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Deep Insight Section

Ataxia-Telangiectasia and variants

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Ataxia-telangiectasia (A-T) is an autosomal recessive multisystem disorder with early-onset cerebellar ataxia as its defining neurologic feature. It is the most common, recessively inherited, cerebellar ataxia in children under 5 years of age, with a prevalence of 1/40,000 to 1/100,000 live births (Swift, 1985). The accompanying extra-neural features aid in its clinical diagnosis and include conjunctival and cutaneous telangiectases, elevated levels of serum alpha-fetoprotein, chromosome aberrations, immunodeficiency with recurrent sinopulmonary infection, cancer susceptibility, and radiation hypersensitivity. Since identification of the causative gene, ATM (for Ataxia-Telangiectasia mutated), on chromosome 11q22-q23 (Gatti et al., 1988; Savitsky et al., 1995), the molecular basis of certain aspects of the disease have become clearer, though others remain to be elucidated (Gatti et al., 1998; Meyn, 1997; Shiloh and Rotman, 1996).

Note: see also cards on genes ATM, and NBS1 , and on cancer prone diseases Ataxia telangectasia and Nijmegen breakage syndrome.

CLINICAL FEATURES

Neurologic Features

Progressive cerebellar ataxia is almost always the presenting symptom and becomes apparent as early as the first year of life. Truncal and gait ataxia are slowly and steadily progressive, although between the ages of 2 and 5 years normal development of motor skills may temporarily mask this decline. This cerebellar degeneration typically leads to wheelchair dependence by the second decade. Migration abnormalities of prenatal Purkinje cell (PC) as well as post-natal PC degeneration have been seen (Vinters et al., 1985), with thinning of the molecular and granule cell layers and minor changes in dentate and olivary nuclei and medullary tracts. Oculomotor abnormalities may also be seen. The typical patient with A-T is of normal intelligence, although the motor abnormalities make formal psychometric testing and standard learning programs difficult.

Telangiectasia

Telangiectases appear an average of two to four years after onset of the neurologic syndrome and are progressive. They are composed of dilated capillaries in the conjunctiva, and, later, on the ears, over the bridge of the nose, in the antecubital fossae, behind the knees, or more diffusely. They do not occur on internal organs nor are they generally associated with bleeding problems.

Cancer Risk

Over the course of their lives, nearly 40% of A-T patients will develop a malignancy (Morrell et al., 1986). Roughly 85% of these malignancies will be either leukemia or lymphoma, which in younger patients may occasionally precede the onset of ataxia. Children will most often develop acute lymphocytic leukemia (ALL) of T-cell origin, rather than the pre-B cell form seen in common childhood ALL. Leukemia in older A-T patients is usually an aggressive T-cell process with morphology similar to a chronic lymphoblastic leukemia (T-CLL, or T-cell prolym-phocytic leukemia, T-PLL) (Taylor et al., 1996). Lymphomas are more often non-Hodgkin's, extra-nodal, infiltrative, B-cell types, and harder to diagnose in their early stages (Murphy et al., 1999). Solid tumors of other tissues occur more commonly as the A-T patient matures, and are being seen in greater numbers as these patients are living longer (Morrell, 1968).

Radiosensitivity

Treatment of A-T patients with cancer with conventional doses of ionizing radiation results in life-threatening sequelae characteristic of much higher doses. *In vitro*, fibroblasts and lymphoblasts from A-T homozygotes show sensitivity to a number of radiomimetic and free-radical-producing agents (Taylor et al., 1985; Shiloh et al., 1985). This finding led to the development of the highly sensitive and reasonably specific diagnostic test, the colony survival assay (CSA) (Huo et al., 1994).

Recurrent infectious disease

Moderate cellular and humoral immunodeficiency, with low levels of certain immunoglobulin classes, in conjunction with difficulties in swallowing, lead to frequent pulmonary infections in A-T patients. The incidence and severity of infections varies widely between patients, with some being severely affected, while others have no particular difficulty.

Other clinical features

A-T, as in other syndromes manifesting chromosomal instability (e.g., Fanconi anemia, xeroderma pigmentosum xeroderma pigmentosum, Bloom syndrome), shows progeroid features (Gatti and Walford, 1981). Young A-T patients may have strands of gray hair or keratoses and basal cell carcinomas. These signs may be related to the accelerated telomeric shortening mentioned above, to increased tissue turnover, and/or to the exaggerated effects of oxidative damage.

Endocrine defects typically result in gonadal abnormalities. Most female patients ultimately begin regular menstrual cycles, but may enter menopause prematurely. Most male patients develop normal secondary sexual characteristics. Retardation in somatic growth is seen in about 75%. Pituitary function studies show no consistent abnormalities. Some patients develop insulin-resistant diabetes in their late teens, with hyperglycemia without glycosuria or ketosis, possibly due to a particular IgM antibody directed against insulin receptors (Gatti and Walford, 1981).

CYTOGENETIC FEATURES

Karyotyping of peripheral lymphocytes from A-T homozygotes shows nonrandom chromosomal rearrangements which preferentially involve chromosomal breakpoints at 14q11, 14q32, 7q35, 7p14, 2pll, and 22q11, and correlate with the regions of the T-cell and B-cell receptor gene complexes (Aurias, 1986). Telomere shortening and fusions, with normal telomerase activity (Pandita et al., 1995), have been observed in peripheral blood lymphocytes of A-T patients, especially in pre-leukemic T-cell clones (Metcalfe et al., 1996).

BIOLOGICAL FEATURES

AFP levels are usually elevated, and are a reliable clinical marker after the age of 2. The high levels of AFP are felt to be of hepatic origin and may be accompanied by elevations of other liver enzymes, with no evidence of liver disease at postmortem (Ishiguro et al., 1986; Gatti and Walford, 1981; McFarlin et al., 1972).

Virtually all A-T homozygotes that have come to postmortem examination have a small, embryonic thymus, but the resulting immunodeficiencies can be quite variable, even within the same family, suggesting a problem with maturation of B and T cell precursors. IgA, IgE, and IgG2 deficiencies are most common, with the accompanying risk of recurrent sinopulmonary infection (Roifman and Gelfand, 1985). Elevated serum IgM levels may occasionally progress to a high blood viscosity syndrome, with splenomegaly, lympho-adenopathy, neutropenia, thrombocytopenia, and congestive heart failure. T-cell deficiencies occur in half the patients, with abnormal skin test antigen and PHA responses (Paganelli et al., 1992). In a British study of 70 patients (Woods and Taylor, 1992), 10% had severe immunodeficiencies, while nearly 40% had normal immunologic function.

