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In some families, predisposition to breast cancer is inherited as a genetic trait. Thus far, a few highly penetrant genes responsible for inherited breast cancer have been identified. An important and unresolved question of breast cancer etiology is whether there are other genes which have a more moderate effect on breast cancer risk, possibly triggering disease only in the presence of specific environmental exposures, and possibly involving more women than do other inherited mutations. It has been suggested that mutations in the Ataxia-Telangiectasia gene (ATM) and cellular damage such as radiation exposure could be involved with breast cancer in this manner. In order to address this question, we are screening a population-based series of African-American and Caucasian breast cancer patients and controls as well as a series of patients with particular phenotypes for mutations in the ATM gene. This study will detect potential mutations in the ATM gene which confer breast cancer risk.

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Introduction

Breast cancer predisposition is inherited in an autosomal dominant manner in some individuals (Newman et al 1988). Currently, the inheritance of breast cancer predisposition is clearly associated with a few highly penetrant genes, most notably BRCA1 and BRCA2, in rare families (reviewed in Szabo and King 1995). In our experience with families who exhibit a high risk for inherited predisposition to cancer (families with at least four cases of breast or ovarian cancer), we estimate that approximately 20% are unresolved after screening for mutations in the BRCA1 and BRCA2 genes (Schubert et al 1997). This indicates that other, as yet unidentified, genes exist which are involved in breast cancer predisposition. Some of these currently unidentified genes may convey only a moderately increased risk of breast cancer, potentially with disease expression among mutation carriers dependent on specific environmental exposures. Such variably penetrant genetic predisposition could account for a greater population risk of breast cancer than the relatively rare highly penetrant gene mutations, although it would convey less risk to individual heterozygotes. One gene that has been suggested to play a role in moderately increased risk of breast cancer is the gene mutated in Ataxia-Telangiectasia (ATM). This study seeks to clarify the role of ATM in breast cancer predisposition. Specifically, this study asks whether ATM heterozygotes are predisposed to breast cancer.

Ataxia-Telangiectasia (AT) is a recessive genetic disorder (reviewed in Lavin and Shiloh, 1997) characterized by progressive cerebellar ataxia, blood vessel lesions (telangiectasias) and immunodeficencies. Patients affected with AT are prone to develop lymphoma and leukemia and are extremely sensitive to ionizing radiation. Various regions of ATM have been identified as specific functional domains, including a carboxy-terminal protein kinase domain (Savitsky et al 1995a, Savitsky et al 1995b). The ATM gene product has been shown to play an important role in cellular response to DNA damage, particularly that from ionizing radiation, as a component of a cell-cycle checkpoint pathway (reviewed in Hoekstra 1997). All AT patients identified to date have inherited two germ-line mutations at the ATM locus and most mutations identified truncate the ATM protein. Multiple mutations in ATM have been discovered in AT patients worldwide (The Ataxia-Telangiectasia Mutation Database), with some founder effects of particular mutations in certain populations (Stankovic et al 1998, Telatar et al 1998, Chessa et al 1997, Gilad et al 1996). Most AT patients have the classically identified severe disease phenotype, however some studies have found evidence of particular ATM mutations which are associated with variant phenotypes (Stankovic et al 1998, Gilad et al 1998, Bar-Shira et al 1997, McConville et al 1996).

Epidemiological studies of the families of children suffering from AT have shown an increased incidence of cancer, particularly breast cancer, in the relatives of such patients (Athma et al 1996, Easton 1994, Pippard et al 1988, Swift et al 1987). Family studies have also suggested that exposure to ionizing radiation increases cancer risk in ATM heterozygotes (Swift et al 1991), which is a compelling idea, particularly given the sensitivity of AT patients to radiation and the known function of the ATM gene product in cellular response to DNA damage. The focus of our study has been to investigate this question by examining breast cancer patients, both at a population level as well as those who have a phenotype that indicates possible involvement of ATM such as previous ionizing radiation exposure or an extreme response to such radiation, for ATM heterozygosity. Such a breast cancer patient-based approach complements the studies of AT families which have already been reported.

