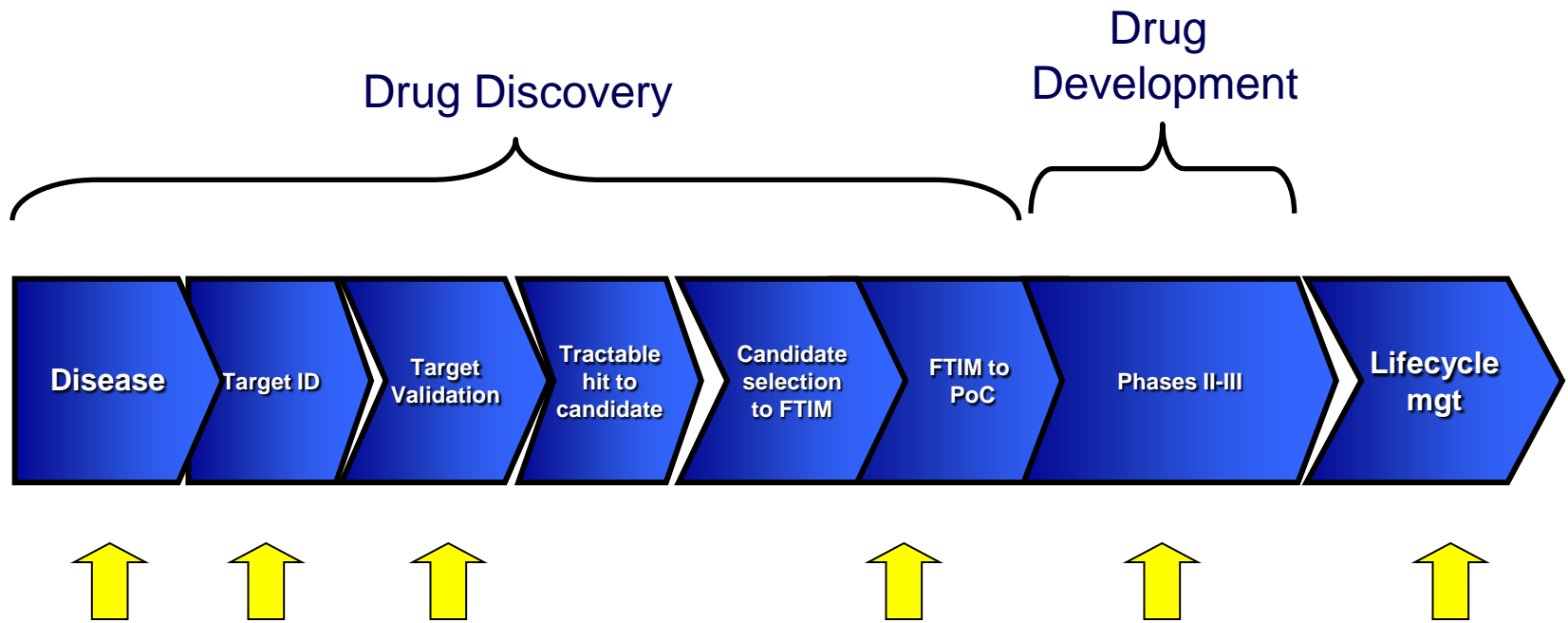




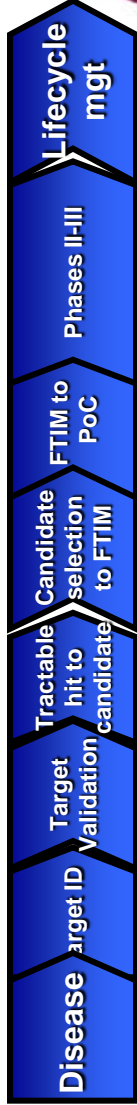
How Genetics Contribute to Drug Discovery and Development

