SPANDIDOS PUBLICATIONS

ATM gene mutations in former uranium miners of SDAG Wismut: A pilot study

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Abstract. Ataxia-telangiectasia is an autosomal recessive disease characterized by neurological and immunological symptoms, radiosensitivity and cancer predisposition. Heterozygous carriers of an ataxia-telangiectasia gene mutation are predisposed to epithelial cancers. We initiated a study to elucidate the frequency and clinical relevance of ATM gene mutations in former uranium miners exposed to high levels of radiation from radon and its decay products. Former uranium miners with Schneeberg lung cancer (n=48), former uranium miners suffering from silicosis (n=60) and uranium miners without occupational lung disorders (n=102) were investigated for nine mutations in the ATM gene. One gastric and one prostate cancer occurred in the group of miners without occupational lung diseases. Mutation analyses for S707P, IVS10-6T→G, 2250G→A, E1978X, R2443X, 3801delG, S49C and D2625E-A2626P were performed using genomic DNA obtained from peripheral blood samples. Three ATM gene alterations (S707P, S49C or IVS10-6T→G) were observed. Of all cancer patients, 8.0% were heterozygous, but only 1.9% of the non-cancer controls were [OR=4.6; 95% confidence interval (CI), 0.8-26.8]. In this pilot study a major role of six ATM gene mutations could not be revealed for cancer predisposition in former uranium miners. The results leave the possibility of a moderate risk associated with more subtle ATM gene alterations.

Introduction

After World War II, in 1946, the Soviet occupation authorities started uranium mining and processing in East Germany. Between 1946 and 1990, the Wismut Company employed between 500,000-600,000 people, with at least half of them exposed to ionising radiation during underground mining and uranium processing. Miners who had been exposed for the first time between 1946 and 1954, the years with the poorest working conditions, showed high mean cumulative radon exposures (709 working level months) (1,2). Due to unsafe working conditions, exposures were in the range of 10-100 mg/m^3 dust with high content of crystalline silica (3). Later on, working conditions were improved and exposure was reduced (1). After German reunification in 1990, uranium mines in Saxony and Thuringia were closed. At present, overall ~20,000 cases of silicosis and ~9,000 cases of lung cancer were reported from this high-risk group (4,5). Of the latter, ~5,300 were compensated as occupational diseases (6). Since 1995 up to ~4,800 additional lung cancer cases have been predicted in the population of exposed former Wismut workers in Saxony (7). The syncarcinogenic effect of radon exposure and smoking has been demonstrated in Wismut employees (8). The carcinogenic effect of crystalline silica is also taken into consideration.

DNA lesions will be evoked followed by a period of repair, mis-repair or non-repair. Analysis of repair processes is problematic owing to the low number of lesions per unit of time that have to be repaired. The effective repair process during chronic exposure makes application of indicator systems of DNA damage very difficult. However, a previous study using the comet assay has uncovered an increase in unrepaired DNA damage in cells from former Wismut employees affected by lung cancer (9).

We would like to initiate a study to elucidate the clinical relevance of genetic susceptibility to lung cancer with regard to the role of DNA damage and repair. For a complex disease such as lung cancer, multiple genes probably act independently or interact with other genes to influence the disease phenotype. Polymorphisms could have functional relevance. Our approach is involved in the DNA repair machinery by analysing the ATM and the X-ray repair cross-complementing gene group. In this pilot study, we focused on the ataxia-telangiectasia (A-T) gene mutations (ATM) in former uranium miners of SDAG Wismut, Germany.

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Ataxia-telangiectasia (A-T) is the classic paradigm of a human genetic disease involving severe ionising radiation sensitivity which has been studied by radiation biologists over many decades (10,11). A-T is an autosomal recessive disorder characterized by progressive cerebellar degeneration, oculocutanous telangiectasia, thymus dysplasia, immunodeficiency and bronchopulmonary infections, gonadal dysgenesis, chromosomal instability, abnormal X-ray sensitivity and cancer predisposition (12,13). The incidence in the USA is approximately 1:100,000.

Cultured cells from AT patients are also hypersensitive to ionising radiation and show defective activation of radiation-induced cell cycle check-points, including retarded p53 stabilisation (14-20). Heterozygous carriers of an A-T mutation (~1% of the population) are clinically unaffected, but there is reported evidence from epidemiological studies that A-T heterozygosity predisposes to some epithelial cancers (21-25). Cancer incidence among A-T heterozygotes has been estimated to be 3- to 4-fold higher than in the general population. It has been suggested that diagnostic exposure to ionizing radiation probably increases the risk of breast cancer in women heterozygous for ataxia-telangiectasia (26).

