The spectrum of *ATM* gene mutations in Iranian patients with ataxia-telangiectasia

Parisa Amirifar[1,2], Mohammad Reza Ranjouri[2], Salar Pashangzadeh[2], Martin Lavin[3], Reza Yazdani[2], Tannaz Moeini Shad[2,4], Mahya Mehrmohamadi[5], Fereshte Salami[2], Samaneh Delavari[2], Soraya Moamer[6], Asghar Aghamohammadi[2], Seyed Mohammad Akrami[1*], Hassan Abolhassani[2,7*]

1 Department of Medical Genetics, School of Medicine, Tehran University of medical sciences, Tehran, Iran

2 Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

3 University of Queensland Centre for Clinical Research (UQCCR), University of Queensland, Herston, Brisbane, QLD, Australia

4 Department of Immunology, Semnan University of Medical Sciences, Semnan, Iran.

5 Department of Biotechnology, College of Science, University of Tehran, Tehran, Iran

6 School of Public Health, Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran

7 Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

*** Corresponding author:** Seyed Mohammad Akrami, MD, PhD.
Address: Medical Genetics Department, Poursina St., Tehran University of Medical Sciences, Tehran 14176-13151, Iran
Tel: + 98 21 88953005
Fax: + 98 21 88953005
Email: akramism@tums.ac.ir

*** Corresponding author:** Hassan Abolhassani, MD, MPH, PhD.
Address: Department of Laboratory Medicine, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden
Tel: +46-(0)8-524 835 90
Email: hassan.abolhassani@ki.se

Running title: *ATM* mutations and Iranian A-T patients

Word count: 3023

Number of tables: 4

Number of figures: 3

Conflict of interest: The authors declare no conflict of interest.

Funding Information: This research was supported by the Tehran University of Medical Sciences (grant no. 40601).

Abstract

Background: Ataxia-telangiectasia (A-T) is a rare genetic disorder characterized by a distinct range of clinical manifestations, including progressive ataxia, immunodeficiency, and radiosensitivity.

Methods: Clinical data, laboratory results, and genetic data were collected from forty-three A-T patients. Whole exome sequencing and Sanger sequencing were done for the patients clinically diagnosed as suffering from A-T. Based on the phenotype severity of the disease, patients were divided into severe and mild sub-groups.

Results: The median (IQR) age of diagnosis in this cohort was 5 (3-7) years and various types of clinical manifestations, including fever (p= 0.005), lower respiratory tract infection (p= 0.033), diarrhea (p= 0.014), and hepatosplenomegaly (p= 0.032) were significantly higher amongst patients diagnosed with the severe phenotype. Our results showed a strong correlation between phenotype severity and mutation type. The chance of having severe phenotype in patients who have severe mutations, including frameshift and nonsense, was 7.3 times higher compared to patients who were categorized in the mild genotype group (odds ratio= 7.3, p= 0.006). Thirty-four types of mutations including 9 novel mutations, were observed in our study.

Conclusion: Molecular analysis provides the opportunity for accurate diagnosis and timely management in A-T patients with chronic progressive disease, especially infections and the risk of malignancies. This study characterizes for the first time, the broad spectrum of mutations and phenotypes in Iranian A-T patients which are required for carrier detection and reducing the burden of disease in future using the patients' families and for the public health care system.

Keywords: Ataxia-telangiectasia (A-T), ATM, Whole-exome sequencing, Class switching recombination (CSR), phenotype severity.

Key massages

We reported the genetic basis of 43 A-T patients and identified 9 novel homozygous mutations in the ATM gene. This study confirmed the wide spectrum of mutations and phenotypes within A-T patients.

Introduction

Ataxia-telangiectasia (A-T; OMIM #208900) is an autosomal recessive multisystem disorder, characterized by progressive cerebellar degeneration, oculocutaneous telangiectasia, variable immunodeficiency, cancer susceptibility, and radiation sensitivity [1, 2]. In general, individuals with A-T present various clinical, immunological, and laboratory features [3]. Different forms of A-T have been described, since a significant subset of patients manifest severe signs/symptoms and are categorized as early-onset or classic A-T, whereas a minority of cases with mild signs/symptoms are classified as late-onset or mild A-T phenotype [4]. The incidence of this monogenic disorder is estimated to be between 1:40,000 to 1:300,000 depending on the degree of consanguinity rate in populations [5].

A-T is caused by mutations in the ataxia telangiectasia mutated (*ATM*) gene localized to chromosomal region 11q22.3-23.1. This gene contains 66 exons (with 62 coding exons) spread over 150 kb of genomic DNA, and has an open reading frame of 9,168 nucleotides [6]. *ATM* encodes the ATM protein, which is a large serine/threonine-protein kinase (~350 KDa) involved in DNA double-strand break (DBS) repair, maintaining genomic stability, cell cycle control, and cell survival [7]. Moreover, ATM function is important to B and T cell receptor development as well as class switching recombination (CSR) in activated B cells [8]. The most common type of *ATM* mutations in A-T patients are null mutations, leading to a truncation of the ATM protein. Patients with these types of *ATM* mutations usually present with the classic form of A-T [9, 10].

In the present study, we performed whole-exome sequencing on patients with a clinical diagnosis of A-T to identify mutations in the affected gene in patients. In addition to identifying mutations in *ATM*, we classified A-T patients based on phenotype severity to evaluate the clinical manifestations and laboratory data in different genotype groups of these patients.

Material and Methods

Patients

This study was performed on all available A-T patients recruited by the Research Center for Immunodeficiencies (RCID) and submitted to the Iranian national registry for primary immunodeficiencies (PIDs) [11] during the period 2018-2020. According to the updated diagnostic criteria of the European Society for Immunodeficiencies (ESID) [12], the presence of ataxia, telangiectasia, and an elevated level of alpha-fetoprotein (AFP) were considered as inclusion criteria. A questionnaire was designed which collected patients' demographical data, family history, consanguinity, clinical manifestations, and laboratory findings. Based on the disease severity, patients were divided into two different groups, (i) a severe group: patients who were diagnosed with the severe form of the disease, including different hospitalization visits due to recurrent infections and other non-infectious complications; (ii) a mild group: patients who experienced only mild forms of infections and were treated as out-patients for the entire course of the disease. Also, based on mutation severity, patients were divided into two groups those with null mutations or non-null mutations and were examined for demographic, clinical and laboratory characteristics. Written informed consent was obtained from all participants. The present study was confirmed by the ethics committee of Tehran University of Medical Sciences (No. 1398042).

Whole-exome sequencing

Peripheral blood was obtained from all patients, and DNA was extracted using the salting-out method, as described previously [13]. The coding and flanking intronic regions were enriched using the Twist Human Core Exome kit according to standard protocols and were sequenced using the Illumina NovaSeq platform, performed by CeGaT GmbH, Germany. The resulting sequencing reads were mapped to the human reference genome (hg19) using the Burrows-Wheeler Aligner (BWA) [14]. In addition, using SAMtools pileup, variants were called and subsequently annotated using ANNOVAR. For analysis of WES, we followed the protocol described previously for prioritizing candidate variants, predicting their effect on protein, homozygosity mapping, large deletion and copy number variation (CNV) detection [15-18]. Updated guidelines of the American College of the Medical Genetics and Genomics (ACMG) were used for interpretation of molecular sequencing and disease variant evaluation regarding

allele frequencies in the population databases, functional and immunological data, and familial segregation [19].

