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Review

Genetic disorders of cellular trafficking

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Cellular trafficking is essential to maintain critical biological functions. Mutations in 346 genes, most of them described in the last 5 years, are associated with disorders of cellular trafficking. Whereas initially restricted to membrane trafficking, the recent detection of many diseases has contributed to the discovery of new biological pathways. Accordingly, we propose to redesign this rapidly growing group of diseases combining biological mechanisms and clinical presentation into the following categories: (i) membrane trafficking (including organelle-related); (ii) membrane contact sites; (iii) autophagy; (iv) cytoskeleton-related. We present the most recently described pathophysiological findings, disorders and phenotypes. Although all tissues and organs are affected, the nervous system is especially vulnerable.

Highlights

The machinery of proteins and the mechanisms that regulate cell trafficking is of great complexity. In the last few years, the discovery of new genetic diseases linked to cell trafficking has enormously grown.

In addition to membrane trafficking, other mechanisms such as membrane contact sites and cytoskeleton transport arise the question of establishing a more inclusive concept of cellular trafficking and related disorders.

The nervous system is particularly affected and includes both early onset encephalopathies and late onset presentations, mostly motor and neurodegenerative disorders.

The prodigious expansion of genetic disorders that impact cellular trafficking raise the question of reclassifying inherited metabolic disorders according to a holistic cell physiological approach rather than to the classic separation between intermediary metabolism, organelles and structural proteins.

General aspects of cellular trafficking and related diseases

The definition of cellular compartmentalization was first based on the anatomical existence of individualized organelles. Recently, it has been extended to the concept of spatial segregation of macromolecules, metabolites, and biochemical pathways connecting organellar structure and function which must be considered both spatially and temporally [1]. Cellular trafficking is a tightly regulated machinery allowing the exchange of signals and metabolites between cellular compartments. Classically, the concept of cellular trafficking and associated diseases was limited to '**membrane trafficking**' (see Glossary) and the major communication process between the compartments: vesicular transport. Vesicular transport enables proteins in membrane-bound vesicles to move between the cell compartments, including the plasma membrane [2]. Today, cutting-edge structural methods, biochemical, computational approaches, and descriptions of new mechanisms and genes involved in these processes, pushes the understanding of cell trafficking and related diseases to unprecedented levels of complexity [3]. The recent discovery of a new mechanism regarding the exchange of signals and metabolites at regions where organelles form functional contacts, 'membrane contact sites' [4] together with other mechanisms of cargo moving and molecular processing such as **autophagy** and transport along the **cytoskeleton**, lead us to propose a more inclusive and clinical oriented concept of 'cell trafficking'.

The number of monogenic diseases of cell trafficking has also exponentially increased from 49 causing genes described in 2011 [5] to 346 genes by now (Table S1 in the supplemental information online). The vast majority of mutations cause a loss of function of transport machinery that involve many organs and systems, especially the nervous system [6]. Monogenic diseases of cell trafficking form the largest group in the recent International Classification of Inherited Metabolic Disorders (ICIMD) [7] and must be included in diagnostic algorithms [8]. Most of these new disorders have been documented in the past 5 years, thanks to the improved use of next-generation genetic sequencing techniques.

This review aims to redesign this category of new diseases focusing on pathophysiological mechanisms, combining the biological basis with a practical medical orientation. In this sense, the angle of the article differs from other reviews that in general, consider cell trafficking as a process

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Table 1. Pathophysiological categories of cell trafficking and IMD

Category	Belongs also to the generic concept of 'membrane trafficking'	Fits into the updated concept of 'IMD'
Membrane trafficking	Yes. It includes 'organelle-related trafficking diseases'	Yes. Not all of them are included in the ICIMD (Table S1)
Membrane contact Sites	No	Yes. Not all of them are included in the ICIMD (Table S1)
Autophagy	Yes	Yes. Not all of them are included in the ICIMD (Table S1)
Cytoskeleton related	Cytoskeleton contributes to almost all types of membrane trafficking	No. Maybe in the future as we have better knowledge on the connection of cytoskeleton and biochemical pathways)
Other types	No. gap junctions (intercellular glial channels) (Table S1 and Table 2) Yes. other types of trafficking not involved yet in human diseases such as exosome formation or **unconventional protein secretion (UPS)**	No
Neuronal trafficking is not an additional category but an example of highly specialized and compartmentalized cellular trafficking that includes the abovementioned categories.		

restricted to membrane trafficking. In order to delineate this inclusive approach, we propose pathophysiological categories that are based on the function of the specific proteins implicated in traffic known to be involved in human disease. These categories are the following: (i) membrane trafficking (vesicular trafficking) including organelle-related; (ii) membrane contact sites; (iii) autophagy; (iv) cytoskeleton-related trafficking. Although these categories may overlap from a mechanistic point of view (Box 1), this stratification aims at being useful for clinicians. In fact, although membrane vesicular trafficking encompasses all membranous vesicle trafficking including autophagy and movement of cargo along the cytoskeleton, the main objective of this

Box 1. Inherited metabolic diseases and cell trafficking disorders

The updated concept of Inborn Metabolic Diseases (IMD) includes any condition in which primary alteration of a biochemical pathway is intrinsic to specific biochemical, clinical and/or pathophysiological features, regardless of whether there are abnormalities in currently available biochemical laboratory tests. The recent ICIMD currently encompasses more than 1400 disorders [7]. The great expansion of IMD as stated in the ICIMD [7] and the simplified classification of IMD [8] is based on the increasing importance of complex molecule metabolism, mostly lipids, and their connection with cell biology processes and intracellular trafficking. The group of IMD that was initially related to cell trafficking was limited to the Congenital Disorders of Glycosylation (CDG) defects in the synthesis of glycans to proteins and lipids. Patients with CDG show a broad spectrum of clinical manifestations, in particular multi-organ disease with neurological symptoms [9]. For a long time, isoelectrofocusing (IEF) of serum transferrin was a biomarker for CDG diagnosis widely available in many clinical laboratories. The generalized introduction of whole exome sequencing allowed to detect not only new CDG without abnormal IEF patterns, but also other disorders of cell trafficking involved in different pathways than glycosylation. However, only certain Golgi trafficking defects are CDG. This could be explained by the fact that some gene mutations alter recycling vesicles that are linked to components of Golgi glycosylation machinery [10]. Additionally, ion homeostasis, vesicular and intraluminal pH is essential for glycosylation. Therefore, cell trafficking disorders that impair ion concentration and/or pH may also affect glycosylation. As an example, patients' cells with mutations in ATP6V0A2 (cutis laxa type II), coding for a subunit of the Golgi-V-ATPase, exhibit glycosylation and membrane trafficking defects.

In this review we will consider the new cell trafficking disorders (beyond CDG), most of them still not included in the ICIMD, which include only some disorders of vesicular trafficking and membrane contact sites. Table S1 highlights those disorders that fit into the definition of IMD but are still not included in the ICIMD. Although we have not considered those defects involved in cytoskeleton transport as IMDs, we have included this category under the umbrella of cellular trafficking because the cytoskeleton has a major role in these processes. However, the interaction with classical biochemical pathways is starting to be described now.

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Glossary

Autophagy: conserved process of degradation of the cell that removes dysfunctional components.
Adaptor proteins: complex of proteins involved in the trafficking of vesicles. They concentrate the cargo molecules in the forming vesicle and travel to the destination, where the cargo is delivered. Defects in these proteins result in adaptinopathies.
COAT protein complex II (COPII): vesicles that move cargo from the ER towards the Golgi (secretory pathway).
Cytoskeleton: complex and dynamic network of interlinking protein filaments, including proteins such as actin, myosin, or tubulin. Dyneins and kinesins bind to the cytoskeleton for the transportation of cargoes.
Endocytosis: process of uptake of a cargo into a cell by a plasma membrane invagination, folding over the substance and enclosing it into a vesicle moved into the cytoplasm.
Endosomes: vesicles that mostly originate from the TGN and are part of endocytic membrane transport pathway.
ER-Golgi intermediate compartment (ERGIC): vesicular-tubular cluster that mediates trafficking between the ER and Golgi complexes. COPII-coated vesicles bud from the exit sites in the ER and fuse to the ERGIC. Retrograde transport in COPI vesicles returns ER-resident proteins back to their origin.
Exocytosis: process of liberation of a vacuole content out of the cell. The vesicle containing the cargo fuses its membrane with the plasma membrane, releasing the content to the extracellular space.
Homotypic fusion and protein sorting (HOPS) complex: structural bridge for the fusion of late endosomes and autophagosomes with lysosomes. Defects on the proteins of this complex produce neurological disorders referred to as HOPSANDs.
Membrane contact sites (MCS): areas of contact between the membranes of two organelles. Fulfilling a specific function, such as transport of molecules or signaling information.
Membrane trafficking: process by which proteins and macromolecules are distributed throughout the cell.
Phosphoinositides (PIPs): acidic phospholipids in cell membranes that interact with proteins. Each cellular membrane compartment uses a

that fit into the definition of IMD but are still not included in the ICIMD. Although we have not considered those defects involved in cytoskeleton transport as IMDs, we have included this category under the umbrella of cellular trafficking because the cytoskeleton has a major role in these processes. However, the interaction with classical biochemical pathways is starting to be described now.

Regarding the stratification of cell trafficking categories suggested in this article, it is important to remark that there is some overlap on the pathophysiological mechanisms. Table 1 clarifies this issue.

categorization is to organize the large number of diseases included, into comprehensive clinical-pathophysiological groups. This categorization may also be useful for therapeutic strategies, since specific therapies that regulate autophagy or cytoskeleton-related disorders are being currently developed.

This review uses a double approach based on classic well-known mechanisms together with the most recent pathophysiological insights and new disorders.

Categories of cellular trafficking

Membrane trafficking

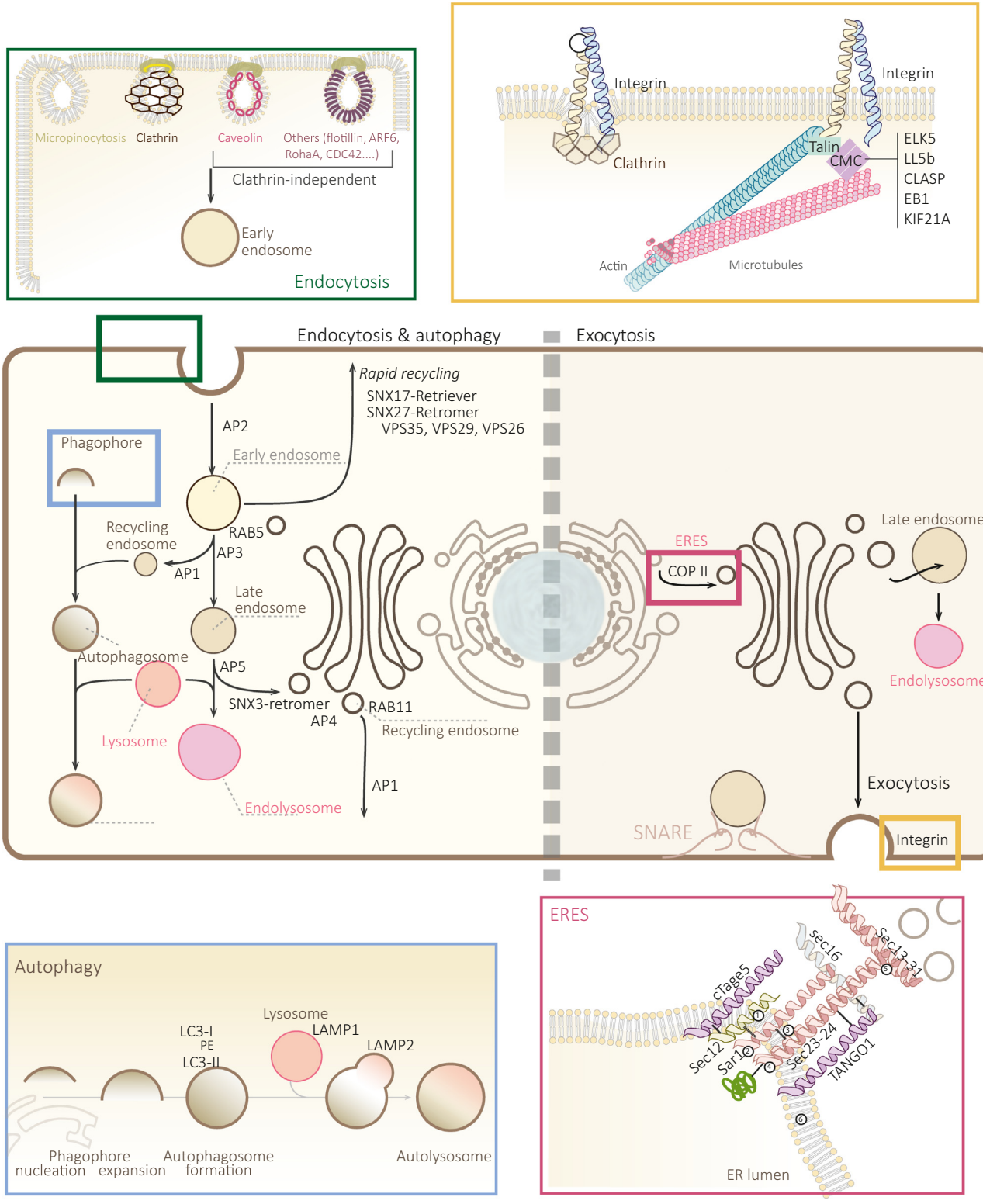
Membrane trafficking includes the full range of processes that go into the movement of cargo using membrane-bound transport vesicles (vesicular trafficking). This transport can take place within different organelles in the same cell, or across the cell membrane [2,11]. Membrane trafficking can be divided into two pathways: **exocytosis** and **endocytosis** (Figure 1).

