

***208900 ATAXIA-TELANGIECTASIA; AT**

Alternative titles; symbols

AT1
LOUIS-BAR SYNDROME

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TEXT

DESCRIPTION

Ataxia-telangiectasia (AT) is an autosomal recessive disorder characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. Chromosomal breakage is a feature. AT cells are abnormally sensitive to killing by ionizing radiation (IR), and abnormally resistant to inhibition of DNA synthesis by ionizing radiation. The latter trait has been used to identify complementation groups for the classic form of the disease ([Jaspers et al., 1988](#)). At least 4 of these (A, C, D, and E) map to chromosome 11q23 ([Sanal et al., 1990](#)) and are associated with mutations in the ATM gene.

CLINICAL FEATURES

HOMOZYGOTES

Patients present in early childhood with progressive cerebellar ataxia and later develop conjunctival telangiectases, other progressive neurologic degeneration, **sinopulmonary infection**, and **malignancies**. Telangiectases typically develop between 3 and 5 years of age. The earlier ataxia can be misdiagnosed as ataxic cerebral palsy before the appearance of oculocutaneous telangiectases. [Gatti et al. \(1991\)](#) contended that oculocutaneous telangiectases eventually occur in all patients, while [Maserati et al. \(1988\)](#) wrote that patients without telangiectases are not uncommon. A **characteristic oculomotor apraxia**, i.e., difficulty in the initiation of voluntary eye movements, frequently precedes the development of telangiectases.

[Thibaut et al. \(1994\)](#) reviewed cases of necrobiosis lipoidica in association with ataxia-telangiectasia.

Gonadal dysfunction in ataxia-telangiectasia was discussed by [Miller and Chatten \(1967\)](#), [Zadik et al. \(1978\)](#), and others.

According to [Boder \(1985\)](#), the oldest known AT patients (as of 1985) were C.P., who died in November 1978 at age 52 years, and his sister M.P., who died in July 1979 at the age of almost 49 years. The sister was the subject of the report by [Saxon et al. \(1979\)](#) on **T-cell leukemia** in AT. *The possibility of heteroalleles at the ataxia-telangiectasia loci might be suggested.*

NEUROLOGIC MANIFESTATIONS

AT may be the most common syndromic **progressive cerebellar ataxia of early childhood**. **Truncal ataxia precedes appendicular ataxia**/Ataksija trupa predhodi ataksiji udova/ ([Gatti et al., 1991](#)). Oculomotor apraxia is progressive and opticokinetic nystagmus is absent. **Choreoathetosis** and/or dystonia occur in 90% of patients and can be severe. Neurologic dysfunction is a clinically invariable feature in homozygotes. [Woods and Taylor \(1992\)](#) studied 70 affected persons in the British Isles, 29 females and 41 males with an age range of 2 to 42 years. Most presented by 3 years of age with truncal ataxia. All had ataxia, ocular motor apraxia, an impassive face, and **dysarthria**, although clinical *immune deficiency was present only in 43 of 70 patients*. Ocular telangiectases was seen in all but one. All 60 tested showed increased sensitivity to ionizing radiation, 43 of 48 had an elevated **alpha-fetoprotein** level, and 14 of 21 had an **immunoglobulin deficiency**.

Deep tendon reflexes become diminished or absent by age 8 and patients later develop diminished large-fiber sensation. [Gatti et al. \(1991\)](#) pointed out that 'a significant proportion

of older patients in their twenties and early thirties develop ***progressive spinal muscular atrophy***, affecting mostly hands and feet, and dystonia.' Interosseous muscular atrophy in the hands in combination with the early-onset dystonic posturing leads to striking combined flexion-extension contractures of the fingers, which they illustrated. ***Mental retardation is not a feature of AT***, although some older patients have a severe loss of short-term memory (Gatti et al., 1991).

MALIGNANCY

Patients with AT have a strong predisposition to malignancy. Hecht et al. (1966) observed **lymphocytic leukemia** in patients with AT. A nonleukemic sib and 2 unrelated patients with AT had multiple chromosomal breaks and impaired responsiveness to phytohemagglutinin. This was the first report of chromosomal breakage in AT. Leukemia and chromosomal abnormalities occur in at least 2 other mendelian disorders--Fanconi pancytopenia (FA; 227650) and Bloom syndrome (BS; 210900).

Saxon et al. (1979) demonstrated thymic origin of the neoplastic cells in a 48-year-old woman with AT and chronic lymphatic leukemia. The neoplastic cells had the specific 14q+ translocation and showed both helper and suppressor function, suggesting that the malignant transformation had occurred in an uncommitted T-lymphocyte precursor that was capable of differentiation. This is a situation comparable to chronic myeloid leukemia in which the Philadelphia chromosome occurs in a stem cell progenitor of both polymorphs and megakaryocytes.

In general, lymphomas in AT patients tend to be of B-cell origin (B-CLL), whereas the leukemias tend to be of the T-CLL type. Rosen and Harris (1987) discussed the case of a 30-year-old man with AT who developed a malignant lymphoma of B-cell type involving the tonsil and lungs. Haerer et al. (1969) described a black sibship of 12, of whom 5 had ataxia-telangiectasia; 2 of those affected died of mucinous adenocarcinoma of the stomach at ages 21 and 19 years. Bigbee et al. (1989) demonstrated an increased frequency of somatic cell mutation in vivo in individuals with AT. Obligate heterozygotes for the disease did not appear to have a significantly increased frequency of such mutations. The authors speculated that the predisposition to somatic cell mutation may be related to the increased susceptibility to cancer in AT homozygotes. Deletion in chromosome bands 11q22-q23 is one of the most frequent chromosomal aberrations in B-CLL. It is associated with extensive lymph node involvement and poor survival. The ATM gene falls within the minimal consensus deletion segment. To investigate the potential pathogenic role of ATM in B-cell tumorigenesis, Schaffner et al. (1999) performed mutation analysis of ATM in 29 malignant lymphomas of B-cell origin (27 cases of B-CLL and 2 cases of mantle cell lymphoma). Twenty-three of the 29 patients carried an 11q22-q23 deletion. In 5 B-CLLs and 1 mantle cell lymphoma with deletion of 1 ATM allele, a point mutation in the remaining allele was detected, which resulted in aberrant transcript splicing, alteration, or truncation of the protein. In addition, mutation analysis identified point mutations in 3 cases without 11q deletion: 2 B-CLLs with 1 altered allele and 1 mantle cell lymphoma with both alleles mutated. In 4 cases analyzed, the ATM alterations were not present in the germline, indicating a somatic origin of the mutations. The study demonstrated somatic disruption of both alleles at the ATM locus by deletion of point mutation and thus its pathogenic role in sporadic B-cell lineage tumors.

Other solid tumors, including medulloblastomas and gliomas, occur with increased frequency in AT (Gatti et al., 1991).

IMMUNE DISORDERS

Defects of the immune mechanism and **hypoplasia of the thymus** have been demonstrated. Serum IgG2 or IgA levels are diminished or absent in 80% and 60% of patients, respectively ([Gatti et al., 1991](#)). IgE levels can be diminished, IgM levels diminished or normal.

Peripheral lymphopenia as well as decreased cellular immunity to **intradermally injected test antigens** can be seen early in the disorder. **Sinopulmonary infections** are frequent, but their severity cannot be simply correlated with the degree of immunodeficiency.

