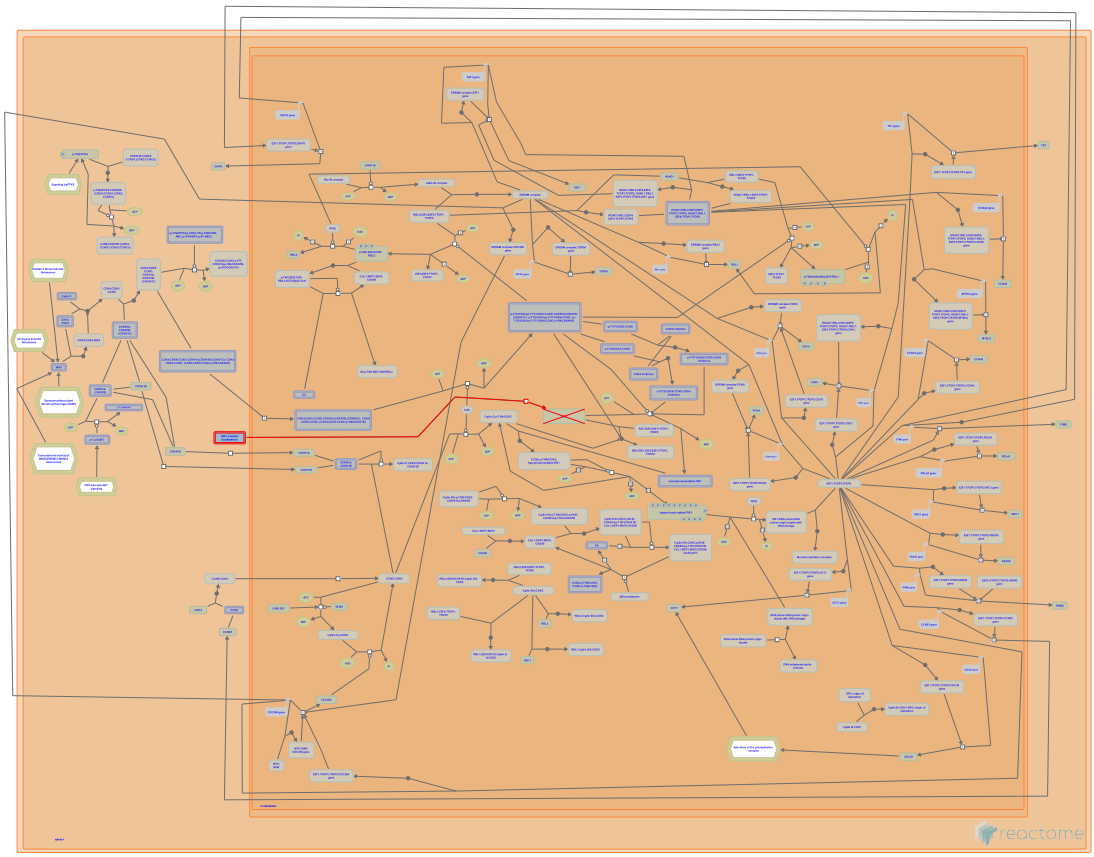
Defective translocation of RB1 mutants to the nucleus



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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. ↗