Exocytosis refers to the movement of cargo to the plasma membrane (PM) or out of the cell (Figure 1). The 'secretory pathway' is a foundational system to distribute membrane and secretory proteins [12]. Recent breakthroughs in understanding the basic building blocks of exocytosis highlight the first step of biosynthetic secretion mediated by **coat protein complex II (COPII)**, the organization of membranes at the endoplasmic reticulum (ER)–Golgi interface, and the regulated biosynthetic secretion from the ER (Box 2). Some of these new aspects include the function of ER exit sites (ERES), the specialized domains on the ER membrane dedicated to the export of proteins [13]. ERES-resident proteins include Sec16A and TANGO1 complexes, which support the nucleation of the coat and function as 'primers' in initiating the cascade of coat assembly, cargo selection, and carrier fission during biosynthetic exit (Box 2). Electron microscopy has recently allowed the discovery of the 3D ultrastructural organization of ERES, an intricate network of tubules connected by a neck to the ER as an inter-organelle transport apparatus that modulates its shape and size while directing diverse cargo types to the Golgi [14]. Many fundamental questions remain unsolved such as how budding sites are defined, what is the structure of native COPII coat, and the details of ER/**ER-Golgi intermediate compartment (ERGIC)** secretory pathway organization and function. In this sense, a working model for COPII-mediated transport includes a series of steps that act in a coordinated fashion at the ER/ERGIC interface [13].

Regarding Golgi to PM carriers (post-Golgi trafficking) information on the molecular machinery involved still remain controversial. Some candidates include Arf1 positive tubular carriers (Arf1is a small GTPase that induces membrane curvature and recruits lipid-modifying enzymes), LAMP1 carriers (LAMP1 is a lysosomal protein that allows post-Golgi tubular carriers to reach the cell surface before being recycled to the endolysosomal compartments), Rab6 associated carriers (Rab6 regulates vesicle fission), CtBP1-S/BARS carriers (with an essential role in vesicular fission), sphingomyelin carriers, and CARTS [CARriers of the trans-Golgi network (TGN) to the cell surface] [15].

Endocytosis is the opposite movement: the cargo moves into the cell from the PM and can be used for the uptake of nutrients or to direct cargo for recycling or degradation via autophagy.

characteristic species of phosphoinositide.
Retromer: complex of proteins that participate in recycling transmembrane receptors from endosomes to the TGN.
SNARE proteins: soluble N-ethylmaleimide–sensitive fusion factor (NSF) attachment protein receptor group of proteins involved in the correct fusion of membranes between vesicles and cell compartments. They are present in both membranes, bringing them together to allow for fusion. Pathological defects due to mutations in any of these proteins are called SNAREopathies.
TRAPP complex: multi-subunit protein complexes that participate in the vesicles transport pathways between intracellular compartments. Disorders in these proteins result in the so called TRAPPC-opathies.
Unconventional protein secretion (UPS): comprises cargoes without a signal peptide or a transmembrane domain that can translocate across the plasma membrane, and cargoes that reach the plasma membrane by bypassing the Golgi despite entering the ER.
Vacuolar Protein Sorting: group of proteins involved in the intracellular sorting and delivery of vacuolar proteins.



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Box 2. Axonal and cytoskeleton-related trafficking defects (axonal, cytoskeleton, synaptic vesicle cycle and dendritic compartments)

Most of the mutated genes associated with neurological defects cause late-onset motor diseases and early-onset encephalopathies with cortical migration abnormalities (Tables S1 and 2 and Figure 3). DYNC1I2 mutations alter the dynein cytoplasmic complex and cause a new disease characterized by congenital microcephaly, brain malformations, and dysmorphic features [82]. DPYSL5 mutations cause a recently described NDD with corpus callosum agenesis and cerebellar abnormalities due to MAP2 and betaIII-tubulin impairment [83]. Dominant or *de novo* mutations in tubulin genes (Tables S1 and 2) are 'tubulinopathies'. They cause a broad spectrum of cortical (lissencephaly, polymicrogyria, dysplasia, simplification) and subcortical (corpus callosum, hindbrain, and basal ganglia) malformations [84].

Synaptic vesicle cycle disorders

At the presynaptic neuron, neurotransmitters are packed into synaptic vesicles (SVs), that translocate to the active zone, where they dock through interaction of the SV protein synaptobrevin 2 and the PM proteins SNAP25 and syntaxin 1, that form the SNARE complex. When membrane depolarization occurs, massive Ca^{2+} influx evokes an ultrafast SV fusion with the PM. The SV proteins, as well as the SV membrane, are then retrieved in an endocytotic process that can be clathrin-independent or -dependent. Mutations in SV exocytosis include SNAREopathies and other genes that may alter NT homeostasis by interacting with SNARE proteins [85,86] (Figure 3). They present as NDDs with developmental delay, epilepsy, movement disorders (mostly hyperkinetic), and neuropsychiatric signs including autism spectrum. The most prevalent are MUNC18-1/STXBP1 and STX1B [86]. Mutations in SV endocytosis are mostly involved with early-onset but also late-onset parkinsonism, although other symptoms may be also present (Figure 3).

Dendrites (Figure 3)

Neuronal dendrites are highly specialized compartments with distinct structures, protein content, secretory organelles, and a unique cytoskeletal organization that includes microtubules of mixed polarity. Mechanisms that control membrane traffic in dendrites and cytoskeleton transport are just being deciphered [87]. Describing the complexity and ultra-specialization of trafficking in dendrites goes beyond the scope of this article. Genetic disorders that occur at the dendritic level include clathrin adaptor protein mutations, reported in patients with ID, epileptic encephalopathy and spastic paraparesis and kinesin-1/KIF5-mediated transport of $GABA_A$ receptors cause epileptic phenotypes [67,88]. Defects in the somatodendritic transport of serotonin (5-HT_{1A}) receptors by kinesin-3/KIF13A and NMDA receptors (NR2B) by kinesin-2/KIF17 are linked to the pathogenesis of anxiety and schizophrenia, respectively [89].

Other diseases related to additional compartments of the nervous system (such as glial trafficking disorders) are included in Figure 3 and Table 2.

Basic mechanisms of endocytosis comprise micropinocytosis, clathrin-mediated and clathrin-independent endocytosis (Figure 1). Recent discoveries show that small GTPases in clathrin- and dynamin-independent endocytosis, the **retromer** complex and the involvement of lipids are relevant contributions to the understanding of the endocytotic machinery [16,17]. The **retromer** complex, a 'master regulator' of protein sorting at endosomal membranes, is formed from **Vacuolar Protein Sorting** protein 35 (VPS35), VPS29, and VPS26. Retromer binds multiple PX proteins [Phox homology (PX) protein family] from the sorting nexin (SNX) family, including dimers of SNX1/SNX2 with SNX5/SNX6 and its most recently identified partner, sorting nexin 27 (SNX2) [18–20]. The role of SNX27/Retromer in Down syndrome, Alzheimer's disease, and tumorigenesis is now being examined [21].

Figure 1. Membrane trafficking pathways. Endocytosis: cargo is internalized by an invagination of the plasma membrane (PM) forming a vesicle, that can be uncoated (micropinocytosis) or coated with different proteins, classified as clathrin dependent or independent processes (green box, upper left). Coated vesicles depend on the GTPase dynamin for the vesicle scission. Molecules are transported through endosomes for either recycling to the plasma membrane or to the Golgi, or for degradation at the lysosome. Cellular proteins can get to lysosomes either from the PM via the endocytic pathway or from the cytoplasm via the autophagy (blue box). The retromer (VPS35,29,26) regulates protein sorting at endosomal membranes. Exocytosis: molecules move from the endoplasmic reticulum (ER) via the Golgi to the PM. ER exit sites (ERES) (pink box) include Sec proteins and TANGO1 which initiate coat assembly and cargo selection. COAT and ADAPTOR proteins self-assemble on the membrane, collect and concentrate the cargo. COPI (coat protein I) surrounds retrograde transport vesicles (Golgi to ER). Coat protein complex II (COPII) vesicles go from the ER towards the Golgi (secretory pathway). Adaptor proteins (cargo adaptor with multiple binding sites) are Sec24 and AP proteins (AP1–AP5). RAB proteins assist in budding, docking, tethering, and fusion. ER-derived cargo enters the Golgi in its cis cisterna (CGN) and moves through the medial and trans cisternae. In the trans Golgi (TGN), proteins are packed into secretory vesicles that subsequently fuse with the PM. In the Golgi, cargo is sorted to the PM, endosomes, lysosomes, and back to the ER. Integrins connect exocytosis to the actin cytoskeleton (yellow box) however, most exocytosis events are integrin-independent.

The main families of vesicle-trafficking proteins that participate in the described pathways include those that coordinate vesicle formation, GTPases of the Rab family, transport and tethering factors, and **SNARE proteins** that mediate vesicle fusion with the target membrane. Table S1 shows a detailed description of these proteins.

Recent discoveries connecting exocytosis, endocytosis, and metabolic pathways involve lipid metabolism and new functions of some particular proteins.

Metabolism and transfer of lipids

Lipid composition, saturation, flip-flop activity, and the participation of **phosphoinositides (PIPs)** are amongst the most relevant contributions.

Lipids that constitute membranes are glycerophospholipids, sphingolipids, and sterols. The composition of a membrane not only affects protein function and curvature, but also the distribution of lipids across the bilayer. New lipid engineering approaches allowing manipulation of fatty acid (FA) unsaturation and sterol biosynthesis, the main regulators of membrane fluidity, have shown that endocytosis is particularly dependent on the lipid properties of cell membranes. In contrast, increased lipid saturation lowers both endocytosis and exocytosis, with the former being more severely affected [22].

Another intriguing feature is the asymmetric distribution of lipids. The inner leaflet of the PM possesses a negative surface charge whereas the exofacial leaflet is mainly uncharged. Due to its abundance and high rates of spontaneous flip-flop between membrane leaflets, cholesterol is proposed to buffer the formation of membrane curvature and is also crucial for maintaining the proper spacing of anionic phospholipids [23].

PIPs are acidic membrane lipids with important roles in cell trafficking. The most common PIP form in the PM is $PI(4,5)P_2$ which is involved in the early steps of endocytic clathrin adaptors recruitment, vesicle fission, and uncoating [24,25]. In exocytosis, $PI(4,5)P_2$ is involved in priming and fusion steps of Ca^{2+}-triggered vesicle release. $PI(4,5)P_2$ recruits and activates specific proteins that regulate SNARE complex assembly and function. The interaction with the cytoskeleton is mediated by phosphatidylinositol 3-kinase signaling at the endosomal compartment, which is regulated by microtubule-associated protein 4 [26], phosphatidylinositol-4-phosphate (PI4P) signaling in the phagolysosome resolution [27], and PI2,3,4P in membrane tubulation and integrin trafficking [28]. PI3P participates in autophagy.

