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ORIGINAL ARTICLE

Identification of a novel *NBN* truncating mutation in a family with hereditary prostate cancer

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Abstract Nibrin (*NBN*), located on chromosome 8q21 is a gene involved in DNA double-strand break repair that has been implicated in the rare autosomal recessive chromosomal instability syndrome known as Nijmegen Breakage Syndrome (NBS). NBS is characterized by specific physical characteristics (microcephaly and dysmorphic facies), immunodeficiency, and increased risk of malignancy. Individuals who are heterozygous for *NBN* mutations are clinically asymptomatic, but may display an elevated risk for certain cancers including, but not limited to, ovarian and prostate cancer as well as various lymphoid malignancies. In this study, 94 unrelated familial prostate cancer cases from the University of Michigan Prostate Cancer Genetics Project ($n = 54$) and Johns Hopkins University ($n = 40$) were subjected to targeted next-generation sequencing of the exons, including UTRs, of *NBN*. One individual of European descent, diagnosed with prostate cancer at age 52, was identified to have a heterozygous 2117 C > G mutation in exon 14 of the gene, that results in a premature stop at codon 706 (S706X). Sequencing of germline DNA from additional male relatives showed partial co-segregation of the *NBN* S706X mutation with prostate cancer. This *NBN* mutation was not observed among 2768 unrelated European men (1859 with prostate cancer and 909 controls). NBN is involved in double-strand break repair as a component of the MRE11 (meiotic recombination 11)/RAD50/NBN genomic stability complex. The S706X mutation truncates the protein in a highly conserved region of NBN near the MRE11 binding site, thus suggesting a role for rare *NBN* mutations in prostate cancer susceptibility.

Keywords Cancer · Hereditary · Prostate · NBN gene

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Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosed among American men and the second leading cause of cancer death with an estimated 241,740 new cases and 28,170 deaths expected in the United States in 2012 [1]. In addition to increasing age and African American race, family history is also a recognized risk factor for prostate cancer. The diagnosis of sporadic prostate cancer cases remains high in the general population, suggesting that disease risk may be influenced by additional risk factors such as diet, obesity, and environment. However, familial aggregation of prostate cancer suggests that in

some cases, heritable genetic factors may play a key role in the development of prostate cancer.

Initial segregation analyses of familial prostate cancer concluded that inherited predisposition was due to the presence of at least one highly penetrant autosomal dominant prostate cancer predisposition gene [2–4]. Though subsequent linkage (e.g. *HPC1* [5], *HPCX* [6], *HPC20* [7]) and association (e.g. [8, 9, 10]) studies have revealed several prostate cancer susceptibility loci, these results have not been strongly replicated nor have they led to the identification of a causative gene mutation(s) capable of explaining a large percentage of familial risk. Evidence from these and other studies suggest that familial prostate cancer is a complex heterogeneous disease that may be influenced by the inheritance of less common risk loci with moderate penetrance. Next-generation sequencing of candidate gene regions can be useful in identifying rare variants that may explain prostate cancer risk in a small number of families.

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder that is characterized by microcephaly, immunodeficiency, chromosomal instability and sensitivity to ionizing radiation [11]. The gene for Nijmegen breakage syndrome (*NBS1*), also known as Nibrin (*NBN*) is located on chromosome 8q21; mutations in *NBN* are known to cause NBS [12]. To date, several NBS-causing mutations have been identified, the most prevalent being the *NBN* founder mutation 657del5 which is estimated to account for more than 90 % of all mutant alleles [13]. This mutation, found in exon 6 of *NBN,* is most often observed in members of the Slavic population which includes people from Poland, Ukraine, and the Czech Republic. Individuals heterozygous for *NBN* mutations are clinically asymptomatic however; there have been reports of increased incidence of various malignancies [14], particularly breast, prostate, colorectal, and lymphoid cancers (especially lymphoblastic leukemia and non-Hodgkin's lymphoma). In the present study, we discuss the identification of a novel truncating mutation in *NBN* as a result of targeted next-generation sequencing of 94 familial prostate cancer cases from the University of Michigan and the Johns Hopkins University.

Materials and methods

Patient selection

University of Michigan prostate cancer genetics project (UM-PCGP)

UM-PCGP prostate cancer cases were restricted to (1) men diagnosed with prostate cancer with at least one living first- or second-degree relative also diagnosed with prostate cancer or (2) men diagnosed with prostate cancer at <56 years of age irrespective of family history. The diagnosis of prostate cancer was confirmed by medical record review whenever possible. All subjects provided written informed consent to participate in the study and all protocol and consent documents were approved by the University of Michigan Medical School Institutional Review Board.

