

AT A GLANCE

# Membrane trafficking in health and disease

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**ABSTRACT**

Membrane trafficking pathways are essential for the viability and growth of cells, and play a major role in the interaction of cells with their environment. In this At a Glance article and accompanying poster, we outline the major cellular trafficking pathways and discuss how defects in the function of the molecular machinery that mediates this transport lead to various diseases in humans. We also briefly discuss possible therapeutic approaches that may be used in the future treatment of trafficking-based disorders.

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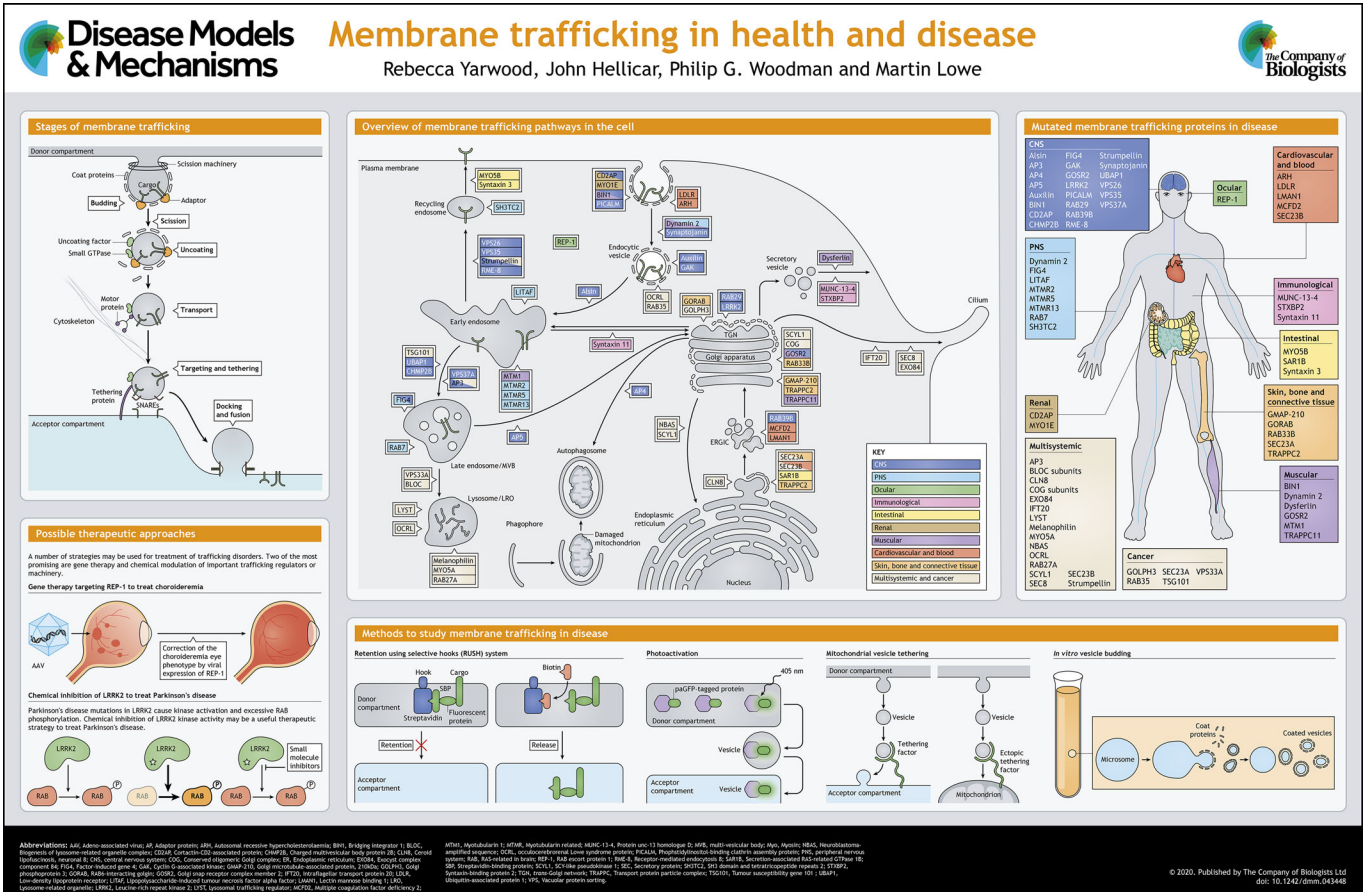
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**KEY WORDS:** Disease, Endocytic pathway, Genetic disorder, Membrane traffic, Secretory pathway, Vesicle

**Introduction**

Membrane trafficking pathways are essential for cells to maintain critical functions, to grow, and to accommodate to their chemical and physical environment. Membrane flux through these pathways is high, and in specialised cells in some tissues can be enormous. For example, pancreatic acinar cells synthesise and secrete amylase, one of the many enzymes they produce, at a rate of approximately 0.5% of cellular protein mass per hour (Allfrey et al., 1953), while in Schwann cells, the rate of membrane protein export must correlate with the several thousand-fold expansion of the cell surface that occurs during myelination (Pereira et al., 2012). The population of cell surface proteins is constantly monitored and modified via the endocytic pathway. In some cells, endocytosis accounts for the complete turnover of surface membrane over a period of an hour or so (Steinman et al., 1976). Given such rates of trafficking, it is not surprising that even subtle alterations in transport caused by mutation or insufficiency of the trafficking machinery can impair cell function and lead to disease over the course of a lifetime.



This At a Glance article describes the essential features of membrane trafficking pathways, including the crucial molecular events that drive transport. We identify instances where the mutation or loss of trafficking machinery components is associated with disease, and attempt to rationalise these effects. Several topics are not covered or are mentioned only briefly due to space limitations, including the folding and quality control of soluble or membrane-bound cargo, as exemplified by cystic fibrosis transmembrane conductance regulator (CFTR) in cystic fibrosis; motor proteins and their adaptors, which move vesicle-bound cargo around the cell; the biogenesis of mitochondria, peroxisomes, or non-membranous organelles; compartment-specific proteins that define essential organelle functions; non-vesicular lipid transport pathways; and exosome trafficking. Similarly, we only briefly discuss autophagy, which relies on membrane input from both the secretory and endocytic pathways and fusion of autophagosomes with lysosomes (Søreng et al., 2018).

### General principles of membrane trafficking

Transport of proteins between compartments is initiated by (1) selection of cargo and its segregation from resident proteins of the donor compartment by the action of ‘adaptors’; (2) encapsulation of cargo-bound adaptors within a protein scaffold or ‘coat’, which drives membrane deformation and ultimately scission to form a transport vesicle, or in some cases a tubular transport intermediate; (3) movement of the vesicle to the target compartment; (4) membrane tethering, in which the vesicle is drawn towards the target membrane by extended proteins/protein complexes that work in conjunction with RAB (RAS-related in brain) GTPases; and (5) docking and membrane fusion, in which the vesicle is first tightly attached to the target membrane, followed by merging of the lipid bilayers, both processes being mediated by soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) protein complexes and supported by accessory factors (see poster). While these steps are generic to transport reactions, the compartmental specificity of the components within protein families ensures transport fidelity. Much of our understanding of these processes stems from important experimental methodologies, which we describe in Box 1.

### The secretory pathway

The biogenesis of most integral membrane proteins, secreted proteins and organelle content markers occurs at the endoplasmic reticulum (ER) (see poster). Correctly folded and post-translationally modified membrane-bound or luminal cargoes are then selected for export by adaptor proteins that engage the coat protein complex (COP) II vesicle machinery, or by binding COPII directly (Jensen and Schekman, 2011; McCaughey and Stephens, 2018). COPII vesicle production is initiated when the ER-associated guanine nucleotide exchange factor (GEF) secretion protein (SEC) 12 (also known as PREB), activates secretion-associated RAS-related GTPase 1 (SAR1) and SAR1-GTP subsequently anchors to the membrane. The COPII coat is formed as SAR1 sequentially recruits multiple SEC23/SEC24 dimers, followed by SEC13/SEC31, to sequester adaptors and drive membrane deformation to produce COPII vesicles. These vesicles tether at and fuse with the ER-Golgi intermediate compartment (ERGIC), from which they are delivered to the *cis*-side of the Golgi apparatus, processes mediated by tethering factors and complexes of ERGIC- and Golgi-associated SNARE proteins (Brandizzi and Barlowe, 2013).

Cargo subsequently moves through the Golgi complex, where it can undergo post-translational modification and processing, most notably at the level of glycosylation, by enzymes that each localise within a narrow range of Golgi cisternae. How cargo moves forward is controversial, but the current consensus is that a Golgi cisterna

moves ‘en bloc’, with cargo encountering Golgi-resident enzymes, as these are distilled backwards via selective incorporation into COPI vesicles (Pantazopoulou and Glick, 2019). COPI works analogously to COPII, with vesicle production initiated by the activation and membrane anchoring of ADP-ribosylation factor (ARF) 1 GTPase (Beck et al., 2009). The COPI coat is recruited en masse, and includes moieties that bind cargo and cargo adaptors, and those that scaffold the assembly and induce membrane curvature. Meanwhile, ARF GTPase activating proteins (ARF-GAPs) sense completion of COPI budding, and facilitate coat disassembly. Conserved oligomeric Golgi complex (COG) is a crucial membrane-tethering complex for COPI vesicles, working in conjunction with RAB GTPases and golgin coiled-coil proteins, while membrane fusion involves Golgi-specific SNAREs (Fisher and Ungar, 2016). In addition to intra-Golgi transport, COPI also recycles proteins from the ERGIC and Golgi apparatus back to the ER (Brandizzi and Barlowe, 2013).

Proteins exit the Golgi at the *trans*-Golgi network en route to the cell surface or towards the endosomal system (discussed below) (De Matteis and Luini, 2008). In the case of secretory/surface cargo, where export is constitutive, carriers appear to be tubular. In contrast, cargoes subject to regulated secretion are concentrated into specialised granules, which fuse with the surface in a Ca<sup>2+</sup>-regulated manner (Anantharam and Kreuzberger, 2019). SNARE-mediated fusion of these granules with the cell surface is facilitated by a range of specialised accessory proteins, including members of the synaptotagmin family of Ca<sup>2+</sup> sensors.

### The endocytic pathway

Surface membrane proteins define the interface between cells and their environment, and cells constantly refine the population of proteins at the surface via rounds of endocytosis and subsequent endosomal sorting (see poster). Endocytosis also brings in soluble proteins, either as ligands to surface receptors or as bulk-flow constituents. The best-characterised uptake pathway is clathrin-mediated endocytosis (McMahon and Boucrot, 2011). Here, clathrin provides the membrane-deforming scaffold, the assembly of which onto the plasma membrane is mediated by cargo-binding adaptor complexes. The best known of these is adaptor protein complex (AP) 2, which is part of a wider family of hetero-tetrameric adaptor complexes, AP1-5. AP2 binds to peptide motifs within the cytoplasmic domains of a range of membrane proteins, while also binding clathrin. Other clathrin adaptors engage client cargoes more selectively. Meanwhile, numerous accessory proteins promote key steps towards vesicle formation, leading ultimately to the recruitment of the scission GTPase, dynamin. Clathrin-coated vesicle formation also relies on local actin dynamics, and on the local generation of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P<sub>2</sub>] which aids both actin and coat protein recruitment. PtdIns(4,5)P<sub>2</sub> phosphatases, notably synaptojanin, complete the vesicle cycle.

Other endocytic mechanisms employ membrane-deforming proteins that selectively engage client membrane cargo while often utilising actin to provide a driving force (Sandvig et al., 2018). Examples include those mediated by flotillin, endophilin and cell division control protein 42 homologue (CDC42). Caveolae, comprised of the membrane protein caveolin and the structural protein cavin, provide a prominent and clinically important example of plasma membrane invagination (Parton, 2018). They primarily appear to function as a reservoir for surface membrane that forms or is dissipated according to alterations in membrane tension, and they are particularly enriched in elastic tissues such as the lung and muscle. Their role may also extend to the sequestration of some signalling

**Box 1. Experimental approaches used to study trafficking**

Many molecular cell biological approaches have been used to study membrane traffic. Historically, cell-free assays that reconstitute transport reactions (Balch et al., 1984) and yeast genetics (Novick and Schekman, 1979) provided great advances in identifying the crucial molecular components, and these approaches are still relevant today for dissecting transport mechanisms (see poster, 'In vitro vesicle budding'). Cell culture models remain a powerful tool, with recent advances including growing cells in 3D to better mimic the tissue environment (Torras et al., 2018), the use of induced pluripotent stem cells that can be isolated from human patients and differentiated into any relevant cell type (Avior et al., 2016), and the use of stem cell-generated organoids, which provide a close approximation of tissue organisation in an *in vitro* setting (Lancaster and Huch, 2019; Rossi et al., 2018). Animal models also remain a valuable tool to study disease mechanisms attributable to trafficking defects, and have been used very successfully in this regard (see, for example, Smits et al., 2010). Analysis of human patients is also a powerful way to assess the functional relevance of gene products in a physiological setting, and provides a direct indication of the importance of trafficking factors for human health (FitzGerald et al., 2018).

A number of more recent or specialised approaches can be applied to the study of membrane traffic, some of which are highlighted in the poster. Various methods have been developed to allow synchronous transport along the secretory pathway (Kreis and Lodish, 1986; Chen et al., 2013; Kuismanen and Saraste, 1989; Rivera et al., 2000). One of the most commonly used is the retention using selective hooks (RUSH) system, in which synchronous transport is triggered by the addition of exogenous biotin, which triggers release of cargo from an organelle-resident 'hook' (Boncompain et al., 2012). The use of split-fluorescent protein technology allows researchers to assess delivery into secretory compartments (Feng et al., 2017). Here, cargo and organelle-resident proteins are separately tagged with two units of a fluorescent protein that, when combined, emit fluorescence, allowing for visualisation of cargo delivery to the organelle of interest. Photo-activation or photo-switching of fluorescently tagged cargo proteins or machinery can also be used to visualise transport dynamics (Sengupta and Lippincott-Schwartz, 2013). Mitochondrial relocation is a useful tool for assessing protein-protein interactions, but more recently has been adapted to allow visualisation of vesicle tethering in intact cells. Here, tethering factors were artificially localised to mitochondria to allow direct visualisation of tethering by light and electron microscopy (Wong and Munro, 2014). Proximity biotinylation is a recently developed and widely used technology to identify closely associated proteins within cells. There are several variations of the method, which all rely on the promiscuous activity of a biotin ligase attached to any protein of interest, allowing for biotinylation of nearby proteins and their isolation and identification by mass spectrometry (Branon et al., 2018; Hung et al., 2016; Roux et al., 2012). The approach can be used in the context of membrane traffic to identify the machinery involved in particular trafficking reactions, cargo components of transport vesicles, or the protein complements of organelles within the endomembrane system. Quantitative proteomics can also be used to identify entire complements of secreted or plasma membrane proteins (Eichelbaum et al., 2012; Steinberg et al., 2013), allowing for unbiased and comprehensive analysis of how these protein complements may change in response to perturbation of various trafficking pathways.

pathway components. Caveolae can also undergo endocytosis, although the mechanisms remain poorly defined (Parton, 2018).

Endocytic vesicles fuse to form early endosomes, which are the major sorting stations within the endocytic pathway. The early (or sorting) endosomes are defined by the presence of RAB5 and phosphatidylinositol 3-phosphate (PtdIns3P), which promote the recruitment of numerous effector proteins to the endosomal membrane (Wandinger-Ness and Zerial, 2014). Eventually, endosomes mature as RAB5 is replaced with RAB7 and PtdIns3P is converted to phosphatidylinositol 3,5-bisphosphate

[PtdIns(3,5)P<sub>2</sub>] to generate late endosomes. These fuse with and discharge into lysosomes, leading to the digestion of luminal content (Wartosch et al., 2015)

To allow the degradation of integral membrane proteins, these must move from the endosomal limiting membrane into the lysosomal luminal space. Hence, these membrane proteins are incorporated into intraluminal vesicles (ILVs), giving rise to the multivesicular body (MVB). The signal for ILV sorting, K63-linked polyubiquitin, is recognised by a series of endosomal sorting complexes required for transport (ESCRT) complexes and accessory factors (Christ et al., 2017), of which ESCRT-0 and ESCRT-I form the principal ubiquitin receptors. Cargo is passed onwards to ESCRT-III, a membrane-deforming polymer that combines with the AAA ATPase vacuolar protein sorting (VPS) 4 to mediate membrane fission and ILV completion.

Endocytic cargo can escape from the MVB-lysosome pathway by recycling to the cell surface or diverting to the Golgi complex (Cullen and Steinberg, 2018). These pathways involve the formation of tubular or vesicular intermediates that bud away from the endosome. The retriever and retromer complexes are important players in recycling from the sorting endosome that interact with sorting nexin proteins. Recycling to the plasma membrane can occur via a 'fast' direct route, or a 'slow' indirect route by which cargo is first delivered to the recycling endosome, marked by RAB11, and utilises a distinct set of molecular machineries such as EH domain-containing protein 1 (EHD1) and molecule interacting with CasL protein-like 1 (MICAL-L1), which remain less well characterised than those at the sorting endosome (Goldenring, 2015).

Synaptic vesicles are the mediators of neurotransmitter release at neuronal synapses. Synaptic vesicle biogenesis within the nerve terminal can occur directly from the plasma membrane via endocytosis, or from pre-existing endosomes through selective budding from this compartment (Saheki and De Camilli, 2012), and is therefore highly dependent upon the endocytic trafficking machinery. Fusion of synaptic vesicles with the plasma membrane for neurotransmitter release is tightly regulated, and occurs in a similar way to the regulated exocytosis of secretory granules described above, being mediated by SNAREs and controlled by Ca<sup>2+</sup> sensors (Südhof, 2013).

**Diseases that are caused by defective membrane traffic**

Diseases associated with defective membrane traffic collectively manifest in practically all tissues and organ systems, with some affecting multiple systems and others restricted to one tissue type or organ. Diseases most often arise from mutations that cause loss of expression or function of transport machinery components, but some are caused by toxic gain-of-function mutations. Diseases attributable to defective trafficking machinery can be developmental in nature, or can arise during the lifespan, often manifesting during ageing. Here, we categorise membrane trafficking-related diseases based upon their tissue and organ system involvement (also see poster). The discussion is not exhaustive; for a more comprehensive list of diseases associated with defective trafficking please consult Table 1.

**Neurological disease**

Major neurodegenerative diseases are strongly associated with defects in membrane traffic, particularly within the endosomal system (Schreij et al., 2016). Genetic association studies link variants or altered expression levels of the clathrin-mediated endocytosis components phosphatidylinositol-binding clathrin assembly protein (PICALM) (Harold et al., 2009; Jun et al.,

**Table 1. Human diseases caused by mutation of membrane trafficking proteins**

| Protein name    | Disease   | Inheritance  | Protein function   | Tissue/organ system affected | Phenotype   | Phenotype Mendelian Inheritance in Man (MIM) number | Reference  |
|-----------------|---|--|--|------------------------------|---|---|--|
| Alpha-synuclein | Parkinson disease 1 (PARK1)<br>Parkinson disease 4 (PARK4)  | Autosomal dominant<br>Autosomal dominant                         | May function as a SNARE regulator in neurons   | Central nervous system       | Bradykinesia, resting tremor, muscular rigidity and postural instability.<br>Bradykinesia, resting tremor, muscular rigidity and postural instability as well as dementia and diffuse Lewy body pathology.  | 168601<br>605543                                    | (Polymeropoulos et al., 1997)<br>(Singleton et al., 2003)              |
| Alsin           | Lewy body dementia (LBD)<br>Juvenile primary lateral sclerosis (JPLS)<br>Amyotrophic lateral sclerosis 2 (ALS2) | Autosomal dominant<br>Autosomal recessive<br>Autosomal recessive | Endosomal trafficking<br>RAB5 GEF  | Central nervous system       | Dementia and parkinsonism, with fluctuating cognitive function. Lewy bodies are more widespread than usually observed in PD.<br>Progressive paralytic disorder resulting from dysfunction of the upper motor neurons.<br>Limb and facial spasticity, spastic dysarthria, subsequent lower motor neuron signs and bladder dysfunction. | 127750<br>606353<br>205100                          | (Zarranz et al., 2004)<br>(Yang et al., 2001)<br>(Hadano et al., 2001) |
| AP1S2           | Infantile-onset ascending spastic paralysis (IAHSP)<br>Pettigrew syndrome                                       | Autosomal recessive<br>X-linked recessive                        | Claithrin vesicle formation and trafficking<br><i>trans</i> -Golgi network (TGN) trafficking | Central nervous system       | Progressive spasticity and weakness of limbs.<br>Mental retardation.  | 607225<br>304340                                    | (Eymard-Pierre et al., 2002)<br>(Tarpey et al., 2006)                  |
| AP2M1           | Intellectual developmental disorder 60 with seizures (MRD60)  | Autosomal dominant   | AP1 complex subunit  | Central nervous system       | Epilepsy with myoclonic-atonic seizures.  | 618587  | (Helbig et al., 2019)  |
| AP3B2           | Early infantile epileptic encephalopathy 48 (EIEE48)  | Autosomal recessive  | AP2 complex subunit<br>TGN/lysosome trafficking<br>AP3 complex subunit                       | Central nervous system       | Refractory seizures, neurodevelopmental impairment. Following onset of seizures, cognitive and motor delays become apparent.<br>Early onset. Progressive lower extremity spasticity and weakness.   | 617276<br>614066                                    | (Assoum et al., 2016)<br>(Bauer et al., 2012)                          |
| AP4B1           | Spastic paraplegia 47 (SPG47)   | Autosomal recessive  | TGN trafficking to endosomal-lysosomal system<br>AP4 complex subunit                         | Central nervous system       | Infantile onset. Progressive lower extremity spasticity and weakness.   | 613744  | (Moreno-De-Luca et al., 2011)  |
| AP4E1           | Spastic paraplegia 51 (SPG51)   | Autosomal recessive  | TGN trafficking to endosomal-lysosomal system<br>AP4 complex subunit                         | Central nervous system       | Frequent repetition or prolongation of sounds or syllables and interruption of speech (blocks).<br>Infantile onset. Progressive lower extremity spasticity and weakness.  | 184450<br>612936                                    | (Raza et al., 2015)<br>(Verkerk et al., 2009)                          |
| AP4M1           | Spastic paraplegia 50 (SPG50)   | Autosomal recessive  | TGN trafficking to endosomal-lysosomal system<br>AP4 complex subunit                         | Central nervous system       | Infantile onset. Progressive lower extremity spasticity and weakness.   | 614067  | (Hardies et al., 2015)   |
| AP4S1           | Spastic paraplegia 52 (SPG52)   | Autosomal recessive  | TGN trafficking to endosomal-lysosomal system<br>AP4 complex subunit                         | Central nervous system       | Progressive lower extremity spasticity and weakness.  | 613647  | (Slabicki et al., 2010)  |
| AP5Z1           | Spastic paraplegia 48 (SPG48)   | Autosomal recessive  | Endosomal trafficking<br>AP5 complex subunit   | Central nervous system       | Developmental disabilities, speech delay, seizures and attention-deficit hyperactivity disorder (ADHD).   | 618185  | (Ge et al., 2016)  |
| ARF1            | Periventricular nodular heterotopia 8 (PVNH8)   | Autosomal dominant   | COPI coat assembly<br>ARF GTPase   | Central nervous system       | Progressive lower extremity spasticity and weakness.  | 182600  | (Zhao et al., 2001)  |
| Atlastin        | Spastic paraplegia 3A (SPG3A)<br>Hereditary sensory neuropathy type 1D (HSN1D)                                  | Autosomal dominant<br>Autosomal dominant                         | ER membrane remodelling<br>GTPase  | Central nervous system       | Adult-onset distal axonal sensory neuropathy leading to mutilating ulcerations as well as hyporeflexia.   | 613708  | (Guelly et al., 2011)  |

|                    |  |  |  |                                   |   |        |   |
|--------------------|--|--|--|-----------------------------------|---|--------|---|
| Auxilin/<br>DNAJC6 | Parkinson disease 19A (PARK19A)  | Autosomal recessive                          | Ciathrin-mediated endocytosis<br>Uncoating chaperone                             | Central nervous system            | Juvenile onset (first or second decade).<br>Bradykinesia, resting tremor, muscular rigidity and postural instability.                                     | 615528 | (Edvardson et al., 2012)  |
|                    | Parkinson disease 19B (PARK19B)  | Autosomal recessive                          |  | Central nervous system            | Early onset (between third and fifth decades).<br>Bradykinesia, resting tremor, muscular rigidity and postural instability.                               |        | (Oligati et al., 2016)  |
| BIN1               | Alzheimer's disease  | Association reported                         | Endocytosis, membrane shaping and t-tubule formation                             | Central nervous system            | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.   | 104300 | (Hu et al., 2011; Seshadri et al., 2010)                            |
|                    | Centronuclear myopathy 2 (CNM2)  | Autosomal recessive                          | Adaptor protein  | Muscular                          | Progressive muscular weakness and wasting involving mainly limb girdle, trunk and neck muscles.   | 255200 | (Nicot et al., 2007)  |
| BIG2               | Periventricular nodular heterotopia 2 (PVNH2)                            | Autosomal recessive                          | TGN trafficking  | Central nervous system            | Microcephaly, severe developmental delay and recurrent infections.  | 608097 | (Sheen et al., 2004)  |
| C9orf72            | Frontotemporal dementia and/or amyotrophic lateral sclerosis 1 (FTDALS1) | Autosomal dominant                           | Autophagy regulator and endosomal trafficking                                    | Central nervous system            | Frontotemporal dementia: frontal and temporal lobe atrophy. Amyotrophic lateral sclerosis: death of motor neurons, resulting in fatal paralysis.          | 105550 | (DeJesus-Hernandez et al., 2011; Renton et al., 2011)               |
| CD2AP              | Alzheimer's disease  | Association reported                         | Ciathrin-mediated endocytosis  | Central nervous system            | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.   | 104300 | (Hollingsworth et al., 2011; Naj et al., 2011)                      |
|                    | Focal segmental glomerulosclerosis 3 (FSGS3)                             | Autosomal recessive                          | Adaptor protein  | Renal                             | Segmental sclerosis in glomeruli, resulting in proteinuria, reduced glomerular filtration rate and progressive decline in renal function.                 | 607832 | (Kim et al., 2003)  |
| CHMP2B             | Chromosome 3-linked frontotemporal dementia (FTD3)                       | Autosomal dominant                           | Endosomal trafficking  | Central nervous system            | Onset of dementia in late 50s initially characterised by behavioural and personality changes.   | 600795 | (Skibinski et al., 2005)  |
|                    | Amyotrophic lateral sclerosis 17 (ALS17)                                 | Autosomal dominant                           | Component of endosomal ESCRT-III complex   | Central nervous system            | Muscle weakness, wasting of the upper and lower limbs, bulbar signs and respiratory insufficiency.  | 614696 | (Parkinson et al., 2006)  |
| cTAGE5             | Familial idiopathic basal ganglia calcification (Fahr's disease)         | Association reported                         | ER-to-Golgi trafficking of large cargo   | Central nervous system            | Basal ganglia calcifications.   |        | (Lemos et al., 2011)  |
| DENND5a            | Early infantile epileptic encephalopathy 49 (EIEE49)                     | Autosomal recessive                          | ER exit site-associated protein<br>Late endosome, lysosome and Golgi trafficking | Central nervous system            | Neonatal onset of seizures, global developmental delay with intellectual disability and lack of speech, hypotonia, spasticity and coarse facial features. | 617281 | (Han et al., 2016)  |
|                    |  |  | GEF for RAB39A and RAB39B  |                                   |   |        |   |
| FIG4               | Bilateral temporoparietal polymicrogyria (BTOP)                          | Autosomal recessive                          | Endosomal trafficking  | Central nervous system            | Polymicrogyria, psychiatric manifestations and epilepsy.  | 612691 | (Baulac et al., 2014)   |
|                    | Amyotrophic lateral sclerosis 11 (ALS11)                                 | Autosomal dominant                           | Vesicle trafficking  | Central nervous system            | Rapid progressive loss of motor neurons, leading to muscle weakness and paralysis.  | 612577 | (Chow et al., 2009)   |
|                    | Charcot-Marie-Tooth disease 4J (CMT4J)                                   | Autosomal recessive                          | RAB-GDP dissociation inhibitor trafficking                                       | Peripheral nervous system         | Recessive demyelinating form of the disease.  | 611228 | (Zhang et al., 2008)  |
|                    |  |  | SNARE  |                                   | Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.  |        |   |
|                    | Yunis-Varon syndrome   | Autosomal recessive                          | Ciathrin-mediated endocytosis  | Multi-systemic                    | Skeletal anomalies, dysmorphism, global developmental delay and intracytoplasmic vacuolation in brain and other tissue.                                   | 216340 | (Campeau et al., 2013)  |
| GAK                | Parkinson's disease  | Association reported                         | Uncoating chaperone  | Central nervous system            | Bradykinesia, resting tremor, muscular rigidity and postural instability.   | 168600 | (Nagle et al., 2016; Nalls et al., 2014)                            |
| GD11               | X-linked 41 mental retardation (MRX41)                                   | X-linked dominant                            | Vesicle trafficking  | Central nervous system            | Below average intelligence.   | 300849 | (Blennu et al., 1998; D'Adamo et al., 1998)                         |
| GOSR2              | Progressive myoclonic epilepsy 6 (EPM6)                                  | Autosomal recessive                          | ER-to-Golgi and intra-Golgi trafficking  | Central nervous system            | Onset of ataxia in the first years of life, followed by action myoclonus and seizures later in childhood.   | 614018 | (Corbett et al., 2011)  |
|                    | Congenital muscular dystrophy  | Autosomal recessive                          | SNARE  | Muscular                          | Mild hypotonia and severe developmental delay.<br>Muscle biopsy shows severe non-specific dystrophic changes.   |        | (Tsai et al., 2013)   |
| HD-PTP             | Developmental and epileptic encephalopathy<br>Cancer                     | Mutations reported<br>Tumour suppressor gene | Endosomal trafficking<br>ESCRT-associated protein                                | Central nervous system<br>Various | Epilepsy, severe and global developmental delay and microcephaly.   |        | (Smigiel et al., 2018; Sowada et al., 2017) (Manteghi et al., 2016) |

