Journal Of Clinical Neurology, Neurosurgery And Spine

SCIENTIFIC LITERATURE

Special Issue Article "Neurodegenerative Diseases" Letter

Inhibitory Effect of Spinocerebellar Ataxia Type 3-Associated Mutant Ataxin-3 on Oligodendroglial Cell Differentiation

Kohei Hattori[1], Arisa Ochiai[1], Marina Tanaka[1], Sui Sawaguchi[1], Rimi Suzuki[1], Natsumi Watanabe[1], Hiroaki Oizumi[2], Katsuya Ohbuchi[2], Yuki Miyamoto[1,3] and Junji Yamauchi[1,3*]

[1]Laboratory of Molecular Neuroscience and Neurology, Tokyo University of Pharmacy and Life, Japan

[2]Department of Neurology, Tsumura Research Laboratories, Japan

[3]Department of Pharmacology, National Research Institute for Child Health and Development, Japan

ARTICLE INFO

Received Date: October 11, 2019
Accepted Date: October 14, 2019
Published Date: October 16, 2019

KEYWORDS

Spinocerebellar ataxia
Ataxin-3
Oligodendrocyte
Lysosome
Rab7

Citation for this article: Kohei Hattori, Arisa Ochiai, Marina Tanaka, Sui Sawaguchi, Rimi Suzuki, Natsumi Watanabe, Hiroaki Oizumi, Katsuya Ohbuchi, Yuki Miyamoto, and Junji Yamauchi. Inhibitory Effect of Spinocerebellar Ataxia Type 3-Associated Mutant Ataxin-3 on Oligodendroglial Cell Differentiation. Journal Of Clinical Neurology, Neurosurgery And Spine. 2019; 2(1):119

Corresponding author:
Junji Yamauchi,
Laboratory of Molecular Neuroscience and Neurology Tokyo University of Pharmacy and Life Sciences 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan, Tel: (+81)-42-676-7164; Fax: (+81)-42-676-8841;
Email: yamauchi@toyaku.ac.jp

LETTER TO THE EDITOR

Spinocerebellar ataxia type 3 (SCA3, also known as Machado-Joseph disease) is an autosomal dominant neurodegenerative disorder [1]. SCA3 is caused by the CAG nucleotide repeat expansion of the ataxin-3 gene, generating polyglutamine-(polyQ-) containing ataxin-3. Normal individuals have up to 44 repeats, whereas patients have between 52 and 86 repeats [2]. Protein aggregation is a hallmark of SCA3 and toxic aggregates are often localized in the nucleus [3]. The clinical features principally involve ataxia, spasticity, and ocular movement abnormalities.

Ataxin-3 is a cytoplasmic protein involved in a protein-metabolizing process, so called the ubiquitin-proteasome system. It often binds more than 4 of polyubiquitin chains to trigger protein degradation [4]. Thus, Ataxin-3 has universal role in various types of cells and indeed exhibits a wide expression in tissues and cells (see the UniGene website, URL. https://www.ncbi.nlm.nih.gov/unigene/). Is it possible that mutant ataxin-3 affects glial cells as well as neuronal cells, as seen in the cases of other neurodegenerative disorders [5,6]?

Cells stably expressing the GFP-tagged mutant ataxin-3 construct with 79 Q repeats did not exhibit myelin multiple web-like structures in FBD-102b cells as the oligodendroglial cell model [7] (Figure 1). Also, cells with mutant ataxin-3 indeed failed to exhibit differentiated phenotypes with processes in N1E-115 cells as the neuronal cell model [8] (Figure S1). Of note, mutant ataxin-3 formed small protein aggregates, which are mainly localized in the lysosome (Figure S2) and the Rab7-positive vesicle (Figure S3) but not in other major organelles such as the endoplasmic reticulum (Figure S4) and the Golgi body (Figure S5). Further studies on cell biological properties for mutant ataxin-3 will possibly allow us to understand how mutant one causes cellular pathological effects not only in neuronal cells but also in glial cells.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-Aid both for Scientific Research from the Japanese MEXT and MHLW.