ATYPICAL CASES

[Ying and Decoteau \(1981\)](#) described a family in which a brother and sister may have had an allelic (and milder) form of AT. The proband, a 58-year-old male of Saskatchewan Mennonite origin, had **spinocerebellar degeneration associated with choreiform movements** beginning at about age 10 years. Despite considerable physical handicap, he was able to work as a delivery man in the family store. **No telangiectases were found at age 44** (they were carefully sought because of typical AT in a niece) or on later examinations. He **showed total absence of IgA** in serum and concentrated saliva and low IgE in serum. He was **anergic on skin testing**. **Glucose tolerance** was markedly decreased. **Serum alpha-fetoprotein** was 840 ng per ml (normal, less than 10 ng per ml). **Lymphocyte response to phytohemagglutinin** was blunted. He died of lymphoma at age 58. He showed **cytogenetic abnormalities** typical of AT; 4 abnormal clones were identified, all involving chromosome 14 in some way. The proband had 4 brothers and 2 sisters. A brother died of leukemia at age 16. A sister was likewise diagnosed as having spinocerebellar degeneration with choreiform movements at age 46; she died at age 55 of breast cancer. The proband's niece with typical AT had telangiectases of the bulbar conjunctivae and earlobes noted at age 3, when she began to have recurrent and severe sinopulmonary infections. She died at age 20 of staphylococcal pneumonia superimposed on bronchiectasis. The brother and sister who died in their 50s may have been genetic compounds. Their parents denied consanguinity.

[Taylor et al. \(1987\)](#) described 3 patients who were atypical in terms of clinical features and cellular features as observed in vitro. One of the patients was a 45-year-old woman with onset of neurologic manifestations in her early twenties. [Maserati et al. \(1988\)](#) described 2 sisters, aged 9 and 11 years, with a progressive neurologic disorder similar to AT, chromosome instability with rearrangements involving chromosomes 7 and 14, but no telangiectases or immunologic anomalies typical of AT. [Byrne et al. \(1984\)](#) reported similar cases of **ataxia without telangiectases with selective IgE deficiency but normal IgA and alpha-fetoprotein**. [Ziv et al. \(1989\)](#) described 2 Turkish sibs with an atypically prolonged course and atypical behavior of cultured fibroblasts. See [208910](#) and [208920](#) for AT-like syndromes.

HETEROZYGOTES

[Welshimer and Swift \(1982\)](#) studied families of homozygotes for AT, Fanconi anemia (FA), and xeroderma pigmentosum (XP; [278700](#)) to test the hypothesis that heterozygotes may be predisposed to some of the same congenital malformations and developmental disabilities that are common among homozygotes. Among XP relatives, 11 of 1,100 had unexplained mental retardation, whereas only 3 of 1,439 relatives of FA and AT homozygotes showed mental retardation. Four XP relatives but no FA or AT relatives had microcephaly. Idiopathic scoliosis and vertebral anomalies occurred in excess in AT relatives, while **genitourinary and distal limb malformations were found in FA families**.

[Swift et al. \(1987\)](#) examined the cancer risk of heterozygotes for AT in 128 families, including 4 of Amish ancestry, 110 white non-Amish families, and 14 black families. They measured documented cancer incidence rather than cancer mortality based solely on death certificates and compared the cancer incidence in adult blood relatives of probands directly with that in spouse controls. The incidence rates in AT relatives were significantly elevated over those in spouse controls. In persons heterozygous for AT, the relative risk of cancer was estimated to be 2.3 for men and 3.1 for women. **Breast cancer in *women was the cancer most clearly associated with heterozygosity for AT.*** [Swift et al. \(1987\)](#) ***estimated that 8 to 18% of patients with breast cancer in the U.S. white population would be heterozygous for AT.***

Intuitively, it is difficult to believe that such a high proportion of breast cancer women are AT heterozygotes. [Pippard et al. \(1988\)](#) confirmed this observation, however. They reported an excess of breast cancer deaths in British mothers of AT patients (significant at the 5% level), but no excess mortality from malignant neoplasms in the grandparents.

[Morrell et al. \(1990\)](#) reported cancer incidence measured retrospectively in 574 close blood relatives of AT patients and 213 spouse controls in 44 previously unreported families. For heterozygous carriers of the AT gene, the relative risk of cancer was estimated to be 6.1 as compared with non-heterozygotes. The most frequent cancer site in the blood relatives was the female breast, with 9 cancers observed. [Gatti et al. \(1991\)](#) provided a review in which they noted the possibly high frequency of breast cancer in AT heterozygotes. [Swift \(1980\)](#) defended, from the viewpoint of not causing anxiety, the usefulness and safety of cancer risk counseling of heterozygotes for AT. [Swift et al. \(1991\)](#) reported the results of a prospective study of 1,599 adult blood relatives of patients with AT and 821 of their spouses distributed in 161 families. Cancer rates were significantly higher among the blood relatives than in their spouses, specifically in the subgroup of 294 blood relatives who were known to be heterozygous for the AT gene. The estimated risk of cancer of all types among heterozygotes as compared with noncarriers was 3.8 in men and 3.5 in women, and that for breast cancer in carrier women was 5.1. Among the blood relatives, women with breast cancer were more likely to have been exposed to selected sources of ionizing radiation than controls without cancer. Male and female blood relatives also had 3-fold and 2.6-fold excess mortality from all causes, respectively, from the ages of 20 through 59 years. [Swift et al. \(1991\)](#) suggested that diagnostic or occupational exposure to ionizing radiation increases the risk of breast cancer in women heterozygous for AT. The work of [Swift et al. \(1991\)](#) on the frequency of breast cancer in AT was critiqued by numerous authors, including [Bridges and Arlett \(1992\)](#).

Since the genes responsible for most cases of AT are located on 11q, [Wooster et al. \(1993\)](#) typed 5 DNA markers in the AT region in 16 breast cancer families. They found no evidence for linkage between breast cancer and these markers and concluded that the contribution of AT to familial breast cancer is likely to be minimal

[Athma et al. \(1996\)](#) determined the AT gene carrier status of 776 blood relatives in 99 AT families by tracing the ATM gene in each family through tightly linked flanking DNA markers. There were 33 women with breast cancer who could be genotyped; 25 of these were AT heterozygotes, compared to an expected 14.9. For 21 breast cancers with onset before age 60, the odds ratio was 2.9 and for 12 cases with onset at age 60 or older, the odds ratio was 6.4. Thus, the breast cancer risk for AT heterozygous women is not limited to young women but appeared to be even higher at older ages. [Athma et al. \(1996\)](#) estimated that, of all breast cancers in the U.S., 6.6% may occur in women who are AT heterozygotes. This proportion is several times greater than the estimated proportion of carriers of BRCA1 mutations ([113705](#)) in breast cancer cases with onset at any age.

The reported increased risk for breast cancer for AT family members has been most evident among younger women, leading to an age-specific relative risk model predicting that 8% of breast cancer in women under age 40 arises in AT carriers, compared with 2% of cases between 40 and 59 years ([Easton, 1994](#)). To test this hypothesis, [FitzGerald et al. \(1997\)](#) undertook a germline mutational analysis of the ATM gene in a population of women with early onset of breast cancer, using a protein truncation (PTT) assay to detect chain-terminating mutations, which account for 90% of mutations identified in children with AT. They detected a heterozygous ATM mutation in 2 of 202 (1%) controls, consistent with the frequency of AT carriers predicted from epidemiologic studies. ATM mutations were present in only 2 of 401 (0.5%) women with early onset of breast cancer ($P = 0.6$). [FitzGerald et al. \(1997\)](#) concluded that heterozygous ATM mutations do not confer genetic predisposition to early onset of breast cancer.

The results of [FitzGerald et al. \(1997\)](#) are discrepant with those of [Athma et al. \(1996\)](#), who conducted a study 'from the other direction' by following identified AT mutations through the families of those with clinically recognized AT. Analysis of DNA markers flanking the AT gene allowed them to identify precisely which female relatives with breast cancer carried the AT mutation. On the basis of the genetic relationship between each case and the AT proband, the a priori probability that these 2 share the AT mutation was calculated. This led to an estimated relative risk of 3.8 as compared to noncarriers. This result was similar to that found by [Easton \(1994\)](#), who reanalyzed the previous studies of breast cancer risk in mothers (and other close relatives) of AT cases. [Bishop and Hopper \(1997\)](#) analyzed these 2 studies and suggested that they may not be discrepant. Indeed, they estimated that the study of [FitzGerald et al. \(1997\)](#) yielded an upper limit of the 95% confidence interval for the proportion of early onset breast cancer occurring in AT heterozygotes as 2.4% (assuming that their assay identified 75% of all mutations).