Vincent Mooser MD
Genetics
University of Michigan Meeting
October 1st, 2009

The Road to a Medicine



Potential of Genetics to Support the Pipeline



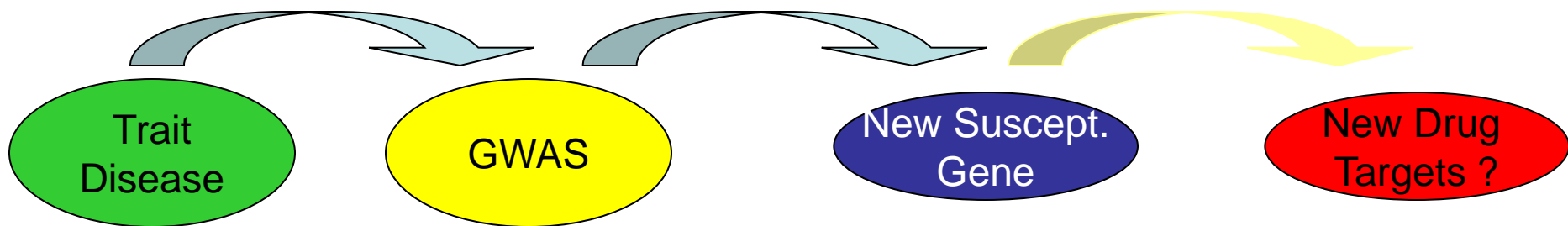
New susceptibility genes → New targets ?

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

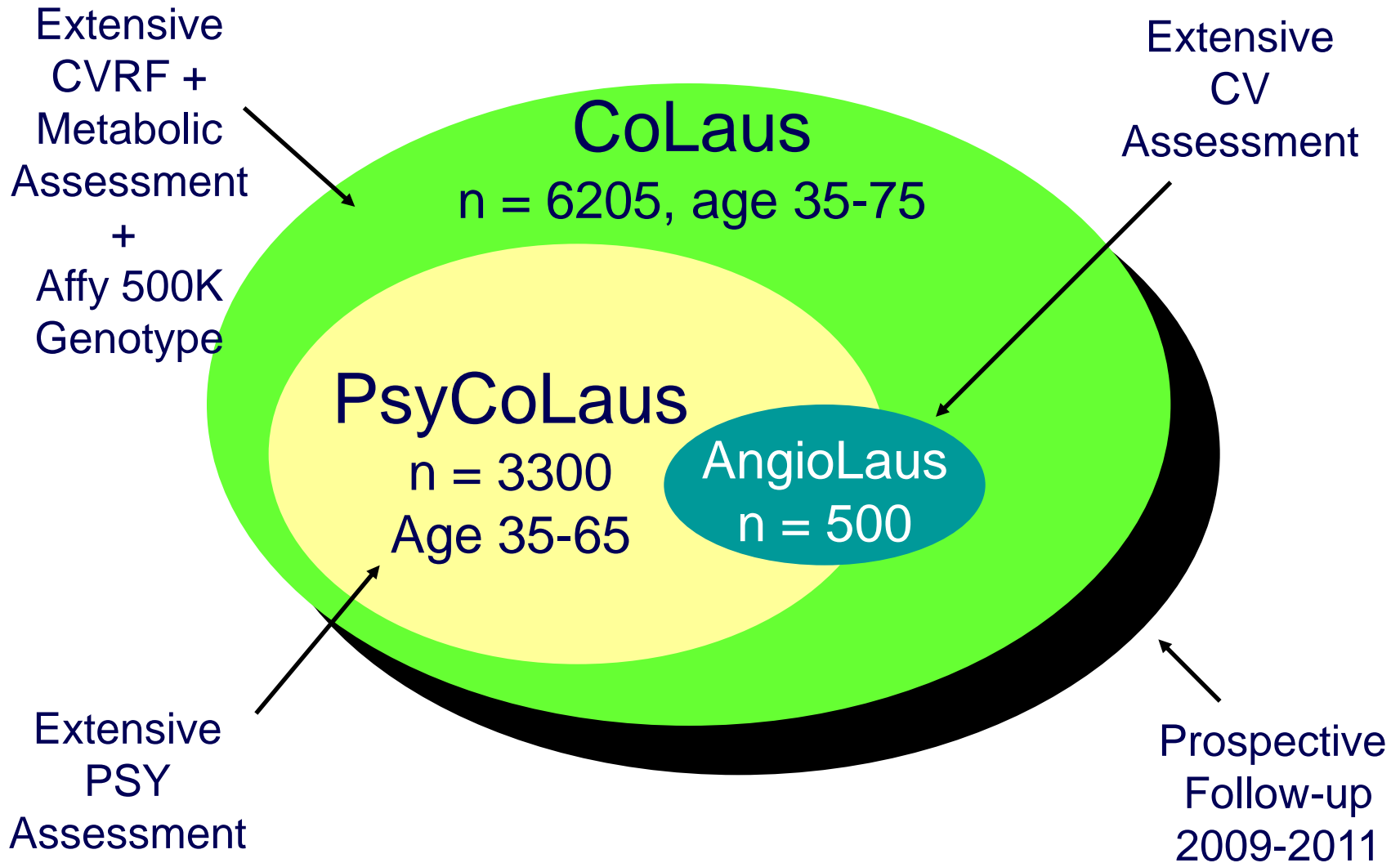
Robert Sladek^{1,2,4}, Ghislain Rocheleau^{1*}, Johan Rung^{4*}, Christian Dina^{5*}, Lishuang Shen¹, David Serre¹, Philippe Boutin⁵, Daniel Vincent⁴, Alexandre Belisle⁴, Samy Hadjadj⁶, Beverley Balkau⁷, Barbara Heude⁷, Guillaume Charpentier⁸, Thomas J. Hudson^{4,9}, Alexandre Montpetit⁴, Alexey V. Pshezhetsky¹⁰, Marc Prentki^{10,11}, Barry I. Posner^{2,12}, David J. Balding¹³, David Meyre⁵, 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.