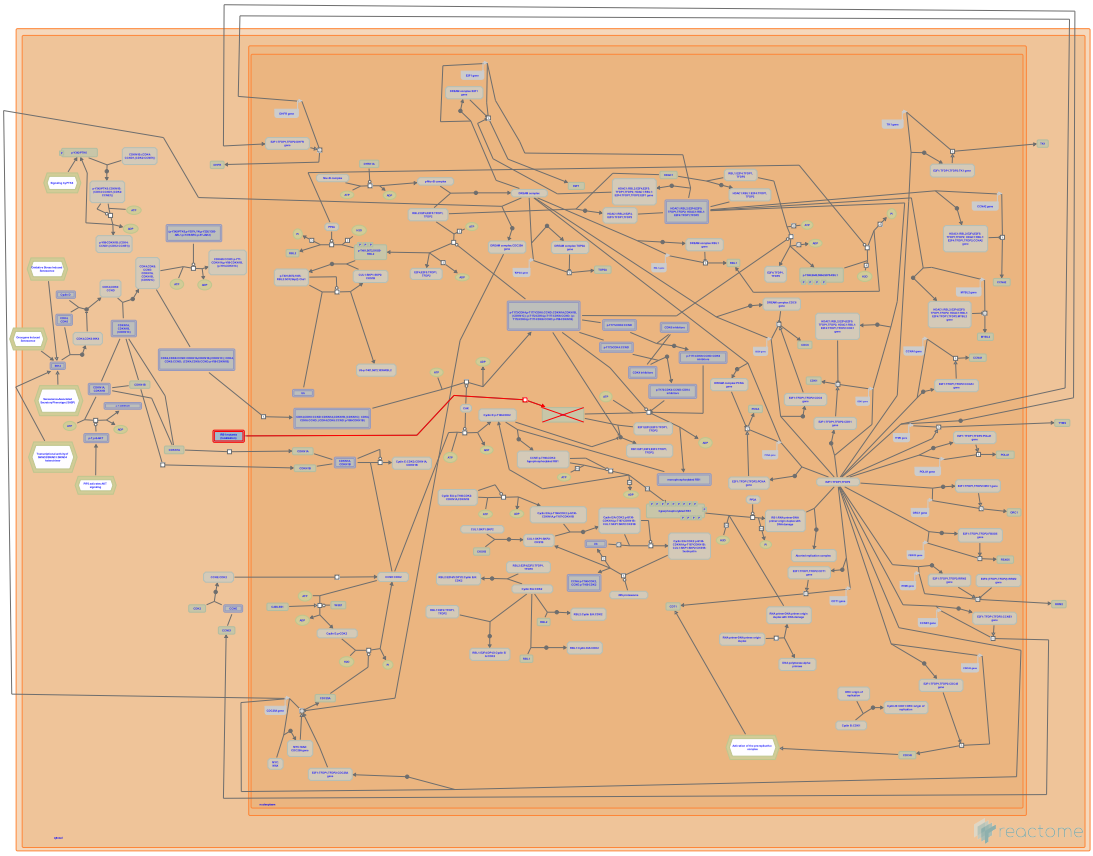
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Defective translocation of RB1 mutants to the nucleus ↗

Stable identifier: R-HSA-9661070

Compartments: cytosol

Diseases: cancer



This pathway describes impaired nuclear localization of RB1 mutants that lack the nuclear localization signal (NLS) (Zacksenhaus et al. 1993, Bremner et al. 1997).

Literature references

Gallie, BL., Zacksenhaus, E., Phillips, RA., Bremner, R. (1993). A bipartite nuclear localization signal in the retinoblastoma gene product and its importance for biological activity. *Mol. Cell. Biol., 13*, 4588-99. ↗

Dunn, JM., Ahmad, KF., Bridge, P., Gallie, BL., Du, DC., Bremner, R. et al. (1997). Deletion of RB exons 24 and 25 causes low-penetrance retinoblastoma. *Am. J. Hum. Genet., 61*, 556-70. ↗

Editions

2020-05-07	Authored	Orlic-Milacic, M.
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Defective RB1 does not translocate to the nucleus ↗

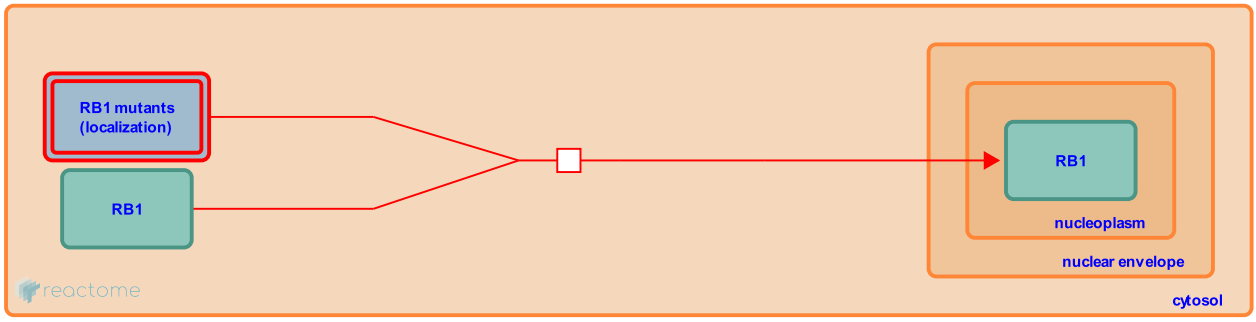
Location: Defective translocation of RB1 mutants to the nucleus

