

## Cancer Prone Disease Section Review

### Ataxia telangiectasia (A-T)

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#### Abstract

Review on Ataxia telangiectasia, with data on clinics, and the gene involved.

#### Keywords

Review on Ataxia telangiectasia, with data on clinics, and the gene involved.

#### Identity

##### Other names

Louis-Bar syndrome

##### Note

See also, in Deep Insight section: Ataxia-Telangiectasia and variants.

##### Inheritance

Autosomal recessive disease. Genome instability syndrome found worldwide with incidence of .0.5. to 2.5/10<sup>5</sup> newborns in different human populations. A founder effect is found in some isolated population. Heterozygotes are estimated to be 1% of the general population. The clinical phenotype of A-T ranges from severe to milder variants of the disease, but is usually portrayed by its classical, severe form (Perlman SL et al., 2012; Lavin MF, 2008; Crawford TO, 1998; Chun HH et al., 2004; Nissenkorn A et al., 2016). However, awareness is growing of the broad clinical variability associated with the causative mutations (Taylor AM et al., 2015).

The primary cause of all variants of the disease is mutations in the autosomal gene ATM (A-T, mutated) at 11q22-23 (Gatti RA et al., 1988; Savitsky K et al., 1995a), which encodes the ATM protein (Savitsky K et al., 1995b; Ziv Y et al., 1997) a multi-functional protein kinase (Shiloh Y et al., 2013; Shiloh Y, 2014; Guleria A et al., 2016; Ditch S et al., 2012).

#### Clinics

Ataxia telangiectasia is a chromosome instability syndrome (Perlman SL et al., 2012; Lavin MF, 2008; Crawford TO, 1998; Chun HH et al., 2004; Taylor AM et al., 1982; Taylor AM et al., 2015; Taylor AM, 1978; Butterworth SV et al., 1986; Kennaugh AA et al., 1986) with cerebellar degeneration, immunodeficiency, and an increased risk of cancers; A-T cells are defective in recognizing double-strand DNA damage to signal for repair.

The cellular phenotype of A-T represents genome instability, deficient DNA damage response (DDR), and elevated oxidative stress, in addition to a premature senescence component (Shiloh Y et al., 1982). A-T patients show a striking sensitivity to the cytotoxic effect of ionizing radiation (Gotoff SP et al., 1967; Morgan JL et al., 1968). Cells from A-T patients exhibit marked chromosomal instability and sensitivity to ionizing radiations and radiomimetic chemicals (Taylor AM, 1978; Taylor AM et al., 1975; Taylor AM et al., 1979; Shiloh Y

et al., 1982; Shiloh Y et al., 1983; Djuzenova CS et al., 1999). This acute sensitivity results from a profound defect in the cellular response to DNA double-strand breaks (DSBs), whose chief mobilizer is the ATM protein. It is important to note, however, that A-T cells are also moderately sensitive to a wide array of other DNA damaging agents suggesting that these cells cope less efficiently with many other DNA lesions besides DSBs.

### **Phenotype and clinics**

Onset of the disease is often noted during the second year of life: there is progressive cerebellar ataxia (initially truncal, with further peripheral extension); ataxia is a constant feature in this disease; oculomotor apraxia, dysarthria, and dystonia; leading to muscular atrophy.

**Cerebellar ataxia.** The prominent symptom of classical A-T is progressive cerebellar ataxia that develops into a general motor dysfunction, eventually confining most patients to a wheelchair around the end of their first decade (Crawford TO, 1998; Chun HH et al., 2004; Nissenkorn A et al., 2016; Boder E et al., 1958; Sedgwick RP et al., 1960; Boder E, 1985; Crawford TO et al., 2000; Gatti RA, 1995; Verhagen MM et al., 2012). The main underlying pathology appears to be progressive cerebellar cortical degeneration that primarily affects Purkinje and granule neurons, but also basket cells (Vinters HV et al., 1985; Gatti RA et al., 1985).

**Impairment of the extrapyramidal** movement system is common in A-T, as are oculomotor abnormalities such as apraxia, strabismus and nystagmus. Swallowing and articulation of speech are often abnormal, and facial expression is limited. Dysfunctional swallowing is often associated with a general nutritional problem as well as clinically unapparent aspiration, which is thought to play a role in the increasing frequency of lower respiratory tract infections in many patients (Lefton-Greif MA et al., 2000; Bhatt JM et al., 2015). An absence of deep reflexes and peripheral neuropathy are common in A-T, but usually develop relatively later than other neurological impairments (Nissenkorn A et al., 2016).

