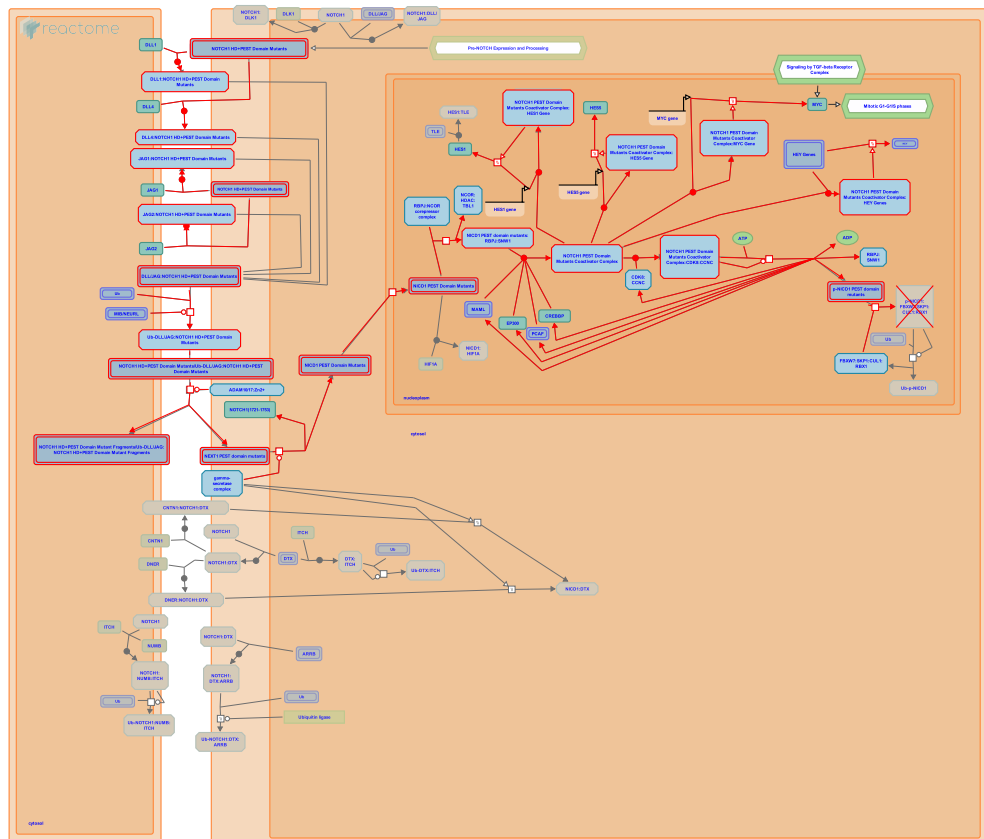


Signaling by NOTCH1 HD+PEST Domain

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.

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).

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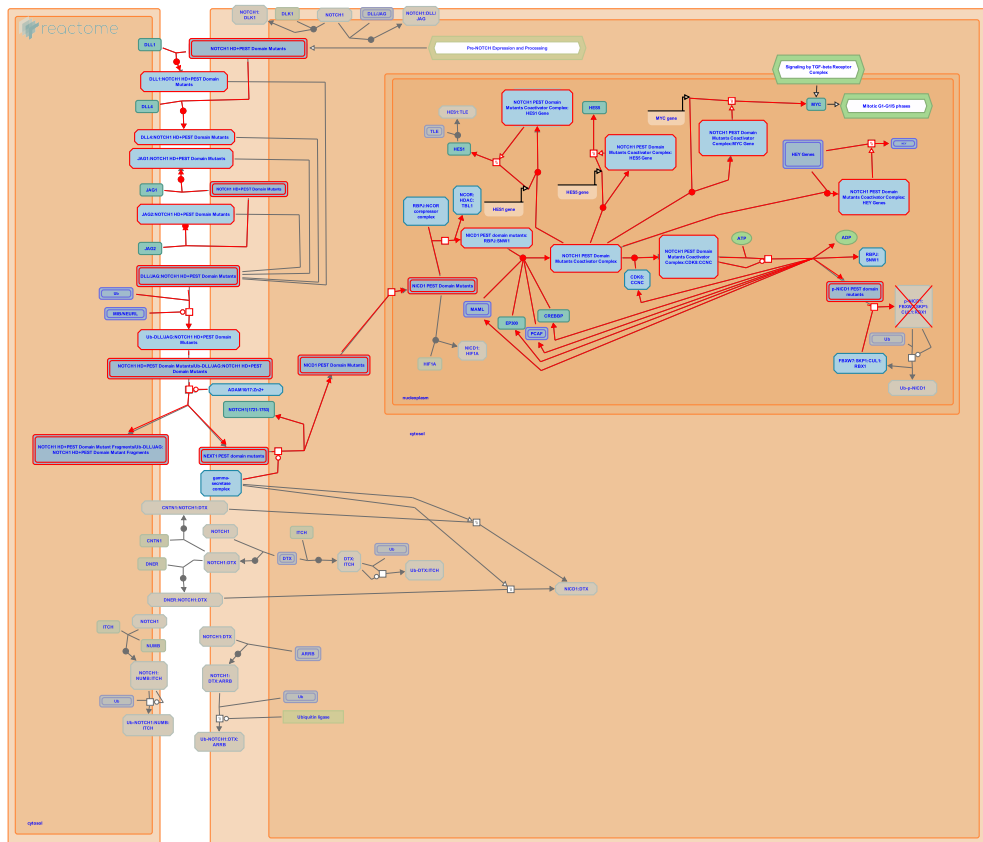
Reactome database release: 70

