UNIVERSITAT DE BARCELONA

Maladies métaboliques du trafic céllulaire: présentations neuropédiatriques

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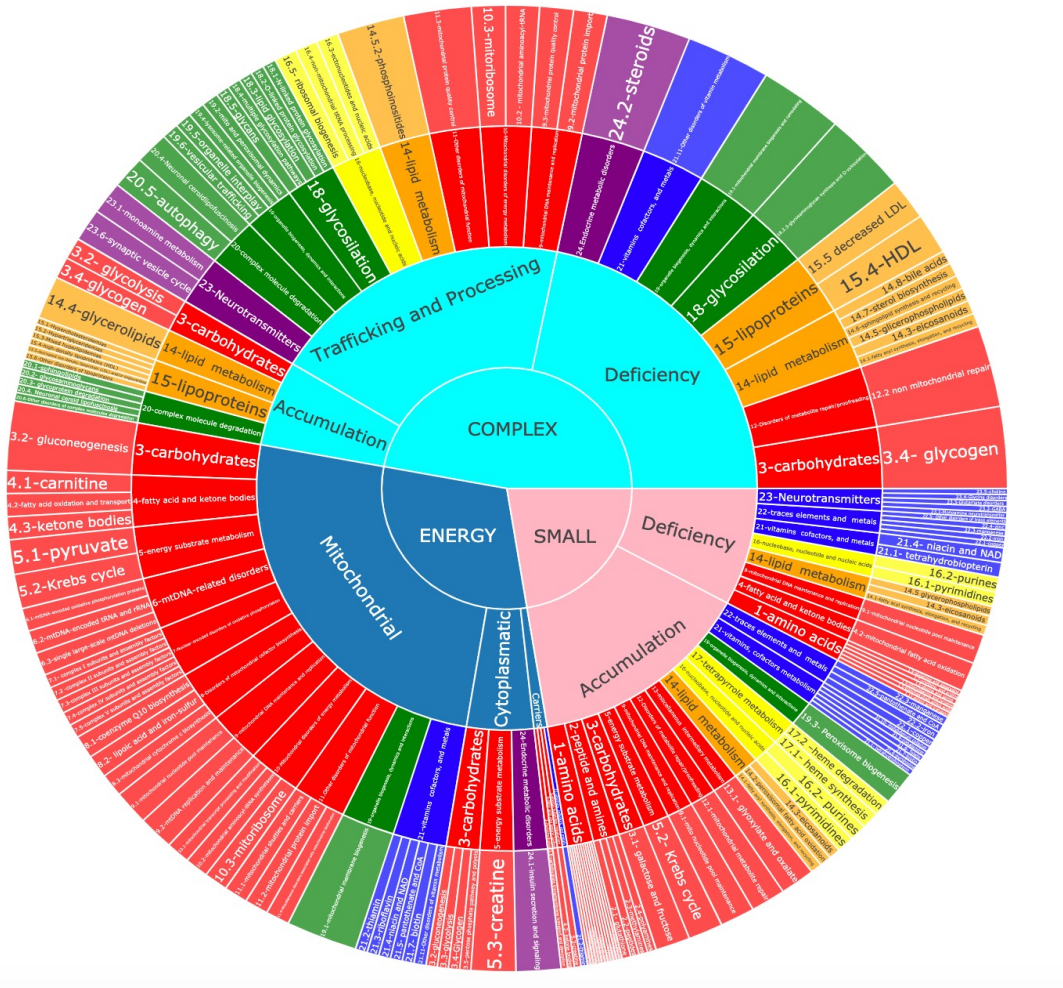
SJD
Sant Joan de Déu
Barcelona · Hospital

1. Small molecules disorders >300
   - Accumulation (catabolism) >200
   - Deficiency (synthesis or transport) >100
2. Complex molecules disorders >650
   - Accumulation (catabolism: storage) >80
   - Deficiency (synthesis, recycling)>300
   - **Trafficking, processing, quality control… >270**
3. Energetic disorders >430
   - Transporters defects of fuel molecules 12
   - Cytoplasmic defects >60
   - Mitochondrial defects >350



1. Intermediary metabolism: Nutrients
2. Intermediary metabolism: Energy
3. **Lipid metabolism and transport**
4. Heterocyclic compounds
5. **Complex molecules and organelles**
6. **Trace elements and vitamins**
7. **Metabolic cell signalling**

What is cell trafficking?

Process that allows the exchange of signals and metabolites between cellular compartments

346 diseases

Trends in Genetics

CellPress OPEN ACCESS

Review

Genetic disorders of cellular trafficking

Angeles García-Cazorla,[1,4,*] Alfonso Oyarzábal,[1,4] Jean-Marie Saudubray,[2] Diego Martinelli,[3] and Carlo Dionisi-Vici[3,*]

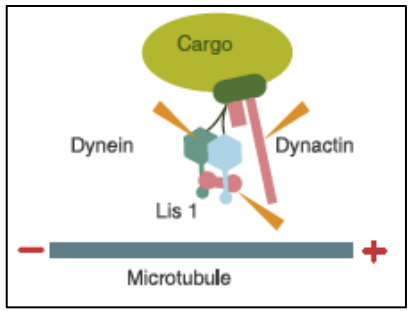
March, 2022

EPG5, WDR45 ,SNX14, SPG11, ZFYVE26, AP5Z1, RAB7, ATG5, SQSTM1

Autophagy related

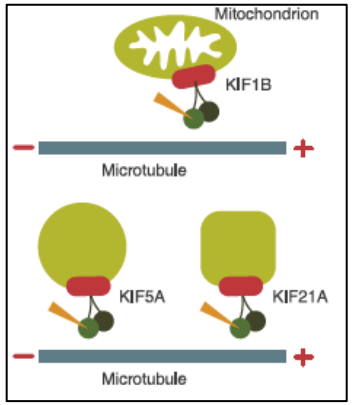
RBSN, SLC9A6, DENND5A, ARFGEF2

RAB7, ATP6AP2, SNAP29



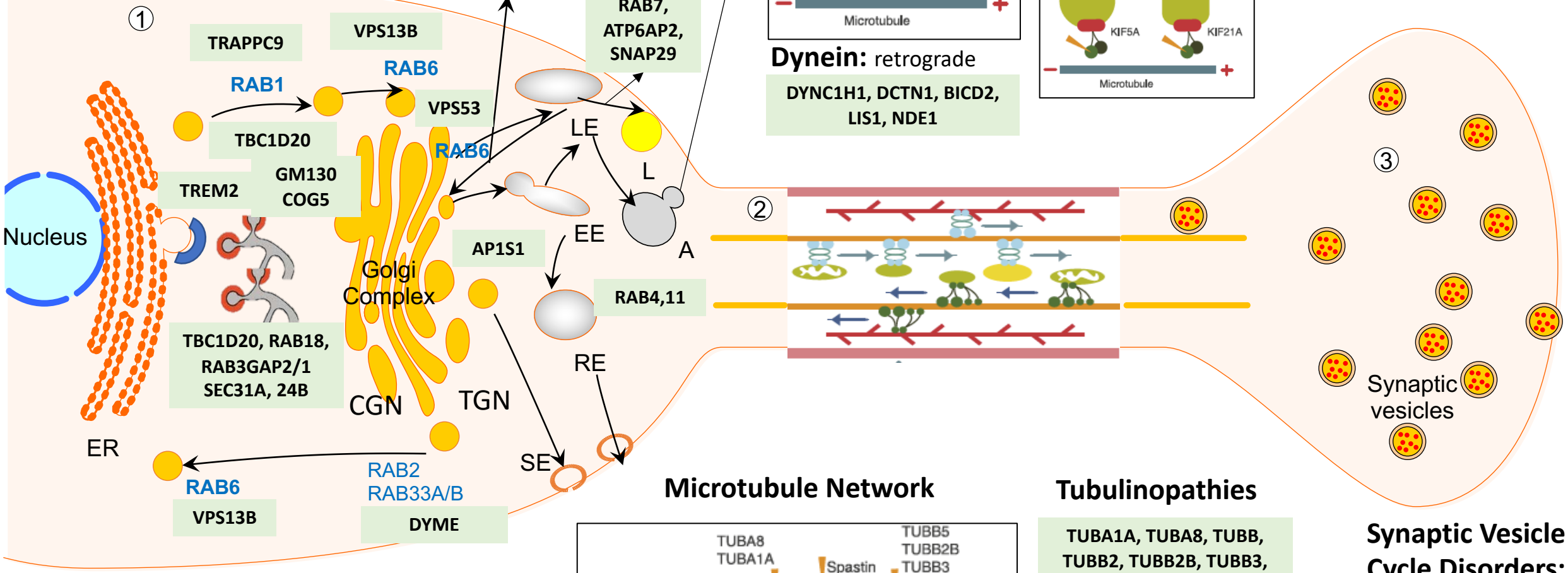
Dynein: retrograde

DYNC1H1, DCTN1, BICD2, LIS1, NDE1



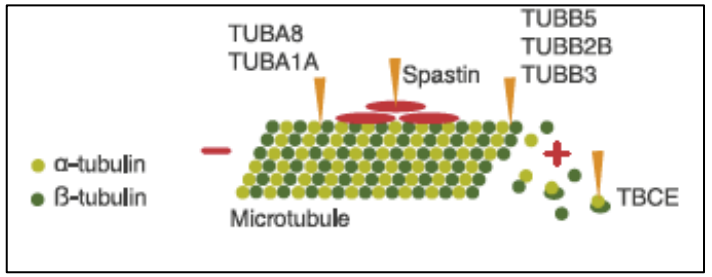
Kinesin: anterograde

KIF5A, KIF5C, KIF1A, KIF1C, KIF14, KIF16A, KIF4A, KIF7, KIF12A, KIF11, KIF10, KIF6, KIF15, KIF2A, KBP



Exo/Endocytosis

Microtubule Network



Tubulinopathies

TUBA1A, TUBA8, TUBB, TUBB2, TUBB2B, TUBB3, TUBB4A, TUBB4B, TUBB6, TUBG1

Synaptic Vesicle Cycle Disorders:

A Garcia-Cazorla et al. Cell trafficking in IMD 7th 2022 chapter 44

EARLY ONSET ENCEPHALOPATHIES

Complex global encephalopathies, **microcephaly ++, brain malformation (+/-), epileptic encephalopathies**

With MULTISYSTEM involvement

SYNAPTOPATHIES

Continuum **ID +/-epilepsy +/- mov. disorders +/-npsy (autism++)**

PREDOMINANT MOTOR DISORDERS

May appear at any age (most childhood-adulthood onset). **Neurodegenerative diseases**

ATAXIA

SPASTIC PARAPARESIS

PARKINSONISM and other MD

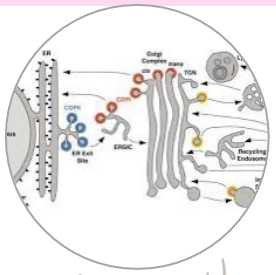
PERIPHERAL NEUROPATHY

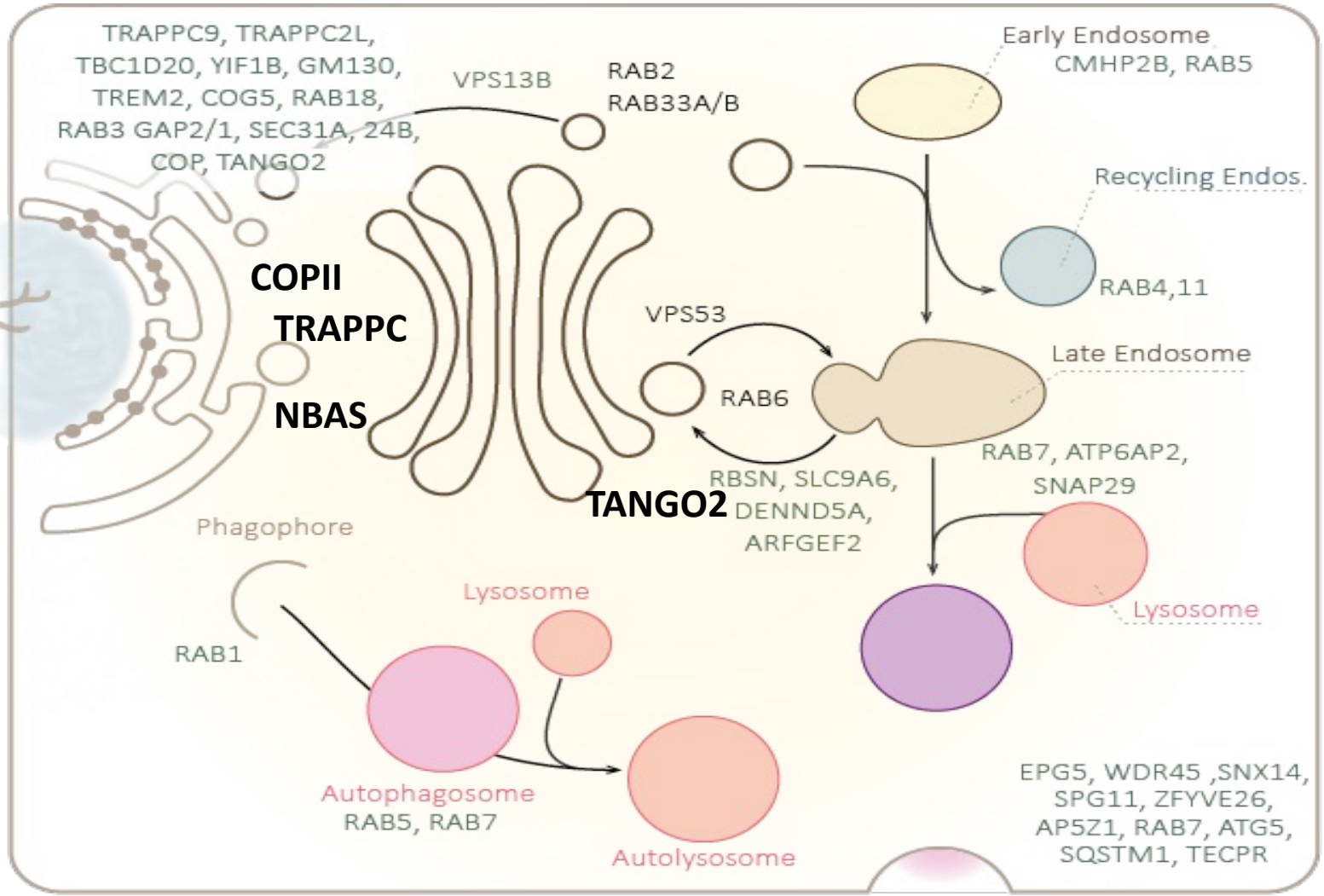
AMIOTROPHIC LATERAL SCLEROSIS

SPINAL MUSCLE ATROPHY

DEMENTIA

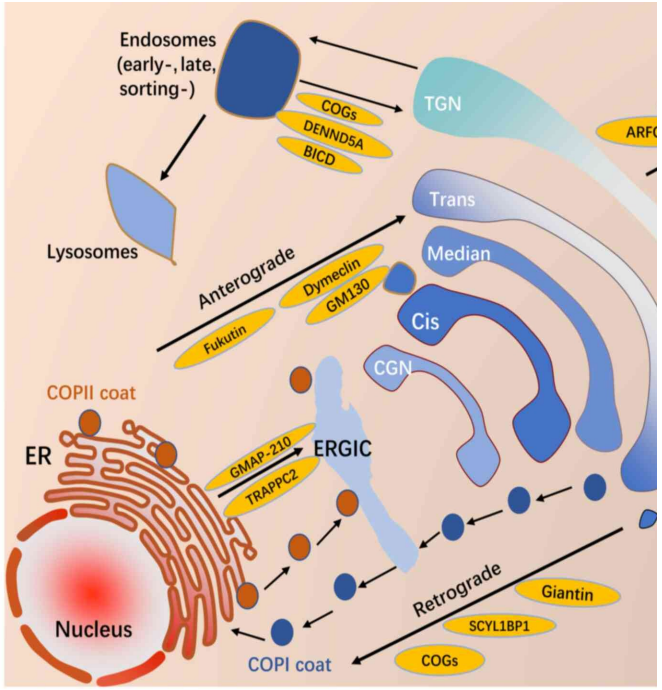
EXOCYTIC COMPARTMENT (vesicular trafficking) : cargo movement out of the cell





CLINICAL CASES

Liu et al, 2021



TRAfficking
Protein
Particle
Complex
subunit 11

TRAPPC11: Vesicle transport from RE to Golgi.

