Traffic

WILEY

Traffic

REVIEW OPEN ACCESS

Disease-Associated Factors at the Endoplasmic Reticulum–Golgi Interface

Miharu Maeda | Masashi Arakawa | Kota Saito

Department of Biological Informatics and Experimental Therapeutics, Graduate School of Medicine, Akita University, Akita, Japan

Correspondence: Kota Saito (ksaito@med.akita-u.ac.jp)

Received: 4 May 2024 | **Revised:** 19 November 2024 | **Accepted:** 17 February 2025

Funding: This work was supported by JSPS Grants-in-Aid for Scientific Research (23K24023 to M.M.; 24K18067 to M.A.; and 23K27123, 24K22065 to K.S.) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Naito Foundation (K.S. and M.M.). K.S. received support from the Takeda Science Foundation, Asahi Glass Foundation, and the Princess Takamatsu Cancer Research Foundation.

Keywords: COPI | COPII | disease-associated factor | endoplasmic reticulum | ER exit site | ERGIC | Golgi | liquid-phase separation | nonvesicular transport | TRAPP complex

ABSTRACT

The endoplasmic reticulum (ER)–Golgi interface is essential for directing the transport of proteins synthesized in the ER to the Golgi apparatus via the ER–Golgi intermediate compartment, as well as for recycling proteins back to the ER. This transport is facilitated by various components, including COPI and COPII coat protein complexes and the transport protein particle complex. Recently, the ER–Golgi transport pathway has gained attention due to emerging evidence of nonvesicular transport mechanisms and the regulation of trafficking through liquid–liquid phase separation. Numerous diseases have been linked to mutations in proteins localized at the ER–Golgi interface, highlighting the need for comprehensive analysis of these conditions. This review examines the disease phenotypes associated with dysfunctional ER–Golgi transport factors and explores their cellular effects, providing insights into potential therapeutic strategies.

1 | Introduction

Intracellular membrane transport is essential for the movement of substances between various cellular organelles. At the heart of this system is the endoplasmic reticulum (ER)–Golgi interface, which serves as the central pathway for transporting proteins synthesized in the ER to other organelles and locations within the cell [1–3].

Historically, transport from the ER to the Golgi apparatus was believed to rely primarily on coat protein complex II (COPII)-coated vesicles. These vesicles form at specific regions of the ER known as ER exit sites and facilitate cargo transport to the Golgi apparatus. This mechanism was thought to be conserved from yeast to humans [4, 5]. However, recent studies have reported alternative transport modes in mammalian cells. Evidence now suggests that, in addition to COPII vesicles, certain materials may also travel from the ER to the Golgi via tubular structures, thereby bypassing traditional COPII vesicle-mediated transport [6–11].

An important structure within this transport pathway is the ER-Golgi intermediate compartment (ERGIC), an organelle positioned between the ER and Golgi apparatus that acts as a relay station for cargo [12–15]. Although ERGIC was initially thought to exist only in higher eukaryotes, recent studies have indicated the possibility of an ERGIC-like organelle in yeast [16]. This discovery underscores the evolving understanding of the ER–Golgi transport system, with several previously accepted concepts now being reconsidered in light of new evidence.

Another recent area of interest is the role of liquid–liquid phase separation (LLPS) in membrane trafficking. It has been found that certain transport machinery and their interacting partners

can undergo LLPS, forming dynamic liquid droplets. This phase separation plays a critical role in regulating the spatial organization and functional dynamics of membrane transport [17].

With these new models and mechanisms emerging for ER–Golgi transport, it has become essential to explore how disruptions in these pathways contribute to disease. In this review, we systematically summarize the cellular functions of key factors at the ER–Golgi interface and the diseases that arise due to their dysfunction. By examining these disease phenotypes in the context of recent findings, we hope to provide new insights into the physiological and pathological roles of these factors, thereby establishing a stage for future therapeutic strategies.

2 | Proteins at ER Exit Sites

The formation of COPII-coated vesicles is initiated by the activation of the small GTPase Sar1. In its GDP-bound state, Sar1 remains in the cytoplasm. However, upon activation by the guanine nucleotide exchange factor (GEF) Sec12, Sar1 binds to GTP and associates with the ER membrane. GTP-bound Sar1 then forms a prebudding complex by interacting with the Sec23/Sec24 complex, thereby enhancing the binding of cargo proteins to Sec24. Recruitment of the outer coat proteins Sec13/31 to the Sec23/24 complex further stimulates the GTPase-activating protein (GAP) activity of Sec23, promoting the GTP hydrolysis of Sar1. Following hydrolysis, Sar1 in its GDP-bound form is released back into the cytoplasm, allowing the cargo to be transported from the ER to the Golgi apparatus (Figure 1) [18–21].

Sec16 serves as a scaffold by binding to multiple COPII components that play an essential role in the formation of ER exit sites [22–25]. In humans, Sec16 exists as two homologs: Sec16A and Sec16B. Sec16A, characterized by its intrinsically disordered regions, is phosphorylated by the dual-specificity kinase DYRK3, which regulates its liquid–liquid phase separation, thereby modulating the physical state and function of ER exit sites [26].

These factors, which are conserved from yeast, have traditionally been regarded as essential for COPII vesicle formation. However, recent studies have uncovered additional factors unique to higher eukaryotes that play critical roles in this process, suggesting an evolutionary divergence in COPII vesicle biogenesis.

One such factor, TANGO1, was initially identified in *Drosophila* S2 cells as essential for secretion through genome-wide screening [27]. Studies in human cells have further elucidated its role as a cargo receptor for collagen at ER exit sites [28–31]. TANGO1 promotes Sar1 activation and efficient collagen secretion by recruiting cTAGE5 and Sec12 to the ER exit sites [32–34]. It forms a ring-like structure at the ER exit sites and recruits ERGIC membranes to facilitate collagen transport [11, 14, 35, 36]. TANGO1 undergoes alternative splicing, resulting in a short form, TANGO1S, and a long

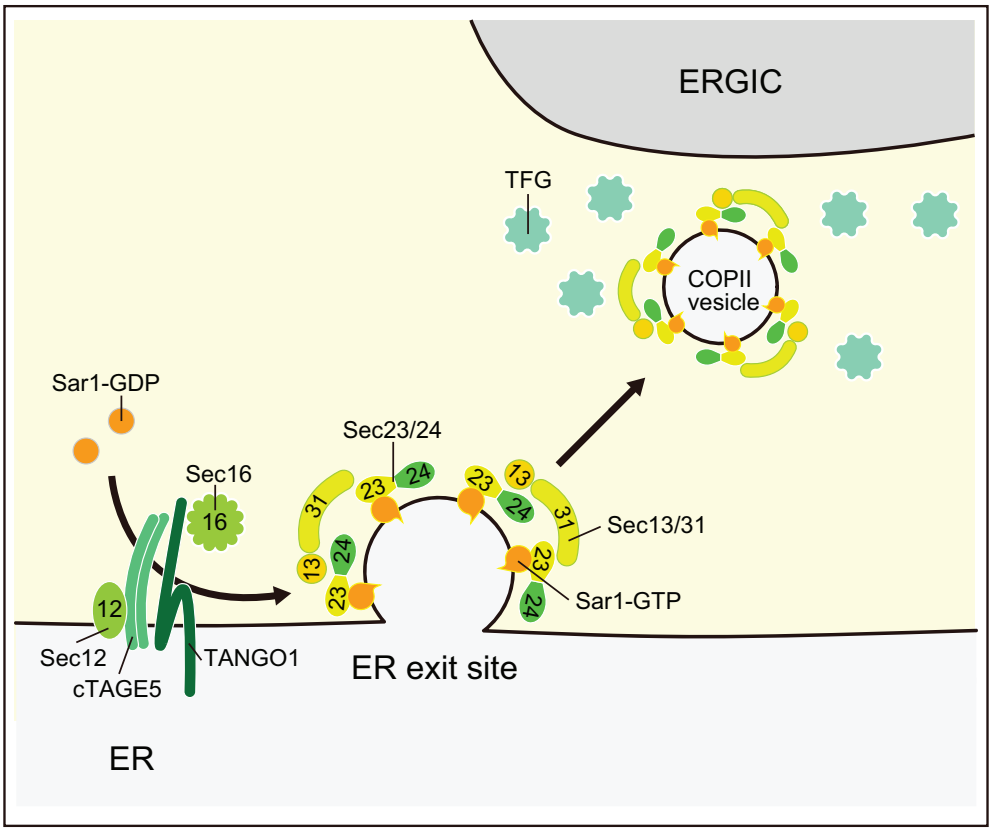

FIGURE 1 | Model of COPII vesicle formation at the ER exit site. The ER exit site is a specialized region of the ER membrane formed by TANGO1 and Sec16. In mammals, TANGO1 forms a complex with cTAGE5 and Sec12, which activates the small GTPase, Sar1. Activated Sar1 binds to the Sec23/24 complex, which then recruits the Sec13/31 complex, leading to COPII vesicle assembly. TFG localizes to the region between the ER and ERGIC, facilitating transport via COPII vesicles.

form, TANGO1L. Both isoforms contribute to ER exit-site organization in conjunction with Sec16A [37, 38]. During mitosis, TANGO1 is phosphorylated by CK1, which modulates its interaction with Sec16A and facilitates ER exit site disassembly [39].

TRK-fused gene (TFG), another critical component, forms an oncogenic fusion gene with TrkA receptor tyrosine kinase [40]. TFG self-assembles into octamers and localizes at the ER/ERGIC interface, where it interacts with multiple factors to regulate the organization of the early secretory pathway and ER export [41–44]. Recent research suggests that the C-terminal region of TFG, which is rich in intrinsically disordered regions, undergoes liquid–liquid phase separation to form liquid droplets, enhancing vesicular transport efficiency at the ER/ERGIC interface [8, 9].

In contrast, recent studies on vesicle-independent transport from the ER have highlighted that, while the precise roles of many factors remain unclear [6, 7], Sar1 activation continues to be recognized as indispensable [45].

2.1 | Sar1

In humans, the Sar1 homolog, Sar1B, is linked to chylomicron retention disease (CMRD; OMIM #246700), an autosomal recessive disorder characterized by impaired fat absorption, growth failure, and steatorrhea [46–49]. Accumulated lipid droplets in enterocytes of affected individuals suggest that Sar1B mutations disrupt chylomicron secretion in the intestine [49]. Many CMRD-associated mutations are located within the GTP-binding domain of Sar1B, indicating a loss-of-function effect [46]. Additionally, some Sar1B mutations significantly reduce protein expression [49].

Sar1B overexpression promotes ApoB-48 secretion, a chylomicron component, while Sar1A overexpression decreases ApoB-48 secretion, suggesting distinct roles of Sar1 homologs in chylomicron secretion [50]. Sar1A cannot compensate for Sar1B in restoring ApoB-48 secretion when Sar1B is suppressed [51]. Sar1B binds more strongly to Sec23/24 and forms gently curved vesicles without oligomerization, suggesting distinct cargo specificities for Sar1A and Sar1B [51].

In contrast, simultaneous suppression of both Sar1A and Sar1B synergistically reduced ApoB and chylomicron secretion, indicating partial functional redundancy [52]. Furthermore, Sar1A and Sar1B participate in regulating the expression of enzymes involved in ApoB and cholesterol biosynthetic pathways [50]. Sar1 regulates lipid biosynthesis pathway enzymes and possibly influences lipid homeostasis through SREBP transport to the Golgi [53].

2.2 | Sec23

In humans, Sec23 exists in two homologous forms, Sec23A and Sec23B, each associated with distinct genetic diseases. Sec23A mutations cause cranio–lenticulo–sutural dysplasia (CLSD; OMIM #607812), a condition characterized by late-closing fontanels, facial dysmorphisms, and skeletal abnormalities. The pathogenic mutations in Sec23A include a homozygous F382L mutation and heterozygous M702V and E599K mutations [54–57]. The F382 and M702 residues are located at interaction sites between Sec23A and Sec31 [55, 58], and these mutations alter the role of Sec23A in membrane recruitment and GAP activity toward Sar1B. Specifically, the F382L mutation disrupts Sec31 recruitment to membranes and inhibits GAP activity, while the M702V mutation enhances GAP activity, leading to Golgi enlargement and impaired collagen secretion [58, 59]. These observations suggest that the altered GAP activity of Sec23A toward Sar1B underlies the abnormalities in collagen trafficking seen in CLSD. The E599K mutation, located at the interaction site between Sec23A and Sar1, is also thought to influence GAP activity, further implicating the Sec23A–Sar1 interaction in disease pathology [56].

