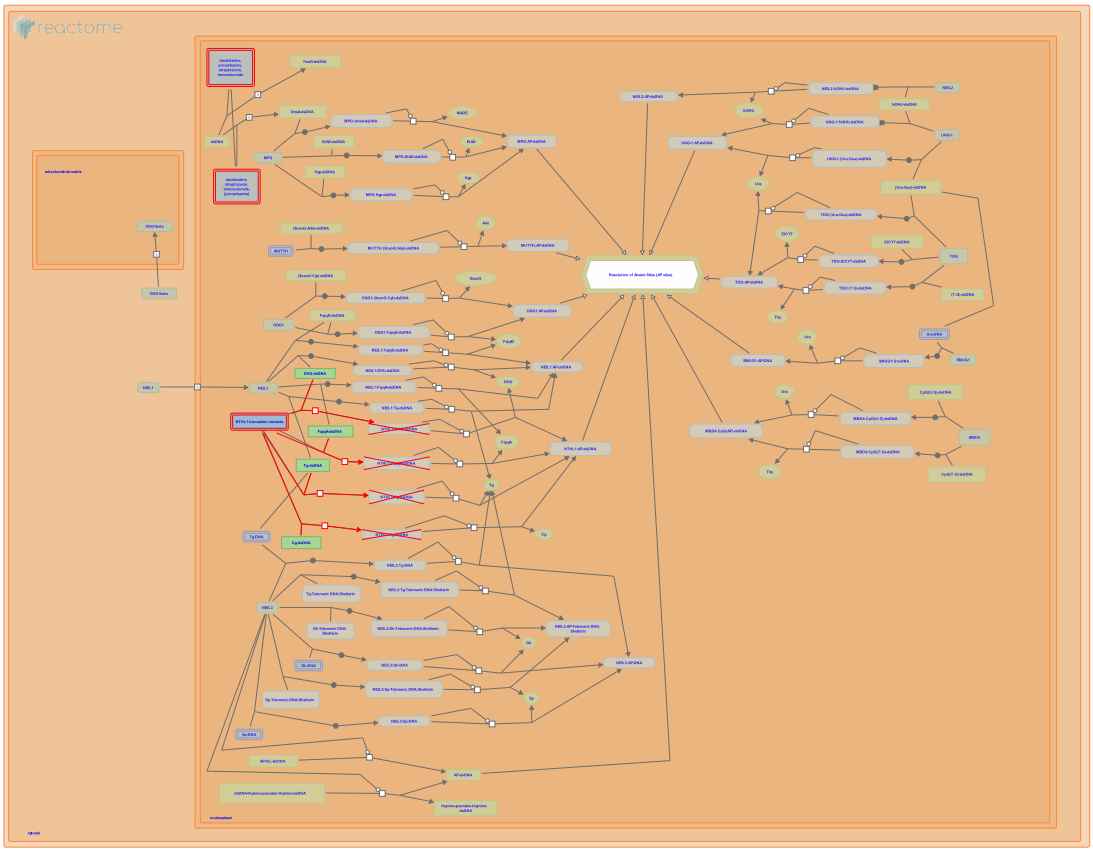
Defective NTHL1 substrate binding



Doetsch, PW., Kuiper, RP., Orlic-Milacic, M., Rivera Polo, B., de Voer, RM.