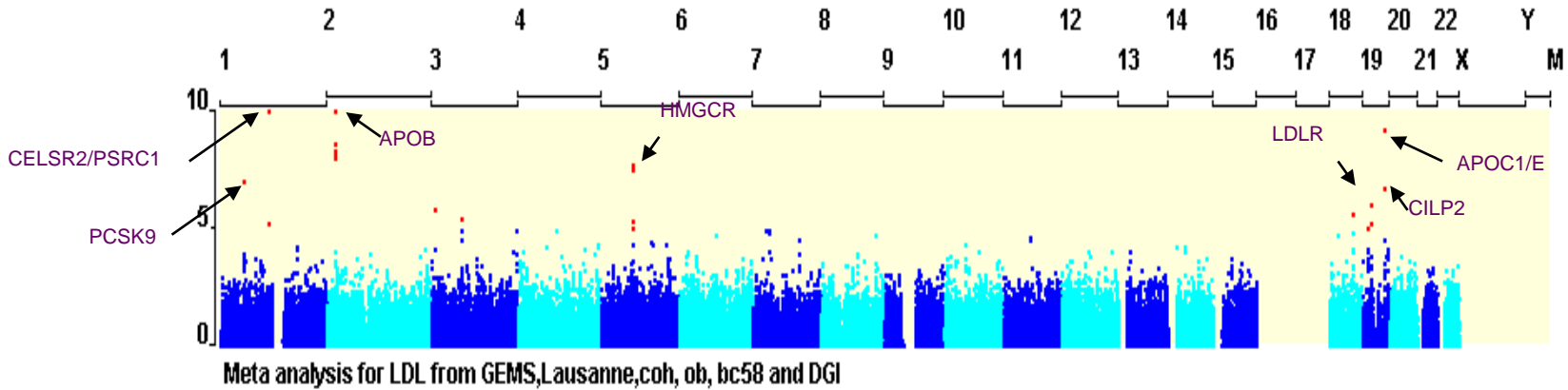
Target Identification : Direct Genetics






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



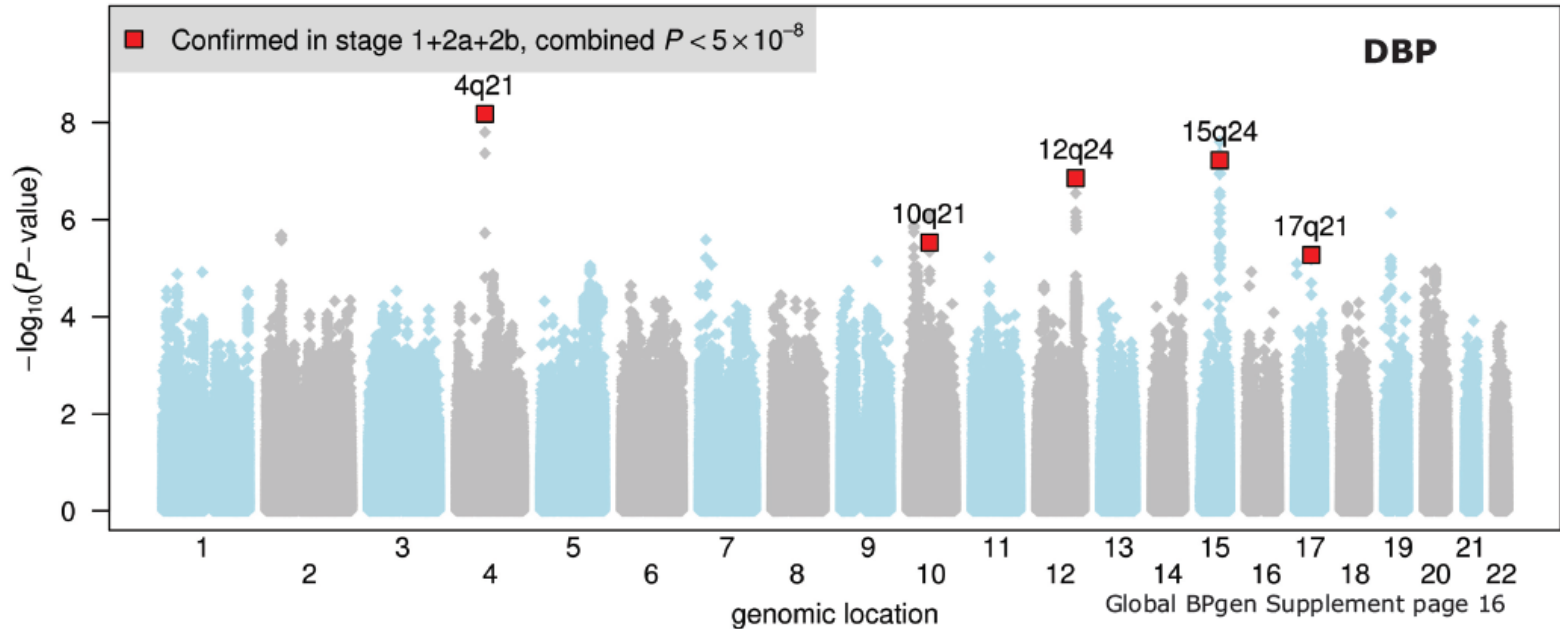


CCGGAAAGGA ACCAGGCTCT EFGAGAAAT ACTTCAGGAG TAGMAAGGG AMGCTAGAGG
 UAGTTAGUAT ATUTUTAGAG UTCUATUAAA CUAAMAACAAS TCTUGANTUG CATACCGCCA
 AGGCAAACTC CAGCCCTCT ATTACTAGAT AGCTTCATC AACAGCTCAA AACCCACAGA
 AATTTGGTTT GGNTOCCATG CCCATGAGCC TGCCAGCTGA CAATTCCTAG CATGCGGAAA
 TGGCCCTTZA TGTGAAGTAC CTGGTTTTTC CATTTCGGT TTTACCNTAG GCCTAGTTC
 FLATINUTAT AGATTAAAG AAAGAAATAC AATGGARGL AAGIGATTAA GCCTTCCTTA
 AACCGTATTA ACCTACAGAA AATGTECAGS GAARTGGTCT ATTTCTERT STATTTTTGA
 TCTCCATCGA CTGCGCTCAG CTTTGGCCTG AAGCTATCTT TAAAGCTACC CTGTACAAGC
 TCTTCGATTA GAGACATCTP CAGTGGCAGH TAAAGAGGAG AGPTATPTTA TGTATCAAGC
