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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. [↗](#)

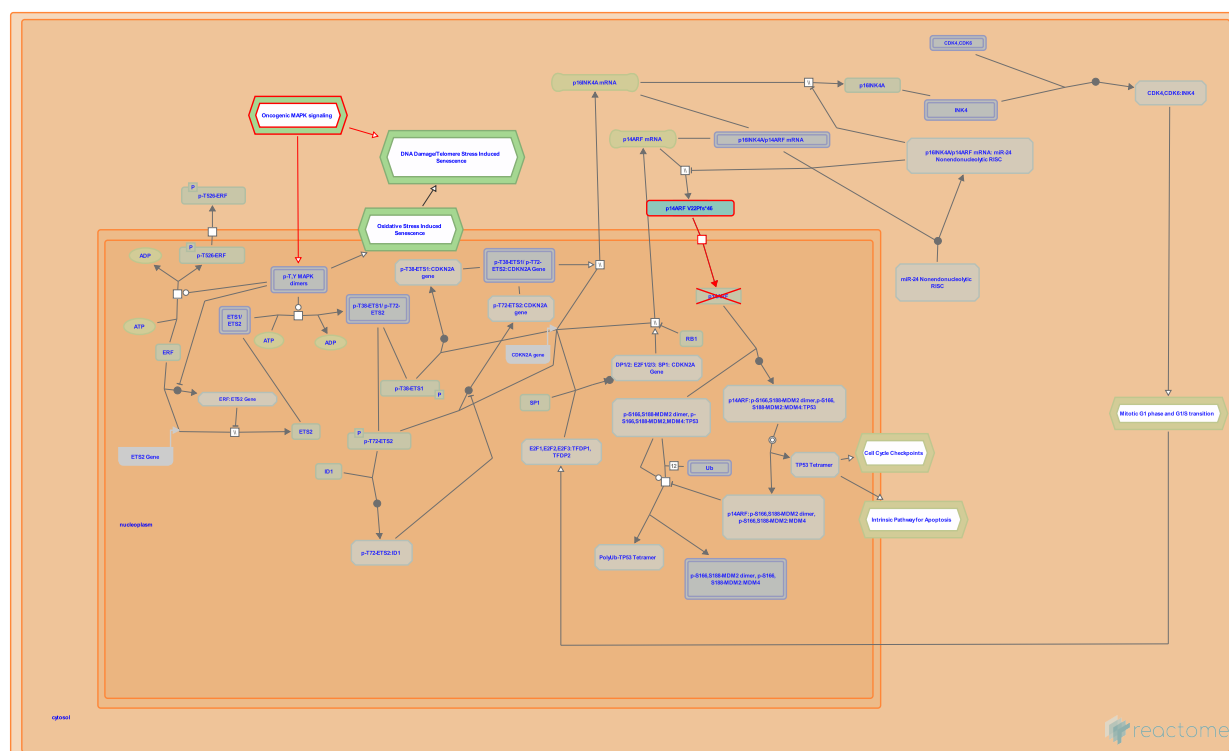
Reactome database release: 88

This document contains 1 pathway and 1 reaction ([see Table of Contents](#))

Evasion of Oncogene Induced Senescence Due to p14ARF Defects ↗

Stable identifier: R-HSA-9646303

Diseases: cancer



In cell culture, p14ARF (CDKN2A transcript 4, CDKN2A-4, ARF), one of the two main protein products of the CDKN2A gene, contributes to oncogene induced senescence by stabilizing TP53 (p53). The function of p14ARF in p53 stabilization through sequestration of MDM2, a p53 ubiquitin ligase, depends on the nuclear localization of p14ARF and its ability to interact with MDM2. The nuclear localization signal and the MDM2 interaction domain map to the first 15 amino acids of the N-terminus of p14ARF. This region is encoded by the p14ARF-specific exon 1beta of CDKN2A. An independent MDM2-binding domain localized to the C-terminus of p14ARF (Lohrum et al. 2000). Insertion of 16 nucleotides in exon 1beta results in a frameshift truncation of p14ARF, responsible for a familial melanoma syndrome in which the p16INK4A product of the CDKN2A gene is unaffected. This mutation is rare and has so far been reported in one family only. The mutant protein, p14ARF V22Pfs*46 has the nucleotide localization signal and the N-terminal MDM2 interaction region preserved, but is unable to translocate from the cytosol to the nucleus, possibly due to aberrant conformation (Rizos, Puig et al. 2001), and also lacks the C-terminal MDM2 interaction region. Relocation of wild type p14ARF to the cytosol has been observed in melanoma (Rizos, Darmanian et al. 2001) and aggressive thyroid papillary carcinoma (Ferru et al. 2006). Genomic deletion of exon 1beta, with exons 1alpha, 2 and 3 intact, has been reported in about 30% of melanoma cases with genomic deletions involving the CDKN2A locus (Freedberg et al. 2008). Several different familial melanoma germline mutations map to the exon 1beta splice donor site (Harland et al. 2005).

