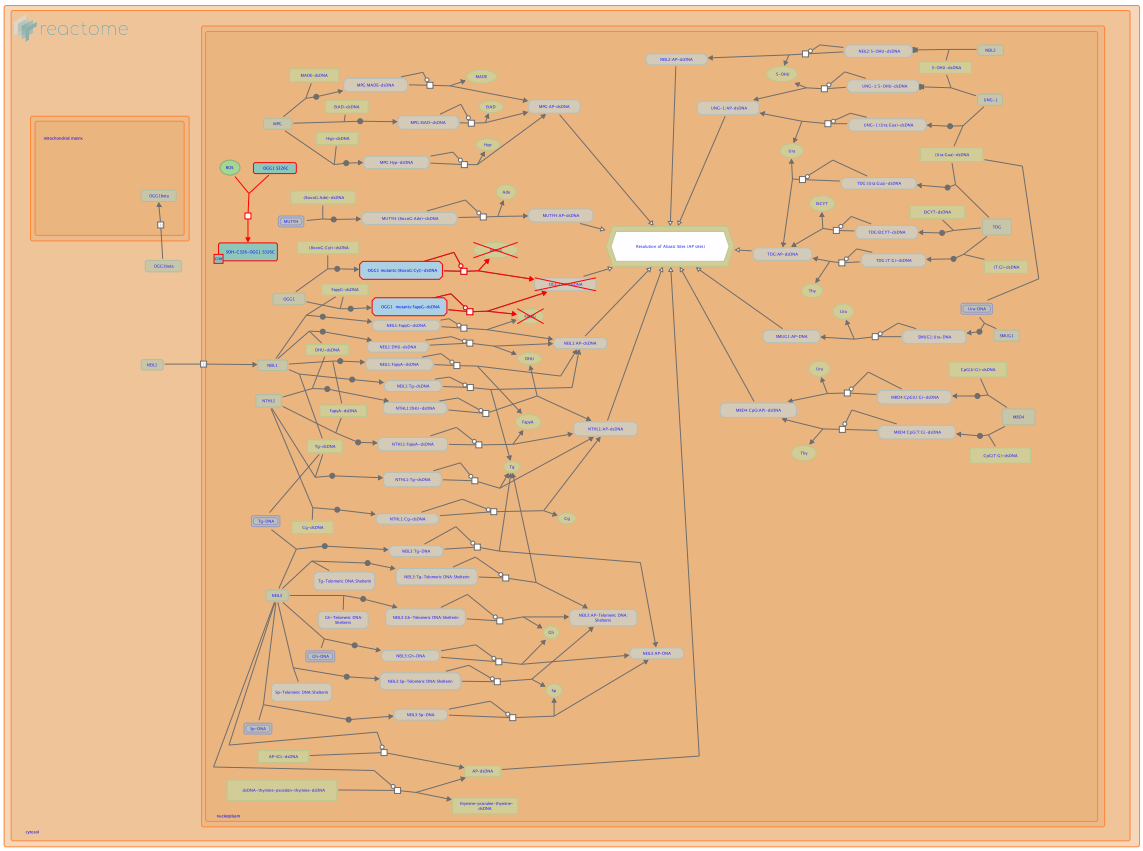
Defective OGG1 Substrate Processing



Boldogh, I., Orlic-Milacic, M., Vlahopoulos, S.