The gene mutated in A-T, designated the ATM gene, has been localized to chromosome 11q23 and contains 66 exons (27-29). The ATM gene encodes a large protein kinase with a PI-3 kinase-related domain. This protein is involved in DNA damage response and cell cycle regulation (11,30-35). Molecular studies have shown that ATM is upstream of p53 in a pathway that activates a G_1-S check-point. In A-T cells, there is a delay in the increase of p53 levels that follows γ irradiation (36,37). The link between the ATM and p53 gene products, and the subsequent identification of several other oncoproteins as targets of ATM (35,38), supports the hypothesis of a tumor-suppressive function of ATM.

Until today numerous different mutations in the ATM gene have been identified in classical A-T patients. The majority of the published mutations in the ATM gene are truncating, although missense substitutions and in-frame deletions have also been found (30,39-48). Most studies have used cDNA for analysing ATM gene mutations. After complete sequence informations are available, mutation-scanning methods using genomic DNA have been possible.

The aim of our study is the analysis of ATM gene alterations that could predispose towards radiation-induced cancer due to a constitutional dysfunction in the cellular DNA damage response pathways. In the pilot phase, we report the screening results of nine tested ATM mutations in former uranium miners.

Patients and methods

Case selection. In this project, n=48 former uranium miners of SDAG Wismut (67.5±5.8 years; 10% actual smokers, 90% ever smokers) with lung cancer and a history of exposure towards ionising radiation (radon and its decay products) were examined [criteria for diagnosis (49)]. The lung cancer patients were recruited from the Klinik für Lungenkrankheiten und Tuberkulose in Bad Berka and the Klinik für Berufskrankheiten in Falkenstein, Germany. Histological classification of the lung carcinoma cases yielded n=14 adenocarcinoma (65.7±8.0 years), n=29 squamous (67.8±8.6), and n=5 large cell, mixed or non-classifiable bronchial carcinoma (65.0±12.7 years).

They were compared to n=102 former uranium miners of SDAG Wismut (66.6±4.5 years; 15% actual smokers, 80% ever smokers, 5% never smokers) without occupational lung disease (i.e., silicosis, asbestosis or chronic obstructive airway diseases). Samples were taken from a multi-center study concerning the effects of radiation-induced illness in former uranium miners of SDAG Wismut. All miners took part in the medical surveillance program by ZeBWis (Zentrale Betreuungsstelle Wismut). The health status of each subject was confirmed in a clinical examination that included X-rays. All patients underwent bronchoscopy. Cancer had occurred in two of these miners (one gastric cancer, one prostate cancer).

The uranium miners (UM) had started their work within the Wismut Company between 1946 and 1978, and over 50% had stopped working as miners before 1980. The mean time of employment at the company was 21.8 years (range 0.4-42.1 years). Work in the underground mine was approximately 14.5 years, and exposure to ionising radiation in uranium processing was calculated at 7.4 years. Cumulative exposure in WLM (WLM, Working Level Month; one WL is the α- energy concentration of radon daughters in equilibrium with 100 pCi/l or 3,700 Bq/m^3 radon) was calculated in each UM by ZeBWis (Central Association of the German Statutory Accidents Insurance Institutions with its special branch for the observation of the health of former Wismut Workers). The mean exposure was calculated at 612±500 WLMs (range 0.7-1954 WLM) or 6.4±9.76 kBqh/m^3 (range 0.06-80 kBqh/m^3) and 53.5±101.7 mSV (range 0-874.3 mSv) respectively. Individual exposure estimates for dust, arsenic or asbestos were not available.

Additionally, n=60 former uranium miners (72.0±2.8 years; 11.7% actual smokers, 76.7% ever smokers, 11.7% never smokers) suffering from silicosis were included as second control group. They underwent clinical treatment at a clinic for occupational diseases to improve rehabilitation. None of the patients showed signs of malignant diseases.

Methods. Peripheral EDTA blood samples were collected. Genomic DNA was extracted from leucocytes of all persons and served as the primary source for mutational screening. Mutation analysis of the coding exons of the ATM gene was performed in the genomic DNA. Mutation analysis for S707P and IVS10-6T→G were performed as described previously (50). The screening of mutations 2250G→A, E1978X, R2443X, 3801delG, S49C and D2625E-A2626P was performed using a newly established hexaplex ARMS (amplification refractory mutation system) [(51) primer sequences available from the authors]. In brief, PCR amplifications were performed in 20-μl reaction volumes containing ~100 ng of genomic DNA, 0.25 mM each dNTP and 2.5 U Taq-DNA polymerase in the reaction buffer supplied by the manufacturer (Qiagen). Primer concentrations were adjusted to allow for the simultaneous detection of six mutant or wild-type ATM fragments, respectively. As the standard procedure, 35 PCR cycles were performed with 1-min denaturation at 95˚C, 1-min annealing at 57 or 62˚C, depending on the primer pairs, and 1-min elongation at 72˚C. Electrophoresis was performed on high-

lutation analysis of the ATM gene in 210 former uranium miners.