Body of Report

This study is based on the hypothesis that ATM heterozygotes have an increased susceptibility to breast cancer, particularly when exposed over the course of a lifetime to cellular damage such as ionizing radiation. We originally proposed to screen a large, population-based series of breast cancer patients completely for alterations in the ATM gene. However, more recent reports that ATM heterozygosity is not found in a large number of breast cancer patients (Chen et al 1998, FitzGerald et al 1997, Vorechovsky et al 1996a, Vorechovsky et al 1996b) and reports of founder mutations in ATM with differing effects (and therefore potentially differing cancer risks; (Stankovic et al 1998, Telatar et al 1998) have lead us to redirect our efforts in a more focused manner than was originally proposed. The studies of Vorechovsky et al, FitzGerald et al and Chen et al examined series of breast cancer patients for ATM gene mutations without finding a significant number of mutations. We feel that these results are important but not definitive; it may be that ATM mutations overall are not common in the general breast cancer population but that some founder mutations are frequent in some populations. Alternatively, it may be that ATM mutations are more prevalent in particular sub-populations of patients who have undergone triggering environmental exposure and who may have distinct cancer phenotypes. Studies indicate that certain ATM mutations lead to distinct sub-phenotypes (Van't Veer et al 1998, Gilad et al 1998, Bar-Shira et al 1997, Taylor et al 1997, McConville et al 1996), leaving open the possibility that breast cancer susceptibility is one such sub-phenotype arising from particular ATM mutation(s). Evidence for such breast cancer predisposing ATM alleles is found in the recent report of Stankovic et al (1998), which describes a founder mutation in Great Britain that may lead to a greater susceptibility to breast cancer due to its particular effects on the ATM protein. This British mutation is also interesting as the increased risk of cancer is associated with a less severe AT phenotype, possibly due to the particular functional domain of the gene which is affected. Similarly, Van't Veer et al (1998) have reported a founder ATM mutation in the Netherlands which is seen in a significant number of breast cancer patients, but not in AT patients or controls. It may be that individuals with particular breast cancer predisposing ATM alleles also have a distinct cancer phenotype, potentially involving environmental triggers to induce disease. We have therefore altered the focus of our study to examine patients at a population level for such founder mutations as well as to completely screen the gene in a targeted group of breast cancer patients with specific environmental exposures and/or phenotypes.

Given the information outlined above, which was not available at the time of writing our original proposal, we have changed the focus of our ATM screening in breast cancer patients. The population of patients that we are now screening for ATM mutations reflects a redefinition of our original hypothesis, which is that ATM heterozygotes with breast cancer may have particular cancer predisposing mutations or exhibit a particular cancer phenotype. We have therefore grouped our study into two parts; the targeted screening of specific portions of the gene encompassing known founder mutations that could predispose to breast cancer at a significant population level in a population-based set of breast cancer patients and controls, and the complete screening of ATM in a selected group of patients with particular environmental exposures or phenotypes which we believe, based on the known biology of ATM, are the most probable to be associated with ATM mutations.

For the targeted screening of particular mutations in a population-based series of breast cancer patients, we have analyzed by single-strand confirmation analysis (SSCA) the 17 regions of ATM with the highest number of founder mutations, based on the Ataxia-Telangiectasia Mutation Database, in 141 patient samples. These targeted regions of ATM encompass 28% of the coding sequence, but contain 43% of all protein truncating ATM mutations and all of the founder mutations reported to date (see Table 1). In September 1998, a new portion of the ATM gene was added to the screening list to detect a founder mutation in the Netherlands which has been hypothesized to specifically predispose to breast cancer (Van't Veer et al 1998). Data from this most recent region is not yet available as the analysis is only recently underway. The patient samples being used in this portion of the study are part of the Carolina Breast Cancer Study (CBCS), a population-based study of both African-American and Caucasian women diagnosed

above and below the age of 50 (Newman et al 1995). CBCS samples are sent to us as anonymously coded DNA samples and the University of Washington Institutional Review Board has approved our use of them in this study. The CBCS samples are ideal for examining the question of ATM in breast cancer susceptibility as extensive clinical and environmental exposure information, including radiation exposure, is already recorded from each participant. Records from any patient who is found to have a mutation in ATM would therefore be able to be examined for unusual environmental exposures or clinical phenotype. Tumor blocks are also available from most CBCS patients for LOH analysis in any patient who was shown to have an ATM mutation. The series of 141 CBCS breast cancer patients being screened for ATM mutations includes 60 African-American and 81 Caucasian women, evenly distributed in age at diagnosis above and below the age of 50. To the best of our knowledge, this series of African-American breast cancer patients is the most extensively studied for ATM mutations to date. In the case of a SSCA variant being detected in the initial patient screen, we also analyze that segment of ATM in a set of 138 CBCS controls (63 African-American and 85 Caucasian women) which were ascertained to match the patients as closely as possible in age. As not all segments of ATM had positive results in the initial SSCA screen, we analyzed 13 regions of ATM in the controls as well as the patients. The SSCA analysis of the CBCS samples is currently three-quarters complete in the cases and controls combined, with all ATM regions being analyzed at least once. Results of the SSCA and variant sequencing to date are in Table 2. If any particular ATM mutation is detected in significant numbers in CBCS patients, it will be the preliminary data needed to expand the set of patients screened to determine the population prevalence of the mutation and estimate its effects to the general US breast cancer patient population.

