Genetic Interactions of Trisomy 21, Carney Complex, and Bloom's Syndrome with Cancer

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Writer's Comment: Many years ago, my younger sister was diagnosed with acute lymphoblastic leukemia. She also had Down syndrome, and, on our many visits to the hospital, my family and I learned that leukemia was more common in people with Down syndrome, though we did not know why. This gap in knowledge informed the topic for my final report for MCB 023. With my background as an undergraduate researcher, I decided to take a more technical approach to my paper to accurately convey and understand how intricate the genetic nature of cancer is. The field of cancer research has been evolving and now there is a greater emphasis on using a person's genetics to see if someone may develop cancer later in life. Using people with genetic disorders as an example, we can see how necessary and revolutionary individualized cancer treatment can be for everyone. Three years after my sister was diagnosed, she was declared cancer-free and has been ever since, and this type of cancer research may provide the same fate for others.

Instructor's Comment: Throughout our time together in the Winter 2022 MCB 23: History of Cancer, Nelly demonstrated a strong interest in developing a better understanding of the biological basis of cancer. I was iteratively impressed with Nelly's inquisitive approach to the course material and how she so gracefully shared the personal significance of the course topic to her and her family. Her motivation to understand the biological connections between Down Syndrome and cancer resulted in this comprehensive research review that provides a detailed and technical synopsis of the molecular mechanisms contributing to increased risks of cancer in individuals with Trisomy 21 and other related conditions.

Nelly exemplifies the true spirit of scholarship, letting curiosity motivate the pursuit of knowledge and disseminating that knowledge with others.

—Marina Crowder, Department of Molecular and Cellular Biology

Introduction

Cancer arises through the accumulation of genetic mutations over a person's lifetime. For this reason, cancer is classified as a genetic disease. There have been over 1,000 genes identified that have a known association with cancer, corresponding with over 1 million possible cancer genotypes (Wishart 2015). Those with genetic disorders already possess specific mutations that cause their particular disorder. Genes, and more importantly mutations, do not have one, single effect on the phenotype of an individual. We have many genes that affect different aspects of our biology or physiology, which are known as pleiotropic genes. Many of the mutations present in individuals with trisomy 21, Bloom syndrome, and Carney complex are also correlated with higher cancer incidence and can be classified as pleiotropic mutations that are present either in a single gene or a chromosome. Identifying specific genetic or chromosomal mutations that predispose an individual to cancer can help in diagnosing and treating cancer earlier.

Trisomy 21

Trisomy 21, commonly known as Down Syndrome, is a genetic disorder caused by a chromosome imbalance that confers a higher risk of developing specific types of cancer. Affected individuals have either a complete or partial extra copy of the 21st chromosome, which causes physical abnormalities and intellectual disability. Every year, about 1/700 births result in a child with trisomy 21, making it one of the most prevalent genetic disorders in the present day (Down Syndrome (Trisomy 21) – Pediatrics). Trisomy 21 can be diagnosed during pregnancy through the use of genetic testing. Beyond the physical characteristics of trisomy 21, affected individuals have an increased risk of developing specific cancers such as leukemia and testicular cancer.

Trisomy 21 and Cancer

One of the physical characteristics of trisomy 21 is weakened immune responses due to irregular thymus function. As a result, the number of T cells, which mature in the thymus, have been observed to be lower than in non-affected individuals. T cells, a type of lymphocyte, are important in preventing autoimmune diseases by regulating the adaptive immune response and recognizing antigens (Cellular Components of the Immune System – Immunology; Allergic Disorders). Trisomy 21 individuals have been observed to have decreased levels of leukocytes and lymphocytes overall, which results in a higher occurrence of acute lymphoblastic leukemia (Bloemers et al. 2009). Genome wide association studies (GWAS) have shown that single nucleotide polymorphisms (SNPs) in the *CDKN2A/B* and *ETV6* genes are commonly present in Down syndrome individuals. These same genes are altered during the development of acute lymphoblastic leukemia (ALL) and are correlated with an increased chance of developing ALL (Hatton et al. 2020).