Statistical analysis

Statistical analysis was performed by SPSS software package, version 24 (SPSS Inc., Chicago, IL, USA). Median and interquartile range (IQR) were calculated and compared for demographical data and laboratory findings of A-T patients using the Mann-Whitney U test. To analyze the categorical variables from the frequency table, the Chi-square test or Fisher's exact test were performed. Logistic regression was used to obtain the odds ratio between phenotype severity and mutation severity. A P-value of less than 0.05 was considered to be statistically significant for all tests.

Result

Clinical data

A total of 43 A-T cases, including 23 females (53.5%) and 20 males (46.5%) with the median (IQR) age of 5.0 (3.0-7.0) years old at the time of diagnosis, were registered in the present study. Thirty-eight (83.87%) of the patients were born in a consanguineous family. The median (IQR) age of ataxia and telangiectasia was 1.5 (1.0-2.2) years and 4.0 (2.0-5.0) years, respectively. The median (IQR) diagnostic delay of the patients was 4.1 (3.6-5.3) years. The major demographic and laboratory findings of the patients with A-T are provided in **Table 1.**

As previously established [20], ataxia-telangiectasia is a rare disease with a broad spectrum of clinical manifestations. Our patients were diagnosed with various clinical presentations, including infections, skin complications, diarrhea, visual impairment, autoimmunity, hepatosplenomegaly, and malignancy. Based on past medical history of all patients, 22 patients were hospitalized and categorized in the severe phenotype group. Ataxia was the most common clinical manifestation, which was reported in all patients. Thirty-five patients (83.3%) experience telangiectasia, which is significantly higher among patients with a severe phenotype (p=0.041). Fever reported in half of the patients was significantly higher in patients with severe phenotype than patients with a mild phenotype (p=0.005). Most patients (n=30) were diagnosed with different types of infections, including otitis media and respiratory tract infection. As expected, lower respiratory tract infection (LRTI) was more common in patients diagnosed with a severe phenotype compared to patients with a mild

phenotype (p=0.033). The detailed clinical manifestations of patients with A-T are summarized in **Table 2**. Moreover, our investigations showed that the incidence rate of diarrhea and hepatosplenomegaly was significantly higher among severe patients (p=0.014) compared to the mild ones (p=0.032), respectively. Immunoglobulin class switch recombination (CSR) defect was observed in 46.5% (n=20) of all patients. Our results also revealed that a defect in the CSR mechanism is significantly higher in patients with a severe phenotype (n=14) than patients with a mild phenotype (n=6, p=0.033) (**Figure 1**). Based on mutation severity, there is no significant difference regarding the phenotype between patients with null mutation and patients with non-null mutation (**Table 2).**

Genetic diagnosis results

Molecular diagnosis was conducted on all the 43 patients who participated in this study. Genetic analysis confirmed the clinical A-T diagnosis for all patients and revealed that 38 out of 43 patients (88.3%) had a homozygous mutation; however, a compound heterozygous mutation was found in five patients (11.6%).

Thirty-four different variants were found in our study, 25 of which have been reported previously in online genetic databases, including (http://www.hgmd.cf.ac.uk, https://asia.ensembl.org). We identified 9 novel *ATM* mutations in our patients (**Figure 3**). Of these nine new variants, six variants (deletion exon1, deletion exons 37-48, c.9097_9101dupAATTT, c.6807+1G>C, c.8741T>A and c.1834C>A) were pathogenic changes, while 3 other variants (c.5003A>G, c.6452G>C, c.1159A>C) were considered as VUS mutations. Taken together, based on the ACMG criteria, 31 of the mutations were pathogenic or likely pathogenic (LP), and 4 of them were classified as VUS mutations (**Figure 2).** The most frequent type of mutation was a nonsense stop-gained mutation, which was observed in 27% of patients. Large deletions and small deletions were also observed in 23% and 13% of patients, respectively. Other types of mutations including missense mutation, small deletion/insertion, splicing, and large duplications were seen in 32% of patients. Altogether, small deletion (13%), small duplication/insertion (9%), large deletion (23%), and large duplication (1%), resulted in frameshift mutations, that were observed in 46% of patients. 73% of patients were identified with nonsense and frameshift mutations, which cause the null deletion mutation. The chance of having severe phenotype in patients who have severe mutations, including frameshift and nonsense, is 7.3 times higher compared to patients who are categorized in the mild phenotype group (OR= 7.3, p= 0.006), that is

statically significant. The detailed genetic analysis results are provided in **Table 3.** Of note, the chance of CSR defect occurrence in patients with severe mutations, including frameshift and nonsense, was 1.3 higher rather than patients with mild mutations; however, the odds ratio (OR) is not significantly different (OR: 1.3, p=0.37).

In this study we found 6 patients with deletion EX62-63 mutations and 5 patients with nonsense c.664C>T mutations. All patients with EX62-63 deletion mutation had a history of recurrent hospitalization due to respiratory tract infections, especially pneumonia. In four patients with the c.664C> T mutation, involvement with recurrent infections including respiratory tract was observed in two patients with skin disorders and in two patients with hepatosplenomegaly. The detailed clinical manifestations of these patients are provided in **Table 4.**

Discussion

A-T is an autosomal recessive disorder with multisystem involvement caused by homozygous or compound heterozygous mutations in the *ATM* gene [21, 22]. To date, more than 600 different mutations have been reported for A-T (www.hgmd.cf.ac.uk), including missense, nonsense, splicing, small indels, large deletions, and duplications in the 62 coding exons of the *ATM* gene [23]. Based on the human gene mutation database or HGMD (www.hgmd.cf.ac.uk), the common type of *ATM* mutations in A-T patients are small deletion (26%), nonsense (19%), missense (18%), and splicing (16%) mutations [24]. In the present study, we report the most common types of ATM mutation in Iranian population. These mutations include nonsense 27%, large deletion 23%, missense 18%, and small deletion 13%. Based on these findings, the frequency of missense mutations in our population is consistent with HGMD reports, whereas the frequency of large deletion mutations in our cohort is significantly higher than in HGMD. In general, the most common type of ATM mutation in A-T patients are null mutations (66% in HGMD vs. 73% in our study) that cause a truncation of the ATM protein.

Identifying mutations using conventional methods in A-T patients is challenging due to the large size of the *ATM* gene without apparent hotspots. Next-generation sequencing [25] technology is an accurate and cost-effective diagnostic method for A-T [26]. Here, we investigated the molecular basis of disease in 43 unrelated A-T patients with different clinical

and immunological features from different regions of Iran for the first time. In general, thirty-four different mutations were found in our study, of which nine variants had not previously been reported. Furthermore, our results demonstrated that there is a significant correlation between phenotype severity and mutation severity. Generally, our findings showed that patients carrying null *ATM* mutations suffer a more severe phenotype than those with missense or splice-site mutations. T

Gait abnormality and telangiectasia are the major diagnostic criteria of A-T patients, appearing at an early age. In our study, all the A-T patients were suffering from gait abnormality, and 83.3% of them had appearance of telangiectasia. Furthermore, the evaluation of serum AFP concentration is another diagnostic marker, as it is increased in approximately 95% of patients with A-T [27]. In this study, all patients at the time of initial diagnosis had high AFP concentrations. The most common manifestation of immunodeficiency in A-T is pulmonary infections that are often progressed by increasing age and neurological deterioration [28, 29]. Based on the findings of this study, it can be concluded that more than 70% of A-T patients suffer from recurrent infections, especially respiratory tract infections. The other types of non-infectious complications such as malignancy and visual impairment have rarely occurred in our patients. Generally, A-T as a monogenic disorder has phenotypic heterogeneity, and the severity of manifestations varies in different patients, even between patients within the same family, which point to the influence of genetic and environmental modifying factors in this disease.

