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# MRE11A Gene Mutations Responsible for the Rare Ataxia Telangiectasia-Like Disorder

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## 1. Introduction

Ataxia telangiectasia like disorder (ATLD) is a rare variant of ataxia telangiectasia (A-T) that share a number of clinical features and similar cellular characteristics with the hallmark of increased sensitivity to ionizing radiation (Taylor et al., 1975; Taylor, 2001; Tauchi et al., 2002). These conditions are typically diagnosed at young age at about the time the affected children start to walk. A-T and ATLD patients develop progressive cerebellar ataxia which is required for their clinical diagnosis. Although classified as another variant of A-T, Nijmegen breakage syndrome (NBS) is characterized by microcephaly and growth retardation without ataxia. The other major clinical characteristics are variable and include dilated blood vessels (telangiectasia) usually in the eyes, immunodeficiency, high level of spontaneously occurring chromosome abnormalities, and predisposition to cancer particularly lymphoreticular malignancies. Genetically, the A-T is caused by biallelic inactivating mutations in the ATM gene at 11q22-23, the NBS is caused by mutation in the NBS1 gene mapped at 8q21, and the ATLD is caused by mutation in the MRE11A gene located at 11q21.

Therefore, a disorder virtually indistinguishable from A-T is caused by mutation in the MRE11A gene. In view of the fact that the ATM and the MRE11A loci are situated nearby (11q22-23 and 11q21) only a very detailed linkage analysis would have historically separated ATLD from A-T on the basis of genetic data. Assuming that the mutation rate is proportional to the length of the coding sequence of the two genes, about 6% of A-T cases might be expected to have MRE11A mutations (Stewart et al., 1999). Thus, ATLD patients were first recognized as a subset of A-T who does not have mutations in the ATM gene. Hence, Stewart *et al.* had designated this syndrome as ataxia-telangiectasia-like disorder (Stewart et al., 1999). The clinical features are very similar to those of A-T; with the clearest similarity being the progressive cerebellar ataxia. In contrast to A-T, however, ATLD patients show no telangiectasia (Hernandez et al., 1993; Klein et al., 1996). In addition, the patients show later onset of the neurological features, and slower progression of the disorder giving the overall appearance of a milder A-T condition in early years.

The function of Mre11 protein is linked to Nbs1 and both are members of the Mre11/Rad50/Nbs1 (MRN) complex involved in different DNA healing mechanisms due to innate processes or in responses to damage induced by ionizing radiation and radiomimetic chemicals (Carney et al., 1998; Petrini, 2000), including complexing with chromatin and

with other damage response proteins, formation of radiation-induced foci, and the induction of cell cycle checkpoints (Figure 1). The MRN complex is among the earliest respondents to DNA damage and acts as sensor of DNA double-strand breaks (DSBs). Upon exposure to ionizing radiation the complex along with ATM becomes rapidly activated and associate with the DNA DSBs (Figure 2). This association holds broken DNA ends until the damage is repaired (Nelms et al., 1998). Loss of functional Nbs1 protein in NBS patients prevents the formation of the radiation-induced Mre11/Rad50 nuclear foci (Carney et al., 1998). In comparison, the loss of function of ATM protein in A-T patients causes abnormal reduction in the formation of MRN foci that is less severe than in NBS cells (Maser et al., 1997). Thus, the function of MRN proteins complex is biochemically linked to ATM, which is a critical component of the cellular response to DNA damage. Since Nbs1 and ATM deficiencies abrogate specific DNA damage-dependent cell cycle checkpoints, the association of MRN complex with DSBs suggests that the DNA damage recognition functions of the complex are linked to the signal transduction pathways required to activate ATM-dependent cell cycle checkpoints. These observations strengthen the molecular connection between DSB recognition by MRN protein complex and the ability of the cell to activate the DNA damage response pathway controlled by ATM.