In contrast, mutations in Sec23B are linked to congenital dyserythropoietic anemia type II (CDAN2; OMIM #224100), a disorder characterized by impaired erythrocyte maturation [60–64]. Zebrafish morpholino-based studies have supported the role of Sec23B in erythrocyte differentiation, demonstrating that Sec23B is essential for proper red blood cell development [60]. These findings emphasize the specialized roles of Sec23 homologs in different tissues, and disease associations reflect these functional distinctions.

Although Sec23A and Sec23B play distinct roles, they exhibit functional redundancy under certain conditions. For example, during erythrocyte maturation, Sec23A expression declines as Sec23B expression becomes predominant, with Sec23B compensating for the absence of Sec23A in this context [60]. Experimental evidence also suggests that the function of Sec23B can be partially rescued by expressing Sec23A under the control of the Sec23B promoter, indicating that these homologs can perform interchangeable roles when appropriately regulated [65–67]. In conditional knockout models targeting Sec23B in T cells, Sec23A can compensate for the loss of Sec23B, restoring T cell proliferation and secretion of cytokines such as IL-2, IL-7 and IFN-γ [68]. This redundancy indicates that tissue-specific transcriptional regulation, rather than intrinsic functional differences, is likely a primary factor in determining the phenotypic consequences of Sec23A and Sec23B mutations.

In addition to their roles in genetic diseases, Sec23 proteins have been implicated in cancer. A homozygous missense mutation in Sec23B has been linked to Cowden's syndrome, an autosomal dominant familial cancer syndrome [69]. Furthermore, both Sec23A and Sec23B are targeted by cancer-associated microRNAs, with expression levels of Sec23A generally reduced in tumors and Sec23B expression elevated [70]. These contrasting expression patterns suggest that the two homologs might have distinct functions in oncogenesis, potentially influencing tumorigenesis in opposite directions.

2.3 | Sec24

The Sec24 family, which includes four paralogs (Sec24A-D), also plays a critical role in ER export by binding to various

cargos and cargo receptors to facilitate protein exit from the ER. Among these, mutations in Sec24D cause Cole–Carpenter syndrome type 2 (CLCRP2; OMIM #616294), a disorder resembling osteogenesis imperfecta, with clinical features including multiple fractures and facial dysmorphisms [71–74]. Cells derived from patients with CLCRP2 exhibit defective collagen secretion and an enlarged ER, implicating impaired collagen trafficking in disease pathology [71]. Similar phenotypes are observed in Sec24D-deficient zebrafish and medaka [75, 76], and the clinical manifestations of CLCRP2 overlap with those of CLSD, caused by Sec23A mutations. These findings suggest that Sec24D mutations disrupt the function of the Sec23/24 complex, thereby contributing to CLCRP2.

2.4 | Sec16

Sec16B interacts with Sec16A and plays a role in peroxisome biogenesis; however, its precise molecular functions remain unclear [22, 77]. Recent studies have shown that homozygous mutations in Sec16B cause a form of osteogenesis imperfecta, characterized by leg bowing, vertebral fractures, low bone mass, musculoskeletal pain, short stature and muscle weakness [78]. In cells from affected individuals, type I collagen accumulates within the ER, leading to increased ER stress, autophagy, and apoptosis. Importantly, expression of wild-type Sec16B can alleviate the collagen secretion defect, highlighting the critical role of Sec16B in collagen processing and ER homeostasis [78].

2.5 | Sec31

In humans, Sec31 exists as two homologs: Sec31A and Sec31B [79]. Homozygous frameshift mutations in Sec31A have been identified through exome sequencing in patients with Halperin–Birk syndrome (HLBKS, OMIM #610257), a disorder characterized by structural brain abnormalities and developmental delays [80]. A similar disease phenotype has been observed in flies with suppressed Sec31A expression, underscoring the critical role of Sec31A in normal brain development. Recently, heterozygous nonsense mutations in Sec31A have been linked to hypopituitarism and gonadal dysgenesis. Some patients with these mutations exhibit milder developmental delays than those observed in HLBKS [81]. ER stress responses were detected in all affected patients, suggesting that Sec31 dysfunction-induced ER stress may play a role in neurodegeneration.

2.6 | Sec13

Conditional knockout of Sec13 specifically in oligodendrocytes in mice disrupts oligodendrocyte differentiation and impairs myelination, underscoring the essential role of Sec13, along with Sec31, in normal brain development [82]. Further studies reveal that the Sec13/31 complex is selectively recruited to intrinsically disordered region-mediated condensation formed by SCOTIN/SHISA-5, where ER-Golgi trafficking is inhibited in response to IFN-γ stimulation or the expression of cancer-associated SCOTIN mutants [83]. Additionally, during influenza infection, Sec13 interacts with the viral protein NS1, suggesting an important role for Sec13 in viral pathogenesis [84].

2.7 | TFG

Mutations in TFG have been implicated in autosomal recessive spastic paraplegia 57 (SPG57; OMIM #615658), a clinically heterogeneous axonopathy characterized by gait abnormalities and neurological symptoms due to upper motor neuron impairment [85–87]. These are primarily missense mutations within the N-terminal Phox and Bem1 (PB1) domains and the coiled-coil regions of TFG. Notably, the R106C mutation in the coiled-coil domain results in defective TFG oligomerization and delayed ER exit [85, 88]. In rat neuronal cells expressing the R106C variant, impaired endosomal cargo trafficking and downregulated inhibitory receptor signaling were observed, highlighting the multifaceted roles of TFG in the nervous system and suggesting its importance in motor neuron maintenance [89].

Heterozygous TFG mutations cause neuropathy, hereditary motor and sensory, Okinawa type (HMSNO; OMIM #604484), a neurodegenerative disorder characterized by muscle weakness, atrophy, and distal sensory loss [90–92]. HMSNO is considered a rare form of Charcot–Marie–Tooth disease [93, 94]. In patients with HMSNO, the motor neurons show TDP-43 inclusion bodies and Golgi fragmentation, indicative of neuronal dysfunction [90]. Disease-causing mutations such as P285L and G269V are missense variants in the PQ-rich domain that are crucial for TFG localization [42]. These mutations induce TFG aggregation in cells [93, 94]. In zebrafish models, TFG suppression impedes neurite outgrowth, triggers neuronal apoptosis, and reduces motor function, indicating that HMSNO is caused by TFG mislocalization, resulting in loss of function and neuronal apoptosis [94].

2.8 | TANGO1

A homozygous mutation in the TANGO1 gene has been identified as the causative factor of severe dentinogenesis imperfecta, short stature, various skeletal abnormalities, insulin-dependent diabetes mellitus, sensorineural hearing loss, and mild intellectual disability, underscoring the essential role of TANGO1 in physiological processes [95]. These findings highlight the broad influence of TANGO1 on normal development and function and emphasize the need for further investigation into its mechanisms.

A missense mutation within exon 8 of TANGO1L, at the amino acid level, disrupts splicing and produces a truncated version of TANGO1L. This mutation may also affect the shorter isoform, TANGO1S, since both TANGO1L and TANGO1S are often affected in patients. However, some affected individuals retain the normal spliced versions of TANGO1L/S, suggesting variable expression outcomes [95].

In a separate study, a distinct mutation involving a 4-base-pair deletion within an exon of TANGO1L was identified in both the parents and offspring. This mutation significantly reduced TANGO1L expression, leading to embryonic lethality and

near-complete bone loss [96]. Interestingly, this deletion did not affect TANGO1S, mirroring the phenotype observed in previously reported TANGO1L-knockout mice [97]. Collectively, these results suggest that TANGO1L, but not TANGO1S, is indispensable for skeletal integrity and viability.

3 | COPI Proteins

COPI vesicles facilitate retrograde transport from the Golgi to the ER and mediate intra-Golgi transport (Figure 2). In humans, the COPI vesicle coat is a hetero-multimeric complex comprising subunits, such as coatomer subunit alpha (COPA), beta 1 (COPB1), beta 2 (COPB2), delta (COPD), epsilon (COPE), gamma 1 (COPG1), gamma 2 (COPG2), zeta 1 (COPZ1) and zeta 2 (COPZ2). These coatomer proteins are recruited to the membrane through the activation of ADP-ribosylation factors (ARFs), a family of small GTPases. Activation of ARFs, including ARF1, is facilitated by ARF guanine nucleotide exchange factors (ARF-GEFs) such as GBF1, which catalyzes the exchange of GDP for GTP.

3.1 | Arf1

ADP-ribosylation factor 1 (Arf1) is predominantly localized on the cis-Golgi, trans-Golgi and ERGIC, where it plays a critical role in maintaining the Golgi structure. Activated Arf1 recruits COPI at the cis-Golgi and ERGIC, thereby facilitating retrograde transport to the ER. At the trans-Golgi, Arf1 recruits coat complexes, such as AP-1 and clathrin, that are involved in different trafficking pathways [98, 99]. Arf1 knockout mice exhibit embryonic lethality [100], and heterozygous missense mutations within the GDP-binding site of Arf1 impair its activation, causing periventricular nodular heterotopia 8 (PVNH8; OMIM #618185), a neurological disorder characterized by abnormal neuronal migration, delayed psychomotor development and intellectual disability [101]. Notably, a similar disorder, periventricular heterotopia with microcephaly (PVNH2), arises due to heterozygous mutations in ARFGEF2, an ARF-GEF that localizes primarily to the trans-Golgi network (TGN) and activates Arf1 and Arf3 [102–104]. This similarity indicates the critical role of Arf1 function in the TGN in PVNH8 pathology. Recently, constitutive activation of Arf1 has also been associated with PVNH8, where monoallelic missense mutations led to Golgi enlargement and increased recruitment of adapter proteins in patient-derived cells, presenting with developmental delay, hypotonia, intellectual disability and motor stereotypies [105].

3.2 | GBF1

Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1 (GBF1) is localized at the ER exit sites, ERGIC, and cis-Golgi, where it activates multiple Arf proteins, including Arf1, and recruits COPI vesicles, thus supporting retrograde transport to the ER [106]. Heterozygous mutations in GBF1 cause Charcot–Marie–Tooth disease, axonal, type 2GG (CMT2GG; OMIM #606483), characterized by peripheral axonal neuropathy, distal sensory impairment, muscle weakness in the lower limbs and gait difficulties [107]. Golgi fragmentation in primary fibroblasts from patients with CMT2GG indicates potential trafficking disruptions. Diseases caused by Arf1 mutations are more strongly linked to ARFGEF2, which localizes to the TGN, than to GBF1 mutations [101–104]. Therefore, future analyses are required to elucidate whether the mechanisms by which GBF1 mutations lead to disease are associated with abnormal activation of Arf1 or the involvement of other Arf proteins.

3.3 | COPA

Coatomer subunit alpha (COPA), a component of the COPI vesicle coat, is essential for retrograde transport from the Golgi to the ER and is recruited to the membrane upon Arf1 activation [108]. The WD40 domain of COPA binds to dilysine motifs on cargo proteins. Watkin et al. identified four heterozygous missense mutations in the WD40 domain of COPA across five families with autoimmune interstitial lung, joint, and kidney disease (AILJK; OMIM #616414) [109]. These mutations impair the ability of COPA to bind to the dilysine motif, thereby disrupting retrograde transport.

Stimulator of interferon genes (STING), a key regulator of innate immune responses, normally resides in the ER, but relocates to the Golgi upon activation by cyclic dinucleotides, leading to

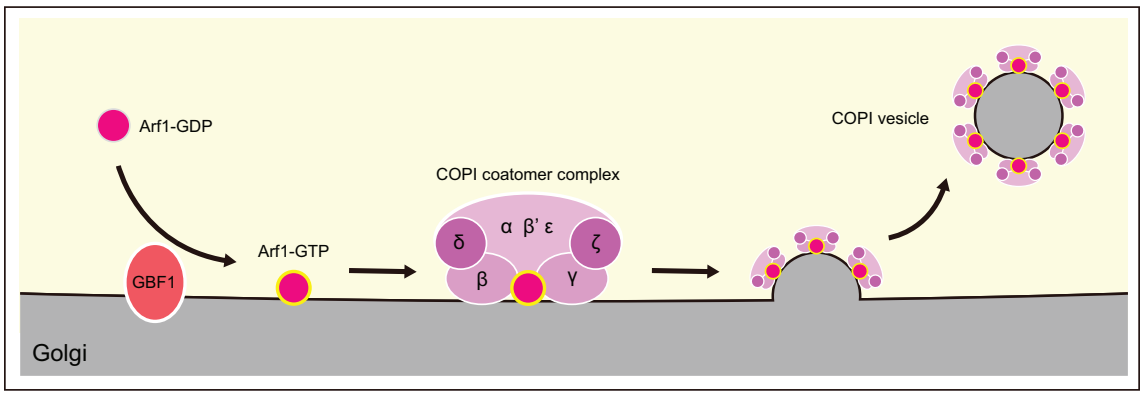

FIGURE 2 | Schematic of COPI vesicle formation. Arf1 is activated by GBF1 on the Golgi membrane, converting it to its GTP-bound state, which in turn recruits the COPI coatomer complex. The COPI coatomer complex comprises the following subunits: Alpha (COPA), beta 1 (COPB1), beta 2 (COPB2), delta (COPD), epsilon (COPE), gamma 1 (COPG1), gamma 2 (COPG2), zeta 1 (COPZ1) and zeta 2 (COPZ2) that form the COPI vesicle.

type I interferon expression [110]. Deng et al. found that STING was mislocalized to the Golgi apparatus in cells with suppressed COPA expression or mutations associated with COPA syndrome. Mutant mice with this syndrome developed type I IFN-driven inflammation, which was not observed in STING-deficient mice [111]. Type I IFN levels and IFN-stimulated gene (ISG) expression were elevated in the blood of patients with COPA syndrome, reflecting STING-dependent IFN production [112]. Thus, the inflammation observed due to COPA mutations may be mediated by STING activation. STING forms a complex with COPA and Surf4 and is transported to the ER. In patients with COPA syndrome, mutant COPA failed to form this complex [113]. Therefore, we inferred that COPA syndrome is caused by ectopic localization and constitutive activation of STING in the Golgi apparatus.