CLINICOPATHOLOGY OF THE A-T HETEROZYGOTE

The carrier frequency for ATM is estimated at 1%. Carriers are normal neurologically, although they have *in vitro* radiosensitivity values that are intermediate between homozygotes and normals (Taylor et al., 1985; Paterson et al., 1985; Weeks et al., 1991). It remains unclear whether this translates to any greater risk during exposure to ionizing radiation clinically (diagnostic X-rays, radiation therapy), although results from Broeks suggest that A-T heterozygotes are more frequent among breast cancer patients who develop a second breast tumor after radiotherapy (Broeks et al., 2000). Studies of mice heterozygous for Atm show an increased frequency of dysplastic breast cells in irradiated animals, supporting an increased cancer risk for heterozygotes that is related to their mutagen exposure (Weil et al., 2001). These data suggest that perhaps Swift's recommendation that female relatives of A-T patients avoid mammography is good advice, although the benefit drawn from early detection is largely thought to outweigh the very small chance that the screening could actually provoke a breast tumor, especially when up-to-date mammography equipment with the lowest possible dose is used. Excessive numbers of ATM heterozygotes have not been identified among patients over-reacting to radiotherapy, nor have ATM heterozygotes diagnosed with cancer been noted to have unusual reactions to irradiation,

suggesting that their radiosensitivity *in vivo* is not great (Clarke et al., 1998; Hall et al., 1998).

CANCER RISK OF AT CARRIERS

Several authors have reported that the incidence of cancer in A-T heterozygotes was higher than that in the general population, most notably breast cancer in female heterozygotes less than 60 years of age (Swift et al., 1991; Pippard et al., 1988; Borreson et al., 1990). Other cancers were also mentioned, such as stomach and liver cancer (Swift et al., 1991; Chessa et al., 1994). Several authors now agree that the relative risk of breast cancer in heterozygotes is between 3.3 and 3.9 (Easton, 1994; Inskip et al., 1999; Athma et al., 1996; Janin et al., 1999), with a greater RR at younger ages and no significantly increased risk above age 60, while the relative risk for other types of cancer is not elevated. This modest risk, however, may correspond to a significant percentage of breast cancer in the population at large being attributable to heterozygosity at *ATM*: if 1% of the population is heterozygous at ATM, and the RR of breast cancer is about 3, then 2 to 4% of new breast cancer cases may be due to defects in ATM.

A few groups have searched for constitutional ATM mutations in circulating lymphocytes from sporadic breast cancer cases, and have not found an increased carrier frequency (Fitzgerald et al., 1996; Bebb et al., 1999). Thus, it seems that heterozygosity for *ATM* is not associated with a tendency toward breast cancer, even though family studies indicate increased risk. There may be several reasons for this discrepancy, first, PTT only identifies 60 to 70% of mutations in A-T homozygotes, and these are not necessarily representative of those associated with breast cancer (Telatar et al., 1996). Secondly, the frequency of A-T heterozygotes in the population is not well defined, although 1% is often cited (Swift et al., 1986; Easton, 1994). Therefore, the low numbers of constitutional mutations found in the above studies do not exclude a role for ATM in breast cancer. Larger study populations and more sensitive techniques to detect *ATM* mutations are needed before any significant difference between the study and control groups can be reliably defined.

Other groups have looked for ATM mutations in familial breast cancer familial breast cancer, again without finding excessive numbers of constitutional heterozygotes (Vorechovsky et al., 1996a; Bay et al., 1998; Chen et al., 1998). It is in fact unlikely that heterozygosity for ATM would lead to identifiable cancer families, due to the low relative risk involved.

Although the truncating mutations found in A-T patients have not been found frequently in breast cancer patients, it is curious that small changes in the ATM sequence are found much more frequently in breast cancer cases than in the healthy population (Gatti et al., 1999). These changes include missense and silent mutations as well as nucleotide changes in the introns. Although some of these will certainly turn out to be innocuous polymorphisms, others may indeed be associated with reduced or altered function of the ATM protein.

Loss of heterozygosity (LOH) at the *ATM* locus has been found in 30 to 60% of cancers, (Hampton et al., 1994; Rio et al., 1998; Uhrhammer et al., 1999), suggesting that ATM may have a role in tumorigenesis, although it is difficult to interpret this type of study due to the large region of chromosome 11q that may be involved in the LOH, and the fact that genes near to *ATM* may also be involved. In addition, in breast and colon cancer the incidence of LOH at the *ATM* locus is not very much higher than background.

The demonstration of the inactivation of the ATM protein in tumors would more precisely define its importance. A few cases have been described, where the wild-type allele of *ATM* is inactivated in the tumor tissue of a heterozygote, but the loss of ATM has not been described generally in breast oncogenesis (Chen et al., 1998; Vorechovsky et al., 1996b; Bay et al., 1999). More definitive studies using antibodies against ATM on tumor tissue sections are underway in several laboratories.

Somatic mutations of both alleles of *ATM* have been found in T-prolymphocytic leukemia, in mantle cell lymphoma and in chronic B-lymphoid leukemias, suggesting that in these types of malignancy ATM does play a tumor-suppressor role (Vorechovsky et al., 1998; Stankovic et al., 1999; Bullrich et al., 1999; Shaffner et al., 2000). This is an interesting finding, because although A-T homozygotes are prone to these types of cancer, they have not been described in A-T heterozygotes.

STRUCTURE AND FUNCTION OF THE ATM PROTEIN

The gene:

The *ATM* gene occupies ~150 kb of 11q22.3-q23.1 (Platzer et al., 1997) (Fig1). *ATM* is transcribed from a bi-directional promoter that also drives expression of the *NPAT/Cand3/E14* gene (Platzer et al., 1997; Imai et al., 1997), although the significance of this co-expression is unknown. There are also two alternative exons 1, although differential expression of the mRNA isoforms in different tissues or in response to different stimuli has not been described, nor is there any change in the amino acid sequence of the resulting protein, since translation is initiated in exon 3. The 13 kb *ATM* mRNA, with its 9168 bp of coding sequence, appears to be expressed in most tissues and stages of development (Savitsky et al., 1995).

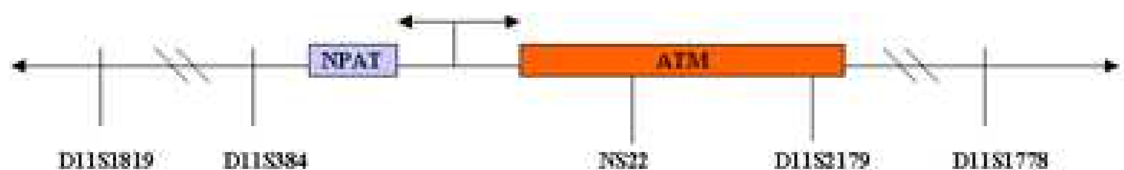

Figure 1: The ATM gene at 11q22.3-q23.1 is transcribed from a bodirectional promoter. Microsatellite loci are found in introns 25 (NS22) and 63 (D11S2179).