In a family with multiple cancers, [Bay et al. \(1999\)](#) described heterozygosity for a mutant allele of ATM that caused skipping of exon 61 in the mRNA ([208900.0020](#)) and was associated with a previously undescribed polymorphism in intron 61. The mutation was inherited by 2 sisters, one of whom developed breast cancer at age 39 years and the second at age 44 years, from their mother, who developed kidney cancer at age 67 years. Studies of irradiated lymphocytes from both sisters revealed elevated numbers of chromatid breaks, typical of AT heterozygotes. In the breast tumor of the older sister, loss of heterozygosity (LOH) was found in the ATM region of 11q23.1, indicating that the normal ATM allele was lost in the breast tumor. LOH was not seen at the BRCA1 ([113705](#)) or BRCA2 ([600185](#)) loci. BRCA2 was considered an unlikely cancer-predisposing gene in this family because each sister inherited different chromosomes 13 from each parent. The findings suggested that haploinsufficiency at ATM may promote tumorigenesis, even though LOH at the ATM locus supported a more classic 2-hit tumor suppressor gene model.

The finding that ATM heterozygotes have an increased relative risk for breast cancer had been supported by some studies but not confirmed by others. [Broeks et al. \(2000\)](#) analyzed germline mutations of the ATM gene in a group of Dutch patients with breast cancer using normal blood lymphocytes and the protein truncation test followed by genomic sequence analysis. A high percentage of ATM germline mutations was demonstrated among patients with sporadic breast cancer. The 82 patients included in this study had developed breast cancer before the age of 45 years and had survived 5 years or more (mean, 15 years), and in 33 (40%) of the patients a contralateral breast tumor had been diagnosed. Among these patients, 7 (8.5%) had germline mutations of the ATM gene, of which 5 were distinct. One splice site mutation, IVS10-6T-G ([208900.0021](#)), was detected 3 times in this series. Four heterozygous carriers had bilateral breast cancer. [Broeks et al. \(2000\)](#) concluded that ATM

heterozygotes have an approximately 9-fold increased risk of developing a type of breast cancer characterized by frequent bilateral occurrence, early age at onset, and long-term survival. They suggested that the characteristics of this population of patients may explain why such a high frequency was found here and not in other series.

BIOCHEMICAL FEATURES

The nature of the basic defect is a mystery but is believed to involve *one or more of the enzymes concerned with DNA repair or processing.*

[Shaham and Becker \(1981\)](#) showed that the AT clastogenic (chromosome breaking) factor present in plasma of AT patients and in the culture medium of AT skin fibroblasts is a peptide with a molecular weight in the range of 500 to 1000. No clastogenic activity could be demonstrated in extracts of cultured AT fibroblasts.

Mutants of the mei-41 gene in *Drosophila melanogaster* were first identified on the basis of a defect in meiotic recombination and subsequently by their mutagen sensitivity to a wide range of mutagens, including ionizing radiation, ultraviolet radiation, methyl methanesulfonate, and hydroxyurea ([Banga et al., 1986](#); [Baker et al., 1976](#)). Indeed, there is no overlap between the x-ray dose-kill curves for wildtype and for mei-41 mutants, and females heterozygous for mei-41 mutations display an intermediate level of mutagen sensitivity ([Boyd et al., 1976](#); [Nguyen et al., 1979](#)). [Hari et al. \(1995\)](#) noted that mutations in the mei-41 gene also cause high levels of chromosome breakage and instability in mitotic cells and in the male germline. A number of gaps and breaks are enhanced following treatment with x-rays to the extent that after 220 R of irradiation, virtually all of the subsequent metaphases possess at least 1 break or rearrangement. They commented that the observation of chromatid breaks and gaps in the metaphase chromosomes of both mutagenized and unmutagenized mei-41 cells is surprising, because many organisms possess cell cycle checkpoint controls that prevent cells with damaged DNA from exiting G2 and entering the M phase. [Hari et al. \(1995\)](#) demonstrated that mei-41 has a similar if not identical effect on G2/M progression of X-irradiated neuroblasts in *Drosophila* as is observed in ataxia-telangiectasia: cells irradiated in G2 fail to display an initial block in cell cycle progression that is characteristic of normal cells. [Hari et al. \(1995\)](#) also showed that the *Drosophila* mei-41 and the human ATM gene are homologous at the level of predicted amino acid sequence. Like the ATM protein, the mei-41 protein belongs to a family of phosphatidylinositol 3-kinase (PI3K)-like proteins that include the yeast rad3 and Mec1p proteins. [Hari et al. \(1995\)](#) concluded that the mei-41 gene of *Drosophila* is a functional homolog of the human ATM gene.

[Greenwell et al. \(1995\)](#) showed that the ATM gene has strong homology to 2 known yeast genes, ESR1/MEC1 of *Saccharomyces cerevisiae* and rad3 of *Schizosaccharomyces pombe*, and to a yeast open reading frame, YBLO88. [Greenwell et al. \(1995\)](#) showed that YBLO88 encodes TEL1, a gene required for maintaining wildtype telomere length. Yeast chromosomes terminate in tracts of simple repetitive DNA, poly-G1-3-T. Mutations in the TEL1 gene result in shortened telomeres. Sequence analysis of TEL1 indicated that it encodes a very large protein (322 kD) with amino acid motifs found in phosphatidylinositol/protein kinases. The authors found that the closest homolog to TEL1 is the human ATM gene. [Morrow et al. \(1995\)](#) presented data indicating that TEL1 and the checkpoint gene MEC1 in *S. cerevisiae* are functionally related and that functions of the human ATM gene are apparently divided between at least 2 *S. cerevisiae* homologs. [Paulovich and Hartwell \(1995\)](#) likewise identified MEC1 as a yeast homolog of ATM.

various ATM-like genes. She pointed out that 'whether or not these ATM-like genes are ATM homologs, continued inquiry in genetically tractable model organisms like yeast and *Drosophila* will surely provide valuable insight into the functions of this family of proteins.'

Telomeres are essential for stable maintenance of linear chromosomes in eukaryotes. As indicated earlier, the ATM family of genes, including TEL1 of budding yeast, rad3+ of fission yeast, and human ATM itself, appear to be involved in telomere length regulation. [Naito et al. \(1998\)](#) cloned another fission yeast ATM homolog, tel1+, and found that a tel1rad3 double mutant lost all telomeric DNA sequences. Thus, the ATM homologs are essential in telomere maintenance. The mutant grew poorly and formed irregular-shaped colonies, probably due to chromosome instability; however, during prolonged culture of double mutants, cells forming normal round-shaped colonies arose at a relatively high frequency. All 3 chromosomes in these derivative cells were circular and lacked telomeric sequences. This appeared to be the first report of eukaryotic cells whose chromosomes were all circular. Upon meiosis, these derivative cells produced few viable spores. Therefore, the exclusively circular genome lacking telomeric sequences is proficient for mitotic growth, but does not permit meiosis.

[Hawley and Friend \(1996\)](#) commented upon the current state of ATM research and concluded that ATM must play crucial roles in normally developing or undamaged cells, as well as the studied role in irradiated cells, in order to explain the neurologic, immune, and reproductive problems observed in AT patients. They also proposed that ATM may be intimately associated with both p53 (TP53; [191170](#)) and the molecular machinery required for chromosomal exchange, perhaps as components of the recombination nodules.

OTHER FEATURES

[Waldmann and McIntire \(1972\)](#) showed *raised alpha-fetoprotein* in the blood of patients with AT. This, they felt, suggests immaturity of the liver and is consistent with the view that the primary defect is in tissue differentiation, specifically, a defect in the interaction necessary for differentiation of gut-associated organs such as the thymus and liver. [Ishiguro et al. \(1986\)](#) concluded that the elevated alpha-fetoprotein in patients with AT probably originates in the liver.

