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A Germline Mutation of Gene ATM P.C1899* is Associated with Family History of Multiple Cancers in a Family in Yunnan Province, China

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Keywords:

ATM; Germline mutation; Family history; Colorectal cancer; Case report

Abbreviations

BC: Breast cancer; CAP: College of American Pathologists; CLIA: Clinical Laboratory Improvement Amendment; CRC: Colorectal cancer; DDR: DNA damage response; GC: Gastric cancer; IC: Immune checkpoint inhibitor

1. Abstract

1.1. Background: Ataxia-Telangiectasia Mutation (ATM) is a well-known gene on chromosome 11q that plays a role in cell cycle checkpoints and DNA damage responses. Heterozygous germline mutations in ATM are considered as one of risk factor of breast cancer (BC), ovarian cancer. There are also some reports that ATM mutations are related to other tumor types, such as prostate cancer. Several pathogenic germline mutations in ATM have been reported included missense mutations, nonsense mutations, frameshift deletions, in-frame deletion, large deletion. However, little was reported about ATM germline mutation in colorectal cancer (CRC).

1.2. Case presentation: Here, we report a patient with colon cancer who carries a novel germline mutation of ATM p.C1899* and has a family history of multiple cancers, including gastric cancer, bowel cancer and pancreatic cancer.

1.3. Conclusion: This is a novel germline mutation of ATM in patient colon cancer, and it may suggest that germline mutation of ATM may associated with genetic or familial high risk of tumors beyond breast cancer, ovarian cancer and pancreatic cancer.

2. Background

ATM plays a key role in the repair of double-strand DNA breaks and the activation of cell cycle checkpoints. Homozygous or compound heterozygous mutations in the ATM gene are the main cause of ataxia telangiectasia (AT), which is a kind of rare autosomal recessive neurological diseases are manifested as progressive cerebellar degeneration and eye skin telangiectasia [1]. For the role

of ATM in the signaling required to initiate DNA repair, therefore, ATM defects can lead to genomic instability and oncogenesis. Hereditary and sporadic ATM mutations occur mainly in the C-terminal end that interacts with the PI3 kinase domain, which is associated with acetylation and activation of ATM [2]. DDR is impaired when the ATM is defective, lead to the accumulation of mutations and finally initiate the process of tumorigenesis. It is frequently documented that obligate or potentially heterozygous ATM mutation are associated with increased risk of cancer, especially, breast cancer [3], and the mutation associated with higher risks of breast cancer were mutation of 7271T>G, c.7429G>A/p.Gly2477Arg, IVS10-6T→G in the ATM gene [4-6]. Germline mutations in ATM result in increased risks of breast cancers, especially, associated with the S707P and S49C mutations [7]. However, there are few reports about ATM germline mutations occurred in the same family with a family history of multiple tumors, especially, a novel germline mutation of ATM.

3. Case Presentation

The proband is a 58-year old male patient with colon cancer, he was scheduled to undergo colectomy, during which a mass was removed from the patient, it was 2.5cm*2.5cm*1.0cm in volume. Pathological analysis of the tissue sample revealed that it was poorly differentiated adenocarcinoma, invading the serosal layer (Figure1). Both tumor tissue samples and peripheral blood sample of the proband was subjected to next generation sequencing (NGS) analysis by 3D Medicines Inc., Shanghai, China, a laboratory accredited by College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA). A novel germ-line mutation was identified, that was heterozygous ATM p.C1899* mutation (c.5697C>A). The proband has two daughters who is healthy, and an uncle with stomach cancer and an aunt with pancreatic cancer. The peripheral blood samples of the two daughters have been collected and sent to 3D Medicines Inc. for NGS analysis. The results showed that both daughters carried heterozygous ATM p.C1899* mutations (c.5697C>A), while other blood relatives refused genetic testing for them (Figure 2).

