How Genetics Contribute to Drug Discovery and Development

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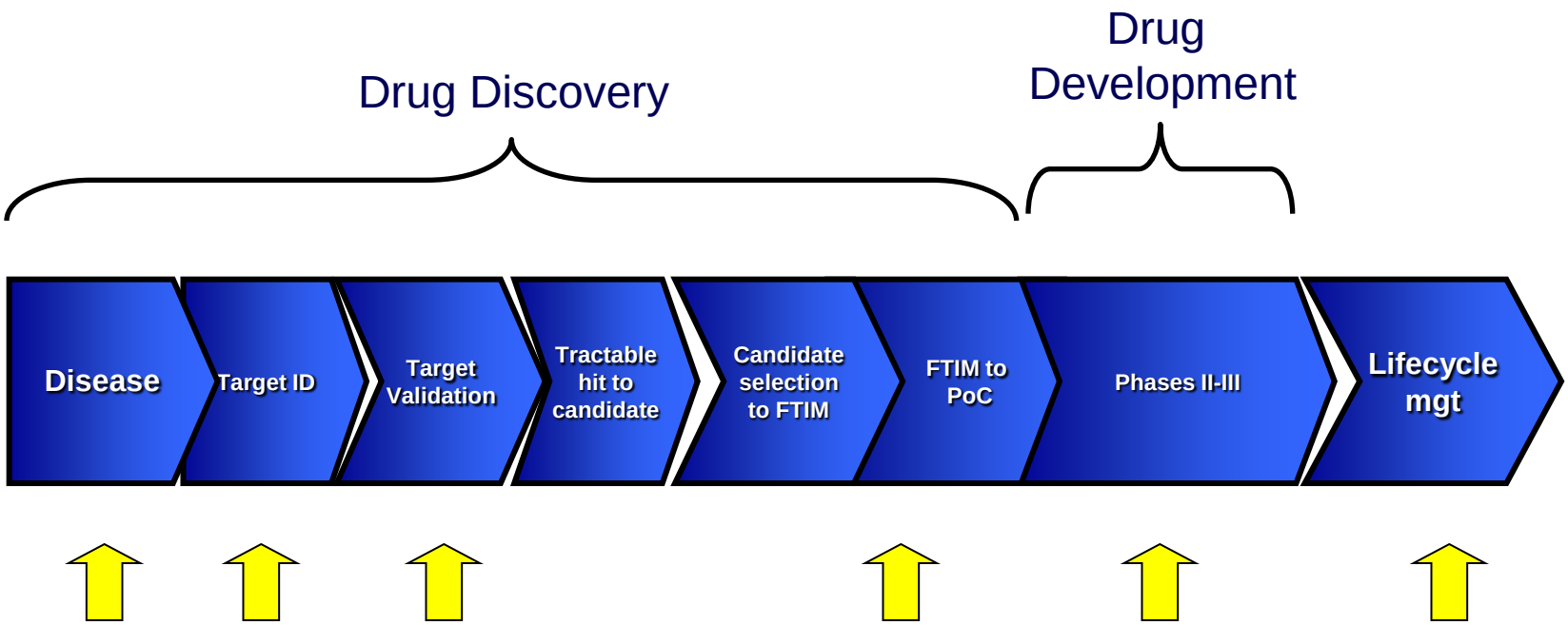
Genetics
University of Michigan Meeting
October 1st, 2009