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

30/04/2024

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. ↗

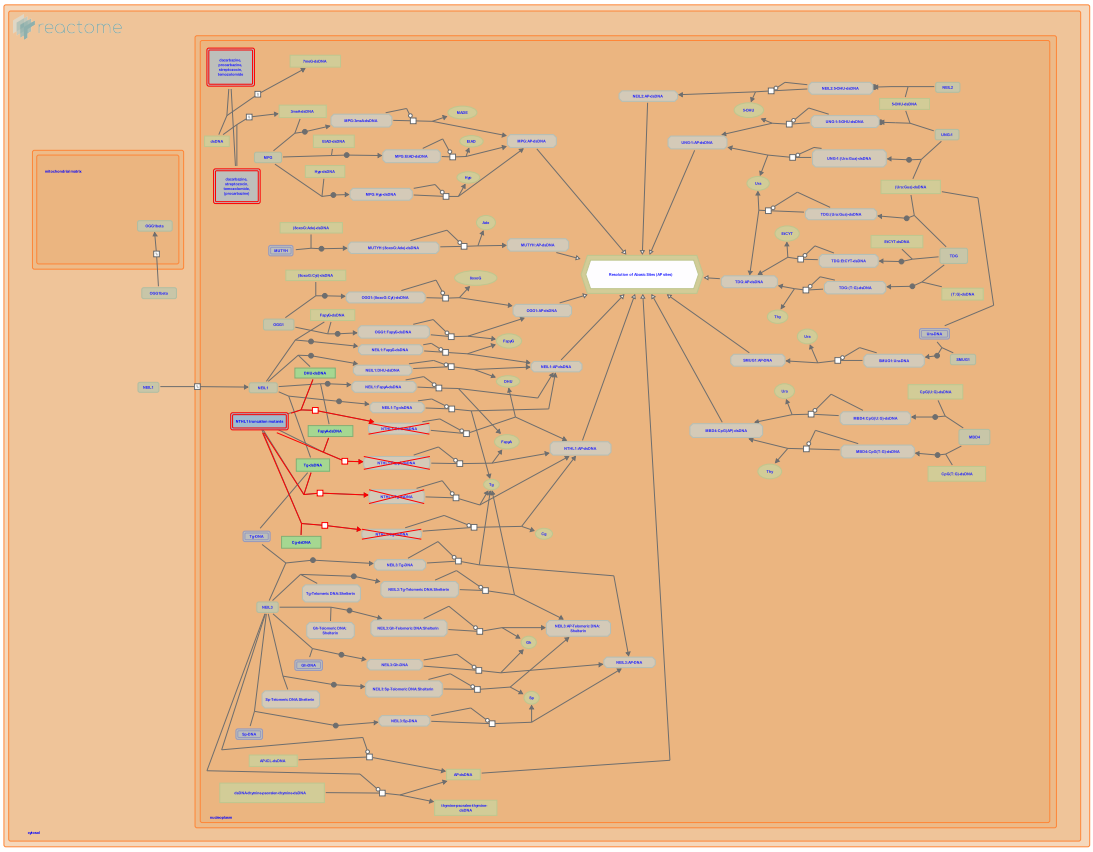
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Defective NTHL1 substrate binding ↗

Stable identifier: R-HSA-9630222

Compartments: nucleoplasm

Diseases: cancer



Several different mutations that result in truncation of NTHL1 protein have been described and associated with cancer. NTHL1 Q90TER (NTHL1 Gln90*) truncation mutant results from a nonsense mutation that replaces codon for glutamine 90 with a STOP codon. NTHL1 Q90TER has not been studied at the protein level, but is predicted to lack the DNA binding domain and the glycosylase domain, thus resulting in a complete loss of the base excision repair (BER) related DNA glycosylase function. Homozygous or compound heterozygous germline NTHL1 Q90TER mutation result in a cancer syndrome (NTHL1 associated tumor syndrome) that involves adenomatous polyposis, colorectal cancer breast cancer and multiple other types of cancer and benign tumors (Weren et al. 2015, Rivera et al. 2015, Grolleman et al. 2019). Apart from NTHL1 Q90TER, at least seven other truncating variants have been identified in patients with NTHL1 associated tumor syndrome, such as NTHL1 A79fs (NTHL1 Ala79fs), NTHL1 Y130TER (NTHL1 Tyr130*), NTHL1 W182TER (NTHL1 Trp182*), NTHL1 c.709+1G>A, NTHL1 I245fs (NTHL1 Ile245fs), NTHL1 W269TER (NTHL1 Trp269*), NTHL1 Q287TER (NTHL1 Gln287*) (Rivera et al. 2015, Broderick et al. 2017, Grolleman et al. 2019).