Continued

**Table 1. Continued**

| Protein name  | Disease  | Inheritance                               | Protein function   | Tissue/organ system affected | Phenotype  | Phenotype Mendelian Inheritance in Man (MIM) number | Reference   |
|---------------|--|---|--|------------------------------|--|---|---|
| Huntingtin    | Huntington disease   | Autosomal dominant                        | Endocytosis, microtubule-mediated transport and autophagic vesicle formation | Central nervous system       | Involuntary movements, motor impairment, psychiatric disorders and dementia.   | 143100  | (MacDonald et al., 1993)                          |
|               | Lopes-Maciel-Rodan syndrome (LOMARS)   | Autosomal recessive                       | Interacts with clathrin-binding protein HIP1                                 | Central nervous system       | Developmental regression in infancy, delayed psychomotor development, severe intellectual disability, and cerebral and cerebellar atrophy.                         | 617435  | (Lopes et al., 2016; Rodan et al., 2016)          |
| LRRK2         | Parkinson disease 8 (PARK8)  | Autosomal dominant                        | Vesicular trafficking and autophagy  | Central nervous system       | Bradykinesia, resting tremor, muscular rigidity, postural instability and neuronal loss in the substantia nigra.   | 607060  | (Paisan-Ruiz et al., 2004; Zimprich et al., 2004) |
|               | Alzheimer's disease  | Association reported                      | TGN trafficking  | Central nervous system       | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.  | 104300  | (Shrivastava-Ranjjan et al., 2009)                |
| NECAP1        | Early infantile epileptic encephalopathy 21 (EIEE21)   | Autosomal recessive                       | ARF adaptor  | Central nervous system       | Intractable seizures, profound global developmental delay and persistent severe axial hypotonia.   | 615833  | (Alazami et al., 2014)                            |
| Optineurin    | Amyotrophic lateral sclerosis 12 (ALS12)   | Autosomal recessive or autosomal dominant | Ciathrin-mediated endocytosis  | Central nervous system       | Slow disease progression. Lower limb onset.  | 613435  | (Manuyama et al., 2010)                           |
|               | Glaucoma 1, open angle, E (GLC1E)  | Autosomal dominant                        | Endocytic trafficking  | Ocular                       | Specific pattern of optic nerve and visual field defects. The angle of the anterior chamber of the eye is open, and usually the intraocular pressure is increased. | 137760  | (Rezaie et al., 2002)                             |
| PICALM        | Alzheimer's disease  | Association reported                      | Interacts with RAB8  | Central nervous system       | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.  | 104300  | (Harold et al., 2009; Jun et al., 2010)           |
| RAB11B        | Neurodevelopmental disorder with ataxic gait, absent speech, and decreased cortical white matter (NDAGSCW) | Autosomal dominant                        | Ciathrin-mediated endocytosis and autophagy                                  | Central nervous system       | Severe intellectual disability with absent speech, epilepsy and hypotonia.   | 617807  | (Lamers et al., 2017)                             |
|               | Parkinson disease 16 (PARK16)  | Association reported                      | Endocytic adaptor  | Central nervous system       | Bradykinesia, resting tremor, muscular rigidity and postural instability.  | 613164  | (MacLeod et al., 2013; Puriyte et al., 2018)      |
| RAB29         | X-linked 72 mental retardation (MRX72)   | X-linked recessive                        | Endocytic recycling  | Central nervous system       | Below average intelligence.  | 300271  | (Giannandrea et al., 2010)                        |
| RAB39B        | Waisman syndrome   | X-linked recessive                        | RAB GTPase   | Central nervous system       | Delayed psychomotor development, intellectual disability and early-onset Parkinson's disease.  | 311510  | (Mata et al., 2015; Wilson et al., 2014)          |
| RME-8/DNAJC13 | Parkinson's disease  | Autosomal dominant                        | Retrograde trafficking   | Central nervous system       | Severe intellectual disability, osseous syndactyly and craniofacial and brain malformations.   | 168600  | (Reuter et al., 2017)                             |
| SEC23IP       | Neurodevelopmental disorder  | Autosomal recessive                       | ER-to-Golgi trafficking  | Central nervous system       | Anencephaly, lumbosacral myelocystocele and hydrocephalus.   |   | (Yang et al., 2013)                               |
| SEC24B        | Neural tube defects  | Missense                                  | ER-to-Golgi trafficking  | Central nervous system       | Intrauterine growth retardation, developmental delay, spastic quadriplegia, epilepsy, optic nerve atrophy, neurosensory deafness and dysmorphisms.                 | 618651  | (Helperin et al., 2019)                           |
|               | Neurodevelopmental disorder with spastic quadriplegia, optic atrophy, anomalies (NEDSOSB)                  | Autosomal recessive                       | COPII inner coat   | Central nervous system       | Muscle weakness that is induced or worsened by exertion.   | 616330  | (Shen et al., 2014)                               |
| SNAP25B       | Congenital myasthenic syndrome 18 (CMS18)  | Autosomal dominant                        | ER-to-Golgi trafficking  | Central nervous system       | Cerebral dysgenesis, neuropathy, ichthyosis and palmoplantar keratoderma.  | 609528  | (Sprecher et al., 2005)                           |
| SNAP29        | Cerebral dysgenesis, neuropathy, ichthyosis and keratoderma (CEDNIK) syndrome                              | Autosomal recessive                       | COPII outer coat   | Central nervous system       |  |   |   |

|                |   |                                 |  |                                   |  |   |
|----------------|---|---------------------------------|--|-----------------------------------|--|---|
| SNX27          | Infantile myoclonic epilepsy and neurodegeneration                            | Homozygous deleterious mutation | Endosomal trafficking Retromer cargo adaptor                 | Central nervous system            | Startle-like movements, myoclonic seizures, axial hypotonia and recurrent aspirations.   | (Damseh et al., 2015)   |
| Spartin        | Spastic paraplegia 20 (SPG20)   | Autosomal recessive             | Endocytic trafficking Associates with microtubules           | Central nervous system            | Early onset. Progressive lower extremity spasticity and weakness.  | (Patel et al., 2002)  |
| Spastin        | Spastic paraplegia 4 (SPG4)   | Autosomal dominant              | Endosome-to-TGN trafficking and endosomal recycling          | Central nervous system            | Progressive lower extremity spasticity and weakness.   | (Hazan et al., 1999)  |
| Spastizin      | Spastic paraplegia 15 (SPG15)   | Autosomal recessive             | Microtubule-severing protein                                 | Central nervous system            | Progressive lower extremity spasticity and weakness.   | (Hanein et al., 2008)   |
| Spatacsin      | Spastic paraplegia 11 (SPG11)   | Autosomal recessive             | Endosome trafficking and autophagy                           | Central nervous system            | Progressive thinning of the corpus callosum.   | (Stevanin et al., 2007)   |
| Strumpellin    | Charcot-Marie-Tooth disease 2X (CMT2X)  | Autosomal recessive             | AP5-associated accessory protein                             | Central nervous system            | Early onset with slow progression. Limb and facial spasticity, spastic dysarthria, subsequent lower motor neuron signs and bladder dysfunction.              | (Oriacchio et al., 2010)  |
| STXBP1         | Spastic paraplegia 8 (SPG8)   | Autosomal dominant              | Endosome trafficking   | Peripheral nervous system         | Slow progression. Progressive lower extremity spasticity and weakness.   | (Montecchiani et al., 2016)   |
| Synapsin 1     | Ritscher-Schinzel syndrome 1 (RTSC1)  | Autosomal recessive             | WASH complex component                                       | Central nervous system            | Adult onset. Progressive lower extremity spasticity and weakness.  | (Valdmanis et al., 2007)  |
| Synapsin 2     | Early infantile epileptic encephalopathy 4 (EIEE4)                            | Autosomal dominant              | Regulation of synaptic vesicle docking and fusion            | Multi-systemic                    | Craniofacial abnormalities, congenital heart defects and cerebellar brain malformations.   | (Elliott et al., 2013)  |
| Synapsin 2     | X-linked epilepsy with variable learning disabilities and behaviour disorders | X-linked recessive              | Syntaxin-binding protein                                     | Central nervous system            | Neonatal or infantile onset of seizures, profound mental retardation and magnetic resonance imaging (MRI) evidence of brain hypomyelination.                 | (Saitou et al., 2008)   |
| Synaplojanin 1 | Susceptibility to schizophrenia   | Autosomal dominant              | Tethering/clustering of synaptic vesicles                    | Central nervous system            | Variable combinations of epilepsy, learning difficulties, macrocephaly and aggressive behaviour.   | (Fassio et al., 2011; Garcia et al., 2004)                                  |
| Synaplojanin 1 | Down's syndrome   | Trisomy 21                      | Neuronal phosphoprotein                                      | Central nervous system            | Disturbances in the form and content of thought, in mind and in behaviour.   | (Chen et al., 2004; Lee et al., 2005)                                       |
| TBC1D23        | Pontocerebellar hypoplasia 11 (PCH11)   | Autosomal recessive             | Tethering/clustering of synaptic vesicles                    | Central nervous system            | Disturbances in the form and content of thought, in mind and in behaviour.   | (Chen et al., 2004; Lee et al., 2005)                                       |
| TECP2          | Spastic paraplegia 49 (SPG49)   | Autosomal recessive             | Neuronal phosphoprotein                                      | Central nervous system            | Bradykinesia, resting tremor, muscular rigidity and postural instability.  | (Krebs et al., 2013; Quadri et al., 2013)                                   |
| TFG            | Hereditary motor and sensory neuropathy, Okinawa type (HMSNO)                 | Autosomal dominant              | Clastrin-mediated endocytosis and synaptic vesicle recycling | Central nervous system            | Cognitive impairment, low muscle tone, loose joints, short stature with small head and neck.   | (Voronov et al., 2008)  |
|                | Spastic paraplegia 57 (SPG57)   | Autosomal recessive             | Phosphoinositide phosphatase                                 | Central nervous system            | Synaplojanin 1 may have link to memory loss in Alzheimer's disease.  | (Miranda et al., 2018)  |
|                |   |                                 | Endosome-to-Golgi trafficking                                | Central nervous system            | Refractory seizures and neurodevelopmental impairment. Development is normal prior to seizure onset, after which cognitive and motor delays become apparent. | (Hardies et al., 2016)  |
|                |   |                                 | Vesicle tethering  | Central nervous system            | Severely delayed psychomotor development with intellectual disability and poor speech, microcephaly, dysmorphic features and pontocerebellar hypoplasia.     | (Harripaul et al., 2018; Ivanova et al., 2017; Marin-Valencia et al., 2017) |
|                |   |                                 | ER-to-Golgi trafficking                                      | Central nervous system            | Slow, gradual, progressive weakness and spasticity of the lower limbs with onset in the first decade.  | (Oz-Levi et al., 2012; Stadel et al., 2015)                                 |
|                |   |                                 | Regulator of COPII-dependent ER exit                         | Central nervous system            | Delayed psychomotor development, mental retardation and dysmorphic features.   | (Ishura et al., 2012)   |
|                |   |                                 | Modulates COPII-dependent ER exit                            | Central/peripheral nervous system | Young adult onset of proximal muscle weakness and atrophy, muscle cramps and fasciculations, with later onset of distal sensory impairment.                  | (604484)  |
|                |   |                                 |  | Central/peripheral nervous system | Slow, gradual, progressive weakness and spasticity of the lower limbs.   | (615658)  |

Continued

**Table 1. Continued**

| Protein name                | Disease   | Inheritance          | Protein function  | Tissue/organ system affected | Phenotype  | Phenotype Mendelian Inheritance in Man (MIM) number | Reference   |
|-----------------------------|---|----------------------|---|------------------------------|--|---|---|
| TRAPPC8B                    | Neurodevelopmental disorder with microcephaly, epilepsy and brain atrophy (NEDMEBA) | Autosomal recessive  | ER-to-Golgi trafficking<br>Member of TRAPP complex  | Central nervous system       | Microcephaly, global developmental delay, hypotonia, intellectual disability, autistic features and generalised tonic-clonic seizures.   | 617862  | (Harpaiu et al., 2018; Marin-Valencia et al., 2018)             |
| TRAPPC9                     | Autosomal recessive mental retardation-13 (MRT13)                                   | Autosomal recessive  | ER-to-Golgi trafficking<br>Member of TRAPP complex  | Central nervous system       | Below average intellectual functioning with impairments in adaptive behaviour.   | 613192  | (Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009) |
| TRAPPC12                    | Early-onset progressive encephalopathy with brain atrophy and spasticity (PEBAS)    | Autosomal recessive  | ER-to-Golgi trafficking<br>Member of TRAPP complex  | Central nervous system       | Progressive encephalopathy (central nervous system atrophy and dysfunction), spasticity, microcephaly, global developmental delay and hearing loss.  | 617669  | (Milev et al., 2017)  |
| UBAP1                       | Spastic paraplegia 80 (SPG80)   | Autosomal dominant   | Endosomal trafficking and MVB sorting   | Central nervous system       | Progressive lower extremity spasticity and weakness  | 618418  | (Farazi Fard et al., 2019)                                      |
| VAC14                       | Childhood-onset striatonigral degeneration (SNDC)                                   | Autosomal recessive  | ESCRT-1 complex component<br>Endosomal trafficking<br>PIKfyve complex component   | Central nervous system       | Impaired movement with dystonia, progressively become non-ambulatory and non-verbal, and striatal abnormalities on MRI.  | 617054  | (Lenk et al., 2016)   |
| VAMP1                       | Yunis-Varon syndrome  | Autosomal recessive  | Synaptic vesicular trafficking<br>SNARE   | Multi-systemic               | Skeletal anomalies, dysmorphism, global developmental delay and intracytoplasmic vacuolation in brain and other tissue.  |   | (Lines et al., 2017)  |
| VIP36-like protein (LMAN2L) | Spastic ataxia 1 (SPAX1)  | Autosomal dominant   | Endosomal trafficking   | Central nervous system       | Lower-limb spasticity and ataxia (head jerks, ocular movement abnormalities, dysphagia, dysarthria and gait disturbance).  | 108600  | (Bourassa et al., 2012)   |
| VPS11                       | Presynaptic congenital myasthenic syndrome 25 (CMS25)                               | Autosomal recessive  | Transport of high mannose glycoproteins from the ER<br>ERGIC-53 regulator<br>Late endosome/lysosome trafficking<br>Subunit of CORVET and HOPS complexes | Muscular                     | Hypotonia and generalised muscle weakness apparent from birth.   | 618323  | (Salpietro et al., 2017; Shen et al., 2017)                     |
| VPS16                       | Autosomal recessive adolescent-onset primary dystonia                               | Autosomal recessive  | Subunit of CORVET and HOPS complexes  | Central nervous system       | Global developmental delay, severe intellectual disability with poor speech and mild seizures in early childhood.  | 616887  | (Rafiuallah et al., 2016)                                       |
| VPS26                       | Alzheimer's disease   | Association reported | Late endosome/lysosome traffic<br>Subunit of CORVET and HOPS complexes  | Central nervous system       | Developmental delay, spasticity, truncal hypotonia, acquired microcephaly, intellectual disability with variable seizure disorder, accompanied by thin corpus callosum, paucity of white matter and delayed myelination. | 616683  | (Edvardson et al., 2015)  |
| VPS26A                      | Atypical parkinsonism   | Association reported | Endosomal sorting<br>Retromer component   | Central nervous system       | Sustained involuntary muscle contractions, often leading to abnormal postures.   |   | (Cai et al., 2016)  |
| VPS35                       | Alzheimer's disease   | Association reported | Endosomal sorting<br>Retromer component   | Central nervous system       | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.  | 104300  | (Small et al., 2005)  |
| VPS37A                      | Parkinson disease 17 (PARK17)   | Autosomal dominant   | Endosomal trafficking and MVB sorting<br>ESCRT-1 complex component  | Central nervous system       | Bradykinesia, resting tremor, muscular rigidity and postural instability. Generally, does not respond to treatment with levodopa.  | 614203  | (Gustavsson et al., 2015)                                       |
|                             | Spastic paraplegia 53 (SPG53)   | Autosomal recessive  | Endosomal trafficking and MVB sorting<br>ESCRT-1 complex component  | Central nervous system       | Progressive dementia, loss of cognitive abilities and deposition of fibrillar amyloid proteins.  | 614898  | (Small et al., 2005; Vilarino-Guell et al., 2011)               |
|                             |   |                      |   |                              | Bradykinesia, resting tremor, muscular rigidity and postural instability.  |   | (Zimprich et al., 2011)   |
|                             |   |                      |   |                              | Pronounced early onset spastic paraparesis of upper and lower limbs, mild intellectual disability, kyphosis, pectus carinatum and hypertrichosis.  |   | (Zivony-Elboum et al., 2012)                                    |



|            |  |  |   |  |  |  |
|------------|--|--|---|--|--|--|
| VPSB3      | Pontocerebellar hypoplasia type 2E<br>Progressive encephalopathy with oedema, hypersarhythmia and optic atrophy (PEHO)-like syndrome | Autosomal recessive<br>Autosomal recessive | Endosome-to-TGN trafficking GARP and EARP complex component                                     | Central nervous system<br>Central nervous system                     | Mental retardation, progressive microcephaly, spasticity and early-onset epilepsy.<br>Infantile hypotonia, myoclonic jerking, infantile spasms and profound psychomotor retardation.   | 615851<br>(Feinstein et al., 2014)<br>(Hady-Cohen et al., 2018)                    |
| Dynamlin 2 | Charcot-Marie-Tooth disease 2M (CMT2M)   | Autosomal dominant                         | Endocytosis and vesicular trafficking<br>Mechano-GTPase   | Peripheral nervous system<br>Peripheral nervous system               | Axonal form of the disease. Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.<br>Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms. Dominant type B intermediate is characterised by clinical and pathological features intermediate between axonal and demyelinating forms.<br>Progressive muscular weakness and wasting involving mainly limb girdle, trunk and neck muscles. | 606482 (Fabrizi et al., 2007)<br>606482 (Zuchner et al., 2005)                     |
|            | Charcot-Marie-Tooth disease dominant intermediate B (CMTDIB)   | Autosomal dominant                         |   | Muscular   |  | 160150 (Bitoun et al., 2005)   |
|            | Centronuclear myopathy 1 (CNM1)  | Autosomal dominant                         |   | Muscular   | Degeneration of anterior horn neurons, extreme skeletal muscle atrophy and congenital non-progressive joint contractures.  | 615368 (Koulopoulos et al., 2013)  |
|            | Lethal congenital contracture syndrome 5 (LCCS5)   | Autosomal recessive                        |   | Muscular   | Sensory loss, distal muscle weakness and slow progressive joint contractures.  | 601098 (Street et al., 2003)   |
| LITAF      | Charcot-Marie-Tooth disease 1C (CMT1C)   | Autosomal dominant                         | Endosomal trafficking   | Peripheral nervous system  | Recessive demyelinating form of the disease. Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.  | 604563 (Azzedine et al., 2003)   |
| MTMR13     | Charcot-Marie-Tooth disease 4B2 (CMT4B2)   | Autosomal recessive                        | Autophagy<br>RAB21 GEF and MTMR2 adaptor  | Peripheral nervous system  | Recessive demyelinating form of the disease. Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.  | 601382 (Bolino et al., 2000)   |
| MTMR2      | Charcot-Marie-Tooth disease 4B1 (CMT4B1)   | Autosomal recessive                        | Endosomal trafficking<br>Phosphoinositide phosphatase [PtdIns3P and PtdIns(3,5)P <sub>2</sub> ] | Peripheral nervous system  | Recessive demyelinating form of the disease. Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.  | 615284 (Nakhro et al., 2013)   |
| MTMR5      | Charcot-Marie-Tooth disease 4B3 (CMT4B3)   | Autosomal recessive                        | Endosomal trafficking<br>MTMR2 adaptor  | Peripheral nervous system  | Dominant axonal form of the disease. Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.  | 600882 (Verhoeven et al., 2003)  |
| RAB7       | Charcot-Marie-Tooth disease 2B (CMT2B)   | Autosomal dominant                         | Endo-lysosomal trafficking<br>RAB GTPase  | Peripheral nervous system  | Progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms.   | 601596 (Senderek et al., 2003)   |
| SH3TC2     | Charcot-Marie-Tooth disease 4C (CMT4C)   | Autosomal recessive                        | Endosomal trafficking<br>RAB11 effector   | Peripheral nervous system  | Median nerve mononeuropathy at the wrist.  | 613353 (Lupski et al., 2010)   |
| PIKfyve    | Mild mononeuropathy of the median nerve (MNMN)<br>Fleck corneal dystrophy  | Autosomal dominant<br>Autosomal dominant   | Endosomal trafficking<br>Required for PtdIns(3,5)P <sub>2</sub> kinase<br>Vesicular traffic     | Ocular<br>Ocular   | Stromal corneal dystrophy (numerous small white flecks scattered in all levels of the stroma).<br>Slow, progressive degeneration of the choroid photoreceptors and retinal pigment epithelium.   | 121850 (Li et al., 2005)<br>303100 (Sankila et al., 1992; Seabra et al., 1993)     |
| REP1       | Choroideremia  | X-linked recessive                         | Chaperone required for the prenylation of RABs  | Ocular   |  |  |
| AAGAB      | Punctate palmoplantar keratoderma 1A (PPKP1A)  | Autosomal dominant                         | Clathrin-mediated endocytosis<br>Required for assembly and stability of AP2 complex.            | Skin, bone and connective tissue                                     | Multiple hyperkeratotic centrally indented papules that develop in early adolescence or later and are irregularly distributed on the palms and soles.  | 148600 (Pohler et al., 2012)   |
| GMAP-210   | Achondrogenesis type 1A (ACG1A)  | Autosomal recessive                        | ER-to-Golgi and intra-Golgi trafficking<br>Golgin   | Skin, bone and connective tissue                                     | Deficient ossification in the lumbar vertebrae and absent ossification in the sacral, pubic and ischial bones.   | 200600 (Smits et al., 2010)  |
| GORAB      | Odontochondrodysplasia (ODCD)<br>Genodermia oosteodysplastica (GO)   | Autosomal recessive<br>Autosomal recessive | Retrograde intra-Golgi traffic<br>COPI scaffolding protein                                      | Skin, bone and connective tissue<br>Skin, bone and connective tissue | Mesomelic shortening of tubular bones, ligamentous laxity, scoliosis and dentinogenesis imperfecta.<br>Lax, wrinkled skin, joint laxity, severe osteoporosis and growth retardation.   | 184260 (Wehrle et al., 2019)<br>231070 (Hennies et al., 2008; Witkos et al., 2019) |

Continued

Table 1. Continued

| Protein name                     | Disease   | Inheritance                                 | Protein function  | Tissue/organ system affected                | Phenotype  | Phenotype Mendelian Inheritance in Man (MIM) number | Reference   |
|----------------------------------|---|---|---|---|--|---|---|
| RAB33B                           | Smith-McCort dysplasia 2  | Autosomal recessive                         | Retrograde traffic and autophagosome formation                                    | Skin, bone and connective tissue            | Short limbs and trunk with barrel-shaped chest.  | 615222  | (Dupuis et al., 2013)                             |
| SEC23A                           | Craniofacial dysplasia (CLSD)<br>Cancer                         | Autosomal recessive<br>Association reported | RAB GTPase<br>COPII inner coat  | Skin, bone and connective tissue<br>Various | Late-closing fontanelles, sutural cataracts, facial dysmorphisms and skeletal defects.   | 607812  | (Boyadjiev et al., 2006)<br>(Korpal et al., 2011) |
| SEC24D                           | Cole-Carpenter syndrome 2 (CLCRP2)                              | Autosomal recessive                         | ER-to-Golgi trafficking<br>COPII inner coat                                       | Skin, bone and connective tissue            | Bone deformities, severe bone fragility, ocular proptosis, craniosynostosis, growth failure and distinctive facial features.   | 616294  | (Garbes et al., 2015)                             |
| Sedlin (TRAPPC2)                 | Spondyloepiphyseal dysplasia tarda (SED)                        | X-linked recessive                          | ER-to-Golgi trafficking<br>TRAPP complex component                                | Skin, bone and connective tissue            | Short stature (evident between 5 and 14 years of age), shortness due to impaired growth of the spine, characteristic flattening of vertebrae with central humping, dysplastic changes of femoral heads and neck, and minor changes in other bones. | 313400  | (Gedeon et al., 1999)                             |
| Alpha-COP                        | Autoimmune interstitial lung, joint, and kidney disease (AILJK) | Autosomal dominant                          | Retrograde traffic  | Immunological                               | Inflammatory arthritis, interstitial lung disease and immune complex-mediated renal disease.   | 616414  | (Watkin et al., 2015)                             |
| AP1S3                            | Pustular psoriasis 15 (PSORS15)                                 | Autosomal dominant                          | Clathrin vesicle formation and TGN trafficking<br>AP1 complex subunit             | Immunological                               | Repeated flares (sudden onset) of diffuse erythematous skin eruptions characterised by rapid coverage with pustules, high-grade fever, asthenia, marked leukocytosis and elevated serum levels of C-reactive protein.                              | 616106  | (Setta-Kaifezi et al., 2014)                      |
| LTK                              | Systemic lupus erythematosus (SLE)                              | Association reported                        | COPII assembly and ER-to-Golgi trafficking  | Immunological                               | Inflammation of multiple organs, glomerulonephritis, dermatitis, thrombosis, vasculitis, seizures and arthritis.   | 152700  | (Centonze et al., 2019; Li et al., 2004)          |
| MUNC-13-4                        | Familial haemophagocytic lymphohistiocytosis (FHL3)             | Autosomal recessive                         | Exocytosis  | Immunological                               | Fever, hepatosplenomegaly, cytopenia and, less frequently, neurological abnormalities.   | 608898  | (Feldmann et al., 2003)                           |
| RAB13                            | Crohn's disease   | Association reported                        | TGN-to-endosome trafficking and tight junction formation                          | Immunological                               | Abdominal pain, diarrhoea, fever and weight loss.  |   | (Ohira et al., 2009)                              |
| Syntaxin 11                      | Familial haemophagocytic lymphohistiocytosis (FHL4)             | Autosomal recessive                         | RAB GTPase<br>Endosome-to-TGN trafficking and exocytosis                          | Immunological                               | Fever, hepatosplenomegaly, cytopenia and, less frequently, neurological abnormalities.   | 603552  | (zur Stadt et al., 2005)                          |
| Syntaxin binding protein 2 MYO5B | Familial haemophagocytic lymphohistiocytosis (FHL5)             | Autosomal recessive                         | Intracellular vesicle trafficking and exocytosis                                  | Immunological                               | Fever, hepatosplenomegaly, cytopenia and, less frequently, neurological abnormalities.   | 613101  | (zur Stadt et al., 2009)                          |
| MYO5B                            | Microvillus inclusion disease                                   | Autosomal recessive                         | Endosome-to-plasma membrane trafficking<br>Unconventional myosin and RAB effector | Intestine                                   | Intractable life-threatening watery diarrhoea during infancy.  | 251850  | (Muller et al., 2008)                             |
| SAR1B                            | Chylomicron retention disease (CMRD/ Anderson Disease)          | Autosomal recessive                         | ER-to-Golgi trafficking<br>COPII component (GTPase)                               | Intestine                                   | Severe fat malabsorption. Deficiency of fat-soluble vitamins, low blood cholesterol level and a selective absence of chylomicrons from blood.  | 246700  | (Jones et al., 2003)                              |
| Syntaxin 3                       | Microvillus inclusion disease                                   | Autosomal recessive                         | Endosome-to-apical plasma membrane trafficking<br>SNARE                           | Intestine                                   | Intractable life-threatening watery diarrhoea during infancy.  |   | (Wiegerinck et al., 2014)                         |
| AP2S1                            | Familial hypocalcaemic hypercalcaemia type III (HHC3)           | Autosomal dominant                          | Clathrin-mediated endocytosis<br>AP2 complex subunit                              | Cardiovascular and blood                    | Elevation of serum calcium concentrations. Associated with inappropriately low urinary calcium excretion and a normal or mildly elevated circulating parathyroid hormone level.  | 600740  | (Nesbit et al., 2013)                             |
| ARH                              | Autosomal recessive hypercholesterolaemia                       | Autosomal recessive                         | Endocytosis<br>Adaptor protein  | Cardiovascular and blood                    | Elevated circulating low-density lipoprotein (LDL) cholesterol.  | 603813  | (Garcia et al., 2001)                             |

|                 |  |   |  |                                     |  |        |   |
|-----------------|--|---|--|-------------------------------------|--|--------|---|
| ERGIC53 (LMAN1) | Combined factor V and VIII deficiency 1<br>Cancer                    | Autosomal recessive<br>Association reported | ER-to-Golgi trafficking<br>Cargo receptor (alongside MCFD2)                      | Cardiovascular and blood<br>Various | Epistaxis, menorrhagia and excessive bleeding during or after trauma.  | 227300 | (Nichols et al., 1999)<br>(Roeckel et al., 2009)  |
| LDL receptor    | Autosomal recessive<br>hypercholesterolaemia                         | Autosomal recessive                         | Endocytosis<br>Receptor  | Cardiovascular and blood            | Elevated circulating low-density lipoprotein (LDL) cholesterol.  | 143890 | (Davis et al., 1986)                              |
| MCFD2           | Combined factor V and VIII deficiency 2                              | Autosomal recessive                         | ER-to-Golgi trafficking<br>Cargo receptor (alongside ERGIC53)                    | Cardiovascular and blood            | Epistaxis, menorrhagia and excessive bleeding during or after trauma.  | 613625 | (Zhang et al., 2003a)                             |
| SEC23B          | Congenital dyserythropoietic anaemia type II (CDaII)                 | Autosomal recessive                         | ER-to-Golgi trafficking<br>COPII inner coat                                      | Cardiovascular and blood            | Erythroblast morphological abnormalities, ineffective erythropoiesis, normocytic anaemia, iron overload and jaundice.  | 224100 | (Bianchi et al., 2009;<br>Schwarz et al., 2009)   |
|                 | Cowden syndrome  | Autosomal dominant                          |  | Multi-systemic                      | Macrocephaly, benign overgrowths, increased risk of thyroid cancer.  | 616858 | (Yehia et al., 2015)                              |
|                 | Cancer   | Autosomal Association reported              |  | Various                             |  |        | (Yehia et al., 2018; Yehia et al., 2015)          |
| MYO1E           | Focal segmental glomerulosclerosis 6 (FSGS6)                         | Autosomal recessive                         | Endocytosis<br>Unconventional myosin and RAB effector                            | Renal                               | Child-onset segmental sclerosis in glomeruli, resulting in proteinuria, reduced glomerular filtration rate and progressive decline in renal function.                              | 614131 | (Mele et al., 2011)                               |
|                 | Dent disease 2   | X-linked recessive                          | Lysosomal, endocytic and endosomal trafficking                                   | Renal                               | Proximal renal tubular defect, hypercalcaemia, nephrocalcinosis and renal insufficiency.   | 300555 | (Hoopes et al., 2005)                             |
|                 | Low eye syndrome   | X-linked recessive                          | Phosphoinositide phosphatase [Ptdlns(4,5)P2]                                     | Multi-systemic                      | Wide range of characteristics that affect the eyes, nervous system and kidney.   | 309000 | (Altree et al., 1992)                             |
| Dysterlin       | Autosomal recessive lamb-girdle muscular dystrophy-2 (LGMDR2)        | Autosomal recessive                         | Vesicle-plasma membrane fusion<br>Calcium-binding protein                        | Muscular                            | Weakness and atrophy starting in the proximal pelvic/ femoral muscles, with onset in the late teens or later. Elevation of serum creatine kinase levels and slow progression.      | 253601 | (Bashir et al., 1998; Liu et al., 1998)           |
|                 | Miyoshi muscular dystrophy 1 (MMD1)                                  | Autosomal recessive                         |  | Muscular                            | Late-onset muscular dystrophy involving the distal lower limb musculature.   | 254130 | (Liu et al., 1998)                                |
|                 | Distal myopathy with anterior tibial onset (DMAT)                    | Autosomal recessive                         |  | Muscular                            | Onset between 14 and 28 years of age, with the anterior tibial muscles the first muscle group involved. Rapidly progressive course involving the lower and upper proximal muscles. | 606768 | (Illa et al., 2001)                               |
| MTM1            | X-linked myotubular myopathy   | X-linked recessive                          | Late endosome to lysosome trafficking  | Muscular                            | Progressive muscular weakness and wasting involving mainly limb girdle, trunk and neck muscles.  | 310400 | (Buj-Bello et al., 1999;<br>Laporte et al., 2000) |
|                 | Autosomal recessive lamb-girdle muscular dystrophy-18 (LGMDR18)      | Autosomal recessive                         | Phosphoinositide phosphatase<br>ER-to-Golgi trafficking<br>TRAPP complex subunit | Muscular                            | Proximal muscle weakness with childhood onset, resulting in gait abnormalities, scapular winging and increased serum creatine kinase.  | 615356 | (Bögershausen et al., 2013)                       |
| AP1S1           | Mental retardation, enteropathy, ichthyosis and keratoderma (MEDNIK) | Autosomal recessive                         | Clathrin vesicle formation and TGN trafficking<br>AP1 complex subunit            | Multi-systemic                      | Erythematous skin lesions and hyperkeratosis, severe psychomotor retardation, peripheral neuropathy and sensorineural hearing loss.  | 609313 | (Montpetit et al., 2008)                          |
| AP3B1 (HPS2)    | Hermansky-Pudlak syndrome type 2                                     | Autosomal recessive                         | TGN/lysosome trafficking<br>AP3 complex subunit                                  | Multi-systemic                      | Oculocutaneous albinism, platelet dysfunction, lysosomal storage deficiency and immunodeficiency.  | 608233 | (Dell'Angelica et al., 1999)                      |
| AP3D1           | Hermansky-Pudlak syndrome type 10                                    | Autosomal recessive                         | TGN/lysosome trafficking<br>AP3 complex subunit                                  | Multi-systemic                      | Oculocutaneous albinism, severe neurological impairment and immunodeficiency.  | 617050 | (Ammann et al., 2016)                             |
| BLOC1S3         | Hermansky-Pudlak syndrome type 8                                     | Autosomal recessive                         | Endolysosomal trafficking<br>BLOC-1 subunit (BLOC1S3)                            | Multi-systemic                      | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.  | 614077 | (Morgan et al., 2006)                             |
| CLN3            | Batten disease (CLN3)  | Autosomal recessive                         | Late endosome/lysosome trafficking   | Multi-systemic                      | Seizures, dementia, visual loss and/or cerebral atrophy.   | 204200 | (Lerner et al., 1995)                             |
| CHS1/LYST       | Chediak-Higashi syndrome   | Autosomal recessive                         | Endolysosomal trafficking<br>regulator   | Multi-systemic                      | Recurrent infections, albinism, peripheral neuropathy.   | 214500 | (Karim et al., 2002)                              |