 CTCTTAAGAC TATAGTAATA TCTTCACTTG AAAAAGDUU CTATTATTCU TATUTAGAT
 TAAAGCCACC TGGCTCTACA AAGCTACTCT GGACAGCAT TTAACANTT ATCTCTTAC
 AAAAACCNAA CTGAGCPTCC CPTCTPTTCC CACTCAATE ACCTAGAGCA AMGGCTAGG
 CAAATGAATT TCGTTTGTAT ATGAGTGAGA GCRAACACTE TTTATTGTAC AACTTGGGTG
 AACGGTTACC TTTGAGTTAR AGCTTAGGAR GAARACCAA GGTATAGGCC TCTTTTCTG
 TGTATATTTT CTAGAAGCAT GCTGTCTTPT GGTTTTGTG TATNIGTLAC TGTGAAGAU
 TFGACAGAT ATAACTCAGH TGTCTACTC AGACCATAGC CCTTCCATC TTTCCATTA
 GGAGACATCT CHTACCCCAH ATAGCTAATA TTTTATAGC TATGATCTG AAGGGGAAA
 TATATTTTAG GCCTTTTCTT TGGCAAGGAT GTTTGGTCAH GGGTTGGLAA AATATATCT
 CACCGGUAH TATAGHACG CCCCAGGAG CANCTCTTG ICAGSAGICA GACTAGCTAC
 CCTGGCCTAA CTAGCCTACT GAGCTGAGS ATGICCAAT TCCCCCRAAT ACACTPACCA
 TCCCAATTCG TTAACAAT ATGPTCAGPT GTAACCAHA ATACCAATAC ATAAAGTGT
 ACCGAGAGS ATGCTTTAT GACCCCTCH CTIACCGAGS GCITTCGACT GAGACAGCTC