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

26/08/2021

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. ↗

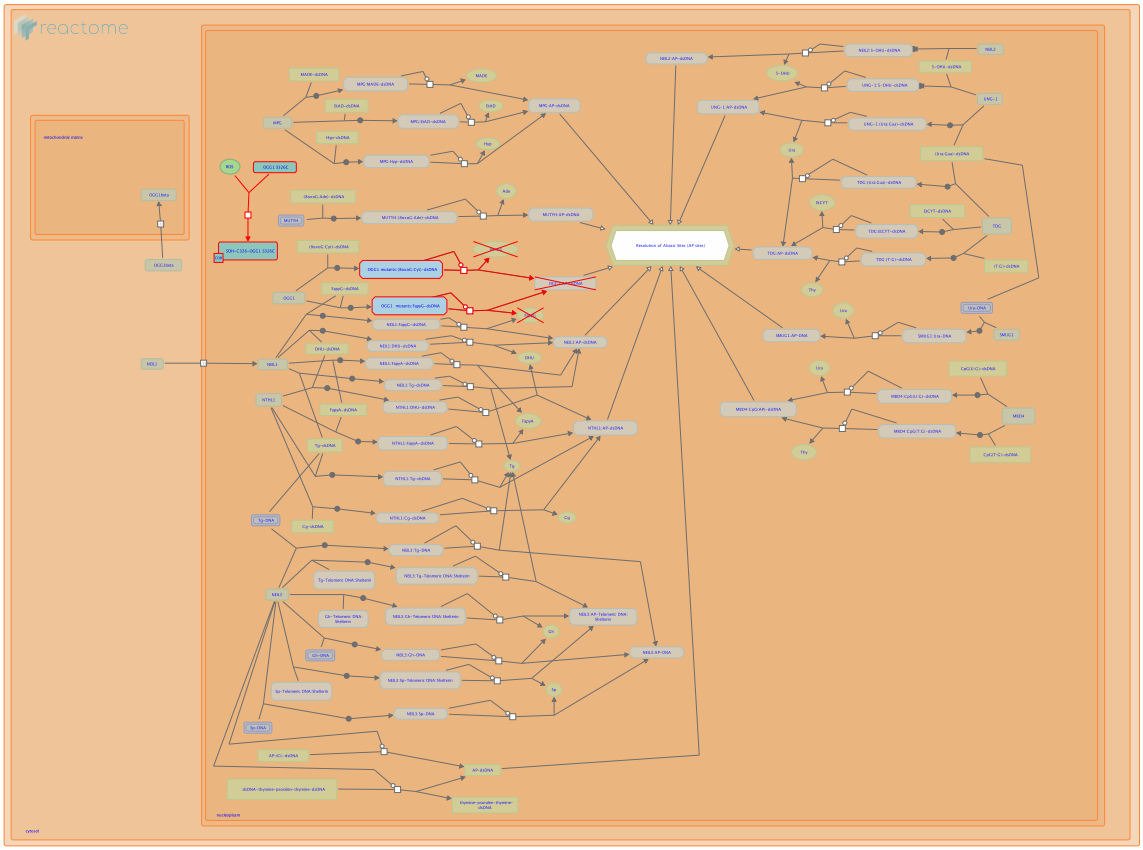
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 OGG1 Substrate Processing ↗

Stable identifier: R-HSA-9656256

Diseases: Alzheimer's disease, cancer



The majority of OGG1 mutants have been tested for their ability to excise 8-oxoguanine (8oxoG) from damaged DNA, while a small number of mutants have been tested for the ability to remove FapyG from DNA.

The following OGG1 mutants show at least a partial loss of their ability to remove 8oxoG:

OGG1 R46Q (Audebert, Chevillard et al. 2000; Audebert, Radicella et al. 2000);

OGG1 R154H (Audebert, Radicella et al. 2000, Bruner et al. 2000);

OGG1 R131Q (Chevillard et al. 1998, Bruner et al. 2000, Anderson and Dagget 2009);

OGG1 R229Q (Hyun et al. 2000, Hyun et al. 2002, Hill and Evans 2007);

OGG1 P266fs139* (Mao et al. 2007).

OGG1 R46L and OGG1 R131G have not been functionally studied but have been reported in cancer and predicted to be pathogenic. They are annotated as candidate disease variants based on their similarity with OGG1 R46Q and OGG1 R131Q, respectively.

OGG1 S326C, a frequent variant in European and Asian populations, is susceptible to oxidation, which diminishes catalytic activity under conditions of oxidative stress (Dherin et al. 1999, Yamane et al. 2004, Kershaw and Hodges 2012, Moritz et al. 2014).

The following OGG1 mutants show at least a partial loss of their ability to remove FapyG:

OGG1 R46Q (Audebert, Radicella et al. 2000);

OGG1 R154H (Audebert, Radicella et al. 2000).

OGG1 R46L has not been functionally studied but has been reported in cancer and predicted to be pathogenic. It is annotated as a candidate disease variant for FapyG excision, based on its similarity with OGG1 R46Q.

Literature references

Bruner, SD., Norman, DP., Verdine, GL. (2000). Structural basis for recognition and repair of the endogenous mutagen 8-oxoguanine in DNA. *Nature, 403*, 859-66. ↗

Hyun, JW., Cheon, GJ., Kim, HS., Lee, YS., Choi, EY., Yoon, BH. et al. (2002). Radiation sensitivity depends on OGG1 activity status in human leukemia cell lines. *Free Radic. Biol. Med., 32*, 212-20. ↗

Chevillard, S., Radicella, JP., Levalois, C., Lebeau, J., Poupon, MF., Oudard, S. et al. (1998). Mutations in OGG1, a gene involved in the repair of oxidative DNA damage, are found in human lung and kidney tumours. *Oncogene, 16* , 3083-6. ↗

Dherin, C., Radicella, JP., Dizdaroglu, M., Boiteux, S. (1999). Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations. *Nucleic Acids Res., 27*, 4001-7. ↗

Kershaw, RM., Hodges, NJ. (2012). Repair of oxidative DNA damage is delayed in the Ser326Cys polymorphic variant of the base excision repair protein OGG1. *Mutagenesis, 27*, 501-10. ↗

Editions

2019-07-30	Authored	Orlic-Milacic, M.
2019-10-02	Reviewed	Vlahopoulos, S.
2019-10-08	Reviewed	Boldogh, I.
2019-10-10	Edited	Orlic-Milacic, M.