Notably, expression does not vary with the cell cycle or increase in response to irradiation (Brown et al., 1997).
Homologs of *ATM* have been identified in other mammals and in fish and amphibians, though no true yeast homolog has been identified. Several proteins with homology to ATM have been found, including the catalytic subunit of DNA-PK and ATR. The greatest similarity between these proteins is in the kinase domain, and together they form a sub-family of PI3-kinase-related proteins.

The protein:

The 350 kDa ATM protein contains a leucine zipper, a domain with homology to the S. pombe Rad3 protein, and a protein kinase domain homologous to the PI3K family (Chen and Lee, 1996). ATM is localized mostly to the nucleus, but is also found in cytoplasmic vesicles (Chen and Lee, 1996; Gately et al., 1998; Watters et al., 1997). ATM has been shown to associate with DNA, with particular affinity for DNA ends (Smith et al., 1999). This DNA end-binding activity suggests that ATM might be the/a primary sensor of DNA double-strand breaks (DSBs). In the presence of DNA DSB damage, ATM phosphorylates a variety of protein targets and activates several different signaling cascades (Figure 2). In contrast to the mRNA, ATM protein does become more abundant in response to IR, although only in cells such as lymphocytes that express low basal levels: no change is seen in cells expressing high levels of ATM (Fang et al., 2001). In addition, ATM becomes more tightly attached to the nuclear matrix and/or chromatin in the presence of DNA damage (Andegeko et al., 2001).

G1 cell cycle arrest: ATM induces G_1 phase arrest through the action of several intermediates. One of the most important targets is the phosphorylation of p53 on ser15 (Canman et al., 1998; Khanna et al., 1998; Watterman et al., 1998). Among the genes whose transcription is induced by p53 is the cdk-inhibitor p21Waf1/Cip1 $p21^{Waf1/Cip1}$, which plays a key role in inhibiting the transition from G_1 to S phase.

ATM also induces G_1 arrest through the phosphorylation of cAbl (Shafman et al., 1997; Baskaran et al., 1997), which in turn activates both the p53 homolog p73 and the SAPK pathway to block progression to S phase.

S phase arrest: the phosphorylation of cAbl also serves to halt progression within S phase by inhibiting Rad51Rad51, a single-stranded DNA binding protein essential for replication. Replication Protein A (RPA), another protein essential for the progression of DNA replication, is inhibited by ATM through phosphor-rylation of its 34 kDa subunit. ATM has been shown to phosphorylate Ser222 of the FANCD2 protien, which is essential for S phase arrest in response to treatment with DNA cross-linking agents (Grompe and D'Andrea, 2001). Two authors have shown that ATM is not, however, required for the decatenation checkpoints in S phase or late G2 phase, underlining the existence of multiple checkpoints throughout the cell cycle (Montecucco et al., 2001; Deming et al., 2001). Abnormalities in S phase lead to the quantifiable phenotype known as 'radiation resistant DNA synthesis', or RDS in cells from A-T homozygotes.

G2 cell cycle arrest: ATM inhibits cells from entering mitosis after irradiation through the phosphorylation of at least two targets, Chk1 and Chk2. The literature is occasionally indistinct on the subject of G_2 arrest in A-T cells, most likely because there are two arrest points, and only one is defective in A-T. Immediately after DNA damage, the defective cell cycle checkpoint can be measured as a failure to diminish the numbers of cells that enter mitosis in the hours that follow irradiation. In contrast, at later times there is clearly an increase in G_2 cells which is readily detectable by FACS analysis. This late G_2 accumulation is due to cells that were in G_1 or S at the time of irradiation, which replicated their DNA in spite of the presence of DSBs, and which have now triggered a distinct G_2 checkpoint.

ATM and radiation-induced apoptosis:

Radiosensitivity is a constant feature of A-T and is thought to be due to excessive apoptosis. How ATM inhibits apoptosis is not completely understood, and may be different according to the type of tissue studied. One route is through the phosphorylation of IkB. IkB is an inhibitor of NFkB, and its phosphorylation leads to the release of NFkB sequestered in the cytoplasm. NFkB now translocates to the nucleus, where it acts as a transcriptional regulator of anti-apoptotic genes. A second level of apoptosis control acts through p53,

