Identification of Regulatory Variation Important for Maternal Metabolism during Pregnancy

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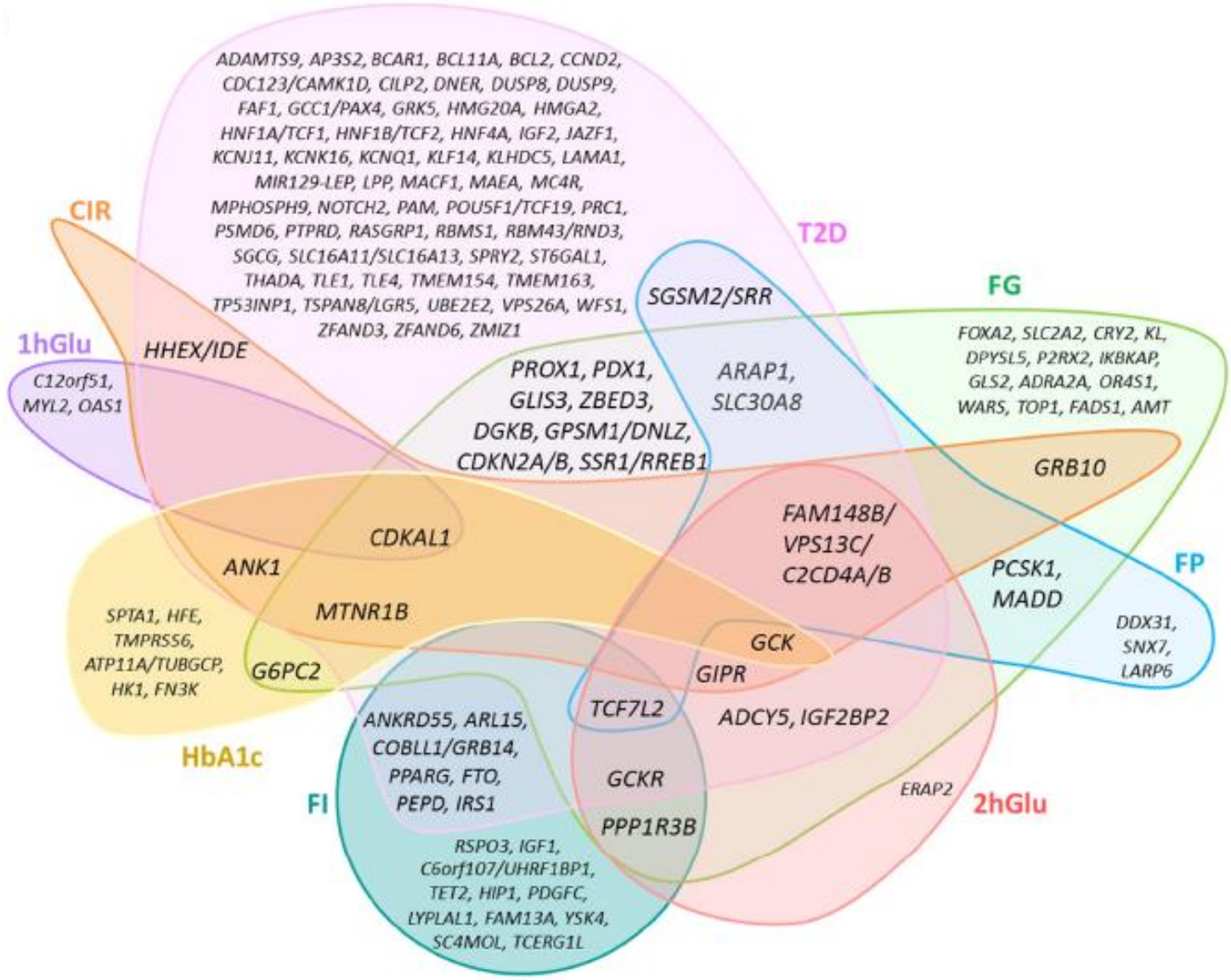
Type 2 Diabetes and Glycemic Trait Loci



