Signaling by ERBB2 TMD/JMD mutants

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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.

16/11/2022
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


Reactome database release: 82

This document contains 1 pathway and 13 reactions (see Table of Contents)
Recurrent missense mutations in regions encoding the transmembrane domain (TMD) and the juxtamembrane domain (JMD) are frequently reported in cancer. The ERBB2 TMD mutants include ERBB2 V659E, ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 S653C, ERBB2 R677L and ERBB2 R678Q. The ERBB2 JMD mutants include ERBB2 E693K and ERBB2 Q709L. ERBB2 TMD mutants ERBB2 V659E, ERBB2 G660D and S653C (de Martino et al. 2014) are known to be activating. ERBB2 TMD/JMD mutants ERBB2 R678Q, ERBB2 E693K, and ERBB2 Q709L mutations may be activating when co-expressed with a wild type ERBB2 receptor (Pahuja et al. 2018). TMD and JMD mutations can activate ERBB2 signaling by improving the active dimer interface or by stabilizing the active conformation. TMD/JMD mutants that are activating in the presence of wild type ERBB2, such as ERBB2 R678Q, may form homodimers with the wild type ERBB2 (Pahuja et al. 2018).

Based on trans-autophosphorylation of ERBB2 and its dimerization partners EGFR and ERBB3, the following ERBB2 TMD/JMD mutants are assumed to form heterodimers with EGFR and ERBB3:

ERBB2 S653C (de Martino et al. 2014)

ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018).

Phosphorylation of tyrosine residues in the C-tail of ERBB2 was shown for the following ERBB2 TMD/JMD mutants:

ERBB2 V659E (Pahuja et al. 2018);

ERBB2 V659K (Pahuja et al. 2018);

ERBB2 G660D (Pahuja et al. 2018);

ERBB2 G660R (Pahuja et al. 2018);

ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1248 demonstrated);

ERBB2 R677L (Pahuja et al. 2018);

ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1248 demonstrated; Pahuja et
Phosphorylation of tyrosine residues in the C-tail of EGFR was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1068) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1068).

Phosphorylation of tyrosine residues in the C-tail of ERBB3 was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1197) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1197).

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1.

Activation of downstream PLCG1 signaling was demonstrated for ERBB2 R678Q, through activating tyrosine phosphorylation on PLCG1 (Bose et al. 2013).

Activation of PI3K/AKT signaling by ERBB2 TMD/JMD mutants has not been tested.

Signaling by ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 R677L, ERBB2 E693K and ERBB2 Q709L has not been sufficiently studied and they are annotated as candidates.

The following ERBB2 TMD/JMD mutants are sensitive to the therapeutic antibody trastuzumab (herceptin):

- ERBB2 V659E (Pahuja et al. 2018);
- ERBB2 G660D (Pahuja et al. 2018);
- ERBB2 G660R (Pahuja et al. 2018);
- ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
- ERBB2 Q709L (Pahuja et al. 2018);

With respect to pertuzumab, a therapeutic antibody that block ligand-driven heterodimerization of ERBB2, ERBB2 R678Q is sensitive to pertuzumab, while ERBB2 V659E, ERBB2 G660D, ERBB2 G660R and probably ERBB2 Q709L are resistant (Pahuja et al. 2018).

The following ERBB2 TMD/JMD mutants are sensitive to lapatinib:

- ERBB2 S653C (de Martino et al. 2014);
- ERBB2 R678Q (Bose et al. 2013);

The following ERBB2 TMD/JMD mutants are sensitive to neratinib:

- ERBB2 V659E (Pahuja et al. 2018);
- ERBB2 G660D (Pahuja et al. 2018);
- ERBB2 G660R (Pahuja et al. 2018);
- ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
- ERBB2 Q709L (Pahuja et al. 2018);

The following ERBB2 TMD/JMD mutants are sensitive to afatinib:
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 S653C (de Martino et al. 2014);
ERBB2 R678Q (Pahuja et al. 2018);
ERBB2 Q709L (Pahuja et al. 2018).