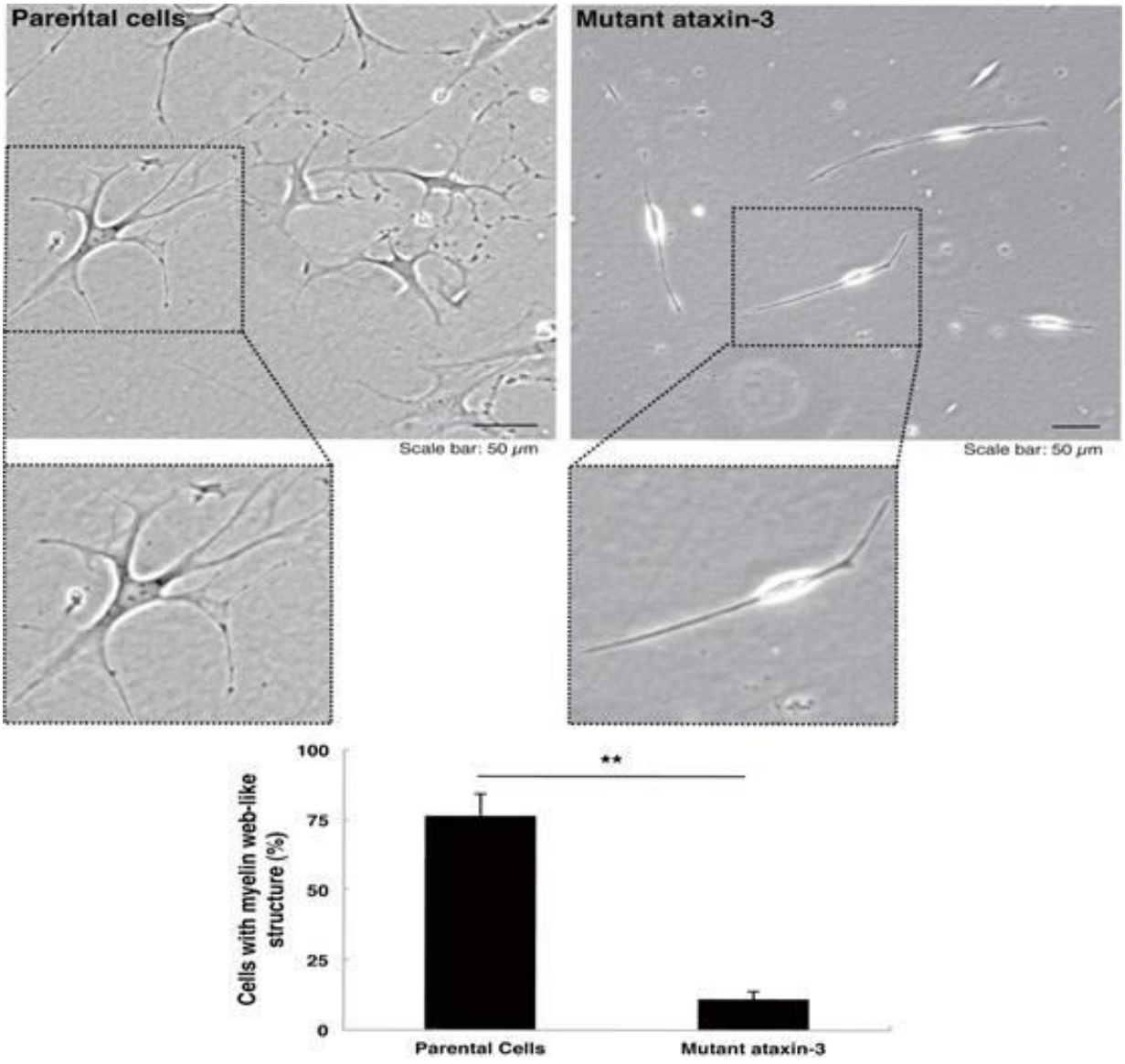

Figure 1: Cells harboring the mutant ataxin-3 construct fail to exhibit differentiated phenotypes in oligodendroglial FBD-102b cells. Parental FBD-102b cells or cells with the mutant construct (79-Q-repeat-containing one) were allowed to be differentiated for 3 days. Representative cells are outlined by white dotted lines. Small images within large ones (upper ones) were magnified in lower images. After 3 days following the induction of differentiation, cells with myelin multiple web-like structures (differentiated cell phenotypes) were counted. They are statistically shown (**, $p<0.01$ of Student's t-test; n=3 fields).

Inhibitory Effect of Spinocerebellar Ataxia Type 3-Associated Mutant Ataxin-3 on Oligodendroglial Cell Differentiation. Journal Of Clinical Neurology, Neurosurgery And Spine. 2019; 2(1):119.

AUTHOR CONTRIBUTION

KH, NW, NM, and MT: search and analysis; and HO, KO, YM, and JY: design, discussion, and writing.

REFERENCES

1. Franca MC Jr, D'Abreu A, Nucci A, Lopes-Cendes I. (2008). Muscle excitability abnormalities in Machado-Joseph disease. Arch Neurol. 65: 525-529.
2. Todd PK, Paulson HL. (2010). RNA-mediated neurodegeneration in repeat expansion disorders. Ann Neurol. 67: 291-300.