The second group of breast cancer patients included in our ATM analysis is that of patients with a distinct phenotype that we believe indicates possible ATM involvement in their cancer based on the known biology of ATM. These patients were selected from the following groups: previous radiation exposure, radiation sensitivity, families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected members, or a breast cancer patient who has had a child with AT. Samples from patients in this targeted series were initially screened by SSCA in the selected regions outlined above (see Table 1 and Table 2), and have also been completely screened for ATM mutations through the entire coding sequence by the protein truncation assay (PTT; Telatar et al 1998). The PTT assay is complementary to SSCA as it is a cDNA based assay that detects splicing variants as well as protein-truncating mutations, while SSCA detects heterozygosity in genomic DNA. Results from the PTT screen were negative, with the exception of the samples from the parents of an AT child, who are of course obligate heterozygotes. Sequencing of these PTT variants is currently underway.

The specific patients screened by PTT for mutations in ATM are: 8 breast cancer patients who exhibited a severe sensitivity to radiation therapy for their cancer, 5 families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected family members, 2 patients who had received radiation therapy for Hodgkin's Lymphoma before being diagnosed with breast cancer, and one set of parents of an AT child. The 5 families included in this study include 3 families with 3 cases of breast cancer, one family with 2 cases of breast and 2 cases of ovarian cancer, and one family with 1 breast, 2 ovarian, 2 colon and 5 prostate cancer cases. This range of cancer types is consistent with those seen in AT families (Morrell et al 1990). Previous BRCA1 and BRCA2 mutation testing in these families was negative. The mother of the AT child reports that she stood next to her son during his radiation therapy for cancer and that her breast subsequently affected with cancer was within the field of this radiation exposure. Her husband was included in this series as a positive control for ATM mutation detection, as the father of an AT child he is an obligate heterozygote. In the aggregate, we believe that screening this series of patients would indicate potential cancer phenotypes associated with ATM mutations and if there is evidence for particular ATM allele(s) which cause a particular susceptibility to breast cancer. The series of radiation sensitive breast cancer patients is particularly interesting, given previous data regarding the radiation sensitivity of cells taken from AT heterozygote patients (West et al 1995, Thacker 1994) and the role of ATM in cellular response to radiation (reviewed in Hoekstra 1997). Two recent reports have examined similarly radiation-sensitive breast cancer patients for ATM

mutations with negative results (Appleby et al 1997, Ramsay et al 1998), however the sum total of patients screened in the two studies was 31, and therefore our 8 patients significantly increase the total number of such patients examined for ATM mutations to date. All patients were enrolled in the study after appropriate informed consent within the structure of our University of Washington Institutional Review Board for Human Subjects agreement.

Since the original submission of this grant, the complete cDNA sequence, genomic organization, and genomic sequence of ATM have been published (Savitsky et al 1995b, Uziel et al 1996, Platzer et al 1997), eliminating the need to obtain this information from other sources. Our preliminary screening strategy for all breast cancer patients included in this study has been targeted screening by single-strand conformational analysis (SSCA) of genomic DNA for protein truncating ATM mutations with known genomic causes reported multiple times (Table 1). Many of the mutations identified in ATM to date are deletions in cDNA for which the genomic basis is unclear, such variants were disregarded in this targeted screen as they have the potential to be artifacts. The polymerase chain reaction (PCR) primers used in this SSCA analysis were those of Vorechovsky et al (1996a). Fragments screened to date include 2581 nucleotides of the 9168 nucleotides of the ATM coding region (Savitsky et al 1995b). This encompasses 43% of the ATM coding region and the adjoining mRNA splicing regions of the exons examined. Results from the initial SSCA screen are described in Table 2.

Future plans are to expand our patient series as warranted from initial results. If there is evidence for ATM mutations in a particular group of breast cancer patients (such as the radiation sensitive patients) or for particular ATM mutation(s) present in the CBCS breast cancer patients, then we will expand the study to include more patients from the relevant group. For example, if we find evidence for ATM mutations in the radiation sensitive breast cancer patients, we will expand our ATM screening to more such patients. With positive preliminary data on ATM mutations in a particular subset of patients, we would be able to embark on collaborations with our clinical colleagues to obtain more such patient samples. Alternatively, if there is evidence for a particular ATM mutation which predisposes to breast cancer, we will expand our screen for that ATM mutation in more breast cancer patients. Functional analysis of any ATM mutation would also be carried out, as discussed in the original proposal. LOH at the ATM locus in tumors from patients with ATM mutations is also planned, as discussed in the original proposal. We have already obtained tumor samples from the families involved in this study, other samples will be available as needed. Although the IDEA grant which partially funded this study has ended, the postdoctoral fellowship (DAMD17-96-1-6248: Elizabeth L. Schubert, Ph.D.) which supports the research is ongoing and the project is continuing as outlined above. We plan to publish our work as soon as the SSCA analysis and variant sequencing of the CBCS patient samples is complete.

