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REVIEW

ATM in breast and brain tumors: a comprehensive review

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ABSTRACT The *ATM* gene is mutated in the syndrome, ataxia-telangiectasia (AT), which is characterized by predisposition to cancer. Patients with AT have an elevated risk of breast and brain tumors Carrying mutations in *ATM*, patients with AT have an elevated risk of breast and brain tumors. An increased frequency of *ATM* mutations has also been reported in patients with breast and brain tumors; however, the magnitude of this risk remains uncertain. With the exception of a few common mutations, the spectrum of *ATM* alterations is heterogeneous in diverse populations, and appears to be remarkably dependent on the ethnicity of patients. This review aims to provide an easily accessible summary of common variants in different populations which could be useful in *ATM* screening programs. In addition, we have summarized previous research on ATM, including its molecular functions. We attempt to demonstrate the significance of ATM in exploration of breast and brain tumors and its potential as a therapeutic target.

KEYWORDS Breast cancer; brain tumor; DNA damage; DNA repair

Introduction

Alterations in the *ATM* gene are the main cause of the rare autosomal recessive disorder, ataxia-telangiectasia (AT). This condition is characterized by neuro-degeneration, cerebellar ataxia, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, frequent infections, immunodeficiency, radiosensitivity, and a predisposition to cancer, and was described as a specific disease entity in 1957. AT occurs early in childhood, and its frequency varies from 1 in 40, 000 to 300, 000 births in various countries and ethnic groups[1,2]. To date more than 400 disease-related mutations have been identified in *ATM*, approximately 70% of which result in the production of truncated protein[3,4] (http://www.vmresearch.org/atm.htm). The majority of mutations are unique and they are uniformly distributed throughout the open reading frame of the gene, without any hotspots. Despite the 100% penetrance of truncating mutations, the low penetrance of missense mutations often leads to an insignificant phenotype[5]. The prevalence of *ATM* mutations ranges from 0.5% to 1% in Western populations[1,6]; however, homozygosity for the same mutation is rare.

Maintaining genomic integrity and stability is essential for all types of cells with the critical function of inhibiting tumor development, and ATM is a key factor in these processes. ATM has various functions, including a key role in the recognition and repair of double-strand breaks (DSBs). The response to DNA damage includes recognition of damaged DNA, recruitment of repair proteins, signaling to cell cycle checkpoints, and facilitation of apoptosis via regulation and activation. Since ATM is involved in many of these processes, it could be considered a master regulator of the DNA damage response[7-9].

In the brain, the processes involved in maintaining genomic stability and integrity are particularly important, since neurons are terminally differentiated and unable to divide. Therefore, they have evolved multiple overlapping mechanisms for DNA damage repair[10]. Consistent with the significance of DNA repair to the health and survival of brain cells, mutations in DNA repair genes often cause syndromes which include pronounced defects in the central nervous system (CNS)[11-13]. AT, caused by mutations in the ataxia-telangiectasia gene, is characterized by progressive degeneration of the cerebellar cortex, and sometimes brain tumors[14], particularly medulloblastomas and gliomas[15-19]. Cytogenetic and molecular deletions of chromosome 11q (the *ATM* gene region) in medulloblastomas suggest the presence of one or more tumor suppressor genes in this region, which could have important roles in brain tumors pathogenesis[20-23]. Therefore, there appear to be two different pathways that contribute to the AT disease process.

Radiation exposure is associated with an elevated risk of breast cancer[24]; therefore, the function of ATM makes it a

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plausible candidate for a role in breast cancer predisposition. Indeed, an association between AT and breast cancer was first reported by Swift et al.[25], before the *ATM* gene was cloned, when they identified an excess of breast cancers in the relatives of individuals with AT.

ATM structure

The *ATM* gene was mapped by genetic linkage analysis to chromosome 11q22–23 in 1988[26] and was identified by positional cloning in 1995[27]. The gene contains 66 exons, of which 62 encode a 350-kDa protein of 3056 amino acid residues. The *ATM* gene covers 160 kb of genomic DNA, and is transcribed in a broad range of tissues to produce an mRNA of approximately 13 kb with a coding sequence of 9168 bp. Exons 1a or 1b are differentially spliced in alternative transcripts, the initiation codon lies within exon 4, and the final 3.8 kb exon contains approximately 3.6 kb of untranslated sequence at the 3' end[28]. ATM is a member of the family of phosphatidylinositol-3-kinase (PI3K)-related protein kinases (PIKK), has serine–threonine protein kinase activity, and includes a PI3K-like domain at its C terminus that comprises almost 10% of the protein. Other important functional domains of ATM are the leucine zipper, which has sequence homology to the *Saccharomyces pombe* Rad3 protein, and a proline-rich region[29-31].

ATM function

ATM is the major initiator of a signaling cascade that responds to DSBs, and which operates not only in humans, but also other eukaryotes (**Table 1**). Normally, ATM is present in cells in the form of an inactive dimer or multimer complexes. Following DNA damage, ATM undergoes autophosphorylation at S1981 leading to the separation of the inactive complex to form highly active monomers. Subsequently, through activation of signaling pathways, and via phosphorylation of numerous substrates, DNA repair can take place[32], during which two central responses to DNA damage, including the activation of cell-cycle checkpoints and the initiation of DNA repair, are facilitated.

Cell-cycle checkpoint function

ATM links the recognition of DNA damage to the maintenance of genomic integrity and stability by activating checkpoints that lead to a delay in the progress of cells carrying damaged DNA through the cell cycle. The progression of the cell cycle is controlled by cyclin-dependent kinase (CDK) complexes (**Figure 1**). Sequential events in the cell cycle rely on checkpoints to guarantee their step by step progression. Also, if the DNA is damaged, checkpoints arrest the cell cycle by delaying the activity of CDKs. ATM is involved in the regulation of these checkpoints after exposure to ionizing radiation (IR)[44-48].