20 patients reported. Limb-girdle muscle dystrophy

Original research

Expanding the phenotypic spectrum of *TRAPPC11*-related muscular dystrophy: 25 Roma individuals carrying a founder variant

Justel et al, 2023. Journal of Medical Genetics

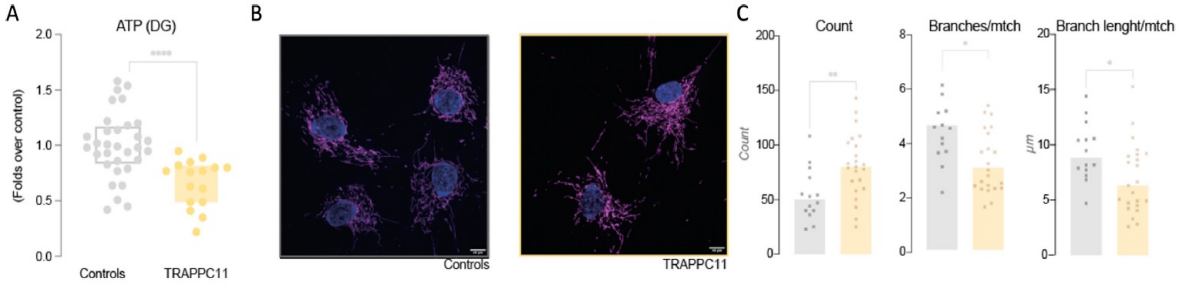
Founder mutation: c.1287+5G>A

-Typical pheatures of Golgipathies: microcephaly

-Decompensations triggered by fever:
Rhabdomyolisis (CPK: from 300 to 3000 UI/L), some times neurological regression.

-Others: epilepsy, cortico-subcortical atrophy (mostly occipital), cataract, achalasia, alacryma, liver dysfunction

-MITOCHONDRIAL DYSFUNCTION
-ABNORMAL AUTHOPHAGY



Increased in mitocondrial counts, networks are less branched and with shorter mitochondria

CLINICAL CASES

Educational videos from a webinar freely available on YouTube
https://www.youtube.com/watch?v=YHKJM0-WBgs

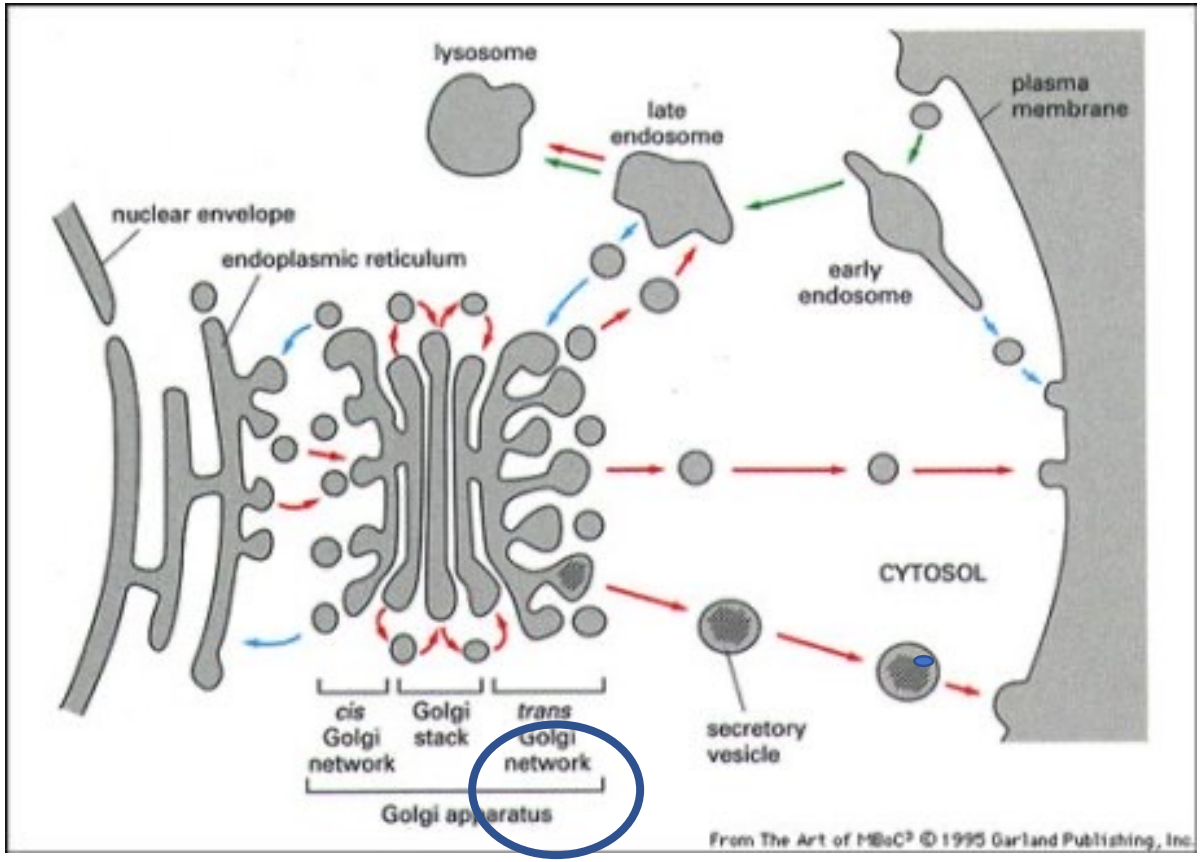
INTERMITTENT and ACUTE-ONSET episodes

Extreme fatigue, weakness
Loss of muscle control
Drooling, Swallowing difficulties
Dystonia
Slurred speech
Episodes mimicking seizures
Metabolic crises

CHRONIC sings

Developmental delay/ID, Motor problems: abnormal gait, poor cordination, Hypotonia, hypertonia, dystonia, Spasticity, Slurred speech, Epilepsy (different types, may be refractory)

TANGO 2 mutations (Trans Golgi Network)



TREATMENT: Limitation of fasting, glucose infusión upon febrile illnesses, starchy foods for dinner. Hyperhydration without potassium, strict ionic and cardiac monitoring. B VITAMINS

Fever, Fasting, Anesthesic Drugs, L-Carnitine?

Bérat, 2020

METABOLIC CRISES
Rhabdomyolisis
+/-
High lactate, ammonia
Low glucose

Cardiac Arrythmias (long Q-T)

Hypothyroidism

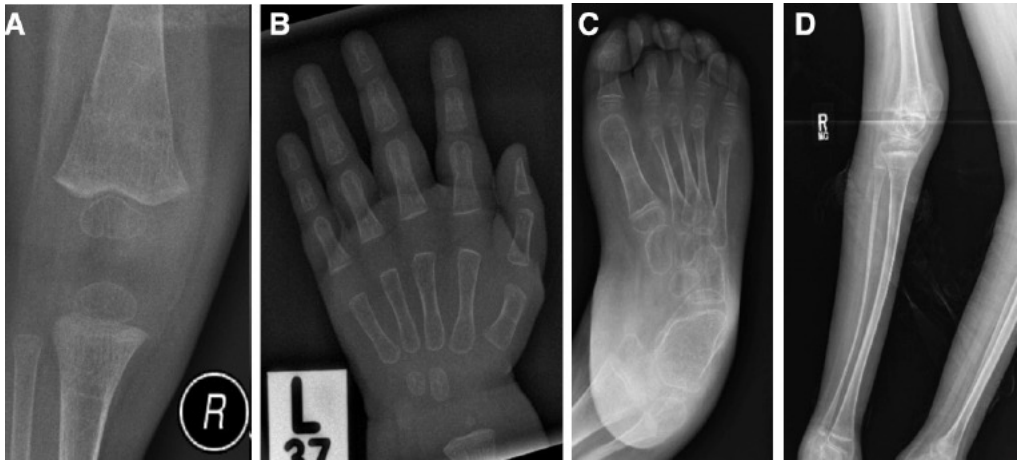
Intellectual Disability
+/-
Complex encephalpathy
Spastic pararesis
Other motor dysfunction
Epilepsy, "Myopathic"
NRL regression

Mingirulli, 2019; Milec, 2020; Bérat, 2020; Sandkuhler et al, 2023

CLINICAL CASE

2 years

- Neurodevelopmental epileptic encephalopathy
- Acquired microcephaly
- **Episodes of transaminitis triggered by fever** with normal lactate, ammonia, aa, organic acids….



OSTEOPOROSIS

ARTICLE *Marom et al, 2021*

COPB2 loss of function causes a coatopathy with osteoporosis and developmental delay

FEVER as a trigger in cellular trafficking defects

RHABDOMYOLISIS

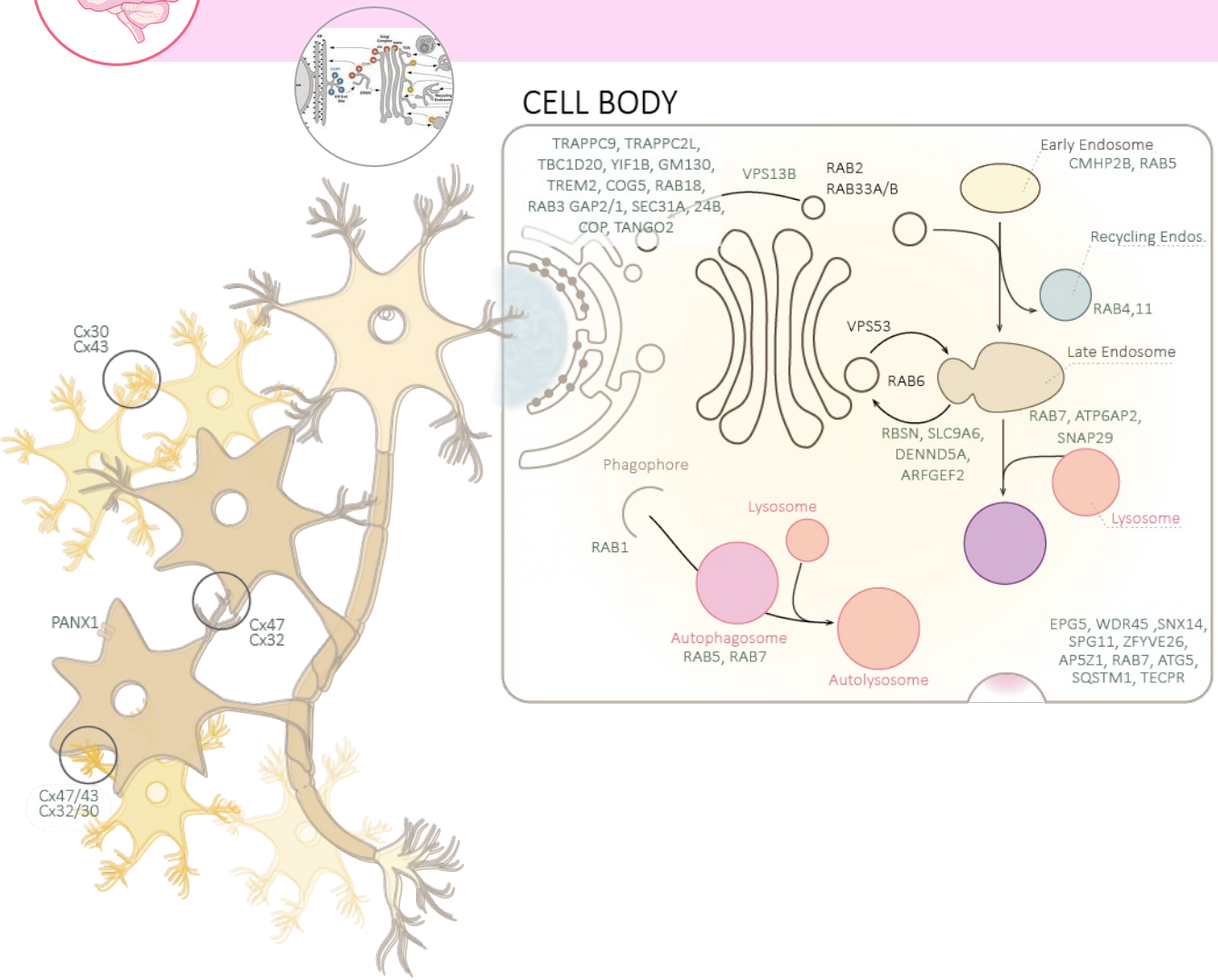
LPIN1, TANGO2,
RYANODIN R
TRAPPC11

RALF

NBAS, SCYL1,
RINT-1, PERK

COPB2
(1 observation)

ENDOCYTIC compartment (vesicular trafficking): movemento of the cargo inside the cell



Golgi - endosomes defects

Complex early-onset encephalopathies that may associate with multisistemic involvement — SLC9A6

Late endosome - lysosome defects

Neonatal seizures	ATP6A2, IER3IP1
Complex multisystemic	SNAP29
Peripheral neuropathy	RAB7
Lysosome biogenesis defects	Lowe syndrome

HOPSANDs (*HOPS Associated Neurological Disorders*)