3.4 | COPB1

COPI coat complex subunit beta 1 (COPB1) is the core component of the COPI coatomer complex. Homozygous mutations in COPB1 cause Baralle–Macken syndrome (BARMACS; OMIM #619255), a rare genetic disorder characterized by global developmental delay, severe intellectual disability and cataracts [114]. Two primary mutation types have been identified in patients with BARMACS: a 36-amino-acid deletion resulting from exon 8 skipping, which mimics human syndrome features in *Xenopus* models, and a F551V missense mutation that disrupts the cellular localization of COPB1. Both mutations impact the β-COP trunk domain, essential for interaction with COPB2. Some patients with BARMACS also exhibit microcephaly, suggesting a potential link with COPB2 mutations, which are also associated with microcephaly.

3.5 | COPB2

COPI coat complex subunit beta 2 (COPB2), another COPI coatomer protein, recognizes cargo dilysine motifs through its N-terminal WD40 propeller domain. The R254C homozygous mutation in COPB2 causes primary autosomal recessive microcephaly 19 (MCPH19; OMIM #617800), a congenital brain malformation [115]. This mutation occurs at a conserved residue within the WD40 domain, indicating its critical role in COPB2 function. In heterozygous mice with the COPB2 R254C mutation and a null allele, cortical dysgenesis resembling human MCPH19 was observed, and the animals exhibited early lethality, highlighting the essential role of COPB2 in brain development [115].

In addition to MCPH19, COPB2 mutations also cause osteoporosis, childhood- or juvenile-onset, with developmental delay (OPDD; OMIM #619884) [116]. Six patients with OPDD were found to harbor various COPB2 mutations, including a homozygous R254C mutation (identical to that observed in MCPH19), two heterozygous frameshift mutations, one heterozygous nonsense mutation and one splicing abnormality. Notably, patients carrying the homozygous R254C mutation also presented with microcephaly, in addition to the characteristic features of OPDD. Partial depletion of COPB2 in cultured cells resulted in the inhibition of procollagen I transport from the endoplasmic reticulum (ER), providing strong evidence that the ER dilation observed in fibroblasts from patients with OPDD reflects impaired collagen secretion due to loss of COPB2 function. This disruption in collagen secretion likely contributes to the reduced bone density observed in these patients. In support of this hypothesis, both heterozygous COPB2 knockout mice and zebrafish homozygous for COPB2 frameshift mutations exhibited reduced collagen secretion and compromised bone density [116].

In cells with suppressed COPB2 expression, disorganization of the Golgi apparatus and ERGIC was observed. Since the ERGIC serves as a critical membrane source for procollagen-containing transport vesicles [14], this disorganization may impair collagen secretion. Alternatively, COPI may play a direct role in the exit of procollagen from the ER, as its involvement in collagen secretion has been previously demonstrated [117, 118]. Recent studies have further demonstrated the association of COPI with transport intermediates extending from ER exit sites [6, 7].

3.6 | COPD

COPD is part of the COPI coatomer complex and is essential for vesicle formation and intracellular transport. Mutations in COPD are linked to short stature–micrognathia syndrome (SSMG; OMIM #617164), characterized by rhizomelic short stature and micrognathia [119–122]. In COPD knockdown cellular models, deficiencies in collagen secretion and increased ER stress have been observed, suggesting that the skeletal abnormalities seen in SSMG are due to impaired collagen transport [119].

Moreover, osteogenesis imperfecta, commonly associated with defective collagen processing, is observed in conditions caused by COPB2 mutations, underscoring the importance of the COPI coatomer in bone development. Patients with SSMG often exhibit microcephaly, a feature shared with conditions involving COPB1 and COPB2 mutations, suggesting the critical role of the COPI coatomer complex in both bone formation and brain development.

4 | Protein Recycling via the ER–Golgi Interface

Cargo receptors cycle between the ER and Golgi, recognizing and transporting specific proteins (Figure 3). This section focuses on three key receptors, ERGIC-53/LMAN1, VIP36/LMAN2, and KDELR that play essential roles in protein transport. These receptors have cargo recognition domains and dilysine motifs that facilitate their retrograde transport from the Golgi to the ER via interaction with the COPI coatomer.

4.1 | ERGIC-53/LMAN1

The ER–Golgi intermediate compartment 53 (ERGIC-53), also known as LMAN1, a mannose-specific lectin, plays a pivotal role as a cargo receptor by recognizing specific glycoprotein cargos and facilitating their transport from the ER. This process is essential for the proper functioning of the ERGIC. ERGIC-53

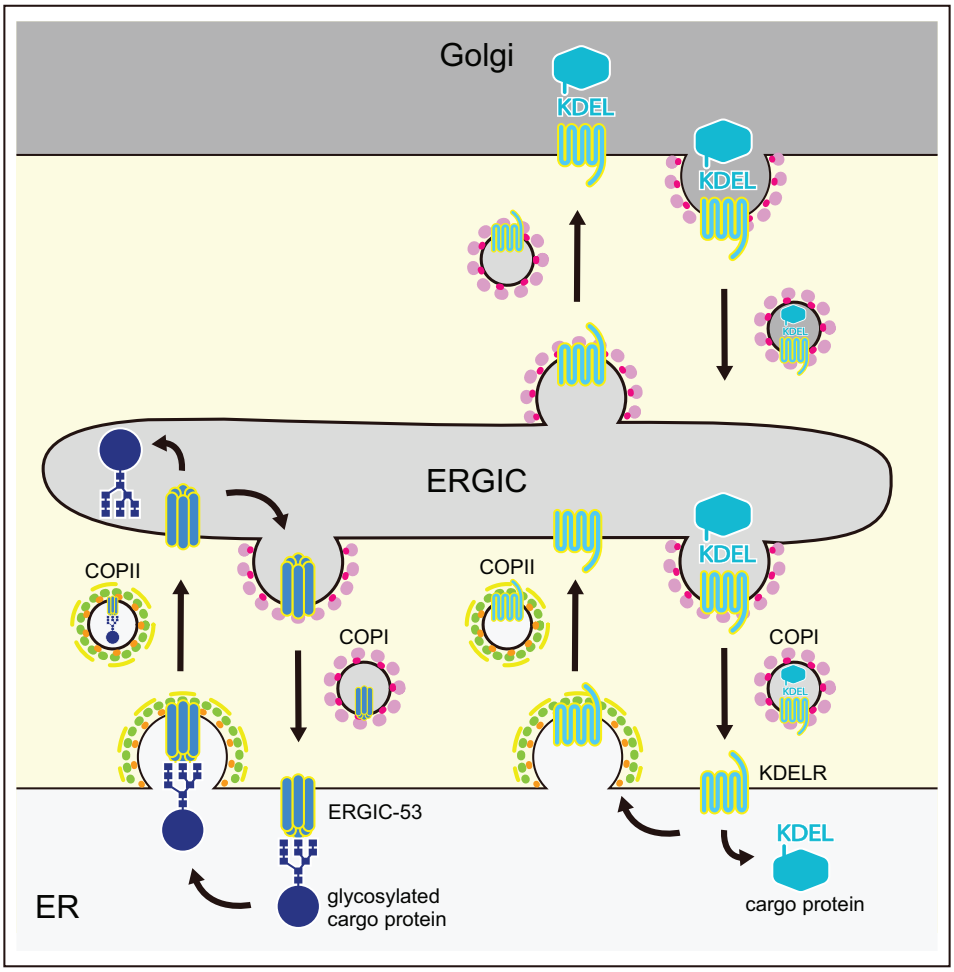

FIGURE 3 | Recycling factors between the ER and Golgi. ERGIC-53 recognizes specific glycans on cargo proteins and mediates their transport from the ER to ERGIC. ERGIC-53 contains a C-terminal motif that interacts with the COPI coatomer complex, enabling its recycling from ERGIC back to the ER via COPI vesicles. The KDEL receptor, a seven-transmembrane-domain protein, recognizes KDEL motifs commonly found in ER-resident proteins and facilitates their transport from the Golgi or ERGIC to the ER, while recycling itself between the ER and Golgi.

contains a C-terminal ER retrieval signal, lys–lys–phe–phe (KKFF), which is believed to interact with COPI coat proteins, enabling its cycling between the ER and ERGIC [123, 124].

Mutations in ERGIC-53 have been associated with factor V and factor VIII combined deficiency 1 (F5F8D1; OMIM #227300) [125–127]. These mutations, which include frameshift, nonsense, and start-codon deletions [127], often result in complete loss of protein expression or loss of function, thereby significantly impacting health. In patient-derived immortalized lymphocytes, ERGIC-53 expression was found to be extremely low [125]. ERGIC-53 knockout mice displayed reduced activity of factor V and factor VIII [128]. In cells expressing mutant forms, introducing mutations in the KKFF motif of ERGIC-53, which disrupt transport between the ER and ERGIC, inhibited the secretion of factor V and factor VIII [129]. The direct binding of factor VIII to ERGIC-53 has been demonstrated, further confirming that factor V and factor VIII are cargos transported from the ER by ERGIC-53 [130].

Mutations in multiple coagulation factor deficiency 2 (MCFD2), the binding partner of ERGIC-53, have also been reported to cause F5F8D2 (OMIM #613625) [131–133]. MCFD2 forms a calcium-dependent complex with ERGIC-53 [131]. Formation of this complex is critical for the efficient secretion of factor V and factor VIII. The W67S mutation in ERGIC-53, observed in F5F8D patients, did not affect its expression but reduced the binding affinity between MCFD2 and D-mannose [134]. These findings suggest that the ERGIC-53 and MCFD2 complex plays a key role in the secretion of factor V and factor VIII.

ERGIC-53 also interacts with other proteins, such as cathepsin C, A1AT, Russell bodies and virus-derived glycoproteins [135, 136], highlighting its diverse roles in protein transport and its potential implications in various diseases. ERGIC-53 knockout mice exhibited perinatal lethality, suggesting its crucial involvement in cargo transport [128].

4.2 | VIP36/LMAN2

VIP36/LMAN2 has been identified as a cargo receptor that recognizes high-mannose glycans [137, 138]. α1-antitrypsin has been reported as a major cargo protein [139]. Proteomic screening following LPS stimulation revealed that the expression of VIP36/LMAN2 regulates macrophage phagocytosis. Future

studies are required to uncover additional immunological roles of VIP36/LMAN2 [140].

4.3 | KDELR

KDEL receptors (KDELRs) are seven-transmembrane-domain proteins with three homologs in humans. They typically bind to the KDEL (lys–asp–glu–leu) sequence or similar motifs commonly found at the C-terminus of ER-resident proteins, facilitating their retrieval back to the ER after exiting. Cela et al. provide a comprehensive review of KDELRs [141]. Recent findings in plant models have suggested that KDELRs might act as gatekeepers in the Golgi apparatus, rather than playing a recycling role as thought previously [142]. Although this hypothesis is based only on observations in plant systems, it raises intriguing questions and warrants further investigation using other models [142, 143]. Mutations in KDELR2 have been identified across multiple pedigrees in patients with osteogenesis imperfecta 21 (OI21) [144, 145]. KDELR2 recognizes KDEL via the PQ motif in its three-dimensional structure. However, mutations observed in OI21 are believed to disrupt this structure, impairing KDELR2 function. Fibroblasts derived from patients with OI21 showed reduced levels of HSP47, a collagen chaperone and cargo protein of KDELR2. This reduction led to abnormal collagen folding and impaired secretion [144].

