Management of Individuals With a Mutation in the Ataxia Telangiectasia Mutated Gene

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Advances in genetic testing have led to the identification of multiple genes associated with a hereditary risk for developing breast and other cancers. One such gene is the ataxia telangiectasia mutated (*ATM*) gene, which is available on many genetic panels offered to individuals with suspected hereditary risk. Genetic testing can often lead to improved understanding and clarification of risk for developing cancer, as well as allow affected individuals to make informed choices about management, including the adoption of primary prevention strategies and more aggressive screening than typically recommended in the general population. This article provides an overview of the role of mutations in the *ATM* gene in developing malignancies, along with emerging research on treatment implications based on genetic testing results.

Physiologic Function

The *ATM* gene is located on the long (q) arm of chromosome 11 between positions 22 and 23, spanning from base pair 108,222,499 to base pair 108,369,101 (Genetics Home Reference, 2015). The *ATM* gene is large; with 63 exons containing about 150 kb of genomic DNA, analyzing the gene is technologically difficult (Graña et al., 2011; Mitui et al., 2009). In addition, the *ATM* gene provides the code to produce a protein that functions in the nucleus of the cell (Genetics Home Reference, 2015).

The function of the ATM protein is to regulate the rate at which cells grow and divide, as well as to promote the normal development and activity of the nervous and immune systems. This protein also plays an important role in recognizing damaged or broken DNA strands and facilitating DNA repair by activating enzymes to repair the damaged DNA strands. The *ATM* gene is considered to be a major guardian of genomic stability (Shiloh, 2014).

The impact of mutations in the *ATM* gene depends on the number of alleles affected. When an individual is homozygous (both alleles are affected) for a mutation in the *ATM* gene, the person will develop ataxia telangiectasia (AT), a rare autosomal recessive disorder (Lindor, McMaster, Lindor, & Greene, 2008). Individuals who are heterozygous (one copy is affected) are at increased risk for developing several malignancies, including breast, colon, stomach, bladder, pancreatic, lung, and ovarian cancers (Gatti, 2010).

Clinical Manifestations

Homozygous: AT occurs because of a germline biallelic (both copies affected) mutation in 1 out of every 40,000 to 100,000 live births (Gatti, 2010). In individuals with suspected AT, germline sequence analysis of

the *ATM* coding region detects about 90% of *ATM* sequence variants (Gatti, 2010). More than 600 different germline mutations have been reported (Chessa et al., 2009). In individuals with AT, about 90% have no detectable ATM protein, and less than 10% have only trace amounts of ATM protein (Gatti, 2010). In about 1% of individuals with AT, a normal amount of ATM protein is present, but the protein is not functional because it lacks ATM serine/threonine kinase activity (Gatti, 2010; Lindor et al., 2008).

The primary clinical sign of biallelic AT is progressive cerebellar ataxia, which is usually first seen from ages 1–4 years (Gatti, 2010). Other clinical manifestations include oculomotor apraxia, telangiectasias of the conjunctivae, immunodeficiency, and frequent infections (Lindor et al., 2008). Individuals with AT are also at increased risk for developing malignancies, particularly leukemia and lymphoma.

Because individuals with AT are unusually sensitive to ionizing radiation, special consideration should be given to limiting exposure to repeated computed tomography scans or other x-rays (Genetics Home Reference, 2015). Increased risks exist when anesthesia is administered, requiring more attention because of impaired swallowing, reduced respiratory capacity, and higher infection risks (Gatti, 2010). Classic AT is treated with IV immunoglobulin replacement therapy to manage the frequent and severe infections and to replace low immunoglobulin G levels. Many individuals with chronic bronchiectasis will require ongoing aggressive pulmonary hygiene (Gatti, 2010). Most affected individuals will require supportive therapy for drooling and physical therapy to help maintain mobility (Gatti, 2010).

Heterozygous: Next-generation sequencing panels for germline mutations associated with hereditary risk for developing breast and colon cancers typically include sequencing of the *ATM* gene. With the increased use of next-generation panels, many more individuals with a heterozygous mutation (one allele affected) in the *ATM* gene have been identified (Aloraifi et al., 2015). Heterozygous germline mutations in the *ATM* gene are considered to be moderate penetrance mutations associated with a 30%–60% lifetime risk of developing breast cancer (Tavtigian et al., 2009). Epidemiologic evidence suggests that one mutation (p.V2424G) has even been estimated to confer a breast cancer risk as high as 52%–69% (Kapoor et al., 2015). Ionizing radiation is a known mutagen associated with increased breast cancer risk. Because the *ATM* gene is a key regulator of cellular responses to the DNA damage induced by ionizing radiation, women with breast cancer treated with radiation may be at increased risk for developing a second breast cancer (Bernstein et al., 2010; Hammond & Muschel, 2014).