3. Bichelmeier U, Schmidt T, Hübener J, Boy J, Rüttiger L, et al. (2007). Nuclear localization of ataxin-3 is required for the manifestation of symptoms in SCA3: *in vivo* evidence. J Neurosci. 27: 7418-7428.
4. Matos CA, de Almeida LP, Nóbrega C. (2019). Machado-Josephdisease/spinocerebellar ataxia type 3: lessons from disease pathogenesis and clues into therapy. JNeurochem. 148: 8-28.
5. Wang J, Ho WY, Lim K, Feng J, Tucker-Kellogg G, et al. (2018). Cell-autonomous requirement of TDP-43, an ALS/FTD signature protein, for oligodendrocyte survival and myelination. Proc Natl Acad Sci USA. 115: E10941-E10950.
6. Alieva AK, Zyrin VS, Rudenok MM, Kolacheva AA, Shulskaya MV, et al. (2018). Whole-Transcriptome Analysis of Mouse Models with MPTP-Induced Early Stages of Parkinson's Disease Reveals Stage-Specific Response of Transcriptome and a Possible Role of Myelin-Linked Genes in Neurodegeneration. Mol Neurobiol. 55: 7229-7241.
7. Miyamoto Y, Yamauchi J, Chan JR, Okada A, Tomooka Y, et al. (2007). Cdk5 regulates differentiation of oligodendrocyte precursor cells through the direct phosphorylation of paxillin. J Cell Sci. 120: 4355-4366.
8. Urai Y, Yamawaki M, Watanabe N, Seki Y, Morimoto T, et al. (2018). Pull down assay for GTP-bound form of Sar1a reveals its activation during morphological differentiation. BiochemBiophys Res Commun. 503: 2047-2053.

Supplementary Figures:

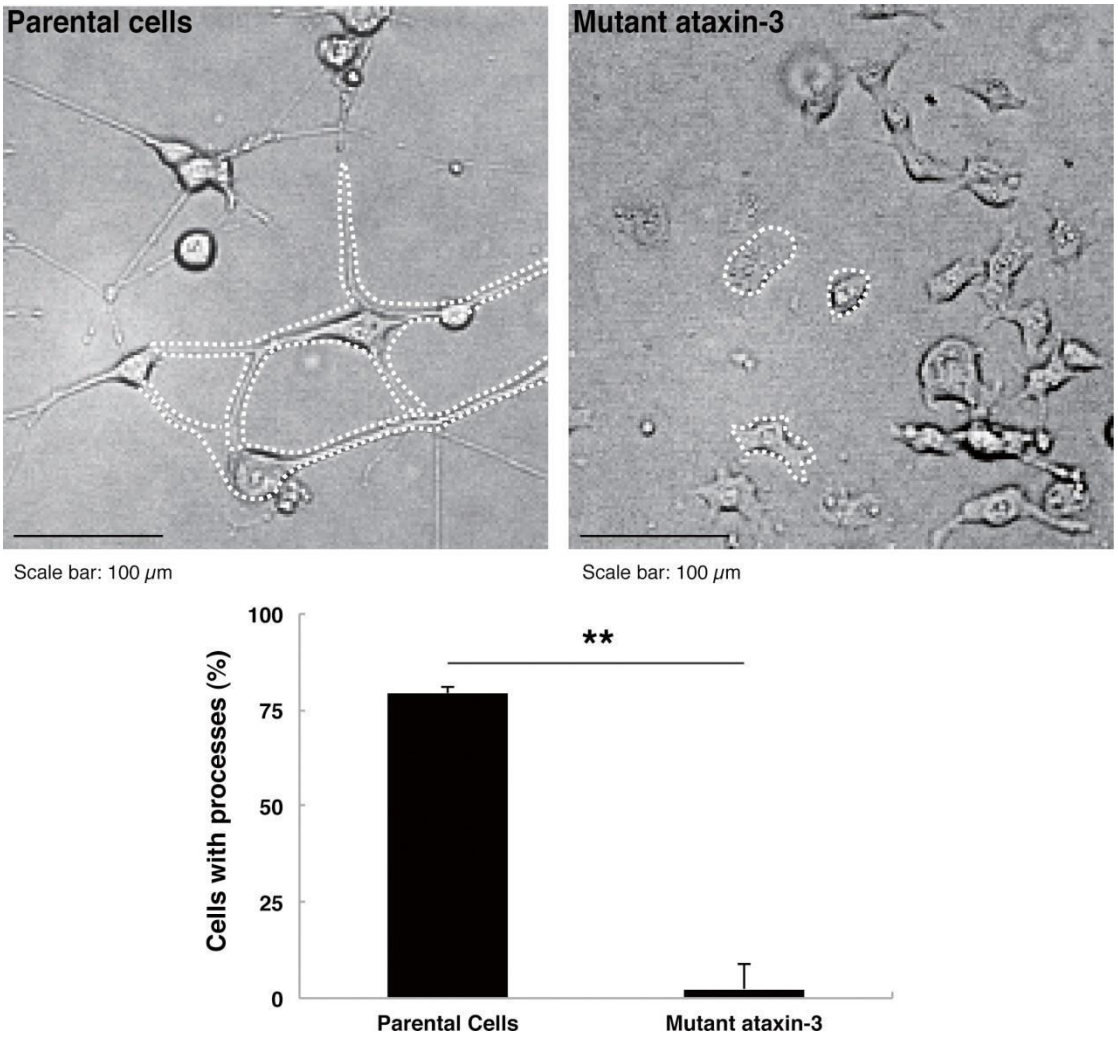

Figure S1: Cells harboring the mutant ataxin-3 construct fail to exhibit differentiated phenotypes in neuronal N1E-115 cells. Parental N1E-115 cells or cells with the mutant construct were allowed to differentiate for 3 days. Representative cells are outlined by white dotted lines. After 3 days following the induction of differentiation, cells with more than one-cell-body-length of processes from the cell bodies were considered differentiated phenotypes (cells with processes) (**, $p<0.01$ of Student's t-test; n=3 fields).

