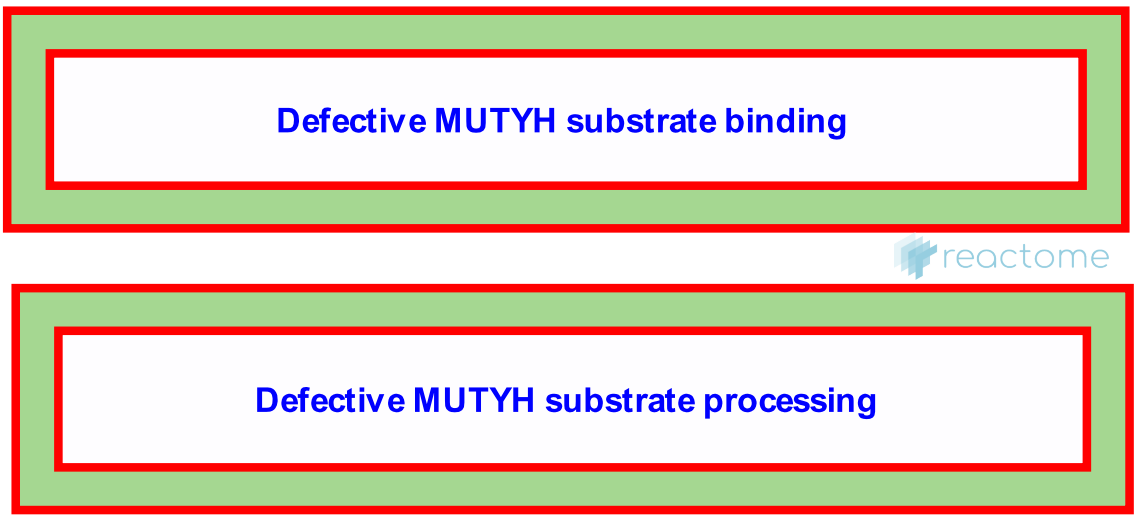
Defective Base Excision Repair Associated with MUTYH



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23/04/2024

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

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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. ↗

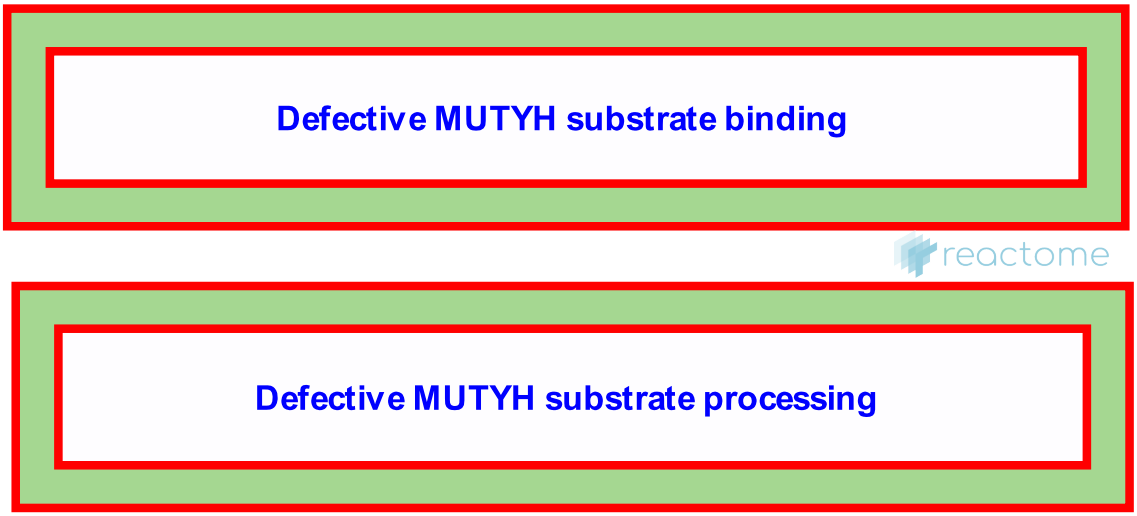
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Defective Base Excision Repair Associated with MUTYH ↗

