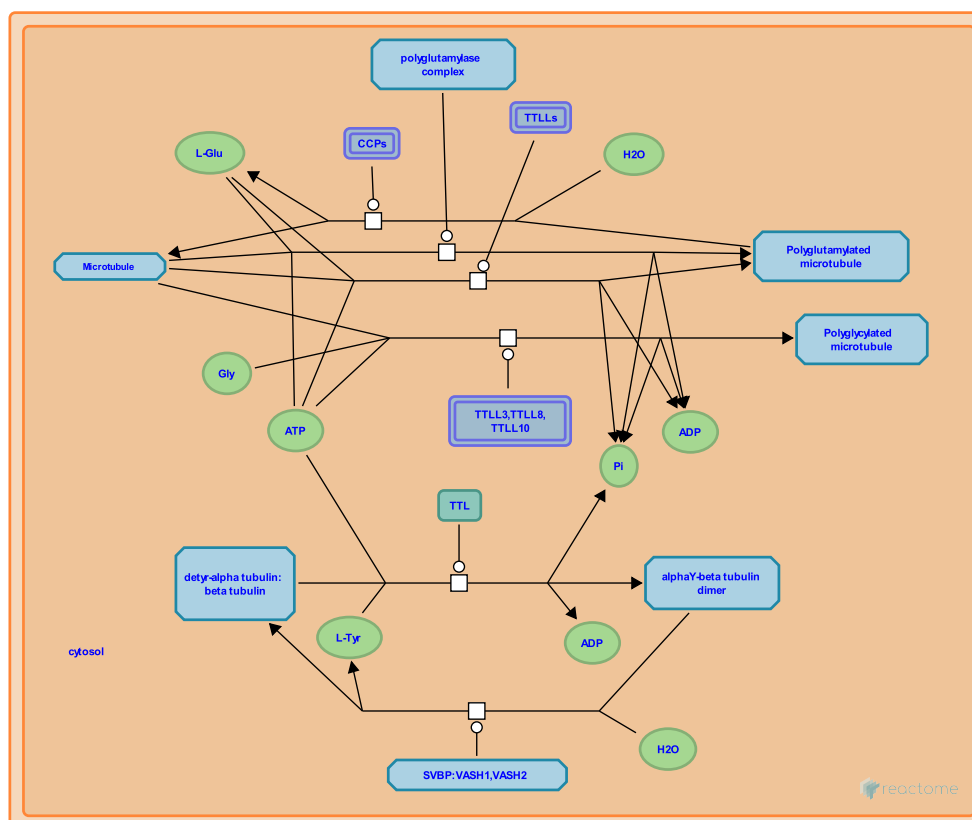


# Carboxyterminal post-translational modifications of tubulin



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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](https://reactome.org/textbook).

27/09/2024

## 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.

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## 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. [↗](#)