Loss of p53 function, which can occur because of mutations in tumor cells, abrogates cell cycle G1/S checkpoints[49]. DNA damage leads to a rapid induction of p53. The demonstration of delayed and reduced induction of p53 in AT cells following IR exposure was the first link between ATM and p53[50,51]. In normal cells, the expression level of p53 is maintained by Mdm2, an E3 ubiquitin ligase[52,53], which prompts p53 ubiquitination and degradation. In cells harboring DNA damage, ATM phosphorylates p53 and Mdm2 on amino acids Ser15 and Ser395, respectively[54,55]. This leads to nuclear accumulation of p53 in response to IR, as a result of reduced Mdm2 activity and consequently inhibits shuttling of p53 from the nucleus to the cytoplasm

Table 1 ATM roles in different species

Eukaryotes	ATM like gene	Function	Reference
Arabidopsis	ATM ortholog	DNA damage response via SOG1 phosphorylation	33
Saccharomyces cerevisiae	Tel 1	Telomere length, DNA damage response	34,35
Caenorhabditis elegans	ATM-1	DNA damage response (lacking the large N-terminal region present in other ATM homologs)	36
Aspergillus nidulans	AtmA	DNA damage response and polarized hyphal growth (formation of a stable axis of hyphal polarity)	37
Zebrafish	zATM	DNA damage response (67% and 66% homology with human ATM and mouse ATM)	38
Drosophila	dATM	DNA damage response and eye and wing development	39
Mouse and mice		DNA damage response, embryonic development, infertility, neurological function	40-43

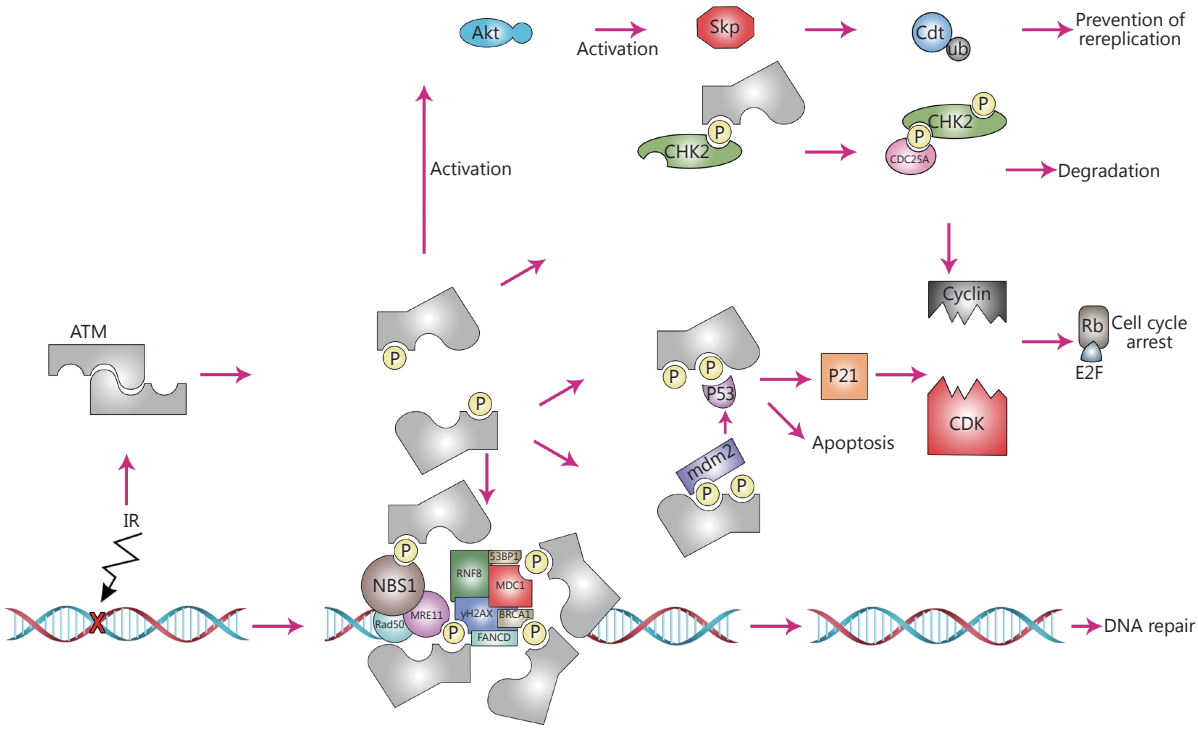

Figure 1 ATM plays multiple roles in human cell biology. To be highly active, ATM disunites to monomers; like other PI3Ks for activation it needs a stimulus and leads to phosphorylation of several different substrates. On the other hand, the activity of ATM can be regulated via some of these substrates. Indeed, they provide a platform for ATM. In the area of damaged DNA, ATM takes part in the phosphorylation of the histone variant H2AX, resulting in production of γH2AX. ATM then phosphorylates the adapter protein MDC1. These phosphorylation events form a docking station for many elements involved in the DNA damage repair system, including the RING-finger ubiquitin ligase, RNF8 that binds to phosphorylated MDC1. RNF8 then leads to ubiquitation of γH2AX, resulting in its stabilization. Stabilized γH2AX is the required platform for recruitment of p53 binding protein 1 (53 BP1) and BRCA1. Following their recruitment, 53BP1 and BRCA1 get phosphorylated by ATM, activating DNA repair processes. ATM also interacts with the MRN complex elements, such as MRE11, NBS1 and Rad50, which bind to double strand DNA and act together as a sensor of DNA damage. This interaction leads to an effective response to DNA damage. In the next levels of ATM dependent mechanisms, p53 transactivates its target genes including CDK inhibitor p21, resulting in the inhibition of the Cyclin-CDK complex formation and hindering G1 to S phase transition. mdm2 which negatively regulates p53, is also phosphorylated by ATM, resulting in abrogation of its interacting potential and stabilization of p53. If occurred in S-phase, DNA DSBs triggers CHK2 activation (phosphorylation on threonine 68) by ATM, leading to the phosphorylation of CDC25A, causing its degradation. Genomic stability is also regulated by ATM where it activates Akt, triggering active Skp that in turn regulates the critical replication licensing factor, Cdt. This process is vital for the maintenance of genome by licensing only one replication event in any given region.

for polyubiquitination and proteasomal degradation. Following DNA damage, in addition to p53 activation and stabilization via modifications[56], ATM also inhibits its nuclear export and the ability of Mdm2 to degrade p53, which is an important step in p53 activation[54,57,58]. Accordingly, the expression of *p53* and *ATM* has been identified as correlated in several cancer cell types[59].

In brain tumors, *p53* risk and protective haplotypes are associated with glioblastoma and *ATM* in meningioma[60]; however, Kheirollahi et al.[61] reported no correlation of expression between *ATM* and *p53* in grade I and II astrocytomas and meningiomas. Accordingly, Barros et al.[62] argued that ATM likely regulates gene expression in an indirect way. It was also suggested by Kheirollahi et al.[61], that various complex mechanisms could contribute to this interaction in brain tumors. In breast cancer, however, Angèle et al.[63] showed a correlation between the expression of *p53* and *ATM*. It has also been demonstrated that patients with tumors containing concomitant *p53* mutations and low *ATM* expression levels exhibit inferior survival rates, compared with those with wild-type *p53* and high *ATM* expression levels[64]. Concannon et al.[65] suggested that a

number of ATM alleles exhibit anti-neoplastic effects, which might be caused by changes in the activity of ATM as a DNA damage initiator or a p53 regulator in breast tumors.

