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Letter-to-the-Editor RE: Nadler RB, McNaughton Collins M, Prokert KJ, Mikolajczyk SD, Knauss JS, Landis J R, Fowler Jr JE, Schaeffer AJ, Alexander RB. Prostate-specific antigen test in diagnostic evaluation of chronic prostatitis/chronic pelvic pain syndrome. *Urology* 67(2): 337-342, 2006

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The world of PSA testing is complex, yet fascinating, and so is the world of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). In this respect, the recent report from the Chronic Prostatitis Collaborative Research Network (CPCRN) of significantly elevated total PSA, free PSA, and [-2] proPSA in CP/CPPS as compared with controls provides tantalizing insights into both worlds.¹ This finding is particularly intriguing in light of the fact that genetic variations in the promoter of the PSA gene have been postulated to contribute to individual variation in serum PSA levels.

One study has implicated the -158 G/A SNP of the PSA promoter in the modulation of serum PSA levels in men without prostatic disease. In that study, men with the AA genotype at the -158 G/A SNP had higher serum PSA levels than men with the AG or GG genotypes.²

In a more recent study,³ linkage disequilibrium and haplotype analyses demonstrated exclusive linkage of the A allele of the -158 G/A SNP of the PSA promoter to the far upstream haplotype, -5429T/-5412T/-4643A, which was associated with reduced serum PSA levels and reduced promoter activity *in vitro*. By contrast, the G allele of the -158 G/A SNP was distributed between far upstream haplotypes, -5429T/-5412T/-4649A and -5429G/-5412C/-4643G and was associated with both lower and higher serum PSA concentrations, respectively. The authors of the study concluded that "the difference in distribution between the -158 G and A alleles with different haplotypes in the far upstream region of the PSA gene may have influenced the association of the -158 SNP with serum PSA levels and that depending on the study group, this association may or may not reach statistical significance."³

The possibility that the observed differences in total PSA, free PSA, and [-2] proPSA in the CPCRN cohort as compared to controls might be associated with linkage disequilibrium at the PSA promoter is certainly intriguing for several reasons. First, if such an association exists, it would aid the definition and diagnosis of CP/CPPS. Second, it would help further refine the cutoff values for PSA testing in benign and malignant prostatic disease. As has already been

suggested, the cutoff value for a man with a PSA promoter genotype associated with reduced serum PSA levels (i.e., the -5429T/-5412T/-4643A haplotype) may be lower (i.e., 4 ng/mL) than that for a man with a genotype that is associated with elevated serum PSA levels (i.e., the -5429G/-5412C/-4643G haplotype).³ The CPCRN, by virtue of being a large and well-defined clinical population, offers the possibility of turning such testing into a reality. Lastly, the possibility of PSA promoter involvement in the pathogenesis of CP/CPPS opens up numerous avenues for research. Given the ability of PSA to cleave insulin-like growth factor binding protein 3, parathyroid hormone-related protein, transforming growth factor-beta, and other prostatic growth factors, the importance of studying linkage disequilibrium and SNP haplotypes in CP/CPPS cannot be overemphasized. The PSA era in CP/CPPS, and prostate cancer, might be just beginning.

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