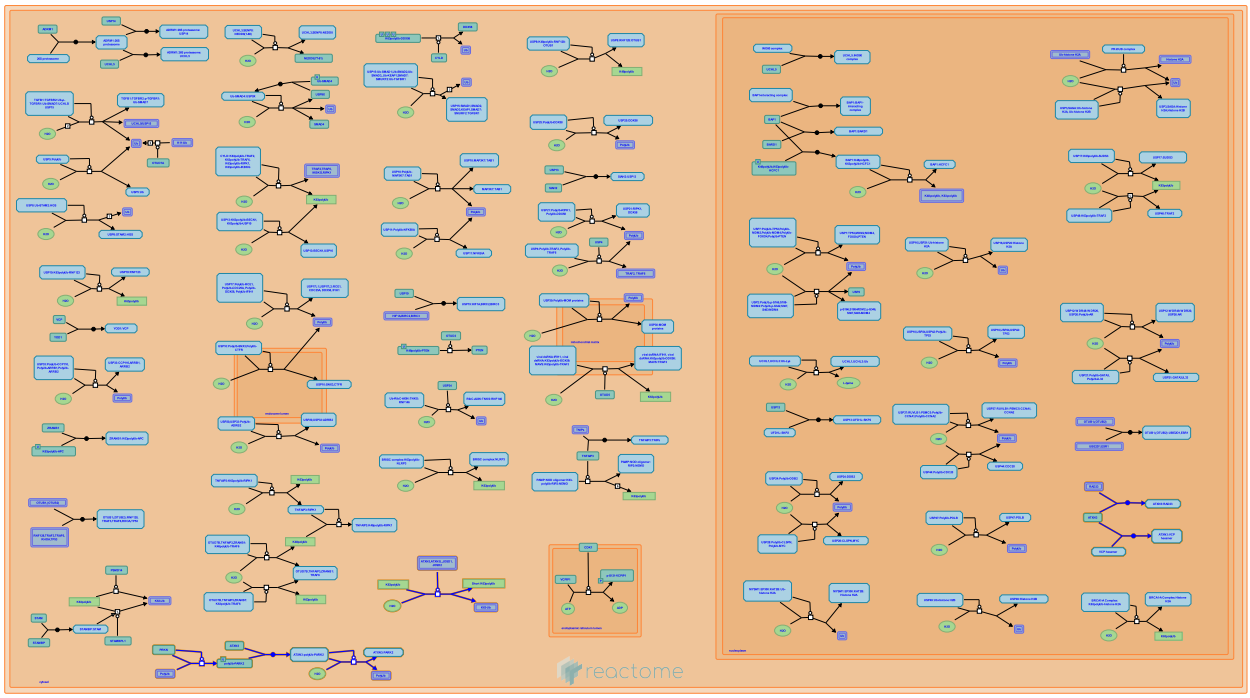
Josephin domain DUBs



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

10/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

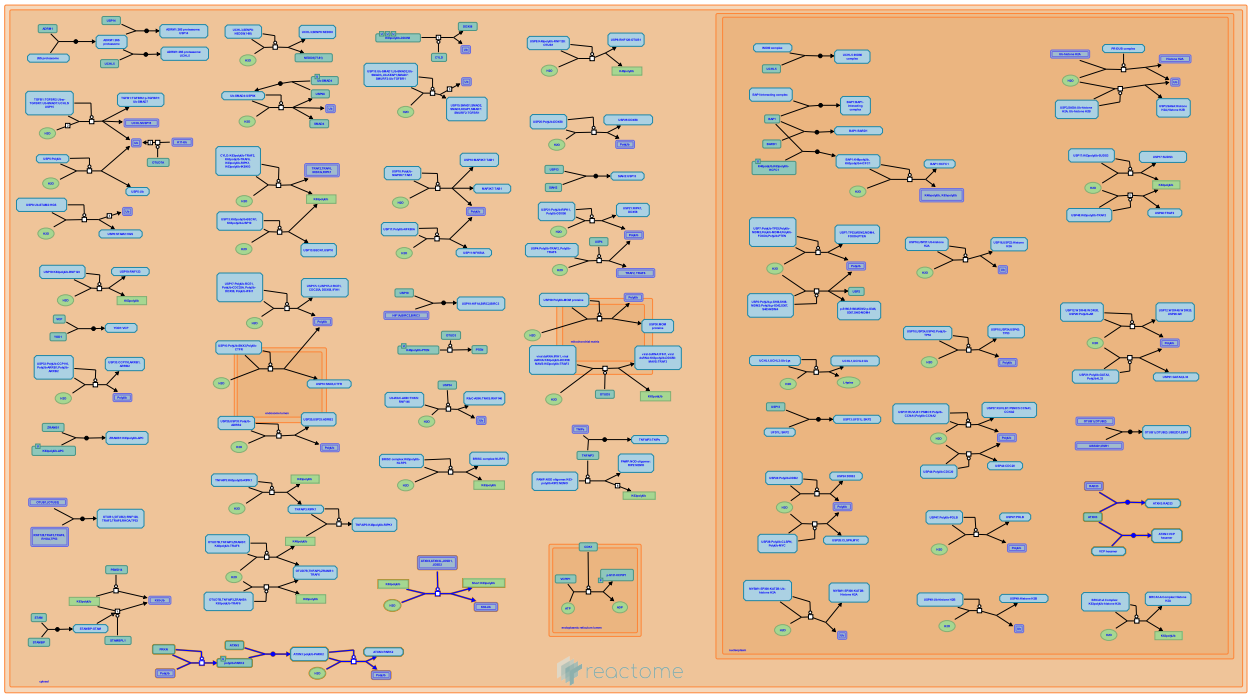
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Josephin domain DUBs ↗

Stable identifier: R-HSA-5689877



The Josephin domain is present in four human DUBs: Ataxin-3 (ATXN3), ATXN3L, Josephin-1 (JOSD1) and JOSD2. All have been shown to possess DUB activity (Tzveltkov & Breuer 