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

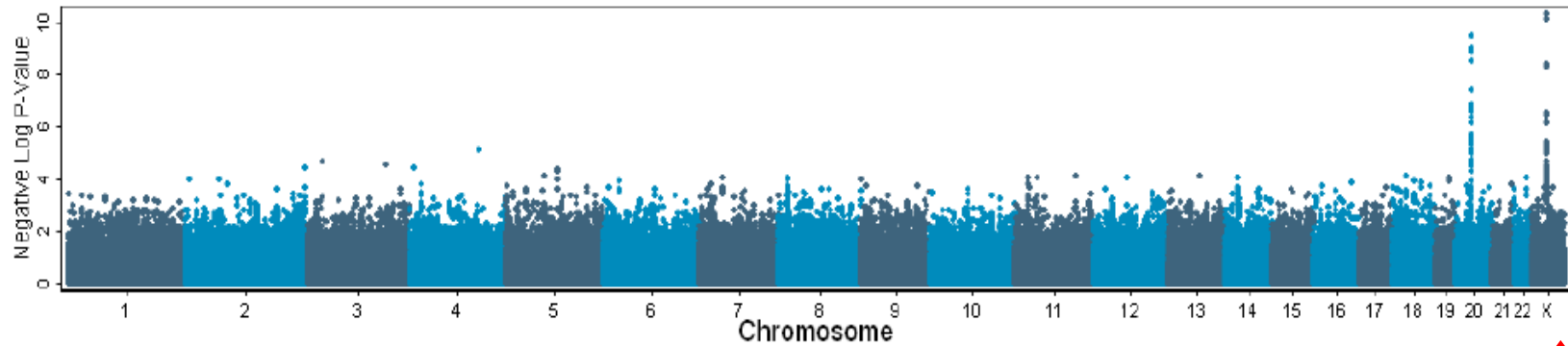


Type VI



Type VII

Androgenic Alopecia : GWAS



Androgen
Receptor

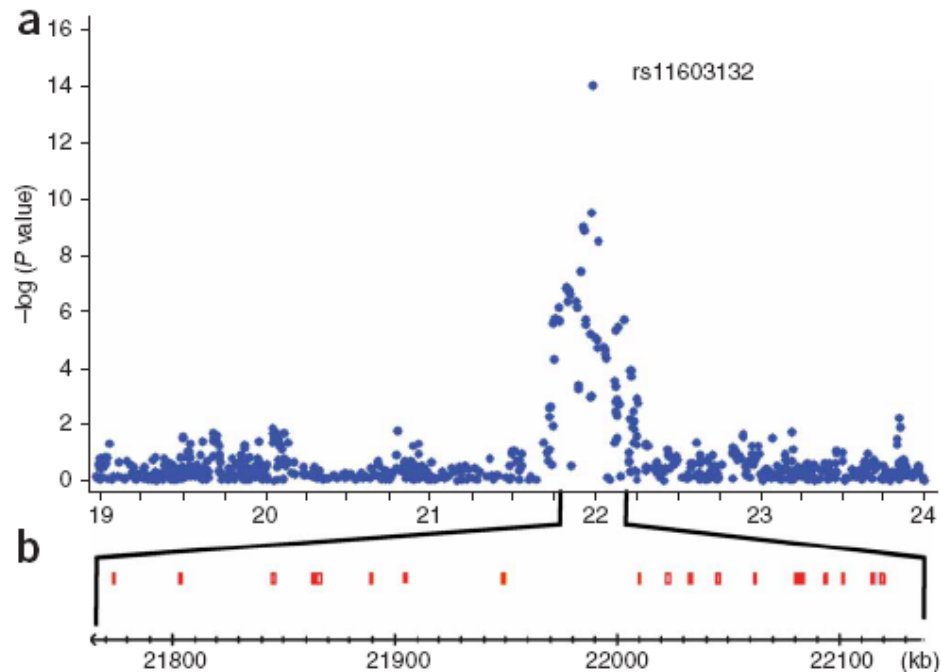


New Locus