There are two pathways that enforce the G1-S checkpoint; the main and delayed response is p53-dependent. Activation, accumulation, and stabilization of p53 leads to transcriptional regulation of a set of genes associated with the cell-cycle. Among those is the CDK inhibitor, p21, which controls the binding of CDK2 to Cyclin D. Binding and activation of CDK2/Cyclin D eventually results in G1/S arrest, a process that requires inactivation of Rb, following progression from G1 to S-phase[66] (**Figure 1**). A study investigating astrocytoma and meningioma brain tumors, revealed that associations between *ATM*, *Cyclin D2*, and *Rb* expression are disordered in higher grade tumors, while in lower grade tumors, different patterns of correlation were observed[61]. In lower grade meningiomas and astrocytomas, the expression levels of *CCND2* (*Cyclin D2*), *P53*, *Rb1*, and *ATM* were significantly positively correlated. *ATM* has been identified as expressed at higher levels in high grade brain tumors, possibly because it is up-regulated in response to DNA damage in higher grade malignancies. The correlation between expression of genes has been demonstrated in various different grades of tumor, indicating a non-specific pattern, even for genes that interact directly[61]. In meningioma tumor cells, ATM and p53 protein levels were found to be low and very low, respectively. In contrast, astrocytoma tumors present a mixture of low and high ATM and p53 protein levels. The existence of tumor cells with high ATM and p53 expression levels is considered a reliable indirect sign of benign status in meningiomas. These observations are comparable with the high expression levels of p53 and ATM proteins in healthy individuals. Interestingly, low levels of ATM protein expression, together with clones of cells with low levels of Rb protein, indicate a harmonic expression pattern in astrocytoma tumors[67].

ATM also prevents entry to S-phase in response to DNA damage, via a second, p53-independent, pathway. CHK2 is a key target of ATM in this pathway, and is activated in response to DNA damage through phosphorylation on various sites, including the Thr68 regulatory residue[68,69]. Activation of CHK2 results in phosphorylation of its target, CDC25A, stimulating its degradation. Reduction of CDC25A blocks entry to S-phase, as it prevents dephosphorylation and activation of CDK2[70]. Mehdipour et al.[71] showed that CDC-25A is up-regulated in breast tumors and associated with poor survival. These authors suggested that CDC25A is a pivotal prognostic cell cycle marker that could be used for diagnosis of high risk breast cancer. High expression levels of *CDC25A* have also been observed in glioma brain tumors[72].

As mentioned above, CDC25A phosphorylation by ATM and CHK2 also controls the intra-S phase checkpoint. In addition, in response to DNA damage, ATM is involved in phosphorylation of multiple factors, providing sufficient time for cells to repair DNA lesions during the intra-S phase checkpoint. In this context, BRCA1, FANCD2, NBS1, and SMC1 are phosphorylated by ATM on residues Ser-1387, -222, -343, and -957 (or -966), respectively[73].

The process that prevents cells containing damaged DNA from entering mitosis is the G2-M checkpoint, which is regulated via several parallel mechanisms. Phosphorylation of BRCA1 on Ser1423 by ATM, inhibits the formation of the CDC2/Cyclin B complex[74]. In addition, BRCA1 catalyzes CtIP ubiquitination, and its subsequent interaction with chromatin leads to G2-M checkpoint control[75]. P53 dependent G2 arrest, CDC25C phosphorylation via ATM, and its subsequent events, are other key mechanisms that are induced in response to DNA damage during the G2-M checkpoint[73].

DNA repair function

As one of the first lines of protection following DNA damage, ATM is rapidly recruited to sites of DSBs (**Figure 1**), accompanied by the MRN complex (MRE11, NBS1, Rad50). The latter acts as a sensor of damaged DNA, and ATM is not required for its localization[76]. In contrast, the MRN complex binds to double stranded DNA and is necessary for the response to DNA damage, which depends on the complete activation of the ATM[77,78], providing a platform and acting as substrate for ATM[79,80]. The endo- and exonuclease activities of ATM are important for stimulation of ATM by the MRN complex[81]. MRE11 leads to production of small DNA fragments which can stimulate ATM activation at the site of DNA DSBs[82]; nevertheless, Lee et al.[83] noted that the nuclease activity of MRE11 in the MRN complex is not crucial for ATM activation. In addition, ATM directly interacts with the MRN complex through the C-terminus of NBS1 (also known NBN)[84]. All these molecular interactions at the site of DNA DSBs result in an effective DNA damage response that can eventually lead to DNA repair. Awasthi et al.[81] proposed that the activation of ATM may be associated with its dephosphorylation. Upon its recruitment, ATM induces the phosphorylation of Ser139 of H2AX, resulting in production of γH2AX[85], which in turn provides a platform for binding of the adapter protein, MDC1, and its phosphorylation by ATM[86,87]. Although dispensable for the initial recruitment of ATM to the site of DNA DSBs, MDC1 is necessary for its

retention. Formation of phosphorylated γH2AX-MDC1 complexes at the site of DSBs provides a docking platform for proteins involved in DNA repair and related signaling pathways, including the RING-finger ubiquitin ligases, RNF168 and RNF8[88-91]. RNF8 recruits p53 binding protein 1 (53BP1) and BRCA1 as a result of ubiquitination of γH2AX, resulting in its stabilization. Moreover, 53BP1 and BRCA1 are phosphorylated by ATM[92]. Thus, phosphorylation events mediated by ATM are essential for the repair of DNA DSBs (**Figure 1**).

Other roles of ATM

Another important role of ATM is its involvement in the cellular response to oxidation state. Following oxidative stress, changes to the integrity of several intermolecular disulfide bonds lead to the induction of ATM. At DNA DSBs, ATM activation is through phosphorylation of Ser1981, which results in dimer dissociation. In contrast, under oxidative conditions, disulfide bonds between the dimer subunits form covalent linkages, resulting in activation of its kinase activity; this function is independent of Ser1981 phosphorylation[93,94].

ATM also prevents re-replication by regulation of Ctd1 stability, and acts as a guardian of genomic integrity and stability during unperturbed cell-cycle progression. Interestingly, depletion of ATM alters the level of Cdt1, which is a critical replication licensing factor (along with p27 in some cells), without changing the expression of Cyclin D1 or p21, factors regulated by Skp2. This results in strict regulation of Cdt1, ensuring that only one replication program occurs. Of several already unanswered questions, "how does ATM regulate Akt activation?" is notable, as it could hold the key to understanding ATM regulated signaling pathways involved in cell growth and inhibition of apoptosis[95,96] (**Figure 1**).