OGG1 S326C is oxidized ↗

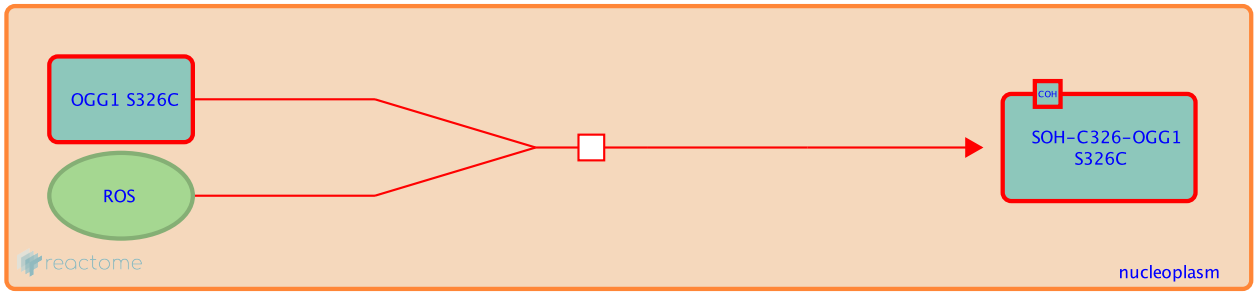
Location: Defective OGG1 Substrate Processing

Stable identifier: R-HSA-9658813

Type: transition

Compartments: nucleoplasm

Diseases: cancer



OGG1 S326C is a frequent genetic polymorphism, present in more than 20% of people of European and Asian descent (Janssen et al. 2001, Moritz et al. 2014). On its own, substitution of serine with cysteine at position 326 does not affect the catalytic activity of OGG1 (Dherin et al. 1999, Janssen et al. 2001, Moritz et al. 2014). However, under oxidative stress, OGG1 S326C variant is more susceptible to oxidation or nitrosation than the wild type enzyme (Moritz et al. 2014), which diminishes catalytic activity and leads to accumulation of genomic 8-oxoguanine (8oxoG) (Yamane et al. 2004, Moritz et al. 2014) under conditions of oxidative stress (Kershaw and Hodges 2012). This may be due to decreased specificity of OGG1 S326C for 8oxoG and FapyG (Dherin et al. 1999).

The frequency of OGG1 S326C allele is increased in NSCLC patients and the level of 8-oxodG is higher in lung tissue and leukocytes of these patients (Janik et al. 2011). OGG1 S326C variant is associated with an increased breast cancer risk (Ali et al. 2015).

Literature references

Moritz, E., Pauly, K., Bravard, A., Hall, J., Radicella, JP., Epe, B. (2014). hOGG1-Cys326 variant cells are hypersensitive to DNA repair inhibition by nitric oxide. *Carcinogenesis, 35*, 1426-33. ↗

Janik, J., Swoboda, M., Janowska, B., Cieśla, JM., Gackowski, D., Kowalewski, J. et al. (2011). 8-Oxoguanine incision activity is impaired in lung tissues of NSCLC patients with the polymorphism of OGG1 and XRCC1 genes. *Mutat. Res., 709*, 21-31. ↗

Ali, K., Mahjabeen, I., Sabir, M., Mehmood, H., Kayani, MA. (2015). OGG1 Mutations and Risk of Female Breast Cancer: Meta-Analysis and Experimental Data. *Dis. Markers, 2015*, 690878. ↗

Editions

2019-07-30	Authored	Orlic-Milacic, M.
2019-10-02	Reviewed	Vlahopoulos, S.
2019-10-08	Reviewed	Boldogh, I.
2019-10-10	Edited	Orlic-Milacic, M.

