Genotype to Target Therapy

Keith R. Walley, MD
St. Paul’s Hospital
University of British Columbia

Conflict: Cyon Therapeutics.
Hypothesis

• Polymorphisms in genes relevant to therapy alter response to therapy – and could be used to target therapy.

• How do we get there?

  1. Response to vasopressin
  2. $\beta_2$- adrenergic receptor
  3. Activated Protein C
Vasopressin and Septic Shock Trial (VASST)
Choose a Therapy to Almost Works
All patients

Log-rank statistic
p = 0.27 day 28
p = 0.10 day 90
Low severity of shock stratum

$5 \mu g/min < NE < 15 \mu g/min$

Log-rank statistic

$p = 0.05$ day 28

$p = 0.03$ day 90
Does genotype play a role?
Vasopressin V1a receptor genetic variation in voles

“In addition, males overexpressing the V1aR in the ventral pallidal region, but not control males, formed strong partner preferences after an overnight cohabitation, without mating, with a female.”

Also in Humans?

Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. Walum H et al. PNAS. 105:14153-6, 2008
Candidate Genes and SNPs

SPH Severe Sepsis Cohort: Vasopressinase rs18059

28-day mortality (%) vs. TT/CT and CC genotypes with p < 0.09.
Identification of 230 SNPs in a huge haplotype block (160 kb) covering the $LNPEP$ region and genotyping

**Identification of 230 SNPs by re-sequencing**

**Genotyping 230 SNPs in the derivation cohort**

**Screening 230 SNPs on 28-day mortality**
LNPEP – Vasopressinase SNPs

rs4869317

$P = 4.4 \times 10^{-4}$

Major allele model

(SP vs. AT+AA)

-28-day mortality (%)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>337</td>
</tr>
<tr>
<td>AT</td>
<td>197</td>
</tr>
<tr>
<td>AA</td>
<td>55</td>
</tr>
</tbody>
</table>
LNPEP – Vasopressinase SNP rs4869317 in Septic Shock

SPH Derivation Cohort

\[ P = 0.0013 \]

Probability of Survival

Days

Number at Risk

AA/AT 252 208 182 175 165

TT 337 244 205 184 165

VASST Replication Cohort

\[ P = 0.026 \]

Probability of Survival

Days

Number at Risk

AA/AT 296 254 229 220 210

TT 316 250 224 207 199
Mechanism: Vasopressinase SNP alters vasopressin clearance

Constant infusion for 72 hours
One-compartment model ($C_p = R \frac{(1-e^{-kt})}{V_Dk}$)

\[ P=0.028 \]
Biological Plausibility: Vasopressinase SNP and serum sodium post cardiac surgery

$\text{LNPEP rs4869317}$

Locus specific heritability $^*$

\[
\frac{\text{Genetic Variance}}{\text{Total Variance}} = 0.800
\]

$P=0.045$

Serum sodium level (mmol/L)

- AA/AT
- TT

$P=0.045$
Treatment effect: replication

SPH

VASST

Mortality (%)
LNPEP genotype
NE n = 139
AVP n = 140

Mortality (%)
LNPEP genotype
NE n = 81
AVP n = 73

Mortality (%)
LNPEP genotype
NE n = 139
AVP n = 140

Mortality (%)
LNPEP genotype
NE n = 81
AVP n = 73
Vasopressinase (LNPEP)

- rs4869317 TT patients have high mortality in septic shock.
- How? rs4869317 TT patients have increased vasopressin clearance.
  - Decreased vasopressin levels in septic shock
  - Increased [Na\(^+\)] before cardiac surgery (decreased ADH)
  - Functional SNP(s) not identified yet
  - Best SNP for response to vasopressin?
Vasopressinase (LNPEP)

- rs4869317 TT patients have high mortality in septic shock.

- **Precision strategy:** Vasopressin for T allele carriers. Not for others.
β2- Adrenergic Receptor

Asthma
Cys/Gly/Gln homozygotes are hypo-responders to salbutamol

Cys/Gly/Gln marked by A allele of ADRB2 rs1042717 G/A polymorphism

Good response to steroids

No Acute Steroids

SPH

Survival

Days

Acute Steroids

SPH

Survival

Days

VASST

Survival

Days

VASST

Survival

Days
β2- Adrenergic receptor genotype

- Cys/Gly/Gln homozygotes (rs1042717 AA) adversely respond to adrenergic agonists, including increased mortality.

- **Precision strategy:** Non-adrenergic vasopressors for AA homozygotes. Steroids may help.
Protein C / PAI-1 combination genotype

Absolute Risk Reduction in 28-day mortality due to rhAPC

Survival ~ Age + APACHEII + Caucasian + rhAPC + genotype

Meta-analysis p<0.0001

p=0.062
p<0.0002
p=0.040

Protein C / PAI-1 genotype

- Response to rhAPC depends on Protein C and PAI-1 genotype.

- **Precision strategy:** Treat severe sepsis patients who have a +/+ Protein C and PAI-1 combination genotype with rhAPC.
Summary

• Genotype could be used to guide sepsis therapy (following confirmatory large prospective studies).
  1. Vasopressin
  2. $\beta_2$-adrenergic receptor
  3. Activated Protein C

• Therapies that don’t work for all might work for some.
Co-investigator
Jim Russell

People
Cheryl Holmes
Lauralynn MacIntyre
Ainsley Sutherland
Dave Shaw
Sanjay Manocha
Horatio Groshaus
Anan Wattanatham
Tony Gordon
Hugh Wellman
Taka Nakada
Emily Nakada
Katherine Thain
Simone Thair
Melissa McConechy
Lynda Lazosky
John Boyd

Databases
VASST Investigators
PROWESS Investigators

Funding
Heart & Stroke Foundation
CIHR
Michael Smith Foundation
Sirius Genomics Inc.

Centre for
Heart Lung Innovation
UBC and St. Paul’s Hospital
# Role of Heredity in Sepsis

<table>
<thead>
<tr>
<th>Parents</th>
<th>Relative Risk of Adoptee Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Death of a biological parent &lt;50 years)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1.2</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>4.5</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>5.8</td>
</tr>
</tbody>
</table>

1. Sorensen TI et al. NEJM 1988; 318: 727
Single Nucleotide Polymorphisms

- Most common genetic variant
- Common SNPs (minor allele frequency > 5%) occur every ~500 base pairs