CRITICAL ILLNESS IS A GENETIC DISEASE

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QUEEN’S UNIVERSITY
KINGSTON, ONTARIO

Critical Care Canada Forum
November 12, 2019

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@DavidMaslove
None
AGENDA

1. WHY?
2. CONSITUTIVE GENOMICS
3. FUNCTIONAL GENOMICS
4. IMPLICATIONS
THE CENTRAL DOGMA

CONSITUTIVE GENOMICS

FUNCTIONAL GENOMICS

DNA → RNA → Protein
AGENDA

1

WHY?
Why even suspect this?
Heritable predisposition to death due to influenza

Albright et al 2008
Evidence for a Heritable Predisposition to Death Due to Influenza

Frederick S. Albright, Patricia Orlando, Andrew T. Pavia, George G. Jackson, and Lisa A. Cannon Albright

1Department of Pharmacotherapy, University of Utah College of Pharmacy, and Departments of 2Pediatrics, 3Internal Medicine, and 4Biomedical Informatics, University of Utah School of Medicine, Salt Lake City

<table>
<thead>
<tr>
<th>Relative</th>
<th>Obs:Exp</th>
<th>P</th>
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<tbody>
<tr>
<td>Spouse</td>
<td>1.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1st degree</td>
<td>1.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2nd degree</td>
<td>1.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3rd degree</td>
<td>1.16</td>
<td>&lt;0.001</td>
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</table>

J Infect Dis 2008
GENETIC AND ENVIRONMENTAL INFLUENCES ON PREMATURE DEATH IN ADULT ADOPTEES

Thorkild I.A. Sørensen, Dr. Med., Gert G. Nielsen, Cand. Stat., Per Kragh Andersen, Lic. Scient., and Thomas W. Teasdale, M.A., Fil. Dr.

NEJM 1988

Biological parents

Adoptive parents

C. 1924

C. 1982

Cause of death ascertained for all
# GENETIC AND ENVIRONMENTAL INFLUENCES ON PREMATURE DEATH IN ADULT ADOPTEES

**Thorkild I.A. Sørensen, Dr.Med., Gert G. Nielsen, Cand.Stat., Per Kragh Andersen, Lic.Scient., and Thomas W. Teasdale, M.A., Fil.Dr.**

**NEJM 1988**

<table>
<thead>
<tr>
<th>Parent</th>
<th>Cause of death</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td>Adoptive</td>
<td>Cancer</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>1.00</td>
</tr>
<tr>
<td>Biologic</td>
<td>Cancer</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>5.00</td>
</tr>
</tbody>
</table>
Critical illness (sepsis) has a heritable component
AGENDA

1. **WHY?**
2. **CONSITUTIVE GENOMICS**
3. **FUNCTIONAL GENOMICS**
4. **IMPLICATIONS**
## TARGET SEQUENCING STUDIES

<table>
<thead>
<tr>
<th>Disease</th>
<th>SNP</th>
<th>Genotype</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Sepsis(^1)</td>
<td>rs4869317 (vasopressinase)</td>
<td>TT</td>
<td>↑ 28-day mortality</td>
</tr>
<tr>
<td>Trauma(^2)</td>
<td>rs1042714 (β2 receptor)</td>
<td>CC</td>
<td>↑ hospital mortality</td>
</tr>
<tr>
<td>Brain injury(^3)</td>
<td>rs3828275 (GAD)</td>
<td>TT</td>
<td>↑ early seizures</td>
</tr>
</tbody>
</table>

\(^1\)Nakada et al. *CHEST* 2010  
\(^2\)Norris et al. *Anesthesiology* 2010  
\(^3\)Darrah et al. *Epilepsy Research* 2012
Mortality from pulmonary sepsis
(2,500 patients 1,000,000 SNPs)

rs4957796 - chromosome 5 - FER

28-day mortality 25% (TT) vs 15% (TC) vs 10% (CC)

Rautanen Lancet Resp Med 2015
AKI in the ICU
(3,000 patients 1,000,000 SNPs)

rs62341639 - chromosome 4 - near IRF2
rs9617814 - chromosome 22 - near TBX1

Zhao AJRCCM 2017
Certain genetic polymorphisms are associated with critical illness and its outcomes.
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3

FUNCTIONAL GENOMICS
Acute leukaemia

AML

ALL
Acute leukaemia
"A genomic storm"

> 80% of leukocyte transcriptome reprioritized

Altered pathways:
- Systemic inflammation
- Innate immunity
- Compensatory inflammation

Xiao et al. JEM 2011
Calvano et al. Nature 2005
Transcriptomic “signature” of sepsis

Scicluna et al. AJRCCM 2015
Transcriptomic “signatures” of sepsis

Scicluna et al. AJRCCM 2015
McHugh et al. PLOS Med 2015
Sweeney et al. Sci Trans Med 2015
Transcriptomic “signatures” of sepsis