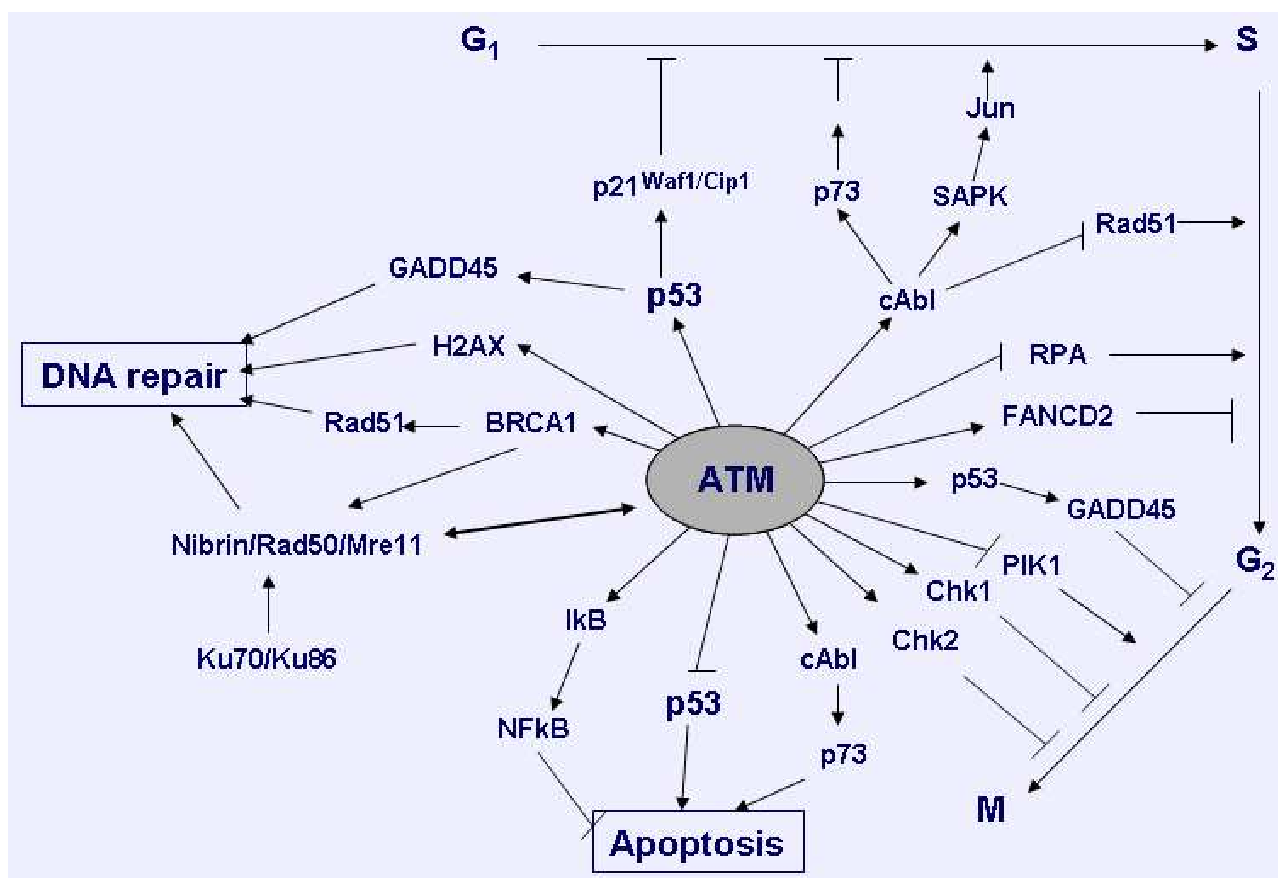

Figure 2. In response to DNA double-strand breaks, ATM interacts with many different proteins to induce cell cycle arrest, increase DNA repair, and inhibits apoptosis.

though the mechanism is likely to be indirect. Cultured A-T fibroblasts undergo apoptosis in response to irradiation, and this process may be inhibited by the inactivation of p53. As we have seen, ATM activates the cell cycle arrest functions of p53, but it is as yet unknown how the inhibition of p53's pro-apoptotic functions works. It is possible that ATM-/- cells allow replication of damaged DNA templates, which in turn trigger p53 through independent mechanisms.

A third pathway through which ATM inhibits apoptosis might be through the ceramide synthesis cascade. This signaling cascade is initiated at the cell membrane in response to irradiation, and is dysregulated in A-T cells. It is not yet known how ATM is involved, and whether the detection of DNA damage is necessary or if ATM might detect some other damage signal.

Most of the functions described above take place in the nucleus, where ATM surveys the DNA for DSBs, and phosphorylates its substrates when necessary. The phosphorylation of IkB (and possibly of cAbl) occurs in the cytoplasm, however, and the proteins of the ceramide signaling pathway are located on membranes accessible from the cytoplasm. Some authors have proposed that the pool of ATM associated with cytoplasmic vesicles performs functions distinct from genomic surveillance. ATM has been shown to associate with beta-adaptin in the cytoplasm and may be involved in vesicle trafficking and intercellular communication, and it is this aspect which may eventually explain the specific degeneration of cerebellar Purkinje cells.

ATM and DSB repair

A-T cells exhibit subtle defects in DSB repair: they take longer to repair DSBs and the repair of plasmid substrates is often inexact. While ATM itself does not seem to play a direct role in the rejoining of DSBs, it is involved in the control of this process. As we have seen, ATM activates GADD45 indirectly though p53. In addition, BRCA1 has been shown to be phosphorylated by ATM in response to DSBs and this phosphorylation is essential to relieve the radiation sensitivity of BRCA1-mutant cells (Cortez et al., 1999). BRCA1 has been described as being necessary for the aggregation of Rad51 complexes or Rad50/Mre11/nibrin at DSB sites, in addition to being a transcriptional activator. Rad50 and Rad51 are both required for the repair of DSBs, and BRCA1 may provide a link in the signaling cascade that activates repair. Finally, ATM probably activates DSB repair through Rad50/Mre11/nibrin independently from

BRCA1. Two groups have now shown that ATM phosphorylates H2AX within seconds of DSB damage (Burma et al., 2001; Andegeko et al., 2001). H2AX-P promotes chromatin decondensation and is a major signal for DNA repair. The speed of this phosphorylation also provides more circumstantial evidence for ATM as an actual sensor of DSBs, although there is as yet no direct evidence for this.

Cells experiencing DSB damage in G_1 or G_0 repair this damage through non-homologous end joining, a process controlled by DNA-PK. The relationship between ATM and DNA-PK is as yet unclear, since the abundant Ku subunits of DNA-PK can bind to DNA ends on their own and recruit DNA-PKcs to the sites for repair. This temporal difference in the choice of DSB repair mechanism may be the main reason why two apparently redundant mechanisms are both essential, another being that some are unrepairable by NHEJ due to the poor quality of the DNA ends. In any case, Atm-/-/SCID double-knockout mice are inviable after 12 days gestation (Gurley 2001), demonstrating the additive effect of these two DSB signaling/repair proteins. Ku70 has been shown now to be essential for the binding of the Rad50 / Mre11 / nibrin complex at DSB sites, however, and the similarities of the cellular phenotypes of A-T and NBS (nibrin-deficient) cells suggests that this may provide the link between ATM and DNA-PK. Cells experiencing DSB damage in G_2 favor homologous recombination between sister chromatids for repair.

ATM and Mre11:

Since the cloning of *ATM*, the vast majority of A-T patients have been found to carry mutations in the *ATM* gene. There are a few cases, however, where no mutation was detectable in the gene, and the ATM protein was present in cellular extracts. Stewart has now described mutations in the *hMre11a* gene in four such patients from two families (1999). Interestingly, cell fusion experiments in the 1980's indicated that there were four complementation groups for A-T (Jaspers et al., 1988). After the cloning of *ATM*, it was shown that mutations in this one gene were present in all four 'complementation groups', sometimes identical mutations, and the multigenic theory of A-T was essentially discarded as an experimental artifact (Savitsky et al., 1995). The *hMre11a* gene is located about 30 cM proximal to *ATM* on the long arm of chromosome 11, at band q22.1.

The phenotypes of human patients with *ATM* and hypomorphic *hMre11* mutations are very nearly identical. ATLD patients (for ataxia-telangiectasia-like disorder) may have a slightly milder phenotype than A-T patients, but still within the range of phenotypes found for classic A-T patients. The phenotypic differences are apparent at the cellular level: the induction of p53 is nearly normal, and clonogenic survival and radioresistant DNA synthesis curves are intermediate between that of A-T patients and normal subjects. Intriguingly, these cellular phenotypes of ATLD are identical to those of NBS patients, even though the neural phenotypes are different (there being no micro-cephaly or mental retardation in ATLD, nor cerebellar ataxia in NBS). Recall that NBS patients have mutations in the gene encoding nibrin, a subunit of Rad50/Mre11/nibrin.

The four patients described with *hMre11* mutations are two homozygotes for a nonsense mutation at codon 633, and two compound heterozygotes for a null mutation and a substitution of serine for asparagine at amino acid 117. Both the nonsense and missense mutated proteins produce stable products that are able to associate with Rad50 and nibrin, although the aggregation of this complex at DSB sites is abnormal. Data from *mMre11* knockout mice indicate that these human mutations are most likely to be partially functional, because a null allele of *mMre11* is lethal during embryogenesis, as are null alleles for *mRad50* (mice with *Nbs1* mutations have are similar to Atm-/- mice, with growth retardation, lymphoid developmental defects, lymphoid thymomas, radiosensitivity and female - though not male - sterility) (Xiao and Weaver, 1997; Kang et al., 2002).

