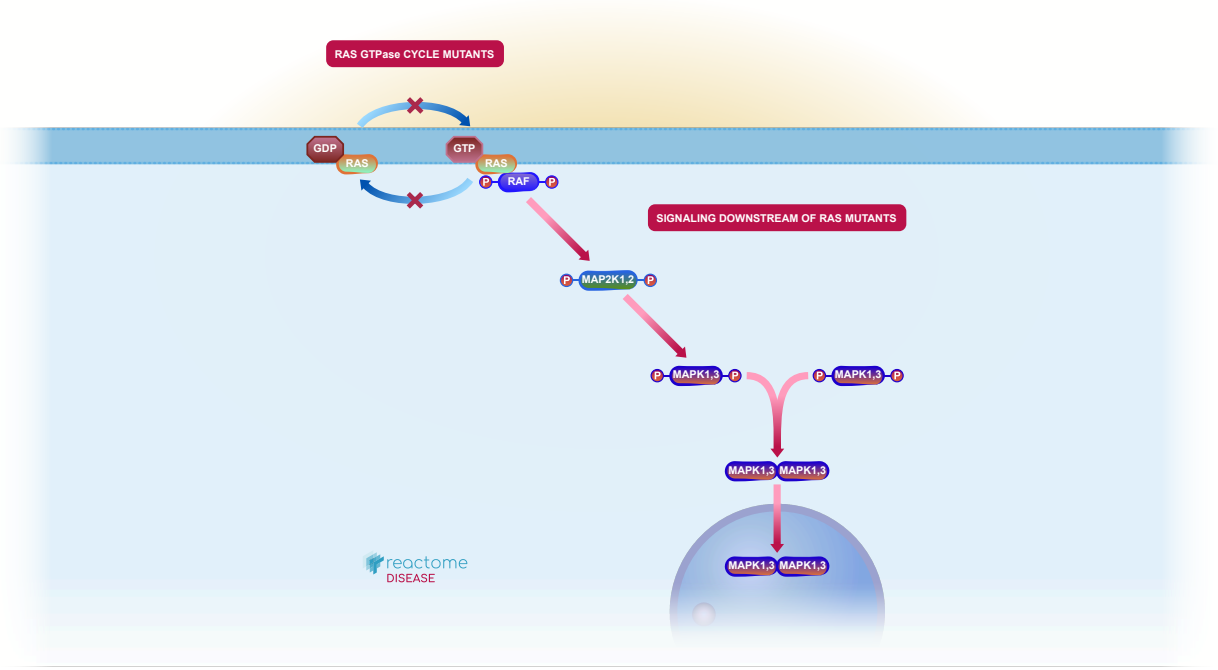
Signaling by RAS mutants



Rothfels, K., Stephens, RM.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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. ↗

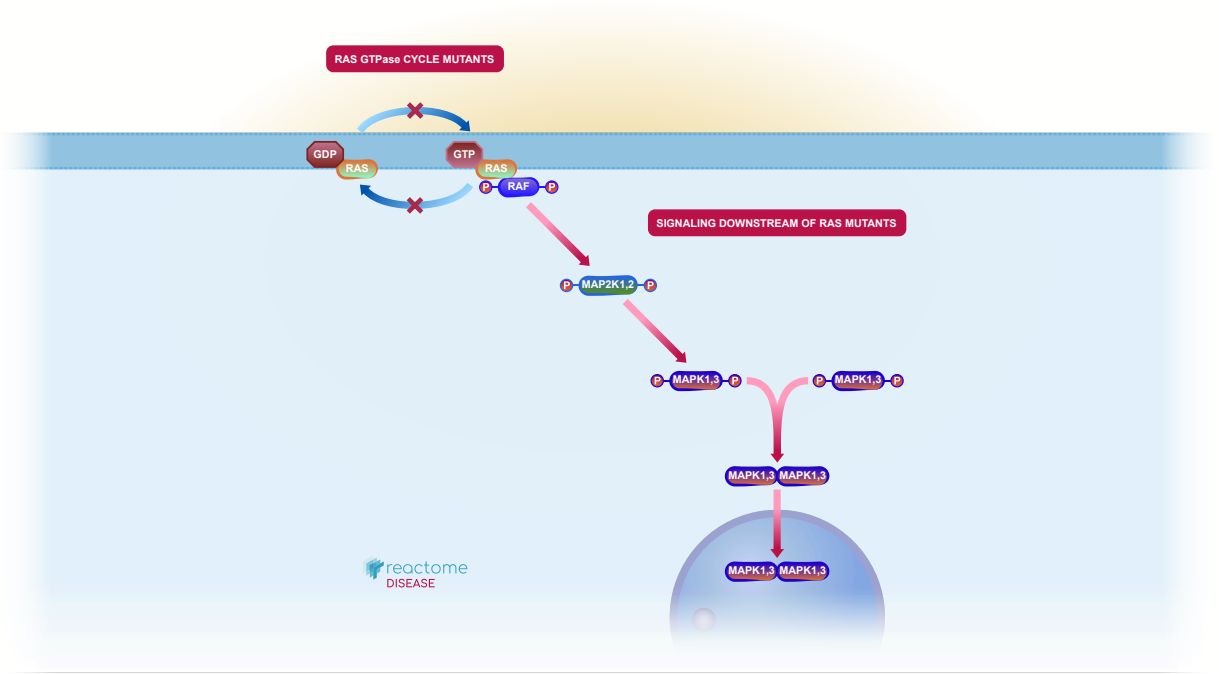
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Signaling by RAS mutants ↗