From: Marullo et al., Curr Diab Rep 14:551, 2014

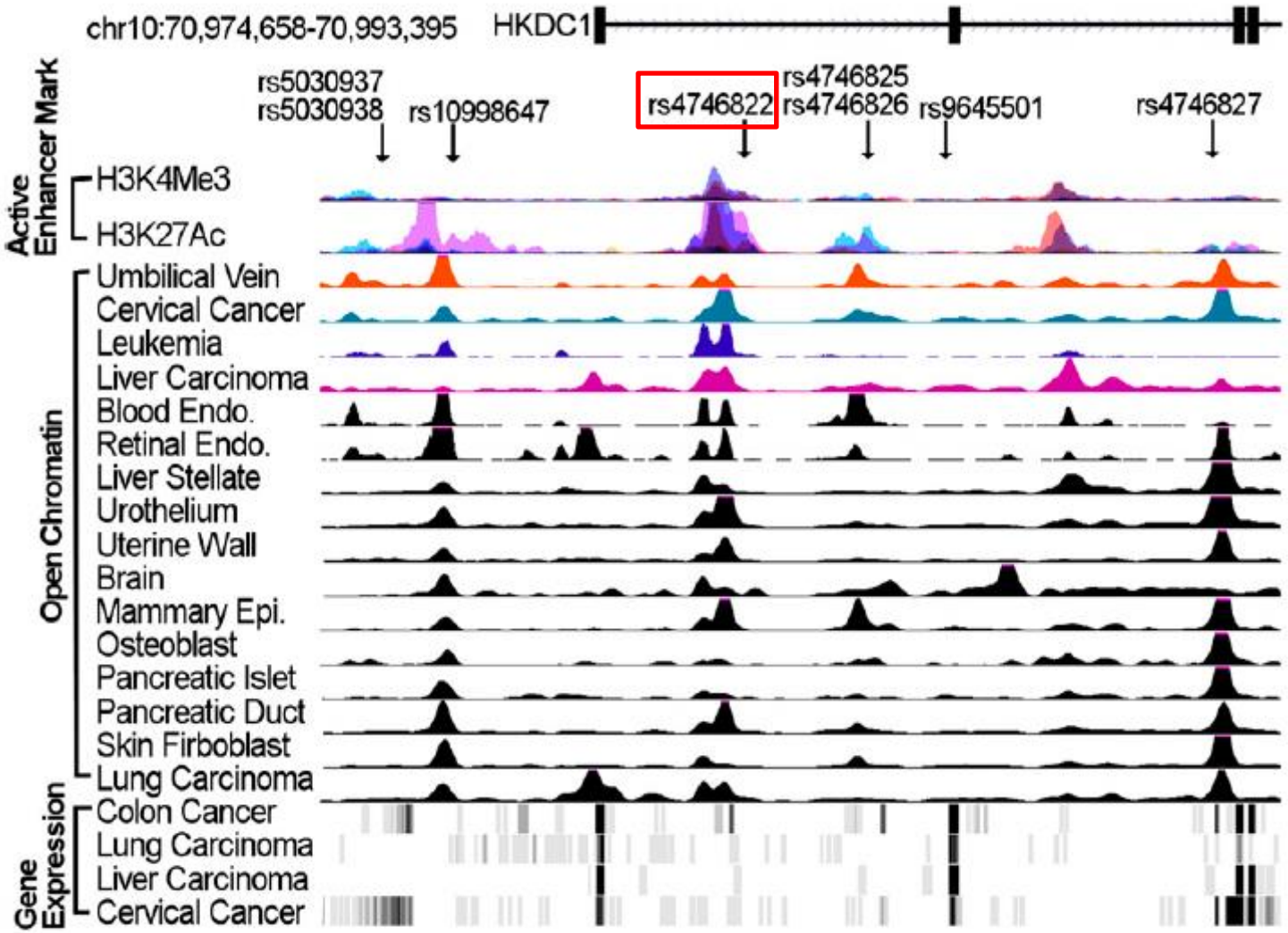
Maternal Metabolism During Pregnancy

- Decreased fasting glucose
- Increased insulin resistance
- Increased fasting insulin
- Increased insulin secretion
- Increased hepatic glucose production

