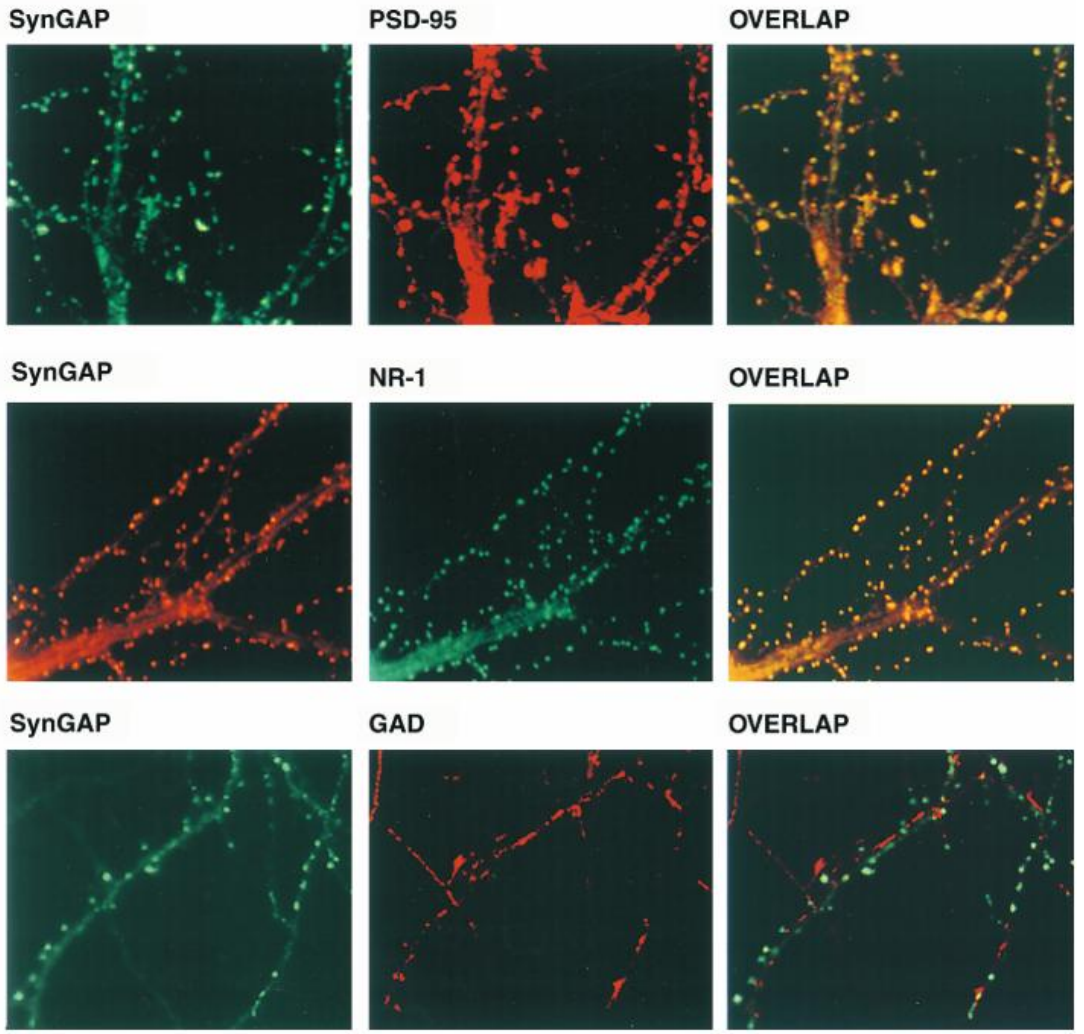
Brain-Specific Expression of SynGAP



SynGAP is localized to membrane fractions



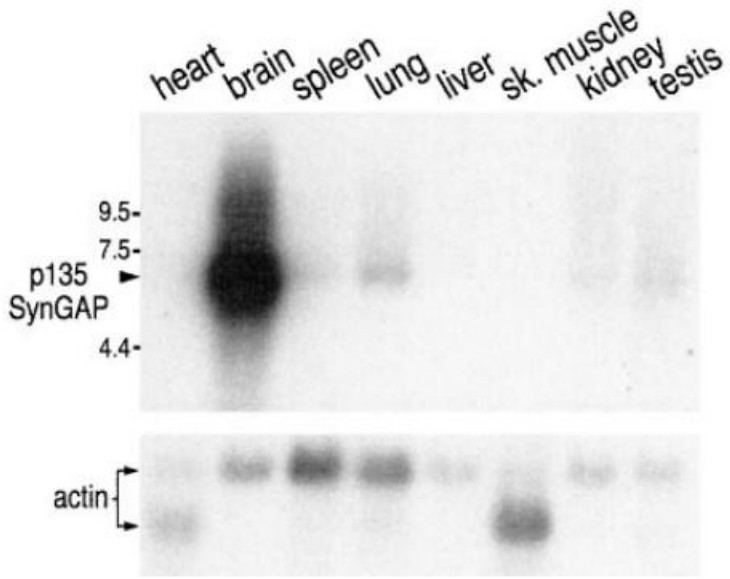
SynGAP is specifically localized at excitatory synapses



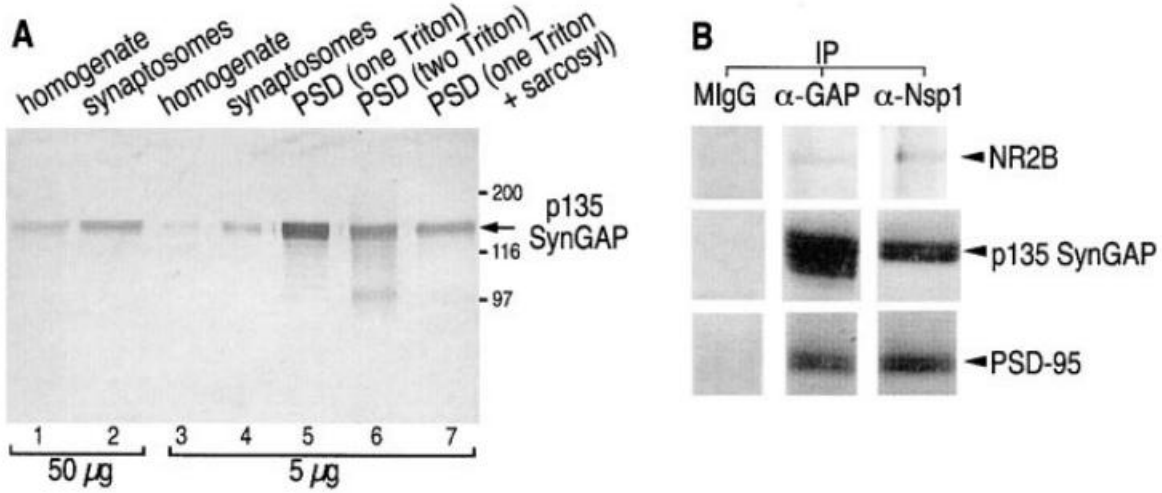
(Kim et al 1998)

SYNGAP1 discovery – Kennedy lab

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

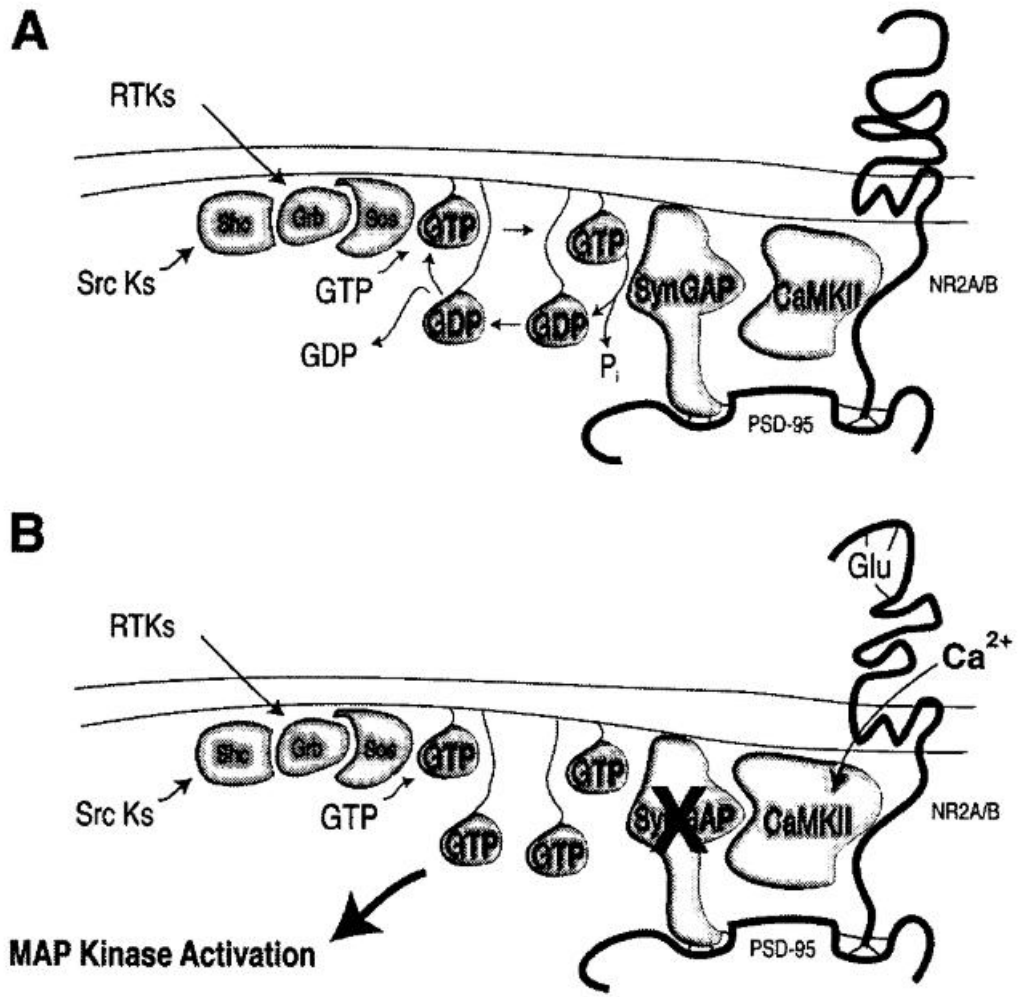


It constitutes 1%–2% of total protein in isolated PSDs and is rapidly phosphorylated upon activation of CaMKII in the PSD.



(Chen et al 1998)

SYNGAP1 discovery – Kennedy lab



Hypothesized Effects of Regulation of p135 SynGAP by NMDA-Receptor Activation at Glutamatergic Synapses.