According to serum immunoglobulin (Ig) level profile, A-T patients can be categorized into various groups, including normal Ig levels, IgA deficiency, IgG subclass deficiency, hypogammaglobulinemia, and hyper IgM (HIgM) phenotypes [30]. Some A-T patients exhibit a HIgM-like phenotype along with the complete Ig CSR defect. In these particular patients, low class-switched Igs such as IgG, IgA, and IgE occur, but a normal or elevated level of IgM and/or IgD are observed [3, 31]. A-T patients with CSR defects have been reported with a more serious disease course, leading to poor quality of life in earlier ages and shorter survival [30, 32-35]. Evidently, the most frequent manifestation of immunodeficiency in this group of A-T patients is respiratory infections that can frequently occur in the first years of life [28, 29]. The results of this study showed that patients in the severe group had a significantly higher incidence rate of the CSR defect than the mild group. It seems that this immunological defect can also significantly impact the aggravation of clinical symptoms,

shorter survival and reduced quality of life in earlier ages in these patients. In addition, it seems that the severe form of the disease may frequently occur in A-T patients with HIgM-like phenotype. Therefore, it is recommended that these patients be monitored accurately and receive more precise therapy.

In our cohort, nine novel homozygous *ATM* variants (c.6452G>C in AT-9, Deletion exon 37-48 in AT-10, Deletion exon 1 in AT-13, c.9097_9101dupAATTT in AT-19, and c.5003A>G in AT-28, c.1159A>C in AT-32, c.6807+1G>C in AT-35, c.8741T>A in AT-40 and c.1834C>A in AT-41) were identified using WES. Based on the criteria of the ACMG, c.6452G>C, c.5003A>G, and c.1159A>C were considered as VUS mutations. c.6452G>C homozygous missense has occurred at the last nucleotide of exon 44, hence it may affect the splicing process. Moreover, the prediction of computational tools such as MutationTaster, CADD, and Polyphen support the deleterious effect of the variant on the gene or gene product. c.5003A>G and c.1159A>C homozygous missense has occurred at exon 33 and 9, respectively, and prediction tools such as MutationTaster, MutationAssessor, DANN, FATHMM-MKL, M-CAP, MVP, and Polyphen confirm the deleterious effect of the variant on the gene or gene product. In our population, we also found c.7308-6T>G homozygous splicing region variant as another VUS, which has been reported in HGMD as pathogenic in an 8-year-old Iranian patient with A-T. However, multiple lines of *in silico* analyses such as MutationTaster and CADD suggest no impact of the variant on the *ATM* gene or gene product. According to the human gene mutation database or HGMD (www.hgmd.cf.ac.uk), the most common type of *ATM* mutations is frameshift and nonsense variant constituting about 70% of A-T cases. As a result, the majority types of *ATM* variants comprise null mutations that lead to a truncation of the ATM protein. Individuals with these types of *ATM* mutations present A-T classical phenotype as its most common form [9, 10]. The classic form of A-T manifest early-onset, severe, multisystem, and progressive disease [4]. Furthermore, missense, in-frame, or leaky splice-site mutations, which lead to some residual ATM kinase activity, result in milder neurological problems, absence of immunodeficiency and longer survival but with higher risk for development of malignancy [9, 10].

In this study, all our patients had the classical type of A-T, but exhibited highly variable clinical symptoms. Hence, we divided the patients into severe and mild phenotypic groups. We observed that patients in the severe group were significantly diagnosed with null mutations, which confirms the effect of ATM genotype on the intensity of the resulting

clinical phenotype. According to our results, the frequency of telangiectasia, fever, lung infection, diarrhea, and hepatosplenomegaly in patients of the severe group was significantly higher than the mild group. Immunologically, in patients of the severe group, IgG level was significantly lower than in the mild group. Also, in this study, we had patients with similar mutations (6 patients with EX62-63 deletion and 5 patients with c.6658C> T). Based on a comparison of their clinical signs, large deletion in the end exons of the ATM gene appears to be significantly associated with severe infection, especially of the lower respiratory tract, but not with skin, organomegaly, and autoimmune disorders. In terms of immunological profile, 66.6% of patients had CSR deficiency. It also appears that patients with the nonsense mutation c.6658C> T are prone to infection (80%), skin disorders (40%) and organomegaly (40%). Also, significantly all patients with this mutation had immunological defects (60% had CSR-D and 40% had IgA-D).

In our study population, the most frequent type of *ATM* mutation was a nonsense and frameshift mutation (in 73% of patients), which is in accordance with previously reported studies [36]. A Chinese cohort reported that 33.33% and 41.66% of *ATM* mutations were missense and frameshift, respectively [37]. In addition, frameshift and missense were the most common types of mutations in the Spanish population [38]. Although Cavalieri et al. [39] reported that 2% of all *ATM* mutations were related to large genomic deletions (LGD) in an Italian cohort, this type of mutation was higher (25% of all *ATM* mutations) in the Japanese population [40]. In our study, 17% of *ATM* mutations were considered as LGD.

Different founder mutations have been identified in various nations, including Norwegian, Costa Rican, Italian, Polish, and Amish/Mennonite [41]. Haplotype analysis in 11 Norwegian families revealed that the similarity of 55% of *ATM* variants with the same haplotype is an affirmation of the founder effect [42]. In contrast, no founder variants were reported in a Chinese study population, which may be related to population diversity [37]. Due to the high rate of consanguinous marriages in Iran [43], founder effects are expected to exist; nevertheless, we did not observe any founder effects in the current cohort even within specific geographical location (data not shown).

Conclusions

We characterized the genetic basis of 43 classical cases of A-T disease and identified 9 novel homozygous mutations in the *ATM* gene. This study confirmed the wide spectrum of

mutations and phenotypes within A-T patients. Early molecular diagnosis of disease provides the opportunity for timely management of symptoms, especially infections and risk of malignancies. Furthermore, molecular diagnosis facilitates genetic counseling, prenatal and preimplantation genetic testing.

References

1. Nissenkorn A, Levy-Shraga Y, Banet-Levi Y, Lahad A, Sarouk I, Modan-Moses D. Endocrine abnormalities in ataxia telangiectasia: findings from a national cohort. Pediatric research. 2016;79:889-94.

2. Teive HA, Moro A, Moscovich M, Arruda WO, Munhoz RP, Raskin S, Ashizawa T. Ataxia-telangiectasia - A historical review and a proposal for a new designation: ATM syndrome. Journal of the neurological sciences. 2015;355:3-6.

3. Amirifar P, Ranjouri MR, Yazdani R, Abolhassani H, Aghamohammadi A. Ataxia-telangiectasia: A review of clinical features and molecular pathology. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2019;30:277-88.

4. Levy A, Lang AE. Ataxia-telangiectasia: A review of movement disorders, clinical features, and genotype correlations. Mov Disord. 2018;33:1238-47.

5. Swift M, Morrell D, Cromartie E, Chamberlin AR, Skolnick MH, Bishop DT. The incidence and gene frequency of ataxia-telangiectasia in the United States. American journal of human genetics. 1986;39:573-83.

6. Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson A, Kampf C, Sjostedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, Ponten F. Proteomics. Tissue-based map of the human proteome. Science. 2015;347:1260419.