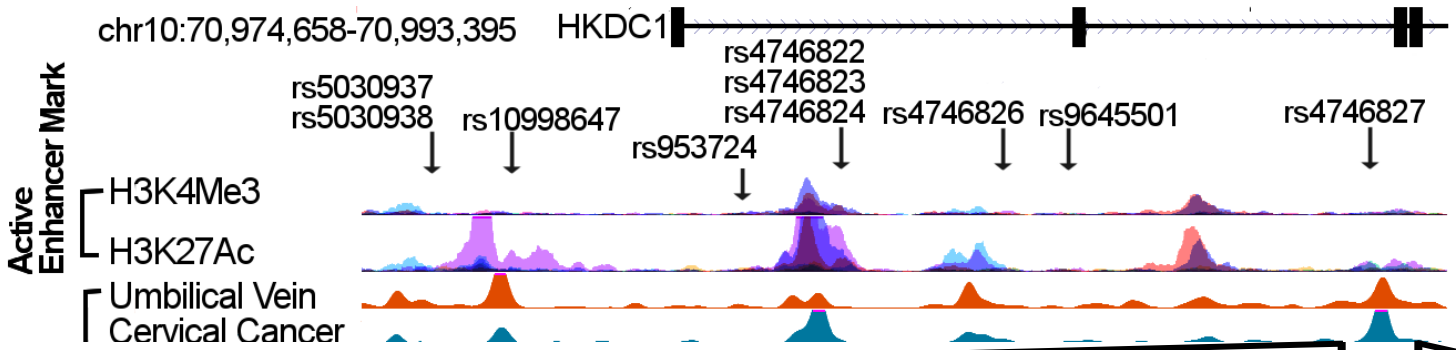
Loci Associated with Maternal Metabolic Traits

- Glucokinase regulator (*GCKR*)
- Glucose-6-phosphatase 2 (*G6PC2*)
- Protein phosphatase 1, regulatory subunit 3B (*PPP1R3B*)
- Preprotein convertase subtilisin/kexin type 1 (*PCSK1*)
- Melatonin receptor 1B (*MTNR1B*)
- Hexokinase Domain Containing 1 (*HKDC1*)
- Beta site amyloid precursor protein cleaving enzyme 2 (*BACE2*)

