

Table S1. List of MAN-associated proteins modified in disease.

Disease	Protein involved	Modifications	Altered MAN	Refs.
PD	Parkin	LOF mutation leading to decrease in DRP-1 degradation	Mitochondrial fission	(Wang et al., 2011; Yu et al., 2011)
	Miro1	LOF mutation leading to impaired calcium homeostasis and increased mitophagy	Calcium signaling	(Grossmann et al., 2020)
	GBA1	LOF mutation abnormally prolonging lysosomal-mitochondrial tethering	Mitochondrial fission	(Kim et al., 2021)
Cancer	DRP-1	Increased activity leading to cell proliferation and migration	Mitochondrial fission	(Kashatus, 2018)
CMT-2A	MFN2	Mutation promoting mitochondrial hyperfusion by increased DRP-1 degradation	Mitochondrial fission	(Cartoni and Martinou, 2009)
	DRP-1	Increased R364W-MFN2-mediated ubiquitination leading to mitochondrial hyperfusion	Mitochondrial fission	(Das et al., 2021)
ALS	Sig-1R	LOF mutation leading to impaired binding to IP3R and mitochondrial dysfunction	Calcium signaling	(Al-Saif et al., 2011; Watanabe et al., 2016)
NASH and cancer	MFN2	Low expression leading to impaired PS transfer	Lipid exchange	(Hernández-Alvarez et al., 2019)
GM1-gangliosidosis	GLB1	LOF mutation leading to lysosomal dysfunction and neurodegeneration	Calcium signaling and Lipid exchange	(Sano et al., 2009)
NPC	NPC1	LOF mutation leading to accumulation of cholesterol at lysosomes causing cell death	Lipid exchange	(Wheeler and Silence, 2020)

Abbreviations: amyotrophic lateral sclerosis (ALS); Charcot-Marie-Tooth disease type2A (CMT-2A); dynamin related protein 1 (DRP-1); β -glucocerebrosidase (GBA1); β -galactosidase (GLB1); Loss-of-function (LOF); mitofusin 2 (MFN2); Non-alcoholic steatohepatitis (NASH); Niemann-Pick type C (NPC); NPC intracellular cholesterol transporter 1 (NPC1); Parkinson's disease (PD); phosphatidylserine (PS); sigma-1R (Sig-1R).

References:

- Al-Saif, A., Al-Mohanna, F. and Bohlega, S.** (2011). A mutation in sigma-1 receptor causes juvenile amyotrophic lateral sclerosis. *Annals of Neurology* **70**, 913–919.
- Cartoni, R. and Martinou, J.-C.** (2009). Role of mitofusin 2 mutations in the physiopathology of Charcot–Marie–Tooth disease type 2A. *Experimental Neurology* **218**, 268–273.
- Das, R., Kamal, I. M., Das, S., Chakrabarti, S. and Chakrabarti, O.** (2021). MITOL-mediated DRP1 ubiquitylation and degradation promotes mitochondrial hyperfusion in CMT2A-linked MFN2 mutant. *Journal of Cell Science* jcs.257808.
- Grossmann, D., Berenguer-Escuder, C., Chemla, A., Arena, G. and Krüger, R.** (2020). The Emerging Role of RHOT1/Miro1 in the Pathogenesis of Parkinson’s Disease. *Front Neurol* **11**, 587.
- Hernández-Alvarez, M. I., Sebastián, D., Vives, S., Ivanova, S., Bartoccioni, P., Kakimoto, P., Plana, N., Veiga, S. R., Hernández, V., Vasconcelos, N., et al.** (2019). Deficient Endoplasmic Reticulum-Mitochondrial Phosphatidylserine Transfer Causes Liver Disease. *Cell* **177**, 881-895.e17.
- Kashatus, D. F.** (2018). The Regulation of Tumor Cell Physiology by Mitochondrial Dynamics. *Biochem Biophys Res Commun* **500**, 9–16.
- Kim, S., Wong, Y. C., Gao, F. and Krainc, D.** (2021). Dysregulation of mitochondria-lysosome contacts by GBA1 dysfunction in dopaminergic neuronal models of Parkinson’s disease. *Nat Commun* **12**, 1807.
- Sano, R., Annunziata, I., Patterson, A., Moshiach, S., Gomero, E., Opferman, J., Forte, M. and d’Azzo, A.** (2009). GM1-Ganglioside Accumulation at the Mitochondria-Associated ER Membranes Links ER Stress to Ca²⁺-Dependent Mitochondrial Apoptosis. *Molecular Cell* **36**, 500–511.
- Wang, X., Winter, D., Ashrafi, G., Schlehe, J., Wong, Y. L., Selkoe, D., Rice, S., Steen, J., Lavoie, M. J. and Schwarz, T. L.** (2011). PINK1 and Parkin target miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell* **147**, 893–906.
- Watanabe, S., Ilieva, H., Tamada, H., Nomura, H., Komine, O., Endo, F., Jin, S., Mancias, P., Kiyama, H. and Yamanaka, K.** (2016). Mitochondria-associated membrane collapse is a common pathomechanism in SIGMAR 1 - and SOD 1 -linked ALS . *EMBO Molecular Medicine* **8**, 1421–1437.
- Wheeler, S. and Sillence, D. J.** (2020). Niemann–Pick type C disease: cellular pathology and pharmacotherapy. *Journal of Neurochemistry* **153**, 674–692.
- Yu, W., Sun, Y., Guo, S. and Lu, B.** (2011). The PINK1/Parkin pathway regulates mitochondrial dynamics and function in mammalian hippocampal and dopaminergic neurons. *Human Molecular Genetics* **20**, 3227–3240.