Literature references


Editions

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ERBB2 TMD/JMD mutants heterodimerize

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665697

Type: dissociation

Compartments: plasma membrane

Diseases: cancer

TMD/JMD mutants that are activating in the presence of wild type ERBB2, such as ERBB2 R678Q, may form homodimers with the wild type ERBB2 (Pahuja et al. 2018).

Based on trans-autophosphorylation of ERBB2 and its dimerization partners EGFR and ERBB3, the following ERBB2 TMD/JMD mutants are assumed to form heterodimers with EGFR and ERBB3:

ERBB2 S653C (de Martino et al. 2014)
ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018).

TMD/JMD mutants that are activating in the presence of wild type ERBB2, such as ERBB2 R678Q, may form homodimers with the wild type ERBB2 (Pahuja et al. 2018).

Signaling by ERBB2 V659E, ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 R677L, ERBB2 E693K and ERBB2 Q709L has not been sufficiently studied and they are annotated as candidates.

Followed by: ERBB2 TMD/JMD heterodimers trans-autophosphorylate

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ERBB2 TMD/JMD heterodimers trans-autophosphorylate

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665709

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer

Phosphorylation of tyrosine residues in the C-tail of ERBB2 was shown for the following ERBB2 TMD/JMD mutants:

ERBB2 V659E (Pahuja et al. 2018);
ERBB2 V659K (Pahuja et al. 2018);
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1248 demonstrated);
ERBB2 R677L (Pahuja et al. 2018);
ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1248 demonstrated; Pahuja et al. 2018); ERBB2 Q709L (Pahuja et al. 2018)

Phosphorylation of tyrosine residues in the C-tail of EGFR was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1068) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1068).

Phosphorylation of tyrosine residues in the C-tail of ERBB3 was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1197) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1197).

Signaling by ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 R677L, ERBB2 E693K and ERBB2 Q709L has not been sufficiently studied and they are annotated as candidates.

Preceded by: ERBB2 TMD/JMD mutants heterodimerize
Followed by: Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind PLCG1, Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind GRB2:SOS1, Phosphorylated ERBB2 TMD/JMD heterodimers bind SHC1

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Phosphorylated ERBB2 TMD/JMD heterodimers bind SHC1

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665701

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1. It is assumed that heterodimers of ERBB2 TMD/JMD mutants, like the wild type ERBB2 heterodimers, bind SHC1.

Preceded by: ERBB2 TMD/JMD heterodimers trans-autophosphorylate

Followed by: Phosphorylated heterodimers of ERBB2 TMD/JMD mutants phosphorylate SHC1

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https://reactome.org
Phosphorylated heterodimers of ERBB2 TMD/JMD mutants phosphorylate SHC1

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665705

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1. It is assumed that heterodimers of ERBB2 TMD/JMD mutants, like the wild type ERBB2 heterodimers, bind to and phosphorylate SHC1.

Preceded by: Phosphorylated ERBB2 TMD/JMD heterodimers bind SHC1

Followed by: Phosphorylated heterodimers of ERBB2 TMD/JMD mutants recruit GRB2:SOS1 through SHC1

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Phosphorylated heterodimers of ERBB2 TMD/JMD mutants recruit GRB2:SOS1 through SHC1

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665699

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1. It is assumed that heterodimers of ERBB2 TMD/JMD mutants, like the wild type ERBB2 heterodimers, bind to and phosphorylate SHC1, leading to the recruitment of the GRB2:SOS1 complex.

**Preceded by:** Phosphorylated heterodimers of ERBB2 TMD/JMD mutants phosphorylate SHC1

**Followed by:** RAS activation by SOS1 bound to phosphorylated heterodimers of ERBB2 TMD/JMD mutants

**Literature references**


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RAS activation by SOS1 bound to phosphorylated heterodimers of ERBB2 TMD/JMD mutants

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665700

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1. It is assumed that heterodimers of ERBB2 TMD/JMD mutants, like the wild type ERBB2 heterodimers, bind to and phosphorylate SHC1, leading to the recruitment of the GRB2:SOS1 complex and activation of RAS through guanyl nucleotide exchange.

