

# [Editorial: golgi pathology in neurodegenerative diseases](https://assignbuster.com/editorial-golgi-pathology-in-neurodegenerative-diseases/)

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The Editorial on the Research Topic   
[Golgi Pathology in Neurodegenerative Diseases](https://www.frontiersin.org/researchtopic/3815/golgi-pathology-in-neurodegenerative-diseases)

The Golgi apparatus is a central organelle that lies at the heart of the secretory pathway sustaining the delivery of proteins from their site of synthesis in the endoplasmic reticulum to their final destination, the extracellular medium, the plasma membrane, and the endo-lysosomal system. It ensures post-translational protein modifications such as glycosylation and proteolytic cleavage and processing and acts as a sorting device including to neuronal axons and dendrites ( [Horton and Ehlers, 2003](#B14) ; [Ye et al., 2007](#B34) ).

The mammalian Golgi apparatus was first described by Camillo Golgi in 1998 as “ apparato reticolare interno,” “ a fine and elegant network within the cell body … completely internal in the nerve cells” ( [Golgi, 1898a](#B11) , [b](#B12) ). This large reticulum comprises stacks of flattened membrane bound compartments called cisternae which are laterally linked to form the so-called Golgi ribbon.

Structural and functional alterations of the Golgi apparatus, which are here collectively termed Golgi pathology, are now recognized as a constant pathological hallmark of various neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Parkinson, Alzheimer, Huntington, and prion diseases ( [Fan et al., 2008](#B9) ). In ALS, structural Golgi alterations have been revealed by the pioneering work of Gonatas and colleagues ( [Mourelatos et al., 1990](#B25) ; [Gonatas et al., 1992](#B13) ; [Fujita et al., 2002](#B10) ). They manifest as fragmentation—transformation of the Golgi ribbon into disconnected stacks, cisternae, tubules and vesicles, and as atrophy—loss of Golgi membrane material.

These morphological changes are often accompanied by functional Golgi alterations, such as those affecting the anterograde and retrograde transport in the early secretory pathway, both in cellular models of Parkinson ( [Cooper et al., 2006](#B7) ; [Cho et al., 2014](#B6) ), Huntington ( [Caviston et al., 2007](#B5) ; [Pardo et al., 2010](#B27) ), and Alzheimer ( [Annaert et al., 1999](#B2) ; [Joshi et al., 2014](#B15) ) diseases as well as in ALS ( [Stieber et al., 2004](#B31) ; [Soo et al., 2015](#B30) ).

At least in ALS, Golgi pathology manifests as an early pre-clinical feature in degenerating neurons both in affected patients and in animal models ( [Mourelatos et al., 1996](#B26) ), suggesting that it may be relevant to the disease process instead of just representing an epiphenomenon. Yet, neither the molecular mechanisms underlying the changes in the functional organization of the Golgi apparatus nor their precise relevance to neurodegeneration have yet been completely elucidated.

These important questions got a new boost by the discovery of mutations in genes encoding Golgi-related proteins as direct causes of neurodegeneration. For instance, mutations in Optineurin ( [Maruyama et al., 2010](#B22) ), VPS54/wobbler ( [Schmitt-John et al., 2005](#B28) ), and TBCE/pmn ( [Martin et al., 2002](#B21) ) have been identified in ALS and related motor neuron diseases. Furthermore, mutations in the Parkinson disease-associated proteins α-Synuclein ( [Cooper et al., 2006](#B7) ; [Thayanidhi et al., 2010](#B32) ), LRRK2 ( [Lin et al., 2009](#B17) ; [Cho et al., 2014](#B6) ), Parkin ( [Shimura et al., 1999](#B29) ; [Kubo et al., 2001](#B16) ), and VPS35 ( [McGough et al., 2014](#B24) ; [Zavodszky et al., 2014](#B35) ; [Malik et al., 2015](#B19) ) have been shown to affect Golgi structure or transport processes to and from the Golgi.

Furthermore, the recognition of Golgi-derived microtubules and their specific functions, the better understanding of Golgi transport processes, the recognition of the Golgi apparatus as a sensor of cellular stress and as trigger of Golgi-specific cell death pathways provide new hints to the molecular mechanisms underlying Golgi pathology.