On the circulating monocytes of AT patients, [Bar et al. \(1978\)](#) demonstrated an 80 to 85% decrease in insulin receptor affinity. This decrease was not observed in the cultured fibroblasts of AT patients or in the monocytes and fibroblasts of relatives of these patients. In addition, they found that whole plasma and immunoglobulin-enriched fractions of plasma from AT patients inhibited the normal binding of insulin to its receptors on cultured human lymphocytes and on human placental membranes. This suggested the presence of antireceptor immunoglobulins. AT and type B acanthosis nigricans have several features in common that suggest the possibility of similar causes for the insulin resistance each demonstrates

[Mohamed et al. \(1987\)](#) found marked reduction of topoisomerase II ([126430](#)) in some but not all AT cell lines. DNA topoisomerases I and II are enzymes that introduce transient single- and double-strand breaks into DNA and thus are capable of interconverting various DNA conformations. The isolation of mutants of the 2 enzymes in yeast and the increased levels of DNA topoisomerase II in cells undergoing DNA synthesis provide evidence for the role of these enzymes in DNA replication and in chromosome segregation and organization.

[Kojis et al. \(1989\)](#) suggested that the very high frequency of lymphocyte-associated rearrangements (LARs) in peripheral blood chromosome preparations is a diagnostic

criterion of the disease. They pointed out a striking difference in the types of rearrangements observed in lymphocytes and fibroblasts. LARs are not commonly observed in fibroblasts, despite the increased but random instability of chromosomes from these cells relative to lymphocytes. The region of location of the AT gene, 11q22-q23, is not involved in site-specific rearrangements in either lymphocytes or fibroblasts.

[Carbonari et al. \(1990\)](#) found that patients with AT have more circulating T cells bearing gamma/delta receptors characteristic of immature cells than alpha/beta receptors typical of mature cells. Normal ratios were found in the patients with other immune deficits, except for 1 child with a primary T-cell defect. [Peterson and Funkhouser \(1990\)](#) proposed that these findings are consistent with a defect in genetic recombination leading to the switch from gamma/delta to alpha/beta. There may also be a defect in DNA ligation or some other aspect of DNA repair. Elucidation of the molecular abnormalities of lymphocytes may demonstrate fundamental molecular mechanisms for cellular differentiation not only of lymphocytes but of other cell systems such as the nervous system.

[Lipkowitz et al. \(1990\)](#) showed that an abnormal V(D)J recombination, joining V segments of the T-cell receptor gamma gene ([186970](#)) with J segments of the T-cell receptor beta gene ([186930](#)), occurs in peripheral blood lymphocytes of AT patients at a frequency 50- to 100-fold higher than normal. This frequency is roughly the same as the increase in the risk for lymphoid malignancy in these individuals. There is also an increase in the frequency of the lymphocyte-specific cytogenetic abnormalities thought to be due to interlocus recombination in non-AT patients with non-Hodgkin lymphoma, further suggesting a relationship between these translocations and lymphoid malignancies. Agriculture workers occupationally exposed to pesticides used in the production and storage of grain have a high frequency of cytogenetic abnormalities in peripheral blood lymphocytes in a pattern reminiscent of those in AT patients. Furthermore, these agriculture workers have an increased risk of developing T- and D-lymphoid malignancies. [Lipkowitz et al. \(1992\)](#) used a PCR-based assay developed for the study of AT patients to demonstrate a 10- to 20-fold increased frequency of hybrid antigen-receptor genes in peripheral blood lymphocytes of agriculture workers with chemical exposure.

INHERITANCE

In a study of 47 families ascertained throughout the United Kingdom, [Woods et al. \(1990\)](#) found a low parental consanguinity rate; no parents were first cousins or more closely related, whereas 10% had been expected. Furthermore, the incidence of the disorder in 79 sibs of index cases was 1 in 7, rather than the expected 1 in 4.

CYTOGENETICS

[Oxford et al. \(1975\)](#) found that chromosome 14 was often involved in rearrangements in AT and that band 14q12 was a highly specific exchange point. In addition to the changes in chromosome 14, a pericentric inversion of chromosome 7 is characteristic. [McCaw et al. \(1975\)](#) described t(14;14)(q11;q32) translocation in T-cell malignancies of patients with AT. T cells show a t(14;14)q12q32 rearrangement in about 10% of AT patients.

[Aurias et al. \(1986\)](#) described a possible 'new' type of chromosome rearrangement, namely, telomere-centromere translocation (tct) followed by double duplication. This type of rearrangement was found between chromosomes 7 and 14 in cases of AT ([Aurias et al., 1986](#)). [Gatti et al. \(1985\)](#) and [Aurias and Dutrillaux \(1986\)](#) found that the sites of breaks in rearrangements (7p14, 7q35, 14q12, 14qter, 2p11, 2p12, and 22q11-q12) are those where

members of the immunoglobulin superfamily are located: IGK, IGH, IGL, TCRA, TCRB, TCRG. The somatic gene rearrangement must precede expression of these genes.

[Kennaugh et al. \(1986\)](#) studied a patient with an inversion of 14q which had been present for many years in T cells. It was found that the breakpoint in 14q32 lay outside the IgH locus and proximal to it. The constant region gene of the T-cell receptor alpha chain (TCRA) locus was translocated to the 14q32 position. [Johnson et al. \(1986\)](#) found that the 14q32 breakpoint in the 14/14 translocation found in T-CLL cells and in an AT patient occurred within the immunoglobulin gene cluster. The AT patient had the characteristic chromosome 14 tandem translocation in 100% of karyotyped T cells 10 years before her death from T-cell leukemia. (This was the same patient described earlier by [Saxon et al. \(1979\)](#).) [Stern et al. \(1988\)](#) used in situ chromosomal hybridization to map the TCRA gene in 3 different nonmalignant T-cell clones derived from patients with AT. The constant region was translocated in each clone; the variable region remained in its original position in 2 clones and was deleted in 1 which lost the derivative chromosome 14

[Stern et al. \(1988\)](#) mapped the 14q32.1 recurrent breakpoint of AT clones by in situ hybridization. They found that the breakpoint lay between D14S1 ([107750](#)) and PI ([107400](#)). In a t(14;14) clone they found an interstitial duplication including D14S1 and a part of the IGH locus. Studying the chromosomes by R-banding, [Zhang et al. \(1988\)](#) concluded that the distal breakpoint in the chromosome 14 inversion in an AT clone was different from that in the chromosome 14 inversion in a malignant T-cell line; specifically, in AT, the breakpoint was centromeric to both the immunoglobulin heavy chain locus and the D14S1 anonymous locus ([107750](#)). They suggested that this finding favors the existence of an unknown oncogene in band 14q32.1

[Russo et al. \(1989\)](#) presented evidence for a cluster of breakpoints in the 14q32.1 region, the site of the putative oncogene TCL1 ([186960](#)), in cases of ataxia-telangiectasia with chronic lymphocytic leukemia. The 14q32.1 breakpoint is at least 10,000 kb centromeric to the immunoglobulin heavy chain locus. In a cell line with a translocation t(14;14)(q11;q32) from an AT patient with T-cell chronic lymphocytic leukemia, [Russo et al. \(1989\)](#) showed that a J(alpha) sequence from the TCRA locus ([186880](#)) was involved. This was again the patient first reported by [Saxon et al. \(1979\)](#). [Humphreys et al. \(1989\)](#) found some rearrangements involving chromosomes 7 and 14 at the usual 4 sites associated with AT--7p14, 7q35, 14q12, and 14q32--all sites of T-cell receptor genes.