5 | TRAPP Complex

The TRAPP (transport protein particle) complex is a multisubunit complex found in two main forms in humans, TRAPPII and TRAPPIII, which share a core structure but interact with different accessory proteins to fulfill distinct cellular functions (Figure 4) [146]. Each TRAPP complex consists of a core complex comprising TRAPPC1, TRAPPC2, TRAPPC2L, TRAPPC3, TRAPPC4, TRAPPC5 and TRAPPC6. TRAPPII is formed by interactions with TRAPPC9 and TRAPPC10, while TRAPPIII is formed by interactions with TRAPPC8, TRAPPC11, TRAPPC12 and TRAPPC13 [147]. The TRAPP complex primarily activates small GTPases, specifically those of the Rab family, which play critical roles in vesicular trafficking. In humans, TRAPPII acts as a guanine nucleotide exchange factor (GEF) for Rab11, while TRAPPIII functions as a GEF for Rab1. Additionally, the TRAPP complex has been reported to interact with Rab18, Rab19, and Rab43; although further studies are required to completely understand these interactions [148–150].

Mutations in components of the TRAPP complex are linked to a variety of diseases collectively known as TRAPPopathies, which present a range of symptoms and phenotypes. This phenotypic diversity raises questions about whether different TRAPP subunits have unique, independent roles or whether variations in their expression and localization contribute to disease-specific manifestations [146].

5.1 | Rab1

Rab1 is a small GTPase from the Rab family that is predominantly localized to the ERGIC [151]. It is activated by the TRAPPIII complex and transitions into its GTP-bound state, where it interacts

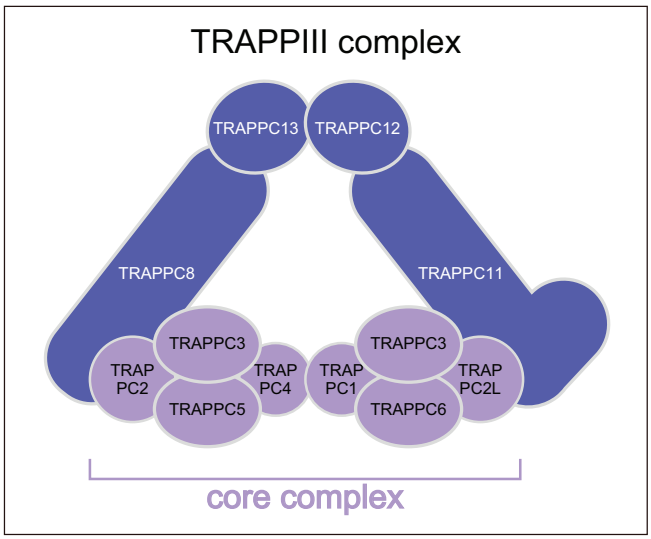

FIGURE 4 | Composition of the TRAPPIII complex. The mammalian TRAPPIII complex, which plays a role in membrane transport between the ER and Golgi, consists of a core complex (TRAPPC1, TRAPPC2, TRAPPC2L, TRAPPC3, TRAPPC4, TRAPPC5 and TRAPPC6) along with TRAPPC8, TRAPPC11, TRAPPC12 and TRAPPC13.

with several effectors, including p115. Rab1 has been implicated in multiple stages of ER–Golgi transport, ranging from vesicle budding to docking. Intriguingly, Golgi fragmentation has been observed in Rab1A knockdown cells, indicating that it is essential for maintaining Golgi structure and integrity [152].

Haploinsufficiency of Rab1A, identified in four unrelated families, has been linked to hereditary spastic paraplegias (HSPs) [153]. These mutations, located within the GTPase domain, result in abnormal Golgi morphology and impaired dendritic development. Considering that mutations in TRAPPIII subunits (discussed later) are also associated with neurocognitive disorders, these findings underscore the critical roles of TRAPPIII and Rab1 in neuronal development.

The Rab1B isoform, which shares a high sequence similarity with Rab1A, plays a role in upregulating the retinoic acid-inducible gene I (RIG-I) pathway, a key viral RNA sensing mechanism. This upregulation enhances IFN-β induction, boosting antiviral responses. Rab1B achieves this by forming a complex with TNF receptor-associated factor 3 (TRAF3) downstream of RIG-I, thereby promoting the interaction between TRAF3 and mitochondrial antiviral signaling protein (MAVS) [154].

5.2 | TRAPPC2

TRAPPC2, a core component of the TRAPP complex, associates with either TRAPPC9 to form the TRAPPII complex or TRAPPC8 to form the TRAPPIII complex. Mutations in TRAPPC2 are associated with spondyloepiphyseal dysplasia tarda (SEDT) (OMIM #313400), an X-linked recessive disorder characterized by short stature due to impaired spinal growth and early-onset osteoarthritis [155–157]. Most disease-associated mutations lead to premature termination codons, resulting in the degradation of truncated peptides [158]. Among the four

identified missense mutations, three induce protein misfolding and subsequent degradation [158]. The D47Y mutation, in particular, markedly reduces the binding affinity of TRAPPC2 for both TRAPPC8 and TRAPPC9, suggesting impaired assembly of TRAPPII and TRAPPIII complexes [159].

In a recent study, TRAPPC2 knockout medaka displayed phenotypes resembling those of human SEDT, supporting its conserved role in vertebrate skeletal development [160]. At the cellular level, TRAPPC2 suppression inhibits collagen secretion, implicating its role in the secretory pathway. Specifically, TRAPPC2 facilitates collagen export from the ER via its TANGO1-mediated recruitment to ER exit sites, where it enhances the cycling of Sar1 and contributes to the formation of COPII vesicles containing collagen [161].

Additionally, TRAPPC8 has been identified as an interacting partner of TMEM-131, a factor known to promote collagen secretion, further implicating TRAPPC2 in collagen transport from the ER [162]. These interactions highlight the potential impact of TRAPPC2 mutations on collagen trafficking, suggesting a molecular basis for the observed phenotypes in SEDT and underscoring the need for further investigation.

5.3 | TRAPPC4

TRAPPC4, a central component of the TRAPP core complex, is essential for the proper assembly and function of both TRAPPII and TRAPPIII complexes [150]. Homozygous mutations in TRAPPC4 have been linked to a neurodevelopmental disorder with epilepsy, spasticity and brain atrophy (NEDESBA) (OMIM #618741) [163–165], a disorder characterized by seizures and severely impaired global development. Patient-derived fibroblasts showed a marked reduction in TRAPPC4 expression, along with altered molecular weights of TRAPPII and TRAPPIII complexes. Functional studies have revealed delayed transport of vesicular stomatitis virus G (VSV G) protein along the secretory pathway as well as impaired autophagy, underscoring the critical role of TRAPPC4 in maintaining the structural integrity of these complexes [165].

Furthermore, magnetic resonance imaging (MRI) scans of patients with NEDESBA displayed abnormalities similar to those observed in individuals with TRAPPC6B and TRAPPC9 variants, highlighting the importance of the TRAPPII complex in normal brain development [165]. These findings suggest that TRAPPC4 is indispensable for the structure and function of TRAPPII and TRAPPIII complexes, as well as for the proper execution of key cellular processes, including vesicular transport and autophagy.

5.4 | TRAPPC6B

The TRAPPC6 subunit, a part of the core TRAPP complex, exists as two homologs in humans: TRAPPC6A and TRAPPC6B. Mutations in TRAPPC6B have been linked to severe neurodevelopmental disorders. In a study involving six patients from three unrelated families, homozygous splice-site mutations in TRAPPC6B were associated with a spectrum of neurological symptoms, including microcephaly, epilepsy and cerebral atrophy [166]. Recently, a larger cohort study identified 29 individuals with biallelic TRAPPC6B mutations in 18 unrelated families, further expanding the clinical spectrum. These patients exhibited non-progressive microcephaly, global developmental delay, intellectual disability, epilepsy and severe speech impairment, along with movement disorders such as stereotypies, spasticity and dystonia [167].

The study by Almousa et al., using patient-derived fibroblasts, suggested that ER–Golgi transport might be impaired, implying a defect in intracellular trafficking [167]. The authors also proposed that TRAPPC6B was predominantly incorporated into the TRAPPII complex, rather than TRAPPIII. However, additional studies are needed to validate these findings and clarify the specific role of TRAPPC6B in these complexes.

5.5 | TRAPPC11

TRAPPC11 interacts with the core complex components TRAPPC2L and TRAPPC3, as well as with TRAPPC12 and TRAPPC13, facilitating the assembly of the TRAPPIII complex [168]. TRAPPC11 knockdown causes partial disassembly of the TRAPP complex, leading to Golgi fragmentation and impaired ER-to-Golgi transport [169]. In addition to its role in vesicular trafficking, TRAPPC11 is involved in autophagosome formation and plays a critical role in lipid metabolism during macroautophagy [170].

In 2013, limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability linked to homozygous mutations in TRAPPC11 were reported in three families comprising eight affected individuals [171]. One family presented with a point mutation, while the other two had deletion mutations resulting from splicing defects. Patient-derived cells showed a significant reduction in TRAPPC11 expression, accompanied by Golgi fragmentation and delayed VSV G transport [171].

Subsequent studies have further characterized this condition, now referred to as TRAPPC11-opathy, which leads to neuromuscular impairment and encompasses a wide array of clinical manifestations, including abnormalities in the central nervous system, ocular defects, muscle weakness, as well as liver, kidney and skeletal abnormalities [172]. These findings highlight the critical role of TRAPPC11 in maintaining cellular and organ homeostasis.

5.6 | TRAPPC12

TRAPPC12 was found to co-purify with TRAPPC8, rather than TRAPPC9 or TRAPPC10, indicating its specific role as a constituent of the human TRAPPIII complex [173]. Depletion of TRAPPC12 using siRNA led to Golgi fragmentation and disrupted ER-to-Golgi transport, highlighting its importance in maintaining Golgi integrity and facilitating vesicular trafficking [169]. In addition to its role in the secretory pathway, TRAPPC12 has been implicated in autophagy and mitotic progression [174, 175].

TABLE 1 | Diseases associated with factors at the ER–Golgi interface.

Gene	Disease	Clinical features	References
Sar1B	Chylomicron retention disease (CMRD) Anderson disease	Fat malabsorption	[46–49]
Sec23A	Cranio-lenticular-sutural dysplasia (CLSD)	Facial dysmorphism, late-closing fontanels Cataract Skeletal dysplasia	[54–59]
Sec23B	Congenital dyserythropoietic anemia type II (CDAN2)	Erythrocyte maturation defect	[60–64]
Sec23B	Cowden's syndrome	A familial cancer syndrome	[69]
Sec24D	Cole–Carpenter syndrome 2 (CLCRP2)	Skeletal dysplasia, low bone mass Facial dysmorphism	[71–74]
Sec16B	Osteogenesis imperfecta (OI)	Skeletal dysplasia	[78]
Sec31A	Halperin–Birk syndrome (HLBKS)	Structural brain defects, seizures Cataract, severe developmental delay	[80]
TFG	Spastic paraplegia 57 (SPG57)	Axonopathies, walking difficulties	[85–87]
TFG	Neuropathy, Hereditary Motor and Sensory, Okinawa type (HMSNO)	Neurodegenerative disorder Muscle weakness	[90–92]
TANGO1		Skeletal dysplasia Insulin-dependent diabetes mellitus Sensorineural hearing loss Mild intellectual disability	[95]
Arf1	Periventricular nodular heterotopia 8 (PVNH8)	Brain developmental disorder	[101]
GBF1	Charcot–Marie–Tooth disease, axonal, type 2GG (CMT2GG)	Axonal peripheral neuropathy, distal sensory impairment, muscle weakness, walking difficulties	[107]
COPA	Autoimmune interstitial lung, joint and kidney disease (AILJK)	Autoimmune disorder Inflammatory arthritis Interstitial lung disease, renal disease	[109, 111–113]
COPB1	Baralle–Macken syndrome (BARMACS)	Walking difficulties, intellectual disability Cataract, microcephaly	[114]
COPB2	Microcephaly 19, primary, autosomal recessive (MCPH19)	Microcephaly, spasticity Severe developmental delay	[115]
COPB2	Osteoporosis, childhood- or juvenile-onset, with developmental delay (OPDD)	Osteoporosis Developmental delay	[116]
COPD	Short stature-micrognathia syndrome (SSMG)	Developmental delay, preterm birth Microcephaly	[119–122]
ERGIC-53	Factor V and Factor VIII combined deficiency 1 (F5F8D1)	Bleeding symptoms	[125–127]
KDELR2	Osteogenesis imperfecta 21 (OI21)	Skeletal dysplasia, scoliosis Walking difficulties	[144, 145]
Rab1A	Hereditary spastic paraplegias (HSPs)	Lower extremity weakness Spasticity	[153]
TRAPPC2	Spondyloepiphyseal dysplasia tarda (SEDT)	Skeletal dysplasia, osteoarthritis	[155–159]
TRAPPC4	Neurodevelopmental disorder with epilepsy, spasticity and brain atrophy (NEDESBA)	Neurological developmental disorders with Global developmental delay Seizures, severe intellectual disability	[163–165]