Johns Hopkins University (JHU)

Hereditary prostate cancer (HPC) families each had at least three first-degree relatives affected with prostate cancer. The diagnosis of prostate cancer was verified by medical record review. Radical prostatectomy cases were men who underwent surgery for treatment of prostate cancer at the Johns Hopkins Hospital (JHH). Controls for this study consisted of men who underwent screening for prostate cancer, including measuring serum prostate-specific antigen (PSA) levels and digital rectal examination at JHH, Johns Hopkins Bayview Medical Center, Johns Hopkins University Applied Physics Laboratory (Columbia, MD) and several other locations in the mid-Atlantic area. Additional inclusion criteria required control subjects to have knowledge of prostate cancer ancestry by self-report and lack a prostate cancer diagnosis. For all JHU studies, research proposals were reviewed and approved by the institutional review board.

Targeted sequencing of NBN gene

We selected the youngest prostate cancer case with available DNA from 94 prostate cancer families (40 families from JHU and 54 from the UM-PCGP) [15]. Seven families were of African descent, 2 were of Asian descent, and the remaining 85 were of European descent. A primer library was designed for amplification of 8068 base pairs (bp) of *NBN* including all coding regions, exons, intron/exon boundaries, and 5′ and 3′ untranslated regions. We used the RainDance RDT 1000 system (RainDance Technologies, Inc., Lexington, MA) to amplify 3 μg of sheared genomic DNA from each sample using our primer library. Purified amplicons were used as templates for sequencing using the Life Technologies SOLiD^{TM} system version 4.0 fragment library methodologies (Life Technologies Corporation, Carlsbad, CA). Sequence data processing was performed using Bioscope to align the sequences to the genomic reference (Build 36, hg18). Variant detection was performed using SamTools 1.3 [16] and SolSNP 1.1. We confirmed and tested all variant sequences in family members using standard Sanger sequencing, capillary electrophoresis technology and BigDye® Terminator chemistry (Applied Biosystems, Carlsbad, CA).

Genotyping of NBN variants

We genotyped identified *NBN* variants using the MassARRAY system (Sequenom, San Diego CA).

Results

Analysis of *NBN* revealed a novel heterozygous 2117 C > G mutation (Fig. 1) in a man diagnosed with prostate cancer at age 52 (NM_002485). The nonsense mutation is a single C to G transversion in exon 14 resulting in a coding change from TCA to TGA (Serine 706 Stop or S706X). This mutation, which codes for a truncated NBN protein that lacks the C-terminal ataxia-telangiectasia mutated (ATM) recruitment motif, was not present in 93 additional HPC probands.

The pedigree of the family in which the *NBN* mutation was identified is depicted in Fig. 2, and features four individuals diagnosed with prostate cancer, as well as one case each of lymphoma, bladder cancer, and melanoma. Subsequent Sanger sequencing of DNA samples collected from three additional family members revealed that the proband's father, who had been diagnosed with prostate and bladder cancer, and a brother who remains unaffected at age 59, were both carriers of the S706X mutation; however the proband's paternal uncle with prostate cancer, diagnosed at age 70, was not a carrier (Fig. 2). Neither of the affected men who were *NBN* S706X carriers had intermediate or high risk prostate cancer based on available clinical information. DNA samples from the proband's paternal aunt with non-Hodgkin's lymphoma and son with melanoma were not available for testing.

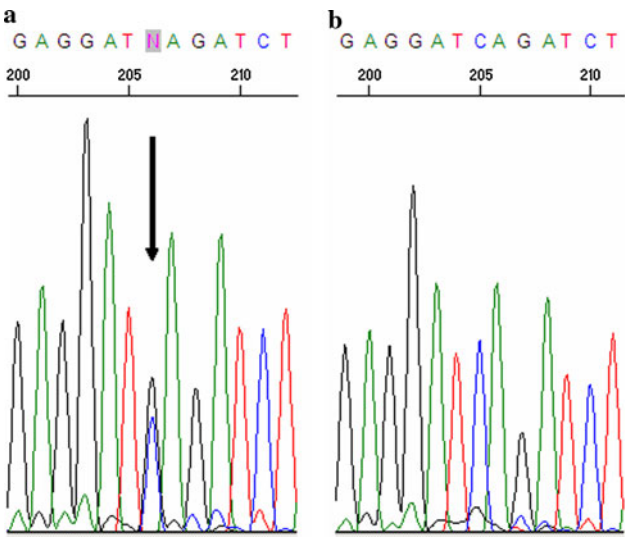

Fig. 1 Sequence chromatogram of exon 14 of *NBN* in the proband demonstrating the 2117 C > G mutation (**a**) and wild-type sequence (**b**). The *arrow* indicates the location of the base substitution

The *NBN* S706X mutation was not observed among 1859 men with prostate cancer (JHU radical prostatectomy cases) and 909 male controls, all of whom describe themselves to be of European descent. Coding variants that were detected as a result of targeted next-generation sequencing of *NBN* in 85 individuals of European descent are summarized in Table 1.

