

ATM Gene Mutations; Hereditary Breast Cancer and Ataxia Telangiectasia

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The number of available hereditary cancer tests increases each year. This gives both patients and providers an increasing number of tools for predicting the likelihood of developing specific types of cancer. Next generation sequencing (NGS), as discussed in an article from June of 2012, is an example of this. Compared to [other/previous type of testing]), NGS allows for the testing of multiple genes, (called panels) with reductions in both cost and results time. Newly discovered gene mutations have emerged with the use of NGS panel testing. The ATM gene is an example of this, and is included on panels offered to patients at increased risk for hereditary breast cancer. In addition to being at increased risk for cancer, the offspring of carriers of one ATM mutation are at increased risk to have a progressively debilitating disorder that begins in infancy called ataxia telangiectasia (A-T). A summary of the clinical manifestation seen among individuals with ATM gene mutations is provided below.

What is an ATM gene mutation carrier?

Everyone has two copies of the ATM gene in each of their cells; these are protective against tumors and cancers. However, some individuals are born with one non-working copy of the ATM gene (i.e. a mutation) in each of their cells. These individuals are called ATM gene mutation carriers. As ATM gene mutations are being discovered in more individuals, the specific risks for cancer are beginning to be better understood.

What are the breast cancer risks?

It has been established that women with ATM gene mutations are at increased risk to develop breast cancer. The lifetime risk for breast cancer in females who are carriers of ATM gene mutations is about 28-50%^{2,3}. Having a relative with breast cancer can further increase these risks. For example, women who carry specific mutations with the ATM gene, such as c.7271T>G and c.1066-6T>G, may have up to a 66% lifetime risk for breast cancer if their mother had been diagnosed with breast cancer⁴.

What are the other cancer risks associated with ATM gene mutations?

The lifetime breast cancer risk for males who carry an ATM gene mutation is not thought to exceed 1%. As more data is gathered from families found to have mutations, the risks for males and females to develop other cancers will be better understood. However, males who have one ATM gene mutation may be at increased risk for prostate cancer.^{7,8} The risk for melanoma and cancers of the mouth, throat, thyroid, and uterus may also be increased.⁸

How can the risks be managed?

It is important for individuals who are carriers for ATM gene mutations to be aware that they may be sensitive to radiation. Hopefully, the radiation sensitivity of carriers of ATM gene mutations will be further clarified as additional clinical data emerges. Radiation from X-rays might cause chromosomal breakage, which could then further increase cancer risk. X-rays should be considered

only if there is no alternative for a particular therapy, treatment, or management option.^{9,10,11}

There is no definitive evidence as to whether mammograms increase the risk of cancer in individuals who have one ATM gene mutation.^{5,6} MRIs, clinical breast exams, and ultrasounds are alternatives to mammograms that do not involve radiation. Annual breast MRI screening is recommended for women with a lifetime risk for breast cancer of 20-25% or greater. It is generally recommended that MRI be used in conjunction with mammogram.

How can the risk for cancer be reduced?

Whereas screening helps enables clinicians to detect cancer that may have otherwise gone unnoticed, there are options to reduce the risk of breast cancer. Prophylactic mastectomy has not been studied extensively in individuals who are carriers for ATM gene mutations. However, in populations with more common gene mutations that increase the risk for breast cancer to similar levels, bilateral mastectomy can reduce the risk of breast cancer by 90-95%^{12,13}. Chemoprevention, such as Tamoxifen and Raloxifene, is another method that is considered for women who are at high risk for breast cancer. This recommendation is based on published data for high-risk women, there is not any evidence concerning the effectiveness of chemoprevention in the ATM gene carrier population. There are currently no guidelines for the management of other cancer risks, relative to carriers of the ATM gene mutation. A personalized screening regimen for these cancers should be established based on the patient's personal and family histories.

What is the risk to relatives?

The relatives of any individual who is a carrier for an ATM mutation are at increased risk to also have the same mutation. Testing can be offered to relatives to determine who else is, and who is not, at increased risk to develop cancer.

What is Ataxia Telangiectasia ?

If two carriers of the ATM gene have children together, each child has a 25% chance of having ataxia telangiectasia (A-T). A-T causes progressive cerebellar ataxia beginning at one to four years of age, which manifests itself as uncoordinated motor function. Other symptoms include the inability for children to track an object visually, Huntington's disease-like writhing movements, oculocutaneous telangiectasias, and frequent infections. The lifetime risk for cancer in individuals with A-T is about 38%. Leukemias and lymphomas account for most of these malignancies. However, as the life expectancy for individuals with A-T increases, other cancers have been observed, including ovarian cancer, breast cancer, gastric cancer, melanoma, and sarcomas. It is also important for individuals with A-T to be aware that they are very sensitive to ionizing radiation, which significantly increases the risk for malignancy.

The life expectancy for individuals with A-T is considerably reduced compared to the general population. However, the life expectancy has increased over the past 20 years. Now most affected individuals live past the age of 25 years, and some have survived into their 50s.

What is the risk to develop A-T?

Individuals who are carriers of an ATM mutation are counseled concerning their risk to have a child with A-T. If a carrier of an ATM mutation wants to prevent having a child with A-T, her partner could undergo testing to see if he is also carrier of an ATM gene mutation. If he is not, their offspring are not at increased risk to have A-T. However, if her partner is a carrier of an ATM

mutation, each of their offspring would have a 25% risk to have two ATM mutations; the cause of A-T. (Half of their offspring would be carriers of ATM mutations, and 25% would be neither carriers nor have A-T).

How can the risk for A-T be reduced?

Partners who are both carriers of ATM mutations can take steps to reduce their risk of having a biologic child with A-T by using Preimplantation Genetic Diagnosis (PGD). Using this method, about 6-9 days after fertilization, eggs are biopsied to determine which do and which do not have A-T. Those that do not have A-T are implanted into the mother. Unfortunately for most couples, the price is cost-prohibitive and can require several cycles of in vitro fertilization.

What are the future expectations?

Clinicians and researchers are finding more and more genes associated with a hereditary predisposition to cancer. It is important for patients and their clinicians to know what the specific risks for cancer are and in what ways these risks can be managed. It is also important patients to realize that their gene mutations, such as ATM mutations, can have an otherwise unexpected health outcomes for other family members. As the link between genetics and health is better understood, patients and clinicians will be able to more adaptively manage and reduce their risks for cancer and other diseases.

As always, if you have any questions or would like to refer a patient to UT Southwestern's cancer genetics team in Dallas or in Fort Worth at the Moncrief Cancer Institute, please call (214) 645-2563.

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