Defective OGG1 mutants do not excise 8-oxoguanine ↗

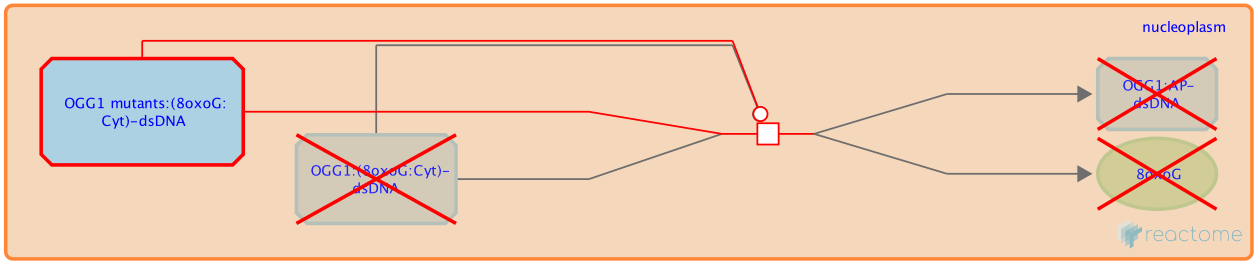
Location: Defective OGG1 Substrate Processing

Stable identifier: R-HSA-9656250

Type: transition

Compartments: nucleoplasm

Diseases: cancer, Alzheimer's disease



OGG1 missense mutants OGG1 R46Q (Audebert, Chevillard et al. 2000; Audebert, Radicella et al. 2000), reported in clear cell renal carcinoma, and OGG1 R154H (Audebert, Radicella et al. 2000), reported in gastric cancer cell line MKN4 (Bruner et al. 2000), show a diminished 8-oxoguanine (8oxoG)-directed DNA glycosylase activity, with the function of OGG1 R154H being more severely impaired. The first functional study of OGG1 R154H reported catalytic activity similar to the wild type OGG1, but promiscuous substrate binding, which could result in a mutator phenotype (Bruner et al. 2000).

OGG1 R131Q mutant, reported in lung cancer, shows the loss of 8oxoG-directed glycolytic activity (Chevillard et al. 1998), which, based on structural studies, is predicted to be the consequence of misfolding of the active site (Bruner et al. 2000, Anderson and Dagget 2009). Distortion of the active site was also found to be the cause of impaired function of OGG1 R46Q and OGG1 R154H.

OGG1 missense mutant, OGG1 R229Q, reported in the acute myeloid leukemia-derived cell line KG-1, shows a loss of 8oxoG-directed DNA glycosylase activity (Hyun et al. 2000, Hyun et al. 2002), which is due to thermolability of the OGG1 R229Q mutant (Hill and Evans 2007).

OGG1 frameshift mutant, OGG1 P266fs139*, reported in Alzheimer's disease, exhibits loss of glycosylase activity and is unable to excise 8oxoG from damaged DNA (Mao et al. 2007).

It is uncertain whether substrate binding is affected in OGG1 R46Q, OGG1 R229Q and OGG1 P266fs139*. Excision of FapyG from dsDNA by OGG1 R46Q, OGG1 R131Q, OGG1 R229Q and OGG1 P266fs139* has not been tested.

OGG1 R46L and OGG1 R131G have not been functionally studied but have been reported in cancer and predicted to be pathogenic. They are annotated as candidate disease variants based on their similarity with OGG1 R46Q and OGG1 R131Q, respectively.

OGG1 S326C is a frequent genetic polymorphism in people of European and Asian descent. OGG1 S326C variant is susceptible to oxidation, leading to diminished catalytic activity and accumulation of 8oxoG (Yamane et al. 2004, Moritz et al. 2014) under conditions of oxidative stress (Kershaw and Hodges 2012). This may be due to decreased specificity of OGG1 S326C for 8oxoG (Dherin et al. 1999).

Lysine 249 (K249) of OGG1 is directly involved in the nucleophilic attack of the N-glycosidic bond while aspartate 268 (D268) of OGG1 primes K249 for the nucleophilic attack. Both K249 and D268 are critical for the excision of 8oxoG lesions from damaged DNA. By directed mutagenesis, OGG1 K249Q (Nash et al. 1997), OGG1 D268A (Bjoras et al. 2002) and OGG1 D268N (Bjoras et al. 2002, Norman et al. 2003, Sebera et

al. 2017) mutants were shown to be non-functional in 8oxoG cleavage. Naturally occurring variant alleles of OGG1 that produce OGG1 K249Q, OGG1 D268A and OGG1 D268N have been reported in human populations (ClinGene Allele Registry - Pawliczek et al. 2018) but have so far not been associated with a specific disease.