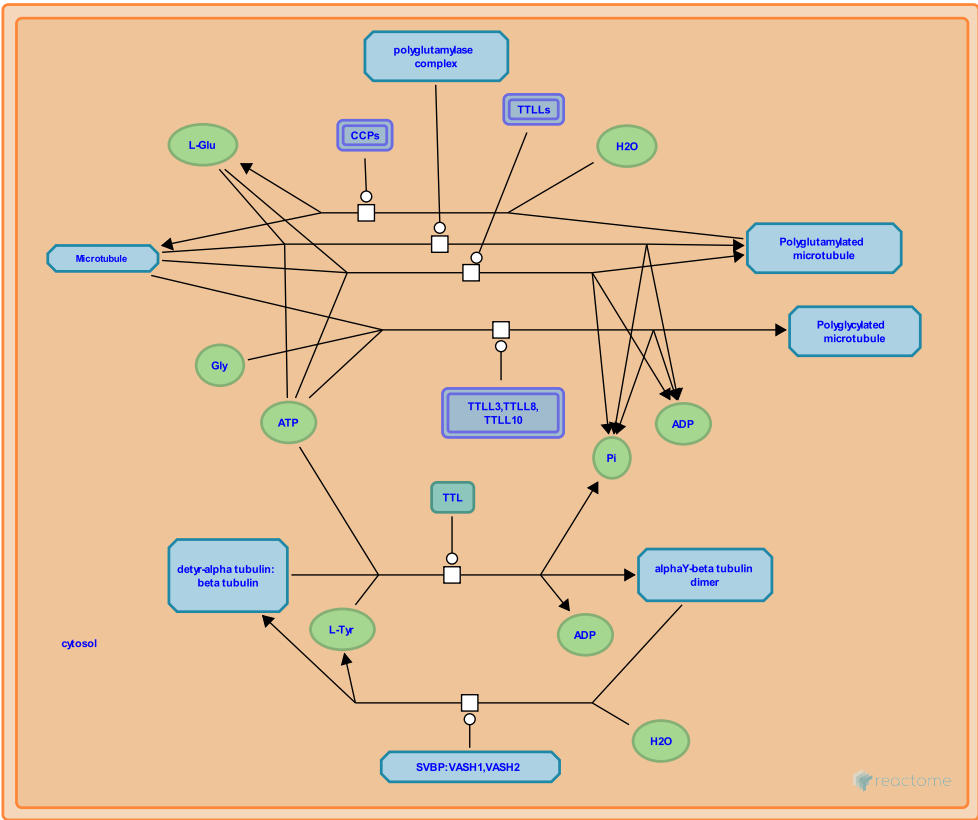
Reactome database release: 89

This document contains 1 pathway and 6 reactions ([see Table of Contents](#))

Carboxyterminal post-translational modifications of tubulin ↗

Stable identifier: R-HSA-8955332

Compartments: cytosol



Tubulins fold into compact globular domains with less structured carboxyterminal tails. These tails vary in sequence between tubulin isoforms and are exposed on the surfaces of microtubules. They can undergo a variety of posttranslational modifications, including the attachment and removal of polyglutamate chains and in the case of alpha-tubulins the loss and reattachment of a terminal tyrosine (Tyr) residue. These modifications are associated with changes in the rigidity and stability of microtubules (Song & Brady 2015; Yu et al. 2015). Mutations affecting these modification processes can have severe effects on phenotype (e.g., Ikegami et al. 2007). Nevertheless, the precise molecular mechanisms by which these changes in tubulin structure modulate its functions remain unclear, so these modification processes are simply annotated here as a series of chemical transformations of tubulins.

Literature references

Roll-Mecak, A., Yu, I., Garnham, CP. (2015). Writing and Reading the Tubulin Code. *J. Biol. Chem.*, 290, 17163-72. ↗

Brady, ST., Song, Y. (2015). Post-translational modifications of tubulin: pathways to functional diversity of microtubules. *Trends Cell Biol.*, 25, 125-36. ↗

Mukai, M., Takagi, H., Setou, M., Hatanaka, K., Campbell, PK., Ikegami, K. et al. (2007). Loss of alpha-tubulin polyglutamylation in ROSA22 mice is associated with abnormal targeting of KIF1A and modulated synaptic function. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 3213-8. ↗

