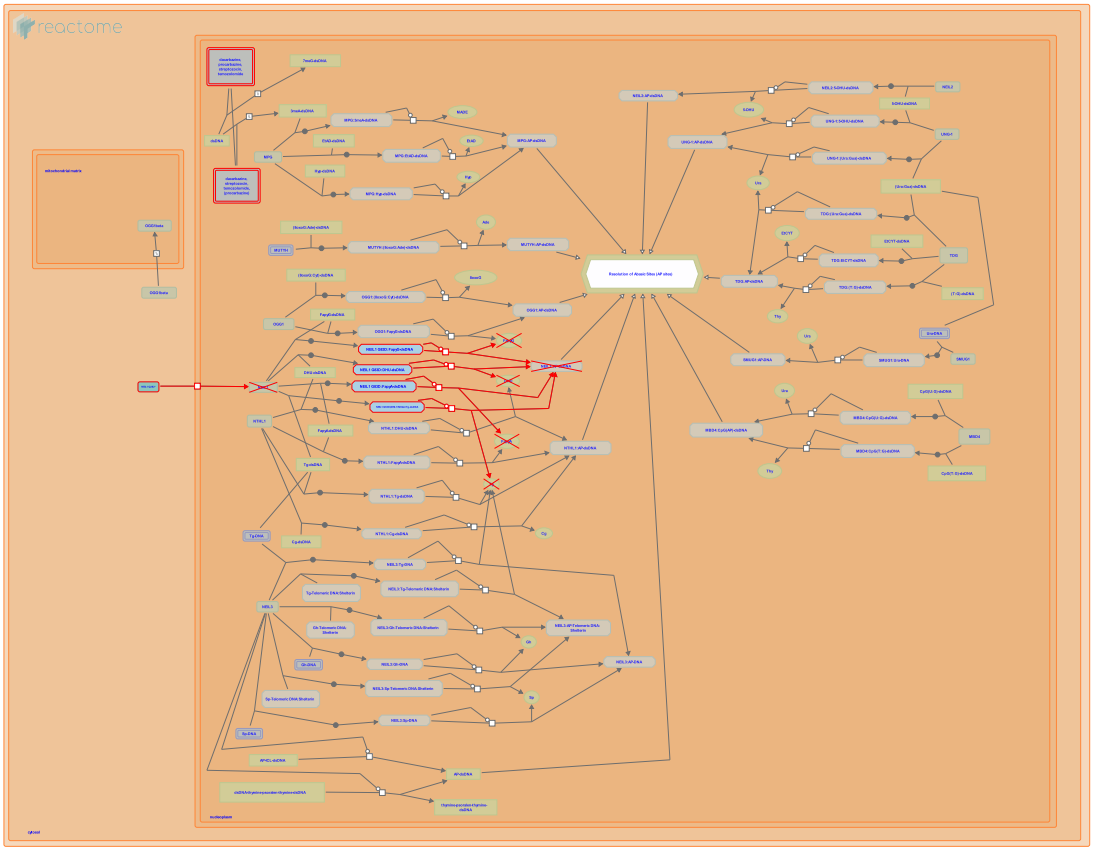
Defective Base Excision Repair Associated with NEIL1



Orlic-Milacic, M., Sampath, H.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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. ↗