The first steps of exocytosis are also mediated by lipids. In fact, COPII vesicle formation needs lysophospholipids and dynamic glycosylation. FAs modulate budding of large COPII cargoes. Additionally, COPII vesicles budded from the ERGIC contribute to autophagosome formation [29–31].

Regarding new functions of some proteins of interest

TANGO 1 (transgolgi network1) recruits Sec16 for efficient secretion, contributes to ring assembly around COPII coats at ERES, and to collagen export [32].

Other recent discoveries include: (i) the involvement of STF-4/Surf4 in ER export control and ERES organization; (ii) the activation of the Rab1 secretory pathway by the **TRAPPIII complex**; (iii) the connection of exocytosis to the actin cytoskeleton by integrins (Figure 1); (iv) the description of specific TBC domains at ER-Golgi-PM trafficking; (v) the involvement of RAB31 in endosomal sorting complexes required for transport (ESCRT)-independent exosome pathways [33–37].

Finally, we accord special mention to membrane trafficking located at specific organelles: 'organelle-related trafficking'. We emphasize this specific subgroup of membrane trafficking in order to connect diseases to organelles, since classically, the concepts of lysosomal, peroxisomal, and mitochondrial disorders and more recently 'golgipathies', are still widely used. Here we highlight some of the recent knowledge in organelle-related membrane trafficking.

There is an overlap in regulatory mechanisms for mitochondrial and peroxisomal trafficking. In the same sense, the role of the mitochondrial Rho-GTPases, Miro, in peroxisomal dynamics has been recently described. Conversely, the microtubule-dependent transport of peroxisomes and mitochondria uses different machineries [38,39].

The newly discovered mitochondrial-derived vesicles (MDVs) are small vesicular carriers that transport mitochondrial proteins and lipids to other organelles. The Parkinson's disease-associated proteins Vps35, Parkin, and PINK1 are involved in the biogenesis of a subset of these MDVs [40]. Similarly, Golgi-derived vesicles regulate late steps of mitochondrial division [41].

The mTOR signaling pathway is involved in organelle trafficking (such as ER, Golgi, and lysosomes). This signaling pathway is related to disorders such as tuberous sclerosis complex [42].

Membrane contact sites

Membrane contact sites (MCS) are areas of close apposition between the membranes of two organelles and can be homotypic (between identical organelles) and heterotypic (between two different organelles or two different membrane types) [43]. Well-studied heterotypic contacts involve the ER such as the ER-mitochondrial [44], ER-PM, ER-Golgi, ER-peroxisomes, and ER-lipid droplets (LDs). In the past couple of years, organelle contacts that do not involve the ER have been discovered: LDs-peroxisomes, and MCS with mitochondria and other organelles (**endosomes**, lysosomes, PM, LDs, peroxisomes, and mitochondria). Metabolic pathways at MCS are tightly regulated and play critical roles such as Ca^{2+} homeostasis, lipid transfer, and regulation of organelle dynamics. In this sense, mitochondrial associated membranes (MAMs) deserve special attention. They play a vital role in the crosstalk between the ER and mitochondria regarding lipid synthesis, regulation of Ca^{2+} homeostasis, mitochondrial dynamics, and signal transduction. Proteomic studies have revealed around 1000 different proteins in MAMs [45]. A number of diseases, mainly neurodegenerative, are due to mutations in genes codifying for MCS proteins (Figure 2).

Autophagy

Autophagy is a highly conserved cellular mechanism involving the clearance of many cytoplasmic constituents. Membrane trafficking and cytoskeletal transport-related processes are included in autophagy. It is a complex process (Figure 1), that starts with a double-membrane precursor (the phagofore) in the cytoplasm to continue with the formation of the autophagosome. The initiation of autophagosome biogenesis is stimulated by changes in energy status and nutrients [46]. Autophagosomes are trafficked along microtubules to facilitate their fusion with lysosomes. The autophagosomal membrane expansion and lipid transport are controlled by the ATG proteins, Atg2 and Atg9. These are novel types of intermembrane and interleaflet lipid transporters, respectively [47,48]. Another recent insight gleaned is the participation of COPII vesicles from the ER in the formation of the autophagosomal membranes [49]. Autophagosome is also induced by different signaling pathways such as mTORC1 inhibition and AMP-activated protein kinase activation, and the ULK complex, Atg3 and Atg101. The ULK complex activates the class III PI3K complex formed by association of VPS34, Beclin1, Atg14L1, and VPS15 [50]. Phosphatidylinositol 3-phosphate (PI3P) allows PI3P-interacting proteins, WIPI2B and Atg16L1 recruitment, and Atg12–Atg5 ubiquitin-like formation.

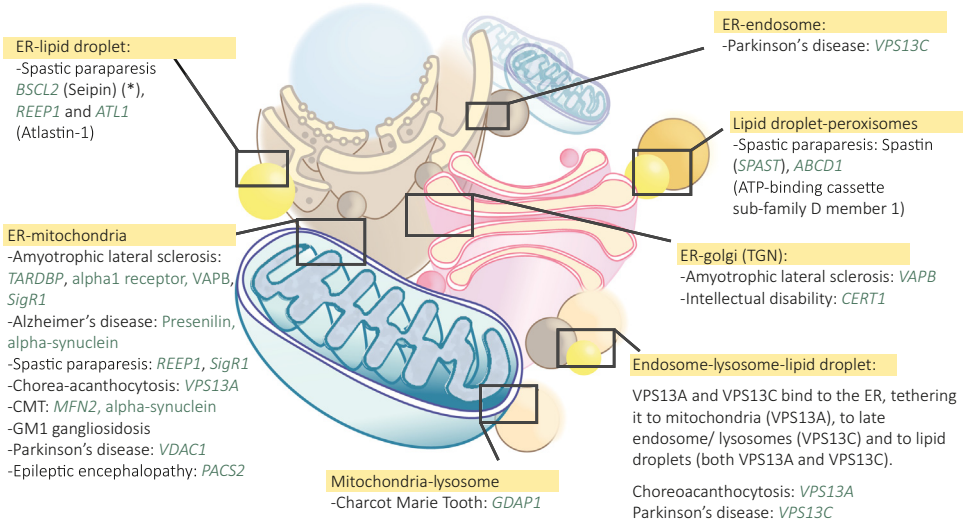

Figure 2. Membrane contact sites and associated diseases. Six membrane contact sites are summarized, with associated genes in green. Genes are in italics. (*) Seipin-related disorders include not only spastic paraparesis, but also a spectrum of clinical manifestations (lipodystrophy with neurodegeneration, epileptic encephalopathy).

This complex stimulates conjugation of LC3 to phosphatidylethanolamine on the autophagic membrane. The last stage is the fusion between autophagosomes and endosomes or lysosomes controlled by Rab GTPases and SNAREs to induce the lysosomal degradation of autophagy cargo. A number of obvious critical issues remain to be addressed such as how different modes of membrane/lipid supply from the ER are coordinated to expand the isolation membrane, mechanisms of membrane shaping and others. Several genes involved in the complex autophagy process have been involved in human diseases [51] and are described later in this review.

Mitophagy, a specific type of autophagy or the degradation of superfluous/damaged mitochondria, has an important role in the pathophysiology of human diseases. Diverse mitophagic regulators and receptors have been identified that vary depending on cargo content and stress. Phosphatase and tensin homologue-induced putative kinase 1 (PINK1) and 1-E3 ubiquitin ligase Parkin-mediated mitophagy is the predominant type of autophagic degradation of mitochondria. PINK1 and parkin have been associated with mitochondrial genome mutations and Parkinson's disease [52] (Table S1).

Trafficking along the cytoskeleton

The cytoskeleton is responsible for moving vesicles throughout the cell and is composed by a dynamic network of actin filaments, microtubules (heterodimers of alpha-tubulin and beta-tubulin) and motor proteins (myosine, dynein, and kinesin families, responsible for anterograde and retrograde transport of cargo). The remodeling of membrane tubules by actomyosin networks is crucial for intracellular trafficking and organelle reshaping. Membrane–cytoskeleton interactions are mediated by actin-binding proteins (ABPs) such as ezrin, a crucial ABP that links membranes to actin filaments [53]. Actin is involved in ER remodeling, mitochondria fusion, and fission, endocytosis and many other cell trafficking processes also through actin-microtubule crosstalk [54]. In general, myosins are actin-dependent motors, whereas dyneins and kinesins are microtubule-dependent motors. Indeed, most vesicle traffic along microtubules use kinesin or dynein motors, although they can also use myosin II and myosin V motors to move along the actin network. Recent insights point towards the involvement of elements such as LIS1, NudE, and HookA for

dynein activation [55,56]. Motor proteins also contribute to organelle and mRNA transport. For this function, the participation of **adaptor proteins** such as the TRACK proteins is important. Additionally, the participation of small GTPases such as Rab and Rho proteins in the cytoskeleton dynamics and the dynamin superfamily is gaining importance as determinants of both pathological and physiological conditions [57].

One of the major challenges of vesicular trafficking is to have a deeper knowledge of all the elements that interact with these motor proteins within the whole network of cell trafficking (such as the interaction between motor proteins and membrane lipids), but also the energy requirements and the ATPases behavior for every protein at different cells and compartments.

Clinical presentations of traffic disorders

Neurological manifestations and related genetic defects

Neurons are the largest known cells, with complex and highly polarized morphologies. Sophisticated transfer mechanisms are required to convey and integrate information within and between sub-neuronal compartments with the double challenge of distance and speed [58]. Here we summarize the trafficking defects on the neuronal soma including information related to other compartments in Box 2. Table 2 includes the whole group of genes and associated disorders. Figure 3 (Key figure) shows a graphic anatomical localization of the most relevant gene products. Neurological manifestations are divided into two categories: early neurodevelopmental encephalopathies (congenital to early infancy) and neurodegenerative disorders (mostly late-onset motor presentations) (Table 2). All categories of cellular trafficking are represented in both.

Trafficking defects in the neuronal soma (ER-Golgi-PM-endosome-lysosome-autophagosome)

Exocytic pathway defects

Some of the most representative and recently described diseases are the following:

ER-to-Cis Golgi defects. These include mutations in genes affecting the COPII machinery.

(i) Early-onset neurodevelopmental disorders (NDDs) with congenital/post-natal microcephaly and intellectual disability (ID) is the presenting sign of mutations affecting diverse proteins such as COP, SEC, TRAPPC, TBC, VPS, and RAB [59,60]. *TANGO2* and some TRAPPopathies [61] cause NDDs, acquired microcephaly, and muscle involvement. *TANGO2* may associate rhabdomyolysis episodes [62] as well as a novel homozygous variant in *TRAPPC2L* that associates post-infectious encephalopathy, developmental arrest, tetraplegia, and rhabdomyolysis [63], and mimics acute metabolic intoxication disorders. Another new reported bi-allelic splicing variant c.454+3A>G in *TRAPPC4* is associated with progressive encephalopathy and muscle involvement [64]. *YIF1B* causes a progressive encephalopathy with movement disorders, microcephaly, and epilepsy with Golgi and primary cilium alterations [65].

(ii) Late-onset presentations (from late childhood to adulthood) are related with motor dysfunctions such spastic paraparesis (i.e., *TANGO2, SLC33A1* defects), and Charcot-Marie-Tooth (CMT) disease (i.e., *TFG, CNPNY3* defects) [66].

Trans Golgi-to-PM defects. These involve complex severe encephalopathies such as diverse adaptinopathies: MEDNIK and MEDNIK-like syndromes (AP1S1 and AP1B1 adaptor protein defects), *AP1S2* (Pettigrew syndrome), *ARFGEF2* (microcephaly, periventricular heterotopia), *ATP7* mutations (Menkes syndrome), and complex spastic paraparesis (*AP4B1, AP4E1*) [67]. *AP1G1* mutations have been recently described as a cause of an NDD consisting of epilepsy and ID [68].