Mutation	Nucleotide	Location	Uranium miners	
			No.	(%)
Amino acid mutations				
S49C	C→G at 146	Exon 5	4 Heterozygote	1.90
S707P	T→C at 2119	Exon 15	2 Heterozygote	0.95
D2625E-A2626P	T→G at 7875			
	G→C at 7876	Exon 55	0 Heterozygote	0.00
Splicing mutation				
IVS10-6T→G	T→G at 1066-6	Intron 10	1 Heterozygote	0.48
2250G→A	G→A at 2250	Exon 16	0 Heterozygote	0.00
Truncating mutation				
3801delG	Deletion of G at 3801-3802	Exon 28	0 Heterozygote	0.00
E1978X	G→T at 5932	Exon 42	0 Heterozygote	0.00
R2443X	C→T at 7327	Exon 52	0 Hetreozygote	0.00
Total mutations			7 Heterozygote	3.33

Mutations are designated according to the recommended nomenclature (65). Nucleotides are numbered according to the published ATM cDNA sequences (66), beginning with the first nucleotide of the start codon.

Table II. Prevalence of ATM mutations in former uranium miners.

Mutation	Wismut cancer patients (n=50)			Wismut non-cancer controls (n=160)			P-value[a]	OR	95% CI
	n	(%)	Diagnosis	n	(%)	Diagnosis			
S49C	1	2.00	Gastric cancer	1	0.63	Healthy	0.04	10.2	0.9-259.4
	2	4.00	Lung cancer				0.14[b]	6.6[b]	0.4-188.8[b]
S707P	1	2.00	Prostate cancer	1	0.63	Silicosis (q/q 3/3 B)[c]	0.42	3.2	0.0-121.2
IVS10-6T→G	-	-	-	1	0.63	Silicosis (p/q 3/2 A)[c]	1.00	-	0.0-56.3
All three mutations	4	8.00		3	1.88		0.04	4.6	0.8-26.8

[a]Fisher's exact test (2-tailed). [b]Analysis restricted to lung cancer. [c]ILO classification of radiographs for pneumoconiosis (small opacities p/q resp. q/q; profusion category 3/2 resp. 3/3, large opacities A resp. B) (67). Carrier frequencies are given as numbers of heterozygotes. Comparison between Wismut cancer patients and all non-cancer controls (healthy persons and patients suffering from silicosis).

resolution agarose gels (2.5% NuSieve agarose, BioWhittaker) including 50 ng/ml ethidium bromide in 0.8X Tris-borate-EDTA at 5 V/cm at room temperature. Bands were visualized by UV light and photographed.

Results

Two hundred and ten former uranium miners were investigated for nine mutations in the ATM gene. As suspected, homozygotes for A-T mutations could not be detected. A total of 7 heterozygotes were identified (Table I).

The most frequent heterozygosity was found for the amino acid substitution S49C in four individuals (1.90%) followed by S707P in two persons (0.95%). A truncating AT mutation, the splicing mutation IVS10-6T→G within the acceptor splice site of intron 10 of the ATM gene, was only detectable in a single person from the non-cancer group (0.48%). Other classic A-T mutations did not occur in either subgroup.

To elucidate whether the mutations predispose to cancer, the prevalence of ATM mutations were grouped into cases suffering from cancer (n=50, including n=48 lung cancer) and controls without cancer (n=160) (Table II).

S49C or S707P are rare in the control group (0.63%) and only seen in single persons. These substitutions were found in a higher percentage in cancer patients than in non-cancer controls (Table II). The differences were not significant for the S707P mutation. The OR of the cumulative frequencies of the S49C heterozygotes between all cancer patients and persons without cancer was elevated (OR=10.2). Using the Fisher's exact test this result was significant (p=0.04). If the analysis was restricted only to lung cancer patients, the OR remained elevated (OR=6.63), but the differences were not significant (p=0.14).

The splicing mutation IVS10-6T→G has only been detected in one silicosis patient, but not in any cancer patient. Three ATM gene alterations (S707P, S49C or IVS10-6T→G) were observed. Heterozygous individuals were observed as 8.0% of all cancer patients but only 1.9% of the non-cancer controls. The calculated crude OR=4.6 may reflect a modest cancer predisposition associated with dysfunctional ATM.

Discussion

In this pilot study we screened for ATM gene alterations in a total of 210 former uranium miners exposed to ionising radiation. More than 46 different ATM mutations and 26 sequence polymorphisms and variants were previously identified in 66 ataxia-telangiectasia patients from German families (48). Only 7 mutations occurred in more than one AT-family. In this preliminary study we focused therefore on nine selected mutations that were commonly observed either in A-T patients or in German breast cancer patients (48,50).