ATM variants in breast cancer

Northern Europe

The most frequent variants of the *ATM* gene in patients from northern Europe (Finland, Denmark, and the Netherlands) include 2572T>C, 3161C>G, 5558A>T, 2119T>C, 4258C>T, and 5557G>A. The 2572T>C variant, is a missense variant causing Phe858Leu amino acid change in exon 19; another variant at this site, 2572insT, was reported in the Netherlands. Two of these variants, 3161C>G (Pro1054Arg) and 5558A>T (p.Asp1853Val), encode amino acid substitutions predicted to have deleterious effects on protein structure. Gutierrez-Enriquez et al.[107] showed that lymphoblastoid cell lines expressing the *ATM* variant, 3161C>G, exhibited chromosomal radiosensitivity *in vitro*, possible due to a dominant-negative effect on ATM function[170]. The alterations, 2119T>C and 4258C>T, are missense variants in exons 15 and 31, respectively, encoding Ser707Pro and Leu1420Phe protein changes. Heikkinen et al.[97] proposed that the 5557G>A *ATM* variant modifies cancer risk when present in cis with the IVS38-8T>C mutation, which is associated with bilateral breast cancer in patients of Finnish origin. They also suggested that such composite alleles lead to low *ATM* expression levels that may influence mis-splicing of exon 39 (**Table 2**).

Table 2 ATM variants have been reported in the breast cancer patients from northern Europe

Country	Variants	References
Finland	5557G>A, 5558A>T, 133C>T, 735C>T, 2119T>C, 2572T>C, 3150C>T, 3161C>G, 4258C>T, 146C>G, 4578C>T, 6779-6780delTA, 6903insA, 7522G>C, 8071C>T, 8710-8715delGAGACA, 9139C>T, IVS62+8A>C, IVS1a-10A>G, IVS11-16delT, IVS14-55T>G, IVS14+3-4delAT, IVS15-68T>C, IVS17-56G>A, IVS24-9delT, IVS25-12insA, IVS27+40G>A, IVS37+9A>G, IVS38-8T>C, IVS38-15G>C, IVS44-61C>G, IVS49-43A>G, IVS62-55T>C, IVS62+60G>A	97-100
Sweden	IVS10-6T>G	101
Denmark	378T>A, 146C>G, 735C>T, 2119T>C, 2572T>C, 3161C>G, 4578C>T, 5557G>A, 5558A>T, 4258C>T, 1899-55T>G, 3285-10delT, 5497-8T>C, 5762+27G>A, 6348-54T>C, 8786+8A>C	65, 102
Norway	3245-3247delATCinsTGAT, 4632-4637delCTTA, 8264-8268delATAAG, 7875-7876TG>GC, 8432delA, 8978-8981delGAAAinsAT	103
The Netherlands	3114A>T, 146C>G, 162T>C, 1009C>T, 1132A>G, 1229T>G, 1562delAG, 1563delAG, 37C>T, 1660delA, 2650C>T, 1810C>T, 378A>T, 2119T>C, 2276G>A, 2336T>C, 2414G>A, 2572T>C, 2572insT, 2614C>T, 3115A>T, 3161C>G, 3925G>A, 4138C>T, 4258C>T, 4324T>C, 4362A>C, 4477C>G, 4664T>A, 4722G>T, 5044G>T, 5071A>C, 5557G>A, 5558A>T, 5741A>G, 6067G>A, 6820G>A, 6919C>T, 7446G>A, 7874A>G, 8659C>G, IVS10-6T>G, IVS14+2T>G	104-106

Southern, central, and western Europe

The most frequent variants of the *ATM* gene in patients from southern, central and western Europe (Switzerland, Britain, Germany, France, and Spain) are 2572T>C and 3161C>G. The 3161C>G variant was not reported in the Polish population, and another frequent variant, 2572T>C, did not vary significantly between cases and controls in the Polish study[115]. In addition, the 2572T>C variant was not reported in Italian population studies (**Table 3**) .

Eastern Europe

The most important and frequent variant of the *ATM* gene in eastern Europe is the nonsense mutation, 5932G>T, which leads to inclusion of a termination of translation at codon at position 1978. It has been reported in the Czech Republic, Austria, Belarus, Ukraine, and Russia. Interestingly, it has rarely been reported in other European countries, other than Poland. Thus, it appears that this variant may have arisen exclusively in eastern Europe. Bogdanova and colleagues, reported a five-fold higher frequency of this mutation in breast cancer patients compared with controls, indicating a role in predisposition to breast cancer susceptibility for the E1978X amino acid change encoded by this allele. This mutation appears to be remarkably frequent in patients from eastern European countries, including Russia, Belarus, and the Ukraine, whereas its incidence is somewhat lower in Poland[114] (**Table 4**).

America

The most frequent variants of the *ATM* gene in the American breast cancer patients, including 5558A>T (D1853V) and 5557G>A (D1853N), which have been reported in all different regions and ethnicities in America; although, 5558A>T

Table 3 ATM variants have been reported in the breast cancer patients from southern, central and western Europe

Country	Variants	References
Switzerland	2119T>C, 1960G>A, 2572T>C, 3161C>G, 4388T>G, 5557G>A, IVS4+37insAA, IVS17-56G>A, IVS20+28insA, IVS22-77T>C, IVS25-15insT, IVS30-2A>G, IVS48-69ins3, IVS56-23insT, IVS59-20del4, IVS63-24delTT	97
Britain	2119T>C, 146C>G, 790delT, 2572T>C, 3161C>G, 3349C>T, 3802delG, 4258C>T, 5290delC, 7271T>G, 7311C>A, 8264delATAAG, IVS40-1050A>G, IVS44+1G>A, IVS59+1delGTGA	4, 6, 108
Germany	5071A>C, 146C>G, 1810C>T, 2119T>C, 2572T>C, 1648A>G, 3161C>G, 3801del G, 4258C>T, 4709T>C, 5557G>A, 5558A>T, 6820G>A, 6860G>C, 7390T>C, 7775C>G, 8314G>A, 735C>T, 1020C>A, 2193C>T, 4578C>T, IVS10-6T>G	106, 109
France	2572T>C, 2614C>T, 5557G>A, 2119T>C, 2572T>C3161C>G, 4148C>T, 4258C>T, 4473T>C, 4578C>T, 5089A>G, 5558A>T, IVS22-77T>C, IVS48+238C>G, IVS38-15G>C, IVS38-8T>C	110, 111
Italy	146C>G, 3161C>G, 4258C>T, 6860G>C, 6235G>A	112
Spain	3161C>G, 146C>G, 2572T>C, 3802delG, 4578C>T, 5557G>A, 1254A>G, 7178C>G, 3763T>G, 6314G>C, 7653T>C, 8156G>A, 10597T>C, 10775T>C, 11250C>T, 12306A>G, 12564T>G, 11686T>A, 72+36insAA, 1802+65T>C, 2125-68T>C, 3285-9delT, 3403-15delA, 3747-34A>G, 5497-8T>C, 6199-61C>G, 6348-54T>C, 6808-69insATT, 8787-56T>C, 8850+60G>A, 6199-57insG, 5497-168T>C, 6573-22A>G, 7629+81T>C	113
Poland	146C>G, 2119T>C, 2572T>C, 4578C>T, 5932G>T	114-116