## 2. Clinical manifestations of ATLD

ATLD is rare with, at present, only 25 published cases, four in the UK (2 of them from Pakistani origin), two in Italy, 15 in Saudi Arabia and four in Japan (Stewart et al., 1999; Pitts et al., 2001; A.M. Taylor et al., 2004; Fernet et al., 2005; Uchisaka et al., 2009; Bohlega et al., 2011; Matsumoto et al., 2011). The 4 British patients belonged to 2 unrelated families. Although none of the affected individuals from either family exhibited ocular telangiectasia, they presented with many clinical features consistent with the diagnosis of A-T, especially progressive cerebellar degeneration (Stewart et al., 1999). The 2 affected Italian patients were born to non-consanguineous parents. They had both normal psychomotor development until the age of 3 - 6 years when they developed progressive unsteadiness, showed diffuse cerebellar signs, i.e. ataxic gait, delayed speech and writing difficulties, choreoathetoid arm movements and oculomotor apraxia (Delia et al., 2004). The disease progressed slowly till the age of 14 and then stabilized. The latest neurological examination of the elder patient at 36 years of age showed cerebellar dysarthria, oculomotor apraxia, ataxic gait with unaided walk for few steps, choreoathetosis of the superior limbs, jerk nystagmus on horizontal and vertical gaze, dysmetria, dyskinetic movements of mouth and slight dystonia of the hands, diffuse hypotonia, reduced tendon reflexes in the arms, and absent ankle jerks with flexor plantar responses.

The 15 Saudi patients represent the largest set of ATLDs identified to date. Consanguinity is a major feature in all these families with affected children with parents were mostly first cousins. Patients were initially presented with clinical features that fall within the Ataxia Oculomotor Apraxia spectrum and exhibited a combination of early-onset, slowly progressive, ataxia plus ocular apraxia. Age at onset is almost similar to that of AT, but disease progression is slower with the absence of telangiectasia. Pedigrees and further details on these families were described previously (Fernet et al., 2005; Bohlega et al., 2011). Clinical features include progressive ataxia that was noted as early as two years old in some patients. Oculomotor apraxia was variable among the affected individuals with very slow saccadic eye movement and impaired vertical and or horizontal pursuit eye movement with