2007, Weeks et al. 2011). Josephin domain DUBs may specialize in distinguishing between polyubiquitin chains of different lengths (Eletr & Wilkinson 2014).

Literature references

Wilkinson, KD., Eletr, ZM. (2014). Regulation of proteolysis by human deubiquitinating enzymes. *Biochim. Biophys. Acta, 1843*, 114-28. ↗

Editions

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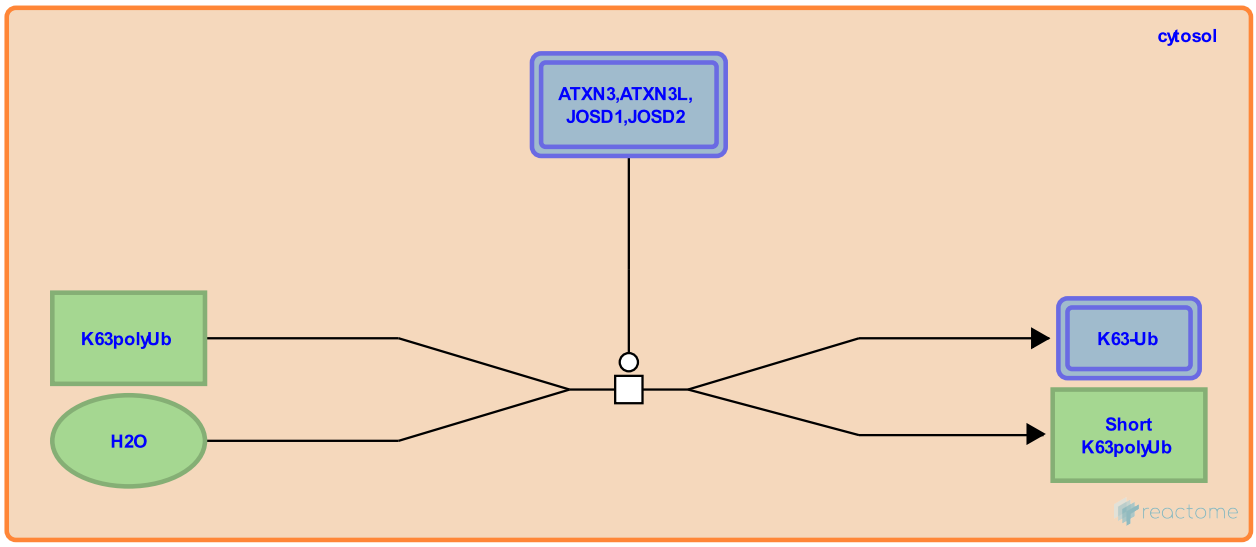
ATXN3 family cleave Ub chains ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5688797