**Oculocutaneous telangiectasia** (dilated blood vessels) appear at various ages, usually in the eyes (conjunctiva) and sometimes on the ears and facial skin exposed to sunlight, (Perlman SL et al., 2012; Greenberger S et al., 2013). Finally, telangiectasia appear in the brain and other internal organs of young adults with A-T, a peculiar finding seen in people without A-T only as a late effect of treatment with ionizing radiation for cancer therapy (Lin DD et al., 2014).

**Combined Immunodeficiency** (in 70 %) is another hallmark of A-T. Typically, IgA, IgE and

various IgG subclasses are reduced; a diminished lymphocyte count is common, affecting B and T but not natural killer cells, and many have impaired antibody responses to vaccines (Gatti RA, 1995), (Nowak-Wegrzyn A et al., 2004; Gatti RA et al., 1982; Weaver M et al., 1985; Härtlova A et al., 2015). The thymus is typically vestigial, as are the gonads.

**Growth/Puberty.** Many children with A-T grow at a diminished rate, and puberty is often delayed; this growth retardation was suggested to result from a primary endocrine defect (Ehlayel M et al., 2014; Voss S et al., 2014; Pommerening H et al., 2015; Ehlayel M et al., 2014), or a primary growth defect (Nissenkorn A et al., 2016), but is probably also a function of swallowing problems making eating an inefficient and exhausting task.

**Dyslipidemia and diabetes.** There was also an increased incidence of dyslipidemia (10/52 = 19%) and diabetes (2/52 = 4%; Nissenkorn A et al., 2016). These abnormalities together with elevated levels of C-reactive protein suggest a diagnosis of metabolic syndrome in a substantial number of young A-T patients. Insulin-resistant diabetes is an important endocrine abnormality in some patients (Nissenkorn A et al., 2016; Schalch DS et al., 1970; Morrell D et al., 1986; Blevins LS Jr et al., 1996).

**Osteoporosis** is common because of a lack of weight bearing, nutritional deficiencies, and early gonadal failure in females. Incapacitating fatigue affects a majority of A-T patients over the age of 30. The etiology of this problem is likely to be multifactorial, with contributions from the extra effort required to function with neurodegeneration, and central nervous system effects of elevated levels of pro-inflammatory cytokines including IL-6 and IL-8 (McGrath-Morrow SA et al., 2016) and chronic, elevated levels of Type I interferons (Härtlova A et al., 2015).

**Senescence**A-T has recently emerged as a premature aging disease. The broad immune system defects in A-T have been regarded as a reflection of premature ageing of this system in these patients (Exley AR et al., 2011; Carney EF et al., 2012). Finding striking similarities between the immune system phenotypes of A-T patients and the elderly (Carney EF et al., 2012), it was concluded that the immune system of A-T patients is congenitally aged, and A-T could be viewed as a model of immune ageing (Exley AR et al., 2011). Similarly, the resemblance between ageing-associated decline of brain functionality and neurodegeneration associated with genome instability has recently been highlighted (Barzilai A et al., 2016). Adolescents and young adults with A-T exhibit an array of health problems that are typically not seen until late middle age or later. Among 53 A-T patients with mean age of 14.6 years (range 5.9 - 26.1), 43% had elevated serum transaminases, 39%

of those patients had fatty liver detected by ultrasound, and 33% of the latter group developed steatohepatitis, fibrosis or cirrhosis (Weiss B et al., 2016). Progeric features of skin include premature greying and thinning of hair, thinning of skin, and vitiligo (Reed WB et al., 1966).

### Neoplastic risk

Another prominent clinical hallmark of A-T is cancer predisposition; risk of cancers is X 100, consisting mainly of T-cell malignancies (a 70-fold and 250-fold increased risks of leukemia of both B cell and T cell origin, and 250-fold increased risks of non-Hodgkin's lymphoma and Hodgkin's lymphoma), but not myeloid leukemia (Loeb DM et al., 2000; Murphy RC et al., 1999; Olsen JH et al., 2001; Taylor AM et al., 1982). There is a striking incidence of gammopathy in A-T (Sadighi Akha AA et al., 1999), another abnormality that is rarely seen in people < 30 years old.