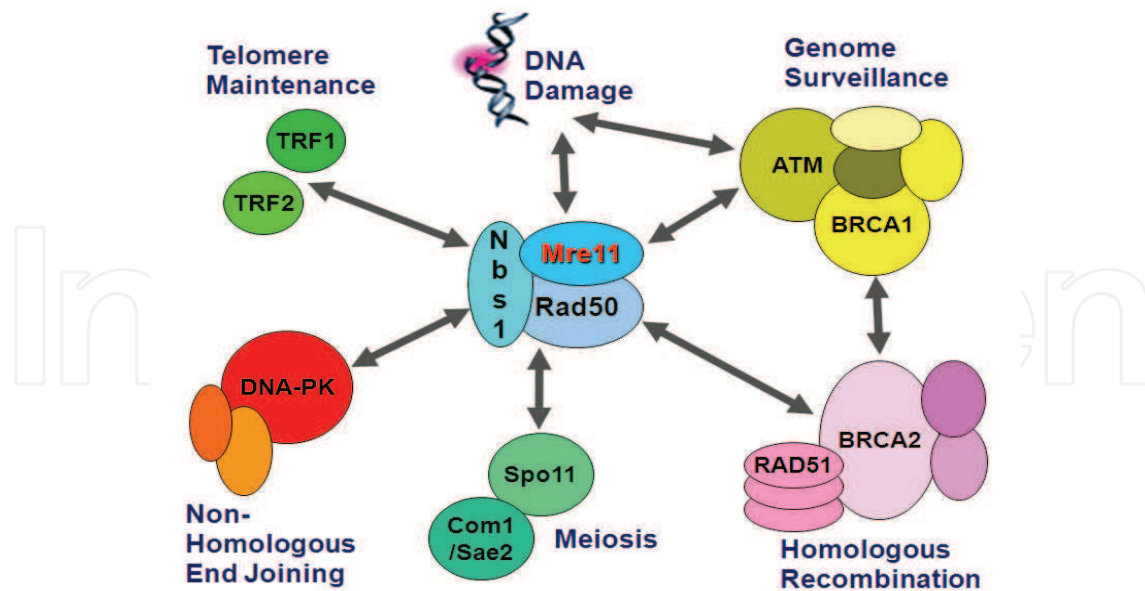


Fig. 1. Role of the Mre11 protein in the cellular response and DNA repair machinery showing the major interacting molecules (Adapted from: [www.lmb.uni-muenchen.de/hopfner/research.html](http://www.lmb.uni-muenchen.de/hopfner/research.html) with modification).

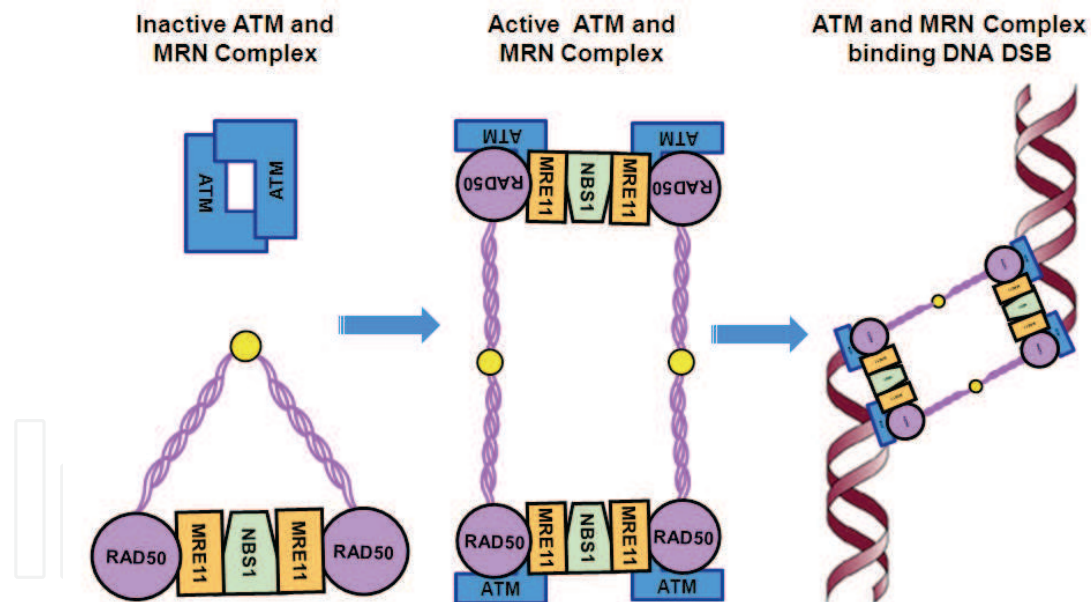


Fig. 2. Representation of the ATM and the Mre11/Rad50/Nbs1 (MRN) complex interacting with a DNA double strand break (DSB). The Mre11 exonuclease directly binds Nbs1, Rad50 and DNA to bridge DSBs and facilitate DNA end processing. The C-terminal of the ataxia telangiectasia mutated (ATM) kinase contributing to MRN regulatory roles in DSB sensing, stabilization, signaling, and effector scaffolding. MRN has 3 coupled critical functions: (1) prompt establishment of protein--nucleic acid tethering scaffolds for the recognition and stabilization of DSBs; (2) initiation of DSB sensing, cell-cycle checkpoint signaling cascades via the ATM kinase; and (3) functional regulation of chromatin remodeling in the vicinity of a DSB (Williams et al., 2007).

head thrusts. Vibration senses were decreased distally and tendon reflexes were absent. Although few patients had no cognitive impairment, others presented cognitive and behavioral problem with forgetfulness, lack of attention, word finding difficulty, emotional liability, impulsivity and disinhibition with fragmented and reversed sleep patterns. Dysarthria in addition to dystonic and choreatic movement were frequently noted. The disease was relentlessly progressive and some patients became wheelchair-bound around age of 18 years. Intra-familial variability was noticeable with some patients were more severely affected. The clinical observations on this set of patients, together with those from previously reported cases, establish that ATLD is not associated with recurrent pulmonary infections due to immune deficiency. However, some patients presented with certain differences with the previously reported ATLD patients, namely the presence of microcephaly in at least four patients, the latter feature being reminiscent of the clinical presentation of NBS. Whether these differences are specific to the W210C mutation found in Saudi patients or only reflect the wide spectrum of the disease needs further investigation.