Literature references

Sweet, K., Hüneburg, R., Høberg-Vetti, H., Morreau, H., Campbell, IG., Cockburn, D. et al. (2019). Mutational Signature Analysis Reveals NTHL1 Deficiency to Cause a Multi-tumor Phenotype. *Cancer Cell, 35*, 256-266.e5. ↗

Broderick, P., Kinnersley, B., Tomlinson, I., Dobbins, SE., Chubb, D., Houlston, RS. et al. (2017). Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology, 152*, 75-77.e4. ↗

Weren, RD., Kuiper, RP., Ligtenberg, MJ., Geurts van Kessel, A., Hoogerbrugge, N., Verwiel, ET. et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet., 47*, 668-71. ↗

Castellsagué, E., Bah, I., van Kempen, LC., Rivera, B., Foulkes, WD. (2015). Biallelic NTHL1 Mutations in a Woman with Multiple Primary Tumors. *N. Engl. J. Med., 373*, 1985-6. ↗

Editions

2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Defective NTHL1 truncation mutants do not bind cytosine glycol (Cg)

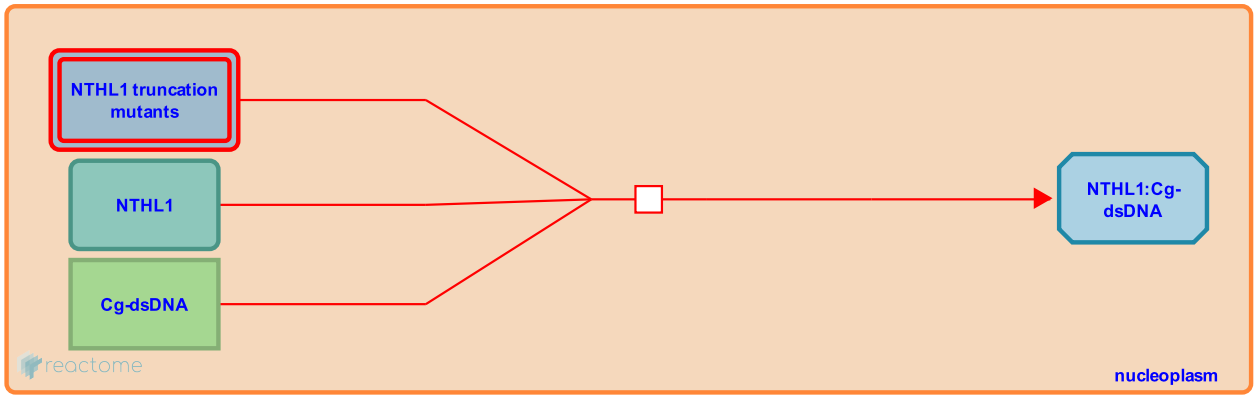
Location: Defective NTHL1 substrate binding

Stable identifier: R-HSA-9630047

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NTHL1 Q90TER (NTHL1 Q90*) truncation mutant (Weren et al. 2015) lacks the DNA binding domain and the glycosylase domain and is thus predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing cytosine glycol (Cg), although this has not been experimentally tested. NTHL1 Q287TER (NTHL1 Q287*) truncation mutant (Broderick et al. 2017) lacks a portion of the DNA binding domain, including glutamine residue Q287, important for substrate recognition (Robey-Bond et al. 2017) and is predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing cytosine glycol (Cg), although this has not been experimentally tested.

Literature references

Broderick, P., Kinnersley, B., Tomlinson, I., Dobbins, SE., Chubb, D., Houlston, RS. et al. (2017). Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology, 152*, 75-77.e4.

Weren, RD., Kuiper, RP., Ligtenberg, MJ., Geurts van Kessel, A., Hoogerbrugge, N., Verwiel, ET. et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet., 47*, 668-71.