Richards *et al*, Nature Genetics 2008

WGAS Androgenic Alopecia

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



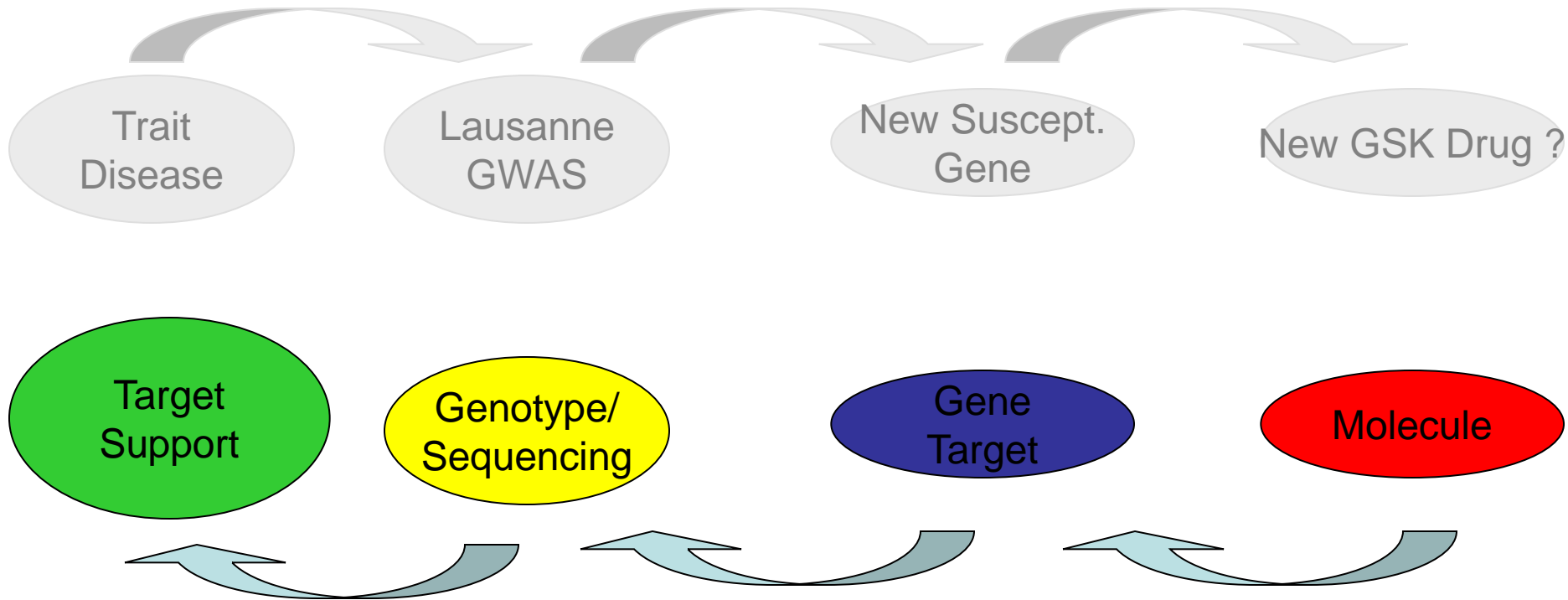
Locus \neq Gene \neq Drug Target \neq IP \neq \$\$\$!!!