The 4 Japanese patients were born to non-consanguineous parents. Two sibling patients were born after healthy pregnancies and deliveries. They had characteristic clinical features of short stature, pointy nose, small jaw, atrophy of the lower legs, and equinus foot deformities (Uchisaka et al., 2009). They had cerebellar ataxia, slurred and explosive speech, and ocular apraxia, but did not show any evidence of involuntary movement such as dystonia or dyskinesia. The patients started to speak at 2 years old where ataxic gait was noted. The cerebellar ataxia with atrophy of the cerebellum and mental retardation had progressed and was more severe in the elder patient who became wheelchair bound at 6 years of age. There was no history of serious infection or evidence of skin or conjunctival telangiectasia. When they were 15 and 9 years old, both patients were diagnosed with nonsmall-cell lung cancer with multiple bone metastases. One Japanese patient was born at 37 weeks of gestation after unremarkable pregnancy. However, the patient showed developmental retardation where he could sit alone but could not stand or walk (Matsumoto et al., 2011). At age 13 years, the patient had severe microcephaly, a bird-like face with sloping forehead, a big nose, large and simple ears, short palpebral fissures, a small mouth, and a small and receding chin with decreased range of motion in shoulders, elbows, hips, and knees. Also noted were scoliosis, subluxation of the left elbow joint, bilateral cryptorchidism, and bilateral talipes equinus. His tendon reflexes were slightly exaggerated. At age 33, the patient does not speak meaningful words, but recognizes people, communicates by gesture, shows fondness by touching, does not show ocular apraxia and had neither malignancy nor severe infections. The 4<sup>th</sup> Japanese patient had intrauterine growth retardation with a small femora and a disproportionately small head (Matsumoto et al., 2011). After caesarian section delivery the patient had severe microcephaly, a bird-headed facial appearance with receding forehead, and a prominent nose. Anterior fontanel was not palpable. He stood holding onto a chair at age 30 months, sat alone and walked at age 3 years. He had no severe or recurrent infections. Now aged 8 years, he is toilet trained, speaks several meaningful words but sentence. He attends a primary school, and is affable and friendly. He is farsighted with astigmatism. He is able to run with a slow pitch and kick a soccer ball. He shows neither ocular apraxia nor cerebellar ataxia.

### 3. MRE11A gene mutations

The 25 genetically confirmed ATLD patients (4 in the UK, 2 in Italy, 4 in Japan and 15 in Saudi Arabia) were either homozygous or compound heterozygous for 10 different



