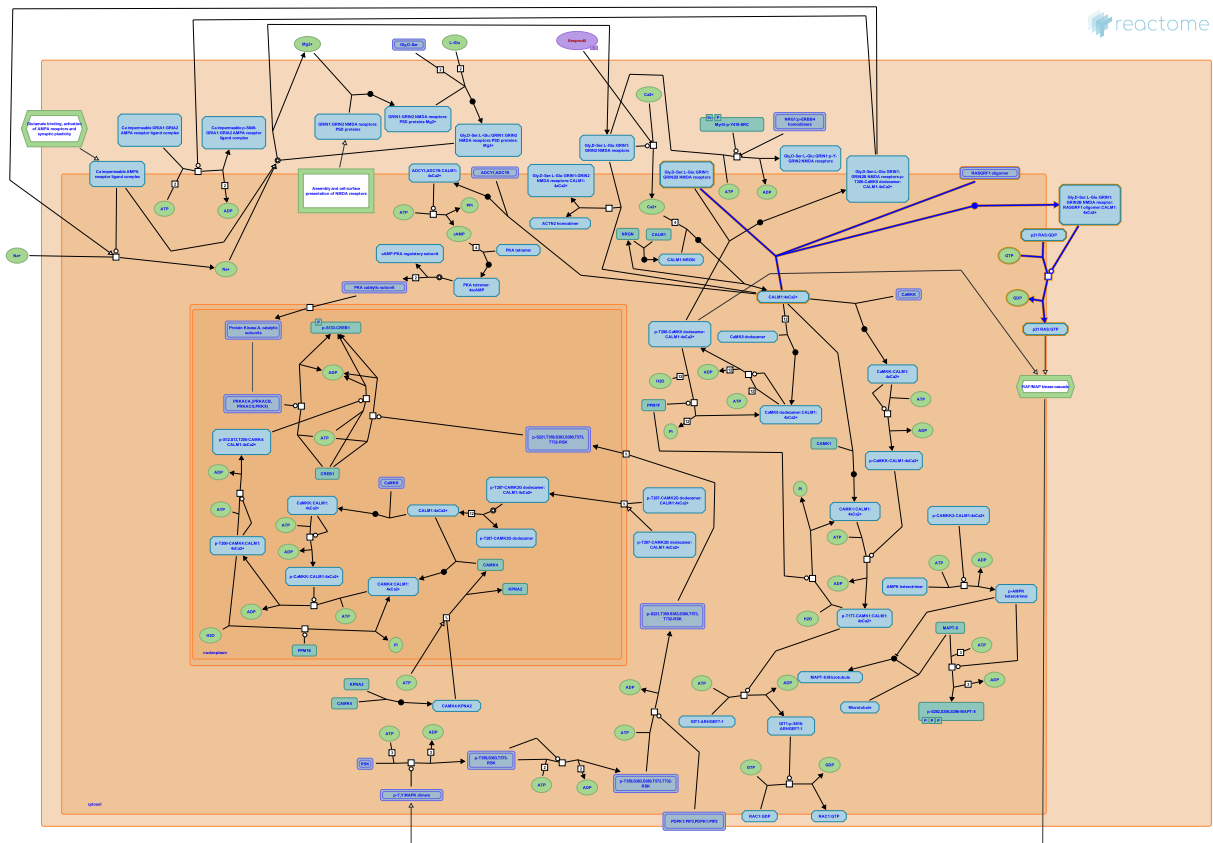


# Ras activation upon Ca<sup>2+</sup> influx through NMDA receptor



Gillespie, ME., Hansen, KB., Mahajan, SS., Orlic-Milacic, M., Tukey, D., Yi, F.

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

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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