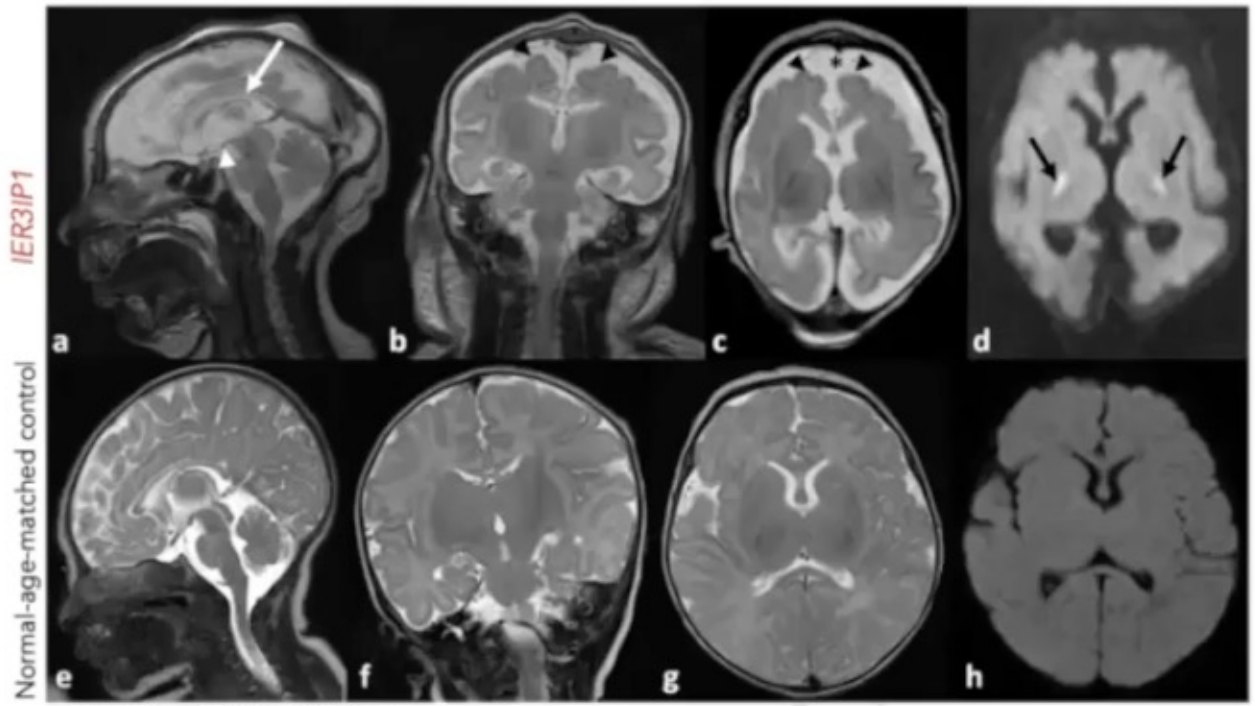
Early-onset dystonia + lysosomal abnormalities

IER3IP1

(Immediate early response-3 interacting protein-1)

Early onset encephalopathies:

Microcephaly, epilepsy, and diabetes (MED)



MRI images from a 5-weeks

Congenital microcephaly with progressive head growth deceleration.

MRI: Simplified gyral pattern, agenesis/hypoplasia of corpus callosum and hypoplastic cerebellar vermis.

Early onset epilepsy: 0-2 months
Refractary epilepsy.
EEG: Burst-suppression or hypsarrythmia

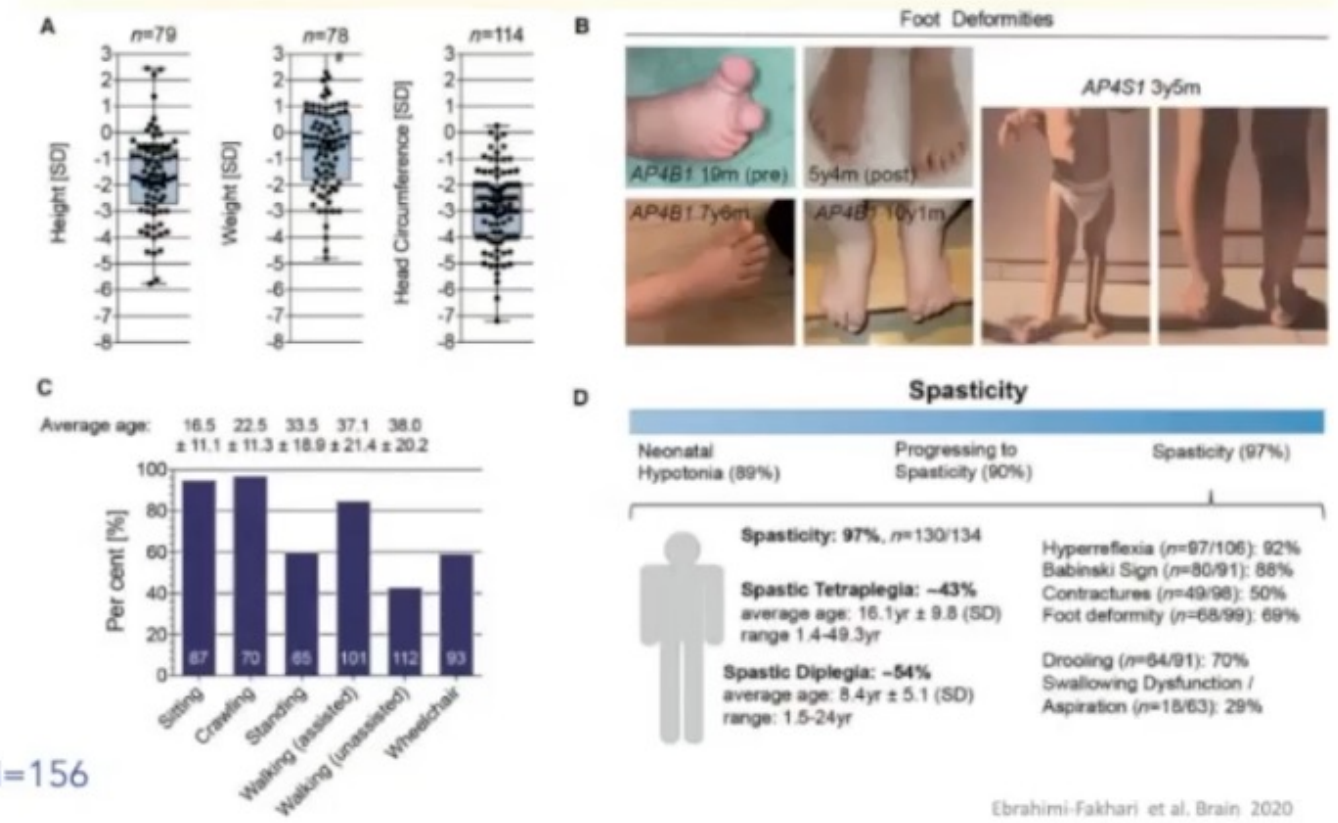
Early onset diabetes: 0-2 months
Severe psychomotor retardation
Death: 7 w- 8 yo

Shalev et al 2014; Valenzuela et al 2017

AP4

(Adaptor protein complex 4)

Defects in this gene are associated with
Complex Hereditary
Spastic Paraplegia
(HSP)



N=156

Ebrahimi-Fakhari et al. Brain 2020

Developmental delay
Infantile hypotonia
Lower limb spasticity
Postnatal microcephaly
Facial dysmorphism
Foot deformity
Epilepsy
Extrapyramidal MDs
Cerebelar signs

Ebrahimi-Fakhari et al 2020 and 2021

CLINICAL CASE

10 yo

Disease onset

Tremor - ULs

11 yo

Tremor – Trunk and limbs

Gait instability

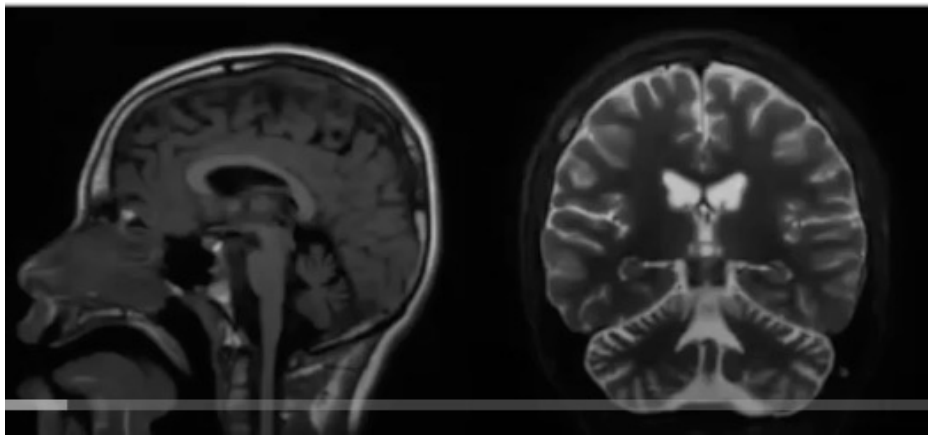
12 yo

Cognitive impairment
Ataxia
OMA
Ophthalmoplegia

13 yo

Global hypokinesia
Hypomimia
Rigidity

Loss of cognitive and motor abilities



- **ATXN2 gene (Ataxin 2**) associated with expansión diseases (CAG repeat expansions)---AD: SCA ataxia and Parkinson's disease. Intermediate expansion increase the susceptibility to ALS

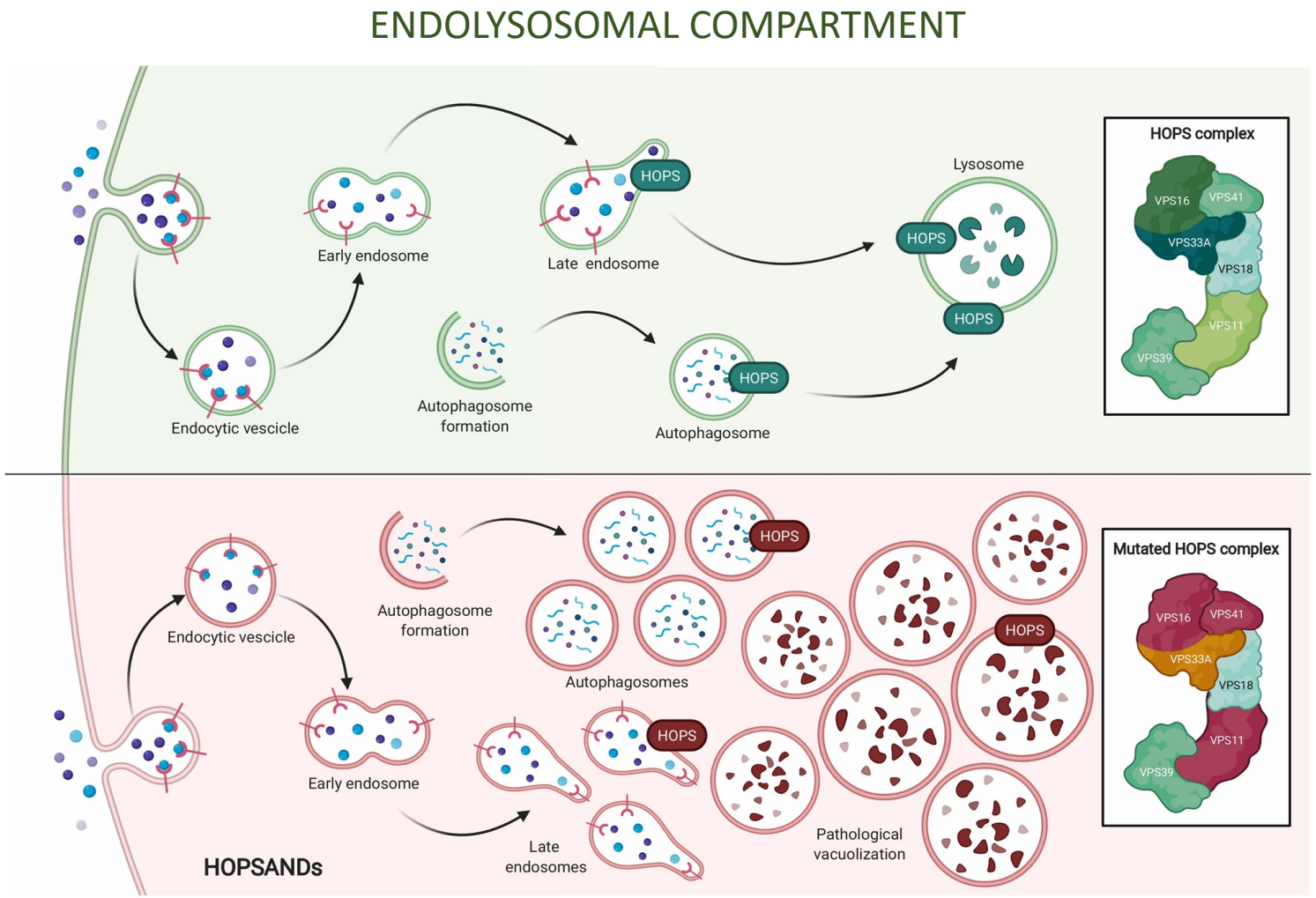
- Localizes to the ER and plasma membrane and is involved in ENDOCYTOSIS

- ATXN2 also modulates mTOR, modifies ribosomal transmaltion and mitochondrial function

HOPS-associated neurological disorders (HOPSANDs): linking endolysosomal dysfunction to the pathogenesis of dystonia

The protein sorting (HOPS) complex is the structural bridge necessary for the **fusion of late endosomes and autophagosomes with lysosomes**

Mutations in genes encoding HOPS complex proteins cause **inherited dystonias** (i.e. **VPS16, VPS41, and VPS11**).