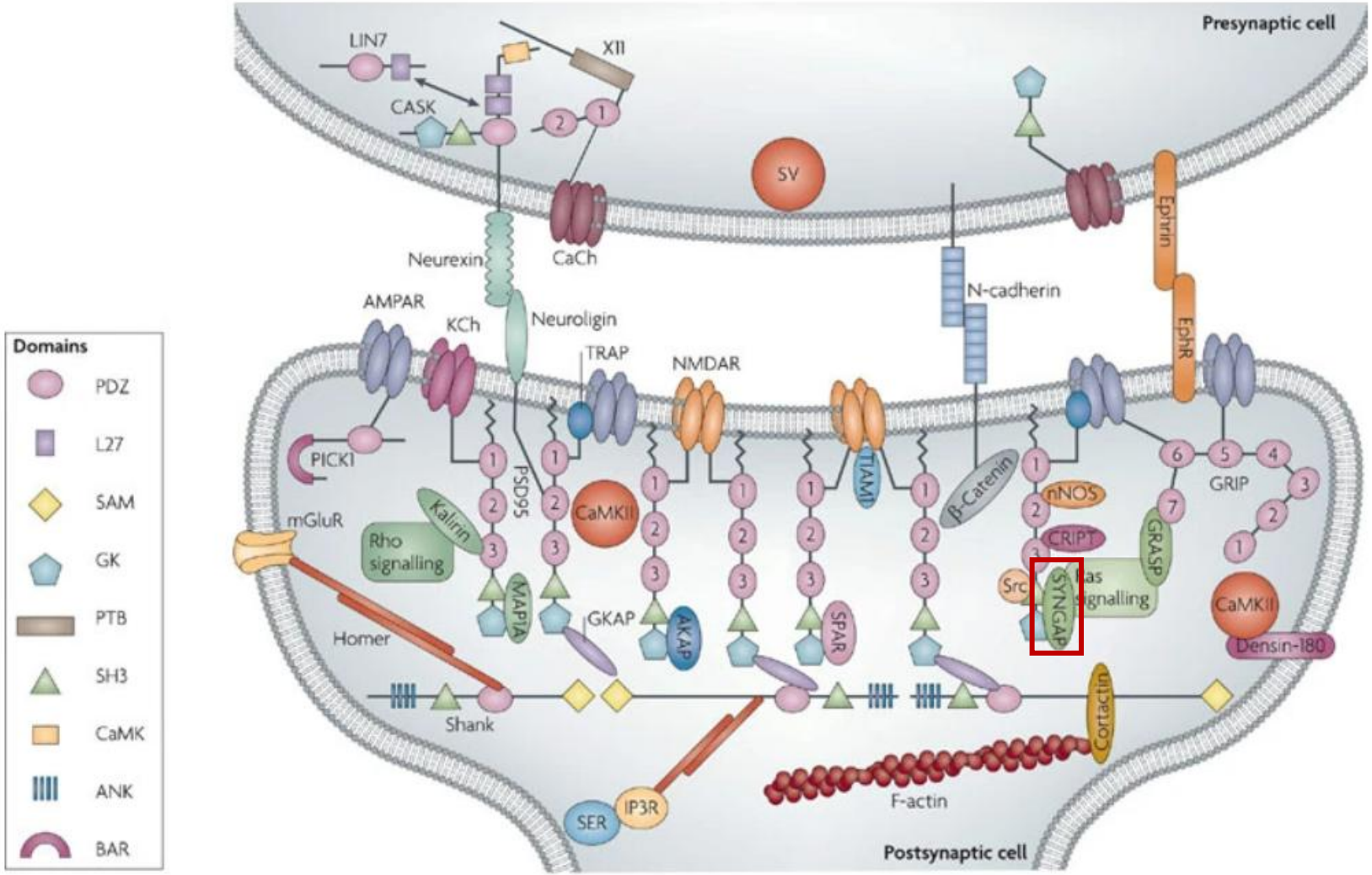
Active p135 SynGAP at postsynaptic densities will keep the steady-state level of active Ras low near the synapse by catalyzing rapid hydrolysis of Ras-GTP to Ras-GDP.

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



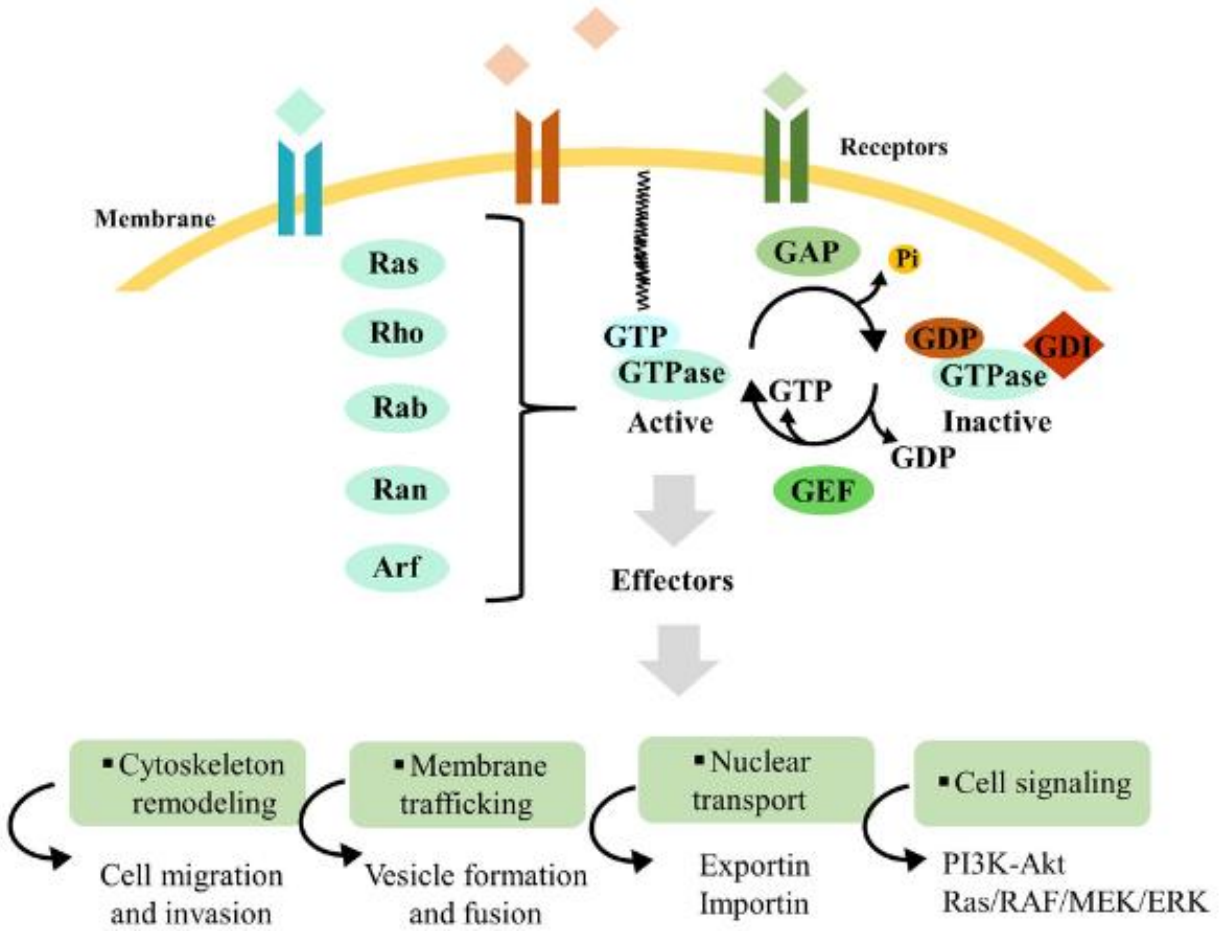
The postsynaptic density is comprised of membrane receptors and ion channels, scaffold and adaptor proteins, signaling proteins, cell-adhesion molecules and components of the cytoskeleton.

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)

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)