HKDC1 Locus on Chromosome 10

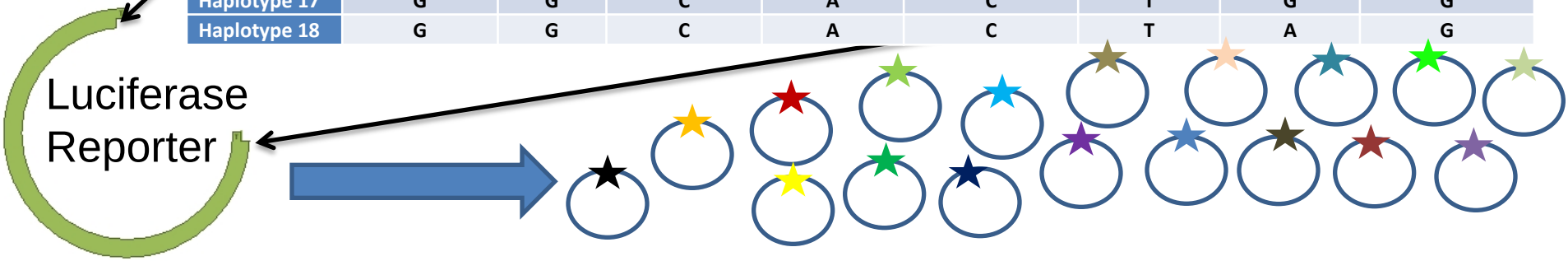


Regulatory Variation in the *HKDC1* Locus

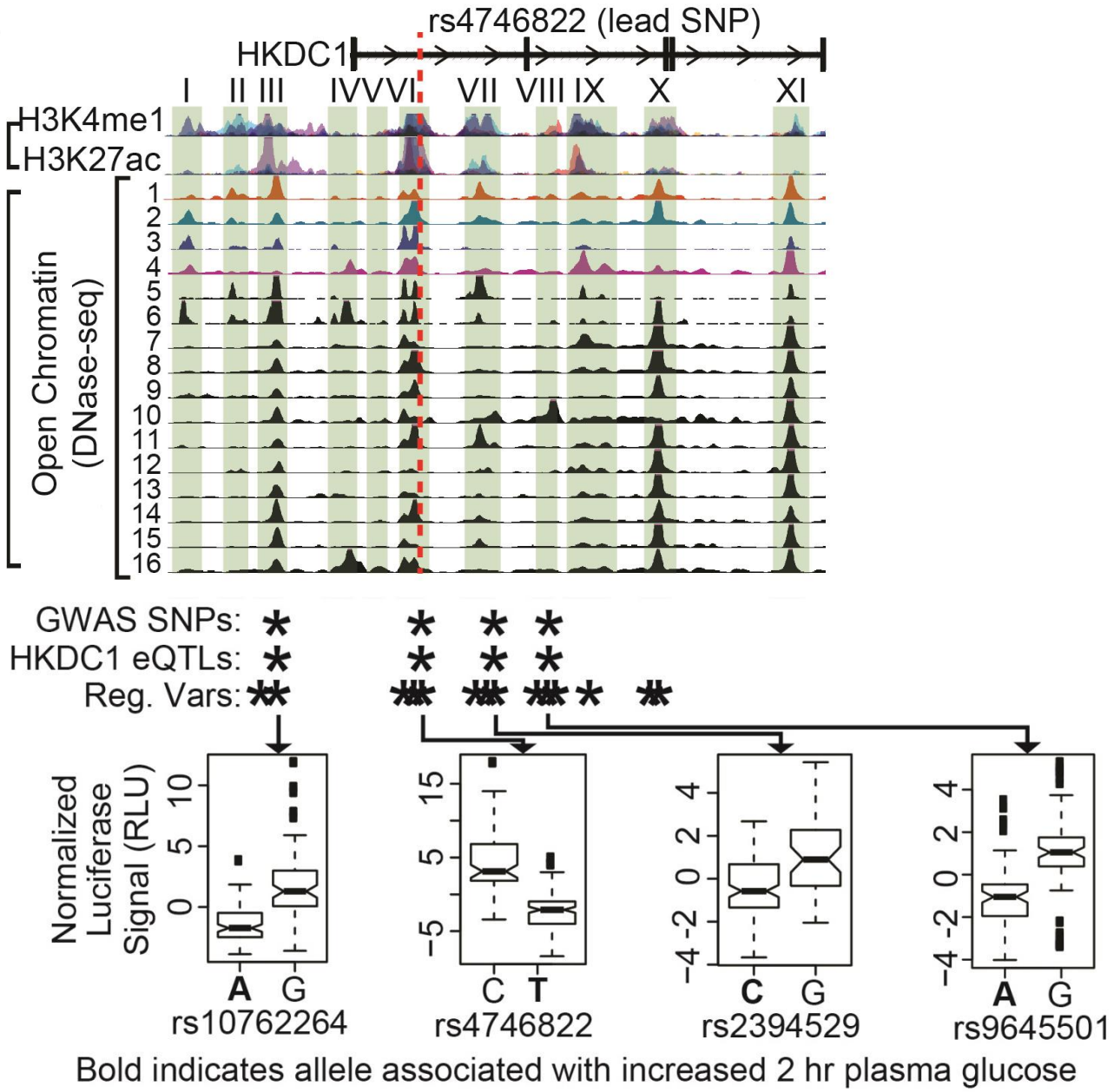


18 "natural" haplotypes

	rs4746827	kg0001	rs5030945	rs5030946	rs144643300	rs4746828	rs874557	rs201928386
Haplotype 1	A	G	C	C	T	T	G	G
Haplotype 2	A	G	C	C	C	T	G	G
Haplotype 3	A	A	C	C	C	T	G	A
Haplotype 4	G	G	C	C	C	T	G	G
Haplotype 5	G	G	C	C	C	C	A	G
Haplotype 6	G	G	C	C	C	T	A	G
Haplotype 7	G	G	C	A	C	C	A	G
Haplotype 8	G	G	T	A	C	C	A	G
Haplotype 9	A	G	T	C	T	T	G	G
Haplotype 10	A	G	T	C	C	T	G	G
Haplotype 11	A	A	T	C	C	T	G	A
Haplotype 12	G	G	T	C	C	T	G	G
Haplotype 13	G	G	T	C	C	C	A	G
Haplotype 14	G	G	T	C	C	T	A	G
Haplotype 15	A	G	C	A	T	T	G	G
Haplotype 16	A	G	C	A	C	T	G	G
Haplotype 17	G	G	C	A	C	T	G	G
Haplotype 18	G	G	C	A	C	T	A	G



