Population Genetics of Chronic Kidney Disease
Convergence of Physiology and Genetics

- Clearances studies
- Isolated Kidney
- Micropuncture
- Isolated tubules and vesicles
- Expression Cloning
- Genetically engineered animal models
- Human Genetics
CLASSIFICATION OF INHERITED DISEASES

Mendelian Inheritance patterns - Monogenic

- Common – e.g. ADPKD
  - Many “private” mutations
- Rare – e.g. ARPKD

Non-Mendelian Inheritance patterns

Single gene – but complex inheritance
  - few common variants
  - many rare variants

Multiple genes with small effects

Epistasis
Environment
Epigenome
Metagenome
### Genetic Epidemiology of Several CKD Risk Loci

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease /Risk Allele Frequency</th>
<th>Genotype Disease/Risk Frequency</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD1</td>
<td>Overall .001 Each allele ~ 0</td>
<td>Overall .001 Each allele ~ 0</td>
<td>&gt;10³</td>
</tr>
<tr>
<td>UMOD*</td>
<td>0.8</td>
<td>0.96</td>
<td>~1.2</td>
</tr>
<tr>
<td>APOL1</td>
<td>0.57 (in at risk populations)</td>
<td>0.13 (in at risk populations)</td>
<td>7-29</td>
</tr>
</tbody>
</table>

* Rare Mendelian with AD inheritance cause Familial Juvenile Hyperuricemic Nephropathy
Disease Associated Variants

- Rare recent variants tend to be associated with high risk for disease picked up in family or whole exome studies.
- Common ancient variants tend to be associated with low risk for disease, with low OR for hundreds of GWAS studies.

Antonorakis et al. et al. NRG 2010
Disease Gene Mapping

- Genome-wide
- Candidate locus
  - Parametric
  - Non-parametric
- Linkage
- Association
- Family-based
- Population-based
What is a Population in Human Genetics?

- A “population” in human genetics can be designated as a group of people who share common ancestry patterns at a “genome wide” or “genetic locus” level.

- “Population genetic architecture” can be measured using DNA diversity markers.
Classification of DNA Diversity Markers

Biological Type
- SNPs, INDELS, STRs, CNVs, other

Evolutionary History

Genomic Location

Choice and combination depends on scientific, historical, genealogical, clinical or forensic question of interest
SNP = Single Nucleotide Polymorphism

*considered a SNP (rather than private mutation)
when minor allele frequency (MAF) > 1 %
(more than 20,000 new private variants per individual – most do not reach the SNP threshold)
Some ~18 million SNPs total:
~3 million* of these differ between individuals
(*depending on population and relatedness)
~95% of these differences have no phenotypic effects

• Smaller percentages influence phenotype
• An even smaller percentage cause or predispose to disease or variable drug response
• Population frequency may be “neutral” or affected by “selection”

Useful to infer human demography and also in Disease Gene Mapping
SNP Allele Frequencies:
Demographic factors affect *genome wide* allele frequencies:
founder, bottleneck, expansion, migration, admixture
Selection: differential effect on allele frequencies at *specific genomic regions*

Genetic variants conferring an advantage and better adaptation will be selected and rise to high frequencies (together with neighbouring variants)

*Evolutionary Medicine*
**Common variants** which passed evolutionary filter may *now* be relevant to **common disease** due to increased life expectancy (or change in adaptive forces: diet, drugs, bugs)

Very many *new* private rare variants may *now* contribute to **common disease** and have not passed evolutionary filter.
Answers will come from Combined Approaches that take into account Evolutionary History, Population Level and Family Studies Combined with Biology.
DISEASE GENE MAPPING

Genome Wide

Positional Cloning:
Family Based, Linkage
Highly Successful in identifying causal mutations
Now combined with or supplanted by whole exome sequencing
In some cases identified locus with rare Mendelian mutations
harbors common variants associated with common disease
(e.g. UMOD, SLC34A1)

