

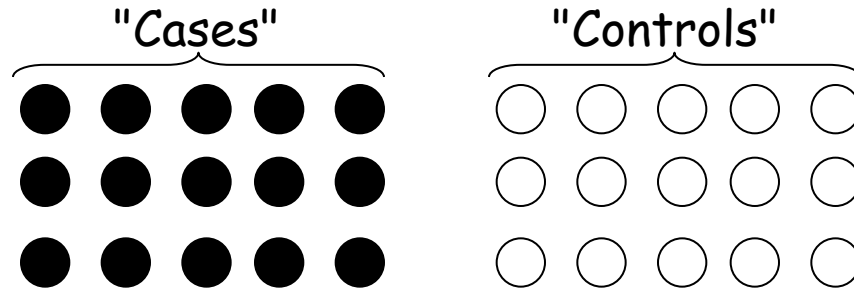
polymorphisms



**GWAS**

traits

# genetic association



? frequency of Brca1 sequence changes

~3% - 5%

< 0.1%

this difference is highly significant !!!

polymorphisms



Functional mutations

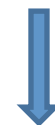


Traits

~18 million in dbSNP

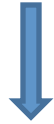


Protein changes  
expression changes



Breast cancer

polymorphisms



Functional mutations



Traits

113 SNPs in actn3



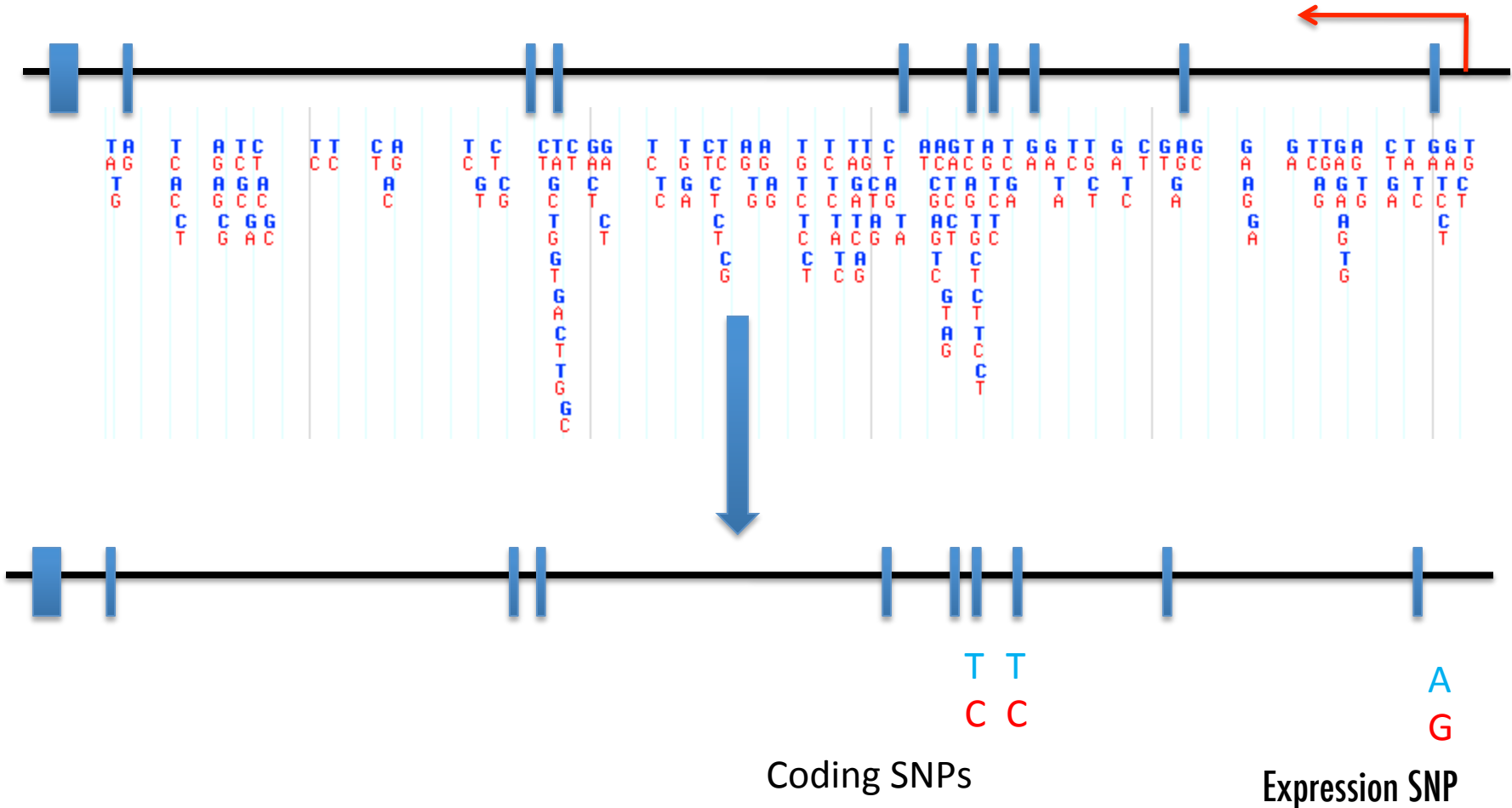
1 SNP is stop codon

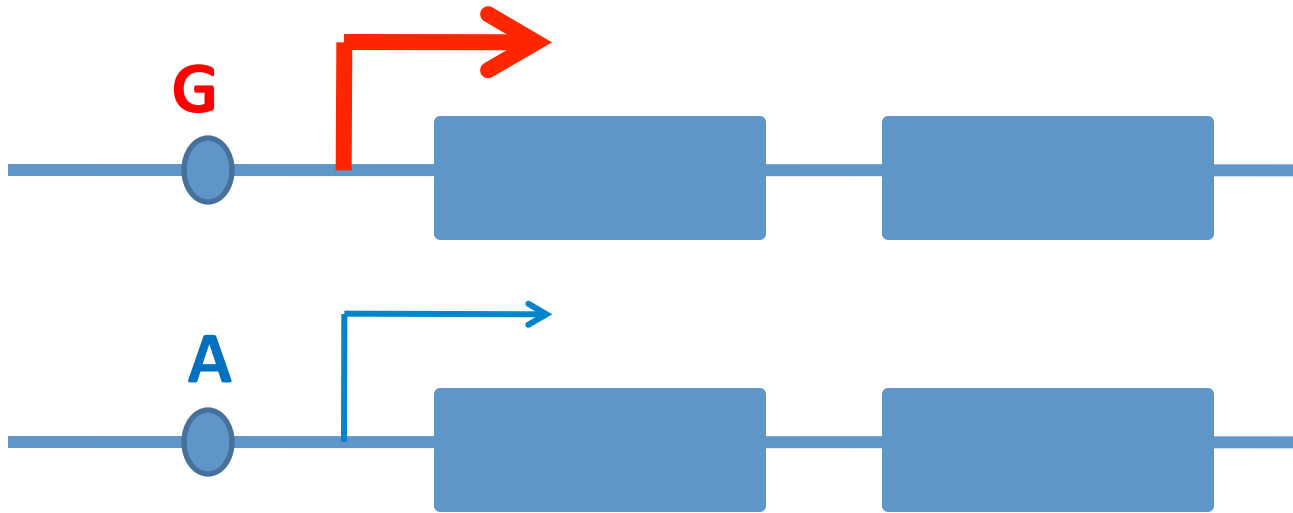


Power muscle

# Functional mutations

MMP20





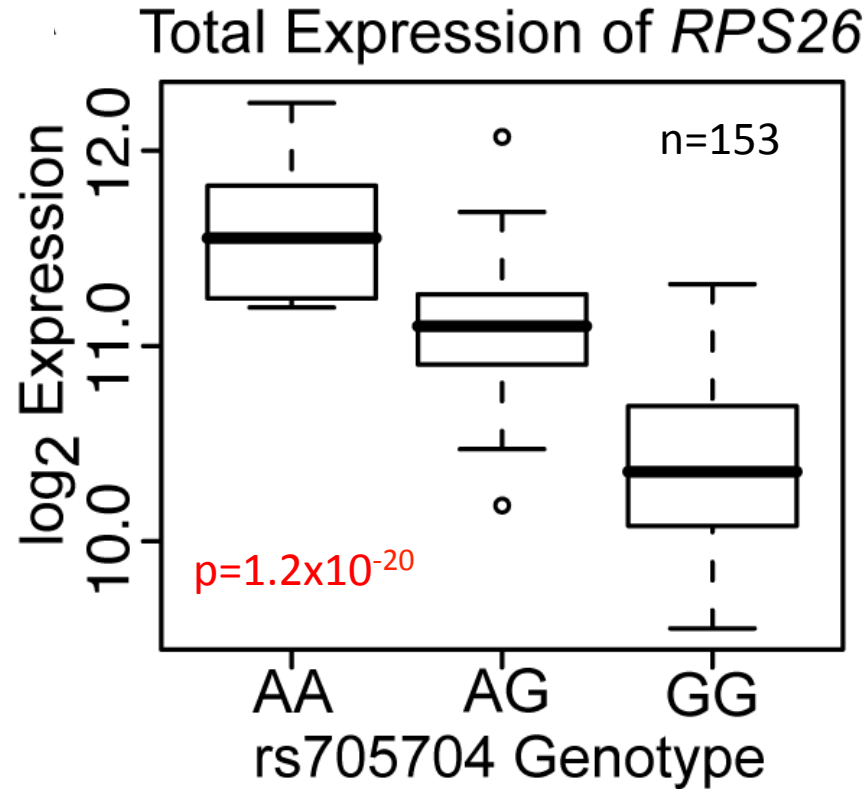
