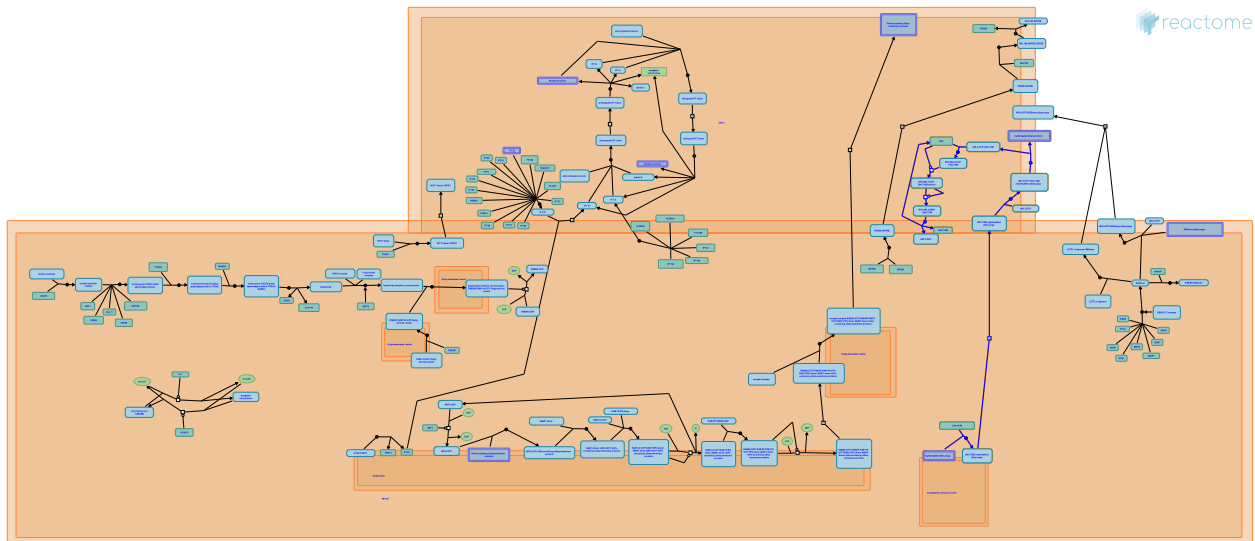


# Trafficking of myristoylated proteins to the cilium



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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).

04/05/2024

## 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

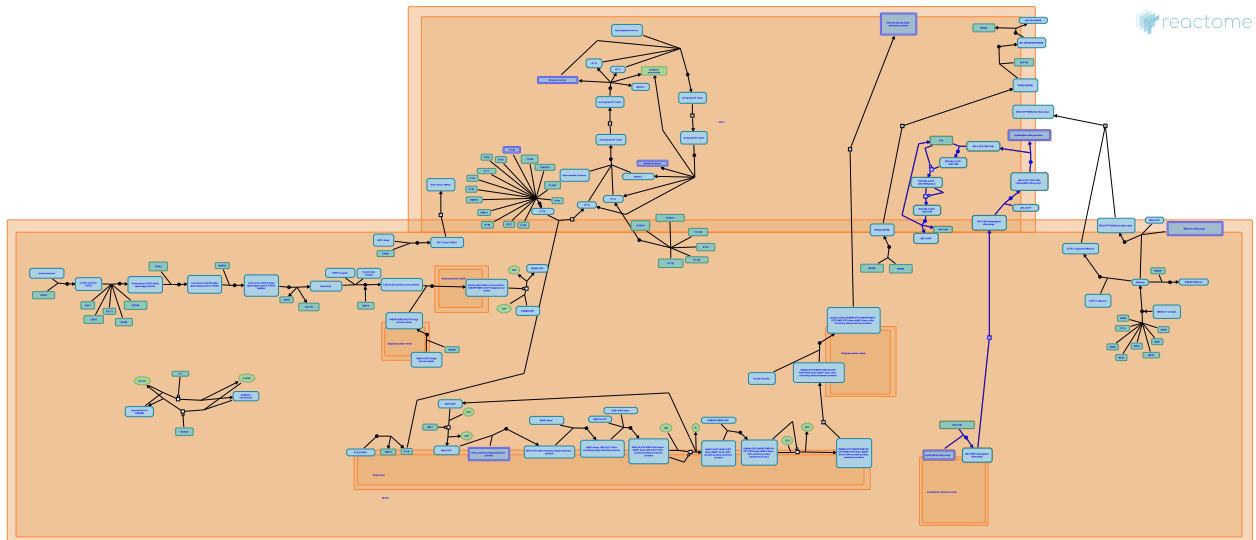
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