Table 2. Neurological manifestations divided into two main groups (early onset encephalopathies, and predominant motor disorders) and are linked to associated predominant clinical signs, related to categories of trafficking, and the corresponding genes

Early onset encephalopathies: clinical signs may appear during the first year of life			Predominant motor disorders		
Clinical signs	Categories of trafficking	Genes	Clinical signs	Categories of trafficking	Genes
Microcephaly as prominent sign Most of these diseases associate brain structure/brain image alterations and are global developmental encephalopathies with multiple neurological symptoms, in particular epilepsy/epileptic encephalopathy. They may have extra-neurological signs (skeletal, multisystem, well-defined genetic syndromes)	Vesicular trafficking *ER3IP1*: microcephaly, epilepsy, and diabetes	*ER3IP1*	**Ataxia** Most of them are spinocerebellar ataxias (SCAs) with onset in adolescence and adulthood. May associate spastic paraparesis (SP), epilepsy	Vesicular trafficking – *AMP1* (synaptic vesicle disorder): spastic ataxia, also causes a congenital myasthenic syndrome – *RUBCN* (SCA15) – *SIL1:* Marinesco-Sjoegren syndrome: SCA with congenital cataract and ID – *VPS13D* (SCA4)	*AMP1* *RUBCN* *SIL1* *VPS13D*
	Vesicular trafficking. Subtype organelles/interorganelle trafficking – *AP1G1:* ID and epilepsy – *AP1S1:* MEDNIK syndrome, high copper excretion – *AP1S2:* Pettigrew syndrome, EE and ID – *CDC42:* Takenouchi-Kosaki syndrome, ID, EE, optic atrophy, macrothrombocytopenia, lymphedema – RAB *proteins* (*RAB3GAP1, 2, RAB18*) and *TBC1D20:* Warburg-Micro syndrome, Marsof syndrome, ID, progressive spasticity, axonal neuropathy, microphthalmia, cataracts – *SLC9A6:* mimics Angelman syndrome. TAU neuronal inclusions; Dandy-Walker, basal ganglia abnormalities – DYM: Dyggve-Melchior-Clausen syndrome (ID, dwarfism) – *VPS13B:* Cohen syndrome, ID, obesity, neutropenia, and retinopathy	*AP1G1* *AP1S1* *AP1S2* *CDC42* *RAB3GAP1, 2* *RAB18,* *SLC9A6,* *TBC1D20* *VPS13B*		Vesicular trafficking. Subtype organelles/interorganelle trafficking Golgipathies: – *ATG5*: SCA – *GORS2* (progressive myoclonic epilepsy with ataxia – *SCYL1* (SCA21) Lysosomal related: – VPS41	*ATG5* *GORS2* *SCYL1* VPS41
	Cytoskeleton *DPYSL5:* NDD with corpus callosum agenesis, Ritscher-Schinzel syndrome: – *KIF14:* Meckel syndrome – *KIF16A:* with blindness – *KIF1BP/KBP:* Golderg-Shprintzen syndrome – *KIF5A:* neonatal seizures, spastic paraparesis – *KIF7:* Acrocallosal and Joubert syndrome – *KIF1BP/KBP:* Golderg-Shprintzen syndrome – *NDE1:* microhydranencephaly, lissencephaly – *TUBA1A:* lissencephaly – *TUBB3:* complex cortical dysplasia with other brain malformations	*DPYSL5* *KIF14* *KIF16A* *KIF1BP/KBP* *KIF5A* *KIF7* *KIF1BP/KBP* *NDE1* *TUBA1A* *TUBB3*		Autophagy – *ATG5* (SCA) – *SNX14* (SCA)	*ATG5* *SNX14*
				Cytoskeleton – *KIF1C* (spastic ataxia) – *SPTBN2* (SCA5 and 14)	*KIF1C* *SPTBN2*
Macrocephaly as prominent sign	Vesicular trafficking – *TBCK* (RABGTPase binding): macrocephaly or normocephaly, hypotonia, dysmorphy, brain atrophy	*TBCK*	**Spastic paraparesis (SPG)** Most of them complex and late-onset	Vesicular trafficking – Complex SP: *AP4B1* – Infantile onset: *AP4E1, AP4M1, AP4S1*	*AP4B1* *AP4E1* *AP4M1* *AP4S1*

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Table 2. (continued)

Early onset encephalopathies: clinical signs may appear during the first year of life			Predominant motor disorders		
Clinical signs	Categories of trafficking	Genes	Clinical signs	Categories of trafficking	Genes
				– Early onset SP with pectus carinatum and hypertrichosis: *VPS37A* – Onset in the first decade: *TGFBR* – *APSZ1*: progressive SP – *AP* related genes in general – MAST syndrome: *SPG21* – *NIPA1* (magnesium transporter): SPG6 – *SPART*: Troyer Syndrome, SPG20. – *WASHC5* (SPG8) – *TANGO2* – *SLC33A1*(SPG42) – Others: *ARL6IP1, UBAP1*	*APSZ* *AP*-related genes *ARL6IP1* *NIPA1* *SLC33A1* *SPART* *TANGO2* *TGFBR1* *UBAP1* *VPS37A* *WASHC5*
				Membrane contact sites *BCSL2* (Seipin), *REEP1*, Atlastin-1 (*ATL-1*) (organelle interplay lipid droplet, fatty acid incorporation in LD): Complex SP *SPAST* and *ABCD1*: fatty acid trafficking from lipid droplets into peroxisomes (different types of SP: SPG4, 52, 47, 50, 51)	*ABCD1* *ATL1* *BCSL2* *REEP1* *SPAST*
	Vesicular trafficking. Subtype: organelles/interorganelle trafficking – *HERC1*: ID, EE, hypotonia, ataxia – *RAB39B* (is also a synaptic vesicle protein): ID, EE, and autism – *RAC1* that may produce microcephaly can also cause macrocephaly	*HERC1* *RAB39B* *RAC1*		Autophagy *SPG11* (spatacsin): Type1 SP type 11; other phenotypes: CMT2; ALS type5. Spastizin (*ZFYVE26*): SP type 15 or Kjellin syndrome. *TECPR2*: SP type 49; *AP5Z1*: SP type 48	*AP5Z1* *SPG11* *TECPR2* *ZFYVE26*
				Cytoskeleton *KIF1A* (SPG30), *KIF1C* (spastic ataxia 2, SPG 58); *KIF5A* (various phenotypes all autosomal dominant: SPG10, CMT2, ALS); *REEP1* (SPG31)	*KIF1A* *KIF1C* *KIF5A* *REEP1*
				Glial trafficking Connexin47 (*C47*), *GJA12*: SP, leukodystrophy	*C47* *GJA12*
Neonatal seizures	Vesicular trafficking – *ATAD1*: AMPA receptor trafficking defect. Neonatal hypertonia ± seizures – *CNPNY3* (ER/co-chaperone): neonatal – first months of life seizures – EE. Progressive brain atrophy. Hippocampal malformation. (ER, lysosome, autophagosome, dendrites/endo-lysosomal): neonatal seizures,	*ATAD1* *CNPNY3* *HCFC1*	**Peripheral neuropathy** Most of them are Charcot-Marie-Tooth (CMT) subtypes but not only	Vesicular trafficking *ATP7, LITAF, MTMR2, SH3TC2, TGF* (HMSN: hereditary motor sensory neuropathy)	*ATP7* *LITAF* *MTMR2* *SH3TC2* *TGF*
				Vesicular trafficking. Subtype organelles/interorganelle trafficking	*FAM134B* *GBF1*

	EE, postnatal microcephaly, spasticity, ID, parkinsonism. brain atrophy, thin corpus callosum. – *HCFC1* (ER, nucleus): neonatal seizures (some cases), EE, microcephaly, choreoathetosis, ID. Cortical malformations (some cases). High homocysteine and methylmalonic acid (mimicking CblC deficiency).			Golgipathies: *FAM134B*: neuropathy hereditary sensory and autonomic type IIB; *RAB18, 39B, RAB7, RAB3GAP1*: CMT. *GBF1*: overlapping phenotype of HMN (hereditary motor neuropathy) and CMT2	*RAB18, RAB3GAP1 RAB7, RAB39B, RAB7*
	Membrane contact sites – *PACS2*: ER-mitochondria MCS defect. Seizures difficult to treat during the first year. Dysmorphism and cerebellar dysgenesis.	*PACS2*		Membrane contact sites *GDAP1:* CMT	*GDAP1*
				Autophagy *DCTN1*: neuropathy, distal hereditary motor, type viib Other genes: *FIG, SPG11*, *RAB7:* CMT2; *TMR13*	*DCTN1* *FIG* *RAB7* *SPG11* *TMR13*
				Cytoskeleton *KIF1A*: Hereditary sensory neuropathy type IIC (AR), spastic paraparesis 30 (AR); *DCTN1* (dynactin1/P150): Distal hereditary motor neuropathy Perry syndrome (AD); *KIF5A*: SPG10; CMT2 ALS; *DNM2*: CMT with neutropenia	*DCTN1* *DNM2* *KIF1A* *KIF5A*
	Cytoskeleton *KIF5A* (kinesin, anterograde transport): intractable neonatal myoclonus	*KIF5A*		Glial trafficking *Connexin32* (*C32*)*:* CMT	*C32*
Complex encephalopathy with multisystem involvement	Vesicular trafficking **– With arthrogryposis:** *ERGIC1, KIAA1109* (Alkuraya-Kucinskas syndrome (arthrogryposis, Dandy-Walker), *SLC35A3* (is a CDG: congenital disorder of glycosylation) **– With diverse organ involvement:** *MADD*: with endocrine dysfunction; *OCRL*: Lowe syndrome, Dent disease 2 and 1 (*CLCN5*); *SNAP29* (CEDNIK syndrome; is an SV), *SUMF1* (multiple sulfatase deficiency), *TBCD*: Hypoparathyroidism-retardation-dysmorphism syndrome; *TBCE:* encephalopathy, progressive, with amyotrophy and optic atrophy; *VPS4A:* with cataract, growth impairment and anemia	*ERGIC1, MADD KIAA1109 OCRL SNAP29 SUMF1 TBCD TBCE, VPS4A*	**Parkinsonism and other movement disorders** Most of them pediatric or juvenile parkinsonism and other early-onset movement disorders	Vesicular trafficking Early-onset parkinsonism (may also cause Leigh-like features): *VPS13C*, *ATP6AP2* Pediatric and juvenile-onset: *SYNJ1* Chorea-achantocytosis: *VPS13A* Early-onset dystonia. *VPS16, VPS4*: these are also lysosome-related disorders With adolescence-onset dystonia: *RME-8; VPS16* Atypical Parkinson's disease, no L-dopa response: *VPS26A* *GAK, LRRK2, VPS35:* diversity of clinical phenotypes SV cycle disorders: mutations in the exocytic pathway are mostly related with hyperkinetic movements whereas parkinsonism is more common in endocytic pathway mutations	*ATP6AP2 GAK LRRK2 RME-8 SYNJ1 VPS13A VPS13C VPS16 VPS4 VPS26A VPS35*

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Table 2. (continued)