Discussion

Targeted next-generation sequencing of the *NBN* gene resulted in the identification of a novel nonsense mutation S706X in one of 94 HPC families. The mutation was identified in two of three family members diagnosed with prostate cancer and therefore demonstrated incomplete segregation with prostate cancer in this pedigree.

A previous study by Cybulski et al. [17] implicated *NBN* as a prostate cancer susceptibility gene due to evidence of increased prostate cancer incidence in homozygous carriers of the 657del5 Eastern European founder mutation. The *NBN* 657del5 mutation was evaluated in Polish individuals and was found in 9 of 340 unselected patients with prostate cancer (2.6 %) compared with only 9 of 1500 (0.6 %) control subjects from the general population (OR = 4.5; 95 % confidence interval (1.7–11.5); $p = 0.002$) A follow-up study by Hebbring et al. [18] could not confirm this hypothesis due to the inability to identify the 657del5 mutation in DNA samples from 293 unaffected members of prostate cancer families and 697 control samples.

Nibrin or NBN is a component of the hMRE11 (meiotic recombination 11)/hRad50/NBN protein complex that is involved in initiating a response to DNA damage and is linked to DNA double-strand break repair [19]. Full length NBN consists of 754 amino acids and has a molecular weight of 95 kDa. The protein has three regions: the N-terminus, the central region, and the C-terminus (Fig. 3a). The N-terminal domain contains a fork-head associated (FHA) domain (amino acids 24–109) and two breast cancer C-terminus (BRCT) domains (amino acids 114–183 and 221–291) [20–22]. The central region is composed of consensus sequences for phosphorylation by ataxia-telangiectasia mutated (ATM) or ataxia-telangiectasia and Rad3-related (ATR) kinases [23]. The C-terminal region contains an MRE11 (amino acids 665–693) binding domain [24] and an ATM (amino acids 734–754) recruitment motif [25].

The S706X mutation results in a truncated NBN protein that lacks the extreme C-terminal ATM recruitment motif (ARM). The ATM protein kinase plays a role in suppressing chromosomal abnormalities by functioning as an agent of DNA damage response [26]. Whereas ATR is activated by single-strand breaks, ATM appears to be

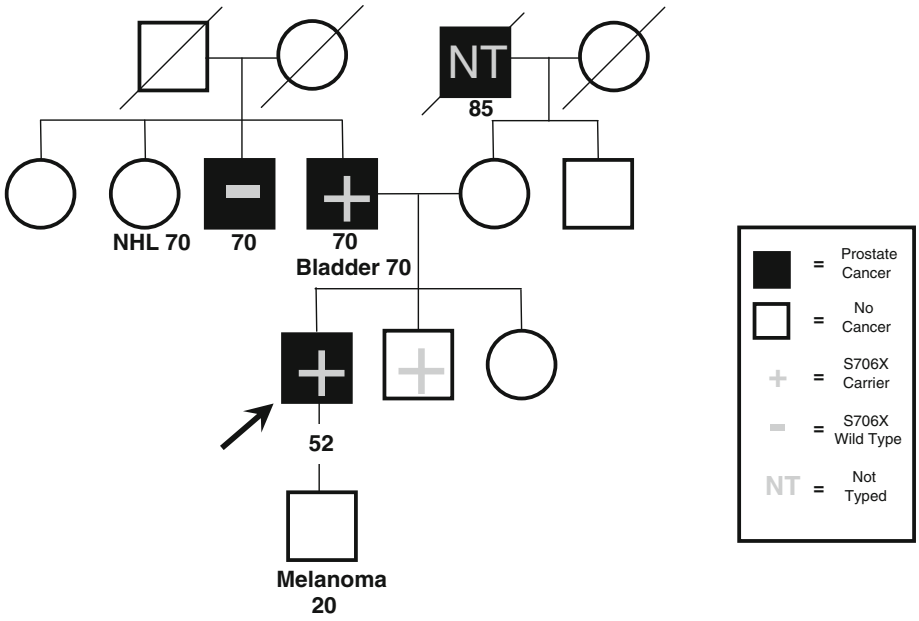

Fig. 2 Pedigree segregating the *NBN* S706X mutation. The proband initially selected for sequencing is indicated by the *arrow*. With the exception of the proband, the ages of diagnosis have been rounded to the nearest 5-year interval and are shown under the subject. The remaining symbols are described in the key. *NHL* non-Hodgkins lymphoma

Table 1 Summary of *NBN* variants from targeted next-generation sequencing of 85 prostate cancer cases of European descent