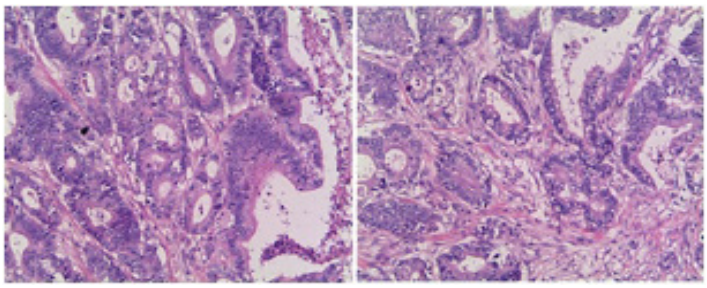

Figure 1: Pathological diagnosis, hematoxylin-eosin staining (HE). A segment of the colon, 13cm long, 4cm in diameter, and a lump can be seen 4cm from the near resection margin, with a volume of 2.5cm*2.5cm*1.0cm

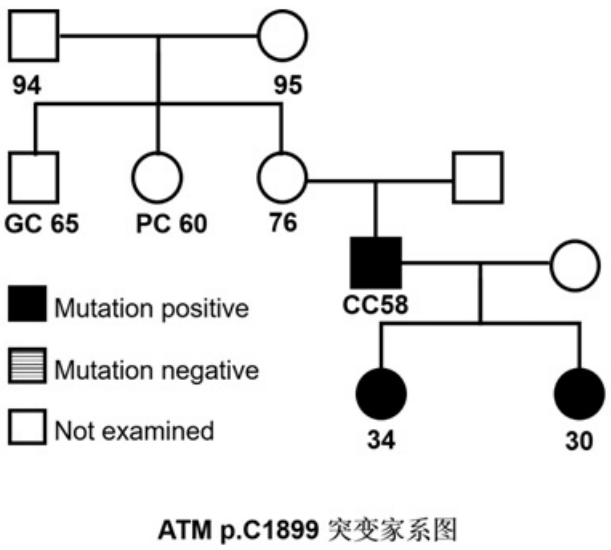

Figure 2: Pedigree of family of case patient with heterozygous ATM p.C1899* mutation (c.5697C>A) (III-1). Boxes and circles indicate males and females, respectively; oblique line shows deceased family members; numbers under boxes or circles indicate age at death or analysis of mutation.GC: Gastric Cancer; CC: Colon Cancer; PC: Pancreatic Cancer.

4. Discussion and conclusion

With the development and application of NGS technology and other genomic technologies, CRC and GC are currently being studied and typed in more detail at the molecular level. ATM mutation was frequently reported in GC and CRC, and the oncogenic role of ATM has also been widely demonstrated in CRC and GC [8, 9]. While insufficient data was available about ATM germline mutation in GC and CRC. Here we firstly report the ATM germline mutation in patients with colorectal cancer, and family history of multiple cancer, what's more, ATM p.C1899* mutation (c.5697C>A) is a novel germline mutation in ATM gene.

Totally, 3 members of the family including the proband underwent NGS analysis, results showed that all these members were carry a germline mutation of gene ATM p.C1899*. Although, genetic information of other blood relatives is missing, the combination of his family history of multiple cancers means this germline mutation may tightly associated with high risk of three different cancer in a family.

DNA damage response (DDR) genes make cancer cells more sensitive to poly-ADP ribose polymerase (PARP) inhibitors, such as olaparib and Rucaparib, ATM is one of the most commonly mutated DDR genes, which imply that patients with ATM mutation may benefit more in using inhibitors of PARP. A previous research found that mantle cell lymphomas cell lines with loss of ATM are sensitive to inhibitors of PARP [10], in addition, In vitro studies have found that colorectal cancer cell lines SK-CO-1 lacking detectable ATM protein expression, and HCT116 colorectal cancer

cells lacking ATM shRNA are all sensitive to olaparib [11]. These findings suggest that ATM mutations may not only be related to an increased risk of cancer, but may also become a marker for tumor therapy.

Since DNA damage activates immune response and improves efficacy of immune checkpoint inhibitors, researchers investigated the effects of ATM inhibition on pancreatic tumor immunogenicity, and results showed inhibition of ATM increased PD-L1 expression, increased tumoral CD8+ T cells, and increased the sensitivity of pancreatic tumors to ICI [12]. This may suggest the ATM mutation may be a potential biomarker for application of ICI in solid tumors, such as CRC, GC.

The mutation of ATM, especially germline mutation, may associated with multiple cancers beyond BC, as GC, CRC and pancreatic cancer happened in the family of the patient. Accurate genetic testing such as germline mutation of gene ATM should be given more attention to better control and manage the risk of familial cancer.

5. Acknowledgements

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