mutations (Figure 3). The four British patients were related to two independent families. The two patients of the 1<sup>st</sup> family were homozygous for a C-to-T transition at nucleotide 1897 (c.1897C>T). This change, CGA>TGA, resulted in an in frame 633R > stop codon, prematurely truncating the Mre11 protein. The two patients of the 2<sup>nd</sup> family were compound heterozygous for two mutations, an A>G missense mutation at nucleotide 350 (c.350A>G), resulting in a Asn to Ser amino acid change at residue 117 (N117S) and C-to-T transition at nucleotide 1714 (c.1714C>T) resulting in a stop codon (572R> stop) (A.M. Taylor et al., 2004). This mutation is predicted to encode a prematurely truncated protein of 65 kDa that was not detected suggesting that this mutation destabilizes the transcript by nonsense-mediated decay (NMD) surveillance mechanism which eliminates the errors in the biogenesis of mRNA (Frischmeyer et al., 2002; Nicholson et al., 2010). The two Italian sibling patients were compound heterozygous for two mutations, a missense mutation at position 1422 (c.1422C>A) resulting in Thr to Lys amino acid change at residue 481 (T481K) and the already known single C>T base change in exon 15, corresponding to nucleotide 1714 in the cDNA sequence (c.1714C>T), which introduces a premature stop codon (Delia et al., 2004). The four Japanese patients belonged to 3 unrelated families. In two brothers with ATLD with lung cancer, genetic studies had looked at alteration in the 20 exons and the flanking intronic sequences of the MRE11A gene. This revealed a T>C substitution in exon 8 at position 727 (c.727T>C) and a G>C base substitution at nucleotide 24994 situated in intron 10 (g.24994G>A; Figure 3), 5bp downstream from exon 10 (Uchisaka et al., 2009). RT-PCR showed the presence of two products. Sequencing of these cDNA products confirmed the T>C base substitution at nucleotide 727 in exon 8 in 1 of the alleles and uncovered an 81 bp deletion in exon 10 on another allele. The alteration of these DNA sequences predicted a Trp to Arg amino acid substitution at residue 243 (W243R) and the loss of 27 amino acids, respectively. The base substitution in intron 10 might have given rise to an alternative splicing of MRE11A, leading to an in frame 81 bp deletion in exon 10. Thus, the two Japanese sibling patients were compound heterozygous for two novel MRE11A gene mutations that have not been reported before, one in exon 8 (c.727 T>C) and one in intron 10 (g.24994 G>A).

The two other unrelated Japanese patients were presented with NBS-like severe microcephaly, bird-like faces, growth and mental retardation remnant of Nijmegen breakage syndrome (NBS). However, genetic studies revealed no mutation in the NBN gene responsible for NBS. Therefore, the MRE11A gene was sequenced in both patients and found to be compound heterozygous for three different types of mutations: an A-to-C transversion in nucleotide 658 (c.658A>C), a G-to-A transition in nucleotide 16513 (g.16513; i.e. c.659+1G>A) and an A-to-G transition in position 338 (c.338A>G). Patient-1 had c.658A>C substitution plus a g.16513 splicing mutation, and patient-2 had c.658A>C and c.338A>G substitutions. Sequencing analysis demonstrated that g.16513G>A resulted in exon 7 skipping leading to a premature termination codon (p.Ser183ValfsX31). The c.658A>C substitution located within exon 7 did not alter amino acids but affected splicing efficiency that contributed to exon 7 skipping. The c.338A>G situated in exon 5 lead to a missense mutation with an amino acid substitution of Asp to Gly at residue 113 (D113G) located within the highly conserved phosphoesterase domain, which is essential for endonuclease activity. The c.658A>C substitution common to both patients and the c.338A>G substitution resulted in a reduced level of normally functioning Mre11 protein.

The 15 Saudi Arabian patients were related to 5 independent families and represent the largest ATLD cohort (Fernet et al., 2005; Khan et al., 2008; Bohlega et al., 2011). Genetic