Stable identifier: R-HSA-9660615

Type: transition

Compartments: cytosol

Diseases: cancer



Amino acid residues 860-876 in the C-terminal part of RB1 constitute a bipartite nuclear localization signal (NLS). An NLS deletion mutant of RB1, generated by directed mutagenesis, shows impaired nuclear localization (Zacksenhaus et al. 1993). RB1 R830_G887 mutant (also known as RB1 delEx24-25), reported in low-penetrance familial retinoblastoma, similarly lacks the NLS and shows primarily cytosolic localization (Bremner et al. 1997). Many loss-of-function mutations in RB1, such as nonsense and frameshift mutations, lead to premature termination of translation and formation of truncated proteins that lack the NLS. Although the subcellular localization has not been examined for these mutants, it is expected for their translocation to the nucleus to be impaired and for them to predominantly localize to the cytosol.

The RB1 nonsense and frameshift mutants reported in cancer that are listed below have been annotated as candidate mutants for impaired translocation to the nucleus based on the absence of the NLS. Please note that some of these nonsense mutants lack more than 90% of their amino acid sequence and are likely to be null mutants, with no protein detectable. Even frameshift mutations that happen close to the 3' end of the RB1 gene have been shown to produce mRNAs that are prone to nonsense-mediated decay (Mitter et al. 2009).
These are the nonsense mutants annotated as candidates for impaired translocation to the nucleus:
RB1 K4*
RB1 Q35*
RB1 E48*
RB1 E54*
RB1 K63*
RB1 E72*
RB1 W75*
RB1 W78*
RB1 E79*
RB1 K80*
RB1 G86*
RB1 K95*
RB1 K96*
RB1 E97*
RB1 W99*
RB1 G100*
RB1 S114*
RB1 Q121*
RB1 E125*
RB1 E137*
RB1 S149*
RB1 L158*
RB1 E166*
RB1 Q176*
RB1 E184*
RB1 W195*

RB1 L199*
RB1 L206*
RB1 E209*
RB1 S215*
RB1 Q217*
RB1 C221*
RB1 S230*
RB1 K240*
RB1 R251*
RB1 R255*
RB1 Q257*
RB1 Q266*
RB1 E275*
RB1 E280*
RB1 E282*
RB1 K289*
RB1 G304*
RB1 G310*
RB1 E313*
RB1 E315*
RB1 R320*
RB1 E322*
RB1 E323*
RB1 K329*
RB1 L335*
RB1 Q344*
RB1 E364*
RB1 Q384*
RB1 L389*
RB1 S391*
RB1 Q395*
RB1 S397*
RB1 K412*
RB1 K429*
RB1 G435*
RB1 Q436*
RB1 E440*
RB1 S443*
RB1 Q444*
RB1 R445*
RB1 Y446*
RB1 Y454*
RB1 R455*
RB1 S463*
RB1 E464*
RB1 E465*
RB1 R467*
RB1 Q471*
RB1 C489*
RB1 E492*
RB1 Y498*
RB1 Q504*
RB1 L512*
RB1 W516*
RB1 L523*
RB1 E533*
RB1 E539*
RB1 R544*
RB1 L550*
RB1 E551*
RB1 R552*
RB1 R556*
RB1 W563*
RB1 S565*