Continued

**Table 1. Continued**

| Protein name | Disease  | Inheritance   | Protein function   | Tissue/organ system affected     | Phenotype   | Phenotype Mendelian Inheritance in Man (MIM) number | Reference                                       |
|--------------|--|---|--|----------------------------------|---|---|---|
| CLN8         | Batten disease (Northern epilepsy syndrome)<br>Batten disease (CLN8)                               | Autosomal recessive<br>Autosomal recessive                                | ER-to-Golgi trafficking<br>Hydrolase cargo receptor  | Multi-systemic<br>Multi-systemic | Seizures and subsequent progressive mental retardation.<br>Seizures, dementia, visual loss and/or cerebral atrophy. | 610003<br>600143                                    | (Ranta et al., 1998)<br>(Ranta et al., 2004)    |
| COG1         | Congenital disorder of glycosylation 2G (CDG2G)  | Autosomal recessive   | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Failure to thrive, generalised hypotonia, growth retardation and mild psychomotor retardation.                      | 611209  | (Foulquier et al., 2006)                        |
| COG2         | Congenital disorder of glycosylation 2Q (CDG2Q)  | Autosomal recessive   | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Delayed development, acquired microcephaly, spastic quadriplegia and tonic seizures.                                | 617395  | (Kodera et al., 2015)                           |
| COG4         | Congenital disorder of glycosylation 2J (CDG2J)  | Autosomal recessive   | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Developmental delay, hypotonia and recurrent respiratory and gastrointestinal infections                            | 613489  | (Miura et al., 2005;<br>Reynders et al., 2009)  |
| COG5         | Saul-Wilson syndrome (SWILS)<br>Congenital disorder of glycosylation 2I (CDG2I)                    | Autosomal dominant<br>Homozygous substitution                             | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Short stature, prominent forehead, prominent eyes with cataracts and developmental delay.                           | 618150  | (Ferreira et al., 2018)                         |
| COG6         | Congenital disorder of glycosylation 2L (CDG2L)  | Autosomal recessive   | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Mild neurological impairments, truncal ataxia and mild hypotonia.   | 613612  | (Paesold-Burda et al., 2009)                    |
| COG7         | Shaheen syndrome (SHNS)  | Autosomal recessive   | Intra-Golgi trafficking<br>COG complex subunit   | Multi-systemic                   | Neonatal intractable focal seizures, vomiting, loss of consciousness, intracranial bleeding and death in infancy.   | 614576  | (Lubbehusen et al., 2010)                       |
| COG8         | Congenital disorder of glycosylation 2E (CDG2E)<br>Congenital disorder of glycosylation 2H (CDG2H) | Autosomal recessive<br>Autosomal recessive compound heterozygous mutation | Intra-Golgi trafficking<br>COG complex subunit<br>COG complex subunit  | Multi-systemic<br>Multi-systemic | Severe intellectual disability, hypohidrosis, dental enamel hypoplasia and hyperkeratosis of the palms and soles.   | 615328  | (Shaheen et al., 2013a)                         |
| Delta-COP    | Rhizomelic short stature with microcephaly, micrognathia and developmental delay (SRMMD)           | Autosomal dominant  | Retrograde trafficking<br>COP1 coat subunit  | Multi-systemic                   | Perinatal asphyxia and dysmorphism, hypotonia, hepatosplenomegaly and progressive jaundice.                         | 608779  | (Wu et al., 2004)                               |
| Dysbindin    | Hermansky-Pudlak syndrome type 7   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-1 subunit  | Multi-systemic                   | Acute encephalopathy, hypotonia and mental retardation.   | 611182  | (Foulquier et al., 2007;<br>Kranz et al., 2007) |
| EXO84        | Joubert syndrome   | Mutation reported   | Exocyst subunit  | Multi-systemic                   | Facial dysmorphism, severe micrognathia, microcephaly, rhizomelic short stature and mild developmental delay.       | 617164  | (Izumi et al., 2016)                            |
| FGD1         | Aarskog-Scott syndrome   | X-linked recessive  | TGN trafficking<br>CDC42 GEF   | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 614076  | (Li et al., 2003)                               |
| HPS1         | Hermansky-Pudlak syndrome type 1   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-3 subunit (BLOC3S1)  | Multi-systemic                   | Hypoplasia of cerebellar vermis, dysregulation of breathing pattern and developmental delay.                        | 213300  | (Dixon-Salazar et al., 2012)                    |
| HPS3         | Hermansky-Pudlak syndrome type 3   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-2 subunit (BLOC2S1)  | Multi-systemic                   | Short stature and multiple facial, limb and genital abnormalities.  | 305400  | (Pasteris et al., 1994)                         |
| HPS4         | Hermansky-Pudlak syndrome type 4   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-3 subunit (BLOC3S2)  | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 203300  | (Oh et al., 1996)                               |
| HPS5         | Hermansky-Pudlak syndrome type 5   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-2 subunit (BLOC2S2)  | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 614072  | (Anikster et al., 2001)                         |
| HPS6         | Hermansky-Pudlak syndrome type 6   | Autosomal recessive   | Endolysosomal trafficking<br>BLOC-2 subunit (BLOC2S3)  | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 614073  | (Suzuki et al., 2002)                           |
| Melanophilin | Griscelli syndrome type 3  | Autosomal recessive   | Melanosome transport<br>RAB27A effector protein  | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 614074  | (Zhang et al., 2003b)                           |
| MYO5A        | Griscelli syndrome type 1  | Autosomal recessive   | Melanosome transport and trafficking to plasma membrane<br>Unconventional myosin that forms complex with RAB27A and melanophilin | Multi-systemic                   | Oculocutaneous albinism, platelet dysfunction and lysosomal storage deficiency.                                     | 609227  | (Ménasché et al., 2003)                         |
|              |  |   |  | Multi-systemic                   | Albinism and neurological defects.  | 214450  | (Pastural et al., 1997)                         |

|          |  |   |  |                |  |   |
|----------|--|---|--|----------------|--|---|
| NBAS     | Multisystem disease  | Autosomal recessive                     | Golgi-to-ER trafficking<br>COPI vesicle-tethering complex  | Multi-systemic | Progeroid appearance, short stature, slender bones, cervical instability, frequent infections, hypogammaglobulinaemia and reduced natural killer cells, retinal dystrophy and optic atrophy. | (Segarra et al., 2015)                    |
|          | Short stature, optic nerve atrophy and Pelger-Huet anomaly (SOPH)  | Autosomal recessive                     |  | Multi-systemic | Postnatal growth retardation, facial dysmorphism with senile face, abnormal nuclear shape in neutrophil granulocytes and optic atrophy.  | (Maksimova et al., 2010)                  |
|          | Infantile liver syndrome 2 (ILFS2)   | Autosomal recessive                     |  | Liver          | Acute liver failure in first few months of life. Anaemia, renal tubulopathy, developmental delay, seizures, liver steatosis and fibrosis.  | (Haack et al., 2015)                      |
|          | Atypical osteogenesis imperfecta   | Compound heterozygous variants reported |  | Multi-systemic | Short stature, bone fragility, developmental delay and immunodeficiency.   | (Balasubramanian et al., 2017)            |
| RAB18    | Warburg micro syndrome 3   | Autosomal recessive                     | Apical endocytosis/recycling, RAB GTPase   | Multi-systemic | Microcephaly, microcornea, congenital cataracts, optic atrophy, cortical dysplasia and severe mental retardation.  | (Ben et al., 2011)                        |
| RAB23    | Carpenter syndrome   | Autosomal recessive                     | Endocytic trafficking, plasma membrane recycling and SHH signalling RAB GTPase                                       | Multi-systemic | Acrocephaly with variable synostosis of the sagittal, lambdoid and coronal sutures, congenital heart defects, growth retardation and mental retardation.                                     | (Josifova, 2007)                          |
| RAB27A   | Griscelli syndrome type 2  | Autosomal recessive                     | Melanosome transport and trafficking to plasma membrane RAB GTPase that can form complex with MYO5A and melanophilin | Multi-systemic | Pigmentary dilution of skin and hair, large clumps of pigment in hair shafts and accumulation of melanosomes in melanocytes. Neurological impairment in some patients.                       | (Ménasché et al., 2000)                   |
| RAB3GAP1 | Warburg micro syndrome 1   | Autosomal recessive                     | Exocytosis RAB3 GAP  | Multi-systemic | Microcephaly, microcornea, congenital cataracts, optic atrophy, cortical dysplasia and severe mental retardation.  | (Aligianis et al., 2005)                  |
| RAB3GAP2 | Warburg micro syndrome 2   | Autosomal recessive                     | Exocytosis RAB3 GAP  | Multi-systemic | Microcephaly, microcornea, congenital cataracts, optic atrophy, cortical dysplasia and severe mental retardation.  | (Borck et al., 2011)                      |
| RIC1     | Martsoff syndrome  | Autosomal recessive                     | Procollagen transport RAB6A GEF  | Multi-systemic | Congenital cataracts, mental retardation and hypogonadism.   | (Aligianis et al., 2006)                  |
|          | Cleft lip, cataract, tooth abnormality, impaired intellectual development, facial dysmorphism and attention-deficit hyperactivity disorder (CATIFA) syndrome | Autosomal recessive                     |  | Multi-systemic | Intellectual disability, facial dysmorphism, tooth abnormality, cleft lip, cataract and ADHD.  | (Unlu et al., 2020)                       |
| Rin2     | Macrocephaly, alopecia, cutis laxa and scoliosis (MACS) syndrome   | Autosomal recessive                     | Endocytic trafficking RAB5 activator/effector.   | Multi-systemic | Elastic tissue characterised by sagging skin.  | (Basel-Vanagaite et al., 2009)            |
| SCYL1    | Low $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN) syndrome   | Autosomal recessive                     | Retrograde trafficking from Golgi ARF and COPI scaffold  | Multi-systemic | Ataxia, peripheral neuropathy, acute liver failure and cholestasis.  | (Lenz et al., 2018; Schmidt et al., 2015) |
| SEC8     | Meckel-Gruber syndrome   | Autosomal recessive                     | Exocytosis Exocyst subunit   | Multi-systemic | Cystic renal disease, central nervous system malformation and hepatic abnormalities.   | (Shaheen et al., 2013b)                   |
| TBC1D20  | Warburg micro syndrome 4   | Autosomal recessive                     | ER-to-Golgi trafficking and autophagy RAB1 and RAB2 GAP  | Multi-systemic | Microcephaly, microcornea, congenital cataracts, optic atrophy, cortical dysplasia and severe mental retardation.  | (Liegel et al., 2013)                     |
| VIPAR    | Arthrogryposis, renal dysfunction and cholestasis 2 (ARCS2)  | Autosomal recessive                     | Endosomal and lysosomal trafficking VPS33B-VIPAR complex interacts with RAB11A                                       | Multi-systemic | Arthrogryposis multiplex congenita, renal tubular abnormalities and cholestasis.   | (Cullinane et al., 2010)                  |
| VPS15    | Ciliopathy   | Autosomal recessive                     | Endosomal trafficking and autophagy Forms complex with GM130   | Multi-systemic | Retinal pigmentosa, progressive renal failure and kidney atrophy and developmental anomalies.  | (Stoetzel et al., 2016)                   |
| VPS33A   | Mucopolysaccharidosis-plus syndrome  | Autosomal recessive                     | Late endosome/lysosome trafficking Subunit of CORVET and HOPS tethering complex                                      | Multi-systemic | Coarse facial features, skeletal abnormalities, respiratory problems, mental retardation and heart, kidney and haematopoietic disorders.   | (Kondo et al., 2017)                      |

Continued

**Table 1. Continued**

| Protein name    | Disease   | Inheritance                     | Protein function   | Tissue/organ system affected | Phenotype  | Phenotype Mendelian Inheritance in Man (MIM) number | Reference  |
|-----------------|---|---------------------------------|--|------------------------------|--|---|--|
| VPS33B          | Arthrogryposis, renal dysfunction and cholestasis 1 (ARCS1) | Autosomal recessive             | Endosomal and lysosomal trafficking with RAB11A<br>VPS33B-VIPAR complex interacts  | Multi-systemic               | Arthrogryposis multiplex congenita, renal tubular abnormalities and cholestasis.   | 208085  | (Gissen et al., 2004)                                    |
| VPS35L          | 3C/Ritscher–Schinzel-like syndrome                          | Compound heterozygous mutations | Endosomal trafficking<br>Retriever complex component   | Multi-systemic               | Cranio-cerebello-cardiac dysplasia, coloboma, microphthalmia, chondrodysplasia punctata and skeletal malformation.   |   | (Kato et al., 2019)                                      |
| VPS51           | Pontocerebellar hypoplasia type 13 (PCH13)                  | Autosomal recessive             | Endosome-to-TGN trafficking<br>Golgi-associated retrograde protein (GARP) and endosome-associated recycling protein (EARP) complex component | Multi-systemic               | Global developmental delay, impaired intellectual development with absent speech, microcephaly and progressive atrophy of the cerebellar vermis and brainstem. | 618606  | (Uwineza et al., 2019; Gershlick et al., 2019)           |
| Endophilin-A2   | Cancer  | Association reported            | Endocytosis<br>Membrane remodelling and scission   | Various                      |  |   | (Baldassarre et al., 2015)                               |
| GOLPH3          | Cancer  | Overexpression                  | Golgi and secretory trafficking<br>Phosphatidylinositol phosphate effector   | Various                      |  |   | (Scott et al., 2009)                                     |
| RAB2A           | Cancer  | Association reported            | ER-to-Golgi trafficking  | Various                      |  |   | (Luo et al., 2015)                                       |
| RAB25           | Various cancers   | Association reported            | RAB GTPase<br>Endosomal trafficking  | Various                      |  |   | (Cheng et al., 2004)                                     |
| RAB35           | Cancer  | Association reported            | RAB GTPase<br>Endosomal trafficking  | Various                      |  |   | (Wheeler et al., 2015)                                   |
| Synaptotagmin 2 | Various cancers   | Association reported            | RAB GTPase<br>Clathrin-mediated endocytosis<br>Phosphoinositide phosphatase  | Various                      |  |   | (Ben-Chehrit et al., 2015; Spaenij-Dekking et al., 2003) |
| TPD52           | Cancer  | Association reported            | Exocytosis   | Various                      |  |   | (Byrne et al., 1998; Byrne et al., 1995)                 |
| TPD53           | Cancer  | Association reported            | Membrane fusion<br>SNARE binding protein   | Various                      |  |   | (Byrne et al., 1996; Byrne et al., 1996)                 |
| TPD54           | Cancer  | Association reported            | Membrane trafficking<br>RAB effector   | Various                      |  |   | (Nourse et al., 1998)                                    |
| TSG101          | Cancer  | Association reported            | Endosomal trafficking<br>ESCRT-I complex component   | Various                      |  |   | (Jiang et al., 2013; Li and Cohen, 1996)                 |
| CHC22           | Type 2 diabetes   | Association reported            | Clathrin-mediated endocytosis and TGN trafficking  | Various                      | Elevated blood sugar level.  | 125853  | (Vassilopoulos et al., 2009)                             |
| DENND4C         | Type 2 diabetes   | Association reported            | Clathrin coat component<br>Golgi-to-plasma membrane trafficking<br>RAB10 GEF   | Various                      | Elevated blood sugar level.  | 125853  | (Johnson and O'Donnell, 2009)                            |
| SAC2            | Type 2 diabetes   | Association reported            | Exocytosis<br>Phosphoinositide phosphatase (PtdIns4P)  | Various                      | Elevated blood sugar level.  | 125853  | (Nguyen et al., 2019)                                    |

2010), bridging integrator 1 (BIN1)/amphiphysin 2 (Hu et al., 2011; Seshadri et al., 2010), cortactin-CD2-associated protein (CD2AP) (Hollingsworth et al., 2011; Naj et al., 2011) and synaptojanin (McMahon and Boucrot, 2011; Miranda et al., 2018), with the risk of acquiring Alzheimer's disease (AD). Additionally, deficiency in VPS26 and VPS35, two subunits of the retromer complex for endosomal recycling, has been observed in AD (Small et al., 2005). In AD, differences in endocytic trafficking and processing of amyloid precursor protein (APP) to its cytotoxic product A $\beta$  can explain the involvement of endocytic traffic in AD pathogenesis (Toh and Gleeson, 2016). Endocytic traffic may also affect AD pathogenesis in other ways; for example, by influencing the susceptibility of neurons to A $\beta$  (which itself can disrupt endocytic traffic), the uptake of toxic A $\beta$  aggregates from the cell exterior, the production of synaptic vesicles or abundance of post-synaptic receptors, or by altering lysosome homeostasis and autophagy pathways that are important for cell viability (Nixon, 2017). Increased processing of APP to A $\beta$  may also arise from altered trafficking at the Golgi apparatus, although the molecular details are less clear (Joshi and Wang, 2015).

Parkinson's disease (PD) is also strongly associated with defective endocytic traffic, including the mutation or altered expression of various endocytic components (Abeliovich and Gitler, 2016). These include cyclin G-associated kinase (GAK) (Nagle et al., 2016; Nalls et al., 2014), auxilin (Edvardson et al., 2012; Olgiati et al., 2016) and synaptojanin (Krebs et al., 2013; Quadri et al., 2013) [which function in clathrin-mediated endocytosis (McMahon and Boucrot, 2011)], the retromer subunit VPS35 (Vilarino-Guell et al., 2011; Zimprich et al., 2011) and the retromer-associated protein receptor-mediated endocytosis 8 (RME-8) (Vilarino-Guell et al., 2014). As in AD, endocytic traffic may lead to PD pathology in several ways; for example, by influencing the uptake of toxic  $\alpha$ -synuclein aggregates, by altering synaptic vesicle or neurotransmitter receptor traffic, or by affecting lysosome homeostasis and autophagy (Abeliovich and Gitler, 2016). Of note, mutations of several lysosomal proteins are strongly associated with PD (Dehay et al., 2013), as is defective autophagic clearance of mitochondria (Ryan et al., 2015).

Defective traffic in the early secretory pathway is also relevant for PD pathogenesis. RAB39B, a mutation of which is associated with early-onset PD as well as X-linked intellectual disability (Giannandrea et al., 2010; Mata et al., 2015; Wilson et al., 2014), is required for ER-to-Golgi transport of the synaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptor subunit GluA2 (Mignogna et al., 2015). Interestingly, excess  $\alpha$ -synuclein can also disrupt ER-to-Golgi traffic, most likely at the level of COPII vesicle tethering or fusion (Cooper et al., 2006; Thayanidhi et al., 2010).  $\alpha$ -Synuclein appears to normally function in synaptic vesicle fusion (Burre et al., 2010; Chandra et al., 2005), hence its aggregation or loss of function likely also directly affect neurotransmitter release (Carstea et al., 1997; Polymeropoulos et al., 1997; Singleton et al., 2003). As for AD, PD pathology may arise from defects in other trafficking pathways. A protein of much current interest is leucine-rich repeat kinase 2 (LRRK2), which is mutated in ~1% of sporadic and ~5% of familial PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). LRRK2 phosphorylates several RAB GTPases (Steger et al., 2016), functioning in diverse trafficking steps, and the most common PD mutations cause LRRK2 activation (West et al., 2005). Excessive LRRK2-mediated phosphorylation alters the ability of these RABs to engage with regulatory factors and effector proteins, thereby disrupting traffic (Steger et al., 2016). Of interest, RAB29 stimulates LRRK2

activation at cellular membranes (Gomez et al., 2019; Purlyte et al., 2018), and is also independently linked to PD, indicating that these proteins (co)operate in a common disease pathway (MacLeod et al., 2013).

Frontotemporal dementia (FTD) is a neurodegenerative disease that is commonly associated with early onset of symptoms (Warren et al., 2013). Mutation of C9orf72, which encodes a RAB GEF, is strongly associated with familial FTD (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Expansion of nucleotide repeats may cause a toxic gain of function at the RNA level, whereas a loss of protein function may also contribute to FTD pathology by altering trafficking to the lysosome, with likely downstream effects upon autophagy (Balendra and Isaacs, 2018). Consistent with this, FTD can be caused by mutation of the ESCRT-III subunit charged multivesicular body protein 2B (CHMP2B), which is involved in MVB sorting (Skibinski et al., 2005).

Amyotrophic lateral sclerosis (ALS), or motor neuron disease, results in progressive degeneration of motor neurons (Hardiman et al., 2017). ALS and FTD represent two extremes of a phenotypic spectrum, and share common pathogenic mechanisms (Ferrari et al., 2011). Thus, C9orf72 mutation causes ALS as well as FTD (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Other endocytic proteins are mutated in ALS, including the RAB5 GEF Alsin (also known as ALS2) and the inositol phosphatase factor-induced gene 4 (FIG4) (Chow et al., 2009; Yang et al., 2001). Dysregulation of endocytic transport, in turn affecting lysosome function and autophagy, is therefore associated with ALS. Of note, mutation of several ALS-associated proteins, including superoxide dismutase 1 (SOD1), RNA-binding protein fused in sarcoma (FUS) and TAR DNA-binding protein 43 (TDP43; also known as TARDBP), have been reported to disrupt the secretory pathway, suggesting additional mechanisms linking defective traffic to ALS (Soo et al., 2015).

Similarly, mutation of endocytic factors is associated with hereditary spastic paraplegia (HSP), a genetically diverse disorder that manifests as progressive loss of lower limb movement control (Blackstone et al., 2011). Notable HSP-involved proteins are spastin (SPG4; also known as SPAST), which couples membrane remodelling with microtubule dynamics, including during endocytic traffic (Hazan et al., 1999), spartin (SPG20; also known as SPART), an endosomal protein that also associates with microtubules (Patel et al., 2002), and strumpellin (SPG8; also known as WASHC5), which is part of the WASH WASP and SCAR (WASH) homologue complex that operates in retromer-mediated endocytic recycling (Valdmanis et al., 2007). Interestingly, spastin also functions at the ER, and mutations in Atlantin (also known as ATL1), another ER membrane remodelling protein, also cause HSP (Zhao et al., 2001). It is currently unclear how changes in ER morphology lead to HSP. Another group of HSPs is caused by mutations within subunits of the AP4 and AP5 adaptor complexes that function in post-Golgi trafficking (Bauer et al., 2012; Hardies et al., 2015; Moreno-De-Luca et al., 2011; Slabicki et al., 2010; Verkerk et al., 2009), which likely affect endolysosomal function (Sanger et al., 2019). Interestingly, AP4 is important for trafficking of the autophagy-initiating factor ATG9A, suggesting a link between HSP and dysregulated autophagy (Mattera et al., 2017; Davies et al., 2018). HSP also results from mutations in ubiquitin-associated protein 1 (UBAP1) and VPS37A (Farazi Fard et al., 2019; Zivony-Elboum et al., 2012), components of ESCRT-I required for MVB sorting (Schmidt and Teis, 2012). Mutations in Trk-fused gene (TFG) and tectonin beta-propeller repeat-containing protein 2 (TECPR2), proteins that associate with COPII and help

mediate ER-to-Golgi transport, also cause HSP, indicating that defective trafficking in the early secretory pathway can also cause this type of disorder (Beetz et al., 2013; Stadel et al., 2015).

Charcot Marie-Tooth (CMT) disease is a genetically and clinically diverse group of peripheral neuropathies (Rossor et al., 2013). Most CMT forms result from altered expression or mutation of myelin components, but mutation of several endocytic proteins is also a cause. For example, recessive demyelinating forms of CMT (CMT4) result from mutation of the endocytic recycling protein SH3 domain and tetratricopeptide repeats 2 (SH3TC2) (Senderek et al., 2003), as well as the myotubularins and FIG4, which influence traffic by acting upon endosomal phosphoinositides (Azzedine et al., 2003; Bolino et al., 2000; Nakhro et al., 2013; Zhang et al., 2008). Lipopolysaccharide-induced tumour necrosis factor alpha factor (LITAF), a protein involved in endocytic protein sorting, causes the autosomal dominant demyelinating CMT1 (also known as SIMPLE) (Street et al., 2003). Meanwhile, mutation of RAB7 causes a dominant axonal form of CMT (Verhoeven et al., 2003).

Mutations in the endocytic machinery are prevalent in other rare neurological disorders (Table 1). The consequent defects in endocytosis and endosomal recycling may alter presynaptic vesicle biogenesis or postsynaptic neurotransmitter receptor availability. Meanwhile, defects in the later stages of the endocytic pathway can affect lysosome homeostasis and autophagy, which, if impaired, result in cytotoxic stress. Defective traffic in the secretory pathway is also associated with several neurological diseases. Here, defective transport may alter axon and dendrite morphogenesis, affect the surface levels of neurotransmitter receptors, or induce cytotoxic ER stress due to cargo accumulation in this compartment.

#### Ocular disease

Eye pathology has been reported in several trafficking-related multi-systemic disorders, including the ciliopathies and the X-linked Lowe syndrome, which are described below. Choroideremia, which is an eye-specific disorder, manifests as degeneration of rod photoreceptors and retinal pigment epithelial cells (Moosajee et al., 2014). It is caused by mutations in RAB escort protein 1 (REP-1), a chaperone required for the prenylation of all RABs, grossly disrupting membrane traffic in the affected cells (Alory and Balch, 2001; Sankila et al., 1992; Seabra et al., 1993). The retinal tissue-restricted nature of choroideremia is likely because a second RAB escort protein, REP-2, compensates for the loss of REP-1 in other cell types, but is not expressed in the retina (Cremers et al., 1994).

