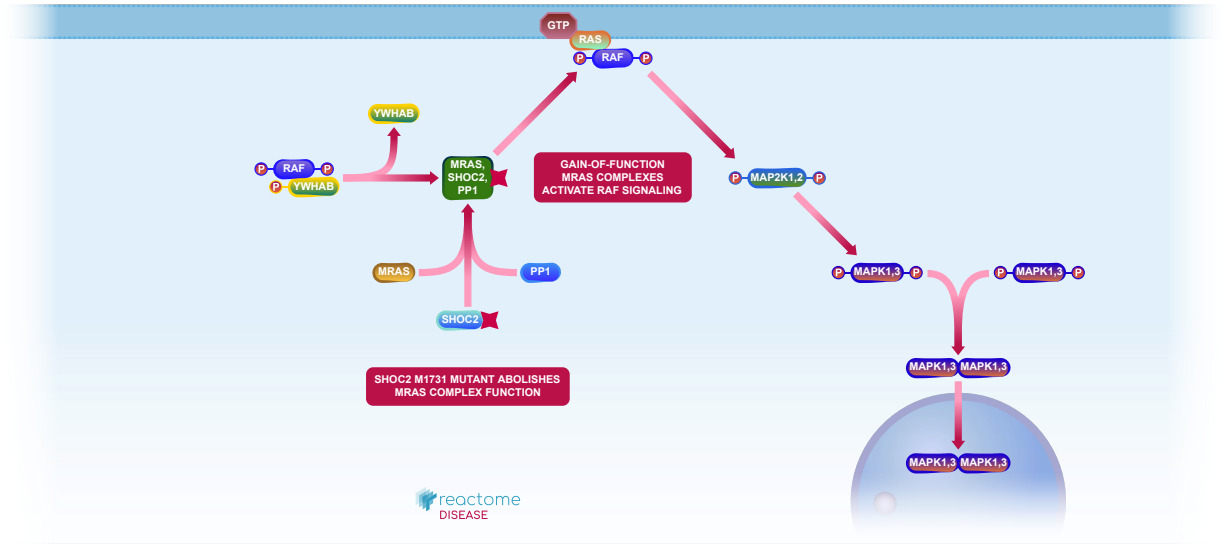
Signaling by MRAS-complex mutants



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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. ↗

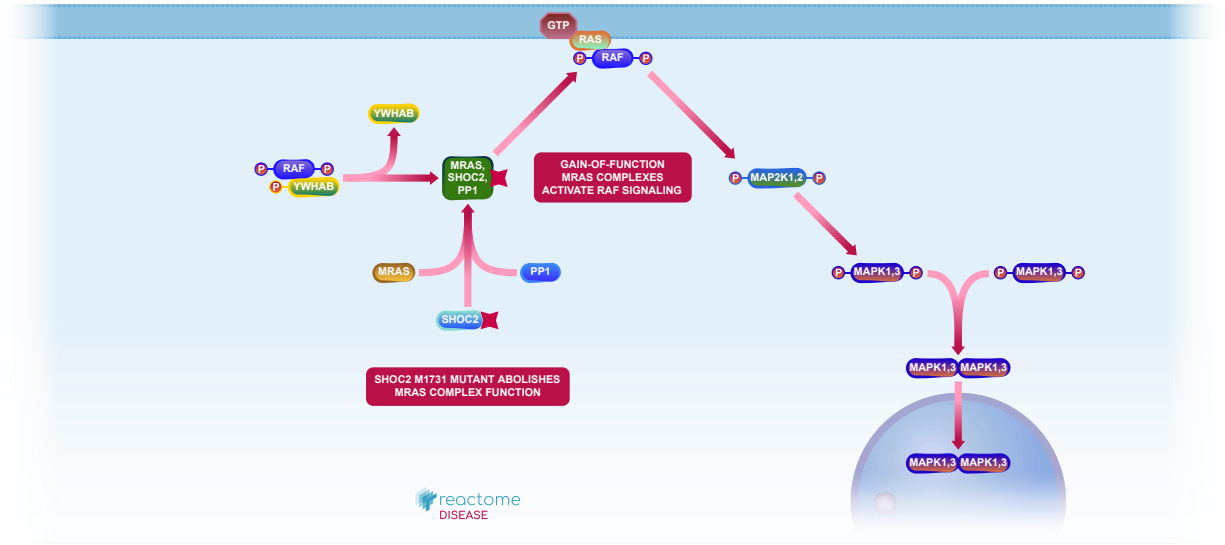
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Signaling by MRAS-complex mutants ↗