The interaction between ATM and Mre11 is becoming more clear. The Rad50/Mre11/nibrin complex has described as containing (an) additional protein(s) of high molecular weight, and probably associates loosely or transiently with several other proteins, including BRCA1 and ATM. Clearly, ATM, Mre11, nibrin, and BRCA1 are all required for the aggregation of Rad50 at DSB sites. ATM phosphorylates both nibrin and Mre11, and in the absence of nibrin, ATM fails to phosphorylate Mre11 (Wu et al., 2000; Kim et al., 1999). Rad50, Mre11, and the yeast analog of nibrin, xrs5, all perform essential repair functions and their loss is lethal. The loss of regulatory proteins such as ATM or BRCA1, or the reduced function of nibrin or Mre11 is tolerated but decreases the efficiency of repair.

How do the known molecular functions of ATM explain the disease?

1. Radiosensitivity: without ATM, DNA damage triggers apoptosis in sensitive cell types. Radiosensitivity is not due to acquired mutations and karyotypic inviability, but to programmed cell elimination.

2. Cancer risk: A-T cells either create or tolerate chromosomal rearrangements more than other cells. These rearrangements may hit genes critical for normal cell growth and thus initiate cancer. The lack of ATM is not directly tumorigenic, but rather allows other mutation events. The stereotypical chromosomal rearrangements seen in A-T lymphocytes are evidence of this problem with genomic stability. A new study in Atm-/- mice, however, showed that spontaneous

mutation rates were not increased in samples of ear and spleen tissue, suggesting that not all tissues are equally sensitive to the effects of ATM loss (Turker et al., 1999).

3. Immunodeficiency: without ATM, the process of V(D)J recombination is not properly supervised, and aberrant chromosomes are created. Most cells recognize the anomaly and commit suicide (leading to the hypoplastic thymus), but others escape this control and are detected as circulating lymphocytes carrying the 7;7, 7;14, and 14;14 rearrangements characteristic of A-T. That the immunodeficiency in A-T is not as severe as other syndromes reflects the ability of A-T cells to create functional V(D)J recombination events at reduced frequency.

4. Cerebellar degeneration: this aspect of A-T is as yet unexplained by the known molecular functions of the protein, though several theories have been advanced. 1) aberrant migration of Purkinje cells 2) oxidative damage leads to cell death; 3) an autoimmune process destroys the Purkinje cells. An excess of oxidative stress in the cerebellum (and elsewhere) is currently the favored hypothesis for this degeneration (Stern et al., 2002).

GENOTYPE/PHENOTYPE CORRELATIONS

Over 300 disease-causing *ATM* mutations have been identified, extending over each of the 66 exons, and patients from non-consanguineous families are typically compound heterozygotes. Although founder effect mutations account for significant proportions of A-T patients in various ethnic populations, they do not account for significant numbers of A-T patients in heterogeneous populations such as the United States.

A-T variants, who do not meet all the clinical criteria for A-T (i.e., relatively late-onset of ataxia or chorea, unusually long survival, absence of telangiectases, normal AFP levels, normal immune status, intermediate levels of radiosensitivity) have been shown for the most part to have *ATM* mutations. These have been homo- or at least heterozygous for milder missense, splice-site, or small, non-critical insertion/deletion abnormalities that could allow production of up to 17% of normal ATM protein. Nonsense, frame-shift, or in-frame changes, causing two truncating mutations, with production of little or no ATM protein in over 85% of patients, result in the more typical A-T phenotype with lower mean survivals.

Many other patients with phenotypes typical of A-T (DiRocco, 1999; Hernandez et al., 1993) have not been shown to have mutations in the *ATM* gene, and may represent mutations in other genes that interact with the ATM protein. One of these proteins has been identified as Mre11, as discussed above.

TREATMENT OF A-T

At present there is no definitive gene-based therapy, neuroprotective therapy, or neural-restorative therapy to halt or reverse progression of the neurologic symptoms of A-T. The extraneural symptoms have many conventional treatment options, especially in the important areas of pulmonary infection and malignancy. Infection is usually with common microbes, not opportunistic organisms (despite the combined immuno-deficiency), so prompt treatment with appropriate antibiotics and attention to aggressive pulmonary hygiene can prevent future complications (resistant infections, bronchiectasis, chronic respiratory failure, and aspiration).

Regular physical examinations with blood counts and blood chemistries can serve as an early screen for leukemia/lymphoma and other cancers. Routine pelvic exams and breast exams in young women, prostate screening in young men, and skin exams in both should be instituted. Non-radiologic imaging studies should be used when any area of concern is raised (MRI, ultrasound). Should a malignancy occur, treatment protocols utilizing lower doses of radiation therapy and alternatives to radiomimetic and neurotoxic agents should be sought, and chemotherapy protocols with a high risk of developing a second malignancy (topoisomerase inhibitors) should be modified. Young children presenting with leukemia or lymphoma, or any other malignancy, should be screened for the presence of A-T before a treatment regimen is begun. Because of the extreme cancer susceptibility of these patients, they should be encouraged to avoid excess sun exposure by keeping skin covered and wearing a hat and sunscreen when outdoors.

Neurorehabilitation strategies and symptomatic medication can improve neurologic performance and reduce the risk of long-term complications from increasing immobility (deconditioning, contractures, decubiti, pneumonia, bladder infections, and constipation). Physical therapy can help the patient maintain independence, continue in school, and enjoy leisure pursuits with family and friends. Pool exercise, speech therapy, remedial learning programs, and appropriate adaptive equipment also reduce the ultimate handicaps of these patients.

Most A-T patients in the United States and Western Europe live well beyond 20 years, thanks to improved health maintenance and rehabilitation options. This is a major change from just a few years ago, when it was unusual for patients to live past their teens, but much work still needs to be done.

References

McFarlin DE, Strober W, Waldmann TA. Ataxia-telangiectasia. Medicine (Baltimore). 1972 Jul;51(4):281-314

Gatti RA, Walford RL. Immune function and features of afing in chromosomal instability syndromes In: Immunological Aspects of Aging, Segre and Smith, Eds. Marcel Dekker, New York 1981, pp449-465.

Paterson MC et al. Cellular hypersensitivity to chronic gamma-radiation in cultured fibroblasts from ataxia-telangiectasia heterozygotes In: Ataxia-Telangiectasia: genetics, neuropathology and immunology of a degenerative disease of childhood. RA Gatti and M Swift, eds. RA Liss, New York, 1985, pp73-87.