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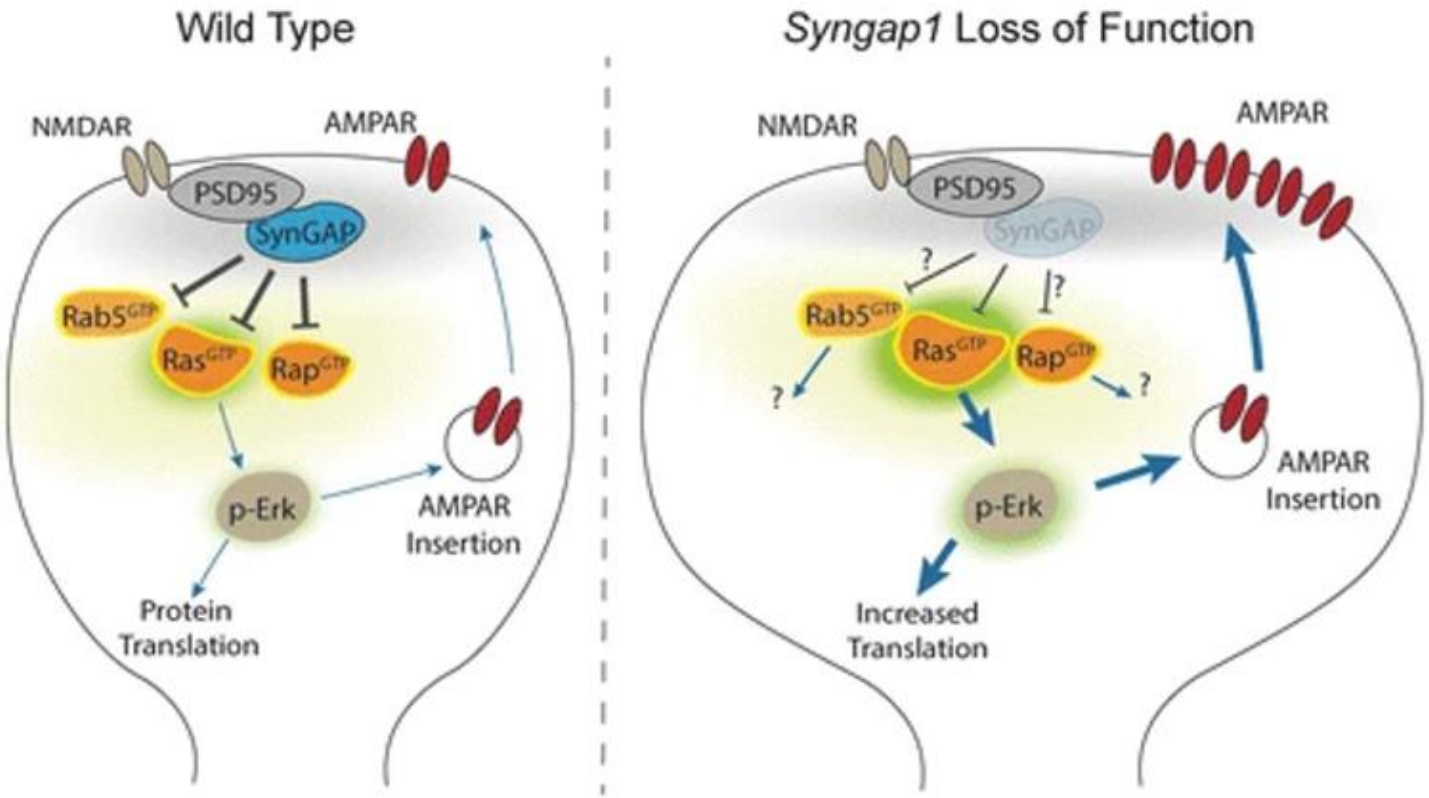
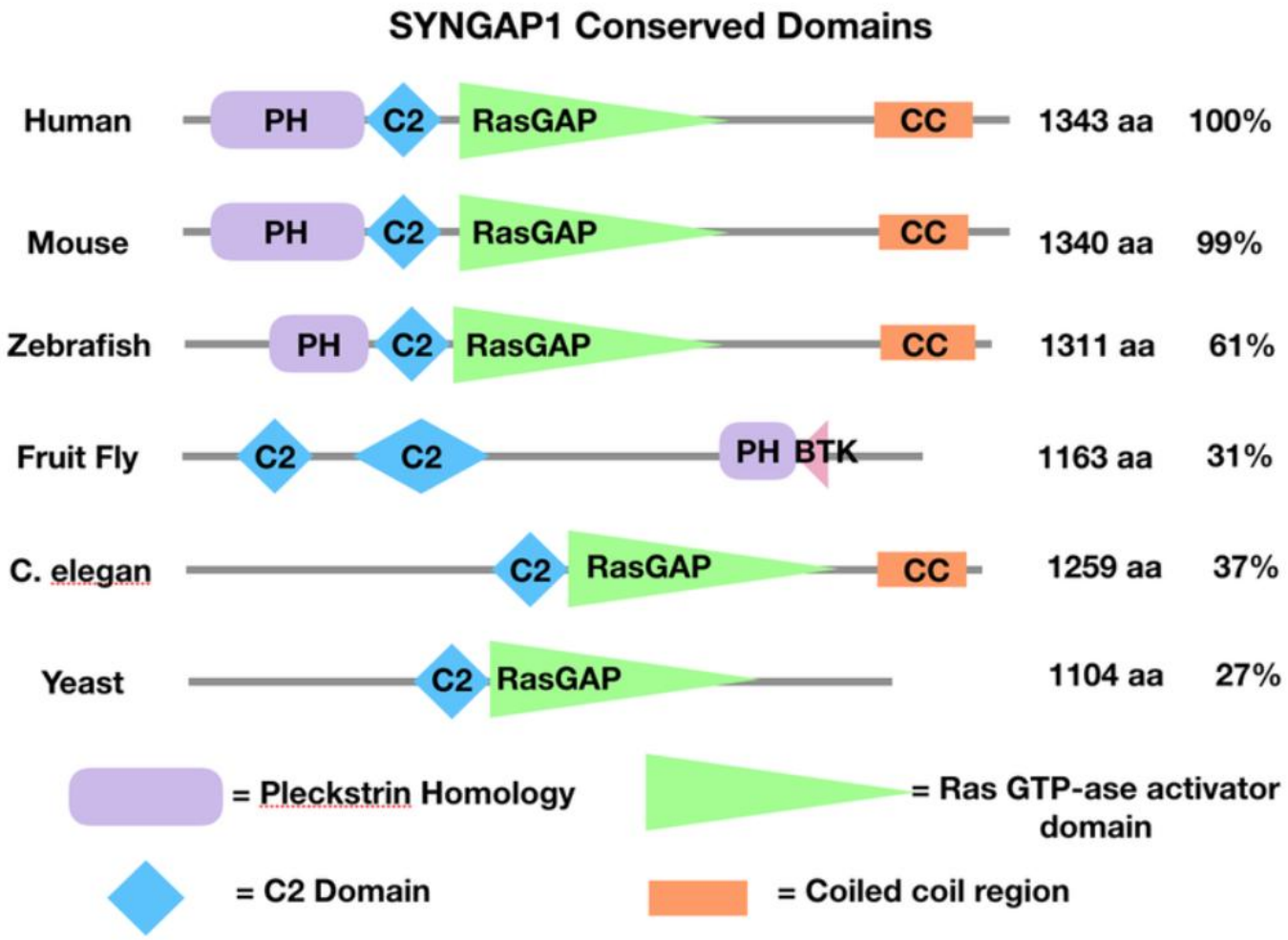


- Influence on PSD composition
- Negative regulator of AMPAR trafficking
- Premature maturation of dendritic spines
- Negative regulator of synaptic plasticity
- Excitation/inhibition imbalance
- Cognitive deficits

(Weldon et al 2018; Brito et al 2020)

The SynGAP protein: today



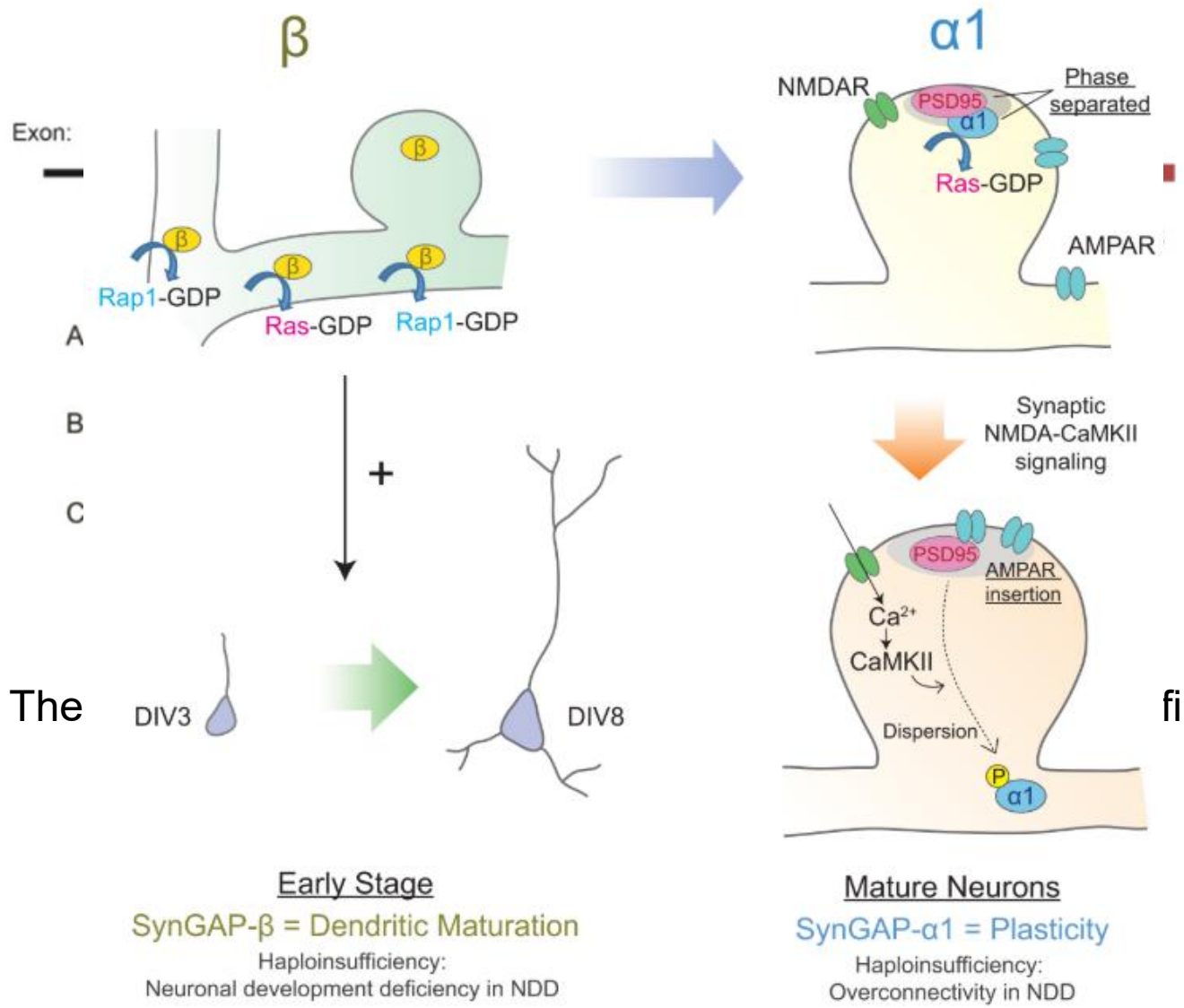
PH → recruiting proteins to different membranes/compartments; binding of inositol phosphates, and various proteins

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

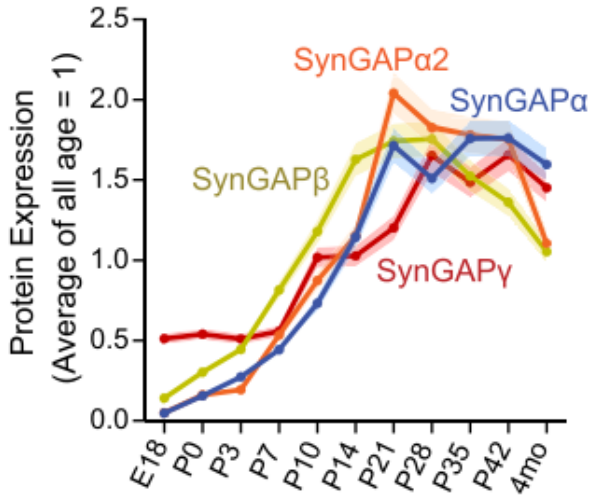
SYNGAP1 alternative splicing and resulting isoforms