Table 4 ATM variants have been reported in the breast cancer patients from eastern Europe

Country	Variants	References
Czech	5177+1G>A, 5932G>T, 6096-9delTTCTT, 1066T>G	117
Slovenia	1960G>A, 2119T>C, 3161C>G, 2572T>C, 4388T>G, 5557G>A, IVS4+37insAA, IVS17-56G>A, IVS20+28insA, IVS22-77T>C, IVS25-15insT, IVS30-2A>G, IVS59-20del4, IVS48-69ins3, IVS56-23insT, IVS59-20del4, IVS63-24delTT	118
Austria	IVS10-6T>G	119
Belarus	5932G>T	114, 116
Ukraine	5932G>T	114, 116
Russia	5932G>T	114, 116
Romania	2572T>C	120

was not reported in Japanese and Mexican Americans. Bretsky et al.[121] noted that 5557G>A is the most important polymorphism, while other missense variants are rare, and do not appear to be overrepresented among breast cancer patients compared with controls in Americans (**Table 5**).

Australia

The most important missense variant of the *ATM* gene in Australian breast cancer patients is 7271T>G. This is a missense variant causes a valine to glycine substitution at position 2424 of the ATM protein (p.Val2424Gly), and has no influence on any recognized functional domain, suggesting that it is deleterious. This variant has also been reported in the USA, Canada and Britain, which are countries with high immigrant populations. Goldgar and his colleagues stated that women with the *ATM* 7271T>G variant are at high risk and that screening for this variant in cancer-prone families, even those lacking changes in *BRCA1* or *BRCA2*, is essential for management and genetic counselling[130]. Another prevalent variant in Australian breast cancer patients is the 3802delG truncating mutation in exon 28. IVS10-6T>G is a further important variant, which has been reported in all regions of the world. This variant leads to incorrect splicing of exon 11, producing ATM mRNA and protein molecules of less than 10% of the full-length versions[144]. Although multiple studies suggest that *ATM* IVS10-6T>G contributes to an elevated risk of breast cancer[105,131], a large meta-analysis revealed it is not correlated with increased risk of breast cancer in the overall study population[145]. The role of the IVS10-6T>G mutation in breast cancer development is suggested to both be determined by its functional consequences and mediated by family history and BRCA1 and BRCA2 mutation status[101,119].

Asia

Mehdipour and colleagues[141] proposed that the polymorphism 5557G>A (located in exon 39 of *ATM*) could be considered a predisposing factor for the development of familial breast cancer. In this study, Iranian women with breast cancers were divided into two subgroups. The first

Table 5 ATM variants have been reported in the breast cancer patients in different regions and ethnic groups of America and Canada

Regions/ethnics	Variants	References
African American	146C>G, 2614C>T, 378T>A, 2119T>C, 2572T>C, 3161C>G, 3383A>G, 5557G>A, 5558A>T, 2685A>G, 1254A>G, 1541G>A, 4939C>T, 2289T>A, 4279G>A	121-123
Latina	378T>A, 2614C>T, 2119T>C, 2572T>C, 3161C>G, 4258C>T, 5557G>A	121
Japanese	2572T>C, 5557G>A	121
Caucasian	146C>G, 378T>A, 2119T>C, 2572T>C, 4258C>T, 3161C>G, 5557G>A, 5558A>T, 5932G>T	121, 123, 124
Hispanic American	5557G>A, 5558A>T, 3161C>G, 146C>G	123
Asian American	5558A>T	123
South American	378T>A, 5557G>A, IVS4+36insAA, IVS17-56G>A, IVS24-9delT, IVS25-12insA, IVS38-15G>C, IVS38-8T>C, IVS47-65G>C, IVS48-69insATT	125
Chile	2572T>C, 5558A>T, 2082T>C, 2256A>G, 378T>A, 1744T>C, 2119T>C, 5557 G>A, IVS4+36insAA, IVS17-56G>A, IVS22-77T>C, IVS24-9delT, IVS25-13insA, IVS25-35T>A, IVS38-8T>C, IVS25-12insA, IVS38-8T>C, IVS47-65G>C, IVS48-69insATT, IVS62+8A>C, IVS64+51delT, IVS38-15G>C	125, 126
Mexico	5557G>A, IVS24-9delT, IVS38-8T>C	127
US (without considering ethnicity)	370A>G, 609C>A, 4138C>T, 4400A>G, 2362A>C, 7397C>T, 6088A>G, 5793T>C, 735C>T, 1176C>G, 4148C>T, 5071A>C, 8734A>G, 9031A>G, 3802delG, 6997dupA, 7831-7835del, 7271T>G, 146C>G, 2119T>C, 2572T>C, 4578C>T, 8473C> A8535G>A, IVS54+8G>T, IVS10-6T>G, 544G>C, 735C>T, 2193C>T, 4066A>G, 6332A>G, 7291A>G, 8071C>T, 2289T>A, 4307A>G, 4388T>G, 4424A>G, 2685A>G, 1541G>A, 2805G>C, 5793T>C, 6088A>G, 6919C>T, 6988C>G, 8000T>C, 1744T>C, 1880T>G, 2614C>T, 3383A>G, 3630G>A, 4138C>T, 7271T>G, 378T>A, 735C>T, 2119T>C, 2572T>C, 3161C>G, 4258C>T, 4578C>T, 5557G>A, 5558A>T, 1899-55T>G, 3285-10delT, 5497-8T>C, 5762+27G>A, 6348-54T>C, 8786+8A>C, IVS4+35insAA, IVS24-9delT, IVS25-12insAA, IVS28+5G>T, IVS7-48T>G, IVS8+38T>C, IVS9+25T>G, IVS15-68T>C, IVS16+78G>A, IVS21+19insA, IVS25-15insT, IVS25-15delT, IVS33-20A>G, IVS43-15T>C, IVS45+30delT, IVS56+30insT, IVS62+8A>C, IVS7+18T>C, IVS16+22A>C, IVS16+34A>C, IVS19-17G>T, IVS25+32delCAT, IVS38-66T>G, IVS38-112G>A, IVS38-15G>C, IVS38-8T>C, IVS62+8A>C	65, 115, 128-135
Canada	7271T>G	132