#### Skin, bone and connective tissue disorders

The extracellular matrix, which surrounds cells in our skin, bone and connective tissues, is a major secreted product in the human body. Consequently, matrix-rich tissues appear particularly susceptible to mutations affecting the secretory pathway that disrupt matrix deposition. Mutations in SEC23A, a component of the COPII coat, cause the skeletal disorder cranio-lenticulo-sutural dysplasia (CLSD) (Boyadjiev et al., 2006). Although COPII is essential for secretion, CLSD is tissue restricted, because most cells also express the functionally analogous SEC23B, sustaining COPII functionality (Khoriaty et al., 2018). Mutations in Sedlin (also known as TRAPPC2), a component of the transport protein particle (TRAPP) complex operating between the ER and Golgi, a RAB GEF and possible vesicle-tethering factor (Barrowman et al., 2010), cause X-linked spondyloepiphyseal dysplasia tarda (SEDT) (Gedeon et al., 1999). Sedlin also regulates SAR1, and both

CLSD and SEDT mutations give rise to defective procollagen export from the ER, causing matrix defects and skeletal dysplasia (Boyadjiev et al., 2011; Venditti et al., 2012). Null and hypomorphic mutations in the Golgi vesicle-tethering factor Golgi microtubule-associated protein of 210 kDa [GMAP-210; also known as thyroid hormone receptor interactor 11 (TRIP11)] are responsible for the lethal skeletal dysplasia achondrogenesis type 1A (ACG1A) and the milder odontochondrodysplasia (ODCD), respectively (Smits et al., 2010; Wehrle et al., 2019). In both cases, the major pathogenic mechanism is defective traffic and improper glycosylation of matrix proteins within the Golgi (Smits et al., 2010; Wehrle et al., 2019). GMAP-210 is also important for cargo traffic to the primary cilium (Follit et al., 2008), and the phenotype may therefore partly arise from defective ciliary signalling that is required to maintain chondrocyte differentiation (Wang et al., 2013). Similarly, mutations in the *trans*-Golgi protein RAB6-interacting golgin (GORAB), which functions in COPI-mediated traffic, cause the skin and bone disorder geroderma osteodysplastica, likely as a consequence of disrupted matrix protein glycosylation (Hennies et al., 2008; Witkos et al., 2019). This not only affects matrix assembly, but is also important for controlling TGF $\beta$  (also known as TGFB1) signalling to prevent cell senescence (Chan et al., 2018). Mutations in Golgi RAB33B cause Smith-McCort syndrome (Dupuis et al., 2013), an osteochondrodysplasia. This is likely due to defects in Golgi traffic and autophagosome formation, both RAB33B-dependent processes (Morgan et al., 2019).

#### Immunological disease

Membrane traffic is vital for innate and adaptive immunity; for example, in mediating phagocytosis of invading microorganisms, supporting the biosynthesis and signalling of the many receptors found on immune cells, and facilitating the secretion of antibodies, cytokines and other immunomodulatory factors. Consequently, several immunological diseases, including immunodeficiencies and autoimmune disorders, can be attributed to defective membrane trafficking. These include familial haemophagocytic lymphohistiocytosis, an immune disorder caused by mutations in protein unc-13 homologue D (MUNC-13-4; also known as UNC13D) (Feldmann et al., 2003), syntaxin 11 (zur Stadt et al., 2005) or syntaxin binding protein 2 (zur Stadt et al., 2009). These proteins control lytic granule release at the T-cell and natural killer (NK) cell immune synapse and platelet granule exocytosis. As a result, cells with these mutations have a compromised ability to mediate cell killing, leading to hyperactivation of the immune system (Gholam et al., 2011). Another interesting example is leukocyte tyrosine kinase receptor (LTK), an ER-associated tyrosine kinase that controls COPII assembly and ER-to-Golgi traffic (Centonze et al., 2019). Gain-of-function mutations in LTK are associated with the autoimmune disorder systemic lupus erythematosus, and it has been proposed that increased LTK activity, and therefore increased COPII-mediated ER export, allows plasma cells to cope better with the increased production and secretion of autoantibodies, thereby contributing to the autoimmune phenotype seen in lupus (Centonze et al., 2019; Li et al., 2004).

#### Intestinal disorders

Defective traffic within both the secretory and endocytic pathways can affect enterocyte function and cause intestinal disease. Enterocytes absorb fats from the intestine and package them into chylomicron particles, which form at the ER and are secreted into the bloodstream. Chylomicron retention disease is a rare disorder



caused by mutation in SAR1B (Jones et al., 2003), which impairs chylomicron particle export from the ER, reducing their secretion and the availability of fats and fat-soluble vitamins throughout the body (Roy et al., 1987). The disease is restricted to enterocytes, most likely because the paralogue SAR1A fulfils SAR1 function in other cell types. Microvillus inclusion disease also affects enterocytes, with a loss of microvilli from the apical surface and impaired nutrient absorption (Davidson et al., 1978). It is caused by mutations in the actin motor myosin (MYO) 5B, which is required for endosomal recycling to the apical membrane (Muller et al., 2008), or in syntaxin 3, which is required for vesicle fusion at the apical membrane (Wiegerinck et al., 2014).

#### Liver disease

Membrane trafficking is important in hepatocytes, which secrete a multitude of proteins into the bloodstream. Mutation of SCY1-like pseudokinase 1 (SCYL1) or neuroblastoma-amplified sequence (NBAS), which function in COPI vesicle traffic, can manifest in the liver, but typically also affect other tissues, and are discussed further in the 'Multi-systemic disorders' section below.

#### Cardiovascular disease and blood disorders

Cholesterol is transported in the blood as low-density lipoprotein (LDL) particles. These are internalised, particularly into hepatocytes, by receptor-mediated endocytosis. Defective LDL uptake causes hypercholesterolaemia, which can manifest as atherosclerosis and premature coronary heart disease (Brown and Goldstein, 1986). Mutations in the LDL receptor (LDLR) that abolish LDL binding have been reported, but of more relevance to this article are LDLR mutations that disrupt binding to disabled homologue 2 (DAB2) and autosomal recessive hypercholesterolaemia (ARH; also known as LDLRAP1), adaptor proteins that mediate LDLR uptake by clathrin-dependent endocytosis (Davis et al., 1986; He et al., 2002; Maurer and Cooper, 2006). Similarly, mutation of ARH itself can also cause hypercholesterolaemia (Garcia et al., 2001).

Defects within the secretory pathway can affect red blood cell production and the production of clotting factors. In the former, mutations within the COPII subunit SEC23B cause congenital dyserythropoietic anaemia type II (Bianchi et al., 2009; Schwarz et al., 2009), likely due to perturbation of ER-to-Golgi traffic in erythroblasts that impairs the delivery and glycosylation of proteins required for red blood cell formation (Denecke and Marquardt, 2009). The widespread expression of the paralogue SEC23A likely accounts for the restricted phenotype of SEC23B mutation. The blood clotting disorder combined factor V and VIII deficiency results from mutations in multiple coagulation factor deficiency 2 (MCFD2) and lectin mannose binding 1 (LMAN1) (Nichols et al., 1998; Zhang et al., 2003a). MCFD2 and LMAN1 combine to form a cargo receptor for the ER-to-Golgi transport of blood clotting factors V and VIII and thus are essential for their secretion (Zhang et al., 2005).

#### Renal disorders

Renal dysfunction occurs in several multi-systemic trafficking disorders, most notably the ciliopathies. Mutations in the actin-associated proteins CD2AP and MYO1E cause focal segmental glomerulosclerosis, which progressively reduces the ability of the glomerulus to filter the blood, ending in renal failure (Kim et al., 2003; Mele et al., 2011). Both proteins participate in endocytosis, which is required to maintain podocyte foot processes and thus effective filtration, but whether defective traffic constitutes a disease mechanism is unclear (Inoue and Ishibe, 2015). The proteins may directly act upon actin within the foot processes (Inoue and Ishibe,

2015), while CD2AP is also a component of the slit diaphragm (Shih et al., 2001). Dent disease and cystinosis are proximal tubulopathies in which the ability of the proximal tubule to re-absorb proteins by endocytosis is disrupted (Ivanova et al., 2015; Piwon et al., 2000; Wang et al., 2000). However, in both diseases, the mutations are not in the trafficking machinery; Dent disease is caused by mutation in the endosomal chloride channel chloride channel protein 5 (CIC-5; also known as CLCN5) (Lloyd et al., 1996), and cystinosis by mutation of a lysosomal cystine transporter (Town et al., 1998).

#### Muscular disorders

Centronuclear myopathies (CNMs) are a group of muscle disorders that derive their name from centrally located muscle cell nuclei. Mutations in the membrane fission protein dynamin 2 or in BIN1, a BAR domain protein able to sculpt membrane shape, cause congenital CNM (Bitoun et al., 2005; Nicot et al., 2007). These two proteins, which physically interact, participate in endocytosis in most cells (Takei et al., 1999). However, in muscle, they are critical for the formation and maintenance of T-tubules, membrane invaginations that penetrate into muscle cells (Chin et al., 2015; Lee et al., 2002). Thus, disruption of T-tubule morphogenesis and function is a major disease mechanism in CNMs. Mutation of myotubularin 1 (MTM1), a member of the myotubularin family of endosomal inositol phosphatases, causes an X-linked CNM (Buj-Bello et al., 1999; Laporte et al., 2000). MTM1 binds to BIN1 (Royer et al., 2013), and, as seen in congenital CNMs, MTM1 mutation disrupts T-tubules, indicating a likely common disease mechanism (Al-Qusairi et al., 2009; Dowling et al., 2009). Mutation of dysferlin, a Ca<sup>2+</sup>-binding protein with homology to the membrane fusion regulator synaptotagmin, causes muscular dystrophy (Bashir et al., 1998; Illa et al., 2001; Liu et al., 1998). The likely pathological mechanism is disruption of muscle cell integrity due to a defect in vesicle fusion and repair of the plasma membrane (Bansal et al., 2003; Lek et al., 2012). Mutations in two proteins required for ER-to-Golgi transport, the TRAPP complex subunit TRAPPC11, and the SNARE Golgi SNAP receptor complex member 2 (GOSR2), are also linked to muscular dystrophy (Bögershausen et al., 2013; Tsai et al., 2013). Hypoglycosylation of  $\alpha$ -dystroglycan occurs in both cases (Larson et al., 2018). Because  $\alpha$ -dystroglycan glycosylation is important for linking the muscle sarcolemma to the extracellular matrix (Barresi and Campbell, 2006), these glycosylation defects can explain the destabilisation of muscle fibres seen in patients.

#### Multi-systemic disorders

There are numerous multi-systemic disorders associated with mutations in the membrane trafficking machinery (Table 1). Several belong to larger disease classes such as congenital disorders of glycosylation (CDGs), ciliopathies and lysosomal storage disorders (LSDs). Many CDGs are caused by loss of Golgi glycosylation enzyme or ion or sugar transporter activity, but mutations within the COG vesicle-tethering complex account for several (Ng and Freeze, 2018). Here, impaired COPI-dependent recycling of glycosylation enzymes in the Golgi stack leads to their inefficient retention, affecting the glycosylation of proteins and lipids (Fisher and Ungar, 2016).

The ciliopathies are a large disease class associated with loss of cilia or defective ciliary signalling (Reiter and Leroux, 2017). The commonly affected tissues include the brain, retina and kidney. Several ciliopathies are associated with defective transport of proteins to or within the cilium, although the latter is not vesicle

mediated (Reiter and Leroux, 2017). Vesicle-mediated transport from the Golgi apparatus to the cilium is important for the generation and maintenance of cilia, with RAB8 and its effector, the exocyst vesicle-tethering complex, constituting the key machinery of this trafficking step (Hsiao et al., 2012). Indeed, mutations in two exocyst subunits, exocyst complex component 84 (EXO84; also known as EXOC8) and SEC8 (also known as EXOC4), have been found in the ciliopathies Joubert syndrome and Meckel–Gruber syndrome (Dixon-Salazar et al., 2012; Shaheen et al., 2013a,b). Intraflagellar transport protein 20 (IFT20) is an important player in Golgi-to-cilium transport of certain membrane proteins (Follit et al., 2008; Monis et al., 2017), and mutation of VPS15, which also causes a ciliopathy, impairs this transport pathway (Stoetzel et al., 2016). Interestingly, IFT20 is anchored to the Golgi by GMAP-210 (Follit et al., 2008), suggesting that the two skeletal dysplasias caused by GMAP-210 mutation (ACG1A and ODCD, discussed above) may have a ciliary component (Smits et al., 2010; Wehrle et al., 2019).

LSDs are a third broad class of disease, defined by impaired lysosome-mediated degradation (Platt et al., 2018). Many LSDs result from the loss of hydrolase expression, but some involve defective hydrolase trafficking. For example, ceroid-lipofuscinosis, neuronal 8 (CLN8) is a cargo receptor for trafficking of newly synthesised hydrolases from the ER to the Golgi (di Ronza et al., 2018), and mutations in CLN8 cause the LSD Batten disease (Ranta et al., 1999). Mutation of VPS33A, a common component of the class C core vacuole/endosome tethering (CORVET) and homotypic fusion and protein sorting (HOPS) multi-subunit vesicle-tethering complexes that operate at the early and late endosome/lysosome, respectively, causes the LSD mucopolysaccharidosis (Kondo et al., 2017).

Lysosome-related organelles (LROs) are found in specific cell types and carry out specialised functions (Marks et al., 2013). Examples include melanosomes in skin melanocytes and retinal pigment epithelial cells, which are important for pigmentation, lytic granules of NK and T-cells that mediate target cell killing, and Weibel–Palade bodies in endothelial cells that contribute to blood clotting. Chediak–Higashi, Griscelli and Hermansky–Pudlak syndromes are all associated with defective LRO biogenesis, and in many cases are due to defects in the relevant LRO trafficking machinery (Huizing et al., 2008). For example, Griscelli syndrome, characterised by hypopigmentation and immunodeficiency, can be caused by mutations in RAB27A, its effector melanophilin, or the actin motor MYO5A, which together facilitate melanosome movement to the cell periphery for delivery of pigment to neighbouring keratinocytes (Ménasché et al., 2003; Ménasché et al., 2000; Pastural et al., 1997). Hermansky–Pudlak syndrome, which presents as hypopigmentation, bleeding and additional symptoms depending on the subtype, is caused by mutations in subunits of the biogenesis of lysosome-related organelle complex (BLOC)-1 (Li et al., 2003; Morgan et al., 2006), BLOC-2 (Anikster et al., 2001; Zhang et al., 2003b), BLOC-3 (Oh et al., 1996; Suzuki et al., 2002) or AP3 (Ammann et al., 2016; Dell’Angelica et al., 1999) complexes that are involved in transport of cargo proteins from endosomes to LROs. Chediak–Higashi syndrome, which manifests as albinism, excessive bleeding and immunodeficiency, is caused by mutations in lysosomal trafficking regulator (LYST) (Karim et al., 2002), which appears to function in endolysosomal trafficking (Gil-Krzewska et al., 2016).

Lysosome dysfunction has also been reported in the rare X-linked disorder Lowe syndrome, which affects the brain, eyes and kidneys, and is caused by mutation of the inositol phosphatase oculocerebrorenal Lowe syndrome protein (OCRL) (Attree et al.,

1992). The aetiology of Lowe is complex, since build-up of the OCRL substrate PtdIns(4,5)P<sub>2</sub> disrupts not only lysosomal function, which results in an additional autophagy defect, but also affects endocytosis, endocytic recycling and trafficking to the cilium (De Matteis et al., 2017). Hence, disruption of several trafficking steps is likely to cause the Lowe syndrome phenotypes seen in patients. Interestingly, mutations in OCRL also cause Dent-2 disease, for which the symptoms are largely restricted to the kidney (Hoopes et al., 2005). The reasons for this dual pathophenotype remain unclear.

Defective COPI-dependent recycling from the Golgi apparatus to the ER is associated with two multi-systemic genetic disorders, both affecting the liver. Mutation of the COPI accessory protein SCYL1 causes low  $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN) syndrome, manifesting as hepatocyte death and liver failure, as well as ataxia resulting from cerebellar neurodegeneration (Lenz et al., 2018; Schmidt et al., 2015). Mutation of NBAS, a component of the NBAS/RINT1/ZW10 (NRZ) ER-localised COPI vesicle-tethering complex results in a nearly identical liver phenotype, and also causes bone, connective tissue, retina and immune system defects (Balasubramanian et al., 2017; Haack et al., 2015; Maksimova et al., 2010; Segarra et al., 2015). These findings suggest a high requirement for the secretory pathway in the affected cell types, including hepatocytes, consistent with them secreting large amounts of material into the bloodstream.

### Cancer

Membrane trafficking is intimately linked with cancer, with trafficking in both the secretory and endocytic pathways playing an important role in many types of cancer. Endocytic trafficking is responsible for the abundance and signalling capacity of mitogenic receptors, adhesion molecules and immune modulators that determine the ability of the immune system to detect cancer cells (Mellman and Yarden, 2013). Hence, changes in the expression levels or degree of phosphorylation of endocytic trafficking machinery can correlate with cancer susceptibility or prognosis. In addition, cancer-causing mutations within the components of the endocytic machinery have been described. A recent example is RAB35, which mediates various endocytic trafficking steps (Klinkert and Ehard, 2016). Oncogenic mutations in RAB35, although extremely rare, have been shown to cause its constitutive activation and promiscuous growth factor signalling from endosomal compartments (Wheeler et al., 2015). Altered expression and splicing of tumour susceptibility gene 101 (TSG101), has been found in cancer (Jiang et al., 2013), whereby impaired growth factor receptor downregulation at the endosome may contribute to tumorigenesis (Lu et al., 2003). Interestingly, toxic gain-of-function mutation of p53 can also promote the recycling of integrins and growth factor receptors, which is responsible for increased cell migration and metastatic potential of tumour cells (Muller et al., 2009).

The secretory pathway can influence cancer susceptibility and disease progression in a number of ways (Dejeans et al., 2014). We know that cell surface glycans, which are generated within the secretory pathway, are important for processes contributing to cancer development and metastasis, including signalling, adhesion and migration (Pinho and Reis, 2015). A particularly interesting example of an oncogenic trafficking protein is Golgi phosphoprotein 3 (GOLPH3), which is highly expressed in several cancers (Scott et al., 2009). GOLPH3 appears to participate in intra-Golgi transport, which is required for Golgi enzyme retention and correct protein

### Box 2. Therapeutic approaches to rescue traffic-dependent phenotypes

We lack effective therapies to treat most of the diseases associated with defective membrane trafficking. In principle, diseases caused by genetic mutation could be treated with gene therapy, but using this approach to successfully treat human disease remains in its infancy (Dunbar et al., 2018). A promising example is gene therapy for retinal dystrophy choroideremia, which is caused by loss of the RAB escort protein REP-1 (Sankila et al., 1992; Seabra et al., 1993). Here, *CHM*, the gene that encodes REP-1, is administered to the eye via a viral delivery vector. The therapy is currently undergoing phase 3 clinical trials following promising results in earlier stages of clinical testing (Xue et al., 2018). Many trafficking regulators, which are enzymes, are potentially amenable to treatment with small-molecule drugs. This approach remains to be explored more fully, but there is significant interest in targeting the protein kinase LRRK2 for treatment of Parkinson's disease (Zhao and Dzakmo, 2019). Pathogenic LRRK2 mutations lead to overactive kinase activity and so chemically inhibiting this activity could protect against Parkinson's disease. As such, clinical trials are underway to test the safety and efficacy of LRRK2 inhibitors in human patients.

glycosylation (Ali et al., 2012; Chang et al., 2013; Isaji et al., 2014; Pereira et al., 2014), as well as export of cargo from the *trans*-Golgi (Rahajeng et al., 2019). GOLPH3 overexpression stimulates a number of mitogenic signalling pathways, which may be a consequence of altering the cell surface glycan profile and thus the signalling capacity of surface receptors (Rizzo et al., 2017). In addition, GOLPH3 has been implicated in a DNA stress response pathway, linking DNA damage to the Golgi apparatus (Farber-Katz et al., 2014). In this context, GOLPH3 overexpression can promote cell survival upon DNA damage, which may be relevant to the cancer phenotype. Another interesting example is mutation of the ER-to-Golgi trafficking protein LMAN1 in colorectal cancers, which causes reduced secretion of the LMAN1 client protein  $\alpha$ -1-antitrypsin (A1AT; also known as SERPINA1), an angiogenesis inhibitor, thereby contributing to tumour blood supply and growth (Roeckel et al., 2009).

### Diabetes

Exocytosis of insulin from pancreatic beta cells, and the endocytic and secretory trafficking of insulin receptors and glucose transporters in target cells, may all directly affect diabetes susceptibility or progression. For example, the inositol phosphatase suppressor of actin 2 (SAC2; also known as INPP5F) functions in insulin granule exocytosis from pancreatic beta cells, and its levels are reduced in type II diabetic patients, suggesting that SAC2 insufficiency might contribute to impaired insulin release in these patients (Nguyen et al., 2019). Another protein of interest is clathrin heavy chain 22 (CHC22), which is involved in the trafficking of glucose transporter type 4 (GLUT4; also known as SLC2A4) in muscle and fat cells, where it mediates glucose uptake in response to insulin signalling (Vassilopoulos et al., 2009). Two CHC22 variants exist in the human population, which differ in their ability to traffic GLUT4 and thus remove glucose from the bloodstream (Fumagalli et al., 2019). The 'new' variant, which appeared later in evolution, increases cell surface levels of GLUT4 and glucose removal from the bloodstream, whereas the 'older' variant has a lower capacity to traffic GLUT4 to the cell surface and therefore to clear blood glucose. However, it remains to be seen whether people carrying the 'older' variant have a greater diabetes risk.

### Summary and conclusions

Membrane trafficking is a ubiquitous process and fundamentally important to all tissues. However, defects in components of the trafficking machinery often manifest as a tissue-specific phenotype. The nature of the observed defect depends upon the tissue expression of the trafficking component in question and its degree of functional redundancy, the rate-limiting trafficking steps within different cell types, and the abundance and types of cargo proteins expressed in different cells. The nature of the mutation itself is also important, as it can result in either a complete loss of expression or function of the trafficking component, a partial loss of expression or function, or, in some cases, a toxic overexpression or gain of function. This is expected to cause corresponding changes in the associated trafficking pathway(s), resulting in the observed phenotype. With regard to the tissue-specific nature of the diseases, it is interesting that the nervous system is particularly sensitive to disruption of the endolysosomal system, possibly due to the importance of endocytic traffic to maintain neurotransmission as well as the sensitivity of neurons to disrupted lysosome function and autophagy. Skin, bone and connective tissues are more sensitive to defective secretory traffic, reflecting the high secretory load in these tissues. Despite these generalisations, it is often hard to predict the phenotype one might expect upon mutation of a particular trafficking component, and understanding the disease mechanisms underlying most trafficking-related disorders is not trivial.

Defective traffic can manifest in a particular phenotype for several reasons. In some cases, it may be the failure to deliver a cargo protein to the correct destination compartment, causing dysfunction of that organelle, or the impaired ability of cells to secrete or internalise cargo effectively, resulting in systemic effects. In other cases, the inability to traffic proteins from their donor compartments may be problematic, as in the case of ER stress induction when proteins fail to exit this compartment. Similarly, the inability to degrade substrates by autophagy is cytotoxic. It is also worth noting that although impaired traffic can cause disease, in some contexts, trafficking might be required to sustain a disease phenotype. This appears to be true in cancer, where endocytic traffic is required to sustain proliferative signalling and cell migration, important for tumour growth and metastasis. Thus, in terms of developing therapeutics for trafficking disorders, a range of strategies is possible (Box 2). Gene therapy is one possible route, but drugs can potentially rescue defective organelle function. Therapeutic strategies could alleviate the cell stress that occurs downstream from organelle dysfunction, restore the disrupted trafficking step, or, in some cases, inhibit a transport step that is driving the disease phenotype. As we identify more rare diseases attributable to defects in membrane traffic, and better understand the mechanisms that underlie these and other more common disorders, we will undoubtedly be able to deliver better treatments and long-term therapies in the future.

### Competing interests

The authors declare no competing or financial interests.

### Funding

R.Y. is supported by a Wellcome Trust PhD studentship (203995/Z/16/Z) and J.H. by a joint University of Manchester and Agency for Science, Technology and Research (Singapore A\*STAR) PhD studentship. Research in the P.G.W. laboratory is supported by grants from the Wellcome Trust (212246/Z/18/Z), the Biotechnology and Biological Sciences Research Council (BBSRC) (BB/R015864/1) and the Leverhulme Trust (RPG-2018-091). Research in the M.L. laboratory is supported by grants from the BBSRC (BB/S014799/1, BB/T000945/1), the Lowe Syndrome Trust (ML/MU/LST NOV/18) and the Leverhulme Trust (RPG-2019-134).

## At a glance

A high-resolution version of the poster is available for downloading in the online version of this article at <http://dmm.biologists.org/content/13/4/dmm043448/F1.poster.jpg>.