Type: transition

Compartments: cytosol



Ataxin-3 (ATXN3) has an N-terminal Josephin domain (JD) that is conserved within a family of around 4 ubiquitin proteases. ATXN3, the best studied, can bind long chains of lysine-63 (K63)-linked and K48-linked poly-ubiquitin (poly-Ub), but its activity is highest for ubiquitin chains with at least four molecules of ubiquitin. It preferentially cleaves linkages between ubiquitin molecules linked through K63 rather than K48 (Winborn et al. 2008). In effect this trims longer polyubiquitin chains down to approximately four residues (Burnett et al. 2003). The other three human JD-containing proteins also have demonstrated deubiquitinase (DUB) activity (Tzvetkov & Breuer 2007). In vitro ATXN3 kinetics are slow when compared to other well-studied deubiquitinating enzymes (Nicastro et al. 2010) but become much faster when ATXN3 is activated by VCP (Laco et al. 2012). JOSD1 partially localizes to the plasma membrane (Seki et al. 2013).

Literature references

Tzvetkov, N., Breuer, P. (2007). Josephin domain-containing proteins from a variety of species are active de-ubiquitination enzymes. *Biol. Chem., 388*, 973-8. ↗

Editions

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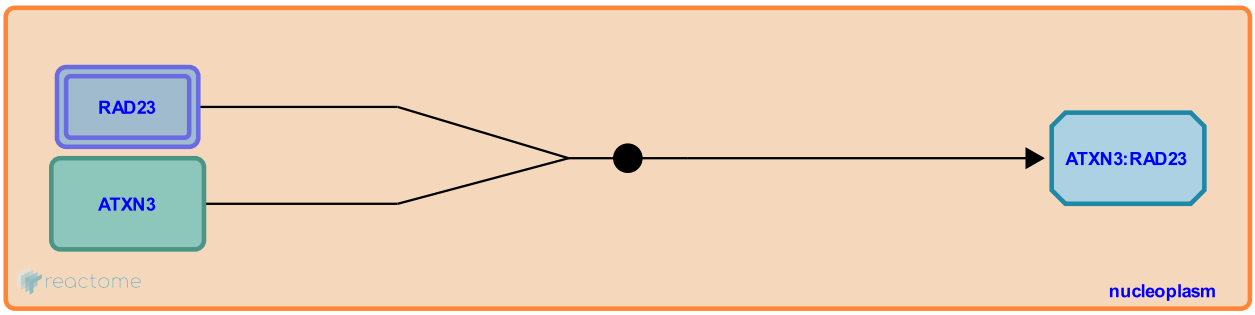
ATXN3 binds RAD23 ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5688786

Type: binding

Compartments: nucleoplasm



Ataxin-3 (ATXN3) is a ubiquitously-expressed deubiqutinating enzyme with important functions in the proteasomal protein degradation pathway and regulation of transcription.