To cover these emerging themes, this Frontiers Research Topic is organized as follows. The issue starts with a summary on Golgi functional organization in neurons [(Valenzuela and Perez)](http://dx.doi.org/10.3389/fnins.2015.00358) and the relation of this organelle with microtubules [(Sanders and Kaverina)](http://dx.doi.org/10.3389/fnins.2015.00431) .

This is followed by pathological, genetic, and mechanistic descriptions of the major neurodegenerative diseases including Parkinson disease [(Wang and Hay)](http://dx.doi.org/10.3389/fnins.2015.00433) , Alzheimer disease by Wang and colleagues [(Joshi et al.)](http://dx.doi.org/10.3389/fnins.2015.00340) and ALS by Atkin and colleagues [(Sundaramoorthy et al.)](http://dx.doi.org/10.3389/fnins.2015.00400) . The Research topic then focuses on Golgi fragmentation brought about by defects in vesicle biogenesis and dynamics to and through the Golgi by Lupashin and colleagues [(Climer et al.)](http://dx.doi.org/10.3389/fnins.2015.00405) and by [Schmitt-John](http://dx.doi.org/10.3389/fnins.2015.00381) , including those caused by defects in Golgi-derived microtubules in ALS [(Haase and Rabouille)](http://dx.doi.org/10.3389/fnins.2015.00448) and microtubule-dependent motors in proximal SMA [(Jaarsma and Hoogenraad](http://dx.doi.org/10.3389/fnins.2015.00397) ; [Wirth and Martinez-Carrera)](http://dx.doi.org/10.3389/fnins.2015.00401) .

The third part of this issue starts by posing the hypothesis of Farhan and colleagues that cellular stress can be the cause of Golgi fragmentation, which in turn amplifies cellular stress and leads to neurodegeneration [(Alvarez-Miranda et al.)](http://dx.doi.org/10.3389/fnins.2015.00435) . This is argued by reviews on the effect of DNA damage on the Golgi by Field and colleagues [(Buschman et al.)](http://dx.doi.org/10.3389/fnins.2015.00362) and on the role of the Golgi as a cell death trigger [(Machamer)](http://dx.doi.org/10.3389/fnins.2015.00421) .

Future studies on Golgi pathology in neurodegenerative diseases will continue to benefit not only from conceptual advances but also from new technical developements that have been gigantic since Golgi's original description of the black reaction (tissue hardening with potassium dichromate and cell staining by silver impregnation) ( [Mazzarello et al., 2009](#B23) ).

Electron microscopy has been used to unravel Golgi fragmentation ( [Mourelatos et al., 1996](#B26) ) and in particular the Golgi fragmentation into tubules and vesicles observed in degenerating motor neurons ( [Bellouze et al., 2014](#B3) ), and its resolution may be further improved in tissues prepared by high pressure freezing ( [Walther et al., 2013](#B33) ). 3D reconstructions of the Golgi and its microtubules ( [Marsh et al., 2001](#B20) ; [Efimov et al., 2007](#B8) ) may illustrate pathological changes in their intricate connections.

Golgi fragmentation can also be monitored by live imaging ( [Altan-Bonnet et al., 2006](#B1) ), and super resolution microscopy ( [Betzig et al., 2006](#B4) ; [Lippincott-Schwartz and Manley, 2009](#B18) ) may help refining the process. Last, system biology approches may shed light on new pathways connecting Golgi fragmentation to neurodegeneration by identifying novel gene networks [(Alvarez-Miranda et al.)](http://dx.doi.org/10.3389/fnins.2015.00435) .

However, this field faces further challenges. It will be crucial to determine whether Golgi pathology is contributory, causative or homeostatic in neurodegeneration. In particular, it is important to understand whether Golgi alterations are linked to axonal degeneration and synapse loss or dysfunction.

It will also be crucial to analyze whether Golgi pathology in each neurodegenerative disease is restricted to the neuron types that are specifically affected, i. e., motor neurons in ALS, dopaminergic neurons in PD, striatal neurons in Huntington. If so, what may be the corresponding mechanisms of vulnerability and resistance?

Furthermore, we will need to determine whether Golgi alterations in degenerating neurons impact on the function of their non-neuronal cellular neighbors, including astrocytes, microglia and Schwann cells. Can this provide a potential explanation for the non-cell autonomous disease spread observed in numerous neurodegenerative diseases?