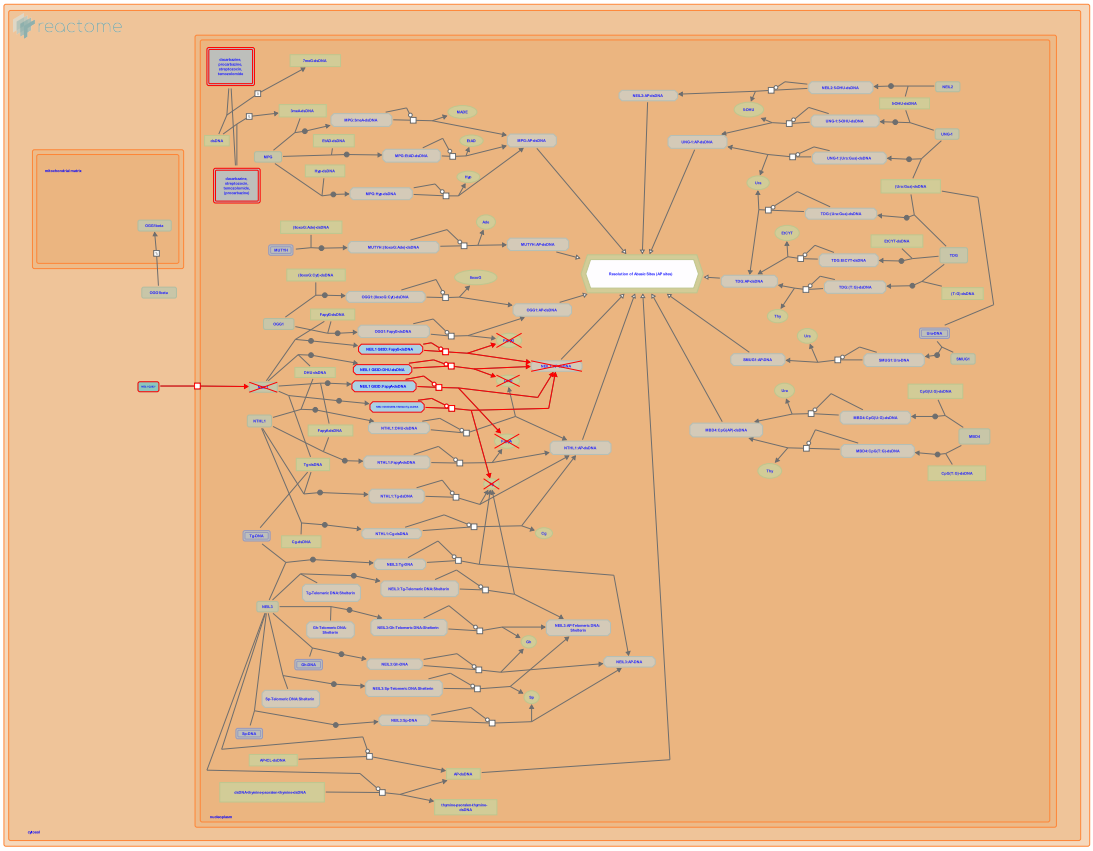
Reactome database release: 90

This document contains 1 pathway and 5 reactions (see Table of Contents)

Defective Base Excision Repair Associated with NEIL1 ↗

Stable identifier: R-HSA-9616334

Diseases: cancer



NEIL1 is an enzyme with dual DNA glycosylase and beta/delta lyase activity involved in base excision repair pathway (BER), the primary repair pathway for oxidative DNA damage. NEIL1 can detect and remove DNA damage resulting from oxidation of adenine, guanine and thymine, in the form of 4,6-diamino-5-formamidopyrimidine (FapyA), 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), and thymine glycol (Tg), respectively. NEIL1 can also detect and remove dihydrouracil (DHU), which results from deamination of cytosine. Several low frequency NEIL1 polymorphisms, present in about 1% of general population in the United States have been reported. Different polymorphisms have different effects on NEIL1 function, and it was suggested that NEIL1 polymorphisms and NEIL1 deficiency or haploinsuficiency may be involved in predisposition to cancer and in metabolic syndrome (Roy et al. 2007, Vartanian et al. 2006, Sampath et al. 2011, Prakash et al. 2014). One polymorphism, NEIL1 G83D, is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL1 G83D variant exhibits impaired DNA glycosylase activity towards different damaged DNA bases (Roy et al. 2007, Prakash et al. 2014) and induces genomic instability (Galick et al. 2017).
NEIL1 E28del, an in frame deletion variant of NEIL1 reported in gastric (stomach) cancer, where glutamate at position 28 is deleted, does not cleave Tg from damaged DNA (Shinmura et al. 2004).
NEIL1 Q282TER, a NEIL1 variant which lacks the putative nuclear localization signal (NLS), localizes to the cytosol and is therefore not able to access damaged DNA substrates, but its involvement in cancer is uncertain (Shinmura et al. 2015).
Reduced expression of NEIL1 and NEIL2 genes, accompanied with increased NEIL3 gene expression was detected in various cancers. NEIL1 gene silencing by promoter hypermethylation may be one of the underlying mechanisms for reduced NEIL1 expression in cancer (Shinmura et al. 2016).
Infection with the Hepatitis C virus (HCV) leads to decreased NEIL1 expression in liver cells, through an unknown mechanism (Pal et al. 2010).
Mice that are double knockout for Neil1 and Nthl1 genes accumulate DNA damage in the form of FapyA and FapyG and are more prone to development of lung adenocarcinoma than single Neil1 or Nthl1 gene knockouts (Chan et al. 2009). Another study reported that Neil1 knockout mice did not show a predisposition to tumour formation, and neither did double knockouts of Neil1 and Neil2, nor triple knockouts of Neil1, Neil2 and Neil3. Neil1 knockout mice are obese, consistent with the metabolic syndrome, but double knockouts of Neil1 and Neil2 do not display obesity (Rolseth et al. 2017).