Early onset encephalopathies: clinical signs may appear during the first year of life			Predominant motor disorders		
Clinical signs	Categories of trafficking	Genes	Clinical signs	Categories of trafficking	Genes
	Vesicular Trafficking. Subtype: organelles/interorganelle trafficking Golgipathies **– With rhabdomyolysis (and epilepsy and microcephaly):** *TRAPPC11* and *TANGO2* (may present with metabolic crises, mild hyperammonemia and hypoglycemia, long QT, but also other late neurological forms such as ID, spastic paraparesis, and myastheniform symptoms). *TRAPPC2L* (ER-Golgi transport): may have also late-onset presentation **– With diverse organ involvement:** *VPS15* (ID, renal failure, retinitis pigmentosa, dysmorphy), *FLNA* [ID, EE, periventricular heterotopia, frontometaphyseal dysplasia, connective tissue abnormalities (Ehlers-Danlos-like)]; *ATP7* (TGN): MENKES syndrome (mild variants: occipital Horn syndrome, peripheral neuropathy); *AP3B1*: Hermansky-Pudlak syndrome 2 (albinism, infections) Other organelles and membrane contact sites: **– With arthrogryposis:** *VPS33B and VIPAS39* (lysosome-interorganelle): ARC1 and ARC2 **– With diverse organ involvement:** seipinopathies (*BSCL2*): include not only SP but EE, lipodystrophy and Celia's disease (neurodegeneration); *VPS33A*: MPS plus, lysosome related. *PPP1R21* (lysosome and endosome related): hypotonia, dysmorphy, mimics storage disorders **– With retinal dystrophy:** interorganelle trafficking and membrane contact sites: *EMC1:* cerebellar atrophy, visual impairment and psychomotor retardation; *ACBD5*: retinal dystrophy with leukodystrophy	*ACBD5* *ATP7* *AP3B1* *BSCL2* *EMC1* *FLNA* *PPP1R21* *TANGO2* *TRAPPC11* *TRAPPC2L* *VPS15* *VPS33A* *VPS33B* *VIPAS39*		Vesicular trafficking. Subtype organelles/interorganelle trafficking Early-onset parkinsonism: *RAB39B* (golgipathy). Early-onset dystonia: lysosomal related: VPS16, 11, 41 (HOPS-associated neurological disorders (HOPSANDs). Leigh syndrome: *SLC39A8*	*RAB39B* *SLC39A8* *VPS16, 11, 41*
				Membrane contact sites alpha-Synuclein, *VDAC1, SigR1; VPS13C; BCAP31* (deafness, dystonia, and cerebellar hypomyelination)	*BCAP31* *SigR* *VDAC1* *VPS13C*
				Autophagy *FIG4*: Yunis-Varon syndrome; type 2 (SDCO): Striatonigral degeneration, childhood-onset; *PRKN:* PARKIN deficiency (Parkinson Disease 2); *PINK1*: Parkinson Disease 6: Neurodegeneration with ataxia, dystonia, and gaze palsy (NADGP)	*FIG4* *NADGP* *PINK1* *PRKN*
				Cytoskeleton Cytoskeleton: *TUBB4A*: torsion dystonia 4 (DYT4), hypomyelinating leukodystrophy; *TUBB6*: congenital facial palsy with ptosis and velopharyngeal dysfunction; *ACTB*: dystonia, juvenile onset	*ACTB* *TUBB4A* *TUBB6*
	Autophagy – *ATG-7*: with muscular, endocrine involvement, cerebellar hypoplasia, ataxia. – *EPG5*: Vici syndrome: agenesis of the corpus callosum, cutaneous hypopigmentation, bilateral cataract, cleft lip and palate, and combined immunodeficiency. ID, seizures – *FIG4* (Yunis-Varon syndrome): hypomyelination, peripheral neuropathy – *WIPI2:* neurodevelopmental disease of variable clinical severity that may associate joint	*ATG-7* *EPG5* *FIG4* *WIPI2*		Others: flippases *ATP8A2*: cerebellar ataxia and atrophy, ID, chorea, severe hypotonia, optic atrophy; *ATP1A3*: cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS), alternating hemiplegia, Dystonia 12 (all AD); rapid-onset parkinsonism Kufor-Rakeb syndrome/SP: *ATP13A2*	*ATP1A3* *ATP13A2* *ATP8A2*

	contractures, subclinical hypothyroidism, and subclinical cardiac arrythmias				
Other neuropediatric diseases that may appear or are mostly detectable beyond the first year of life	Vesicular trafficking – *CLTN* (*collectrin*)*:* Hartnup-like – *EIF2AK3:* Wolcott-Rallison syndrome – *GET4* (*VT*)*:* 1 case, EE, thin corpus callosum, brain atrophy – *GD1I:* X-linked ID – *FGD1:* Aarskog-Scott syndrome – *INPP5E:* ID, truncal obesity, retinal dystrophy, and micropenis – *ITSN1:* ID, autism, and epilepsy – *NPC1, NPC2:* Niemann-Pick disease, type C1/C2 – *PACS1:* Schuurs-Hoeijmakers syndrome (SHMS) – *PAX3, MITF, TYR:* Waardenburg syndrome (different types) – *SCARB2:* epilepsy with or without renal failure – *Synaptic vesicle disorders:* comprise ID, epilepsy, movement disorders, and neuropsychiatric symptoms in different combinations	*CLTN* *EIF2AK3* *GET4* *GD1I* *FGD1* *INPP5E* *ITSN1* *MITF* *NPC1, NPC2* *PACS1* *SCARB2* *PAX3* *Synaptic vesicle disorders* *TYR*	**Amyotrophic lateral sclerosis (ALS)**	Vesicular trafficking *OPTN*	*OPTN*
				Membrane contact sites *VAP9, VAPB, SigR1*: ALS and SMA	*SigR1* *VAP9* *VAPB*
				Cytoskeleton: *KIF5A*	*KIF5A*
				Autophagy *CHMP2B*: ALS type 17; *Spatacsin* (ALS type5) (SPG11 type 3); *ALSJ* (ALS2); *FIG4*: type 1 (BTOP): polymicrogyria bilateral temporo-occipital; type 2 (*ASL11*): ASL type 11; type 3 *(CMT4J*): CMT type 4	*ALSJ* *ASL11* *CHMP2B* *CMT4J*
	Vesicular trafficking. Subtype: organelles/interorganelle trafficking **– Post-infectious encephalopathy** (developmental arrest, followed by pyramidal signs ± rhabdomyolysis): Golgipathies: TRAPPcopathies (including new variants in *TRAPPC2L, TRAPPC4*) and TANGO2 **– Cognitive impairment, autistic features, and mitochondrial myopathy:** *APOO* (MICOS complex, mitochondrial) **– Seizures with gingival overgrowth:** *TBC1D2B* **– Febrile seizures:** *HERC1* **– Neurodevelopmental and neurodegenerative disorder with myoclonus:** *DHDDS* ID associated with behavioral abnormalities ± epilepsy: TRAPPC9 (Golgi trafficking disorder I)	*APOO* *DHDDS* *HERC1* *TANGO2* *TRAPPcopathies* *TBC1D2B*	**Spinal muscle atrophy (SMA)**	Vesicular trafficking	*ATP7*
				Membrane contact sites	*VAPB*
				Cytoskeleton	*Bicaudal* *dync1h1*

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Table 2. (continued)

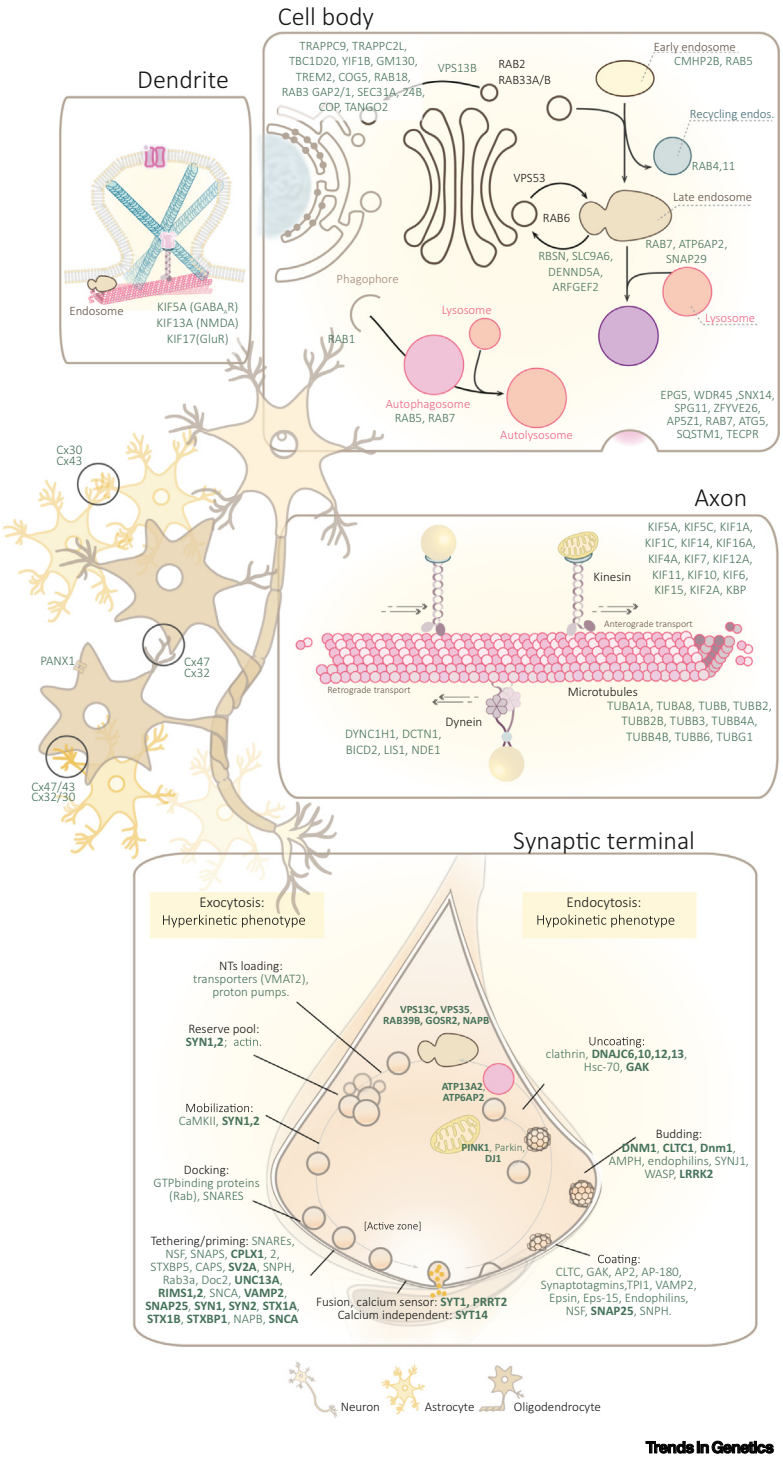
Early onset encephalopathies: clinical signs may appear during the first year of life			Predominant motor disorders		
Clinical signs	Categories of trafficking	Genes	Clinical signs	Categories of trafficking	Genes
	Autophagy – *WDR45*: autistic traits, Rett-like phenotype, evolution towards NBIA (neurodegeneration with brain iron accumulation) – *ATP6VOA:* Rett-like phenotype, neurodevelopmental disorder with epilepsy, and ID – *WIPI2:* moderate ID, autistic features, and ataxic gait.	*ATP6VOA* *WIPI2* *WDR45*	**Other clinical manifestations**	Vesicular trafficking *CHMP2B, 4B*: frontotemporal dementia, cataracts; *TREM2:* Nasu-Hakola disease (early-onset fronto-temporal dementia and recurrent bone fractures; *BIN1*: progressive dementia and amyloid deposition	**Dementias** *BIN1* *CHMP2B, 4B* *TREM2*
			Dementias	Vesicular trafficking. Subtype organelles/interorganelle trafficking *TMEM106B* (lysosome related): FTD and a hypomyelination disorder	**Dementias** *TMEM106B*:
				Membrane contact sites Presenilin (*PSEN-1*), amyloid precursor protein: Alzheimer's disease	**Dementias** *PSEN-1*
				Autophagy *TBK1* (TANK binding kinase 1): susceptibility to encephalopathy infection-induced; *C9orf72*: frontotemporal dementia. Also involved in endosomal trafficking	**Dementias** *C9orf72* *TBK1*
	Astrocytic trafficking – *NLGN1, NLGN3, NLGN4*: autism spectrum disorders – *SLITRK1*: obsessive compulsive disorder. Late-onset, adolescence/adulthood – *SLITRK4:* schizophrenia. Late-onset, adolescence/adulthood	*NLGN1* *NLGN3* *NLGN4* *SLITRK1* *SLITRK4*	**Deafness**	Diversity of mechanisms	**Deafness** Related genes: *WFS1, UNCA5A, AP1S1, VPS33B, VPAS39, RFTL, MYH9, PAA3, MTF, TYR, SUMF1, MYC58, RAB23, MYO5B, BCAP31, ATP6V1B2*
	Membrane contact sites – *CERT1: ID*	*CERT1*	**Demyelinating disorders**	Glial trafficking disorders: Connexin32 (C32) (*GJB1*): multiple sclerosis; Connexin47 (C47) (*GJC12*): leukodystrophy, multiple sclerosis; *Pannexin* (*PANX1*): demyelination	(*GJB1*), *GJC12*), *(PANX1*):