Heterozygous mutations in the *ATM* gene may account for about 5%–15% of hereditary breast cancer (Aloraifi et al., 2015; Kapoor et al., 2015). The risk of breast cancer is at least twice as high in *ATM* carriers than in the general population (Economopoulou, Dimitriadis, & Psyrri, 2015). Epidemiologic evidence suggests that the risk of breast cancer in heterozygotes with *ATM* mutations is higher in women younger than age 50 years and may be as high as five times the risk in the general population (Ahmed & Rahman, 2006; Economopoulou et al., 2015). Whether some mutations are associated with different risks of developing breast and other cancers is unclear (Ahmed & Rahman, 2006). Breast cancers diagnosed in women who are heterozygous for the *ATM* mutation may be more aggressive than those in noncarriers (Economopoulou et al., 2015).

The risk of gastric cancer may be increased in individuals with a germline *ATM* mutation (Kim, Choi, Min, Kim, & Kim, 2013). Gastric cancer in *ATM* carriers typically is associated with older age, larger tumor size, distal location in the stomach, more extensive invasion, and lower recurrence rate. Risk for ovarian cancer in *ATM* germline mutation carriers is also possibly increased, but the exact increase in risk is not clear (Pennington et al., 2014). A three-fold increased risk for developing colon cancer has been reported, as have small increased risks for developing bladder, lung, prostate, gallbladder, and esophageal cancers (Thompson et al., 2005) The risk of pancreatic cancer is also increased (Roberts et al., 2012).

Emerging Research in Somatic Mutations

Somatic mutations, or acquired mutations that occur after conception, in the *ATM* gene have been detected in cancer biopsy specimens from a small fine-needle aspiration (Beltran et al., 2013; Kanagal-Shamanna et al., 2014). Early research suggests that somatic mutations in the *ATM* gene may be sensitive to inhibition of poly(adenosine diphosphate-ribose) polymerase (PARP), playing an important role in base excision DNA repair. Somatic *ATM* mutations have been found in breast, lung, prostate, and colorectal cancers, as well as in hematologic malignancies (Ouillette et al., 2012; Skowronska et al., 2012; Weber & Ryan, 2015). Identifying loss of *ATM* function in somatic tumor mutations may allow for the identification of a patient subset that could receive increased benefit from targeted PARP inhibitor therapy.

Management of a Heterozygous Germline Mutation

Because of the size of the *ATM* gene and the relatively new ability to perform germline mutation genetic testing, variants of unknown significance (VUS) are detected frequently (Kapoor et al., 2015). This potential outcome of testing should be addressed in pretest genetic counseling. The detection of a VUS can be confusing, is largely uninformative, and may increase anxiety and stress levels (Mahon, 2015). Oncology nurses need to be prepared to address these concerns.

No specific recommendations exist for screening and early detection in heterozygous *ATM* carriers. Given that the risk of breast cancer is at least 20% and perhaps as high as 60% in *ATM* germline mutation carriers, the National Comprehensive Cancer Network ([NCCN], 2015) recommends considering adding breast magnetic resonance imaging to screening. The NCCN (2015) has stated that inadequate evidence exists to support prophylactic mastectomies in *ATM* germline mutation carriers. Because the risks of developing colon, gastric, pancreatic, and ovarian cancers may also be increased in germline mutation carriers, consideration should be given to the modification of screening recommendations. Family and personal history of cancer is an important consideration when developing recommendations for prevention and early detection. Oncology nurses should ensure that patients and families understand the importance of complying with these recommendations.

Knowing if a patient carries a germline *ATM* mutation may help to guide treatment decisions (Stagni et al., 2014). Those with a germline *ATM* mutation being treated for ovarian cancer may have a better response to platinum-based therapy or PARP inhibitors, according to a few small retrospective reviews (Gilardini Montani et al., 2013; Pennington et al., 2014). Oncology nurses should anticipate more research in this area and be willing to provide basic information to patients and families about how knowing whether an individual carries a mutation may aid in the selection of the best treatment plan.

Conclusion

Although routine testing for germline and somatic mutations in the *ATM* gene is relatively new, knowledge is quickly emerging about the gene's role as one of the primary caretakers of genomic stability and its part in DNA damage response and repair. A heterozygous mutation in the *ATM* gene can lead to cancer initiation and progression. More widespread identification of this gene should lead to the development of more effective therapeutic choices for those diagnosed with malignancy. Oncology nurses should anticipate that recommendations for the management of individuals with an *ATM* mutation will be refined and updated, as well as ensure that those who have an *ATM* mutation are provided with this information.

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