7. Lavin MF. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. Nature reviews Molecular cell biology. 2008;9:759-69.

8. Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature. 2003;421:499-506.

9. Taylor AM, Lam Z, Last JI, Byrd PJ. Ataxia telangiectasia: more variation at clinical and cellular levels. Clinical genetics. 2015;87:199-208.

10. Verhagen MM, Last JI, Hogervorst FB, Smeets DF, Roeleveld N, Verheijen F, Catsman-Berrevoets CE, Wulffraat NM, Cobben JM, Hiel J, Brunt ER, Peeters EA, Gomez Garcia EB, van der Knaap MS, Lincke CR, Laan LA, Tijssen MA, van Rijn MA, Majoor-Krakauer D, Visser M, van 't Veer LJ, Kleijer WJ, van de Warrenburg BP, Warris A, de Groot IJ, de Groot R, Broeks A, Preijers F, Kremer BH, Weemaes CM, Taylor MA, van Deuren M, Willemsen MA. Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study. Human mutation. 2012;33:561-71.

11. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, Yazdani R, Azizi G, Habibi S, Gharagozlou M, Movahedi M, Hamidieh AA, Behniafard N, Nabavi M, Bemanian MH, Arshi S, Molatefi R, Sherkat R, Shirkani A, Amin R, Aleyasin S, Faridhosseini R, Jabbari-Azad F, Mohammadzadeh I, Ghaffari J, Shafiei A, Kalantari A, Mansouri M, Mesdaghi M, Babaie D, Ahanchian H, Khoshkhui M, Soheili H, Eslamian MH, Cheraghi T, Dabbaghzadeh A, Tavassoli M, Kalmarzi RN, Mortazavi SH, Kashef S, Esmaeilzadeh H, Tafaroji J, Khalili A, Zandieh F, Sadeghi-Shabestari M, Darougar S, Behmanesh F, Akbari H, Zandkarimi M, Abolnezhadian F, Fayezi A, Moghtaderi M, Ahmadiafshar A, Shakerian B, Sajedi V, Taghvaei B, Safari M, Heidarzadeh M, Ghalebaghi B, Fathi SM, Darabi B, Bazregari S, Bazargan N, Fallahpour M, Khayatzadeh A, Javahertrash N, Bashardoust B, Zamani M, Mohsenzadeh A, Ebrahimi S, Sharafian S, Vosughimotlagh A, Tafakoridelbari M, Rahimi M, Ashournia P, Razaghian A, Rezaei A, Mamishi S, Parvaneh N, Rezaei N, Hammarstrom L, Aghamohammadi A. Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis. J Clin Immunol. 2018;38:816-32.

12. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, Scheible R, Rusch S, Gasteiger LM, Grimbacher B, Mahlaoui N, Ehl S, Party ERW, collaborators. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract. 2019;7:1763-70.

13. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic acids research. 1988;16:1215.

14. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics (Oxford, England). 2009;25:1754-60.

15. Fang M, Abolhassani H, Lim CK, Zhang J, Hammarstrom L. Next Generation Sequencing Data Analysis in Primary Immunodeficiency Disorders - Future Directions. Journal of clinical immunology. 2016;36 Suppl 1:68-75.

16. Abolhassani H, Hammarstrom L, Cunningham-Rundles C. Current genetic landscape in common variable immune deficiency. Blood. 2020;135:656-67.

17. Abolhassani H, Aghamohammadi A, Fang M, Rezaei N, Jiang C, Liu X, Pan-Hammarstrom Q, Hammarstrom L. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. Genet Med. 2019;21:243-51.

18. Abolhassani H, Chou J, Bainter W, Platt CD, Tavassoli M, Momen T, Tavakol M, Eslamian MH, Gharagozlou M, Movahedi M, Ghadami M, Hamidieh AA, Azizi G, Yazdani R, Afarideh M, Ghajar A, Havaei A, Chavoshzadeh Z, Mahdaviani SA, Cheraghi T, Behniafard N, Amin R, Aleyasin S, Faridhosseini R, Jabbari-Azad F, Nabavi M, Bemanian MH, Arshi S, Molatefi R, Sherkat R, Mansouri M, Mesdaghi M, Babaie D, Mohammadzadeh I, Ghaffari J, Shafiei A, Kalantari N, Ahanchian H, Khoshkhui M, Soheili H, Dabbaghzadeh A, Shirkani A, Nasiri Kalmarzi R, Mortazavi SH, Tafaroji J, Khalili A, Mohammadi J, Negahdari B, Joghataei MT, Al-Ramadi BK, Picard C, Parvaneh N, Rezaei N, Chatila TA, Massaad MJ, Keles S, Hammarstrom L, Geha RS, Aghamohammadi A. Clinical, immunologic, and genetic spectrum of 696 patients with combined immunodeficiency. J Allergy Clin Immunol. 2018;141:1450-8.

19. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, Committee ALQA. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics. 2015;17:405-24.

20. Akturk H, Sutcu M, Somer A, Piskin S, Acar M, Ozmen M, Altinoglu U, Tatli B, Salman N. Ataxia telangiectasia in Turkey: multisystem involvement of 91 patients. World journal of pediatrics : WJP. 2017;13:465-71.

21. Chaudhary MW, Al-Baradie RS. Ataxia-telangiectasia: future prospects. The application of clinical genetics. 2014;7:159-67.

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

23. Amirifar P, Ranjouri MR, Lavin M, Abolhassani H, Yazdani R, Aghamohammadi A. Ataxia-telangiectasia: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management. Expert Review of Clinical Immunology. 2020.

24. Amirifar P, Ranjouri MR, Lavin M, Abolhassani H, Yazdani R, Aghamohammadi A. Ataxia-telangiectasia: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Expert review of clinical immunology. 2020:1-13.

25. Karczewski KJ, Weisburd B, Thomas B, Solomonson M, Ruderfer DM, Kavanagh D, Hamamsy T, Lek M, Samocha KE, Cummings BB, Birnbaum D, Daly MJ, MacArthur DG. The ExAC browser: displaying reference data information from over 60 000 exomes. Nucleic acids research. 2017;45:D840-d5.

26. Carranza D, Vega AK, Torres-Rusillo S, Montero E, Martinez LJ, Santamaría M, Santos JL, Molina IJ. Molecular and functional characterization of a cohort of Spanish patients with ataxia-telangiectasia. Neuromolecular medicine. 2017;19:161-74.

27. Stray-Pedersen A, Borresen-Dale AL, Paus E, Lindman CR, Burgers T, Abrahamsen TG. Alpha fetoprotein is increasing with age in ataxia-telangiectasia. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2007;11:375-80.

28. Bott L, Lebreton J, Thumerelle C, Cuvellier J, Deschildre A, Sardet A. Lung disease in ataxia−telangiectasia. Acta paediatrica. 2007;96:1021-4.

29. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. Immunodeficiency and infections in ataxia-telangiectasia. The Journal of pediatrics. 2004;144:505-11.

30. Ghiasy S, Parvaneh L, Azizi G, Sadri G, Zaki Dizaji M, Abolhassani H, Aghamohammadi A. The clinical significance of complete class switching defect in Ataxia telangiectasia patients. Expert review of clinical immunology. 2017;13:499-505.

31. Noordzij JG, Wulffraat NM, Haraldsson A, Meyts I, van't Veer LJ, Hogervorst FB, Warris A, Weemaes CM. Ataxia-telangiectasia patients presenting with hyper-IgM syndrome. Archives of disease in childhood. 2009;94:448-9.