Potential of Genetics to Support the Pipeline

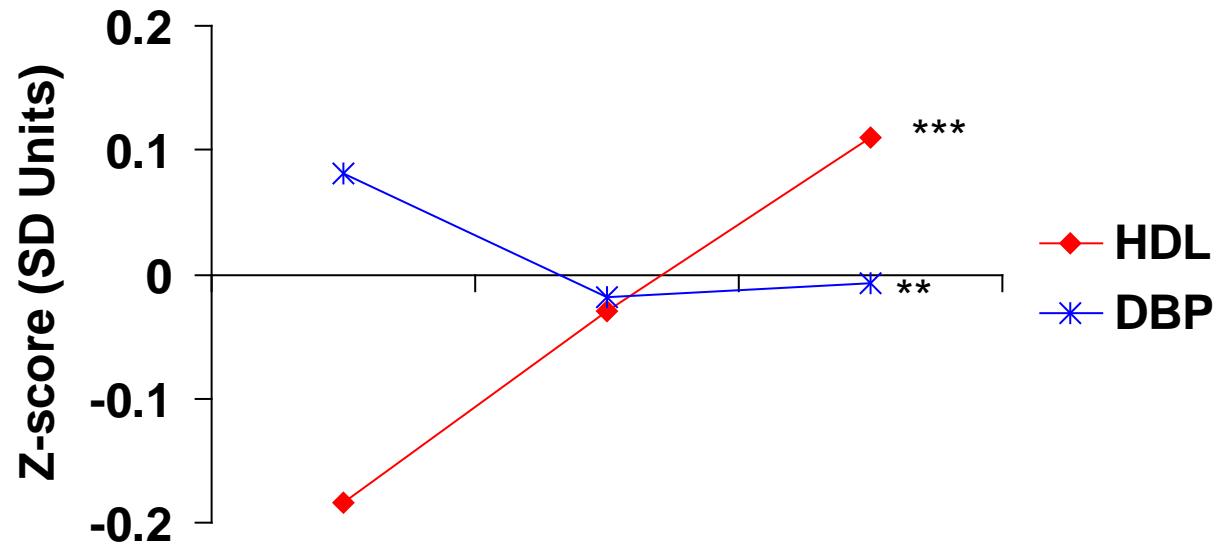


Knowledge expansion on targets, target validation

Reverse Genetics



Common Variants for Target Validation



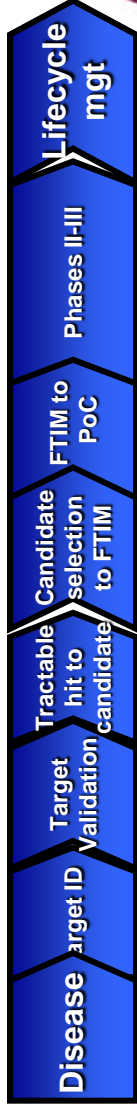
CETP RS9989419 Genotype

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)

Potential of Genetics to Support the Pipeline



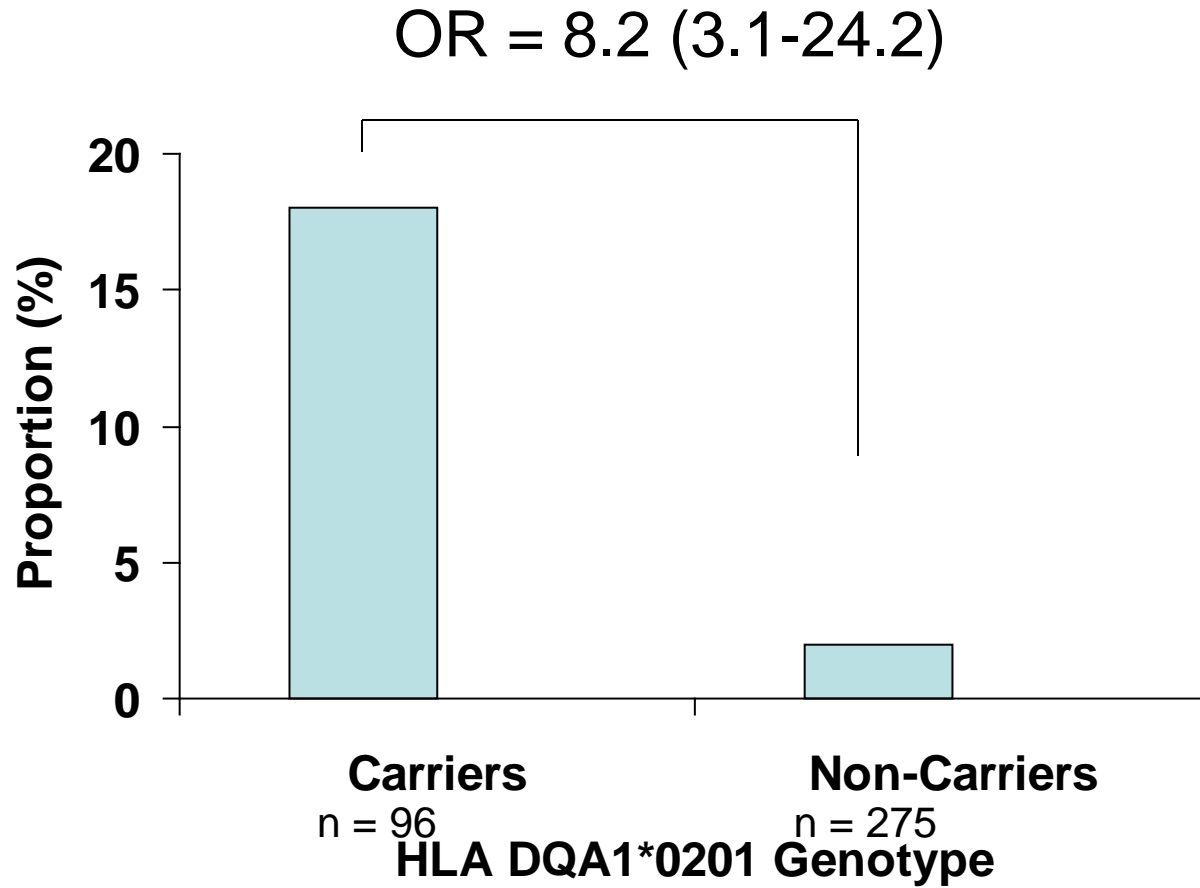
Elucidation of molecular basis of efficacy