ATXN3 interacts with RAD23A and RAD23B, multiubiquitin chain receptors involved in modulation of proteasomal degradation. RAD23 binds to Lysine-48-linked (K48) polyubiquitin chains, and with a lower affinity to K63-linked chains, in a length-dependent manner. RAD23 is proposed to bind simultaneously to the 26S proteasome and polyubiquitinated substrates, thereby assisting their delivery to the proteasome (Wang et al. 2000).

The C-terminus of ATXN3 contains a polyglutamine (PolyQ) region that, when mutationally expanded to over 52 glutamines, causes the protein to form aggregates that are a hallmark of the neurodegenerative disease spinocerebellar ataxia 3 (SCA3) (Kawaguchi et al. 1994, Evers et al. 2014).

Literature references

Kanazawa, I., Kotliarova, S., Wang, G., Nukina, N., Sawai, N. (2000). Ataxin-3, the MJD1 gene product, interacts with the two human homologs of yeast DNA repair protein RAD23, HHR23A and HHR23B. *Hum. Mol. Genet., 9*, 1795-803. ↗

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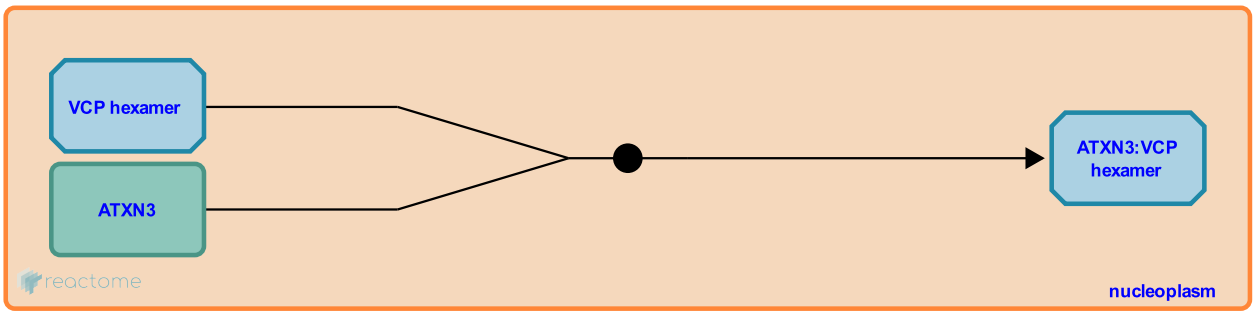
ATXN3 binds VCP ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5688834

Type: binding

Compartments: nucleoplasm



Ataxin-3 (ATXN3) binds Valosin-containing protein (VCP) (Dos-Pepe et al. 2003), a 26S proteasome-associated multiubiquitin chain-targeting factor required for protein degradation by the ubiquitin-proteasome pathway (Dai & Li 2001). One of the functions of VCP is the regulation of misfolded endoplasmic reticulum (ER) proteins a process named ER-associated degradation (ERAD) (Zhong & Pittman 2006, Liu & Ye 2012). VCP increases the ubiquitinase activity of ATXN3 (Laco et al. 2012) and may act as an 'uncoupling factor' that transfers ubiquitinated substrates from RAD23 to ATXN3 (Doss-Pepe et al. 2003). In this model multiubiquitinated proteolytic substrates bind to RAD23 through its UBA domains, while VCP associates with ATXN3 at the proteasome. RAD23 plus substrate would bind to the proteasome (conceivably an ataxin-3-containing proteasome) via its UbL domain. VCP would transfer multiubiquitinated substrates from RAD23 to ATXN3 (Doss-Pepe et al. 2003). VCP is found as a component of abnormal protein aggregates (Hirabayashi et al. 2001) and has been identified as a modulator of polyglutamine-induced neurodegeneration (Higashiyama et al. 2002). Mutant ATXN3 with an expanded polyQ tract binds VCP more efficiently than wild-type ATXN3, interfering with the degradation of ubiquitinated substrates (Laco et al. 2012).