The most common malignancies in A-T patients of all ages are of lymphocytic origin. However, among those from 18-40 years old with cancer, 11/21 (52%) had cancers of solid organs (stomach, esophagus, liver, parotid gland, thyroid, skin, breast and lung) that are rarely seen in that age group among people without A-T (HM Lederman, L Chessa, unpublished observations).

Cancer treatment is complicated by radiation- and chemo-sensitivity.

### Evolution

Progressive cerebellar degeneration: patients are usually in a wheelchair by the age of ten.

### Prognosis

Respiratory infection is the common cause of death, with cancer being the second most common.

Survival is often into fourth decade today where optimal medical care is available.

## Cytogenetics

Difficulty to grow cells with phytohemagglutinin: karyotypes should be performed with interleukine 2 in 4 days cultures.

Lymphocyte cultures from A-T patients often contain clonal translocations that mainly involve the loci of the T-cell receptor and immunoglobulin heavy-chain genes (Butterworth SV et al., 1986; Kennaugh AA et al., 1986; Taylor AM et al., 1986; Heppell A et al., 1988; Kojis TL et al., 1991), pointing to a defect in the maturation of these genes via V(D)J and class-switch recombination in the adaptive immune system. Such clones usually herald the onset of malignancy and expand as malignancy progresses. Cultured A-T cell strains exhibit elevated rates of chromosome end associations and reduced telomere length (Pandita TK et al., 1995; Smilenov LB et al., 1999; Wood

LD et al., 2001; Metcalfe JA et al., 1996; Vaziri H, 1997). A-T fibroblast strains exhibit similar growth properties to wild-type cells at early passage levels but senesce prematurely (Shiloh Y et al., 1982).

### Inborn conditions

Spontaneous chromatid/chromosome breaks, triradials, quadriradials (less prominent phenomenon than in Fanconi anaemia); telomeric associations.

The best diagnosis test is on the (pathognomonic) highly elevated level (10% of mitoses) of inv(7)(p14q35), t(14;14)(q11;q32), and other non clonal stable chromosome rearrangements involving 2p12, 7p14, 7q 35, 14q11, 14q32, and 22q11 (illegitimate recombinations between immunoglobulin superfamily genes Ig and TCR); normal level of those rearrangements are: 1/500 (inv(14)), 1/200 (t(7;14)), 1/10 000 (inv(7)).

Clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14).