## Trafficking of myristoylated proteins to the cilium ↗

Stable identifier: R-HSA-5624138



A number of myristoylated proteins have been shown to traffic to the cilium in a myristoyl- and UNC119B:ARL3:RP2-dependent fashion. These include the ciliary proteins Nephrocystin 3 (NPHP3) and Cystin 1 (CYS1) (Wright et al, 2011; reviewed in Schwarz et al, 2012). Myristoyl-binding by the ARL3 effector UNC119B is required in an unknown fashion for the transport of the myristoylated cargo to the cilium. At the cilium, a GTPase cycle involving the ARF-like small GTPase ARL3 and its GAP protein RP2 promote the release of the myristoylated proteins into the ciliary membrane and the recycling and ciliary exit of UNC119B (Wright et al, 2011; reviewed in Schwarz et al, 2012). ARL3 plays additional roles in the cilium coordinating the association of IFT A and IFT B complexes with the kinesin motors (Li et al, 2010; reviewed in Li et al, 2012).

### Literature references

- Ling, K., Hu, J., Li, Y. (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. *J. Cell. Biochem.*, 113, 2201-7. ↗
- Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. ↗
- Ling, K., Wei, Q., Hu, J., Li, Y., Zhang, Y. (2010). The small GTPases ARL-13 and ARL-3 coordinate intraflagellar transport and ciliogenesis. *J. Cell Biol.*, 189, 1039-51. ↗
- Cheetham, ME., Schwarz, N., Hardcastle, AJ. (2012). Arl3 and RP2 mediated assembly and traffic of membrane associated cilia proteins. *Vision Res.*, 75, 2-4. ↗

### Editions

2014-09-15	Authored	Rothfels, K.
2014-10-13	Edited	Jassal, B.
2014-11-10	Reviewed	Lorentzen, E.
2014-11-14	Reviewed	Goncalves, J.

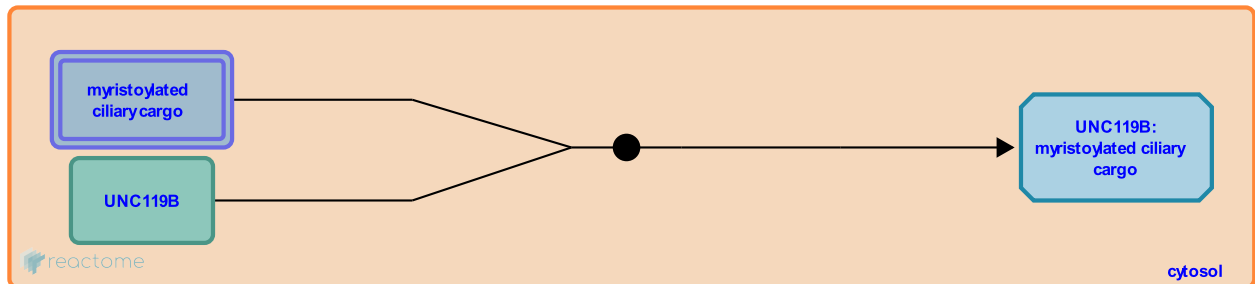
## UNC119B binds myristoylated proteins ↗

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5624131

**Type:** binding

**Compartments:** cytosol



UNC119B is an ARL3 effector that binds directly to the myristoyl moieties at glycine 2 of NPHP3 and CYS1 (Wright et al, 2011). Myristoylation is required for the ciliary localization of these proteins (Wright et al, 2011; Tao et al, 2006), and both mutation of the glycine 2 myristoylation target in NPHP3 and siRNA knockdown of UNC119B dramatically reduce the ciliary localization of NPHP3 and CYS1 (Tao et al, 2006; Wright et al, 2011; reviewed in Schwarz et al, 2012).