The ability of p14ARF to localize to the nucleolus also plays a role in p14ARF-mediated stabilization of p53. Mutations in exon 2 of the CDKN2A gene can lead to missense mutations in p14ARF that affect its nucleolar localization and p53 stabilization, but the exact mechanism has not been fully elucidated (Zhang and Xiong 1999, reviewed by Fontana et al. 2019).

Literature references

- Ashcroft, M., Vousden, KH., Kubbutat, MH., Lohrum, MA. (2000). Contribution of two independent MDM2-binding domains in p14(ARF) to p53 stabilization. *Curr. Biol.*, 10, 539-42. ↗
- Busam, K., Randerson-Moor, JA., Rigas, SH., Polsky, D., Turner, F., Gai, W. et al. (2008). Frequent p16-independent inactivation of p14ARF in human melanoma. *J. Natl. Cancer Inst.*, 100, 784-95. ↗
- Mann, GJ., Darmanian, AP., Holland, EA., Kefford, RF., Rizos, H. (2001). Mutations in the INK4a/ARF melanoma susceptibility locus functionally impair p14ARF. *J. Biol. Chem.*, 276, 41424-34. ↗

Fontana, R., Vivo, M., Ranieri, M., La Mantia, G. (2019). Dual Role of the Alternative Reading Frame ARF Protein in Cancer. *Biomolecules*, 9. [↗](#)

Randerson-Moor, JA., Chambers, PA., Bishop, DT., Goldstein, AM., Taylor, CF., ter Huurne, JA. et al. (2005). A mutation hotspot at the p14ARF splice site. *Oncogene*, 24, 4604-8. [↗](#)

Editions

2019-06-28	Authored	Orlic-Milacic, M.
2019-07-08	Reviewed	Rizos, H.
2019-07-16	Edited	Orlic-Milacic, M.
2019-08-12	Reviewed	Bennett, DC.
2019-08-14	Edited	Orlic-Milacic, M.

p14ARF mutant does not translocate to the nucleus

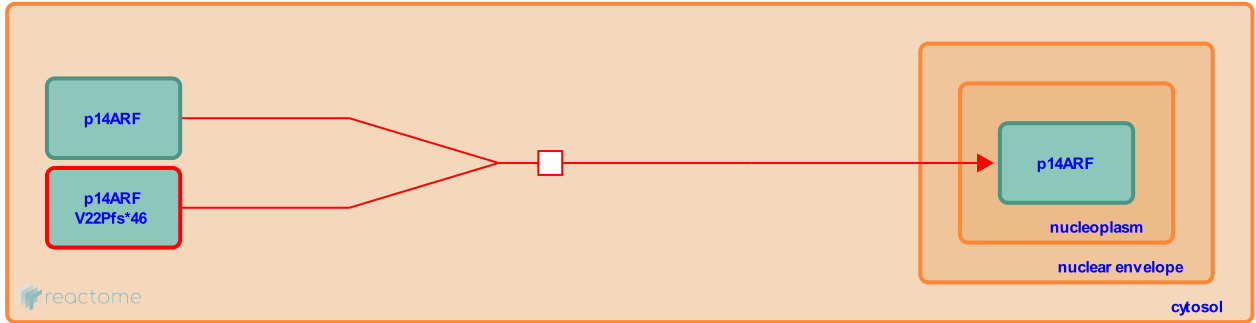
Location: [Evasion of Oncogene Induced Senescence Due to p14ARF Defects](#)

Stable identifier: R-HSA-9646295

Type: transition

Compartments: cytosol

Diseases: cancer



A germline mutation affecting exon 1beta of the CDKN2A locus is associated with a familial melanoma syndrome. The mutation represents an insertion of 16 nucleotides (CGGCCCGCCGCGAGTG) between coding bases 60 and 61 in exon 1beta. This insertion results in a frameshift, starting at arginine codon at position 21 of p14ARF, with the first amino acid changed being valine at position 22, and ending with a premature stop codon at position 67. The mutant protein p14ARF V22Pfs*46 (p14ARF 60ins16) is unable to translocate to the nucleus and stabilize TP53 (Rizos, Puig et al. 2001).

Literature references

Puig, S., Milà, M., Darmanian, AP., Badenas, C., Kefford, RF., Rizos, H. et al. (2001). A melanoma-associated germline mutation in exon 1beta inactivates p14ARF. *Oncogene*, 20, 5543-7. [↗](#)

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