Additionally, infants with trisomy 21 are 500 times more likely to develop acute megakaryoblastic leukemia (AMKL), a subset of acute myeloid leukemia, due to a variety of mutations (Satge and Bernard 2008). A common somatic mutation present in trisomy 21 individuals results in a shortened GATA1 transcription factor, which affects the development of blood progenitor cells. Specifically, megakaryoblasts are arrested in a premature development state and proliferate uncontrollably, leading to AMKL (Mansaro et al 2011). Furthermore, this GATA1 mutation phenotype has been observed exclusively in trisomy 21 individuals with AMKL. However, it has also been noted that trisomy 21 and GATA1 mutations alone are not enough to cause AMKL in affected individuals (Roy et al 2009). This further illustrates how no one single mutation is responsible for the development of any cancer, making the behavior of cancer more difficult to decipher and predict.

AML/RUNX1 is another transcription factor gene present on chromosome 21 that is involved in the development of blood progenitor cells. Mutations in this gene have been observed to contribute to the development of acute myeloid leukemia. Though the mutation is not exclusive to trisomy 21 individuals, when it is present, it usually confers a poor prognosis for the patient (Taketami et al 2003).

Affected individuals also have a higher risk of developing testicular cancer because of delayed and increased expression of POUSF1, a transcription factor that results in the under-expression of a gene that controls the formation of germ cells (Satge and Bernard 2008). This results in testicular germ cells that are unable to mature properly and have increased genomic instability. This instability causes an increased rate of mutations that can ultimately cause testicular cancer.

Trisomy 21 individuals are at a higher risk of developing other diseases besides cancer and have higher chances of developing complications from disease. When a trisomy 21 individual presents with cancer-like symptoms, the genetic interactions between extant mutations and cancer mutations that may have developed must be considered to obtain a complete clinical picture.

Carney Complex

In addition to trisomy 21, Carney Complex (CNC) is a rare syndrome that has also been associated with an increased risk of cancer. CNC is caused by mutations or deletions of the *PRKAR1A* gene on chromosome 17. This gene codes for the regulation of protein kinase A (PKA), which regulates several biological processes through phosphorylation. *PRKAR1A* is also classified as a tumor suppressor gene that, when mutated, produces an incomplete protein product.

Carney Complex and Cancer

When PKA is mutated, proteins are indiscriminately phosphorylated and cell division continues uncontrollably, allowing cancer the opportunity to develop (Caretta and Mucignat-Caretta 2011). Affected individuals develop "pigmented lesions" on the skin and in several other tissues as well as benign growths in the heart, known as myxomas. This syndrome is autosomal dominant, meaning that parents who are carriers are likely to have an affected child. However, because of the variety of ways that CNC presents itself phenotypically, the precise incidence is unknown (Correa et al. 2015). Currently, less than 400 people have been officially diagnosed with Carney complex, so many of the genetic interactions that contribute to the development of cancer in affected individuals have not been completely elucidated.

Because CNC presents itself in several parts of the body, one of the leading causes of death in affected individuals is the presence of metastatic tumors. This disorder has many complex interactions with the endocrine system which increases the risk of ovarian cancer in female patients (Siordia 2015). Thyroid cancer is one of the most common cancers observed in affected individuals due to the role of tumorigenesis caused by the mutation of the *PRKAR1A* gene (Boikos and Stratakis 2006).

Bloom's Syndrome

Bloom's syndrome is an autosomal recessive disorder caused by single-gene mutation in any of the genes in the Bloom syndrome complex: *BLM, TOP3A, RMI1, RM12*. This complex codes for many enzymes that maintain genomic stability during DNA repair by homologous recombination. Any mutations in the complex compromises the accuracy and precision of recombination and leads to the accumulation of further mutations (Bythell-Douglas et al. 2020). High rates of sister chromatid exchange have also been observed as a result of mutations in the *BLM* gene, which

results in a shortened or nonfunctional RecQ helicase, a protein that is important in stabilizing the unwinding of DNA (Cuniff et al. 2017). Bloom's has many clinical and biological manifestations including growth deficiency, reduced life span, dermatological abnormalities, and increased cancer incidence.