32. Chen L, Guo L, Tian J, Zheng B, Han S. Deficiency in activation-induced cytidine deaminase promotes systemic autoimmunity in lpr mice on a C57BL/6 background. Clinical and experimental immunology. 2010;159:169-75.

33. Aghamohammadi A, Imai K, Moazzami K, Abolhassani H, Tabatabaeiyan M, Parvaneh N, Nasiri Kalmarzi R, Nakagawa N, Oshima K, Ohara O, Nonoyama S, Rezaei N. Ataxia-telangiectasia in a patient presenting with hyper-immunoglobulin M syndrome. Journal of investigational allergology & clinical immunology. 2010;20:442-5.

34. Amirifar P, Mozdarani H, Yazdani R, Kiaei F, Moeini Shad T, Shahkarami S, Abolhassani H, Delavari S, Sohani M, Rezaei A. Effect of Class Switch Recombination Defect on the Phenotype of Ataxia-Telangiectasia Patients. Immunological Investigations. 2020:1-15.

35. Moeini Shad T, Yousefi B, Amirifar P, Delavari S, Rae W, Kokhaei P, Abolhassani H, Aghamohammadi A, Yazdani R. Variable Abnormalities in T and B Cell Subsets in Ataxia Telangiectasia. Journal of clinical immunology. 2020.

36. Concannon P, Gatti RA. Diversity of ATM gene mutations detected in patients with ataxia-telangiectasia. Human mutation. 1997;10:100-7.

37. Huang Y, Yang L, Wang J, Yang F, Xiao Y, Xia R, Yuan X, Yan M. Twelve novel Atm mutations identified in Chinese ataxia telangiectasia patients. Neuromolecular Med. 2013;15:536-40.

38. Carranza D, Vega AK, Torres-Rusillo S, Montero E, Martinez LJ, Santamaría M, Santos JL, Molina IJ. Molecular and Functional Characterization of a Cohort of Spanish Patients with Ataxia-Telangiectasia. Neuromolecular Med. 2017;19:161-74.

39. Cavalieri S, Funaro A, Pappi P, Migone N, Gatti RA, Brusco A. Large genomic mutations within the ATM gene detected by MLPA, including a duplication of 41 kb from exon 4 to 20. Annals of human genetics. 2008;72:10-8.

40. Mitui M, Campbell C, Coutinho G, Sun X, Lai CH, Thorstenson Y, Castellvi-Bel S, Fernandez L, Monros E, Carvalho BT, Porras O, Fontan G, Gatti RA. Independent mutational events are rare in the ATM gene: haplotype prescreening enhances mutation detection rate. Human mutation. 2003;22:43-50.

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

42. Laake K, Telatar M, Geitvik GA, Hansen RO, Heiberg A, Andresen AM, Gatti R, Børresen-Dale AL. Identical mutation in 55% of the ATM alleles in 11 Norwegian AT families: evidence for a founder effect. European journal of human genetics : EJHG. 1998;6:235-44.

43. Saadat M, Ansari-Lari M, Farhud DD. Consanguineous marriage in Iran. Ann Hum Biol. 2004;31:263-9.

44. Podralska MJ, Stembalska A, Ślęzak R, Lewandowicz−Uszyńska A, Pietrucha B, Kołtan S, Wigowska−Sowińska J, Pilch J, Mosor M, Ziółkowska−Suchanek I. Ten new ATM alterations in Polish patients with ataxia−telangiectasia. Molecular genetics & genomic medicine. 2014;2:504-11.

45. Huang D-S, Tao H-Q, He X-J, Long M, Yu S, Xia Y-J, Wei Z, Xiong Z, Jones S, He Y. Prevalence of deleterious ATM germline mutations in gastric cancer patients. Oncotarget. 2015;6:40953.

46. Sawyer SL, Schwartzentruber J, Beaulieu CL, Dyment D, Smith A, Chardon JW, Yoon G, Rouleau GA, Suchowersky O, Siu V. Exome sequencing as a diagnostic tool for pediatric−onset ataxia. Human mutation. 2014;35:45-9.

47. Mortaz E, Marashian SM, Ghaffaripour H, Varahram M, Mehrian P, Dorudinia A, Garssen J, Adcock IM, Taylor M, Mahdaviani SA. A new ataxia-telangiectasia mutation in an 11-year-old female. Immunogenetics. 2017;69:415-9.

48. Castellví-Bel S, Sheikhavandi S, Telatar M, Tai LQ, Hwang M, Wang Z, Yang Z, Cheng R, Gatti RA. New mutations, polymorphisms, and rare variants in the ATM gene detected by a novel SSCP strategy. Human mutation. 1999;14:156-62.

49. Heidari M, Soleyman-Nejad M, Taskhiri MH, Shahpouri J, Isazadeh A, Ahangari R, Mohamadi AR, Ebrahimi M, Karimi H, Bolhassani M, Karimi Z, Heidari M. Identification of Two Novel Mutations in the ATM Gene from Patients with Ataxia-Telangiectasia by Whole Exome Sequencing. Current genomics. 2019;20:531-4.

50. Fang M, Abolhassani H, Lim CK, Zhang J, Hammarström L. Next Generation Sequencing Data Analysis in Primary Immunodeficiency Disorders - Future Directions. Journal of clinical immunology. 2016;36 Suppl 1:68-75.

51. Stankovic T, Kidd AM, Sutcliffe A, McGuire GM, Robinson P, Weber P, Bedenham T, Bradwell AR, Easton DF, Lennox GG, Haites N, Byrd PJ, Taylor AM. ATM mutations and phenotypes in ataxia-telangiectasia families in the British Isles: expression of mutant ATM and the risk of leukemia, lymphoma, and breast cancer. American journal of human genetics. 1998;62:334-45.

52. Martin-Rodriguez S, Calvo-Ferrer A, Ortega-Unanue N, Samaniego-Jimenez L, Sanz-Izquierdo MP, Bernardo-Gonzalez I. Two novel variants in the ATM gene causing ataxia-telangiectasia, including a duplication of 90 kb: Utility of targeted next-generation sequencing in detection of copy number variation. Annals of human genetics. 2019;83:266-73.

53. Broeks A, de Klein A, Floore AN, Muijtjens M, Kleijer WJ, Jaspers NG, van 't Veer LJ. ATM germline mutations in classical ataxia-telangiectasia patients in the Dutch population. Human mutation. 1998;12:330-7.

54. Saeidi K, Saleh Gohari N, Mansouri Nejad SE. A Novel Splice Site Mutation of the ATM Gene Associated with Ataxia Telangiectasia. Iranian journal of child neurology. 2018;12:111-9.

55. Tabatabaiefar MA, Alipour P, Pourahmadiyan A, Fattahi N, Shariati L, Golchin N, Mohammadi-Asl J. A novel pathogenic variant in an Iranian Ataxia telangiectasia family revealed by next-generation sequencing followed by in silico analysis. Journal of the neurological sciences. 2017;379:212-6.

56. Micol R, Slama LB, Suarez F, Le Mignot L, Beauté J, Mahlaoui N, d'Enghien CD, Laugé A, Hall J, Couturier J. Morbidity and mortality from ataxia-telangiectasia are associated with ATM genotype. Journal of Allergy and Clinical Immunology. 2011;128:382-9. e1.

57. Yurgelun MB, Allen B, Kaldate RR, Bowles KR, Judkins T, Kaushik P, Roa BB, Wenstrup RJ, Hartman AR, Syngal S. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected Lynch Syndrome. Gastroenterology. 2015;149:604-13.e20.