RB1 S567*
RB1 S576*
RB1 E580*
RB1 G581*
RB1 Q597*
RB1 Y606*
RB1 K615*
RB1 S618*
RB1 Q631*
RB1 S634*
RB1 Q637*
RB1 Q639*
RB1 S648*
RB1 K652*
RB1 Y655*
RB1 E672*
RB1 E675*
RB1 E677*
RB1 W681*
RB1 Q685*
RB1 Q689*
RB1 E691*
RB1 E693*
RB1 Q702*
RB1 Y709*
RB1 K715*
RB1 K720*
RB1 Y728*
RB1 Q736*
RB1 E737*
RB1 K745*
RB1 E747*
RB1 E748*
RB1 Y749*
RB1 Y756*
RB1 S758*
RB1 Q762*
RB1 R763*
RB1 K765*
RB1 Q770*
RB1 L779*
RB1 R787*
RB1 Y790*
RB1 K791*
RB1 G801*
RB1 S807*
RB1 E817*
RB1 S829*
RB1 L832*
RB1 S834*
RB1 E837*
RB1 S838*
RB1 E843*
RB1 Q846*
RB1 Q850*

These are the frameshift mutants annotated as candidates for impaired translocation to the nucleus:
RB1 R7Efs*58
RB1 R7Pfs*24
RB1 T9Rfs*56
RB1 A11Rfs*20
RB1 A15Pfs*3
RB1 A17Pfs*3
RB1 P28Lfs*37

RB1 D32Tfs*33
RB1 P39Rfs*26
RB1 P39Sfs*10
RB1 L44Rfs*4
RB1 T58Yfs*52
RB1 C61Vfs*4
RB1 K63Rfs*38
RB1 I66Dfs*44
RB1 I66Yfs*11
RB1 R71Efs*39
RB1 E72Vfs*34
RB1 R73Sfs*36
RB1 A74Efs*4
RB1 L76*
RB1 T77Lfs*34
RB1 E97Gfs*13
RB1 E97Nfs*14
RB1 W99Lfs*11
RB1 W99Yfs*5
RB1 G100Efs*11
RB1 C102Yfs*7
RB1 F104Lfs*7
RB1 E112Dfs*6
RB1 T116Lfs*8
RB1 N123Tfs*2
RB1 I124*
RB1 I124Rfs*6
RB1 E125Kfs*11
RB1 N133*
RB1 N133Tfs*3
RB1 L134*
RB1 L135Tfs*5
RB1 E137Rfs*3
RB1 T140Nfs*6
RB1 K143Mfs*19
RB1 D145Ifs*8
RB1 M148Hfs*9
RB1 M148Ifs*8
RB1 M148Vfs*8
RB1 R150Kfs*7
RB1 D156Mfs*19
RB1 D156Vfs*19
RB1 L158Mfs*19
RB1 Y173Ffs*11
RB1 S182Ifs*3
RB1 S182Yfs*2
RB1 N186Ifs*6
RB1 S194Ffs*7
RB1 W195*
RB1 L199Ffs*4
RB1 L199Yfs*2
RB1 Q207Tfs*5
RB1 E209Vfs*3
RB1 D224Afs*40
RB1 P232Rfs*4
RB1 Y239Lfs*25
RB1 S249Ffs*22
RB1 P250Afs*16
RB1 P250Sfs*20
RB1 P253Gfs*5
RB1 N258Efs*11
RB1 Q266Hfs*2
RB1 N269*
RB1 L277Pfs*9

RB1 C278*
RB1 H281Qfs*6
RB1 H281Sfs*2
RB1 E287Rfs*2
RB1 N290Kfs*20
RB1 V291Ifs*9
RB1 F299Lfs*4
RB1 G310Dfs*22
RB1 L317*
RB1 S318*
RB1 S318Nfs*13
RB1 R320Dfs*12
RB1 E323Kfs*9
RB1 I324Mfs*17
RB1 L326*
RB1 N328*
RB1 N328Ifs*4
RB1 A333Ffs*13
RB1 R334*
RB1 L337Wfs*12
RB1 D340Yfs*5
RB1 L343Sfs*3
RB1 D346Rfs*4
RB1 D346Vfs*17
RB1 S360Pfs*2
RB1 N367*
RB1 P370Lfs*10
RB1 Q383Nfs*3
RB1 Q384Tfs*11
RB1 L385*
RB1 M386Ifs*11
RB1 L389Ffs*3
RB1 Q395Pfs*11
RB1 N406Kfs*4
RB1 E413Kfs*4
RB1 S414Kfs*14
RB1 I415Nfs*13
RB1 K417Wfs*23
RB1 R418Sfs*9
RB1 V419*
RB1 C438Vfs*19
RB1 G442Dfs*15
RB1 G449Efs*8
RB1 V450Sfs*13
RB1 Y453*
RB1 M460Ifs*3
RB1 N472Ifs*6
RB1 L477Mfs*17
RB1 D479Efs*16
RB1 D479Vfs*14
RB1 N480Kfs*13
RB1 F482Sfs*10
RB1 H483Ifs*12
RB1 H483Sfs*10
RB1 H483Yfs*9
RB1 M484Vfs*8
RB1 L486Ifs*6
RB1 C489Lfs*5
RB1 E492Lfs*4
RB1 T497Hfs*22
RB1 T502Nfs*17
RB1 F514Pfs*8
RB1 N522Ifs*2
RB1 K524Rfs*28

