Genetics of Kidney Disease

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Research Summary
End-stage renal disease necessitating renal transplantation or dialysis affects one in a 700 Americans. The molecular bases of renal failure are largely unknown but evidence suggests that genetic susceptibility is an important causative factor. By taking advantage of the dense linkage maps of mammalian genomes now available, we can now map and identify genes conferring susceptibility to renal failure in humans or in animal models. The process of gene identification has been greatly facilitated by the availability of the sequence of the human genome. My laboratory is focused on several projects in humans and the mouse:

- **Research Projects in Humans:**
  IgA nephropathy is the most common form of glomerulonephritis and a significant cause of renal failure worldwide. Starting with a collection of kindreds with familial disease, we have mapped the first locus for IgA nephropathy to chromosome 6q22-23 and our efforts are now geared towards identifying the underlying genes using approaches such as disequilibrium mapping and sequencing of positional candidates. In addition, mapping projects in newer families recruited are expected to identify additional loci responsible for IgA nephropathy.

  Renal developmental abnormalities account for the majority of pediatric end-stage renal disease (ESRD). Renal developmental abnormalities can occur in isolation, but often aggregate in the same individual. For example the most common disorder, vesicoureteral reflux (VUR) may present in isolation or in association with other anomalies such as renal aplasia, multicystic dysplastic kidney, duplicated ureters or ureteropelvic junction obstruction, suggesting a common pathogenic between these clinical entities. Familial aggregation suggests that genetic factors are important to the development of these disorders. We are performing genome-wide search to map and identify the susceptibility genes in large kindreds with these traits.

- **Research Projects in the Mouse:**
  HIV nephropathy (HIVAN) is the most common cause of renal failure in African American adults after diabetes and hypertension. Familial and ethnic clustering suggests that genetic susceptibility is involved in the pathogenesis of HIVAN. Using a transgenic mouse model of HIVAN, we identified strains with contrasting susceptibility and by genome-wide analysis of linkage, we have identified a major susceptibility gene on mouse chromosome 3. We expect that identification of the underlying gene will permit elucidation of pathways leading to HIVAN and glomerulosclerosis in humans.

Searching for models of glomerulopathy that display strong gene-environment interaction, we examined the determinants of anthracycline induced nephropathy, a classic, strain dependent experimental model applied to rodents in the past four decades. We surprisingly found that this widely studied model segregates as a single gene defect with recessive inheritance. By genome-wide analysis of linkage, we mapped the trait locus to chromosome 16A1-B1 (DOXNPH locus, peak lod score of 92.7, p=1x10^-65); this interval represents a novel susceptibility locus for nephropathy. Elucidation of DOX nephropathy may simultaneously provide novel insight into the pathogenesis of renal failure and mechanisms of cytotoxicity induced by chemotherapeutic agents.
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