The Road to a Medicine



Potential of Genetics to Support the Pipeline

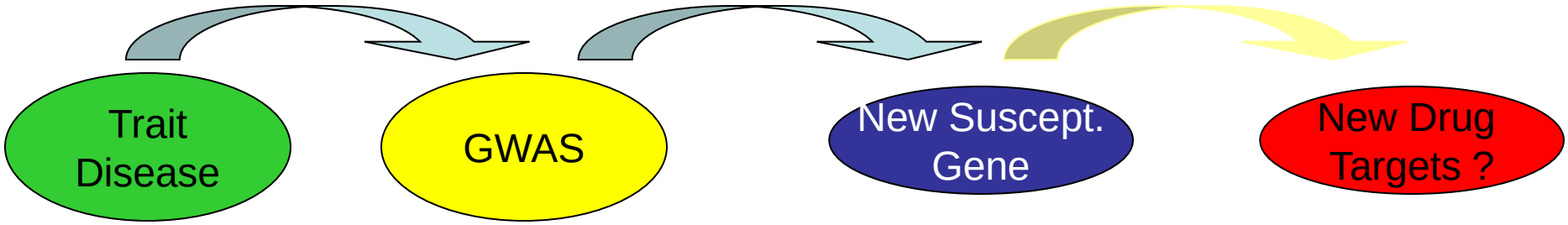
New susceptibility genes → New targets ?

A genome-wide association study identifies novel risk loci for type 2 diabetes

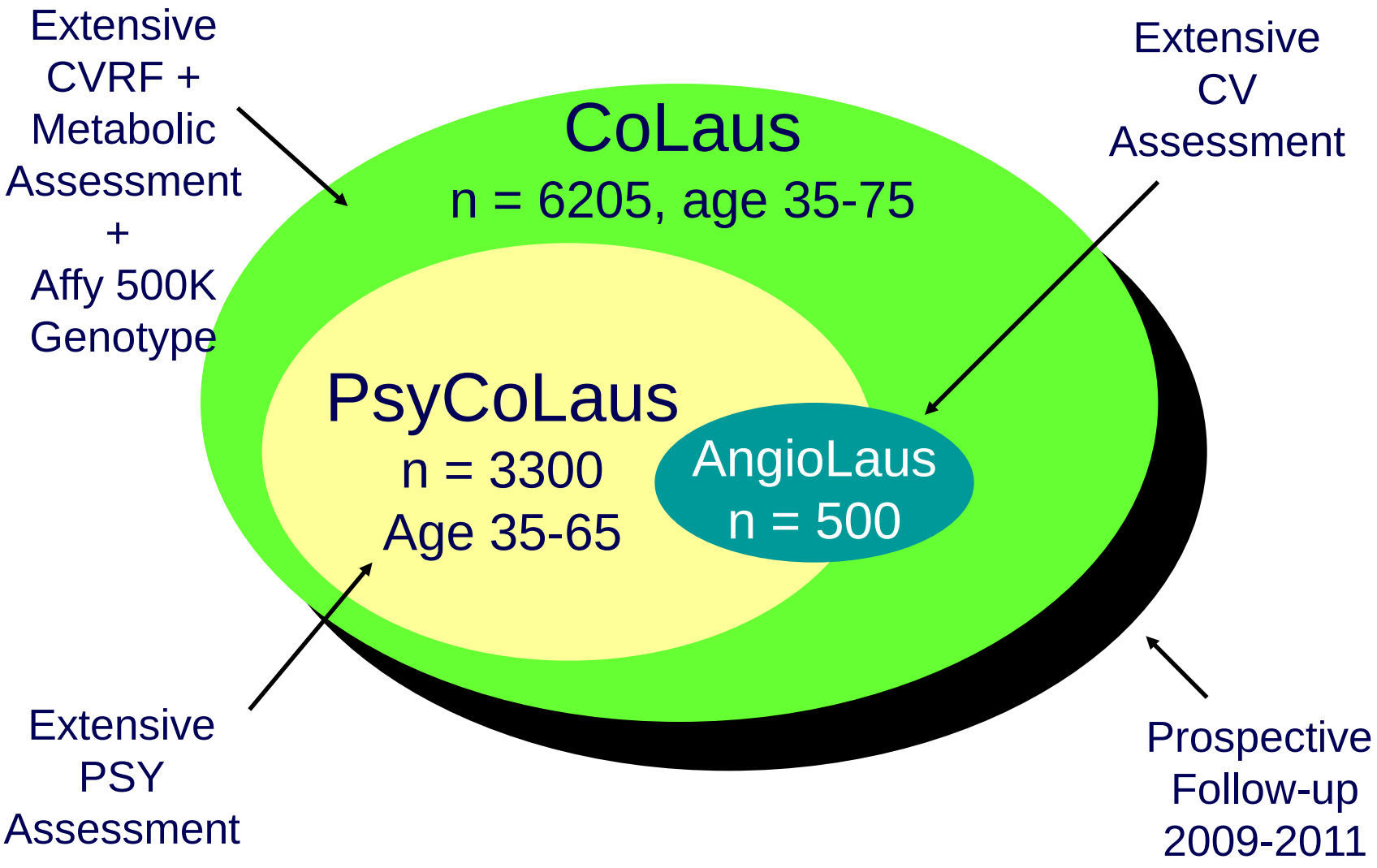
Robert Sladek[1,2,4], Ghislain Rocheleau[1]*, Johan Rung[4]*, Christian Dina[5]*, Lishuang Shen[1], David Serre[1], Philippe Boutin[5], Daniel Vincent[4], Alexandre Belisle[4], Samy Hadjadj[6], Beverley Balkau[7], Barbara Heude[7], Guillaume Charpentier[8], Thomas J. Hudson[4,9], Alexandre Montpetit[4], Alexey V. Pshezhetsky[10], Marc Prentki[10,11], Barry I. Posner[2,12], David J. Balding[13], David Meyre[5], Constantin Polychronakos[1,3] & Philippe Froguel[5,14]