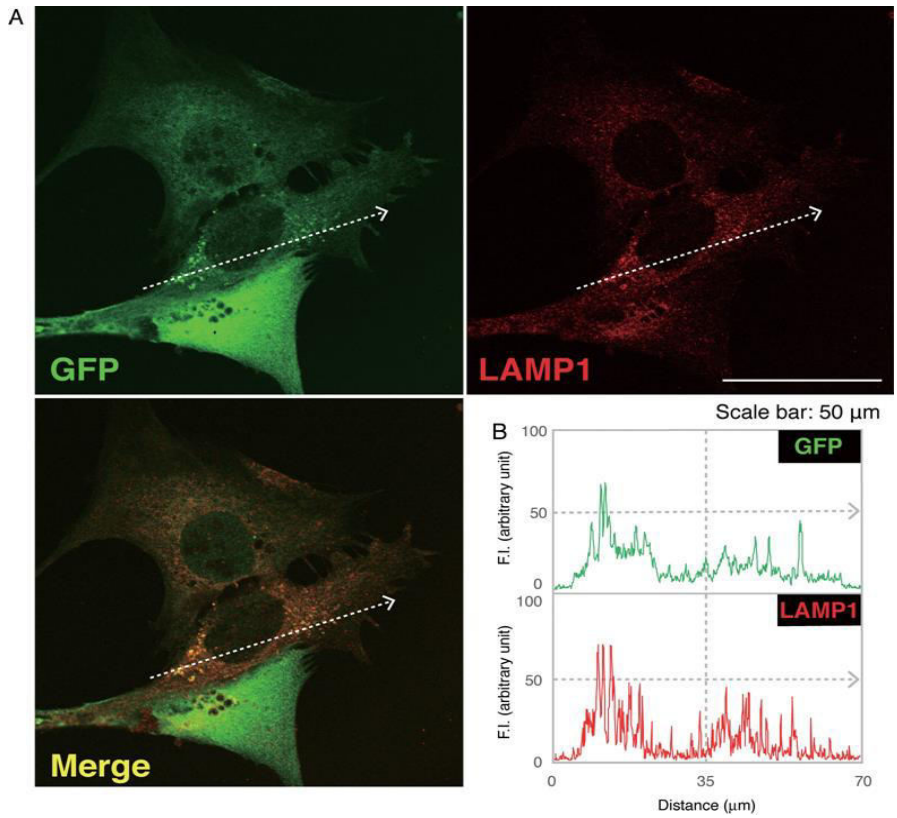

Figure S2: Mutant ataxin-3 is localized in the lysosome. (A) FBD-102b transfected with the plasmid encoding the mutant construct (green) were immunostained with an anti-lysosomal-associated membrane protein 1 (LAMP1) antibody (red). Merged images (yellow) are also shown. (B) Fluorescence intensities (F.I., arbitrary unit) of green and red along dotted arrows in upper left and right images, respectively, are shown.