Editions

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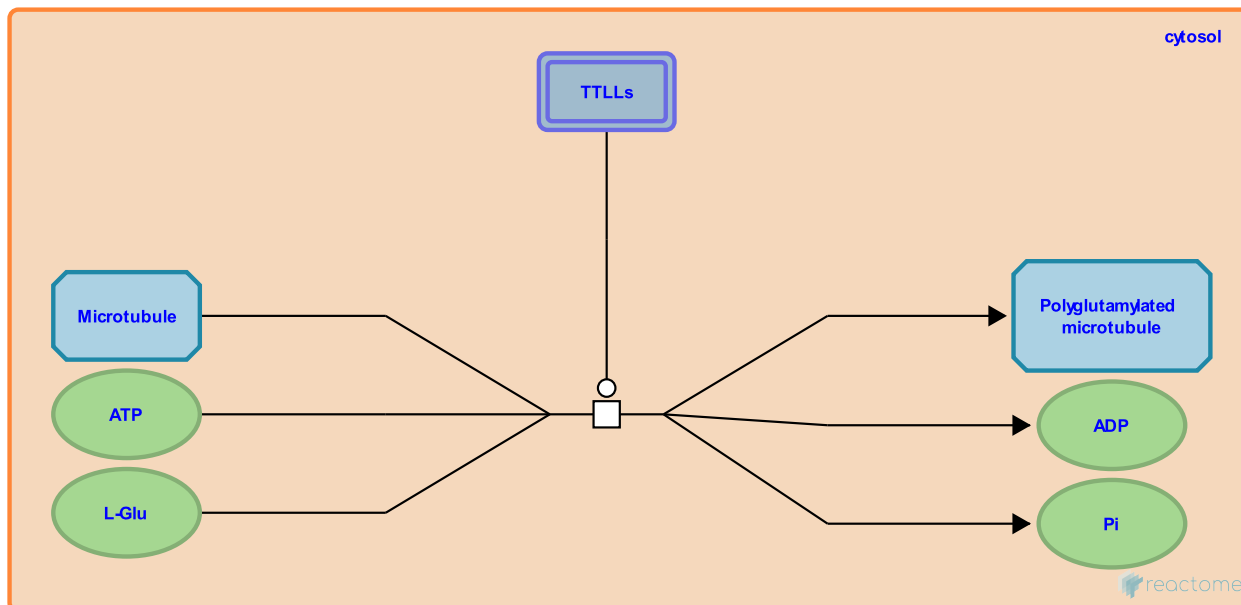
## TTLLs polyglutamate tubulin ↗

**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8865774

**Type:** transition

**Compartments:** cytosol



Tubulin is modified by glutamylation and glycylation, the addition of peptide branches made of glutamyl or glycyl residues respectively, which are attached to the gamma-carboxyl group of glutamic acids within the C-terminal tail domains of alpha- and beta-tubulin. Glutamylation, the most prevalent tubulin posttranslational modification, marks stable microtubules and regulates recruitment and activity of microtubule-interacting proteins. Hyperglutamylation in Purkinje cell degeneration (pcd) mice leads to neurodegeneration (Rogowski et al. 2010).

Nine enzymes of the tubulin tyrosine ligase-like (TTLL) family catalyze glutamylation (Garhnam & Roll-Mecak 2012, Garnham et al. 2015). TTLLs can have a preference for either alpha- or beta-tubulin, although many are able to modify either (Janke et al. 2005, Ikegami et al. 2006, van Dijk et al. 2007). Initial characterization of the mouse TTLL family showed that TTLL1, 5, 6, 11, and 13 preferentially poly-glutamylate alpha-tubulin, while TTLL4 and 7 prefer beta-tubulin. While TTLL1 has a preference for alpha-tubulin (Janke et al. 2005), TTLL1 knockout mice displayed decreased glutamylation on alpha- and beta-tubulin (Ikegami et al. 2010). The molecular determinants for specificity are poorly understood and specificity can differ between organisms, preventing an unambiguous classification of TTLLs by their alpha/beta preference. TTLL4, 5, and 7 have been described as initiases, adding a branched glutamic acid to the tubulin tail, while TTLL6, 11, and 13 were suggested to be elongases, adding poly-Glu chains of variable lengths to the branched glutamic acid (Garhnam & Roll-Mecak 2012). The specificity of mammalian TTLL2, 9, and TTLL12 are unknown.

TTLL3, 8, and 10 are glycylation enzymes that glycate rather than glutamylate tubulin (Ikegami et al. 2008, Ikegami & Setou 2009, Rogowski et al. 2009, Wloga et al. 2009), with TTLL3 and 8 serving as initiases, and TTLL10 serving as an elongase.

TTLL7, the most abundant glutamylase in neurons, modifies both alpha- and beta-tubulin tail peptides in isolation but shows a preference for beta-tubulin when presented with microtubules. TTLL7 catalyzes the initial glutamylation of Beta-tubulin glutamates at multiple internal positions in the Beta-tail, and also the addition of subsequent glutamates to existing branched glutamates (Mukai et al. 2009).