ing 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.

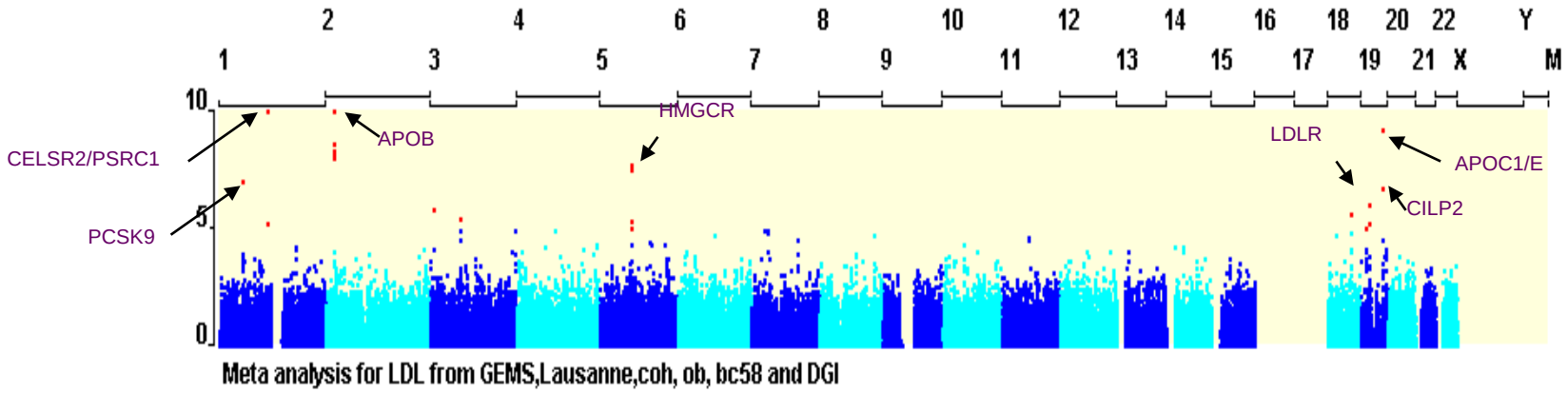
Target Identification : Direct Genetics



The Lausanne Constellation



Genes Associated with LDL-C, GWAS



HMGCoA-R

Target for Statins

	CC	CT	TT
LDL-C (mM)	3.29	3.36	3.42

TT-CC = 4%