## References

- Abeliovich, A. and Gitler, A. D.** (2016). Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature* **539**, 207-216. doi:10.1038/nature20414
- Alazami, A. M., Hijazi, H., Kentab, A. Y. and Alkuraya, F. S.** (2014). NECA1 loss of function leads to a severe infantile epileptic encephalopathy. *J. Med. Genet.* **51**, 224-228. doi:10.1136/jmedgenet-2013-102030
- Ali, M. F., Chachadi, V. B., Petrosyan, A. and Cheng, P. W.** (2012). Golgi phosphoprotein 3 determines cell binding properties under dynamic flow by controlling Golgi localization of core 2 N-acetylglucosaminyltransferase 1. *J. Biol. Chem.* **287**, 39564-39577. doi:10.1074/jbc.M112.346528
- Aligianis, I. A., Johnson, C. A., Gissen, P., Chen, D. R., Hampshire, D., Hoffmann, K., Maina, E. N., Morgan, N. V., Tee, L., Morton, J. et al.** (2005). Mutations of the catalytic subunit of RAB3GAP cause Warburg Micro syndrome. *Nat. Genet.* **37**, 221-223. doi:10.1038/ng1517
- Aligianis, I. A., Morgan, N. V., Mione, M., Johnson, C. A., Rosser, E., Hennekam, R. C., Adams, G., Trembath, R. C., Pilz, D. T., Stoodley, N. et al.** (2006). Mutation in Rab3 GTPase-activating protein (RAB3GAP) noncatalytic subunit in a kindred with Martsolf syndrome. *Am. J. Hum. Genet.* **78**, 702-707. doi:10.1086/502681
- Allfrey, V., Daly, M. M. and Mirsky, A. E.** (1953). Synthesis of protein in the pancreas. II. The role of ribonucleoprotein in protein synthesis. *J. Gen. Physiol.* **37**, 157-175. doi:10.1085/jgp.37.2.157
- Alory, C. and Balch, W. E.** (2001). Organization of the Rab-GDI/CHM superfamily: the functional basis for choroideremia disease. *Traffic* **2**, 532-543. doi:10.1034/j.1600-0854.2001.20803.x
- Al-Qusairi, L., Weiss, N., Toussaint, A., Berbey, C., Messaddeq, N., Kretz, C., Sanoudou, D., Beggs, A. H., Allard, B., Mandel, J.-L. et al.** (2009). T-tubule disorganization and defective excitation-contraction coupling in muscle fibers lacking myotubularin lipid phosphatase. *Proc. Natl. Acad. Sci. USA* **106**, 18763-18768. doi:10.1073/pnas.0900705106
- Ammann, S., Schulz, A., Krageloh-Mann, I., Dieckmann, N. M., Niethammer, K., Fuchs, S., Eckl, K. M., Plank, R., Werner, R., Altmüller, J. et al.** (2016). Mutations in AP3D1 associated with immunodeficiency and seizures define a new type of Hermansky-Pudlak syndrome. *Blood* **127**, 997-1006. doi:10.1182/blood-2015-09-671636
- Anantharam, A. and Kreutzberger, A. J. B.** (2019). Unraveling the mechanisms of calcium-dependent secretion. *J. Gen. Physiol.* **151**, 417-434. doi:10.1085/jgp.201812298
- Anikster, Y., Huizing, M., White, J., Shevchenko, Y. O., Fitzpatrick, D. L., Touchman, J. W., Compton, J. G., Bale, S. J., Swank, R. T., Gahl, W. A. et al.** (2001). Mutation of a new gene causes a unique form of Hermansky-Pudlak syndrome in a genetic isolate of central Puerto Rico. *Nat. Genet.* **28**, 376-380. doi:10.1038/ng576
- Assoum, M., Philippe, C., Isidor, B., Perrin, L., Makrythanasis, P., Sondheimer, N., Paris, C., Douglas, J., Lesca, G., Antonarakis, S. et al.** (2016). Autosomal-recessive mutations in AP3B2, adaptor-related protein complex 3 Beta 2 subunit, cause an early-onset epileptic encephalopathy with optic atrophy. *Am. J. Hum. Genet.* **99**, 1368-1376. doi:10.1016/j.ajhg.2016.10.009
- Attree, O., Olivios, I. M., Okabe, I., Bailey, L. C., Nelson, D. L., Lewis, R. A., McInnes, R. R. and Nussbaum, R. L.** (1992). The Lowe's oculocerebrorenal syndrome gene encodes a protein highly homologous to inositol polyphosphate-5-phosphatase. *Nature* **358**, 239-242. doi:10.1038/358239a0
- Avior, Y., Sagi, I. and Benvenisty, N.** (2016). Pluripotent stem cells in disease modelling and drug discovery. *Nat. Rev. Mol. Cell Biol.* **17**, 170-182. doi:10.1038/nrm.2015.27
- Azzedine, H., Bolino, A., Taieb, T., Birouk, N., Di Duca, M., Bouhouche, A., Benamou, S., Mrabet, A., Hammadouche, T., Chkili, T. et al.** (2003). Mutations in MTMR13, a new pseudophosphatase homologue of MTMR2 and Sbf1, in two families with an autosomal recessive demyelinating form of Charcot-Marie-Tooth disease associated with early-onset glaucoma. *Am. J. Hum. Genet.* **72**, 1141-1153. doi:10.1086/375034
- Balasubramanian, M., Hurst, J., Brown, S., Bishop, N. J., Arundel, P., DeVile, C., Pollitt, R. C., Crooks, L., Longman, D., Caceres, J. F. et al.** (2017). Compound heterozygous variants in NBAS as a cause of atypical osteogenesis imperfecta. *Bone* **94**, 65-74. doi:10.1016/j.bone.2016.10.023
- Balch, W. E., Dunphy, W. G., Braell, W. A. and Rothman, J. E.** (1984). Reconstitution of the transport of protein between successive compartments of the Golgi measured by the coupled incorporation of N-acetylglucosamine. *Cell* **39**, 405-416. doi:10.1016/0092-8674(84)90019-9
- Baldassarre, T., Watt, K., Truesdell, P., Meens, J., Schneider, M. M., Sengupta, S. K. and Craig, A. W.** (2015). Endophilin A2 promotes TNBC cell invasion and tumor metastasis. *Mol. Cancer Res.* **13**, 1044-1055. doi:10.1158/1541-7786.MCR-14-0573
- Balendra, R. and Isaacs, A. M.** (2018). C9orf72-mediated ALS and FTD: multiple pathways to disease. *Nat. Rev. Neurol.* **14**, 544-558. doi:10.1038/s41582-018-0047-2
- Bansal, D., Miyake, K., Vogel, S. S., Groh, S., Chen, C. C., Williamson, R., McNeil, P. L. and Campbell, K. P.** (2003). Defective membrane repair in dysferlin-deficient muscular dystrophy. *Nature* **423**, 168-172. doi:10.1038/nature01573
- Barresi, R. and Campbell, K. P.** (2006). Dystroglycan: from biosynthesis to pathogenesis of human disease. *J. Cell Sci.* **119**, 199-207. doi:10.1242/jcs.02814
- Barrowman, J., Bhandari, D., Reinisch, K. and Ferro-Novick, S.** (2010). TRAPP complexes in membrane traffic: convergence through a common Rab. *Nat. Rev. Mol. Cell Biol.* **11**, 759-763. doi:10.1038/nrm2999
- Basel-Vanagaite, L., Sarig, O., Hershkovitz, D., Fuchs-Telem, D., Rapaport, D., Gat, A., Isman, G., Shirazi, I., Shohat, M., Enk, C. D. et al.** (2009). RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. *Am. J. Hum. Genet.* **85**, 254-263. doi:10.1016/j.ajhg.2009.07.001
- Bashir, R., Britton, S., Strachan, T., Keers, S., Vafiadaki, E., Lako, M., Richard, I., Marchand, S., Bourg, N., Argov, Z. et al.** (1998). A gene related to Caenorhabditis elegans spermatogenesis factor fer-1 is mutated in limb-girdle muscular dystrophy type 2B. *Nat. Genet.* **20**, 37-42. doi:10.1038/1689
- Bauer, P., Leshinsky-Silver, E., Blumkin, L., Schlipf, N., Schröder, C., Schicks, J., Lev, D., Riess, O., Lerman-Sagie, T. and Schöls, L.** (2012). Mutation in the AP4B1 gene cause hereditary spastic paraplegia type 47 (SPG47). *Neurogenetics* **13**, 73-76. doi:10.1007/s10048-012-0314-0
- Baulac, S., Lenk, G. M., Dufresnois, B., Ouled Amer Bencheikh, B., Couarch, P., Renard, J., Larson, P. A., Ferguson, C. J., Noe, E., Poirier, K. et al.** (2014). Role of the phosphoinositide phosphatase FIG4 gene in familial epilepsy with polymicrogyria. *Neurology* **82**, 1068-1075. doi:10.1212/WNL.0000000000000241
- Beck, R., Rawat, M., Wieland, F. T. and Cassel, D.** (2009). The COPI system: molecular mechanisms and function. *FEBS Lett.* **583**, 2701-2709. doi:10.1016/j.febslet.2009.07.032
- Beetz, C., Johnson, A., Schuh, A. L., Thakur, S., Varga, R. E., Fothergill, T., Hertel, N., Bomba-Warczak, E., Thiele, H., Nurnberg, G. et al.** (2013). Inhibition of TFG function causes hereditary axon degeneration by impairing endoplasmic reticulum structure. *Proc. Natl. Acad. Sci. USA* **110**, 5091-5096. doi:10.1073/pnas.1217197110
- Bem, D., Yoshimura, S.-I., Nunes-Bastos, R., Bond, F. F., Kurian, M. A., Rahman, F., Handley, M. T. W., Hadzhiev, Y., Masood, I., Straatman-Iwanowska, A. A. et al.** (2011). Loss-of-function mutations in RAB18 cause Warburg Micro syndrome. *Am. J. Hum. Genet.* **88**, 499-507. doi:10.1016/j.ajhg.2011.03.012
- Ben-Chetrit, N., Chetrit, D., Russell, R., Körner, C., Mancini, M., Abdul-Hai, A., Itkin, T., Carvalho, S., Cohen-Dvashi, H., Koestler, W. J. et al.** (2015). Synaptotagmin 2 is a druggable mediator of metastasis and the gene is overexpressed and amplified in breast cancer. *Sci. Signal.* **8**, ra7. doi:10.1126/scisignal.2005537
- Bianchi, P., Fermo, E., Vercellati, C., Boschetti, C., Barcellini, W., Iurlo, A., Marcello, A. P., Righetti, P. G. and Zanella, A.** (2009). Congenital dyserythrocytic anemia type II (CDAlI) is caused by mutations in the SEC23B gene. *Hum. Mutat.* **30**, 1292-1298. doi:10.1002/humu.21077
- Bienvu, T., des Portes, V., Saint Martin, A., McDonnell, N., Billuart, P., Carrie, A., Vinet, M. C., Couvert, P., Toniolo, D., Ropers, H. H. et al.** (1998). Non-specific X-linked semidominant mental retardation by mutations in a Rab GDP-dissociation inhibitor. *Hum. Mol. Genet.* **7**, 1311-1315. doi:10.1093/hmg/7.8.1311
- Bitoun, M., Maugeure, S., Jeannot, P. Y., Lacene, E., Ferrer, X., Laforet, P., Martin, J. J., Laporte, J., Lochmuller, H., Beggs, A. H. et al.** (2005). Mutations in dynamin 2 cause dominant centronuclear myopathy. *Nat. Genet.* **37**, 1207-1209. doi:10.1038/ng1657
- Blackstone, C., O'Kane, C. J. and Reid, E.** (2011). Hereditary spastic paraplegias: membrane traffic and the motor pathway. *Nat. Rev. Neurosci.* **12**, 31-42. doi:10.1038/nrn2946
- Bolino, A., Muglia, M., Conforti, F. L., LeGuern, E., Salih, M. A., Georgiou, D. M., Christodoulou, K., Hausmanowa-Petrusewicz, I., Mandich, P., Schenone, A. et al.** (2000). Charcot-Marie-Tooth type 4B is caused by mutations in the gene encoding myotubularin-related protein-2. *Nat. Genet.* **25**, 17-19. doi:10.1038/75542
- Boncompain, G., Divoux, S., Gareil, N., de Forges, H., Lescure, A., Latreche, L., Mercanti, V., Jollivet, F., Raposo, G. and Perez, F.** (2012). Synchronization of secretory protein traffic in populations of cells. *Nat. Methods* **9**, 493-498. doi:10.1038/nmeth.1928
- Bögershausen, N., Shahrzad, N., Chong, J. X., von Kleist-Retzow, J.-C., Stanga, D., Li, Y., Bernier, F. P., Loucks, C. M., Wirth, R., Puffenberger, E. G. et al.** (2013). Recessive TRAPPC11 mutations cause a disease spectrum of limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability. *Am. J. Hum. Genet.* **93**, 181-190. doi:10.1016/j.ajhg.2013.05.028
- Borck, G., Wunram, H., Steiert, A., Volk, A. E., Korber, F., Roters, S., Herkenrath, P., Wollnik, B., Morris-Rosendahl, D. J. and Kubisch, C.** (2011). A homozygous RAB3GAP2 mutation causes Warburg Micro syndrome. *Hum. Genet.* **129**, 45-50. doi:10.1007/s00439-010-0896-2

- Bourassa, C. V., Meijer, I. A., Merner, N. D., Grewal, K. K., Stefanelli, M. G., Hodgkinson, K., Ives, E. J., Pryse-Phillips, W., Jog, M., Boycott, K. et al. (2012). VAMP1 mutation causes dominant hereditary spastic ataxia in Newfoundland families. *Am. J. Hum. Genet.* **91**, 548-552. doi:10.1016/j.ajhg.2012.07.018
- Boydjiev, S. A., Fromme, J. C., Ben, J., Chong, S. S., Nauta, C., Hur, D. J., Zhang, G., Hamamoto, S., Schekman, R., Ravazzola, M. et al. (2006). Cranio-lenticulo-sutural dysplasia is caused by a SEC23A mutation leading to abnormal endoplasmic-reticulum-to-Golgi trafficking. *Nat. Genet.* **38**, 1192-1197. doi:10.1038/ng1876
- Boydjiev, S. A., Kim, S. D., Hata, A., Haldeman-Englert, C., Zackai, E. H., Naydenov, C., Hamamoto, S., Schekman, R. W. and Kim, J. (2011). Cranio-lenticulo-sutural dysplasia associated with defects in collagen secretion. *Clin. Genet.* **80**, 169-176. doi:10.1111/j.1399-0004.2010.01550.x
- Brandizzi, F. and Barlowe, C. (2013). Organization of the ER-Golgi interface for membrane traffic control. *Nat. Rev. Mol. Cell Biol.* **14**, 382-392. doi:10.1038/nrm3588
- Branon, T. C., Bosch, J. A., Sanchez, A. D., Udeshi, N. D., Svinikina, T., Carr, S. A., Feldman, J. L., Perrimon, N. and Ting, A. Y. (2018). Efficient proximity labeling in living cells and organisms with TurboID. *Nat. Biotechnol.* **36**, 880-887. doi:10.1038/nbt.4201
- Brown, M. S. and Goldstein, J. L. (1986). A receptor-mediated pathway for cholesterol homeostasis. *Science* **232**, 34-47. doi:10.1126/science.3513311
- Buj-Bello, A., Biancalana, V., Moutou, C., Laporte, J. and Mandel, J. L. (1999). Identification of novel mutations in the MTM1 gene causing severe and mild forms of X-linked myotubular myopathy. *Hum. Mutat.* **14**, 320-325. doi:10.1002/(SICI)1098-1004(199910)14:4<320::AID-HUMU7>3.0.CO;2-O
- Burre, J., Sharma, M., Tsetsenis, T., Buchman, V., Etherton, M. R. and Südhof, T. C. (2010). Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. *Science* **329**, 1663-1667. doi:10.1126/science.1195227
- Byrne, J. A., Tomasetto, C., Garnier, J. M., Rouyer, N., Mattei, M. G., Bellocq, J. P., Rio, M. C. and Basset, P. (1995). A screening method to identify genes commonly overexpressed in carcinomas and the identification of a novel complementary DNA sequence. *Cancer Res.* **55**, 2896-2903.
- Byrne, J. A., Mattei, M.-G. and Basset, P. (1996). Definition of the tumor protein D52 (TPD52) gene family through cloning of D52 homologues in human (hD53) and mouse (mD52). *Genomics* **35**, 523-532. doi:10.1006/geno.1996.0393
- Byrne, J. A., Nourse, C. R., Basset, P. and Gunning, P. (1998). Identification of homo- and heteromeric interactions between members of the breast carcinoma-associated D52 protein family using the yeast two-hybrid system. *Oncogene* **16**, 873-881. doi:10.1038/sj.onc.1201604
- Cai, X., Chen, X., Wu, S., Liu, W., Zhang, X., Zhang, D., He, S., Wang, B., Zhang, M., Zhang, Y. et al. (2016). Homozygous mutation of VPS16 gene is responsible for an autosomal recessive adolescent-onset primary dystonia. *Sci. Rep.* **6**, 25834. doi:10.1038/srep25834
- Campeau, P. M., Lenk, G. M., Lu, J. T., Bae, Y., Burrage, L., Turnpenny, P., Roman Corona-Rivera, J., Morandi, L., Mora, M., Reutter, H. et al. (2013). Yunis-Varon syndrome is caused by mutations in FIG4, encoding a phosphoinositide phosphatase. *Am. J. Hum. Genet.* **92**, 781-791. doi:10.1016/j.ajhg.2013.03.020
- Carstea, E. D., Morris, J. A., Coleman, K. G., Loftus, S. K., Zhang, D., Cummings, C., Gu, J., Rosenfeld, M. A., Pavan, W. J., Krizman, D. B. et al. (1997). Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* **277**, 228-231. doi:10.1126/science.277.5323.228
- Centonze, F. G., Reiterer, V., Nalbach, K., Saito, K., Pawlowski, K., Behrends, C. and Farhan, H. (2019). LTK is an ER-resident receptor tyrosine kinase that regulates secretion. *J. Cell Biol.* **218**, 2470-2480. doi:10.1083/jcb.201903068
- Chan, W. L., Steiner, M., Witkos, T., Egerer, J., Busse, B., Mizumoto, S., Pestka, J. M., Zhang, H., Hausser, I., Khayal, L. A. et al. (2018). Impaired proteoglycan glycosylation, elevated TGF- $\beta$  signaling, and abnormal osteoblast differentiation as the basis for bone fragility in a mouse model for geroderma osteodysplastica. *PLoS Genet.* **14**, e1007242. doi:10.1371/journal.pgen.1007242
- Chandra, S., Gallardo, G., Fernández-Chacón, R., Schlüter, O. M. and Südhof, T. C. (2005). Alpha-synuclein cooperates with CSP $\alpha$  in preventing neurodegeneration. *Cell* **123**, 383-396. doi:10.1016/j.cell.2005.09.028
- Chang, W.-L., Chang, C.-W., Chang, Y.-Y., Sung, H.-H., Lin, M.-D., Chang, S.-C., Chen, C.-H., Huang, C.-W., Tung, K.-S. and Chou, T.-B. (2013). The Drosophila GOLPH3 homolog regulates the biosynthesis of heparan sulfate proteoglycans by modulating the retrograde trafficking of exostosins. *Development* **140**, 2798-2807. doi:10.1242/dev.087171
- Chen, Q., He, G., Qin, W., Chen, Q.-Y., Zhao, X.-Z., Duan, S.-W., Liu, X.-M., Feng, G.-Y., Xu, Y.-F., St Clair, D. et al. (2004). Family-based association study of synapsin II and schizophrenia. *Am. J. Hum. Genet.* **75**, 873-877. doi:10.1086/425588
- Chen, D., Gibson, E. S. and Kennedy, M. J. (2013). A light-triggered protein secretion system. *J. Cell Biol.* **201**, 631-640. doi:10.1083/jcb.201210119
- Cheng, K. W., Lahad, J. P., Kuo, W.-L., Lapuk, A., Yamada, K., Auersperg, N., Liu, J., Smith-McCune, K., Lu, K. H., Fishman, D. et al. (2004). The RAB25 small GTPase determines aggressiveness of ovarian and breast cancers. *Nat. Med.* **10**, 1251-1256. doi:10.1038/nm1125
- Chin, Y. H., Lee, A., Kan, H. W., Laiman, J., Chuang, M. C., Hsieh, S. T. and Liu, Y. W. (2015). Dynamin-2 mutations associated with centronuclear myopathy are hypermorphic and lead to T-tubule fragmentation. *Hum. Mol. Genet.* **24**, 5542-5554. doi:10.1093/hmg/ddv285
- Chow, C. Y., Landers, J. E., Bergsen, S. K., Sapp, P. C., Grant, A. E., Jones, J. M., Everett, L., Lenk, G. M., McKenna-Yasek, D. M., Weisman, L. S. et al. (2009). Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. *Am. J. Hum. Genet.* **84**, 85-88. doi:10.1016/j.ajhg.2008.12.010
- Christ, L., Raiborg, C., Wenzel, E. M., Campsteijn, C. and Stenmark, H. (2017). Cellular functions and molecular mechanisms of the ESCRT membrane-scission machinery. *Trends Biochem. Sci.* **42**, 42-56. doi:10.1016/j.tibs.2016.08.016
- Cooper, A. A., Gitler, A. D., Cashikar, A., Haynes, C. M., Hill, K. J., Bhullar, B., Liu, K., Xu, K., Strathearn, K. E., Liu, F. et al. (2006). Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. *Science* **313**, 324-328. doi:10.1126/science.1129462
- Corbett, M. A., Schwake, M., Bahlo, M., Dibbens, L. M., Lin, M., Gandolfo, L. C., Vears, D. F., O'Sullivan, J. D., Robertson, T., Bayly, M. A. et al. (2011). A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. *Am. J. Hum. Genet.* **88**, 657-663. doi:10.1016/j.ajhg.2011.04.011
- Cremers, F. P., Armstrong, S. A., Seabra, M. C., Brown, M. S. and Goldstein, J. L. (1994). REP-2, a Rab escort protein encoded by the choroideremia-like gene. *J. Biol. Chem.* **269**, 2111-2117.
- Cullen, P. J. and Steinberg, F. (2018). To degrade or not to degrade: mechanisms and significance of endocytic recycling. *Nat. Rev. Mol. Cell Biol.* **19**, 679-696. doi:10.1038/s41580-018-0053-7
- Cullinane, A. R., Straatman-Iwanowska, A., Zaucker, A., Wakabayashi, Y., Bruce, C. K., Luo, G., Rahman, F., Gürkan, F., Utine, E., Özkan, T. B. et al. (2010). Mutations in VIPAR cause an arthrogyposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. *Nat. Genet.* **42**, 303-312. doi:10.1038/ng.538
- D'Adamo, P., Menegon, A., Lo Nigro, C., Grasso, M., Gulisano, M., Tamanini, F., Bienvuut, T., Gedeon, A. K., Oostra, B., Wu, S. K. et al. (1998). Mutations in GDI1 are responsible for X-linked non-specific mental retardation. *Nat. Genet.* **19**, 134-139. doi:10.1038/487
- Damseh, N., Danson, C. M., Al-Ashhab, M., Abu-Libdeh, B., Gallon, M., Sharma, K., Yaacov, B., Coulthard, E., Caldwell, M. A., Edvardson, S. et al. (2015). A defect in the retromer accessory protein, SNX27, manifests by infantile myoclonic epilepsy and neurodegeneration. *Neurogenetics* **16**, 215-221. doi:10.1007/s10048-015-0446-0
- Davidson, G. P., Cutz, E., Hamilton, J. R. and Gall, D. G. (1978). Familial enteropathy: a syndrome of protracted diarrhea from birth, failure to thrive, and hypoplastic villus atrophy. *Gastroenterology* **75**, 783-790. doi:10.1016/0016-5085(78)90458-4
- Davies, A. K., Itzhak, D. N., Edgar, J. R., Archuleta, T. L., Hirst, J., Jackson, L. P., Robinson, M. S. and Borner, G. H. H. (2018). AP-4 vesicles contribute to spatial control of autophagy via RUSC-dependent peripheral delivery of ATG9A. *Nat. Commun.* **9**, 3958. doi:10.1038/s41467-018-06172-7
- Davis, C. G., Lehman, M. A., Russell, D. W., Anderson, R. G., Brown, M. S. and Goldstein, J. L. (1986). The J.D. mutation in familial hypercholesterolemia: amino acid substitution in cytoplasmic domain impedes internalization of LDL receptors. *Cell* **45**, 15-24. doi:10.1016/0092-8674(86)90533-7
- De Matteis, M. A. and Luini, A. (2008). Exiting the Golgi complex. *Nat. Rev. Mol. Cell Biol.* **9**, 273-284. doi:10.1038/nrm2378
- De Matteis, M. A., Staiano, L., Emma, F. and Devuyst, O. (2017). The 5-phosphatase OCRL in Lowe syndrome and Dent disease 2. *Nat. Rev. Nephrol.* **13**, 455-470. doi:10.1038/nrneph.2017.83
- Dehay, B., Martinez-Vicente, M., Caldwell, G. A., Caldwell, K. A., Yue, Z., Cookson, M. R., Klein, C., Vila, M. and Bezdard, E. (2013). Lysosomal impairment in Parkinson's disease. *Mov. Disord.* **28**, 725-732. doi:10.1002/mds.25462
- Dejeans, N., Manié, S., Hetz, C., Bard, F., Hupp, T., Agostinis, P., Samali, A. and Chevet, E. (2014). Addicted to secrete - novel concepts and targets in cancer therapy. *Trends Mol. Med.* **20**, 242-250. doi:10.1016/j.molmed.2013.12.003
- DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M., Rutherford, N. J., Nicholson, A. M., Finch, N. A., Flynn, H., Adamson, J. et al. (2011). Expanded GGGGCC hexanucleotide repeat in noncoding region of C9orf72 causes chromosome 9p-linked FTD and ALS. *Neuron* **72**, 245-256. doi:10.1016/j.neuron.2011.09.011
- Dell'Angelica, E. C., Shotelersuk, V., Aguilar, R. C., Gahl, W. A. and Bonifacino, J. S. (1999). Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the  $\beta$ 3A subunit of the AP-3 adaptor. *Mol. Cell* **3**, 11-21. doi:10.1016/S1097-2765(00)80170-7
- Denecke, J. and Marquardt, T. (2009). Congenital dyserythropoietic anemia type II (CDAIL/HEMPAS): where are we now? *Biochim. Biophys. Acta* **1792**, 915-920. doi:10.1016/j.bbadis.2008.12.005
- di Ronza, A., Bajaj, L., Sharma, J., Sanagasetti, D., Lotfi, P., Adamski, C. J., Collette, J., Palmieri, M., Amawi, A., Popp, L. et al. (2018). CLN8 is an endoplasmic reticulum cargo receptor that regulates lysosome biogenesis. *Nat. Cell Biol.* **20**, 1370-1377. doi:10.1038/s41556-018-0228-7

- Dixon-Salazar, T. J., Silhavy, J. L., Udpa, N., Schroth, J., Bielas, S., Schaffer, A. E., Olvera, J., Bafna, V., Zaki, M. S., Abdel-Salam, G. H. et al. (2012). Exome sequencing can improve diagnosis and alter patient management. *Sci. Transl. Med.* **4**, 138ra78. doi:10.1126/scitranslmed.3003544
- Dowling, J. J., Vreede, A. P., Low, S. E., Gibbs, E. M., Kuwada, J. Y., Bonnemann, C. G. and Feldman, E. L. (2009). Loss of myotubularin function results in T-tubule disorganization in zebrafish and human myotubular myopathy. *PLoS Genet.* **5**, e1000372. doi:10.1371/journal.pgen.1000372
- Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K. and Sadelain, M. (2018). Gene therapy comes of age. *Science* **359**, eaan4672. doi:10.1126/science.aan4672
- Dupuis, N., Lebon, S., Kumar, M., Drunat, S., Graul-Neumann, L. M., Gressens, P. and El Ghouzzi, V. (2013). A novel RAB33B mutation in smith-McCort dysplasia. *Hum. Mutat.* **34**, 283-286. doi:10.1002/humu.22235
- Edvardson, S., Cinnamon, Y., Ta-Shma, A., Shaag, A., Yim, Y.-I., Zenvirt, S., Jalas, C., Lesage, S., Brice, A., Taraboulos, A. et al. (2012). A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. *PLoS ONE* **7**, e36458. doi:10.1371/journal.pone.0036458
- Edvardson, S., Gerhard, F., Jalas, C., Lachmann, J., Golan, D., Saada, A., Shaag, A., Ungermann, C. and Elpeleg, O. (2015). Hypomyelination and developmental delay associated with VPS11 mutation in Ashkenazi Jewish patients. *J. Med. Genet.* **52**, 749-753. doi:10.1136/jmedgenet-2015-103239
- Eichelbaum, K., Winter, M., Berriel Diaz, M., Herzig, S. and Krijgsveld, J. (2012). Selective enrichment of newly synthesized proteins for quantitative secretome analysis. *Nat. Biotechnol.* **30**, 984-990. doi:10.1038/nbt.2356
- Elliott, A. M., Simard, L. R., Coghlan, G., Chudley, A. E., Chodirker, B. N., Greenberg, C. R., Burch, T., Ly, V., Hatch, G. M. and Zelinski, T. (2013). A novel mutation in KIAA0196: identification of a gene involved in Ritscher-Schinzel/3C syndrome in a First Nations cohort. *J. Med. Genet.* **50**, 819-822. doi:10.1136/jmedgenet-2013-101715
- Eymard-Pierre, E., Lesca, G., Dollet, S., Santorelli, F. M., di Capua, M., Bertini, E. and Boespflug-Tanguy, O. (2002). Infantile-onset ascending hereditary spastic paralysis is associated with mutations in the alsin gene. *Am. J. Hum. Genet.* **71**, 518-527. doi:10.1086/342359
- Fabrizi, G. M., Ferrarini, M., Cavallaro, T., Cabrini, I., Cerini, R., Bertolasi, L. and Rizzuto, N. (2007). Two novel mutations in dynamin-2 cause axonal Charcot-Marie-Tooth disease. *Neurology* **69**, 291-295. doi:10.1212/01.wnl.0000265820.51075.61
- Farazi Fard, M. A., Rebelo, A. P., Buglo, E., Nemat, H., Dastsooz, H., Gehweiler, I., Reich, S., Reichbauer, J., Quintans, B., Ordóñez-Ugalde, A. et al. (2019). Truncating mutations in UBAP1 cause hereditary spastic paraplegia. *Am. J. Hum. Genet.* **104**, 767-773. doi:10.1016/j.ajhg.2019.03.001
- Farber-Katz, S. E., Dippold, H. C., Buschman, M. D., Peterman, M. C., Xing, M., Noakes, C. J., Tat, J., Ng, M. M., Rahajeng, J., Cowan, D. M. et al. (2014). DNA damage triggers Golgi dispersal via DNA-PK and GOLPH3. *Cell* **156**, 413-427. doi:10.1016/j.cell.2013.12.023
- Fassio, A., Patry, L., Congia, S., Onofri, F., Piton, A., Gauthier, J., Pozzi, D., Messa, M., Defranchi, E., Fadda, M. et al. (2011). SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function. *Hum. Mol. Genet.* **20**, 2297-2307. doi:10.1093/hmg/ddr122
- Feinstein, M., Flusser, H., Lerman-Sagie, T., Ben-Zeev, B., Lev, D., Agamy, O., Cohen, I., Kadir, R., Sivan, S., Leshinsky-Silver, E. et al. (2014). VPS53 mutations cause progressive cerebello-cerebral atrophy type 2 (PCCA2). *J. Med. Genet.* **51**, 303-308. doi:10.1136/jmedgenet-2013-101823
- Feldmann, J., Callebaut, I., Raposo, G., Certain, S., Bacq, D., Dumont, C., Lambert, N., Ouachée-Chardin, M., Chedeville, G., Tamary, H. et al. (2003). Munc13-4 is essential for cytotylic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). *Cell* **115**, 461-473. doi:10.1016/S0092-8674(03)00855-9
- Feng, S., Sekine, S., Pessino, V., Li, H., Leonetti, M. D. and Huang, B. (2017). Improved split fluorescent proteins for endogenous protein labeling. *Nat. Commun.* **8**, 370. doi:10.1038/s41467-017-00494-8
- Ferrari, R., Kapogiannis, D., Huey, E. D. and Momeni, P. (2011). FTD and ALS: a tale of two diseases. *Curr. Alzheimer Res.* **8**, 273-294. doi:10.2174/156720511795563700
- Ferreira, C. R., Xia, Z.-J., Clément, A., Parry, D. A., Davids, M., Taylan, F., Sharma, P., Turgeon, C. T., Blanco-Sánchez, B., Ng, B. G. et al. (2018). A recurrent de novo heterozygous COG4 substitution leads to saul-wilson syndrome, disrupted vesicular trafficking, and altered proteoglycan glycosylation. *Am. J. Hum. Genet.* **103**, 553-567. doi:10.1016/j.ajhg.2018.09.003
- Fisher, P. and Ungar, D. (2016). Bridging the gap between glycosylation and vesicle traffic. *Front. Cell Dev. Biol.* **4**, 15. doi:10.3389/fcell.2016.00015
- FitzGerald, G., Botstein, D., Califf, R., Collins, R., Peters, K., Van Bruggen, N. and Rader, D. (2018). The future of humans as model organisms. *Science* **361**, 552-553. doi:10.1126/science.aau7779
- Follit, J. A., San Agustín, J. T., Xu, F., Jonassen, J. A., Samtani, R., Lo, C. W. and Pazour, G. J. (2008). The Golgin GMAP210/TRIP11 anchors IFT20 to the Golgi complex. *PLoS Genet.* **4**, e1000315. doi:10.1371/journal.pgen.1000315
- Foulquier, F., Vasile, E., Schollen, E., Callewaert, N., Raemaekers, T., Quelhas, D., Jaeken, J., Mills, P., Winchester, B., Krieger, M. et al. (2006). Conserved oligomeric Golgi complex subunit 1 deficiency reveals a previously uncharacterized congenital disorder of glycosylation type II. *Proc. Natl. Acad. Sci. USA* **103**, 3764-3769. doi:10.1073/pnas.0507685103
- Foulquier, F., Ungar, D., Reynders, E., Zeevaert, R., Mills, P., Garcia-Silva, M. T., Briones, P., Winchester, B., Morelle, W., Krieger, M. et al. (2007). A new inborn error of glycosylation due to a Cog8 deficiency reveals a critical role for the Cog1-Cog8 interaction in COG complex formation. *Hum. Mol. Genet.* **16**, 717-730. doi:10.1093/hmg/ddl476
- Fumagalli, M., Camus, S. M., Diekmann, Y., Burke, A., Camus, M. D., Norman, P. J., Joseph, A., Abi-Rached, L., Benazzo, A., Rasteiro, R. et al. (2019). Genetic diversity of CHC22 clathrin impacts its function in glucose metabolism. *Elife* **8**, e41517. doi:10.7554/eLife.41517.028
- Garbes, L., Kim, K., Riess, A., Hoyer-Kuhn, H., Beleggia, F., Bevot, A., Kim, M. J., Huh, Y. H., Kweon, H. S., Savarirayan, R. et al. (2015). Mutations in SEC24D, encoding a component of the COPII machinery, cause a syndromic form of osteogenesis imperfecta. *Am. J. Hum. Genet.* **96**, 432-439. doi:10.1016/j.ajhg.2015.01.002
- Garcia, C. K., Wilund, K., Arca, M., Zuliani, G., Fellin, R., Maioli, M., Calandra, S., Bertolini, S., Cossu, F., Grishin, N. et al. (2001). Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* **292**, 1394-1398. doi:10.1126/science.1060458
- Garcia, C. C., Blair, H. J., Seager, M., Coulthard, A., Tennant, S., Buddles, M., Curtis, A. and Goodship, J. A. (2004). Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. *J. Med. Genet.* **41**, 183-186. doi:10.1136/jmg.2003.013680
- Ge, X., Gong, H., Dumas, K., Litwin, J., Phillips, J. J., Waisfisz, Q., Weiss, M. M., Hendriks, Y., Stuurman, K. E., Nelson, S. F. et al. (2016). Missense-depleted regions in population exomes implicate ras superfamily nucleotide-binding protein alteration in patients with brain malformation. *NPJ Genom. Med.* **1**, 16036. doi:10.1038/npjgenmed.2016.36
- Gedeon, A. K., Colley, A., Jamieson, R., Thompson, E. M., Rogers, J., Sillence, D., Tiller, G. E., Mulley, J. C. and Géczy, J. (1999). Identification of the gene (SEDL) causing X-linked spondyloepiphyseal dysplasia tarda. *Nat. Genet.* **22**, 400-404. doi:10.1038/11976
- Gershlick, D. C., Ishida, M., Jones, J. R., Bellomo, A., Bonifacino, J. S. and Everman, D. B. (2019). A neurodevelopmental disorder caused by mutations in the VPS51 subunit of the GARP and EARP complexes. *Hum. Mol. Genet.* **28**, 1548-1560. doi:10.1093/hmg/ddy423
- Gholam, C., Grigoriadou, S., Gilmour, K. C. and Gaspar, H. B. (2011). Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin. Exp. Immunol.* **163**, 271-283. doi:10.1111/j.1365-2249.2010.04302.x
- Giannandrea, M., Bianchi, V., Mignogna, M. L., Sirri, A., Carrabino, S., D'Elia, E., Vecellio, M., Russo, S., Cogliati, F., Larizza, L. et al. (2010). Mutations in the small GTPase gene RAB39B are responsible for X-linked mental retardation associated with autism, epilepsy, and macrocephaly. *Am. J. Hum. Genet.* **86**, 185-195. doi:10.1016/j.ajhg.2010.01.011
- Gil-Krzewska, A., Wood, S. M., Murakami, Y., Nguyen, V., Chiang, S. C. C., Cullinane, A. R., Peruzzi, G., Gahl, W. A., Coligan, J. E., Introne, W. J. et al. (2016). Chediak-Higashi syndrome: Lysosomal trafficking regulator domains regulate exocytosis of lytic granules but not cytokine secretion by natural killer cells. *J. Allergy Clin. Immunol.* **137**, 1165-1177. doi:10.1016/j.jaci.2015.08.039
- Gissen, P., Johnson, C. A., Morgan, N. V., Stapelbroek, J. M., Forshe, T., Cooper, W. N., McKiernan, P. J., Klomp, L. W. J., Morris, A. A. M., Wraith, J. E. et al. (2004). Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogyrosis-renal dysfunction-cholestasis (ARC) syndrome. *Nat. Genet.* **36**, 400-404. doi:10.1038/ng1325
- Goldenring, J. R. (2015). Recycling endosomes. *Curr. Opin. Cell Biol.* **35**, 117-122. doi:10.1016/j.cob.2015.04.018
- Gomez, R. C., Wawro, P., Lis, P., Alessi, D. R. and Pfeffer, S. R. (2019). Membrane association but not identity is required for LRRK2 activation and phosphorylation of Rab GTPases. *J. Cell Biol.* **218**, 4157-4170. doi:10.1083/jcb.201902184
- Guelly, C., Zhu, P.-P., Leonardis, L., Papić, L., Zidar, J., Schabhüttl, M., Strohmaier, H., Weis, J., Strom, T. M., Baets, J. et al. (2011). Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. *Am. J. Hum. Genet.* **88**, 99-105. doi:10.1016/j.ajhg.2010.12.003
- Gustavsson, E. K., Guella, I., Trinh, J., Szu-Tu, C., Rajput, A., Rajput, A. H., Steele, J. C., McKeown, M., Jeon, B. S., Aasly, J. O. et al. (2015). Genetic variability of the retromer cargo recognition complex in parkinsonism. *Mov. Disord.* **30**, 580-584. doi:10.1002/mds.26104
- Haack, T. B., Stauffer, C., Köpke, M. G., Straub, B. K., Kölker, S., Thiel, C., Freisinger, P., Baric, I., McKiernan, P. J., Dikow, N. et al. (2015). Biallelic mutations in NBAS cause recurrent acute liver failure with onset in infancy. *Am. J. Hum. Genet.* **97**, 163-169. doi:10.1016/j.ajhg.2015.05.009
- Hadano, S., Hand, C. K., Osuga, H., Yanagisawa, Y., Otomo, A., Devon, R. S., Miyamoto, N., Showguchi-Miyata, J., Okada, Y., Singaraja, R. et al. (2001). A

