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Golgi trafficking defects in postnatal microcephaly: the evidence for "Golgipathies"

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1 **Abstract**

2

3 The Golgi apparatus plays a central role in cell homeostasis, not only in processing and
4 maturing newly synthesized proteins and lipids but also in orchestrating their sorting, packing,
5 routing and recycling on the way to their final destination. These multiple secretory pathways
6 require a complex ballet of vesicular and tubular carriers that continuously bud off from donor
7 membranes and fuse to acceptor membranes. Membrane trafficking is particularly prominent in
8 axons, where cargo molecules have a long way to travel before they reach the synapse, and in
9 oligodendrocytes, which require an immense increase in membrane surface in order to sheathe
10 axons in myelin. Interestingly, in recent years, genes encoding Golgi-associated proteins with a
11 role in membrane trafficking have been found to be defective in an increasing number of
12 inherited disorders whose clinical manifestations include postnatal-onset microcephaly (POM),
13 white matter defects and intellectual disability. Several of these genes encode RAB GTPases,
14 RAB-effectors or RAB-regulating proteins, linking POM and intellectual disability to RAB-
15 dependent Golgi trafficking pathways and suggesting that their regulation is critical to postnatal
16 brain maturation and function. Here, we review the key roles of the Golgi apparatus in post-
17 mitotic neurons and the oligodendrocytes that myelinate them, and provide an overview of
18 these Golgi-associated POM-causing genes, their function in Golgi organization and trafficking
19 and the likely mechanisms that may link dysfunctions in RAB-dependent regulatory pathways
20 with POM.

21

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1 **1. Introduction**

2 Microcephaly affects about 2% of the population worldwide and represents the most
3 frequent neurological sign encountered in developmental brain disorders. It is characterized by
4 a small brain size, indirectly diagnosed by an occipito-frontal or head circumference (OFC)
5 smaller than the age- and gender-adjusted mean by more than 2 standard deviations (SD) at
6 birth and/or 3 SD as measured at 6 months of age or later; it is frequently associated with
7 intellectual disability of variable severity. Among the many kinds of microcephaly, genetic
8 forms have yielded essential information as to how the human brain develops during
9 embryonic/fetal and postnatal periods. While primary microcephaly is defined by a congenital
10 failure of brain growth detectable before birth, secondary (or postnatal-onset) microcephaly
11 (POM) is characterized by normal brain size at birth and the subsequent deceleration of brain
12 growth, and in particular the white matter, during infancy and/or childhood. In the past 15
13 years, considerable efforts have led to the identification of genes and pathways whose
14 deficiency causes hereditary primary microcephaly, also known as MCPH. The vast majority of
15 MCPH genes (17 identified to date, see updated review by (Alcantara and O'Driscoll, 2014))
16 play a role in the regulation of cell division and/or centrosome function in neural progenitors,
17 and a large number of functional studies now converge on common mechanisms that affect the
18 mode and/or extent of cortical progenitor division and their subsequent survival and
19 differentiation during the development of the neocortex. In contrast, POM or acquired
20 microcephaly, which often appears to be only one of many clinical signs in complex and
21 divergent syndromes, is not always considered a disorder on its own. As such, it is
22 underdiagnosed and underinvestigated, and the cellular mechanisms leading to it are poorly
23 understood.

24 The timing of POM suggests that these cellular mechanisms presumably involve
25 processes and pathways that occur later during development than neuronal progenitor division,
26 the major process implicated in primary microcephaly. Indeed, several principally postnatal

1 mechanisms that could lead to POM, such as defective gliogenesis or myelination, the
2 impairment of neuronal maturation or synaptic pruning, the arrest of normal development or
3 degenerative processes, have received much attention from the scientific community in recent
4 years. One candidate process worth noting is membrane trafficking and secretion through the
5 Golgi apparatus. Indeed, several recent studies have implicated Golgi-associated proteins in
6 genetic disorders that include POM among their characteristics, suggesting that the regulation
7 of Golgi trafficking and secretory functions are critical to postnatal brain maturation.
8 Intriguingly, a number of these POM-causing genes encode either RAB proteins - members of
9 the RAS superfamily of small GTPases which play a central role in membrane trafficking
10 including Golgi organization, vesicle formation, transport and fusion – or RAB-associated or
11 RAB-tethering factors whose fast and reversible recruitment facilitates such trafficking.
12 Interestingly, all these POM-causing genes are associated with the defective development of
13 white matter, which consists principally of the axons of neurons and the myelinating
14 oligodendrocytes that ensheath them, highlighting the link between the heavy membrane
15 trafficking and secretory activity of these two interdependent cellular components and postnatal
16 brain development.

17 In this review, we describe the key roles played by the Golgi apparatus in post-mitotic
18 neurons and oligodendrocytes, describe recently identified POM-causing genes associated with
19 the Golgi apparatus, and discuss the intriguing fact that many of these appear to encode RAB
20 proteins or their molecular partners. In light of their role in Golgi organization and trafficking
21 and the mechanistic links between RAB proteins, white matter defects and the development of
22 POM, we propose a new term for these disorders based on their similar pathophysiology:
23 "Golgipathies"/"Golgipathic microcephalies".

24

2. The Golgi apparatus in post-mitotic neurons and oligodendrocytes

The Golgi apparatus is a multifunctional organelle essential to ensure differentiated cellular functions as well as to maintain cell homeostasis. In mammalian cells, about one-third of newly synthesized proteins are destined to be secreted following the conventional secretory pathway. The Golgi apparatus is primarily involved in the processing of secretory proteins and lipids as they transit through it, effecting posttranslational modifications such as glycosylation, sulfation and proteolytic cleavage. The Golgi apparatus also acts in the sorting, packing, routing and recycling of these cargo molecules for their final destination. Depending on the cell type and stage of development, Golgi-dependent trafficking routes and secretory cargos have become diversified to fulfill specific secretory functions (Boncompain and Perez, 2013a). This is especially true of two cell types that are heavily affected in POM: post-mitotic projection neurons and the oligodendrocytes that enwrap their axons in myelin, with several studies showing that the Golgi apparatus plays a key role in the dynamic trafficking specific to the axonal and dendritic compartments of these neurons, as well as the extensive plasma membrane extensions of oligodendrocytes required for myelin formation. Besides its involvement in protein and lipid trafficking/processing in these two cell types, the Golgi apparatus is also involved in the determination and maintenance of neuronal polarity, as well as in autophagy, another process essential both for brain development and homeostasis of mature neural cells.

2.1 Role of the Golgi apparatus in neuronal polarity

In mammalian cells, the Golgi apparatus is a ribbon-shaped organelle made up of flattened cisternae organized into polarized stacks, flanked on either side by fenestrated tubular reticular membranes called the *cis*-Golgi network (CGN) and the *trans*-Golgi network (TGN) (Nakamura *et al.*, 2012; Papanikou and Glick, 2014). In most cells, the Golgi apparatus is positioned near or around the centrosome, with which it is dynamically associated through the action of cytoplasmic dynein motor proteins and Golgi anchor proteins (Yadav and Linstedt, 2011). In developing neurons, centrosomes, the Golgi apparatus and endosomes cluster

1 together at one pole of the cell body before neurites form, and play a key role in axon
2 specification (Caceres, 2007). Although the existence of a direct correlation between
3 Golgi/centrosome positioning and the area where the future axon will form has remained
4 controversial (de Anda *et al.*, 2005; Distel *et al.*, 2010; Horton *et al.*, 2005; Lowenstein *et al.*,
5 1994; Zmuda and Rivas, 1998), this asymmetric pericentrosomal confinement of the Golgi
6 apparatus likely leads to a local concentration of neuronal growth potential both in terms of
7 cytoskeletal infrastructure and of newly synthesized proteins, two components essential for the
8 elongation of the axon. Axonal outgrowth also requires a huge expansion of the plasma
9 membrane surface (Horton and Ehlers, 2003), which is achieved by the progressive integration
10 of Golgi-derived vesicles. Such vesicles have been shown to accumulate and polarize before
11 axonogenesis in cultured hippocampal neurons (Bradke and Dotti, 1997). In line with this
12 mechanism, brefeldin A treatment, which disassembles the Golgi apparatus, results in the
13 selective inhibition of axonal growth (Jareb and Banker, 1997). Similarly, the genetic
14 invalidation of certain Golgi-related proteins leads to altered neuronal polarity and death and/or
15 dysfunction. For instance, in mice in which the expression of the golgin GM130 is invalidated
16 by shRNA treatment or genetically knocked out, the polarity of the Golgi apparatus is altered,
17 leading to altered dendritic polarization in granule cells of the hippocampus (Huang *et al.*,
18 2014), as well as altered ER-to-Golgi transport, inducing the atrophy and death of Purkinje
19 cells of the cerebellum, and consequently, ataxia (Liu *et al.*, 2017). The loss of expression of
20 two other golgins, Golgin-160 and GMAP210, which disrupt pericentrosomal Golgi positioning
21 without affecting either the microtubule network or general secretion, also strongly affects cell
22 polarity in vitro (Yadav *et al.*, 2009). However, the effect of GMAP120 deletion on Golgi
23 structure or function might depend on the cellular subtype being examined (Smits *et al.*, 2010).