Editions

2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Defective NTHL1 truncation mutants do not bind dihydrouracil (DHU) ↗

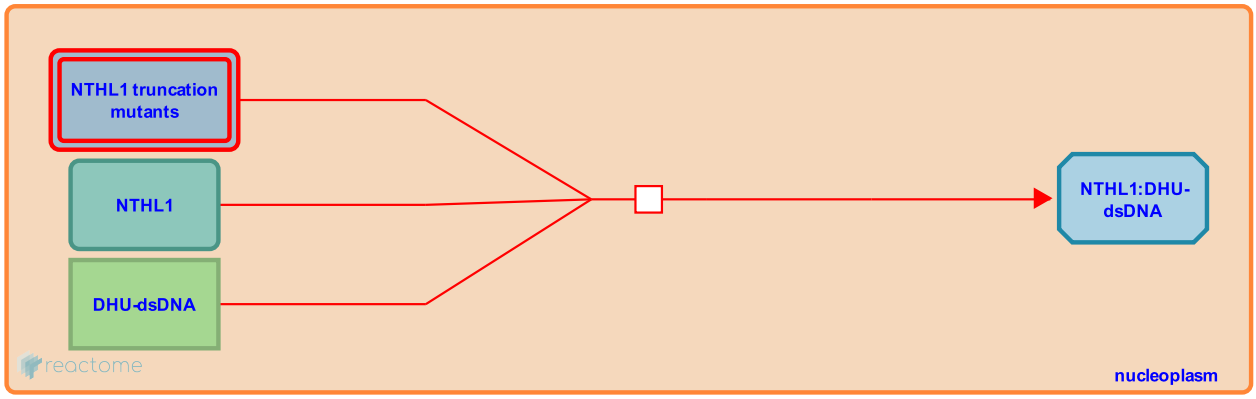
Location: Defective NTHL1 substrate binding

Stable identifier: R-HSA-9630045

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NTHL1 Q90TER (NTHL1 Q90*) truncation mutant (Weren et al. 2015) lacks the DNA binding domain and the glycosylase domain and is thus predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing dihydrouracil (DHU), although this has not been experimentally tested. NTHL1 Q287TER (NTHL1 Q287*) truncation mutant (Broderick et al. 2017) lacks a portion of the DNA binding domain, including glutamine residue Q287, important for substrate recognition (Robey-Bond et al. 2017) and is predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing dihydrouracil (DHU), although this has not been experimentally tested.

Literature references

Broderick, P., Kinnersley, B., Tomlinson, I., Dobbins, SE., Chubb, D., Houlston, RS. et al. (2017). Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology, 152*, 75-77.e4. ↗

Weren, RD., Kuiper, RP., Ligtenberg, MJ., Geurts van Kessel, A., Hoogerbrugge, N., Verwiel, ET. et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet., 47*, 668-71. ↗

Editions

2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Defective NTHL1 truncation mutants do not bind formamidopyrimidine (FapyA)

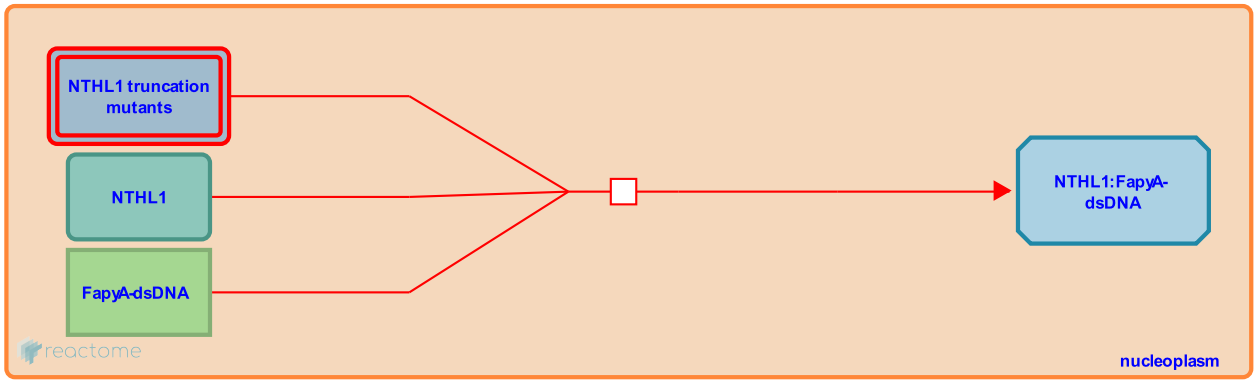
Location: Defective NTHL1 substrate binding

