Role of the Nijmegen Breakage Syndrome 1 Gene in Familial and Sporadic Prostate Cancer

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Abstract

The Nijmegen breakage syndrome 1 (*NBS1*) gene, which participates in DNA double strand break repair, has been postulated to be a susceptibility factor for a number of cancers, including prostate cancer. Numerous mutations have been identified in *NBS1*, including the founder mutation 657del5. In this study, a number of analyses were done to determine whether mutations in *NBS1* are associated with an increased risk for prostate cancer. The frequency of the 657del5 mutation in both familial prostate cancer cases (1,819 affected men among 909 families) and sporadic prostate cancer cases (1,218 affected men) collected from five centers participating in the International Consortium for Prostate Cancer Genetics were compared with that found in 697 normal controls. Seven individuals were identified to carry the mutation among the 3,037 cases screened: four in the familial group (three from one family and one from another) and three in the sporadic cases. The carrier frequency was 0.22% (2 of 909) for the probands and 0.25% (3 of 1,218) for the sporadic cases of prostate cancer. The 657del5 mutation was not detected in either the 293 unaffected members of the prostate cancer families or in the 697 control samples tested. The entire *NBS1* gene was also sequenced in 20 of the youngest affected individuals from the Finnish group of familial cases to identify the presence of possible mutations in this high-risk group. One rare (D95N) and one common (E185Q) missense alteration was identified. More detailed analyses of the E185Q polymorphism, along with a third rare variant (R215W), failed to show an association with prostate cancer. Because the 657del5 mutation was absent from the control population, we are unable to determine if this alteration predisposes to prostate cancer. However, our data does suggest that mutations within *NBS1*, and in particular, 657del5, do not significantly contribute to the overall prostate cancer burden within our patient samples. (Cancer Epidemiol Biomarkers Prev 2006;15(5):935–8)

Introduction

Prostate cancer is one of the most common malignancies among men in western countries and the second most frequent for deaths due to cancer (1). In the U.S., there are approximately 232,000 newly diagnosed cases and 30,000 deaths annually. The lifetime probability of developing invasive disease is ~18%. Although older age and African-American ancestry have long been recognized as important risk factors, there is extensive evidence supporting the notion that genetics plays a key role. This evidence comes from a wide range of studies including familial aggregation, twin studies, family-based linkage studies, and molecular epidemiologic studies of both rare and common polymorphisms of candidate genes (2, 3). However, the evidence also points towards a much more complex genetic basis than initially anticipated. Early results from linkage analyses provided targeted candidate regions for prostate cancer susceptibility loci, including *HPC1* on chromosome 1q23-25, *PCAP* on chromosome 1q42-43, *CAPB* on chromosome 1p36, chromosome 8p22-23, *HPC2* on chromosome 17p, *HPC20* on chromosome 20q13, and *HPCX* on chromosome Xq27-28. A few of the targeted linkage studies led to the identification of candidate susceptibility genes including *RNASEL* (HPC1) on chromosome 1, *ELAC2* (HPC2) on chromosome 17, and *MSR1* on chromosome 8 (2, 3). However, confirmatory studies for these genes, along with multiple microsatellite-based genome-wide linkage screens have provided mixed results (2, 3). A number of studies provide strong support, both functional and epidemiologic, yet other studies suggest that their role may be small (2-4). As is the case with other complex genetic disorders, familial prostate cancer is likely to be very heterogeneous, with the presence of several lower penetrant susceptibility genes.

The Nijmegen breakage syndrome 1 (*NBS1*) gene, located on chromosome 8q21, has recently been postulated to be a prostate cancer susceptibility gene (5). NBS1, also known as p95, is part of the MRE11/RAD50 complex and is involved in DNA double strand break repair (6). Individuals carrying biallelic mutations in *NBS1* have an autosomal recessive disorder, Nijmegen breakage syndrome, and are characterized by the presence of microcephaly, facial deformities, mental retardation, impaired immunity, and increased risk to multiple

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cancers. Numerous mutations have been identified for Nijmegen breakage syndrome, including a common founder mutation in exon 6, 657del5. This founder mutation has been found with a high frequency in the Slavic population, which includes individuals primarily from Poland, Ukraine, and the Czech Republic. A number of studies suggest that heterozygosity for a mutation in *NBS1* may be associated with elevated risk for some cancers (7-13), including prostate cancer (5). Cybulski et al. (5) showed an increased risk for prostate cancer among carriers of the 657del5 mutation in both familial and non-familial cases from Poland. Among the familial cases, this mutation co-segregated with disease and tumor analysis showed that *NBS1* mutation carriers lost the wild-type allele, suggesting a possible mechanism within the tumor.