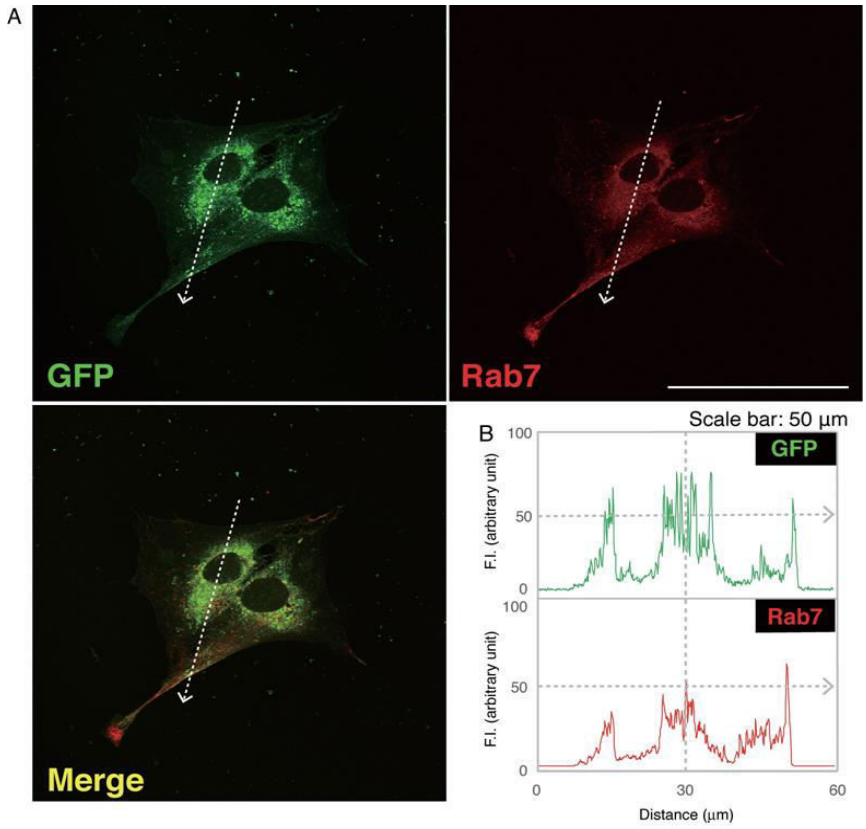

Figure S3: Mutant ataxin-3 is localized in the Rab7-positive vesicle. (A, B) FBD-102b transfected with the plasmid encoding the mutant construct (green) were immunostained with an anti-Rab7 antibody (red,). Rab7 is present around the lysosome. Merged images (yellow) are also shown. Fluorescence intensities (F.I., arbitrary unit) of green and red along dotted arrows in upper left and right images, respectively, are shown.