(Continues)

TABLE 1 | (Continued)

Gene	Disease	Clinical features	References
TRAPPC6B	Neurodevelopmental disorder with microcephaly, epilepsy and brain atrophy (NEDMEBA)	Neurological developmental disorders with Global developmental delay Seizures, microcephaly, severe intellectual disability	[166, 167]
TRAPPC11	Muscular dystrophy, limb-girdle, autosomal recessive 18 (LGMDR18)	Proximal muscle weakness, walking difficulties Hyperkinetic movement disorder, developmental delay	[171, 172]
TRAPPC12	Encephalopathy, progressive, early-onset, with brain atrophy and spasticity (PEBAS)	Global developmental delay, hearing loss Microcephaly	[176, 177]

Recently, two families reported cases of individuals harboring distinct TRAPPC12 mutations [176, 177]. One patient carried a homozygous frameshift mutation, while two siblings from another family presented with compound heterozygous mutations, one frameshift mutation and one single-nucleotide substitution. Both types of mutations resulted in a marked decrease in TRAPPC12 expression, suggesting that the single-nucleotide substitution may affect protein stability. The affected individuals exhibited similar clinical phenotypes, including global developmental delay, severe intellectual disabilities, microcephaly, hearing loss, seizures, brain atrophy and encephalopathy.

Patient-derived fibroblasts exhibited a fragmented Golgi phenotype, which was rescued upon expression of wild-type TRAPPC12, confirming that Golgi defects were directly attributable to TRAPPC12 dysfunction. Additionally, these fibroblasts exhibited delayed ER-to-Golgi transport and impaired mitotic progression [176, 177]. These findings underscore the critical role of TRAPPC12 in vesicular trafficking, mitosis and overall cellular homeostasis and highlight its potential involvement in severe neurodevelopmental disorders.

6 | Conclusion

This review systematically examines and organizes diseases arising from mutations in proteins situated at the ER–Golgi interface, categorizing them based on their localization and cellular function (Table 1). By exploring the roles of each protein and summarizing recent discoveries, we provide a comprehensive perspective on how mutations affect ER–Golgi trafficking and contribute to various pathologies. This review also emphasizes both shared and unique disease mechanisms linked to similar functional proteins, illustrating the complexity of genotype–phenotype relationships.

Proteins with similar cellular roles can cause vastly different diseases. For instance, while mutations in various proteins involved in collagen processing lead to similar bone disorders such as osteogenesis imperfecta, other cases demonstrate marked phenotypic differences despite functional redundancy. For example, Sec23A and Sec23B proteins, which are functionally interchangeable yet associated with distinct diseases, exemplify how transcriptional regulation, temporal expression, tissue specificity and posttranslational modifications can contribute to diverse clinical outcomes. This underscores that the phenotypic expression of cellular dysfunction is influenced by more than just the primary role of the protein.

Moreover, some ER–Golgi interface proteins have not yet been linked to specific diseases, suggesting the possibility of undiscovered pathologies. It is plausible that mutations in certain essential factors are incompatible with survival, thereby masking their pathological effects. Nevertheless, this review highlights the therapeutic potential of targeting proteins at the ER–Golgi interface. By deepening our understanding of the roles of these proteins in diseases, we open new avenues for the development of targeted drug therapies and personalized medicine approaches tailored to the molecular underpinnings of these conditions.

Acknowledgments

This work was supported by JSPS Grants-in-Aid for Scientific Research (23K24023 to M.M.; 24K18067 to M.A.; and 23K27123, 24K22065 to K.S.) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Naito Foundation (K.S. and M.M.). K.S. received support from the Takeda Science Foundation, Asahi Glass Foundation, and the Princess Takamatsu Cancer Research Foundation.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. M. Aridor, "A Tango for Coats and Membranes: New Insights Into ER-To-Golgi Traffic," *Cell Reports* 38, no. 3 (2022): 110258.

2. M. Aridor, "COPII Gets in Shape: Lessons Derived From Morphological Aspects of Early Secretion," *Traffic* 19, no. 11 (2018): 823–839.

3. F. Brandizzi and C. Barlowe, "Organization of the ER-Golgi Interface for Membrane Traffic Control," *Nature Reviews Molecular Cell Biology* 14 (2013): 382–392.

4. E. A. Miller and R. Schekman, "COPII—A Flexible Vesicle Formation System," *Current Opinion in Cell Biology* 25, no. 4 (2013): 420–427.

5. J. G. D'Arcangelo, K. R. Stahmer, and E. A. Miller, "Vesicle-Mediated Export From the ER: COPII Coat Function and Regulation," *Biochimica et Biophysica Acta* 1833 (2013): 2464–2472.

6. A. V. Weigel, C. L. Chang, G. Shtengel, et al., "ER-To-Golgi Protein Delivery Through an Interwoven, Tubular Network Extending From ER," *Cell* 184, no. 9 (2021): 2412–2429.e2416.

7. O. Shomron, I. Nevo-Yassaf, T. Aviad, et al., "COPII Collar Defines the Boundary Between ER and ER Exit Site and Does Not Coat Cargo Containers," *Journal of Cell Biology* 220, no. 6 (2021): e201907224.

8. H. Qiu, X. Wu, X. Ma, et al., "Short-Distance Vesicle Transport via Phase Separation," *Cell* 187, no. 9 (2024): 2175-2193.e21.

9. W. R. Wegeng, S. M. Bogus, M. Ruiz, et al., "A Hollow TFG Condensate Spatially Compartmentalizes the Early Secretory Pathway," *bioRxiv* (2024): 03.26.586876.

10. J. McCaughey, N. L. Stevenson, S. Cross, and D. J. Stephens, "ER-To-Golgi Trafficking of Procollagen in the Absence of Large Carriers," *Journal of Cell Biology* 218, no. 3 (2019): 929–948.

11. I. Raote and V. Malhotra, "Protein Transport by Vesicles and Tunnels," *Journal of Cell Biology* 218, no. 3 (2019): 737–739.

12. A. Schweizer, K. Matter, C. M. Ketcham, and H. P. Hauri, "The Isolated ER-Golgi Intermediate Compartment Exhibits Properties That Are Different From ER and Cis-Golgi," *Journal of Cell Biology* 113, no. 1 (1991): 45–54.

13. S. Yu, A. Satoh, M. Pypaert, K. Mullen, J. C. Hay, and S. Ferro-Novick, "mBet3p Is Required for Homotypic COPII Vesicle Tethering in Mammalian Cells," *Journal of Cell Biology* 174, no. 3 (2006): 359–368.

14. A. J. Santos, I. Raote, M. Scarpa, N. Brouwers, and V. Malhotra, "TANGO1 Recruits ERGIC Membranes to the Endoplasmic Reticulum for Procollagen Export," *eLife* 4 (2015): e10982.

15. J. Peotter, W. Kasberg, I. Pustova, and A. Audhya, "COPII-Mediated Trafficking at the ER/ERGIC Interface," *Traffic* 20, no. 7 (2019): 491–503.

16. T. Tojima, Y. Suda, N. Jin, K. Kurokawa, and A. Nakano, "Spatiotemporal Dissection of the Golgi Apparatus and the ER-Golgi Intermediate Compartment in Budding Yeast," *eLife* 13 (2024): e92900.

17. F. Campelo, J. V. Lillo, and J. von Blume, "Protein Condensates in the the Secretory Pathway: Unraveling Biophysical Interactions and Function," *Biophysical Journal* 123, no. 12 (2024): 1531–1541.

18. S. E. Van der Verren and G. Zanetti, "The Small GTPase Sar1, Control Centre of COPII Trafficking," *FEBS Letters* 597, no. 6 (2023): 865–882.

19. X. Bi, J. D. Mancias, and J. Goldberg, "Insights Into COPII Coat Nucleation From the Structure of Sec23.Sar1 Complexed With the Active Fragment of Sec31," *Developmental Cell* 13 (2007): 635–645.

20. S. Fath, J. D. Mancias, X. Bi, and J. Goldberg, "Structure and Organization of Coat Proteins in the COPII Cage," *Cell* 129 (2007): 1325–1336.

21. S. M. Stagg, C. Gurkan, D. M. Fowler, et al., "Structure of the Sec13/31 COPII Coat Cage," *Nature* 439 (2006): 234–238.

22. D. Bhattacharyya and B. S. Glick, "Two Mammalian Sec16 Homologues Have Nonredundant Functions in Endoplasmic Reticulum (ER) Export and Transitional ER Organization," *Molecular Biology of the Cell* 18 (2007): 839–849.

23. H. Hughes, A. Budnik, K. Schmidt, et al., "Organisation of Human ER-Exit Sites: Requirements for the Localisation of Sec16 to Transitional ER," *Journal of Cell Science* 122 (2009): 2924–2934.

24. P. Watson, A. K. Townley, P. Koka, K. J. Palmer, and D. J. Stephens, "Sec16 Defines Endoplasmic Reticulum Exit Sites and Is Required for Secretory Cargo Export in Mammalian Cells," *Traffic* 7 (2006): 1678–1687.

25. T. Iinuma, A. Shiga, K. Nakamoto, et al., "Mammalian Sec16/p250 Plays a Role in Membrane Traffic From the Endoplasmic Reticulum," *Journal of Biological Chemistry* 282 (2007): 17632–17639.

26. R. Gallo, A. K. Rai, A. B. R. McIntyre, K. Meyer, and L. Pelkmans, "DYRK3 Enables Secretory Trafficking by Maintaining the Liquid-Like State of ER Exit Sites," *Developmental Cell* 58, no. 19 (2023): 1880–1897 e1811.

27. F. Bard, L. Casano, A. Mallabiabarrena, et al., "Functional Genomics Reveals Genes Involved in Protein Secretion and Golgi Organization," *Nature* 439 (2006): 604–607.

28. K. Saito and M. Maeda, "Not Just a Cargo Receptor for Large Cargoes; an Emerging Role of TANGO1 as an Organizer of ER Exit Sites," *Journal of Biochemistry* 166, no. 2 (2019): 115–119.

29. K. Saito, M. Maeda, and T. Katada, "Regulation of the Sar1 GTPase Cycle Is Necessary for Large Cargo Secretion From the Endoplasmic Reticulum," *Frontiers in Cell and Developmental Biology* 5 (2017): 75.

30. K. Saito and T. Katada, "Mechanisms for Exporting Large-Sized Cargoes From the Endoplasmic Reticulum," *Cellular and Molecular Life Sciences: CMLS* 72 (2015): 3709–3720.

31. K. Saito, M. Chen, F. Bard, et al., "TANGO1 Facilitates Cargo Loading at Endoplasmic Reticulum Exit Sites," *Cell* 136 (2009): 891–902.

32. T. Tanabe, M. Maeda, K. Saito, and T. Katada, "Dual Function of cTAGE5 in Collagen Export From the Endoplasmic Reticulum," *Molecular Biology of the Cell* 27 (2016): 2008–2013.

33. K. Saito, K. Yamashiro, N. Shimazu, T. Tanabe, K. Kontani, and T. Katada, "Concentration of Sec12 at ER Exit Sites via Interaction With cTAGE5 Is Required for Collagen Export," *Journal of Cell Biology* 206 (2014): 751–762.

34. K. Saito, K. Yamashiro, Y. Ichikawa, et al., "cTAGE5 Mediates Collagen Secretion Through Interaction With TANGO1 at Endoplasmic Reticulum Exit Sites," *Molecular Biology of the Cell* 22 (2011): 2301–2308.

35. I. Raote, M. Ortega-Bellido, A. J. Santos, et al., "TANGO1 Builds a Machine for Collagen Export by Recruiting and Spatially Organizing COPII, Tethers and Membranes," *eLife* 7 (2018): e32723.

36. I. Raote, M. Ortega Bellido, M. Pirozzi, et al., "TANGO1 Assembles Into Rings Around COPII Coats at ER Exit Sites," *Journal of Cell Biology* 216 (2017): 901–909.

