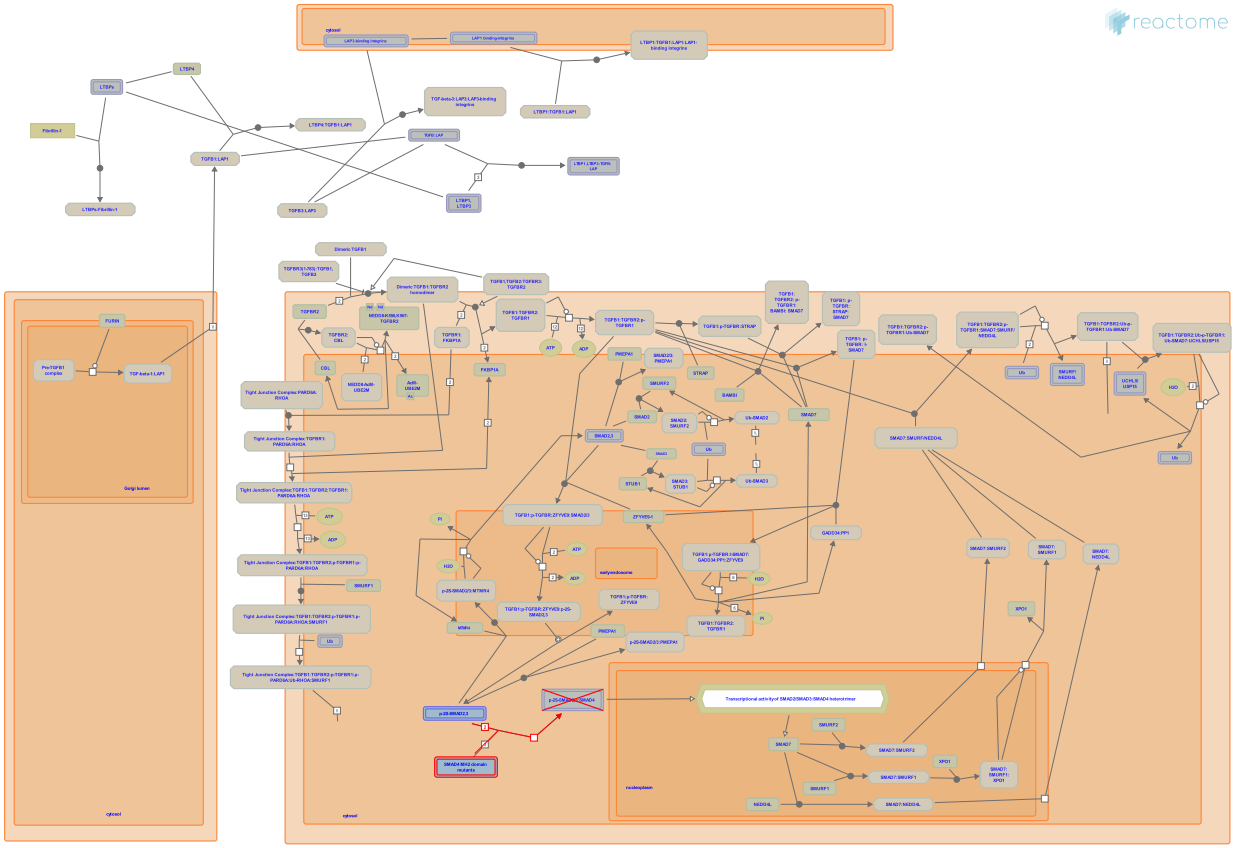
SMAD4 MH2 Domain Mutants in Cancer



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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.

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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. ↗