MAPPING

By linkage to RFLP markers, [Gatti et al. \(1988\)](#) localized the AT gene to 11q22-q23. They had previously excluded 171 markers, comprising approximately 35% of the genome. The most promising marker in a large Amish pedigree was found to be THY1 ([188230](#)), which is located at 11q22.3; it showed linkage with maximum lod = 1.8 at theta = 0.00. When data from the other 4 informative group A AT families were added, the maximum lod score rose to 3.63 with no observed recombinants. The maximum lod score for all 31 families studied for linkage of AT to THY1 was 4.34 at theta = 0.10. The large Amish pedigree diagrammed in their Figure 1 is the kindred reported by [McKusick and Cross \(1966\)](#), [Ginter and Tallapragada \(1975\)](#), and [Rary et al. \(1975\)](#). By further mapping with a panel of 10 markers, [Sanal et al. \(1990\)](#) concluded that the AT locus is in band 11q23. It is of interest that the site of the AT1 gene (11q22-q23) is the same as or adjacent to the region occupied by the CD3 ([186790](#)), THY1, and NCAM ([116930](#)) genes, all of which are members of the immunoglobulin-gene superfamily and therefore may be subject to the same defect that afflicts the T-cell receptor and immunoglobulin molecules in AT. [Concannon et al. \(1990\)](#) excluded the AT1 gene from a region extending 15 cM to either side of ETS1 ([164720](#)),

which maps to 11q24. According to [Gatti \(1990\)](#), the gene in families from complementation groups A, C, and D, representing approximately 97% of all families, has been mapped to 11q23. Thus, a single gene may exist with various intragenic defects permitting complementation

In studies of 35 consecutively obtained families in the British Isles, [McConville et al. \(1990\)](#) found support for linkage with THY1 at zero recombination. They found evidence suggesting a second AT locus on 11q, centromeric to the site previously postulated. With 3 exceptions, the families had not been assigned to complementation groups. The series of families included the only group E family described to date. They quoted [Jaspers et al. \(1988\)](#) as giving the proportion of group A, group C, and group D cases as approximately 56%, 28%, and 14%, respectively.

By linkage studies in a Jewish-Moroccan family with AT of the group C type, [Ziv et al. \(1991\)](#) found that the disorder was linked to the same region (11q22-q23) as found in group A families. [McConville et al. \(1990\)](#) located the AT1 gene to a 5-cM region in 11q22-q23, flanked by NCAM and DRD2 ([126450](#)) on one side and STMY1 ([185250](#)) on the other.

On the basis of an 18-point map of the 11q23 region of 11q, derived from linkage analysis of 40 CEPH families, [Foroud et al. \(1991\)](#) analyzed 111 AT families from Turkey, Israel, England, Italy, and the United States, localizing the gene to an 8-cM sex-averaged interval between the markers STMY1 and D11S132/NCAM. [Ziv et al. \(1992\)](#) obtained results from linkage study indicating that the ATA gene in 3 large Arab families was located in 11q23. However, in a Druze family unassigned to a specific complementation group, several recombinants between AT and the same markers were observed.

[Sobel et al. \(1992\)](#) pointed to linkage evidence suggesting that there are 2 AT loci on 11q and that group D AT may be located distal to the site of groups A and C in the 11q23 region. [Kapp et al. \(1992\)](#) reported the cloning of a putative group D gene that mapped, by means of radiation hybrids, to the region between markers THY1 and D11S83. In linkage studies of 14 Turkish families, 12 of which were consanguineous, [Sanal et al. \(1992\)](#) obtained results indicating that the most likely location for a single AT locus is within a 6-cM sex-averaged interval defined by STMY and the marker CJ77. However, it appeared that there are at least 2 distinct AT loci (ATA and ATD) at 11q22-q23, with perhaps a third locus, ATC, located very near the ATA gene.

[Hernandez et al. \(1993\)](#) described a large inbred family in which 2 adult cousins had AT with a somewhat milder clinical course than usual. Since genetic linkage analysis did 'not provide any evidence that the gene for AT in this family is located at 11q22-23,' further locus heterogeneity was suggested.

In 2 families clinically diagnosed with AT and previously reported by [Hernandez et al. \(1993\)](#) and [Klein et al. \(1996\)](#), respectively, [Stewart et al. \(1999\)](#) identified mutations in the MRE11A gene ([600814](#)). Consistent with the clinical outcome of these mutations, cells established from the affected individuals within the 2 families exhibited many of the features characteristic of both AT and Nijmegen breakage syndrome ([251260](#)), including chromosomal instability, increased sensitivity to ionizing radiation, defective induction of stress-activated signal transduction pathways, and radioresistant DNA synthesis. The authors designated the disorder ATLD, for AT-like disorder ([604391](#)). Because the MRE11A gene maps to 11q21 and the ATM gene maps to 11q23, [Stewart et al. \(1999\)](#) concluded that only a very detailed linkage analysis would separate ATLD from AT purely on the basis of genetic data. Assuming that the mutation rate is proportional to the length of the coding sequences of

the 2 genes, they suggested that approximately 6% of AT cases might be expected to have MRE11A mutations

[Gatti et al. \(1993\)](#) reported prenatal genotyping in this disorder. They pointed out that although at least 5 complementation groups have been defined, linkage studies of more than 160 families from various parts of the world have failed to show linkage heterogeneity. All but 2 families were linked to a 6-cM (sex-averaged) region at 11q22.3 defined by the markers STMY1 and D11S385. A further analysis of 50 British families narrowed the localization to a 4-cM (sex-averaged) region defined by D11S611 and D11S535. The demonstrated complementation groups may represent different intragenic mutations or separate ataxia-telangiectasia genes clustered within the 11q22.3 region, neither of which would challenge the validity of linkage or haplotyping studies. A possible reinterpretation of the complementation data is that the radiosensitivity of AT fibroblasts can be complemented by many genes besides the AT gene or genes. [Gatti et al. \(1993\)](#) used the flanking markers to show that the haplotypes in a fetus were identical to those in a previously born affected child. The parents chose to continue the pregnancy.

[Matsuda et al. \(1996\)](#) determined the chromosomal locations of the *Atm* and *Acat1* (mitochondrial acetoacetyl-CoA thiolase; [203750](#)) genes in mouse, rat, and Syrian hamster by direct R-banding fluorescence in situ hybridization. The 2 genes colocalized to mouse 9C-D, the proximal end of rat 8q24.1, and 12qa4-qa5 of Syrian hamster. The regions in the mouse and rat are homologous to human chromosome 11q. In the study of interspecific backcross mice, no recombinants were found among *Atm*, *Npat* ([601448](#)), and *Acat1*. NPAT is a gene identified by positional cloning in the AT region and the gene product may be transported into the nucleus because it has sequences matching the nuclear localization signals. Therefore, the gene was tentatively designated NPAT, for 'nuclear protein mapped to the ataxia-telangiectasia locus' ([Imai, 1996](#)

[Pecker et al. \(1996\)](#) also mapped the mouse *Atm* gene to band 9C by FISH. Using a panel of 67 progeny derived from an interspecific backcross, [Xia et al. \(1996\)](#) demonstrated that the mouse homolog maps to chromosome 9.

MOLECULAR GENETICS

At least 2 stages in the cell cycle are regulated in response to DNA damage, the G1-S and the G2-M transitions ([Hartwell, 1992](#)). These transitions serve as checkpoints at which cells delay progress through the cell cycle to allow repair of damage before entering either S-phase, when damage would be perpetuated, or M-phase, when breaks would result in the loss of genomic material. Checkpoints are thought to consist of surveillance mechanisms that can detect DNA damage, signal transduction pathways that transmit and amplify the signal to the replication or segregation machinery, and possibly repair activities. Both the G1-S and G2-M checkpoints are known to be under genetic control, since there are mutants that abolish the arrest or delay occurring in normal cells in response to DNA damage. [Painter et al. \(1982\)](#) showed that the G1-S checkpoint is abolished in cells from AT patients. [Kastan et al. \(1992\)](#) provided strong evidence that p53 is necessary for the G1-S checkpoint. They found that the AT gene(s) is upstream of the p53 gene in a pathway that activates the G1-S checkpoint. p53 levels increase 3- to 5-fold by a posttranscriptional mechanism after gamma-irradiation, coincident with a delay of the G1-S transition ([Kastan et al., 1991](#)); the induction of p53 does not occur in AT cells ([Kastan et al., 1992](#)). Induction by ionizing radiation of the GADD45 gene ([126335](#)), an induction that is also defective in AT cells, is dependent on wildtype p53 function ([Kastan et al., 1992](#)). Thus, [Kastan et al. \(1992\)](#) identified 3 participants--AT gene(s), p53, and GADD45--in a signal transduction pathway that controls cell cycle arrest following DNA damage. Abnormalities in this pathway probably contribute to tumor

development. [Kastan et al. \(1992\)](#) pointed out that lymphoid malignancies are the most common tumor seen both in AT patients and in p53-deficient mice. Lymphoid cells normally experience DNA strand breaks during gene rearrangements. The G1 checkpoint may be important in the avoidance of errors in that process. Breast cancer and other nonlymphoid cancers are increased in individuals heterozygous for germline mutations of either p53 (e.g., the Li-Fraumeni syndrome; [191170.0001](#)) or the AT gene(s) (Swift et al., [1987](#), [1991](#)).