37. M. Maeda, T. Katada, and K. Saito, "TANGO1 Recruits Sec16 to Coordinately Organize ER Exit Sites for Efficient Secretion," *Journal of Cell Biology* 216 (2017): 1731–1743.

38. M. Maeda, K. Saito, and T. Katada, "Distinct Isoform-Specific Complexes of TANGO1 Cooperatively Facilitate Collagen Secretion From the Endoplasmic Reticulum," *Molecular Biology of the Cell* 27 (2016): 2688–2696.

39. M. Maeda, Y. Komatsu, and K. Saito, "Mitotic ER Exit Site Disassembly and Reassembly Are Regulated by the Phosphorylation Status of TANGO1," *Developmental Cell* 55 (2020): 237–250.e5.

40. A. Greco, C. Mariani, C. Miranda, et al., "The DNA Rearrangement That Generates the TRK-T3 Oncogene Involves a Novel Gene on Chromosome 3 Whose Product Has a Potential Coiled-Coil Domain," *Molecular and Cellular Biology* 15, no. 11 (1995): 6118–6127.

41. M. G. Hanna, S. Block, E. B. Frankel, et al., "TFG Facilitates Outer Coat Disassembly on COPII Transport Carriers to Promote Tethering and Fusion With ER-Golgi Intermediate Compartments," *Proceedings of the National Academy of Sciences of the United States of America* 114 (2017): E7707–E7716.

42. A. Johnson, N. Bhattacharya, M. Hanna, et al., "TFG Clusters COPII-Coated Transport Carriers and Promotes Early Secretory Pathway Organization," *EMBO Journal* 34 (2015): 811–827.

43. J. McCaughey, V. J. Miller, N. L. Stevenson, et al., "TFG Promotes Organization of Transitional ER and Efficient Collagen Secretion," *Cell Reports* 15 (2016): 1648–1659.

44. K. Witte, A. L. Schuh, J. Hegermann, et al., "TFG-1 Function in Protein Secretion and Oncogenesis," *Nature Cell Biology* 13 (2011): 550–558.

45. M. Maeda, M. Arakawa, Y. Komatsu, and K. Saito, "Small GTPase ActIvitY ANalyzing (SAIYAN) System: A Method to Detect GTPase Activation in Living Cells," *Journal of Cell Biology* 223, no. 10 (2024): e202403179.

46. B. Jones, E. L. Jones, S. A. Bonney, et al., "Mutations in a Sar1 GTPase of COPII Vesicles Are Associated With Lipid Absorption Disorders," *Nature Genetics* 34 (2003): 29–31.

47. G. Annesi, U. Aguglia, P. Tarantino, et al., "SIL1 and SARA2 Mutations in Marinesco-Sjögren and Chylomicron Retention Diseases," *Clinical Genetics* 71, no. 3 (2007): 288–289.

48. S. Treepongkaruna, N. Chongviriyaphan, U. Suthutvoravut, D. Charoenpipop, L. Choubtum, and D. Wattanasirichaigoon, "Novel Missense Mutations of SAR1B Gene in an Infant With Chylomicron Retention Disease," *Journal of Pediatric Gastroenterology and Nutrition* 48, no. 3 (2009): 370–373.

49. A. Georges, J. Bonneau, D. Bonnefont-Rousselot, et al., "Molecular Analysis and Intestinal Expression of SAR1 Genes and Proteins in Anderson's Disease (Chylomicron Retention Disease)," *Orphanet Journal of Rare Diseases* 6 (2011): 1.

50. L. G. Fryer, B. Jones, E. J. Duncan, et al., "The Endoplasmic Reticulum Coat Protein II Transport Machinery Coordinates Cellular Lipid Secretion and Cholesterol Biosynthesis," *Journal of Biological Chemistry* 289 (2014): 4244–4261.

51. D. B. Melville, S. Studer, and R. Schekman, "Small Sequence Variations Between Two Mammalian Paralogs of the Small GTPase SAR1 Underlie Functional Differences in Coat Protein Complex II Assembly," *Journal of Biological Chemistry* 295, no. 25 (2020): 8401–8412.

52. A. T. Sané, E. Seidman, N. Peretti, et al., "Understanding Chylomicron Retention Disease Through Sar1b Gtpase Gene Disruption: Insight From Cell Culture," *Arteriosclerosis, Thrombosis, and Vascular Biology* 37, no. 12 (2017): 2243–2251.

53. E. Levy, E. Harmel, M. Laville, et al., "Expression of Sar1b Enhances Chylomicron Assembly and Key Components of the Coat Protein Complex II System Driving Vesicle Budding," *Arteriosclerosis, Thrombosis, and Vascular Biology* 31, no. 11 (2011): 2692–2699.

54. S. A. Boyadjiev, J. C. Fromme, J. Ben, et al., "Cranio-Lenticulo-Sutural Dysplasia Is Caused by a SEC23A Mutation Leading to Abnormal Endoplasmic-Reticulum-to-Golgi Trafficking," *Nature Genetics* 38 (2006): 1192–1197.

55. S. A. Boyadjiev, S. D. Kim, A. Hata, et al., "Cranio-Lenticulo-Sutural Dysplasia Associated With Defects in Collagen Secretion," *Clinical Genetics* 80 (2011): 169–176.

56. K. Cisarova, L. Garavelli, S. G. Caraffi, et al., "A Monoallelic SEC23A Variant E599K Associated With Cranio-Lenticulo-Sutural Dysplasia," *American Journal of Medical Genetics. Part A* 188, no. 1 (2022): 319–325.

57. J. C. Fromme, L. Orci, and R. Schekman, "Coordination of COPII Vesicle Trafficking by Sec23," *Trends in Cell Biology* 18 (2008): 330–336.

58. S. D. Kim, K. B. Pahuja, M. Ravazzola, et al., "The [Corrected] SEC23-SEC31 [Corrected] Interface Plays Critical Role for Export of Procollagen From the Endoplasmic Reticulum," *Journal of Biological Chemistry* 287 (2012): 10134–10144.

59. J. C. Fromme, M. Ravazzola, S. Hamamoto, et al., "The Genetic Basis of a Craniofacial Disease Provides Insight Into COPII Coat Assembly," *Developmental Cell* 13 (2007): 623–634.

60. K. Schwarz, A. Iolascon, F. Verissimo, et al., "Mutations Affecting the Secretory COPII Coat Component SEC23B Cause Congenital Dyserythropoietic Anemia Type II," *Nature Genetics* 41 (2009): 936–940.

61. P. Bianchi, E. Fermo, C. Vercellati, et al., "Congenital Dyserythropoietic Anemia Type II (CDAII) is Caused by Mutations in the SEC23B Gene," *Human Mutation* 30 (2009): 1292–1298.

62. R. Russo, C. Langella, M. R. Esposito, et al., "Hypomorphic Mutations of SEC23B Gene Account for Mild Phenotypes of Congenital Dyserythropoietic Anemia Type II," *Blood Cells, Molecules & Diseases* 51, no. 1 (2013): 17–21.

63. M. Méndez, M. I. Moreno-Carralero, V. L. Peri, et al., "Congenital Dyserythropoietic Anemia Types Ib, II, and III: Novel Variants in the CDIN1 Gene and Functional Study of a Novel Variant in the KIF23 Gene," *Annals of Hematology* 100, no. 2 (2021): 353–364.

64. M. M. Musri, V. Venturi, X. Ferrer-Cortès, et al., "New Cases and Mutations in SEC23B Gene Causing Congenital Dyserythropoietic Anemia Type II," *International Journal of Molecular Sciences* 24, no. 12 (2023): 9935.

65. R. Khoriaty, G. G. Hesketh, A. Bernard, et al., "Functions of the COPII Gene Paralogs SEC23A and SEC23B Are Interchangeable In Vivo," *Proceedings of the National Academy of Sciences of the United States of America* 115, no. 33 (2018): E7748–E7757.

66. S. Pellegrin, K. L. Haydn-Smith, L. A. Hampton-O'Neil, et al., "Transduction With BBF2H7/CREB3L2 Upregulates SEC23A Protein in Erythroblasts and Partially Corrects the Hypo-Glycosylation Phenotype Associated With CDAII," *British Journal of Haematology* 184, no. 5 (2019): 876–881.

67. R. King, Z. Lin, G. Balbin-Cuesta, et al., "SEC23A Rescues SEC23B-Deficient Congenital Dyserythropoietic Anemia Type II," *Science Advances* 7, no. 48 (2021): eabj5293.

68. S. Kim, R. Khoriaty, L. Li, et al., "ER-to-Golgi Transport and SEC23-Dependent COPII Vesicles Regulate T Cell Alloimmunity," *Journal of Clinical Investigation* 131, no. 2 (2021): e136574.

69. L. Yehia, F. Niazi, Y. Ni, et al., "Germline Heterozygous Variants in SEC23B Are Associated With Cowden Syndrome and Enriched in Apparently Sporadic Thyroid Cancer," *American Journal of Human Genetics* 97, no. 5 (2015): 661–676.

70. J. Jing, B. Wang, and P. Liu, "The Functional Role of SEC23 in Vesicle Transportation, Autophagy and Cancer," *International Journal of Biological Sciences* 15, no. 11 (2019): 2419–2426.

71. L. Garbes, K. Kim, A. Riess, et al., "Mutations in SEC24D, Encoding a Component of the COPII Machinery, Cause a Syndromic Form of Osteogenesis Imperfecta," *American Journal of Human Genetics* 96 (2015): 432–439.

72. H. Zhang, H. Yue, C. Wang, et al., "Novel Mutations in the SEC24D Gene in Chinese Families With Autosomal Recessive Osteogenesis Imperfecta," *Osteoporosis International* 28, no. 4 (2017): 1473–1480.

73. S. Moosa, B. H. Chung, J. Y. Tung, et al., "Mutations in SEC24D Cause Autosomal Recessive Osteogenesis Imperfecta," *Clinical Genetics* 89, no. 4 (2016): 517–519.

74. S. Takeyari, T. Kubota, K. Miyata, et al., "Japanese Patient With Cole-Carpenter Syndrome With Compound Heterozygous Variants of SEC24D," *American Journal of Medical Genetics. Part A* 176, no. 12 (2018): 2882–2886.

75. S. Ohisa, K. Inohaya, Y. Takano, and A. Kudo, "sec24d Encoding a Component of COPII Is Essential for Vertebra Formation, Revealed by the Analysis of the Medaka Mutant, Vbi," *Developmental Biology* 342 (2010): 85–95.

76. S. Sarmah, A. Barrallo-Gimeno, D. B. Melville, J. Topczewski, L. Solnica-Krezel, and E. W. Knapik, "Sec24D-Dependent Transport of Extracellular Matrix Proteins Is Required for Zebrafish Skeletal Morphogenesis," *PLoS One* 5 (2010): e10367.

77. S. Yonekawa, A. Furuno, T. Baba, et al., "Sec16B Is Involved in the Endoplasmic Reticulum Export of the Peroxisomal Membrane

Biogenesis Factor Peroxin 16 (Pex16) in Mammalian Cells," *Proceedings of the National Academy of Sciences of the United States of America* 108, no. 31 (2011): 12746–12751.

78. A. El-Gazzar, B. Voraberger, F. Rauch, et al., "Bi-Allelic Mutation in SEC16B Alters Collagen Trafficking and Increases ER Stress," *EMBO Molecular Medicine* 15, no. 4 (2023): e16834.

79. M. C. Stankewich, P. R. Stabach, and J. S. Morrow, "Human Sec31B: A Family of New Mammalian Orthologues of Yeast Sec31p That Associate With the COPII Coat," *Journal of Cell Science* 119, no. Pt 5 (2006): 958–969.

80. D. Halperin, R. Kadir, Y. Perez, et al., "SEC31A Mutation Affects ER Homeostasis, Causing a Neurological Syndrome," *Journal of Medical Genetics* 56, no. 3 (2019): 139–148.

81. E. S. Tobias, A. K. Lucas-Herald, D. Sagar, et al., "SEC31A May Be Associated With Pituitary Hormone Deficiency and Gonadal Dysgenesis," *Endocrine* 84 (2024): 345–349.

82. Z. Liu, M. Yan, W. Lei, et al., "Sec13 Promotes Oligodendrocyte Differentiation and Myelin Repair Through Autocrine Pleiotrophin Signaling," *Journal of Clinical Investigation* 132, no. 7 (2022): e155096.

83. N. Kim, T. H. Kim, C. Kim, et al., "Intrinsically Disordered Region-Mediated Condensation of IFN-Inducible SCOTIN/SHISA-5 Inhibits ER-to-Golgi Vesicle Transport," *Developmental Cell* 58, no. 19 (2023): 1950–1966 e1958.