### Literature references

- Gaertig, J., Eddé, B., Strub, JM., Boucher, D., Temurak, N., Suryavanshi, S. et al. (2005). Tubulin polyglutamylase enzymes are members of the TTL domain protein family. *Science*, 308, 1758-62. ↗
- Mukai, M., Setou, M., Tsuchida, J., Macgregor, GR., Heier, RL., Ikegami, K. (2006). TTLL7 is a mammalian beta-tubulin polyglutamylase required for growth of MAP2-positive neurites. *J. Biol. Chem.*, 281, 30707-16. ↗

Lacroix, B., Eddé, B., Rogowski, K., Janke, C., Miro, J., van Dijk, J. (2007). A targeted multienzyme mechanism for selective microtubule polyglutamylation. *Mol. Cell*, 26, 437-48. [↗](#)

## Editions

2016-03-24	Authored	Jupe, S.
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**Polyglutamylase complex (TTLL1) polyglutamylates alpha subunits of tubulin ↗**

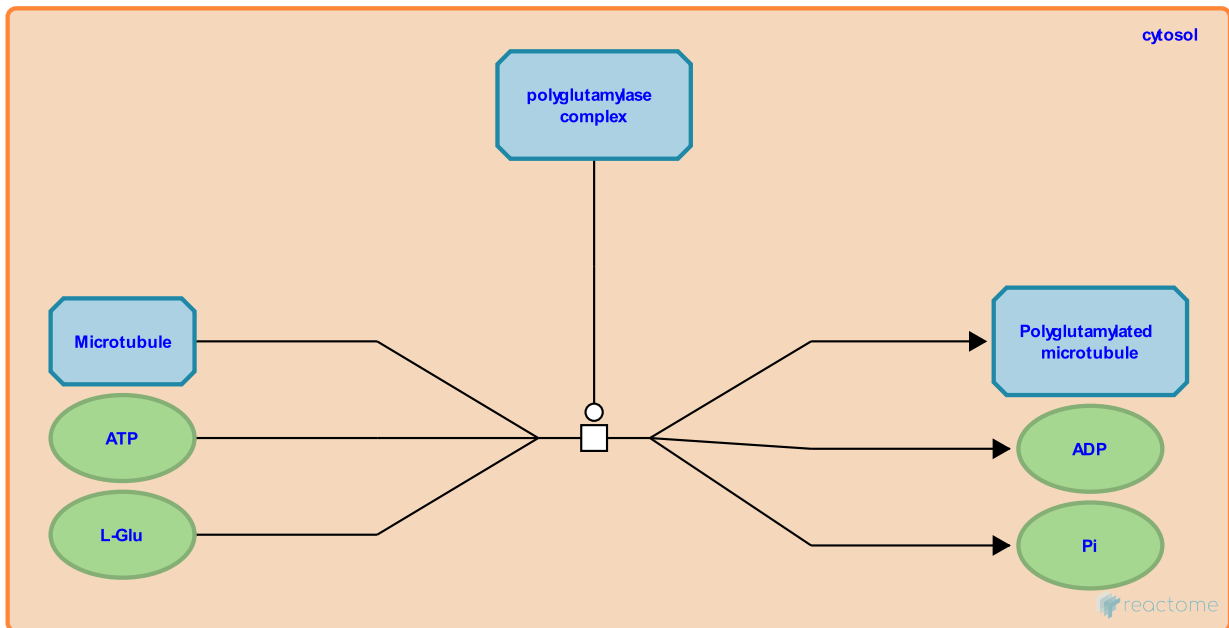
**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8955869

**Type:** transition

**Compartments:** cytosol

**Inferred from:** [Polyglutamylase complex \(Ttl1\) polyglutamylates alpha subunits of tubulin \(Homo sapiens\)](#)



Polyglutamylase complex polyglutamylates alpha subunits of tubulin in the brain. The complex contains TTLL1 (Tubulin tyrosine ligase-like 1) protein. The human complex has not been characterized experimentally. Its organization and function have been inferred from biochemical and genetic studies of its mouse counterpart. The mouse complex has been isolated and four additional protein components have been identified (Janke et al. 2005). A mouse mutation that disrupts one of these, Tpgs1, is associated with failure of polyglytamylation of alpha-chains in microtubules (Ikegami et al. 2007). In this event polyglutamylation is arbitrarily shown on only one tubulin protofilament within the microtubule.