Stable identifier: R-HSA-6802949

Diseases: cancer, Noonan syndrome



Members of the RAS gene family were the first oncogenes to be identified, and mutations in RAS are present in ~20-30% of human cancers (reviewed in Prior et al, 2012). Mutations in the KRAS gene are the most prevalent, and are found with high frequency in colorectal cancer, non-small cell lung cancer and pancreatic cancer, among others. The reasons for the lower prevalence of HRAS and NRAS mutations in human cancers are not fully understood, but may reflect gene-specific functions as well as differential codon usage and spatio-temporal regulation (reviewed in Prior et al, 2012; Stephen et al, 2014; Pylayeva-Gupta et al, 2011). Activating RAS mutations contribute to cellular proliferation, transformation and survival by activating the MAPK signaling pathway, the AKT pathway and the RAL GDS pathway, among others (reviewed in Stephen et al, 2014; Pylayeva-Gupta et al, 2011).

Although the frequency and distribution varies between RAS genes and cancer types, the vast majority of activating RAS mutations occur at one of three residues - G12, G13 and Q61. Mutations at these sites favour the RAS:GTP bound form and yield constitutively active versions of the protein (reviewed in Prior et al, 2012).

Literature references

Grabocka, E., Pylayeva-Gupta, Y., Bar-Sagi, D. (2011). RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer, 11*, 761-74. ↗

Lewis, PD., Mattos, C., Prior, IA. (2012). A comprehensive survey of Ras mutations in cancer. *Cancer Res., 72*, 2457-67. ↗

McCormick, F., Stephen, AG., Bagni, RK., Esposito, D. (2014). Dragging ras back in the ring. *Cancer Cell, 25*, 272-81. ↗

Editions

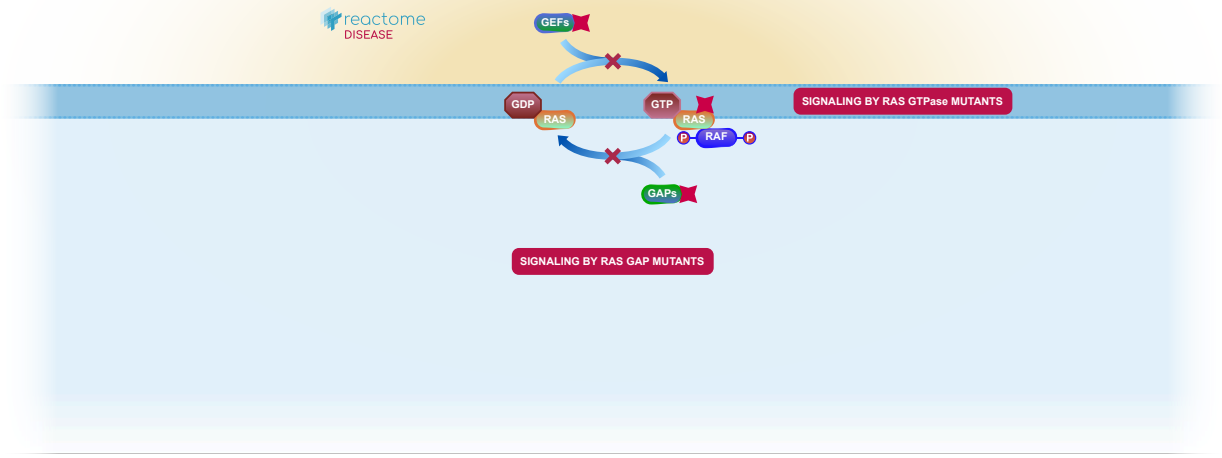
2015-05-18	Authored	Rothfels, K.
2015-08-10	Edited	Rothfels, K.
2016-08-05	Reviewed	Stephens, RM.