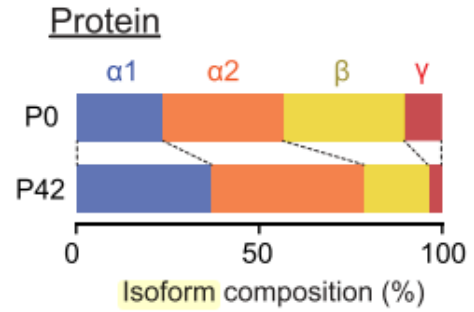


The files

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

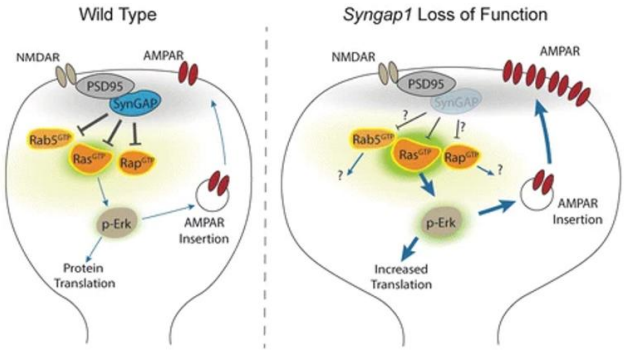
Isoforms expression in mice over time

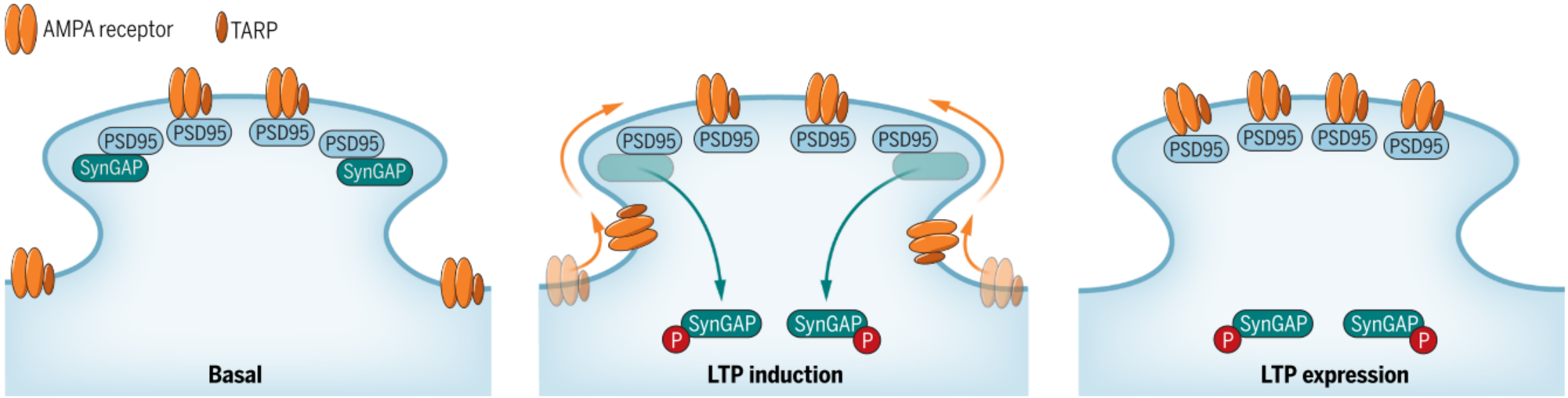




(Kilinc et al 2018; Araki et al 2020)

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

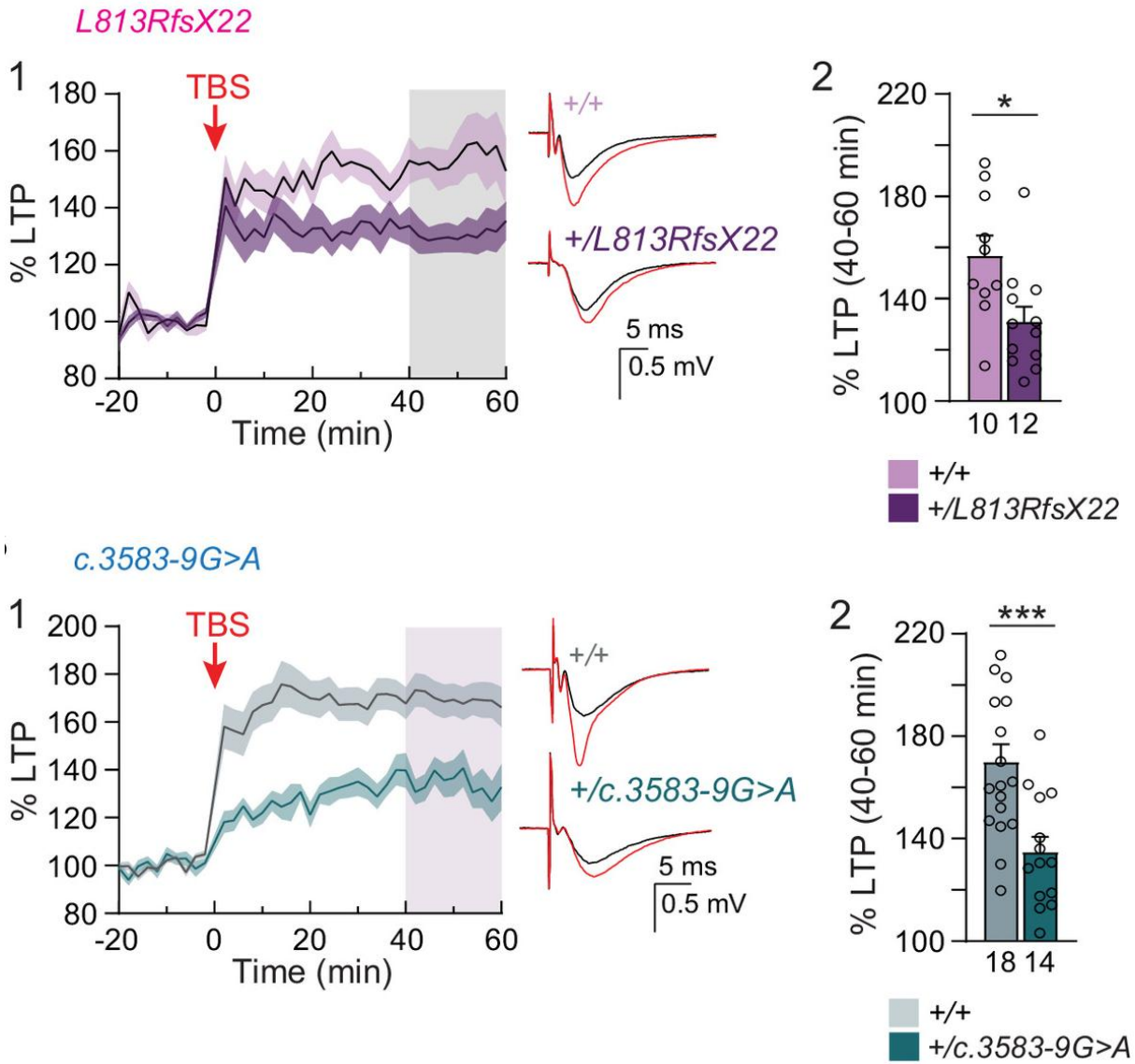




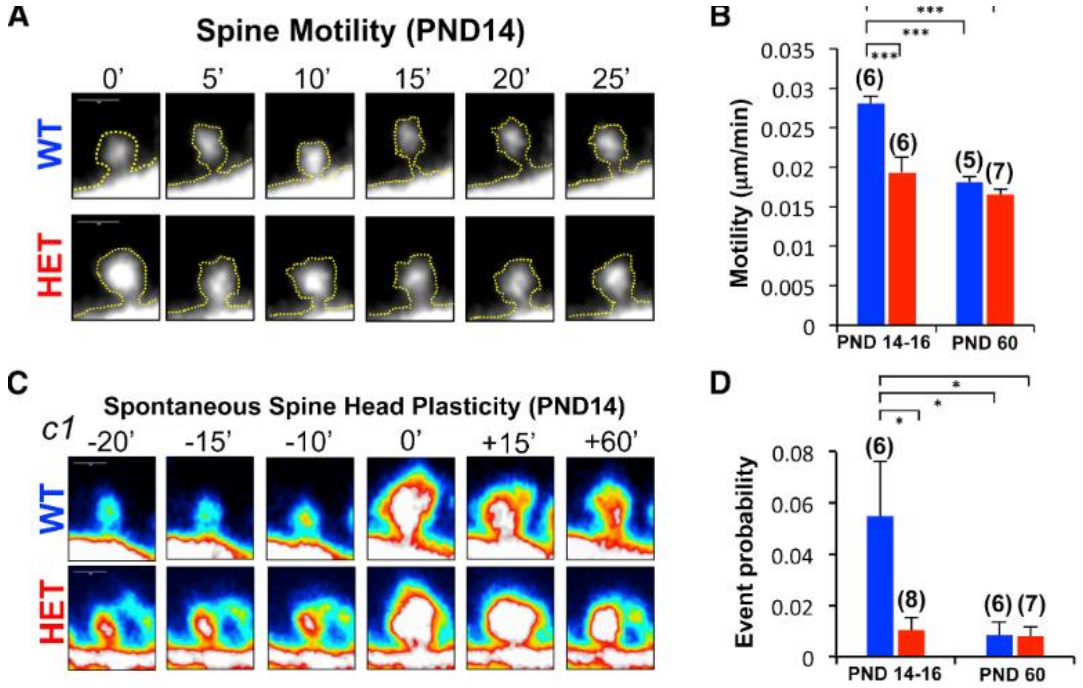
Model of SynGAP regulation of synaptic plasticity. SynGAP regulates synapses by competing with AMPAR-TARP complexes to form LLPS condensates with PSD95. During LTP induction, phosphorylation of SynGAP promotes the dispersal of SynGAP from the synapse and is replaced with AMPAR-TARP complexes, resulting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

(Araki et al 2024)

