Association of common missense changes in \textit{ELAC2} (\textit{HPC2}) with prostate cancer in a Japanese case–control series

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**Abstract** The recently identified prostate cancer susceptibility gene \textit{ELAC2} (\textit{HPC2}) harbors two common missense variants, a serine to leucine substitution at residue 217 (Leu217) and an alanine to threonine substitution at residue 541 (Thr541). We genotyped the two variants in a Japanese cohort consisting of 350 prostate cancer patients 242 male population controls, and 114 male low-risk controls. Both missense alleles, Leu217 and Thr541, were carried at higher frequency in Japanese patients than in the controls (Leu217, $P = 0.0012$; Thr541, $P = 0.0145$), and the odds ratios associated with carrying these sequence variants were higher in Japanese than in Caucasians. Although the Leu217 and Thr541 variants of \textit{ELAC2} are less common in Japanese than in Caucasians, both variants confer significantly increased risk of prostate cancer in Japanese. Carriage of these variants was not associated with age at diagnosis, tumor stage, or tumor grade in these Japanese prostate cancer patients. The allele-specific pattern of risk observed in Japanese and familial Caucasian patients was qualitatively similar; however, the magnitude of that risk was considerably greater in Japanese than in Caucasians.

**Key words** \textit{ELAC2} · \textit{HPC2} · Modest risk variant · Prostate cancer · Genetics

**Introduction**

\textit{ELAC2} (\textit{HPC2}), the first prostate cancer susceptibility gene identified through genetic linkage and positional cloning, was described in late 2000 (Tavtigian et al. 2000). Orthologs of \textit{ELAC2} are readily identifiable among all eukaryotes for which complete genome sequences are available. In addition, the carboxy half of \textit{ELAC2} is very similar to a gene, typified by \textit{Escherichia coli} elaC, present in all prokaryotes. Sequence analysis suggests that \textit{ELAC2} encodes a metal-dependent hydrolase. However, the function of the gene product remains unknown, as does the mechanism by which the altered function influences the risk of prostate cancer (CaP).

Initial mutation screening of \textit{ELAC2} in prostate cancer patients from Utah (Tavtigian et al. 2000, 2001) revealed four nucleotide sequence variants that altered the predicted amino acid sequence of the protein. Two of these variants, the frameshift mutation 1641insG and the missense variant Arg781His, are rare or pedigree-specific changes associated
with a high risk of CaP. The other two variants are common missense variants: Ser217Leu (S217L), with a Leu217 allele frequency of about 30% in Caucasians of northern European ancestry, and Ala541Thr (A541T), with a Thr541 allele frequency of about 5% in the same population. Two primary hypotheses emerged from the initial case–control association study to examine these common missense changes (Tavtigian et al. 2001): (1) Thr541 is in very strong linkage disequilibrium with Leu217 such that virtually all Thr541 carriers also carry Leu217. If confirmed, the two missense variants could be considered to define a three-allele system: Ser217/Ala541 (SA allele), Leu217/Ala541 (LA allele), and Leu217/Thr541 (LT allele). (2) Both Leu217 and Thr541 confer a modestly increased risk of CaP, with the risk of prostate cancer conferred by the individual alleles decreasing in the order LT > LA > SA.

Subsequent studies have both screened familial prostate cancer patients for germline mutations in ELAC2 (Xu et al. 2001; Rokman et al. 2001; Wang et al. 2001) and looked for associations between common sequence variants in this gene and CaP-related phenotypes (Xu et al. 2001; Rokman et al. 2001; Wang et al. 2001; Rebbeck et al. 2000; Vesprini et al. 2001; Suarez et al. 2001). Rare novel sequence variants that alter the protein coding sequence of ELAC2 have been found in familial CaP patients (Rokman et al. 2001; Wang et al. 2001). However, as these resequencing studies have focused on variant discovery in CaP patients without measuring the summed frequency of such variants in controls, it is not known whether such variants are actually more common in patients than in controls. In addition, the variants that have been found are less than 100% penetrant and do not account for all of the cases in the pedigrees in which they are present, making it difficult to link them with risk of disease. While association studies have confirmed strong linkage disequilibrium between the common missense variants Thr541 and Leu217, they have left the relationship between carriage of these common ELAC2 missense variants and risk of CaP ambiguous. For instance, Rebbeck et al. (2000) observed an association between carriage of the LT allele of ELAC2 and risk of CaP in a hospital-based CaP case–control series, and Suarez et al. observed an association between carriage of the LT allele of ELAC2 and risk of CaP in a series of familial CaP cases vs. low-risk controls (Suarez et al. 2001). In contrast, other studies have seen no significant evidence for an association between the common missense variants in ELAC2 and risk of CaP (Xu et al. 2001; Rokman et al. 2001; Wang et al. 2001; Vesprini et al. 2001).

Age-adjusted incidence rates of CaP vary dramatically between Caucasian men residing in the United States. Therefore, as one might expect that the genetic component of susceptibility to CaP is less confounded by these factors, and consequently easier to detect, in Asian men residing in Asia than in Caucasian men residing in the United States. Therefore, even though point estimates of allele frequencies of the missense variants of ELAC2 are numerically lower in Asians than in Caucasians (Vesprini et al. 2001), we undertook to analyze these variants in a Japanese case–control series.

Subjects and methods

Study subjects

Three groups of male Japanese adults were identified for this study.

Prostate cancer cases. This group consisted of 350 patients over the age of 45 who were diagnosed with prostate cancer in Nippon Medical School Hospital, Yokohama City University Hospital, Akita University Hospital, Kyoto University Hospital, Kouchi Medical school Hospital, Nagoya City University Hospital, or Chiba University Hospital over the period 1995–2001. All of the patients had prostatectomy with postoperative pathological validation of the diagnosis; however, information on age at diagnosis, tumor stage, and tumor grade were available only for subsets of patients, as follows: age at diagnosis, 255 (72.9%); tumor stage, scored by the Jewett staging system, where stages A and B describe locally confined prostate tumors, stage C describes tumors that have spread across the prostatic capsule or involve the seminal vesicles but without evidence of more distant metastasis, and stage D describes node-positive tumors and tumors that have metastasized to distant sites, 295 (84.3%); tumor grade, by Gleason score (range of 2–10), 257 (73.4%); tumor grade, by a summary description of well differentiated, moderately differentiated, or poorly differentiated, 177 (50.6%). These clinical data are summarized in Table 1.

Low-risk controls. This group consisted of 114 adult male Japanese with a mean age of 64.5 (52–78), who were negative for prostate cancer after urological examination, which included digital rectal examination (DRE) and rectal ultrasound echography, and had normal serum PSA levels (less than 4 ng/ml).