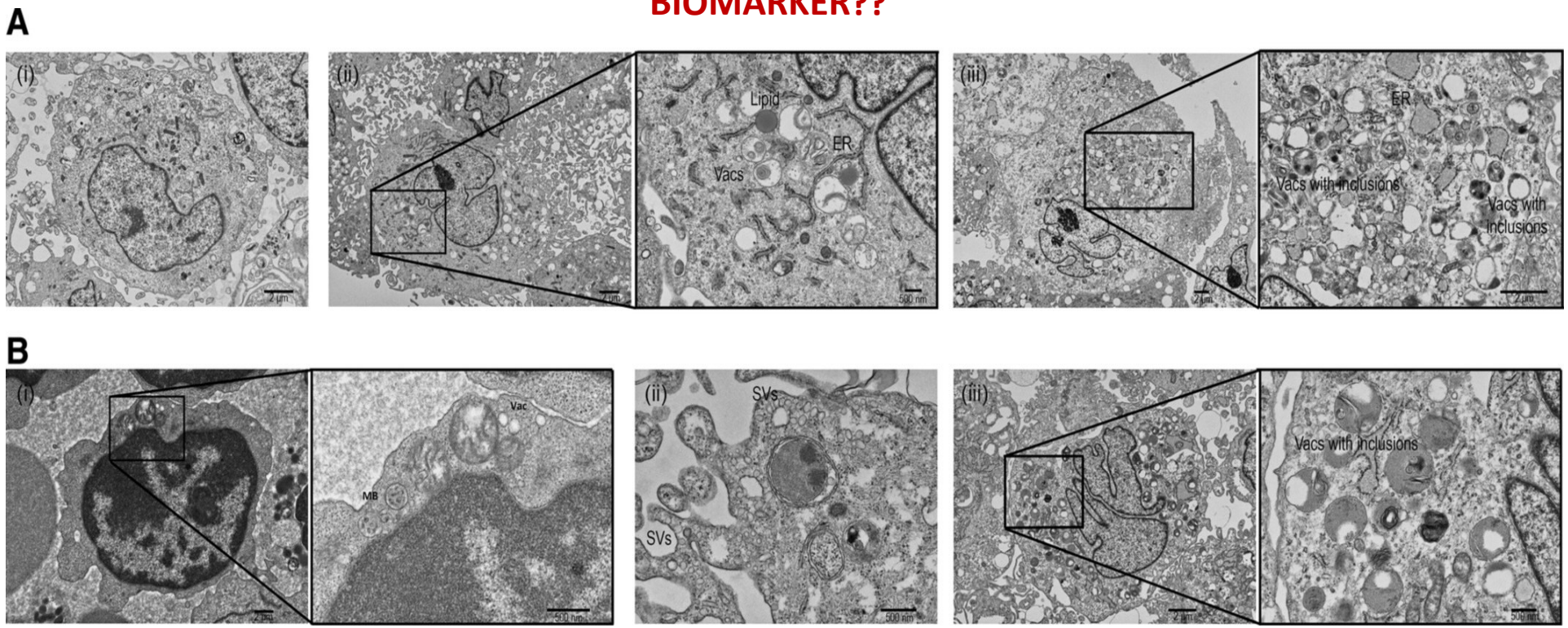


Monfrini et al, 2021

Functional and microstructural studies on patient-derived fibroblasts carrying mutations of HOPS complex subunits displayed clear abnormalities of the lysosomal and autophagic compartments

SMALL VACUOLES, MULTIVESICULAR BODIES, ABNORMAL INCLUSIONS

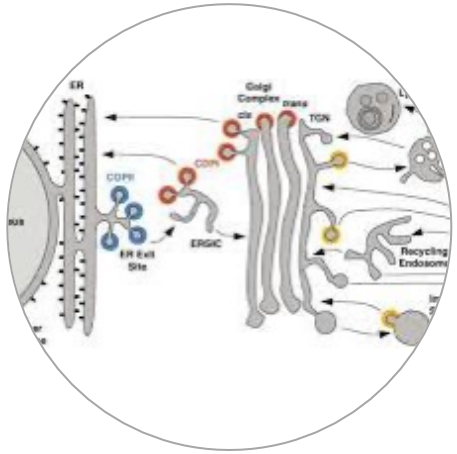
BIOMARKER??



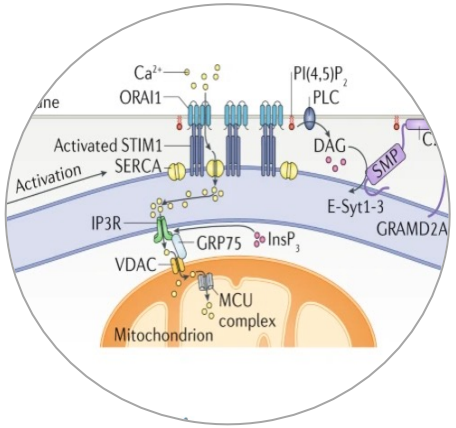
Monfrini et al, 2021

Pathophysiological categories of cell trafficking

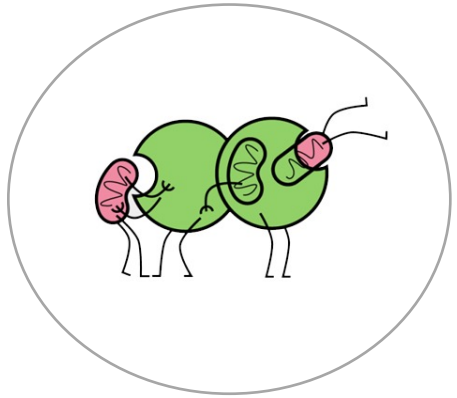
Membrane trafficking : Vesicular Trafficking



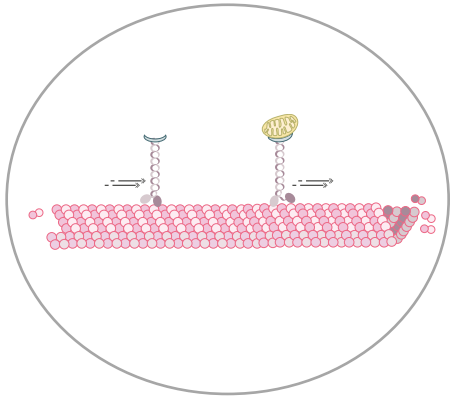
Membrane contact sites (MCS)

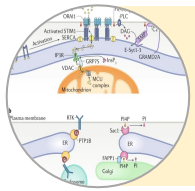


Autophagy (self eating vesicular process)



Cytoskeleton related trafficking

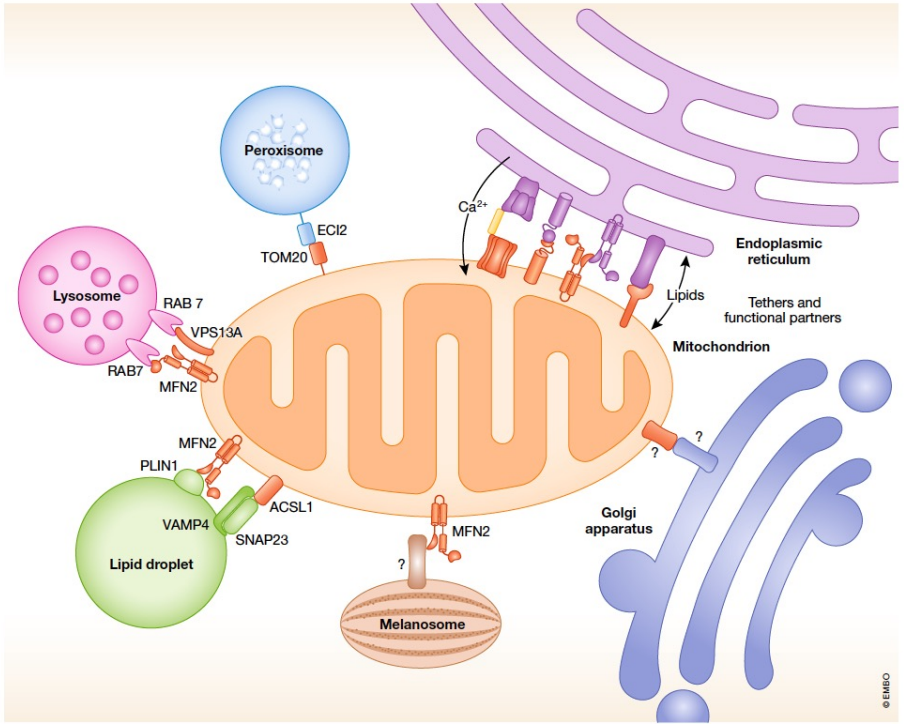


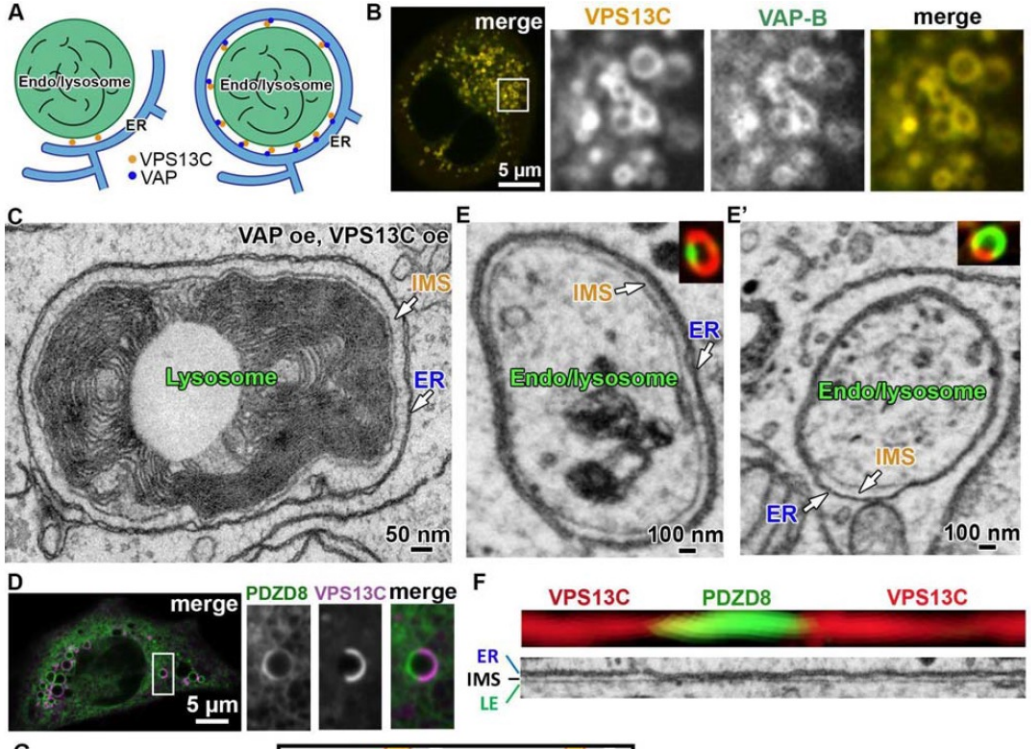


MEMBRANE CONTACT SITES (homotypic, heterotypic)

-Tethering forces
-Lack of fusion
-Specific function
-Defined proteome/lipidome

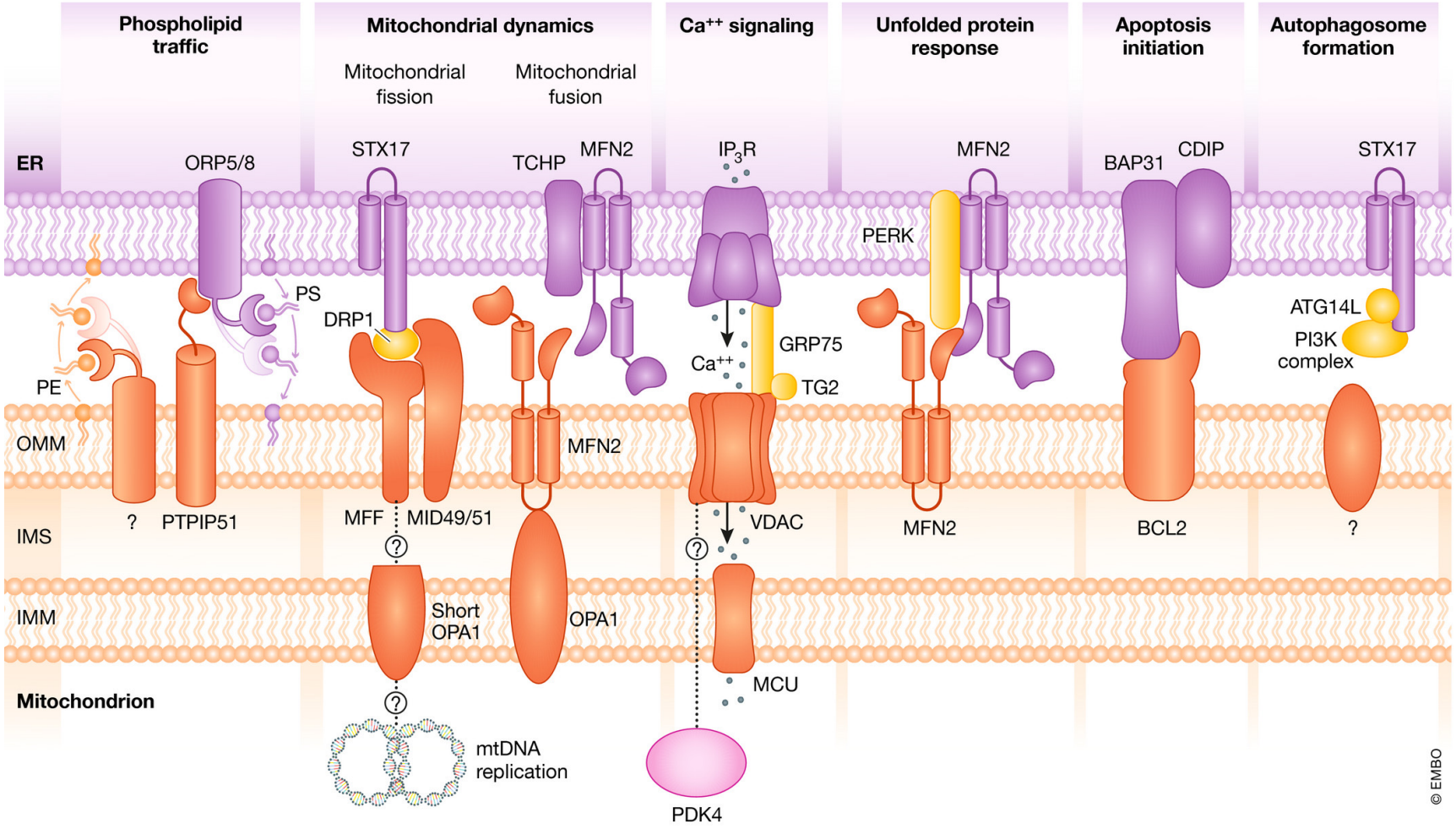
The most common distance: from 10 to 80 nm
although some MCS are much larger (over 300 nm)