24

25 In addition to its involvement in neuronal development, the Golgi apparatus is required
26 for the maintenance of axodendritic polarity throughout the lifespan of mature post-mitotic

1 neurons. These highly specialized cells possess specific architectural features that make the
2 secretory pathway central to their structural maintenance, dynamics and function. In particular,
3 their strongly polarized axons and dendrites are characterized by morphologically and
4 functionally distinct components and pathways. This necessitates the asymmetric transport of
5 membranes and the continuous targeting of distinct repertoires of cargo proteins and lipids to
6 these distinct subcellular compartments. Mature neurons also often develop extensive dendritic
7 branching accompanied by a huge increase in membrane surface area (Ye *et al.*, 2006). In
8 addition, the long axons possessed by some neurons pose a perennial challenge to the
9 movement of proteins, lipids, vesicles and organelles between cell bodies and synaptic sites.
10 Although the mechanisms through which this differential targeting is specifically achieved and
11 regulated are complex and only partially understood, a number of key findings show that the
12 Golgi apparatus lies at the core of processes that elicit distinct secretory features in the axons
13 and dendrites of post-mitotic neurons, thereby maintaining neuronal polarity.

14

15 *2.1.1 Distribution of microtubules in neurons and their relationship to the Golgi* 16 *apparatus*

17 Microtubules, which themselves are polarized and serve as rails for active vesicular
18 cargo transport driven by molecular motors, are asymmetrically distributed in axons and
19 dendrites. While axons usually display long, uniformly oriented microtubules with their minus
20 ends towards the soma and the plus ends facing outwards, proximal dendrites contain shorter
21 microtubules oriented in both directions (Baas, 1999) (Figure 1A). In dendrites, the minus-end-
22 out microtubules are generally more stable (Yau *et al.*, 2016), which contributes to generating
23 directionality. This implies a difference in the organization of molecular motors involved in
24 trafficking in the two compartments. For example, dynein, which moves along microtubules
25 towards their minus end, drives retrograde transport in axons but bidirectional transport in
26 dendrites, while kinesin motors seem to predominantly drive anterograde transport in axons

1 (Kapitein *et al.*, 2010). Interestingly, the Golgi apparatus not only sorts and provides the
2 various cargos to be conveyed to specific destinations but also acts as a microtubule-organizing
3 center (MTOC), independently of the centrosome (Chabin-Brion *et al.*, 2001; Zhu and
4 Kaverina, 2013), and itself generates a distinct population of microtubules called Golgi-derived
5 microtubules. During the development of rodent hippocampal neurons, the centrosome actually
6 loses its function as an MTOC, and it is microtubules of non-centrosomal origin that enable
7 axon extension and serve as rails for directional post-Golgi trafficking (Stiess *et al.*, 2010).
8 Similarly, microtubule organization is independent of the centrosome in developing and mature
9 *Drosophila* neurons (Nguyen *et al.*, 2011), and the Golgi apparatus has been proposed as a
10 possible source of dendritic microtubules (Ori-McKenney *et al.*, 2012), a process promoted by
11 the golgin GM130 (Zhou *et al.*, 2014). Interestingly, directional trafficking defects have been
12 observed in human RPE1 cells lacking Golgi-derived microtubules, suggesting that the latter
13 are essential for post-Golgi transport (Miller *et al.*, 2009; Vinogradova *et al.*, 2012). Thus,
14 while further evidence is still required to confirm this possibility, the Golgi apparatus might
15 also be directly involved in the maintenance of neuronal polarity in postmitotic neurons
16 through its role as an MTOC.

17

18 2.1.2 *Specificity of Golgi-derived carriers*

19 The differential distribution of cargo proteins and lipids between dendrites and axons is
20 largely due to specific and reciprocal interactions between cargos, their carriers and molecular
21 motors. This occurs through the docking of motor proteins onto their specific cargos either
22 directly or via adaptor molecules, including scaffolding proteins, receptors and Rab GTPases
23 that regulate neuronal transport (Franker and Hoogenraad, 2013; Maeder *et al.*, 2014; Schlager
24 and Hoogenraad, 2009). Interestingly, the identity of the various carriers is in large part
25 conferred by the specific cargos they carry. The sorting of axonal and dendritic cargo proteins
26 and lipids occurs in the TGN, where they are physically segregated into specific clusters that

1 define specific dynamic TGN subdomains, ultimately leading to vesicle budding. This physical
2 segregation of cargos appears to rely on both the intrinsic affinity of different cargos for
3 specific lipid microenvironments provided by the TGN (Brugger *et al.*, 2000; Klemm *et al.*,
4 2009; Orci *et al.*, 1987; Paladino *et al.*, 2004; Schuck and Simons, 2004); reviewed in (Anitei
5 and Hoflack, 2011; De Matteis and Luini, 2008; Guo *et al.*, 2014; Lingwood and Simons, 2010;
6 Surma *et al.*, 2012), and the presence of sorting signals on cargo molecules that target them to
7 TGN-specific adaptors such as small ADP ribosylation factors, Rab and Rho GTPases, and
8 Golgi-localized tethering factors (De Matteis and Luini, 2008). In other words, the selective
9 targeting of cargos that contribute to the axodendritic polarity of neurons starts as soon as the
10 cargos reach the TGN (Guo *et al.*, 2014).

11

12 2.1.3. Golgi outposts in dendrites

13 In addition to the somatic Golgi apparatus, the Golgi complex forms smaller satellite
14 structures called Golgi outposts that are found in about 20% of the dendrites of mature neurons
15 (Gardiol *et al.*, 1999; Horton *et al.*, 2005; Pierce *et al.*, 2001) (Figure 1A). Several studies have
16 provided evidence that these Golgi outposts lack continuity with the somatic Golgi apparatus
17 and are functionally independent. Golgi outposts ensure the post-translational modifications,
18 trafficking and sorting of locally synthesized proteins (Horton *et al.*, 2005; Jeyifous *et al.*,
19 2009; Torre and Steward, 1996; Ye *et al.*, 2007), as well as local microtubule nucleation (Ori-
20 McKenney *et al.*, 2012), thereby playing a major role both in shaping dendritic arbor
21 morphology and in serving as platforms for the local delivery of postsynaptic molecules such as
22 synaptic receptors. In line with this role, and consistent with the recent demonstration that
23 Golgi outposts destined for the major dendrite are generated by a sequential process that
24 involves the polarized deployment and fission of tubules derived from the somatic Golgi
25 (Quassollo *et al.*, 2015), markers of *cis*, *medial* and *trans* Golgi compartments have all been
26 detected in dendrites (Horton *et al.*, 2005; Pierce *et al.*, 2001). Reinforcing the role of the Golgi

1 apparatus in the functional specialization of dendrites, a recent study by Mikhaylova provides
2 evidence for a Golgi-related satellite microsecretory system in dendrites that is even more
3 widespread than Golgi outposts and would permit the autonomous local control of membrane
4 protein synthesis and processing within dendrites (Mikhaylova *et al.*, 2016).

5

6 2.1.4. *Golgi components in axons*

7 Besides the well-described transport mechanisms that direct cargos to axons through
8 molecular motors and microtubules, and ensure their activity, function and plasticity (Hirokawa
9 and Takemura, 2005), growing evidence suggests that a number of axonal proteins are locally
10 synthesized from mRNAs and ribosomes present in axons and presynaptic elements (Sotelo-
11 Silveira *et al.*, 2006; Yoo *et al.*, 2010). The existence of such decentralized protein synthesis
12 could allow axons to meet local demands in a fast and energy-efficient manner, as is the case
13 with dendrites (Donnelly *et al.*, 2010; Holt and Bullock, 2009; Jung *et al.*, 2012). However,
14 whether this process also involves the presence of Golgi outpost-like structures in axons is a
15 matter of debate. The presence of early secretory components, including markers of the ER, the
16 ER-Golgi intermediate compartment (ERGIC), Golgi apparatus and TGN, has been observed
17 by some authors in the distal axoplasm of rat peripheral axons (Gonzalez *et al.*, 2016; Merianda
18 *et al.*, 2009), raising the possibility that these components self-organize into small functional
19 organelles in situ. Although rough ER and Golgi stacks have not so far been observed in axons
20 at the ultrastructural level (reviewed in (Ramirez and Couve, 2011)), the occurrence of local
21 protein synthesis suggests that protein processing and secretory needs could also be met locally,
22 rendering axons at least partially independent of the somatic early secretory pathway and
23 facilitating, for example, fast membrane receptor recycling in response to local conditions.

24

25

26

27

2.2 *Role of the Golgi apparatus in myelination*

1 Most neurons are characterized by a myelin sheath that enwraps their axons and is
2 responsible for the whitish appearance of the white matter of the brain. In the central nervous
3 system (CNS), the myelin sheath is a multilamellar structure consisting of the plasma
4 membrane extensions of oligodendrocytes, with a single mature oligodendrocyte ensheathing
5 several axons. These lipid-rich processes are extremely long and packed in tight spirals around
6 axons, forming a dense sheath to protect and insulate them and thus ensure the high-speed
7 propagation of electrical impulses. A stereological study carried out in a 20 year-old man has
8 revealed a total myelinated fiber length of 170,000 kilometers (Marner *et al.*, 2003); the
9 dimensions of the oligodendrocytic processes required to ensheath these fibers must therefore
10 be many times greater. The biogenesis and maintenance of this vast quantity of myelin implies
11 an intensive and sustained supply of membrane proteins and lipids. In oligodendrocytes, as in
12 neurons, this is achieved both through the local synthesis of myelin components close to the
13 site of their assembly, and through intensive vesicle trafficking mechanisms involving the
14 traditional ER-Golgi-TGN pathway (Kramer *et al.*, 2001). For example, myelin basic protein
15 (MBP), which represents approximately 30 percent of myelin proteins and plays a major role in
16 myelin compaction (Privat *et al.*, 1979) and composition by regulating its protein to lipid ratio
17 (Aggarwal *et al.*, 2011), is synthesized on the spot by the local translation of MBP mRNAs
18 (Colman *et al.*, 1982), following their packing in a translationally repressed state (Bauer *et al.*,
19 2012; Kosturko *et al.*, 2006) into large ribonucleoprotein complexes called RNA transport
20 granules (Muller *et al.*, 2013), and their transport along microtubules into the myelin
21 compartment (Ainger *et al.*, 1993; Carson *et al.*, 1997). In contrast, myelin-specific lipids and
22 other major myelin proteins, such as the proteolipid protein PLP, are synthesized in the soma of
23 mature oligodendrocytes and pass through the Golgi where they are processed and self-
24 assemble with cholesterol and sphingolipids to form a type of preformed myelin modules called
25 lipid-enriched liquid ordered membrane microdomains or lipid "rafts", which are transported
26 through the secretory pathway (Gielen *et al.*, 2006; Simons *et al.*, 2000). However, the