The p53 tumor-suppressor protein is a sequence-specific DNA-binding transcription factor that induces cell cycle arrest or apoptosis in response to genotoxic stress. Activation of p53 by DNA-damaging agents is critical for eliminating cells with damaged genomic DNA and underlies the apoptotic response of human cancers treated with ionizing radiation and radiomimetic drugs. Both the levels of p53 protein and its affinity for specific DNA sequences increase in response to genotoxic stress. In vitro, the affinity of p53 for DNA is regulated by its carboxyl terminus. [Waterman et al. \(1998\)](#) therefore examined whether this region of p53 is targeted by DNA-damage signaling pathways in vivo. In nonirradiated cells, serines 376 and 378 of p53 were phosphorylated. IR led to dephosphorylation of ser376, creating a consensus binding site for 14-3-3 proteins ([113508](#)) and leading to association of p53 with 14-3-3. In turn, this increased the affinity of p53 for sequence-specific DNA. Consistent with the lack of p53 activation by ionizing radiation in AT, neither ser376 dephosphorylation nor the interaction of p53 with 14-3-3 proteins occurred in AT cells.

Using 2 recombination vectors to study recombination in AT and control human fibroblast lines, [Meyn \(1993\)](#) found that the spontaneous intrachromosomal recombination rates were 30 to 200 times higher in AT fibroblast lines than in normal cells, whereas extrachromosomal recombination frequencies were near normal. Increased recombination is thus a component of genetic instability in AT and may contribute to the cancer risk. Other evidence of in vitro and in vivo genomic instability includes increased frequencies of translocations and other chromosomal aberrations in lymphocytes and fibroblasts, micronucleus formation in epithelial cells, and loss of heterozygosity in erythrocytes. Hyperrecombination is a specific feature of the AT phenotype rather than a genetic consequence of defective DNA repair because a xeroderma pigmentosum cell line exhibited normal spontaneous recombination rates

[Croce et al. \(1985\)](#) assigned the gene for the alpha subunit of the T-cell antigen receptor ([186880](#)) to the region of one of the common breakpoints in AT (14q11.2) and suggested that the oncogene TCL1 ([186960](#)) is located in the region of the other breakpoint (14q32.3). It is thought that the TCL1 gene may be activated by chromosome inversion or translocation, either of which results in juxtaposition of the TCL1 gene and the TCRA gene. In AT, circulating lymphocytes show characteristic rearrangements involving the site of the T-cell receptor gamma genes (7p15), T-cell receptor beta genes (7q35), T-cell receptor alpha genes (14q11), and immunoglobulin heavy chain genes (14q32) ([McFarlin et al., 1972](#); [Ying and Decoteau, 1981](#)).

[Jung et al. \(1995\)](#) isolated cDNA that corrected the radiation sensitivity and DNA synthesis defects in fibroblasts from an AT1 group D patient by expression cloning, and showed that the cDNA encoded NFKB1, a truncated form of I-kappa-B ([164008](#)), which is an inhibitor of NFKB1, the nuclear factor kappa-B transcriptional activator ([164011](#)). The parental AT1 fibroblast expressed large amounts of the NFKB1 transcript and showed constitutive activation of NFKB1. The AT1 fibroblast transfected with the truncated NFKB1 expressed normal amounts of the NFKB1 transcript and showed regulated activation of NFKB1. Since the NFKB1 gene is located on chromosome 14 and not chromosome 11, it is probably not the

site of the primary defect; [Jung et al. \(1995\)](#) hypothesized that its contribution to the ataxia-telangiectasia phenotype may work downstream of the gene representing the primary defect.

[Kapp et al. \(1992\)](#) rescued the integrated cosmid sequences that partially restored resistance to ionizing radiation in an AT cell line of complementation group D. In this way they found a previously unidentified gene, which they called ATDC. Southern blot analysis indicated that the gene is present in single copy in the human genome. However, RNA blot analysis showed mRNA of several sizes (1.8, 2.6, 3.0, 4.7, and 5.7 kb), varying among different cell lines. Because no large rearrangements were detected by Southern or RNA blot analysis in the group D cell line, abnormality in the gene must involve a point mutation or a small rearrangement.

By the strategy of positional cloning, [Savitsky et al. \(1995\)](#) identified a gene that they designated ATM (for 'AT mutated'). ATM, which has a transcript of 12 kb, was found to be mutated in AT patients from all complementation groups, indicating that it is probably the sole gene responsible for this disorder. A partial ATM cDNA clone of 5.9 kb encoded a putative protein that is similar to several yeast and mammalian phosphatidylinositol 3-prime (PI-3) kinases (e.g., [171833](#), [171834](#)) that are involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. [Savitsky et al. \(1995\)](#) speculated that the discovery of ATM may allow the identification of AT heterozygotes who are at increased risk of cancer

In order to clone ATM, [Savitsky et al. \(1995\)](#) constructed a YAC contig and cosmid contigs spanning the interval between D11S384 and D11S1818, known from linkage studies to contain the AT1 gene. Two complementary methods were used for identification of transcribed sequences: hybrid selection based on direct hybridization of genomic DNA with cDNAs, and exon amplification to identify putative exons in genomic DNA by their splicing capacity. One cDNA clone had an open reading frame that predicted a protein of 1,708 amino acids, beginning with the first available methionine and ending in a termination codon. Southern blot analysis revealed homozygous deletion in this gene in affected members of family ISAT9, an extended Palestinian-Arab AT family that had not been assigned to a complementation group ([Ziv et al., 1992](#)). The deletion detected by [Savitsky et al. \(1995\)](#) included almost the entire genomic region spanned by the original cDNA clone and segregated with the disease. This finding led to a systematic search for mutations in additional AT patients. The restriction endonuclease fingerprinting (REF) method was applied to DNA products of RT-PCR-amplified RNA derived from AT cell lines. When an abnormal REF pattern was found, the relevant portion of the transcript was directly sequenced. Most of the mutations identified in 14 patients, including 3 sib pairs, were predicted to lead to premature truncation of the protein product. Three mutations were predicted to create in-frame deletions of 1, 2, or 3 amino acid residues; see [208900.0001](#), [208900.0002](#), and [208900.0003](#).

[Pecker et al. \(1996\)](#) showed that the mouse *Atm* gene encodes a 3,066-amino acid predicted protein with 84% identity to the human sequence. Northern blots showed a 13-kb transcript in brain, skeletal muscle, and testis with lower amounts in other tissues. A 10.5-kb band was also seen in testis mRNA.

[Brzoska et al. \(1995\)](#) isolated a candidate AT gene (which they called ATDC) on the basis of its ability to complement the ionizing radiation sensitivity of AT group D fibroblasts. They found that the ATDC protein physically interacts with the intermediate-filament protein vimentin ([193060](#)), which is a protein kinase C ([176960](#)) substrate and colocalizing protein, and with an inhibitor of protein kinase C, PKCII ([601314](#)). Indirect immunofluorescence analysis of cultured cells transfected with a plasmid encoding an epitope-tagged ATDC

protein localized the protein to vimentin filaments. [Brzoska et al. \(1995\)](#) suggested that the ATDC and PKCII proteins may be components of a single transduction pathway that is induced by ionizing radiation and mediated by protein kinase C. The fact that the ATM gene encodes a protein with a putative phosphatidylinositol 3-kinase domain and functions as a lipid-mediated signaling molecule is consistent with a model in which ATDC and PKC function downstream from ATM in this pathway.

