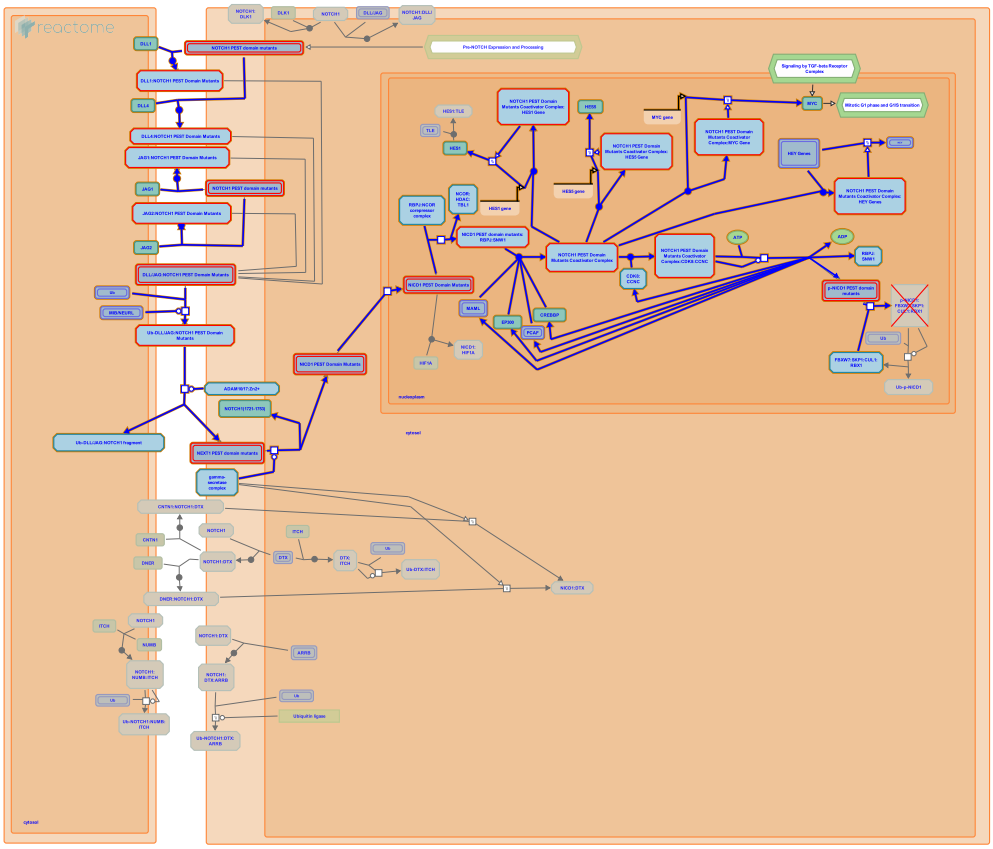
Constitutive Signaling by NOTCH1 PEST Domain Mutants



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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.

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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. ↗

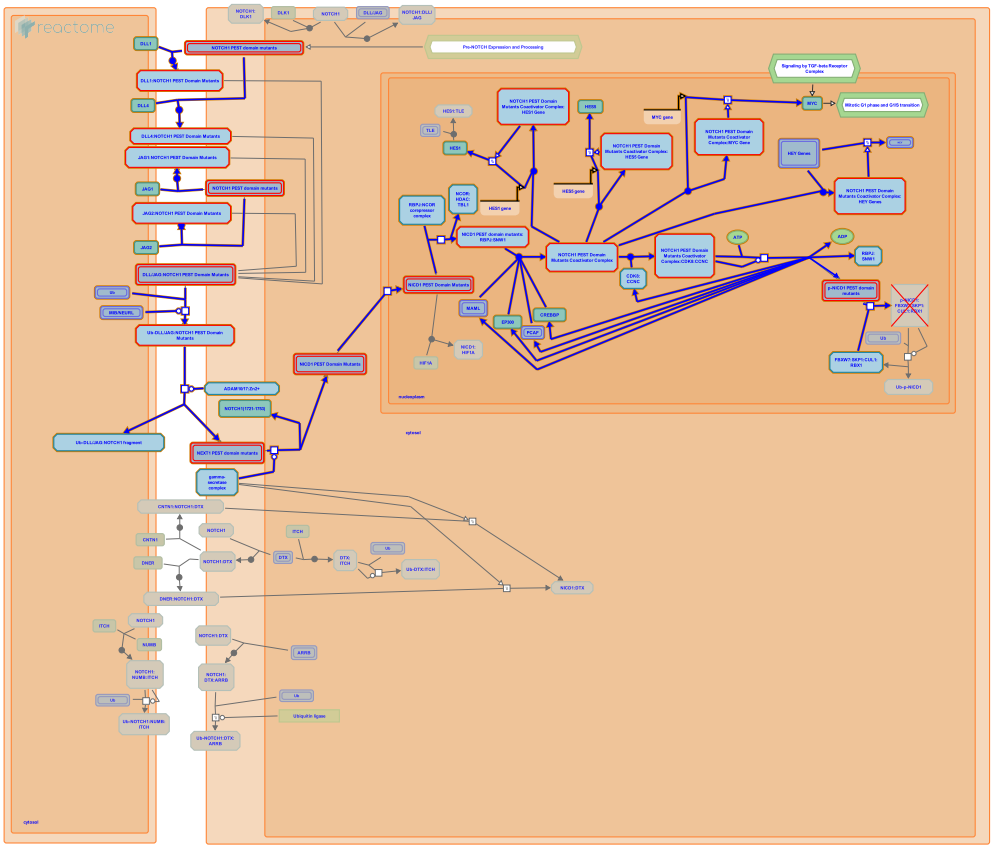
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Constitutive Signaling by NOTCH1 PEST Domain Mutants ↗

Stable identifier: R-HSA-2644606

Diseases: cancer, T-cell leukemia



As NOTCH1 PEST domain is intracellular, NOTCH1 PEST domain mutants are expected to behave as the wild-type NOTCH1 with respect to ligand binding and proteolytic cleavage mediated activation of signaling. However, once the NICD1 fragment of NOTCH1 is released, PEST domain mutations prolong its half-life and transcriptional activity through interference with FBXW7 (FBW7)-mediated ubiquitination and degradation of NICD1 (Weng et al. 2004, Thompson et al. 2007, O'Neil et al. 2007). All NOTCH1 PEST domain mutants annotated here (NOTCH1 Q2395*, NOTCH1 Q2440*, NOTCH1 P2474Afs*4 and NOTCH1 P2514Rfs*4) either have a truncated PEST domain or lack the PEST domain completely.

Literature references

Thompson, BJ., Buonamici, S., Sulis, ML., Palomero, T., Vilimas, T., Basso, G. et al. (2007). The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. *J Exp Med, 204*, 1825-35. ↗

O'Neil, J., Grim, J., Strack, P., Rao, S., Tibbitts, D., Winter, C. et al. (2007). FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. *J Exp Med, 204*, 1813-24. ↗

Weng, AP., Ferrando, AA., Lee, W., Morris JP, 4th., Silverman, LB., Sanchez-Irizarry, C. et al. (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science, 306*, 269-71. ↗

Editions

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2013-01-09	Edited	Jassal, B.
2013-02-10	Reviewed	Haw, R.

NOTCH1 PEST domain mutants bind DLL1 ↗

Location: Constitutive Signaling by NOTCH1 PEST Domain Mutants

Stable identifier: R-HSA-2769008

Type: binding

Compartments: plasma membrane

Diseases: T-cell leukemia, cancer