Loss of Function of SMAD4 in Cancer

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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Reactome database release: 88

This document contains 2 pathways (see Table of Contents)

Loss of Function of SMAD4 in Cancer ↗

Stable identifier: R-HSA-3304347

Diseases: cancer

SMAD4 was identified as a gene homozygously deleted in ~30% of pancreatic cancers and was named DPC4 (DPC stands for deleted in pancreatic cancer). SMAD4 maps to the chromosomal band 18q21.1, and about 90% of pancreatic carcinomas show allelic loss at chromosomal arm 18q (Hahn et al. 1996), while ~50% of pancreatic cancers show some alteration of the SMAD4 gene (reviewed by Schutte et al. 1999).

Based on COSMIC database (Catalogue Of Somatic Mutations In Cancer) (Forbes et al. 2011), mutations in the coding sequence of SMAD4 gene are frequently found in pancreatic cancer, biliary duct carcinoma and colorectal cancer (reviewed by Schutte et al. 1999). Germline SMAD4 mutations are the cause of juvenile polyposis, an autosomal dominant disease that predisposes affected individuals to hamartomatous polyps and gastrointestinal cancer (Howe et al. 1998). Homozygous Smad4 loss is embryonic lethal in mice (Takaku et al. 1998). Smad4 +/- heterozygotes appear normal but develop intestinal polyps between 6 and12 months of age and these polyps can progress to cancer. Loss of the remaining wild-type Smad4 allele is detectable only at later stages of tumor progression in Smad4+/- mice (Xu et al. 2000). Compound Apc+/-;Smad4+/- mice develop malignant tumors from intestinal polyps more rapidly than Apc+/- mice (Takaku et al. 1998).

SMAD4 coding sequence mutations are most frequently found in the MH2 domain and impair the formation of SMAD4 heterotrimers with phosphorylated SMAD2 and SMAD3 (Shi et al. 1997, Fleming et al. 2013), thereby impairing SMAD4:SMAD2/3 heterotrimer-mediated transcriptional regulation of TGF-beta responsive genes. MH2 domain is also involved in the formation of SMAD4 homotrimers which may play a role in SMAD4 protein stability (Shi et al. 1997).

Coding sequence mutations are also found in the MH1 domain of SMAD4. MH1 domain is involved in DNA binding (Dai et al. 1999) and it is also involved in the formation of SMAD4 homotrimers (Hata et al. 1997).

Literature references

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Editions

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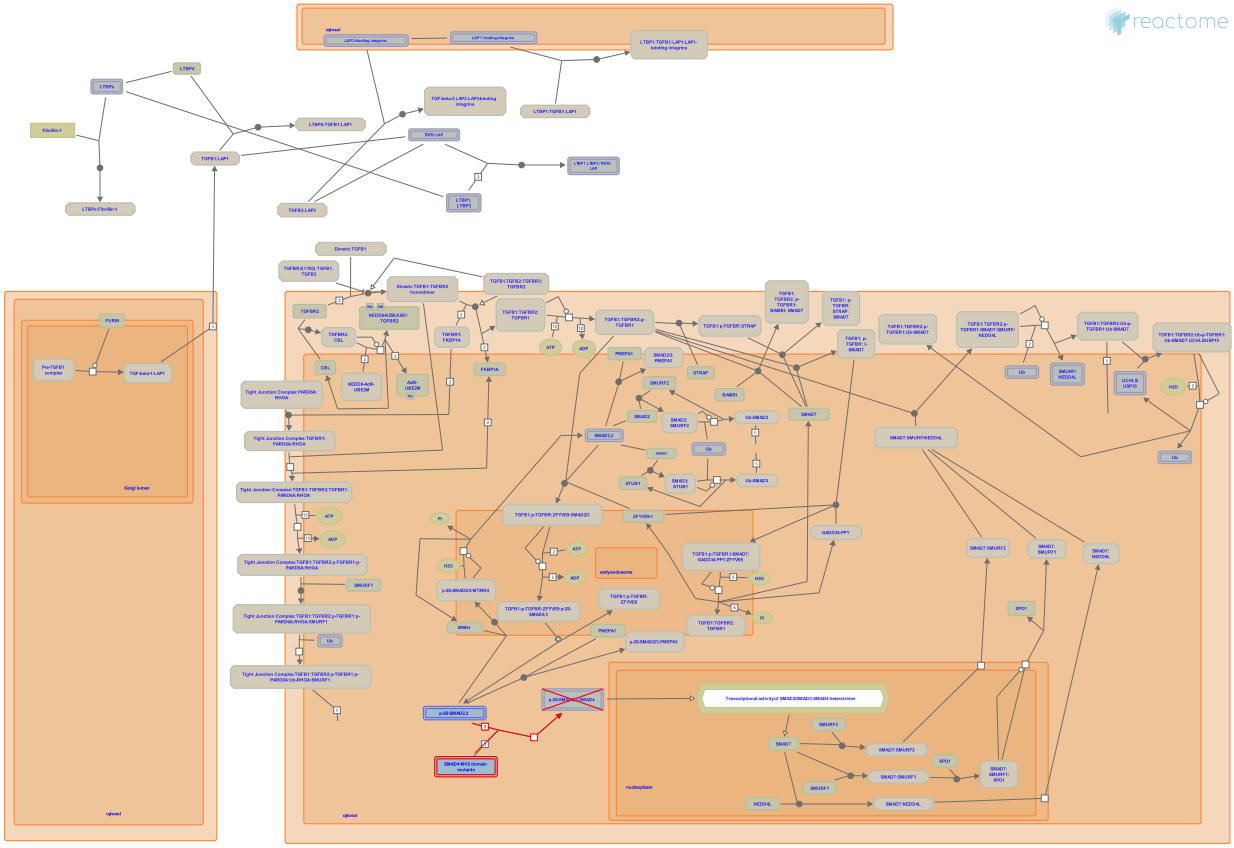
SMAD4 MH2 Domain Mutants in Cancer ↗

Location: Loss of Function of SMAD4 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

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