Stable identifier: R-HSA-9605310

Diseases: familial adenomatous polyposis, colorectal cancer, cancer



MUTYH gene is located on chromosome 1 and encodes a DNA glycosylase involved in base excision repair (BER). MUTYH (MYH) functions as an adenine DNA glycosylase and removes adenines and 2-hydroxyadenines on the newly synthesized DNA strand mispaired with guanines or 8-oxoguanines. 8-oxogunanines are produced by oxidation of guanines in DNA or by incorporation of 8-oxodGTP from the nucleotide pool into the newly synthesized DNA strand. Germline mutations in MUTYH cause the MUTYH-associated polyposis (MAP), a syndrome that resembles the familial adenomatous polyposis (FAP) syndrome, caused by mutations in the APC tumor suppressor gene. MAP is also known as the familial adenomatous polyposis 2 (FAP2) (OMIM:608456). MAP-affected individuals are predisposed to development of multiple colorectal adenomas and colorectal cancer. MAP is largely inherited in an autosomally recessive manner, with both MUTYH alleles affected. The predisposition of heterozygous MUTYH mutation carriers to MAP has not been completely ruled out (Fleischmann et al. 2004).

MUTYH is most frequently affected by missense mutations in MAP patients, with two major mutations, Y165C and G382D, reported in about 80% of MAP patients of European origin. In Japanese patients, the most frequently reported mutation was Q324H (Yanaru-Fujisawa et al. 2008). Residues Y165C and G382D in the abundant MUTYH isoform MUTYH alpha-3 (MUTYH-3), used in the majority of functional studies, correspond to Y176C and G393D, respectively, in the canonical UniProt isoform (MUTYH alpha-1) and to Y179C and G396, respectively, in the longest NCBI isoform, which is used as a reference isoform in the database InSiGHT (International Society for Gastrointestinal Hereditary Tumours Database). However, both the canonical UniProt and NCBI MUTYH isoforms are expressed at very low levels or not at all (Plotz et al. 2012). In addition to the isoform MUTYH alpha-3, the other two abundant MUTYH isoforms are MUTYH beta-3 and MUTYH gamma-3 (Plotz et al. 2012), which differ from MUTYH alpha-3 in the first exon used. Exons 1-alpha and 1-beta contain sequences that resemble a mitochondrial targeting signal (MTS). It was reported that MUTYH alpha-3 and MUTYH beta-3 predominantly localize to mitochondria, while MUTYH gamma-3 predominantly localizes to the nucleus (Takao et al. 1999). However, a nuclear localization signal is located at the C-terminus of all MUTYH isoforms and other studies suggested that all isoforms can localize to the nucleus and only a small fraction of MUTYH is targeted to the mitochondria (Ohtsubo et al. 2000, Ichinoe et al. 2004). A small number of functional studies of MUTYH mutants uses the MUTYH isoform gama-3 (Goto et al. 2010, Shinmura et al. 2012). Nuclear localization of MUTYH may be affected by a splicing site variant (Tao et al. 2004).

MAP, compared with APC-associated FAP, is characterized by a later age of onset and a smaller number and size of polyps. Germline MUTYH mutations are associated with an increased incidence of duodenal polyps, gastric cancer, melanoma, breast cancer, dental and dermoid cysts, and osteomas. MUTYH mutations are rarely reported in the sporadic colorectal cancer. Tumors that develop in MAP patients are characterized with an excess of G:C -> T:A transversions in tumor suppressor genes, such as APC, and oncogenes, such as KRAS, which is a consequence of MUTYH functional impairment.

A single nucleotide polymorphism (SNP) at the splice donor site was reported to affect translation efficiency of

MUTYH transcript, but its relevance for cancer predisposition has not been clarified (Yamaguchi et al. 2002). Catalytic activity of MUTYH and its mutants may be affected by posttranslational modifications (Parker et al. 2003, Kundu et al. 2010). Some MUTYH mutations reported in colorectal cancer do not affect MUTYH catalytic activity but disrupt the interaction of MUTYH with other proteins involved in DNA repair (Tominaga et al. 2004, Turco et al. 2013).