**Look at expression in :**

**G/G**  
**High**

**G/A**  
**Medium**

**A/A**  
**Low**

# Total Expression Analysis



# 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

a

Sequence 1: ENSHUS00000022346  
Sequence 2: ENS000000136997

```

133537 : aggt--at-cgtCCATAAAACgagggatgaataaactctctctaccactaagggtg
164885 : -gtccocta--tCCATAAAACgagggacgaataaactctctctaccactaagggtg
133594 : tagccaggttaataaccctaccctcctttgagctccgcSATGAAAAGTactgagaaaa
164842 : tagccaggttaataaccctaccctcctttgagctccgcSATGAAAAGTactgagaaaa
133604 : gtacaaagtATTTTTATGtctattgacTTTTTTTTTTTTATg:ggggagggaggttg
165002 : gtacaaagtATTTTTATGtctattgacTTTTTTTTTTTTATg:ggggagggagccgg
133714 : ccccagctggaagtTGCCTTTtctgAAACAAGgaggaaccAGCAAGTTTCCAGG
165002 : ccccagctggaagtTGCCTTTtctgAAACAAGgaggaaccAGCAAGTTTCCAGG
133774 : AcaggaccttaggcTGGCTGTGtatcaga--gtgccaccaccaccacagttcagtt
165122 : AtggggccttagacTGGCTGTGtatcagacagctgccagccaccaccacagttcagtt
133832 : tctttaacctggtCTCCAGGCataaactgtccaactctgaaTTTAACAATgtgttg
165182 : tctttaacctggtCTCCAGGCataaactgtccaactctgaaTTTAACAATgtgttg
133892 : ttgtcccCAACTGTgtgtttcgcaatgccaggtaatatgttggccctgtaggaa
165242 : ttgtcccCAACTGTgtgtttctcaactgccaggtaatatgttggccctgtaggaa
133902 : gagtcAAATAGTTatgTGGAAAgggttggcat
165302 : gagtcAAATAGTTatgTGGAAAgggttggcat

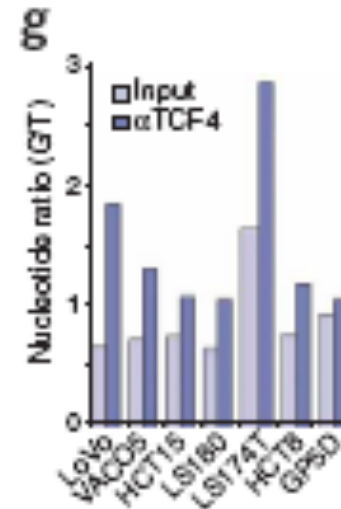
```