Stable identifier: R-HSA-9660537

Diseases: esophageal carcinoma, Noonan syndrome



A complex of MRAS, SHOC2 and the phosphatase PP1 contributes to the activation of RAF proteins by removing an inhibitory phosphorylation that mediates binding to 14-3-3 (also known as YWHAB) proteins (Rodriguez-Viciano et al, 2006; Young et al, 2013;reviewed in Simanshu et al, 2017; Lavoie and Therrien, 2015). Activating and inactivating mutations in each of the components of this dephosphorylating complex have been identified in RASopathies as well as at low frequency in some cancers (Cordeddu et al, 2009; Hannig et al, 2014; Gripp et al, 2016; Higgin et al, 2017; Motta et al, 2016; Motta et al, 2019a,b).

Literature references

De Luca, A., Petrini, S., Pantaleoni, F., Mastromoro, G., D'Ambrosio, V., Pinna, V. et al. (2019). Clinical and functional characterization of a novel RASopathy-causing SHOC2 mutation associated with prenatal-onset hypertrophic cardiomyopathy. *Hum. Mutat., 40*, 1046-1056. ↗

Zenker, M., Martinelli, S., Di Schiavi, E., Cordeddu, V., Ferrero, GB., Cardinale, A. et al. (2009). Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. *Nat. Genet., 41*, 1022-6. ↗

Young, LC., Ghatrora, R., Gewinner, C., Bender, S., Hartig, N., Burlingame, AL. et al. (2013). An MRAS, SHOC2, and SCRIB complex coordinates ERK pathway activation with polarity and tumorigenic growth. *Mol. Cell, 52*, 679-92. ↗

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Aldinger, KA., Bennett, JT., Sol-Church, K., Baker, L., Timms, AE., Powell-Hamilton, N. et al. (2016). A novel rasopathy caused by recurrent de novo missense mutations in PPP1CB closely resembles Noonan syndrome with loose anagen hair. *Am. J. Med. Genet. A, 170*, 2237-47. ↗

Editions

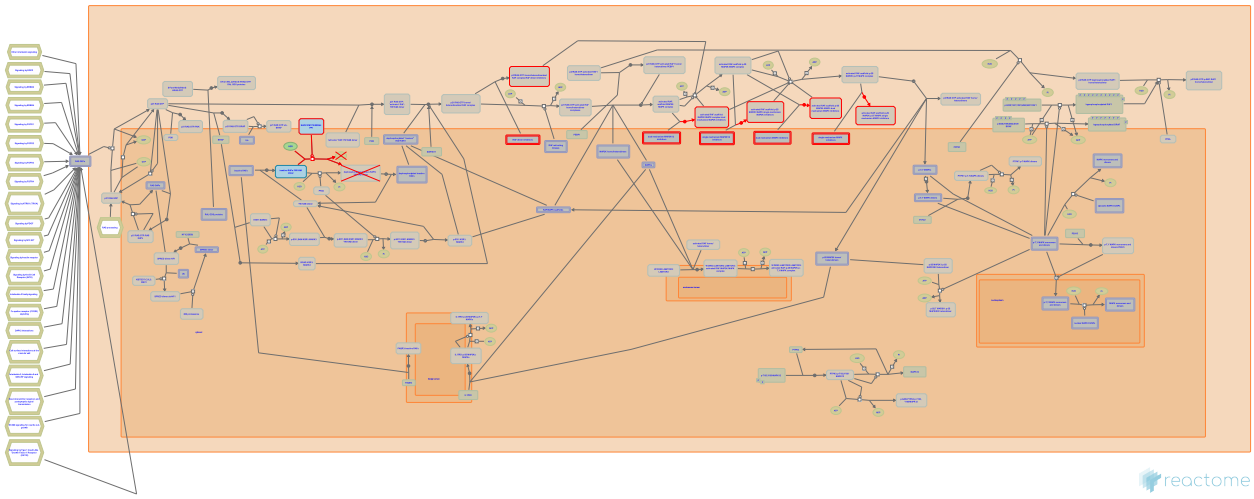
2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