84. S. C. J. H. Chua, J. Cui, K. Sachaphibulkij, et al., "The ER-Golgi Transport of Influenza Virus Through NS1-Sec13 Association During Virus Replication," *Microbiology Spectrum* 12, no. 1 (2024): e0260923.

85. C. Beetz, A. Johnson, A. L. Schuh, et al., "Inhibition of TFG Function Causes Hereditary Axon Degeneration by Impairing Endoplasmic Reticulum Structure," *Proceedings of the National Academy of Sciences of the United States of America* 110, no. 13 (2013): 5091–5096.

86. G. V. Harlalka, M. E. McEntagart, N. Gupta, et al., "Novel Genetic, Clinical, and Pathomechanistic Insights Into TFG-Associated Hereditary Spastic Paraplegia," *Human Mutation* 37, no. 11 (2016): 1157–1161.

87. L. Xu, Y. Wang, W. Wang, et al., "Novel TFG Mutation Causes Autosomal-Dominant Spastic Paraplegia and Defects in Autophagy," *Journal of Medical Genetics* 61, no. 4 (2024): 325–331.

88. E. L. Slosarek, A. L. Schuh, I. Pustova, et al., "Pathogenic TFG Mutations Underlying Hereditary Spastic Paraplegia Impair Secretory Protein Trafficking and Axon Fasciculation," *Cell Reports* 24, no. 9 (2018): 2248–2260.

89. J. L. Peotter, I. Pustova, M. M. Lettman, et al., "TFG Regulates Secretory and Endosomal Sorting Pathways in Neurons to Promote Their Activity and Maintenance," *Proceedings of the National Academy of Sciences of the United States of America* 119, no. 40 (2022): e2210649119.

90. H. Ishiura, W. Sako, M. Yoshida, et al., "The TRK-Fused Gene Is Mutated in Hereditary Motor and Sensory Neuropathy With Proximal Dominant Involvement," *American Journal of Human Genetics* 91, no. 2 (2012): 320–329.

91. S. S. Lee, H. J. Lee, J. M. Park, et al., "Proximal Dominant Hereditary Motor and Sensory Neuropathy With Proximal Dominance Association With Mutation in the TRK-Fused Gene," *JAMA Neurology* 70, no. 5 (2013): 607–615.

92. A. Alavi, H. Shamshiri, S. Nafissi, et al., "HMSN-P Caused by p.Pro-285Leu Mutation in TFG Is Not Confined to Patients With Far East Ancestry," *Neurobiology of Aging* 36, no. 3 (2015): 1606.e1601–1606.e1607.

93. P.-C. Tsai, Y.-H. Huang, Y.-C. Guo, et al., "A Novel TFG Mutation Causes Charcot-Marie-Tooth Disease Type 2 and Impairs TFG Function," *Neurology* 83, no. 10 (2014): 903–912.

94. X. Chen, F. Liu, K. Chen, et al., "TFG Mutation Induces Haploinsufficiency and Drives Axonal Charcot-Marie-Tooth Disease by Causing Neurite Degeneration," *CNS Neuroscience & Therapeutics* 28, no. 12 (2022): 2076–2089.

95. C. Lekszas, O. Foresti, I. Raote, et al., "Biallelic TANGO1 Mutations Cause a Novel Syndromal Disease due to Hampered Cellular Collagen Secretion," *eLife* 9 (2020): e51319.

96. B. Guillemyn, S. Nampoothiri, D. Syx, F. Malfait, and S. Symoens, "Loss of TANGO1 Leads to Absence of Bone Mineralization," *JBMR Plus* 5, no. 3 (2021): e10451.

97. D. G. Wilson, K. Phamluong, L. Li, et al., "Global Defects in Collagen Secretion in a Mia3/TANGO1 Knockout Mouse," *Journal of Cell Biology* 193 (2011): 935–951.

98. P. Adarska, L. Wong-Dilworth, and F. Bottanelli, "ARF GTPases and Their Ubiquitous Role in Intracellular Trafficking Beyond the Golgi," *Frontiers in Cell and Developmental Biology* 9 (2021): 679046.

99. C. L. Jackson, "Activators and Effectors of the Small G Protein Arf1 in Regulation of Golgi Dynamics During the Cell Division Cycle," *Frontiers in Cell and Developmental Biology* 6 (2018): 29.

100. N. Hayakawa, H. Ogoh, M. Sumiyoshi, et al., "The Gene Is Indispensable for Mouse Embryonic Development After Implantation," *Biochemical and Biophysical Research Communications* 453, no. 4 (2014): 748–753.

101. X. Ge, H. Gong, K. Dumas, et al., "Missense-Depleted Regions in Population Exomes Implicate Ras Superfamily Nucleotide-Binding Protein Alteration in Patients With Brain Malformation," *NPJ Genomic Medicine* 1 (2016): 16036.

102. V. L. Sheen, V. S. Ganesh, M. Topcu, et al., "Mutations in ARFGEF2 Implicate Vesicle Trafficking in Neural Progenitor Proliferation and Migration in the Human Cerebral Cortex," *Nature Genetics* 36, no. 1 (2004): 69–76.

103. E. Banne, O. Atawneh, M. Henneke, et al., "West Syndrome, Microcephaly, Grey Matter Heterotopia and Hypoplasia of corpus Callosum due to a Novel ARFGEF2 Mutation," *Journal of Medical Genetics* 50, no. 11 (2013): 772–775.

104. E. J. Bardón-Cancho, L. Muñoz-Jiménez, M. Vázquez-López, Y. Ruíz-Martín, M. García-Morín, and E. Barredo-Valderrama, "Periventricular Nodular Heterotopia and Dystonia due to an ARFGEF2 Mutation," *Pediatric Neurology* 51, no. 3 (2014): 461–464.

105. M. Ishida, M. G. Otero, C. Freeman, et al., "A Neurodevelopmental Disorder Associated With an Activating de Novo Missense Variant in ARF1," *Human Molecular Genetics* 32, no. 7 (2023): 1162–1174.

106. J. Wright, R. A. Kahn, and E. Sztul, "Regulating the Large Sec7 ARF Guanine Nucleotide Exchange Factors: The When, Where and How of Activation," *Cellular and Molecular Life Sciences: CMLS* 71, no. 18 (2014): 3419–3438.

107. N. Mendoza-Ferreira, M. Karakaya, N. Cengiz, et al., "De Novo and Inherited Variants in GBF1 Are Associated With Axonal Neuropathy Caused by Golgi Fragmentation," *American Journal of Human Genetics* 107, no. 4 (2020): 763–777.

108. E. C. Arakel and B. Schwappach, "Formation of COPI-Coated Vesicles at a Glance," *Journal of Cell Science* 131, no. 5 (2018): jcs209890.

109. L. B. Watkin, B. Jessen, W. Wiszniewski, et al., "COPA Mutations Impair ER-Golgi Transport and Cause Hereditary Autoimmune-Mediated Lung Disease and Arthritis," *Nature Genetics* 47, no. 6 (2015): 654–660.

110. T. Taguchi, K. Mukai, E. Takaya, and R. Shindo, "STING Operation at the ER/Golgi Interface," *Frontiers in Immunology* 12 (2021): 646304.

111. Z. Deng, Z. Chong, C. S. Law, et al., "A Defect in COPI-Mediated Transport of STING Causes Immune Dysregulation in COPA Syndrome," *Journal of Experimental Medicine* 217, no. 11 (2020): e20201045.

112. A. Lepelley, M. J. Martin-Niclós, M. Le Bihan, et al., "Mutations in COPA Lead to Abnormal Trafficking of STING to the Golgi and Interferon Signaling," *Journal of Experimental Medicine* 217, no. 11 (2020): e20200600.

113. K. Mukai, E. Ogawa, R. Uematsu, et al., "Homeostatic Regulation of STING by Retrograde Membrane Traffic to the ER," *Nature Communications* 12, no. 1 (2021): 61.

114. W. L. Macken, A. Godwin, G. Wheway, et al., "Biallelic Variants in COPB1 Cause a Novel, Severe Intellectual Disability Syndrome With Cataracts and Variable Microcephaly," *Genome Medicine* 13, no. 1 (2021): 34.

115. A. DiStasio, A. Driver, K. Sund, et al., "Copb2 Is Essential for Embryogenesis and Hypomorphic Mutations Cause Human Microcephaly," *Human Molecular Genetics* 26, no. 24 (2017): 4836–4848.

116. R. Marom, L. C. Burrage, R. Venditti, et al., "COPB2 Loss of Function Causes a Coatopathy With Osteoporosis and Developmental Delay," *American Journal of Human Genetics* 108, no. 9 (2021): 1710–1724.

117. D. J. Stephens and R. Pepperkok, "Imaging of Procollagen Transport Reveals COPI-Dependent Cargo Sorting During ER-To-Golgi Transport in Mammalian Cells," *Journal of Cell Science* 115 (2002): 1149–1160.

118. A. A. Mironov, A. A. Mironov, Jr., G. V. Beznoussenko, et al., "ER-to-Golgi Carriers Arise Through Direct En Bloc Protrusion and Multistage Maturation of Specialized ER Exit Domains," *Developmental Cell* 5 (2003): 583–594.

119. K. Izumi, M. Brett, E. Nishi, et al., "ARCN1 Mutations Cause a Recognizable Craniofacial Syndrome due to COPI-Mediated Transport Defects," *American Journal of Human Genetics* 99, no. 2 (2016): 451–459.

120. J. Reunert, S. Rust, M. Gruneberg, et al., "Transient N-Glycosylation Abnormalities Likely due to a de Novo Loss-of-Function Mutation in the delta Subunit of Coat Protein I," *American Journal of Medical Genetics. Part A* 179, no. 7 (2019): 1371–1375.

121. T. Tidwell, M. Deshotel, J. Palumbos, C. Miller, P. Bayrak-Toydemir, and J. C. Carey, "Novel De Novo ARCN1 Intronic Variant Causes Rhizomelic Short Stature With Microretrognathia and Developmental Delay," *Cold Spring Harbor Molecular Case Studies* 6, no. 6 (2020): a005728.

122. A. L. Ritter, J. Gold, H. Hayashi, et al., "Expanding the Phenotypic Spectrum of ARCN1-Related Syndrome," *Genetics in Medicine* 24, no. 6 (2022): 1227–1237.

123. C. Appenzeller-Herzog and H. P. Hauri, "The ER-Golgi Intermediate Compartment (ERGIC): In Search of Its Identity and Function," *Journal of Cell Science* 119, no. Pt 11 (2006): 2173–2183.

124. S. Watanabe, Y. Kise, K. Yonezawa, et al., "Structure of Full-Length ERGIC-53 in Complex With MCFD2 for Cargo Transport," *Nature Communications* 15, no. 1 (2024): 2404.

125. W. C. Nichols, U. Seligsohn, A. Zivelin, et al., "Mutations in the ER-Golgi Intermediate Compartment Protein ERGIC-53 Cause Combined Deficiency of Coagulation Factors V and VIII," *Cell* 93, no. 1 (1998): 61–70.

126. W. C. Nichols, V. H. Terry, M. A. Wheatley, et al., "ERGIC-53 Gene Structure and Mutation Analysis in 19 Combined Factors V and VIII Deficiency Families," *Blood* 93, no. 7 (1999): 2261–2266.

127. M. Neerman-Arbez, K. M. Johnson, M. A. Morris, et al., "Molecular Analysis of the ERGIC-53 Gene in 35 Families With Combined Factor V-Factor VIII Deficiency," *Blood* 93, no. 7 (1999): 2253–2260.

128. B. Zhang, C. Zheng, M. Zhu, et al., "Mice Deficient in LMAN1 Exhibit FV and FVIII Deficiencies and Liver Accumulation of α1-Antitrypsin," *Blood* 118, no. 12 (2011): 3384–3391.

129. M. Moussalli, S. W. Pipe, H. P. Hauri, W. C. Nichols, D. Ginsburg, and R. J. Kaufman, "Mannose-Dependent Endoplasmic Reticulum (ER)-Golgi Intermediate Compartment-53-Mediated ER to Golgi Trafficking of Coagulation Factors V and VIII," *Journal of Biological Chemistry* 274, no. 46 (1999): 32539–32542.

130. M. A. Cunningham, S. W. Pipe, B. Zhang, H. P. Hauri, D. Ginsburg, and R. J. Kaufman, "LMAN1 Is a Molecular Chaperone for the Secretion of Coagulation Factor VIII," *Journal of Thrombosis and Haemostasis* 1, no. 11 (2003): 2360–2367.

131. B. Zhang, M. A. Cunningham, W. C. Nichols, et al., "Bleeding due to Disruption of a Cargo-Specific ER-to-Golgi Transport Complex," *Nature Genetics* 34, no. 2 (2003): 220–225.