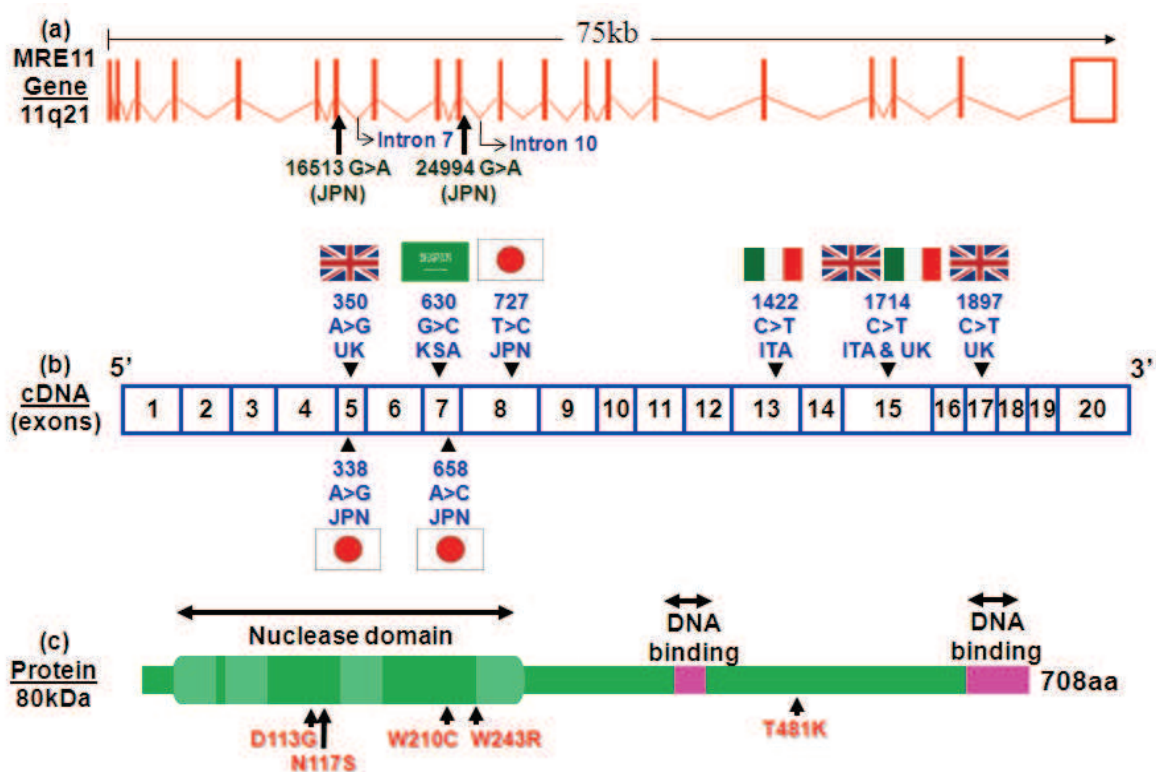


Fig. 3. Representation of the human (a) MRE11A gene, (b) cDNA and (c) protein. Location of the exonic (cDNA) and intronic mutations causing the 25 confirmed cases of ATLD from United Kingdom (UK), Italy (ITA), Japan (JPN) and the Kingdom of Saudi Arabia (KSA), are indicated. Only mutations detectable in a full-length Mre11 protein are indicated at the protein level. (Assembled from *www.ensembl.org* and Taylor et al., 2004 with substantial modifications and update).

studies have identified in all patients the same G to C transversion at position 630 (c.630G>C) located in exon 7, which results in the missense change of Trp to Cys (W210C). No other nucleotide change was identified in the coding sequences or flanking intronic sequences of MRE11A. Tryptophan at position 210 is a highly conserved residue in the Mre11 protein, being invariable from yeast to mammals and its replacement by the small polar residue cysteine is likely to affect the structure or function of the protein. In addition, this residue lies between motifs III and IV of the N-terminal nuclease domain of the Mre11 protein, a region where another missense mutation (N117S) had been identified in ATLD patients (Figure 3). Thus, all patients were homozygous for a novel missense mutation (c.630 G>C) of the MRE11A gene that seems to be specific to Saudi Arabia. The resulting amino acid change (W210C) does not seem to affect the level of Mre11 protein expression but results in an inability of the mutant Mre11 protein to interact with Nbs1 protein leading to destabilization of the MRN complex and the loss of its normal function.