**Followed by:** [UNC119B stimulates translocation of myristoylated ciliary cargo to the primary cilium](#)

### Literature references

- Kispert, A., Tao, B., Siroky, B., Guay-Woodford, LM., Kappes, JC., Bu, S. et al. (2009). Cystin localizes to primary cilia via membrane microdomains and a targeting motif. *J. Am. Soc. Nephrol.*, 20, 2570-80. ↗
- Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. ↗
- Cheetham, ME., Schwarz, N., Hardcastle, AJ. (2012). Arl3 and RP2 mediated assembly and traffic of membrane associated cilia proteins. *Vision Res.*, 75, 2-4. ↗

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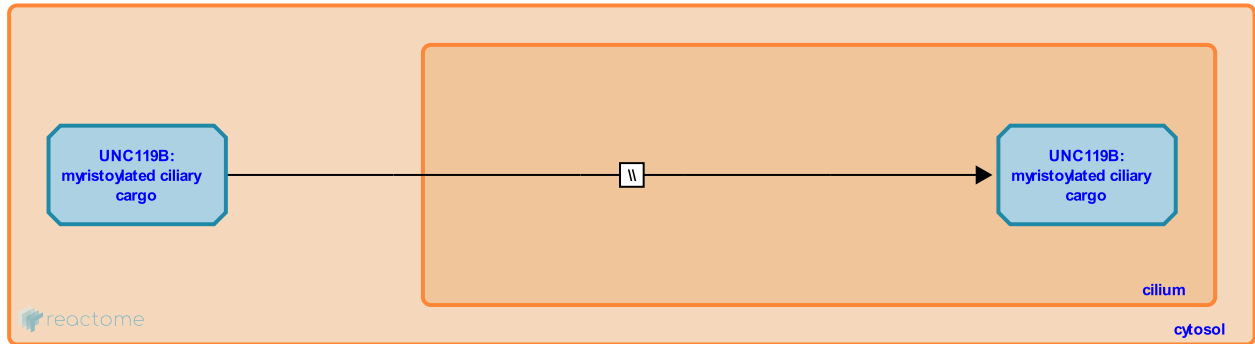
## UNC119B stimulates translocation of myristoylated ciliary cargo to the primary cilium ↗

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5624132

**Type:** omitted

**Compartments:** cilium



UNC119B promotes the translocation of myristoylated NPHP3 from the ER membrane to the cilium by an unknown mechanism. Ciliary localization depends both on myristoylation and UNC119B, as mutation of the glycine 2 acceptor site or siRNA knockdown of UNC119B drastically reduces the amount of NPHP3 or CYS1 in the cilium (Wright et al, 2011).

**Preceded by:** [UNC119B binds myristoylated proteins](#)

**Followed by:** [ARL3:GTP binds the UNC119B complex](#)

### Literature references

Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. ↗

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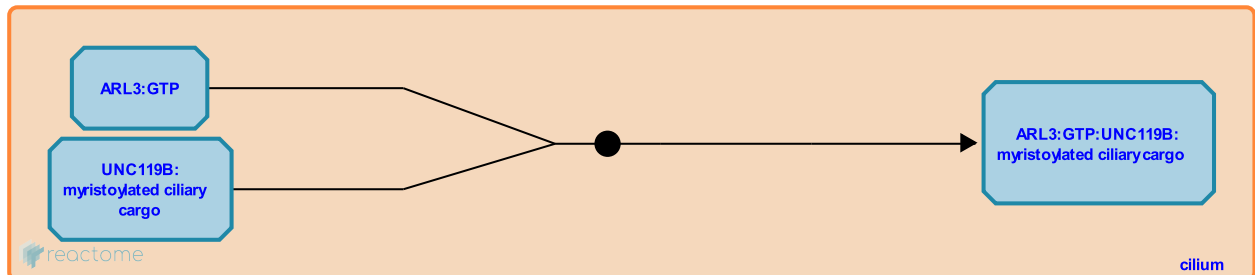
## ARL3:GTP binds the UNC119B complex ↗