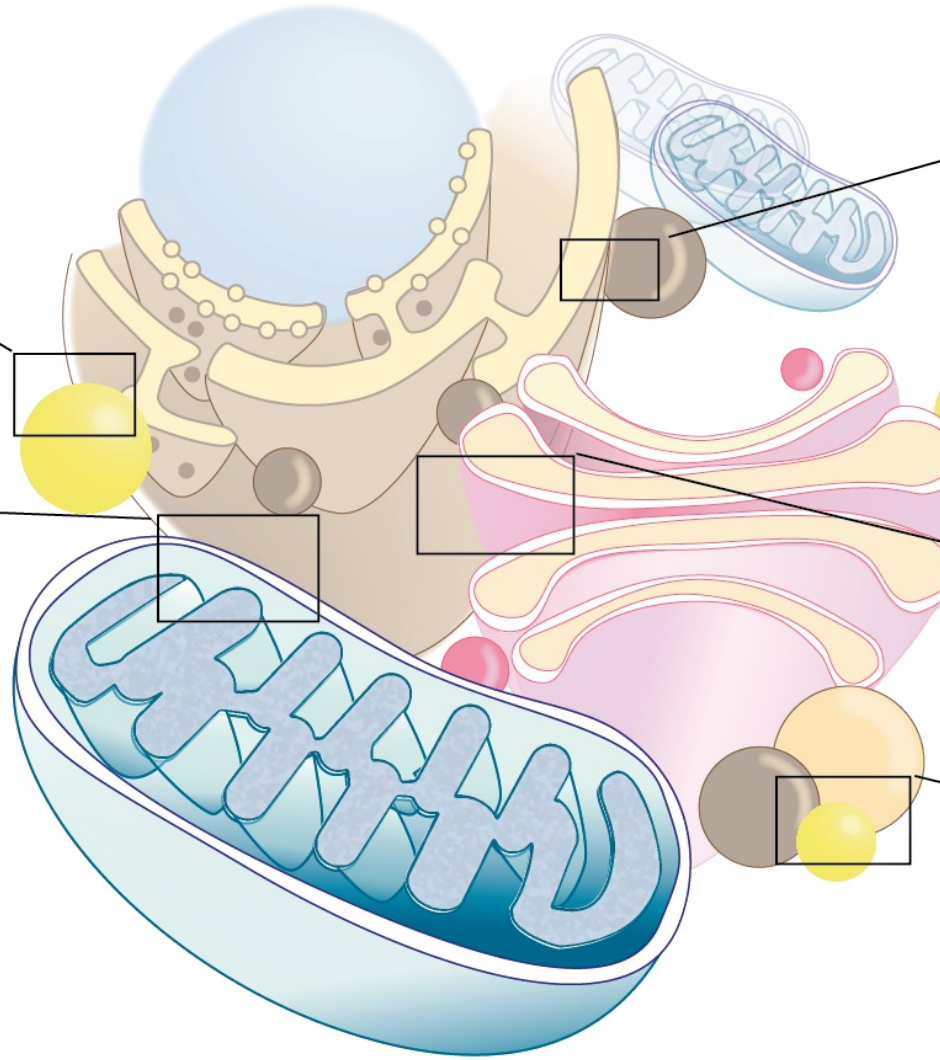
MAM. Metabolic implications of organelle–mitochondria communication

- Phospholipid traffic
- Mitochondrial dynamics
- Ca++ signaling
- Unfolded protein response
- Apoptosis initiation
- Autophagosome formation



EMBO Reports, Volume: 20, Issue: 9, First published: 14 August 2019, DOI: (10.15252/embr.201947928)

Most Membrane Contac Sites (MCS) defects are NEURODEGENERATIVE disorders



ER-Lipid droplet:
-Spastic Paraparesis *BSCL2* (Seipin) (*), *REEP1* and *ATL1* (Atlas-tin-1)

ER-Mitochondria
-Amyotrophyc Lateral Sclerosis: *TARDBP*, alpha1 receptor, VAPB, *SigR1*
-Alzheimer's Disease: Presenilin, alpha-synuclein
-Spastic Paraparesis: *REEP1*, *SigR1*
-Chorea-Acanthocytosis: *VPS13A*
-CMT: *MFN2*, alpha-synuclein
-GM1 gangliosidosis
-Parkinson's Disease: *VDAC1*
-Epileptic encephalopathy: *PACS2*

ER-Endosome:
-Parkinson Disease: *VPS13C*

Lipid droplet-peroxisomes
-Spastic Paraparesis: Spastin (*SPAST*), *ABCD1* (ATP-binding cassette sub-family D member 1)

ER-Golgi (TGN):
-Amyotrophyc Lateral Sclerosis: *VAPB*
-Intellectual disability: *CERT1*

Endosome-Lysosome-Lipid droplet:

VPS13A and VPS13C bind to the ER, tethering it to mitochondria (VPS13A), to late endosome/ lysosomes (VPS13C) and to lipid droplets (both VPS13A and VPS13C).

Choreoacanthocytosis: *VPS13A*
Parkinson's Disease: *VPS13C*

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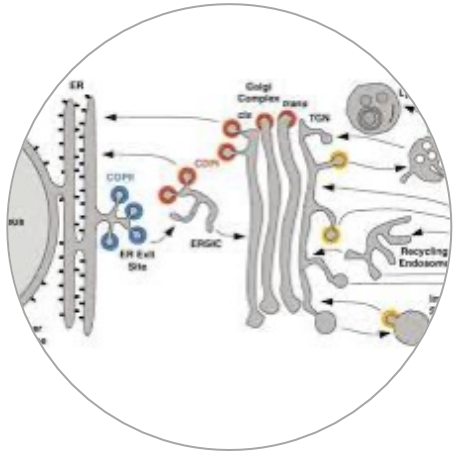

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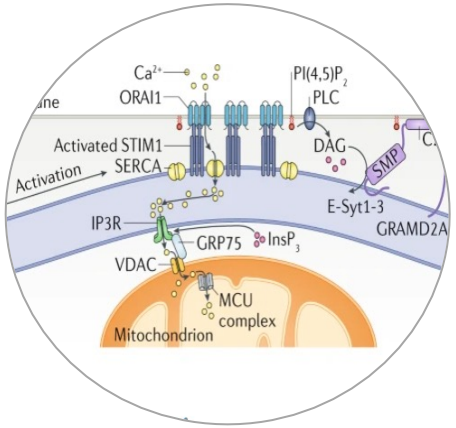

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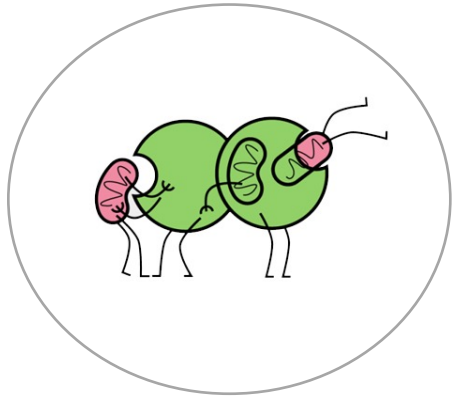
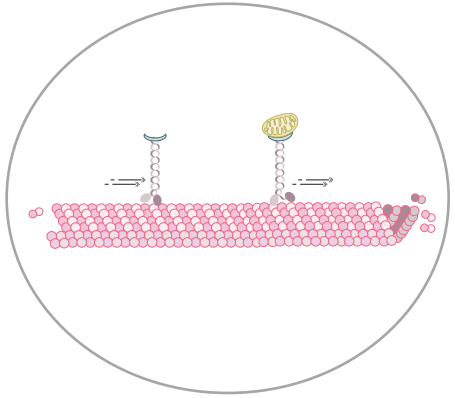
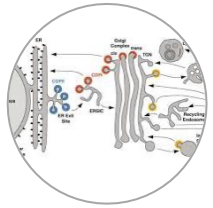


Cytoskeleton related trafficking

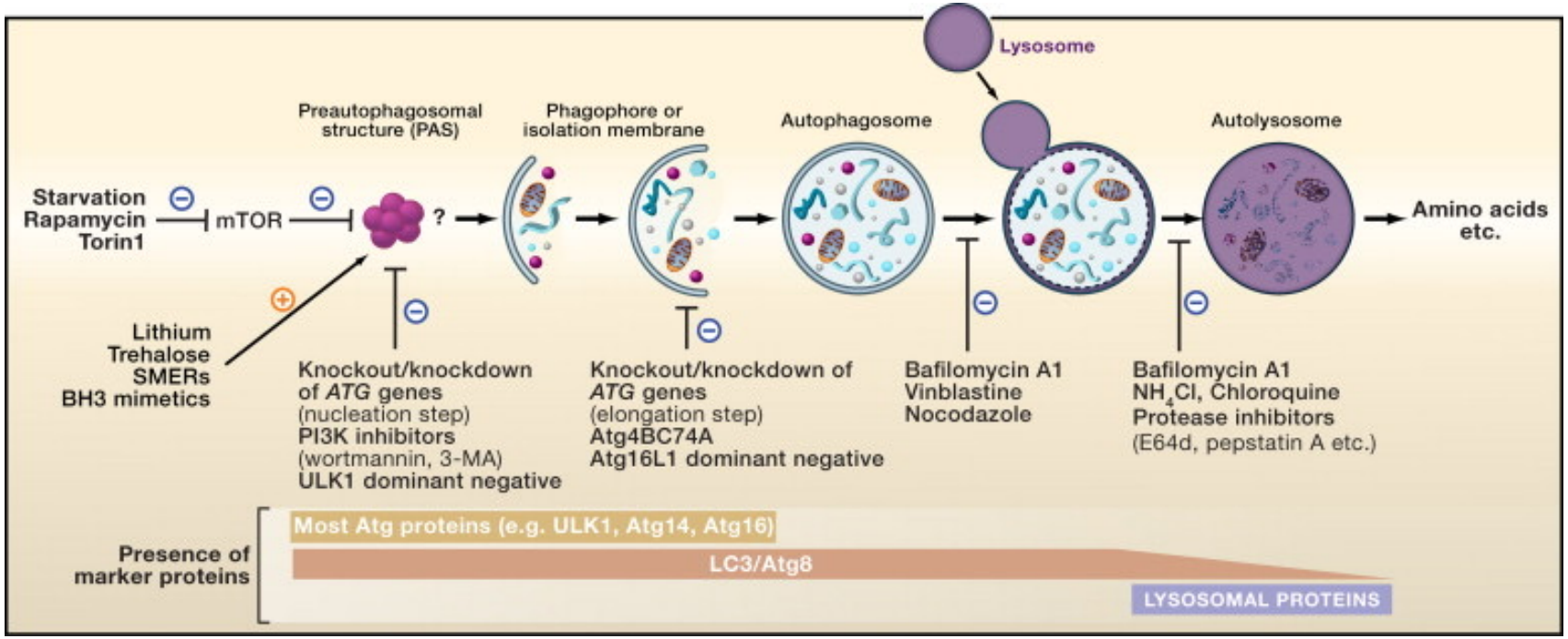


AUTOPHAGY



Complex process that starts with a double-membrane precursor (the phagofore) in the cytoplasm to continue with the formation of the autophagosome and autolysosome:

allows recycling amino acids, lipids, and carbohydrates during periods of nutrient starvation

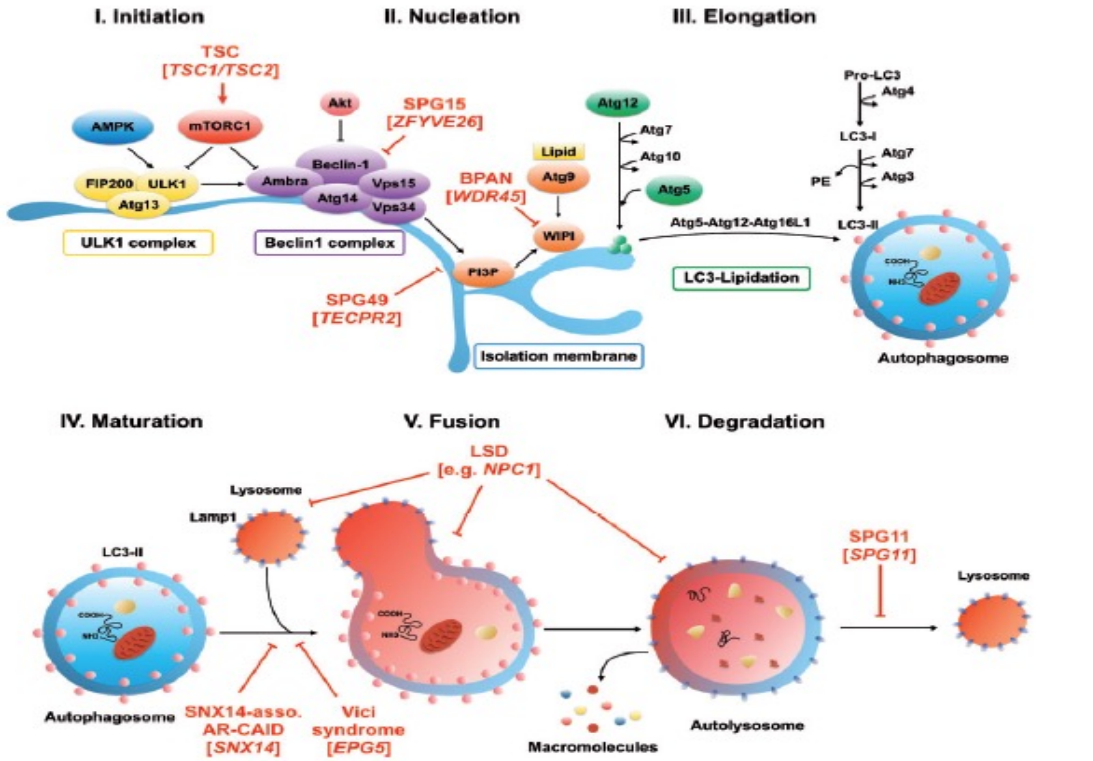


Mizushima, Cell 2010

Recessive mutations in *EPG5* cause Vici syndrome, a multisystem disorder with defective autophagy

Thomas Cullup[1,28], Ay Lin Kho[2,3,28], Carlo Dionisi-Vici[4,5], Birgit Brandmeier[2,3], Frances Smith[1], Zoe Urry[6], Michael A Simpson[6], Shu Yau[1], Enrico Bertini[5], Verity McClelland[7], Mohammed Al-Owain[8,9], Stefan Koelker[10], Christian Koerner[10], Georg F Hoffmann[10], Frits A Wijburg[11], Amber E ten Hoedt[11], R Curtis Rogers[12], David Manchester[13], Rie Miyata[14], Masaharu Hayashi[15], Elizabeth Said[16,17], Doriette Soler[18], Peter M Kroisel[19], Christian Windpassinger[19], Francis M Filloux[20], Salwa Al-Kaabi[21], Jozef Hertecant[21], Miguel Del Campo[22], Stefan Buk[23], Istvan Bodi[23], Hans-Hilmar Goebel[24], Caroline A Sewry[25], Stephen Abbs[1], Shehla Mohammed[26], Dragana Josifova[26], Mathias Gautel[2,3,29] & Heinz Jungbluth[7,27,29]

Nat Genet 2013



Disorders of autophagy

-Multisystemic disorders
-Neurodevelopmental----Neurodegenerative disorders
-Late onset neurodegenerative

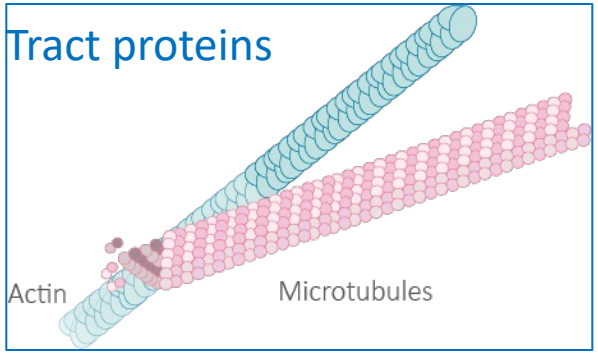
- **EPG5-**associated Vici syndrome,
- **WDR45**-associated β-propeller protein associated neurodegeneration,(BPAN)
- **WIPI2:** neurodevelopmental disorder
- **SNX14**-associated autosomal-recessive spinocerebellar ataxia 20,
- **ATG5**-associated autosomal-recessive ataxia syndrome,
- **SQSTM1**/p62-associated childhood-onset neurodegeneration,
- Several forms of the **hereditary spastic paraplegias**.