Roifman CM, Gelfand EW. Heterogeneity of the immunological deficiency in ataxia-telangiectasia: absence of a clinical-pathological correlation. Kroc Found Ser. 1985;19:273-85

Shiloh Y, Tabor E, Becker Y. Cells from patients with ataxia telangiectasia are abnormally sensitive to the cytotoxic effect of a tumor promoter, phorbol-12-myristate-13-acetate. Mutat Res. 1985 Apr;149(2):283-6

Swift M. Genetics and epidemiology of ataxia-telangiectasia. Kroc Found Ser. 1985;19:133-46

Taylor AM, Laher HB, Morgan GR. Unscheduled DNA synthesis induced by streptonigrin in ataxia telangiectasia fibroblasts. Carcinogenesis. 1985 Jun;6(6):945-7

Vinters HV, Gatti RA, Rakic P. Sequence of cellular events in cerebellar ontogeny relevant to expression of neuronal abnormalities in ataxia-telangiectasia. Kroc Found Ser. 1985;19:233-55

Aurias A. Aspects cytogénétiques de l'ataxie télangiectasie. Med Sci. 1986 ;2:298-303.

Ishiguro T, Taketa K, Gatti RA. Tissue of origin of elevated alpha-fetoprotein in ataxia-telangiectasia. Dis Markers. 1986 Dec;4(4):293-7

Morrell D, Cromartie E, Swift M. Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. J Natl Cancer Inst. 1986 Jul;77(1):89-92

Swift M, Morrell D, Cromartie E, Chamberlin AR, Skolnick MH, Bishop DT. The incidence and gene frequency of ataxia-telangiectasia in the United States. Am J Hum Genet. 1986 Nov;39(5):573-83

Gatti RA, Berkel I, Boder E, Braedt G, Charmley P, Concannon P, Ersoy F, Foroud T, Jaspers NG, Lange K. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. Nature. 1988 Dec 8;336(6199):577-80

Jaspers NG, Gatti RA, Baan C, Linssen PC, Bootsma D. Genetic complementation analysis of ataxia telangiectasia and Nijmegen breakage syndrome: a survey of 50 patients. Cytogenet Cell Genet. 1988;49(4):259-63

Pippard EC, Hall AJ, Barker DJ, Bridges BA. Cancer in homozygotes and heterozygotes of ataxia-telangiectasia and xeroderma pigmentosum in Britain. Cancer Res. 1988 May 15;48(10):2929-32

Børresen AL, Andersen TI, Tretli S, Heiberg A, Møller P. Breast cancer and other cancers in Norwegian families with ataxia-telangiectasia. Genes Chromosomes Cancer. 1990 Nov;2(4):339-40

Gatti RA, Boder E, Vinters HV, Sparkes RS, Norman A, Lange K. Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. Medicine (Baltimore). 1991 Mar;70(2):99-117

Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med. 1991 Dec 26;325(26):1831-6

Weeks DE, Paterson MC, Lange K, Andrais B, Davis RC, Yoder F, Gatti RA. Assessment of chronic gamma radiosensitivity as an in vitro assay for heterozygote identification of ataxia-telangiectasia. Radiat Res. 1991 Oct;128(1):90-9

Kastan MB, Zhan Q, el-Deiry WS, Carrier F, Jacks T, Walsh WV, Plunkett BS, Vogelstein B, Fornace AJ Jr. A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. Cell. 1992 Nov 13;71(4):587-97

Paganelli R, Scala E, Scarselli E, Ortolani C, Cossarizza A, Carmini D, Aiuti F, Fiorilli M. Selective deficiency of CD4+/CD45RA+ lymphocytes in patients with ataxia-telangiectasia. J Clin Immunol. 1992 Mar;12(2):84-91

Woods CG, Taylor AM. Ataxia telangiectasia in the British Isles: the clinical and laboratory features of 70 affected individuals. Q J Med. 1992 Feb;82(298):169-79

Hernandez D, McConville CM, Stacey M, Woods CG, Brown MM, Shutt P, Rysiecki G, Taylor AM. A family showing no evidence of linkage between the ataxia telangiectasia gene and chromosome 11q22-23. J Med Genet. 1993 Feb;30(2):135-40

Chessa L, Lisa A, Fiorani O, Zei G. Ataxia-telangiectasia in Italy: genetic analysis. Int J Radiat Biol. 1994 Dec;66(6 Suppl):S31-3

Easton DF. Cancer risks in A-T heterozygotes. Int J Radiat Biol. 1994 Dec;66(6 Suppl):S177-82

Hampton GM, Mannermaa A, Winqvist R, Alavaikko M, Blanco G, Taskinen PJ, Kiviniemi H, Newsham I, Cavenee WK, Evans GA. Loss of heterozygosity in sporadic human breast carcinoma: a common region between 11q22 and 11q23.3. Cancer Res. 1994 Sep 1;54(17):4586-9

Huo YK, Wang Z, Hong JH, Chessa L, McBride WH, Perlman SL, Gatti RA. Radiosensitivity of ataxia-telangiectasia, X-linked agammaglobulinemia, and related syndromes using a modified colony survival assay. Cancer Res. 1994 May 15;54(10):2544-7

Lange E, Borresen AL, Chen X, Chessa L, Chiplunkar S, Concannon P, Dandekar S, Gerken S, Lange K, Liang T. Localization of an ataxia-telangiectasia gene to an approximately 500-kb interval on chromosome 11q23.1: linkage analysis of 176 families by an international consortium. Am J Hum Genet. 1995 Jul;57(1):112-9

Pandita TK, Pathak S, Geard CR. Chromosome end associations, telomeres and telomerase activity in ataxia telangiectasia cells. Cytogenet Cell Genet. 1995;71(1):86-93

Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Sartiel A, Gatti RA, Chessa L, Sanal O, Lavin MF, Jaspers NG, Taylor AM, Arlett CF, Miki T, Weissman SM, Lovett M, Collins FS, Shiloh Y. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science. 1995 Jun 23;268(5218):1749-53

Athma P, Rappaport R, Swift M. Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer. Cancer Genet Cytogenet. 1996 Dec;92(2):130-4

Chen G, Lee EYHP. The product of the ATM gene is a 370-kDa nuclear phosphoprotein. J Biol Chem. 1996 Dec 27;271(52):33693-7

Metcalfe JA, Parkhill J, Campbell L, Stacey M, Biggs P, Byrd PJ, Taylor AM. Accelerated telomere shortening in ataxia telangiectasia. Nat Genet. 1996 Jul;13(3):350-3

Shiloh Y, Rotman G. Ataxia-telangiectasia and the ATM gene: linking neurodegeneration, immunodeficiency, and cancer to cell cycle checkpoints. J Clin Immunol. 1996 Sep;16(5):254-60

Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood. 1996 Jan 15;87(2):423-38

Vorechovský I, Luo L, Lindblom A, Negrini M, Webster AD, Croce CM, Hammarström L. ATM mutations in cancer families. Cancer Res. 1996 Sep 15;56(18):4130-3