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5624133

**Type:** binding

**Compartments:** cilium



ARL3 is an ARF-like small GTPase that is localized to the cilium in both the GDP- and the GTP-bound form (Zhou et al, 2006; Wright et al, 2011). ARL3 binds UNC119B in a GTP-dependent fashion and is required for the ciliary localization of NPHP3 and CYS1. Upon GTPase activation, ARL3 promotes the transfer of the myristoylated cargo into the ciliary membrane (Wright et al, 2011).

**Preceded by:** [UNC119B stimulates translocation of myristoylated ciliary cargo to the primary cilium](#)

**Followed by:** [Myristoylated NPHP3 translocates into the ciliary membrane](#)

### Literature references

Zhou, C., Li, Y., Kahn, RA., Marcus, AI., Cunningham, L. (2006). Arl2 and Arl3 regulate different microtubule-dependent processes. *Mol. Biol. Cell*, 17, 2476-87. ↗

Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. ↗

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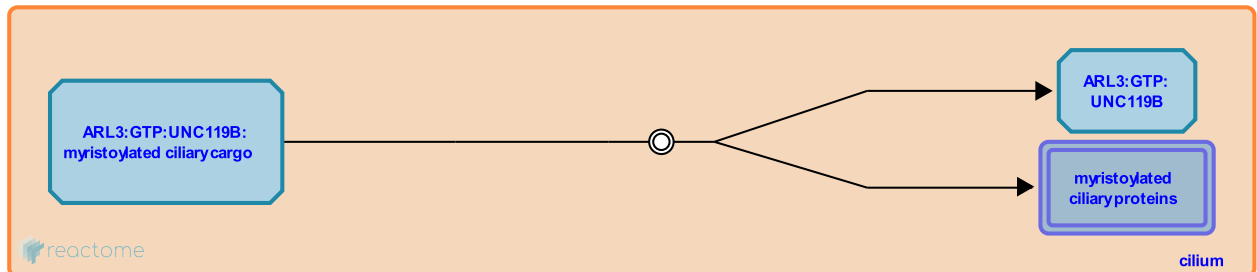
## Myristoylated NPHP3 translocates into the ciliary membrane [↗](#)

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5624130

**Type:** dissociation

**Compartments:** cilium



Binding of ARL3 to UNC119B induces a conformational change that obstructs UNC119B cargo-binding and promotes the release of the myristoylated cargo into the ciliary membrane (Wright et al, 2011; Ismail et al, 2012).

**Preceded by:** [ARL3:GTP binds the UNC119B complex](#)

**Followed by:** [RP2 binds ARL3:GTP:UNC119B](#)

### Literature references

Miertzschke, M., Wittinghofer, A., Chen, YX., Ismail, SA., Vetter, IR., Koerner, C. (2012). Structural basis for Arl3-specific release of myristoylated ciliary cargo from UNC119. *EMBO J.*, 31, 4085-94. [↗](#)

Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. [↗](#)

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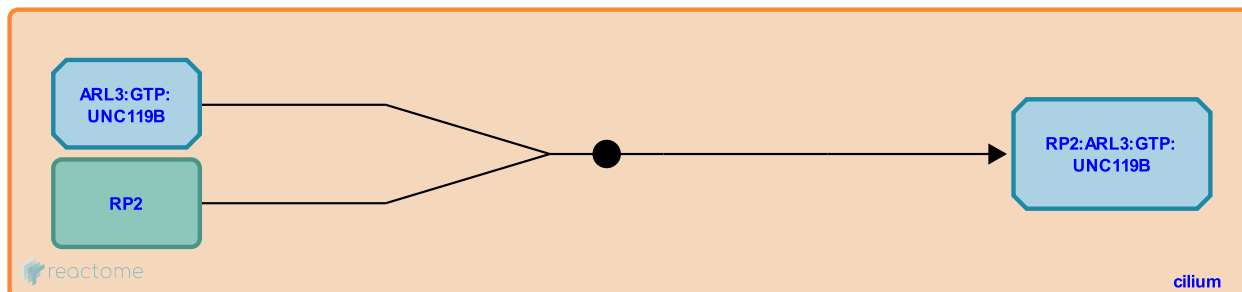
## RP2 binds ARL3:GTP:UNC119B ↗

