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See related article, “Distinct Macrophage Phenotypes Contribute to Kidney Injury and Repair,” on pages 317–326.

Identification of a Major Chronic Renal Failure Susceptibility Locus in Mice: Perhaps EGFR Determines What Happens to eGFR

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One of the most challenging issues facing modern renal science is finding at-risk genes for kidney disease, particularly those predisposing to the development or progression of chronic kidney disease (CKD). In human populations, the use of Genome Wide Association Screening (GWAS) has identified a number of loci associated with CKD.^{1,2} Further refinements to GWAS techniques using admixture-mapping linkage disequilibrium also allowed for the identification of a locus on chromosome 22q12 that predisposes individuals of African descent to nondiabetic glomerular injury,^{3,4} and recent analyses strongly indicate that the affected gene is *ApoL1*.^{5,6} Undoubtedly, other genes are involved in development of progressive kidney disease.

Given the genetic complexity of essentially all modern human populations, investigators have also turned to model organisms to uncover mechanisms that predispose to renal progression. In this regard, the mouse provides distinct advan-

tages⁷ in that genetically well-characterized inbred strains abound and previous studies identified marked differences in susceptibility to the development of progressive kidney injury among strains.^{8–11} In this issue of *JASN*, Laouari *et al.*¹² have taken advantage of this differential susceptibility and performed a genetic linkage analysis in mice to identify genes that predispose to renal progression after subtotal nephrectomy.

In previous studies, the authors identified the FVB/N mouse strain as susceptible to development of renal injury in response to either subtotal nephrectomy or continuous angiotensin II infusion.^{13,14} In the current studies,¹² the authors phenotyped three other mouse strains and two F1 hybrids—C57BL/6, DBA/2, 129S2/Sv, (C57BL/6xDBA/2)F1 (B6D2F1), and (C57BL/6xSJL)F1—and found that all of these strains were resistant to development of injury within 8 weeks after $\frac{3}{4}$ nephrectomy, whereas FVB/N mice developed progressive worsening of renal function, proteinuria, and glomerular and tubulointerstitial damage. They then intercrossed FVB/N mice with B6D2F1 mice and found that 96% of male F1 offspring inherited the renal failure phenotype, whereas only 4% of females did. This gender-dependent phenotype was observed regardless of the direction of the crosses, arguing against gender-linked inheritance. To establish that this remarkable difference in sensitivity by gender was not the result of either X or Y chromosome transmission, they backcrossed F1 females to male FVB/N and B6D2F1 mice. The proportion of affected male and female offspring indicated autosomal transmission and suggested gender-specific penetrance, manifesting as a dominant trait in males and a recessive trait in females.

The authors then used these informative backcrosses to perform a GWAS using 64 microsatellite markers and identified a quantitative trait locus (QTL) on chromosome 6, called *Ckdp1*, which contains more than 400 genes. They were then able to refine the QTL further with additional markers, but the identified locus still spans a relatively large, gene-rich region. A total of 125,294 single-nucleotide polymorphisms were identified within the critical region, among which 9668 (7.7%) were polymorphic between FVB/N and both C57BL/6 and DBA/2. Of these 9668 single-nucleotide polymorphisms, 3904 are located within 104 previously annotated genes. It is noteworthy that this locus is syntenic with regions on human chromosome 2 and chromosome 3 that have also associated with CKD.^{1,2,15,16}

The authors also previously reported an important role for the EGF receptor (EGFR) in mediating progressive renal injury.¹⁷ EGFR can be activated by a family of growth factors in addition to EGF,¹⁸ and in FVB/N mice, one of these EGF-like growth factors, TGF- α , increases in response to progressive renal injury, whereas blocking EGFR activation significantly decreases progressive kidney damage.^{14,17} Of note, TGF- α is one of the genes that resides in the *Ckdp1* locus on chromosome 6.¹²

In further studies, Laouari *et al.* confirmed that renal expression of TGF- α increases in FVB/N mice after subtotal ne-

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phrectomy but not in resistant B6D2F1 mice.¹² Likewise, inhibition of EGFR with a specific tyrosine kinase inhibitor¹⁴ decreases proteinuria and renal injury. However, they failed to identify a specific mutation or polymorphism in the TGF- α gene. Therefore, it may be premature to claim that differential expression of TGF- α underlies the increased susceptibility of FVB/N mice to development of renal progression. It is still quite possible that a variant in a regulatory region of the TGF- α gene was not identified in this analysis. Alternatively, another gene variant in the chromosome 6 locus may regulate expression of TGF- α . Finally, the possibility must also be considered that although TGF- α is activated in response to progressive renal injury and will further accelerate progression, it is only a coincidence that it is in the linkage region of interest; that is, the authors did not provide information about whether subtotal nephrectomy-induced expression of TGF- α tracked with susceptibility to injury in the F1 and F2 intercrosses.