- gene encoding a putative GTPase regulator is mutated in familial amyotrophic lateral sclerosis 2. *Nat. Genet.* **29**, 166-173. doi:10.1038/ng1001-166
- Hady-Cohen, R., Ben-Pazi, H., Adir, V., Yosovich, K., Blumkin, L., Lerman-Sagie, T. and Lev, D.** (2018). Progressive cerebello-cerebral atrophy and progressive encephalopathy with edema, hypsarrhythmia and optic atrophy may be allelic syndromes. *Eur. J. Paediatr. Neurol.* **22**, 1133-1138. doi:10.1016/j.ejpn.2018.07.003
- Halperin, D., Kadir, R., Perez, Y., Drabkin, M., Yogev, Y., Wormser, O., Berman, E. M., Eremenko, E., Rotblat, B., Shorer, Z. et al.** (2019). SEC31A mutation affects ER homeostasis, causing a neurological syndrome. *J. Med. Genet.* **56**, 139-148. doi:10.1136/jmedgenet-2018-105503
- Han, C., Alkhatir, R., Froukh, T., Minassian, A. G., Galati, M., Liu, R. H., Fotouhi, M., Sommerfeld, J., Albrook, A. J., Marshall, C. et al.** (2016). Epileptic encephalopathy caused by mutations in the guanine nucleotide exchange factor DENND5A. *Am. J. Hum. Genet.* **99**, 1359-1367. doi:10.1016/j.ajhg.2016.10.006
- Hanein, S., Martin, E., Boukhris, A., Byrne, P., Goizet, C., Hamri, A., Benomar, A., Lossos, A., Denora, P., Fernandez, J. et al.** (2008). Identification of the SPG15 gene, encoding spastizin, as a frequent cause of complicated autosomal-recessive spastic paraplegia, including Kjellin syndrome. *Am. J. Hum. Genet.* **82**, 992-1002. doi:10.1016/j.ajhg.2008.03.004
- Hardies, K., May, P., Djemie, T., Tarta-Arsene, O., Deconinck, T., Craiu, D., AR working group of the EuroEPINOMICS RES Consortium, Helbig, I., Suls, A., Balling, R. et al.** (2015). Recessive loss-of-function mutations in AP4S1 cause mild fever-sensitive seizures, developmental delay and spastic paraplegia through loss of AP-4 complex assembly. *Hum. Mol. Genet.* **24**, 2218-2227. doi:10.1093/hmg/ddu740
- Hardies, K., Cai, Y., Jardel, C., Jansen, A. C., Cao, M., May, P., Djemie, T., Hachon Le Camus, C., Keymolen, K., Deconinck, T., (2016).** Loss of SYNJ1 dual phosphatase activity leads to early onset refractory seizures and progressive neurological decline. *Brain* **139**, 2420-2430. doi:10.1093/brain/aww180
- Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E. M., Logroscino, G., Robberecht, W., Shaw, P. J., Simmons, Z. and van den Berg, L. H.** (2017). Amyotrophic lateral sclerosis. *Nat. Rev. Dis. Primers* **3**, 17071. doi:10.1038/nrdp.2017.71
- Harlalka, G. V., McEntagart, M. E., Gupta, N., Skrzypiec, A. E., Mucha, M. W., Chioza, B. A., Simpson, M. A., Sreekantan-Nair, A., Pereira, A., Günther, S. et al.** (2016). Novel genetic, clinical, and pathomechanistic insights into TFG-associated hereditary spastic paraplegia. *Hum. Mutat.* **37**, 1157-1161. doi:10.1002/humu.23060
- Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., Pahwa, J. S., Moskvin, V., Dowzell, K., Williams, A. et al.** (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet.* **41**, 1088-1093. doi:10.1038/ng.440
- Harripaul, R., Vasli, N., Mikhailov, A., Rafiq, M. A., Mittal, K., Windpassinger, C., Sheikh, T. I., Noor, A., Mahmood, H., Downey, S. et al.** (2018). Mapping autosomal recessive intellectual disability: combined microarray and exome sequencing identifies 26 novel candidate genes in 192 consanguineous families. *Mol. Psychiatry* **23**, 973-984. doi:10.1038/mp.2017.60
- Hazan, J., Fonknechten, N., Mavel, D., Paternotte, C., Samson, D., Artiguenave, F., Davoine, C. S., Craud, C., Durr, A., Wincker, P. et al.** (1999). Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. *Nat. Genet.* **23**, 296-303. doi:10.1038/15472
- He, G., Gupta, S., Yi, M., Michaely, P., Hobbs, H. H. and Cohen, J. C.** (2002). ARH is a modular adaptor protein that interacts with the LDL receptor, clathrin, and AP-2. *J. Biol. Chem.* **277**, 44044-44049. doi:10.1074/jbc.M208539200
- Helbig, I., Lopez-Hernandez, T., Shor, O., Galer, P., Ganesan, S., Pendiwiat, M., Rademacher, A., Ellis, C. A., Humper, N., Schwarz, N. et al.** (2019). A recurrent missense variant in AP2M1 impairs clathrin-mediated endocytosis and causes developmental and epileptic encephalopathy. *Am. J. Hum. Genet.* **104**, 1060-1072. doi:10.1016/j.ajhg.2019.04.001
- Hennies, H. C., Kornak, U., Zhang, H., Egerer, J., Zhang, X., Seifert, W., Kühnisch, J., Budde, B., Nätebus, M., Brancati, F. et al.** (2008). Geroderma osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting coiled-coil. *Nat. Genet.* **40**, 1410-1412. doi:10.1038/ng.252
- Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., Abraham, R., Hamshere, M. L., Pahwa, J. S., Moskvin, V. et al.** (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat. Genet.* **43**, 429-435. doi:10.1038/ng.803
- Hoopes, R. R., Jr, Shrimpton, A. E., Knohl, S. J., Hueber, P., Hoppe, B., Matyus, J., Simckes, A., Tasic, V., Toenshoff, B., Suchy, S. F. et al.** (2005). Dent Disease with mutations in OCLRL1. *Am. J. Hum. Genet.* **76**, 260-267. doi:10.1086/427887
- Hsiao, Y.-C., Tuz, K. and Ferland, R. J.** (2012). Trafficking in and to the primary cilium. *Cilia* **1**, 4. doi:10.1186/2046-2530-1-4
- Hu, X., Pickering, E., Liu, Y. C., Hall, S., Fournier, H., Katz, E., Dechairo, B., John, S., Van Eerdewegh, P., Soares, H. et al.** (2011). Meta-analysis for genome-wide association study identifies multiple variants at the BIN1 locus associated with late-onset Alzheimer's disease. *PLoS ONE* **6**, e16616. doi:10.1371/journal.pone.0016616
- Huizing, M., Helip-Wooley, A., Westbroek, W., Gunay-Aygun, M. and Gahl, W. A.** (2008). Disorders of lysosome-related organelle biogenesis: clinical and molecular genetics. *Annu. Rev. Genomics Hum. Genet.* **9**, 359-386. doi:10.1146/annurev.genom.9.081307.164303
- Hung, V., Udeshi, N. D., Lam, S. S., Loh, K. H., Cox, K. J., Pedram, K., Carr, S. A. and Ting, A. Y.** (2016). Spatially resolved proteomic mapping in living cells with the engineered peroxidase APEX2. *Nat. Protoc.* **11**, 456-475. doi:10.1038/nprot.2016.018
- Illa, I., Serrano-Munuera, C., Gallardo, E., Lasa, A., Rojas-Garcia, R., Palmer, J., Gallano, P., Baiget, M., Matsuda, C. and Brown, R. H.** (2001). Distal anterior compartment myopathy: a dysferlin mutation causing a new muscular dystrophy phenotype. *Ann. Neurol.* **49**, 130-134. doi:10.1002/AID-ANA22>3.0.CO;2-0
- Inoue, K. and Ishibe, S.** (2015). Podocyte endocytosis in the regulation of the glomerular filtration barrier. *Am. J. Physiol. Renal. Physiol.* **309**, F398-F405. doi:10.1152/ajprenal.00136.2015
- Isaji, T., Im, S., Gu, W., Wang, Y., Hang, Q., Lu, J., Fukuda, T., Hashii, N., Takakura, D., Kawasaki, N. et al.** (2014). An oncogenic protein Golgi phosphoprotein 3 up-regulates cell migration via sialylation. *J. Biol. Chem.* **289**, 20694-20705. doi:10.1074/jbc.M113.542688
- Ishiuira, H., Sako, W., Yoshida, M., Kawarai, T., Tanabe, O., Goto, J., Takahashi, Y., Date, H., Mitsui, J., Ahsan, B. et al.** (2012). The TRK-fused gene is mutated in hereditary motor and sensory neuropathy with proximal dominant involvement. *Am. J. Hum. Genet.* **91**, 320-329. doi:10.1016/j.ajhg.2012.07.014
- Ivanova, E. A., De Leo, M. G., Van Den Heuvel, L., Pastore, A., Dijkman, H., De Matteis, M. A. and Levtschenko, E. N.** (2015). Endo-lysosomal dysfunction in human proximal tubular epithelial cells deficient for lysosomal cystine transporter cystinosin. *PLoS ONE* **10**, e0120998. doi:10.1371/journal.pone.0120998
- Ivanova, E. L., Mau-Them, F. T., Riazuddin, S., Kahrizi, K., Laugel, V., Schaefer, E., de Saint Martin, A., Runge, K., Iqbal, S., Spitz, M.-A. et al.** (2017). Homozygous truncating variants in TBC1D23 cause pontocerebellar hypoplasia and alter cortical development. *Am. J. Hum. Genet.* **101**, 428-440. doi:10.1016/j.ajhg.2017.07.010
- Izumi, K., Brett, M., Nishi, E., Drunat, S., Tan, E.-S., Fujiki, K., Lebon, S., Cham, B., Masuda, K., Arakawa, M. et al.** (2016). ARCN1 mutations cause a recognizable craniofacial syndrome due to COPI-mediated transport defects. *Am. J. Hum. Genet.* **99**, 451-459. doi:10.1016/j.ajhg.2016.06.011
- Jensen, D. and Schekman, R.** (2011). COP11-mediated vesicle formation at a glance. *J. Cell Sci.* **124**, 1-4. doi:10.1242/jcs.069773
- Jiang, Y., Ou, Y. and Cheng, X.** (2013). Role of TSG101 in cancer. *Front. Biosci. (Landmark Ed)* **18**, 279-288. doi:10.2741/4176
- Johnson, A. D. and O'Donnell, C. J.** (2009). An open access database of genome-wide association results. *BMC Med. Genet.* **10**, 6. doi:10.1186/1471-2350-10-6
- Jones, B., Jones, E. L., Bonney, S. A., Patel, H. N., Mensenkamp, A. R., Eichenbaum-Voline, S., Rudling, M., Myrdal, U., Annesi, G., Naik, S. et al.** (2003). Mutations in a Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders. *Nat. Genet.* **34**, 29-31. doi:10.1038/ng1145
- Joshi, G. and Wang, Y.** (2015). Golgi defects enhance APP amyloidogenic processing in Alzheimer's disease. *BioEssays* **37**, 240-247. doi:10.1002/bies.201400116
- Josifova, D.** (2007). RAB23 mutations in carpenter syndrome imply an unexpected role for hedgehog signaling in cranial-suture development and obesity (vol 80, pg 1162, 2007). *Am. J. Hum. Genet.* **81**, 1114-1114. doi:10.1086/522891
- Jun, G., Naj, A. C., Beecham, G. W., Wang, L. S., Buros, J., Gallins, P. J., Buxbaum, J. D., Ertekin-Taner, N., Fallin, M. D., Friedland, R. et al.** (2010). Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch. Neurol.* **67**, 1473-1484. doi:10.1001/archneurol.2010.201
- Karim, M. A., Suzuki, K., Fukai, K., Oh, J., Nagle, D. L., Moore, K. J., Barbosa, E., Falik-Borenstein, T., Filipovich, A., Ishida, Y. et al.** (2002). Apparent genotype-phenotype correlation in childhood, adolescent, and adult Chediak-Higashi syndrome. *Am. J. Med. Genet.* **108**, 16-22. doi:10.1002/ajmg.10184
- Kato, K., Oka, Y., Muramatsu, H., Vasilev, F. F., Otomo, T., Oishi, H., Kawano, Y., Kidokoro, H., Nakazawa, Y., Ogi, T. et al.** (2019). Biallelic VPS35L pathogenic variants cause 3C/Ritscher-Schinzel-like syndrome through dysfunction of retriever complex. *J. Med. Genet.* **57**, 245-253. doi:10.1136/jmedgenet-2019-106213
- Khoriaty, R., Hesketh, G. G., Bernard, A., Weyand, A. C., Mellacheruvu, D., Zhu, G., Hoenerhoff, M. J., McGee, B., Everett, L., Adams, E. J. et al.** (2018). Functions of the COPII gene paralogs SEC23A and SEC23B are interchangeable in vivo. *Proc. Natl. Acad. Sci. USA* **115**, E7748-E7757. doi:10.1073/pnas.1805784115
- Kim, J. M., Wu, H., Green, G., Winkler, C. A., Kopp, J. B., Miner, J. H., Unanue, E. R. and Shaw, A. S.** (2003). CD2-associated protein haploinsufficiency is linked to glomerular disease susceptibility. *Science* **300**, 1298-1300. doi:10.1126/science.1081068
- Klinkert, K. and Echard, A.** (2016). Rab35 GTPase: a central regulator of phosphoinositides and F-actin in endocytic recycling and beyond. *Traffic* **17**, 1063-1077. doi:10.1111/tra.12422
- Kodera, H., Ando, N., Yuasa, I., Wada, Y., Tsurusaki, Y., Nakashima, M., Miyake, N., Saitoh, S., Matsumoto, N. and Saito, H.** (2015). Mutations in COG2

- encoding a subunit of the conserved oligomeric golgi complex cause a congenital disorder of glycosylation. *Clin. Genet.* **87**, 455-460. doi:10.1111/cge.12417
- Kondo, H., Maksimova, N., Otomo, T., Kato, H., Imai, A., Asano, Y., Kobayashi, K., Nojima, S., Nakaya, A., Hamada, Y. et al. (2017). Mutation in VPS33A affects metabolism of glycosaminoglycans: a new type of mucopolysaccharidosis with severe systemic symptoms. *Hum. Mol. Genet.* **26**, 173-183. doi:10.1093/hmg/ddw377
- Korpal, M., Eli, B. J., Buffa, F. M., Ibrahim, T., Blanco, M. A., Celià-Terrassa, T., Mercatali, L., Khan, Z., Goodarzi, H., Hua, Y. et al. (2011). Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. *Nat. Med.* **17**, 1101-1108. doi:10.1038/nm.2401
- Koutsopoulos, O. S., Kretz, C., Weller, C. M., Roux, A., Mojzisova, H., Böhm, J., Koch, C., Toussaint, A., Heckel, E., Stemkens, D. et al. (2013). Dynamin 2 homozygous mutation in humans with a lethal congenital syndrome. *Eur. J. Hum. Genet.* **21**, 637-642. doi:10.1038/ejhg.2012.226
- Kranz, C., Ng, B. G., Sun, L., Sharma, V., Eklund, E. A., Miura, Y., Ungar, D., Lupashin, V., Winkel, R. D., Cipollo, J. F. et al. (2007). COG8 deficiency causes new congenital disorder of glycosylation type IIh. *Hum. Mol. Genet.* **16**, 731-741. doi:10.1093/hmg/ddm028
- Krebs, C. E., Karkheiran, S., Powell, J. C., Cao, M., Makarov, V., Darvish, H., Di Paolo, G., Walker, R. H., Shahidi, G. A., Buxbaum, J. D. et al. (2013). The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. *Hum. Mutat.* **34**, 1200-1207. doi:10.1002/humu.22372
- Kreis, T. E. and Lodish, H. F. (1986). Oligomerization is essential for transport of vesicular stomatitis viral glycoprotein to the cell surface. *Cell* **46**, 929-937. doi:10.1016/0092-8674(86)90075-9
- Kuismanen, E. and Saraste, J. (1989). Low temperature-induced transport blocks as tools to manipulate membrane traffic. *Methods Cell Biol.* **32**, 257-274. doi:10.1016/S0091-679X(08)61174-7
- Lamers, I. J. C., Reijnders, M. R. F., Venselaar, H., Kraus, A., Jansen, S., de Vries, B. B. A., Houge, G., Gradek, G. A., Seo, J., Choi, M. et al. (2017). Recurrent De Novo mutations disturbing the GTP/GDP binding pocket of RAB11B cause intellectual disability and a distinctive brain phenotype. *Am. J. Hum. Genet.* **101**, 824-832. doi:10.1016/j.ajhg.2017.09.015
- Lancaster, M. A. and Hutch, M. (2019). Disease modelling in human organoids. *Dis. Model. Mech.* **12**, dmm039347. doi:10.1242/dmm.039347
- Laporte, J., Biancalana, V., Tanner, S. M., Kress, W., Schneider, V., Wallgren-Pettersson, C., Herger, F., Buj-Bello, A., Blondeau, F., Liechti-Gallati, S. et al. (2000). MTM1 mutations in X-linked myotubular myopathy. *Hum. Mutat.* **15**, 393-409. doi:10.1002/(SICI)1098-1004(200005)15:5<393::AID-HUMU1>3.0.CO;2-R
- Larson, A. A., Baker, P. R., II, Milev, M. P., Press, C. A., Sokol, R. J., Cox, M. O., Lekostaj, J. K., Stence, A. A., Bossler, A. D., Mueller, J. M. et al. (2018). TRAPPC11 and GOSR2 mutations associate with hypoglycosylation of alpha-dystroglycan and muscular dystrophy. *Skelet Muscle* **8**, 17. doi:10.1186/s13395-018-0163-0
- Lee, E., Marcucci, M., Daniell, L., Pypaert, M., Weisz, O. A., Ochoa, G. C., Farsad, K., Wenk, M. R. and De Camilli, P. (2002). Amphiphysin 2 (Bin1) and T-tubule biogenesis in muscle. *Science* **297**, 1193-1196. doi:10.1126/science.1071362
- Lee, H. J., Song, J. Y., Kim, J. W., Jin, S.-Y., Hong, M. S., Park, J. K., Chung, J.-H., Shibata, H. and Fukumaki, Y. (2005). Association study of polymorphisms in synaptic vesicle-associated genes, SYN2 and CPLX2, with schizophrenia. *Behav. Brain Funct.* **1**, 15. doi:10.1186/1744-9081-1-15
- Lek, A., Evesson, F. J., Sutton, R. B., North, K. N. and Cooper, S. T. (2012). Ferlins: regulators of vesicle fusion for auditory neurotransmission, receptor trafficking and membrane repair. *Traffic* **13**, 185-194. doi:10.1111/j.1600-0854.2011.01267.x
- Lemos, R. R., Oliveira, D. F., Zatz, M. and Oliveira, J. R. M. (2011). Population and computational analysis of the MGEA6 P521A variation as a risk factor for familial idiopathic basal ganglia calcification (Fahr's Disease). *J. Mol. Neurosci.* **43**, 333-336. doi:10.1007/s12031-010-9445-7
- Lenk, G. M., Szymanska, K., Debska-Vielhaber, G., Ryzanicz, M., Walczak, A., Bekiesinska-Figatowska, M., Vielhaber, S., Hallmann, K., Stawinski, P., Buehring, S. et al. (2016). Biallelic mutations of VAC14 in pediatric-onset neurological disease. *Am. J. Hum. Genet.* **99**, 188-194. doi:10.1016/j.ajhg.2016.05.008
- Lenz, D., McClean, P., Kansu, A., Bonnen, P. E., Ranucci, G., Thiel, C., Straub, B. K., Harting, I., Alhaddad, B., Dimitrov, B. et al. (2018). SCYL1 variants cause a syndrome with low  $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN). *Genet. Med.* **20**, 1255-1265. doi:10.1038/gim.2017.260
- Lerner, T. J., Boustany, R. M. N., Anderson, J. W., Darigo, K. L., Schlumpf, K., Buckler, A. J., Gusella, J. F., Haines, J. L., Kremmidiotis, G., Lensink, I. L. et al. (1995). Isolation of a novel gene underlying batten-disease, CLN3. *Cell* **82**, 949-957. doi:10.1016/0092-8674(95)90274-0
- Li, L. and Cohen, S. N. (1996). Tsg101: a novel tumor susceptibility gene isolated by controlled homozygous functional knockout of allelic loci in mammalian cells. *Cell* **85**, 319-329. doi:10.1016/S0092-8674(00)81111-3
- Li, W., Zhang, Q., Oiso, N., Novak, E. K., Gautam, R., O'Brien, E. P., Tinsley, C. L., Blake, D. J., Spritz, R. A., Copeland, N. G. et al. (2003). Hermansky-Pudlak syndrome type 7 (HPS-7) results from mutant dysbindin, a member of the biogenesis of lysosome-related organelles complex 1 (BLOC-1). *Nat. Genet.* **35**, 84-89. doi:10.1038/ng1229
- Li, N., Nakamura, K., Jiang, Y., Tsurui, H., Matsuoka, S., Abe, M., Ohtsui, M., Nishimura, H., Kato, K., Kawai, T. et al. (2004). Gain-of-function polymorphism in mouse and human Ltk: implications for the pathogenesis of systemic lupus erythematosus. *Hum. Mol. Genet.* **13**, 171-179. doi:10.1093/hmg/ddh020
- Li, S., Tiab, L., Jiao, X., Munier, F. L., Zografos, L., Frueh, B. E., Sergeev, Y., Smith, J., Rubin, B., Meallet, M. A. et al. (2005). Mutations in PIP5K3 are associated with Francois-Neetens mouchetee fleck corneal dystrophy. *Am. J. Hum. Genet.* **77**, 54-63. doi:10.1086/431346
- Liegel, R. P., Handley, M. T., Ronchetti, A., Brown, S., Langemeyer, L., Linford, A., Chang, B., Morris-Rosendahl, D. J., Carpanini, S., Posmyk, R. et al. (2013). Loss-of-function mutations in TBC1 D20 cause cataracts and male infertility in blind sterile mice and warburg micro syndrome in humans. *Am. J. Hum. Genet.* **93**, 1001-1014. doi:10.1016/j.ajhg.2013.10.011
- Lines, M. A., Ito, Y., Kernohan, K. D., Mears, W., Hurteau-Miller, J., Venkateswaran, S., Ward, L., Khatchadourian, K., McClintock, J., Bhola, P. et al. (2017). Yunis-Varon syndrome caused by biallelic VAC14 mutations. *Eur. J. Hum. Genet.* **25**, 1049-1054. doi:10.1038/ejhg.2017.99
- Liu, J., Aoki, M., Ila, I., Wu, C., Fardeau, M., Angelini, C., Serrano, C., Urtizberea, J. A., Hentati, F., Hamida, M. B. et al. (1998). Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi myopathy and limb girdle muscular dystrophy. *Nat. Genet.* **20**, 31-36. doi:10.1038/1682
- Lloyd, S. E., Pearce, S. H., Fisher, S. E., Steinmeyer, K., Schwappach, B., Scheinman, S. J., Harding, B., Bolino, A., Devoto, M., Goodyer, P. et al. (1996). A common molecular basis for three inherited kidney stone diseases. *Nature* **379**, 445-449. doi:10.1038/379445a0
- Lopes, F., Barbosa, M., Ameur, A., Soares, G., de Sá, J., Dias, A. I., Oliveira, G., Cabral, P., Temudo, T., Calado, E. et al. (2016). Identification of novel genetic causes of Rett syndrome-like phenotypes. *J. Med. Genet.* **53**, 190-199. doi:10.1136/jmedgenet-2015-103568
- Lu, Q., Hope, L. W., Brasch, M., Reinhard, C. and Cohen, S. N. (2003). TSG101 interaction with HRS mediates endosomal trafficking and receptor down-regulation. *Proc. Natl. Acad. Sci. USA* **100**, 7626-7631. doi:10.1073/pnas.0932599100
- Lubbehun, J., Thiel, C., Rind, N., Ungar, D., Prinsen, B. H. C. M. T., de Koning, T. J., van Hasselt, P. M. and Korner, C. (2010). Fatal outcome due to deficiency of subunit 6 of the conserved oligomeric Golgi complex leading to a new type of congenital disorders of glycosylation. *Hum. Mol. Genet.* **19**, 3623-3633. doi:10.1093/hmg/ddq278
- Luo, M. L., Gong, C., Chen, C. H., Hu, H., Huang, P., Zheng, M., Yao, Y., Wei, S., Wulf, G., Lieberman, J. et al. (2015). The Rab2A GTPase promotes breast cancer stem cells and tumorigenesis via Erk signaling activation. *Cell Rep* **11**, 111-124. doi:10.1016/j.celrep.2015.03.002
- Lupski, J. R., Reid, J. G., Gonzaga-Jauregui, C., Rio Deiros, D., Chen, D. C., Nazareth, L., Bainbridge, M., Dinh, H., Jing, C., Wheeler, D. A. et al. (2010). Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. *N. Engl. J. Med.* **362**, 1181-1191. doi:10.1056/NEJMoa0908094
- MacDonald, M. E., Ambrose, C. M., Duyao, M. P., Myers, R. H., Lin, C., Srinidhi, L., Barnes, G., Taylor, S. A., James, M., Groot, N. et al. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* **72**, 971-983. doi:10.1016/0092-8674(93)90585-E
- MacLeod, D. A., Rhinn, H., Kuwahara, T., Zolin, A., Di Paolo, G., McCabe, B. D., Marder, K. S., Honig, L. S., Clark, L. N., Small, S. A. et al. (2013). RAB7L1 interacts with LRRK2 to modify intraneuronal protein sorting and Parkinson's disease risk. *Neuron* **77**, 425-439. doi:10.1016/j.neuron.2012.11.033
- Maddirevula, S., Alzahrani, F., Al-Owain, M., Al Muhaizea, M. A., Kayyali, H. R., AlHashem, A., Rahbeeni, Z., Al-Otaibi, M., Alzaidan, H. I., Balobaid, A. et al. (2019). Autozygome and high throughput confirmation of disease genes candidacy. *Genet. Med.* **21**, 736-742. doi:10.1038/s41436-018-0138-x
- Maksimova, N., Hara, K., Nikolaeva, I., Chun-Feng, T., Usui, T., Takagi, M., Nishihira, Y., Miyashita, A., Fujiwara, H., Oyama, T. et al. (2010). Neuroblastoma amplified sequence gene is associated with a novel short stature syndrome characterised by optic nerve atrophy and Pelger-Huet anomaly. *J. Med. Genet.* **47**, 538-548. doi:10.1136/jmg.2009.074815
- Manteghi, S., Gingras, M. C., Kharitidi, D., Galarneau, L., Marques, M., Yan, M., Cencic, R., Robert, F., Paquet, M., Witcher, M. et al. (2016). Haploinsufficiency of the ESCRT component HD-PTP predisposes to cancer. *Cell Rep* **15**, 1893-1900. doi:10.1016/j.celrep.2016.04.076
- Marin-Valencia, I., Gerondopoulos, A., Zaki, M. S., Ben-Omran, T., Almureikhi, M., Demir, E., Guemez-Gamboa, A., Gregor, A., Issa, M. Y., Appelhof, B. et al. (2017). Homozygous mutations in TBC1D23 lead to a non-degenerative form of pontocerebellar hypoplasia. *Am. J. Hum. Genet.* **101**, 441-450. doi:10.1016/j.ajhg.2017.07.015
- Marin-Valencia, I., Novarino, G., Johansen, A., Rosti, B., Issa, M. Y., Musaev, D., Bhat, G., Scott, E., Silhavy, J. L., Stanley, V. et al. (2018). A homozygous founder mutation in TRAPPC6B associates with a neurodevelopmental disorder