1 technical complications inherent in observing nanoscale molecular organizations such as lipid
2 microdomains in a reliable manner, i.e. without altering the object of the observation, has no
3 doubt contributed to their being viewed by some authors as hypothetical rather than real
4 structures for the present (see (Guo *et al.*, 2014)). Reciprocal communication between axons
5 and oligodendrocytes is also required for the generation of the myelin sheath. In
6 oligodendrocytes, such lipid microdomains, in addition to being components of myelin, behave
7 as dynamic signaling modules in recruiting specific signaling proteins that integrate axon-
8 derived soluble or membrane-bound signals to regulate myelination spatiotemporally (White
9 and Kramer-Albers, 2014). The nodes of Ranvier, non-myelinated axon segments that are
10 regularly placed along myelinated fibers, constitute privileged zones where molecular
11 interchanges take place across the axonal membrane. In addition to specific cell adhesion
12 molecules and cytoskeletal scaffold molecules that maintain the proper function and
13 architecture of nodes (Susuki and Rasband, 2008), these nodes are also the sites of release of
14 several axon-derived signaling molecules that have been shown to regulate the proliferation,
15 differentiation and survival of oligodendrocytes, and control the onset and timing of myelin
16 membrane growth (Simons and Trajkovic, 2006). For example, both the stability and the site-
17 specific translation of MBP mRNA are promoted by the recruitment of the tyrosine kinase Fyn
18 by oligodendrocytic lipid microdomains (White and Kramer-Albers, 2014), and its activation
19 occurs in response to the binding of the axonal cell adhesion molecule L1 (White *et al.*, 2008).
20 Interestingly, the myelin membrane protein TPO1, which has also been proposed to activate
21 Fyn, is highly enriched both in the Golgi and in the Fyn-positive sheets of myelinating
22 oligodendrocytes (Fukazawa *et al.*, 2006; Jain and Ganesh, 2016). Thus, the fine regulation of
23 myelin formation and maintenance appear to depend on trafficking through the Golgi-
24 dependent secretory pathway and microtubule network and signaling pathways in both
25 oligodendrocytes and the neurons, and on their functional interactions at specific sites.

26

2.3 Role of the Golgi apparatus in autophagy

Autophagy or "self-eating" is an evolutionarily conserved catabolic process by which cytosolic contents are delivered to acidic lysosomes for degradation. It serves various purposes: the maintenance of cellular homeostasis by eliminating waste or toxic products and recycling cellular components and nutrients, especially during conditions of starvation, for protection against certain pathogens, as well as the facilitation of cellular remodeling. In contrast to the ubiquitin-proteasome system (which achieves the regulated degradation of individual ubiquitinated proteins), autophagy leads to the bulk degradation of whole organelles and large amounts of proteins. Of the three main types of autophagy – microautophagy, chaperone-mediated autophagy and macroautophagy – the last is the best studied, and is characterized by a newly formed "isolation membrane" or "phagophore" that grows to envelop the components to be degraded in a double-walled structure called the autophagosome, which subsequently fuses with the lysosome (for a broad review, see (Feng *et al.*, 2014; Mizushima and Komatsu, 2011)). For this reason, the term "autophagy" is often used to refer specifically to macroautophagy.

In the central nervous system with its specialized long-lived cells characterized by extensive membrane processes, in addition to its traditional role in maintaining cellular homeostasis (Hu *et al.*, 2015; Tooze and Schiavo, 2008), autophagy plays several other roles: the modulation of synaptic plasticity (Hernandez *et al.*, 2012), the maintenance of the pool of neural stem cells required for postnatal neurogenesis (Wang *et al.*, 2013), and finally, the normal development of the CNS, including neural progenitor proliferation, neuronal maturation, connectivity and myelination (Ban *et al.*, 2013; Hara *et al.*, 2006; Jang *et al.*, 2015; Kadir *et al.*, 2016; Kim *et al.*, 2016; Komatsu *et al.*, 2006; Liang *et al.*, 2010; Rangaraju *et al.*, 2010; Schwarz *et al.*, 2012; Smith *et al.*, 2013; Song *et al.*, 2008). As could be expected, defects in autophagy-related genes or dysfunctions of autophagy are reflected in a number of human neurological disorders (for review, see (Bockaert and Marin, 2015; Ebrahimi-Fakhari *et al.*, 2016; Yamamoto and Yue, 2014)).

1 Despite the fact that neurons were among the first cell types in which autophagosomes were
2 observed (Dixon, 1967; Holtzman and Novikoff, 1965), most of the research into the
3 mechanisms of autophagy has focused on other cell types and/or non-mammalian species.
4 However, keeping in mind the highly conserved nature of this process, there is evidence from
5 neuronal and non-neuronal models to show that, at the structural level, the nucleation and the
6 elongation of the phagophore or isolation membrane might occur directly from the Golgi
7 apparatus, although, depending on the cell type involved, the ER or the ERGIC have been
8 proposed as alternative sources (Ge *et al.*, 2015; Lamb *et al.*, 2013). In alternative forms of
9 autophagy (Atg5/Atg7-independent autophagy (Nishida *et al.*, 2009) or the recently discovered
10 Golgi membrane-associated degradation (Yamaguchi *et al.*, 2016)), autophagosomes have been
11 shown to bud directly from Golgi membranes. Using 3D electron tomography of cryopreserved
12 brain tissue, Fernandez-Fernandez *et al.* have further described distinct engulfing Golgi
13 structures as a potential site for the degradation of cytoplasmic contents in neurons (Fernandez-
14 Fernandez *et al.*, 2017). At the functional level also, there are numerous links between Golgi-
15 related proteins and autophagic processes. Beclin1 is involved in endosome-to-Golgi recycling
16 but also plays a crucial early role in autophagosome formation (reviewed in (He and Levine,
17 2010)). The membrane-bound protein Atg9, normally involved in TGN-to-endosome transport,
18 is found in vesicles that contribute to autophagosome formation (Longatti *et al.*, 2012), and the
19 regulation of its trafficking plays a crucial role in the induction of autophagy pathways (Young
20 *et al.*, 2006; Zhou *et al.*, 2017). The clathrin adaptor proteins AP1/2, involved in the clathrin
21 coating of secretory vesicles and known to interact with Atg9, are also necessary for
22 autophagosome formation at specific TGN domains (Guo *et al.*, 2012). UVRAG (UV radiation
23 resistance-associated gene), which normally mediates Golgi-to-ER retrograde transport through
24 the tethering of COPI-coated vesicles, is dissociated from the ER and used for the generation of
25 autophagosomes during autophagy (He *et al.*, 2013). As discussed further below, several Golgi-
26 associated RAB GTPases and their partners, involved in various stages of trafficking, also play

1 key roles in the formation of the autophagosome (Geng *et al.*, 2010; Itoh *et al.*, 2008; Longatti
2 *et al.*, 2012; Oda *et al.*, 2016; Wen *et al.*, 2017) (see also **Table I**). In addition, SNAREs
3 (soluble *N*-ethylmaleimide-sensitive fusion protein attachment proteins), small membrane-
4 bound protein labels that help target vesicles to the Golgi apparatus, are also involved in the
5 fusion of autophagosomes (reviewed in (Reggiori and Ungermann, 2017)). It appears thus that
6 the membrane trafficking role of the Golgi apparatus and its role in autophagy are two sides of
7 the same coin, with the molecular machinery involved in one function being requisitioned to
8 serve the other according to cellular needs.

9
10

11 ***2.4 Role of Golgi-associated RAB proteins in the brain***

12 RAB proteins are small GTPases that regulate the docking of cargo vesicles to their
13 target compartments through specific interactions with tether, motor, and coat proteins at
14 almost every step of membrane trafficking, and in both anterograde (secretory) and retrograde
15 (endocytic and recycling) pathways. RAB proteins are considered to be molecular switches,
16 cycling between an active form (bound to GTP) and an inactive form (bound to GDP). The
17 switching between the two forms is regulated by guanine nucleotide exchange factors (GEFs),
18 which promote the active GTP-bound state, and by GTPase-activating proteins (GAPs), which
19 inactivate RABs by promoting hydrolysis of GTP to GDP (Barr and Lambright, 2010). Among
20 the ~60 RAB GTPases identified so far in mammalian cells, 20 have been localized to the
21 Golgi complex (Golgi-associated RABs) and 12 appear to be enriched in TGN membranes or to
22 act between the TGN and recycling endosomes (**Table I**).

