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Convergence of Reproductive and Cancer Genetic Counseling: A Case Report

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I. Introduction and Purpose

A 34 year old patient under evaluation for infertility was referred for genetic counseling to discuss results of expanded carrier screening (ECS). ECS revealed she is a carrier for Ataxia-telangiectasia (ATM) mutation c.8977C>T(p.Arg2993X). Although ECS was recommended to the patient for the purpose of fetal risk assessment, the ATM mutation is also associated with an increased cancer risk for carriers of a pathogenic variant. This case report illustrates the counseling process involved in assisting a patient to understand, accept, and incorporate this unexpected information into her personal health management and reproductive decision making.

II. Case Overview

The patient and her partner were initially informed of their ECS results during results reporting phone calls. Following the initial results disclosure to the patient, comprehensive genetic counseling was recommended to discuss both reproductive and cancer risks. Given the significantly different implications of the reproductive and cancer risks, two separate counseling appointments were scheduled.

The cancer counseling session focused on family history, personal health cancer risks associated with the ATM mutation and implications for medical management. The family history was unremarkable for associated cancers. The only reported cancer history was a 70 year old maternal aunt diagnosed with osteosarcoma at age 64.

ATM is considered a moderate-risk cancer gene, with ATM pathogenic variants accounting for about 4% of hereditary breast cancers. The patient's results revealed a pathogenic variant c.8977C>T (pArg2993X) associated with an increased risk for female breast cancer. In addition, some studies have suggested an increased risk for pancreatic cancer. The risk for breast cancer is 17-52%, and the risk for pancreatic cancer, though it may be increased, could not be quantified. Although specific information was not available for the patient's mutation, since it is a truncating mutation it is expected to have a less detrimental effect on a cell than a missense mutation which produces an abnormal protein. Current recommendations regarding surveillance and risk reduction were reviewed with the patient (**Table 1**).

The reproductive session centered on reviewing the couple's ECS results, including the significance of the ATM mutation as it relates to reproductive options. In addition to identifying the patient as an ATM carrier by ECS, the partner was identified as a carrier for the galactosemia Duarte mutation. Homozygous ATM mutations cause ataxia-telangiectasia, signs and symptoms of which include: early-onset progressive cerebellar ataxia, telangiectasia of the conjunctivae, recurrent infections, and cancer susceptibility. Duarte variant galactosemia causes a partial deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT). Due to the presence of residual enzyme activity, Duarte variant galactosemia with another GALT mutation may be asymptomatic or show minor manifestations of clinical disease. The residual fetal risks for ataxia-telangiectasia of 1/664 and for galactosemia of less than 1/1050 were discussed with the patient and her partner. Of note, the reproductive risks to future offspring for homozygous disease related to these mutations was significantly lower than the risks identified for the patient and her offspring for related hereditary cancer (**Table 2**). The couple declined further carrier testing for galactosemia and ATM by sequencing and deletion/duplication analysis based on their perception of fetal risk for homozygous ATM and galactosemia, which they found acceptable.

Table 1. Cancer risks and recommendations

NCCN Risk and Management Recommendations for ATM Mutation Carrier		
	Risk	**Management**
Breast Cancer	Increased risk	• Annual mammogram starting at age 40 with consideration of tomosynthesis and breast MRI with contrast • Insufficient evidence for recommendation of risk reducing mastectomy
Ovarian Cancer	Potential increase in risk	Insufficient evidence for management recommendations
Other Cancers	Unknown or insufficient evidence for pancreatic or prostate cancer	Insufficient evidence for management recommendations

Table 2. Reproductive and cancer risks

Reproductive Risks for Offspring		Hereditary Cancer Risks for Patient related to ATM variant	
Inheriting ATM pathogenic variant	50%	**Breast Cancer**	17-52% (increased risk)
Ataxia Telangiectasia (homozygous ATM mutation)	1/664	**Ovarian Cancer**	Potential increase in risk
Galactosemia (including Duarte variant)	1/1050	**Other Cancers**	Unknown or insufficient evidence for pancreatic or prostate cancer

III. Discussion and Conclusion

Given the dominant mode of inheritance of ATM cancer risks, family members as well as the patient's offspring are at risk to inherit the mutation and subsequently be at risk for hereditary cancer. The patient found this information to be unsettling and alarming and expressed this in both genetic counseling sessions. She was able to accept her own cancer risk but was not willing to gamble with passing this on to the next generation. The benefits, limitations and risks of various modes of prenatal diagnosis including preimplantation genetic testing were discussed. The patient elected to utilize preimplantation genetic testing (PGT-M) for the known ATM mutation. This case demonstrates the complexities of helping a patient navigate unexpected genetic screening results, increased personal cancer risk and decision making concerning assisted reproductive technologies and prenatal diagnosis. By providing the patient with separate reproductive and cancer counseling sessions, the couple was able to focus on each issue separately, thereby reducing the feeling of being overwhelmed and allowing them to feel empowered to make decisions about the patient's health and the health of future offspring.

IV. References

Tung N, et al. Counselling framework for moderate-penetrance cancer susceptibility mutations. *Nat Rev Clin Oncol* 2016 Sept; 13(9):581-8

GeneReviews 2016: BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer

NCCN.org (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian-Version 2.2019)

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