Pharmacogenomics as a Guide for Treating Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) suffer from a lack of therapeutic options. CP/CPPS constitutes a major public health burden due to its high prevalence and crippling effects on quality of life. Although the last decade has seen progress toward understanding the etiology, pathogenesis and optimal treatment, the picture remains cloudy.

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Pharmacogenomic techniques have great potential to elucidate disease mechanisms for conditions such as CP/CPPS and establish individualized, target oriented treatments. Pharmacogenetics research has made great strides in recent years with the identification of gene alleles that influence drug effects in humans. Some examples from other areas of pharmacogenomic success include the VKORC1 haplotypes and CYP2C9 alleles which, when combined with clinical factors, can be used to establish an initial dosing protocol for warfarin; the beta-2-adrenergic receptor polymorphisms that predict decreased efficacy of the bronchodilator albuterol; and SLC01B1 polymorphisms in the gene encoding the organic anion transporter that determines blood levels of statin drugs producing myopathies.[1]

The precise role of genetic predisposition in CP/CPPS is unknown, but multiple lines of evidence suggest its potential importance. We have previously presented evidence of familial clustering of interstitial cystitis/painful bladder syndrome or CP/CPPS.[2] A study of risk factors in CP/CPPS showed an increased incidence of cardiovascular, neurological, psychiatric and several other conditions in patients with CP/CPPS.[3] A recent meta-analysis revealed significant overlap between urological unexplained syndromes, such as CP/CPPS, and nonurological unexplained syndromes such as fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome.[4]

The frequent occurrence of CP/CPPS with other comorbities implicates genetically determined systemic mechanisms in the pathogenesis of CP/CPPS symptoms. A recent study demonstrated a unique adrenocortical profile in men with CP/CPPS in a manner suggestive of nonclassic CYP21A2 deficiency.[5] For the first time to our knowledge this study highlighted the importance of pharmacogenomics as a potential tool for CP/CPPS phenotyping and defining a homogeneous group of patients that can be targeted for a specific therapeutic intervention. While none of these studies proves a specific level of genetic influence, they generally suggest a genetic predisposition that may respond to environmental triggers, manifesting in CP/CPPS and potentially other related conditions.

Genomic profiling of patients with CP/CPPS in the context of the National Institute of Diabetes and Digestive and Kidney Diseases sponsored MAPP (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) Research Network will enormously enhance patient phenotyping and help identify subgroups for targeted interventions. There has been substantial improvement in CP/CPPS studies in the last decade, largely due to the National Institutes of Health (NIH) consensus definition of CP/CPPS, the universal acceptance of the National Institutes of Health Chronic Prostatitis Symptom Index as the gold standard for the diagnosis of the condition and the large cohorts of patients with CP/CPPS that have been established. Obtaining genomic data such as single nucleotide polymorphism (SNP) genotypes should be a priority in CP/CPPS research, especially in large-scale clinical trials. Conducting genome-wide association studies (GWAS) using these data will help to probe disease etiology and pathogenesis, and assign specific therapies to patients who stand to benefit the most from them.

GWAS could produce several types of useful results. If 1 or several genes showed high associations with CP/CPPS, these hits might direct us toward specific biological pathways whose perturbation is at the root of the disease. The products of these genes could also serve as potential drug targets, as could other proteins in the affected pathways. However, even if there are no hits with high associations, GWAS could produce sets of diagnostic fingerprints associated with particular forms of disease.

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For example, there might be a subset of individuals with CP/CPPS who have several smaller gene associations all within a particular pathway or biological process, such as inflammation or pain processing. These patients would fit into a well-defined category and therapy would be directed at the implicated pathway or process. Furthermore, even if the genes do not clearly fit into a well-defined category, bioinformatic analysis could identify fingerprints consisting of certain groups of haplotypes that tend to group together in individuals with CP/CPPS. Each of these fingerprints might represent a subtype of patients with particular etiological and pathogenic characteristics, even if the role of the genes is not yet understood. Clinical trial data could be used to determine whether particular fingerprints were associated with successful response to particular therapies, which is why coupling genomic analysis with clinical trials has such great potential.

While it is important to approach CP/CPPS from many angles, a pharmacogenomic approach holds particular promise with regard to improving therapy. Proteomics, metabonomics and transcriptomics are other valuable approaches to studying CP/CPPS but they have some practical limitations. These assays tend to be more sensitive to experimental error than genomic assays and, thus, it is more difficult to replicate results and obtain consistency among research groups. This will be particularly important if diagnostic fingerprints are to be used for optimal therapy determination. These other approaches also require a biological specimen from a particular anatomical location, whether it is tissue or bodily fluid.

With the emerging view of CP/CPPS as a systemic, nonprostatocentric condition, obtaining data that pertain to every cell in every organ system may provide the most direct insight to underlying etiology. Extracting genomic DNA from leukocytes and running SNP arrays are relatively straightforward methods of accomplishing this task. This is not to undermine the importance of discovering the proteins, small molecule metabolites and gene transcripts that have a role in disease pathogenesis, but merely to suggest the particular importance of genomic data in moving toward individualized therapies in the near future.

Pharmacogenomics will help with the rational design and implementation of therapy in many clinical conditions. The etiology, pathogenesis and optimal treatment of CP/CPPS have proved elusive, probably due to the complexity and breadth of factors that contribute to the disease in different individuals. Given the evidence of genetic influences in CP/CPPS, genomic data will likely prove useful in several respects. The discovery of associated genes will help elucidate the etiology and pathogenesis of CP/CPPS and identify possible drug targets. Potentially most promising is the prospect of obtaining genomic fingerprints characteristic of patient subsets that will respond to particular therapies. Clinical trials in conjunction with genomic studies will be needed and should be considered an important priority in CP/CPPS research. ◆

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