23 Golgi-associated RABs play critical roles in two tightly linked processes that jointly
24 contribute to Golgi homeostasis - Golgi structural organization and membrane trafficking - as
25 the maintenance of ribbon organization is essential for cargo proteins to be correctly modified
26 and efficiently sorted (Liu and Storrie, 2012). An increasing number of studies show that each
27 Golgi-associated RAB fulfils more than one function and can recruit a large number of

1 effectors in several different locations of the Golgi apparatus. Interestingly, many RABs,
2 including several that are associated with the Golgi apparatus, appear to play a role in the
3 morphogenesis or function of post-mitotic neurons, for example by promoting neurite
4 elongation and/or enhancing dendritic growth and branching in neuronal cultures (Villarroel-
5 Campos *et al.*, 2014). The involvement of some of these Golgi-associated RABs in the
6 autophagic pathway could also be important for the maturation and maintenance of post-mitotic
7 neurons and glia, as mentioned in the previous section (see also **Table I**). The flip side of this
8 observation is that defects in some of these RABs or their effectors could be expected to lead to
9 the abnormal morphogenesis or function of post-mitotic neurons, as seen for instance in
10 disorders characterized by POM. This is precisely the case with RAB6, RAB1, RAB18,
11 RAB33 and RAB39, which we will examine further below.

12
13 RAB6 is one of the most abundant and best-characterized Golgi-associated RABs
14 (Goud, 2012). The RAB6 subfamily consists of 4 different isoforms, RAB6A, RAB6A',
15 RAB6B and RAB6C. RAB6A and A', two isoforms encoded by the same gene, localize to the
16 *medial* and *trans*-Golgi cisternae, cytoplasmic vesicles and TGN, and can recruit at least 15
17 different effectors through which they regulate Golgi vesicle biogenesis (Miserey-Lenkei *et al.*,
18 2010), vesicle tethering at the Golgi (Short *et al.*, 2002), intra-Golgi transport and retrograde
19 transport from late endosomes via the Golgi to the ER (Heffernan and Simpson, 2014). Recent
20 studies, however, suggest that the main function of RAB6 is to ensure the generation of post-
21 Golgi carriers and their exocytosis (Grigoriev *et al.*, 2007; Grigoriev *et al.*, 2011).
22 Nevertheless, in the context of microcephaly, the role of RAB6 in regulating retrograde
23 transport and its functional interactions with other molecules involved in this process, RAB33B
24 and the COG complex (Starr *et al.*, 2010; Sun *et al.*, 2007), are particularly intriguing (see next
25 section). A second gene encodes the brain-specific isoform RAB6B, which is localized to
26 structures similar to RAB6A/A', but is preferentially expressed in neuronal cells (Opdam *et al.*,

1 2000), where it also mediates retrograde membrane transport in neurites (Opdam *et al.*, 2000;
2 Wanschers *et al.*, 2007); however, whether this transport also involves the Golgi-to-ER
3 compartment has not been confirmed. Interestingly, RAB6A/A' and B are thought to play a key
4 role in the regulation of neurite outgrowth during the early phase of neuronal differentiation,
5 through the recruitment Bicaudal-D-related protein 1 and dynamic interactions with the kinesin
6 motor Kif1C and the dynein/dynactin retrograde motor complex (Schlager *et al.*, 2010).
7 RAB6C is encoded by a primate-specific intronless gene and is expressed in a limited number
8 of human tissues (including brain). In contrast to other RAB6 proteins, RAB6C associates with
9 the centrosome and is involved in cell cycle progression (Young *et al.*, 2010).

10 RAB1 is known to regulate anterograde membrane trafficking mediated by vesicles
11 coated with the coatomer COPII between the ER and the Golgi, where its two isoforms RAB1A
12 and RAB1B are predominantly expressed (Plutner *et al.*, 1991; Saraste *et al.*, 1995), but it is
13 also present in lipid microdomains and in autophagosomes (Wang *et al.*, 2010; Zoppino *et al.*,
14 2010). As for RAB6, RAB1 can recruit many different effectors such as the golgins p115,
15 GM130, GIANTIN, GRASP65 and GOLGIN-84, which act as tethers to help COPII-coated
16 vesicles dock to *cis*-Golgi membranes (Alvarez *et al.*, 2001; Diao *et al.*, 2003; Moyer *et al.*,
17 2001; Satoh *et al.*, 2003; Weide *et al.*, 2001). Interestingly, *Drosophila* neurons lacking a
18 functional *dar6* gene (the *Drosophila* RAB1 homolog) show reduced dendritic arborization (Ye
19 *et al.*, 2007). Conversely, over-expression of RAB1 rescues defective vesicular trafficking in
20 models of Parkinson disease with α -Synuclein-induced disruption of ER-to-Golgi transport
21 (Cooper *et al.*, 2006). This suggests that RAB1 is critical to both neuronal differentiation and
22 homeostasis.

23 RAB18, although less well studied, appears to have multiple roles as well, depending on
24 cell type and differentiation stage, and a combination of effectors (Vazquez-Martinez and
25 Malagon, 2011). In certain non-neuronal cells, e.g. adipocytes and hepatic stellate cells, RAB18
26 is associated with lipid droplets and functions in cell activation and lipid metabolism (Martin *et*

1 *al.*, 2005; O'Mahony *et al.*, 2015; Ozeki *et al.*, 2005). In neuroendocrine cells, RAB18 cycles
2 between the cytosol and the surface of a discrete population of secretory granules to reduce
3 their transport, and thereby negatively modulates the secretory activity of the cells (Vazquez-
4 Martinez *et al.*, 2007). In most cells, RAB18 is also present in the *cis*-Golgi and ER
5 compartments (Dejgaard *et al.*, 2008) and is required to maintain the morphology of the
6 perinuclear ER (Gerondopoulos *et al.*, 2014). There is good evidence that RAB18 can bind the
7 ER-resident Dsl1 protein complex (Gillingham *et al.*, 2014), which tethers and fuses vesicles
8 returning from the Golgi. This suggests that RAB18 may participate in the tethering of COPI-
9 coated vesicles to the ER (Gillingham *et al.*, 2014; Schroter *et al.*, 2016). Interestingly, RAB18
10 is expressed in the developing mouse brain from E14.5, and its expression markedly increases
11 around birth (Wu *et al.*, 2016). The depletion of RAB18 impairs the radial migration of neurons
12 to the cortical plate *in vivo* and alters cortical neuron morphogenesis *in vitro* (Wu *et al.*, 2016),
13 providing evidence that RAB18 is critical to neuronal positioning and maturation.

14 RAB33, another RAB of particular interest for brain maturation, exists as two closely
15 related and conserved proteins encoded by distinct genes, *RAB33A* and *RAB33B*. Both are
16 Golgi-associated proteins but *RAB33A* is found only in the brain, lymphocytes and
17 melanocytes (Cheng *et al.*, 2006; Lee *et al.*, 2006; Zheng *et al.*, 1997), whereas *RAB33B* is
18 ubiquitous (Zheng *et al.*, 1998). In the mouse brain, *RAB33A* is particularly highly expressed
19 throughout all cell layers of the cortex and hippocampus (Cheng *et al.*, 2006). In neurons, the
20 protein preferentially accumulates in growing axons and is found both in Golgi membranes and
21 in synaptophysin-positive vesicles that are transported along the growing axons (Nakazawa *et*
22 *al.*, 2012). *RAB33A* downregulation inhibits the anterograde axonal transport of these vesicles
23 while its overexpression results in their excessive accumulation and the formation of
24 supernumerary axons (Nakazawa *et al.*, 2012), suggesting that *RAB33A* mediates
25 axonogenesis and anterograde axonal transport of post-Golgi vesicles. Although *RAB33B*
26 shares strong sequence homology with *RAB33A* (especially in the effector domain, which is

1 perfectly conserved), functional studies have assigned a role for RAB33B in the regulation of
2 the retrograde transport of vesicles between the Golgi and the ER (Starr *et al.*, 2010).
3 Interestingly, RAB33B and RAB6A cooperate in regulating Golgi-to-ER trafficking and are
4 thought to act through a common RAB cascade in which the active form RAB33B recruits the
5 GEFs necessary to activate RAB6A (Pusapati *et al.*, 2012). In addition, RAB33B plays a role in
6 autophagy by modulating autophagosome formation through an interaction with Atg16L (Ao *et*
7 *al.*, 2014).

8 Like RAB33B, RAB39B is a neuron-specific protein that is localized to the Golgi
9 apparatus (Giannandrea *et al.*, 2010). Interestingly, both its downregulation and overexpression
10 in mouse primary hippocampal neurons significantly affect neuronal branching, the density of
11 presynaptic boutons and subsequent synapse formation (Giannandrea *et al.*, 2010;
12 Vanmarsenille *et al.*, 2014; Wilson *et al.*, 2014). This suggests that the tightly tuned expression
13 of RAB39B is required for proper neuronal maturation and further illustrates the direct link
14 between Golgi-associated RABs and the specification and maintenance of post-mitotic neurons.

15

16 **3. Syndromes with postnatal onset microcephaly (POM) and causative genes**

17 ***3.1 Postnatal-onset microcephaly***

18 Postnatal-onset microcephaly (POM) reflects a failure of the brain to achieve its normal
19 growth after birth, implicating mechanisms occurring during infancy or childhood and involved
20 in its maturation rather than those involved in its formation. At birth, the human brain is only at
21 around 60% of its adult size. The processes critical to ensure the establishment of a functional
22 neuronal network largely take place postnatally, throughout childhood, adolescence and even
23 into adulthood (**Figure 2**): while most neurons are produced and migrate during corticogenesis
24 (i.e. during the first two trimesters), synaptogenesis, which starts at mid-gestation, massively
25 increases during the first two years of life and continues throughout childhood. Synaptic
26 pruning, the process by which extra synapses are selectively eliminated, starts during the third

1 trimester, increases in childhood and lasts until adulthood. Similarly, the myelination process,
2 by which oligodendrocytes enwrap axons to generate a myelin sheath, starts during the third
3 trimester of gestation and peaks around two to three years of age, but persists throughout
4 childhood and adolescence and continues into adulthood (Back *et al.*, 2002; Bercury and
5 Macklin, 2015). In line with this prolonged role of glial cells, gliogenesis, though very active
6 around 32-40 weeks of gestation, largely continues after birth, especially during the first two
7 years of life (Stiles and Jernigan, 2010). POM, which likely results from the impairment of one
8 or several of these maturation processes, thus consistently becomes apparent during the first
9 two years of age (**Figure 2**). In most cases, POM is associated with cognitive impairments of
10 variable severity and outcome, collectively referred as to intellectual disability. Regardless of
11 the pathophysiological mechanism involved, as for primary microcephaly, POM has multiple
12 etiologies that may be genetic or environmental. A good classification has been proposed in the
13 review by Ashwal and colleagues (Ashwal *et al.*, 2009), and distinguishes, among the genetic
14 causes of POM, inborn errors of metabolism from the syndromic forms of POM.