Defective LTP



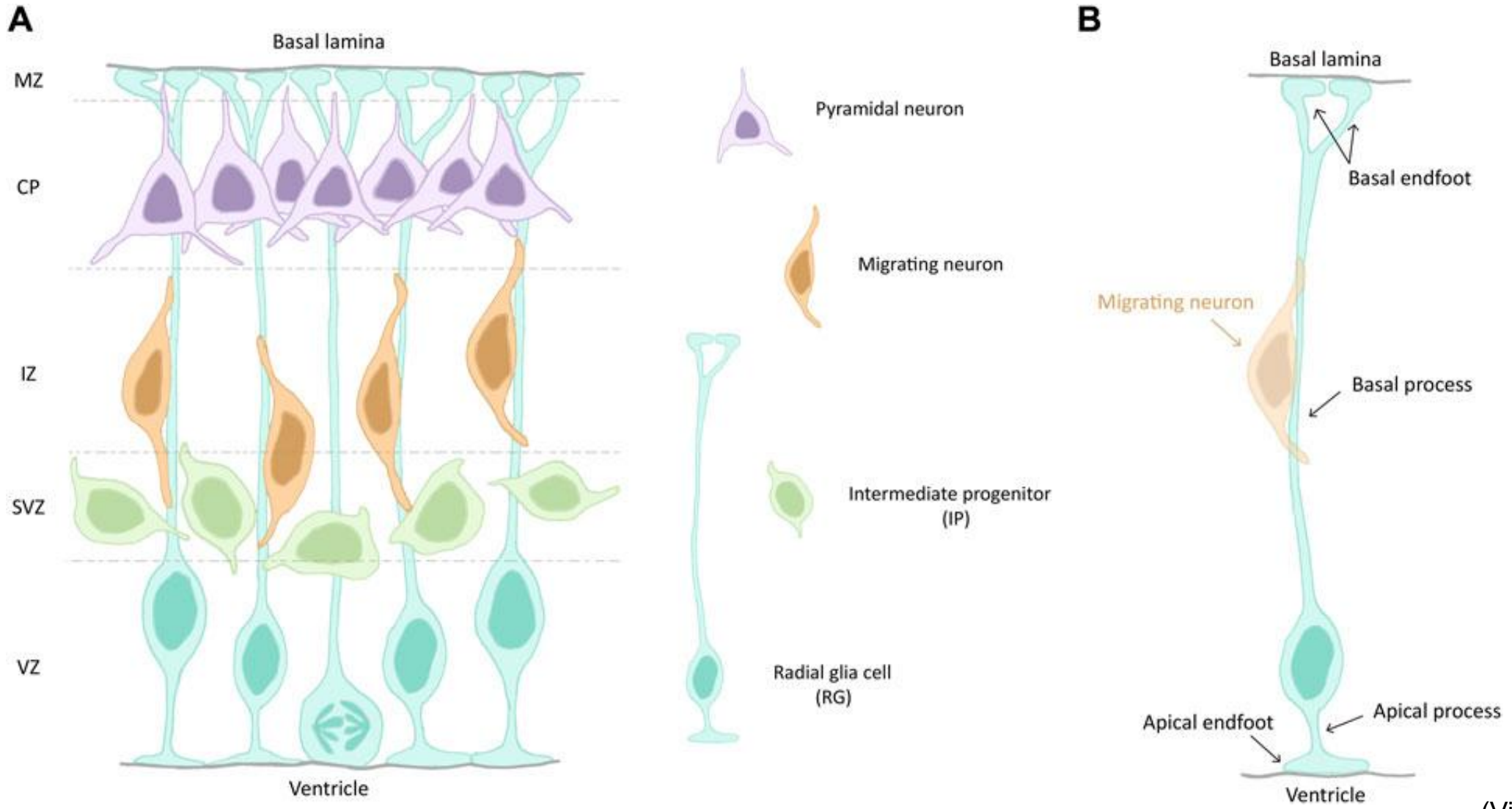
Defective structural plasticity



Thanks to animal studies…
(Clement et al 2012;
Araki et al 2023)

SYNGAP1 – Non-canonical role during brain development

New finding : *SYNGAP1* is expressed already in radial glia progenitors

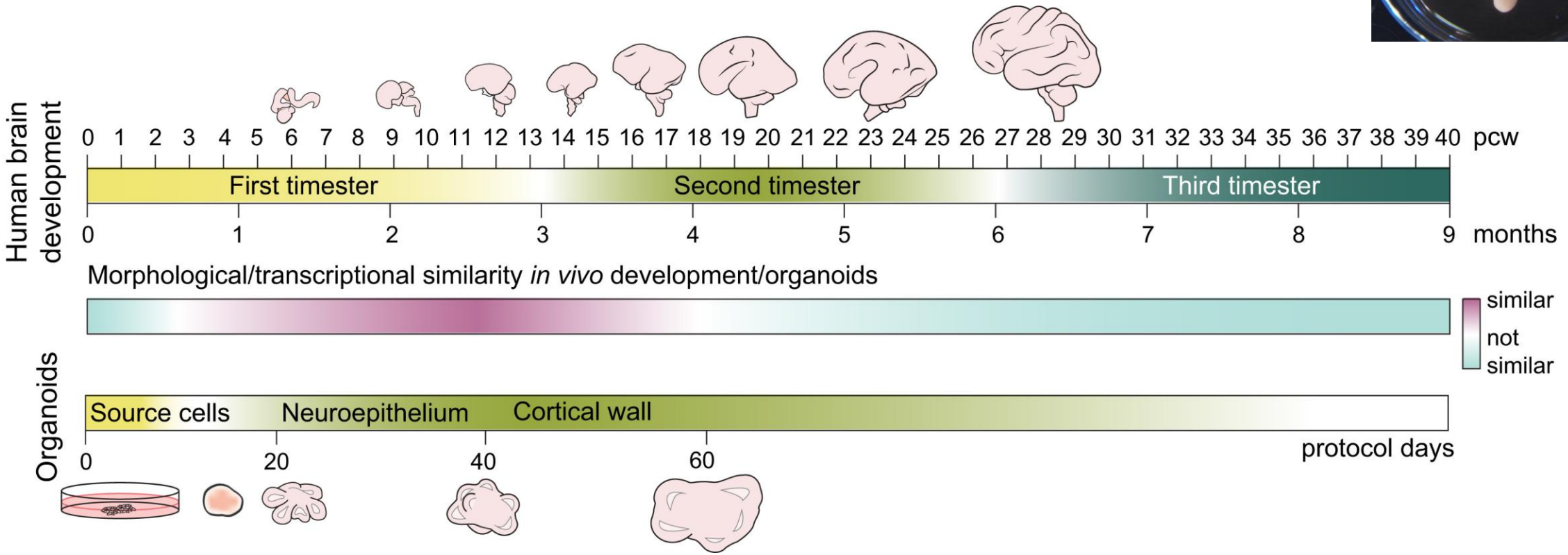


(Viola et al 2024)

Similarities between human brain and organoids development: the concept of mini-brains

Mini-brains in a dish

We are currently able to model early human neocortical development accurately



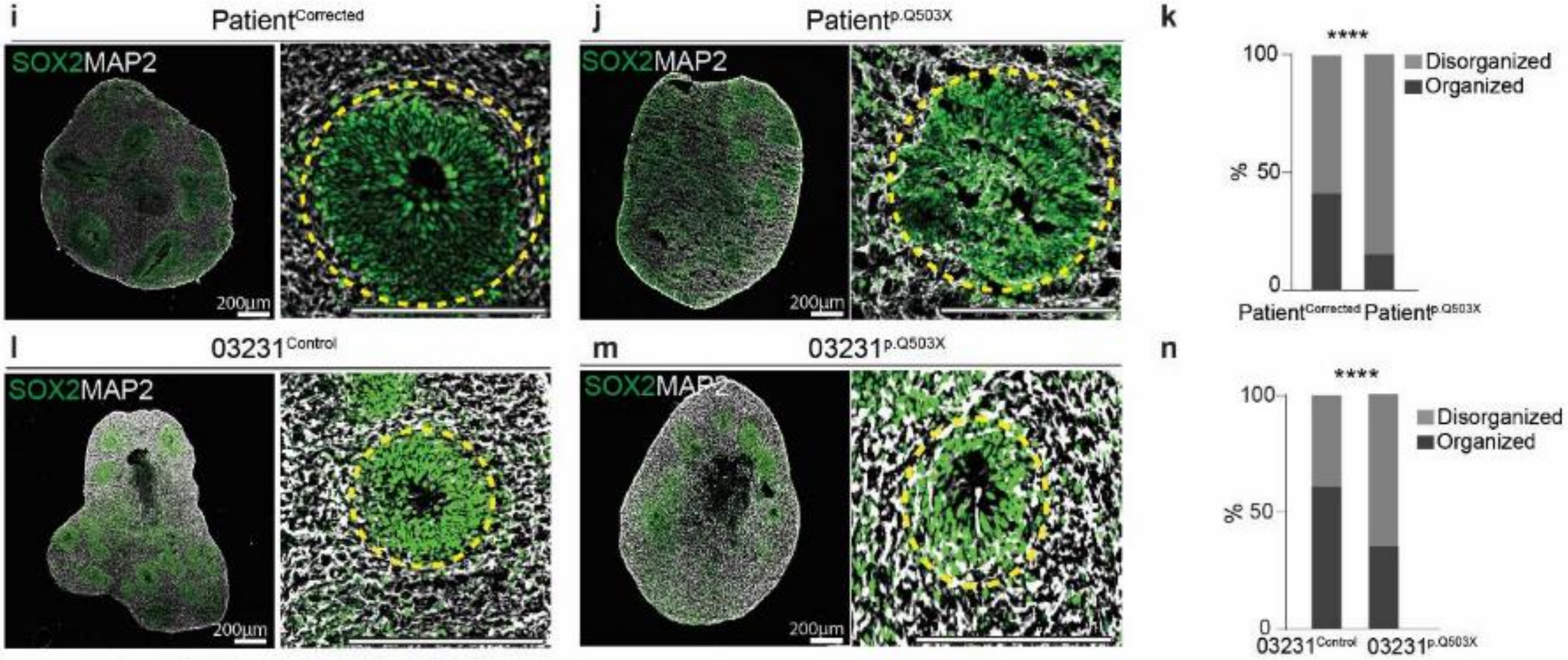
Similarities are based on cell biology and transcriptional (RNA-seq and single-cell RNA-seq) features. However, there are methods' limitations, such as the inability to vascularize the cultures and the possible lack of some intrinsic and extrinsic cues, which are not replicated with the current protocols .

(Kelava and Lancaster, 2016)

SYNGAP1 – Non-canonical role in brain development

New finding : SYNGAP1 is expressed already in radial glia progenitors

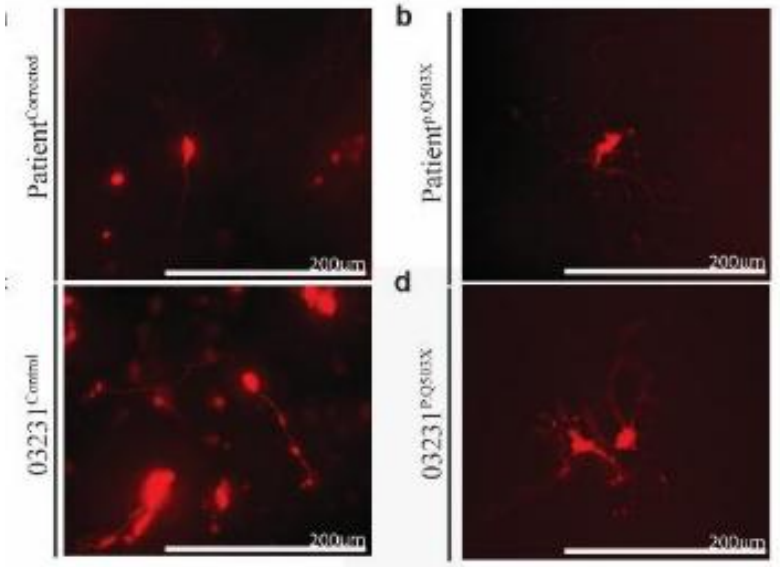
Cortical plate disorganization during development affecting cell division mode

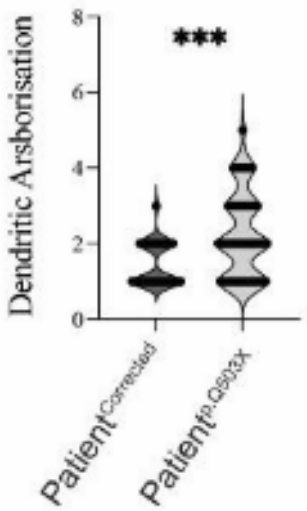


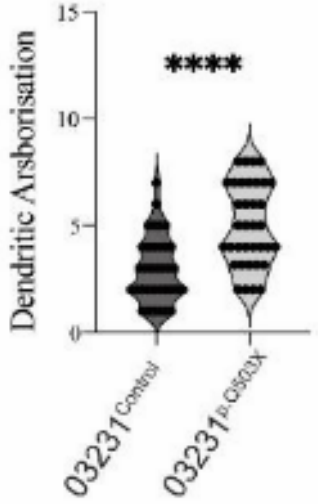
(Birtele et al 2023)

