

## Complex Renal Traits: Role of Adrenergic Genetic Polymorphism

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Many if not most of the common disease states encountered in internal medicine, nephrology in particular, are complex traits<sup>1</sup>: Typically poorly understood and likely to be multifactorial, with etiologic contributions from both heredity and environment. Family or twin studies can establish the relative roles of heredity or environment trait determination, and indeed, familial aggregation or heritability is documented for such traits as hypertension<sup>2</sup> and chronic kidney disease,<sup>3</sup> whereas less common traits, including adult and juvenile polycystic kidney disease, display simpler, Mendelian hereditary patterns. The contribution of polymorphisms at specific loci are now documented for hypertensive ESRD, including the nonmuscle myosin variant, *MYH9*,<sup>4</sup> and the catecholamine storage vesicle protein chromogranin A, *CHGA*.<sup>5</sup> Systematic family studies have not been conducted in acute kidney injury (AKI), perhaps because of the transient nature of the illness coupled with unavailability of appropriate first-degree relatives for study during hospitalization.

Despite a recent explosion of studies and investigations of complex diseases, results have been mixed, incomplete, and inconsistent.<sup>6</sup> Such studies are compelling insofar as they aim to tackle important medical questions regarding traits that are likely influenced by genes, the environment, or interaction between the genes and the environment, highlighting the difficulty and intricacy of such traits. Since 2007, developments in nanotechnology have enabled genome-wide association (GWA) studies, which typically study very large numbers (many hundreds to several thousands) of disease cases and controls at up to approximately  $5$  to  $10 \times 10^5$  single-nucleotide polymorphisms (SNPs) at once.<sup>7</sup> In such hypothesis-free approaches, many new susceptibility traits have been revealed, unveiling novel molecular pathways that contribute to complex diseases. Such studies identify genomic regions for further analysis but are limited in their ability to detect causative variants and are unable to identify rare variants that may highly

influence disease processes.<sup>8</sup> Effect size, gauged by odds ratios, for the common variants identified have typically been modest (often  $<2.0$ ), and the ability to detect associations is compromised by a decrement in power introduced by multiple statistical comparisons inherent in genome wide searches.<sup>9</sup> In addition, the GWA approach currently employs only common, relatively high minor allele frequency SNPs to “tag” haplotype blocks across the genome, rendering this a technique for discovery of relatively common (rather than rare) variants that influence a trait. Because complex traits also represent the cumulative effect of the action of relatively rare genetic variants,<sup>8</sup> the search for improved methods of genetic analysis continues.<sup>7</sup>

By contrast, the candidate gene approach may be a practical and logical alternative to GWA in complex genetic traits.<sup>10</sup> In using previous hypotheses regarding genes and proteins that are likely involved in the disease, as well as previous knowledge of functional polymorphisms in such regions, increased statistical efficiency may be achieved in seeking marker-on-trait associations for complex diseases, in part by minimizing multiple comparisons. With recognition that the GWA approach may be unable to uncover much of the source of genetic variation for many clearly heritable traits,<sup>7</sup> especially rare genetic variation,<sup>8</sup> the candidate gene approach is increasingly appreciated for complex diseases.<sup>10</sup> Explicit hypothesis testing may then facilitate appropriate molecular testing to confirm results and demonstrate functionality for better understanding of biologic causality.

Kidney diseases, both chronic and acute, present examples of heterogeneous disease processes resulting from different etiologies and pathologies influenced by one's own genetic background, eventuating in particular disease traits or predispositions for certain ailments, with modification by environmental conditions, such as medications, diet, stress, and comorbid illnesses. Candidate genetic pathways have already been investigated in renal disease, particularly within the renin-angiotensin and adrenergic systems. The adrenergic system has been an active area of study in complex traits, particularly in cardiorenal diseases, given long-standing acknowledgment of overactivity contributing to hypertension, the metabolic syndrome, and cardiovascular morbidity.<sup>2,11</sup> A growing body of literature implicates sympathetic nervous system hyperactivity as a mechanism of renal injury and disease progression.<sup>12</sup> Adrenergic genetic variation has been noted to influence renal traits; for example,  $\beta_2$ -adrenoreceptor polymorphisms predict future renal damage,<sup>13</sup> and haplotypes across the catecholamine storage vesicle glycoprotein chromogranin A (*CHGA*) are predictive of both estimated GFR in healthy control subjects<sup>14</sup> and of ESRD as a result of hypertension in black patients.<sup>5</sup> Adrenergic gene polymorphisms that alter catecholamine metabolism may also be of importance in AKI. A recent abstract associated the terminal gene in biosynthesis of the catecholamine epinephrine, phenylethanolamine N-methyltransferase (*PNMT*), with disease severity and in-hospital mortality among patients with AKI.<sup>15</sup>