15 The most famous syndrome consistently associated with POM is undoubtedly Rett
16 syndrome (RTT). Among the many neurological and behavioral features that characterize the
17 complex clinical spectrum of this neurodevelopmental disorder, typical criteria include a
18 normal period of development followed by a deceleration of head growth in the first two years
19 of life, associated with cognitive deterioration and seizures (Liyanage and Rastegar, 2014;
20 Pohodich and Zoghbi, 2015). Neuropathological examinations reveal reduced cortical thickness
21 associated with smaller and more closely packed neuronal cell bodies, but no active
22 neurodegeneration (Bauman *et al.*, 1995). Local myelin abnormalities and abnormal
23 membrane-bound inclusions in oligodendrocytes have also been reported in several RTT cases,
24 suggesting an involvement of white matter defects in the microcephaly associated with RTT
25 patients (Lekman *et al.*, 1991; Papadimitriou *et al.*, 1988). *MeCP2*, the major RTT gene,
26 encodes a methyl-CpG binding protein that binds methylated DNA. Initially thought to act as a

1 transcriptional repressor to modulate the transcription of target neuronal genes (Ausio *et al.*,
2 2014), MeCP2 has turned out to be a multifunctional protein with many interactors and several
3 roles in the CNS. It is expressed in microglia, astrocytes and oligodendrocytes in addition to
4 neurons (Cronk *et al.*, 2016), and is located in cellular compartments other than the nucleus,
5 such as the cytosol (Miyake and Nagai, 2007), the post-synaptic compartments of neurons
6 (Aber *et al.*, 2003) and even the centrosome (Bergo *et al.*, 2015). In line with this, a role for
7 MeCP2 in microtubule stability and vesicular transport has been suggested recently (Delepine
8 *et al.*, 2013; Roux *et al.*, 2012).

9

10 ***3.2 Golgi-associated proteins implicated in POM***

11 Vesicular routing within the cell is highly dependent on microtubules, and the Golgi
12 apparatus is central to this process as it not only drives translational modifications of freshly
13 synthesized proteins and lipids but also orchestrates the complex process that allows them to be
14 packed into specific transport vesicles and routed to their final destinations (Boncompain and
15 Perez, 2013b). As detailed in the introduction, this is even more relevant in the case of neurons
16 and oligodendrocytes. In line with the involvement of the secretory pathway in brain
17 maturation, an increasing number of genes that have been recently associated with syndromic
18 or isolated POM appear to encode Golgi proteins involved in the regulation of the Golgi-
19 mediated traffic machinery, including vesicle targeting and membrane recycling (**Table II**).

20

21 ***3.2.1 Cohen syndrome and COH1/VPS13B***

22 Cohen syndrome (COH, MIM 216550) is an autosomal recessive disorder characterized
23 by motor delays, retinal dystrophy appearing by mid-childhood, progressive severe myopia,
24 hypotonia, joint hypermobility and progressive POM associated with intellectual disability
25 (Wang *et al.*, 1993). Brain MRI reveals a relatively large corpus callosum in some patients,
26 associated with markedly smaller sagittal diameters of the brain stem (Kivitie-Kallio *et al.*,

1 1998). While the neurological signs are most prominent, additional features such as short
2 stature, small hands and feet or childhood-onset obesity have also been reported in some
3 patients but are not constant (Falk *et al.*, 2004). COH1, the only gene associated with Cohen
4 syndrome so far, encodes VPS13B, a large peripheral membrane protein that displays regions
5 homologous to yeast vacuolar protein sorting-associated protein 13 (Vps13p), and is active in
6 the Golgi (Seifert *et al.*, 2011). VPS13B has recently been found to colocalize and interact
7 physically with the active form of RAB6 (Seifert *et al.*, 2015). Depletion experiments using
8 RNAi against RAB6 show that it is required for VPS13B recruitment to Golgi membranes.
9 Conversely, the downregulation of VPS13B or a blockade of its recruitment to the Golgi
10 apparatus results in the fragmentation of Golgi ribbons and a simultaneous inhibition of neurite
11 outgrowth in hippocampal neurons (Seifert *et al.*, 2011; Seifert *et al.*, 2015). Thus, the gene
12 responsible for Cohen syndrome likely encodes an effector protein of RAB6 with a specific
13 role in the dynamics and function of the Golgi apparatus in particular during neuronal
14 maturation (**Figure 1B**).

15

16 3.2.2 *PCCA2* syndrome and *VPS53*

17 Progressive Cerebello-Cerebral Atrophy type 2, also named Ponto-Cerebellar
18 Hypoplasia type 2E (*PCCA2/PCH2E*, MIM 615851) is an autosomal recessive
19 neurodegenerative disorder characterized by normal development during the first three to five
20 months of life, followed by motor delays, progressive POM, progressive spasticity leading to
21 contracture and epileptic seizures prior to two years of age (Ben-Zeev *et al.*, 2003). Patients
22 have a normal head circumference at birth and undergo progressive growth deceleration,
23 resulting in microcephaly during the first year of life. Brain MRI reveals a gradual decrease in
24 cerebral white matter associated with delayed myelination and thinning of the corpus callosum
25 (Ben-Zeev *et al.*, 2003). The responsible gene, mapped and identified in 2014, encodes *VPS53*,
26 a vacuolar protein-sorting protein that participates in the transport and recycling of endosome-

1 derived transport vesicles (Feinstein *et al.*, 2014). VPS53 is part of two large multisubunit
2 complexes named Golgi-associated retrograde protein (GARP) and Endosome-associated
3 recycling protein (EARP). Both GARP and EARP ensure the proper tethering between
4 endosomes and their acceptor compartment. GARP is a peripheral complex associated with the
5 TGN and is involved in tethering retrograde transport carriers from endosomes to the TGN
6 (Bonifacino and Hierro, 2011). EARP, characterized more recently, is localized to recycling
7 endosomes and promotes their fast recycling back to the plasma membrane (Schindler *et al.*,
8 2015). Both complexes cooperate with SNAREs for subsequent membrane fusion. RAB
9 proteins play an essential role during these tethering-fusion steps as they recruit the required
10 tethering factors. In line with this role, GARP has been found to interact with RAB6A at the
11 TGN (Liewen *et al.*, 2005) and EARP associates with RAB4-containing vesicles (Schindler *et*
12 *al.*, 2015). Thus, the gene responsible for PCCA2 syndrome encodes a subunit of tethering
13 complex proteins that specifically interact with RAB GTPases during endosomal transport in
14 between the TGN and the plasma membrane (**Figure 1B**).

15

16 3.2.3 Warburg-Micro syndrome and *RAB3GAP1/2*, *RAB18* and *TBC1D20*

17 Warburg-Micro syndrome (WARBM1, MIM 600118) is an autosomal recessive
18 disorder characterized by neurodevelopmental defects, severe visual impairment and
19 hypogonadism (Warburg *et al.*, 1993). Neurodevelopmental features generally include POM
20 with profound intellectual disability and progressive limb spasticity associated with progressive
21 peripheral axonal neuropathy (Bem *et al.*, 2011). Brain MRI shows predominantly frontal
22 polymicrogyria bilaterally, and hypoplasia of the corpus callosum and cerebellar vermis
23 (Handley *et al.*, 2013; Liegel *et al.*, 2013). Loss-of-function mutations in four distinct genes,
24 *RAB3GAP1*, *RAB3GAP2*, *RAB18* and *TBC1D20*, have been implicated in WARBM1 in
25 recent years (Aligianis *et al.*, 2005; Borck *et al.*, 2011; Liegel *et al.*, 2013). *RAB18* has been
26 linked to several distinct membrane-bound organelles such as endosomes (Lutcke *et al.*, 1994),

1 peroxisomes (Gronemeyer *et al.*, 2013), secretory granules (Vazquez-Martinez *et al.*, 2007) and
2 the ER, and to lipid droplet formation (Martin *et al.*, 2005; Ozeki *et al.*, 2005), depending upon
3 circumstances and cell types. More recent studies have confirmed its localization in the ER and
4 the *cis*-Golgi compartment (Dejgaard *et al.*, 2008). The RAB3GAP complex, initially identified
5 as a GTPase activating protein (GAP) specific to the RAB3 subfamily of small G proteins
6 (Fukui *et al.*, 1997; Nagano *et al.*, 1998), is also a GEF (guanine nucleotide exchange factor) of
7 RAB18 (Gerondopoulos *et al.*, 2014). TBC1D20, an ER-localized GAP that promotes the
8 hydrolysis of RAB1 GTP (Haas *et al.*, 2007; Sklan *et al.*, 2007), is thought to act on RAB18 as
9 well (Handley *et al.*, 2015). Thus, RAB3GAP1, RAB3GAP2 and TBC1D20 all play a role in
10 the regulation of the RAB18 activity, directly linking WARBM1 to RAB18 deficiency or
11 dysregulation. RAB3GAP and TBC1D20 also regulate the ER localization of RAB18, an
12 essential step to support the function of RAB18 in the control of ER structural integrity and
13 retrograde membrane recycling from the Golgi apparatus to the ER (Gerondopoulos *et al.*,
14 2014; Handley *et al.*, 2015). Thus, the genes involved in WARBM1 all pinpoint a specific
15 RAB-dependent pathway directly associated with ER-Golgi trafficking (**Figure 1B**).