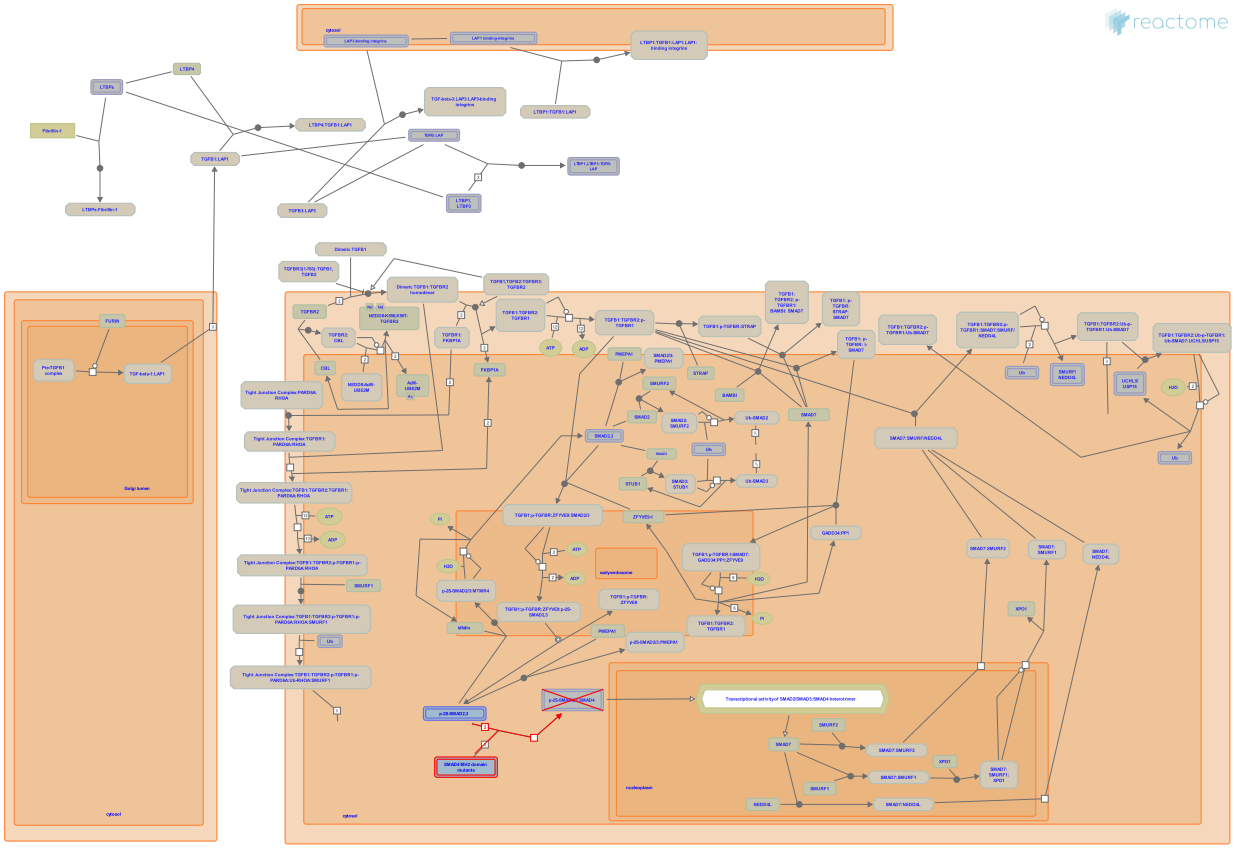
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

SMAD4 MH2 Domain Mutants in Cancer ↗

Stable identifier: R-HSA-3311021

Diseases: cancer



The MH2 domain of SMAD4 is the most frequently mutated SMAD4 region in cancer. MH2 domain mutations result in the loss of function of SMAD4 by abrogating the formation of transcriptionally active heterotrimers of SMAD4 and TGF-beta receptor complex-activated R-SMADs - SMAD2 and SMAD3 (Shi et al. 1997, Chacko et al. 2001, Chacko et al. 2004, Fleming et al. 2013).

The hotspot MH2 domain amino acid residues that are targeted by missense mutations are Asp351 (D351), Pro356 (P356) and Arg361 (R361). These three hotspot residues map to the L1 loop which is conserved in SMAD2 and SMAD3 and is involved in intermolecular interactions that contribute to the formation of SMAD heterotrimers and homotrimers (Shi et al. 1997, Fleming et al. 2013). Other frequently mutated residues in the MH2 domain of SMAD4 - Ala406 (A406), Lys428 (K428) and Arg515 (R515) - are involved in binding the phosphorylation motif (Ser-Ser-X-Ser) of SMAD2 and SMAD3, with Arg515 in the L3 loop being critical for this interaction (Chacko et al. 2001, Chacko et al. 2004, Fleming et al. 2013).

Literature references

Shi, G., De Caestecker, M., Lin, K., Chacko, BM., Hayward, LJ., Tiwari, A. et al. (2004). Structural basis of heteromeric smad protein assembly in TGF-beta signaling. *Mol Cell, 15*, 813-23. ↗

Pavletich, NP., Lo, RS., Hata, A., Shi, Y., Massagué, J. (1997). A structural basis for mutational inactivation of the tumour suppressor Smad4. *Nature, 388*, 87-93. ↗

Correia, JJ., Lam, SS., de Caestecker, MP., Qin, B., Chacko, BM., Lin, K. (2001). The L3 loop and C-terminal phosphorylation jointly define Smad protein trimerization. *Nat. Struct. Biol., 8*, 248-53. ↗

Mouradov, D., Jorissen, RN., Jones, IT., Tsui, C., Palmieri, M., Sieber, OM. et al. (2013). SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. *Cancer Res., 73*, 725-35. ↗

Editions

2013-05-03	Edited	Jassal, B.
2013-08-08	Authored, Reviewed	Akhurst, RJ.
2013-08-08	Authored, Reviewed	Meyer, S.
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SMAD4 MH2 Domain Mutants do not bind phosphorylated SMAD2 and SMAD3 ↗