Literature references

Andersen, JM., Esbensen, Y., Graupner, A., Neurauter, CG., Slupphaug, G., Hildrestrand, GA. et al. (2017). No cancer predisposition or increased spontaneous mutation frequencies in NEIL DNA glycosylases-deficient mice. *Sci Rep, 7*, 4384. ↗

Galick, HA., Sweasy, JB., Volk, L., Prakash, A., Marsden, CG., Nemec, AA. et al. (2017). The NEIL1 G83D germline DNA glycosylase variant induces genomic instability and cellular transformation. *Oncotarget, 8*, 85883-85895. ↗

Lloyd, RS., Dizdaroglu, M., Jaruga, P., Roy, LM., Wood, TG., McCullough, AK. (2007). Human polymorphic variants of the NEIL1 DNA glycosylase. *J. Biol. Chem., 282*, 15790-8. ↗

Carroll, BL., Sweasy, JB., Prakash, A., Doublié, S., Wallace, SS. (2014). Genome and cancer single nucleotide polymorphisms of the human NEIL1 DNA glycosylase: activity, structure, and the effect of editing. *DNA Repair (Amst.), 14*, 17-26. ↗

Shinmura, K., Maekawa, M., Igarashi, H., Takezaki, T., Taniguchi, T., Goto, M. et al. (2004). Inactivating mutations of the human base excision repair gene NEIL1 in gastric cancer. *Carcinogenesis, 25*, 2311-7. ↗

Editions

2018-11-27	Authored	Orlic-Milacic, M.
2019-01-03	Reviewed	Sampath, H.
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NEIL1 Q282TER does not translocate to the nucleus ↗

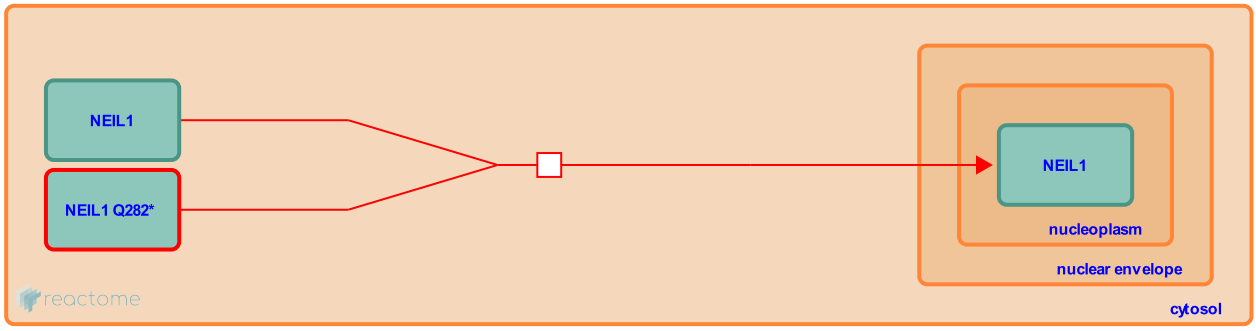
Location: Defective Base Excision Repair Associated with NEIL1

Stable identifier: R-HSA-9629917

Type: transition

Compartments: cytosol

Diseases: cancer



A rare NEIL1 variant reported in the Japanese population results in a truncated NEIL1 protein, NEIL1 Q282TER, which lacks the putative nuclear localization signal (NLS). NEIL1 Q282TER localizes to the cytosol and, due to this mislocalization, is not able to access damaged DNA substrates. Several NEIL truncation mutations that remove the NLS have been reported in different cancer types and correlate with increased mutational loads, but they have not been functionally studied. NEIL1 Q282TER has not yet been associated with any specific cancer type or cancer predisposition, but is the only functionally studied NEIL1 truncation mutant that lacks the NLS (Shinmura et al. 2015).