group were selected at random and the second group had a positive family history; both were compared with a group of healthy controls. The study revealed a carrier frequency of 31% in the disease group, compared with 18.6% in controls. In the randomly selected group, the carrier frequency was 12.5%, whereas the rate was 26.9% in subjects with a family history of breast cancer[141]. To address the clinical significance of this polymorphism, a meta-analysis study by Gao and colleagues[146] concluded that there was no association between the 5557G>A polymorphism and disease. In contrast, Tapia and colleagues[126] found a clear positive association between this polymorphism and a high risk of bilateral breast cancer development. They analyzed the frequency of 5557G>A and the intronic variant, IVS24-9delT, individually or in combination, and found a frequency of 20.3% heterozygosity among patients and 7.5% in controls, while only 1% homozygosity was detected in both groups. Furthermore, this variant was described in European countries by Angéle and colleagues[110]. The authors found that homozygotes were more frequent among patients with breast cancer who had received radiotherapy. This finding led to the proposal of the association of this variant with elevated radiosensitivity in breast tissue, and the suggestion that this alteration is a predisposing factor for reaction effects occurring after radiotherapy[110]. In another study, González-Hormazábal and colleagues[125] found three *ATM* polymorphism, IVS24-9delT, IVS38-8T>C, and 5557G>A (the latter more common, at 20.6%), among Chilean patients with familial breast cancer, who were negative for mutations in BRCA1/2. They suggest that these three alterations, either alone or in combination, together with environmental factors, could increase the risk of breast cancer, as a result of raised chance of genetic instability or failure of the DNA damage response. Youlden et al.[147] reported variable mortality rates among different regions, with huge increases in some Asian countries compared with low rates in Australia. Although all breast cancer patients with *ATM* mutations, who had inferior survival rates and died during the follow-up period, carried the 5557G>A variant, this was not a statistically significant finding[148] (**Table 6**).

ATM variants in brain tumors

To date, 739 mutations have been identified in the *ATM* gene (HGMD 2015). Patients with AT and CNS involvement and patients with CNS tumors can have *ATM* gene disruption. In response to DNA damage, requirement for special mechanism in terminally differentiated cells and also localization of ATM at a key biochemical node[10] indicate strong evidence of a link between *ATM* and CNS; however, adequate studies are lacking. To date, the evidence for the influence of specific *ATM* mutations and polymorphisms in different types of brain tumor is limited (**Table 7, Figure 3**). The first study of the association between *ATM* variants and brain tumors was performed by Liberzon and colleagues[14], who screened 13 medulloblastomas and found that the only altered *ATM* sequences were the known polymorphisms, F858L and D1853N, which were present in five patients (38%). The reported frequency of the D1853N polymorphism was consistent with that in a previously published study of patients with medulloblastoma[149]. Moreover, D1853N has been reported in the majority of studies[65, 109, 127, 150, 151], and is considered the most important fundamental alteration identified by genotyping of the *ATM* gene in patients with brain tumors[152].

In glioma, four variants have been reported, with 4578C>T the only exonic polymorphism identified in a patient population from the north of the UK[153]. This variant was also detected in patients with breast cancer from Finland, Denmark, Germany, France, Spain, Poland, and the USA, and at the amino acid level encodes Pro1526Pro (exon 30). Zhao et al.[154] identified a novel polymorphism in the *ATM* promoter region in gliomas. This variant, 111G>A, is located in the non-coding region of the *ATM* gene and has no direct influence on the amino acid sequence of the ATM protein; however, it may effect splicing, modification, or RNA stability, and thereby the mode of expression of the ATM protein[155]. Bioinformatics analysis to explore the potential mechanism of *ATM* mRNA expression regulation by this polymorphism suggested that, *ATM* sequences containing the SNP, rs189037, were transcriptionally repressed by AP-

Table 6 ATM variants have been reported in the breast cancer patients in Asia, Australia and New Zealand

Country	Variants	References
Australia and New Zealand	7271T>G, 4258C>T, 2119T>C, 3161C>G, IVS10-6T>G, 3802delG, 5623C>T, 7886-7890del, 8851-1G>T, IVS10-6T>G	101, 130, 132, 136-140
Iran	5557G>A	141
China	IVS34+60G>A, IVS1+19A>T	142
South Korea	5144A>T, 3393T>G, IVS21+1049T>C, IVS33-55T>C, IVS34+60G>A	143

Table 7 ATM variants have been reported in different types of brain tumors

Brain tumor types	Year and country	Samples	Results
Glioma	2011: UK, Sweden and Denmark[153]	188 cases with grade II and III glioma	4 SNPs mapped to *ATM* had significant association with survival
	2013: China[154]	384 glioma patients and 384 cancer-free controls	186 cases and 203 controls were heterozygote and 58 cases and 56 controls were homozygote for rs189037 SNP
	2016: China[158]	771 glioma cases and 752 cancer-free controls	3-locus interaction model involving NBS1 rs1805794, MRE11 rs10831234, and ATM rs227062 is the best model for the prediction of the risk of glioma
	2007: Nordik-UK[60]	680 glioma cases and 1555 controls were analyzed for five *ATM* polymorphisms	No significant association between cases and controls. No significant difference in *ATM* haplotypes distribution between cases and controls
	2008: Iran[152]	One case with astrocytoma and in her 14 relatives. Regarding the group II controls 12 out of 129 were revealed to carry D1853N.	Two novel (IVS38-63T>A and IVS38-30A>G) alterations were found in proband
		10 astrocytoma and 40 other types of brain tumors screened for D1853N.	D1853N was observed in 50% of astrocytoma cases and 27.5% of other brain tumor types
Medulloblastoma	2003: Israel[14]	13 tumors screened for *ATM* mutations and 9 for loss of heterozygosity	They identified four with the D1853N and one with F858L. The LOH of the 11q region detected in 25% of informative cases
Meningioma	2007: Nordik-UK[60]	503 meningioma cases and 1555 controls were analyzed for five *ATM* polymorphisms	T10182A and G142798A variants were significantly less common in cases than in controls. A significant difference in ATM haplotype distribution was observed between cases and controls
Pediatric brain tumors	2016: Denmark, Sweden, Norway, and Switzerland[159]	Saliva DNA from 245 cases and 489 controls, aged 7-19 years at diagnosis was genotyped.	An increased risk of non-astrocytoma subtype of PBTs associated with ATM rs170548 (IVS63 + 97)

2a[156]. To date, the ATM protein kinase has been referred to as a DNA damage sensor and a therapeutic target in tumors[157].