BIOMARKERS: Brain Image	BIOMARKERS: Biochemical/Metabolic Markers
Brain atrophy: *ATP6AP2, AP4E1, TBCD, VPS1, TBCK,* TRAPPCpathies **Thin corpus callosum (cc) and cc agenesis:** most golgipathies with microcephaly. *PPP1R21*. Tubulinopathies with hypomyelination. Others: atp6ap2; cc agenesis: cdk5rap2, *DPYSL5* **Cortical malformations:** most golgipathies with microcephaly. Tubulinopathies; *NDE1* (dynamin): microhydranencephaly, lissencephaly **Posterior fossa involvement:** cerebellar atrophy: *ZNHIT3* (PEHO-like syndrome), *AP4E1, SLC9A6;* pontocerebellar hypoplasia: *VPS53, 51, TBC1D23, PCLO* (with optic atrophy) Joubert malformation: *AP4E1;* Dandy-Walker: *AP1S2, KIAA1109, DPYSL5;* other cerebellar dysplasia: *PACS2.* Cerebellar hypoplasia: *ATG-7,* hypoplasia of the cerebellar vermis: *WIPI2.* **Leukodistrophy:** hypomyelination: Tubulinopathies, *VPS11, FOLR1, SLC33A;* Pelizaeus-Merzbacher-like: *GJB1, GJA12;* demyelination: pannexin (*Panx1*): demyelination, *ACBD5* **Basal ganglia involvement:** *AP1S2, AP1S1, SLC39A8, WIPI2* (abnormal dentate nuclei)	Very few diseases have biomarkers. In particular, some synaptic vesicle disorders have been described to have biomarkers: – Macrocytosis, transient neutropenia, severe dyslipidemia with ketogenic diet, signs of B12 deficiency: *Rabenosyn-5* – Hyperphenylalaninemia: *DNAJC12* – High levels of free sialic acid: *SLC17A5* – Low levels of homovanillic acid in the cerebrospinal fluid (CSF): *DNAJC6, CLCT, SYNJ*, and may respond, at least partially or transiently, to L-dopa treatment, mimicking dopamine biosynthesis defects. VPS35 also responds to L-dopa. – Low levels of homovanillic acid and 5-hydroxiindolacetic acid in the CSF: *VMAT2* (some patients have normal levels) – Low levels of homovanillic acid, 5-hydroxiindolacetic acid and high levels of biopterin and neopterin in the CSF: *DNAJC12* – *HCFC1*: high levels of plasma homocysteine and low levels of urine methylmalonic acid – Low levels of copper and ceruloplasmin in plasma: *AP1S1, AP1B1* – MEDNIK syndrome, high copper excretion – Lactic acidosis: *APOO* (MIC26) mutations characterized by mitochondrial myopathy, cognitive impairment, and autistic features – Abnormal profile of urinary oligosaccharides (elevated Glc4 tetrasaccharide); *EPG5, FIG4, VAC14*

Abbreviation: AD, autosomal dominant; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; EE, epileptic encephalopathy.

Key figure

Neuronal compartments and associated diseases



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Endocytic pathway defects

Golgi to endosomes trafficking defects. These often present as complex early-onset encephalopathies that may associate multisystem involvement. This is the case of Rabenosyn-5 deficiency and *SLC9A6, DENND5A,* and *ARFGEF2* mutations. A recently described disorder caused by mutations in *PPP1R21* causes an NDD that associates dysmorphism, loss of white matter, and thin corpus callosum and appears to be related to the endosomal sorting process [69].

Late endosome to lysosome and trafficking defects. The endolysosomal vesicle and autophagosomes communicate to each other and some proteins involved in this pathway can also have roles in autophagy. Clinical presentations include neonatal seizures (*ATP6AP2*) [70], complex multisystem syndromes such as CEDNIK (*SNAP29* mutations) and ARC syndrome (*VPS33B* and *VIPAS39* defects) [71] and peripheral neuropathy (CMT) as in *RAB7* defects (late endosome to lysosome: pathway) [72]. Recently, new VPS disorders that compose the **homotypic fusion and protein sorting (HOPS) complex** (VPS11, 16, 18, 33A, 39, 41) have been described to cause early-onset dystonia associated with lysosomal abnormalities (*VPS16, VPS11,* and *VPS41*) [73]. *VPS41* cause also an NDD with cerebellar ataxia [74]. HOPS-associated neurological disorders (HOPSANDs) has been the name proposed for these group of diseases [75].

Lysosome biogenesis defects (type 7 and 8 Hermansky-Pudlak syndrome) and several phosphoinositide-phosphatase-producing myopathies, Lowe syndrome and CMT types 4B1 and 4B2, also belong to this category.

De novo DHDDS variants alter the endolysosomal pathway and cause a recently reported disease linked to a neurodevelopmental and neurodegenerative disorder with myoclonus [76].

Autophagy defects. Disorders present as early complex encephalopathies with multisystem involvement such as Vici syndrome (*EPG5*) [77], NDDs with brain iron accumulation (*WDR45*); spastic paraparesis (spastin, *ABCD1*, spastacsin, spastizin, *TECPR2*, *AP5Z1*), amyotrophic lateral sclerosis (*CHMP2B, FIG4* mutations), peripheral neuropathy (CMT disease) due to *DCTN*1, *FIG4*, spactacsin, and *RAB7* mutations, parkinsonism and other movement disorders (*FIG4, PRKN*, *PINK1*, *RAB39B*), and dementia (*TBK1*, *FTD3*) [78]. A new NDD characterized by cerebellar hypoplasia, ataxia, developmental delay, musculoskeletal abnormalities, facial dysmorphia and endocrine involvement has been linked to *ATG-7* mutations [79]. Mutations in *ATP6V01* have been recently described to impair autophagy and lysosomal acidification and cause a Rett-like encephalopathy with developmental delay and epilepsy [80]. The protein codified by this gene belongs to the V-ATPase complex, located at the endolysosomal compartment. WIPI2 variants have been recently described to cause a new autophagy neurodevelopmental disease of variable clinical severity [81].

Figure 3. Some of the most representative genes responsible for neurological diseases and their predominant cellular localization are shown. Four cellular compartments are included. Dendrites: microtubule-associated proteins involved in the transport of receptors to the dendritic button are shown. Cell body: gene products causing pathologies are in green. Other RAB and VPS proteins (in black) are also shown to indicate their behavior in different cellular exocytic and endocytic processes. Axon: gene products/proteins are in green and placed depending on different types of transport (anterograde – kynesin mediated and retrograde – dynein mediated). Tubulins compose the microtubule network and genes related to diseases are also shown. Pre-synaptic terminal: genes causing disease are in green bold. Although genes involved in the exocytic pathway are mostly associated with neurodevelopmental disorders with hyperkinetic movements and those involved in the endocytic pathway are responsible for parkinsonian syndromes, sometimes phenotypes overlap. It is also possible that the phenotype changes over time as is the case for *STXBP1* mutations that can appear as a neurodevelopmental disorder with hyperkinetic movements but may evolve over time towards parkinsonism. In the middle part, cell contacts and representative proteins are schematized: PANX1 and Connexins (Cx) 30, 32, 43, and 47.

Systemic manifestations of cell-trafficking disorders

Systemic symptoms often present as multisystem diseases or well-defined syndromic phenotypes [6] (Table 3 includes the whole list of diseases). Only a few characteristic syndromes are described below.

Immuno-hematological symptoms

These include immune deficiencies, familial hemophagocytic lymphohistiocytosis, and specific abnormalities of blood cells. Vici syndrome (*EPG5*) is characterized by agenesis of the corpus callosum, skin and hair hypopigmentation, cataracts, cleft lip and palate, cardio/myopathy, and immunodeficiency [77]. Chediak-Higashi syndrome is an autosomal recessive (AR) disorder caused by *LYST* (lysosomal trafficking regulator gene) mutations characterized by partial oculocutaneous albinism, severe immunodeficiency, neurological dysfunction, and lymphoproliferative disorder lethal in the absence of bone marrow transplantation [90].

Skin and hair abnormalities

These include a wide spectrum of clinical manifestations such as hypopigmentation/albinism, ichthyosis, eruptions, nodular and papular lesions, cutis laxa, and lipodystrophy, and structural hair abnormalities with or without pigmentary changes. Hermansky Pudlak syndrome (HPS) is an AR multisytemic disorder characterized by an oculocutaneous albinism and a bleeding tendency [91]. There are 10 types of HPS each caused by a different dysfunctional gene. CEDNIK syndrome (Cerebral Dysgenesis, Neuropathy, Ichthyosis, and palmoplantar Keratoderma) is an AR disorder linked to mutations of *SNAP29* which encodes a SNARE protein involved in vesicle fusion. Recently, hypomyelination, seizures, and early puberty have also been described. Due to reduce penetrance of the cutaneous symptoms, cerebral dysgenesis, and neuropathy, it has been proposed renaming this syndrome *SNAP29*-related disorder [92].

Musculoskeletal signs

These include myopathies with structural muscle abnormalities, recurrent myoglobinuria, skeletal dysplasia, structural bone abnormalities, arthrogryposis, and joint laxity. Dyggve-Melchior-Clausen disease caused by mutations of *DYM* is a rare spondylo-epi-metaphyseal dysplasia characterized by progressive short-trunked dwarfism, protruding sternum, microcephaly, ID, and pathognomonic radiological findings (generalized platyspondyly, irregularly ossified femoral heads, a hypoplastic odontoid, and a lace-like appearance of iliac crests) [93]. A novel ARCN1 intronic variant has been described to rhizomelic short stature with microretrognathia and ID [94]. Craniofacial diseases have been recently related to a number of genes involved in both exocytic and endocytic pathways [95]. TMEM251 mutations cause a recently described skeletal dysplasia [96].

Digestive-hepatic symptoms

These include acute and chronic liver disease, diarrhea, and inflammatory bowel disease. Recurrent acute liver failure (RALF) triggered by febrile illnesses is a common presenting sign in *NBAS* and *SCYL1* mutations. Mutations in *NBAS* (involved in retrograde transport) cause a complex disease with a wide clinical spectrum ranging from isolated RALF to a multisystemic phenotype [97]. Thermal susceptibility of the syntaxin 18 complex is the basis of fever dependency of RALF episodes [98]. *SCYL1* mutations underlie a syndrome characterized by RALF, peripheral neuropathy, cerebellar atrophy, and ataxia [99]. *ATP6AP1* and *ATP6AP2* mutations are involved in acute liver failure. *STX3* and *Munc18.2* mutations are genetic enteropathies that are microvillous disorders and cause congenital diarrhea by defective apical vesicular transport [100,101].

Table 3. Systemic manifestations of trafficking disorders

Clinical manifestations	Categories	Genes	Clinical manifestations	Categories	Genes
Immunohematological			**Skin and hair**		
Immune dysfunction Chediak-Higashi syndrome (*LYST*) Griscelli syndrome (*MYO5A, RAB27A*) Takenouchi-Kosaki syndrome (*CDC42*) Vici syndrome (*EPG5*) Wiskott-Aldrich syndrome (*WAS*) Immunodeficiency type 47 (*ATP6AP1*)	Vesicular trafficking	*DKC1, FLI1, HYOU1, JAGN1, MAGT1, NBAS, PACS1, PRF1, RAB27A, STXBP2, TMEM173, TTC37, UNC13D, VIPAS39, VPS13B*	**Hypopigmentation** Griscelli syndrome (*MYO5A, RAB27A, MLPH*) Hermansky-Pudlak syndrome (*AP3B1, AP3D1, BLOC1S3, BLOC1S6, DTNBP1*) Menkes disease (*ATP7A*) Vici syndrome (*EPG5*) Waardenburg syndrome (*MITF, PAX3*)	Vesicular trafficking	*DTNBP1, GPNMB, RAB27A, TYR*
	VOIT	*ATP6AP1, COG1, COG4, COG6, MYO5A, SLC35A1, SLC35C1, AP3B1, AP3D1, BLOC156, COPA, LAMTOR2, LRBA, LYST, STX11, VPS33B, VPS45*		VOIT	*AP3B1, AP3D1, ATP7A, BLOC1S3, BLOC1S6, LYST*
				Autophagy	*EPG5*
	Autophagy	*ATP6AP1, EPG5, TBK1*		Cytoskeleton	*MLPH*
	Cytoskeleton	*WAS*		VOIT and cytoskeleton	*MYO5A*
	Others	*ITK, MBL2, NFE2L2, SH2D1A, SKIV2L, XIAP*		Others	*MITF, PAX3*
HLH Chediak-Higashi syndrome (*LYST, BLOC1S* subtypes) Familial HLH (*PRF1, STX11, STXBP2, UNC13D*) Griscelli syndrome (*MYO5A, RAB27A*) Lymphoproliferative syndrome (*CD27, ITK, SH2DA1, XIAP*) STING-associated vasculopathy (*TMEM173*)	Vesicular trafficking	*AP3B1, CD27, ITK, LYST, NBAS, PRF1, RAB27A, STX11, STXBP2, TMEM173, UNC13D, BLOC1S* subtypes	**Hyperpigmentation** Alstrom syndrome (*ALMS1*) Craniolenticulosutural dysplasia (*SEC23A*)	Vesicular trafficking	*GPNMB, SEC23A*
				Cytoskeleton	*ALMS1, KIF1B*
	VOIT	*MYO5A*	**Ichthyosis** ARC syndrome (*VIPAS39, VPS33B*) CEDNIK syndrome (*SNAP29*) MEDNIK syndrome (*AP1S1*) Multiple sulfatase deficiency (*SUMF1*)	Vesicular trafficking	*SNAP29, SUMF1, VIPAS39*
	Others	*SH2D1A, XIAP*		VOIT	*AP1S1, VPS33B*
Specific erythrocyte abnormalities Congenital dyserythropoietic anemia type II (*SEC23B*) SLC35C1-CDG, lack of erythrocyte H-antigen (*SLC35C1*) Rabenosyn-5 deficiency, macrocytosis, megaloblastoid erythropoiesis (*RBSN*)	Vesicular trafficking	*RBSN, SEC23B*	**Nodular/papular lesions** Lowe syndrome (*OCRL*) Lymphoproliferative syndrome X-linked (*XIAP*)	VOIT	*AP1S3, OCRL*
	VOIT	*SLC35C1*		Others	*XIAP*
	Cytoskeleton	*TBCE*	**Eruptions** Dyskeratosis congenita X-linked (*DKC1*) MEDNIK syndrome (*AP1S1*) Palmoplantar punctate keratoderma (*AAGAB*) Wiskott-Aldrich syndrome (*WAS*)	Vesicular trafficking	*AAGAB, DKC1, FLI1, GPNMB, PRF1, RAC1, TMEM173*
Specific platelet abnormalities Hermansky-Pudlak syndrome (*AP3B1, DTNBP1, BLOC1S3, BLOC1S6*) Macrothrombocytopenia (*MYH9*) Platelet-type bleeding disorder (*ACTN1, FLI1*) Wiskott-Aldrich syndrome (*WAS*) Thrombocytopenia (*MADD*)	Vesicular trafficking	*DTNBP1, FLI1, NBEAL2, MADD*		VOIT	*AP1S1, ATP2C1, COG6*
	VOIT	*BLOC1S3, BLOC1S6, LRBA, TMEM165*		Cytoskeleton	*WAS*