To confirm that alterations within the *NBS1* gene increase the risk of prostate cancer, we compared the frequency of the 657del5 mutation in both familial (1,819 affected individuals among 909 families) and sporadic prostate cancer cases (1,218 affected individuals) from five separate study populations to that found in 697 unaffected controls. In a smaller subset, we also examined the frequency of both common and rare *NBS1* variants for associations with prostate cancer. Lastly, to explore if there are other unknown mutations and/or polymorphisms associated with prostate cancer, the entire *NBS1* gene was sequenced in 20 men with familial prostate cancer.

Materials and Methods

Sample Collection. Samples from five separate study populations were used in this study. These include the following.

Mayo Clinic. Four hundred and twenty-eight affected men from 178 prostate cancer families, 492 men with sporadic prostate cancer, and 489 population-based controls (14) were tested for the 657del5 mutation. Individuals from this group are primarily Caucasian (three of the familial cases, five of the sporadic cases, and three of the controls were non-Caucasian: seven Hispanic, one African-American, and three other). The mean age at diagnosis for the familial and sporadic cases was 66 years (range, 45-84) and 64 years (range, 46-79), respectively.

Tampere. For the 657del5 mutation, 164 probands from 164 prostate cancer families and 380 unselected cases of prostate cancer (15, 16) were analyzed. For D95N, 121 familial cases (probands), 613 unselected cases, and 440 population-based controls were analyzed. For E185Q, 121 familial cases (probands), 200 unselected cases, and 200 population-based controls were analyzed. Lastly, the entire gene was sequenced from the youngest affected patient available from 20 of the families with prostate cancer. These were selected so that four families had five or more affected first- or second-degree relatives, eight families had four affected first- or second-degree relatives and eight families had three or two affected first- or second-degree relatives. The mean age at diagnosis for the patients was 58.3 years (range, 44-72.6).

Michigan. Seven hundred and thirty-four affected men and 182 unaffected men from 261 prostate cancer families from the University of Michigan Prostate Cancer Genetics Project were tested for the 657del5 mutation. The prostate cancer families that were selected for this analysis include 167 of the 175 families used for a genome-wide scan for prostate cancer susceptibility loci (17) and 94 additional families that met the same criteria as the families used for the genome-wide scan (families with three or more confirmed cases of prostate cancer or families in which there were two men affected with prostate cancer before age 55 years). DNA samples were available from at least two affected men (excluding father/son pairs) in each of the families. Eight additional samples from eight unrelated men with prostate cancer were also tested. These men were selected based on age at diagnosis, <40 years. Consistent with the racial/ethnic distribution of participants in the Prostate Cancer Genetics Project, 78 of 1,107 samples came from African-American individuals and 7 of 1,107 samples were from Asian individuals.

Ulm. Two hundred and ninety-nine affected men and 111 unaffected men from 139 prostate cancer families, 338 cases of sporadic prostate cancer, and 208 normal controls (18) were tested for the 657del5 and R215W mutations. Individuals from this group were Caucasian from Central Europe (Germany). The mean age at diagnosis was 64.6 years (range, 47-89) for the familial cases and 63.7 years (range, 42-84) for the sporadic patients.

Johns Hopkins. A single affected man from 167 prostate cancer families and all family members from five families reporting Polish descent were tested (a total of 27 additional samples; ref. 19) were tested for the 657del5 mutation. Individuals from this group are primarily North European Caucasian.

Genotyping. For the majority of samples, genotyping was done at each individual center. Samples were genotyped for the 657del5 alteration using either an ABI3100 (Applied Biosystems, Foster City, CA) and fluorescently-labeled PCR product (Mayo, Michigan, and Ulm), direct sequencing using an Amersham Megabase (Johns Hopkins University), or by DNA sequencing (Tampere). E185Q and D95N genotypes were obtained using minisequencing (Tampere; ref. 20), whereas ddNTP-primer extension (Applied Biosystems) was used to determine the R215W genotypes (Ulm). Reaction conditions and primer sequences are available upon request.

Statistical Analysis. Association of the *NBS1* variants, E185Q and D95N, with prostate cancer was tested by logistic regression analysis using the SPSS statistical software package (SPSS 11.0).