RAS GTPase cycle mutants ↗

Location: Signaling by RAS mutants

Stable identifier: R-HSA-9649913

Diseases: cancer



RAS proteins cycle between an active GTP-bound state and an inactive GDP-bound state. GTPase activating proteins (GAPs) stimulate the low intrinsic GTPase activity of RAS proteins, converting the active to the inactive form, while guanine nucleotide exchange factors (GEFs) stimulate the intrinsic dissociation of GDP, allowing its replacement with GTP and consequent activation of RAS. Disease-causing mutations in RAS promote constitutive signaling by favouring the accumulation of RAS:GTP. The vast majority of these mutations are loss of function mutations at G12, G13 and Q61. These mutations disrupt the GTPase activity of RAS proteins by interfering with nucleophilic attack on the gamma phosphate of GTP. A smaller proportion of RAS mutations increase the intrinsic GDP dissociation rate, while other mutations interfere with RAS interactions with GAPs (reviewed in Prior et al, 2012; Pylayeva-Gupta et al, 2011; Stephen et al, 2014; Samatar and Poulikakos, 2014).

Literature references

Grabocka, E., Pylayeva-Gupta, Y., Bar-Sagi, D. (2011). RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer, 11*, 761-74. ↗

Lewis, PD., Mattos, C., Prior, IA. (2012). A comprehensive survey of Ras mutations in cancer. *Cancer Res., 72*, 2457-67. ↗

Poulikakos, PI., Samatar, AA. (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov, 13*, 928-42. ↗

McCormick, F., Stephen, AG., Bagni, RK., Esposito, D. (2014). Dragging ras back in the ring. *Cancer Cell, 25*, 272-81. ↗

Editions

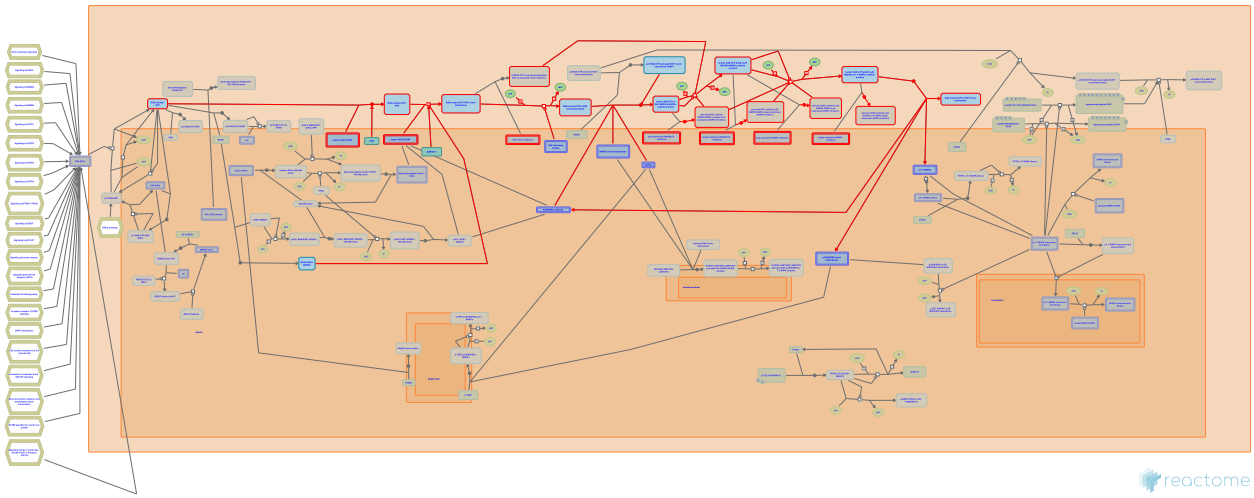
2015-05-18	Authored	Rothfels, K.
2016-08-05	Reviewed	Stephens, RM.

Signaling downstream of RAS mutants ↗

Location: Signaling by RAS mutants

Stable identifier: R-HSA-9649948

Diseases: cancer



Disease-causing mutations in RAS favour the active RAS:GTP bound form and yield constitutively active forms of the protein (reviewed in Prior et al, 2011; Maertens and Cichowski, 2014). Mutations in RAS contribute to cellular proliferation, transformation and survival by activating the MAPK signaling pathway, the AKT pathway and the RAL GDS pathway, among others (reviewed in Stephen et al, 2014; Pylayeva-Gupta et al, 2011)

Literature references

Grabocka, E., Pylayeva-Gupta, Y., Bar-Sagi, D. (2011). RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer, 11*, 761-74. ↗

Cichowski, K., Maertens, O. (2014). An expanding role for RAS GTPase activating proteins (RAS GAPs) in cancer. *Adv Biol Regul, 55*, 1-14. ↗

Lewis, PD., Mattos, C., Prior, IA. (2012). A comprehensive survey of Ras mutations in cancer. *Cancer Res., 72*, 2457-67. ↗

McCormick, F., Stephen, AG., Bagni, RK., Esposito, D. (2014). Dragging ras back in the ring. *Cancer Cell, 25*, 272-81. ↗

Editions

2015-05-18	Authored	Rothfels, K.
2016-08-05	Reviewed	Stephens, RM.

Table of Contents