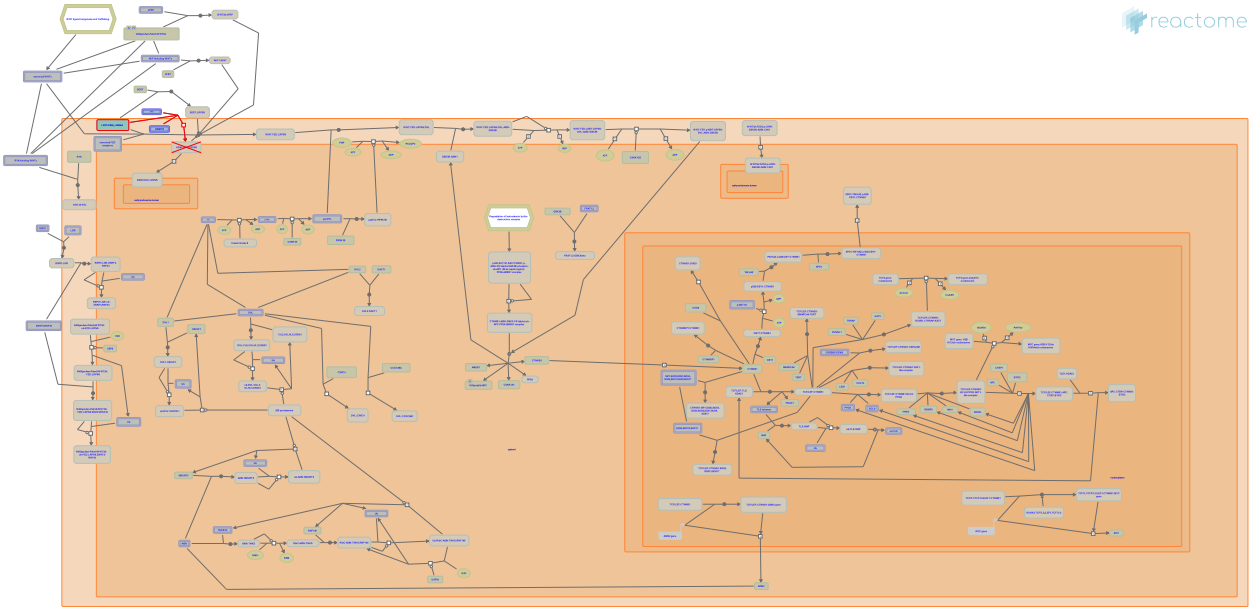
Signaling by LRP5 mutants



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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

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. ↗

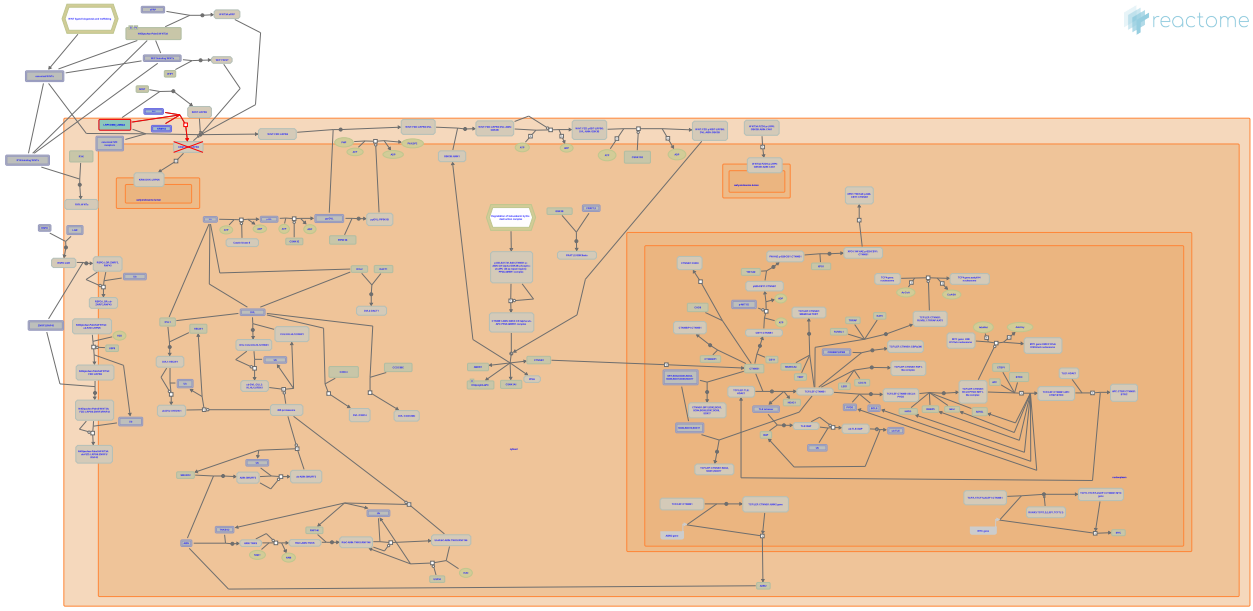
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by LRP5 mutants

Stable identifier: R-HSA-5339717

Compartments: cytosol

Diseases: parathyroid carcinoma, breast cancer



LRP5 is subject to an in-frame missplicing event in breast and parathyroid cancers that renders the protein insensitive to inhibition by the WNT antagonist DKK1. Expression of the mutant protein results in elevated levels of active, unphosphorylated beta-catenin and enhanced TCF-dependent WNT-signaling, promoting cellular proliferation (Bjorklund et al 2007a, b; Bjorklund et al, 2009).