**Literature references**

Gaertig, J., Eddé, B., Strub, JM., Boucher, D., Temurak, N., Suryavanshi, S. et al. (2005). Tubulin polyglutamylase enzymes are members of the TTL domain protein family. *Science*, 308, 1758-62. ↗

Mukai, M., Takagi, H., Setou, M., Hatanaka, K., Campbell, PK., Ikegami, K. et al. (2007). Loss of alpha-tubulin polyglutamylation in ROSA22 mice is associated with abnormal targeting of KIF1A and modulated synaptic function. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 3213-8. ↗

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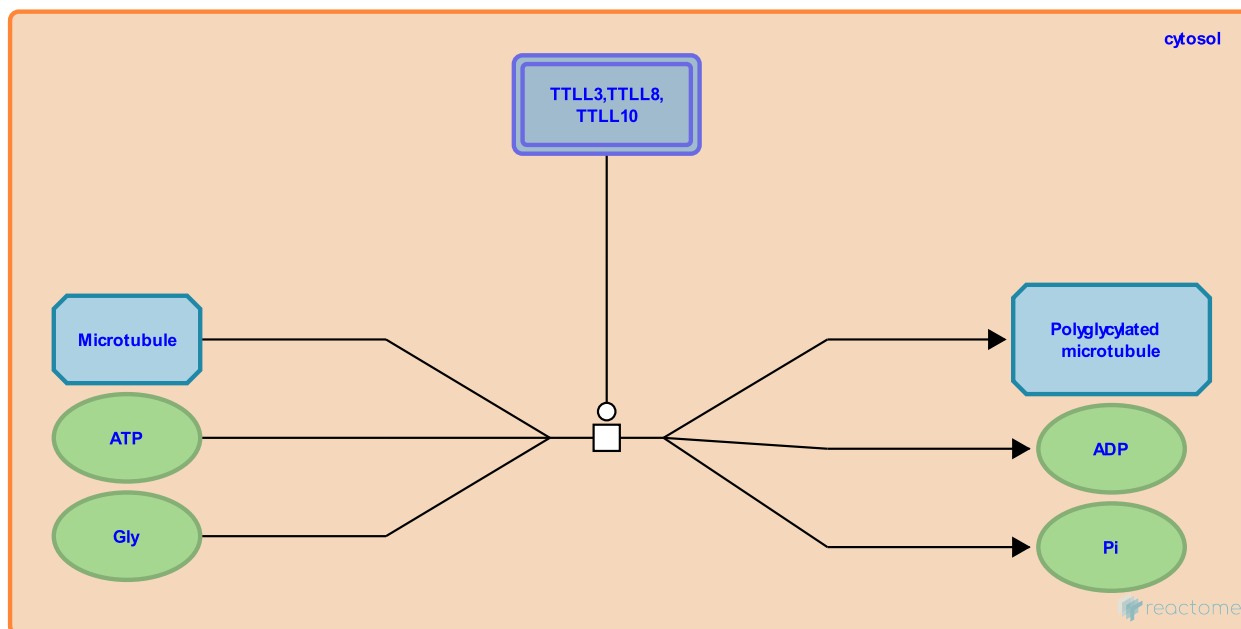
## TTLL3, TTLL8, TTLL10 polyglycylate tubulin ↗

**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8867370

**Type:** transition

**Compartments:** cytosol



Tubulin is modified by glutamylation and glycylation, the addition of peptide branches made of glutamyl or glycy residues respectively, which are attached to the gamma-carboxyl group of glutamic acids within the C-terminal tail domains of alpha- and beta-tubulin. They are added by members of the tubulin tyrosine ligase (TTL family). TTLL3, 8, and 10 are glycyases (Ikegami et al. 2008, Ikegami and Setou, 2009; Rogowski et al. 2009; Wloga et al. 2009) with TTLL3 and 8 serving as initiases, and TTLL10 serving as an elongase. In this event polyglycylation is arbitrarily shown on only one tubulin protofilament within the microtubule.