Results

We compared the frequency of the 657del5 mutation in both familial (1,819 affected individuals among 909 families) and sporadic cases of prostate cancer (1,218 affected individuals) from five separate study samples to that found in 697 normal controls (Table 1). A total of seven carriers of the 657del5 mutation were identified among 3,037 cases screened. Among the familial cases (n = 1819), four carriers were identified in

Table 1. Frequency of 657del5 mutation in familial prostate cancer, sporadic prostate cancer and in normal controls

	No. of 657del5 carriers/total tested by group					
	Tampere	Johns Hopkins	Michigan	Ulm	Mayo Clinic	Total
Affected familial	0 of 164 (164 fam)	0 of 194 (167 fam)	1 of 734 (261 fam)	0 of 299 (139 fam)	3 of 428 (178 fam)	4 of 1,819 (909 fam)
Unaffected familial			0 of 182	0 of 111		0 of 293
Sporadic	0 of 380		0 of 8	1 of 338	2 of 492	3 of 1,218
Control				0 of 208	0 of 489	0 of 697

Table 2. *NBS1* mutation spectrum in 20 cases of familial prostate cancer

Mutation	Amino acid change	Exon/Intron
102 A→G	L34 (silent)	Exon 2
283 G→A	D95N	Exon 3
553 G→C	E185Q	Exon 5
702 + 149 T→C	—	Intron 6
896 + 36 G→A	—	Intron 7
1,124 + 18 C→T	—	Intron 9
1,124 + 91 C→A	—	Intron 9
1,197 C→T	D399 (silent)	Exon 10
1,919-7 A→G	—	Intron 12
2,017 G→A	P673 (silent)	Exon 13
2,072-30 A→T	—	Intron 13
2,235 + 88 C→G	—	Intron 15
2,266 + 273 G→A	—	3-Untranslated region

two families (three from one family and one from another). The carrier frequency for the probands was 0.22% (2 of 909). Among the sporadic cases (n = 1218), three carriers were identified for a carrier frequency of 0.25%. The 657del5 mutation was not detected in either the 293 unaffected members of the prostate cancer families or in the 697 control samples tested.

To determine if there are other unknown mutations in *NBS1*, the entire *NBS1* gene was sequenced in 20 of the youngest affected cases from the Finnish group of familial cases. Two missense alterations were identified, one common (E185Q) and one rare (D95N). No other plausible causative mutations were identified within the coding region of *NBS1*. These results are summarized in Table 2.

For the Finnish subset of patients, the frequencies of the two *NBS1* alterations (D95N and E185Q) were examined for associations with prostate cancer (Table 3). Similarly, the frequency of another rare alteration, R215W (643 C>T), was examined within the Ulm subset of patients (Table 3). No significant associations were observed for either the E185Q or the R215W variant. Testing D95N for an association with prostate cancer was not possible because this alteration was not detected in the control population.

Discussion

In this study, we have taken advantage of samples collected from five centers participating in the International Consortium for Prostate Cancer Genetics (University of Tampere, University of Michigan, Johns Hopkins University, Universitätsklinikum Ulm, and the Mayo Clinic) to confirm that mutations in *NBS1* confer susceptibility to either sporadic or familial prostate cancer. The International Consortium for Prostate Cancer Genetics is a working group of investigators, consisting of approximately 11 independent groups from >20 institutions from North America, Europe, and Australia who share a common interest in genetic susceptibility for prostate cancer, and all of whom have major ongoing, individual research efforts in this area (19). The International Consortium for Prostate Cancer Genetics was formed in 1996 to explore collaborative studies in the area of prostate cancer, and in particular, to provide a mechanism by which large-scale pooled analyses could be done. Given the heterogeneity and complexity of prostate cancer and the historical difficulties of replicating results, the International Consortium for Prostate Cancer Genetics provides a valuable resource to perform large-scale genetic studies in hereditary prostate cancer.

