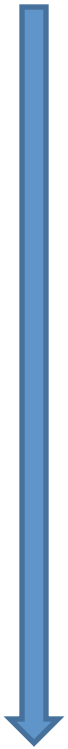
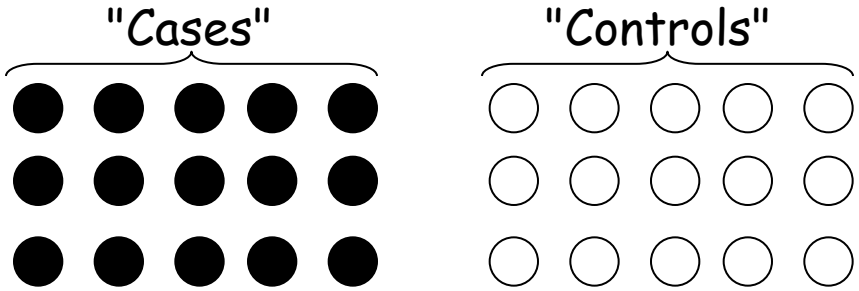
polymorphisms



GWAS

traits

genetic association



? frequency of Brca1 sequence changes

~3% – 5% < 0.1%

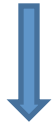
this difference is highly significant !!!

polymorphisms

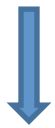
Functional mutations

Traits

~18 million in dbSNP



Protein changes
expression changes