58. Méneret A, Ahmar-Beaugendre Y, Rieunier G, Mahlaoui N, Gaymard B, Apartis E, Tranchant C, Rivaud-Péchoux S, Degos B, Benyahia B. The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia. Neurology. 2014;83:1087-95.

59. Mangone FR, Miracca EC, Feilotter HE, Mulligan LM, Nagai MA. ATM gene mutations in sporadic breast cancer patients from Brazil. Springerplus. 2015;4:23.

Table 1. Demographic and laboratory features of patients with ataxia-telangiectasia.

Parameter	All patients (n=43)	Patients with severe form (n=22)	Patients with mild form (n=21)	*P*-value	Patients with null mutations (n=31)	Patients with non-null mutations (n=12)	*P*-value
Age at diagnosis, years (IQR†)	5.0 (3.0-7.0)	5.0 (3.0-8.0)	5.0 (3.0-7.0)	0.446	5.0 (3..0-7.0)	5.5 (3.0-7.0)	0.935
Age at onset of ataxia, years (IQR)	1.5 (1.0-2.2)	1.5 (1.0-3.0)	1.7 (1.0-2.0)	0.915	1.5 (1.0-3.0)	1.0 (1.0-2.0)	0.454
Age at onset of infection, years (IQR)	3.0 (1.0-6.5)	3.0 (1.0-5.5)	2.0 (0.7-7.0)	0.842	2.5 (1.2-5.5)	5.0 (1.8-10.0)	0.390
Age at onset of telangiectasia, years (IQR)	4.0 (2.0-5.0)	3.0 (1.6-5.0)	4.5 (3.0-6.0)	0.134	3.0 (2.0-5.0)	4.0 (1.7-6.2)	0.854
Delay diagnosis, years (IQR)	3.0 (1.0-5.0)	4.0 (1.7-5.2)	1.9 (0.4-4.7)	0.093	3.0 (1.0-5.0)	2.0 (0.2-6.1)	0.830
Sex, N (%) Male Female	 20 (46.50) 23 (53.50)	 7 (31.8) 13 (61.9)	 15 (68.2) 8 (38.1)	0.06	 14 (45.2) 17 (54.8)	 7 (58.3) 5 (41.7)	0.510
Consanguinity, N (%)	38 (88.4)	19 (86.4)	19 (90.5)	0.674	28 (90.3)	10 (83.3)	0.593
Mortality, N (%) Alive Dead	 37(86) 4 (9.3)	 18 (81.8) 3 (13.6)	 19 (90.5) 1 (4.8)	0.653	 26 (83.9) 3 (9.7)	 11 (91.7) 1 (8.3)	0.653
AFP	133.0 (93.7-290.7)	153.5 (88.2-321.7)	124.5 (95.7-191.0)	0.554	148.5 (90.0-314.0)	124.0 (98.0-244.5)	0.731
IgG‡, mg/dl (IQR)	656.0 (155.7-915.0)	242.0 (66.2-849.2)	750.0 (502.0-981.7)	0.014 *	644 (108.0-910.0)	668 (500.0-990.0)	0.168
IgA, mg/dl (IQR)	7.0 (4.0-15.7)	5.5 (2.3-15.2)	7.5 (5.0-17.2)	0.160	6.5 (3.6-8.0)	7 (5.0-74.0)	0.246
IgM, mg/dl (IQR)	194.0 (109.5-360.2)	209.5 (85.5-552.0)	184 (112.5-262.5)	0.546	220 (115.5-442.5)	150 (71.2-200.0)	0.077
IgE, IU/ml (IQR)	1.0 (1.0-4.1)	1.0 (1.0-4.1)	1.0 (1.0-4.2)	0.777	1.0 (1.0-4.5)	1.0 (1.0-3.4)	0.575

†IQR, interquartile range rang; ‡Ig, immunoglobulin.

* *P value* < 0.05 is statistically significant.

552 **Table 2.** Clinical manifestations of patients with ataxia-telangiectasia.

Variable	All patients (n=43)	Patients with severe phenotype (n=22)	Patients with mild phenotype (n=21)	*P*-value	Patients with null mutations (n=31)	Patients with non-null mutations (n=12)	*P*-value
Ataxia	43 (100%)	22 (100%)	21 (100%)	-	31 (100%)	12 (100%)	-
Telangiectasia	35 (83.3%)	21 (95.5%)	14 (70.0%)	0.041 *	26 (83.9%)	9 (75%)	0.279
Fever	21 (48.9%)	16 (72.7%)	5 (25.0%)	0.005 *	17 (54.8%)	4 (33.3%)	0.185
Cold	19 (44.2%)	10 (45.5%)	9 (45.0%)	0.619	16 (51.6%)	3 (27.3%)	0.273
Infection	30 (70.0%)	18 (81.8%)	12 (60.0%)	0.081	24 (77.4%)	6 (50%)	0.061
Otitis media	14 (32.5%)	9 (40.9%)	5 (25.0%)	0.259	10 (32.3%)	4 (33.3%)	0.820
URTI†	14 (32.5%)	9 (40.9%)	5 (25.0%)	0.338	8 (25.8%)	6 (50%)	0.592
LRTI‡	18 (41.8%)	13 (59.1%)	5 (25.0%)	0.033 *	10 (32.2%)	8 (66.6%)	0.814
Skin manifestation	13 (30.2%)	9 (40.9%)	4 (21.1)	0.200	10 (32.2%)	3 (27.3)	0.719
Diarrhea	14 (32.5%)	11 (50.0%)	3 (15.0%)	0.014 *	10 (32.2%)	4 (33.3%)	0.803
Hepatosplenomegaly	5 (11.6%)	5 (22.7%)	0 (0%)	0.032 *	3 (9.6%)	2 (16.6%)	0.674
Malignancy	2 (4.6%)	2 (9.1%)	0 (0%)	0.489	1 (3.2%)	1 (8.3%)	-
Autoimmunity	8 (18.6%)	6 (27.3%)	2 (10.0%)	0.243	5 (16.12%)	3 (27.3%)	0.768

553 †URTI, *Upper respiratory tract infection;* ‡*LRTI, lower respiratory tract infection*.

554 * *P value* < 0.05 is statistically significant.