Finally and most importantly, can our burgeoning knowledge on the molecular mechanisms of Golgi pathology in neurodegenerative diseases be translated into earlier disease diagnosis and new therapies for these severe and hitherto untreatable disorders?

## Author Contributions

CR and GH prepared and wrote the manuscript.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

Altan-Bonnet, N., Sougrat, R., Liu, W., Snapp, E. L., Ward, T., and Lippincott-Schwartz, J. (2006). Golgi inheritance in mammalian cells is mediated through endoplasmic reticulum export activities. *Mol. Biol. Cell* 17, 990–1005. doi: 10. 1091/mbc. E05-02-0155

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16314396) | [CrossRef Full Text](http://dx.doi.org/10.1091/mbc.E05-02-0155) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Altan-Bonnet&author=R.+Sougrat&author=W.+Liu&author=E.+L.+Snapp&author=T.+Ward&author=J.+Lippincott-Schwartz+&publication_year=2006&title=Golgi+inheritance+in+mammalian+cells+is+mediated+through+endoplasmic+reticulum+export+activities&journal=Mol.+Biol.+Cell&volume=17&pages=990-1005)

Annaert, W. G., Levesque, L., Craessaerts, K., Dierinck, I., Snellings, G., Westaway, D., et al. (1999). Presenilin 1 controls gamma-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons. *J. Cell Biol.* 147, 277–294. doi: 10. 1083/jcb. 147. 2. 277

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10525535) | [CrossRef Full Text](http://dx.doi.org/10.1083/jcb.147.2.277) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=W.+G.+Annaert&author=L.+Levesque&author=K.+Craessaerts&author=I.+Dierinck&author=G.+Snellings&author=D.+Westaway+&publication_year=1999&title=Presenilin+1+controls+gamma-secretase+processing+of+amyloid+precursor+protein+in+pre-golgi+compartments+of+hippocampal+neurons&journal=J.+Cell+Biol.&volume=147&pages=277-294)

Bellouze, S., Schaefer, M. K., Buttigieg, D., Baillat, G., Rabouille, C., and Haase, G. (2014). Golgi fragmentation in pmn mice is due to a defective ARF1/TBCE cross-talk that coordinates COPI vesicle formation and tubulin polymerization. *Hum. Mol. Genet.* 23, 5961–5975. doi: 10. 1093/hmg/ddu320

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24951541) | [CrossRef Full Text](http://dx.doi.org/10.1093/hmg/ddu320) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Bellouze&author=M.+K.+Schaefer&author=D.+Buttigieg&author=G.+Baillat&author=C.+Rabouille&author=G.+Haase+&publication_year=2014&title=Golgi+fragmentation+in+pmn+mice+is+due+to+a+defective+ARF1%2FTBCE+cross-talk+that+coordinates+COPI+vesicle+formation+and+tubulin+polymerization&journal=Hum.+Mol.+Genet.&volume=23&pages=5961-5975)

Betzig, E., Patterson, G. H., Sougrat, R., Lindwasser, O. W., Olenych, S., Bonifacino, J. S., et al. (2006). Imaging intracellular fluorescent proteins at nanometer resolution. *Science* 313, 1642–1645. doi: 10. 1126/science. 1127344

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16902090) | [CrossRef Full Text](http://dx.doi.org/10.1126/science.1127344) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=E.+Betzig&author=G.+H.+Patterson&author=R.+Sougrat&author=O.+W.+Lindwasser&author=S.+Olenych&author=J.+S.+Bonifacino+&publication_year=2006&title=Imaging+intracellular+fluorescent+proteins+at+nanometer+resolution&journal=Science&volume=313&pages=1642-1645)

Caviston, J. P., Ross, J. L., Antony, S. M., Tokito, M., and Holzbaur, E. L. (2007). Huntingtin facilitates dynein/dynactin-mediated vesicle transport. *Proc. Natl. Acad. Sci. U. S. A.* 104, 10045–10050. doi: 10. 1073/pnas. 0610628104