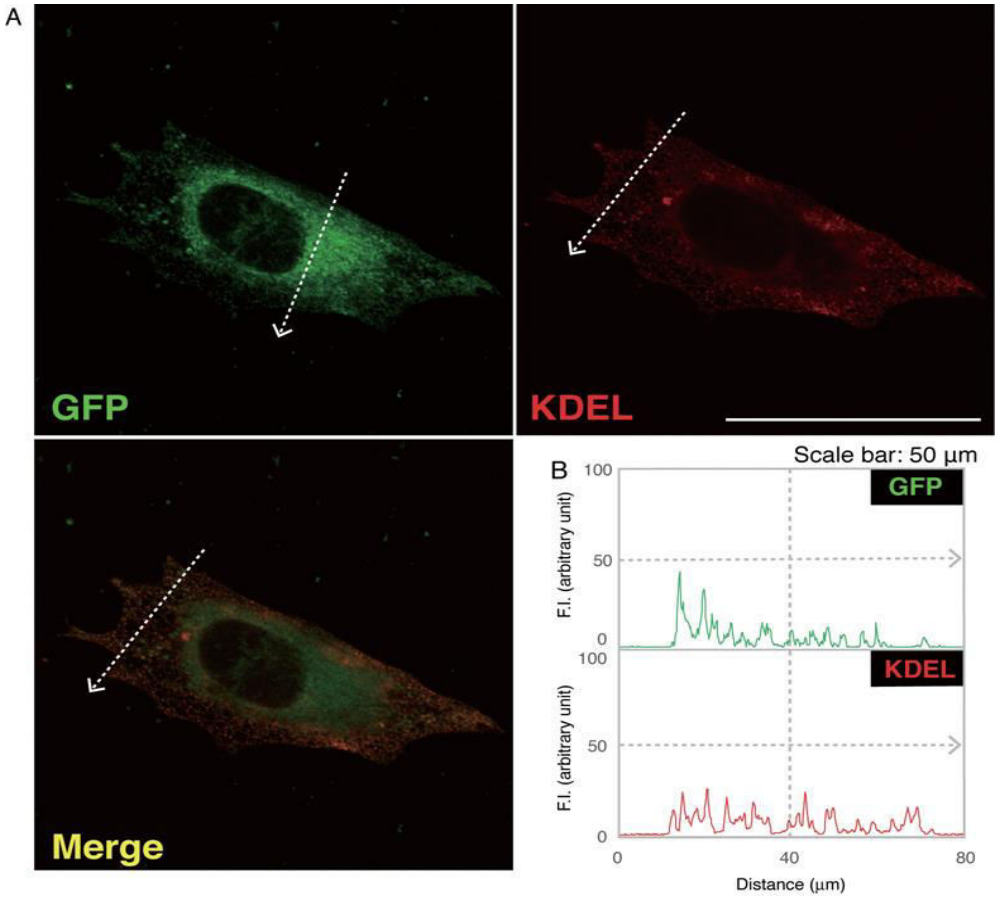

Figure S4: Mutant ataxin-3 is not localized in the endoplasmic reticulum. (A, B) FBD-102b transfected with the plasmid encoding the mutant construct (green) were immunostained with an antibody (red) against endoplasmic reticulum-resident KDEL antigen. Merged images (yellow) are also shown. Fluorescence intensities (F.I., arbitrary unit) of green and red along dotted arrows in upper left and right images, respectively, are shown.

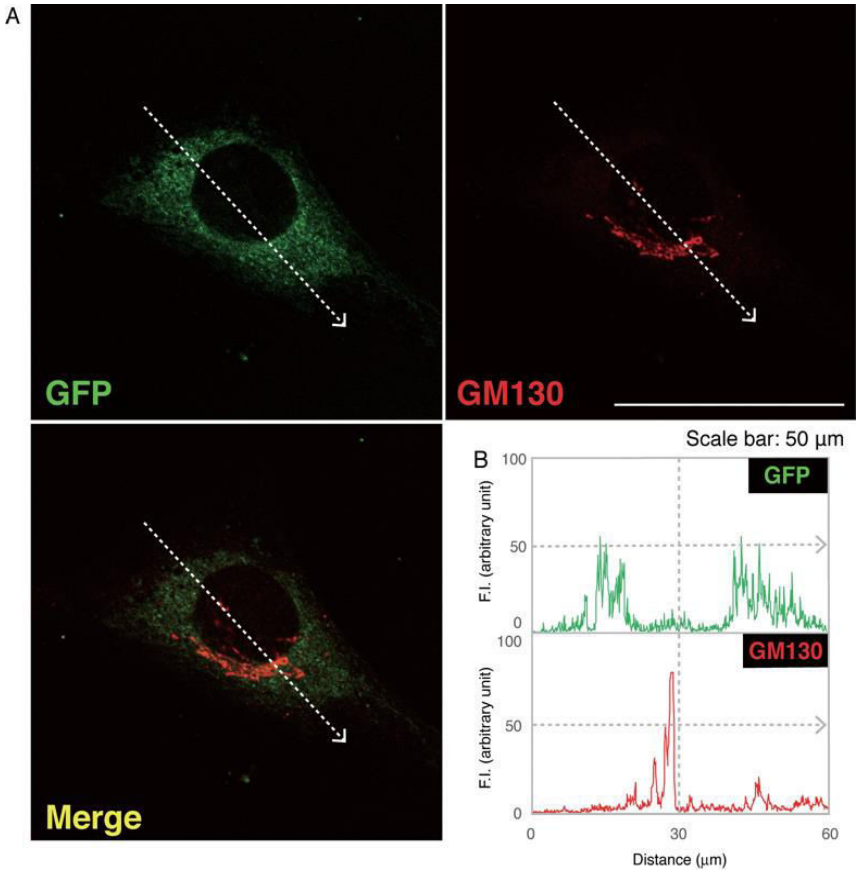

Figure S5: Mutant ataxin-3 is not localized in the Golgi body. (A, B) FBD-102b transfected with the plasmid encoding the mutant construct (green) were immunostained with an anti-Golgi matrix 130 kDaprotein (GM130) antibody (red). Merged images (yellow) are also shown. Fluorescence intensities (F.I., arbitrary unit) of green and red along dotted arrows in upper left and right images, respectively, are shown.