[Kastan \(1995\)](#) reviewed the implications of the cloning of the ATM gene.

[Savitsky et al. \(1995\)](#) sequenced the 3-prime half of the ATM gene; [Byrd et al. \(1996\)](#) reported the 1,348-amino acid sequence of the N-terminal half of the ATM gene product. No homology with other genes was found within the N-terminal half of the AT protein. They also identified 6 mutations affecting this half of the protein. One of these mutations was found to be associated with a haplotype that is common to 4 apparently unrelated families of Irish descent. All the patients so far examined for both AT alleles had been shown to be compound heterozygotes. None of these mutations affected the putative promoter region which made direct divergent transcription of both the ATM gene and a novel gene, E14 ([601448](#)). All of the mutations identified by [Byrd et al. \(1996\)](#) were deletions except for 1 insertion

[Savitsky et al. \(1995\)](#) reported the sequence of a cDNA contig spanning the entire open reading frame of the ATM gene. The predicted protein of 3,056 amino acids showed significant sequence similarities to several large proteins in yeast, *Drosophila*, and mammals, all of which share the PI 3-kinase domain. Many of these proteins are involved in the detection of DNA damage and the control of cell cycle progression. Mutations in the genes confer a variety of phenotypes with features similar to those observed in human AT cells.

[Uziel et al. \(1996\)](#) determined the genomic organization of ATM using long distance PCR between exons. The gene contains 66 exons spanning approximately 150 kb of genomic DNA. The initiating methionine occurs in exon 4. The first 2 exons, 1a and 1b, are used differentially in alternative transcripts; the initiation codon lies within exon 4; and the final, 3.8-kb exon has about 3.6 kb of 3-prime untranslated sequence.

[Gilad et al. \(1996\)](#) performed mutation analysis in 55 families with AT, using RT-PCR of total RNA from cultured fibroblasts or lymphoblasts, followed by restriction endonuclease fingerprinting of PCR products. Of the 44 AT mutations identified, 39 (89%) were expected to inactivate the ATM protein by truncating it, abolishing correct initiation or termination of translation, or deleting large segments. Additional mutations included 4 smaller in-frame deletions and insertions, and 1 substitution of a highly conserved amino acid at the PI-3 kinase domain.

[Wright et al. \(1996\)](#) assayed 38 cell lines, including 36 from unrelated AT patients and 2 control cell lines, for ATM gene mutations. They detected 30 mutations. Twenty-five of these were distinct, and most of the patients were compound heterozygotes. The mutations included nucleotide substitutions (2 cases), inserti

Ataxia Telangiectasia

LS and MS were concerned about their third, youngest child, TS, because his ability to walk steadily has not developed properly even at age 20 months. During earlier visits to the pediatrician for immunizations and mild bouts of otitis media (ear infections), the parents' concern about his unsteady gait was never dealt with satisfactorily, until recently. After an evaluation by a pediatric neurologist, the possibility of ataxia telangiectasia (AT) was raised as part of the differential diagnosis. Although their son TS appeared to have ataxia (incoordination) when walking, there was no sign of telangiectasia (an abnormality of the blood vessels).

As part of the evaluation for AT, blood was sent for measurement of two embryonic genes, **alpha-fetoprotein** (AFP) and **carcinoembryonic antigen** (CEA), the most consistent markers associated with AT. TS's levels were found to be markedly elevated, compatible with the diagnosis of AT. The parents are besides themselves, because prior to seeking genetic counseling, they learn that their son is at risk for a host of medical illness, including different forms of cancer that are virtually untreatable, and that he is likely to die in childhood because of AT.

At the time of genetic counseling, the parents present with a series of questions concerning AT:

- [What is ataxia telangiectasia?](#)
- [Why is our son afflicted with this disease?](#)
- [Why us, why did we have a son afflicted with AT?](#)
- [Are we at risk for this to happen again, if we should decide to have more children? And, what about the risk to our other children?](#)
- [What is going to happen to TS?](#)
- [What is the risk that TS will develop cancer? And, what kind?](#)
- [What does the AT gene do in our cells?](#)
- [Are there tests to determine who is a carrier of AT gene mutations? If future pregnancies are actually at risk for AT?](#)
- [Are we as parents at any increased risk for the medical problems associated with persons affected with AT?](#)
- [Are there any therapies that can cure AT, such as gene therapy?](#)

What is ataxia telangiectasia?

Ataxia telangiectasia (AT) is a complex genetic disease characterized by:

- **progressive cerebellar degeneration** leading to ataxia,
- **abnormal eye movements**, and
- **deterioration of speech.**

Other features include:

- an increased predisposition to [malignant neoplasms](#), particularly T cell leukemia and lymphoma;
- [okular Telangiectasia](#) (blood-vessel lesions that are formed by a dilatation of a group of small blood vessels);
- high serum AFP (alpha-fetoprotein) levels;
- selective immunoglobulin deficiency with increased susceptibility to infection (usually consisting of a deficiency of IgA, IgE, IgG2, and IgG4 and disturbed T-cell immunity);
- growth retardation;
- hypersensitivity to ionizing radiation;
- spontaneous chromosome instability; and
- premature aging.

The ophthalmological findings involve:

- Telangiectasia of the horizontal conjunctival vessels in the exposed bulbar conjunctivae and
- oculomotor signs, such as dissociated nystagmus, failure of gaze holding, and convergence.

Ataxia is the first symptom and becomes apparent when the child starts to walk, whereas the pathognomonic Telangiectasia (the characteristic for which the disease is named) at the light-exposed areas of the bulbar conjunctiva appear several years later, but can point the way to the diagnosis.

Why is our son afflicted with this disease?

Ataxia Telangiectasia (AT) is generally considered to be an [autosomal recessive](#) disorder.

The birth incidence of AT is approximately 1 in 300,000.

In autosomal recessive disorders, the affected person has one pair of altered genes, each member of the pair inherited from each of the parents.

- The disturbance in development, in this case AT, is caused by that pair of altered (mutated) genes.

- Thus, both alleles of a pair of genes are mutant, and there is no normal partner allele to carry on the function of the particular gene.

Generally, autosomal recessive disorders have less clinical (phenotypic) variation than other forms of inherited disorders. However, AT is unusual in this respect. There is considerable clinical variation when patients with AT are compared.

There are several variants of AT, probably caused by *different allelic mutations*, because affected sibs resemble the index patients:

- classical AT with marked radiation sensitivity;
- classical AT with intermediate levels of radiation sensitivity;
- mild AT with intermediate levels of radiation sensitivity;
- AT without Telangiectasia;
- AT without oculomotor apraxia (an inability to carry out purposeful movements); and
- AT with microcephaly

In one report (Wright et. al., 1996), 25 or 30 mutations in the AT gene (ATM) were distinct, and therefore most patients were compound heterozygotes.

Why us, why did we have a son afflicted with AT?

AT, being an [autosomal recessive](#) disorder, is inherited from clinically normal parents who both have a mutated form of the gene ATM, but in a single dose.

In order for parents to have a child affected with AT, both must be carriers of mutations in the AT gene.

Most individuals have several mutated forms of genes that cause no medical problems because each mutated allele is counterbalanced by its normal gene partner.

Parents with a child affected with AT happen to share the common feature of each having one altered allele in the ATM gene.

It is likely that parents with an affected child carry different mutations within the ATM locus, because:

- mutations in the AT gene are relatively rare, and

- there is a high frequency of distinct ATM gene mutations in AT that may account for [phenotypic variability](#) between families with offspring affected with AT.

Are we at risk for this to happen again, if we should decide to have more children? And, what about the risk to our other children?

For parents who carry altered mutations common to one gene, the chance of any given offspring (*izdanak*) receiving both of the altered gene mutations is 25%.

- In other words, the recurrence risk from the same parentage for an autosomal recessive disorder is 1 in 4.
- It is important to stress that this risk is the same for each and every pregnancy, regardless of previous outcomes.