Breast to brain metastases

Brain metastases are the most common form of intracranial spread of tumors, accounting for 15%–40% of patients with metastatic conditions[160-162], whereas 42% of metastatic breast tumors are solitary[163]. Overall, breast and lung cancers are the most likely to progress to brain metastases[164]. Patients with breast cancer are remarkably likely to develop brain metastases, leading to a disease state with undesirable consequences for quality of life and more complicated responses to therapy. The incidence of brain metastases varies between 140, 000 and 170, 000 cases per year, and in recent years has risen, seemingly because of the prolonged survival of patients with primary tumors who have undergone aggressive treatment[162,165].

Gachechiladze et al.[166] reported a significant correlation between shorter survival and phosphorylation of BRCA1 in patients with brain metastases of lung cancer. The role of ATM in BRCA1 phosphorylation and the interaction of these proteins is established[166,167]. In addition, variants of ATM and BRCA1 have functional effects in breast cancer[141,168]. Thus, ATM may have a crucial role in tumors involving breast-brain metastases. Studies investigating *ATM* variants in this type of breast tumor will shed new light on this field; however, no such study has been published to date. Recently, the D1853N mutation in *ATM* was reported in tumors with ovarian to brain metastases, and *ATM* and *BRCA1* were found to be the most commonly altered genes[169]. Mehdipour et al.[141] explored the role of D1853N in disease susceptibility among breast cancer patients and healthy individuals, and found this variant is a risk factor for metastatic progression. Furthermore, metastatic progression has been classified as a stepwise molecular alteration process of cancer development which requires three hits, D1853N, IVS38-63T>A, and IVS38-30A>G, occurring sequentially in astrocytes[152] (**Figure 4**). In addition, Mehdipour et al.[67] found a triangular

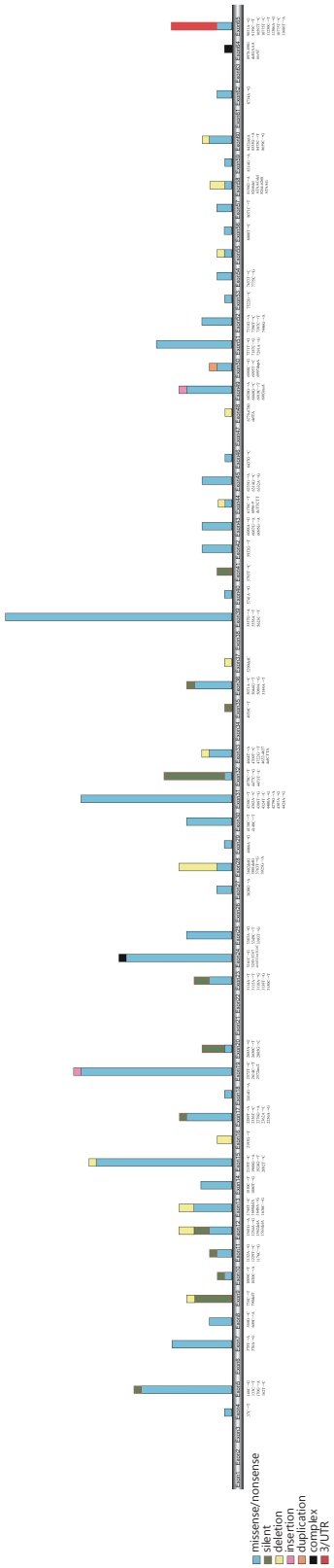

Figure 2 Mutations of ATM gene in exonic region according to their repetition in different studies in breast cancer patients.

correlation between methylation of the *ATM* promoter and protein expression of *ATM* with the D1853N variant. Evaluation of the D1853N variant alongside other alterations in patients with breast cancer, particularly those with breast to brain metastases, could lead to development of appropriate clinical management approaches.

Heikkinen and colleagues[97] proposed a cancer risk-modifying consequence of the IVS38-8T>C alteration occurring *in cis*, as it was reported as associated with bilateral breast cancer in patients of Finnish origin. They suggested that the function of such a composite allele leads to low *ATM* expression levels, that may be related to the mis-splicing of a region of exon 39. These data emphasize the importance of evaluation of ATM expression, in addition to exploration of its variants. The only study to do this was that of Salhia et al.[170] who demonstrated that *ATM* gene expression was commonly down-regulated in patients with breast cancer and brain metastases. Combined functional assays, including copy number variation and gene expression analyses, demonstrated the down-regulation of *ATM*, revealed cell cycle and G2-M pathway enrichment, and have potential to lead to innovative therapeutic strategies. These findings are of particular importance, since they suggest rare therapeutic options for tumors involving breast to brain metastases.

Therapeutic opportunities

Given its broad range of functions, in processes from cell cycle regulation to DNA repair, ATM represents a therapeutic target molecule in tumors of the brain and breast. The discovery and introduction of anticancer drugs targeting molecules involved in the cell-cycle and checkpoint regulation, such as cell-cycle or checkpoint inhibitors[171], can also influence ATM indirectly. The majority of cancer therapy studies related to ATM have focused on its significance in radiotherapy[172-175]. Molecular mechanisms that cause resistance to radiotherapy in glioma cells have been linked to the expression of ATM, in cooperation with other pro-survival networks[176]. A key mechanism leading to inactivation of tumor suppressor genes is methylation of their promoters. The methylation pattern of the *ATM* promoter has been investigated in a few studies of different types of brain tumors[177,178]. For example, Mehdipour et al.[67] found that more than 73% of brain tumors exhibit methylation of the *ATM* promoter. A strong correlation between *ATM* promoter methylation and its protein expression has also been established. In another study, in which three glioblastoma cell lines (U87, T98G, and U118) were analyzed, methylation of the *ATM* promoter was only