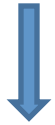
Breast cancer

polymorphisms

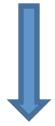
Functional mutations

Traits

113 SNPs in actn3

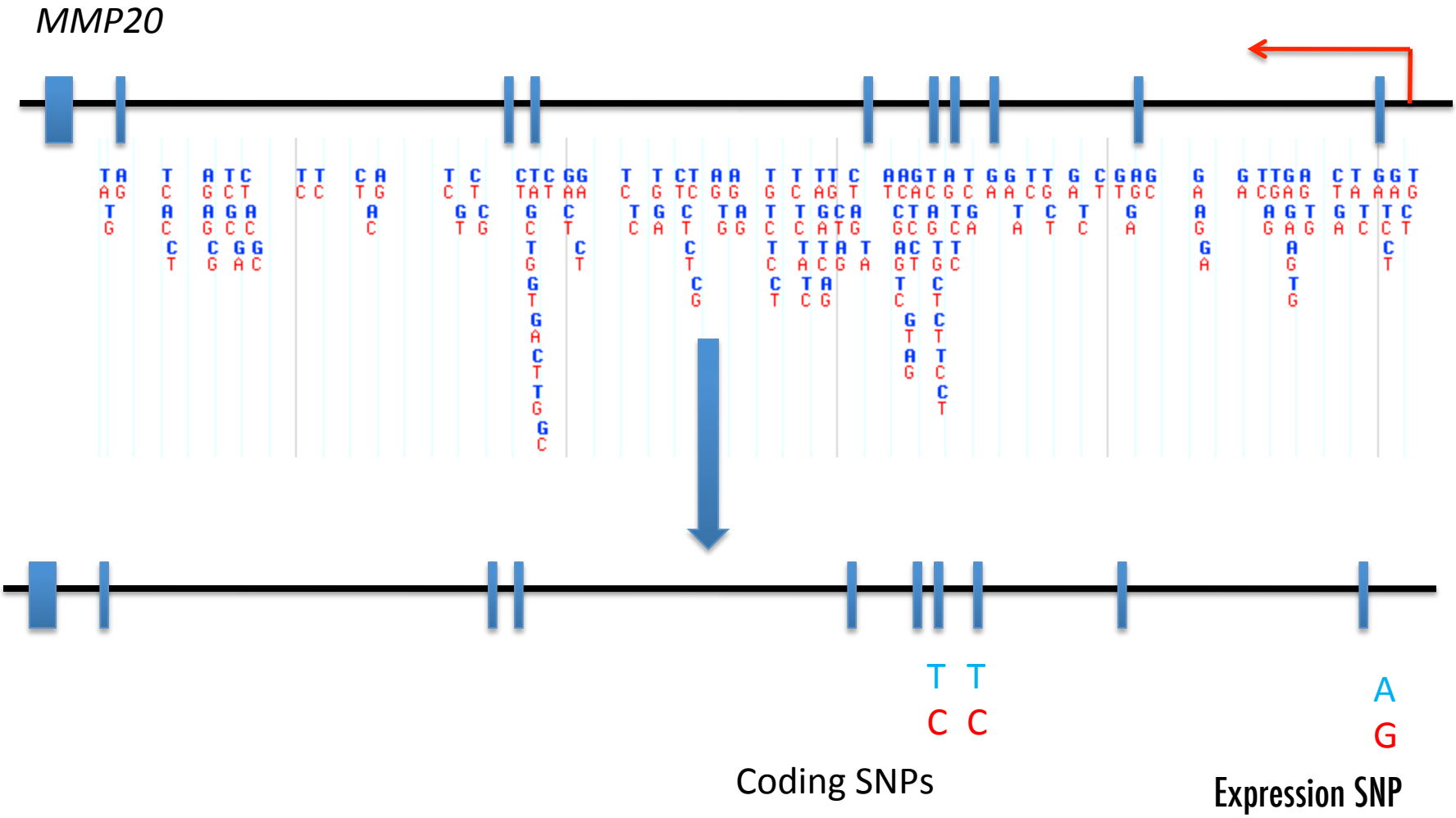


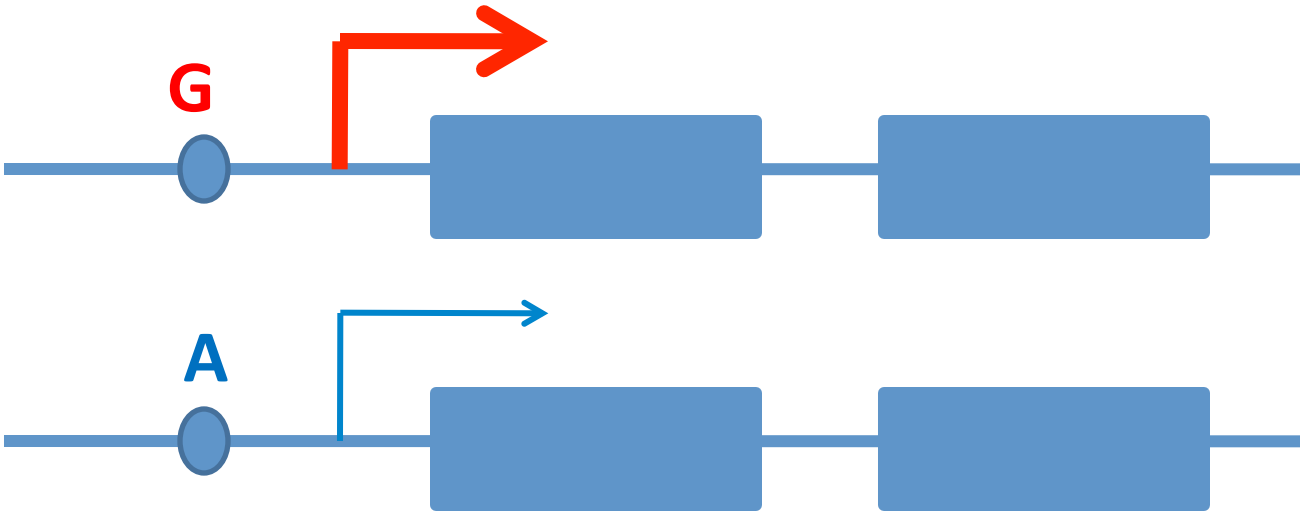
1 SNP is stop codon



Power muscle

Functional mutations

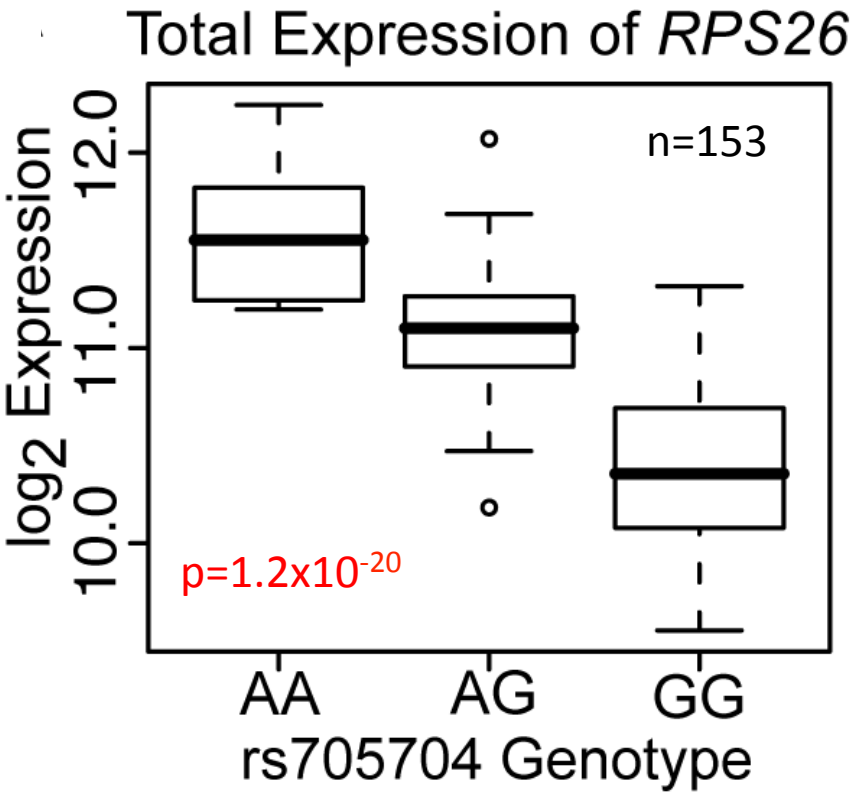




Look at expression in :

G/G	G/A	A/A
High	Medium	Low