16

17 3.2.4 Autosomal recessive mental retardation 13 (*MRT13*) and *TRAPPC9*

18 Loss-of-function mutations in the *TRAPPC9* gene were originally identified by
19 autozygosity mapping in four families with a nonsyndromic autosomal recessive intellectual
20 disability (*MRT13*, MIM 613192) (Mir *et al.*, 2009; Mochida *et al.*, 2009; Philippe *et al.*,
21 2009). Since then, 3 additional cases have been reported. Although initially referred to as
22 nonsyndromic, the phenotype that is starting to emerge appears to be quite distinctive,
23 including moderate to severe POM, a peculiar facial appearance, obesity and hypotonia.
24 Reported brain anomalies consistently include a reduced volume of the cerebral white matter
25 with a hypersignal on FLAIR sequences, and a marked thinning of the corpus callosum (Abou
26 Jamra *et al.*, 2011; Kakar *et al.*, 2012; Marangi *et al.*, 2013). *TRAPPC9* is one of the subunits

1 of the Trafficking Protein Particle (TRAPP) complex, which mediates the tethering of COPII-
2 coated ER-derived vesicles to allow their fusion with *cis*-Golgi membranes (Barrowman *et al.*,
3 2010). The TRAPP complex acts through the recruitment and activation of the GTPase RAB1,
4 which in turn recruits specific *cis*-Golgi effectors such as p115 and GM130, allowing the
5 tethering of the vesicles to Golgi membranes (Barnekow *et al.*, 2009). During this anterograde
6 ER-to-Golgi transport, the TRAPP complex is dynamically associated with the microtubules
7 through a physical interaction with p150^{Glued}, a subunit of dynactin. A recent study has
8 proposed that TRAPPC9 in particular mediates the interaction between p150^{Glued} and COPII-
9 coated vesicles until they reach their target membrane (Zong *et al.*, 2012), evoking an
10 additional paradigm in which RAB-associated ER-Golgi trafficking linked to POM and white
11 matter defects (**Figure 1B**).

12

13 3.2.5 A neuromuscular syndrome with microcephaly and *GOLGA2/GM130*

14 A homozygous frame-shift deletion in the *GOLGA2* gene that results in a loss of gene
15 function has recently been identified in an individual with a neuromuscular phenotype
16 characterized by developmental delays, seizures, progressive microcephaly starting at 4 months
17 of age, hypotonia and muscular dystrophy (Shamseldin *et al.*, 2016). Here also, brain MRI has
18 revealed delayed myelination and a thinning of the corpus callosum, but with no other specific
19 loss of cerebral volume. *GOLGA2* encodes the Golgi matrix protein GM130, which is a
20 peripheral membrane protein located on the *cis*-side of the Golgi apparatus and involved in
21 both the assembly/maintenance of Golgi structure and the regulation of the secretory pathway
22 (Nakamura, 2010). As mentioned above in the case of TRAPPC9, GM130 participates in
23 membrane-tethering events at the Golgi complex through dynamic interactions with RAB1 and
24 other tethering proteins such as p115, to ensure efficient anterograde cargo delivery to the *cis*-
25 Golgi compartment. Moreover, GM130 binds to other RAB proteins involved in membrane
26 traffic regulation at the ER/Golgi interface, such as RAB2 and RAB33B (Short *et al.*, 2001;

1 Valsdottir *et al.*, 2001). Thus, GOLGA2/GM130 deficiency appears to be yet another situation
2 highlighting the link between Golgi-associated RABs, POM and white matter defects (**Figure**
3 **1B**).

4

5 3.2.6 Dyggve-Melchior-Clausen syndrome and DYMECLIN

6 Dyggve-Melchior-Clausen syndrome (DMC, MIM #223800) is an autosomal recessive
7 skeletal dysplasia associated with POM and intellectual disability, and caused by loss-of-
8 function mutations in the *DYM* gene encoding DYMECLIN, a Golgi protein involved in
9 intracellular trafficking (Dimitrov *et al.*, 2009; Osipovich *et al.*, 2008; Paupe *et al.*, 2004).
10 Brain MRI in DMC patients with a truncating mutation in *DYM* reveals a marked thinning of
11 the corpus callosum and brain stem (Dupuis *et al.*, 2015). In line with this finding, recent data
12 from our group show a significant reduction in white matter volume associated with defects in
13 the way the myelin sheath is wrapped, and a reduced thickness of myelinated axons in *Dym*^{-/-}
14 mutant mice (Dupuis *et al.*, 2015). Interestingly, *Dym*-deficient neurons display a fragmented
15 Golgi apparatus and impaired ER-to-Golgi trafficking (Dupuis *et al.*, 2015). However, an
16 impairment of the retrograde transport of vesicles from the Golgi to the ER has also been
17 suggested in *Dym*^{-/-} mouse embryonic fibroblasts (Osipovich *et al.*, 2008). Although
18 DYMECLIN function is still elusive at the molecular level, several lines of evidence suggest
19 that it has a tethering role during vesicle trafficking between the ER and the Golgi: (i)
20 DYMECLIN localizes to both the cytosol and the periphery of *cis*-Golgi membranes, and
21 permanently shuttles between these two compartments (Dimitrov *et al.*, 2009), (ii)
22 DYMECLIN colocalizes and directly interacts with GIANTIN (Dimitrov *et al.*, 2009;
23 Osipovich *et al.*, 2008), a giant Golgi-resident protein of the golgin family that forms
24 complexes with RAB1 or RAB6 to tether Golgi membranes with membrane structures derived
25 from the ER (anterograde pathway) or returning to the ER (retrograde pathway), respectively
26 (Goud and Gleeson, 2010; Koreishi *et al.*, 2013; Rosing *et al.*, 2007) (**Figure 1B**).

1 Interestingly, Smith McCort dysplasia, a clinical variant of DMC syndrome with identical
2 skeletal defects but normal intelligence and no microcephaly, has been found to result either
3 from specific missense mutations in *DYM* that could result in some residual activity of the
4 protein (SMC1, MIM #607326) (Cohn *et al.*, 2003; Dimitrov *et al.*, 2009) or from loss-of-
5 function mutations in the small GTPase RAB33B (SMC2, MIM #615222) (Alshammari *et al.*,
6 2012; Dupuis *et al.*, 2013). Given that the main functional domains of RAB33A and RAB33B
7 proteins are perfectly conserved (Zheng *et al.*, 1998), it is tempting to speculate that the
8 cerebral phenotype in SMC is rescued by the partial activity of DYMECLIN (SMC1) or a
9 complementation of RAB33B deficiency by RAB33A in the brain (SMC2). Interestingly, both
10 RAB33A and RAB33B are present in the Golgi complex (Cheng *et al.*, 2006; Zheng *et al.*,
11 1998) and are involved in the regulation of vesicular transport: while RAB33B functions in
12 concert with RAB6 to coordinate bidirectional intra-Golgi and retrograde Golgi-to-ER transport
13 (Starr *et al.*, 2010), RAB33A has been shown to mediate the anterograde transport of post-
14 Golgi vesicles in growing hippocampal axons (Nakazawa *et al.*, 2012). Although the precise
15 link between *DYM*, RAB33A/B and RAB6 is yet to be understood, these factors likely function
16 in the regulation of common Golgi-driven secretory pathways.

17

18 3.2.7 Congenital disorders of glycosylation and the COG complex

19 Congenital Disorders of Glycosylation (CDG) represent a huge and still growing family
20 of multisystemic autosomal recessive pathologies involving dysfunctions in the processing of
21 N- and O-linked glycans, with most of the genes identified so far encoding glycosylation
22 enzymes (Freeze and Ng, 2011). However, one subgroup of these diseases involves the
23 Conserved Oligomeric Golgi (COG) complex, a hetero-octameric protein complex, which, as
24 its name suggests, is localized to the *cis* and medial Golgi as well as surrounding vesicles
25 (Climer *et al.*, 2015). The COG complex is thought to act as a tethering factor, in particular
26 during intra-Golgi and retrograde Golgi-to-ER trafficking, where it mediates the recycling of

1 Golgi glycosyltransferases (Shestakova *et al.*, 2006). Loss-of-function mutations in seven of the
2 eight COG subunits have been associated with CDG, possibly due to the accumulation of COG
3 complex-dependent vesicles, likely resulting in the segregation of Golgi glycosylation enzymes
4 from their target proteins (Climer *et al.*, 2015). Mutations affecting the COG complex thus
5 result in multiple protein glycosylation deficiencies. Among the many neurological
6 manifestations described in COG-associated CDG, POM has been reported in patients carrying
7 mutations in COG1, COG2, COG7 and COG8 (Foulquier *et al.*, 2007; Foulquier *et al.*, 2006;
8 Kodera *et al.*, 2015; Morava *et al.*, 2007). In addition, hypoplasia of the corpus callosum has
9 been observed on brain MRI in four patients (Kodera *et al.*, 2015; Morava *et al.*, 2007) and
10 brainstem atrophy has been reported in one case (Foulquier *et al.*, 2007). Interestingly, the
11 COG complex has been shown to interact with molecules at all levels of Golgi organization and
12 trafficking, including several Golgi-associated SNAREs (Laufman *et al.*, 2013a; Laufman *et*
13 *al.*, 2011, 2013b; Laufman *et al.*, 2009; Shestakova *et al.*, 2007), golgins such as p115, GM130,
14 GIANTIN and GOLGIN-84 (Miller *et al.*, 2013; Shestakova *et al.*, 2007; Sohda *et al.*, 2010;
15 Sohda *et al.*, 2007), vesicular coatomers such as COPI, and molecular motors (Kristensen *et al.*,
16 2012; Miller *et al.*, 2013) as well as a number of Golgi-associated RABs. Among the latter are
17 RAB1A/B, RAB2A, RAB6A/B, RAB10, RAB14, RAB30, RAB36, RAB39 and RAB41
18 (reviewed in (Willett *et al.*, 2013)), again pointing to the relationship between defects in these
19 functionally important Golgi-associated proteins on the one hand, and POM and white matter
20 defects on the other (**Figure 1B**).