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Table 3. (continued)

Clinical manifestations	Categories	Genes	Clinical manifestations	Categories	Genes
	Vesicular trafficking and cytoskeleton	*CDC42*	**Cutis Laxa** *ATP6V1A1, ATP6V1E1* Menkes disease (*ATP7A*) Wrinkly skin syndrome (*ATP6V0A2*) Geroderma osteodysplasticum (*GORAB*)	Vesicular trafficking	*ATP6V0A2, NBAS*
	Autophagy	*AP3B1*		VOIT	*ATP6V1A1, ATP6V1E1, COG7, GORAB, SLC39A13, ATP7A*
	Cytoskeleton	*ACTN1, MYH9, WAS*			
	Others	*RUNX1*	**Increased skin thickness – lipodystrophy** CDG syndromes (*COG4, COG6, COG7, SLC35C1, TMEM165*) Lipoid proteinosis (*ECM1*) MPS-plus syndrome (*VPS33A*) Mucolipidosis II (*GNPTAB*)	Vesicular trafficking	*KIAA1109*
Specific white blood cell abnormalities Charcot-Marie-Tooth disease 2M: neutropenia (*DNM2*) Chediak-Higashi syndrome (*LYST*) NBAS deficiency (*NBAS*): *Pelger-Huet anomaly* Severe congenital neutropenia (*JAGN1, VPS45, WAS*)	Vesicular trafficking	*JAGN1, NBAS, VPS13B*		VOIT	*SLC35C1 GNPTAB, TMEM165*
	VOIT	*SLC35C1, LYST, VPS45*		Cytoskeleton	*ECM1, KIF11*
	Cytoskeleton	*WAS*		VOIT and autophagy	*VPS33A*
	Autophagy and cytoskeleton	*DNM2*			
Musculoskeletal					
Muscular abnormalities Acute recurrent myoglobinuria (*LPIN1*) Centronuclear myopathy (*MTMR14*) Danon disease (*LAMP2*) Marinesco-Sjogren syndrome (*SIL1*) *MECRCN* (*TANGO2*) Vici syndrome (*EPG5*) Congenital muscular dystrophy (*BET1*)	Vesicular trafficking	*DYSF, LPIN1, PIK3R4, RFT1, SIL1, SLC33A1, STRADA, TMEM173, VIPAS39*	**Hair abnormalities** Menkes disease (*ATP7A*) Trichohepatoenteric syndrome (*SKIV2L, TTC37*) Warburg micro syndrome (*RAB3GAP1, RAB18, TBC1D20*) Yunis-Varon syndrome (*FIG4, VAC14*)	Vesicular trafficking	*DTNBP1, RAB18, RAB3BAP1, SEC23A, TTC37, TYR*
	VOIT	*ACBD5, BET1, COG8, CTNS, SLC35A1, SLC35C1 ARCN1, CAV3, ERGIC1, LAMP2, LYST, TANGO2, TMEM165, TRAPPC11, TRAPPC2L, VPS33B*		VOIT	*COG4, COG7, CTNS AP1S1, ATP7A, BLOC1S3, CAV1, TBC1D20*
	Autophagy	*EPG5, MTMR14, SQSTM10, TBCD, VPS13D*		VOIT and cytoskeleton	*MYO5A*
	Cytoskeleton	*ACTB, BIN1, KIF5C, TUBB3*		Autophagy	*EPG5, FIG4, VAC14*
	Autophagy and cytoskeleton	*DNM2*		Cytoskeleton	*ALMS1, KIFBP, MLPH*
Skeletal dysplastic changes Dyggve-Melchior-Clausen disease (*DYM*) Short stature, amelogenesis imperfecta (*SLC10A7*) Multiple sulfatase deficiency (*SUMF1*) Spondyloepiphyseal dysplasia tarda (*TRAPPC2*) Yunis-Varon syndrome (*FIG4*, *VAC14*) Skeletal dysplasia and short stature (*TMEM251*)	Vesicular trafficking	*ATPV06A2, CDC42, EIF2AK3, HYOU1, PIK3R4, RAB18, RAB3GAP1, RAB3GAP2, RFT1, SEC23A, SUMF1, TRAPPC2, VPS13B*	**Digestive–hepatic**		

Table 3. (continued)

Clinical manifestations	Categories	Genes	Clinical manifestations	Categories	Genes
	VOIT	*COG1, COG6, COG7, DYM, PACS1, RAB33B, SLC10A7, SLC35A2, VPS33A AP3D1, ARCN1, ATP7A, GNPTAB, TBC1D20, TMEM165, TMEM251, TRIP11*	**Chronic liver disease** ARC syndrome (*VPS33B, VIPAS39*) CDG type II (*COG2, COG4, COG5, COG6, COG7, COG8, RFT1, TMEM165, TMEM199*) MEDNIK syndrome (*AP1S1*) Trichohepatoenteric syndrome (*SKIV2L, TTC37*) Liver disease (*ATP6AP1, VMA21*) Hepatic steatosis (*ATP6AP2, CCDC115*) Liver fibrosis (*CCDC115*)	Vesicular trafficking	*CCDC115, DCK1, NGLY1, RFT1, TMEM199, TTC37, UNC45A, VIPAS39*
	Autophagy	*FIG4, VAC14*		VOIT	*ATP6AP1, ATP6AP2, COG2, COG4, COG5, COG6, COG7, COG8, AP1S1, CAV1, IGF2R, NPC1, NPC2, PEX13, TMEM165, TRAPPC11, VPS33A, VPS33B*
				Autophagy	*ATP6AP1, VMA21*
	Cytoskeleton	*ACTB, DYNC2H1, KIFBP*		Cytoskeleton	*ALMS1, DYNC2H1*
Other skeletal signs Primary intraosseous vascular malformation (*ELMO2*) Skeletal defect and joint laxity (*GORAB*) Osteogenesis imperfecta (*KDELR2*) Paget disease (*SQSTM1*) STING-associated vasculopathy (*TMEM173*)	Vesicular trafficking	*ELMO2, TMEM173*		Others	*ITK, SKIV2L,*
	VOIT	*COPA, GORAB, LRBA, KDELR2*			
	VT and autophagy	*SQSTM1*	**Acute liver failure and hepatitis-like attacks** *ATPSAP1, ATPSAP2* Familial HLH (*PRF1, UNC13D, STX11, STXBP2*) RALF (recurrent acute liver failure) (*NBAS, SCYL1*) Wilson disease (*ATP7B*)	Vesicular trafficking	*ATP7B, BCAP31, HYOU1, NBAS, PRF1, UNC13D*
Structural bone abnormalities Hypoparathyroidism-retardation-dysmorphism syndrome (*TBCE*) Osteopetrosis type 1, 3 (*PLEKHM1, TCIRG1*) Waardenburg syndrome (*PAX3*) **Craniofacial features** Wide-open calvarian sutures, dysmorphism, cataracts (*Sec23A*) Ocular proptosis with craniosynostosis and hydrocephalus (*Sec24D*) Severe micrognatia and dwarfism (*ARCN1*) Enamel abnormalities, dysmorphy, mandibular hypoplasia (*SCL10A7*) Ritscher-Schinzel syndrome (*CCDC22*) Cleft palate (*AP2beta1*); Other genes involved in craniofacial abnormalities: *INPPL1, PHETA1/2, PPP3CA, RBSN-5*	Vesicular trafficking	*AP2S1, HERC1, NBAS, UNC45A, Sec23A, 24D, RBSN-5*		VOIT	*ATPSAP1, ATPSAP2, COG4, STX11, SCYL1,*
	VOIT	*COG1, CTNS, GORAB IL17RD, OCRL, STX16, ARCN1*		Others	*SH2D1A, STXBP2, XIAP*
	Autophagy	*TBCE*	**Hepato(spleno) megaly** Mucolipidosis II (*GNPTAB*) Multiple sulfatase deficiency (*SUMF1*) Niemann-pick disease type C (*NPC1, NPC2*) Trichohepatoenteric syndrome (*SKIV2L, TTC37*)	Vesicular trafficking	*EIF2AK3, PRF1, RFT1, SUMF1*
	VOIT and autophagy	*PLEKHM1*		VOIT	*COG4 AP3B1, AP3D1, CAV1, GNPTAB, LYST, NPC1, NPC2, TRAPPC11, VPS33A, VPS45*
	VOIT and autophagy	*SQSTM1, TCIRG1*			
	Cytoskeleton	*ALMS1, CCDC2*		VOIT and autophagy	*PLEKHM1, TCIRG1*
	Others	*PAX3, SCL10A7, AP2beta1, INPPL1*		VT and cytoskeleton	*CD27*
Arthrogryposis ARC syndrome (*VPS33B, VIPAS39*) Neurogenic multiplex arthrogryposis (*ERGIC1*) Progressive encephalopathy brain atrophy and thin corpus callosum (*TBCD*)	Vesicular trafficking	*KIAA1109, VIPAS39*		Others	*ITK, SKIV2L*
	VOIT	*SLC35A3 ERGIC1, VPS33B*	**Gastrointestinal signs** Chylomicron retention disease (*SAR1B*) Goldberg-Shprintzen megacolon syndrome (*KIFBP*) MEDNIK syndrome (*AP1S1*)	Vesicular trafficking	*HYOI1, TTC37, UNC45A, STX3, Munc18.2*
	Cytoskeleton	*BICD2, KIF5C, TBCD*		VOIT	*AP1S1, ARCN1, LRBA, SAR1B, TMEM165 COG4, COG6, COG8, SLC35A2*
Joint laxity SLC35A1-CDG (*SLC35A1*) Cutis laxa type IIA (*ATP6V0A2*) SSASKS syndrome (*SLC10A7*)	Vesicular trafficking	*ATP6V0A2, RAB3GAP1*			

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Table 3. (continued)