SYNGAP1 – Non-canonical role during brain development

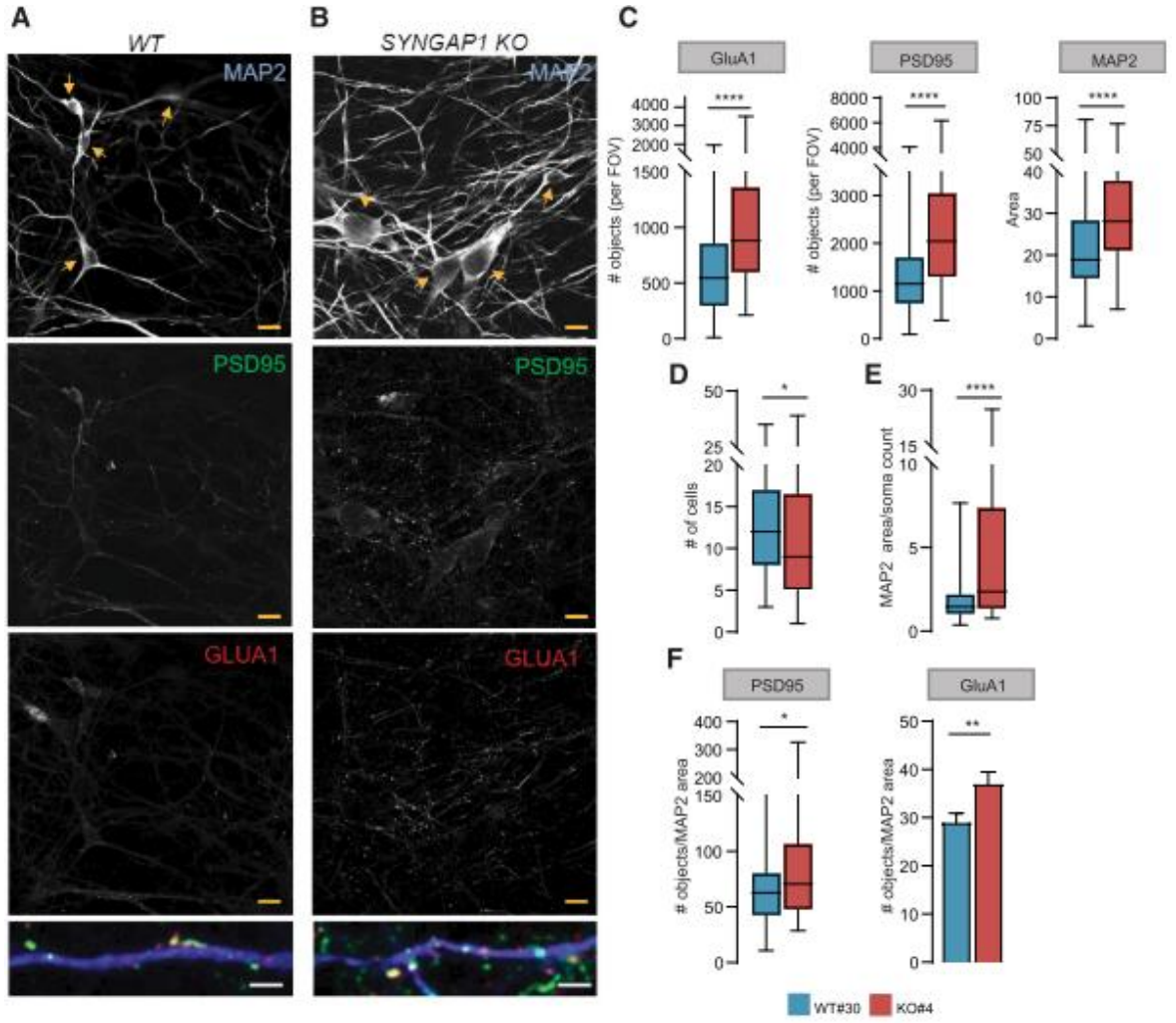
Accelerated maturation of cortical projection neurons and iNeurons







(Birtele et al 2023)



(Llamosas et al 2020)

SYNGAP1 – Non-canonical role in brain development

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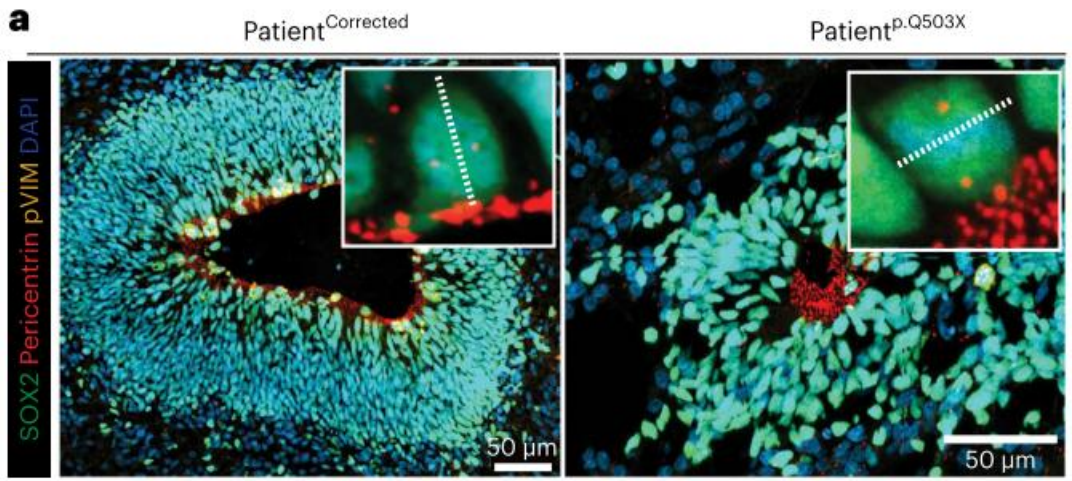

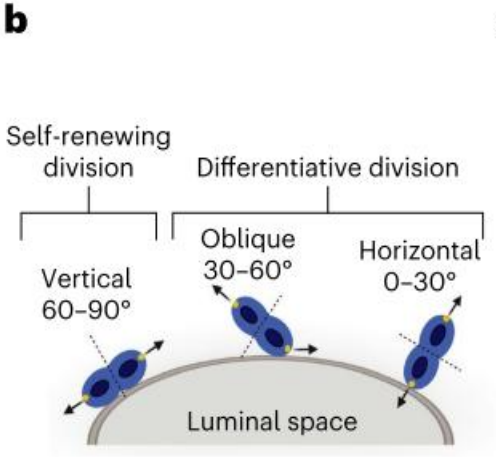

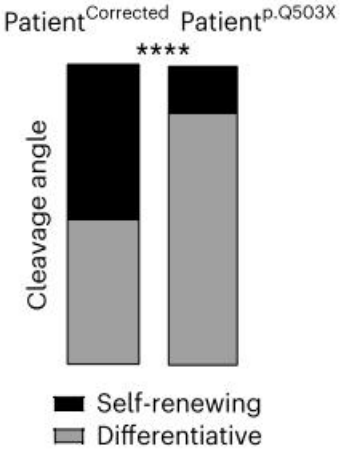

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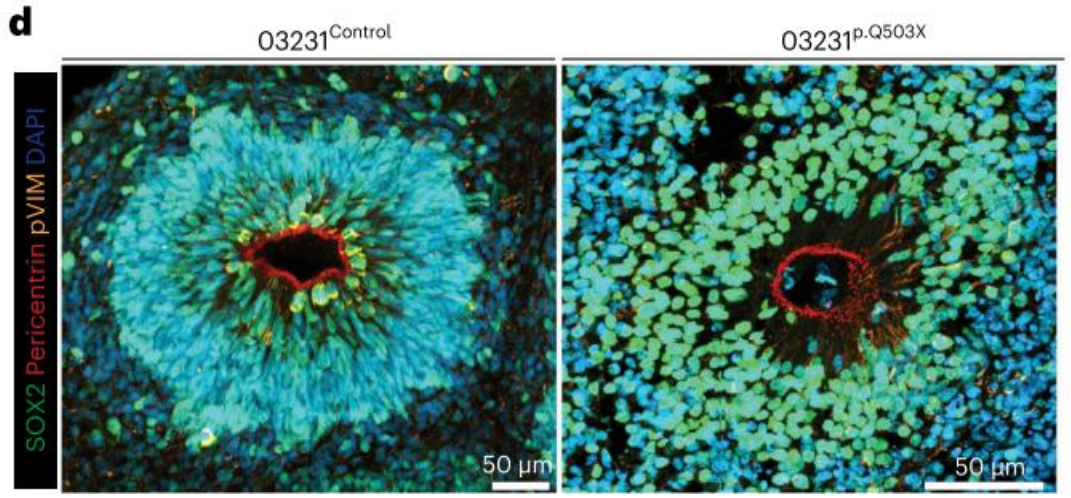
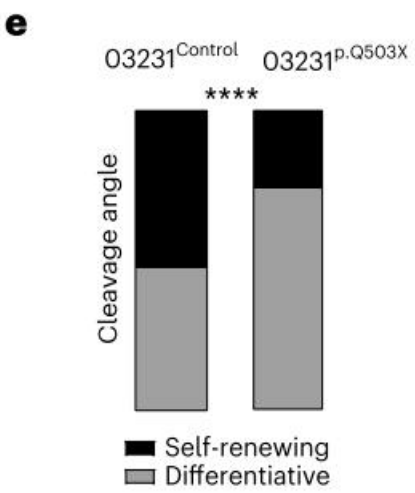