Chr. position GRCh37	Reference	Variant	dbSNP ID	Substitution	SNP Type	# of individuals	MAF[a] (%)	ESP [29] MAF[a] (%)
90955548	G	C	Novel	S706X	Nonsense	1	1.06	0
90955583	A	C	rs7823648	P694P	Synonymous	1	1.06	0.1
90958422	T	C	rs1061302	P672P	Synonymous	50	53.19	31.36
90967711	A	G	rs709816	D399D	Synonymous	54	57.44	35.56
90990479	C	G	rs1805794	E185Q	Missense	46	48.94	31.41
90990534	A	G	Novel	I166I	Synonymous	1	1.06	0
90993061	A	G	rs61754795	A127A	Synonymous	3	3.19	0.41
90995019	C	T	rs1063045	L34L	Synonymous	54	57.44	31.5

[a] *MAF* minor allele frequency, *ESP* MAF are listed for individuals of European descent

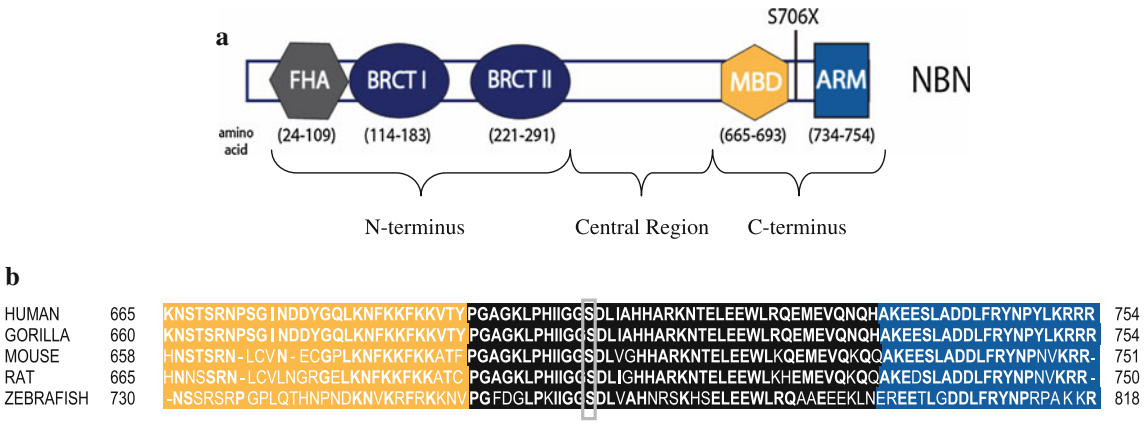

Fig. 3 The NBN S706X mutation results in deletion of the ATM recruitment motif. **a** The N-terminus of the NBN protein contains a fork-head associated (FHA) domain and two breast cancer C-terminus (BRCT) domains. The C-terminal region contains an MRE11 binding domain (MBD) and an ATM recruitment motif (ARM). **b** Novel nonsense mutation S706X affects an amino acid located in the C-terminus in a highly conserved region of NBN

specific to double strand breaks (DSBs). The hMRE11/hRad50/NBN protein complex requires the highly conserved C-terminal 20 amino acids of NBN (Fig. 3b), which comprise the ARM, for interaction with ATM [25]. In the absence of the full-length protein, ATM is not actively recruited to the site of DNA damage, thus preventing efficient DSB repair. In addition, though heterozygous carriers of *NBN* mutations maintain the ability to produce full length NBN, the resulting truncation may be sufficient to promote tumorigenesis by means of haplo-insufficiency. Note that in the original report by Cybulski et al. [17], the majority (seven of eight) of the prostate cancer tumors from men who were heterozygous carriers of the founder *NBN* 657del5 mutation demonstrated loss of heterozygosity suggesting that *NBN* is acting as a classical tumor suppressor gene to promote cancer growth. Future tumor as well as in vitro studies and animal models should address this issue [27].

In the present study, we focused on identifying germline variants in *NBN*, an established prostate cancer candidate gene. Heterozygous carriers of deleterious *NBN* mutations have been shown to be at increased risk for several common malignancies including prostate cancer. Based on its deletion of the ATM recruitment motif, the S706X mutation is expected to impair the function of the highly conserved protein complex necessary for DNA damage response and subsequent DSB repair. Mutations in genes involved in DSB repair such as *BRCA1*, *BRCA2* [28], and *BRIP1* [29] have also been shown to increase risk of prostate cancer in some pedigrees. Exome sequencing of multiplex prostate cancer pedigrees may uncover additional deleterious variants in DNA repair genes that may contribute to this common disease. Although these variants are expected to be rare, knowledge of these mutations may be useful for risk assessment and may provide unique insights into potential therapeutic strategies [30].

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