<table>
<thead>
<tr>
<th>Test</th>
<th>AUROC</th>
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<tbody>
<tr>
<td>SMS</td>
<td>0.88</td>
</tr>
<tr>
<td>FAIM3:PLAC8</td>
<td>0.74</td>
</tr>
<tr>
<td>Septicyte Lab</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Arms-length validation from PREVAIL data
Maslove et al. J Crit Care 2019
Patterns of gene expression can identify sepsis subtypes
“Endotypes”

Type 1

Type 2

Type 3

Wong et al. BMC Med 2009
Wong et al. Crit Care Med 2011
Validation cohort clustering

Maslove et al. Crit Care 2012
A

B

C

D

E

Discovery cohort

HR = 2.4, 95% CI 1.3-4.5, p = 0.005

Number at risk

Survival (days)

Patients surviving (%)
Patterns of gene expression can identify sepsis subtypes
Agenda

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Agenda
A case for therapeutic nihilism?
<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Expression Ratio (Type2:Type1)</th>
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<tr>
<td>drotrecogin alpha</td>
<td>1.74</td>
</tr>
<tr>
<td>TFPI</td>
<td>1.52</td>
</tr>
<tr>
<td>SERPINB2</td>
<td>1.61</td>
</tr>
<tr>
<td>CP</td>
<td>1.49</td>
</tr>
<tr>
<td>GGCX</td>
<td>1.58</td>
</tr>
<tr>
<td>SERPIND1</td>
<td>1.82</td>
</tr>
<tr>
<td>SERPINB6</td>
<td>1.43</td>
</tr>
<tr>
<td>SERPINE1</td>
<td>1.52</td>
</tr>
<tr>
<td>THBD</td>
<td>0.53</td>
</tr>
<tr>
<td>F5</td>
<td>0.48</td>
</tr>
<tr>
<td>vasopressin</td>
<td></td>
</tr>
<tr>
<td>GNG11</td>
<td>1.73</td>
</tr>
<tr>
<td>GNG5</td>
<td>1.43</td>
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<tr>
<td>GNAQ</td>
<td>0.58</td>
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<tr>
<td>hydrocortisone</td>
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<tr>
<td>5-LOX</td>
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<td>ANXA1</td>
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<td>NNMT</td>
<td>1.32</td>
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<tr>
<td>MOXD1</td>
<td>1.42</td>
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**Validation cohort clustering**

Reduction of the multiple organ injury and dysfunction caused by hemorrhagic shock and trauma in 5-lipoxygenase knockout mice and by the 5-lipoxygenase inhibitor zileuton

Flavocoxid, a dual inhibitor of COX-2 and 5-LOX of natural origin, attenuates the inflammatory response and protects mice from sepsis

*Marta Lattari, University of Lecce, Italy; \^Carmine Scuderi, University of Lecce, Italy; \^Giovanni Di Paola, Regina Fabbi, Università di Pisa, Italy; and \^Umberto P.C. Zucchi, Institute of Immunology, University of Naples, Italy*
Hoekstra et al. Crit Care Med 2019

# differentially expressed genes (vs Day 0)

- Placebo
- Lactoferrin
Take-home messages
1. Take a family history!

2. Reject nihilism! We might use genomics to our advantage.

3. Bank some blood samples!
QUESTIONS & COMMENTS

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@DavidMaslove
Transcriptomic “signature” of sepsis

Arms-length validation from PREVAIL data

Maslove et al. J Crit Care 2019
Critical illness is a genetic disease
Fig. 1. Labeled PCA comparing sterile SIRS/trauma versus sepsis patients. (A) Sterile SIRS/trauma and sepsis patients appear to be largely separable in the transcriptomic space, with only a minimal non-separable set. (B) The same labeled PCA is shown, with labels updated to reflect patients in recovery from noninfectious SIRS/trauma and patients with hospital-acquired sepsis; the late group (>48 hours after hospital admission) is much harder to separate. $n = 1094$ combined from 15 studies.
# Genetic and Environmental Influences on Premature Death in Adult Adoptees

Thorkild I.A. Sørensen, Dr.Med., Gert G. Nielsen, Cand.Stat., Per Kragh Andersen, Lic.Scient., and Thomas W. Teasdale, M.A., Fil.Dr.

**NEJM 1988**

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“GWAS”
Gene Expression

Environment & stimuli

Expression quantitative trait loci (eQTLs)

DNA methylation
Transcriptomic “signature” of sepsis

Scicluna et al. AJRCCM 2015
Higher prevalence of severe sepsis in subtype 2
Figure 2. Differences in gene expression trajectory between placebo and lactoferrin groups. A, Volcano plot showing the fold change and p values for the differences in gene expression between time points. There were more genes differentially expressed in the lactoferrin group than in the placebo group. B, Venn diagram showing the areas of overlap between differentially expressed genes in the lactoferrin and placebo groups. BH = Benjamini.