Literature references

Shinmura, K., Inoue, Y., Nakamura, S., Goto, M., Sugimura, H., Kato, H. et al. (2015). NEIL1 p.Gln282Stop variant is predominantly localized in the cytoplasm and exhibits reduced activity in suppressing mutations. *Gene, 571,* 33-42. ↗

Editions

2018-11-27	Authored	Orlic-Milacic, M.
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NEIL1 G83D does not cleave DHU ↗

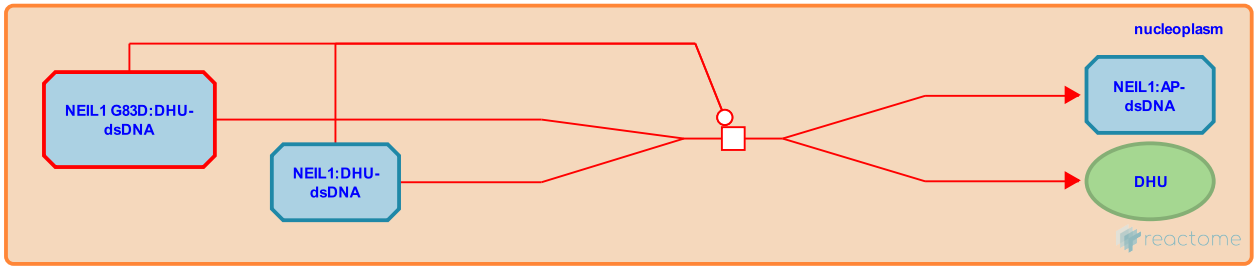
Location: Defective Base Excision Repair Associated with NEIL1

Stable identifier: R-HSA-9628737

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NEIL1 G83D variant is a low frequency polymorphism, estimated to occur in ~1% of US population (Roy et al. 2007), and is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL G83D shows 3-8 fold reduced activity in excising DHU (dihydrouracil) from damaged DNA (Prakash et al. 2014).

Literature references

Carroll, BL., Sweasy, JB., Prakash, A., Doublié, S., Wallace, SS. (2014). Genome and cancer single nucleotide polymorphisms of the human NEIL1 DNA glycosylase: activity, structure, and the effect of editing. *DNA Repair (Amst.), 14*, 17-26. ↗

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NEIL1 G83D does not cleave FapyG ↗

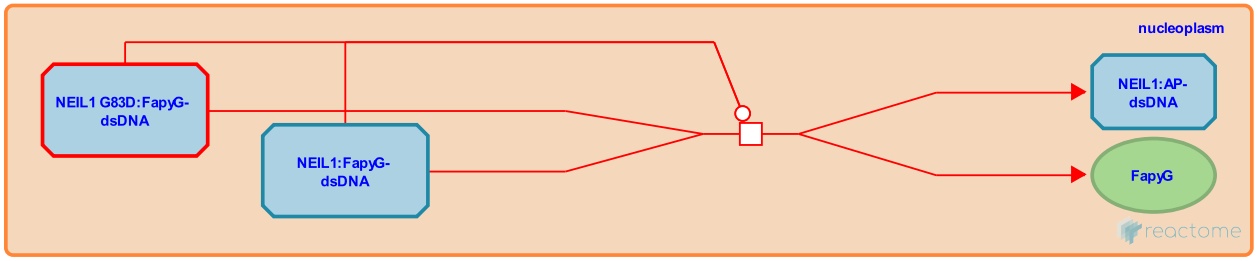
Location: Defective Base Excision Repair Associated with NEIL1

Stable identifier: R-HSA-9628758

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NEIL1 G83D variant is a low frequency polymorphism, estimated to occur in ~1% of US population (Roy et al. 2007), and is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL G83D does not cleave FapyG from damaged DNA (Roy at al. 2007).