RB1 A525Pfs*7
RB1 Y529Lfs*26
RB1 Y529Tfs*3
RB1 I532Nfs*57
RB1 K537Nfs*14
RB1 G540Afs*3
RB1 L542Kfs*11
RB1 K548Nfs*3
RB1 C553Vfs*58
RB1 C553Wfs*53
RB1 A562Hfs*49
RB1 L564Sfs*47
RB1 S565*
RB1 D571Lfs*41
RB1 K574*
RB1 S576Rfs*34
RB1 K577Rfs*34
RB1 R579Qfs*29
RB1 D584Nfs*2
RB1 S588Ffs*6
RB1 N593Sfs*5
RB1 N593Tfs*11
RB1 P595Lfs*16
RB1 Y606Lfs*47
RB1 P609Cfs*43
RB1 R611Lfs*43
RB1 G617Rfs*36
RB1 N623Qfs*15
RB1 N627Mfs*16
RB1 A635Gfs*6
RB1 P641Afs*12
RB1 L647Ffs*5
RB1 S648Tfs*4
RB1 L649Ffs*11
RB1 F650Lfs*5
RB1 Y651Ifs*7
RB1 V654Cfs*4
RB1 V654Sfs*14
RB1 Y655Ifs*3
RB1 Y655Lfs*13
RB1 Y655Lfs*4
RB1 Y659Ifs*4
RB1 R661*
RB1 T664Nfs*4
RB1 C666*
RB1 L670Cfs*7
RB1 L676Ffs*16
RB1 E677Dfs*19
RB1 I679*
RB1 E693Nfs*3
RB1 M695Rfs*10
RB1 D697Qfs*23
RB1 R698Afs*22
RB1 I723Nfs*28
RB1 T726Nfs*25
RB1 P732Lfs*12
RB1 K740Tfs*10
RB1 L743*
RB1 E747Gfs*3
RB1 E748Dfs*6
RB1 V754Sfs*4
RB1 M761Nfs*21
RB1 I768Cfs*23
RB1 L769Cfs*41

RB1 Y771Cfs*23
RB1 Y771Lfs*24
RB1 R775Gfs*35
RB1 P777Lfs*33
RB1 L797*
RB1 L797Ffs*14
RB1 L797Ffs*18
RB1 R798Qfs*4
RB1 R798Tfs*17
RB1 I799Ffs*11
RB1 N803Tfs*7
RB1 I806Lfs*10
RB1 P808Kfs*12
RB1 L809Rfs*17
RB1 Y813Kfs*12
RB1 Y813Qfs*10
RB1 S816Qfs*10
RB1 P822Qfs*4
RB1 M825*
RB1 M825Ifs*13
RB1 R828Kfs*10
RB1 L832Ffs*5
RB1 E837Dfs*12
RB1 S842*
RB1 K844Sfs*5
RB1 N854*
RB1 D856Efs*17

Literature references

Dunn, JM., Ahmad, KF., Bridge, P., Gallie, BL., Du, DC., Bremner, R. et al. (1997). Deletion of RB exons 24 and 25 causes low-penetrance retinoblastoma. *Am. J. Hum. Genet., 61,* 556-70. ↗

Editions

2020-05-07	Authored	Orlic-Milacic, M.
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