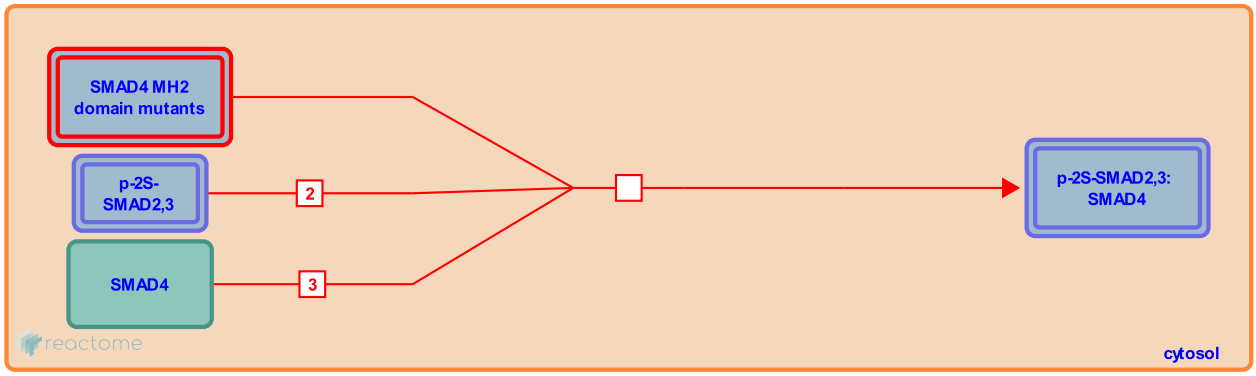
Location: SMAD4 MH2 Domain Mutants in Cancer

Stable identifier: R-HSA-3311014

Type: transition

Compartments: cytosol

Diseases: cancer



SMAD4 MH2 domain mutants are not able to form heterotrimers with phosphorylated SMAD2 and SMAD3 (Shi et al. 1997, Fleming et al. 2013) and regulate transcription of TGF-beta responsive genes, which leads to aberrant cell differentiation and proliferation even in the presence of tumor suppressive TGF-beta signaling.

The following SMAD4 MH2 domain mutants are annotated as members of the SMAD4 MH2 Domain Mutants set based on functional and structural studies that demonstrated their loss-of-function (LOF):
SMAD4 A406T (Fleming et al. 2013)
SMAD4 D351G (Fleming et al. 2013)
SMAD4 D351H (Shi et al. 1997, Fleming et al. 2013)
SMAD4 D351Y (Fleming et al. 2013)
SMAD4 D351del (Fleming et al. 2013)
SMAD4 K428T (Fleming et al. 2013)
SMAD4 P356L (Fleming et al. 2013)
SMAD4 P356R (Fleming et al. 2013)
SMAD4 R361C (Shi et al. 1997, Fleming et al. 2013)
SMAD4 R361H (Fleming et al. 2013)
SMAD4 R515T (Fleming et al. 2013)
The following SMAD4 MH2 domain missense mutants are annotated as candidate LOF mutants based on their similarity with characterized mutants:
SMAD4 K428R
SMAD4 R361G
SMAD4 R361S
The following SMAD4 MH2 domain nonsense mutants are annotated as candidate LOF mutants based on complete absence or truncation of the MH2 domain (amino acids 323-552):
SMAD4 G30*
SMAD4 E33*
SMAD4 E49*
SMAD4 E53*
SMAD4 Q83*
SMAD4 Y95*
SMAD4 W101*
SMAD4 E108*
SMAD4 Q116*
SMAD4 K122*
SMAD4 R135*
SMAD4 S138*
SMAD4 S144*
SMAD4 L146*
SMAD4 S154*
SMAD4 G168*

SMAD4 S171*
SMAD4 L172*
SMAD4 E175*
SMAD4 S178*
SMAD4 Q183*
SMAD4 Y195*
SMAD4 E205*
SMAD4 Q224*
SMAD4 Q239*
SMAD4 S242*
SMAD4 Q245*
SMAD4 Q248*
SMAD4 Q249*
SMAD4 Q250*
SMAD4 Q256*
SMAD4 Y260*
SMAD4 W268*
SMAD4 Y276*
SMAD4 Q289*
SMAD4 W302*
SMAD4 E307*
SMAD4 Q311*
SMAD4 E321*
SMAD4 Y322*
SMAD4 Y328*
SMAD4 E330*
SMAD4 Q334*
SMAD4 S343*
SMAD4 G352*
SMAD4 G358*
SMAD4 Q366*
SMAD4 E390*
SMAD4 W398*
SMAD4 Q410*
SMAD4 Y412*
SMAD4 E417*
SMAD4 Y430*
SMAD4 L440*
SMAD4 Q442*
SMAD4 C443*
SMAD4 R445*
SMAD4 Q448*
SMAD4 Q455*
SMAD4 G473*
SMAD4 G477*
SMAD4 W509*
SMAD4 G510*
SMAD4 Y513*
SMAD4 R515*
SMAD4 Q516*
SMAD4 E520*
SMAD4 W524*
SMAD4 E526*
SMAD4 Q534*
SMAD4 E538*

Literature references

Pavletich, NP., Lo, RS., Hata, A., Shi, Y., Massagué, J. (1997). A structural basis for mutational inactivation of the tumour suppressor Smad4. *Nature, 388*, 87-93. ↗

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