Human Molecular Genetics 2017 vol.26 N8, pages 1432-1443

ATpase-deficient mitochondrial inner membrane protein ATAD3a disturbs mitochondrial dynamics in dominant hereditary spastic paraplegia

Cooper H., Yang Y., Ylikallio E., Khairullin R., Woldegebriel R., Lin K., Euro L., Palin E., Wolf A., Trokovic R., Isohanni P., Kaakkola S., Auranen M., Lonqvist T., Wanrooij S., Tyynismaa H.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© The Author 2017. Published by Oxford University Press. All rights reserved. De novo mutations in ATAD3A (ATPase family AAA-domain containing protein 3A) were recently found to cause a neurological syndrome with developmental delay, hypotonia, spasticity, optic atrophy, axonal neuropathy, and hypertrophic cardiomyopathy. Using whole-exome sequencing, we identified a dominantly inherited heterozygous variant c.1064G > A (p. G355D) in ATAD3A in a mother presenting with hereditary spastic paraplegia (HSP) and axonal neuropathy and her son with dyskinetic cerebral palsy, both with disease onset in childhood. HSP is a clinically and genetically heterogeneous disorder of the upper motor neurons. Symptoms beginning in early childhood may resemble spastic cerebral palsy. The function of ATAD3A, a mitochondrial inner membrane AAA ATPase, is yet undefined. AAA ATPases form hexameric rings, which are catalytically dependent on the co-operation of the subunits. The dominant-negative patient mutation affects the Walker A motif, which is responsible for ATP binding in the AAA module of ATAD3A, and we show that the recombinant mutant ATAD3A protein has a markedly reduced ATPase activity. We further show that overexpression of the mutant ATAD3A fragments the mitochondrial network and induces lysosome mass. Similarly, we observed altered dynamics of the mitochondrial network and increased lysosomes in patient fibroblasts and neurons derived through differentiation of patient-specific induced pluripotent stem cells. These alterations were verified in patient fibroblasts to associate with upregulated basal autophagy through mTOR inactivation, resembling starvation. Mutations in ATAD3A can thus be dominantly inherited and underlie variable neurological phenotypes, including HSP, with intrafamiliar variability. This finding extends the group of mitochondrial inner membrane AAA proteins associated with spasticity.

http://dx.doi.org/10.1093/hmg/ddx042

References

[1] Tesson, C., Koht, J. and Stevanin, G. (2015) Delving into the complexity of hereditary spastic paraplegias: How unexpected phenotypes and inheritance modes are revolutionizing their nosology. Hum. Genet., 134, 511-538.

[2] McDermott, C., White, K., Bushby, K. and Shaw, P. (2000) Hereditary spastic paraparesis: A review of new developments. J. Neurol. Neurosurg. Psychiatry, 69, 150-160.

[3] Harding, A.E. (1983) Classification of the hereditary ataxias and paraplegias. Lancet, 1, 1151-1155.

[4] Colver, A., Fairhurst, C. and Pharoah, P.O. (2014) Cerebral palsy. Lancet, 383, 1240-1249.

[5] McMichael, G., Bainbridge, M.N., Haan, E., Corbett, M., Gardner, A., Thompson, S., van Bon, B.W., van Eyk, C.L., Broadbent, J., Reynolds, C., et al. (2015) Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. Mol. Psychiatry, 20, 176-182.

[6] Rainier, S., Sher, C., Reish, O., Thomas, D. and Fink, J.K. (2006) De novo occurrence of novel SPG3A/atlastin mutation presenting as cerebral palsy. Arch. Neurol., 63, 445-447.

[7] Casari, G., De Fusco, M., Ciarmatori, S., Zeviani, M., Mora, M., Fernandez, P., De Michele, G., Filla, A., Cocozza, S., Marconi, R., et al. (1998) Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell, 93, 973-983.

[8] Le, D.T., Eckert, T. and Woehlke, G. (2013) Computer simulation of assembly and co-operativity of hexameric AAA ATPases. PLoS One, 8, e67815.

[9] Pierson, T.M., Adams, D., Bonn, F., Martinelli, P., Cherukuri, P.F., Teer, J.K., Hansen, N.F., Cruz, P., Mullikin For The Nisc Comparative Sequencing Program, J.C., Blakesley, R.W., et al. (2011) Whole-exome sequencing identifies homozygous AFG3L2 mutations in a spastic ataxia-neuropathy syndrome linked to mitochondrial m-AAA proteases. PLoS Genet., 7, e1002325.

