

# Defective MUTYH mutants do not cleave adenine mispaired with 8-oxoguanine

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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

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Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)

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Reactome database release: 88

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

## Defective MUTYH mutants do not cleave adenine mispaired with 8-oxoguanine ↗

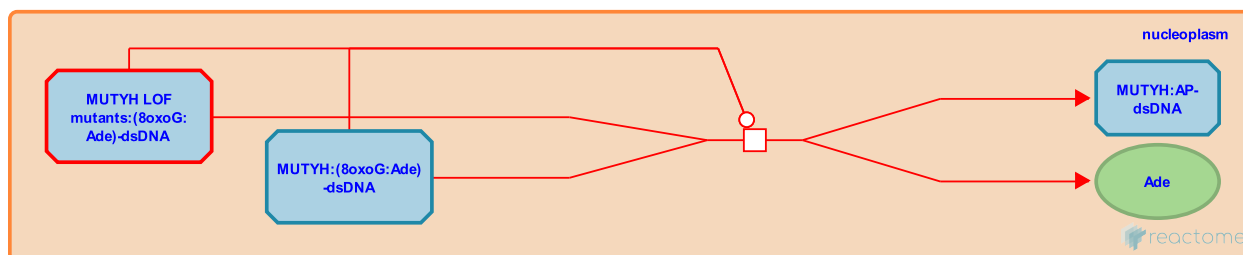
**Stable identifier:** R-HSA-9605313

**Type:** transition

**Compartments:** nucleoplasm

**Diseases:** familial adenomatous polyposis, colorectal cancer, cancer

**Inferred from:** Defective Mutyh mutants do not cleave adenine mispaired with 8-oxoguanine (Mus musculus)



MUTYH alpha-3 isoform (MUTYH-3) mutants MUTYH-3 Y165C and MUTYH-3 G382D have impaired ability to cleave adenine mispaired with 8-oxoguanine (OGUA:Ade, also known as 8-oxoG:A), and also show a reduced binding to the OGUA:Ade substrate (Jones et al. 2002, Chmiel et al. 2003, Wooden et al. 2004, Parker et al. 2005, Ali et al. 2008, Molatore et al. 2010, D'Agostino et al. 2010, Raetz et al. 2012). Impairment of catalytic activity was confirmed for the corresponding MUTYH gamma-3 isoform (MUTYH-6) mutants, MUTYH-6 Y151C and MUTYH-6 G368D (Gotto et al. 2010). Residues Y165 and G382 are conserved in mutY of *Escherichia coli* (Y82 and G253). Introduction of Y82C and G253D mutations into *E. coli* mutY significantly reduces the catalytic activity of bacterial mutY towards the OGUA:Ade substrate (Al-Tassan et al. 2002, Chmiel et al. 2003). MUTYH-3 Y165C and MUTYH-3 G382D are the two most common MUTYH mutations in patients of European origin affected by MUTYH-associated polyposis (MAP), also known as familial adenomatous polyposis 2 (FAP2) (Sieber et al. 2003, Sampson et al. 2003).

MUTYH-3 Q324H was reported as the most prevalent mutant in Japanese MAP patients (Yanaru-Fujisawa et al. 2008), and results in partial impairment of MUTYH DNA glycosylase activity (Ali et al. 2008). Q324H is a common polymorphism in some populations (Sampson et al. 2003, Raetz et al. 2012) but is associated with reduced catalytic activity of MUTYH and predisposition to cancer (Raetz et al. 2012).

MUTYH mutant MUTYH-3 R227W is unable to bind and process the OGUA:Ade substrate, while the MUTYH-3 V232F mutant shows severely reduced binding and catalytic activity towards OGUA:Ade. Neither MUTYH-3 R227W nor MUTYH-3 V232F can complement the mutY deficient *E. coli* cells (Bai et al. 2005). Mutation R231L lies in the same region and MUTYH-3 R231L mutants also show impaired binding to OGUA:Ade and no glycosylase activity. As expected, MUTYH-3 R231L was unable to complement *E. coli* mutY mutants (Bai et al. 2007). MUTYH-3 R231H mutant, defective in DNA binding and glycosylase activity, was reported in both adenomatous polyposis (Ali et al. 2008) and lung squamous cell carcinoma.

MUTYH-3 A459D mutant shows significantly reduced repair of OGUA:Ade mismatch and cannot complement the defective mutY in *E. coli* (Alhopuro et al. 2005).

Mutants MUTYH-3 G272E and MUTYH-3 A359V, reported in Japanese patients with adenomatous polyposis and wild-type APC gene, have impaired DNA glycosylase activity, based on studies with mouse Mutyh proteins carrying synonymous mutations. Affected residues, G272 and A359, are conserved in prokaryotic mutY and mouse Mutyh (Yanaru-Fujisawa et al. 2008). MUTYH-3 A359S mutant was reported in medulloblastoma (Pugh et al. 2012). This mutant has not been functionally tested, but is predicted to be pathogenic and is annotated as a candidate LOF mutant.

Mutants MUTYH-3 R260Q and MUTYH-3 P281L show impaired DNA binding and glycosylase activity, with MUTYH-3 P281L being more severely affected (Ali et al. 2008). In addition to adenomatous polyposis, MUTYH-3 R260Q was reported in stomach cancer and primary sclerosing cholangitis, a risk factor for development of cholangiocarcinoma (Forsbring et al. 2009). MUTYH-3 R260W mutant was detected in melanoma, skin squamous cell carcinoma, and chondrosarcoma (Tarpey et al. 2013, Pickering et al. 2014, Li et al. 2015). R260W substitution is predicted to be pathogenic, but has not been functionally tested, and therefore MUTYH-3 R260W was annotated as a candidate LOF mutant.

Mutants MUTYH-3 P391L and MUTYH-3 Q324R show reduced DNA glycosylase activity. While MUTYH-3 Q324R is able to complement E. coli mutY mutants, MUTYH-3 P391L is not (Kundu et al. 2009). MUTYH-6 P377L, a gamma-3 isoform mutant corresponding to MUTYH-3 P391L, is also not functional (Goto et al. 2010, Shinmura et al. 2012).

Loss-of-function of MAP-associated MUTYH mutants MUTYH-3 R171W, MUTYH-3 W138\_M139insIW (also known as MUTYH 137insIW) and MUTYH-3 E466del was confirmed by expression of recombinant human proteins in Mutyh knockout mouse cells and measuring accumulation of OGUA in the genome and hypersensitivity to oxidative stress (Molatore et al. 2010), as well as by in vitro evaluation of their catalytic activity using the surface plasmon resonance technology (D'Agostino et al. 2010). Loss-of-function was also confirmed for MUTYH-6 E452del mutant, which corresponds to MUTYH-3 E466del (Goto et al. 2010).

Frameshift mutations in MUTYH, which result in MUTYH protein truncation, also occur in MAP patients. The nonsense mutants MUTYH-3 Y90\*, MUTYH-3 Q377\* and MUTYH-3 E466\*, and frameshift mutant MUTYH-3 A368fs26\* (commonly known as MUTYH 1103delC) are neither able to bind target DNA nor excise adenine mispaired with OGUA (Ali et al. 2008).

Impaired catalytic activity was shown for MUTYH gamma-3 isoform mutants MUTYH-6 I195V, MUTYH-6 M255V, MUTYH-6 R154H and MUTYH-3 L360P, but the corresponding alpha-3 isoform mutants have not been tested (Goto et al. 2010, Shinmura et al. 2012). A MUTYH missense mutation corresponding to R154H was reported in pancreatic ductal adenocarcinoma (Witkiewicz et al. 2015).

Literature references

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Editions

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