Bloom's Syndrome and Cancer

Colorectal cancer is one of the most common neoplasms observed in the population of Ashkenazi Jews, who have the highest prevalence of Bloom's syndrome. Approximately 1.8% of this population was observed to carry a mutation in the *BLM* gene as compared to 0.8% in a control group, suggesting a correlation between the development of mucinous colorectal cancer and *BLM* mutations. Sporadic colorectal cancer, cancer that is not due to inherited mutations, also frequently contains somatic mutations in *BLM* (Hodgson et al. 2014).

Leukemia and lymphoma are also common neoplasms observed in Bloom's syndrome individuals. *BLM* is important in the proper development of the immune system and affected individuals usually present with generalized immunodeficiency. This immunodeficiency is partially attributed to abnormal B and T cell development (Ababou 2021). Apart from having a greater risk of developing cancer, affected individuals develop cancer at an earlier median age and can develop multiple cancers at the same time. 20% of all affected individuals develop neoplasms with about half being diagnosed before the age of 20. Dermatological manifestations of the syndrome and extreme sensitivity to sun exposure also contribute to a higher risk of skin cancer, specifically basal cell carcinomas. Cancer is the most common cause of death for Bloom's syndrome individuals and has prompted increased and systematic surveillance of affected individuals in order to improve patient outcomes (Cuniff et al. 2017).

Genetic Screening

Genetic screening is an incredibly powerful public health tool that has the potential to save lives through prevention. Because of the correlation between genetic disorders and cancer, many people choose to undergo genetic testing to determine their or their children's risk of developing cancer. Most of the mutations that we have are present in our somatic cells and cannot be passed down to children. However, mutations present in our germ line cells have the possibility of being passed down. Many of the genetic disorders presented here also have a hereditary element where parents can be carriers of a disorder-causing gene. Because of this, each of these disorders have screening procedures to determine if individuals have the disorder or are likely to develop it.

Trisomy 21 Screening

Trisomy 21 can be diagnosed during pregnancy and as early as 10 weeks of gestation. One screening method is known as amniocentesis and can only be performed after the 14th week of pregnancy. This procedure involves inserting a needle into the abdomen and the amniotic sac to collect amniotic fluid and fetal cells. Chorionic Villus Sampling (CVS) is another prenatal screening method. Chorionic villi are present on the surface of the placenta, which are collected using a syringe and then cultured. This procedure can be performed between 10 and 12 weeks (Genetic Evaluation – Gynecology and Obstetrics). Both procedures examine the cells collected to detect the percent of chromosome 21 fragments present. A higher-than-normal percentage indicates a third copy of the chromosome, confirming a diagnosis of trisomy 21 (Burke et al. 2011).

Carney Complex Screening

Diagnosis of Carney complex is usually performed by observing a patient's clinical manifestations and determining whether they

meet the diagnostic criteria of CNC. These include the presence of dispersed skin pigmentation, myxomas, and acromegaly. Histological analysis confirming the necessary mutation in the *PRKAR1A* gene must also be performed to confirm the diagnosis. Not all patients have a complete null mutation of *PRKAR1A*, but they will still have the same clinical manifestations as those who do. Many of the manifestations of Carney complex appear, on average, at age 18. Diagnosis is usually made at the median age of 20, but there have been some cases of diagnosis at birth (Boikos and Stratakis 2006). If an individual is diagnosed with CNC, their family members may be prompted to undergo genetic screening as well to determine whether they are carriers of the mutation and prevent unnecessary interventions if found to be non-carriers.

Once Carney complex is diagnosed, several additional screenings are recommended across a person's lifetime to detect malignancies early. Over half of individuals with Carney complex die due to cardiac-related issues and 30% of related deaths are due to cardiac myxomas. Echocardiograms, cortisol urine analysis, and thyroid ultrasonography are recommended to be performed annually, with additional screenings being performed as manifestations of malignancies develop (Stratakis et al. 2001).

