New Genetic Developments in Steroid Sensitive Nephrotic Syndrome

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• Presented with edema
  • 4+ proteinuria
  • Hypoalbuminemia
  • Hypercholesterolema

• Mom’s questions
  • Why did this happen?
  • What’s going to happen?
  • Can you help him?
Current classification-descriptive & imprecise

Response to Steroids
- Steroid Sensitive NS “SSNS”
- Steroid Resistant NS “SRNS”

Histologic Description
- Minimal Change Disease “MCD”
- Focal Segmental Glomerulosclerosis “FSGS”

Tyagi 2013; Dijkman 2005
What’s going to happen?

• Variable outcomes
  • Single event (no relapses)
  • Relapses
  • Chronic kidney disease (CKD)/End stage (ESRD)
    • +/-Recurrence of NS in transplanted kidney

• Morbidity and mortality from;
  • NS itself (quality of life, infection, venous thromboembolism, end stage renal disease)
  • Treatment of the NS
    • Steroids, cyclophosphamide, calcineurin inhibitors, mycophenolate, rituximab

*Swaminathan 2006; El-Bakkali 2007*
Benefits of a genetic understanding of nephrotic syndrome

• Deliver novel insights regarding NS biology
• Identification of new targets for medicines
• Discover clinical impact for those harboring disease variants
• Support the selection of patients for clinical trials
• Ultimately, match patients with treatments most likely to benefit them
Genomic discovery in nephrotic syndrome: Conceptual model
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**STEP 1: DISCOVER KNOWN AND NOVEL NS-ASSOCIATED GENETIC VARIANTS**

**STEP 2A: GENETIC EPIDEMIOLOGY**

**STEP 2B: MOLECULAR & MECHANISTIC CHARACTERIZATION**

- Define biology & molecular subtypes
- Send to specific clinical trials
- Identify targets for therapeutic intervention

Demographics characteristics

Baseline characteristics

Longitudinal outcomes

Molecular Mechanisms

Genomic discovery in nephrotic syndrome: Conceptual model

- STEP 1: DISCOVER KNOWN AND NOVEL NS-ASSOCIATED GENETIC VARIANTS
- STEP 2A: GENETIC EPIDEMIOLOGY
- STEP 2B: MOLECULAR & MECHANISTIC CHARACTERIZATION
Nephrotic syndrome discovery from a population-based, complex trait approach
Genome-wide association study (GWAS) - discover genomic regions that differ between cases & controls

GWAS of Membranous Nephropathy
Stanescu et al, NEJM
# Nephrotic syndrome as a rare, complex disease: small sample size & big effects

<table>
<thead>
<tr>
<th>Glomerular disease</th>
<th>N\textsubscript{cases}</th>
<th>Loci</th>
<th>Odds ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous nephropathy</td>
<td>75-335</td>
<td>HLA-DQA1, PLA2R1</td>
<td>4.3, 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>188-430</td>
<td>APOL1</td>
<td>6-11</td>
</tr>
</tbody>
</table>

Stanescu et al, 2011  
Winkler et al 2008  
Genovese et al 2010  
Tzur et al 2010
HLA-DQA1 and PLCG2 Are Candidate Risk Loci for Childhood-Onset Steroid-Sensitive Nephrotic Syndrome


Due to the number of contributing authors, the affiliations are listed at the end of this article.
Exome-chip association study pediatric SSNS

Common Allele
214 Cases, 149 Controls
OR: 2.1

Gbadegesin et al, 2015
Limitations

• Sparse markers for Exome Chip done in Sri Lankan population
  • no imputation
  • No fine-mapping at HLA region
Outstanding questions

• What are genetic risk factors for SSNS outside of those with South Asian Ancestry?

• If we can find risk alleles for SSNS, what are the
  • Molecular consequences
  • Clinical consequences
Transethnic, Genome-Wide Analysis Reveals Immune-Related Risk Alleles and Phenotypic Correlates in Pediatric Steroid-Sensitive Nephrotic Syndrome

Hanna Debiec,1 Claire Dossier,2 Eric Letouzé,3–6 Christopher E. Gillies,7 Marina Vivarelli,8 Rosemary K. Putler,7 Elisabet Ars,9 Evelyne Jacqz-Aigrain,10 Valery Elie,10 Manuela Colucci,8 Stéphanie Debette,11 Philippe Amouyel,12 Siham C. Elalaoui,13 Abdelaziz Sefiani,14 Valérie Dubois,15 Tabassome Simon,16,17 Matthias Kretzler ©,18 Jose Ballarin,19 Francesco Emma,7 Matthew G. Sampson,7 Georges Deschênes,2,20 and Pierre Ronco1,21

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Leveraging Ancestral Heterogeneity to Map Shared Genetic Risk Loci in Pediatric Steroid-Sensitive Nephrotic Syndrome

Rebecca Hjorten1 and Karl Skorecki2,3
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Challenges
1. Small sample sizes
2. Diverse ancestries

Discovery
273 Children
- 132 EUR
- 85 North African
- 54 Sub-Saharan African

Replication
112 EUR Children
Rationale for trans-ethnic meta-analysis

Figure 1. The long trek of our ancestors from the beginnings in Africa ~150,000 years ago to their emergence out of Africa about 50,000 years ago to colonize the Levant, Europe, Asia, Australia, Americas, and eventually, Oceania. (From Gluckman et al. 2009 [Fig. 6.6, p. 142]; reprinted, with express permission, from the authors in conjunction with Oxford University Press © 2009.)
Fixed effects, trans-ethnic meta-analysis (385 children, three ancestries)
Odds ratio: 3.3
Odds ratio: 2.2
Controlling for rs1063348 and rs28366266

Odds ratio: 3.5
Genomic position of SSNS risk alleles

Chromosome 6 position (Mb)

LOC101929163-HCG23-BTNL2

rs9348883

HLA-

DRB1

DQA1

DQB1

rs28366266

rs1063348

Pleiotropy with other immune dysregulation disorders
• Epidemiologic associations: 97 children
• Glomerular transcriptomic associations: children
• *Note: children mostly FSGS/MCD, small % with IgA
rs1063348 → decreased glomerular expression of HLA transcripts
Risk alleles across GWAS SNPs

• Combined affects of rs1063348 & rs28366266
  • younger age of onset (also in GWAS cohort)
  • complete remission?
SSNS risk alleles are associated with complete remission across NS conditions.

Increased odds of complete remission, regardless of child’s histologic diagnosis.
Conclusion

• SSNS impacts a large percentage of our patients with NS
  • Substantial morbidity associated with this condition as well
• We can use GWAS to pinpoint the genetic contributors to SSNS
  • A first step towards mechanistic understanding & ”cleaner” treatments
• A patient’s genetic signature may lead to more accurate prognoses & effective therapies than histologic appearance