Genome Wide Association (GWAS):
Population Based, Linkage Disequilibrium
Generally $\rightarrow$ Low Odds Ratios, Missing Heritability
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Gene product</th>
<th>Is living related donor transplantation appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital nephrotic syndrome (Finnish type)</td>
<td>NPHS1</td>
<td>Nephrin</td>
<td>Yes</td>
</tr>
<tr>
<td>Autosomal recessive SRNS</td>
<td>NPHS2</td>
<td>Podocin</td>
<td>Yes—an after genetic testing to exclude the Arg229Gln (p.R229Q) variant in the donor</td>
</tr>
<tr>
<td>Autosomal recessive SRNS</td>
<td>NPHS3 (PLCE1)</td>
<td>Phospholipase Cε</td>
<td>Yes</td>
</tr>
<tr>
<td>Pierson syndrome</td>
<td>LAMB2</td>
<td>Laminin β2</td>
<td>Yes</td>
</tr>
<tr>
<td>Schimke's immuno-osseous dystrophy</td>
<td>SMARCAL1</td>
<td>HepA-related protein</td>
<td>Yes</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>NPHP1 to NPHP9</td>
<td>Nephrocystines 1 to 9</td>
<td>Yes</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>CNTS</td>
<td>Lysosomal cystine transporter</td>
<td>Yes</td>
</tr>
<tr>
<td>ARPKD</td>
<td>PKHD1</td>
<td>Fibrocystin</td>
<td>Yes</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>COL4A3, COL4A4</td>
<td>α3 and α4 type IV collagen</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>AGXT</td>
<td>Alanine glyoxylate aminotransferase</td>
<td>No</td>
</tr>
<tr>
<td>Atypical HUS</td>
<td>CFH, CFHR1, CFHR3, CD46</td>
<td>Complement factor H, complement factor H-related proteins 1 and 3</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; HUS, hemolytic uremic syndrome; SRNS, steroid-resistant nephrotic syndrome.
### Table 2 | Autosomal dominant diseases that progress to end-stage renal disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Gene product</th>
<th>Is living related donor transplantation appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD type 1</td>
<td><em>PKD1</em></td>
<td>Polycystin 1</td>
<td>Yes—for unaffected relatives</td>
</tr>
<tr>
<td>ADPKD type 2</td>
<td><em>PKD2</em></td>
<td>Polycystin 2</td>
<td>Yes—for unaffected relatives</td>
</tr>
<tr>
<td>Atypical HUS</td>
<td><em>CFH, CFHR1, CFHR3, CFB, CFI, C3</em></td>
<td>Complement proteins</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; HUS, hemolytic uremic syndrome.
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<th>Disease</th>
<th>Gene</th>
<th>Gene product</th>
<th>Is living donor related transplantation appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alport syndrome</td>
<td>COL4A5</td>
<td>α5 type IV collagen</td>
<td>Yes—for unaffected males or females and for heterozygous females without proteinuria, aged &gt;45 years and after information is provided on the long-term risks of renal disease after donation</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>GLA</td>
<td>α-Galactosidase</td>
<td>A risk of renal dysfunction exists in heterozygous female donors; living related transplantation is possible in donors who do not have the mutation</td>
</tr>
</tbody>
</table>
Genetic Loci with Rare Mutations that Cause Severe Mendelian Disease that also Harbor Common Variants Associated with Common Disease
A Cluster of Mutations in the UMOD Gene Causes Familial Juvenile Hyperuricemic Nephronophptisis with Abnormal Expression of Uromodulin

Dahan et al JASN 2003
\( -\log_{10}(P) \)

**eGFRcrea**

- ANXA9
- GCKR
- CPS1
- NAT8
- TFDP2
- SHROOM3
- SLC34A1
- DAB2
- SLC22A2
- PRKAG2
- RNASEH2C
- DACH1
- PIP5K1B
- TMEM60
- STC1
- WDR72
- SLC9A13
- BCAS3
- SLC7A9

**CKD**

- SOX11
- PRKAG2
- UMOD

Köttgen et al. Nature Genetics, 2010
Association of Variants at *UMOD* with Chronic Kidney Disease and Kidney Stones—Role of Age and Comorbid Diseases

Gudbjartsson DF et al 2011
Unfolded Protein Response and ERAD Damage
A Loss-of-Function Mutation in NaPi-IIa and Renal Fanconi’s Syndrome

Daniella Magen, M.D., Liron Berger, M.Sc., Michael J. Coady, Ph.D., Anat Ilivitzki, M.D., Daniela Militianu, M.D., Martin Tieder, M.D., Sara Selig, Ph.D., Jean Yves Lapointe, Ph.D., Israel Zelikovic, M.D., and Karl Skorecki, M.D., F.R.C.P.C.
Does Mapping of Mutations in Genes Causing Rare Monogenic Disease Shed Light on Common Health and Disease Phenotypes (e.g. Stones, Bones, CKD)