[10] Harel, T., Yoon, W.H., Garone, C., Gu, S., Coban-Akdemir, Z., Eldomery, M.K., Posey, J.E., Jhangiani, S.N., Rosenfeld, J.A., Cho, M.T., et al. (2016) Recurrent de novo and biallelic variation of ATAD3A, encoding a mitochondrial membrane protein, results in distinct neurological syndromes. Am. J. Hum. Genet., 99, 831-845.

[11] Gilquin, B., Taillebourg, E., Cherradi, N., Hubstenberger, A., Gay, O., Merle, N., Assard, N., Fauvarque, M.O., Tomohiro, S., Kuge, O., et al. (2010) The AAA ATPase ATAD3A controls mitochondrial dynamics at the interface of the inner and outer membranes. Mol. Cell. Biol., 30, 1984-1996.

[12] Issop, L., Fan, J., Lee, S., Rone, M.B., Basu, K., Mui, J. and Papadopoulos, V. (2015) Mitochondria-associated membrane formation in hormone-stimulated leydig cell steroidogenesis: Role of ATAD3. Endocrinology, 156, 334-345.

[13] Gerhold, J.M., Cansiz-Arda, S., Lohmus, M., Engberg, O., Reyes, A., van Rennes, H., Sanz, A., Holt, I.J., Cooper, H.M. and Spelbrink, J.N. (2015) Human mitochondrial DNAprotein complexes attach to a cholesterol-rich membrane structure. Sci. Rep., 5, 15292.

[14] He, J., Mao, C.C., Reyes, A., Sembongi, H., Di Re, M., Granycome, C., Clippingdale, A.B., Fearnley, I.M., Harbour, M., Robinson, A.J., et al. (2007) The AAA protein ATAD3 has displacement loop binding properties and is involved in mitochondrial nucleoid organization. J. Cell Biol., 176, 141-146.

[15] He, J., Cooper, H.M., Reyes, A., Di Re, M., Sembongi, H., Litwin, T.R., Gao, J., Neuman, K.C., Fearnley, I.M., Spinazzola, A., et al. (2012) Mitochondrial nucleoid interacting proteins support mitochondrial protein synthesis. Nucleic Acids Res., 40, 6109-6121.

[16] Bogenhagen, D.F., Rousseau, D. and Burke, S. (2008) The layered structure of human mitochondrial DNA nucleoids. J. Biol. Chem., 283, 3665-3675.

[17] Hubstenberger, A., Merle, N., Charton, R., Brandolin, G. and Rousseau, D. (2010) Topological analysis of ATAD3A insertion in purified human mitochondria. J. Bioenerg. Biomembr., 42, 143-150.

[18] Walker, J.E., Saraste, M., Runswick, M.J. and Gay, N.J. (1982) Distantly related sequences in the alpha-and beta-subunits of ATP synthase, myosin, kinases and other ATP-requiring enzymes and a common nucleotide binding fold. embo J., 1, 945-951.

[19] Sauer, R.T. and Baker, T.A. (2011) AAA proteases: ATPfueled machines of protein destruction. Annu. Rev. Biochem., 80, 587-612.

[20] Gomes, L.C., Di Benedetto, G. and Scorrano, L. (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nat. Cell Biol., 13, 589-598.

[21] Bjorkoy, G., Lamark, T., Brech, A., Outzen, H., Perander, M., Overvatn, A., Stenmark, H. and Johansen, T. (2005) p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death. J. Cell Biol., 171, 603-614.

[22] Gingras, A.C., Raught, B. and Sonenberg, N. (2001) Regulation of translation initiation by FRAP/mTOR. Genes Dev., 15, 807-826.

[23] Jung, C.H., Jun, C.B., Ro, S.H., Kim, Y.M., Otto, N.M., Cao, J., Kundu, M. and Kim, D.H. (2009) ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol. Biol. Cell, 20, 1992-2003.

[24] Kim, J., Kundu, M., Viollet, B. and Guan, K.L. (2011) AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat. Cell Biol., 13, 132-141.