Literature references

Kanazawa, I., Kotliarova, S., Wang, G., Nukina, N., Sawai, N. (2000). Ataxin-3, the MJD1 gene product, interacts with the two human homologs of yeast DNA repair protein RAD23, HHR23A and HHR23B. *Hum. Mol. Genet., 9*, 1795-803. ↗

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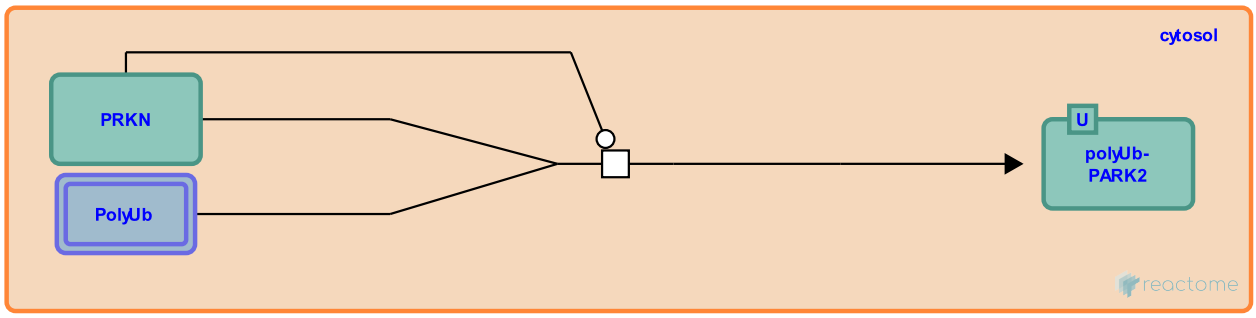
PARK2 autoubiquitinates ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5689111

Type: transition

Compartments: cytosol



Ubiquitin conjugates linked via lysine-48 (K48) target substrates to the proteasome, whereas those linked via any of the six other ubiquitin lysines can alter the function of the modified protein without leading to degradation. Parkin (PARK2) was found to autoubiquitinate itself predominantly via K6, K27, K29 and K63-linked ubiquitination, rather than via K48 (Durcan et al. 2011).

Followed by: ATXN3 binds polyUb-PARK2

Literature references

Durcan, TM., Fon, EA., Williams, AJ., Djarmati, A., Fantaneanu, T., Kontogiannea, M. et al. (2011). The Machado-Joseph disease-associated mutant form of ataxin-3 regulates parkin ubiquitination and stability. *Hum. Mol. Genet. , 20*, 141-54. ↗

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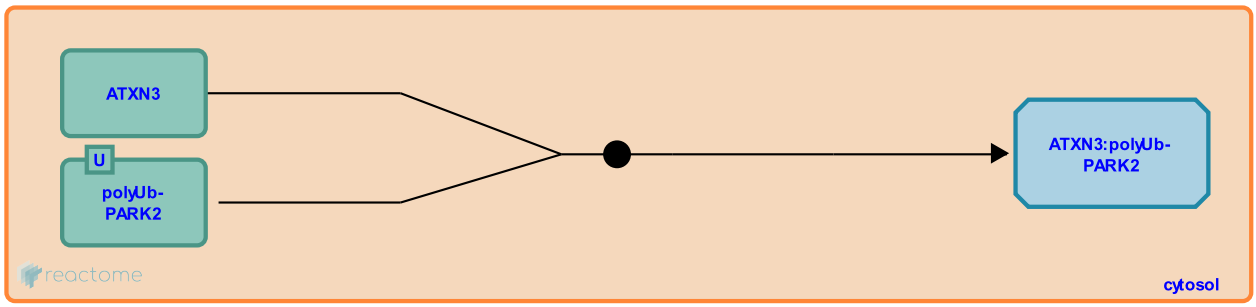
ATXN3 binds polyUb-PARK2 ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5689085

Type: binding

Compartments: cytosol



Ataxin-3 (ATXN3) binds to poly-ubiquitinated Parkin (PARK2) but not unubiquitinated or mono-ubiquitinated PARK2 (Durcan et al. 2011).