#### 4. Frequency of MRE11A gene mutations

While the frequency of the different mutations in the MRE11A gene is unknown, the high number of Saudi ATLD patients with the 630 G>C particular mutation would suggest noticeable frequency of heterozygous carriers in the Arabic peninsula. This may have

impact on premarital and preimplantation screening to limit genetic diseases and to provide informed genetic counseling. Therefore, a study was initiated to assess the allelic frequency of this mutation (Alsbeih et al., 2008). Currently, a cohort of 528 phenotypically normal individuals was included in the study. There were 146 females and 382 males. The methodological procedures to detect the G to C missense mutation at nucleotide 630 of the MRE11A gene and the PCR primers used were described previously (Alsbeih et al., 2008). Briefly, genomic DNA was extracted from 3-5 ml peripheral whole blood or cultured skin fibroblasts, using Puregene DNA Purification Kit (Gentra System, Minneapolis, MN). Relevant segments of DNA were amplified by thermal cycling (95 °C for 15 min, 39 rounds of 95 °C for 1 min, 55 °C for 1 min and 72 °C for 1 min and final extension at 72 °C for 7 min) using HotStarTaq DNA polymerase (Qiagen, Venlo, Netherlands), and 50 ng template DNA in 25 microliter volume with standard reaction conditions. The quality of the PCR product was checked by running 5 microliter of the reaction in 1% agarose gel. The amplified fragment was directly sequenced using the DYEnamic ET Dye Terminator Cycle Sequencing Kit (Amersham Biosciences, Piscataway, NJ) according to the manufacturer's instruction, and were run on the MegaBase 1000 sequencer (Applied Biosystems, Fostercity, CA). Sequencing results were aligned to the corresponding reference sequence and the missense mutation was genotyped using SeqManII sequence analysis software (DNASTAR Inc., Madison, WI). Out of the 528 individuals, only two were heterozygous (G630C) for the missense mutation, while the remaining 526 were all wild-type. The genotype and allelic distributions of the missense mutation in the MRE11A are listed in Table 1. This gives a frequency of 99.6 for the G/G wild-type and 0.4% for the heterozygous G/C. In addition, one individual was heterozygous for a new SNP in intron 6, position 18026 (*Ensembl* annotation), 131 nucleotides upstream of the G630C mutation (Alsbeih et al., 2008).

Genotype and allele	Individuals <i>n</i>	Frequencies (%)
MRE11A g.18157 mutation G>C		
G/G	526	99.6
G/C	2	0.4
C/C	0	0
G	1054	99.8
C	2	0.2

Table 1. Genotype and allele frequencies of the MRE11A 630G>C (g.18157, p.210 Trp>Cys) missense mutation in 528 Saudi individuals. Sequence reported on the negative strand as per the gene direction.

The presence of two heterozygous individuals indicates the existence of this rare mutation in the population with an estimated heterozygous genotype G/C of 0.4% and estimated mutant C allele frequency of 0.2%. Therefore, the diagnosis of MRE11A ATLD should be in the mind of physicians whenever they encounter an A-T like disorder and genetic study should be carried out to confirm the diagnosis. This is how the 5 patients reported by Bohlega and colleagues were diagnosed (Bohlega et al., 2011). The fact that the 10 previously described Saudi ATLD patients (Fernet et al., 2005) are from the central region of Saudi Arabia could suggest higher frequency of this mutation in geographically isolated families



with high level of consanguineous marriages. However, larger studies with members from different regions are required to precisely estimate the exact frequency of this mutation in Saudi Arabia.

## 5. ATLD and other ataxia causing disorders

Ataxia occurs when parts of the nervous system that control movement are damaged. Most disorders that result in ataxia cause cells in the cerebellum, and sometimes in the spine or even the peripheral nervous systems, to degenerate or atrophy. Cerebellar and spinocerebellar degeneration have many different causes. Genetic causes form a heterogeneous group with different pattern of inheritance and onset of the symptoms. Currently this group encompasses the following distinct conditions: ataxia telangiectasia (A-T), ataxia telangiectasia-like disorder (ATLD), ataxia oculomotor apraxias (AOA), and the two "A-T variants", Nijmegen breakage syndrome (NBS) with microcephaly but without ataxia, and A-T (Fresno) that combines features of both NBS and A-T. This is in addition to other hereditary ataxia such as Friedreich ataxia (FA) and Machado-Joseph Disease (MJD) caused by triplet repeat expansion, spastic ataxia of the Charlevoix-Saguenay, Autosomal recessive ataxia associated with isolated vitamin E deficiency, Infantile onset spinocerebellar ataxia, ataxia with hearing loss and optic atrophy, spinocerebellar ataxia with axonal neuropathy, Cayman ataxia, cerebellar ataxia with mental retardation optic atrophy and skin abnormalities, Salla syndrome, Marinesco-Sjögren and the childhood spinocerebellar ataxia (Bouhhal et al., 2005). Table 2 summarizes some of the genetic disorders grouped under hereditary ataxias and its variants of relevance to ATLD.