555

556 **Table 3.** *ATM* mutations detected in patients with ataxia-telangiectasia

Name	Zygosity	ATM mutation	AA change	Exon/Intron	Type of mutation	Pathogenicity (ACMG)	Ref.
AT-1	Homo	Deletion EX62-63	-	62-63	Frameshift	P †	[44]
AT-2	Homo	c.67C>T	p.R23*	2	Nonsense	P	[45]
AT-3	Compound hetero	c.1537C>T c.8050C>T	p.Q513* p.Q2689*	10 55	Nonsense Nonsense	P P	[46] VCV000479048
AT-4	Homo	c.3244-3245insG	p.H1082Rfs*14	22	Frameshift	P	[47]
AT-5	Homo	c.3895delG	p.A1299Pfs*50	26	Frameshift	P	SCV000217647.4
AT-6	Homo	c.6658C>T	p.Q2220*	46	Nonsense	P	VCV000407464
AT-7	Homo	c.3600-3601delTT	p.F1201Wfs*3	25	Frameshift	P	[48]
AT-8	Compound hetero	c.8907T>G c.8050C>T	p.Q2684* p.Q2969*	55 62	Nonsense Nonsense	P P	[49] VCV000479048
AT-9	Homo	c.6452G>C	p.R2151T	44	Missense	VUS §	Novel
AT-10	Homo	Deletion EX37-48	-	37-48	Frameshift	P	Novel
AT-11	Homo	c.5585delA	p.S1863Lfs*54	37	Frameshift	P	[50]
AT-12	Homo	c.6658C>T	p.Q2220*	46	Nonsense	P	VCV000407464
AT-13	Homo	Deletion EX1	-	1	Frameshift	P	Novel
AT-14	Compound hetero	c.6259delG c.6658C>T	p.E2087Kfs*9 p.Q2220*	43 46	Frameshift Nonsense	P P	[50] VCV000407464
AT-15	Homo	c.5552_5553insC	p.Q1852Pfs*5	37	Frameshift	P	[50]
AT-16	Homo	c.6047A>G	p.D2016G	41	Missense	LP ‡	VCV000140823
AT-17	Compound hetero	c.6198+1G>A c.6047A>G	Splice donor p.D2016G	IVS 42 41	Splicing error missense	P LP	[51] VCV000140823
AT-18	Compound hetero	18-61 duplication c.7788G>A	- p.E2596=	18-61 52	Frameshift synonymous	P LP	[52, 53]
AT-19	Homo	c.9097_9101dupAATTT	p.L3035Ifs*8	63	Frameshift	P	Novel
AT-20	Homo	c.7308-6T>G	-	IVS 49	Splicing error	VUS	[54]
AT-21	Homo	c.8046-8047delTA	p.I2683Tfs*4	55	Frameshift	P	[55]
AT-22	Homo	c.6658C>T	p.Q2220*	46	Nonsense	P	VCV000407464
AT-23	Homo	c.829G>T	p.E277*	7	Nonsense	P	[56]
AT-24	Homo	c.6658C>T	p.Q2220*	46	Nonsense	P	VCV000407464
AT-25	Homo	Deletion EX62-63	-	62-63	Frameshift	P	[44]
AT-26	Homo	Deletion EX62-63	-	62-63	Frameshift	P	[44]
AT-27	Homo	c.3600_3601delTT	p.F1201Wfs*3	25	Frameshift	P	[48]
AT-28	Homo	c.5003A>G	p.L1668P	33	Missense	VUS	Novel
AT-29	Homo	c.3102T>G	p.Y1034*	21	Nonsense	P	VCV000556315

AT-30	Homo	Deletion EX62-63	-	62-63	Frameshift	P	[44]
AT-31	Homo	c.5712dupA	p.S1905fs*12	38	Frameshift	P	VCV000141416
AT-32	Homo	c.1159A>C	p.K387Q	9	Missense	VUS	Novel
AT-33	Homo	Deletion EX62-63	-	62-63	Frameshift	P	[44]
AT-34	Homo	Deletion EX61-62	-	61-62	Frameshift	P	[57]
AT-35	Homo	c.6807+1G>C	-	IVS 46	Splicing error	P	Novel
AT-36	Homo	c.829G>T	p.E277*	7	Nonsense	P	[56]
AT-37	Homo	Deletion EX62-63		62-63	Frameshift	P	[44]
AT-38	Homo	c.6199-1G>T	-	IVS 42	Splicing error	P	[44]
AT-39	Homo	c.664C>T	p.Q222*	7	Nonsense	P	[58]
AT-40	Homo	c.8741T>A	p.I2914N	60	Missense	LP	Novel
AT-41	Homo	c.1834C>A	p.L612I	12	Missense	LP	Novel
AT-42	Homo	c.6067G>C	p.G2023R	41	Missense	LP	[59]
AT-43	Homo	Deletion EX37-48	-	37–48	Frameshift	P	Novel

† *P: Pathogenic,* ‡ *LP: Likely pathogenic,* § *VUS:* Variant *of uncertain significance*

Table 1 Clinical features of A-T patients with same *ATM* mutations.

Mutation	***Deletion EX62-63***						***c.6658C>T (p.Q2220*)***				
Patient	**AT-1**	**AT-25**	**AT-26**	**AT-30**	**AT-33**	**AT-37**	**AT-6**	**AT-12**	**AT-14**	**AT-22**	**AT-24**
Ataxia	+	+	+	+	+	+	+	+	+	+	+
Telangiectasia	+	+	+	+	+	+	+	+	+	+	+
Fever	+	+	-	+	+	-	+	+	+	-	-
Cold	+	-	+	+	-	-	+	+	+	-	-
Recurrent infection	+	+	+	+	+	+	+	+	+	-	+
URTI †	+	-	-	-	-	-	-	+	+	-	-
LRTI ‡	+	+	+	+	+	+	+	+	+	-	-
Pneumonia	+	+	+	+	+	+	+	+	+	-	-
Otitis media	+	-	-	-	-	-	-	+	+	-	-
Skin manifestation	-	-	-	-	-	-	-	-	-	+	+
Diarrhea	+	-	-	-	-	-	+	-	+	-	-
Hepatosplenomegaly	-	-	-	-	-	-	+	-	+	-	-
Malignancy	-	-	-	-	-	+	-	-	-	-	-
Autoimmunity	-	-	-	-	-	-	-	-	-	+	-
Immunologic profile	CSR-D §	CSR-D	CSR-D	IgA-D¶	N ‼	CSR-D	CSR-D	CSR-D	CSR-D	IgA-D	IgA-D

† *URTI, upper respiratory tract infection;* ‡ *LRTI, lower respiratory tract infection;* § *CSR-D, class switching recombination defect;* ¶ *IgA-D, IgA deficiency;* ‼ *N, Normal Ig level*