- characterised by microcephaly, epilepsy and autistic features. *J. Med. Genet.* **55**, 48-54. doi:10.1136/jmedgenet-2017-104627
- Marks, M. S., Heijnen, H. F. and Raposo, G.** (2013). Lysosome-related organelles: unusual compartments become mainstream. *Curr. Opin. Cell Biol.* **25**, 495-505. doi:10.1016/j.ceb.2013.04.008
- Maruyama, H., Morino, H., Ito, H., Izumi, Y., Kato, H., Watanabe, Y., Kinoshita, Y., Kamada, M., Nodera, H., Suzuki, H. et al.** (2010). Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* **465**, 223-226. doi:10.1038/nature08971
- Mata, I. F., Jang, Y., Kim, C. H., Hanna, D. S., Dorschner, M. O., Samii, A., Agarwal, P., Roberts, J. W., Klepitskaya, O., Shprecher, D. R. et al.** (2015). The RAB39B p.G192R mutation causes X-linked dominant Parkinson's disease. *Mol. Neurodegener.* **10**, 50. doi:10.1186/s13024-015-0045-4
- Mattera, R., Park, S. Y., De Pace, R., Guardia, C. M. and Bonifacino, J. S.** (2017). AP-4 mediates export of ATG9A from the trans-Golgi network to promote autophagosome formation. *Proc. Natl. Acad. Sci. USA* **114**, E10697-E10706. doi:10.1073/pnas.1717327114
- Maurer, M. E. and Cooper, J. A.** (2006). The adaptor protein Dab2 sorts LDL receptors into coated pits independently of AP-2 and ARH. *J. Cell Sci.* **119**, 4235-4246. doi:10.1242/jcs.03217
- McCaughy, J. and Stephens, D. J.** (2018). COPII-dependent ER export in animal cells: adaptation and control for diverse cargo. *Histochem. Cell Biol.* **150**, 119-131. doi:10.1007/s00418-018-1689-2
- McMahon, H. T. and Boucrot, E.** (2011). Molecular mechanism and physiological functions of clathrin-mediated endocytosis. *Nat. Rev. Mol. Cell Biol.* **12**, 517-533. doi:10.1038/nrm3151
- Ménasché, G., Pastural, E., Feldmann, J., Certain, S., Ersoy, F., Dupuis, S., Wulffraat, N., Bianchi, D., Fischer, A., Le Deist, F. et al.** (2000). Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. *Nat. Genet.* **25**, 173-176. doi:10.1038/76024
- Mele, C., Iatropoulos, P., Donadelli, R., Calabria, A., Maranta, R., Cassis, P., Buelli, S., Tomasoni, S., Piras, R., Krendel, M. et al.** (2011). MYO1E mutations and childhood familial focal segmental glomerulosclerosis. *N. Engl. J. Med.* **365**, 295-306. doi:10.1056/NEJMoa1101273
- Mellman, I. and Yarden, Y.** (2013). Endocytosis and cancer. *Cold Spring Harb. Perspect. Biol.* **5**, a016949. doi:10.1101/cshperspect.a016949
- Ménasché, G., Ho, C. H., Sanal, O., Feldmann, J., Tezcan, I., Ersoy, F., Houdusse, A., Fischer, A. and de saint Basile, G.** (2003). Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *J. Clin. Investig.* **112**, 450-456. doi:10.1172/JCI200318264
- Mignogna, M. L., Giannandrea, M., Gurgone, A., Fanelli, F., Raimondi, F., Mapelli, L., Bassani, S., Fang, H., Van Anken, E., Alessio, M. et al.** (2015). The intellectual disability protein RAB39B selectively regulates GluA2 trafficking to determine synaptic AMPAR composition. *Nat. Commun.* **6**, 6504. doi:10.1038/ncomms7504
- Milev, M. P., Grout, M. E., Saint-Dic, D., Cheng, Y. H., Glass, I. A., Hale, C. J., Hanna, D. S., Dorschner, M. O., Prematilake, K., Shaag, A. et al.** (2017). Mutations in TRAPPC12 manifest in progressive childhood encephalopathy and golgi dysfunction. *Am. J. Hum. Genet.* **101**, 291-299. doi:10.1016/j.ajhg.2017.07.006
- Mir, A., Kaufman, L., Noor, A., Motazacker, M. M., Jamil, T., Azam, M., Kahrizi, K., Rafiq, M. A., Weksberg, R., Nasr, T. et al.** (2009). Identification of mutations in TRAPPC9, which encodes the NIK- and IKK- $\beta$ -binding protein, in nonsyndromic autosomal-recessive mental retardation. *Am. J. Hum. Genet.* **85**, 909-915. doi:10.1016/j.ajhg.2009.11.009
- Miranda, A. M., Herman, M., Cheng, R., Nahmani, E., Barrett, G., Micevska, E., Fontaine, G., Potier, M. C., Head, E., Schmitt, F. A. et al.** (2018). Excess synaptotagmin 1 contributes to place cell dysfunction and memory deficits in the aging hippocampus in three types of Alzheimer's disease. *Cell Rep* **23**, 2967-2975. doi:10.1016/j.celrep.2018.05.011
- Miura, Y., Tay, S. K., Aw, M. M., Eklund, E. A. and Freeze, H. H.** (2005). Clinical and biochemical characterization of a patient with congenital disorder of glycosylation (CDG) IIx. *J. Pediatr.* **147**, 851-853. doi:10.1016/j.jpeds.2005.07.038
- Mochida, G. H., Mahajnah, M., Hill, A. D., Basel-Vanagaite, L., Gleason, D., Hill, R. S., Bodell, A., Crosier, M., Straussberg, R. and Walsh, C. A.** (2009). A truncating mutation of TRAPPC9 is associated with autosomal-recessive intellectual disability and postnatal microcephaly. *Am. J. Hum. Genet.* **85**, 897-902. doi:10.1016/j.ajhg.2009.10.027
- Monis, W. J., Faundez, V. and Pazour, G. J.** (2017). BLOC-1 is required for selective membrane protein trafficking from endosomes to primary cilia. *J. Cell Biol.* **216**, 2131-2150. doi:10.1083/jcb.201611138
- Montecchiani, C., Pedace, L., Lo Giudice, T., Casella, A., Mearini, M., Gaudiello, F., Pedroso, J. L., Terracciano, C., Caltagirone, C., Massa, R. et al.** (2016). ALS5/SPG11/KIAA1840 mutations cause autosomal recessive axonal Charcot-Marie-Tooth disease. *Brain* **139**, 73-85. doi:10.1093/brain/awv320
- Montpetit, A., Côté, S., Brustein, E., Drouin, C. A., Lapointe, L., Boudreau, M., Meloche, C., Drouin, R., Hudson, T. J., Drapeau, P. et al.** (2008). Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. *PLoS Genet.* **4**, e1000296. doi:10.1371/journal.pgen.1000296
- Moosajee, M., Ramsden, S. C., Black, G. C., Seabra, M. C. and Webster, A. R.** (2014). Clinical utility gene card for: choroideremia. *Eur. J. Hum. Genet.* **22**, 572. doi:10.1038/ejhg.2013.183
- Moreno-De-Luca, A., Helmers, S. L., Mao, H., Burns, T. G., Melton, A. M. A., Schmidt, K. R., Fernhoff, P. M., Ledbetter, D. H. and Martin, C. L.** (2011). Adaptor protein complex-4 (AP-4) deficiency causes a novel autosomal recessive cerebral palsy syndrome with microcephaly and intellectual disability. *J. Med. Genet.* **48**, 141-144. doi:10.1136/jmg.2010.082263
- Morgan, N. V., Pasha, S., Johnson, C. A., Ainsworth, J. R., Eady, R. A., Dawood, B., McKeown, C., Trembath, R. C., Wilde, J., Watson, S. P. et al.** (2006). A germline mutation in BLOC1S3/reduced pigmentation causes a novel variant of Hermansky-Pudlak syndrome (HPS8). *Am. J. Hum. Genet.* **78**, 160-166. doi:10.1086/499338
- Morgan, N. E., Cutrona, M. B. and Simpson, J. C.** (2019). Multitasking Rab proteins in autophagy and membrane trafficking: a focus on Rab33b. *Int. J. Mol. Sci.* **20**, 3916. doi:10.3390/ijms20163916
- Muller, T., Hess, M. W., Schiefermeier, N., Pfaller, K., Ebner, H. L., Heinz-Erian, P., Pönstingl, H., Patsch, J., Rollinghoff, B., Kohler, H. et al.** (2008). MYO5B mutations cause microvillus inclusion disease and disrupt epithelial cell polarity. *Nat. Genet.* **40**, 1163-1165. doi:10.1038/ng.225
- Muller, P. A., Caswell, P. T., Doyle, B., Iwanicki, M. P., Tan, E. H., Karim, M., Lukashchuk, N., Gillespie, D. A., Ludwig, R. L., Gosselin, P. et al.** (2009). Mutant p53 drives invasion by promoting integrin recycling. *Cell* **139**, 1327-1341. doi:10.1016/j.cell.2009.11.026
- Nagle, M. W., Latourelle, J. C., Labadorf, A., Dumitriu, A., Hadzi, T. C., Beach, T. G. and Myers, R. H.** (2016). The 4p16.3 Parkinson disease risk locus is associated with GAK expression and genes involved with the synaptic vesicle membrane. *PLoS ONE* **11**, e0160925. doi:10.1371/journal.pone.0160925
- Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., Gallins, P. J., Buxbaum, J. D., Jarvik, G. P., Crane, P. K. et al.** (2011). Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat. Genet.* **43**, 436-441. doi:10.1038/ng.801
- Nakhro, K., Park, J.-M., Hong, Y. B., Park, J. H., Nam, S. H., Yoon, B. R., Yoo, J. H., Koo, H., Jung, S.-C., Kim, H.-L. et al.** (2013). SET binding factor 1 (SBF1) mutation causes Charcot-Marie-Tooth disease type 4B3. *Neurology* **81**, 165-173. doi:10.1212/WNL.0b013e31829a3421
- Nalls, M. A., Pankratz, N., Lill, C. M., Do, C. B., Hernandez, D. G., Saad, M., DeStefano, A. L., Kara, E., Bras, J., Sharma, M. et al.** (2014). Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat. Genet.* **46**, 989-993. doi:10.1038/ng.3043
- Nesbit, M. A., Hannan, F. M., Howles, S. A., Reed, A. A., Cranston, T., Thakker, C. E., Gregory, L., Rimmer, A. J., Rust, N., Graham, U. et al.** (2013). Mutations in AP2S1 cause familial hypocalcaemic hypercalcaemia type 3. *Nat. Genet.* **45**, 93-97. doi:10.1038/ng.2492
- Ng, B. G. and Freeze, H. H.** (2018). Perspectives on glycosylation and its congenital disorders. *Trends Genet.* **34**, 466-476. doi:10.1016/j.tig.2018.03.002
- Nguyen, P. M., Gandasi, N. R., Xie, B., Sugahara, S., Xu, Y. and Idevall-Hagren, O.** (2019). The PI(4)P phosphatase Sac2 controls insulin granule docking and release. *J. Cell Biol.* **218**, 3714-3729. doi:10.1083/jcb.201903121
- Nichols, W. C., Seligsohn, U., Zivelin, A., Terry, V. H., Hertel, C. E., Wheatley, M. A., Moussalli, M. J., Hauri, H.-P., Ciavarella, N., Kaufman, R. J. et al.** (1998). Mutations in the ER-Golgi intermediate compartment protein ERGIC-53 cause combined deficiency of coagulation factors V and VIII. *Cell* **93**, 61-70. doi:10.1016/S0092-8674(00)81146-0
- Nichols, W. C., Terry, V. H., Wheatley, M. A., Yang, A., Zivelin, A., Ciavarella, N., Stefanile, C., Matsushita, T., Saito, H., de Bosch, N. B. et al.** (1999). ERGIC-53 gene structure and mutation analysis in 19 combined factors V and VIII deficiency families. *Blood* **93**, 2261-2266.
- Nicot, A.-S., Toussaint, A., Tosch, V., Kretz, C., Wallgren-Pettersson, C., Iwarsson, E., Kingston, H., Garnier, J.-M., Biancalana, V., Oldfors, A. et al.** (2007). Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. *Nat. Genet.* **39**, 1134-1139. doi:10.1038/ng2086
- Nixon, R. A.** (2017). Amyloid precursor protein and endosomal-lysosomal dysfunction in Alzheimer's disease: inseparable partners in a multifactorial disease. *FASEB J.* **31**, 2729-2743. doi:10.1096/fj.201700359
- Nourse, C. R., Mattei, M.-G., Gunning, P. and Byrne, J. A.** (1998). Cloning of a third member of the D52 gene family indicates alternative coding sequence usage in D52-like transcripts. *Biochim. Biophys. Acta* **1443**, 155-168. doi:10.1016/S0167-4781(98)00211-5
- Novick, P. and Schekman, R.** (1979). Secretion and cell-surface growth are blocked in a temperature-sensitive mutant of *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **76**, 1858-1862. doi:10.1073/pnas.76.4.1858
- Oh, J., Bailin, T., Fukai, K., Feng, G. H., Ho, L., Mao, J. I., Frenk, E., Tamura, N. and Spritz, R. A.** (1996). Positional cloning of a gene for Hermansky-Pudlak syndrome, a disorder of cytoplasmic organelles. *Nat. Genet.* **14**, 300-306. doi:10.1038/ng1196-300

- OHIRA, M., OSHITANI, N., HOSOMI, S., WATANABE, K., YAMAGAMI, H., TOMINAGA, K., WATANABE, T., FUJIWARA, Y., MAEDA, K., HIRAKAWA, K. et al. (2009). Dislocation of Rab13 and vasodilator-stimulated phosphoprotein in inactive colon epithelium in patients with Crohn's disease. *Int. J. Mol. Med.* **24**, 829-835. doi:10.3892/ijmm\_00000300
- OLGIATI, S., QUADRI, M., FANG, M., ROOD, J. P., SAUTE, J. A., CHIEN, H. F., BOUWKAMP, C. G., GRAAFLAND, J., MINNEBOO, M., BREEDVELD, G. J. et al. (2016). DNAJC6 mutations associated with early-onset Parkinson's disease. *Ann. Neurol.* **79**, 244-256. doi:10.1002/ana.24553
- ORLACCHIO, A., BABALINI, C., BORRECA, A., PATRONO, C., MASSA, R., BASARAN, S., MUNHOZ, R. P., ROGAEVA, E. A., ST GEORGE-HYSLOP, P. H., BERNARDI, G. et al. (2010). SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis. *Brain* **133**, 591-598. doi:10.1093/brain/awp325
- OZ-LEVI, D., BEN-ZEEV, B., RUZZO, E. K., HITOMI, Y., GELMAN, A., PELAK, K., ANIKSTER, Y., REZNIK-WOLF, H., BAR-JOSEPH, I., OLENDER, T. et al. (2012). Mutation in TECPR2 reveals a role for autophagy in hereditary spastic paraparesis. *Am. J. Hum. Genet.* **91**, 1065-1072. doi:10.1016/j.ajhg.2012.09.015
- PAESOLD-BURDA, P., MAAG, C., TROXLER, H., FOULQUIER, F., KLEINERT, P., SCHNABEL, S., BAUMGARTNER, M. and HENNET, T. (2009). Deficiency in COG5 causes a moderate form of congenital disorders of glycosylation. *Hum. Mol. Genet.* **18**, 4350-4356. doi:10.1093/hmg/ddp389
- PAISAN-RUIZ, C., JAIN, S., EVANS, E. W., GILKS, W. P., SIMON, J., VAN DER BRUG, M., LOPEZ DE MUNAIN, A., APARICIO, S., GIL, A. M., KHAN, N. et al. (2004). Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron* **44**, 595-600. doi:10.1016/j.neuron.2004.10.023
- PANTAZOPOULOU, A. and GLICK, B. S. (2019). A kinetic view of membrane traffic pathways can transcend the classical view of golgi compartments. *Front. Cell Dev. Biol.* **7**, 153. doi:10.3389/fcell.2019.00153
- PARKINSON, N., INCE, P. G., SMITH, M. O., HIGHLEY, R., SKIBINSKI, G., ANDERSEN, P. M., MORRISON, K. E., PALL, H. S., HARDIMAN, O., COLLINGE, J. et al. (2006). ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). *Neurology* **67**, 1074-1077. doi:10.1212/01.wnl.0000231510.89311.8b
- PARTON, R. G. (2018). Caveolae: structure, function, and relationship to disease. *Annu. Rev. Cell Dev. Biol.* **34**, 111-136. doi:10.1146/annurev-cellbio-100617-062737
- PASTERIS, N. G., CADLE, A., LOGIE, L. J., PORTEOUS, M. E., SCHWARTZ, C. E., STEVENSON, R. E., GLOVER, T. W., WILROY, R. S. and GORSKI, J. L. (1994). Isolation and characterization of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: a putative Rho/Rac guanine nucleotide exchange factor. *Cell* **79**, 669-678. doi:10.1016/0092-8674(94)90552-5
- PASTURAL, E., BARRAT, F. J., DUFOURCQ-LAGELOUSE, R., CERTAIN, S., SANAL, O., JABADO, N., SEGER, R., GRISCELLI, C., FISCHER, A. and DE SAINT BASILE, G. (1997). Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. *Nat. Genet.* **16**, 289-292. doi:10.1038/ng0797-289
- PATEL, H., CROSS, H., PROUKAKIS, C., HERSHBERGER, R., BORK, P., CICCARELLI, F. D., PATTON, M. A., MCKUSICK, V. A. and CROSBY, A. H. (2002). SPG20 is mutated in Troyer syndrome, an hereditary spastic paraplegia. *Nat. Genet.* **31**, 347-348. doi:10.1038/ng937
- PEREIRA, J. A., LEBRUN-JULIEN, F. and SUTER, U. (2012). Molecular mechanisms regulating myelination in the peripheral nervous system. *Trends Neurosci.* **35**, 123-134. doi:10.1016/j.tins.2011.11.006
- PEREIRA, N. A., PU, H. X., GOH, H. and SONG, Z. (2014). Golgi phosphoprotein 3 mediates the Golgi localization and function of protein O-linked mannose beta-1,2-N-acetylglucosaminyltransferase 1. *J. Biol. Chem.* **289**, 14762-14770. doi:10.1074/jbc.M114.548305
- PHILIPPE, O., RIO, M., CARIoux, A., PLAZA, J. M., GUIGUE, P., MOLINARI, F., BODDAERT, N., BOLE-FEYSOT, C., NITSCHKE, P., SMAHI, A. et al. (2009). Combination of linkage mapping and microarray-expression analysis identifies NF- $\kappa$ B signaling defect as a cause of autosomal-recessive mental retardation. *Am. J. Hum. Genet.* **85**, 903-908. doi:10.1016/j.ajhg.2009.11.007
- PINHO, S. S. and REIS, C. A. (2015). Glycosylation in cancer: mechanisms and clinical implications. *Nat. Rev. Cancer* **15**, 540-555. doi:10.1038/nrc3982
- PIWON, N., GUNTHER, W., SCHWAKE, M., BOSL, M. R. and JENTSCH, T. J. (2000). CIC-5 Cl<sup>-</sup> channel disruption impairs endocytosis in a mouse model for Dent's disease. *Nature* **408**, 369-373. doi:10.1038/35042597
- PLATT, F. M., D'AZZO, A., DAVIDSON, B. L., NEUFELD, E. F. and TIFFT, C. J. (2018). Lysosomal storage diseases. *Nat. Rev. Dis. Primers* **4**, 27. doi:10.1038/s41572-018-0025-4
- POHLER, E., MAMAI, O., HIRST, J., ZAMIRI, M., HORN, H., NOMURA, T., IRVINE, A. D., MORAN, B., WILSON, N. J., SMITH, F. J. et al. (2012). Haploinsufficiency for AAGAB causes clinically heterogeneous forms of punctate palmoplantar keratoderma. *Nat. Genet.* **44**, 1272-1276. doi:10.1038/ng.2444
- POLYMERPOULOS, M. H., LAVEDAN, C., LEROY, E., IDE, S. E., DEHEJIA, A., DUTRA, A., PIKE, B., ROOT, H., RUBENSTEIN, J., BOYER, R. et al. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045-2047. doi:10.1126/science.276.5321.2045
- PURLEY, E., DHEKNE, H. S., SARHAN, A. R., GOMEZ, R., LIS, P., WIGHTMAN, M., MARTINEZ, T. N., TONELLI, F., PFEFFER, S. R. and ALESSI, D. R. (2018). Rab29 activation of the Parkinson's disease-associated LRRK2 kinase. *EMBO J.* **37**, 1-18. doi:10.15252/emj.201798099
- QUADRI, M., FANG, M., PICILLO, M., OLGIATI, S., BREEDVELD, G. J., GRAAFLAND, J., WU, B., XU, F., ERRO, R., AMBONI, M. et al. (2013). Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism. *Hum. Mutat.* **34**, 1208-1215. doi:10.1002/humu.22373
- RAFIULLAH, R., ASLAMKHAH, M., PARAMASIVAM, N., THIEL, C., MUSTAFA, G., WIEMANN, S., SCHLESNER, M., WADE, R. C., RAPPOLD, G. A. and BERKEL, S. (2016). Homozygous missense mutation in the LMAN2L gene segregates with intellectual disability in a large consanguineous Pakistani family. *J. Med. Genet.* **53**, 138-144. doi:10.1136/jmedgenet-2015-103179
- RAHAJENG, J., KUNA, R. S., MAKOWSKI, S. L., TRAN, T. T. T., BUSCHMAN, M. D., LI, S., CHENG, N., NG, M. M. and FIELD, S. J. (2019). Efficient golgi forward trafficking requires GOLPH3-driven, PI4P-dependent membrane curvature. *Dev. Cell* **50**, 573-585.e5. doi:10.1016/j.devcel.2019.05.038
- RANTA, S., ZHANG, Y., ROSS, B., LONKA, L., TAKKUNEN, E., MESSER, A., SHARP, J., WHEELER, R., KUSUMI, K., MOLE, S. et al. (1999). The neuronal ceroid lipofuscinoses in human EPMR and mnd mutant mice are associated with mutations in CLN8. *Nat. Genet.* **23**, 233-236. doi:10.1038/13868
- RANTA, S., TOPCU, M., TEGELBERG, S., TAN, H., USTUBUTUN, A., SAATICI, I., DUFKE, A., ENDERS, H., POHL, K., ALEMBIK, Y. et al. (2004). Variant late infantile neuronal ceroid lipofuscinosis in a subset of Turkish patients is allelic to Northern epilepsy. *Hum. Mutat.* **23**, 300-305. doi:10.1002/humu.20018
- RAZA, M. H., MATTERA, R., MORELL, R., SAINZ, E., RAHN, R., GUTIERREZ, J., PARIS, E., ROOT, J., SOLOMON, B., BREWER, C. et al. (2015). Association between rare variants in AP4E1, a component of intracellular trafficking, and persistent stuttering. *Am. J. Hum. Genet.* **97**, 715-725. doi:10.1016/j.ajhg.2015.10.007
- REITER, J. F. and LEROUX, M. R. (2017). Genes and molecular pathways underpinning ciliopathies. *Nat. Rev. Mol. Cell Biol.* **18**, 533-547. doi:10.1038/nrm.2017.60
- RENTON, A. E., MAJOUNIE, E., WAITE, A., SIMON-SANCHEZ, J., ROLLINSON, S., GIBBS, J. R., SCHYMIK, J. C., LAAKSOVIRTA, H., VAN SWIETEN, J. C., MYLLYKANGAS, L. et al. (2011). A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* **72**, 257-268. doi:10.1016/j.neuron.2011.09.010
- REUTER, M. S., TAWAMIE, H., BUCHERT, R., HOSNY GEBRIL, O., FROUKH, T., THIEL, C., UEBE, S., EKICI, A. B., KRUMBIEGEL, M., ZWEIER, C. et al. (2017). Diagnostic yield and novel candidate genes by exome sequencing in 152 consanguineous families with neurodevelopmental disorders. *JAMA Psychiatry* **74**, 293-299. doi:10.1001/jamapsychiatry.2016.3798
- REYNDERS, E., FOULQUIER, F., LEÃO TELES, E., QUELHAS, D., MORELLE, W., RABOUILLE, C., ANNAERT, W. and MATTHIJS, G. (2009). Golgi function and dysfunction in the first COG4-deficient CDG type II patient. *Hum. Mol. Genet.* **18**, 3244-3256. doi:10.1093/hmg/ddp262
- REZAIE, T., CHILD, A., HITCHINGS, R., BRICE, G., MILLER, L., COCA-PRADOS, M., HEON, E., KRUPIN, T., RITCH, R., KREUTZER, D. et al. (2002). Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* **295**, 1077-1079. doi:10.1126/science.1066901
- RIVERA, V. M., WANG, X., WARDWELL, S., COURAGE, N. L., VOLCHUK, A., KEENAN, T., HOLT, D. A., GILMAN, M., ORCI, L., CERASOLI, F. JR et al. (2000). Regulation of protein secretion through controlled aggregation in the endoplasmic reticulum. *Science* **287**, 826-830. doi:10.1126/science.287.5454.826
- RIZZO, R., PARASHURAMAN, S., D'ANGELO, G. and LUINI, A. (2017). GOLPH3 and oncogenesis: What is the molecular link? *Tissue Cell* **49**, 170-174. doi:10.1016/j.tice.2016.06.008
- RODAN, L. H., COHEN, J., FATEMI, A., GILLIS, T., LUENTE, D., GUSELLA, J. and PICKER, J. D. (2016). A novel neurodevelopmental disorder associated with compound heterozygous variants in the huntingtin gene. *Eur. J. Hum. Genet.* **24**, 1826-1827. doi:10.1038/ejhg.2016.74
- ROECKEL, N., WOERNER, S. M., KLOOR, M., YUAN, Y.-P., PATSOS, G., GROMES, R., KOPITZ, J. and GEBERT, J. (2009). High frequency of LMAN1 abnormalities in colorectal tumors with microsatellite instability. *Cancer Res.* **69**, 292-299. doi:10.1158/0008-5472.CAN-08-3314
- ROSSI, G., MANFRIN, A. and LUTOLF, M. P. (2018). Progress and potential in organoid research. *Nat. Rev. Genet.* **19**, 671-687. doi:10.1038/s41576-018-0051-9
- ROSSOR, A. M., POLKE, J. M., HOULDEN, H. and REILLY, M. M. (2013). Clinical implications of genetic advances in Charcot-Marie-Tooth disease. *Nat. Rev. Neurol.* **9**, 562-571. doi:10.1038/nrneurol.2013.179
- ROUX, K. J., KIM, D. I., RAIDA, M. and BURKE, B. (2012). A promiscuous biotin ligase fusion protein identifies proximal and interacting proteins in mammalian cells. *J. Cell Biol.* **196**, 801-810. doi:10.1083/jcb.201112098
- ROY, C. C., LEVY, E., GREEN, P. H., SNIDERMAN, A., LETARTE, J., BUTS, J. P., ORQUIN, J., BROCHU, P., WEBER, A. M., MORIN, C. L. et al. (1987). Malabsorption, hypocholesterolemia, and fat-filled enterocytes with increased intestinal apolipoprotein B. Chylomicron retention disease. *Gastroenterology* **92**, 390-399. doi:10.1016/0016-5085(87)90133-8
- ROYER, B., HANIA, K., GAVRIILIDIS, C., TRONCHÈRE, H., TOSCH, V. and LAPORTE, J. (2013). The myotubularin-amphiphysin 2 complex in membrane tubulation and centronuclear myopathies. *EMBO Rep.* **14**, 907-915. doi:10.1038/embor.2013.119