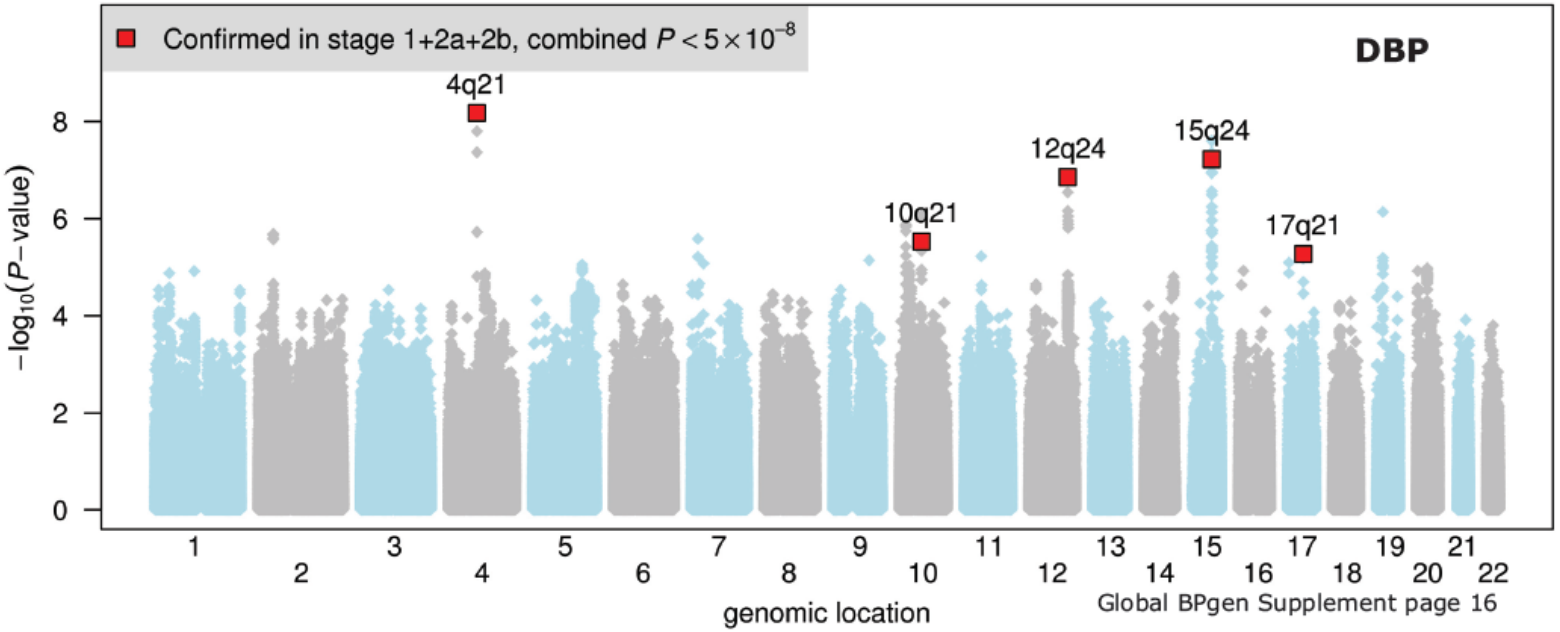
Sandhu, Lancet 2008


Ceci n'est pas une pipe.


Ceci n'est pas une pipe.


Ceci n'est pas un médicament.

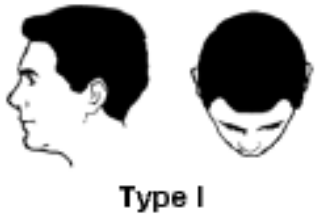
WGAS on Blood Pressure
Global BPGen, n = 34433, Nat Gen May 10, 2009



→ No gene encoding for anti-hypertensives !!!