Literature references

Lloyd, RS., Dizdaroglu, M., Jaruga, P., Roy, LM., Wood, TG., McCullough, AK. (2007). Human polymorphic variants of the NEIL1 DNA glycosylase. *J. Biol. Chem., 282,* 15790-8. ↗

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NEIL1 G83D does not cleave FapyA ↗

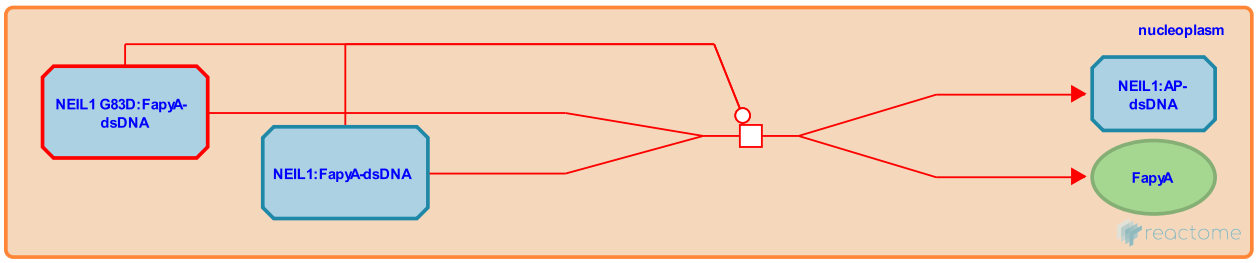
Location: Defective Base Excision Repair Associated with NEIL1

Stable identifier: R-HSA-9628756

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NEIL1 G83D variant is a low frequency polymorphism, estimated to occur in ~1% of US population (Roy et al. 2007), and is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL1 G83D does not cleave FapyA from damaged DNA (Roy at al. 2007).

Literature references

Lloyd, RS., Dizdaroglu, M., Jaruga, P., Roy, LM., Wood, TG., McCullough, AK. (2007). Human polymorphic variants of the NEIL1 DNA glycosylase. *J. Biol. Chem., 282,* 15790-8. ↗

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Defective NEIL1 variants do not cleave Tg ↗

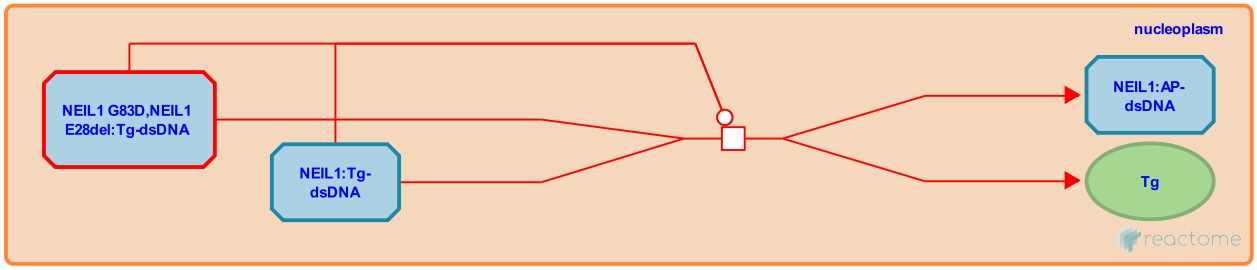
Location: Defective Base Excision Repair Associated with NEIL1

Stable identifier: R-HSA-9629166

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NEIL1 G83D variant is a low frequency polymorphism, estimated to occur in ~1% of US population (Roy et al. 2007), and is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL1 G83D does not cleave thymine glycol (Tg) from damaged DNA (Prakash et al. 2014).
NEIL1 E28del, an in-frame deletion variant of NEIL1 reported in gastric (stomach) cancer, where glutamate at position 28 is deleted, does not cleave Tg from damaged DNA (Shinmura et al. 2008).

Literature references

Carroll, BL., Sweasy, JB., Prakash, A., Doublié, S., Wallace, SS. (2014). Genome and cancer single nucleotide polymorphisms of the human NEIL1 DNA glycosylase: activity, structure, and the effect of editing. *DNA Repair (Amst.), 14*, 17-26. ↗

Shinmura, K., Maekawa, M., Igarashi, H., Takezaki, T., Taniguchi, T., Goto, M. et al. (2004). Inactivating mutations of the human base excision repair gene NEIL1 in gastric cancer. *Carcinogenesis, 25*, 2311-7. ↗

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