Literature references

Mao, G., Pan, X., Zhu, BB., Zhang, Y., Yuan, F., Huang, J. et al. (2007). Identification and characterization of OGG1 mutations in patients with Alzheimer's disease. *Nucleic Acids Res., 35*, 2759-66. ↗

Hyun, JW., Choi, JY., Zeng, HH., Lee, YS., Kim, HS., Yoon, SH. et al. (2000). Leukemic cell line, KG-1 has a functional loss of hOGG1 enzyme due to a point mutation and 8-hydroxydeoxyguanosine can kill KG-1. *Oncogene, 19*, 4476-9. ↗

Hill, JW., Evans, MK. (2007). A novel R229Q OGG1 polymorphism results in a thermolabile enzyme that sensitizes KG-1 leukemia cells to DNA damaging agents. *Cancer Detect. Prev., 31*, 237-43. ↗

Hyun, JW., Cheon, GJ., Kim, HS., Lee, YS., Choi, EY., Yoon, BH. et al. (2002). Radiation sensitivity depends on OGG1 activity status in human leukemia cell lines. *Free Radic. Biol. Med., 32*, 212-20. ↗

Audebert, M., Chevillard, S., Levalois, C., Gyapay, G., Vieillefond, A., Klijanienko, J. et al. (2000). Alterations of the DNA repair gene OGG1 in human clear cell carcinomas of the kidney. *Cancer Res., 60*, 4740-4. ↗

Editions

2019-07-30	Authored	Orlic-Milacic, M.
2019-10-02	Reviewed	Vlahopoulos, S.
2019-10-08	Reviewed	Boldogh, I.
2019-10-10	Edited	Orlic-Milacic, M.

Defective OGG1 mutants do not excise FapyG ↗

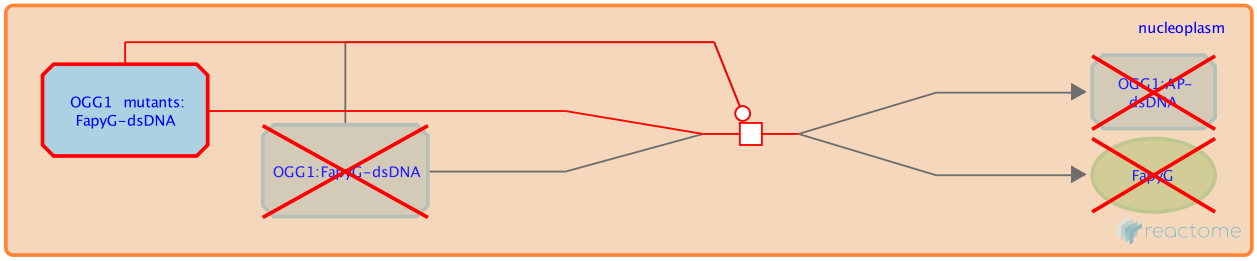
Location: Defective OGG1 Substrate Processing

Stable identifier: R-HSA-9656252

Type: transition

Compartments: nucleoplasm

Diseases: cancer



OGG1 R46Q mutant, reported in renal carcinoma, and OGG1 R154H mutant, reported in stomach cancer cell line MKN4 (Bruner et al. 2000), show decreased excision of FapyG from dsDNA (Audebert, Radicella et al. 2000), with the function of OGG1 R154H being more severely impaired. It is uncertain whether binding to FapyG in dsDNA substrate is affected in OGG1 R46Q and OGG1 R154H.

OGG1 R46L has not been functionally studied but has been reported in cancer and predicted to be pathogenic. It is annotated as a candidate disease variant based on its similarity with OGG1 R46L.

OGG1 S326C is a frequent genetic polymorphism in people of European and Asian descent. OGG1 S326C variant is susceptible to oxidative modifications, leading to diminished catalytic activity (Yamane et al. 2004, Moritz et al. 2014) under conditions of oxidative stress (Kershaw and Hodges 2012). This may be due to decreased specificity of OGG1 S326C for FapyG (Dherin et al. 1999).

Literature references

Audebert, M., Radicella, JP., Dizdaroglu, M. (2000). Effect of single mutations in the OGG1 gene found in human tumors on the substrate specificity of the Ogg1 protein. *Nucleic Acids Res., 28*, 2672-8. ↗

Dherin, C., Radicella, JP., Dizdaroglu, M., Boiteux, S. (1999). Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations. *Nucleic Acids Res., 27*, 4001-7. ↗

Editions

2019-07-30	Authored	Orlic-Milacic, M.
2019-10-02	Reviewed	Vlahopoulos, S.
2019-10-08	Reviewed	Boldogh, I.
2019-10-10	Edited	Orlic-Milacic, M.

Table of Contents