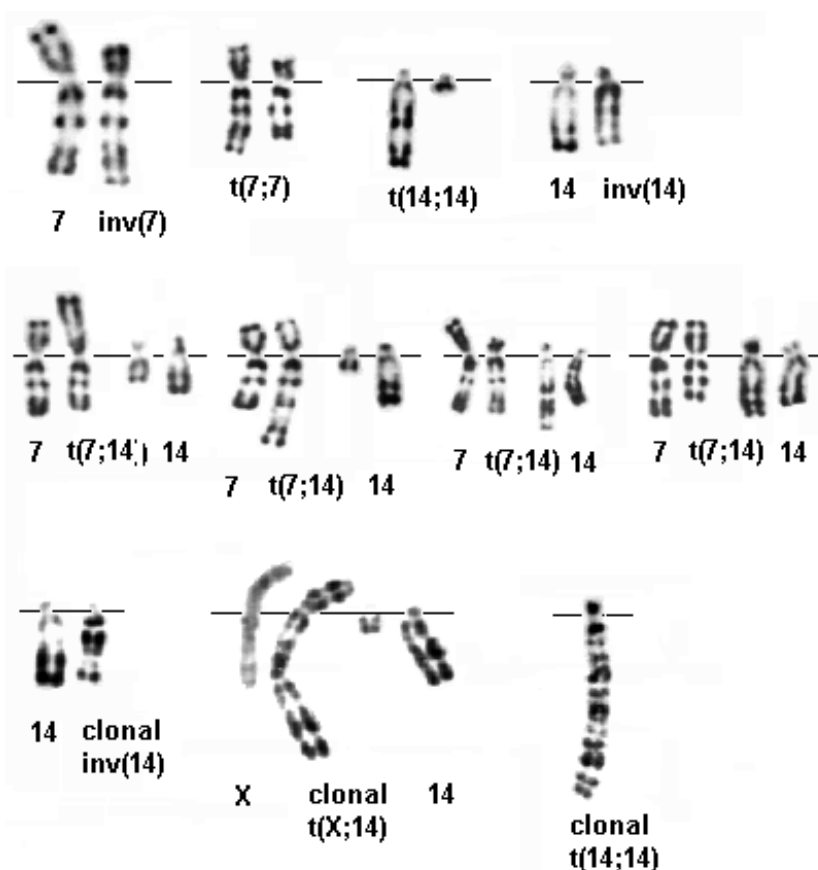
### Cytogenetics of cancer

Clonal rearrangements in T-cell ALL and T-PLL (prolymphocytic leukaemia) in AT patients are complex, with the frequent involvement of t(14;14)(q11;q32)(q11;q32), or t(X;14)(q28;q11), implicating the genes TCL1 or MTCPI1 respectively, as is found in T-Pro Lymphocytic Leukemia in non-AT patients.

## Other findings

**High sensitivity to ionizing radiations** and to radiomimetic drugs (diagnostic may in part be based on the hypersensitivity of AT lymphocytes to killing by gamma irradiation); cell irradiation does not inhibit S phase (DNA synthesis): this is quite pathognomonic of AT, and shows that G1 checkpoint is deficient; there is a lack of TP53, GADD45 and CDKN1A (P21) induction, and a fall in radiation-induced apoptosis; TP53 phosphorylation at ser15 is deficient.

**Telomeres.** The observation of accelerated telomere shortening and telomere fusions in peripheral blood lymphocytes (Metcalfe JA et al., 1996) and cultured fibroblasts (Xia SJ et al., 1996; Smilenov LB et al., 1997) from A-T patients and cell lines expressing dominant-negative ATM fragments (Smilenov LB et al., 1997) exposed an important possible contributor to premature senescence of ATM-deficient cells. The wealth of information currently available on telomere maintenance and the role of the DDR in telomere dynamics (reviewed in (Webb CJ et al., 2013; Dokhani Y et al., 2014; Arnoult N et al., 2015) has tightly linked ATM to telomere homeostasis and added an important component to the ageing aspect of A-T.



Sporadic (rows 1 and 2) and clonal (row 3) rearrangements in ataxia telangiectasia (R- banding). Row 1, from left to right: *inv(7)(p14q35)*, *t(7;7)(p14;q35)*, *t(14;14)(q11;q32)*, *inv(14)(q11q32)*; Row 2, from left to right: *t(7;14)(p14;q11)*, *t(7;14)(q35;q11)*, *t(7;14)(p14;q32)*, *t(7;14)(q35;q32)*; Row 3, from left to right: *inv(14)(q11;q32)*, *t(X;14)(q28;q11)* (note the late replicating X on the left), *t(14;14)(q11;q32)* - Courtesy Alain Aurias (modified figure reprinted from *Médecine/Sciences* 1986; 2: 298-303., by permission of the publisher Masson).

### Lenthening of the cell cycle.

**Oxidative stress.** Increasing numbers of reports have described elevated readouts of oxidative stress in plasma of A-T patients (Reichenbach J et al., 2002), in cultured A-T fibroblasts (Gatei M et al., 2001; Lee SA et al., 2001) and lymphocytes (Ludwig LB et al., 2013), and in tissues and cultured cells from *Atm*-deficient mice (Barlow C et al., 1999; Kamsler A et al., 2001; Gage BM et al., 2001; Ziv S et al., 2005; Chen P et al., 2003; Reliene R et al., 2004; Reliene R et al., 2007; Liu N et al., 2005; McDonald CJ et al., 2011). Notably, the response of A-T fibroblast strains to induced oxidative stress was found defective (Yi M et al., 1990; Ward AJ et al., 1994). These observations were later linked to the role of ATM in regulating cellular oxidative stress.

**Alpha fetoprotein/serum carcinoembryonic antigen** Notable laboratory findings are elevation of serum alpha fetoprotein and serum carcinoembryonic antigen. Further aspects of A-T, which entail segmental premature ageing.

## Genes involved and proteins

### Gene

#### ***ATM (ataxia telangiectasia mutated)***

#### Location

11q22.3

#### DNA/RNA

#### Description

66 exons spanning 184 kb of genomic DNA.

#### Transcription

Northern blot analysis shows two transcript: the first-one, TRIM37a of about 4.5-kb and the second-one, TRIM37b of approximately 3.9 kb.

#### Protein

#### Description

3056 amino acids; 350 kDa; contains a PI 3-kinase-like domain.