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5638004

**Type:** binding

**Compartments:** cilium



RP2 is an ARL3 GAP that is localized to the cilium and plays a role in trafficking proteins from the Golgi to the ciliary membrane (Veltel et al, 2008a; Hurd et al, 2011; Evans et al, 2010; Wright et al, 2011). RP2 forms a ternary complex with UNC119B and ARL3, activating the ARL3 GTPase activity and promoting the release of UNC119B (Veltel et al, 2008b; Wright et al, 2011; Kuhnel et al, 2006; reviewed in Schwarz et al, 2012; Li et al, 2012)

**Preceded by:** [Myristoylated NPHP3 translocates into the ciliary membrane](#)

**Followed by:** [RP2 activates the GTPase activity of ARL3](#)

### Literature references

- Cheetham, ME., Wolfrum, U., Schwarz, N., Hardcastle, AJ., Nagel-Wolfrum, K., Evans, RJ. (2010). The retinitis pigmentosa protein RP2 links pericentriolar vesicle transport between the Golgi and the primary cilium. *Hum. Mol. Genet.*, 19, 1358-67. ↗
- Schlichting, I., Kühnel, K., Wittinghofer, A., Veltel, S. (2006). Crystal structure of the human retinitis pigmentosa 2 protein and its interaction with Arl3. *Structure*, 14, 367-78. ↗
- Eisenacher, E., Gasper, R., Wittinghofer, A., Veltel, S. (2008). The retinitis pigmentosa 2 gene product is a GTPase-activating protein for Arf-like 3. *Nat. Struct. Mol. Biol.*, 15, 373-80. ↗
- Hurd, TW., Margolis, BL., Fan, S. (2011). Localization of retinitis pigmentosa 2 to cilia is regulated by Importin beta2. *J. Cell. Sci.*, 124, 718-26. ↗
- Ling, K., Hu, J., Li, Y. (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. *J. Cell. Biochem.*, 113, 2201-7. ↗

### Editions

2014-10-13	Edited	Jassal, B.
2014-10-30	Authored	Rothfels, K.
2014-11-10	Reviewed	Lorentzen, E.
2014-11-14	Reviewed	Goncalves, J.



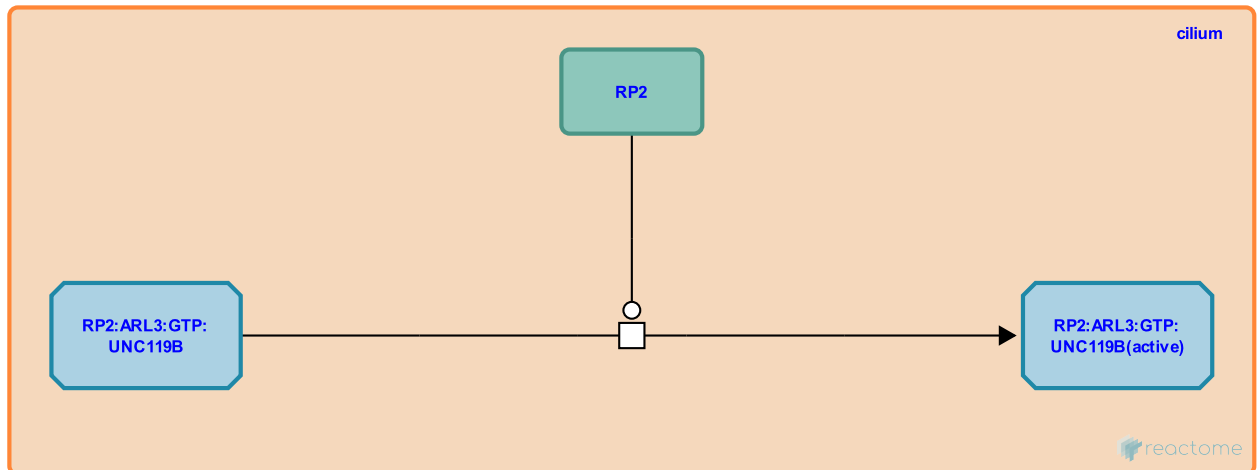
## RP2 activates the GTPase activity of ARL3 [↗](#)