### Literature references

- Gaertig, J., Webster, DM., Jerka-Dziadosz, M., Bré, MH., Levilliers, N., Rogowski, K. et al. (2009). TTLL3 Is a tubulin glycine ligase that regulates the assembly of cilia. *Dev. Cell*, 16, 867-76. ↗
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### Editions

2016-04-14	Authored	Jupe, S.
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2017-01-19	Reviewed	Jassal, B.

## CCPs deglutamylate tubulin ↗

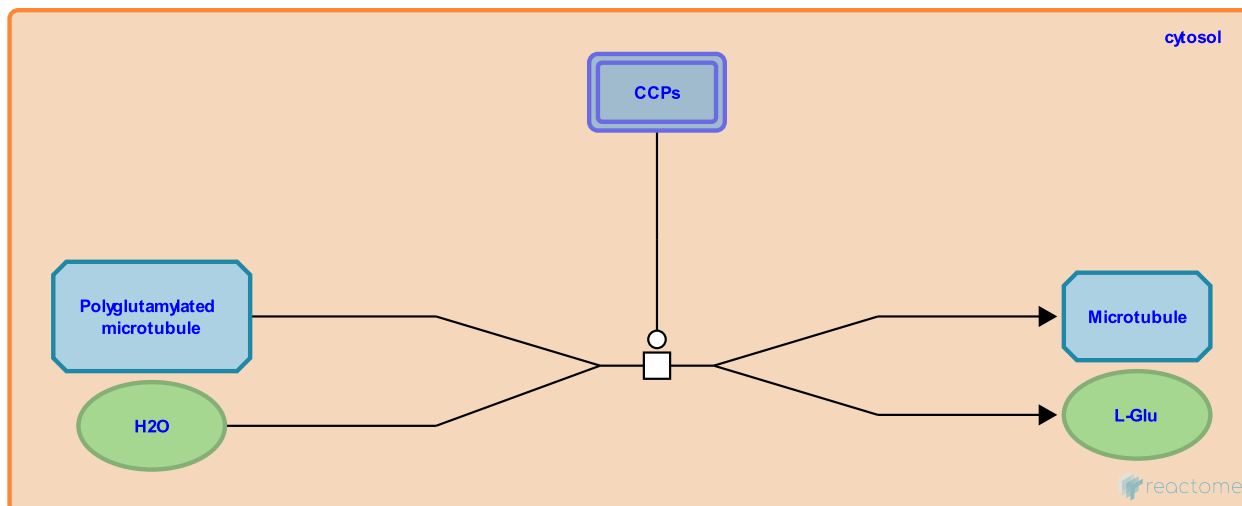
**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8866105

**Type:** transition

**Compartments:** cytosol

**Inferred from:** [Ccps deglutamylate tubulin \(Homo sapiens\)](#)



Cytosolic carboxypeptidases (CCPs) catalyze the removal of glutamate residues from the C-terminal tails of both alpha- and beta-tubulin. These glutamate residues are either enzymatically added in the polyglutamylation reaction, or gene-encoded glutamate residues are removed from alpha-tubulin after detyrosination to generate delta2-tubulin (Kimura et al. 2010, Rogowski et al. 2010). CCPs are members of the MC clan, M14 family, subfamily M14D of metallopeptidases (Kalinina et al. 2007, Rodriguez de la Vega et al. 2007). Mouse Ccp1, 2, 3, 4, and 6 are functionally homologous and remove linearly added glutamates from tubulin (alpha-peptide bonds), while Ccp5 specifically removes branching-point glutamates (gamma-peptide bonds) which are generated as first step of the polyglutamylation reaction (Rogowski et al. 2010; Tort et al. 2014). The catalytic activities of the human proteins are inferred from the properties of their mouse homologues and limited studies of human proteins expressed in cultured cells (Rogowski et al. 2010). In this event polyglutamylation is arbitrarily shown on only one tubulin protofilament within the polyglutamylated microtubule.