This document contains 2 pathways ([see Table of Contents](#))

Signaling by NOTCH1 HD+PEST Domain Mutants in Cancer ↗

Stable identifier: R-HSA-2894858

Diseases: cancer, T-cell leukemia



Mutations in the heterodimerization domain (HD) and PEST domain of NOTCH1 are frequently found in cis in T-cell acute lymphoblastic leukemia. While HD mutations alone result in up to ~10-fold increase in NOTCH1 transcriptional activity and PEST domain mutations alone result in up to ~2-fold increase in NOTCH1 transcriptional activity, in cis mutations of HD and PEST domains act synergistically, increasing NOTCH1 transcriptional activity up to ~40-fold (Weng et al. 2004).

Literature references

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

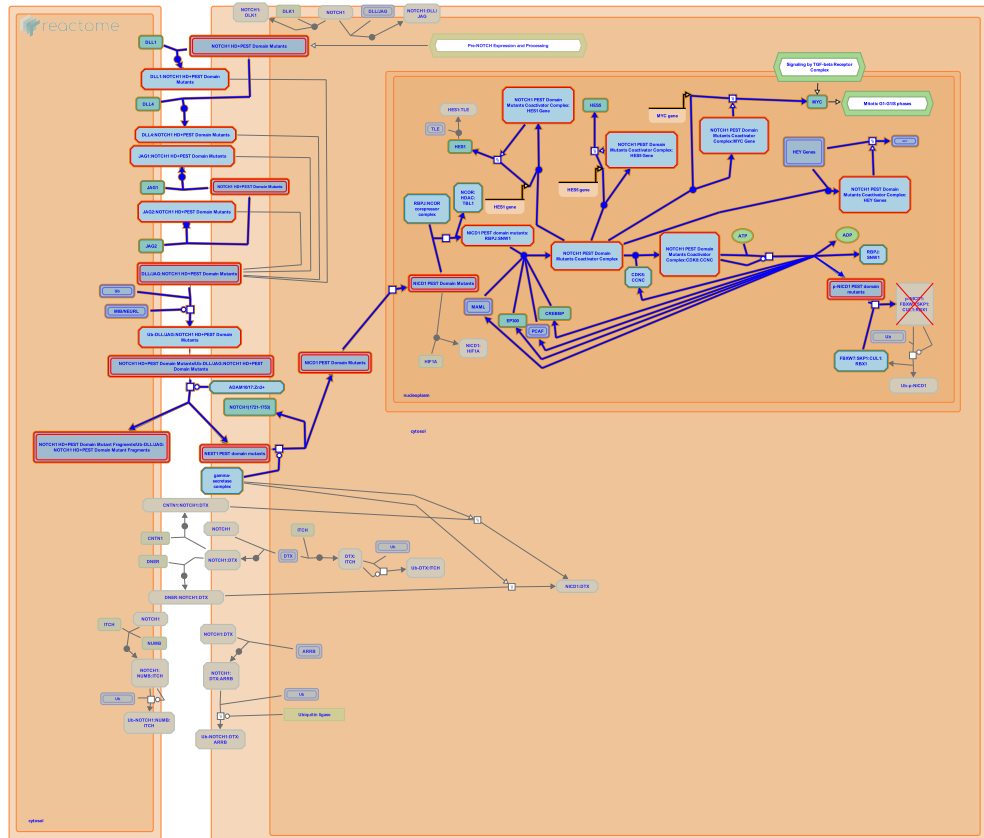
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|------------|----------|-------------------|
| 2013-01-04 | Authored | Orlic-Milacic, M. |
| 2013-01-09 | Edited | Jassal, B. |
| 2013-02-10 | Reviewed | Haw, R. |

Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants ↗

Location: Signaling by NOTCH1 HD+PEST Domain Mutants in Cancer

Stable identifier: R-HSA-2894862

Diseases: T-cell leukemia, cancer



When found in cis, HD and PEST domain mutations act synergistically, increasing NOTCH1 transcriptional activity up to ~40-fold, compared with up to ~10-fold and up to ~2-fold increase with HD mutations alone and PEST domain mutations alone, respectively (Weng et al. 2004). HD domain mutations enable spontaneous, ligand-independent, proteolytic release of the NICD1 fragment, although mutants remain responsive to ligand binding (Malecki et al. 2006), while PEST domain mutations prolong NICD1 half-life and transcriptional activity through interference with FBXW7 (FBW7)-mediated ubiquitination and degradation (Thompson et al. 2007, O'Neil et al. 2007). NOTCH1 HD+PEST domain mutants annotated here are NOTCH1 L1600P;P2514Rfs*4, NOTCH1 L1600P;Q2440*, NOTCH1 L1600P;Q2395* and NOTCH1 L1574P;P2474Afs*4.

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Editions

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|------------|----------|-------------------|
| 2013-01-04 | Authored | Orlic-Milacic, M. |
| 2013-01-09 | Edited | Jassal, B. |
| 2013-02-10 | Reviewed | Haw, R. |

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