Vorechovský I, Rasio D, Luo L, Monaco C, Hammarström L, Webster AD, Zaloudik J, Barbanti-Brodani G, James M, Russo G. The ATM gene and susceptibility to breast cancer: analysis of 38 breast tumors reveals no evidence for mutation. Cancer Res. 1996 Jun 15;56(12):2726-32

Baskaran R, Wood LD, Whitaker LL, Canman CE, Morgan SE, Xu Y, Barlow C, Baltimore D, Wynshaw-Boris A, Kastan MB, Wang JY. Ataxia telangiectasia mutant protein activates c-Abl tyrosine kinase in response to ionizing radiation. Nature. 1997 May 29;387(6632):516-9

Brown KD, Ziv Y, Sadanandan SN, Chessa L, Collins FS, Shiloh Y, Tagle DA. The ataxia-telangiectasia gene product, a constitutively expressed nuclear protein that is not up-regulated following genome damage. Proc Natl Acad Sci U S A. 1997 Mar 4;94(5):1840-5

FitzGerald MG, Bean JM, Hegde SR, Unsal H, MacDonald DJ, Harkin DP, Finkelstein DM, Isselbacher KJ, Haber DA. Heterozygous ATM mutations do not contribute to early onset of breast cancer. Nat Genet. 1997 Mar;15(3):307-10

Imai T, Sugawara T, Nishiyama A, Shimada R, Ohki R, Seki N, Sagara M, Ito H, Yamauchi M, Hori T. The structure and organization of the human NPAT gene. Genomics. 1997 Jun 15;42(3):388-92

Jung M, Kondratyev A, Lee SA, Dimtchev A, Dritschilo A. ATM gene product phosphorylates I kappa B-alpha. Cancer Res. 1997 Jan 1;57(1):24-7

Meyn MS. Chromosome instability syndromes: lessons for carcinogenesis. Curr Top Microbiol Immunol. 1997;221:71-148

Platzer M, Rotman G, Bauer D, Uziel T, Savitsky K, Bar-Shira A, Gilad S, Shiloh Y, Rosenthal A. Ataxia-telangiectasia locus: sequence analysis of 184 kb of human genomic DNA containing the entire ATM gene. Genome Res. 1997 Jun;7(6):592-605

Shafman T, Khanna KK, Kedar P, Spring K, Kozlov S, Yen T, Hobson K, Gatei M, Zhang N, Watters D, Egerton M, Shiloh Y, Kharbanda S, Kufe D, Lavin MF. Interaction between ATM protein and c-Abl in response to DNA damage. Nature. 1997 May 29;387(6632):520-3

Vorechovský I, Luo L, Dyer MJ, Catovsky D, Amlot PL, Yaxley JC, Foroni L, Hammarström L, Webster AD, Yuille MA. Clustering of missense mutations in the ataxia-telangiectasia gene in a sporadic T-cell leukaemia. Nat Genet. 1997 Sep;17(1):96-9

Watters D, Khanna KK, Beamish H, Birrell G, Spring K, Kedar P, Gatei M, Stenzel D, Hobson K, Kozlov S, Zhang N, Farrell A, Ramsay J, Gatti R, Lavin M. Cellular localisation of the ataxia-telangiectasia (ATM) gene product and discrimination between mutated and normal forms. Oncogene. 1997 Apr 24;14(16):1911-21

Xiao Y, Weaver DT. Conditional gene targeted deletion by Cre recombinase demonstrates the requirement for the double-strand break repair Mre11 protein in murine embryonic stem cells. Nucleic Acids Res. 1997 Aug 1;25(15):2985-91

Bay JO, Grancho M, Pernin D, Presneau N, Rio P, Tchirkov A, Uhrhammer N, Verrelle P, Gatti RA, Bignon YJ. No evidence for constitutional ATM mutation in breast/gastric cancer families. Int J Oncol. 1998 Jun;12(6):1385-90

Canman CE, Lim DS, Cimprich KA, Taya Y, Tamai K, Sakaguchi K, Appella E, Kastan MB, Siliciano JD. Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. Science. 1998 Sep 11;281(5383):1677-9

Chen J, Birkholtz GG, Lindblom P, Rubio C, Lindblom A. The role of ataxia-telangiectasia heterozygotes in familial breast cancer. Cancer Res. 1998 Apr 1;58(7):1376-9

Clarke RA, Goozee GR, Birrell G, Fang ZM, Hasnain H, Lavin M, Kearsley JH. Absence of ATM truncations in patients with severe acute radiation reactions. Int J Radiat Oncol Biol Phys. 1998 Jul 15;41(5):1021-7

Gately DP, Hittle JC, Chan GK, Yen TJ. Characterization of ATM expression, localization, and associated DNA-dependent protein kinase activity. Mol Biol Cell. 1998 Sep;9(9):2361-74

Gatti RA. Ataxia-telangiectasia In: The genetic basis of human cancer by Vogelstein B. and Kinzler K. W. McGraw-Hill 1998 New York pp 275-300.

Hall EJ, Schiff PB, Hanks GE, Brenner DJ, Russo J, Chen J, Sawant SG, Pandita TK. A preliminary report: frequency of A-T heterozygotes among prostate cancer patients with severe late responses to radiation therapy. Cancer J Sci Am. 1998 Nov-Dec;4(6):385-9

Khanna KK, Keating KE, Kozlov S, Scott S, Gatei M, Hobson K, Taya Y, Gabrielli B, Chan D, Lees-Miller SP, Lavin MF. ATM associates with and phosphorylates p53: mapping the region of interaction. Nat Genet. 1998 Dec;20(4):398-400

Rio PG, Pernin D, Bay JO, Albuisson E, Kwiatkowski F, De Latour M, Bernard-Gallon DJ, Bignon YJ. Loss of heterozygosity of BRCA1, BRCA2 and ATM genes in sporadic invasive ductal breast carcinoma. Int J Oncol. 1998 Oct;13(4):849-53

Telatar M, Teraoka S, Wang Z, Chun HH, Liang T, Castellvi-Bel S, Udar N, Borresen-Dale AL, Chessa L, Bernatowska-Matuszkiewicz E, Porras O, Watanabe M, Junker A, Concannon P, Gatti RA. Ataxia-telangiectasia: identification and detection of founder-effect mutations in the ATM gene in ethnic populations. Am J Hum Genet. 1998 Jan;62(1):86-97

Waterman MJ, Stavridi ES, Waterman JL, Halazonetis TD. ATM-dependent activation of p53 involves dephosphorylation and association with 14-3-3 proteins. Nat Genet. 1998 Jun;19(2):175-8

Bay JO, Uhrhammer N, Pernin D, Presneau N, Tchirkov A, Vuillaume M, Laplace V, Grancho M, Verrelle P, Hall J, Bignon YJ. High incidence of cancer in a family segregating a mutation of the ATM gene: possible role of ATM heterozygosity in cancer. Hum Mutat. 1999;14(6):485-92