### Literature references

- Desagher, S., Bosson, A., Rogowski, K., van Dijk, J., Bosc, C., Larroque, C. et al. (2010). A family of protein-deglutamylating enzymes associated with neurodegeneration. *Cell*, 143, 564-78. ↗
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- Setou, M., Kurabe, N., Kimura, Y., Konishi, Y., Iino, Y., Kaplan, OI. et al. (2010). Identification of tubulin deglutamylase among *Caenorhabditis elegans* and mammalian cytosolic carboxypeptidases (CCPs). *J. Biol. Chem.*, 285, 22936-41. ↗
- Avilés, FX., Rocha, C., Tort, O., Lorenzo, J., Seixas, C., Bièche, I. et al. (2014). The cytosolic carboxypeptidases CCP2 and CCP3 catalyze posttranslational removal of acidic amino acids. *Mol. Biol. Cell*, 25, 3017-27. ↗

### Editions

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## TTL ligates L-Tyr to the carboxy terminus of detyr-alpha tubulin:beta tubulin ↗

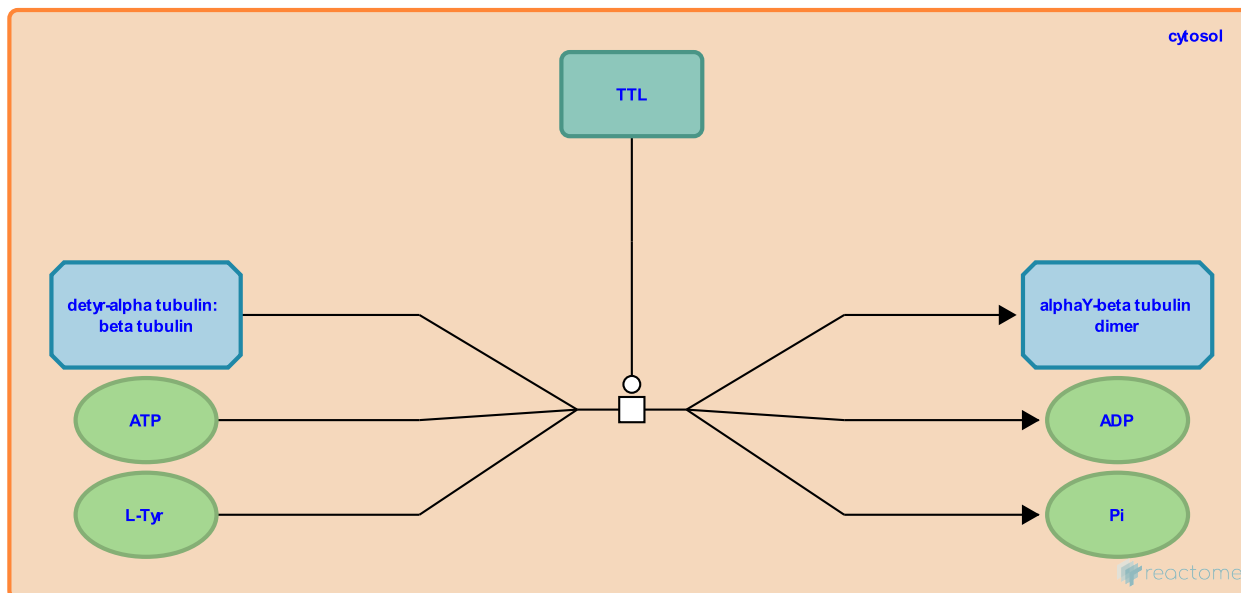
**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8955706

**Type:** transition

**Compartments:** cytosol

**Inferred from:** [TTL ligates L-Tyr to the carboxy terminus of alpha-tubulin \(Bos taurus\)](#)



TTL (tubulin tyrosine ligase) ligates tyrosine (L-Tyr) to the carboxy terminus of the alpha-tubulin subunit of an alpha tubulin:beta tubulin dimer in an ATP-dependent reaction. Human TTL has not been characterized in detail; the reaction mechanism annotated here has been worked out with bovine proteins (Deans et al. 1992), and structural studies with chicken proteins demonstrate the basis of the enzyme's specificity for the carboxy terminus of tubulin alpha chains (Prota et al. 2013).