The risk to any unaffected child whose sibling has AT of themselves having an affected child is calculated as follows:

- Their risk of being a carrier = $2/3$.
- Their risk of marrying a carrier (not a relative) = $1/70$ (the frequency of ATM in the general population in a heterozygous state).
- The chance of two carrier parents having an affected offspring = $1/4$.
- Risk of having an affected child = $2/3 \times 1/70 \times 1/4 = 1$ in 420 (0.24%).

These figures would apply, for example, to TS's older sister, who shows no signs of AT at 5 years of age.

What is going to happen to TS?

Children affected with AT are expected to undergo:

- neurodegeneration,
- recurrent infections due to immunodeficiencies, and
- development of cancer as a consequence of radiosensitivity and [genetic instability](#).

Growth deficiency,

although it may be prenatal in onset, more commonly becomes evident in later infancy or in childhood.

Progressive ataxia

usually develops during infancy and is commonly accompanied by features of choreoathetosis and by **dysrhythmic speech**, drooling ([dr̂] v intr balaviti), aberrant okular movements, stooped posture plus dull sad facies, and occasional seizures.

Instability,

suggesting **vestibular deficit**, often becomes so severe that ambulation is no longer possible in later childhood.

Personalities of children with AT

are usually affable ([ˈaefÁbÁl] a ljubazan , prijatan) and pleasant despite the progression of their handicaps.

Mental deficiency

characterizes up to half of all AT children.

Immune deficiency

results in frequent respiratory infections and bronchiectasis.

Cancer, along with lung infections and neurologic deficits, frequently leads to death in later childhood.

What is the risk that TS will develop cancer? and, what kind?

Approximately 10% of children diagnosed with AT will develop a malignancy in childhood or early adulthood.

The majority of tumors are either [lymphoid leukemias or lymphomas](#).

AT patients with leukemia have markers for T cell leukemia, with cases of T-cell lymphoma, T-cell acute lymphoblastic leukemia (T-ALL), and T-cell prolymphocytic leukemia (T-PLL) reported.

It appears that the gene defect in AT patients allows the formation of a much higher level of **chromosome translocations** involving recombination of T-cell receptors gene in T lymphocytes than in non-AT patients.

- The occurrence of chromosome translocations explains the potential for the development of any of the several forms of T-cell tumors in a population of AT patients.

- There is a suggestion that families with more than one child affected develop either T-ALL or P-ALL, which may reflect the effect of [different AT mutations](#).

Since there is variation in the level of **sensitivity to radiation**, is there any association with the likelihood of developing malignant disease?

- There is no evidence that the lymphoid tumors in AT patients are caused by an increased sensitivity of patients to the effects of ionizing radiation.
- Evidence does point to the importance of particular chromosome translocations in the development of leukemia/lymphoma.

The basic defect in AT cells has the effect of producing both the abnormal chromosomal response to ionizing radiation *and* producing a high level of specific chromosome translocations. But, these responses appear to be independent.

What does the AT gene do in our cells?

The AT gene has been cloned and shown to encode (*[en'koud], [i] v tr šifrovati*) a multi-domain protein with homology to cell-cycle regulators. The gene for AT (ATM) is located on chromosome 11 (11q22→q23). The gene spans (*obuhvata*) a region of approximately 70–80 kb and is composed of 37 [exons](#) ranging in size from 64 to 324 bp.

Abnormalities of [DNA repair](#), genetic recombination, chromatin structure, and [cell-cycle checkpoint](#) control have been proposed as the underlying defect in AT.

AT is a genetic disorder whose clinical and cellular phenotype points to a defect in the signaling system which normally slows down the [cell cycle](#) in the presence of DNA damage, facilitating, in turn, [DNA repair](#) and preventing the accumulation of mutations leading to malignant transformation.

After exposure to ionizing radiation, cells for patients with AT demonstrate:

- an extended [G₁-phase](#) checkpoint and
- prolonged accumulation of cells at G₂.

The AT gene product appears to be upstream (that is, before) a series of [tumor-suppressor genes](#) (for example, TP53, TP21) in

the signalling of the presence of DNA strand breaks produced by ionizing radiation. With mutation in the AT gene, there is a defect in response to [chromosome breakage](#), contributing to the high cancer risk and radiosensitivity observed in AT.

It has been proposed that the AT protein is involved in [DNA damage](#) response at different cell cycle checkpoints.

- The normal protein coded for by the AT gene apparently acts a sensor of DNA damage and binds to [p53](#).
- In cells carrying two mutations for the AT gene, this association of the AT protein with p53 is defective, compatible with the defective p53 response in these cells.
- A defective p53 response in cells whose DNA has been damaged results in the failure to slow down or halt cell division to allow time for DNA repair and permits the accumulation of gene mutations, the initial hallmark of malignant transformation and cancer.
- Inappropriate p53-mediated [apoptosis](#) is the major cause of death in AT cells irradiated in culture.

Most mutations in the AT gene are small deletions or insertions, resulting in premature termination of the [translation](#) product.

The only specific DNA repair defect in AT is mis-repair of cleaved DNA. DNA recombination, which plays a role in DNA repair and genetic stability, is remarkably high in AT, more than 100 times normal. AT cells have a high frequency of chromosomal recombination and also exhibit error-prone recombination of cleaved DNA.

Mutations in the ATM gene appear to be responsible for [chromosomal instability](#), with a high frequency of [telomere](#) fusion.

- Telomeric fusions are associated with large preleukemic translocation clones in T cells.
- AT mutation in the homozygous state (that is, no normal gene present) also accelerates telomere shortening with increasing age of peripheral blood lymphocytes, which may be linked to premature senescence.

- However, there is no evidence that either accelerated telomere loss per se or telomeric fusions are important in tumorigenesis.

A Damage Surveillance Network model has been proposed (Meyn, 1995):

A lack of a functional AT protein results in an *inability* to:

- halt division at multiple cell cycle checkpoints in response to DNA damage.
- activate damage-inducible DNA repair.
- prevent triggering of programmed cell death by spontaneous and induced DNA damage.

Absence of damage-sensitive cell-cycle checkpoints and damage-induced repair disrupts immune gene rearrangements and leads to genetic instability and cancer,

- Triggering apoptosis (cell "suicide") by otherwise nonlethal DNA damage is primarily responsible for the radiation sensitivity of AT affecteds and results in loss of cells, leading to cerebellar ataxia and neurological deterioration, as well as thymic atrophy, lymphocytopenia, and a paucity of germ cells.

**Are there tests to determine who is a carrier of AT gene mutations?
If future pregnancies are actually at risk for AT?**

DNA-based methods are available for [detection of mutations](#) in the AT gene.

It is therefore possible to identify:

- carriers of the AT mutation and
- whether a pregnancy is at risk for AT.

At least 30 different mutations in the AT gene have been identified.

Are we as parents at any increased risk for the medical problems associated with persons affected with AT?

It has been suggested that carriers of mutations in the AT gene are at significantly increased risk for breast cancer, but this is controversial at the present time.

The gene for AT is located at a region (11q22→q23) of frequent [loss of constitutional heterozygosity](#) in breast cancer and other

tumors. Deletions at 11q23→q23, resulting in loss of heterozygosity for genes in the region, has been found in 50% to 60% of cases of breast and lung carcinomas in non-affected family members.

In one study (Athma et al., 1996), it was estimated that the risk of breast cancer for carriers of AT gene mutations ranged from 2.9 times greater for women less than 60 years of age to 6.4 times greater for women 60 years of age or older, when compared to the general population

Of all [breast cancers](#) in the United States, 6.6% may occur in women who are carriers of mutations in the AT gene.

[Epidemiological studies](#) have suggested that carriers of AT mutations, similar to AT affecteds with hypersensitivity to ionizing radiation, may be at increased risk for malignancy possibly as a consequence of radiation exposure.

Are there any therapies that can cure AT, such as gene therapy?

There are no therapies currently available to cure AT.

Treatments are directed toward managing specific medical problems, such as treating infections with antibiotics.

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