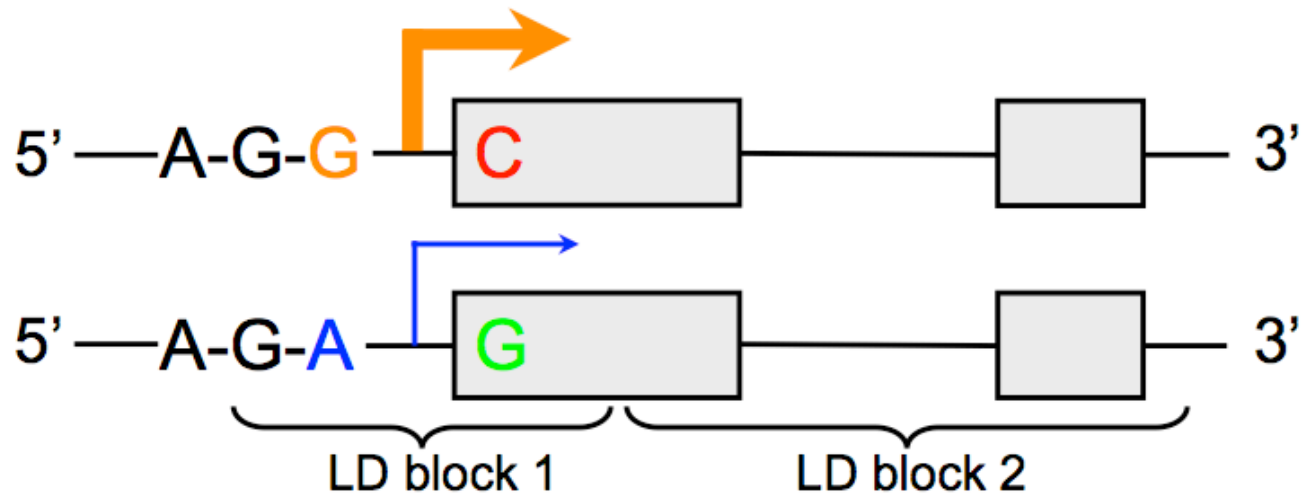
The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling



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



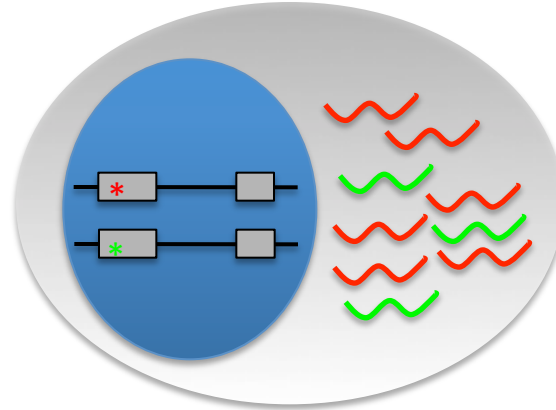
# Allele-specific Expression



**Look at expression in :**

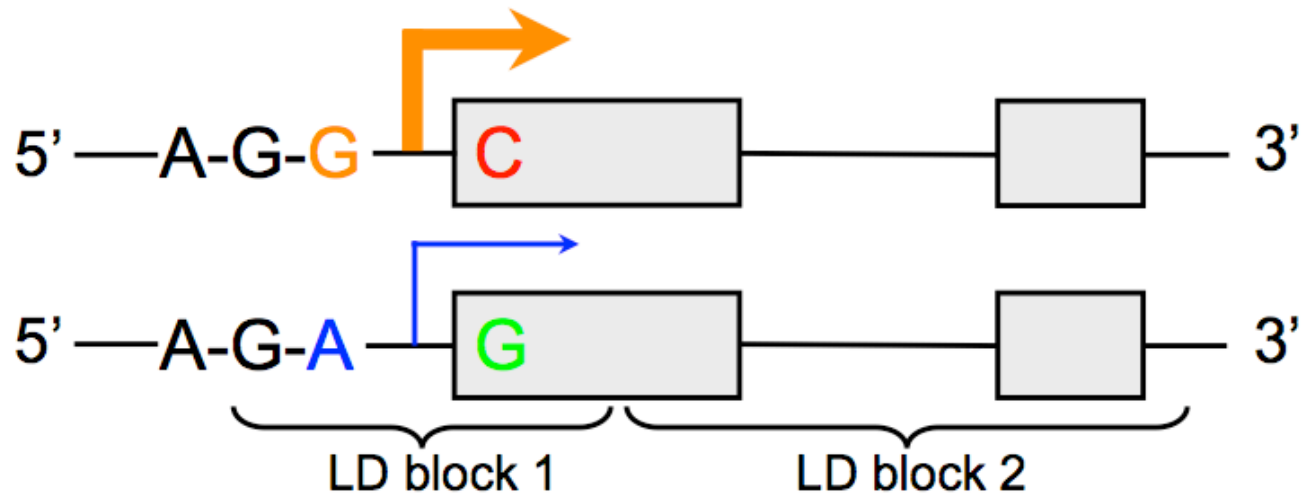
**G/A heterozygotes**  
**G allele is expressed**  
**higher than the A allele**

# 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.

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

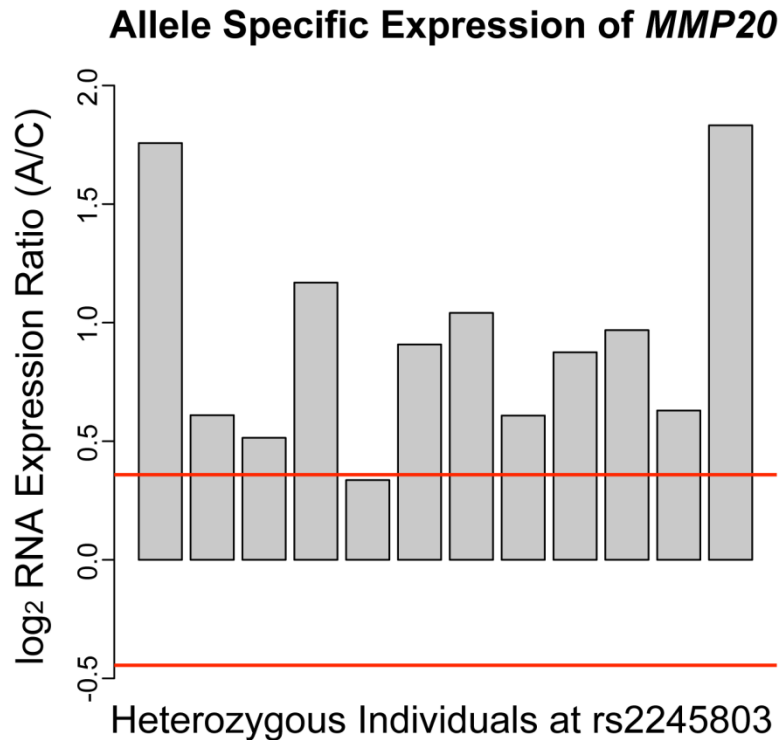
Heather E. Wheeler<sup>1</sup>, E. Jeffrey Metter<sup>2,3</sup>, Toshiko Tanaka<sup>2,3</sup>, Devin Absher<sup>4</sup>, John Higgins<sup>5</sup>, Jacob M. Zahn<sup>6</sup>, Julie Wilhelmy<sup>6</sup>, Ronald W. Davis<sup>6</sup>, Andrew Singleton<sup>7</sup>, Richard M. Myers<sup>4</sup>, Luigi Ferrucci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

**1** Department of Genetics, Stanford University Medical Center, Stanford, California, United States of America, **2** Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, United States of America, **3** Medstar Research Institute, Baltimore, Maryland, United States of America, **4** HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, United States of America, **5** Department of Pathology, Stanford University Medical Center, Stanford, California, United States of America, **6** Stanford Genome Technology Center, Palo Alto, California, United States of America, **7** Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, United States of America, **8** Department of Developmental Biology, Stanford University Medical Center, Stanford, California, United States of America



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

# 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