Preceded by: PARK2 autoubiquitinates

Followed by: ATXN3 deubiquitinates polyUb-PARK2

Literature references

Durcan, TM., Fon, EA., Williams, AJ., Djarmati, A., Fantaneanu, T., Kontogiannea, M. et al. (2011). The Machado-Joseph disease-associated mutant form of ataxin-3 regulates parkin ubiquitination and stability. *Hum. Mol. Genet. , 20*, 141-54. ↗

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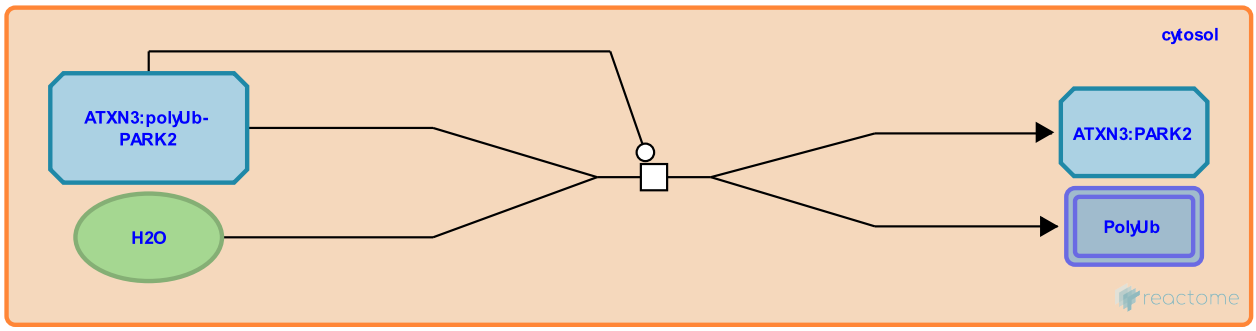
ATXN3 deubiquitinates polyUb-PARK2 ↗

Location: Josephin domain DUBs

Stable identifier: R-HSA-5688837

Type: transition

Compartments: cytosol



Ataxin-3 (ATXN3) deubiquitinates the C-terminus of PARK2 (Parkin) (Winborn et al. 2008, Durcan et al. 2011). This promotes the degradation of PARK2.

An unstable CAG trinucleotide repeat expansion in the ATXN3 gene leads to elongation of the polyglutamine (polyQ) tract within the ATXN3 protein, and is believed to be the cause of Machado-Joseph disease (MJD) or spinocerebellar ataxia type 3 (SCA3), the most common dominantly inherited form of ataxia (Martins et al. 2007). Both wild-type and polyQ-expanded ATXN3 can deubiquitinate PARK2, regardless of the lysine residue used to assemble poly-Ub chains. The polyQ-expanded ATXN3 deubiquitinates PARK2 more efficiently than wild-type ATXN3, but the mutant rather than the wild-type ATXN3 promoted the clearance of PARK2 via the autophagy pathway. This apparent contradiction may be due to increased removal of K27- and K29-linked Ub conjugates on PARK2 by the polyQ-expanded ATXN3; Ub conjugates linked in this manner to PARK2 may protect it from autophagic degradation (Durcan et al. 2011).

Preceded by: ATXN3 binds polyUb-PARK2

Literature references

Durcan, TM., Fon, EA., Williams, AJ., Djarmati, A., Fantaneanu, T., Kontogiannea, M. et al. (2011). The Machado-Joseph disease-associated mutant form of ataxin-3 regulates parkin ubiquitination and stability. *Hum. Mol. Genet. , 20*, 141-54. ↗

Cohen, RE., Xu, P., Scaglione, KM., Peng, J., Williams, AJ., Winborn, BJ. et al. (2008). The deubiquitinating enzyme ataxin-3, a polyglutamine disease protein, edits Lys63 linkages in mixed linkage ubiquitin chains. *J. Biol. Chem., 283*, 26436-43. ↗

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