The Future of Whole-Genome Sequencing: MGMT Mutations in a Family Could Be Linked to Cervical Cancer

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1. Abstract

In 2008, the CDC reported 4,008 cervical cancer-related deaths in the US (1). Researchers at MCW used Whole Genome Sequencing technology to sequence the DNA of a mother and daughter diagnosed with a rapidly progressing cervical cancer. Identifying the genetic underpinnings could explain how their cancer developed and progresses, and help develop a specific treatment. One candidate gene, O-6-methylguanine-DNA-methyltransferase (MGMT), is a DNA repair enzyme that removes alkylated lesions that can lead to tumor formation (2). Alkylating agents are formed through exposure to alkylating agents, which are produced in small quantities in numerous industrial reactions. MGMT removes a methyl group from methylated Guanines in the DNA lesion via its Cysteine 145 residue; the normal Guanine properly pairs with Cytosine (3). Alteration of MGMT, such as the mutations found in this family (p.Ile143Val and p.Lys178Arg), may prevent this reaction, leaving improperly pairing methylguanines in the lesion in place. If these uncorrected lesions are in a region responsible for regulation of cell growth, they may lead to cancer development. Understanding MGMT’s structure, specifically at these altered positions, will assist MCW researchers in determining whether the variant MGMT is a likely cause of disease. The Greenfield SMART Team (Students Modeling A Research Topic) modeled MGMT using 3D printing technology to analyze the likely effect of these mutations to assist in understanding their possible role in the development of cervical cancer in this family.

2. A Family with Cervical Cancer

A mother and her daughter have been diagnosed with cervical cancer, the third most common type of cancer in women. Cervical cancer occurs as the squamous cells of the cervix lining (see figures to the right) mutate and overgrow, slowly spreading deeper into the wall of the cervix (1). While there are a few symptoms of cervical cancer (abnormal vaginal bleeding, pelvic pain, etc.), these are often missed resulting in a later diagnosis and poorer outcome. Diagnostic tests such as a Pap smear are used to diagnose a patient in an earlier stage to improve the outcome (1). Surgical removal or radiation of the cancer is necessary to prevent spreading to other parts of the body (1).

Researchers at the Medical College of Wisconsin applied the technique of whole genome sequencing of the mother and daughter’s genomes to attempt to identify genetic causes for their disease. They located two variants (mutations) in their genomes relative to the reference genome that could contribute to their cervical cancer (see graphs in Section 4 below).

The two variants are found in a protein called MGMT, which corrects specific types of errors in the DNA that could lead to tumor formation. These mutations could alter MGMT’s function as seen below.

3. Comparing Normal MGMT to Improperly Functioning MGMT

How might these mutations impact the structure of MGMT?

Two variants (Ile143Val and Lys178Arg) were found: Ile143Val is located adjacent to the alkyl group (such as a methyl group) acceptor Cys145 in the active site of MGMT (3). Although similar in many ways, we hypothesize that there is an effect due to replacement of a polar group with a smaller Valine in this critical region.

In addition, we use that in our 3D model, Lys178Arg lies close to Cys145. Once again this change is between two similar amino acids, but altered hydrophylicity might add to the altered conformation in this critical region.

Alteration of a protein’s shape is known to lead to changes in function and in this case of MGMT, alteration in the region of the active site is known to lead to inability to correct DNA mutations, as shown in the right (5).

4. Genome Sequencing Data Showing the Two Variants in the Mother and Daughter with Cervical Cancer

• It is unclear what the role of these specific MGMT mutations are in the cervical cancer in these individuals. There is growing evidence to support that they are not causative in other types of cancers. However, the techniques performed to study the likely impact on function due to altered structure are very powerful tools in making links between an individual’s diseases and genetics.

• Through DNA sequencing, our mentor and collaborators hope to be able to discover the cause of the mother and daughter’s cervical cancer. Providing this link between genome sequence and disease can be used to identify others at risk for developing cancer due to presence of specific mutations. These individuals can be screened earlier and more frequently to detect cancers sooner. This information can potentially be used to assist in the development of specific treatments for individuals with these types of mutations.

• Doctors are using Whole Genome Sequencing to try to determine the genetic causes of diseases, including cancers, that cannot be figured out otherwise. Being able to identify the genetic basis of various medical issues can help diagnose and possibly lead to personalized treatments for many people who have been left without an explanation or help in the past (5).

5. What Does All of This Mean For the Future of Medicine?

6. References