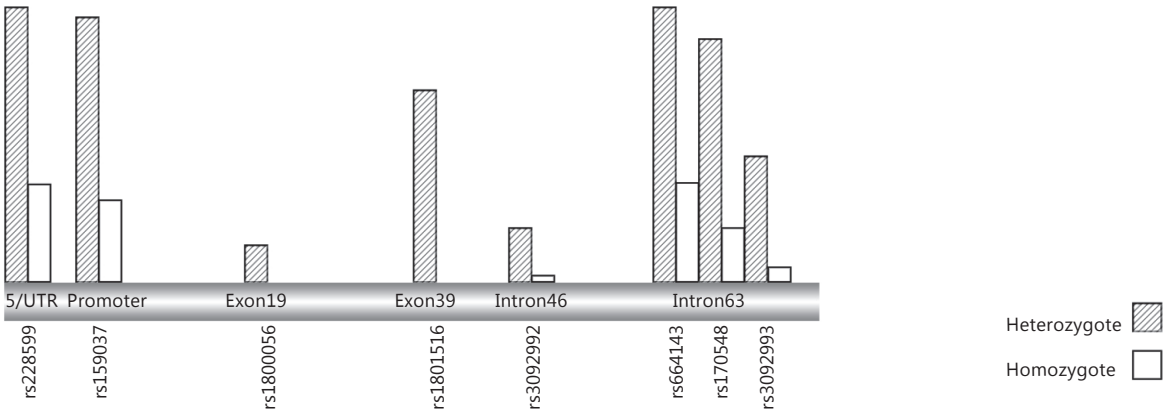

Figure 3 ATM gene variants in brain tumors.

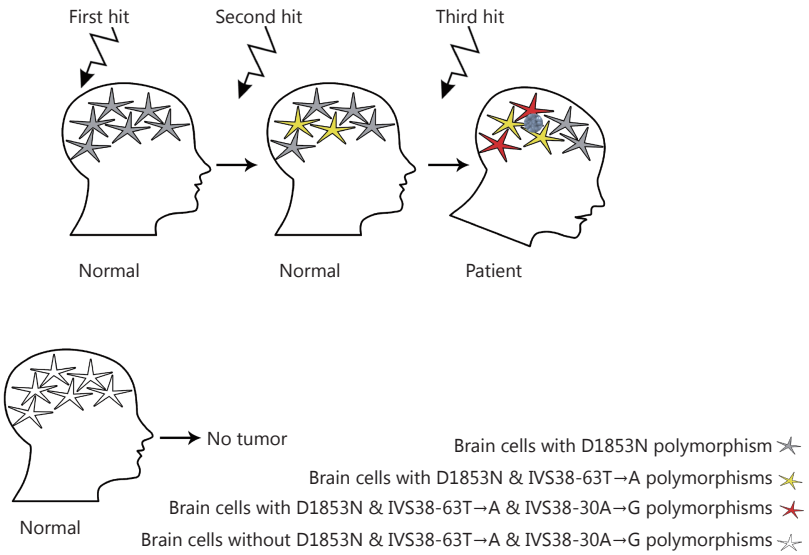

Figure 4 Three hit hypothesis. Two novel heterozygously intronic alteration, i.e., IVS 38- 63 T>A and IVS 38-30 A> was found in proband located within 3 regions of splicing site. Two non-inherited events including IVS38-63T>A and IVS38-30A>G, resulting from two separate courses of evolution in proband occurred on the same chromosome which was different from the inherited D1853N polymorphism (data is adopted from Mehdipour, et al. 2008).

found in the T98G cell line[178]; however, despite its normal methylation status, the level of ATM protein was decreased in U87 and U118 glioma cells, which also exhibited elevated sensitivity to radiation. The use of siRNA to silence ATM expression can increase tumor cell radiosensitivity, as reported recently[175]. In brain metastases from the majority of epithelial cancers, the blood brain barrier (BBB) limits the use of chemotherapy as the first-line treatment option, with radiotherapy considered most effective. However, resistance to radiotherapy leads to disease recurrence and therapeutic failure. Yang et al.[179] reported increased radiosensitivity in response to treatment with the CHK1 inhibitor, AZD7762, in lung cancer cell lines and a xenograft model. In lung cancer cell lines, the mechanism underlying this phenomenon was identified as the interaction of AZD7762 with ATR/ATM-mediated CHK1 phosphorylation, stabilization of CDC25A, and suppression of cyclin expression. In addition, in a lung cancer xenograft model of brain metastases, the median survival period was enhanced by AZD7762[179].

Tumors with DNA repair pathway deficiency are sensitized to platinum drugs that induce such double strand breaks[180]. Hence, breast cancer patients with *BRCA1* mutations exhibit increased responses to treatment with cisplatin[181]. Tumors with *ATM* mutations are also highly sensitive and responsive

to platinum chemotherapy[182].

Recently, Fann et al.[183] evaluated the small molecule, NSC745887, in glioblastoma cells and found that it caused high expression of γH2AX, leading to DNA fragmentation, enhanced G2-M arrest, and apoptosis via induction of DNA damage responses.

Future perspective

Adequately informative gene expression/polymorphism profiles of human brain tumors are not available, because of disease heterogeneity and lack of comprehensive studies. Thus, comprehensive understanding of tumorigenic processes requires additional complementary investigations and pedigree-based analyses. Hence, more studies are required to fully address the etiology of brain tumors and differences in ATM variations, particularly in brain metastases. Nevertheless, monitoring of ATM alterations in brain tumors is a rather limited approach that has been restricted to a few types of brain tumors. Some reports of evaluation of *ATM* gene expression are available in different tumors, particularly brain tumors. Neurons are unable to enter the cell cycle; however, cancerous brain cells lose this feature and reactivate cycling, indicating that their templates of activation or inactivation differ fundamentally to normal ones. Accordingly, there does not appear to be a specific template for the correlation of the expression pattern of key factors in the DNA repair process, even among genes known to closely interact, including *p53*, *ATM*, *Rb* and *Cyclin D*. Studying the mRNA expression level of the above-mentioned genes in human brain tumors is necessary. To clarify any relationship between ATM functions and its variants, complementary research studies are required. The newly discovered function of ATM in response to oxidative conditions blurs any clear distinction between the DNA repair process and other cellular functions of ATM.

According to available data on breast tumors, it could be concluded that *ATM* gene status, is highly variable depending on the available data on the patient's population origin and pedigree. In addition, a primary obstacle to effective therapy for brain tumors, specifically higher grade tumors, is rooted in resistance to radiotherapy. The remarkable resistance of cells lacking ATM to radiation is a key finding worthy of consideration. What are the expectations of the clinicians and scientists fighting to eradicate breast cancer and brain tumors? Comprehensive insights into the molecular involvement of the *ATM* gene have the potential to facilitate more reliable clinical management, including improvement of patient survival.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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