For review, please refer to Chow et al. 2004, Nielsen et al. 2011, Venesio et al. 2012, Mazzei et al. 2013.

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Editions

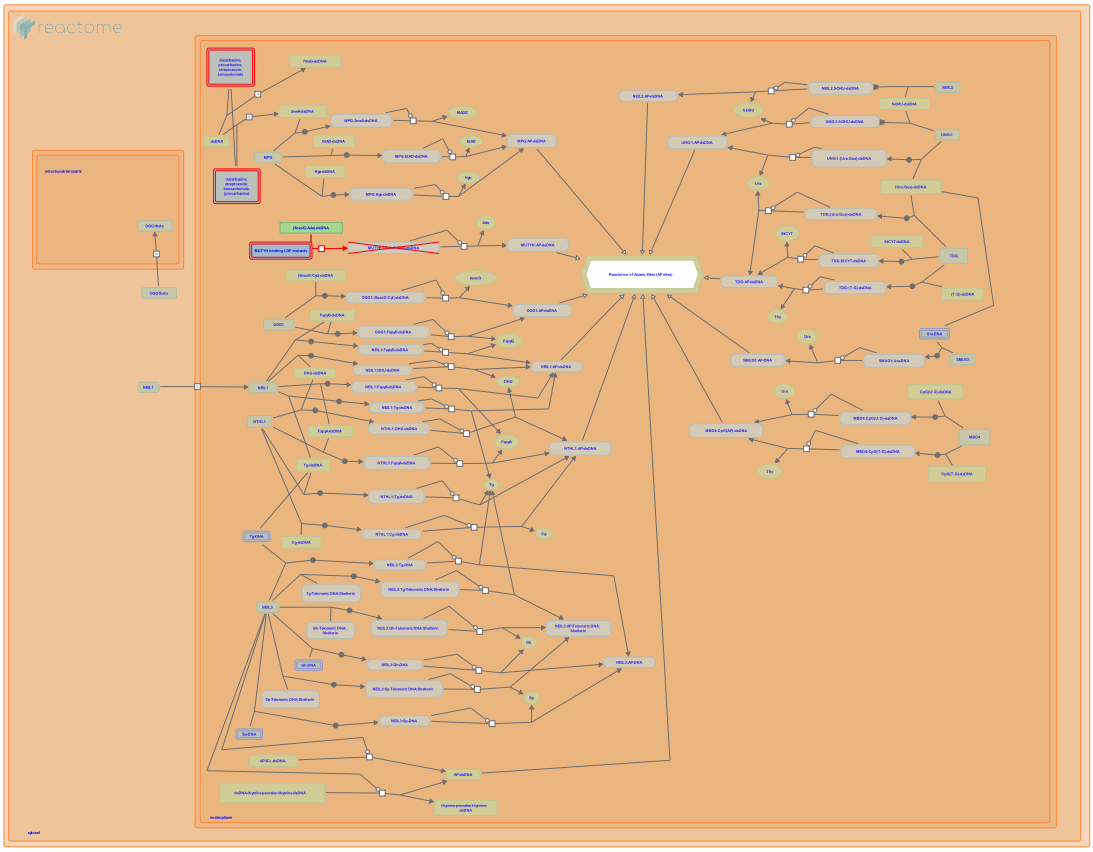
2018-05-12	Authored	Orlic-Milacic, M.
2018-06-28	Reviewed	Nakabeppu, Y.
2018-06-29	Edited	Orlic-Milacic, M.