Among the genes in the refined chromosome 6 locus, 13 also harbored nonsynonymous coding polymorphisms between FVB/N and C57BL/6 and DBA/2 mice. Ten of the genes are known to express in adult mouse kidney, but none of them have been implicated previously in the pathophysiology of CKD. However, one of these genes, *Tprkb*, a p53-related protein kinase-binding protein of unknown function, was identified as a candidate gene in recent GWAS analyses of human renal disease.^{1,2}

Because the genome of the FVB/N strain has not yet been completely sequenced, it remains possible that additional genes could be involved. Further delineation of the QTL on chromosome 6 with congenic strains may be necessary to identify the genes mediating the susceptibility to renal injury and the increase in TGF- α expression. Further studies will also be required to determine the underlying mechanisms for the striking gender dimorphism seen in the intercrosses. However, this new study provides exciting hypotheses to be tested and highlights the potential use of mouse genetics to help identify mechanisms underlying the development and progression of kidney injury in humans.

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DISCLOSURES

None.

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See related article, "TGF- α Mediates Genetic Susceptibility to Chronic Kidney Disease," on pages 327–335.

Atrial Fibrillation in Dialysis Patients: A Neglected Comorbidity

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Atrial fibrillation is the most common and potentially difficult to treat cardiac arrhythmia encountered in clinical practice. It is classified according to its temporal pattern as paroxysmal (self-limiting), persistent (amenable to cardio-

version), or permanent.¹ Although the frequency of each type depends on the population studied, it is estimated that paroxysmal fibrillation accounts for 35% to 66% of all cases of atrial fibrillation.^{2–4} The prevalence of this disorder increases with age, rising above 5% in people older than 65 years of age.⁵

Independent risk factors for fibrillation, from long-term follow-up data of the Framingham study, include male sex, hypertension, diabetes, heart failure, and valvular heart disease.⁶ Because of its high prevalence, hypertension accounts for most cases of fibrillation in the population compared with all other risk factors. Among chronic kidney disease patients starting dialysis, 36% have heart failure, and an additional 7% develop heart failure while receiving dialysis.⁷ Consequently, it is not unexpected that those patients on renal replacement therapy are at a particularly increased risk for the development of atrial fibrillation compared with the general population.

The prevalence of atrial fibrillation in dialysis patients is also driven by the changing age distribution of this population. Thirty years ago, approximately 27% of new end-stage kidney disease patients in the United States who began chronic renal replacement therapy were ≥ 65 years of age. In 2005, the total number of patients who started renal replacement therapy in the United States was 106,912, of which 52,434 (49%) were > 65 years of age.⁸ Although the incidence rates between 2000 and 2005 have been relatively stable for most age groups (changing $< 3.0\%$), the incidence rate has grown 10% from 1570 to 1725 per million for patients ≥ 75 years of age.

In the general population, atrial fibrillation may affect longevity because it is associated with approximately doubling all-cause and cardiovascular mortality rates.^{9,10} Mortality, as expected in this setting, is driven by cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. In addition, age-adjusted incidence of stroke in the Framingham study after 34 years of follow-up was nearly five-fold higher when nonrheumatic atrial fibrillation was present compared with those without atrial fibrillation.¹¹

The mechanism that triggers most atrial premature beats that initiate frequent paroxysms of fibrillation originates in the pulmonary veins, which has generated interest in ablative therapy of this region in selected patients.¹² Despite its important clinical relevance and potential effect on morbidity and mortality, there have been very limited data studying this comorbidity in dialysis patients in the United States and only a few worldwide published reports in this population.^{13–16}

In this issue, Winkelmayr *et al.* examine the epidemiology (including prevalence, risk factors, and mortality) of atrial fibrillation in patients on maintenance dialysis in the United States over a period of 15 years (1992 to 2006) using the U.S. Renal Data System annual cohorts. The overall prevalence of atrial fibrillation in this patient population exceeded 10% in 2006. In older patients, the prevalence was 13.2% in patients aged 65 to 75 years, 19.2% in those aged 75 to 85 years, and 22.5% in those > 85 years of age. More importantly, atrial fibrillation was associated with considerable excess mortality in

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