Overall, our data indicate that mutation in *NBS1*, in particular, 657del5, does not significantly contribute to the overall cancer burden among either the sporadic or the familial prostate cancers tested in this study. Although a number of published reports have suggested that mutations in *NBS1*, especially 657del5, is associated with elevated risk for some cancers, including ovarian (13), breast (7, 8, 10), melanoma (7, 9), and lymphoid malignancies (7, 11, 12), such findings have not been replicated in other studies (21-24). For prostate cancer, Cybulski et al. (5) found that the 657del5 mutation was a risk factor. They screened 56 familial prostate cancer patients, 305 sporadic cases, and 1,500 normal controls within a Slavic population. Five of the familial cases (9%, $P < 0.0001$), seven of the non-familial cases (2.2%, $P = 0.01$), and nine control subjects (0.6%) carried the 657del5 mutation. Data from our study show a significantly lower frequency of the 657del5 alteration among cases and controls than that reported by Cybulski et al. In this current study, both the familial and sporadic groups had approximately the same frequency, 0.22% and 0.25%, respectively, but this mutation was not found in any of the 697 controls tested. Because the 657del5 mutation was absent in our control population, testing for an association was not possible. The lack of this alteration among the controls is not necessarily surprising as the prevalence of this alteration is low and varies considerably between different geographic regions, the highest being in the Slavic population due to a founder effect (25). As a result, our ability to determine if the *NBS1* 657del5 mutation truly increases risk for prostate cancer cannot be determined with our study populations. In non-Slavic populations, in which the frequency is lower and poorly defined, large population sizes will be necessary to achieve the power needed to detect an association, if present. Even in the current study of 3,000 cases and 697 controls, the number of cases and controls is not sufficient to adequately address this

Table 3. Association-based analysis for D95N, E185Q, and R215W

Sample and variant	No. of carriers/total (frequency)	Odds ratio (95% confidence interval)	*P*
D95N (Tampere)			
Controls	0 of 440 (0%)	—	—
Unselected prostate cancer	1 of 613 (0.16%)	—	—
Familial prostate cancer	1 of 121 (0.83%)	—	—
E185Q (Tampere)			
Controls (G/C)	79 of 200 (39.5%)	1	
Controls (C/C)	32 of 200 (16.0%)	1	
Unselected prostate cancer (G/C)	94 of 200 (47.0%)	1.59 (0.86-2.91)	0.14
Unselected prostate cancer (C/C)	24 of 200 (12.0%)	1.23 (0.67-2.26)	0.51
Familial prostate cancer (G/C)	63 of 121 (52.07%)	1.42 (0.73-2.76)	0.30
Familial prostate cancer (C/C)	18 of 121 (14.9%)	0.80 (0.40-1.59)	0.52
R215W (Ulm)			
Controls	3 of 208 (1.44%)	1	
Unaffected familial	1 of 111 (0.90%)		
Sporadic prostate cancer	6 of 338 (1.78%)	1.24 (0.31-4.99)	0.77
Familial prostate cancer	2 of 139 (1.44%)	1.0 (0.17-6.05)	1.0

question. For example, to have 90% power to detect a difference of 0.25% among cases versus 0.1% among controls, >12,000 subjects would be needed for each group. However, of more importance, would it be necessary to detect such a small difference? Probably not. Although we cannot determine if the 657del5 mutation increases risk for prostate cancer, we can conclude that this alteration is so rare that it has little, if any, contribution to the overall risk for prostate cancer in the cases examined in this study.

Data from additional analyses done in this study, however, also failed to support the involvement of *NBS1* among our prostate cancer cases. First, sequencing of *NBS1* in a subset of the Finnish group of familial prostate cancer (n = 20) revealed one common (E185Q) and one rare (D95N) missense variant. However, it is important to note that our power to detect rare variants in this small group is limited. For this sample size, the variant frequency would have to be at least 3.94% in order to have an 80% chance of finding at least one variant among 40 chromosomes. The D95N alteration is found within the forkhead-associated domain, a putative nuclear signaling domain, of the *NBS1* gene. Although this amino acid position is highly conserved among a variety of species, this amino acid substitution is not necessarily predicted to be highly damaging. Thus, the clinical significance of this alteration is uncertain. Although a statistical analysis was not possible, the D95N alteration also does not seem to significantly contribute to either sporadic or familial prostate cancer, having identified only two carriers among both groups of cases (n = 734). A follow-up case-control analysis for E185Q and R215W did not show a significant association with prostate cancer. In other published reports, the common polymorphism, E185Q, showed an association with lung cancer (26), but not with breast (27-29), bladder (30), or non-Hodgkin lymphoma (31). The rare variant, R215W, has also been implicated as a pathogenic mutation in Nijmegen breakage syndrome (32). Conservation studies also show that this position is highly conserved and that this change is predicted to be damaging (8, 13).

In summary, based on the low frequency of mutations observed in this study, we are not able to determine if *NBS1* is truly a susceptibility gene for prostate cancer. However, these data do suggest that the attributable risk for the 657del5 in a non-Slavic population is quite low. This mutation was responsible for less than a fraction of 1% of the prostate cancer in the population tested.

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