Androgenic Alopecia

Controls



Type I

Type II

Type III

Type III Vertex

Cases

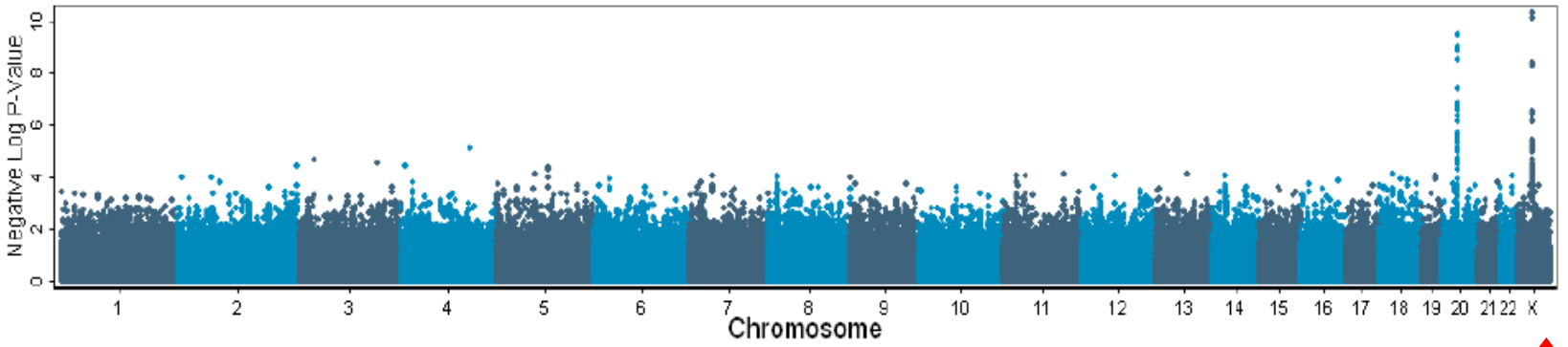
Type IV

Type V

Type VI

Type VII

Androgenic Alopecia : GWAS



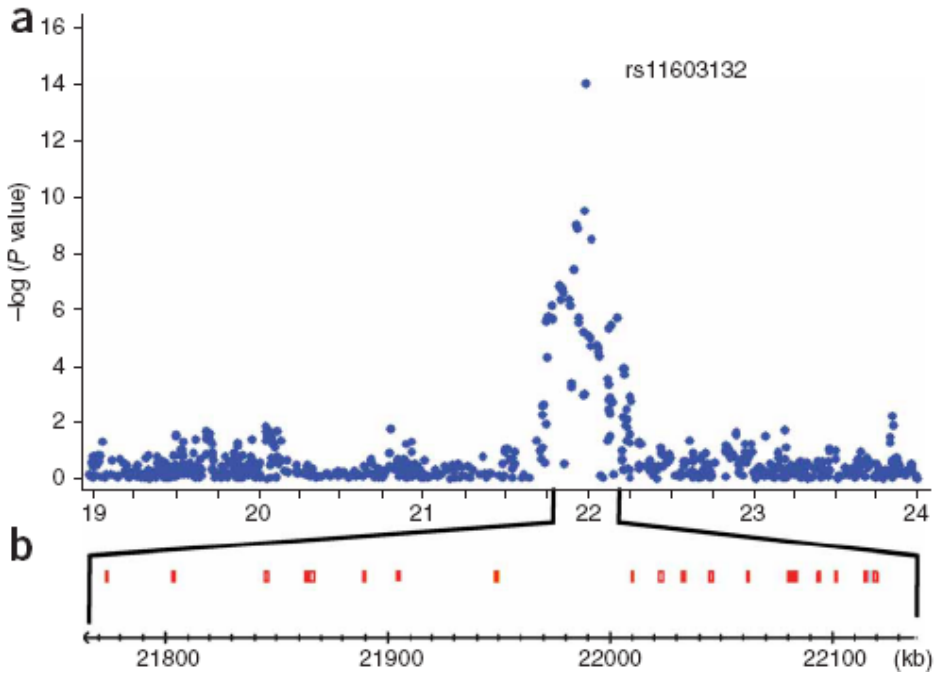
Androgen Receptor

New Locus

Richards *et al,* Nature Genetics 2008

WGAS Androgenic Alopecia

Androgenic Alopecia : Signal in a Gene Desert !!!!!