Defective MUTYH substrate binding ↗

Location: Defective Base Excision Repair Associated with MUTYH

Stable identifier: R-HSA-9608287

Diseases: familial adenomatous polyposis, colorectal cancer, cancer



For a subset of MUTYH disease variants underlying MUTYH-associated polyposis (MAP), also known as familial adenomatous polyposis 2 (FAP2), it was shown that, in addition to impaired catalytic activity, they also exhibit reduced binding to their substrate, adenine mispaired with 8-oxoguanine (OGUA:Ade, also known as 8-oxoG:A). MUTYH alpha-3 isoform (MUTYH-3) mutants with demonstrated deficient binding to OGUA:Ade include missense variants MUTYH-3 Y165C, MUTYH-3 R227W, MUTYH-3 R231L, MUTYH-3 R231H, MUTYH-3 V232F, MUTYH-3 R260Q, MUTYH-3 P281L and MUTYH-3 G382D, nonsense variants MUTYH-3 Y90*, MUTYH-3 Q377*, MUTYH-3 E466*, and frameshift variant MUTYH-3 A368fs26* (commonly known as MUTYH 1103delC) (Chmiel et al. 2003, Parker et al. 2005, Ali et al. 2008, Molatore et al. 2010, D'Agostino et al. 2010).

Literature references

Albertini, AM., Bossa, C., Mazzei, F., Ranzani, GN., D'Agostino, VG., Torreri, P. et al. (2010). Functional analysis of MUTYH mutated proteins associated with familial adenomatous polyposis. *DNA Repair (Amst.), 9*, 700-7. ↗

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Ali, M., Bristow, R., Gallinger, S., Cleary, S., Kim, H., Cupples, C. (2008). Characterization of mutant MUTYH proteins associated with familial colorectal cancer. *Gastroenterology, 135*, 499-507. ↗

Chmiel, NH., David, SS., Livingston, AL. (2003). Insight into the functional consequences of inherited variants of the hMYH adenine glycosylase associated with colorectal cancer: complementation assays with hMYH variants and pre-steady-state kinetics of the corresponding mutated E.coli enzymes. *J. Mol. Biol., 327*, 431-43. ↗

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Editions

2018-05-12	Authored	Orlic-Milacic, M.
2018-06-28	Reviewed	Nakabeppu, Y.
2018-06-29	Edited	Orlic-Milacic, M.