Bloom's Syndrome Screening

Screening for Bloom's syndrome involves determining the rate of sister chromatid exchanges (SCE) occurring in the patient's cells and sequencing of the *BLM* gene, which is present on chromosome 15. To determine the rate of SCE, chromosomes are visualized during cell reproduction. DNA sequencing, PCR, and Southern blots are used to analyze abnormal *BLM* gene products (Arora et al. 2014). Bloom's is an autosomal recessive disorder, so parents can be carriers for the mutations that cause the syndrome. Bloom's syndrome is more common in populations with higher rates of consanguineous relationships (Ababou 2021). Overall, there are

less than 400 people who are affected by Bloom's syndrome (Bloom Syndrome).

Cancer Screening

Family history has always been part of a standard clinical examination. Present day genetic cancer risk assessments are considered an extension and application of a family history, taken to the genetic level. Genetic mutations are the driving force behind cancer development, so genetic risk assessments have become more appreciated as another tool in the fight against cancer. Genetic cancer risk assessment is different from screening because it does not seek to diagnose a person with any one cancer. Rather, it can indicate whether a person is likely to develop a specific kind of cancer due to mutations present in their genome. In adults, cancer screening may provide information on whether one or both parents are carriers of a mutation that may predispose their child to a specific type of cancer.

Genetic risk assessment usually includes taking blood and tissue samples and sequencing the DNA from those samples. Commonly, whole genome sequencing is performed, mutations are identified, and those mutations are compared to known cancer-associated mutations. If cancer-associated mutations are identified, proper risk reduction practices can be implemented, treatment options can be discussed, and informed health decisions can be made (Aiello-Laws 2011).

However, genetic risk assessment, like any other screening method, is not a perfect prediction tool. Many non-genetic environmental factors can affect the likelihood that someone will develop cancer. Health behaviors such as smoking and exposure to carcinogens may still cause cancer in an individual not considered "at risk" from risk assessment. The field of cancer genetic screening is still evolving and being optimized to accurately portray an individual's risk for developing cancer.

Conclusion

As a genetic disease, cancer has a complex relationship with pre-existing genetic disorders in an individual. Trisomy 21, Carney complex, and Bloom's syndrome are just some examples of how inherent mutations can cause a greater risk for cancer. The interactions between these inherent mutations and cancer incidence have not been completely elucidated, but they are a good clinical tool to assess whether someone has an increased risk of developing cancer.

However, not all cancer-causing mutations are equal. In the genetic disorders presented, the risk of developing mutations varies widely and varies for different types of cancer. Therefore, it is important to individualize observation and treatment for each patient. In recent years, scientists and oncologists have gained an appreciation for the heterogeneous nature that cancer can have. Genetic risk assessment technology has helped in elucidating the complex genetic interactions of cancer with mutations and in determining an individual's likelihood of developing specific types of cancer. Evaluating a person's genome can help in highly individualizing treatment and do what is best for patients.

There are several other genetic disorders that have not been presented here that may also confer a higher likelihood of developing cancer. Being aware of the correlation between genetic abnormalities and mutations that can lead to cancer can be a useful tool for both physicians and family members. For caretakers of people with genetic disorders, it is instrumental to know what to expect when taking care of that person. This can cause changes such as becoming more vigilant of neoplasia symptoms and undergoing cancer screening more often or at an earlier age. This knowledge can also provide comfort if a genetic cancer risk assessment shows that someone does not have an increased risk of cancer.

Although several genetic disorders are rare, the information that can be obtained from a genetic risk assessment can greatly contribute to the field of cancer research. Efforts are being made

today to diversify the genetic information available for research to find more effective and targeted therapies for everyone. In doing so, in the near future, we may be able to identify more cancer-associated mutations and develop targeted therapies against them and reduce the mortality caused by cancer in people with trisomy 21, Bloom's syndrome, and Carney complex.

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