

MEETING ABSTRACT



Functional *in silico* analysis of missense mutations in the MSH6 gene

controls.

Katarzyna Gajdel^{1*}, Grzegorz Kurzawski²

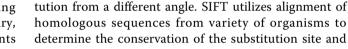
From Annual Conference on Hereditary Cancers 2013 Szczecin, Poland. 26-27 September 2013

Missense mutations of mismatch repair (MMR) genes – MLH1, MSH2, MSH6 and PMS2 – may (but do not necessarily) play a role in the etiology of the Lynch syndrome (LS) which is one of the hereditary cancer susceptibility syndromes. Pathogenic mutations in one of those genes result in a higher risk of developing cancer in colon, endometrium, small intestine, ovary, urinary tract, stomach or breast. One in ten patients with LS have a germline mutation in MSH6, and 40% of all mutations in that gene are single amino acid substitutions.

One of the elements taking part in the MMR process is the MSH6 protein which, along with MSH2, is a component of a protein dimer - MutSa. MMR function is critical in maintaining cellular DNA integrity. Loss of that function results in increased number of uncorrected mutations which may lead to malignant tissue transformation. This is why it is crucial to determine whether the detected change is located in a DNA sequence coding the MMR protein and if it impairs the repair function. Alas, the consequences of single amino acid substitution are often harder to evaluate than outcomes of deletions, insertions or nonsense mutations. Moreover, performing a functional and molecular analysis for each detected alteration would be too expensive and unrealistic. This is where the use of prediction software would be of assistance.

The intent of this thesis was to determine the pathogenic significance of a set of missense mutations using selected *in silico* analysis tools and to evaluate their utility in everyday use.

Twenty-one *MSH6* missense mutations were analyzed, three of them already classified as non-pathogenic



thereby estimates the potential pathogenicity of a mutation. PolyPhen-2 prediction is based on the sequence, protein structure and position of each mutation. The last of the used programs was ESEfinder which tested the impact of a mutation on the presence of ESEs (Exonic Splicing Enhancers) in the examined sequence.

polymorphisms, and two had confirmed pathogenic status.

They were used accordingly as negative and positive

Three online programs were used for the analysis of

those mutations, which allowed to evaluate each substi-

After performing the *in silico* analysis and confronting the results with data available in literature and the Internet databases, it was established that next to one of the changes confirmed as non-pathogenic polymorphisms, there are probably eight further non-pathogenic ones. Likewise, beside the two confirmed pathogenic alterations, in the analyzed set there were probably five additional pathogenic mutations. The last group is formed by substitutions that remain uncertain because of their ambiguous results.

Following the analysis of the results and available data, a conclusion was reached that the sole use of *in silico* prediction is not sufficient for a complete classification of the mutations, but they may be helpful for decision making in choosing or prioritizing the variants worth further analysis.

Authors' details



© 2015 Gajdel and Kurzawski This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/ publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

^{*} Correspondence: k.gajdel@wp.pl

¹Pomeranian Medical University, Faculty of Medical Biotechnology, Szczecin, Poland

Full list of author information is available at the end of the article

¹Pomeranian Medical University, Faculty of Medical Biotechnology, Szczecin, Poland. ²Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland.

Published: 9 September 2015

doi:10.1186/1897-4287-13-S1-A10 Cite this article as: Gajdel and Kurzawski: Functional *in silico* analysis of missense mutations in the MSH6 gene. *Hereditary Cancer in Clinical Practice* 2015 13(Suppl 1):A10.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit

BioMed Central