How Genetics Contribute to Drug Discovery and Development

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Genetics
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The Road to a Medicine

Drug Discovery

Disease → Target ID → Target Validation → Tractable hit to candidate → Candidate selection to FTIM → FTIM to PoC → Phases II-III → Lifecycle mgt

Drug Development
Potential of Genetics to Support the Pipeline

- New susceptibility genes → New targets?
A genome-wide association study identifies novel risk loci for type 2 diabetes

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In a more complex scenario of pleiotropic effects. We anticipate that identification of the causal variants at these genetic loci and their functional consequences will reveal unexpected players in T2DM pathogenesis, and will point to novel mechanisms and targeted therapeutics.
Target Identification: Direct Genetics

- Trait Disease
- GWAS
- New Suscept. Gene
- New Drug Targets?
The Lausanne Constellation

CoLaus
n = 6205, age 35-75

Extensive CVRF + Metabolic Assessment + Affy 500K Genotype

PsyCoLaus
n = 3300
Age 35-65

Extensive PSY Assessment

AngioLaus
n = 500

Extensive CV Assessment

Prospective Follow-up 2009-2011
Genes Associated with LDL-C, GWAS

- CELSR2/PSRC1
- APOB
- PCSK9
- APOC1/E
- LDLR
- CILP2
- HMGCR

Target for Statins: HMGCoA-R

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<th>CC</th>
<th>CT</th>
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<td>LDL-C (mM)</td>
<td>3.29</td>
<td>3.36</td>
<td>3.42</td>
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TT-CC = 4%

Sandhu, Lancet 2008
Ceci n’est pas une pipe.
Leci n'est pas une pipe.

Leci n'est pas un médicament.
No gene encoding for anti-hypertensives !!!
Androgenic Alopecia

Controls

Cases

Type I

Type IV

Type II

Type V

Type III

Type VI

Type III Vertex

Type VII
Androgenic Alopecia: GWAS

Richards et al, Nature Genetics 2008
Androgenic Alopecia: Signal in a Gene Desert !!!!
Knowledge expansion on targets, target validation
CETP RS9989419 Genotype

HDL-raising SNP in CETP gene associated with lower DBP

*** : p < 0.001, ** : P < 0.01, Lausanne n = 5749

→ Genetic evidence for Pfizer torcetrapib-induced elevation in BP = off-target effect (confirmed with Merck anacetrapib, no effect on BP)

Pharmacogenetics 2008
Potentioal of Genetics to Support the Pipeline

Elucidation of molecular basis of efficacy
Elucidation of molecular basis of adverse effects → *Differentiation* – better, safer drugs
Risk of ALT 3x ULN Elevation in GSK Drug -Treated Patients

OR = 8.2 (3.1-24.2)

Proportion (%)

Carriers
n = 96
HLA DQA1*0201 Genotype

Non-Carriers
n = 275

Genotype
Genetic-based clinical trial enrichment

→ Faster development
Prevalence of Type 2 Diabetes by Quintiles of BMI and Weighted Genetic Score - Lausanne

Diabetologia 2009
Summary

Elucidation of molecular basis of AE
→ Safety – better, safer drugs

Elucidation of molecular basis of efficacy
→ Differentiation - personalized medicine

Clinical trial enrichment
→ Faster development

Knowledge expansion on targets
→ Target Support

New susceptibility genes → New targets?
→ Portfolio replenishment