Clinical manifestations	Categories	Genes	Clinical manifestations	Categories	Genes
Warburg micro syndrome (*RAB3GAP1*)	VOIT	*SLC35A1 ATP7A, SLC10A7*	Microvillus inclusion disease (*MYO5B, STX3, Munc18.2*)	Autophagy	*FIG4, VAC14*
				Cytoskeleton	*KIFBP, MYO5B, WAS*
	Others	*SKIV2L, SLC2A10, XIAP*		Others	*SKIV2L, SLC2A10, XIAP*
Cardiological			**Ocular**		
Congenital heart disease Carpenter syndrome (*RAB23*) Saladino Noonan syndrome (*DYNC2H1*) Schuurs-Hoeijmakers syndrome (*PACS1*)	Vesicular trafficking	*RAB23, STRADA, VPS13B*	**Cataract** Lowe syndrome (*OCRL*) Multiple sulfatase deficiency (*SUMF1*) Vici syndrome (*EPG5*) Warburg micro syndrome (RAB3GAP1, *RAB18, TBC1D20*) Yunis-Varon syndrome (*FIG4, VAC14*) NDD, growth impairment, and anemia (*VPS4A*)	Vesicular trafficking	*DKC1, KIAA1109, RAB18, RAB23, RAB3GAP1, RAB3GAP2, RNF13, SEC23A, SIL1, SLC33A1, SUMF1, WFS1*
	VOIT	*COG1, PACS1, SLC35A1 ARCN1*		VOIT	*AP1S1, ARCN1, FYCO1, GNPTAB, INPP5E, ORCL, PEX13, TBC1D20, TRAPPC11, VPS4A*
				Autophagy	*EPG5, FIG4, VAC14*
	Cytoskeleton	*DYNC2H1, FLNA*		VOIT and autophagy	*CHMP4B*
Cardiomyopathy Danon disease (*LAMP2*) Familial hypertrophic cardiomyopathy (*CAV3*) Martsolf syndrome (*RAB3GAP2*) Vici syndrome (*EPG5*) Wolfram syndrome (*WFS1*)	Vesicular trafficking	*RAB3GAP2, WFS1*		Cytoskeleton	*ACTB, ALMS1, KIF11, KIF1B, TUBG1*
	Others	*NFE2L2*	**Retinopathy** Alkuraya-Kucinskas syndrome (*KIAA1109*) Choroideremia (*CHM*) Cohen syndrome (*VPS13B*) Leber amaurosis with deafness (*TUBB4B*) Wolfram syndrome (*WFS1*) Cone-Rode retinopathy (*RIMS2*)	Vesicular trafficking	*ATXN2, CHM, KIAA1109, PIK3R4, SUMF1, TYR, VPS13B, WFS1,*
Arrhythmia Long QT syndrome type 9 and 11 (*CAV3, AKAP9*) *MECRCN* (*TANGO2*)	VOIT	*CAV3, TANGO2 AKAP9*		VOIT	*SLC35A2 AP3B2, BLOC1S3, RIMS2*
Other cardiac abnormalities MATINS (macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss) (*MYH9*)	Cytoskeleton	*MYH9*		Autophagy	*AP5Z1, FIG4, VAC14*
Renal				VOIT and autophagy	*SPG11*
Tubulopathy ARC syndrome (*VIPAS39, VPS33B*) SLC35A1-*CDG* (*SLC35A1*) Dent disease type 2 (*OCRL*) Lowe syndrome (*OCRL*)	Vesicular trafficking	*VIPAS39, VPS33B*	**Corneal abnormalities** Carpenter syndrome (*RAB23*) Congenital stromal corneal dystrophy (*DCN*) Cystinosis nephropathic (*CTNS*) Multiple sulfatase deficiency (*SUMF1*)	Vesicular trafficking	*DCN, RAB23, SUMF1, TRAPPC2*
	VOIT	*SLC35A1* and *OCRL*		VOIT	*CTNS GNPTAB, TBC1D20*
Chronic kidney disease CDG type II (*COG1, COG6, COG7, SLC35A1, SLC35A2*) Cystinosis nephropathic (*CTNS*) Lowe syndrome (*OCRL*) Wolcott-Rallison syndrome (*EIF2AK3*)	VOIT	*EIF2AK3, LPIN1, STRADA,* and *CTNS, SCARB2, SLC35A1, SLC35A2, OCRL, VPS33A*	**Hypopigmentation** Chediak-Higashi syndrome (*LYST*) Hermansky-Pudlak syndrome (*AP3B1, AP3D1, DTNBP1*) Waardenburg syndrome (*MITF*)	Vesicular trafficking	*DTNBP1*
				VOIT	*AP3B1, AP3D1, LYST*

Table 3. (continued)

Clinical manifestations	Categories	Genes	Clinical manifestations	Categories	Genes
	Cytoskeleton and others	*KIF14, WAS,* and *NUP107*		Others	*MITF, PAX3*
Renal dysplasia/malformation Alkuraya-Kucinskas syndrome (*KIAA1109*) Saladino-Noonan syndrome (*DYNC2H1*) Trichohepatoenteric syndrome (*TTC37*) Zellweger syndrome (*PEX13*)	Vesicular trafficking	*KIAA1109, RAB23, TTC37, WFS1*	**Coloboma** Baraitser-Winter syndrome (*ACTB*) Pontocerebellar hypoplasia type 11 (*TBC1D23*) Schuurs-Hoeijmakers syndrome (*PACS1*)	VOIT	*PACS1, TBC1D23*
	VOIT	*PACS1* and *PEX13, VPS33A*		Cytoskeleton	*ACTB*
	Cytoskeleton	*DYNC2H1*	**Other ocular abnormalities** Achromatopsia-7 (*ATF6*) Glaucoma open angle (*OPTN*) Goldberg-Shprintzen megacolon syndrome (*KIFBP*)	Vesicular trafficking	*NGLY1, RAB18, RAB3GAP1, SFB2WFS1*
				VOIT	*ATF6, COG5, SLC39A13 LAMP2, OCRL, OPTN, TMEM165*
				Cytoskeleton	*KIF14, KIF1B, KIFBP, TUBG1*
Endocrine, reproductive, neoplasia					
Endocrinological abnormalities Cohen syndrome (*VPS13B*) (short stature, truncal obesity) Kenny-Caffey syndrome (*TBCE*) (hypoparathyroidism) Osteopetrosis type 1 and 3 (*TCIRG1, PLEKHM1*) Pseudohypoparathyroidism IB (*STX16*) Wolfram syndrome (*WFS1*) (diabetes) Male infertility (*TBC1D25, RABL2*) Hypothyroidism, growth hormone failure, pancreatic dysfunction (*MADD*); diabetes (*RIMS2, IER3IP*)*1*	Vesicular trafficking	*STRADA, VPS13B, WFS1, MADD, IER3IP1, YIF1B*	**Neoplasia** Adenocarcinoma of lung (*PRKN*) Hepatocellular carcinoma somatic (*IGF2R*) Lymphoproliferative syndrome 1 and 2 (*ITK, CD27*) Pheochromocytoma (*KIF1B*)	Vesicular trafficking	*CD27, DKC1, ITK, MAGT1*
	VOIT	*LRBA, PLEKHM1, STX16, TANGO2, TBC1D25, RABL2, RIMS2*		VOIT	*COG1, COG4, COG6, SLC35A1, SLC35C1 IGF2R*
	VOIT and autophagy	*TCIRG1*			
	Cytoskeleton	*TBCE*		Autophagy	*PRKN*
Genital/reproductive abnormalities Carpenter syndrome (*RAB23*) Globozoospermia 6 (*SPATA16*) Marinesco-Sjogren syndrome (*SIL1*) Martsolf syndrome (*RAB3GAP2*) Warburg micro syndrome (*RAB3GAP1 RAB18, TBC1D20*)	Vesicular trafficking	*PANX1, RAB18, RAB23, RAB3GAP1, RAB3GAP2, RAC1, SIL1, WFS1*		Cytoskeleton	*KIF1B*
	VOIT	*TBC1D20*		Others	*RUNX1, SH2D1A, XIAP*
	Autophagy	*PRKN, VAC14*			
	Cytoskeleton	*TBCE*			
	Others	*SPATA16*			
Neoplasia Adenocarcinoma of lung (*PRKN*) Hepatocellular carcinoma somatic (*IGF2R*) Lymphoproliferative syndrome 1 and 2 (*ITK, CD27*) Pheochromocytoma (*KIF1B*)	Vesicular trafficking	*CD27, DKC1, ITK, MAGT1*			
	VOIT	*COG1, COG4, COG6, SLC35A1, SLC35C1, IGF2R*			
	Autophagy	*PRKN*			
	Cytoskeleton	*KIF1B*			
	Others	*RUNX1, SH2D1A, XIAP*			

Abbreviations: CDG, congenital disorder of glycosylation; HLH, hemophagocytic lymphohistiocytosis; Others: traffic mechanisms are complex or not clearly defined according to current knowledge; VOIT, vesicular and organelle/interorganelle trafficking.

Cardiac manifestations

These include congenital heart disease due to *PACS1* mutations, cardiomyopathy (dilated and hypertrophic; i.e., Vici syndrome: *EPG5* mutations; Danon disease: *LAMP2*), and arrhythmia. *CAV3, AKAP9*, and *TANGO2* mutations cause long QT syndrome [6].

Kidney disease

This may manifest as tubular dysfunction with or without renal failure, as chronic kidney disease, or with renal dysplastic changes. Oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked multisystem disorder due to *OCRL* mutations, leading to phosphatidylinositol-4,5-bisphosphate accumulation. It is characterized by congenital cataracts, glaucoma, ID, postnatal growth retardation, and renal tubular dysfunction of the Fanconi type [102].

The endocrine and reproductive systems may also be involved. Finally, some disorders of cellular trafficking are associated with specific types of cancer or with increased risk of neoplasia.

Concluding remarks

The study of cell trafficking and their related disorders is a great challenge that will probably open a new era of knowledge creating networks between cell biology, biochemistry, metabolism and genetic medicine. Given the large number of diseases and the complex pathophysiology of the biological processes involved, we have proposed a tentative approach aimed to link mechanisms and clinical manifestations. However, many Outstanding questions are still to be revealed.

How classic metabolic pathways such as energy metabolism, lipid and protein synthesis and catabolism are interconnected with membrane trafficking and crucial functions such as autophagy? How are transport intermediates organized at different interfaces? Most of the mutations involved in these diseases are linked to a loss-of-function, how will this fact impact possible therapeutic strategies? The great importance of cell trafficking in the nervous system and the marked vulnerability of neurons to cell trafficking defects give rise to many questions. In particular, the discovery of biomarkers that could detect dysfunctions in these pathways should allow an early diagnosis and possible personalized treatments.

The future should usher in new CryoEM-based techniques and other high-resolution imaging-based approaches that will enable a deeper understanding of the cell trafficking machinery. Additionally, the prodigious expansion of genetic disorders linked to cellular trafficking defects raises the possibility of reclassifying inherited metabolic disorders according to a holistic cell physiological approach rather than the classic separation between intermediary metabolism, organelles and structural proteins. Localization of the mutated gene product, where in the cell, in which compartment and at which point of the three-dimensional structure of every cellular structure, will also be also a matter of importance to pathophysiology and symptoms of these diseases.

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The authors declare no competing interests regarding the topic of this article.

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Outstanding questions

How can we better develop a pathophysiological based approach to disorders of cellular trafficking and accordingly, is it possible to establish a link between the fundamental mechanisms of disease and the clinical manifestations?

How the advances made at the scientific level, mostly through electron microscopy and other ultra-high resolution image techniques that would enable a deeper understanding of the cell trafficking machinery, will impact the clinical approach to these disorders?

Would it be necessary a combination of high-resolution cell image techniques and multi-omic analysis to describe new biomarkers for these diseases, and would these biomarkers be useful for an early diagnosis and targeted treatment?

Given that all compartments are dynamically polymorphic, how could we investigate cellular trafficking both spatially and temporally by looking at serial metabolic signatures in subcellular fractions?

How are cellular trafficking processes regulated by biochemical, metabolic pathways such as energy consumption, lipid synthesis and remodeling, amino acid synthesis and catabolism?

Would the description of novel pathways connecting cellular processes and intermediary metabolism lead to the definition of new therapies and what consequences for the development of new treatments will have the fact that these disorders are mostly loss-of-function defects?

Given the extreme vulnerability of neurons to these type of disorders, would it be possible that any kind of neurological disease, regardless the genetic or environmental origin, would end up having some kind of cell trafficking impairment?

How a better knowledge of mechanisms of cell trafficking will transform both, the field of inborn errors of metabolism and neurology in terms of classifications and understanding of these diseases as an interconnected network?

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Author contributions

A.G-C. and A.O. conceived of, wrote, and edited the manuscript. C.D-V. and D.M. wrote and edited the article. J-M.S., D.M. and C.D-V. have contributed to the original idea and the critical review providing important information for the content of the article.

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