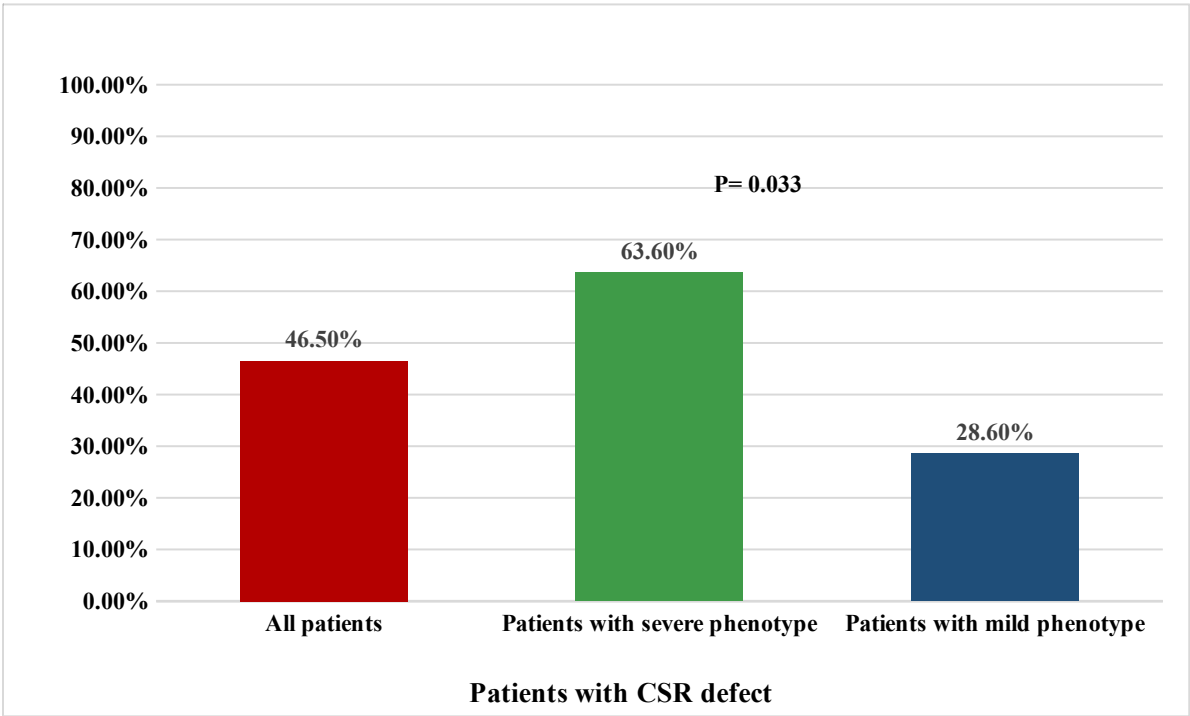


Figure 1. Frequency of CSR defect in the study groups of Ataxia-telangiectasia. CSR defect is significantly higher in patients with severe phenotype than patients with a mild phenotype.

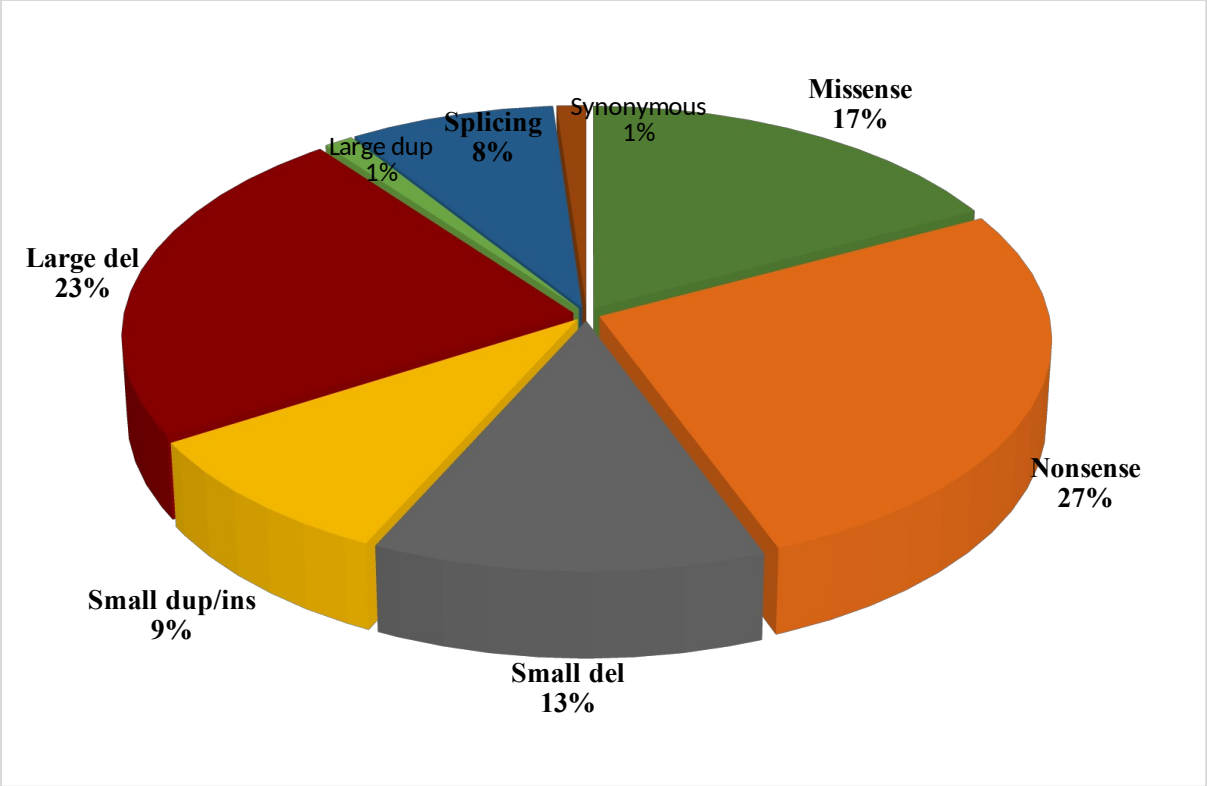
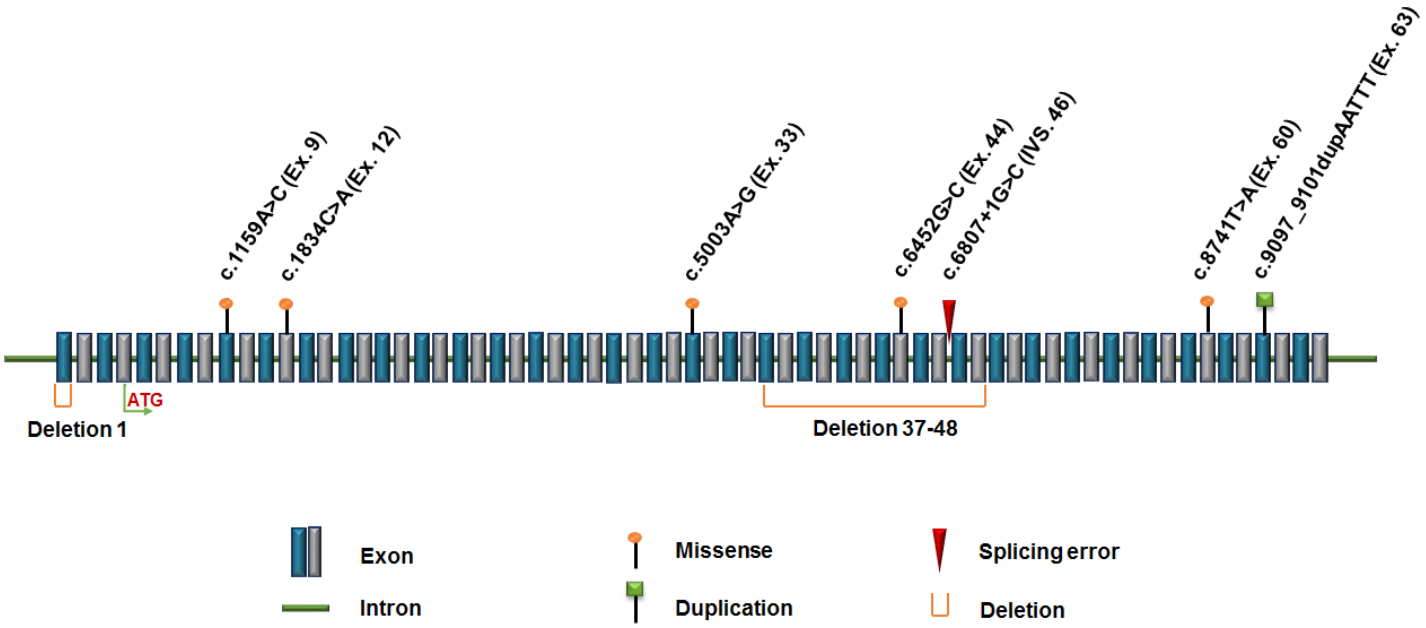


Figure 2. Frequency of *ATM* mutations in patients with ataxia-telangiectasia.



588

589 **Figure 3.** Nine novel *ATM* mutations in Iranian patients with ataxia-telangiectasia.

590

591

592

593