Genomics
The future Biomarkers

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Conflicts of Interest

- None
Genomic achievements since the Human Genome Project

- 1950: Watson & Crick discover the DNA double helix
- 1960: Crick & Watson write the DNA code
- 1965: Human genome sequencing begins
- 1977: Human genome sequencing begins
- 1980: Human genome sequencing begins
- 1990: Human Genome Project launched
- 1995: Human genome sequencing begins
- 1999: Human genome sequencing begins
- 2000: Human genome sequencing begins
- 2001: Human genome sequencing begins
- 2002: Human genome sequencing begins
- 2003: Human genome sequencing begins
- 2004: Human genome sequencing begins
- 2005: Human genome sequencing begins
- 2006: Human genome sequencing begins
- 2007: Human genome sequencing begins
- 2008: Human genome sequencing begins
- 2009: Human genome sequencing begins
- 2010: Human genome sequencing begins

Key achievements:
- 2000: First draft human genome sequence
- 2003: First complete human genome sequence
- 2004: First draft mouse genome sequence
- 2005: First draft rat genome sequence
- 2006: First draft dog genome sequence
- 2007: First draft plant genome sequence
- 2008: First draft fruit fly genome sequence
- 2009: First draft yeast genome sequence
- 2010: First draft Escherichia coli genome sequence

Legal and regulatory:
- 2008: Genetic Information Non-Discrimination Act (GINA) passed in US

- 2009: 23andMe introduces personalized healthcare

- 2010: southern African genome sequences

- 600ths genome-variant association study published

- 1,000 mouse knockout mutations

- ENCODE publications

- Nobel Prize in Physiology or Medicine

- Indian Genome Research Fund (IGRF)

- Korean Genome sequencing

- Nuffield Council on Bioethics publication on personalized healthcare
<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotides in the genome</td>
<td>$3.2 \times 10^{9}$</td>
</tr>
<tr>
<td>Protein-coding genes in the genome</td>
<td>23,500</td>
</tr>
<tr>
<td>DSVs</td>
<td>$4 \times 10^6$</td>
</tr>
<tr>
<td>SNPs</td>
<td>$3.5 \times 10^6$</td>
</tr>
<tr>
<td>nsSNPs</td>
<td>10,000</td>
</tr>
<tr>
<td>SV/CNVs</td>
<td>$10^3$–$10^5$</td>
</tr>
<tr>
<td>Variants known to be associated with inherited diseases</td>
<td>50–100</td>
</tr>
<tr>
<td>De novo variants</td>
<td>30</td>
</tr>
</tbody>
</table>
PARN mediates 3'-end maturation of TERC

Diane Moon et al.

Suneet Agarwal and colleagues use somatic cells and induced pluripotent stem cells from patients with PARN mutations to show that PARN is required for the 3'-end maturation of the telomerase RNA component (TERC). Their findings provide a mechanism linking PARN mutations to telomere diseases.

GWAS for alcohol-related cirrhosis

Stephan Buch, Felix Stickel, Eric Trépo et al.

GWAS for atopic dermatitis

Lavinia Paternoster, Marie Standl et al.

Mutations in RAS and PRC2 in juvenile myelomonocytic leukemia

Aurélie Caye et al.

Genomic landscape of juvenile myelomonocytic leukemia

Elliot Stieglitz et al.
Meeting report

The PIRO concept: P is for predisposition

Derek C Angus¹, David Burgner², Richard Wunderink³, Jean-Paul Mira⁴, Herwig Gerlach⁵,
Christian J Wiedermann⁶ and Jean-Louis Vincent⁷

How to choose candidate genes?
Invasive Aspergillosis
## Human Genetic Susceptibility to Invasive Aspergillosis