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17548833) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.0610628104) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+P.+Caviston&author=J.+L.+Ross&author=S.+M.+Antony&author=M.+Tokito&author=E.+L.+Holzbaur+&publication_year=2007&title=Huntingtin+facilitates+dynein%2Fdynactin-mediated+vesicle+transport&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&volume=104&pages=10045-10050)

Cho, H. J., Yu, J., Xie, C., Rudrabhatla, P., Chen, X., Wu, J., et al. (2014). Leucine-rich repeat kinase 2 regulates Sec16A at ER exit sites to allow ER-Golgi export. *EMBO J.* 33, 2314–2331. doi: 10. 15252/embj. 201487807

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25201882) | [CrossRef Full Text](http://dx.doi.org/10.15252/embj.201487807) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+J.+Cho&author=J.+Yu&author=C.+Xie&author=P.+Rudrabhatla&author=X.+Chen&author=J.+Wu+&publication_year=2014&title=Leucine-rich+repeat+kinase+2+regulates+Sec16A+at+ER+exit+sites+to+allow+ER-Golgi+export&journal=EMBO+J.&volume=33&pages=2314-2331)

Cooper, A. A., Gitler, A. D., Cashikar, A., Haynes, C. M., Hill, K. J., Bhullar, B., et al. (2006). Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. *Science* 313, 324–328. doi: 10. 1126/science. 1129462

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16794039) | [CrossRef Full Text](http://dx.doi.org/10.1126/science.1129462) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+A.+Cooper&author=A.+D.+Gitler&author=A.+Cashikar&author=C.+M.+Haynes&author=K.+J.+Hill&author=B.+Bhullar+&publication_year=2006&title=Alpha-synuclein+blocks+ER-Golgi+traffic+and+Rab1+rescues+neuron+loss+in+Parkinson's+models&journal=Science&volume=313&pages=324-328)

Efimov, A., Kharitonov, A., Efimova, N., Loncarek, J., Miller, P. M., Andreyeva, N., et al. (2007). Asymmetric CLASP-dependent nucleation of noncentrosomal microtubules at the trans-Golgi network. *Dev. Cell* 12, 917–930. doi: 10. 1016/j. devcel. 2007. 04. 002

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17543864) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.devcel.2007.04.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Efimov&author=A.+Kharitonov&author=N.+Efimova&author=J.+Loncarek&author=P.+M.+Miller&author=N.+Andreyeva+&publication_year=2007&title=Asymmetric+CLASP-dependent+nucleation+of+noncentrosomal+microtubules+at+the+trans-Golgi+network&journal=Dev.+Cell&volume=12&pages=917-930)

Fan, J., Hu, Z., Zeng, L., Lu, W., Tang, X., Zhang, J., et al. (2008). Golgi apparatus and neurodegenerative diseases. *Int. J. Dev. Neurosci.* 26, 523–534. doi: 10. 1016/j. ijdevneu. 2008. 05. 006

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18599251) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.ijdevneu.2008.05.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+Fan&author=Z.+Hu&author=L.+Zeng&author=W.+Lu&author=X.+Tang&author=J.+Zhang+&publication_year=2008&title=Golgi+apparatus+and+neurodegenerative+diseases&journal=Int.+J.+Dev.+Neurosci.&volume=26&pages=523-534)

Fujita, Y., Okamoto, K., Sakurai, A., Kusaka, H., Aizawa, H., Mihara, B., et al. (2002). The Golgi apparatus is fragmented in spinal cord motor neurons of amyotrophic lateral sclerosis with basophilic inclusions. *Acta Neuropathol. (Berl.)* 103, 243–247. doi: 10. 1007/s004010100461

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11907804) | [CrossRef Full Text](http://dx.doi.org/10.1007/s004010100461) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Y.+Fujita&author=K.+Okamoto&author=A.+Sakurai&author=H.+Kusaka&author=H.+Aizawa&author=B.+Mihara+&publication_year=2002&title=The+Golgi+apparatus+is+fragmented+in+spinal+cord+motor+neurons+of+amyotrophic+lateral+sclerosis+with+basophilic+inclusions&journal=Acta+Neuropathol.+(Berl.)&volume=103&pages=243-247)

Golgi, C. (1898a). Sur la structure des cellules nerveuses. *Arch. Ital. Biol.* 30, 60–71.

Golgi, C. (1898b). Interno alle struttura delle cellule nervose. *Boll. Soc. Med. Chir. Pavia* 13, 1–14.