Disorder	Acronym	Inheritance	Chromosomal location	Protein affected	Reference
Ataxia telangiectasia	A-T	Recessive	11q22-23	ATM	(Savitsky et al., 1995)
Ataxia telangiectasia-like disorder	ATLD	Recessive	11q21	Mre11	(Stewart et al., 1999)
Ataxia oculomotor apraxia 1	AOA1	Recessive	9p13	Aprataxin	(Date et al., 2001)
Ataxia oculomotor apraxia 2	AOA2	Recessive	9q34	Senataxin	(Moreira et al., 2004)
Nijmegen breakage syndrome	NBS	Recessive	8q21	Nbs1 (nibrin)	(Varon et al., 1998)
Ataxia telangiectasia Fresno*	A-T Fresno	Recessive	11q23	ATM	(Gilad et al., 1998)
Friedreich ataxia	FRDA	Recessive	9q13-q21	Frataxin	(Campuzano et al., 1996)
Machado-Joseph Disease	MJD	Dominant	14q32	Ataxin-3	(Kawaguchi et al., 1994)

\* A-T Fresno combines features of A-T and NBS with mutation in ATM.

Table 2. Genetic disorders grouped under hereditary ataxias and its variants

Diagnosis is usually suggested by the clinical manifestations. Non-specific complementary tests may be done to differentiate between them or to exclude other disorders or conditions that may cause ataxia. The molecular characterization of these different disorders allows genetic tests to confirm a clinically suggested diagnosis. In general, there are no specific treatments available for most of the inherited ataxia disorders. Symptoms are treated with physical and occupational therapy, assistive devices, and medication for muscle pain or spasms that may occur. Genetic counseling provides education to parents of individuals with an inherited ataxia disorder to be aware that they may pass the disorder on to their children. Some affected families may choose to test members to see if they have inherited the gene responsible for the disorder.

## 6. Conclusions

Hereditary ataxias are a heterogeneous group of cerebellar degeneration causing failure of muscle control, resulting in a lack of coordination, imbalance and ataxic gait. ATLD is a rare variant of A-T with only 25 confirmed cases worldwide, 4 in the UK, 2 in Italy, 4 in Japan and 15 in Saudi Arabia. The patients were either homozygous or compound heterozygous for 10 different hypomorphic mutations in exons and splice sites. The 15 Saudi Arabian patients were related to 5 independent families and represent the largest ATLD cohort which would suggest the presence of a noticeable frequency of heterozygous carriers of MRE11A gene mutation in the population. Therefore, the diagnosis of ATLD should be in the mind of physicians whenever they encounter an A-T like disorder and genetic study should be carried out to confirm the diagnosis. Testing for MRE11A gene mutations could ultimately be incorporated to premarital, pre-implementation or prenatal screening to reduce the risk of transmission of genetic diseases.

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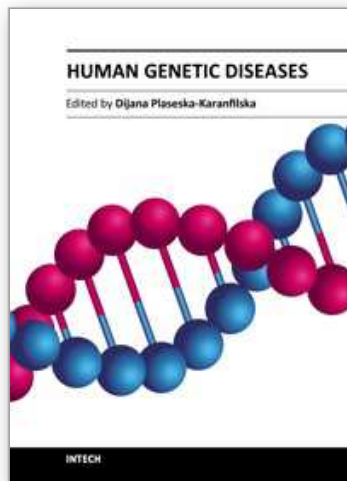


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## Human Genetic Diseases

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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the “genetic approach” to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

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