Bebb DG, Yu Z, Chen J, Telatar M, Gelmon K, Phillips N, Gatti RA, Glickman BW. Absence of mutations in the ATM gene in forty-seven cases of sporadic breast cancer. Br J Cancer. 1999 Aug;80(12):1979-81

Bullrich F, Rasio D, Kitada S, Starostik P, Kipps T, Keating M, Albitar M, Reed JC, Croce CM. ATM mutations in B-cell chronic lymphocytic leukemia. Cancer Res. 1999 Jan 1;59(1):24-7

Cortez D, Wang Y, Qin J, Elledge SJ. Requirement of ATM-dependent phosphorylation of brca1 in the DNA damage response to double-strand breaks. Science. 1999 Nov 5;286(5442):1162-6

Gatti RA, Tward A, Concannon P. Cancer risk in ATM heterozygotes: a model of phenotypic and mechanistic differences between missense and truncating mutations. Mol Genet Metab. 1999 Dec;68(4):419-23

Inskip HM, Kinlen LJ, Taylor AM, Woods CG, Arlett CF. Risk of breast cancer and other cancers in heterozygotes for ataxia-telangiectasia. Br J Cancer. 1999 Mar;79(7-8):1304-7

Janin N, Andrieu N, Ossian K, Laugé A, Croquette MF, Griscelli C, Debré M, Bressac-de-Paillerets B, Aurias A, Stoppa-Lyonnet D. Breast cancer risk in ataxia telangiectasia (AT) heterozygotes: haplotype study in French AT families. Br J Cancer. 1999 Jun;80(7):1042-5

Kim ST, Lim DS, Canman CE, Kastan MB. Substrate specificities and identification of putative substrates of ATM kinase family members. J Biol Chem. 1999 Dec 31;274(53):37538-43

Lavin MF, Khanna KK. ATM: the protein encoded by the gene mutated in the radiosensitive syndrome ataxia-telangiectasia. Int J Radiat Biol. 1999 Oct;75(10):1201-14

Murphy RC, Berdon WE, Ruzal-Shapiro C, Hall EJ, Kornecki A, Daneman A, Brunelle F, Campbell JB. Malignancies in pediatric patients with ataxia telangiectasia. Pediatr Radiol. 1999 Apr;29(4):225-30

Smith GC, Cary RB, Lakin ND, Hann BC, Teo SH, Chen DJ, Jackson SP. Purification and DNA binding properties of the ataxia-telangiectasia gene product ATM. Proc Natl Acad Sci U S A. 1999 Sep 28;96(20):11134-9

Stankovic T, Weber P, Stewart G, Bedenham T, Murray J, Byrd PJ, Moss PA, Taylor AM. Inactivation of ataxia telangiectasia mutated gene in B-cell chronic lymphocytic leukaemia. Lancet. 1999 Jan 2;353(9146):26-9

Stewart GS, Maser RS, Stankovic T, Bressan DA, Kaplan MI, Jaspers NG, Raams A, Byrd PJ, Petrini JH, Taylor AM. The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. Cell. 1999 Dec 10;99(6):577-87

Turker MS, Gage BM, Rose JA, Ponomareva ON, Tischfield JA, Stambrook PJ, Barlow C, Wynshaw-Boris A. Solid tissues removed from ATM homozygous deficient mice do not exhibit a mutator phenotype for second-step autosomal mutations. Cancer Res. 1999 Oct 1;59(19):4781-3

Uhrhammer N, Bay J, Pernin D, Rio P, Grancho M, Kwiatkowski F, Gosse-Brun S, Daver A, Bignon Y. Loss of heterozygosity at the ATM locus in colorectal carcinoma. Oncol Rep. 1999 May-Jun;6(3):655-8

Broeks A, Urbanus JH, Floore AN, Dahler EC, Klijn JG, Rutgers EJ, Devilee P, Russell NS, van Leeuwen FE, van 't Veer LJ. ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. Am J Hum Genet. 2000 Feb;66(2):494-500

Schaffner C, Idler I, Stilgenbauer S, Döhner H, Lichter P. Mantle cell lymphoma is characterized by inactivation of the ATM gene. Proc Natl Acad Sci U S A. 2000 Mar 14;97(6):2773-8

Wu X, Ranganathan V, Weisman DS, Heine WF, Ciccone DN, O'Neill TB, Crick KE, Pierce KA, Lane WS, Rathbun G, Livingston DM, Weaver DT. ATM phosphorylation of Nijmegen breakage syndrome protein is required in a DNA damage response. Nature. 2000 May 25;405(6785):477-82

Andegeko Y, Moyal L, Mittelman L, Tsarfaty I, Shiloh Y, Rotman G. Nuclear retention of ATM at sites of DNA double strand breaks. J Biol Chem. 2001 Oct 12;276(41):38224-30

Burma S, Chen BP, Murphy M, Kurimasa A, Chen DJ. ATM phosphorylates histone H2AX in response to DNA double-strand breaks. J Biol Chem. 2001 Nov 9;276(45):42462-7

Deming PB, Cistulli CA, Zhao H, Graves PR, Piwnica-Worms H, Paules RS, Downes CS, Kaufmann WK. The human decatenation checkpoint. Proc Natl Acad Sci U S A. 2001 Oct 9;98(21):12044-9

Fang ZM, Lee CS, Sarris M, Kearsley JH, Murrell D, Lavin MF, Keating K, Clarke RA. Rapid radiation-induction of ATM protein levels in situ. Pathology. 2001 Feb;33(1):30-6

Grompe M, D'Andrea A. Fanconi anemia and DNA repair. Hum Mol Genet. 2001 Oct 1;10(20):2253-9

Gurley KE, Kemp CJ. Synthetic lethality between mutation in Atm and DNA-PK(cs) during murine embryogenesis. Curr Biol. 2001 Feb 6;11(3):191-4

Montecucco A, Rossi R, Ferrari G, Scovassi AI, Prosperi E, Biamonti G. Etoposide induces the dispersal of DNA ligase I from replication factories. Mol Biol Cell. 2001 Jul;12(7):2109-18

Weil MM, Kittrell FS, Yu Y, McCarthy M, Zabriskie RC, Ullrich RL. Radiation induces genomic instability and mammary ductal dysplasia in Atm heterozygous mice. Oncogene. 2001 Jul 19;20(32):4409-11

Kang J, Bronson RT, Xu Y. Targeted disruption of NBS1 reveals its roles in mouse development and DNA repair. EMBO J. 2002 Mar 15;21(6):1447-55

Stern N, Hochman A, Zemach N, Weizman N, Hammel I, Shiloh Y, Rotman G, Barzilai A. Accumulation of DNA damage and reduced levels of nicotine adenine dinucleotide in the brains of Atm-deficient mice. J Biol Chem. 2002 Jan 4;277(1):602-8

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