Reading skills_MSH2_part1

Created by Dr. Dongfang Wang, Jan 2014

Please work as a group and submit a single document before class on Week2day2, with following components:

1. Section number, group number, name of all participating group members.
2. Answers to the questions (see below).

Assignment Description:

Please read the information between the dashed lines, and answer the following questions. You will need to do additional literature and Google search to answer all the questions.

Functional Characterization of Pathogenic Human MSH2 Missense Mutations in *Saccharomyces cerevisiae*

Alison E. Gammie, Naz Erdeniz, Julia Beaver, Barbara Devlin, Afshan Nanji and Mark D. Rose

Genetics 177: 707–721 (October 2007)

ABSTRACT
Hereditary nonpolyposis colorectal cancer (HNPCC) is associated with defects in DNA mismatch repair. Mutations in either hMSH2 or hMLH1 underlie the majority of HNPCC cases. Approximately 25% of annotated hMSH2 disease alleles are missense mutations, resulting in a single change out of 934 amino acids. We engineered 54 missense mutations in the cognate positions in yeast MSH2 and tested for function. Of the human alleles, 55% conferred strong defects, 8% displayed intermediate defects, and 38% showed no defects in mismatch repair assays. Fifty percent of the defective alleles resulted in decreased steady-state levels of the variant Msh2 protein, and 49% of the Msh2 variants lost crucial protein–protein interactions. Finally, nine positions are predicted to influence the mismatch recognition complex ATPase activity. In summary, the missense mutations leading to loss of mismatch repair defined important structure–function relationships and the molecular analysis revealed the nature of the deficiency for Msh2 variants expressed in the tumors. Of medical relevance are 15 human alleles annotated as pathogenic in public databases that conferred no obvious defects in mismatch repair assays. This analysis underscores the importance of functional characterization of missense alleles to ensure that they are the causative factor for disease.

Questions (please answer in your own words):

1. What is the title of the article? When was it published?
2. How many authors contributed to this work? Who contributed the most?

3. What is the name of the journal? What are the volume number and page number of this article?
4. Find the PubMed link for this article (Try NCBI PubMed advanced search, by author, date, etc).
5. In this article, what was identified as the putative **cause** for hereditary nonpolyposis colorectal cancer (HNPCC)? What is the nature of this **cause** (genetic predisposition, environment, or pathogen)?
6. Find a piece of evidence from this abstract to support the claim "the putative **cause** is linked to HNPCC". Describe the evidence and argue for the claim.
7. What is MSH2? What is the function of MSH2 protein (find out as much as you can bout MSH2)?
8. Which MSH2 was analyzed in this article, human or yeast?
9. What is the meaning of "cognate positions in yeast MSH2"?
10. Describe a significant new discovery about MSH2 presented in this abstract.