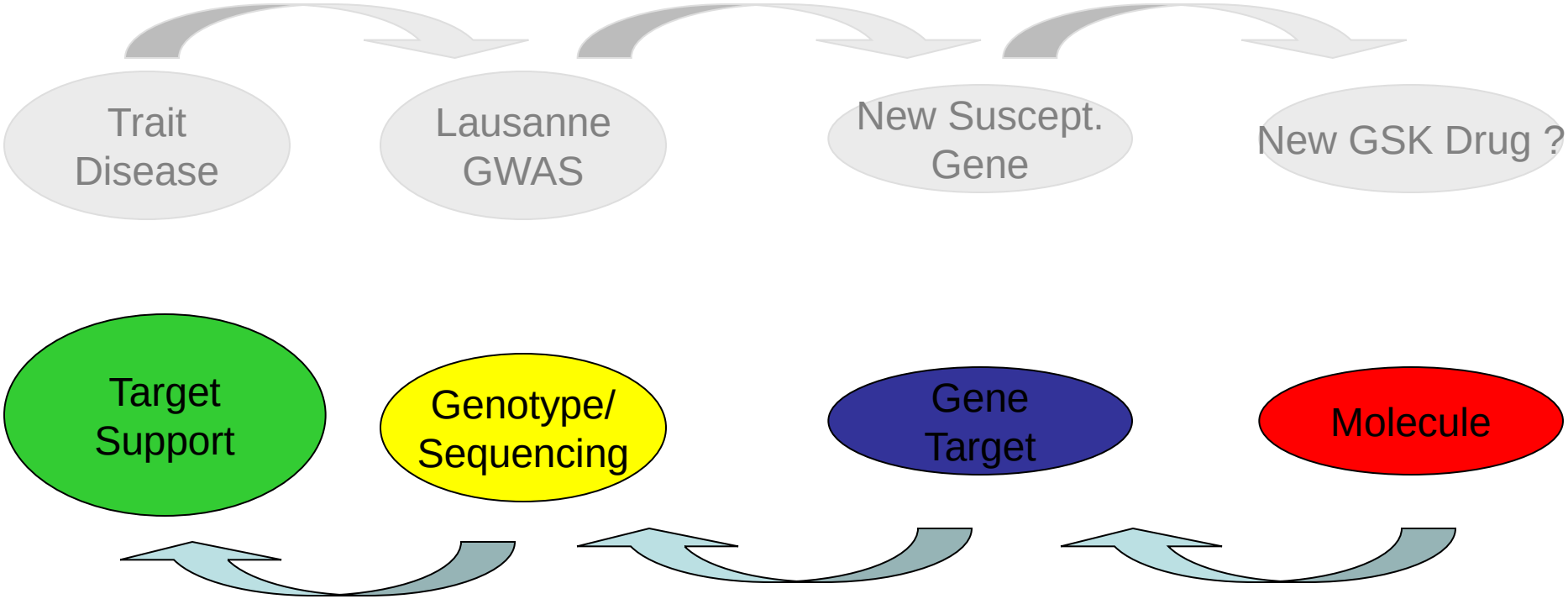


Locus ≠Gene ≠ Drug Target ≠ IP ≠ $$$!!!

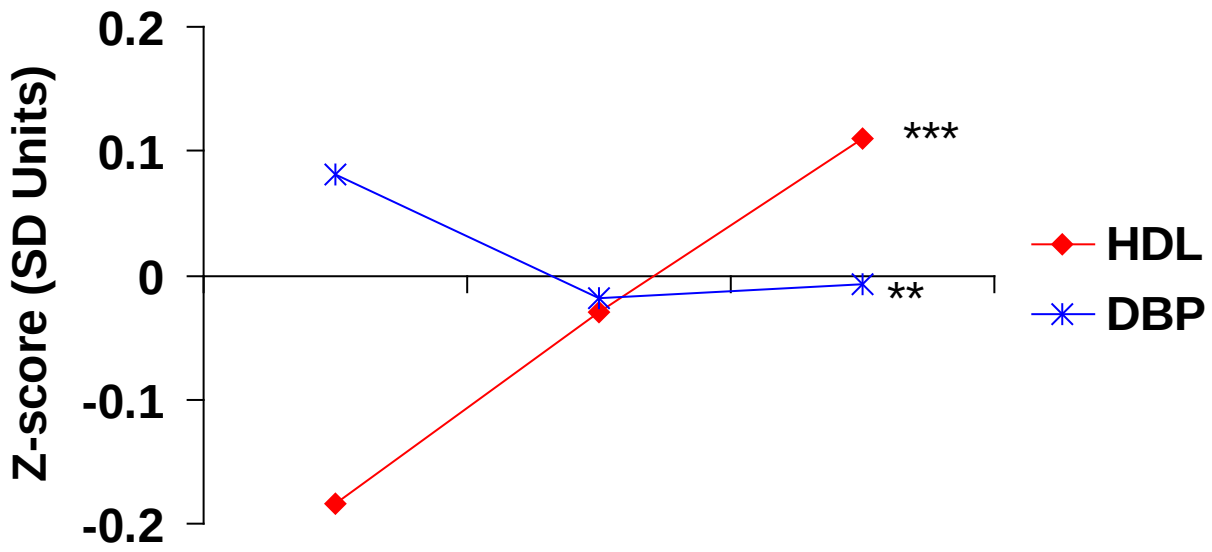
Potential of Genetics to Support the Pipeline