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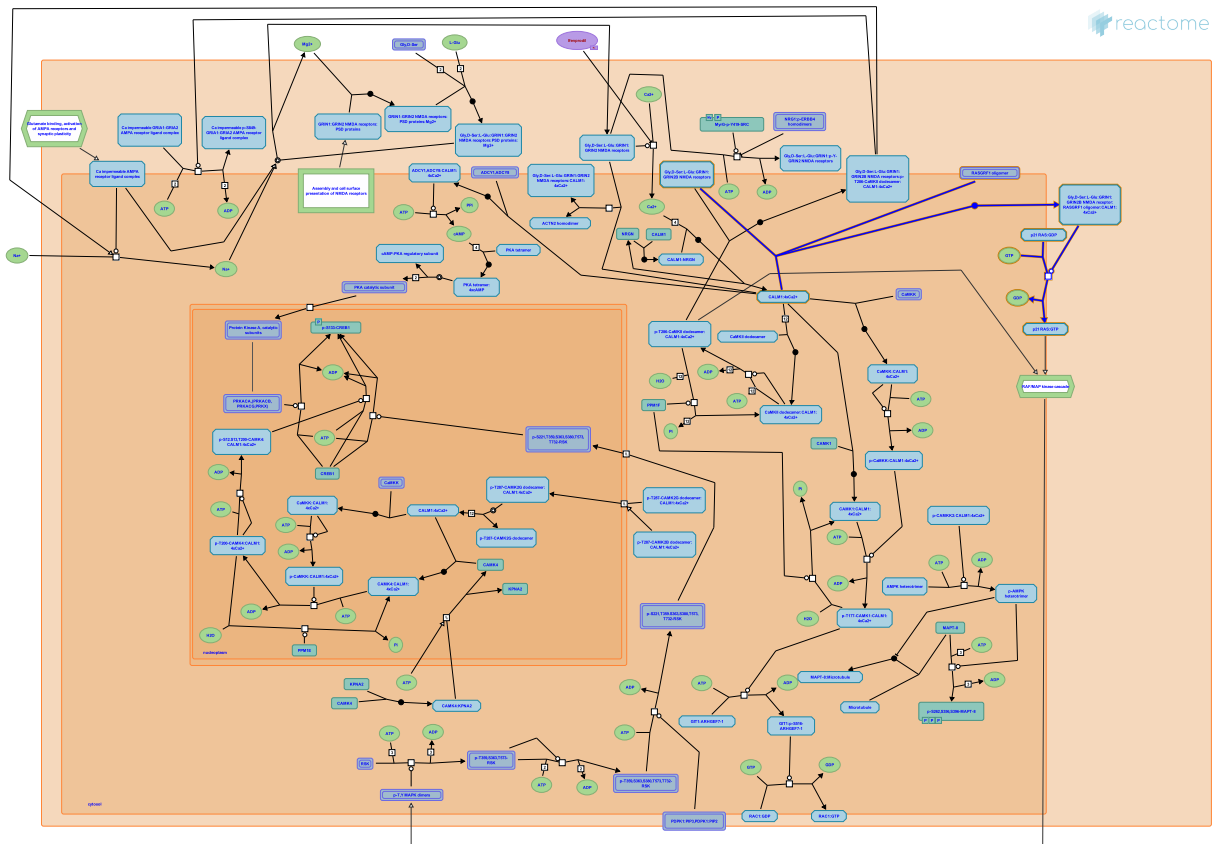
Reactome database release: 74

This document contains 1 pathway and 2 reactions ([see Table of Contents](#))

# Ras activation upon Ca<sup>2+</sup> influx through NMDA receptor ↗

Stable identifier: R-HSA-442982

Compartments: plasma membrane, cytosol



Ca<sup>2+</sup> influx through the NMDA receptor triggers RAS signaling through the activation of RAS guanyl nucleotide exchange factor RasGRF (Krapivinsky et al. 2003).

## Literature references

Krapivinsky, G., Krapivinsky, L., Manasian, Y., Ivanov, A., Tyzio, R., Pellegrino, C. et al. (2003). The NMDA receptor is coupled to the ERK pathway by a direct interaction between NR2B and RasGRF1. *Neuron*, 40, 775-84. ↗

## Editions

2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2009-11-19	Edited	Gillespie, ME.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

## Activation of RasGRF ↗

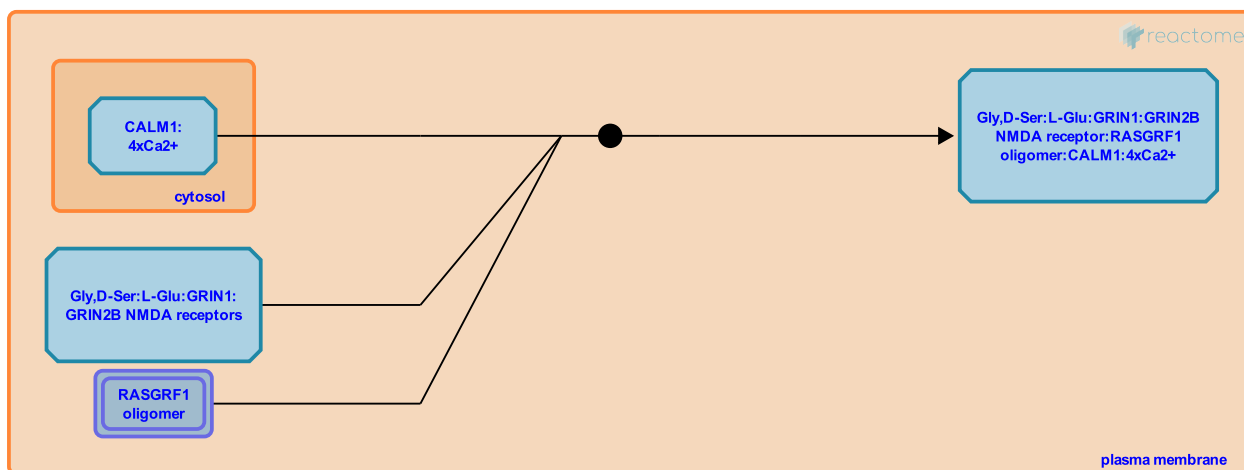
**Location:** [Ras activation upon Ca<sup>2+</sup> influx through NMDA receptor](#)