Literature references

Björklund, P., Akerström, G., Olsson, AK., Westin, G., Svedlund, J. (2009). The internally truncated LRP5 receptor presents a therapeutic target in breast cancer. *PLoS ONE, 4*, e4243.

Björklund, P., Akerström, G., Westin, G. (2007). An LRP5 receptor with internal deletion in hyperparathyroid tumors with implications for deregulated WNT/beta-catenin signaling. *PLoS Med., 4*, e328.

Björklund, P., Akerström, G., Westin, G. (2007). Accumulation of nonphosphorylated beta-catenin and c-myc in primary and uremic secondary hyperparathyroid tumors. *J. Clin. Endocrinol. Metab., 92*, 338-44.

Editions

2014-02-22	Authored	Rothfels, K.
2014-04-03	Edited	Matthews, L.
2014-05-12	Reviewed	Salahshor, S.
2014-05-22	Reviewed	Woodgett, J.

misspliced mutants of LRP5 support enhanced beta-catenin-dependent signaling

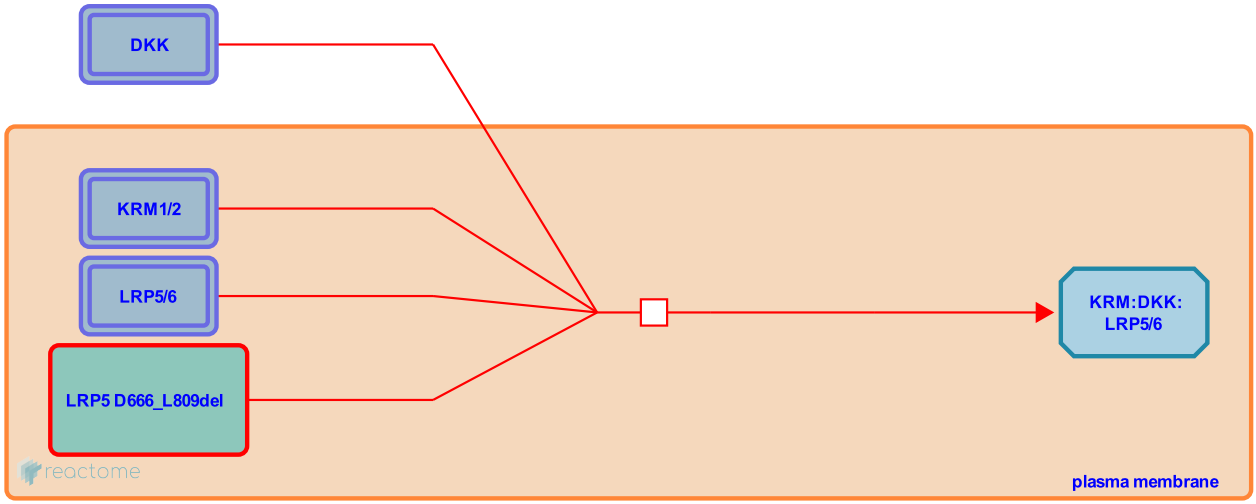
Location: Signaling by LRP5 mutants

Stable identifier: R-HSA-5339711

Type: transition

Compartments: plasma membrane

Diseases: cancer, parathyroid carcinoma, breast cancer



Frequent expression of an internally deleted LRP5 has been identified in parathyroid and breast cancers. Expression of the internally deleted LRP5 protein results in elevated levels of the active, unphosphorylated beta-catenin, enhanced expression of the both WNT-dependent reporter genes and the endogenous WNT-target gene MYC, and is required for cellular proliferation (Bjorklund et al, 2007a, b; Bjorklund et al, 2009). The in-frame internal deletion, which removes residues 666-809, arises through the aberrant use of cryptic splice sites in imperfect direct repeat sequences in exons 9 and 11 (Bjorklund et al, 2007b). This region has been shown to contain residues required for inhibition of beta-catenin activity by the negative regulator DKK1; consistent with this, expression of LRP5del666-809 is insensitive to inhibition by DKK1 (Zhang et al, 2004; Bjorklund et al, 2007b; Bjorklund et al, 2009). It has not been determined whether the LRP666-809del affects the interaction with SOST.

Literature references

Björklund, P., Akerström, G., Olsson, AK., Westin, G., Svedlund, J. (2009). The internally truncated LRP5 receptor presents a therapeutic target in breast cancer. *PLoS ONE, 4*, e4243.

Björklund, P., Akerström, G., Westin, G. (2007). An LRP5 receptor with internal deletion in hyperparathyroid tumors with implications for deregulated WNT/beta-catenin signaling. *PLoS Med., 4*, e328.

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