Ebrahimi-Fakhari et al, 2016, 2019

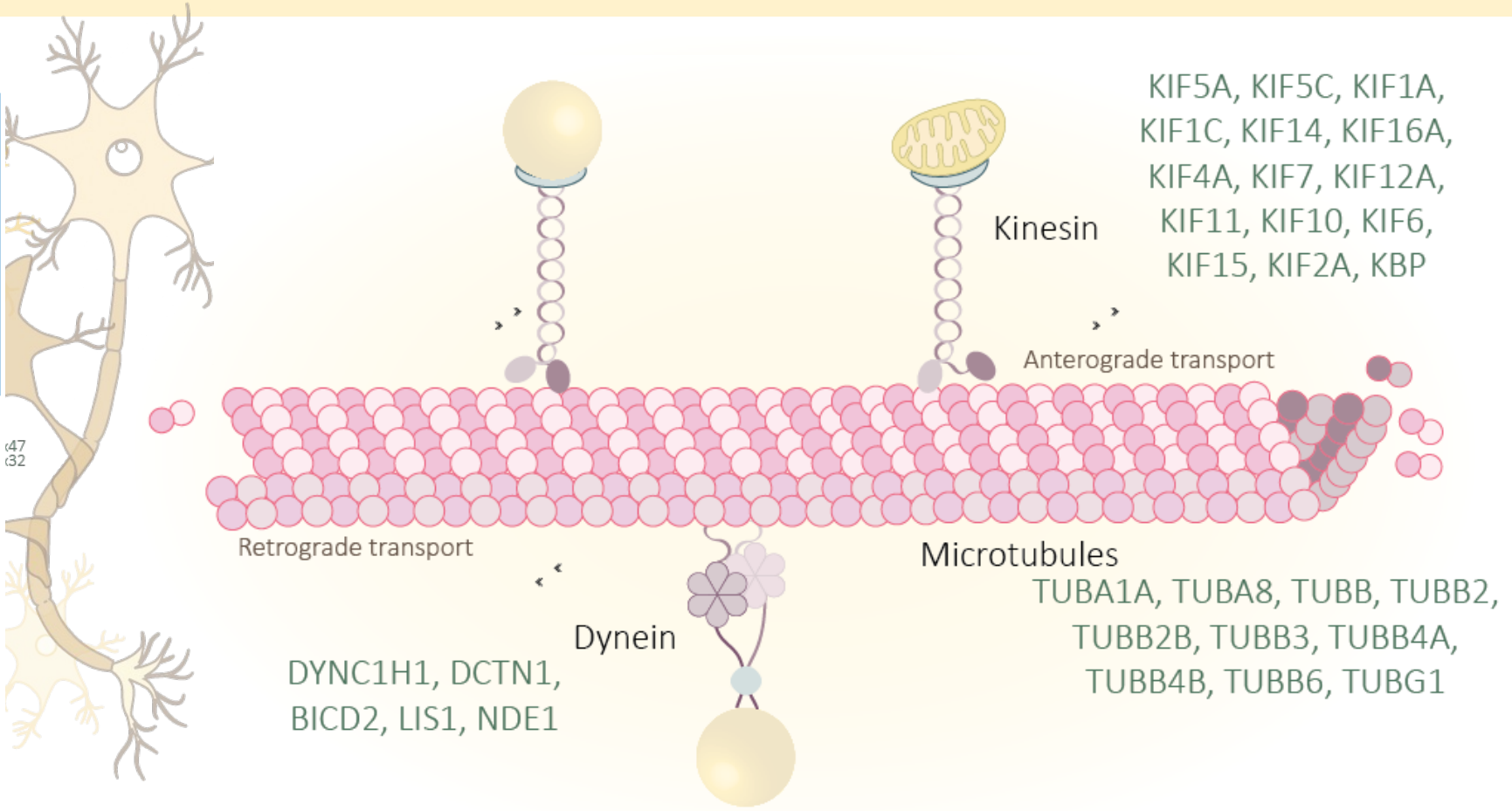
TRAFFICK ALONG CYTOSKELETON

“Cellular Highways”

Tract proteins



Motor proteins
KINESIN:
Anterograde
DYNEIN:
Retrogade



CLINICAL CASE, 15 year-old girl

10 years

Previos developmental delay. Acute presentation/ tone loss and falls episodes, bradykinesia, hypokinesia, upper limb rigidity and shoulder dystonia

12 years

Slow progression of symptoms ---Hypokinetic-Rigid pattern and later Dystonia-Parkinsonism

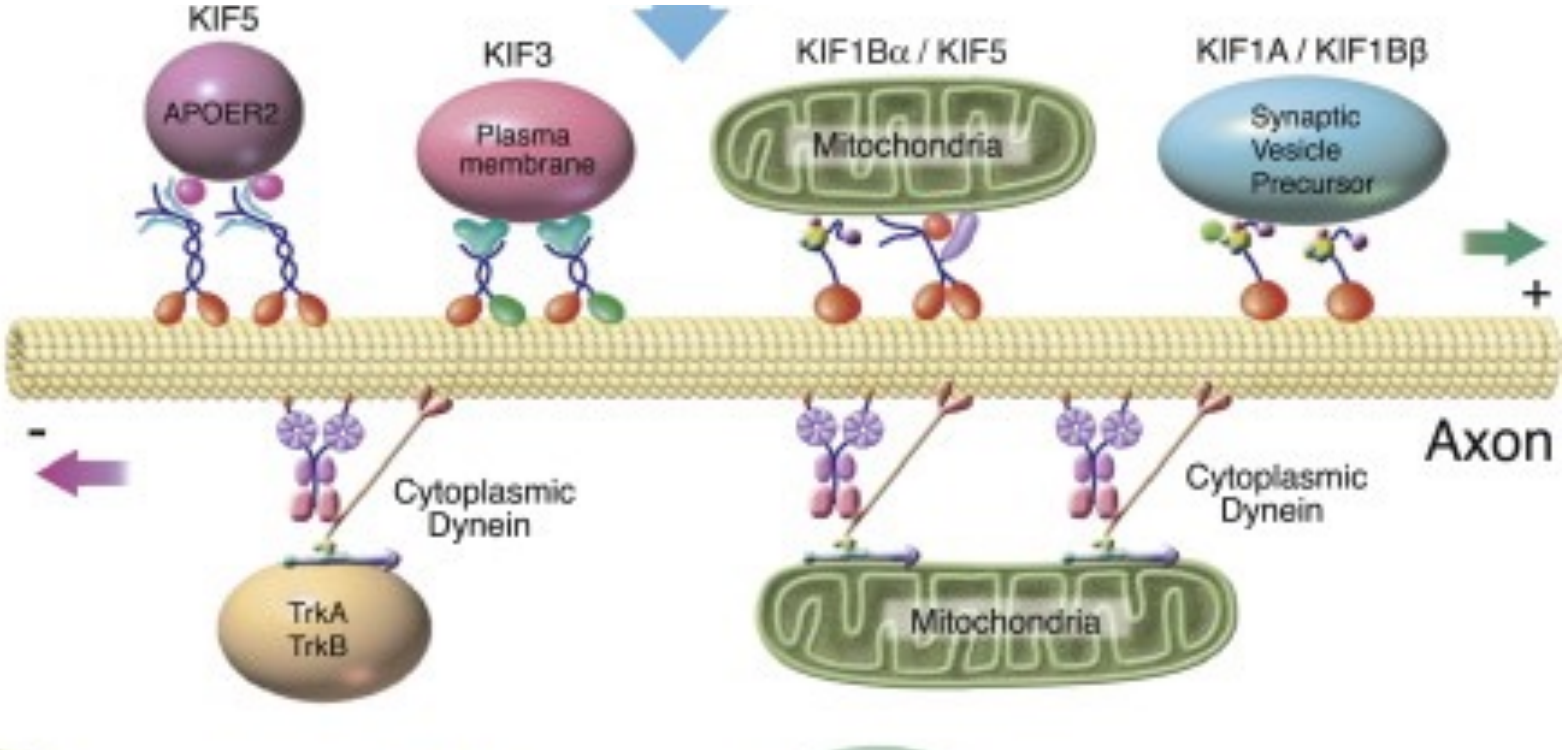
14 years

Motor regression, mild psychiatric symptoms (anxiety, insomnia), mild ID, obesity,
axonal neuropathy

Complementary exams--only abnormal finding:
CSF: low levels of HVA and 5-HIAA
Brain MRI: thalamus dysplasia

KIF1A (p.Ser104Phe/c.311C>T, heterozygous, DE NOVO

Confirmed by functional studies



Less synaptic vesicles availability

Less NT release???

Low concentration of NTs

6/15 patients show mitochondrial dysfunction in muscle biopsy studies
-Lipid accumulation
-Respiratory chain abnormalities (II+III)
-Low CoQ10 levels

Energy dysfunction in kinesin related disorders

GENERAL TRAITS OF CLINICAL PRESENTATIONS OF CYTOSKELETON TRAFFICKING DISEASES

Cortical Malformations

Early-onset encephalopathies

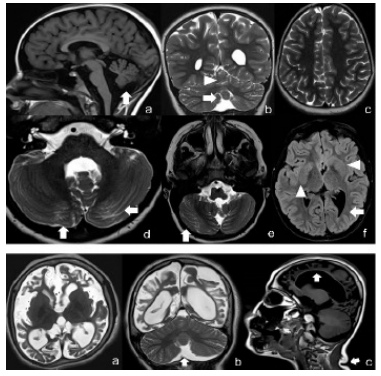
Late onset predominant
MOTOR symptoms

Neurodenerative conditions

Tubulinopathies

TUBB Variants Underlying Different Phenotypes Result in Altered Vesicle Trafficking and Microtubule Dynamics

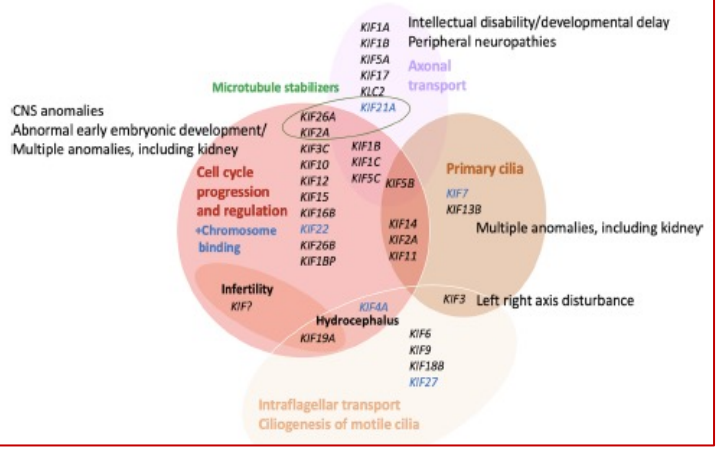
Antonella Sferra [1,*], Stefania Petrini [2], Emanuele Bellacchio [3], Francesco Nicita [1], Francesco Scibelli [4], Maria Lisa Dentici [5], Paolo Alfieri [4], Gianluca Cestra [6], Enrico Silvio Bertini [1] and Ginevra Zanni [1,*] *2020*

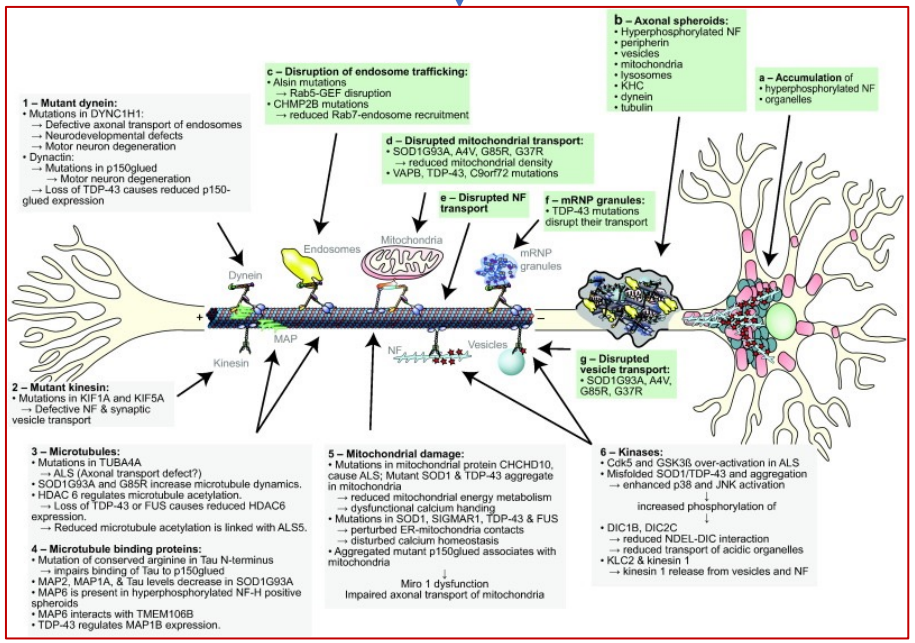


Kinesinopathies

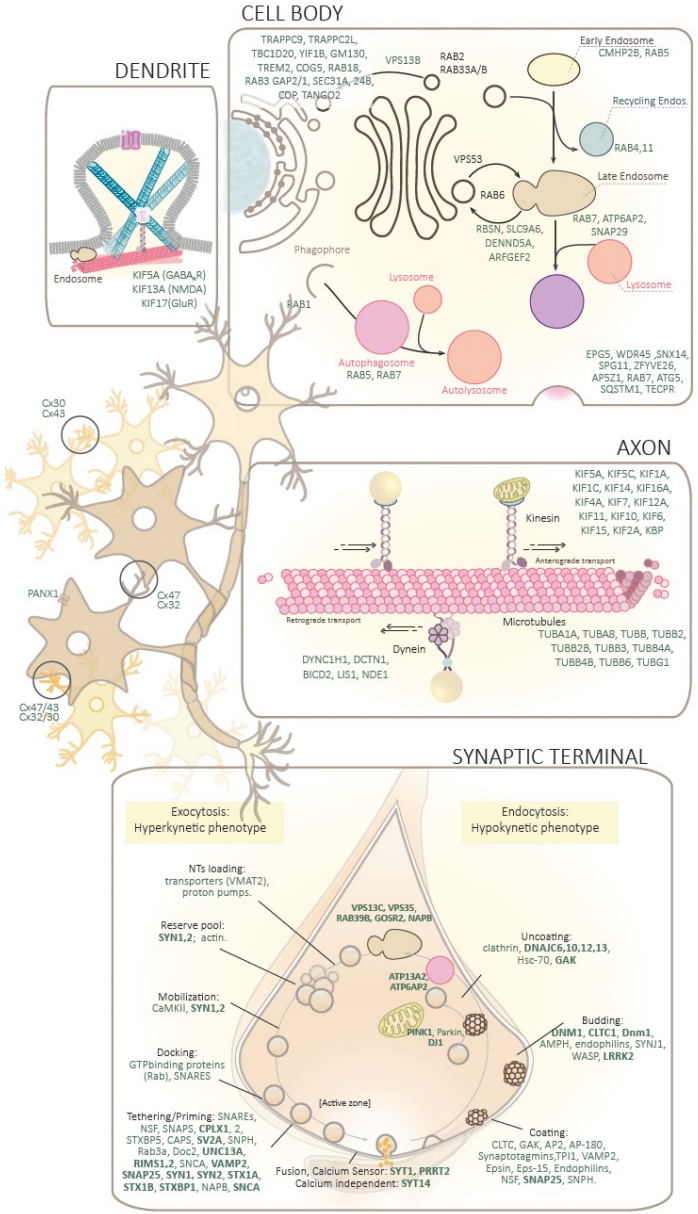
'Kinesinopathies': emerging role of the kinesin family member genes in birth defects