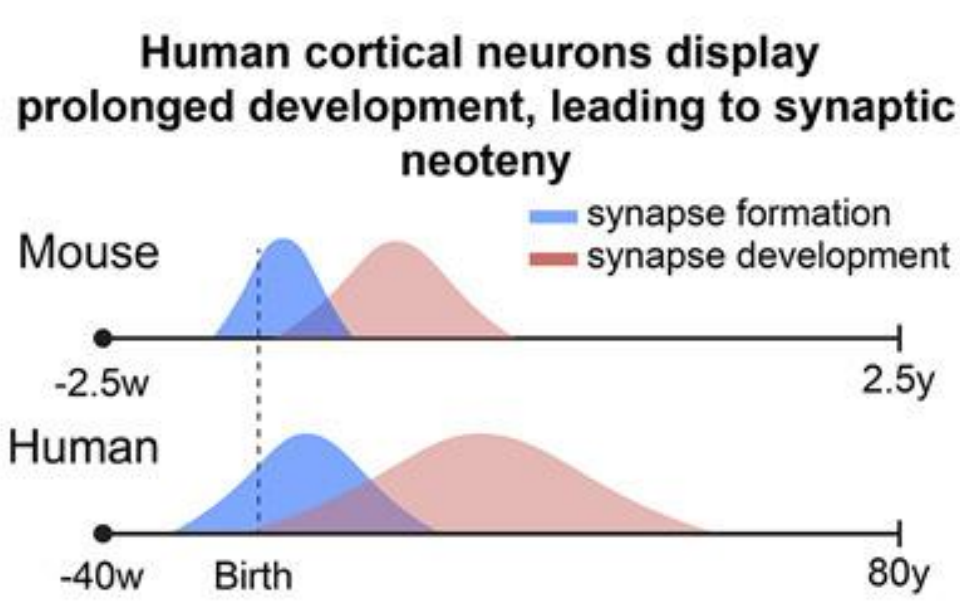


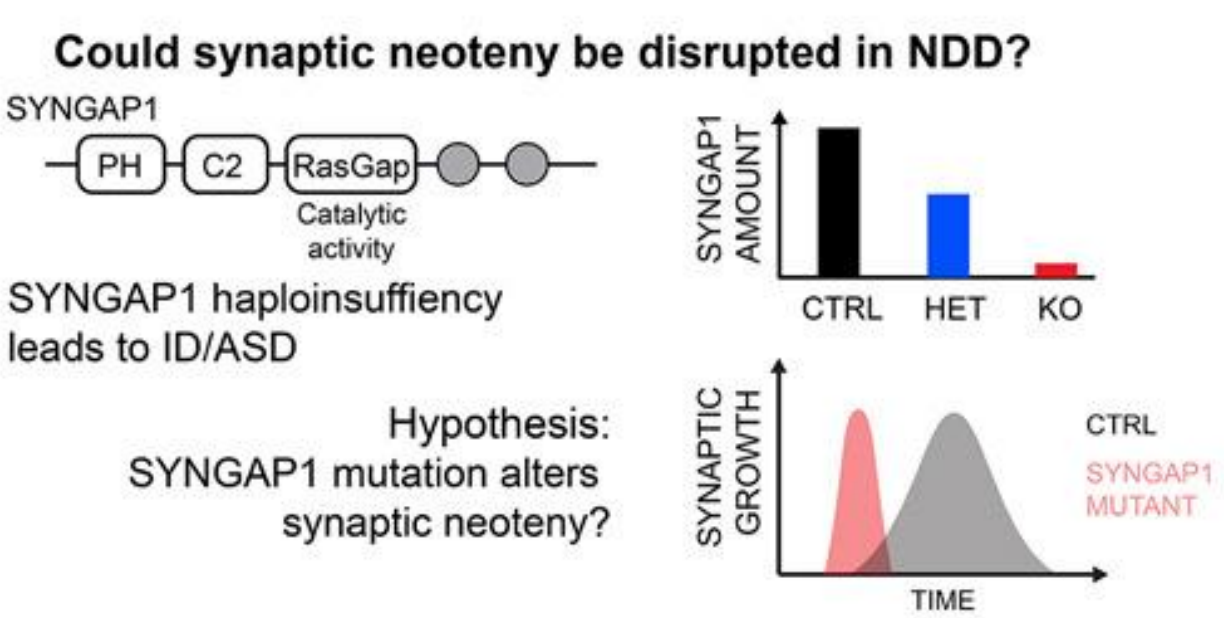
(Birtele et al 2023)

SYNGAP1 – Non-canonical role during brain development

New finding: SYNGAP1 regulates neoteny

"Neoteny" is the retention of the juvenile features in an adult animal/individual. Genetic factors influence the degree of neoteny in individuals.





(Vermaercke et al 2024)

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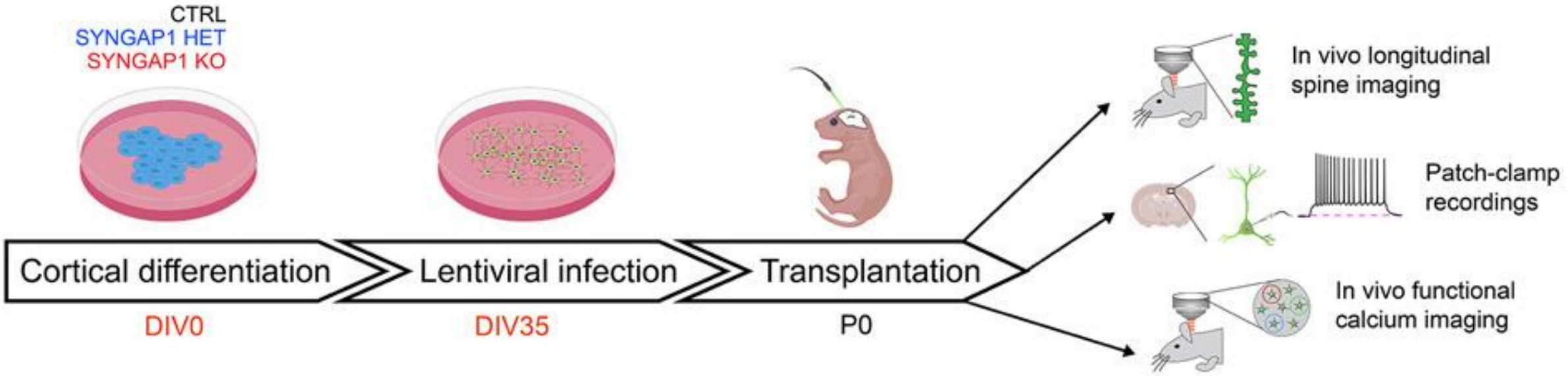
Studying human neoteny *in vivo*