Candidate Regulatory Variants in the *HKDC1* Locus



Nat Commun, 2015

Causal Chain from DNA Variant to Phenotype: Identifying Regulatory Variation

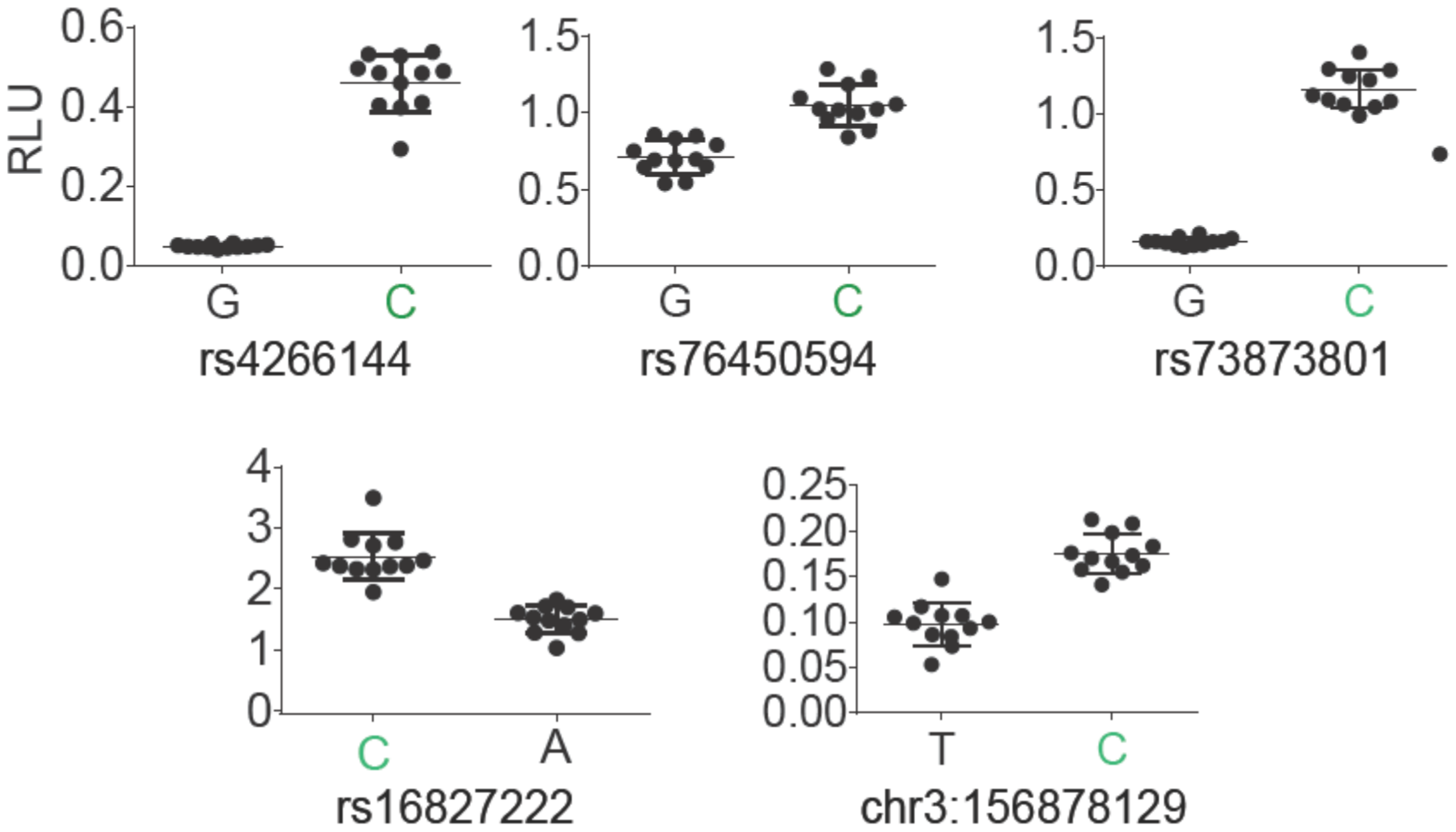
To move from donor DNA to causal variant(s) and function more rapidly and efficiently need new high throughput technologies that allow:

- Functional assays of gene expression
- Personal and rare variants to be tested more directly
- Haplotypes to be tested directly