Stable identifier: R-HSA-9630044

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NTHL1 Q90TER (NTHL1 Q90*) truncation mutant (Weren et al. 2015) lacks the DNA binding domain and the glycosylase domain and is thus predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing formamidopyrimidine (FapyA), although this has not been experimentally tested. NTHL1 Q287TER (NTHL1 Q287*) truncation mutant (Broderick et al. 2017) lacks a portion of the DNA binding domain, including glutamine residue Q287, important for substrate recognition (Robey-Bond et al. 2017) and is predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing formamidopyrimidine (FapyA), although this has not been experimentally tested.

Literature references

Broderick, P., Kinnersley, B., Tomlinson, I., Dobbins, SE., Chubb, D., Houlston, RS. et al. (2017). Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology, 152*, 75-77.e4.

Weren, RD., Kuiper, RP., Ligtenberg, MJ., Geurts van Kessel, A., Hoogerbrugge, N., Verwiel, ET. et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet., 47*, 668-71.

Editions

2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Defective NTHL1 truncation mutants do not bind thymine glycol (Tg)

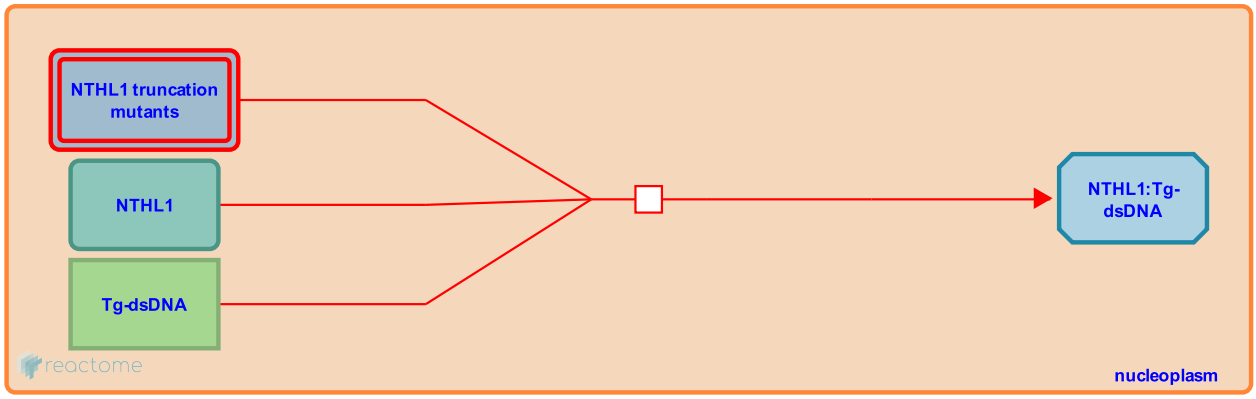
Location: Defective NTHL1 substrate binding

Stable identifier: R-HSA-9630043

Type: transition

Compartments: nucleoplasm

Diseases: cancer



NTHL1 Q90TER (NTHL1 Q90*) truncation mutant (Weren et al. 2015) lacks the DNA binding domain and the glycosylase domain and is thus predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing thymine glycol (Tg), although this has not been experimentally tested. NTHL1 Q287TER (NTHL1 Q287*) truncation mutant (Broderick et al. 2017) lacks a portion of the DNA binding domain, including glutamine residue Q287, important for substrate recognition (Robey-Bond et al. 2017) and is predicted to be unable to recognize and bind damaged DNA, including damaged DNA containing thymine glycol (Tg), although this has not been experimentally tested.

Literature references

Broderick, P., Kinnersley, B., Tomlinson, I., Dobbins, SE., Chubb, D., Houlston, RS. et al. (2017). Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology, 152*, 75-77.e4.

Weren, RD., Kuiper, RP., Ligtenberg, MJ., Geurts van Kessel, A., Hoogerbrugge, N., Verwiel, ET. et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet., 47*, 668-71.

Editions

2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Table of Contents