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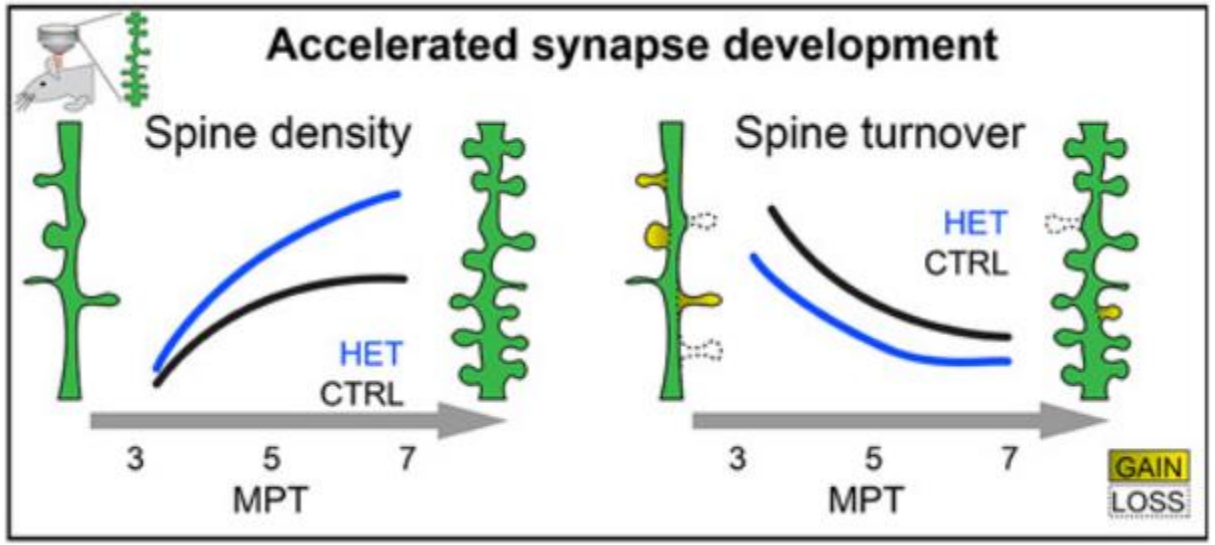
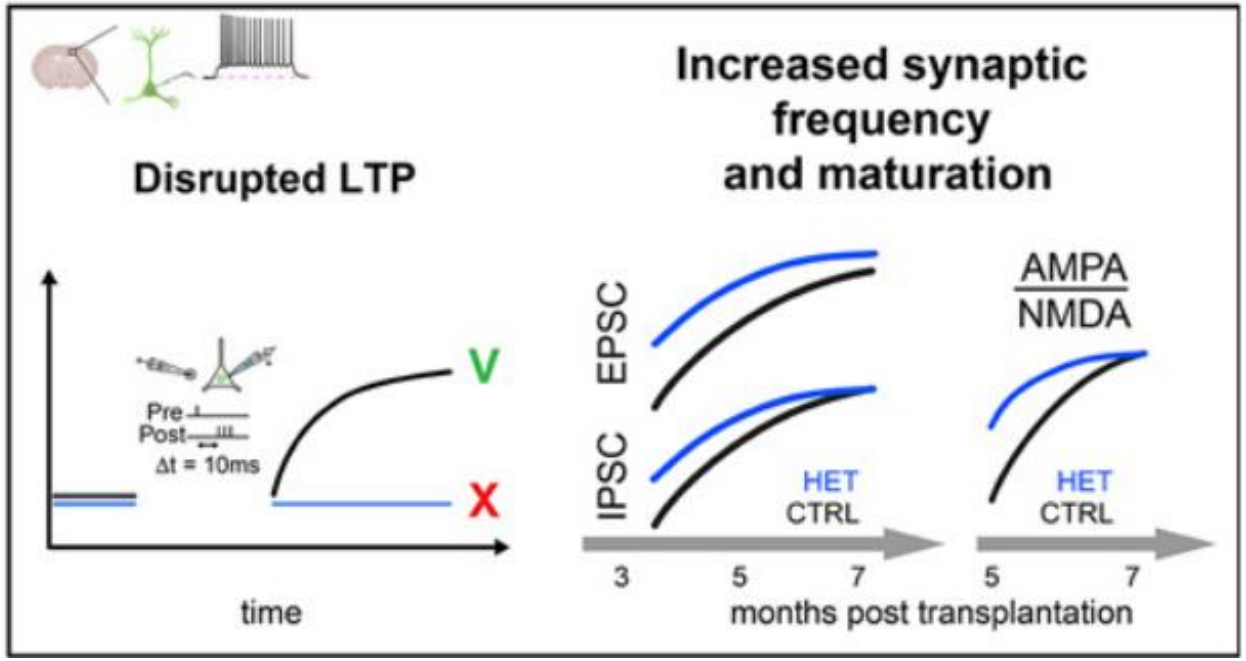
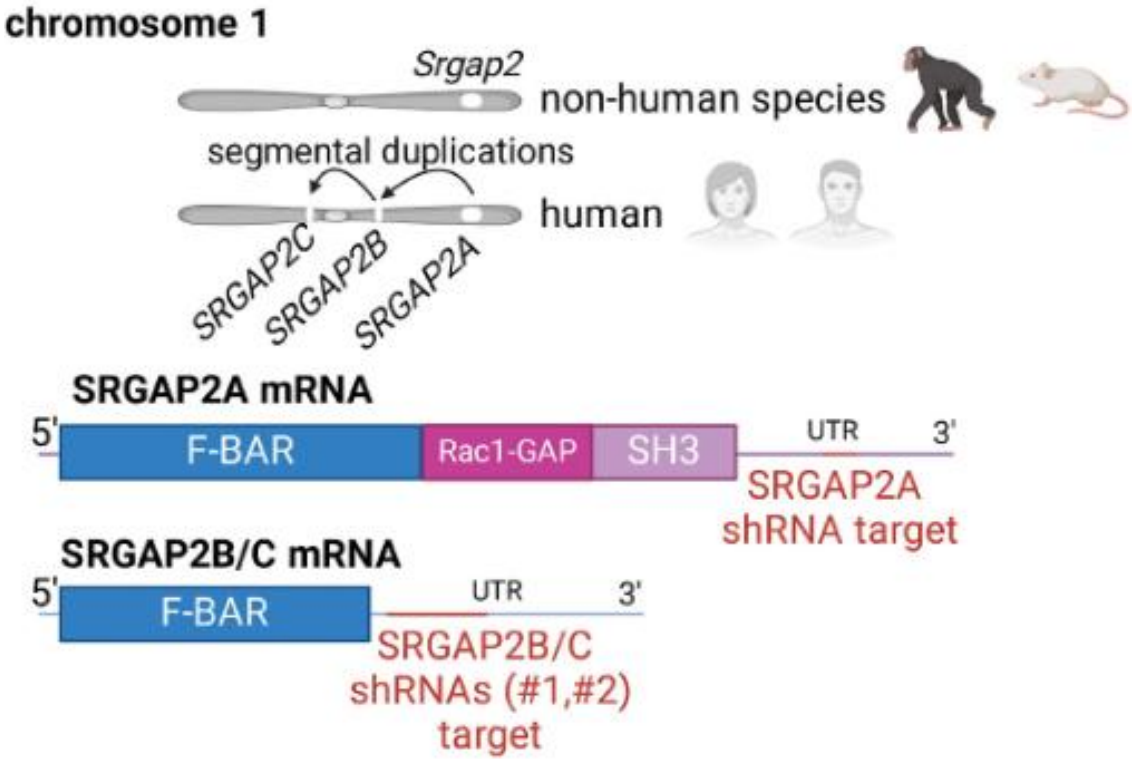
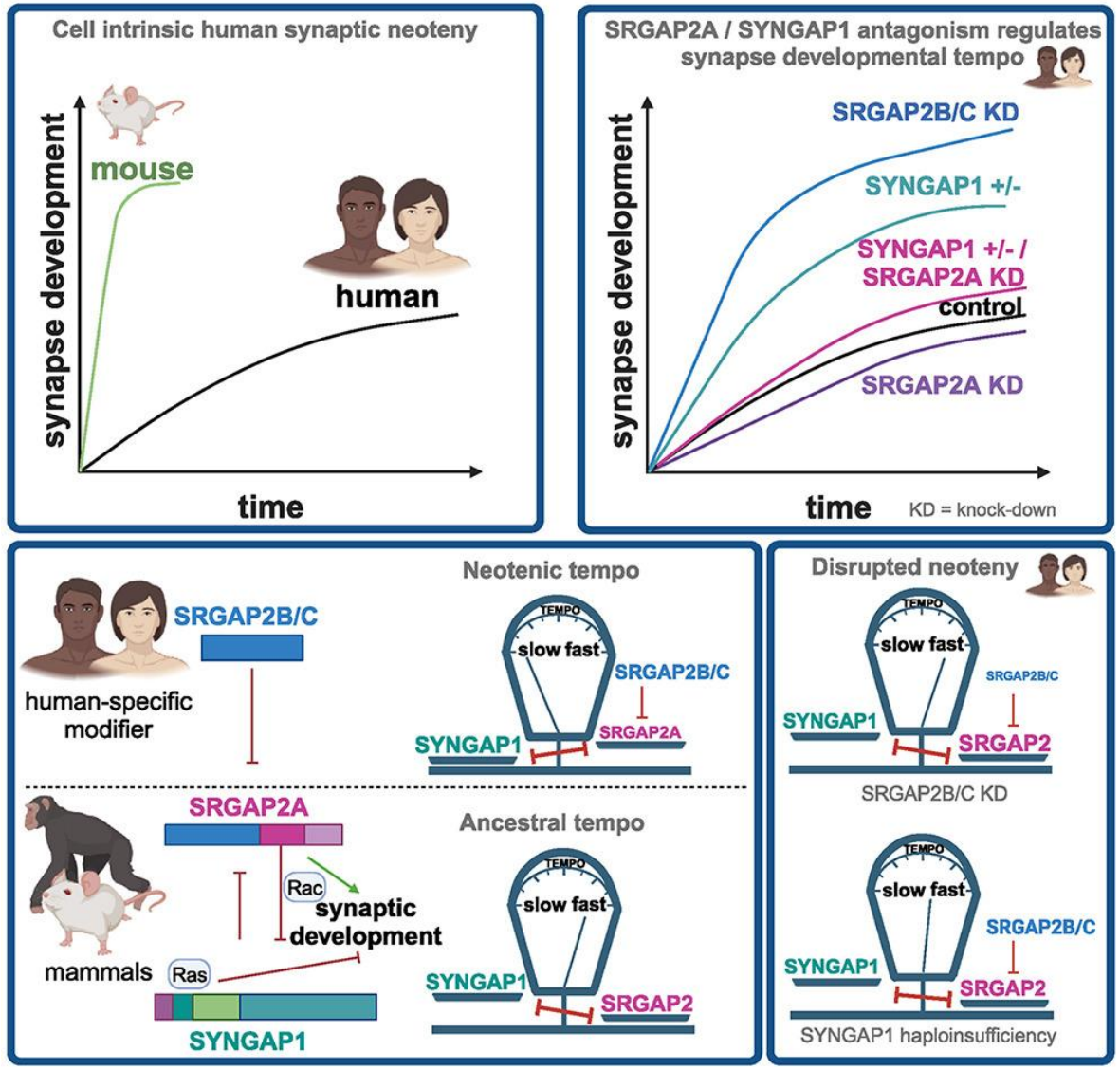




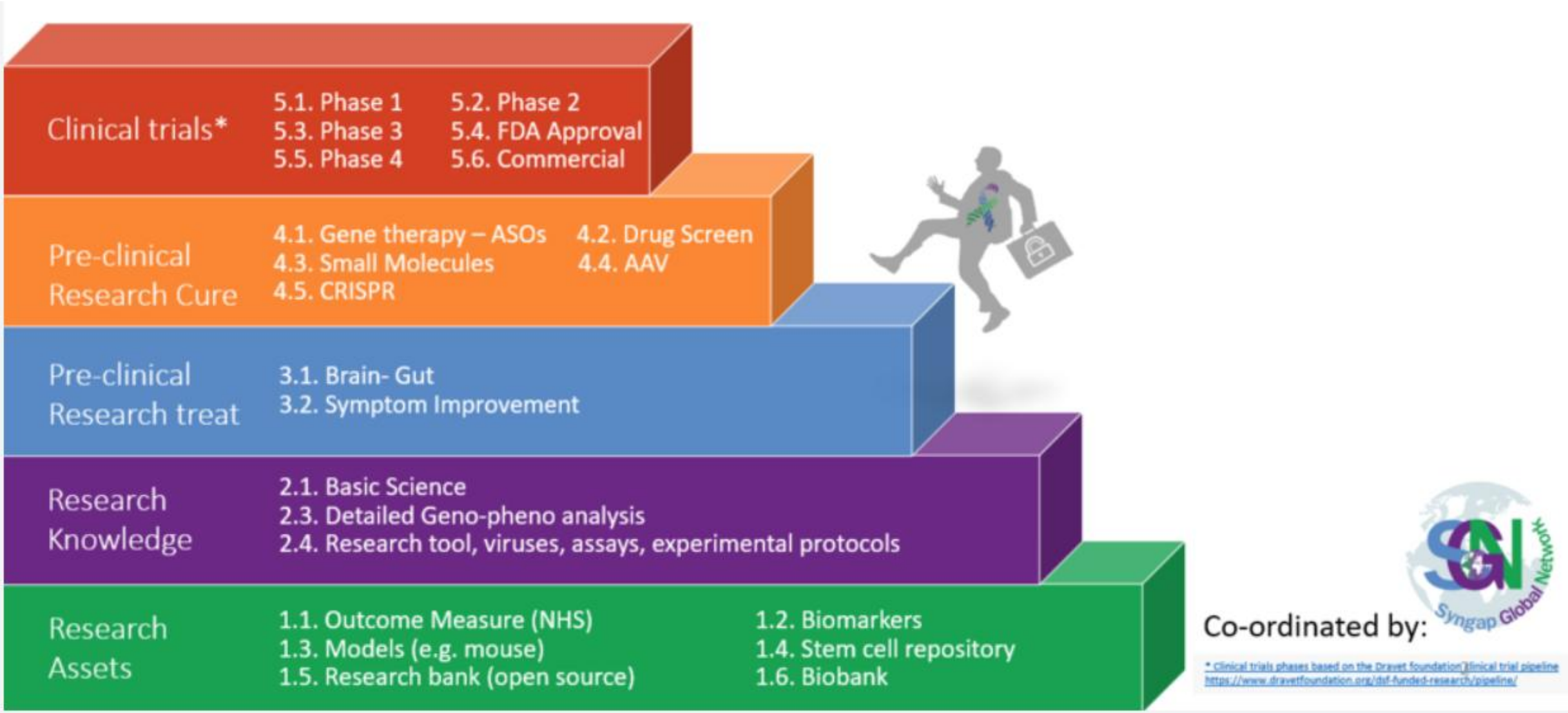
(Vermaercke et al 2024)

How can SynGAP control neoteny?





(Libé-Philippot et al 2024)



The SynGAP Research Roadmap. Source: SynGAP Global Network

Is there a treatment for SYNGAP1–related disorders?

A complex answer:

- There are treatments, medicines and medical procedures that help control the symptoms of *SYNGAP1*-related disorders.
- Some drugs can improve downstream effects of the *SYNGAP1* condition.
- At present there are **no approved therapies** that correct the main defect: the reduced amount of SynGAP protein (haploinsufficiency). Several strategies are in development and are approaching the clinical trial phase.
- There are **still no approved therapies** that directly repair the genetic error causing the syndrome. However, several gene-therapy techniques are already available that could do this in the future.