Silvia Kalantari [1], Isabel Filges [1,2] *2020*





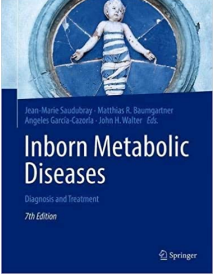
De Vos, 2017



Exocytosis/Endocytosis/Autophagy

Cytoskeleton

Synaptic vesicle cycle



Autophagosome

Endosome

Transmitter Loading: transporters (**VMAT2**), proton pumps

Reserve pool: synapsins, actin

Budding

Mobilisation: CaMKII, synapsins

Synapsin

RAB

VPS

PARK2

LRRK2

PINK1

DJ1

CPSα

SLC18A2

Uncoating: **clathrin**, **auxilin (DNAJC6),** Hsc-70

Budding: **dynamin1** **clathrin**, endodynamin, amphiphysin, endophilin, **synaptojanin 1**, WASP

Endocytosis

Clathrin CLTC

Docking: **GTPbinding proteins (Rab), SNARES**

Exocytosis

Active zones

Tethering/Priming: **SNAREs,** NSF, SNAPS, **Complexin 1**, 2, Tomosyn, CAPS, **SV2A**, Syntaphilin, Rab3a, Doc2. **STXBP1, UNC13A, RIMS1,**2, **SCNA, VAMP2, SNAP25, SYN1, SYN2, STX1B, NAPB**

Ca^{2+}

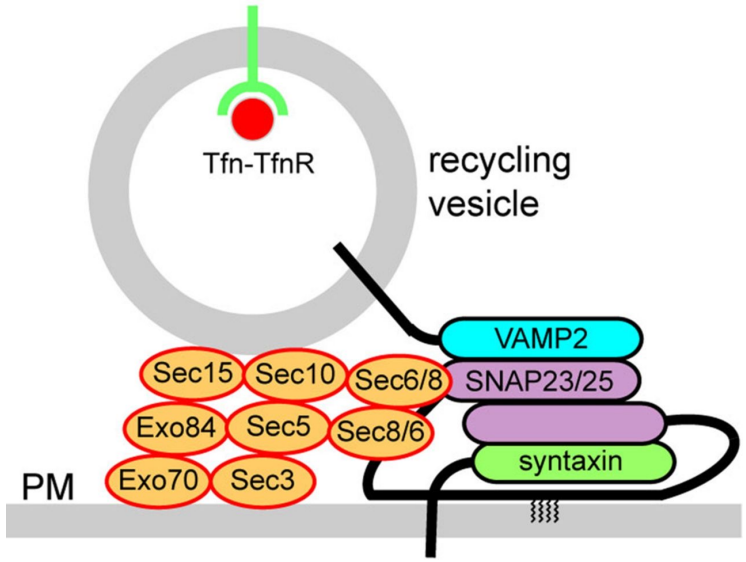
Fusion, Calcium Sensor: **Synaptotagmin: SYT1**

Coating: **clathrin, GAK**, AP2, AP-180, Synaptotagmins,**TPI1** Synaptobrevin, Epsin, Eps-15, Endophilin, NSF, SNAPS, Syntaphilin.

García-Cazorla et al, 2022

Mutations in the Neuronal Vesicular SNARE *VAMP2* Affect Synaptic Membrane Fusion and Impair Human Neurodevelopment

Salprieto et al, 2019



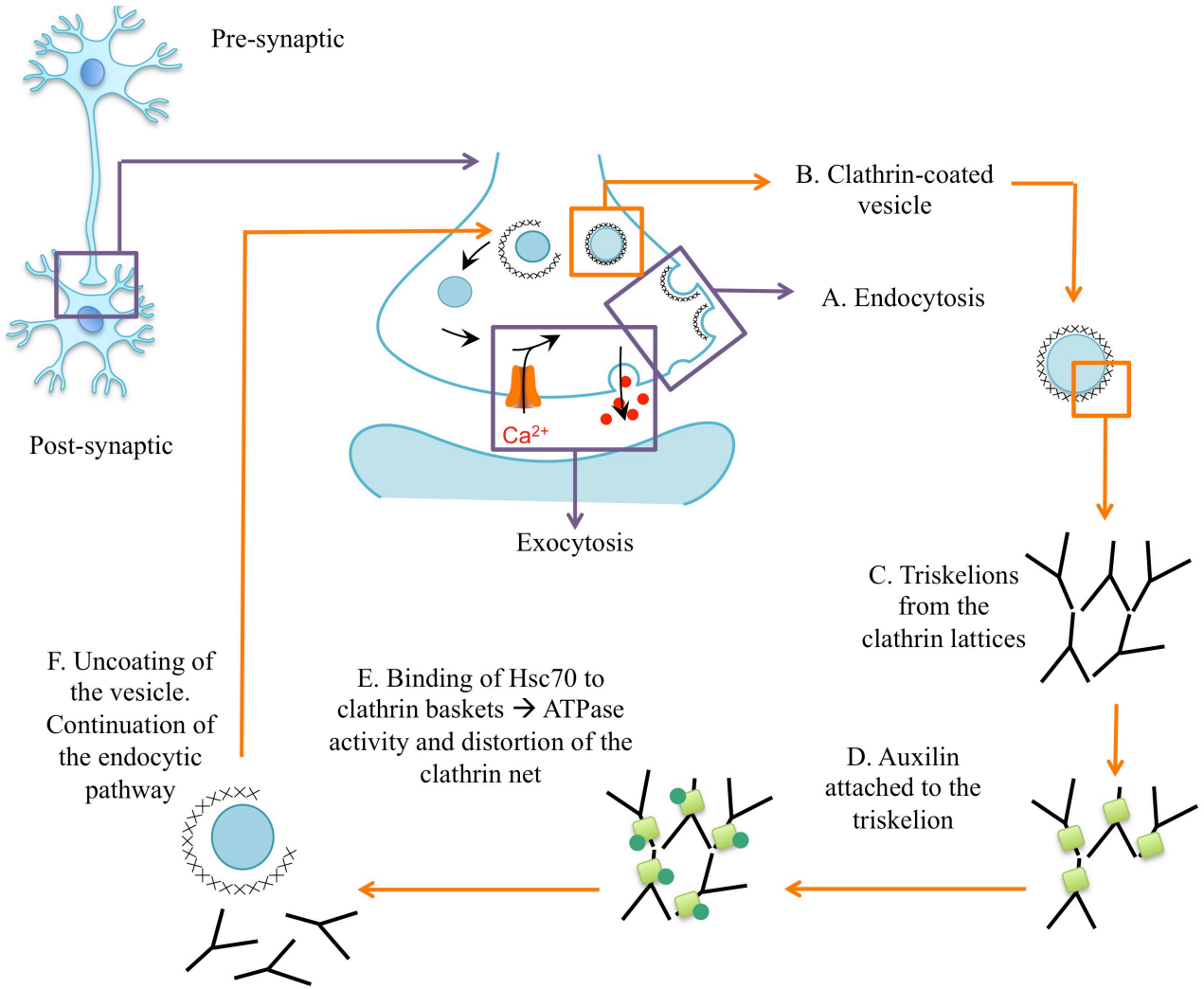
Kubo et al, 2015

VAMP1 (vesicle fusión at NM synapses)
-Spastic Ataxia
-Congenital myasthenic syndrome

DNAJC6 Mutations Disrupt Dopamine Homeostasis in Juvenile Parkinsonism-Dystonia

STARTING AT 7-10 YEARS

LOW HVA



DNAJC6 encodes **auxilin**, a chaperone protein that plays a major role in clathrin-coated vesicle dynamics.

Ng and Cortès-Saladelafont, 2020

MESSAGES, ALGORITHMS

Overview of proteins and genes involved in cell trafficking

VESICULAR TRAFFICKING

Families of proteins involved in membrane trafficking diseases:

-**COAT** protein complex related
-TRAFFICKING PROTEIN PARTICLE COMPLEX (TRAPPCpathies)
-VACUOLAR PROTEIN SORTING (VPS)
-**SNARE** related proteins
-ADAPTOR RELATED PROTEIN COMPLEX defects, "Adaptinopathies":
-CAVEOLIN proteins
-TBC proteins
-RAB proteins
-SCL (solute carrier family) proteins
-ATP (ATPases) proteins

Other proteins involved in vesicular trafficking :

OCRL1, UNC45A, PRF1 , ARFGEF2 , TRIP11, NBEAL2 , MBL, MCFD2, DYM, SH2D1A, XIAP, ITK, CD27, MAGT1, SKIV2L, TTC37, ACTN1, RUNX1, FLY1, PAX3, MITF,TYR, EIF2AK3, SAR1B , SUMF1 , MCFD2, SPATA16, GORAB, FGD1, INPP5E, MORMS; MYO5B, BIN1, MTMR14, HCFC1 , CHMP2B, 4B, ELMO2, EPS15L1, GPNMB, IQCF, CNPY3, KIAA1109, ERGIC1, CLTRN, DYSF, DKC1, NFE2L2, WFS1, NUP107, HYOU1, ALMS1, ARCN1, ATF6, DCN, FYCO1, IGF2R, IL17RD, LMAN2L, LRBA, OPTN, OSBPL2 ,PLEKHM1, SORT1, STX16, GET4

ORGANELLE AND INTERORGANELLE TRAFFICKING

GOLGI-RELATED DEFECTS ("golgipahies")

-TRAPPC: *TRAPPC6B, 6A, C12, C9 , C11*
-VPS: *VPS13B, VPS53, VPS51, VPS15*
-RAB: *RAB3GAP1, RAB3GAP2, RAB18*
-OTHER proteins that interact with RAB are codified by the genes: *RUSC2, COL4A3BP, BIG2, COSR2, CDC42, TBC1D20, TBC1D23*. CDGs (COG complex, SLC35A and TMEM165): see Chapter X (CDG);
-Other Golgipathies: *WDR62, CDK5RAP2, SLC9A6, DENND5A, HERC1, STRADA, RAC1, GD1, PACS1, BICD1, KIF1C, TANGO2, GOSR2, FAM134B, OSBPL2*

LYSOSOME RELATED DEFECTS

-Biogenesis of lysosomal related organelles complex (**BLOC**)
-Lysosomal Trafficking Regulators
-MYO5A; **-RAB27A**

MEMBRANE CONTACT SITES

CERT, EMC1, ACBD5, BCAP31, VAPB, TDP-43, ADRA1A, VAP9, PSEN1, REEP1, VPS13A, MFN2, SNCA, VPS13C, PACS2, VDAC1, SigR1

LIPID DROPLET RELATED

BSCL2, REEP1, ATL-1, SPAST, ABCD1, VPS13A,VPS13C.

AUTOPHAGY

EPG5, WDR45 ,SNX14, SPG11, ZFYVE26, AP5Z1, TECPR2, RAB7, ATG5, PARK2 , PINK, SQSTM1
SPG52, 47, 50, 51, ALSJ, ALS17, FIG4, CHMP2B, MTMR13

CYTOSKELETON PROTEINS INVOLVED IN AUTOPHAGY

DCTN1, MTMR14, DNM2

CYTOSKELETON RELATED

ANTEROGRADE TRANSPORT (KINESIN DEFECTS)

KIF5A, KIF5C, KIF1A, KIF1C, KIF14, KIF16A, KIF4A, KIF7, KIF12A, KIF11, KIF10, KIF6, KIF15, KIF2A, KIF1BP/KBP

RETROGRADE TRANSPORT (DYNEIN DEFECTS)

DYNC1H1, DCTN1, BICD2, LIS1, NDE1

MICROTUBULE NETWORK DEFECTS

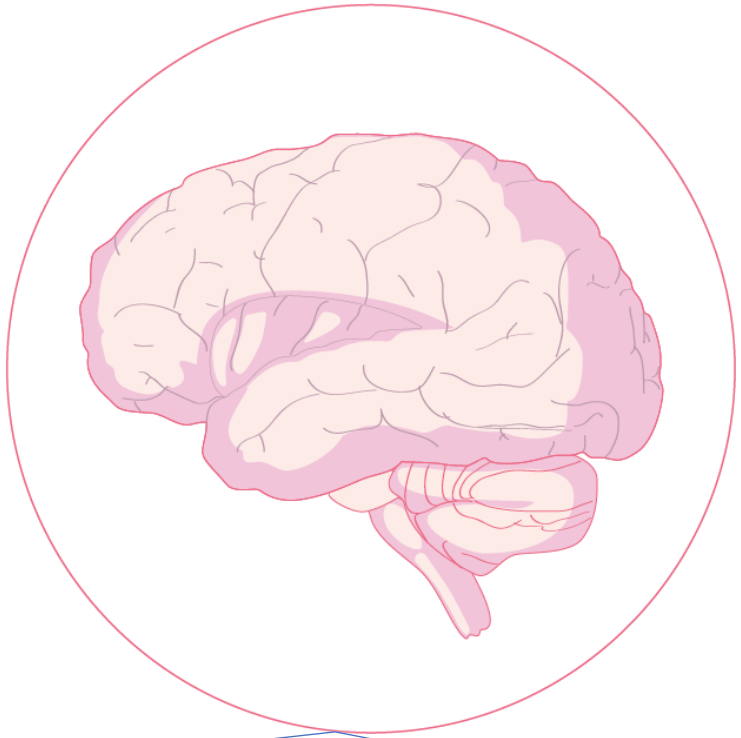
Tubulinopathies: *TUBA1A, TUBA8, TUBB, TUBB2, TUBB2B, TUBB3, TUBB4A, TUBB4B, TUBB6, TUBG1*
Related to other cytoskeleton proteins: *MTMR14, DNM2*