Common Genetic Variants Associate with Serum Phosphorus Concentration

Kestenbaum et al. JASN 2010
Control of Phosphate Excretion in Uremic Man

E. Slatopolsky, A. M. Robson, I. Elkan, and N. S. Bricker

From the Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110

ON THE PATHOGENESIS OF THE UREMIC STATE

An Exposition of the "Trade-off Hypothesis"

Neal S. Bricker, M.D.
**DISEASE GENE MAPPING**

**Genome Wide**

**Positional Cloning:**
- Family Based, Linkage
- Highly Successful in identifying causal mutations
- Now combined with or supplanted by whole exome sequencing
- In some cases identified locus with rare Mendelian mutations harbors common variants associated with common disease (e.g. UMOD, SLC34A1) and in other misleading (e.g. MYH9)

**Genome Wide Association (GWAS):**
- Population Based, Linkage Disequilibrium
- Low Odds Ratios, Missing Heritability
Pace of genome-wide association study publications since 2005

Manolio T A. Nat Rev Genet, 2013
Published Genome-Wide Associations through 12/2012
Published GWA at $p \leq 5 \times 10^{-8}$ for 17 trait categories

NHGRI GWA Catalog
www.genome.gov/GWASTudies
www.ebi.ac.uk/fgpt/gwas/
Linkage Disequilibrium (LD) is the nonrandom association (at the population level) of two alleles on the same chromosome:

\[ P_{AB} = P_A \times P_B \]

In disequilibrium:

\[ P_{AB} > P_A \times P_B \]
Linkage Disequilibrium (LD)

If marker A is found in significant LD with a disease risk causative variant (B), we should detect association of marker A to the examined phenotype A → B.

In genome wide association (GWAS), only markers (A) in sufficient physical proximity to causative variant B to mitigate recombination will be associated with the health or disease phenotype of interest.

Power to detect and ROC weak unless

1. admixture, 2. selection
Meiotic Recombination Breaks Down Linkage Disequilibrium (LD) & Genetic Association into smaller and smaller regions

Admixture restores LD genetic association

Confers to GWAS the power of family based linkage mapping
Success depends on:

1. Population Admixture
   African American

2. Disparity in disease frequency between parent populations
   Chronic Kidney Disease

3. Causal risk variant(s) have risen to high frequency in the at risk parent population =
   (Common Variant – Common Disease)
   Evolutionary Selection
- Identify “ancestry” of chromosomal regions using DNA markers whose allele frequencies differ markedly between parent populations

- Discover genomic region(s) with significant enrichment of ancestry markers in disease (Chronic Kidney Disease) compared to control cohort
Chronic Kidney Disease in African Americans: Admixture Scan

(Kao et al. 2008)

(Kopp et al. 2008)

(Shlush et al. 2010)
Admixture peak: >30 other genes were found in the 2 mb 95% interval.
Odds Ratio for markers in the region 7-29 depending on etiology of kidney disease

Adapted from Kopp et al 2008 and NIDDK 2010, Kao et al 2008
Approaches to Finding “Causative” Gene in the Region

- 1,000 Genomes Data Mining
- Clinical Observation
- Evolution, Biology, and Function
Resequence the Region 1000 Genomes

- Much more strongly associated with disease phenotypes than variants in MYH9
- Explain the associations observed with MYH9
- Explains a population level discrepancy
- Evolutionary Medicine

Genovese et al. 2010
Tzur et al. 2010

**APOL1 (15kbp)**
- S342G and I384M
- LD 279/280 Chromosomes
- del.N388/Y389

**MYH9** was a gene with highly associated tag SNPs and known monogenic Mendelian disease (GPS) at the time, but sequence showed no candidate functional variants within the gene itself

- BUT the gene anchored and tagged even more highly associated functional variants outside of MYH9 in the next gene over – APOL1
The APOL1 variants are more strongly associated with ESKD risk than the leading MYH9 risk variants, both in terms of OR and p values.

<table>
<thead>
<tr>
<th>Odds Ratio (recessive mode)</th>
<th>African American</th>
<th>Hispanic American</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>APOL1 G1+G2</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>APOL1 G1+G2</td>
<td>1.5E-10 (Fisher exact test)</td>
<td></td>
</tr>
<tr>
<td>MYH9</td>
<td>1.74E-10</td>
<td></td>
</tr>
</tbody>
</table>

Modifier Loci (e.g. Podocin, CFH)
The MYH9 Signals are attenuated to near insignificance when association is conditioned upon APOL1 G1 + G2.