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5638007

**Type:** transition

**Compartments:** cilium



RP2 is an ARL3 GAP that is localized to the cilium and plays a role in trafficking proteins from the Golgi to the ciliary membrane (Veltel et al, 2008a; Hurd et al, 2011; Evans et al, 2010; Wright et al, 2011). RP2 forms a ternary complex with UNC119B and ARL3, activating the ARL3 GTPase activity and promoting the release of UNC119B (Veltel et al, 2008b; Wright et al, 2011; Kuhnel et al, 2006; reviewed in Schwarz et al, 2012; Li et al, 2012)

**Preceded by:** [RP2 binds ARL3:GTP:UNC119B](#)

**Followed by:** [ARL3 hydrolyzes GTP](#)

### Literature references

- Cheetham, ME., Wolfrum, U., Schwarz, N., Hardcastle, AJ., Nagel-Wolfrum, K., Evans, RJ. (2010). The retinitis pigmentosa protein RP2 links pericentriolar vesicle transport between the Golgi and the primary cilium. *Hum. Mol. Genet.*, 19, 1358-67. [↗](#)
- Schlichting, I., Kühnel, K., Wittinghofer, A., Veltel, S. (2006). Crystal structure of the human retinitis pigmentosa 2 protein and its interaction with Arl3. *Structure*, 14, 367-78. [↗](#)
- Eisenacher, E., Gasper, R., Wittinghofer, A., Veltel, S. (2008). The retinitis pigmentosa 2 gene product is a GTPase-activating protein for Arf-like 3. *Nat. Struct. Mol. Biol.*, 15, 373-80. [↗](#)
- Hurd, TW., Margolis, BL., Fan, S. (2011). Localization of retinitis pigmentosa 2 to cilia is regulated by Importin beta2. *J. Cell. Sci.*, 124, 718-26. [↗](#)
- Ling, K., Hu, J., Li, Y. (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. *J. Cell. Biochem.*, 113, 2201-7. [↗](#)

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2014-10-13	Edited	Jassal, B.
2014-11-10	Reviewed	Lorentzen, E.
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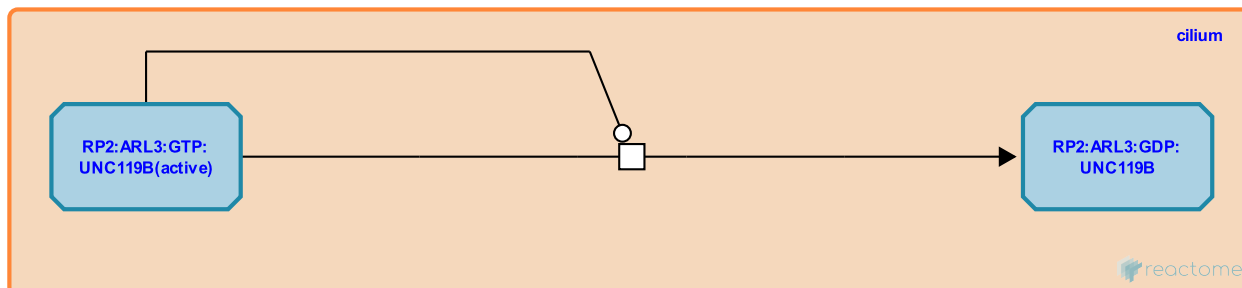
## ARL3 hydrolyzes GTP ↗