SHOC2 M1731 mutant abolishes MRAS complex function ↗

Location: Signaling by MRAS-complex mutants

Stable identifier: R-HSA-9726840

Diseases: Noonan syndrome



This pathway describes the effect of a loss-of-function mutation in SHOC2 on RAF activation (Rodriguez-Viciano et al, 2006; Hannig et al, 2014). How both loss- and gain-of-function SHOC2 mutants can contribute to RAF pathway activation remains to be elucidated.

Literature references

Hannig, V., Galperin, E., Phillips, JA., Jeoung, M., Jang, ER. (2014). A Novel SHOC2 Variant in Rasopathy. *Hum. Mutat., 35*, 1290-4. ↗

McCormick, F., Fried, M., Burlingame, A., Oses-Prieto, J., Rodriguez-Viciana, P. (2006). A phosphatase holoenzyme comprised of Shoc2/Sur8 and the catalytic subunit of PP1 functions as an M-Ras effector to modulate Raf activity. *Mol. Cell, 22*, 217-30. ↗

Editions

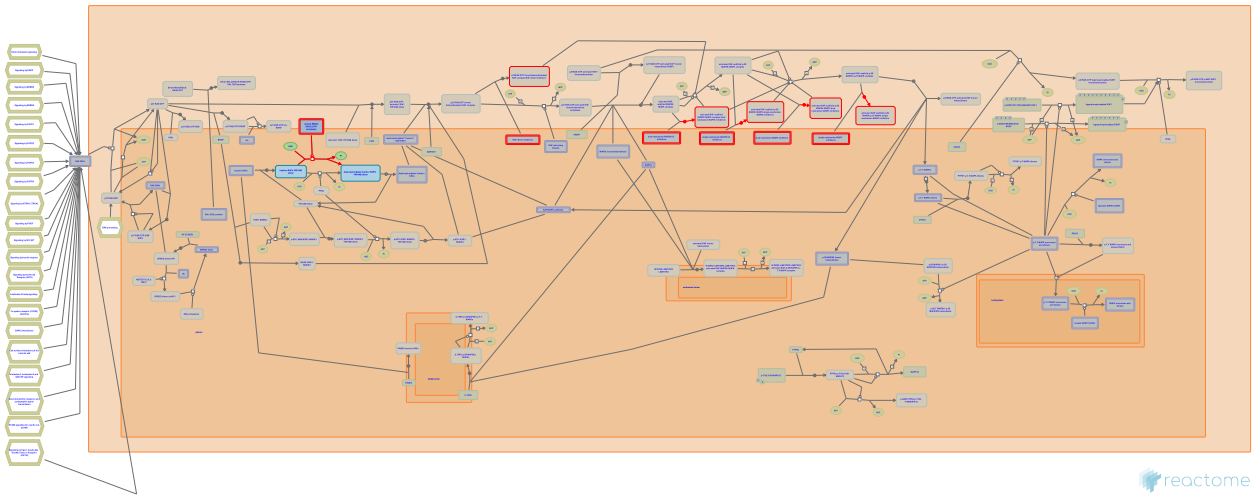
2019-10-25	Authored, Edited	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.

Gain-of-function MRAS complexes activate RAF signaling ↗

Location: Signaling by MRAS-complex mutants

Stable identifier: R-HSA-9726842

Diseases: esophageal carcinoma, Noonan syndrome



This pathway describes the effect of activating mutations of MRAS-complex components on RAF activation (reivewed in Simanshu et al, 2017).

Literature references

McCormick, F., Nissley, DV., Simanshu, DK. (2017). RAS Proteins and Their Regulators in Human Disease. *Cell, 170*, 17-33. ↗

Editions

2019-10-25	Authored, Edited	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.

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