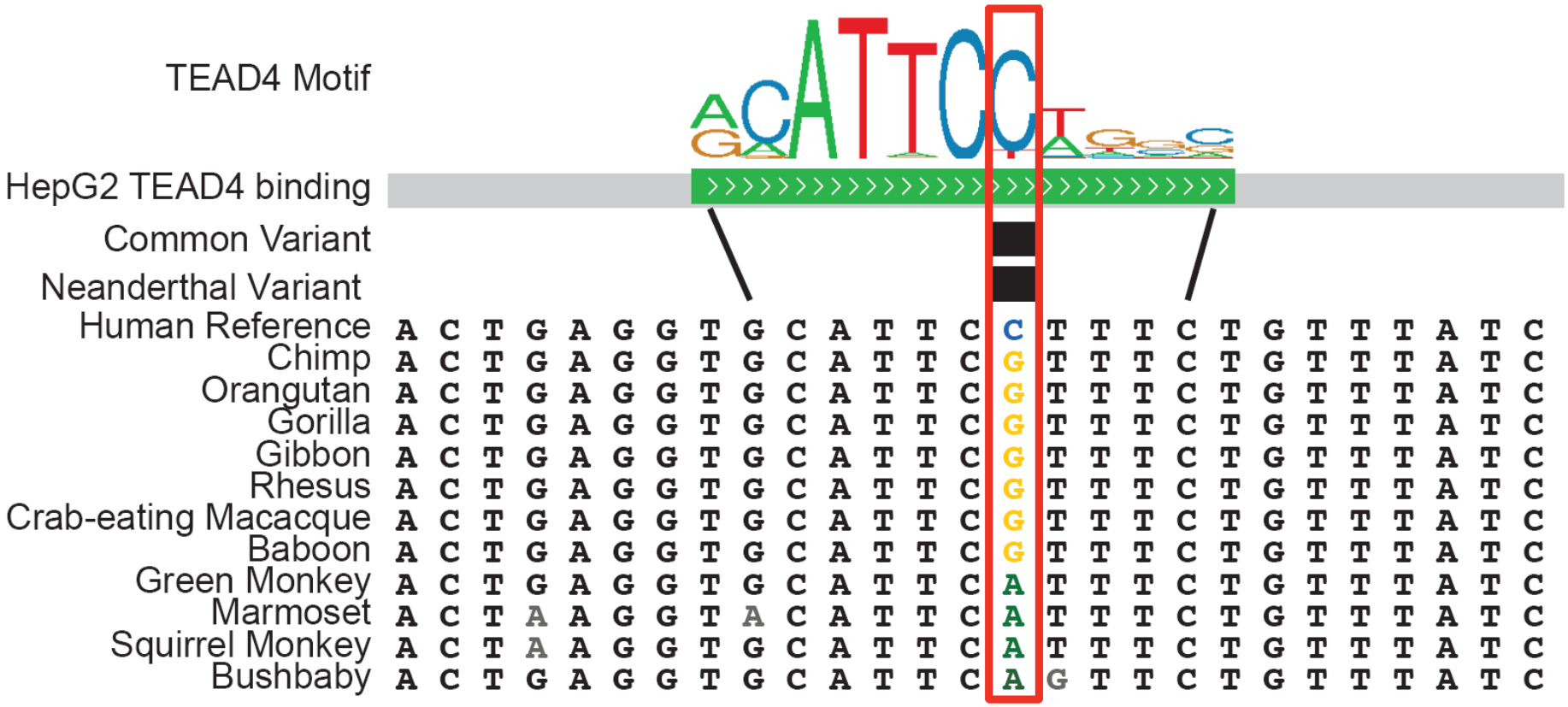
High Throughput Screening of a GWAS-Associated Locus

- Using a new approach we have:
  - Successfully assayed 283 of 321 SNPs in a GWAS-associated locus in a high throughput screen
  - Performed replication to demonstrate high concordance between replicates
  - Successfully assayed both common and rare variation
  - Identified 27 common and 9 rare SNPs which demonstrated significant changes in regulatory activity

Results


RLU
0.6
0.4
0.2
0.0
G
C
rs4266144
1.5
1.0
0.5
0.0
G
C
rs76450594
1.5
1.0
0.5
0.0
G
C
rs73873801
4
3
2
1
0
C
A
rs16827222
0.25
0.20
0.15
0.10
0.05
0.00
T
C
chr3:156878129

Disruption of TEAD4 Binding Site by rs4266144



Summary

- What gap does your proposed project fill and why is it a high priority?
  - New technologies to directly screen haplotypes in phenotyped populations for functional variation
- Why is this project appropriate for NHGRI vs other ICs
- What new technological breakthroughs/resources would be transformative?
  - Relevant cell types for functional studies – resource of iPS-derived or primary cells
- What additional unbiased data generation efforts would facilitate these studies?
  - eQTLs identified in largely healthy individuals to date
    - How do these compare to findings in disease states or extremes of phenotype
    - eQTL x environment interactions
- Would this project benefit from a particular scale and/or organizational structure?

HAPO Genetics Studies

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