MLH1 variants-defective DNA mismatch repair

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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

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. ↗

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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. ↗

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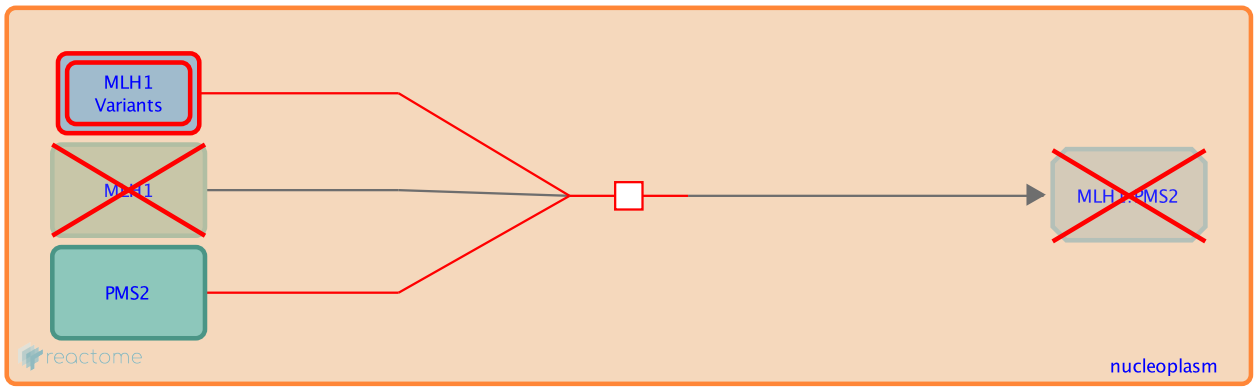
Stable identifier: R-HSA-5545484

Type: transition

Compartments: nucleoplasm

Diseases: colorectal cancer



MLH1 heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative DNA mismatch repair system (MMR). This system assembles in a stepwise fashion, with the MutL complex recruited after the the dsDNA mismatch has been identified.

Two representative MLH1 variants are described, MLH1 HIS329PRO and MLH1 SER252TER. The MLH1 HIS329PRO variant was identified in a family that fulfilled the Amsterdam criteria (a set of diagnostic criteria used to help identify families likely to carry gene variants predisposing them to hereditary nonpolyposis colorectal cancer (HNPCC)) of HNPCC as well as its identification as a his329-to-pro germline mutation (Vasen et al., 1991, Wang et al. 1997). The mutations' pathogenic significance was supported by the identification of the same missense mutation as a somatic event ('second hit') in colonic tumors of 2 other HNPCC patients who had germline mutations at different sites of the MLH1 gene.

The MLH1 SER252TER variant was identified in a colorectal tumor cell line manifesting microsatellite instability (Papadopoulos et al, 1994). Sequence analysis of the cDNA revealed a C-to-A transversion at codon 252, resulting in the substitution of a stop codon for serine.

Literature references

Papadopoulos, N., Nicolaides, NC., Wei, YF., Ruben, SM., Carter, KC., Rosen, CA. et al. (1994). Mutation of a mutL homolog in hereditary colon cancer. *Science, 263*, 1625-9. ↗

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Editions

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