The most frequent truncating AT mutation in breast cancer is a splicing mutation, polypyrimidine tract substitution IVS10-6T→G within the acceptor splice site of intron 10 of the ATM gene (50,52). However in former uranium miners this mutation could only be found in one single patient suffering from severe silicosis. Respirable quartz dust was classified as a carcinogen. Epidemiological studies revealed an association between lung cancer and exposure to quartz dust. Meta-analysis of epidemiological studies (53,54) showed high risks (RR>2.0) for developing lung cancer in patients suffering from silicosis. So the heterozygous silicosis patient has to be followed-up with respect to a possible development of lung cancer.

In two previous studies of breast cancer patients (50,55) the S707P substitution was significantly more frequent in cases than in the general population. We did not detect this mutation in n=100 healthy uranium miners but ATM heterozygosity for S707P was found in one (0.63%) patient with silicosis and in one patient with prostate cancer. How far this result can be interpreted in terms of cancer predisposition needs further investigation. In a family study of AT patients, in which the risk of cancer according to ATM heterozygosity status was estimated, prostate cancer was not significantly increased (56). Studies of workers exposed to ionising radiation usually focus on mortality in relation to the whole body exposure. The relation to neutron and surface exposure has also been examined (57). Surface exposure was significantly (p<0.001) related to prostate cancer. Among prostate cancer a clearly increased mortality in relation to exposure was described (58). Because other relevant information was not available, the reason for the increased mortality from prostate cancer could not be determined. Epidemiological studies failed to correlate significant excess of prostate cancer with high exposure to ionising radiation (59). However A-T heterozygous individuals have been identified among patients with prostate cancer (60). Patients carrying a significant mutation in the ATM gene are over-represented in prostate cancer that developed serious late responses to high-dose external-beam conformal radiation therapy (60).

The most prominent trend was observed for the S49C amino acid substitution in exon 5 of the ATM gene. Three of the n=50 cancer patients but only one of the n=160 control subjects were heterozygous for this mutation. One former uranium miner died at the age of 72 years according to a gastric cancer. The adenocarcinoma of the stomach was progressive and metastasis could be found in skin, lung and muscles.

Extra pulmonary tumors due to ionising radiation have been reported (59). A statistically significant excess risk for cancers of the stomach was demonstrated in atomic bomb survivors. In a collaborative analysis of 11 studies in underground miners, statistically significant increases in mortality for cancers of the stomach were observed (61). The authors concluded that the increases in mortality from stomach cancers were unlikely to have been caused by radon, since they were unrelated to cumulative exposure. Also the risk of gastric cancer was assumed to be elevated in former uranium miners of SDAG Wismut (62). Bay *et al* (63) did not produce evidence for constitutional ATM mutations in breast or gastric cancer families. Nevertheless breast and gastric cancers appear to be the most frequent malignancies in A-T carriers and one ATM germ-line mutation has been described in a cancer family (63). However, further investigation did not reveal cosegregation of the A-T mutations with gastric cancer in the family (63).

In our study two (4.0%) heterozygous ATM carriers for S49C mutation had Schneeberg lung cancer accepted as occupational disease. The odds ratio (OR) of the cumulative frequencies of this amino acid substitution between lung cancer patients (n=48) and all other uranium miners without cancer (n=160) was OR=6.63 (95% CI, 0.46-188.88). This difference was not significant at this low number of cases.

Carrier frequencies of any heterozygous ATM mutation, i.e., S707P, S49C or IVS10-6T→G, were observed at a higher rate in cancer patients (8.0%) than in non-cancer controls (1.88%). The elevated odds ratio (OR=4.55) may support an association of malignancies with heterozygosity for A-T mutations (22) but these preliminary findings need to be replicated in larger cohorts.

In the study of Kim *et al* (64) only one ATM genotype (IVS62160G>A) showed an association with lung cancer risk. Subjects with the A allele at this site had a significantly higher risk of lung cancer than those with the G allele (OR=1.6; 95% CI, 1.1-2.1). However the allele frequencies of four loci (24518A>G, IVS21277C>T, IVS61255T>C and IVS62160G>A) of the ATM gene in the Korean population were shown to be different from those of the SNP500Cancer database. In the study of Jialin *et al* (65) it was found that the genetic instability measured with the comet assay in lung cancer patients was significantly higher than that in the controls. On the contrary ATM protein expression levels in lung cancer patients were significantly lower than in controls.

 g correlation was found between ATM protein n and ionizing radiation induced mean tail moment or micronucleus rate.

Further investigation is focusing on the identification of other ATM gene alterations in the wide spectrum of possible A-T mutations. The clinical impact and magnitude of the cancer risk in former uranium miners will need to be corroborated by studies screening high-risk populations with respect to lung cancer.

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