Genovese et al. 2011
Ethiopian Jews in Israel
Low Prevalence of CKD – Absence of HIVAN
[We now know this to be valid for Ethiopian non-Jews]
Leading APOL1 Causative SNPs

Evolutionary Pressure held MYH9 tagging SNPs in strong LD with APOL1 G1 and G2 which had risen to high frequency in sub-Saharan Africa.

MYH9 tag SNPs allele frequencies of 0.35 in Ethiopia, yet no HIVAN.
Human African Trypanosomiasis
African Sleeping Sickness

Pays and colleagues and Raper and colleagues have shown that most human APOL1 efficiently kills many (but not all) Trypanosoma species

SRA – present in *T. Brucei Rhodesiense* binds, sequesters and confers resistance to APOL1

What can we learn from what is already known about APOL1 regarding the Evolutionary Selection Pressure?
ApoL1 G1 and G2 Variants modify protein structure so as to confer protection from Trypanosoma B. Rhodesiense Sleeping Sickness in Subsaharan Africa

Protein Structure Models for Apoliproteins L:
I-TASSER and CHIMERA
Tm>0.5 for all predictions
Evolutionary Medicine

1. Rise to high frequency of G1 and G2
   - single allele protection against pathogen
   - two alleles associated with increased risk of later onset disease

2. Hitchhiking of Tag markers in neighboring genes (MYH9)

Permissive to High Odds Ratio for a Common Variants in a Common Disease
Ethiopian SNPs reflect a different population genetic history and thereby clarify the phylogenetic branch upon which the actual “causative” mutation resides.
Population Genetics of APOL1 Associated Chronic Kidney Disease

Clues to Pathobiology from Clinical Observations and Genetic Epidemiology
The *APOL1* Gene and Allograft Survival after Kidney Transplantation

* Reeves-Daniel et al.  
  Am. J. Transplant 2011

* Two risk allele state of donor kidney
The APOL1 Genotype of African American Kidney Transplant Recipients Does Not Impact 5-Year Allograft Survival

Lee et al.
Am. J. Transplantation 2012
Taken together these two studies suggest that:

APOL1 risk allele association is mediated by gene product isoform endogenously expressed within the kidney

Caveats:

- The “disease” is “transplant loss” and not one of the “classical” APOL1-Associated Nephropathies (APANs)
- Neither study measured both donor and recipient genotype together
Disease travels with Kidney: Mechanistically suggests that effect is due to intra-renal APOL1. Is APOL1 actually expressed:

- in the kidney?
- in the glomerulus?
- in the podocyte?

Apolipoprotein L1  
Apolipoprotein L2

**Correlation with ISH:**
Proximal Tubule: not endogenous  
Podocyte: endogenous
**IFNγ markedly and robustly induces the expression of APOL1 in human podocytes**

Intracellular Injury Mechanisms in the setting of a *Second Hit* which also induces a rise in IFNγ and other cytokines

Sharon Aviram
Specificity of APOL1 Disease Associations

Robust Associations:

- Hypertension with Chronic Kidney Disease in African Ancestry population (Hypertension “Misattributed” Chronic Kidney Disease)
- FSGS – primary non-monogenic [especially Collapsing Glomerular Nephropathy (CGN)]
- HIV Associated Nephropathy (HIVAN) → Combine with inheritance mode
- Progression of SLE Nephropathy
- Sickle Cell Nephropathy

Weak or no associations:

- Diabetic Nephropathy – Shlush et al and 2010 and multiple studies
  Diabetic Nephropathy is already a state of mTOR, Sirt1 and AMPK mediated autophagy inhibition → Consistent with a role of autophagy inhibition in APOL1 nephropathy

- IgA Nephropathy (Patera et al. JASN 2012)
Inheritance Mode, Phylogeny, and Genetic Risk Epidemiology

- Confidence intervals for dominant (single risk allele association) or additive (2 risk > 1) frequently overlap.