21
22

4. Possible mechanisms underlying postnatal microcephaly

A consistent finding in all the disorders described above is the presence of white matter defects, and in particular of abnormalities of the corpus callosum, which, thanks to its relatively high visibility in live imaging modalities as well as conventional histology, could rightly be considered a window into the diseased brain. Although white matter, which is made up of millions of axon bundles that interconnect neurons throughout the brain into functional circuits, accounts for half the volume of the human brain, its role in brain maturation and homeostasis is still far less studied than that of the cortex. Yet, it is essential for impulse conduction, and is thought to participate actively in higher functions such as learning, reasoning (in particular mathematical thinking (Matejko and Ansari, 2015)), and memory (Fields, 2010). Consistent with this broad involvement, axonal transport defects are now being described in an increasing number of degenerative disorders such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease and hereditary spastic paraplegia etc. (Duncan and Goldstein, 2006; Neefjes and van der Kant, 2014). The fragmentation and dispersal of the Golgi apparatus has been documented as an early event in these degenerative processes (Gonatas *et al.*, 2006; Haase and Rabouille, 2015; Joshi *et al.*, 2015), and the Golgi, in addition to being a sensor of stress signals in cell death pathways (Machamer, 2015; Nakagomi *et al.*, 2008), may be actively involved in degeneration (Rabouille and Haase, 2015).

However, defective Golgi trafficking is not only an important issue in neurodegenerative conditions but during development, including in predominantly postnatal processes such as the maturation of white matter, as indicated by its involvement in POM highlighted in the present review. The demand for secretory traffic increases exponentially as axons elongate, dendrites multiply and myelination increases. If even a single link in the supply chain is deficient, whether in neurons or the oligodendrocytes that myelinate them, the Golgi apparatus likely detects this stress, which, beyond a certain threshold, becomes detrimental and affects cell

1 maturation and maintenance. Additionally, in many cases of POM, as detailed above, the
2 deficient link appears to be none other than a member of the Golgi-mediated secretory traffic
3 machinery. The implication of several Golgi-associated RABs in the pathophysiology of POM
4 highlights the central role of the Golgi apparatus in dynamically receiving and generating
5 specific membrane vesicles both in large quantities and in a highly controlled manner. Thus,
6 one possible mechanism responsible for the development of POM could be an insufficient
7 supply of synaptic and/or oligodendrocytic cargos due to a defective secretory pathway in these
8 highly demanding cells (Dupuis *et al.*, 2015). Such a defect may be due to ineffective transport,
9 alteration in cargo maturation (e.g. glycosylation, proteolysis) or problems in routing to the
10 proper target compartment. Defective secretory trafficking combined with hypomyelination
11 likely leads to an impairment of synaptic transmission, contributing to the intellectual disability
12 observed in POM patients and perhaps further weakening diseased neurons. Thus, while POM
13 or acquired microcephaly is not traditionally considered a disorder on its own but rather as a
14 clinical feature present in various genetic syndromes, and several syndromes featuring POM
15 are associated with genes and functions that do not directly involve membrane trafficking
16 (Seltzer and Paciorkowski, 2014), we believe that there exists a distinct subset of POM with
17 similar pathophysiological mechanisms and clinical manifestations. We propose that this
18 distinct and coherent ensemble of causes and effects – defects in Golgi-associated RABs or
19 their partners, altered trafficking of molecules, vesicles and membrane components essential
20 for neuronal and oligodendrocytic activity, the resulting defective myelination and synaptic
21 function and finally, microcephaly with a postnatal onset independent of neural progenitor
22 proliferation or migration – be named "Golgipathic microcephalies".

23 The impairment of autophagic pathways is also likely implicated in the pathophysiology of
24 POM and may be related to defects in the conventional secretory pathway. Among the
25 autophagy-related molecules involved in POM, the tethering complex GARP (of which VPS53,
26 involved in PCCA2, is a subunit) is recruited at the phagophore membrane during

1 autophagosome assembly (Yang and Rosenwald, 2016). TBC1D20, one of the genes associated
2 with Warburg-Micro syndrome, plays an essential role in the maturation of autophagosomes
3 via its RAB1BGAP function (Sidjanin *et al.*, 2016). RAB33A and B are known to modulate
4 autophagosome formation through their interaction with ATG16L (Itoh *et al.*, 2008). The
5 vesicle-tethering golgin GM130 has also been shown to participate in the regulation of
6 autophagy through dynamic interactions with GABARAP and WAC proteins (Joachim *et al.*,
7 2015). It is also likely that some syndromes involving defective autophagy do indeed include
8 POM among their symptoms, but that this link has been missed among the multitude of other
9 symptoms involved, or ignored because of a lack of understanding regarding the underlying
10 cause. For instance, a form of hereditary spastic paraplegia linked to mutations in TECPR2,
11 which regulates COPII-dependent vesicle formation (Stadel *et al.*, 2015), has recently been
12 shown to include progressive microcephaly among its symptoms (Heimer *et al.*, 2016; Oz-Levi
13 *et al.*, 2012), although it is not yet known whether this is due to neurodevelopmental or
14 neurodegenerative processes. As mentioned previously, several other ER/Golgi-associated
15 RAB proteins such as RAB1, RAB11 and RAB24, are also involved in the regulation of
16 autophagy, further highlighting the crosstalk, if not the overlap, between Golgi membrane
17 trafficking and autophagy pathways (Jain and Ganesh, 2016) (**Table I**).

18 The clinical manifestations of "Golgiopathies" may not be restricted to the white matter or
19 myelinated neurons predominantly affected in POM. The Golgi apparatus obviously plays a
20 crucial role in numerous cell types, a fact supported by the diversity of other symptoms
21 displayed by patients with "Golgiopathies": stunted growth, neuromuscular dysfunctions,
22 metabolic disorders, pubertal anomalies etc. It is unclear at present in what cells and to what
23 extent Golgi trafficking deficits in other organs and tissues contributes to the phenotype in
24 these syndromes. Besides, with regard to disorders of the autophagic pathway and the putative
25 overlap between the molecular machinery involved in this pathway and that traditionally
26 associated with trafficking, other symptoms that have been overlooked until now may also turn

1 out to form part of the clinical spectrum. In addition, although neurodegeneration has not been
2 shown to be involved in the types of POM described in the present review, it cannot be ruled
3 out, as the long-term evolution of the cases reported so far is unknown. However, it is worth
4 noting that retinal degeneration has been documented in Cohen syndrome (North *et al.*, 1995),
5 and sensory axon degeneration associated with a deletion of RAB18 has recently been
6 described in a mouse model of Warburg-Micro syndrome (Cheng *et al.*, 2015). Future
7 investigations into POM-related syndromes where the responsible gene has not been identified
8 should therefore be carried out in light of the notion of Golgi trafficking defects as a possible
9 etiology.

11 **5. Conclusion**

12 The newly identified defects in certain Golgi-associated proteins, including RABs and
13 their interactors, that we have highlighted in the present review and propose to name
14 "Golgipathic microcephalies" or "Golgipathies", and more broadly, the notion that the primary
15 deregulation of the trafficking machinery is itself a mechanism leading to POM, is clearly an
16 emerging research area that it would be important to investigate in coming years. Future studies
17 in this field will surely improve our understanding of the molecular mechanisms linking Golgi
18 function and the maturation of white matter, in addition to extending the predicted and
19 observed phenotype of patients with these disorders and creating new avenues to optimize
20 cognitive outcome by reversing part of the maturation defects.

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Legends to Figures

Figure 1.

Golgi-associated postnatal microcephaly-causing factors and their link with RAB proteins in anterograde and retrograde neuronal trafficking

A. Schematic representation of the somatic Golgi apparatus, dendritic Golgi outposts and differential organization of microtubules in axons and dendrites. B. Subcellular localization of the proteins whose encoding genes have been associated with postnatal-onset microcephaly, and their known link with Golgi-associated RAB GTPases.

EE = Early Endosome. ER = Endoplasmic Reticulum. ERGIC = Endoplasmic Reticulum-Golgi Intermediate Compartment. GA = Golgi Apparatus. GO = Golgi Outposts. GS = Golgi Satellites. L/A = Lysosome/Autophagosome. LE = Late Endosome. MT = MicroTubules. Nu = Nucleus. RE = Recycling Endosome. TGN = Trans Golgi Network.

Figure 2.

Time-course of the main neurodevelopmental steps in human and correspondence with the Occipito-Frontal Circumference progression

Schematic representation of the main neurodevelopmental mechanisms contributing to brain growth illustrating that gliogenesis, synaptogenesis, myelination and synaptic pruning mainly occur during childhood (although initiated before birth) and significantly contribute to postnatal brain growth (black curve). The red and blue curves illustrate the progression of occipito-frontal circumference (OFC) in patients affected with postnatal microcephaly (POM) and primary microcephaly (PM) respectively.