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In this issue of *JASN*, Haase-Fielitz *et al.*<sup>16</sup> use the candidate gene approach to investigate the association between AKI after cardiac surgery and a SNP in the catechol-O-methyltransferase (*COMT*) gene that plays an important role in metabolism of catecholamines. A *COMT* Val-to-Met amino acid substitution at codon 158 is known to result in an unstable *COMT* protein with reduced enzymatic activity.<sup>17,18</sup> Homozygotes for the loss-of-function allele (Met/Met) display alterations in postoperative catecholamine concentrations in association with an increased frequency of prolonged vasodilator shock, AKI requiring renal replacement therapy, and prolongation of hospital stay. The results of this large series of 260 European-ancestry patients after cardiopulmonary bypass surgery reinforce the importance of the adrenergic system in acute renal disease.

Particular advantages or strengths of this study include a schema of prospective longitudinal enrollment; a relatively large number ( $n = 260$ ) of patients; the functional change<sup>18</sup> already attributable to the assayed SNP (Val158Met); cross-validation in two subsets of the cohort; and the effects of Val158Met on a plausible, very proximate trait in the same patients: Catecholamine metabolism.

The study Haase-Fielitz *et al.*<sup>16</sup> immediately suggests several lines of follow-up investigation. Replication in an independent AKI cohort would enable generalization of the results to larger numbers of patients in different clinical settings. Polymorphisms at other points in the catecholaminergic pathway might also be expected to influence the course of AKI; indeed, the effect of genetic variation at *PNMT* has already been reported to play a role.<sup>15</sup> Pleiotropic (one gene affecting many traits) consequences of the *COMT* Val158Met variant in these patients with AKI may be of interest, given the multitude of phenotypic consequences already reported for genetic variation at *COMT* (see the *COMT* entry at Online Mendelian Inheritance in Man at <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=116790>).

Even though the *COMT* Val158Met polymorphism already has well-documented effects on *COMT* protein stability and hence enzymatic activity,<sup>18</sup> the *COMT* local genetic region on chromosome 22q11.2 displays a complex pattern of linkage disequilibrium across populations, perhaps harboring additional functional variation<sup>19</sup>; indeed, multiple SNPs across the *COMT* coding region are already appreciated to give rise to haplotypes that alter *COMT* mRNA secondary structure and hence overall gene expression.<sup>20</sup> Further resequencing across the *COMT* locus<sup>18</sup> may yield additional, associated genetic variations that contribute to changes in enzymatic activity; given the complex and likely heterogeneous nature of AKI, this form of injury might be an example of the common disease/rare variant category of marker-on-trait relationships.<sup>8</sup> The availability of a mouse model of targeted gene ablation of the *COMT* locus<sup>21</sup> should enable even more mechanistic investigations of the route whereby *COMT* genetic variation influences the course of AKI.

Future GWA studies may complement the report by Haase-

Fielitz *et al.*<sup>16</sup> on *COMT* by implicating loci currently unsuspected in AKI on the basis of known biologic pathways.<sup>22</sup> Continued advances in the development of molecular and statistical tools<sup>22</sup> will be essential for further investigation of complex traits such as AKI. Finally, the information from association studies such as that by Haase-Fielitz *et al.*<sup>16</sup> will need explanation in a manner useful to clinicians and patients ultimately to aid in prevention or treatment of human disease.

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## DISCLOSURES

None.

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