Cristina Cunha¹, Franco Aversa², Luigina Romani¹, Agostinho Carvalho¹*

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>SNP(s)</th>
<th>Amino acid change</th>
<th>Type of patients¹</th>
<th>Cases (total patients)</th>
<th>Association [OR (95% CI), P value]</th>
<th>Probable mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGER</td>
<td>rs1800624</td>
<td>-</td>
<td>HSCT (D/R)</td>
<td>41 (223)</td>
<td>2.0 (1.0–3.8), P = 0.04 (D) 2.0 (1.0–4.1), P = 0.05 (R)</td>
<td>Enhanced expression of RAGE</td>
</tr>
<tr>
<td>CLEC7A</td>
<td>rs16910526</td>
<td>Y238X</td>
<td>HSCT (D/R) Hematological</td>
<td>39 (205) 21 (138)²</td>
<td>2.5 (1.0–6.5), P = 0.05 (D) 3.9 (1.5–10.0), P = 0.005 (D+R) n.a., P = 0.02</td>
<td>Defective cell surface expression of dectin-1 and cytokine production</td>
</tr>
<tr>
<td>CLEC7A</td>
<td>rs7309123</td>
<td>-</td>
<td>Hematological</td>
<td>57 (182)</td>
<td>5.5 (1.9–16.4), P = 0.001</td>
<td>Impaired expression of dectin-1 mRNA</td>
</tr>
<tr>
<td>CXCL10</td>
<td>rs1554013</td>
<td>-</td>
<td>HSCT (D)</td>
<td>81 (139)</td>
<td>2.2 (1.2–3.8), P = 0.007 2.6 (1.4–5.0), P = 0.003 2.8 (1.6–5.2), P = 0.001</td>
<td>Impaired expression of CXCL10</td>
</tr>
<tr>
<td>IL1A</td>
<td>rs1800587</td>
<td>-</td>
<td>Hematological³</td>
<td>59 (110)</td>
<td>15.4 (1.4–171.2), P = 0.02</td>
<td>Unknown</td>
</tr>
<tr>
<td>IL1B</td>
<td>rs16944</td>
<td>VNTR 86-bp(n)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL1RN</td>
<td>rs1800896</td>
<td>-</td>
<td>HSCT (R)⁴</td>
<td>9 (105)</td>
<td>9.3 (1.6–52.8), P = 0.01</td>
<td>Unknown</td>
</tr>
<tr>
<td>IL10</td>
<td>rs1800871</td>
<td>-</td>
<td>HSCT (R)⁴</td>
<td>59 (120)</td>
<td>4.5 (1.6–12.9), P = 0.001</td>
<td>Unknown</td>
</tr>
<tr>
<td>IL10</td>
<td>rs1800872</td>
<td>-</td>
<td>Hematological</td>
<td>59 (120)</td>
<td>4.5 (1.6–12.9), P = 0.001</td>
<td>Unknown</td>
</tr>
<tr>
<td>MBL2</td>
<td>*MBL-low genotypes⁵</td>
<td>-</td>
<td>HSCT (D)</td>
<td>15 (106)</td>
<td>7.3 (1.9–27.3), P = 0.003</td>
<td>Unknown</td>
</tr>
<tr>
<td>MASP2</td>
<td>rs72550870</td>
<td>D120G</td>
<td>HSCT (R)</td>
<td>59 (194)</td>
<td>6.4 (2.0–20.6), P = 0.002</td>
<td>Unknown</td>
</tr>
<tr>
<td>PLG</td>
<td>rs4252125</td>
<td>D472N</td>
<td>HSCT (R)</td>
<td>59 (194)</td>
<td>3.0 (1.5–6.1), P&lt;0.001 5.6 (1.9–16.5), P&lt;0.001⁶</td>
<td>Unknown</td>
</tr>
<tr>
<td>S100B</td>
<td>rs9722</td>
<td>-</td>
<td>HSCT (D)</td>
<td>41 (223)</td>
<td>3.15 (1.61–6.15), P&lt;0.001</td>
<td>Enhanced secretion of S100B</td>
</tr>
<tr>
<td>TLR1</td>
<td>rs5743611</td>
<td>R80T N248S S249P</td>
<td>HSCT (R)</td>
<td>22 (127)</td>
<td>1.2 (1.0–1.5), P = 0.04 1.2 (1.0–1.5), P = 0.02 1.3 (1.1–1.5), P&lt;0.001⁷</td>
<td>Unknown</td>
</tr>
<tr>
<td>TLR6</td>
<td>rs483095</td>
<td>N248S S249P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TLR3</td>
<td>rs3775296</td>
<td>-</td>
<td>HSCT (D)</td>
<td>42 (223)</td>
<td>2.4 (1.3–4.6), P = 0.007</td>
<td>Defective antigen presentation and activation of CD8(+) T-cell responses</td>
</tr>
<tr>
<td>TLR4</td>
<td>rs4986790</td>
<td>D299G T399I</td>
<td>HSCT (D)⁸</td>
<td>33 (336) 103 (366)</td>
<td>6.2 (2.0–19.3), P = 0.002 (discovery study) 2.5 (1.2–5.4), P = 0.02 (validation study)</td>
<td>Unknown</td>
</tr>
<tr>
<td>TNFR1</td>
<td>rs4149570</td>
<td>-</td>
<td>Hematological</td>
<td>77 (144)</td>
<td>n.a., P = 0.02</td>
<td>Impaired expression of TNFR1 mRNA</td>
</tr>
<tr>
<td>TNFR2</td>
<td>rs5745946</td>
<td>-</td>
<td>Hematological</td>
<td>54 (102)</td>
<td>2.5 (1.1–5.0), P = 0.03</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Protective role of interleukin-10 promoter gene polymorphism in the pathogenesis of invasive pulmonary aspergillosis after allogeneic stem cell transplantation