Knowledge expansion on targets, target validation

Reverse Genetics



Common Variants for Target Validation



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)

Potential of Genetics to Support the Pipeline

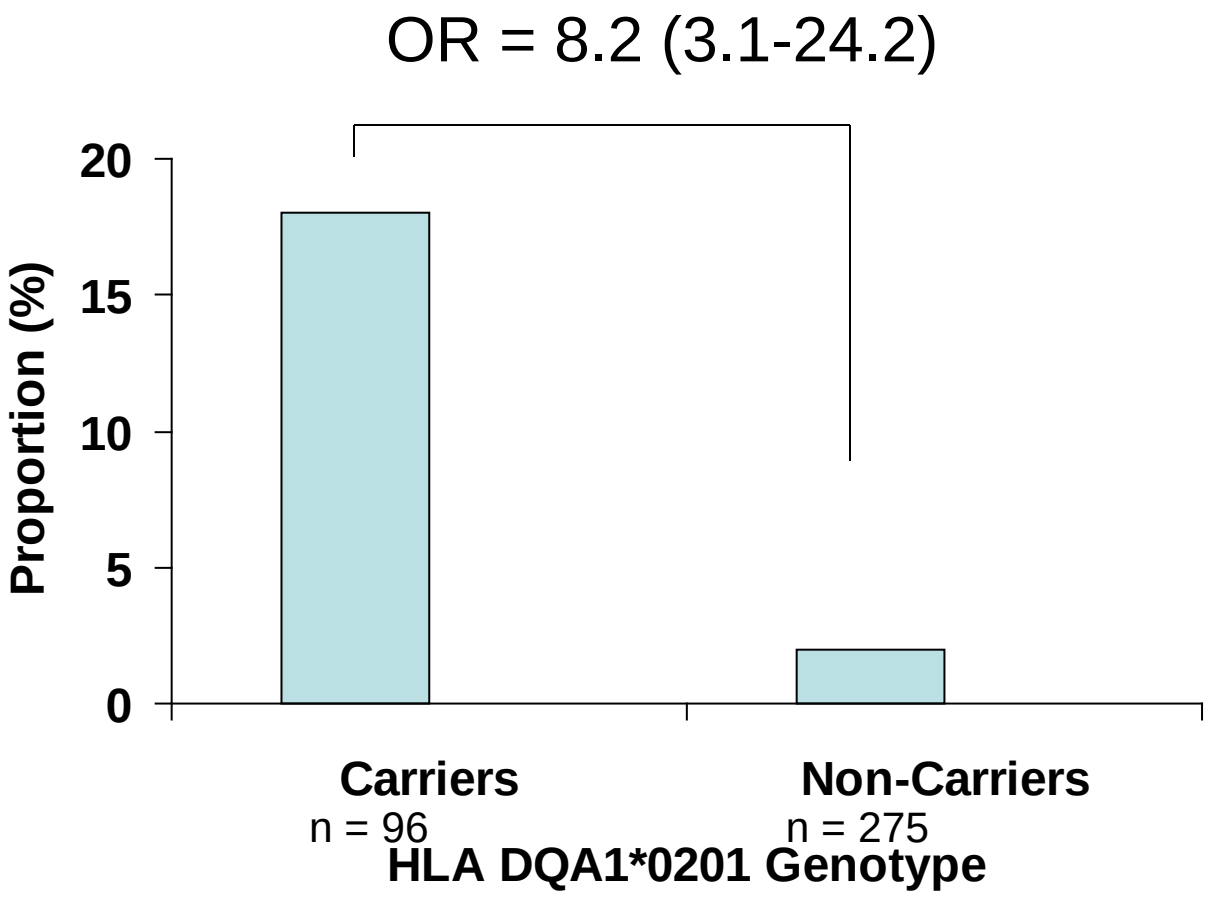
Elucidation of molecular basis of efficacy