[25] Hamalainen, R.H., Manninen, T., Koivumaki, H., Kislin, M., Otonkoski, T. and Suomalainen, A. (2013) Tissue-and celltype-specific manifestations of heteroplasmic mtDNA 3243A>G mutation in human induced pluripotent stem cellderived disease model. Proc. Natl. Acad. Sci. U. S. A, 110, E3622-E3630.

[26] Rugarli, E.I. and Langer, T. (2012) Mitochondrial quality control: A matter of life and death for neurons. embo J., 31, 1336-1349.

[27] Chen, Y.C., Umanah, G.K., Dephoure, N., Andrabi, S.A., Gygi, S.P., Dawson, T.M., Dawson, V.L. and Rutter, J. (2014) Msp1/ATAD1 maintains mitochondrial function by facilitating the degradation of mislocalized tail-anchored proteins. embo J., 33, 1548-1564.

[28] Merle, N., Feraud, O., Gilquin, B., Hubstenberger, A., Kieffer-Jacquinot, S., Assard, N., Bennaceur-Griscelli, A., Honnorat, J. and Baudier, J. (2012) ATAD3B is a human embryonic stem cell specific mitochondrial protein, re-expressed in cancer cells, that functions as dominant negative for the ubiquitous ATAD3A. Mitochondrion, 12, 441-448.

[29] Li, S. and Rousseau, D. (2012) ATAD3, a vital membrane bound mitochondrial ATPase involved in tumor progression. J. Bioenerg. Biomembr., 44, 189-197.

[30] Goller, T., Seibold, U.K., Kremmer, E., Voos, W. and Kolanus, W. (2013) Atad3 function is essential for early postimplantation development in the mouse. PLoS One, 8, e54799.

[31] Fink, J.K. (2013) Hereditary spastic paraplegia: Clinicopathologic features and emerging molecular mechanisms. Acta Neuropathol., 126, 307-328.

[32] Hansen, J.J., Durr, A., Cournu-Rebeix, I., Georgopoulos, C., Ang, D., Nielsen, M.N., Davoine, C.S., Brice, A., Fontaine, B., Gregersen, N., et al. (2002) Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. Am. J. Hum. Genet., 70, 1328-1332.

[33] Nolden, M., Ehses, S., Koppen, M., Bernacchia, A., Rugarli, E.I. and Langer, T. (2005) The m-AAA protease defective in hereditary spastic paraplegia controls ribosome assembly in mitochondria. Cell, 123, 277-289.

[34] Chen, T.C., Hung, Y.C., Lin, T.Y., Chang, H.W., Chiang, I.P., Chen, Y.Y. and Chow, K.C. (2011) Human papillomavirus infection and expression of ATPase family AAA domain containing 3A, a novel anti-autophagy factor, in uterine cervical cancer. Int. J. Mol. Med., 28, 689-696.

[35] Desai, B.N., Myers, B.R. and Schreiber, S.L. (2002) FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. Proc. Natl. Acad. Sci. U. S. A, 99, 4319-4324.

[36] Whitney, M.L., Jefferson, L.S. and Kimball, S.R. (2009) ATF4 is necessary and sufficient for ER stress-induced upregulation of REDD1 expression. Biochem. Biophys. Res. Commun., 379, 451-455.

[37] Li, H. and Durbin, R. (2009) Fast and accurate short read alignment with burrows-wheeler transform. Bioinformatics, 25, 1754-1760.

[38] Li, H., Handsaker, B., Wysoker, A., Fennell, T., Ruan, J., Homer, N., Marth, G., Abecasis, G. and Durbin, R. and 1000 Genome Project Data Processing Subgroup (2009) The sequence alignment/map format and SAMtools. Bioinformatics, 25, 2078-2079.

[39] Okita, K., Matsumura, Y., Sato, Y., Okada, A., Morizane, A., Okamoto, S., Hong, H., Nakagawa, M., Tanabe, K., Tezuka, K., et al. (2011) A more efficient method to generate integrationfree human iPS cells. Nat. Methods, 8, 409-412.

[40] Mikkola, M., Toivonen, S., Tamminen, K., Alfthan, K., Tuuri, T., Satomaa, T., Natunen, J., Saarinen, J., Tiittanen, M., Lampinen, M., et al. (2013) Lectin from erythrina cristagalli supports undifferentiated growth and differentiation of human pluripotent stem cells. Stem Cells Dev., 22, 707-716.