### Localisation

Mostly in the nucleus in replicating cells, cytoplasm in differentiating cells.

### Function

Homeostatic protein kinase involved in many cellular circuits. A primary role in the DNA damage response. Activated vigorously by DNA double-strand breaks and activates a broad network of responses. ATM initiates cell cycle checkpoints in response to double-strand DNA breaks by phosphorylating TP53, BRCA1, H2AFX ID: 40783,

**Double strand breaks.** The most widely documented function of ATM, and the one associated with its most vigorous activation, is the mobilization of the complex signaling network that responds to DSBs in the DNA (Shiloh Y et al., 2013; Cremona CA et al., 2014; Awasthi P et al., 2016; Thompson LH, 2012; McKinnon PJ, 2012). DSBs are induced by exogenous DNA breaking agents or endogenous reactive oxygen species (Schieber M et al., 2014), and are an integral part of physiological processes including meiotic recombination (Borde V et al., 2013; Lange J et al., 2011) and the rearrangement of antigen receptor genes in the adaptive immune system (Alt FW et al., 2013). DSBs are repaired via nonhomologous end-joining (NHEJ), or homologous recombination repair (HRR; Shibata A et al., 2014; Chapman JR et al., 2012; Jasin M et al., 2013; Radhakrishnan SK et al., 2014). Once ATM mobilizes the vast DDR network in response to a DSB (McKinnon PJ, 2012; Shiloh Y et al., 2013; Bhatti S et al., 2011), its protein kinase activity is rapidly enhanced. ATM subsequently phosphorylates key players in various arms of the DSB response network (Shiloh Y et al., 2013; Bensimon A et al., 2010; Matsuoka S et al., 2007; Mu JJ et al., 2007; Bensimon A et al., 2011), including other protein kinases that in turn phosphorylate still other targets (Bensimon A et al., 2011).

**Single-strand break repair and base excision repair.** A broader, overarching role for ATM in maintaining genome stability was recently suggested in addition to mobilizing the DSB response (Shiloh Y, 2014). According to this conjecture, ATM supports other DNA repair pathways that respond to various genotoxic stresses, among them single-strand break repair (SSBR; Khoronenkova SV et al., 2015) and base excision repair (BER) - a cardinal pathway in dealing with the daily nuclear and mitochondrial DNA damage caused by endogenous agents (Wallace SS, 2014; Bauer NC et al., 2015). ATM's involvement in these processes is based on its ability to phosphorylate proteins that function in these pathways.

This ongoing role of ATM is its routine function in the daily maintenance of genome stability, while its powerful role in the DSB response is reserved for when this harmful lesion interferes with the daily life of a cell. Thus, when ATM is missing, not only is there markedly reduced response to DSBs, the ongoing modulation of numerous pathways in response to occasional stresses becomes suboptimal. All of these lesions are part of the daily wear and tear on the genome that contributes to ageing.

An additional role for ATM in genome dynamics was proposed following evidence that ATM is involved in shaping the epigenome in neurons by regulating the localization of the histone deacetylase 4 (HDAC4; Li J et al., 2012; Herrup K et al., 2013; Herrup K, 2013), targeting the EZH2 component of the polycomb repressive complex 2 (Li J et al., 2013), and regulating the levels of 5-hydroxymethylcytosine in Purkinje cells (Jiang D et al., 2015).

### Oxidative stress/Cellular homeostasis.

**Cytoplasmic fraction of ATM.** ATM's role in cellular homeostasis is further expanded by its cytoplasmic fraction. Specifically, cytoplasmic ATM was found to be associated with peroxisomes (Watters D et al., 1999; Tripathi DN et al., 2016; Zhang J et al., 2015) and mitochondria (Valentin-Vega YA et al., 2012). In view of the evidence of increased oxidative stress in ATM-deficient cells, it has long been suspected that ATM senses and responds to oxidative stress (Gatei M et al., 2001; Rotman G et al., 1997; Rotman G et al., 1997; Barzilai A et al., 2002; Watters DJ, 2003; Takao N et al., 2000; Alexander A et al., 2010). This conjecture was validated by work from the Paull lab (Guo Z et al., 2010a), which identified an MRN-independent mode of ATM activation, differentiating it from DSB-induced activation, stimulated by reactive oxygen species (ROS) and leading to ATM oxidation (Paull TT, 2015; Guo Z et al., 2010a; Guo Z et al., 2010b; Lee JH et al., 2014).

