Ataxia-Telangiectasia and variants

Nancy Uhrhammer¹, Jacques-Olivier Bay¹, Susan Perlman², Richard A Gatti³
1. Centre Jean Perrin, Departement d'Oncologie Moléculaire, Clermont-Ferrand, France
2. UCLA School of Medicine, Dept of Neurology, Los Angeles, CA 90095
3. UCLA School of Medicine, Dept of Pathology, Los Angeles, CA 90095

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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 1988, Savitsky 1995], the molecular basis of certain aspects of the disease have become clearer, though others remain to be elucidated [Gatti 1998, Meyn 1997, Shiloh 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 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 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 prolymphocytic leukemia, T-PLL) [Taylor 1996]. Lymphomas are more often non-Hodgkin's, extra-nodal, infiltrative, B-cell types, and harder to diagnose in their early stages [Murphy 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 1985, Shiloh 1985]. This finding led to the development of the highly sensitive and reasonably specific diagnostic test, the colony survival assay (CSA) [Huo 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, [10004] https://www.k-prone.org/xerodermaID10004.txt xeroderma pigmentosum xeroderma pigmentosum, Bloom syndrome), shows progeroid features [Gatti 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 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 1995], have been observed in peripheral blood lymphocytes of A-T patients, especially in pre-leukemic T-cell clones [Metcalfe 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 1986, Gatti 1981, McFarlin 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 1985]. Elevated serum IgM levels may occasionally progress to a high blood viscosity syndrome, with splenomegaly, lymphadenopathy, neutropenia, thrombocytopenia, and congestive heart failure. T-cell deficiencies occur in half the patients, with abnormal skin test antigen and PHA responses [Paganelli 1992]. In a British study of 70 patients [Woods 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 1985, Paterson 1985, Weeks 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 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 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 1998, Hall 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 1991, Pippard 1988, Borreson 1990]. Other cancers were also mentioned, such as stomach and liver cancer [Swift 1991, Chessa 1994]. Several authors now agree that the relative risk of breast cancer in heterozygotes is between 3.3 and 3.9 [Easton 1994, Inskip 1999, Athma 1996, Janin 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 1996, Bebb 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 1996]. Secondly, the frequency of A-T heterozygotes in the population is not well defined, although 1% is often cited [Swift 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, again without finding excessive numbers of constitutional heterozygotes [Vorechovsky 1996a, Bay 1998, Chen 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 [see Gatti 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 1994, Rio 1998, Uhrhammer 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 1998, Vorechovsky 1996b, Bay 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 1998, Stankovic 1999, Bulrich 1999, Shaffner 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 1997] (Fig1). *ATM* is transcribed from a bi-directional promoter that also drives expression of the *NPAT/Cand3/E14* gene [Platzer 1997, Imai 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 1995]. Notably, expression does not vary with the cell cycle or increase in response to irradiation [Brown 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 1996]. ATM is localized mostly to the nucleus, but is also found in cytoplasmic vesicles [Chen 1996, Gately 1998, Watters 1997]. ATM has been shown to associate with DNA, with particular affinity for DNA ends [Smith 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 2001). In addition, ATM becomes more tightly attached to the nuclear matrix and/or chromatin in the presence of DNA damage (Andegeko 2001).

G1 cell cycle arrest: ATM induces G1 phase arrest through the action of several intermediates. One of the most important targets is the phosphorylation of p53 on ser15 [Canman 1998, Khanna 1998, Watterman 1998]. Among the genes whose transcription is induced by p53 is the cdk-inhibitor [139] GENE:::CDKN1AID139.txt p21Waf1/Cip1 p21Waf1/Cip1, which plays a key role in inhibiting the transition from G1 to S phase. ATM also induces G1 arrest through the phosphorylation of cAbl [Shafman 1997, Baskaran 1997], which in turn activates both the p53 homolog [150]

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 phosphorylation of its 34 kDa subunit. ATM has been shown to phosphorylate Ser222 of the FANCD2 protein, 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 2001, Deming 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 G2 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 G2 cells which is readily detectable by FACS analysis. This late G2 accumulation is due to cells that were in G1 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 G2 checkpoint.

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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.
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 B, and its B is an inhibitor of NF B through the phosphorylation of I B sequestered in the cytoplasm. NF phosphorylation leads to the release of NF 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, 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 IκB (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 through 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 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 2001, Andegeko 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 G1 or G0 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 /

**Contributor(s)**

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