Gonatas, N. K., Stieber, A., Mourelatos, Z., Chen, Y., Gonatas, J. O., Appel, S. H., et al. (1992). Fragmentation of the Golgi apparatus of motor neurons in amyotrophic lateral sclerosis. *Am. J. Pathol.* 140, 731–737.

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=1546747) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+K.+Gonatas&author=A.+Stieber&author=Z.+Mourelatos&author=Y.+Chen&author=J.+O.+Gonatas&author=S.+H.+Appel+&publication_year=1992&title=Fragmentation+of+the+Golgi+apparatus+of+motor+neurons+in+amyotrophic+lateral+sclerosis&journal=Am.+J.+Pathol.&volume=140&pages=731-737)

Horton, A. C., and Ehlers, M. D. (2003). Neuronal polarity and trafficking. *Neuron* 40, 277–295. doi: 10. 1016/S0896-6273(03)00629-9

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14556709) | [CrossRef Full Text](http://dx.doi.org/10.1016/S0896-6273(03)00629-9) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+C.+Horton&author=M.+D.+Ehlers+&publication_year=2003&title=Neuronal+polarity+and+trafficking&journal=Neuron&volume=40&pages=277-295)

Joshi, G., Chi, Y., Huang, Z., and Wang, Y. (2014). Abeta-induced Golgi fragmentation in Alzheimer's disease enhances Abeta production. *Proc. Natl. Acad. Sci. U. S. A.* 111, E1230–E1239. doi: 10. 1073/pnas. 1320192111

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24639524) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.1320192111) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=G.+Joshi&author=Y.+Chi&author=Z.+Huang&author=Y.+Wang+&publication_year=2014&title=Abeta-induced+Golgi+fragmentation+in+Alzheimer's+disease+enhances+Abeta+production&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&volume=111&pages=E1230-E1239)

Kubo, S. I., Kitami, T., Noda, S., Shimura, H., Uchiyama, Y., Asakawa, S., et al. (2001). Parkin is associated with cellular vesicles. *J. Neurochem.* 78, 42–54. doi: 10. 1046/j. 1471-4159. 2001. 00364. x

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11432972) | [CrossRef Full Text](http://dx.doi.org/10.1046/j.1471-4159.2001.00364.x) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+I.+Kubo&author=T.+Kitami&author=S.+Noda&author=H.+Shimura&author=Y.+Uchiyama&author=S.+Asakawa+&publication_year=2001&title=Parkin+is+associated+with+cellular+vesicles&journal=J.+Neurochem.&volume=78&pages=42-54)

Lin, X., Parisiadou, L., Gu, X. L., Wang, L., Shim, H., Sun, L., et al. (2009). Leucine-rich repeat kinase 2 regulates the progression of neuropathology induced by Parkinson's-disease-related mutant alpha-synuclein. *Neuron* 64, 807–827. doi: 10. 1016/j. neuron. 2009. 11. 006

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20064389) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.neuron.2009.11.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=X.+Lin&author=L.+Parisiadou&author=X.+L.+Gu&author=L.+Wang&author=H.+Shim&author=L.+Sun+&publication_year=2009&title=Leucine-rich+repeat+kinase+2+regulates+the+progression+of+neuropathology+induced+by+Parkinson's-disease-related+mutant+alpha-synuclein&journal=Neuron&volume=64&pages=807-827)

Lippincott-Schwartz, J., and Manley, S. (2009). Putting super-resolution fluorescence microscopy to work. *Nat. Methods* 6, 21–23. doi: 10. 1038/nmeth. f. 233

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19116610) | [CrossRef Full Text](http://dx.doi.org/10.1038/nmeth.f.233) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+Lippincott-Schwartz&author=S.+Manley+&publication_year=2009&title=Putting+super-resolution+fluorescence+microscopy+to+work&journal=Nat.+Methods&volume=6&pages=21-23)

Malik, B. R., Godena, V. K., and Whitworth, A. J. (2015). VPS35 pathogenic mutations confer no dominant toxicity but partial loss of function in Drosophila and genetically interact with parkin. *Hum. Mol. Genet.* 24, 6106–6117. doi: 10. 1093/hmg/ddv322