132. D. Mohanty, K. Ghosh, S. Shetty, M. Spreafico, I. Garagiola, and F. Peyvandi, "Mutations in the MCFD2 Gene and a Novel Mutation in the LMAN1 Gene in Indian Families With Combined Deficiency of Factor V and VIII," *American Journal of Hematology* 79, no. 4 (2005): 262–266.

133. B. Zhang, B. McGee, J. S. Yamaoka, et al., "Combined Deficiency of Factor V and Factor VIII Is due to Mutations in Either LMAN1 or MCFD2," *Blood* 107, no. 5 (2006): 1903–1907.

134. T. Yamada, Y. Fujimori, A. Suzuki, et al., "A Novel Missense Mutation Causing Abnormal LMAN1 in a Japanese Patient With Combined Deficiency of Factor V and Factor VIII," *American Journal of Hematology* 84, no. 11 (2009): 738–742.

135. L. Mattioli, T. Anelli, C. Fagioli, C. Tacchetti, R. Sitia, and C. Valetti, "ER Storage Diseases: A Role for ERGIC-53 in Controlling the Formation and Shape of Russell Bodies," *Journal of Cell Science* 119, no. Pt 12 (2006): 2532–2541.

136. J. P. Klaus, P. Eisenhauer, J. Russo, et al., "The Intracellular Cargo Receptor ERGIC-53 Is Required for the Production of Infectious Arenavirus, Coronavirus, and Filovirus Particles," *Cell Host & Microbe* 14, no. 5 (2013): 522–534.

137. S. Hara-Kuge, T. Ohkura, A. Seko, and K. Yamashita, "Vesicular-Integral Membrane Protein, VIP36, Recognizes High-Mannose Type Glycans Containing alpha1→2 Mannosyl Residues in MDCK Cells," *Glycobiology* 9, no. 8 (1999): 833–839.

138. K. Fiedler, R. G. Parton, R. Kellner, T. Etzold, and K. Simons, "VIP36, a Novel Component of Glycolipid Rafts and Exocytic Carrier Vesicles in Epithelial Cells," *EMBO Journal* 13, no. 7 (1994): 1729–1740.

139. V. Reiterer, B. Nyfeler, and H. P. Hauri, "Role of the Lectin VIP36 in Post-ER Quality Control of Human alpha1-Antitrypsin," *Traffic* 11, no. 8 (2010): 1044–1055.

140. K. Shirakabe, S. Hattori, M. Seiki, S. Koyasu, and Y. Okada, "VIP36 Protein Is a Target of Ectodomain Shedding and Regulates Phagocytosis in Macrophage Raw 264.7 Cells," *Journal of Biological Chemistry* 286, no. 50 (2011): 43154–43163.

141. I. Cela, B. Dufrusine, C. Rossi, et al., "KDEL Receptors: Pathophysiological Functions, Therapeutic Options, and Biotechnological Opportunities," *Biomedicine* 10, no. 6 (2022): 1234.

142. J. C. Alvim, R. M. Bolt, J. An, et al., "The K/HDEL Receptor Does Not Recycle but Instead Acts as a Golgi-Gatekeeper," *Nature Communications* 14, no. 1 (2023): 1612.

143. J. Denecke, "Reply to: Does the KDEL Receptor Cycle Between the Golgi and the ER?," *Nature Communications* 15, no. 1 (2024): 2454.

144. F. S. van Dijk, O. Semler, J. Etich, et al., "Interaction Between KDELR2 and HSP47 as a Key Determinant in Osteogenesis Imperfecta Caused by Bi-Allelic Variants in KDELR2," *American Journal of Human Genetics* 107, no. 5 (2020): 989–999.

145. S. Efthymiou, I. Herman, F. Rahman, et al., "Two Novel Bi-Allelic KDELR2 Missense Variants Cause Osteogenesis Imperfecta With Neurodevelopmental Features," *American Journal of Medical Genetics. Part A* 185, no. 7 (2021): 2241–2249.

146. M. Sacher, N. Shahrzad, H. Kamel, and M. P. Milev, "TRAPPopathies: An Emerging Set of Disorders Linked to Variations

in the Genes Encoding Transport Protein Particle (TRAPP)-associated Proteins," *Traffic* 20, no. 1 (2019): 5–26.

147. A. Galindo and S. Munro, "The TRAPP Complexes: Oligomeric Exchange Factors That Activate the Small GTPases Rab1 and Rab11," *FEBS Letters* 597, no. 6 (2023): 734–749.

148. C. Li, X. Luo, S. Zhao, et al., "COPI-TRAPPII Activates Rab18 and Regulates Its Lipid Droplet Association," *EMBO Journal* 36, no. 4 (2017): 441–457.

149. N. J. Harris, M. L. Jenkins, U. Dalwadi, et al., "Biochemical Insight Into Novel Rab-GEF Activity of the Mammalian TRAPPIII Complex," *Journal of Molecular Biology* 433, no. 18 (2021): 167145.

150. M. L. Jenkins, N. J. Harris, U. Dalwadi, et al., "The Substrate Specificity of the Human TRAPPII Complex's Rab-Guanine Nucleotide Exchange Factor Activity," *Communications Biology* 3, no. 1 (2020): 735.

151. J. Saraste, U. Lahtinen, and B. Goud, "Localization of the Small GTP-Binding Protein rab1p to Early Compartments of the Secretory Pathway," *Journal of Cell Science* 108, no. Pt 4 (1995): 1541–1552.

152. B. Goud, S. Liu, and B. Storrie, "Rab Proteins as Major Determinants of the Golgi Complex Structure," *Small GTPases* 9, no. 1–2 (2018): 66–75.

153. J. J. Rios, Y. Li, N. Paria, et al., "RAB1A Haploinsufficiency Phenocopies the 2p14-p15 Microdeletion and Is Associated With Impaired Neuronal Differentiation," *American Journal of Human Genetics* 110, no. 12 (2023): 2103–2111.

154. D. C. Beachboard, M. Park, M. Vijayan, et al., "The Small GTPase RAB1B Promotes Antiviral Innate Immunity by Interacting With TNF Receptor-Associated Factor 3 (TRAF3)," *Journal of Biological Chemistry* 294, no. 39 (2019): 14231–14240.

155. A. K. Gedeon, G. E. Tiller, M. Le Merrer, et al., "The Molecular Basis of X-Linked Spondyloepiphyseal Dysplasia Tarda," *American Journal of Human Genetics* 68, no. 6 (2001): 1386–1397.

156. A. K. Gedeon, A. Colley, R. Jamieson, et al., "Identification of the Gene (SEDL) Causing X-Linked Spondyloepiphyseal Dysplasia Tarda," *Nature Genetics* 22 (1999): 400–404.

157. E. Grunebaum, E. Arpaia, J. J. MacKenzie, J. Fitzpatrick, P. N. Ray, and C. M. Roifman, "A Missense Mutation in the SEDL Gene Results in Delayed Onset of X Linked Spondyloepiphyseal Dysplasia in a Large Pedigree," *Journal of Medical Genetics* 38, no. 6 (2001): 409–411.

158. M. Y. Choi, C. C. Chan, D. Chan, K. D. Luk, K. S. Cheah, and J. A. Tanner, "Biochemical Consequences of Sedlin Mutations That Cause Spondyloepiphyseal Dysplasia Tarda," *Biochemical Journal* 423, no. 2 (2009): 233–242.

159. M. Zong, X. G. Wu, C. W. Chan, et al., "The Adaptor Function of TRAPPC2 in Mammalian TRAPPs Explains TRAPPC2-Associated SEDT and TRAPPC9-Associated Congenital Intellectual Disability," *PLoS One* 6, no. 8 (2011): e23350.

160. F. Zappa, D. Intartaglia, A. M. Guarino, et al., "Role of Trafficking Protein Particle Complex 2 in Medaka Development," *Traffic* 25, no. 1 (2024): e12924.

161. R. Venditti, T. Scanu, M. Santoro, et al., "Sedlin Controls the ER Export of Procollagen by Regulating the Sar1 Cycle," *Science* 337 (2012): 1668–1672.

162. Z. Zhang, M. Bai, G. O. Barbosa, et al., "Broadly Conserved Roles of TMEM131 Family Proteins in Intracellular Collagen Assembly and Secretory Cargo Trafficking," *Science Advances* 6, no. 7 (2020): eaay7667.

163. P. Majethia, M. C. Do Rosario, P. Kaur, et al., "Further Evidence of Muscle Involvement in Neurodevelopmental Disorder With Epilepsy, Spasticity, and Brain Atrophy," *Annals of Human Genetics* 86, no. 2 (2022): 94–101.

164. S. G. Ghosh, M. Scala, C. Beetz, et al., "A Relatively Common Homozygous TRAPPC4 Splicing Variant Is Associated With an Early-Infantile Neurodegenerative Syndrome," *European Journal of Human Genetics* 29, no. 2 (2021): 271–279.

165. N. J. Van Bergen, Y. Guo, N. Al-Deri, et al., "Deficiencies in Vesicular Transport Mediated by TRAPPC4 Are Associated With Severe Syndromic Intellectual Disability," *Brain* 143, no. 1 (2020): 112–130.

166. I. Marin-Valencia, G. Novarino, A. Johansen, et al., "A Homozygous Founder Mutation in TRAPPC6B Associates With a Neurodevelopmental Disorder Characterised by Microcephaly, Epilepsy and Autistic Features," *Journal of Medical Genetics* 55, no. 1 (2018): 48–54.

167. H. Almousa, S. A. Lewis, S. Bakhtiari, et al., "TRAPPC6B Biallelic Variants Cause a Neurodevelopmental Disorder With TRAPP II and Trafficking Disruptions," *Brain* 147, no. 1 (2024): 311–324.

168. A. Galindo, V. J. Planelles-Herrero, G. Degliesposti, and S. Munro, "Cryo-EM Structure of Metazoan TRAPPIII, the Multi-Subunit Complex That Activates the GTPase Rab1," *EMBO Journal* 40, no. 12 (2021): e107608.

169. P. J. Scrivens, B. Noueihed, N. Shahrzad, S. Hul, S. Brunet, and M. Sacher, "C4orf41 and TTC-15 Are Mammalian TRAPP Components With a Role at an Early Stage in ER-To-Golgi Trafficking," *Molecular Biology of the Cell* 22, no. 12 (2011): 2083–2093.

170. D. Stanga, Q. Zhao, M. P. Milev, D. Saint-Dic, C. Jimenez-Mallebrera, and M. Sacher, "TRAPPC11 Functions in Autophagy by Recruiting ATG2B-WIPI4/WDR45 to Preautophagosomal Membranes," *Traffic* 20, no. 5 (2019): 325–345.

171. N. Bögershausen, N. Shahrzad, J. X. Chong, et al., "Recessive TRAPPC11 Mutations Cause a Disease Spectrum of Limb Girdle Muscular Dystrophy and Myopathy With Movement Disorder and Intellectual Disability," *American Journal of Human Genetics* 93, no. 1 (2013): 181–190.

172. J. R. Corona-Rivera, I. Martinez-Duncker, E. Morava, et al., "TRAPPC11-CDG Muscular Dystrophy: Review of 54 Cases Including a Novel Patient," *Molecular Genetics and Metabolism* 142, no. 1 (2024): 108469.

173. M. C. Bassik, M. Kampmann, R. J. Lebbink, et al., "A Systematic Mammalian Genetic Interaction Map Reveals Pathways Underlying Ricin Susceptibility," *Cell* 152, no. 4 (2013): 909–922.

174. C. A. Lamb, S. Nuhlen, D. Judith, et al., "TBC1D14 Regulates Autophagy via the TRAPP Complex and ATG9 Traffic," *EMBO Journal* 35, no. 3 (2016): 281–301.

175. M. P. Milev, B. Hasaj, D. Saint-Dic, S. Snounou, Q. Zhao, and M. Sacher, "TRAMM/TrappC12 Plays a Role in Chromosome Congression, Kinetochore Stability, and CENP-E Recruitment," *Journal of Cell Biology* 209, no. 2 (2015): 221–234.

176. M. P. Milev, M. E. Grout, D. Saint-Dic, et al., "Mutations in TRAPPC12 Manifest in Progressive Childhood Encephalopathy and Golgi Dysfunction," *American Journal of Human Genetics* 101, no. 2 (2017): 291–299.

177. A. D. Aslanger, E. Demiral, S. Sonmez-Sahin, et al., "Expanding Clinical Phenotype of TRAPPC12-Related Childhood Encephalopathy: Two Cases and Review of Literature," *Neuropediatrics* 51, no. 6 (2020): 430–434.