- Consistently the highest association ORs with G1 and G2 occurs under a 2-risk allele mode (G1G1, G1G2, G2G2).
**APOL1 Genetic Variants in Focal Segmental Glomerulosclerosis and HIV-Associated Nephropathy**

Kopp et al. JASN 2011

[Diagram showing odds ratios for different genotypes: Heterozygote (single risk allele), Homozygote or Compound Heterozygote (two risk alleles), with N values for each genotype category.]
More than 10 Studies Across Multiple Etiologies of Kidney Disease Show Highly Significant Odds Ratio under a “Recessive” inheritance mode (two APOL1 risk alleles)

* Odds Ratio were recalculated for two risk alleles combined based on available genotype frequency data.
APOL1 seems Dispensable in most Mammalian Species

TH-PO655

APOL1 Null Alleles from a Village in India Do Not Correlate with Glomerulosclerosis

Duncan B. Johnstone,1 V. Shegokar,2 Deepak Nihalani,1 Yogendra Singh Rathore,3 Leena Mallik,3 Fnu Ashish,3 Halil O. Ikizler,1 V. Zare,4 Rajaram Powar,2 Lawrence B. Holzman.1

1Renal, U Pennsylvania; 2Microbiology, GMH, Nagpur, India; 3CSIR-IMTech, Chandigarh, India;
How to Reconcile Recessive Inheritance with Apparent Dispensability of APOL1 for Mammalian Kidney Integrity

It’s not APOL1 but rather another gene tagged by MYH9 and APOL1

1. Calculations based on all variants found to date in 1000 Genomes would not explain the APOL1 Signal
2. Unlikely to yield associations with both G1 and G2 on separate lineages
3. Not consistent with absence of HIVAN in Ethiopia

“Gain of Injury” for G1/G2 risk alleles in which two doses of risk allele product are needed to cross kidney disease threshold

Even a single non-risk (G0) APOL1 “protects” from a human-specific “second hit”
Genetic Epidemiology Examples of One Allele Effect

Mild effect of Single Risk Allele on Age of Dialysis Onset

Two risk alleles: dialysis onset 12 years earlier
One G1 risk allele: dialysis onset 5 years earlier

Data from Papeta et al. JASN 2011

APOL1 Variants Increase Risk for FSGS and HIVAN but not IgA Nephropathy

Data from Tzur et al. NDT 2012
Transient Viral Transduction of G1-Risk APOL1 Gene Delivery Constructs Induce Significant Proteinuria and Foot Process Effacement

Reiser, Wei, Magen, Skorecki and colleagues
How to Reconcile Recessive Inheritance with Apparent Dispensability of APOL1 for Mammalian Kidney Integrity

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1. Calculations based on all variants found to date in 1000 Genomes would not explain the APOL1 Signal
2. Unlikely to yield associations with both G1 and G2 on separate lineages
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“Gain of Injury” for G1/G2 risk alleles in which two doses of risk allele product are needed to cross kidney disease threshold

Weakly supported and may contribute to pathogenesis under some specific states (e.g. recurrent FSGS following transplantation)

Even a single non-risk (G0) APOL1 “protects” from a human-specific “second hit”
Family History - APOL1 and risk for ESKD

- ~40% have two APOL1 risk alleles (compared to 13% in general AA population)
- Other non-APOL1 genetic or non-genetic factors

- Hispanic American
- African American

Controls | ESKD
---|---
2% | 2%
3% | 5%
5% | 18%

~ Only ESKD and not early kidney disease is associated with APOL1 two risk allele state in first degree relatives (Freedman et al. 2012)

- Second hit transforms genetic risk to progressive kidney disease in APOL1 two risk allele family members

- Use HIV as the prototype “second hit” to understand mechanism(s)
Algorithm for screening of CKD upon diagnosis of HIV

1. Microalbuminuria present?
   - Yes: Can HIV-unrelated causes be excluded?
     - Yes: Referral of patient to a nephrologist possible?
       - Yes: Proceed with referral
       - No: Proceed to Proteinuria still present after 1 month by dipstick?
     - No: Repeat algorithm after 1 year
   - No: Repeat algorithm after 1 year

2. Proteinuria still present after 1 month by dipstick?
   - Yes: Treat cause of proteinuria
   - No: Repeat algorithm after 1 year

3. Proteinuria present after 3 months?
   - Yes: Initiate ART and adjust dose if eGFR <60 ml/min/1.73 m²
   - No: Commence treatment with antiproteinuric agents

4. eGFR* <60 ml/min/1.73 m²?
   - Yes: Proceed with referral
   - No: Repeat algorithm after 1 year

5. Plasma potassium <5.0 mmol/L?
   - Yes: Commence ACE-I or ARB therapy and check potassium levels in 1–2 weeks
   - No: Prescribe potassium binding resin given orally or as an enema or administer non-dihydropyridine CCBs verapamil or diltiazem. Check potassium levels in 1–2 weeks