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26251041) | [CrossRef Full Text](http://dx.doi.org/10.1093/hmg/ddv322) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+R.+Malik&author=V.+K.+Godena&author=A.+J.+Whitworth+&publication_year=2015&title=VPS35+pathogenic+mutations+confer+no+dominant+toxicity+but+partial+loss+of+function+in+Drosophila+and+genetically+interact+with+parkin&journal=Hum.+Mol.+Genet.&volume=24&pages=6106-6117)

Marsh, B. J., Mastronarde, D. N., Buttle, K. F., Howell, K. E., and McIntosh, J. R. (2001). Organellar relationships in the Golgi region of the pancreatic beta cell line, HIT-T15, visualized by high resolution electron tomography. *Proc. Natl. Acad. Sci. U. S. A.* 98, 2399–2406. doi: 10. 1073/pnas. 051631998

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11226251) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.051631998) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+J.+Marsh&author=D.+N.+Mastronarde&author=K.+F.+Buttle&author=K.+E.+Howell&author=J.+R.+McIntosh+&publication_year=2001&title=Organellar+relationships+in+the+Golgi+region+of+the+pancreatic+beta+cell+line,+HIT-T15,+visualized+by+high+resolution+electron+tomography&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&volume=98&pages=2399-2406)

Martin, N., Jaubert, J., Gounon, P., Salido, E., Haase, G., Szatanik, M., et al. (2002). A missense mutation in Tbce causes progressive motor neuronopathy in mice. *Nat. Genet.* 32, 443–447. doi: 10. 1038/ng1016

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12389029) | [CrossRef Full Text](http://dx.doi.org/10.1038/ng1016) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Martin&author=J.+Jaubert&author=P.+Gounon&author=E.+Salido&author=G.+Haase&author=M.+Szatanik+&publication_year=2002&title=A+missense+mutation+in+Tbce+causes+progressive+motor+neuronopathy+in+mice&journal=Nat.+Genet.&volume=32&pages=443-447)

Maruyama, H., Morino, H., Ito, H., Izumi, Y., Kato, H., Watanabe, Y., et al. (2010). Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* . 7295, 223–226. doi: 10. 1038/nature08971

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20428114) | [CrossRef Full Text](http://dx.doi.org/10.1038/nature08971) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Maruyama&author=H.+Morino&author=H.+Ito&author=Y.+Izumi&author=H.+Kato&author=Y.+Watanabe+&publication_year=2010&title=Mutations+of+optineurin+in+amyotrophic+lateral+sclerosis&journal=Nature&volume=7295&pages=223-226)

Mazzarello, P., Garbarino, C., and Calligaro, A. (2009). How Camillo Golgi became “ the Golgi.” *FEBS Lett.* 583, 3732–3737. doi: 10. 1016/j. febslet. 2009. 10. 018

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19833130) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.febslet.2009.10.018) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Mazzarello&author=C.+Garbarino&author=A.+Calligaro+&publication_year=2009&title=How+Camillo+Golgi+became+“ the+Golgi.”&journal=FEBS+Lett.&volume=583&pages=3732-3737)

McGough, I. J., Steinberg, F., Jia, D., Barbuti, P. A., McMillan, K. J., Heesom, K. J., et al. (2014). Retromer binding to FAM21 and the WASH complex is perturbed by the Parkinson disease-linked VPS35(D620N) mutation. *Curr. Biol.* 24, 1670–1676. doi: 10. 1016/j. cub. 2014. 06. 024

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24980502) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.cub.2014.06.024) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=I.+J.+McGough&author=F.+Steinberg&author=D.+Jia&author=P.+A.+Barbuti&author=K.+J.+McMillan&author=K.+J.+Heesom+&publication_year=2014&title=Retromer+binding+to+FAM21+and+the+WASH+complex+is+perturbed+by+the+Parkinson+disease-linked+VPS35(D620N)+mutation&journal=Curr.+Biol.&volume=24&pages=1670-1676)

Mourelatos, Z., Adler, H., Hirano, A., Donnenfeld, H., Gonatas, J. O., and Gonatas, N. K. (1990). Fragmentation of the Golgi apparatus of motor neurons in amyotrophic lateral sclerosis revealed by organelle-specific antibodies. *Proc. Natl. Acad. Sci. U. S. A.* 87, 4393–4395. doi: 10. 1073/pnas. 87. 11. 4393