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

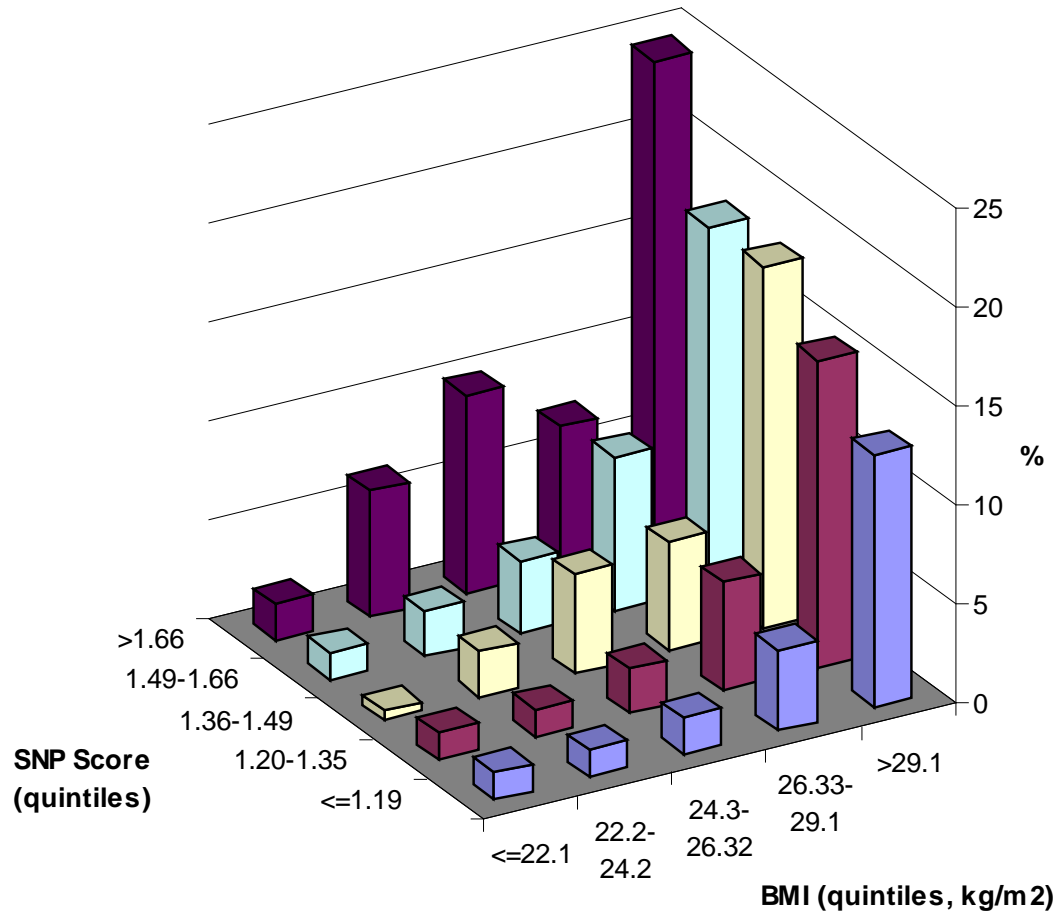


Clinical Trial Enrichment



Genetic-based clinical trial enrichment
→ *Faster development*

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



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*