TABLE I. GA/TGN-associated RAB GTPases and their associated function(s).

RAB GTPase Sub-family	Subcellular location	Known intracellular function	References
RAB1	Cis-Golgi - ER/Intermediate compartment	ER-Golgi trafficking, Cell signaling, Autophagy	(Ao <i>et al.</i> , 2014; Yang and Rosenwald, 2016)
RAB2	Cis-Golgi, Intermediate compartment, vesicles	Regulation of GA morphology, Axonal transport	(Aizawa and Fukuda, 2015; White <i>et al.</i> , 2015)
RAB3	Golgi, TGN, secretory vesicles	Exocytosis	(Kogel <i>et al.</i> , 2013; Nishimura <i>et al.</i> , 2008)
RAB6	Golgi, TGN, peroxisomes	Golgi vesicle biogenesis, Anterograde & retrograde vesicle transport from the trans-Golgi/TGN to the plasma membrane or ER	(Heffernan and Simpson, 2014; Majeed <i>et al.</i> , 2014)
RAB7	TGN, late endosomes	Transport to late endocytic compartments, Cell signaling, Autophagy	(Ao <i>et al.</i> , 2014; Guerra and Bucci, 2016)
RAB8	TGN, vesicles, tubular structures	Membrane trafficking from the TGN, Exocytosis, Membrane recycling, Autophagy	(Ao <i>et al.</i> , 2014; Peranen, 2011)
RAB9	Golgi, TGN, late endosomes	Endosome-to-TGN transport, Transport within the endolysosomal system, Golgi targeting of glycosphingolipids, Autophagy	(Ao <i>et al.</i> , 2014; Kucera <i>et al.</i> , 2016)
RAB10	Golgi, ER tubular intermediates, peroxisomes	Membrane trafficking from the Golgi/ER, the TGN and recycling endosomes, Dendritic transport	(Homma and Fukuda, 2016; Zou <i>et al.</i> , 2015)
RAB11	Golgi, ER tubular intermediates, TGN, recycling endosomes	Recycling endosomes, Exocytosis, Autophagy	(Ao <i>et al.</i> , 2014; Takahashi <i>et al.</i> , 2012; Wilson <i>et al.</i> , 2016)
RAB12	Golgi, early endosomes, toxin-induced membrane invaginations	Transport within the endolysosomal system, Retrograde transport to TGN, Autophagy	(Matsui and Fukuda, 2011, 2013; Rydell <i>et al.</i> , 2014)
RAB13	TGN, endosomes, plasma membrane	Recycling endosomes, Membrane trafficking from the TGN	(Kobayashi <i>et al.</i> , 2014; Nokes <i>et al.</i> , 2008)
RAB14	Golgi, TGN, early endosomes, peroxisomes	membrane trafficking between the Golgi complex and endosomes, Autophagy	(Junutula <i>et al.</i> , 2004; Okai <i>et al.</i> , 2015)
RAB15	TGN, early and recycling endosomes	Early endocytic trafficking	(Zuk and Elferink, 2000)
RAB18	Cis-Golgi - ER, <i>endosomes, peroxisomes, secretory granules, lipid droplets</i>	ER structure, ER-Golgi trafficking, secretory granule transport	(Dejgaard <i>et al.</i> , 2008; Gerondopoulos <i>et al.</i> , 2014; Vazquez-Martinez and Malagon, 2011)
RAB19	Golgi, vesicles	Axonal transport	(Sinka <i>et al.</i> , 2008; White <i>et al.</i> , 2015)
RAB21	TGN, endosomes	Neurite Outgrowth Early endocytic pathway, Autophagy	(Burgo <i>et al.</i> , 2009; Jean <i>et al.</i> , 2015; Simpson <i>et al.</i> , 2004)
RAB22	Trans-Golgi, TGN, endosomes	Neurite Outgrowth Early endocytic pathway	(Dutta and Donaldson, 2015; Rodriguez-Gabin <i>et al.</i> , 2001; Wang <i>et al.</i> , 2011)

RAB24	ER, Cis-Golgi, late endosomes, Autophagosomes, midbody	endosome-lysosome degradative pathway, Cytokinesis, Autophagy	(Amaya <i>et al.</i> , 2016; Militello <i>et al.</i> , 2013; Olkkonen <i>et al.</i> , 1993; Yla-Anttila <i>et al.</i> , 2015)
RAB26	Golgi, synaptic vesicles, Lysosomes	Golgi-to-cell surface traffic, lysosome traffic, Autophagy	(Binotti <i>et al.</i> , 2015; Jin and Mills, 2014; Li <i>et al.</i> , 2012)
RAB27	TGN, secretory granules	secretory granule transport and exocytosis	(Fukuda, 2013)
RAB29	Golgi, TGN, recycling endosomes	Integrity of the TGN, Recycling from late endosomes to the TGN	(Onnis <i>et al.</i> , 2015; Wang <i>et al.</i> , 2014)
RAB30	Golgi	Integrity of the Golgi apparatus, Autophagy	(Kelly <i>et al.</i> , 2012; Oda <i>et al.</i> , 2016)
RAB33	Golgi, synaptic vesicles	axonal transport (RAB33A), Retrograde Golgi-to-ER transport (RAB33B), Autophagy	(Ao <i>et al.</i> , 2014; Itoh <i>et al.</i> , 2008)
RAB34	Golgi, Lysosomes	Intra-Golgi anterograde transport, lysosomes trafficking, Autophagy	(Goldenberg <i>et al.</i> , 2007; Kasmapour <i>et al.</i> , 2012; Starling <i>et al.</i> , 2016)
RAB35	TGN, endosomes, plasma membrane	Endocytic recycling, Neurite Outgrowth, Exosome release, Cytokinesis & cell polarity	(Klinkert and Echard, 2016)
RAB36	Golgi, Lysosomes, recycling endosomes	Endosomes and lysosomes trafficking, Neurite Outgrowth	(Chen <i>et al.</i> , 2010; Kobayashi <i>et al.</i> , 2014)
RAB38	ER, Golgi, TGN, post-Golgi vesicles	biogenesis of lysosomes/melanosomes	(Bultema and Di Pietro, 2013; Osanai <i>et al.</i> , 2005; Wasmeier <i>et al.</i> , 2006)
RAB39	Golgi	Neurite morphology, Autophagy	(Chen <i>et al.</i> , 2003; Corbier and Sellier, 2016; Mori <i>et al.</i> , 2013; Seto <i>et al.</i> , 2013)
RAB40	Golgi, plasma membrane, recycling endosomes	Vesicle transport in oligodendrocytes, cell signaling	(Lee <i>et al.</i> , 2007; Rodriguez-Gabin <i>et al.</i> , 2004)
RAB41	Golgi	Golgi apparatus organization, ER-Golgi trafficking	(Liu <i>et al.</i> , 2013)
RAB43	Golgi	Integrity of the Golgi apparatus, anterograde trafficking of cargo through the medial Golgi, Retrograde transport from endosomes to Golgi	(Cox <i>et al.</i> , 2016; Dejgaard <i>et al.</i> , 2008)

ER=Endoplasmic Reticulum. GA=Golgi apparatus. TGN=Trans Golgi Network.

TABLE II. Genetic disorders associated with POM and Golgi-associated factors.

Disorder	OMIM (disease)	Mode of inheritance	Causing-gene(s)	Gene product	Type(s) of mutation	References (gene identification)
Cohen syndrome	216550	Autosomal Recessive	COH1	VPS13B	nonsense, frameshift, splice site, larger in-frame deletions, missense, complex rearrangement, intragenic heterozygous deletions	(Seifert <i>et al.</i> , 2011)
PCCA2 syndrome	615851	Autosomal Recessive	VPS53	VPS53	splice site, missense	(Feinstein <i>et al.</i> , 2014)
Warburg-Micro syndrome	600118	Autosomal Recessive	RAB3GAP1	RAB3GAP1	nonsense, frameshift, large insertions/deletions, missense, splice site	(Aligianis <i>et al.</i> , 2005)
			RAB3GAP2	RAB3GAP2	in-frame deletions, missense mutations	(Borck <i>et al.</i> , 2011)
			RAB18	RAB18	missense, frameshift, deletions	(Bem <i>et al.</i> , 2011)
			TBC1D20	TBC1D20	large deletions, missense, frameshift	(Liegel <i>et al.</i> , 2013)
MRT13	613192	Autosomal Recessive	MRT13	TRAPPC9	missense, frameshift	(Mir <i>et al.</i> , 2009; Mochida <i>et al.</i> , 2009; Philippe <i>et al.</i> , 2009)
Neuromuscular syndrome	602580*	Autosomal Recessive	GOLGA2	GM130	missense, frameshift mutations	(Shamseldin <i>et al.</i> , 2016)
Dyggve-Melchior-Clausen syndrome	223800	Autosomal Recessive	DYM	DYMECLIN	nonsense, splice site, frameshift, missense, complex duplications	(Cohn <i>et al.</i> , 2003; El Ghouzzi <i>et al.</i> , 2003)
Congenital disorders of glycosylation (COG subgroup)	611209 (<i>CDG type 2G</i>)	Autosomal Recessive	COG1	COG1	nonsense, frameshift	(Foulquier <i>et al.</i> , 2006)
	606974*		COG2	COG2	nonsense, missense	(Foulquier <i>et al.</i> , 2007)
	608779 (<i>CDG type 2E</i>)		COG7	COG7	nonsense, splice site	(Wu <i>et al.</i> , 2004)
	611182 (<i>CDG type 2H</i>)		COG8	COG8	nonsense	(Foulquier <i>et al.</i> , 2007)

* OMIM reference corresponds to the gene instead of the disease