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=2349244) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.87.11.4393) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Mourelatos&author=H.+Adler&author=A.+Hirano&author=H.+Donnenfeld&author=J.+O.+Gonatas&author=N.+K.+Gonatas+&publication_year=1990&title=Fragmentation+of+the+Golgi+apparatus+of+motor+neurons+in+amyotrophic+lateral+sclerosis+revealed+by+organelle-specific+antibodies&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&volume=87&pages=4393-4395)

Mourelatos, Z., Gonatas, N. K., Stieber, A., Gurney, M. E., and Dal Canto, M. C. (1996). The Golgi apparatus of spinal cord motor neurons in transgenic mice expressing mutant Cu, Zn superoxide dismutase becomes fragmented in early, preclinical stages of the disease. *Proc. Natl. Acad. Sci. U. S. A.* 93, 5472–5477. doi: 10. 1073/pnas. 93. 11. 5472

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=8643599) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.93.11.5472) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Mourelatos&author=N.+K.+Gonatas&author=A.+Stieber&author=M.+E.+Gurney&author=M.+C.+Dal+Canto+&publication_year=1996&title=The+Golgi+apparatus+of+spinal+cord+motor+neurons+in+transgenic+mice+expressing+mutant+Cu,+Zn+superoxide+dismutase+becomes+fragmented+in+early,+preclinical+stages+of+the+disease&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&volume=93&pages=5472-5477)

Pardo, R., Molina-Calavita, M., Poizat, G., Keryer, G., Humbert, S., and Saudou, F. (2010). pARIS-htt: an optimised expression platform to study huntingtin reveals functional domains required for vesicular trafficking. *Mol. Brain* 3: 17. doi: 10. 1186/1756-6606-3-17

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20515468) | [CrossRef Full Text](http://dx.doi.org/10.1186/1756-6606-3-17) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Pardo&author=M.+Molina-Calavita&author=G.+Poizat&author=G.+Keryer&author=S.+Humbert&author=F.+Saudou+&publication_year=2010&title=pARIS-htt%3A+an+optimised+expression+platform+to+study+huntingtin+reveals+functional+domains+required+for+vesicular+trafficking&journal=Mol.+Brain&volume=3&pages=17)

Schmitt-John, T., Drepper, C., Mussmann, A., Hahn, P., Kuhlmann, M., Thiel, C., et al. (2005). Mutation of Vps54 causes motor neuron disease and defective spermiogenesis in the wobbler mouse. *Nat. Genet.* 37, 1213–1215. doi: 10. 1038/ng1661

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16244655) | [CrossRef Full Text](http://dx.doi.org/10.1038/ng1661) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Schmitt-John&author=C.+Drepper&author=A.+Mussmann&author=P.+Hahn&author=M.+Kuhlmann&author=C.+Thiel+&publication_year=2005&title=Mutation+of+Vps54+causes+motor+neuron+disease+and+defective+spermiogenesis+in+the+wobbler+mouse&journal=Nat.+Genet.&volume=37&pages=1213-1215)

Shimura, H., Hattori, N., Kubo, S., Yoshikawa, M., Kitada, T., Matsumine, H., et al. (1999). Immunohistochemical and subcellular localization of Parkin protein: absence of protein in autosomal recessive juvenile parkinsonism patients. *Ann. Neurol.* 45, 668–672.

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10319893)

Soo, K. Y., Halloran, M., Sundaramoorthy, V., Parakh, S., Toth, R. P., Southam, K. A., et al. (2015). Rab1-dependent ER-Golgi transport dysfunction is a common pathogenic mechanism in SOD1, TDP-43 and FUS-associated ALS. *Acta Neuropathol.* 130, 679–697. doi: 10. 1007/s00401-015-1468-2

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26298469) | [CrossRef Full Text](http://dx.doi.org/10.1007/s00401-015-1468-2) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=K.+Y.+Soo&author=M.+Halloran&author=V.+Sundaramoorthy&author=S.+Parakh&author=R.+P.+Toth&author=K.+A.+Southam+&publication_year=2015&title=Rab1-dependent+ER-Golgi+transport+dysfunction+is+a+common+pathogenic+mechanism+in+SOD1,+TDP-43+and+FUS-associated+ALS&journal=Acta+Neuropathol.&volume=130&pages=679-697)