- Ryan, B. J., Hoek, S., Fon, E. A. and Wade-Martins, R. (2015). Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease. *Trends Biochem. Sci.* **40**, 200-210. doi:10.1016/j.tibs.2015.02.003
- Saheki, Y. and De Camilli, P. (2012). Synaptic vesicle endocytosis. *Cold Spring Harb. Perspect. Biol.* **4**, a005645. doi:10.1101/cshperspect.a005645
- Saitsu, H., Kato, M., Mizuguchi, T., Hamada, K., Osaka, H., Tohyama, J., Uruno, K., Kumada, S., Nishiyama, K., Nishimura, A. et al. (2008). De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nat. Genet.* **40**, 782-788. doi:10.1038/ng.150
- Salpietro, V., Lin, W., Delle Vedove, A., Storbeck, M., Liu, Y., Efthymiou, S., Manole, A., Wiethoff, S., Ye, Q., Saggari, A. et al. (2017). Homozygous mutations in *VAMP1* cause a presynaptic congenital myasthenic syndrome. *Ann. Neurol.* **81**, 597-603. doi:10.1002/ana.24905
- Sandvig, K., Kavaliuskiene, S. and Skotland, T. (2018). Clathrin-independent endocytosis: an increasing degree of complexity. *Histochem. Cell Biol.* **150**, 107-118. doi:10.1007/s00418-018-1678-5
- Sanger, A., Hirst, J., Davies, A. K. and Robinson, M. S. (2019). Adaptor protein complexes and disease at a glance. *J. Cell Sci.* **132**, jcs222992. doi:10.1242/jcs.222992
- Sankila, E.-M., Tolvanen, R., van den Hurk, J. A. M., Cremers, F. P. and de la Chapelle, A. (1992). Aberrant splicing of the CHM gene is a significant cause of choroideremia. *Nat. Genet.* **1**, 109-113. doi:10.1038/ng0592-109
- Schmidt, O. and Teis, D. (2012). The ESCRT machinery. *Curr. Biol.* **22**, R116-R120. doi:10.1016/j.cub.2012.01.028
- Schmidt, W. M., Rutledge, S. L., Schule, R., Mayerhofer, B., Zuchner, S., Boltshauser, E. and Bittner, R. E. (2015). Disruptive SCYL1 mutations underlie a syndrome characterized by recurrent episodes of liver failure, peripheral neuropathy, cerebellar atrophy, and ataxia. *Am. J. Hum. Genet.* **97**, 855-861. doi:10.1016/j.ajhg.2015.10.011
- Schrijf, A. M., Fon, E. A. and McPherson, P. S. (2016). Endocytic membrane trafficking and neurodegenerative disease. *Cell. Mol. Life Sci.* **73**, 1529-1545. doi:10.1007/s00018-015-2105-x
- Schwarz, K., Iolascon, A., Verissimo, F., Trede, N. S., Horsley, W., Chen, W., Paw, B. H., Hopfner, K. P., Holzmann, K., Russo, R. et al. (2009). Mutations affecting the secretory COPII coat component SEC23B cause congenital dyserythropoietic anemia type II. *Nat. Genet.* **41**, 936-940. doi:10.1038/ng.405
- Scott, K. L., Kabbarah, O., Liang, M. C., Ivanova, E., Anagnostou, V., Wu, J., Dhakal, S., Wu, M., Chen, S., Feinberg, T. et al. (2009). GOLPH3 modulates mTOR signalling and rapamycin sensitivity in cancer. *Nature* **459**, 1085-1090. doi:10.1038/nature08109
- Seabra, M. C., Brown, M. S. and Goldstein, J. L. (1993). Retinal degeneration in choroideremia: deficiency of rab geranylgeranyl transferase. *Science* **259**, 377-381. doi:10.1126/science.8380507
- Segarra, N. G., Ballhausen, D., Crawford, H., Perreau, M., Campos-Xavier, B., van Spaendonck-Zwarts, K., Vermeer, C., Russo, M., Zambelli, P.-Y., Stevenson, B. et al. (2015). NBAS mutations cause a multisystem disorder involving bone, connective tissue, liver, immune system, and retina. *Am. J. Med. Genet. A* **167**, 2902-2912. doi:10.1002/ajmg.a.37338
- Senderek, J., Bergmann, C., Stendel, C., Kirfel, J., Verpoorten, N., De Jonghe, P., Timmerman, V., Chrast, R., Verheijen, M. H., Lemke, G. et al. (2003). Mutations in a gene encoding a novel SH3/TPR domain protein cause autosomal recessive Charcot-Marie-Tooth type 4C neuropathy. *Am. J. Hum. Genet.* **73**, 1106-1119. doi:10.1086/379525
- Sengupta, P. and Lippincott-Schwartz, J. (2013). Photohighlighting approaches to access membrane dynamics of the Golgi apparatus. *Methods Cell Biol.* **118**, 217-234. doi:10.1016/B978-0-12-417164-0.00013-6
- Seshadri, S., Fitzpatrick, A. L., Ikram, M. A., DeStefano, A. L., Gudnason, V., Boada, M., Bis, J. C., Smith, A. V., Carassquillo, M. M., Lambert, J. C. et al. (2010). Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* **303**, 1832-1840. doi:10.1001/jama.2010.574
- Setta-Kaffetzi, N., Simpson, M. A., Navarini, A. A., Patel, V. M., Lu, H.-C., Allen, M. H., Duckworth, M., Bachelez, H., Burden, A. D., Choon, S.-E. et al. (2014). AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am. J. Hum. Genet.* **94**, 790-797. doi:10.1016/j.ajhg.2014.04.005
- Shaheen, R., Ansari, S., Alshammari, M. J., Alkhalidi, H., Alrukban, H., Eyaid, W. and Alkuraya, F. S. (2013a). A novel syndrome of hypohidrosis and intellectual disability is linked to COG6 deficiency. *J. Med. Genet.* **50**, 431-436. doi:10.1136/jmedgenet-2013-101527
- Shaheen, R., Faqeih, E., Alshammari, M. J., Swaid, A., Al-Gazali, L., Mardawi, E., Ansari, S., Sogaty, S., Seidahmed, M. Z., AlMotairi, M. I. et al. (2013b). Genomic analysis of Meckel-Gruber syndrome in Arabs reveals marked genetic heterogeneity and novel candidate genes. *Eur. J. Hum. Genet.* **21**, 762-768. doi:10.1038/ejhg.2012.254
- Sheen, V. L., Ganesh, V. S., Topcu, M., Sebire, G., Bodell, A., Hill, R. S., Grant, P. E., Shugart, Y. Y., Imitola, J., Khoury, S. J. et al. (2004). Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nat. Genet.* **36**, 69-76. doi:10.1038/ng1276
- Shen, X.-M., Selcen, D., Brengman, J. and Engel, A. G. (2014). Mutant SNAP25B causes myasthenia, cortical hyperexcitability, ataxia, and intellectual disability. *Neurology* **83**, 2247-2255. doi:10.1212/WNL.0000000000001079
- Shen, X.-M., Scola, R. H., Lorenzoni, P. J., Kay, C. S., Werneck, L. C., Brengman, J., Selcen, D. and Engel, A. G. (2017). Novel synaptobrevin-1 mutation causes fatal congenital myasthenic syndrome. *Ann. Clin. Transl. Neurol.* **4**, 130-138. doi:10.1002/acn3.387
- Shih, N.-Y., Li, J., Cotran, R., Mundel, P., Miner, J. H. and Shaw, A. S. (2001). CD2AP localizes to the slit diaphragm and binds to nephrin via a novel C-terminal domain. *Am. J. Pathol.* **159**, 2303-2308. doi:10.1016/S0002-9440(10)63080-5
- Shrivastava-Ranjan, P., Faundez, V., Fang, G., Rees, H., Lah, J. J., Levey, A. I. and Kahn, R. A. (2008). Mint3/X11γ is an ADP-ribosylation factor-dependent adaptor that regulates the traffic of the Alzheimer's Precursor protein from the trans-Golgi network. *Mol. Biol. Cell* **19**, 51-64. doi:10.1091/mbc.e07-05-0465
- Singleton, A. B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R. et al. (2003). alpha-Synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841. doi:10.1126/science.1090278
- Skibinski, G., Parkinson, N. J., Brown, J. M., Chakrabarti, L., Lloyd, S. L., Hummerich, H., Nielsen, J. E., Hodges, J. R., Spillantini, M. G., Thusgaard, T. et al. (2005). Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat. Genet.* **37**, 806-808. doi:10.1038/ng1609
- Slabicki, M., Theis, M., Krastev, D. B., Samsonov, S., Mundwiler, E., Junqueira, M., Paszkowski-Rogacz, M., Teyra, J., Heninger, A. K., Poser, I. et al. (2010). A genome-scale DNA repair RNAi screen identifies SPG48 as a novel gene associated with hereditary spastic paraplegia. *PLoS Biol.* **8**, e1000408. doi:10.1371/journal.pbio.1000408
- Slosarek, E. L., Schuh, A. L., Pustova, I., Johnson, A., Bird, J., Johnson, M., Frankel, E. B., Bhattacharya, N., Hanna, M. G., Burke, J. E. et al. (2018). Pathogenic TFG mutations underlying hereditary spastic paraplegia impair secretory protein trafficking and axon fasciculation. *Cell Rep.* **24**, 2248-2260. doi:10.1016/j.celrep.2018.07.081
- Small, S. A., Kent, K., Pierce, A., Leung, C., Kang, M. S., Okada, H., Honig, L., Vonsattel, J. P. and Kim, T. W. (2005). Model-guided microarray implicates the retromer complex in Alzheimer's disease. *Ann. Neurol.* **58**, 909-919. doi:10.1002/ana.20667
- Smigiel, R., Landsberg, G., Schilling, M., Rydzanicz, M., Pollak, A., Walczak, A., Stodolak, A., Stawinski, P., Mierzewska, H., Sasiadek, M. M. et al. (2018). Developmental epileptic encephalopathy with hypomyelination and brain atrophy associated with PTPN23 variants affecting the assembly of UsnRNPs. *Eur. J. Hum. Genet.* **26**, 1502-1511. doi:10.1038/s41431-018-0179-2
- Smits, P., Bolton, A. D., Funari, V., Hong, M., Boyden, E. D., Lu, L., Manning, D. K., Dwyer, N. D., Moran, J. L., Prysak, M. et al. (2010). Lethal skeletal dysplasia in mice and humans lacking the golgin GMAP-210. *N. Engl. J. Med.* **362**, 206-216. doi:10.1056/NEJMoa0900158
- Soo, K. Y., Halloran, M., Sundaramoorthy, V., Parakh, S., Toth, R. P., Southam, K. A., McLean, C. A., Lock, P., King, A., Farg, M. A. et al. (2015). Rab1-dependent ER-Golgi transport dysfunction is a common pathogenic mechanism in SOD1, TDP-43 and FUS-associated ALS. *Acta Neuropathol.* **130**, 679-697. doi:10.1007/s00401-015-1468-2
- Søreng, K., Neufeld, T. P. and Simonsen, A. (2018). Membrane trafficking in autophagy. *Int. Rev. Cell Mol. Biol.* **336**, 1-92. doi:10.1016/bs.ircmb.2017.07.001
- Sowada, N., Hashem, M. O., Yilmaz, R., Hamad, M., Kakar, N., Thiele, H., Arnold, S. T., Bode, H., Alkuraya, F. S. and Borck, G. (2017). Mutations of PTPN23 in developmental and epileptic encephalopathy. *Hum. Genet.* **136**, 1455-1461. doi:10.1007/s00439-017-1850-3
- Spainij-Dekking, E. H., Van Delft, J., Van Der Meijden, E., Hiemstra, H. S., Falkenburg, J. H., Koning, F., Drijfhout, J. W. and Kluijn-Nelemans, J. C. (2003). Synaptotagmin 2 is recognized by HLA class II-restricted hairy cell leukemia-specific T cells. *Leukemia* **17**, 2467-2473. doi:10.1038/sj.leu.2403174
- Sprecher, E., Ishida-Yamamoto, A., Mizrahi-Koren, M., Rapaport, D., Goldsher, D., Indelman, M., Topaz, O., Chefetz, I., Keren, H., O'Brien, T. J. et al. (2005). A mutation in SNAP29, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. *Am. J. Hum. Genet.* **77**, 242-251. doi:10.1086/432556
- Stadel, D., Millarte, V., Tillmann, K.-D., Huber, J., Tamin-Yecheskel, B. C., Akutsu, M., Demishtein, A., Ben-Zeev, B., Anikster, Y., Perez, F. et al. (2015). TECPR2 cooperates with LC3C to regulate COPII-dependent ER export. *Mol. Cell* **60**, 89-104. doi:10.1016/j.molcel.2015.09.010
- Steger, M., Tonelli, F., Ito, G., Davies, P., Trost, M., Vetter, M., Wachter, S., Lorentzen, E., Duddy, G., Wilson, S. et al. (2016). Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases. *Elife* **5**, e12813. doi:10.7554/eLife.12813.023
- Steinberg, F., Gallon, M., Winfield, M., Thomas, E. C., Bell, A. J., Heesom, K. J., Tavaré, J. M. and Cullen, P. J. (2013). A global analysis of SNX27-retromer assembly and cargo specificity reveals a function in glucose and metal ion transport. *Nat. Cell Biol.* **15**, 461-471. doi:10.1038/ncb2721
- Steinman, R. M., Brodie, S. E. and Cohn, Z. A. (1976). Membrane flow during pinocytosis. A stereologic analysis. *J. Cell Biol.* **68**, 665. doi:10.1083/jcb.68.3.665

- Stevanin, G., Santorelli, F. M., Azzedine, H., Coutinho, P., Chomilier, J., Denora, P. S., Martin, E., Ouvrard-Hernandez, A. M., Tessa, A., Bouslam, N. et al. (2007). Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat. Genet.* **39**, 366-372. doi:10.1038/ng1980
- Stoetzel, C., Bär, S., De Craene, J.-O., Scheidecker, S., Etard, C., Chicher, J., Reck, J. R., Perrault, I., Geoffroy, V., Chennen, K. et al. (2016). A mutation in VPS15 (PIK3R4) causes a ciliopathy and affects IFT20 release from the cis-Golgi. *Nat. Commun.* **7**, 13586. doi:10.1038/ncomms13586
- Street, V. A., Bennett, C. L., Goldy, J. D., Shirk, A. J., Kleopa, K. A., Tempel, B. L., Lipe, H. P., Scherer, S. S., Bird, T. D. and Chance, P. F. (2003). Mutation of a putative protein degradation gene LITAF/SIMPLE in Charcot-Marie-Tooth disease 1C. *Neurology* **60**, 22-26. doi:10.1212/WNL.60.1.22
- Südhof, T. C. (2013). Neurotransmitter release: the last millisecond in the life of a synaptic vesicle. *Neuron* **80**, 675-690. doi:10.1016/j.neuron.2013.10.022
- Suzuki, T., Li, W., Zhang, Q., Karim, A., Novak, E. K., Sviderskaya, E. V., Hill, S. P., Bennett, D. C., Levin, A. V., Nieuwenhuis, H. K. et al. (2002). Hermansky-Pudlak syndrome is caused by mutations in HPS4, the human homolog of the mouse light-ear gene. *Nat. Genet.* **30**, 321-324. doi:10.1038/ng835
- Takei, K., Slepnev, V. I., Haucke, V. and De Camilli, P. (1999). Functional partnership between amphiphysin and dynamin in clathrin-mediated endocytosis. *Nat. Cell Biol.* **1**, 33-39. doi:10.1038/9004
- Tarpey, P. S., Stevens, C., Teague, J., Edkins, S., O'Meara, S., Avis, T., Barthorpe, S., Buck, G., Butler, A., Cole, J. et al. (2006). Mutations in the gene encoding the Sigma 2 subunit of the adaptor protein 1 complex, AP1S2, cause X-linked mental retardation. *Am. J. Hum. Genet.* **79**, 1119-1124. doi:10.1086/510137
- Thayanidhi, N., Helm, J. R., Nycz, D. C., Bentley, M., Liang, Y. and Hay, J. C. (2010). Alpha-synuclein delays endoplasmic reticulum (ER)-to-Golgi transport in mammalian cells by antagonizing ER/Golgi SNAREs. *Mol. Biol. Cell* **21**, 1850-1863. doi:10.1091/mbc.e09-09-0801
- Toh, W. H. and Gleeson, P. A. (2016). Dysregulation of intracellular trafficking and endosomal sorting in Alzheimer's disease: controversies and unanswered questions. *Biochem. J.* **473**, 1977-1993. doi:10.1042/BCJ20160147
- Torras, N., García-Díaz, M., Fernández-Majada, V. and Martínez, E. (2018). Mimicking epithelial tissues in three-dimensional cell culture models. *Front Bioeng Biotechnol* **6**, 197. doi:10.3389/fbioe.2018.00197
- Town, M., Jean, G., Cherqui, S., Attard, M., Forestier, L., Whitmore, S. A., Callen, D. F., Gribouval, O., Broyer, M., Bates, G. P. et al. (1998). A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat. Genet.* **18**, 319-324. doi:10.1038/ng0498-319
- Tsai, L., Schwake, M., Corbett, M. A., Gecz, J., Berkovic, S. and Shieh, P. B. (2013). P.1.20 GOSR2: a novel form of congenital muscular dystrophy. *Neuromuscul. Disord.* **23**, 748. doi:10.1016/j.nmd.2013.06.404
- Unlu, G., Qi, X., Gamazon, E. R., Melville, D. B., Patel, N., Rushing, A. R., Hashem, M., Al-Faifi, A., Chen, R., Li, B. et al. (2020). Phenome-based approach identifies RIC1-linked Mendelian syndrome through zebrafish models, biobank associations and clinical studies. *Nat. Med.* **26**, 98-109. doi:10.1038/s41591-019-0705-y
- Uwineza, A., Caberg, J.-H., Hitayezu, J., Wenric, S., Mutesa, L., Vial, Y., Drunat, S., Passemard, S., Verloes, A., El Ghouzzi, V. et al. (2019). VPS51 biallelic variants cause microcephaly with brain malformations: a confirmatory report. *Eur. J. Med. Genet.* **62**, 103704. doi:10.1016/j.ejmg.2019.103704
- Valdmanis, P. N., Meijer, I. A., Reynolds, A., Lei, A., MacLeod, P., Schlesinger, D., Zatz, M., Reid, E., Dion, P. A., Drapeau, P. et al. (2007). Mutations in the KIAA0196 gene at the SPG8 locus cause hereditary spastic paraplegia. *Am. J. Hum. Genet.* **80**, 152-161. doi:10.1086/510782
- Vassilopoulos, S., Esk, C., Hoshino, S., Funke, B. H., Chen, C. Y., Plocik, A. M., Wright, W. E., Kucherlapati, R. and Brodsky, F. M. (2009). A role for the CHC22 clathrin heavy-chain isoform in human glucose metabolism. *Science* **324**, 1192-1196. doi:10.1126/science.1171529
- Venditti, R., Scanu, T., Santoro, M., Di Tullio, G., Spaar, A., Gaibisso, R., Beznoussenko, G. V., Mironov, A. A., Mironov, A., Jr, Zelante, L. et al. (2012). Sedlin controls the ER export of procollagen by regulating the Sar1 cycle. *Science* **337**, 1668-1672. doi:10.1126/science.1224947
- Verhoeven, K., De Jonghe, P., Coen, K., Verpoorten, N., Auer-Grumbach, M., Kwon, J. M., FitzPatrick, D., Schmedding, E., De Vriendt, E., Jacobs, A. et al. (2003). Mutations in the small GTP-ase late endosomal protein RAB7 cause Charcot-Marie-Tooth type 2B neuropathy. *Am. J. Hum. Genet.* **72**, 722-727. doi:10.1086/367847
- Verkerk, A. J., Schot, R., Dumee, B., Schellekens, K., Swagemakers, S., Bertoli-Avella, A. M., Lequin, M. H., Dudink, J., Govaert, P., van Zwol, A. L. et al. (2009). Mutation in the AP4M1 gene provides a model for neuroaxonal injury in cerebral palsy. *Am. J. Hum. Genet.* **85**, 40-52. doi:10.1016/j.ajhg.2009.06.004
- Vilarino-Guelli, C., Wider, C., Ross, O. A., Daxsel, J. C., Kachergus, J. M., Lincoln, S. J., Soto-Ortolaza, A. I., Cobb, S. A., Wilhoite, G. J., Bacon, J. A. et al. (2011). VPS35 mutations in Parkinson disease. *Am. J. Hum. Genet.* **89**, 162-167. doi:10.1016/j.ajhg.2011.06.001
- Vilarino-Guelli, C., Rajput, A., Milnerwood, A. J., Shah, B., Szu-Tu, C., Trinh, J., Yu, I., Encarnacion, M., Munsie, L. N., Tapia, L. et al. (2014). DNAJC13 mutations in Parkinson disease. *Hum. Mol. Genet.* **23**, 1794-1801. doi:10.1093/hmg/ddt570
- Voronov, S. V., Frere, S. G., Giovedi, S., Pollina, E. A., Borel, C., Zhang, H., Schmidt, C., Akeson, E. C., Wenk, M. R., Cimasoni, L. et al. (2008). Synaptotagmin 1-linked phosphoinositide dyshomeostasis and cognitive deficits in mouse models of Down's syndrome. *Proc. Natl. Acad. Sci. USA* **105**, 9415-9420. doi:10.1073/pnas.0803756105
- Wandinger-Ness, A. and Zerial, M. (2014). Rab proteins and the compartmentalization of the endosomal system. *Cold Spring Harb. Perspect. Biol.* **6**, a022616. doi:10.1101/cshperspect.a022616
- Wang, S. S., Devuyt, O., Courtoy, P. J., Wang, X. T., Wang, H., Wang, Y., Thakker, R. V., Guggino, S. and Guggino, W. B. (2000). Mice lacking renal chloride channel, CLC-5, are a model for Dent's disease, a nephrolithiasis disorder associated with defective receptor-mediated endocytosis. *Hum. Mol. Genet.* **9**, 2937-2945. doi:10.1093/hmg/9.20.2937
- Wang, C., Yuan, X. and Yang, S. (2013). IFT80 is essential for chondrocyte differentiation by regulating Hedgehog and Wnt signaling pathways. *Exp. Cell Res.* **319**, 623-632. doi:10.1016/j.yexcr.2012.12.028
- Warren, J. D., Rohrer, J. D. and Rossor, M. N. (2013). Clinical review. Frontotemporal dementia. *BMJ* **347**, f4827. doi:10.1136/bmj.f4827
- Wartosch, L., Bright, N. A. and Luzio, J. P. (2015). Lysosomes. *Curr. Biol.* **25**, R315-R316. doi:10.1016/j.cub.2015.02.027
- Watkin, L. B., Jessen, B., Wiszniewski, W., Vece, T. J., Jan, M., Sha, Y., Thamsen, M., Santos-Cortez, R. L., Lee, K., Gambin, T. et al. (2015). COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. *Nat. Genet.* **47**, 654-660. doi:10.1038/ng.3279
- Wehrle, A., Witkos, T. M., Unger, S., Schneider, J., Follit, J. A., Hermann, J., Welting, T., Fano, V., Hietala, M., Vatanavicharn, N. et al. (2019). Hypomorphic mutations of TRIP11 cause odontochondroplasia. *JCI Insight* **4**, e124701. doi:10.1172/jci.insight.124701
- West, A. B., Moore, D. J., Biskup, S., Bugayenko, A., Smith, W. W., Ross, C. A., Dawson, V. L. and Dawson, T. M. (2005). Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. *Proc. Natl. Acad. Sci. USA* **102**, 16842-16847. doi:10.1073/pnas.0507360102
- Wheeler, D. B., Zoncu, R., Root, D. E., Sabatini, D. M. and Sawyers, C. L. (2015). Identification of an oncogenic RAB protein. *Science* **350**, 211-217. doi:10.1126/science.aaa4903
- Wiegerinck, C. L., Janecke, A. R., Schneeberger, K., Vogel, G. F., van Haften-Visser, D. Y., Escher, J. C., Adam, R., Thoni, C. E., Pfaller, K., Jordan, A. J. et al. (2014). Loss of syntaxin 3 causes variant microvillus inclusion disease. *Gastroenterology* **147**, 65-68.e10. doi:10.1053/j.gastro.2014.04.002
- Wilson, G. R., Sim, J. C., McLean, C., Giannandrea, M., Galea, C. A., Riseley, J. R., Stephenson, S. E., Fitzpatrick, E., Haas, S. A., Pope, K. et al. (2014). Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with alpha-synuclein pathology. *Am. J. Hum. Genet.* **95**, 729-735. doi:10.1016/j.ajhg.2014.10.015
- Witkos, T. M., Chan, W. L., Joensuu, M., Rhiel, M., Pallister, E., Thomas-Oates, J., Mould, A. P., Mironov, A. A., Biot, C., Guerardel, Y. et al. (2019). GORAB scaffolds COPI at the trans-Golgi for efficient enzyme recycling and correct protein glycosylation. *Nat. Commun.* **10**, 127. doi:10.1038/s41467-018-08044-6
- Wong, M. and Munro, S. (2014). Membrane trafficking. The specificity of vesicle traffic to the Golgi is encoded in the golgin coiled-coil proteins. *Science* **346**, 1256898. doi:10.1126/science.1256898
- Wu, X., Steet, R. A., Bohorov, O., Bakker, J., Newell, J., Krieger, M., Spaapen, L., Kornfeld, S. and Freeze, H. H. (2004). Mutation of the COG complex subunit gene COG7 causes a lethal congenital disorder. *Nat. Med.* **10**, 518-523. doi:10.1038/nm1041
- Xue, K., Jolly, J. K., Barnard, A. R., Rudenko, A., Salvetti, A. P., Patrício, M. I., Edwards, T. L., Groppe, M., Orleans, H. O., Tolmachova, T. et al. (2018). Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia. *Nat. Med.* **24**, 1507-1512. doi:10.1038/s41591-018-0185-5
- Yang, Y., Hentati, A., Deng, H.-X., Dabbagh, O., Sasaki, T., Hirano, M., Hung, W.-Y., Ouahchi, K., Yan, J., Azim, A. C. et al. (2001). The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis. *Nat. Genet.* **29**, 160-165. doi:10.1038/ng1001-160
- Yang, X.-Y., Zhou, X.-Y., Wang, Q. Q., Li, H., Chen, Y., Lei, Y.-P., Ma, X.-H., Kong, P., Shi, Y., Jin, L. et al. (2013). Mutations in the COPII vesicle component gene SEC24B are associated with human neural tube defects. *Hum. Mutat.* **34**, 1094-1101. doi:10.1002/humu.22338
- Yehia, L., Niazi, F., Ni, Y., Ngeow, J., Sankunny, M., Liu, Z., Wei, W., Mester, J. L., Keri, R. A., Zhang, B. et al. (2015). Germline heterozygous variants in SEC23B are associated with cowden syndrome and enriched in apparently sporadic thyroid cancer. *Am. J. Hum. Genet.* **97**, 661-676. doi:10.1016/j.ajhg.2015.10.001
- Yehia, L., Jindal, S., Komar, A. A. and Eng, C. (2018). Non-canonical role of cancer-associated mutant SEC23B in the ribosome biogenesis pathway. *Hum. Mol. Genet.* **27**, 3154-3164. doi:10.1093/hmg/ddy226
- Zarranz, J. J., Alegre, J., Gómez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B. et al. (2004). The new

- mutation, E46K, of  $\alpha$ -synuclein causes parkinson and Lewy body dementia. *Ann. Neurol.* **55**, 164-173. doi:10.1002/ana.10795
- Zhang, B., Cunningham, M. A., Nichols, W. C., Bernat, J. A., Seligsohn, U., Pipe, S. W., McVey, J. H., Schulte-Overberg, U., de Bosch, N. B., Ruiz-Saez, A. et al. (2003a). Bleeding due to disruption of a cargo-specific ER-to-Golgi transport complex. *Nat. Genet.* **34**, 220-225. doi:10.1038/ng1153
- Zhang, Q., Zhao, B., Li, W., Oiso, N., Novak, E. K., Rusiniak, M. E., Gautam, R., Chintala, S., O'Brien, E. P., Zhang, Y. et al. (2003b). Ru2 and Ru encode mouse orthologs of the genes mutated in human Hermansky-Pudlak syndrome types 5 and 6. *Nat. Genet.* **33**, 145-153. doi:10.1038/ng1087
- Zhang, B., Kaufman, R. J. and Ginsburg, D. (2005). LMAN1 and MCFD2 form a cargo receptor complex and interact with coagulation factor VIII in the early secretory pathway. *J. Biol. Chem.* **280**, 25881-25886. doi:10.1074/jbc.M502160200
- Zhang, X., Chow, C. Y., Sahenk, Z., Shy, M. E., Meisler, M. H. and Li, J. (2008). Mutation of FIG4 causes a rapidly progressive, asymmetric neuronal degeneration. *Brain* **131**, 1990-2001. doi:10.1093/brain/awn114
- Zhao, X., Alvarado, D., Rainier, S., Lemons, R., Hedera, P., Weber, C. H., Tukul, T., Apak, M., Heiman-Patterson, T., Ming, L. et al. (2001). Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nat. Genet.* **29**, 326-331. doi:10.1038/ng758
- Zhao, Y. and Dзамко, N. (2019). Recent developments in LRRK2-targeted therapy for Parkinson's disease. *Drugs* **79**, 1037-1051. doi:10.1007/s40265-019-01139-4
- Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R. J., Calne, D. B. et al. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* **44**, 601-607. doi:10.1016/j.neuron.2004.11.005
- Zimprich, A., Benet-Pagès, A., Struhal, W., Graf, E., Eck, S. H., Offman, M. N., Haubenberger, D., Spielberger, S., Schulte, E. C., Lichtner, P. et al. (2011). A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. *Am. J. Hum. Genet.* **89**, 168-175. doi:10.1016/j.ajhg.2011.06.008
- Zivony-Elboun, Y., Westbroek, W., Kfir, N., Savitzki, D., Shoval, Y., Bloom, A., Rod, R., Khayat, M., Gross, B., Samri, W. et al. (2012). A founder mutation in Vps37A causes autosomal recessive complex hereditary spastic paraparesis. *J. Med. Genet.* **49**, 462-472. doi:10.1136/jmedgenet-2012-100742
- Zuchner, S., Noureddine, M., Kennerson, M., Verhoeven, K., Claeys, K., De Jonghe, P., Merory, J., Oliveira, S. A., Speer, M. C., Stenger, J. E. et al. (2005). Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot-Marie-Tooth disease. *Nat. Genet.* **37**, 289-294.
- zur Stadt, U., Schmidt, S., Kasper, B., Beutel, K., Diler, A. S., Henter, J. I., Kabisch, H., Schneppenheim, R., Nurnberg, P., Janka, G. et al. (2005). Linkage of familial hemophagocytic lymphohistiocytosis (FHL) type-4 to chromosome 6q24 and identification of mutations in syntaxin 11. *Hum. Mol. Genet.* **14**, 827-834. doi:10.1093/hmg/ddi076
- zur Stadt, U., Rohr, J., Seifert, W., Koch, F., Grieve, S., Pagel, J., Strauss, J., Kasper, B., Nurnberg, G., Becker, C. et al. (2009). Familial hemophagocytic lymphohistiocytosis type 5 (FHL-5) is caused by mutations in Munc18-2 and impaired binding to syntaxin 11. *Am. J. Hum. Genet.* **85**, 482-492. doi:10.1016/j.ajhg.2009.09.005