Potential of Genetics to Support the Pipeline

Elucidation of molecular basis of adverse effects

→ *Differentiation – better, safer drugs*

Risk of ALT 3x ULN Elevation in GSK Drug -Treated Patients

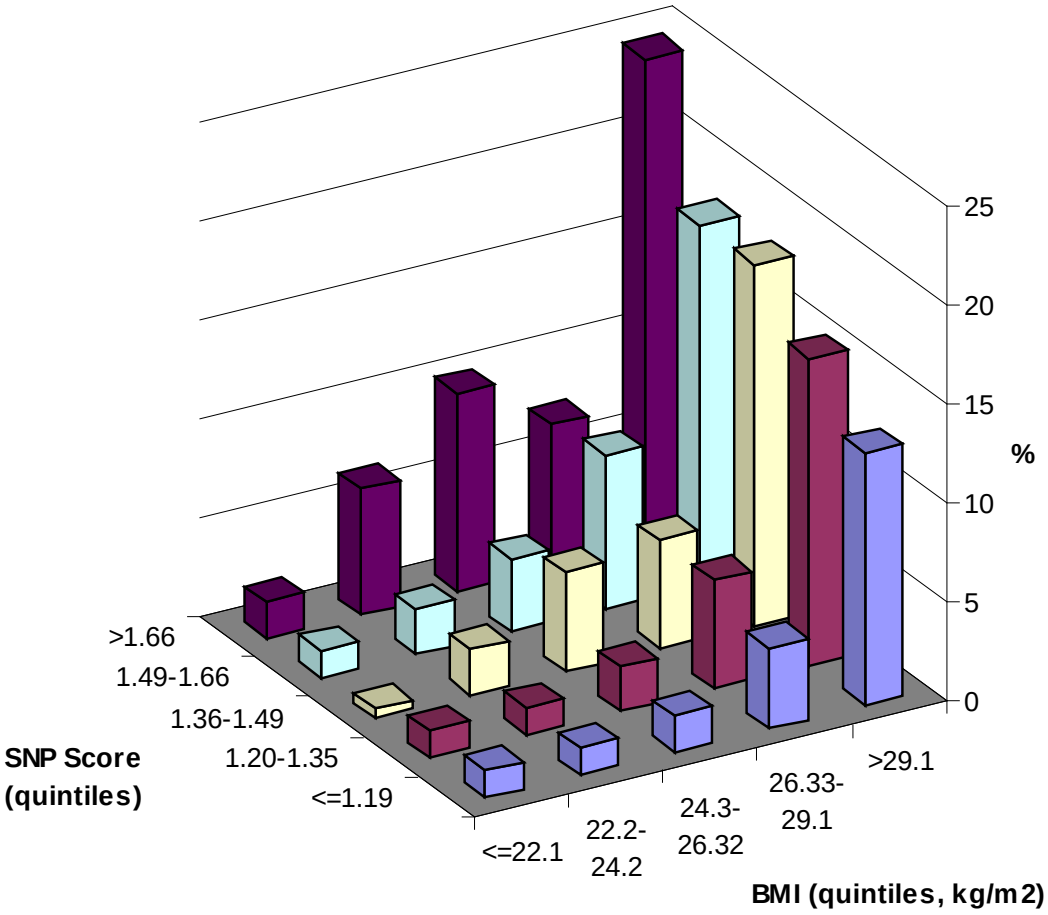


Clinical Trial Enrichment

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*