### Literature references

Steinmetz, MO., Kammerer, RA., Jaussi, R., Kuijpers, M., Magiera, MM., Prota, AE. et al. (2013). Structural basis of tubulin tyrosination by tubulin tyrosine ligase. *J. Cell Biol.*, 200, 259-70. ↗

Allison, RD., Deans, NL., Purich, DL. (1992). Steady-state kinetic mechanism of bovine brain tubulin: tyrosine ligase. *Biochem. J.*, 286, 243-51. ↗

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## SVBP:VASH1,VASH2 hydrolyzes the terminal L-Tyr residue from alphaY-beta tubulin dimer ↗

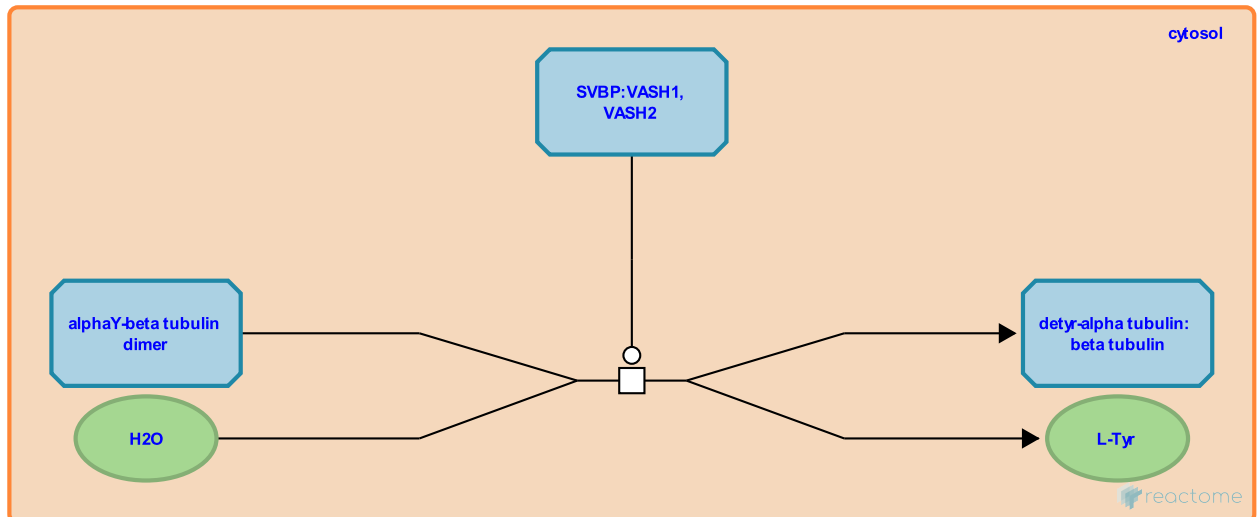
**Location:** [Carboxyterminal post-translational modifications of tubulin](#)

**Stable identifier:** R-HSA-8955712

**Type:** transition

**Compartments:** cytosol

**Inferred from:** [TTCP hydrolyzes the terminal L-Tyr residue from alpha-tubulin \(Bos taurus\)](#)



TTCP (tubuliny-tyrosine carboxypeptidase) hydrolyzes the terminal L-Tyr residue from the alpha-tubulin subunit of an alpha tubulin:beta tubulin dimer to yield deY-alpha tubulin and L-tyrosine (L-Tyr). Although TTCP enzyme has not been purified from any species, studies of material partially purified from chicken brain have allowed its activity to be defined and distinguished from those of widely expressed carboxypeptidases with broader substrate specificities (Argarana et al. 1980). This reaction is known to occur in humans (Song & Brody 2015; Yu et al. 2015) and its properties have been inferred from those of its chicken counterpart.

### Literature references

- Roll-Mecak, A., Yu, I., Garnham, CP. (2015). Writing and Reading the Tubulin Code. *J. Biol. Chem.*, 290, 17163-72. ↗
- Brady, ST., Song, Y. (2015). Post-translational modifications of tubulin: pathways to functional diversity of microtubules. *Trends Cell Biol.*, 25, 125-36. ↗
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### Editions

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