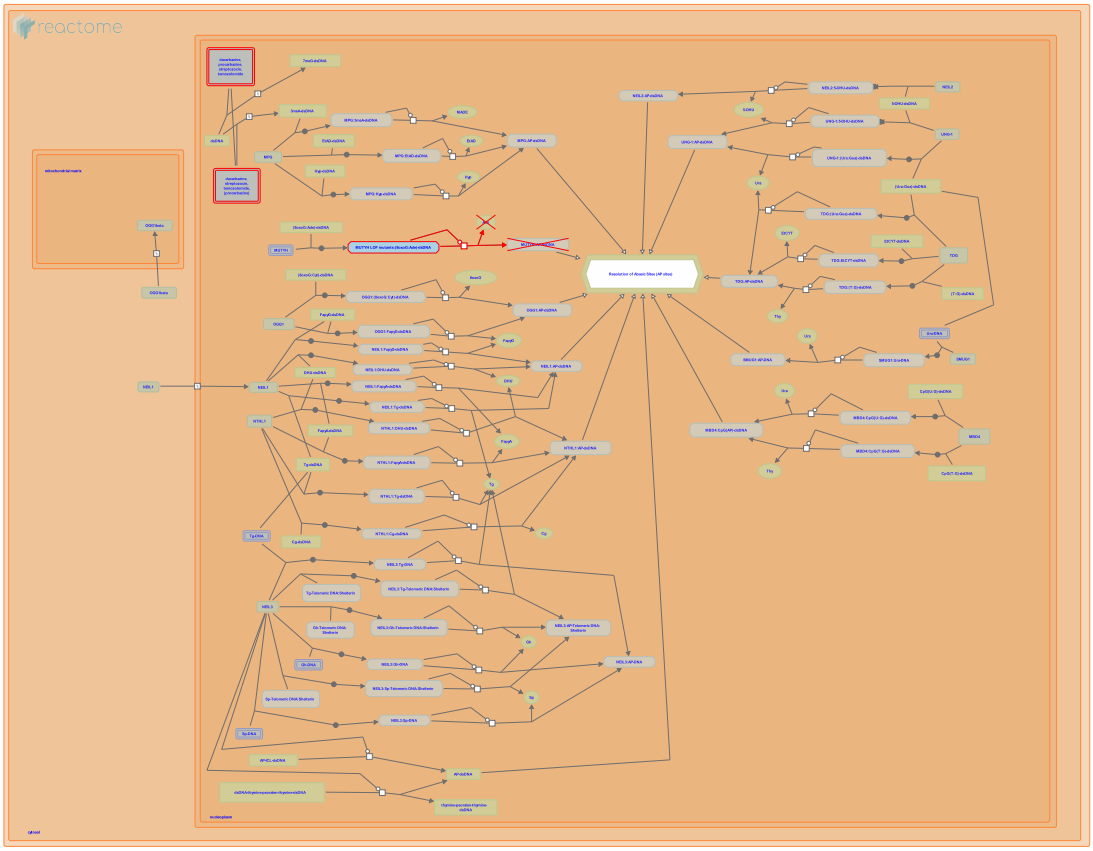
Defective MUTYH substrate processing ↗

Location: Defective Base Excision Repair Associated with MUTYH

Stable identifier: R-HSA-9608290

Compartments: nucleoplasm

Diseases: familial adenomatous polyposis, colorectal cancer, cancer



MUTYH disease variants underlying the MUTYH-associated polyposis (MAP), also known as familial adenomatous polyposis 2 (FAP2), show impaired catalytic activity with respect to cleaving adenine mispaired with 8-oxoguanine (OGUA:Ade, also known as 8-oxoG:A). For some of the mutants, defective substrate processing is further aggravated by reduced substrate binding. MUTYH alpha-3 isoform (MUTYH-3) mutants and MUTYH gamma-3 isoform (MUTYH-6) mutants with experimentally demonstrated deficiency in catalytic activity include missense mutants MUTYH-3 Y165C (MUTYH-6 Y151C), MUTYH-3 R171W, MUTYH-3 R227W, MUTYH-3 R231H, MUTYH-3 R231L, MUTYH-3 V232F, MUTYH-3 R260Q, MUTYH-3 G272E, MUTYH-3 P281L, MUTYH-3 P391L (MUTYH-6 P377L), MUTYH-3 Q324H, MUTYH-3 Q324R,, MUTYH-3 A359V, MUTYH-3 G382D (MUTYH-6 G368D), MUTYH-3 A459D, MUTYH-6 R154H, MUTYH-6 I195V, MUTYH-6 M255V and MUTYH-3 L360P, in-frame indel mutants MUTYH-3 W138_M139insIW (also known as MUTYH 137insIW) and MUTYH-3 E466del (MUTYH-6 E452del), nonsense mutants MUTYH-3 Y90*, MUTYH-3 Q377*, and MUTYH-3 E466*, and frameshift mutant MUTYH-3 A368fs26* (commonly known as MUTYH 1103delC) (Jones et al. 2002, Chmiel et al. 2003, Wooden et al. 2004, Parker et al. 2005, Bai et al. 2005, Alhopuro et al. 2005, Bai et al. 2007, Ali et al. 2008, Yanaru-Fujisawa et al. 2008, Kundu et al. 2009, Forsbring et al. 2009, Molatore et al. 2010, D'Agostino et al. 2010, Goto et al. 2010, Raetz et al. 2012, Shinmura et al. 2012).

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Albertini, AM., Bossa, C., Mazzei, F., Ranzani, GN., D'Agostino, VG., Torreri, P. et al. (2010). Functional analysis of MUTYH mutated proteins associated with familial adenomatous polyposis. *DNA Repair (Amst.), 9*, 700-7. ↗

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Editions

2018-05-11	Authored	Orlic-Milacic, M.
2018-06-28	Reviewed	Nakabeppu, Y.
2018-06-29	Edited	Orlic-Milacic, M.

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