Stieber, A., Gonatas, J. O., Moore, J. S., Bantly, A., Yim, H. S., Yim, M. B., et al. (2004). Disruption of the structure of the Golgi apparatus and the function of the secretory pathway by mutants G93A and G85R of Cu, Zn superoxide dismutase (SOD1) of familial amyotrophic lateral sclerosis. *J. Neurol. Sci.* 219, 45–53. doi: 10. 1016/j. jns. 2003. 12. 004

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15050437) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.jns.2003.12.004) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Stieber&author=J.+O.+Gonatas&author=J.+S.+Moore&author=A.+Bantly&author=H.+S.+Yim&author=M.+B.+Yim+&publication_year=2004&title=Disruption+of+the+structure+of+the+Golgi+apparatus+and+the+function+of+the+secretory+pathway+by+mutants+G93A+and+G85R+of+Cu,+Zn+superoxide+dismutase+(SOD1)+of+familial+amyotrophic+lateral+sclerosis&journal=J.+Neurol.+Sci.&volume=219&pages=45-53)

Thayanidhi, N., Helm, J. R., Nycz, D. C., Bentley, M., Liang, Y., and Hay, J. C. (2010). Alpha-synuclein delays endoplasmic reticulum (ER)-to-Golgi transport in mammalian cells by antagonizing ER/Golgi SNAREs. *Mol. Biol. Cell* 21, 1850–1863. doi: 10. 1091/mbc. E09-09-0801

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20392839) | [CrossRef Full Text](http://dx.doi.org/10.1091/mbc.E09-09-0801) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Thayanidhi&author=J.+R.+Helm&author=D.+C.+Nycz&author=M.+Bentley&author=Y.+Liang&author=J.+C.+Hay+&publication_year=2010&title=Alpha-synuclein+delays+endoplasmic+reticulum+(ER)-to-Golgi+transport+in+mammalian+cells+by+antagonizing+ER%2FGolgi+SNAREs&journal=Mol.+Biol.+Cell&volume=21&pages=1850-1863)

Walther, P., Schmid, E., and Höhn, K. (2013). High-pressure freezing for scanning transmission electron tomography analysis of cellular organelles. *Methods Mol. Biol.* 931, 525–535. doi: 10. 1007/978-1-62703-056-4\_28

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23027022) | [CrossRef Full Text](http://dx.doi.org/10.1007/978-1-62703-056-4_28) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Walther&author=E.+Schmid&author=K.+Höhn+&publication_year=2013&title=High-pressure+freezing+for+scanning+transmission+electron+tomography+analysis+of+cellular+organelles&journal=Methods+Mol.+Biol.&volume=931&pages=525-535)

Ye, B., Zhang, Y., Song, W., Younger, S. H., Jan, L. Y., and Jan, Y. N. (2007). Growing dendrites and axons differ in their reliance on the secretory pathway. *Cell* 130, 717–729. doi: 10. 1016/j. cell. 2007. 06. 032

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17719548) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.cell.2007.06.032) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+Ye&author=Y.+Zhang&author=W.+Song&author=S.+H.+Younger&author=L.+Y.+Jan&author=Y.+N.+Jan+&publication_year=2007&title=Growing+dendrites+and+axons+differ+in+their+reliance+on+the+secretory+pathway&journal=Cell&volume=130&pages=717-729)

Zavodszky, E., Seaman, M. N., Moreau, K., Jimenez-Sanchez, M., Breusegem, S. Y., Harbour, M. E., et al. (2014). Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. *Nat. Commun.* 5, 3828. doi: 10. 1038/ncomms4828

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24819384) | [CrossRef Full Text](http://dx.doi.org/10.1038/ncomms4828) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=E.+Zavodszky&author=M.+N.+Seaman&author=K.+Moreau&author=M.+Jimenez-Sanchez&author=S.+Y.+Breusegem&author=M.+E.+Harbour+&publication_year=2014&title=Mutation+in+VPS35+associated+with+Parkinson's+disease+impairs+WASH+complex+association+and+inhibits+autophagy&journal=Nat.+Commun.&volume=5&pages=3828)