**Stable identifier:** R-HSA-442760

**Type:** binding

**Compartments:** plasma membrane, cytosol, extracellular region

**Inferred from:** [Rasgrf1 oligomers bind GluN1:GluN2B \(Grin1:Grin2b\) di-heterotetramers \(Rattus norvegicus\)](#)



After Ca<sup>2+</sup> influx through the activated NMDA receptors, RASGRF1 homooligomers and heterooligomers with RASGRF2 are activated by binding to the Ca<sup>2+</sup>:Calmodulin complex (CALM1:4xCa<sup>2+</sup>) and by associating with the GluN1:GluN2B (GRIN1:GRIN2B) NMDA receptors through direct interaction between GluN2B and RASGRF1 (Anborgh et al. 1999, Krapivinsky et al. 2003).

**Followed by:** [NMDA-activated RASGRF1 activates RAS](#)

## Literature references

Anborgh, PH., Qian, X., Papageorge, AG., Vass, WC., DeClue, JE., Lowy, DR. (1999). Ras-specific exchange factor GRF: oligomerization through its Dbl homology domain and calcium-dependent activation of Raf. *Mol Cell Biol*, 19, 4611-22. ↗

Krapivinsky, G., Krapivinsky, L., Manasian, Y., Ivanov, A., Tyzio, R., Pellegrino, C. et al. (2003). The NMDA receptor is coupled to the ERK pathway by a direct interaction between NR2B and RasGRF1. *Neuron*, 40, 775-84. ↗

## Editions

2009-06-02	Edited	Gillespie, ME.
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2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

## NMDA-activated RASGRF1 activates RAS ↗

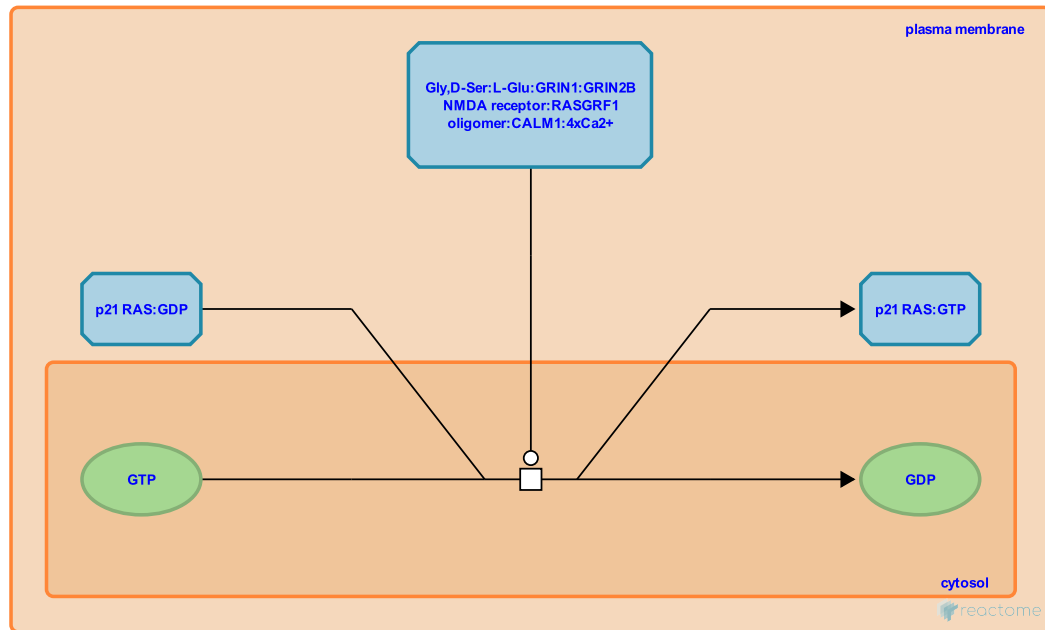
**Location:** Ras activation upon Ca<sup>2+</sup> influx through NMDA receptor

**Stable identifier:** R-HSA-442732

**Type:** transition

**Compartments:** cytosol, plasma membrane, extracellular region

**Inferred from:** Rasgrf1 promotes activation of HRAS (Rattus norvegicus)



Binding of RASGRF1 oligomers (Anborgh et al. 1999) to calcium-activated calmodulin (CALM1:4xCa<sup>2+</sup>) stimulates GDP to GTP exchange on RAS, resulting in RAS activation (Farnsworth et al. 1995). Binding of RASGRF1 to the GluN2B (GRIN2B, NR2B) subunit of NMDA receptors is needed for activation of RAS downstream of NMDA receptor activation (Krapivinsky et al. 2003).

Activated CaMKII can contribute to activation of RAS/RAF/MAPK signaling by phosphorylation of RAF1 (Salzano et al. 2012).

**Preceded by:** Activation of RasGRF

### Editions

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2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-10-10	Revised	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

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