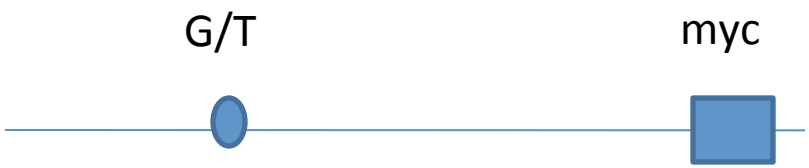
Total Expression Analysis



ARTICLES

nature genetics

The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling



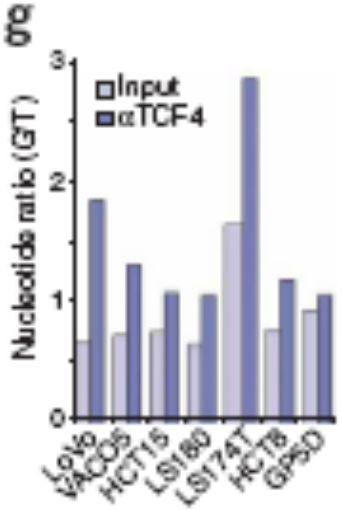
rs6983267 is a G/T SNP in a TCF4 binding site near the myc oncogene

Nature Genetics 41, 885, 2009

ARTICLES

nature genetics

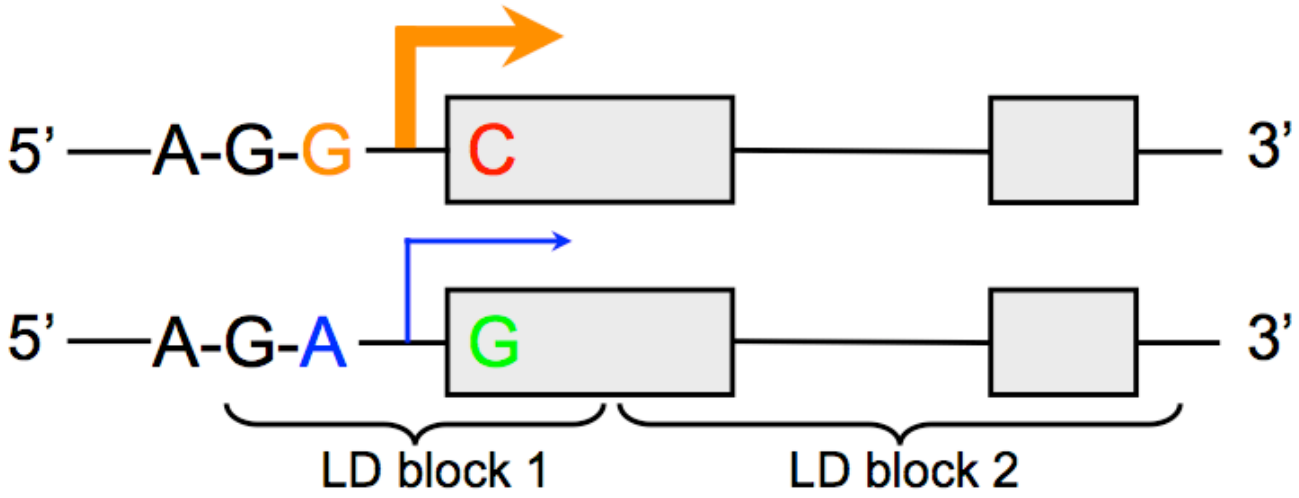
The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling



The G allele shows stronger binding to TCF4 than the T allele

Nature Genetics 41, 885, 2009

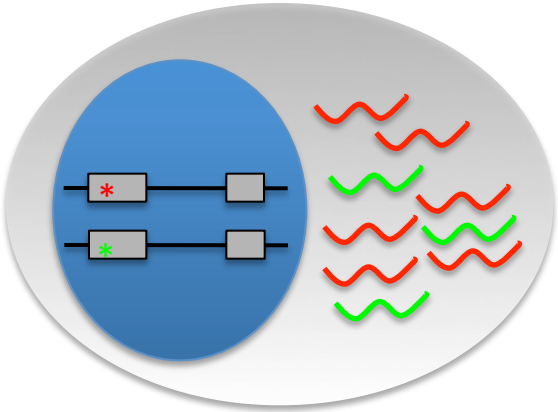
Allele-specific Expression



Look at expression in :

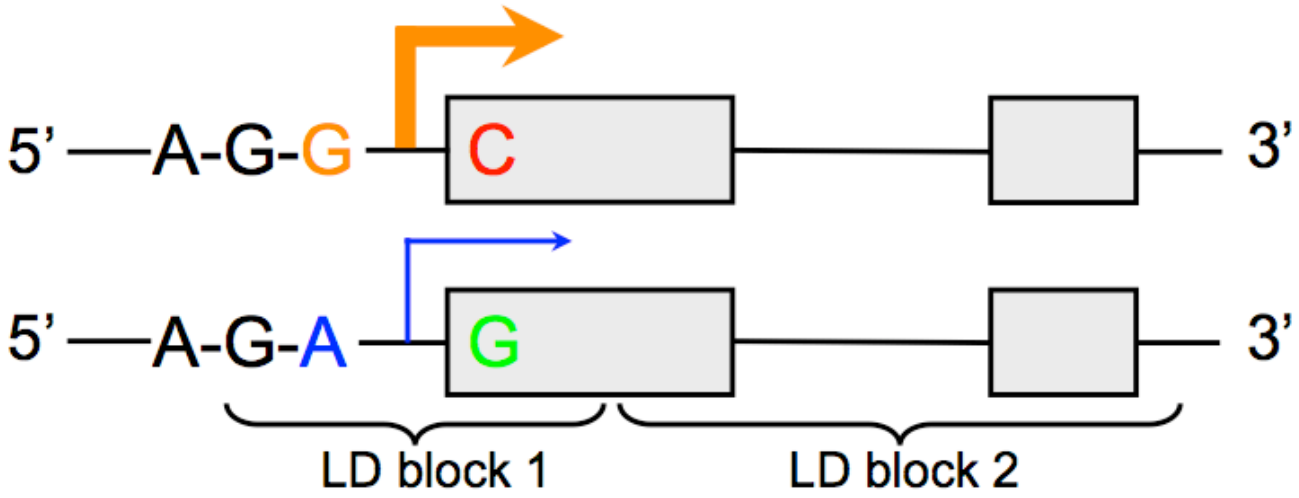
G/A heterozygotes
G allele is expressed higher than the A allele

Allele-specific Expression



- Expressed in the same nucleus
- Same genetic background
- Same environment
- Extremely sensitive

Allele-specific Expression



- Make cDNA
- Method 1: sequence cDNAs and count if C allele is more abundant than the G allele.
- Method 2: use DNA arrays and see if the C oligo is more intense than the G oligo.