**Preceded by:** Phosphorylated heterodimers of ERBB2 TMD/JMD mutants recruit GRB2:SOS1 through SHC1

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Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind GRB2:SOS1

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665698

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3). It is assumed that heterodimers of ERBB2 TMD/JMD mutants and EGFR, like the wild type ERBB2:EGFR heterodimers, directly bind to GRB:SOS1 complex.

Preceded by: ERBB2 TMD/JMD heterodimers trans-autophosphorylate

Followed by: RAS activation by SOS1 bound to phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR

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RAS activation by SOS1 bound to phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665707

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3). It is assumed that heterodimers of ERBB2 TMD/JMD mutants and EGFR, like the wild type ERBB2:EGFR heterodimers, directly bind to GRB:SOS1 complex, resulting in activation of RAS signaling to guanyl nucleotide exchange on RAS.

**Preceded by:** Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind GRB2:SOS1

**Literature references**


Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind PLCG1

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665706

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** cancer

Activation of downstream PLCG1 signaling was demonstrated for ERBB2 R678Q, through activating tyrosine phosphorylation on PLCG1 (Bose et al. 2013). It is assumed that the heterodimer of ERBB2 R678Q and EGFR, like the wild type ERBB2:EGFR heterodimer, binds PLCG1.

**Preceded by:** ERBB2 TMD/JMD heterodimers trans-autophosphorylate

**Followed by:** Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR phosphorylate PLCG1

**Literature references**

Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR phosphorylate PLCG1

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665704

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

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Activation of downstream PLCG1 signaling was demonstrated for ERBB2 R678Q, through activating tyrosine phosphorylation on PLCG1 (Bose et al. 2013). It is assumed that the heterodimer of ERBB2 R678Q and EGFR, like the wild type ERBB2:EGFR heterodimer, binds to and phosphorylates PLCG1, leading to activation of PLCgamma1 signaling.

**Preceded by:** Phosphorylated heterodimers of ERBB2 TMD/JMD mutants and EGFR bind PLCG1

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ERBB2 TMD/JMD mutants bind TKIs

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665702

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

The following ERBB2 TMD/JMD mutants are sensitive to lapatinib:

- ERBB2 S653C (de Martino et al. 2014);
- ERBB2 R678Q (Bose et al. 2013);

The following ERBB2 TMD/JMD mutants are sensitive to neratinib:

- ERBB2 V659E (Pahuja et al. 2018);
- ERBB2 G660D (Pahuja et al. 2018);
- ERBB2 G660R (Pahuja et al. 2018);
- ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
- ERBB2 Q709L (Pahuja et al. 2018);

The following ERBB2 TMD/JMD mutants are sensitive to afatinib:

- ERBB2 G660D (Pahuja et al. 2018);
- ERBB2 G660R (Pahuja et al. 2018);
- ERBB2 S653C (de Martino et al. 2014);
- ERBB2 R678Q (Pahuja et al. 2018);
- ERBB2 Q709L (Pahuja et al. 2018).

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ERBB2 TMD/JMD mutants bind trastuzumab

**Location:** Signaling by ERBB2 TMD/JMD mutants

**Stable identifier:** R-HSA-9665696

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Diseases:** cancer

The following ERBB2 TMD/JMD mutants are sensitive to the therapeutic antibody trastuzumab (herceptin):

ERBB2 V659E (Pahuja et al. 2018);
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
ERBB2 Q709L (Pahuja et al. 2018);

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ERBB2 TMD/JMD mutants bind pertuzumab

Location: Signaling by ERBB2 TMD/JMD mutants

Stable identifier: R-HSA-9665703

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: cancer

ERBB2 R678Q is sensitive to pertuzumab (Pahuja et al. 2018).

Literature references

Editions

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