**Mitochondrial fraction of ATM.** Still another arm of the ATM-mediated response to oxidative stress operates in the mitochondrial fraction of ATM. ATM is thus emerging also as a regulator of mitochondrial homeostasis. Evidence is accumulating of its involvement in mitochondrial function, mitophagy, and the integrity of mitochondrial DNA (Valentin-Vega YA et al., 2012; Ambrose M et al., 2007; Eaton JS et al., 2007; Fu X et al., 2008; Valentin-Vega YA et al., 2012; D'Souza AD et al., 2013; Sharma NK et al., 2014) and further work is needed to identify its substrates in mitochondria and the mechanistic aspects of its action in this arena.



**Links between ATM and the SASP (senescence-associated secretory phenotype).** Several laboratories recently described direct links between ATM and the SASP - a cardinal feature of cell senescence. Work from the Gamble lab (Chen H et al., 2015) showed that the histone variant macroH2A.1 is required for full transcriptional activation of SASP-promoting genes, driving a positive feedback loop that enhances cell senescence. This response is countered by a negative feedback loop that involves ATM activation by endoplasmic reticulum stress, elevated ROS levels or DNA damage. ATM's activity is required for the removal of macroH2A.1 from sites of SASP genes, thus leading to SASP gene repression.

#### **Insulin response and lipoprotein metabolism.**

**IGF-1 receptor.** Another pathway by which ATM may impact on cellular senescence is the dependence of IGF1R (IGF-1 receptor) expression on ATM (Peretz S et al., 2001; Goetz EM et al., 2011; Ching JK et al., 2013).

**Beta-adrenergic receptor.** Another series of observations assigned ATM a protective role in cardiac myocyte apoptosis stimulated by  $\beta$ -adrenergic receptor and myocardial remodeling.

#### **Mutations**

##### **Germinal**

Various types of mutations, dispersed throughout the gene, and therefore most patients are compound heterozygotes; however, most mutations appear to inactivate the ATM protein by truncation, large deletions, or annulation of initiation or termination. Missense mutations have been described in breast cancer patients, but do not seem to contribute to ataxia-telangiectasia.

Patients with the severe form of A-T are homozygous or compound heterozygous for null ATM alleles. The corresponding mutations usually lead to truncation of the ATM protein and subsequently to its loss due to instability of the truncated derivatives; a smaller portion of the mutations create amino acid substitutions that abolish ATM's catalytic activity (Taylor AM et al., 2015; Gilad S et al., 1996; Sandoval N et al., 1999; Barone G et al., 2009) (see also [http://chromium.liacs.nl/LOVD2/home.php?select\\_db=ATM](http://chromium.liacs.nl/LOVD2/home.php?select_db=ATM)).

Careful inspection of the neurological symptoms of A-T patients reveals variability in their age of onset and rate of progression among patients with different combinations of null ATM alleles (Taylor AM et al., 2015; Crawford TO et al., 2000; Alterman N et al., 2007). Thus, despite the identical outcome in terms of ATM function, additional genes may affect the most cardinal symptom of A-T. Other, milder types of ATM mutations further extend this variability, and account for forms of the

disease with extremely variable severity and age of onset of symptoms.

The corresponding ATM genotypes are combinations of hypomorphic alleles or combinations of null and hypomorphic ones. Many of the latter are leaky splicing mutations and others are missense mutations, eventually yielding low amounts of active ATM (Taylor AM et al., 2015; Alterman N et al., 2007; Soresina A et al., 2008; Verhagen MM et al., 2009; Silvestri G et al., 2010; Saunders-Pullman R et al., 2012; Verhagen MM et al., 2012; Worth PF et al., 2013; Claes K et al., 2013; Méneret A et al., 2014; Nakamura K et al., 2014; Gilad S et al., 1998).

## **To be noted**

Heterozygote cancer risk: the relative risk of breast cancer in A-T heterozygote women has been estimated through epidemiological studies to be 3.9 (CI 2.1-7.1), and through haplotype analysis to be 3.32 (CI 1.75-6.38); since the A-T heterozygote frequency is about 1 %, 2-4 % of breast cancer cases may be due to ATM heterozygosity; the risk of other types of cancer in A-T heterozygotes is low.

The A-T variant Nijmegen breakage syndrome does not involve the same gene, but, instead, NBN or RAD50, involved in the MRE11/RAD50/NBN double-strand break repair complex.

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