OPEN ACCESS Freely available online PLoS GENETICS

Sequential Use of Transcriptional Profiling, Expression Quantitative Trait Mapping, and Gene Association Implicates *MMP20* in Human Kidney Aging

Heather E. Wheeler[1], E. Jeffrey Metter[2,3], Toshiko Tanaka[2,3], Devin Absher[4], John Higgins[5], Jacob M. Zahn[6], Julie Wilhelmy[6], Ronald W. Davis[6], Andrew Singleton[7], Richard M. Myers[4], Luigi Ferrucci[2,3], Stuart K. Kim[1,8]*

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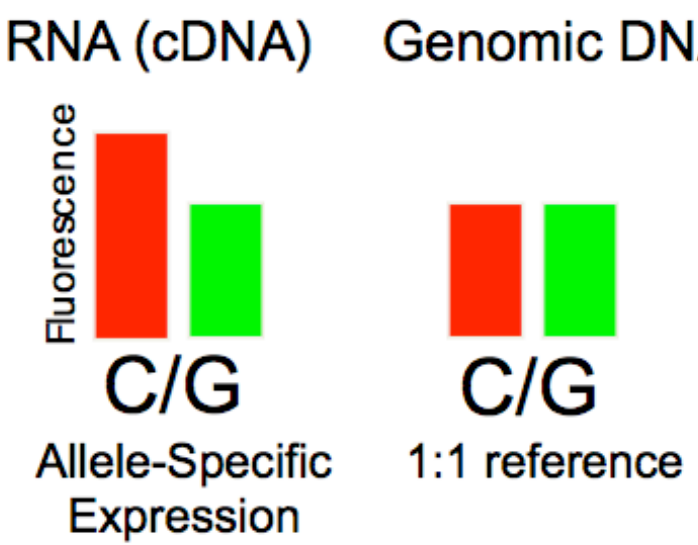
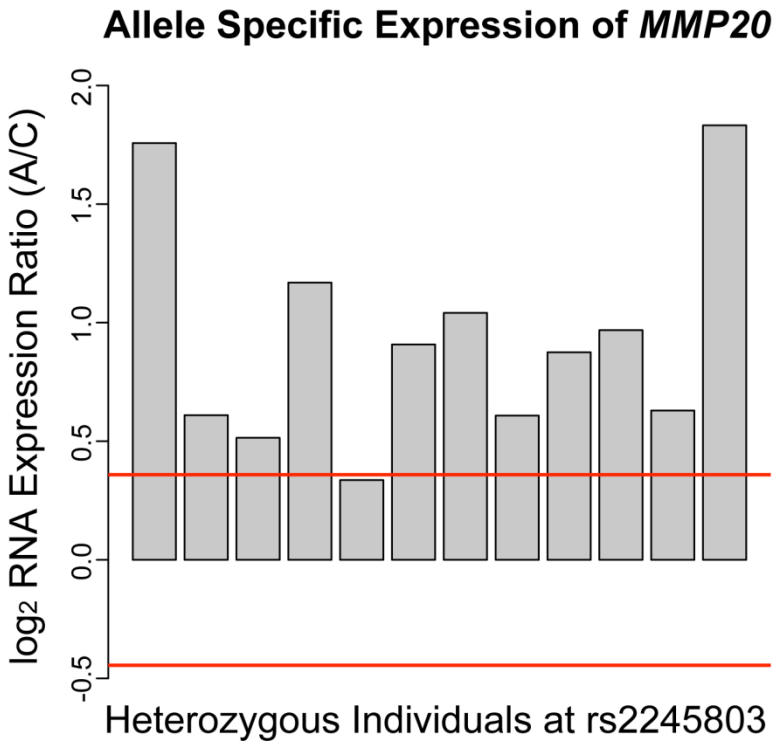


- 96 kidney cortex samples
- For ASE:
  - ≥5 expressing heterozygotes
  - ≥50% hets outside DNA-defined confidence interval
  - meta-p $<10^{-6}$

Allele-Specific Expression



- Red lines indicate 95% confidence intervals
- Example shows 11/12 heterozygotes have higher expression of A allele than C allele.

Functional mutations

- Coding:
  - About 2000-5000 missense SNPs that affect conserved amino acids
- Expression:
  - At least 40% of genes have SNPs that affects expression in cis.
  - The median change in expression between alleles is about 2 fold