OTHERS

Membrane phospholipid regulators defects: Flippases defects (*ATP8A2, ATP8B1, ATP11C, ATP13A2, ATP1A3*);
Brain barriers transcytosis defects: *FOLR1*;
Glial trafficking defects: *GJB1, GJC2, Panx1*; Neuronal receptors and cell adhesion molecules (CAM) trafficking defects: Neuroligins, *SLITRK1, JAKMIP1, CNTNAP2*

(A Garcia Cell trafficking in IMD 7th 2022 chapter 44)

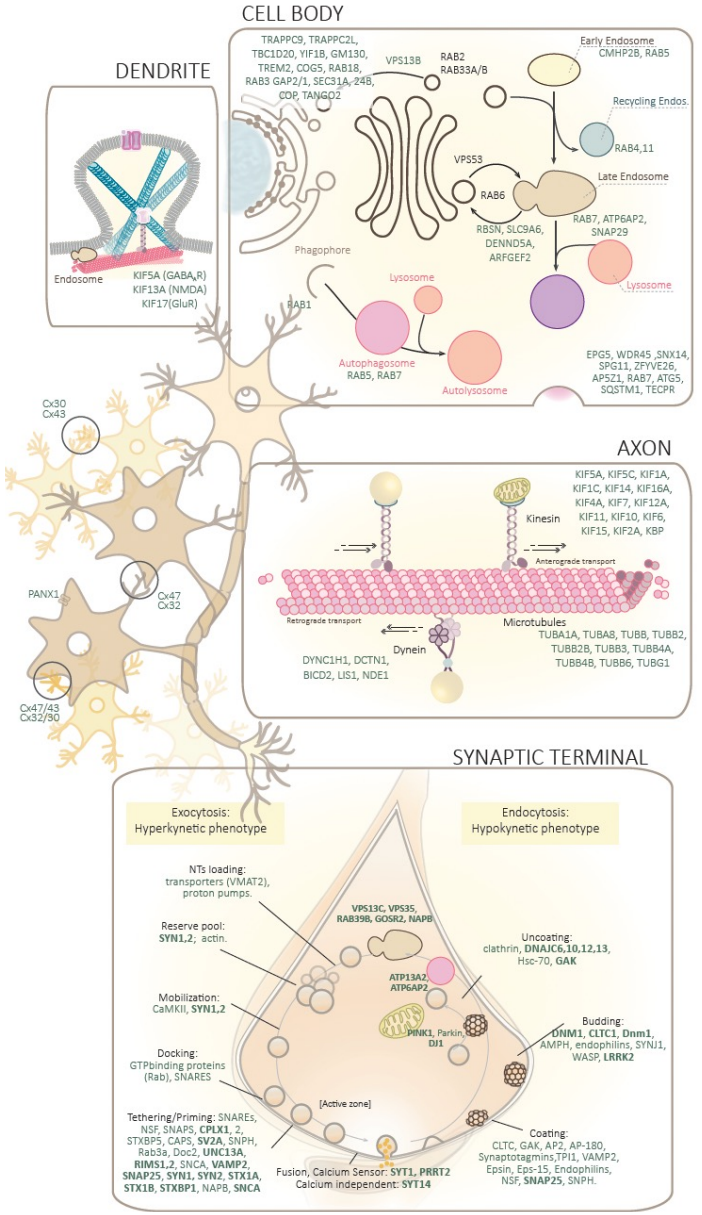
NEUROLOGICAL SYMPTOMS++++



Early onset

Microcephaly
Complex Neurodevelopmental encephalopathies

Late onset: MOTOR disorders



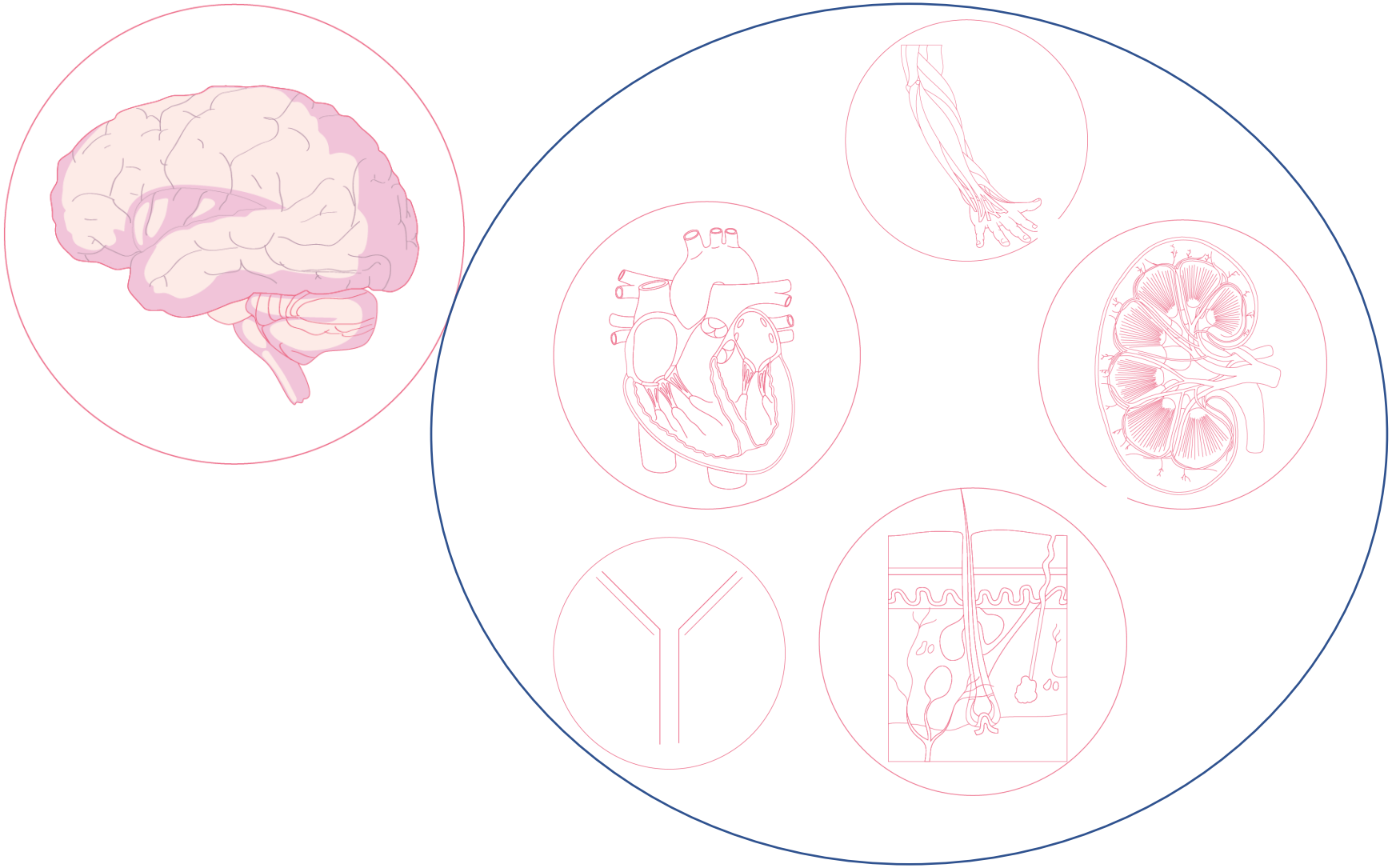
-NRL+ExtraNRL
Endocytic:
-Neurodegenerative

-Brain Malformations
-Spastic Paraparesis
-Motor Symptoms

“Synaptopathies”

Combination ID+/-Epilepsy+/-MovDis +/-Neuropsychiatric symptoms (autism)

MULTISYSTEM DISORDERS



EARLY ONSET ENCEPHALOPATHIES

Complex global encephalopathies, **microcephaly ++, brain malformation (+/-), epileptic encephalopathies**

GOLGIPATHIES

COPB2, COPD, CDK5RAP2, ZNHIT3, AP4E1, WDR62, SLC9A6, AP1S2, DENNDA, RAC1, DYM, RAB proteins (*RAB3GAP1, 2, RAB18*), TRAPPCpathies (*TRAPPC9,11,12,6A, 6B, 4), COL4A3BP, AP1S1 ARFGEF2, CDC42, VPS13B,VPS53, VPS51, VPS1, TBC1D23, TBC1D20.*

CYTOSKELETON DISORDERS

-Kinesin (Anterograde Transport) deficiencies and NDE1 deficiency (Dynein Retrograde Transport): NudE neurodevelopmental protein 1): *KIF5C, KIF10, KIF2A, KIF14, KIF16A, KIF7, KIF15*, Kinesin-binding protein *KIF1BP/KBP, KIF5A, NDE1*.

-Tubulins (microtubule network): *TUBA1A, TUBA8, TUBB, TUBB2A, TUBB2B, TUBB3, TBCD, TUBG1*

With MULTISYSTEM involvement

WITH ARTHROGRYPOSIS: *SLC35A3* (is a CDG), *ERGIC1*, *KIAA1109* (Alkuraya-Kucinskas syndrome (arthrogryposis, Dandy-Walker) VPS33B and VIPAS39 (lysosome-interorganelle): ARC1 and ARC2

WITH RHABDOMYOLISIS (and Epilepsy and microcephaly): TRAPPC2L (ER-Golgi transport): may have also late-onset presentation. TRAPPC11 and TANGO2 (may present with metabolic crises, mild hyperammonaemia and hypoglycemia, long QT, but also other late NRL forms such as ID, spastic paraparesis and myastheniform symptoms)

WITH DIVERSE ORGAN INVOLVEMENT: SUMF1 (Multiple sulfatase deficiency), SNAP29 (CEDNIK syndrome; is a SV), OCRL: Lowe syndrome, Dent disease 2 and 1 (CLCN5); TBCD: Hypoparathyroidism-retardation-dysmorphism syndrome; TBCE: Encephalopathy, progressive, with amyotrophy and optic atrophy

SYNAPTOPATHIES
SV cycle

PREDOMINANT MOTOR DISORDERS

May appear at any age (most childhood-adulthood onset). **Neurodegenerative diseases**

ATAXIA

VPS13D (SCA4), *RUBCN* (SCA15), *SIL1, SCYL1 (SCA21), GORS2* SNX14, ATG5, SPTBN2 (SCA5 and 14), KIF1C (spastic ataxia)

SPASTIC PARAPARESIS

SPAST and *ABCD1*: FA trafficking from LDs into peroxisomes (different types of SP: SPG4, 52, 47, 50, 51) *SPG11* (spatacsin): Type1 SP type 11; Other phenotypes: CMT2; ALS type5.Spastizin *(ZFYVE26)*: SP type 15 or Kjellin síndrome; *TECPR2*: SP type 49; *AP5Z1*: SP type 48 REEP1 (SPG31), KIF1C (spastic ataxia 2, SPG 58); KIF5A (various phenotypes all AD: SPG10, CMT2, ALS); KIF1A (SPG30), TANGO2, SLC33A1(SPG42), AP related genes are also Golgipathies, ATL1 (atlastin); AP4B1, AP4E1(Complex Spastic Paraparesis), WASHC5 (SPG8), NIPA1 (magnesium transporter): SPG6; MAST syndrome: SPG21; SPART: Troyer Syndrome, SPG20. Infantile onset: AP4E1, AP4M1, AP4S1. APSZ1: progressive SP;MTGFBR1:onset in the first decade; VPS37A: early onset SP with pectus carinatum and hypertrichosis; ARL6IP1, UBAP1

PARKINSONISM and other MD

FIG4: Yunis-Varon syndrome; type 2 (SDCO): Striatonigral degeneration, childhood-onset; *PRKN:* PARKIN deficiency (Parkinson Disease 2); *PINK1*: Parkinson Disease 6: *NADGP*: Neurodegeneration with ataxia, dystonia and gaze palsy VPS13C: Early-onset parkinsonism (may also cause Leigh-like features); ATP6AP2: Early-onset PARKINSONISM; VPS13A: chorea-achantocytosis; VPS16, VPS4: early-onset dystonia. These are also lysosome-related disorders; GAK. LRRK2: diversity of clinical phenotypes; RME-8; SYNJ1: pediatric-juvenile onset PD; VPS16: adolescence-onset dystonia; VPS26A: atypical PD, no L-Dopa response. VPS35: parkinsonism, ATP8A2: cerebellar ataxia and atrophy, ID, chorea, severe hypotonia, optic atrophy; ATP1A3: Cerebellar ataxia, areflexia, pes cavus

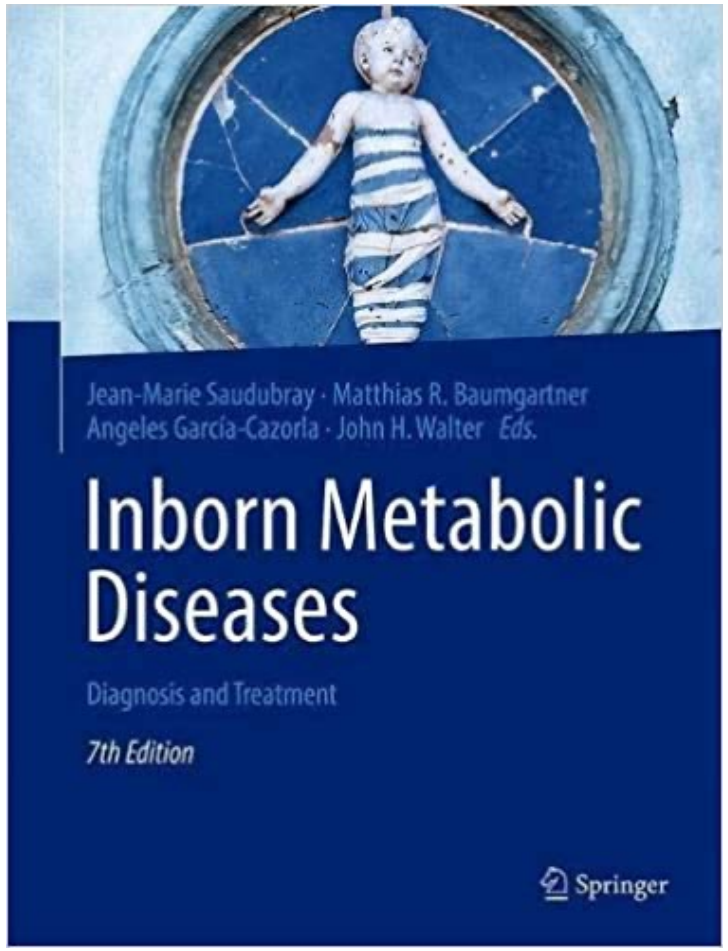
AMIOTROPHIC LATERAL SCLEROSIS

SPINAL MUSCLE ATROPHY

PERIPHERAL NEUROPATHY

DEMENTIA

(A Garcia Cell trafficking in IMD 7th 2022 chapter 44 in press)



Trends in Genetics

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Review

Genetic disorders of cellular trafficking

Angeles García-Cazorla,[1,4,*] Alfonso Oyarzábal,[1,4] Jean-Marie Saudubray,[2] Diego Martinelli,[3] and Carlo Dionisi-Vici[3,*]