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5638006

**Type:** transition

**Compartments:** cilium



RP2 is an ARL3 GAP that is localized to the cilium and plays a role in trafficking proteins from the Golgi to the ciliary membrane (Veltel et al, 2008a; Hurd et al, 2011; Evans et al, 2010; Wright et al, 2011). RP2 forms a ternary complex with UNC119B and ARL3, activating the ARL3 GTPase activity and promoting the release of UNC119B (Veltel et al, 2008b; Wright et al, 2011; Kuhnel et al, 2006; reviewed in Schwarz et al, 2012; Li et al, 2012)

**Preceded by:** [RP2 activates the GTPase activity of ARL3](#)

**Followed by:** [RP2:ARL3:GDP:UNC119B dissociates](#)

## Literature references

- Cheetham, ME., Wolfrum, U., Schwarz, N., Hardcastle, AJ., Nagel-Wolfrum, K., Evans, RJ. (2010). The retinitis pigmentosa protein RP2 links pericentriolar vesicle transport between the Golgi and the primary cilium. *Hum. Mol. Genet.*, 19, 1358-67. ↗
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- Ling, K., Hu, J., Li, Y. (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. *J. Cell. Biochem.*, 113, 2201-7. ↗

## Editions

2014-09-15	Authored	Rothfels, K.
2014-10-13	Edited	Jassal, B.
2014-11-10	Reviewed	Lorentzen, E.
2014-11-14	Reviewed	Goncalves, J.

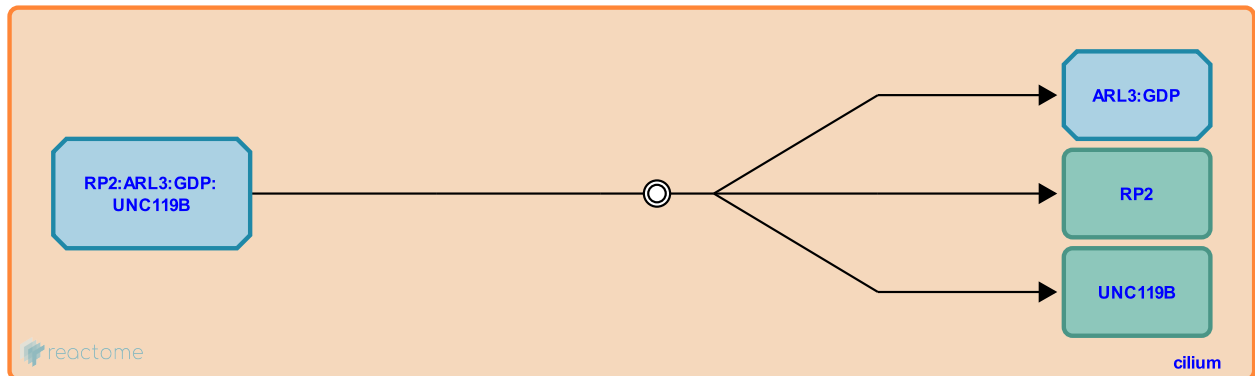
## RP2:ARL3:GDP:UNC119B dissociates [↗](#)

**Location:** [Trafficking of myristoylated proteins to the cilium](#)

**Stable identifier:** R-HSA-5638016

**Type:** dissociation

**Compartments:** cilium



ARL3 hydrolysis of GTP promotes the release of UNC119B, dissociating the complex (Wright et al, 2011; reviewed in Schwarz et al, 2012).

**Preceded by:** [ARL3 hydrolyzes GTP](#)

### Literature references

Sengupta, P., Kwong, M., Baye, LM., Sang, L., Sheffield, VC., Wright, KJ. et al. (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.*, 25, 2347-60. [↗](#)

Cheetham, ME., Schwarz, N., Hardcastle, AJ. (2012). Arl3 and RP2 mediated assembly and traffic of membrane associated cilia proteins. *Vision Res.*, 75, 2-4. [↗](#)

### Editions

2013-10-16	Edited	Jupe, S.
2014-10-30	Authored	Rothfels, K.
2014-11-10	Reviewed	Lorentzen, E.
2014-11-14	Reviewed	Goncalves, J.

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