Table 1: Regions of ATM with Common Protein Truncating Mutations
(The ATM Mutation Database, July 6 1998 update)

Region	Number of individual mutations reported	Total number of mutations reported
exon 12	6	11
exon 15	2	2
exon 16	2	4
exon 20	2	5
exon 24	3	3
exon 39	3	3
intron 40	1	3
exon 43	4	5
exon 46	5	8
exon 51	3	5
exon 52	2	2
exon 53	1	7
exon 54	3	10
exon 55	6	10
exon 58	3	6
exon 63	4	5
exon 64	4	4
17 fragments	54 individual mutations	93 total mutations

The sum total of truncating mutations reported in these genomic regions is 93, or 43% of a total number of 216 truncating mutations reported in the ATM Mutation Database. These regions encompass 2581 bp of the ATM coding sequence, or 28% of the entire 9168 bp.

As of September 1998, exon 11 was added to the analysis to detect a founder mutation seen in breast cancer patients in the Netherlands (Van't Veer et al 1998).

Table 2: Data from SSCA analysis of selected genomic regions of ATM

A. CBCS Patients

Region	Times the same variant was detected (by race)	Sequencing results[1]
exon 12	African-American and Caucasian	1236-3 T_N polymorphism
exon 15	1 (African-American)	2096 A>G (Glu>Gly)[2]
exon 16	1 (Caucasian)	2125+22 A>C
exon 39	1 (Caucasian)	5558 A>T (silent)[2]
exon 39	1 (African-American)	incomplete
exon 43	6 (3 African-American / 3 Caucasian)	6025 T>G (Tyr>Asp)[2,3]
exon 46	1 (African-American)	incomplete
exon 52	1 (African-American)	incomplete
exon 53	3 (1 African-American / 2 Caucasian)	incomplete
exon 54	2 (1 African-American / 1 Caucasian)	incomplete
exon 58	1 (Caucasian)	incomplete
exon 63	10 (7 African-American / 3 Caucasian)	8847 A>T (silent)[2,3]

B. CBCS Controls[4]

Region	Times the same variant was detected (by race)	Sequencing results[1]
exon 12	African-American and Caucasian	1236-3 T_N polymorphism
exon 16	1 (Caucasian)	2125+22 A>C
exon 39	3 (Caucasian)	5558 A>T (silent)[2]
exon 43	1 (African-American)	incomplete
exon 52	1 (Caucasian)	incomplete
exon 53	1 (Caucasian)	incomplete
exon 63	3 (2 African-American / 1 Caucasian)	incomplete

C. Non-CBCS patients (selected by phenotype)

Region	Times the same variant was detected (phenotype)	Sequencing results[1]
exon 12	3 (Radiation sensitive)	1544 G>A (Ser>Asn)[2,3]
exon 12	1 (AT heterozygote)	1591 G>C (Ala>Pro)[2,3]
exon 39	7 (radiation sensitive, AT heterozygote, family)	incomplete
exon 55	1 (family; does not segregate with disease)	incomplete
exon 63	1 (family; does not segregate with disease)	8847 A>T (silent)[2,3]
exon 64	1 (family; does not segregate with disease)	incomplete

[1] Numbers given are based on the ATM cDNA, nt 1 is the start of translation. Sequencing of variants is still underway and is not complete in all cases.
[2] Previously unreported variant (Ataxia-Telangiectasia Mutation Database)
[3] Unconfirmed variant; resequencing is underway to confirm initial sequence results
[4] CBCS controls were not analyzed in regions where no variants were detected in patients

Conclusions

This study is still in progress, however after significant screening we have not yet uncovered a truncating ATM mutation in any breast cancer patient except in an obligate ATM mutation heterozygote. The variants that we have identified to date have all been silent or missense variants, and do not clearly result in loss of function of the ATM protein. Final results of the CBCS population portion of this study will indicate if any variant is seen in significantly higher numbers in breast cancer cases than in controls. Final results in the selected patient portion of this study will indicate if ATM mutations predispose to particular cancer phenotypes. It is premature at this time to make final conclusions, but with much of the study complete, data so far indicates that protein truncating ATM mutations are not extremely common in breast cancer patients from the CBCS population series or in phenotypic groups analyzed in this study.

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