ApoL1 genotyping
Population Epidemiology of FSGS and HIV with Kidney Disease

Revision of biopsies → no bona fide HIVAN in absence of 2 risk allele state for APOL1
→ 100% risk for HIVAN in un/undertreated HIV infected individuals with APOL1 2 risk allele state
Effect of ART on GFR decline (all HIV patients)

Data from Kalayjian et al. AIDS 2012

Spontaneous resolution of HIV-associated nephropathy in an elite controller

Blankson, Basseth, Kuperman and Fine AIDS 2010
**Recessive Inheritance Model: Non-risk APOL1 Protective**

- Viral Protein (e.g. Nef) in Podocyte
- Induction of APOL1 in Podocyte
- At least one APOL1 non-risk allele
- Two APOL1 risk alleles
- Glomerulus protected
- Glomerulus injured

**Additive Inheritance Model: Risk APOL1 - Podocyte Injury**

- Induction of 2 APOL1 risk allele exceeds a threshold level for podocyte injury (+/- interaction with viral protein)
- 0/1 APOL1 risk allele below threshold level for podocyte injury
Additional Human Viral Nephrotropic Candidate Second Hits

Association of parvovirus B19 infection with idiopathic collapsing glomerulonephropathy


Table 3. PVB19 DNA detection in renal specimens by PCR

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sample N</th>
<th>PVB19 DNA (+) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>23</td>
<td>18 (78.3)²</td>
</tr>
<tr>
<td>HIVAN</td>
<td>19</td>
<td>3 (15.7)</td>
</tr>
<tr>
<td>FSGS</td>
<td>27</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Controls</td>
<td>27</td>
<td>7 (25.9)</td>
</tr>
</tbody>
</table>

²P < 0.01, CG vs. HIVAN, FSGS and controls

Majority African American \(\rightarrow\) APOL1 Genotype

ISH confirmation of Parvo B19 Viral Genome detection
Population Genetics of Focal Segmental Glomerulosclerosis

**GENETIC RISK**

- **APOL1** genetic susceptibility (perhaps other loci)
- Modifier Loci (e.g. CFH) Gene – Gene interactions
- Modifiable Environmental Second Hit
  - Human Nephrotopic Virus

**FSGS → CKD → ESKD**

**Major Public Health Challenge Especially in Sub-Saharan Africa affecting tens of millions with markedly increased susceptibility to Kidney Disease**

- Prevention and treatment of APOL1 associated FSGS will involve:
  - prevention and treatment of the second hit
  - restoring protection to the unsecured podocyte in the face of the “second hit”

Schema adapted from Barry Freedman
Chronic Disease Vaccines Need Shot in the Arm

Genotype for Susceptibility  
Vaccinate to Prevent Second Hit
Redefining Chronic Viral Infection

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2Immunology Program, The Wistar Institute, Philadelphia, PA 19104, USA
3Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: virgin@wustl.edu (H.W.V.), jwherry@wistar.org (E.J.W.), ra@microbio.emory.edu (R.A.)
DOI 10.1016/j.cell.2009.06.036

Table 1. Chronic Virus Infections in Humans

<table>
<thead>
<tr>
<th>Virus, Primary Nucleic Acid, Estimated Percent of Humans Infected</th>
<th>Major Site of Persistence (Organ or Cell)</th>
<th>Acute Infection Examples</th>
<th>Within Normal Hosts</th>
<th>Within Immunocompromised Hosts</th>
<th>References</th>
</tr>
</thead>
</table>

### Viral strategies
- Rapid replication
- Immune evasion and subversion
- Immune privilege
- Tissue damage
- Viral adaptation (genetic, mutation)

### ACUTE INFECTION
- Entry
- Primary replication
- Spread
- Secondary replication
- Tissue damage
- Shedding

### Immune strategies
- Innate immunity
- Antigen presentation
- Cytokines
- Clonal expansion of lymphocytes
- Antireviral effector mechanisms
- Regulatory cell interactions

#### DECISION POINT
- Recovery
  - Clearance of damaged cells
  - Elimination of virus
  - Re-establish immune system
  - Re-establish homeostasis

- Chronic infection
  - Continuous/intermittent antigen
  - Tissue damage
  - Altered immune system
  - Altered homeostasis

- Viral strategies
  - Latency
  - Niche-specific evasion genes
  - Niche-specific regulatory genes
  - Mutation
  - Immunoprivilege

- Immune effects
  - DAMP responses
  - Chronic activation
  - Immunopathology
  - Lymphocyte function/dysfunction
  - Repertoire contraction
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