KW Seo¹, DH Kim¹,², SK Sohn¹,², NY Lee²,³, HH Chang⁴, SW Kim⁴, SB Jeon¹, JH Baek¹, JG Kim¹,², JS Suh²,³ and KB Lee¹,²

Bone Marrow Transplantation (2005) 36, 1089–1095

Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation


Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation

Cristina Cunha, Ph.D., Franco Aversa, M.D., João F. Lacerda, M.D., Ph.D.,
Genetics and ARDS
Assessing the quality of studies supporting genetic susceptibility and outcomes of ARDS

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARC, F5</td>
<td></td>
</tr>
<tr>
<td>NFE2L2, STAT1</td>
<td>1</td>
</tr>
<tr>
<td>GP5</td>
<td>2</td>
</tr>
<tr>
<td>EGF, CXCL2, PPARGC1A</td>
<td>3</td>
</tr>
<tr>
<td>TLR1, SOD3, NFkB1</td>
<td>4</td>
</tr>
<tr>
<td>LTA, TNF</td>
<td>5</td>
</tr>
<tr>
<td>SERPINE1</td>
<td>6</td>
</tr>
<tr>
<td>NAMPT</td>
<td>7</td>
</tr>
<tr>
<td>ANGPT2</td>
<td>8</td>
</tr>
<tr>
<td>PLAU, SETD2, SFTP42, SFTP42</td>
<td>9</td>
</tr>
<tr>
<td>FAS</td>
<td>10</td>
</tr>
<tr>
<td>MBL2</td>
<td>11</td>
</tr>
<tr>
<td>IRAK3</td>
<td>12</td>
</tr>
<tr>
<td>DIO2</td>
<td>13</td>
</tr>
<tr>
<td>NFkB1</td>
<td>14</td>
</tr>
<tr>
<td>IL32, HMOX2, NQO1</td>
<td>15</td>
</tr>
<tr>
<td>ACE</td>
<td>16</td>
</tr>
<tr>
<td>FTL</td>
<td>17</td>
</tr>
<tr>
<td>PI3</td>
<td>18</td>
</tr>
<tr>
<td>MIF, HMOX1</td>
<td>19</td>
</tr>
</tbody>
</table>

Number of independent study samples reporting statistically significant associations
Recent advances in genetic predisposition to clinical acute lung injury

First network:

- ACE
- IL6
- IL8
- IL10
- TNF
- LTA
- NFKB1
- NFKBIA
- SFTPBP
- VEGFA
- PLAU
- F5

Second network:

- FTL
- HMOX2
- MBL2
- MIF
- MYLK
- PBEF1 (NAMPT)
- NFE2L2
- SOD3
- NQO1

Gao L and Barnes KC. Am J Physiol Lung Cell Mol Physiol 2009; 296: L713
Severe *Plasmodium malariae* Malaria in a Patient With Multiple Susceptibility Genes
Anne-Pauline Bellanger, PharmD,* Fabrice Bruneel, MD,† Olivier Barbot, MD,‡
Jean-Paul Mira, MD PhD,§ Laurence Millon, PharmD, PhD,* Pascal Houzé, PharmD,‖
Jean-François Faucher, MD PhD,‖ and Sandrine Houzé, PharmD#

**BMC Infectious Diseases**

Case report

*Lemierre's syndrome and genetic polymorphisms: a case report*
Jean-Michel Constantin*¹, Jean-Paul Mira², Renaud Guerin¹, Sophie Cayot-Constantin¹, Olivier Lesens³, Florence Gourdon³, Jean-Pierre Romaszko⁴, Philippe Linval⁵, Henri Laurichesse³ and Jean-Etienne Bazin¹

**Pachymeningitis after meningococcal infection**

Julie Toubiana, Claire Heilbronner, Cyril Gitiaux, Mehdi Oualha, Muhamed-Kheir Taha, Christophe Rousseau, Capucine Picard, Jean-Paul Mira,
Nice...
We have so many options!
- Deep whole genome
- Low pass whole genome
- Deep whole exome
- Genomewide array
- Exome array

How would you like to be sequenced?
Study Design: Multiple Step Design

1. GWAS: genome wide association study
2. Replication of most significant Markers from Step 1
<table>
<thead>
<tr>
<th></th>
<th>GenOSept/GAinS; Discovery</th>
<th>VASST; Discovery</th>
<th>PROWESS; Discovery</th>
<th>GAinS; Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1766</td>
<td>361</td>
<td>407</td>
<td>1002</td>
</tr>
<tr>
<td><strong>N deaths</strong></td>
<td>328 (18.6%)</td>
<td>115 (31.9%)</td>
<td>129 (31.7%)</td>
<td>174 (17.4%)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>1055 (59.7%)</td>
<td>226 (62.6%)</td>
<td>247 (60.7%)</td>
<td>505 (50.4%)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>711 (40.3%)</td>
<td>135 (37.4%)</td>
<td>160 (39.3%)</td>
<td>497 (49.6%)</td>
</tr>
<tr>
<td><strong>Age (mean)</strong></td>
<td>63.1</td>
<td>62.2</td>
<td>63.1</td>
<td>63.8</td>
</tr>
<tr>
<td><strong>N Pneumonia</strong></td>
<td>1035 (58.6%)</td>
<td>217 (60.1%)</td>
<td>301 (74.0%)</td>
<td>538 (53.7%)</td>
</tr>
<tr>
<td><strong>N deaths among patients with pneumonia</strong></td>
<td>185 (17.9%)</td>
<td>74 (34.1%)</td>
<td>100 (33.2%)</td>
<td>106 (19.7%)</td>
</tr>
<tr>
<td><strong>APACHE II score; median (range)</strong></td>
<td>17 (2-44)</td>
<td>26 (10-49)</td>
<td>24 (10-50)</td>
<td>16 (3-41)</td>
</tr>
<tr>
<td><strong>Pathogen identified</strong>*</td>
<td>60.2%</td>
<td>81.1%</td>
<td>61.5%</td>
<td>44.4%</td>
</tr>
<tr>
<td><strong>Bacterial infection</strong>*</td>
<td>33.6%</td>
<td>62.7%</td>
<td>56.5%</td>
<td>32.4%</td>
</tr>
<tr>
<td><strong>Gram positive infection</strong>*</td>
<td>23.5%</td>
<td>51.2%</td>
<td>36.3%</td>
<td>22.3%</td>
</tr>
<tr>
<td><strong>Gram negative infection</strong>*</td>
<td>11.7%</td>
<td>25.3%</td>
<td>30.9%</td>
<td>11.0%</td>
</tr>
<tr>
<td><strong>Viral infection</strong>*</td>
<td>3.3%</td>
<td>1.8%</td>
<td>0</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

*among patients with sepsis due to pneumonia
FER plays a role in the regulation of the actin cytoskeleton, cell adhesion, migration and invasion, and chemotaxis.

Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study

Effect on FER rs4957796 on pneumonia mortality

Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Deaths n/N</th>
<th>C/T alleles non-survivors</th>
<th>C/T alleles survivors</th>
<th>FER rs4957796</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1: GenOSept/GAinS</td>
<td>185/1035</td>
<td>35/335</td>
<td>308/1392</td>
<td></td>
<td>0.52 (0.38–0.72)</td>
</tr>
<tr>
<td>Cohort 2: VASST²²</td>
<td>74/217</td>
<td>11/137</td>
<td>52/234</td>
<td></td>
<td>0.44 (0.25–0.76)</td>
</tr>
<tr>
<td>Cohort 3: PROWESS²³,²⁴</td>
<td>100/301</td>
<td>25/175</td>
<td>79/323</td>
<td></td>
<td>0.60 (0.37–0.95)</td>
</tr>
<tr>
<td>Cohort 4: GAinS</td>
<td>101/525</td>
<td>26/176</td>
<td>148/700</td>
<td></td>
<td>0.70 (0.45–1.10)</td>
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<tr>
<td>Combined</td>
<td>460/2078</td>
<td>97/823</td>
<td>587/2649</td>
<td></td>
<td>0.56 (0.45–0.69)</td>
</tr>
</tbody>
</table>
Potential Application of Pharmacogenomics

- Discover better drugs
- Improve the safety and efficacy of new drugs in development
- Improve the safety and efficacy of licensed drugs
- Target the right patients - theragnostics
Pharmacogenomic information in drug labels: European Medicines Agency perspective

F Ehmann1, L Caneva1, K Prasad2,3, M Paulmichi2,4, M Maliepaard2,5,6, A Llerena2,7, M Ingelman-Sundberg8 and M Papaluca-Amati1

EMA evaluated medicinal products containing PGx biomarker in their label under Therapeutic Indication (1999 and 2014)

- Total number of authorized products with PGx biomarkers
- Ratio of products with PGx biomarkers to total number of products

The Pharmacogenomics Journal (2015), 1–10
SPECIAL REPORT

Cardiovascular disease gets personal

Gene-association studies hint at better ways of treating the leading cause of death

β-blocking agents

Clin Pharmacol Ther 2011; 89(3): 366-78

ACE inhibitors

Heart Fail Rev 2010; 15(3): 209-17

Warfarin

Blood 2009 113: 784-792

Statins


Antiplatelet therapy

Clin Pharmacol Ther 2011; 89(3): 455-59
Clinical Translation of Findings from Whole Genome Studies

Identification of susceptibility variants

- Novel biological insights
  - Clinical advances
    - Therapeutic targets
    - Biomarkers
    - Prevention
  - Improved measures of individual aetiological processes
    - Personalized medicine
      - Diagnostics
      - Prognostics
      - Therapeutic optimization
MinION USB stick gene sequencer finally comes to market

By John Hewitt on September 19, 2014 at 2:10 pm | 22 Comments
More breakthroughs coming

MINION = USB connection, minimal sample preparation, $1000 device + consumables

20-node installation = complete human genome in 15 minutes

Google Genomics

Explore genetic variation interactively. Compare entire cohorts in seconds with SQL-like queries. Compute transition/transversion ratios, genome-wide association, allelic frequency and more.

Process big genomic data easily. Run batch analyses like principal component analysis and Hardy-Weinberg equilibrium on as many samples as you like, in minutes or hours, with just a little code.

Use Google’s infrastructure and big data expertise. Store one genome or a million using Google Genomics and take advantage of the same infrastructure that powers Search, Maps, YouTube, Gmail and Drive.

Cell 157, March 27, 2014
“I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning”

Steve Jobs
1955-2011
MERCI!
THANK YOU!