

polymorphisms

3 million/person



GWAS

10K-100K people

traits

polymorphisms



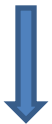
Functional mutations



genes



Pathways



Traits

~18 million in dbSNP



Protein changes
expression changes



HMG CoA reduct.
LPA



Cholesterol levels



Cardiovascular disease

polymorphisms



Functional mutations



Traits

113 SNPs in *actn3*



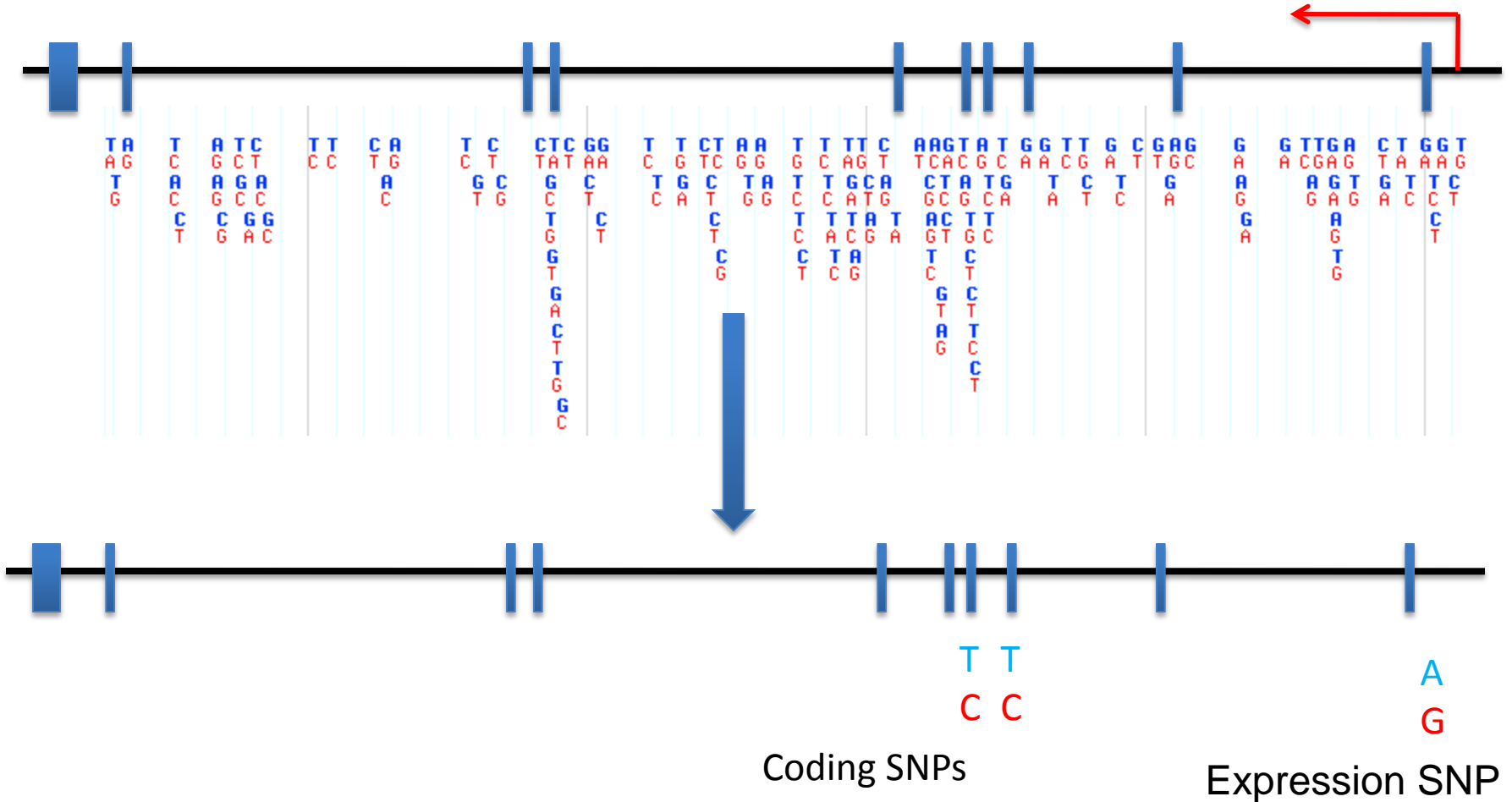
1 SNP is stop codon



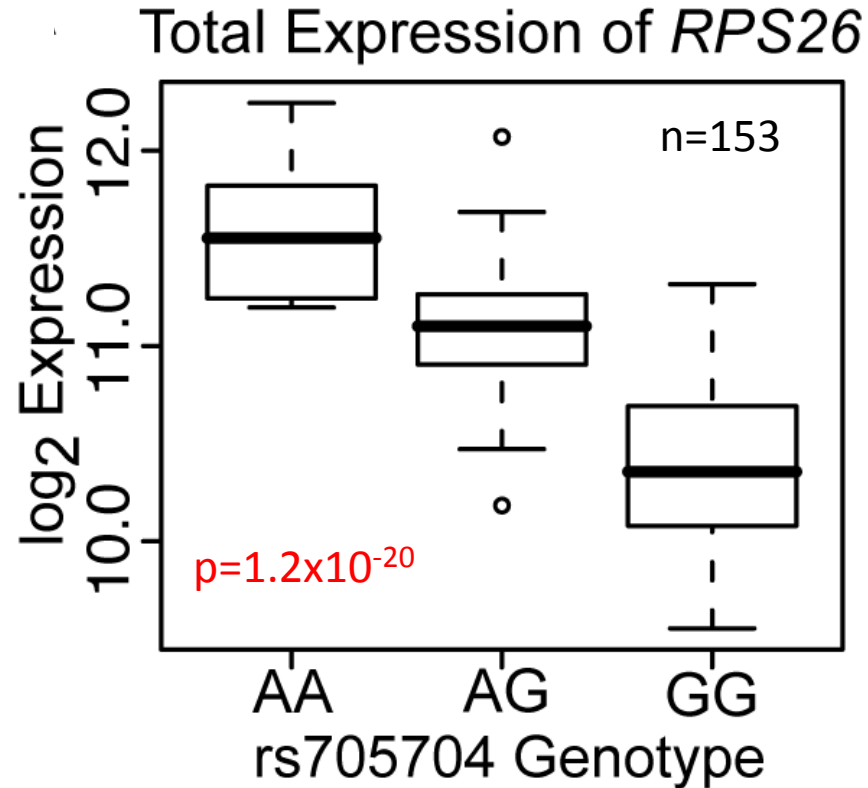
Power muscle

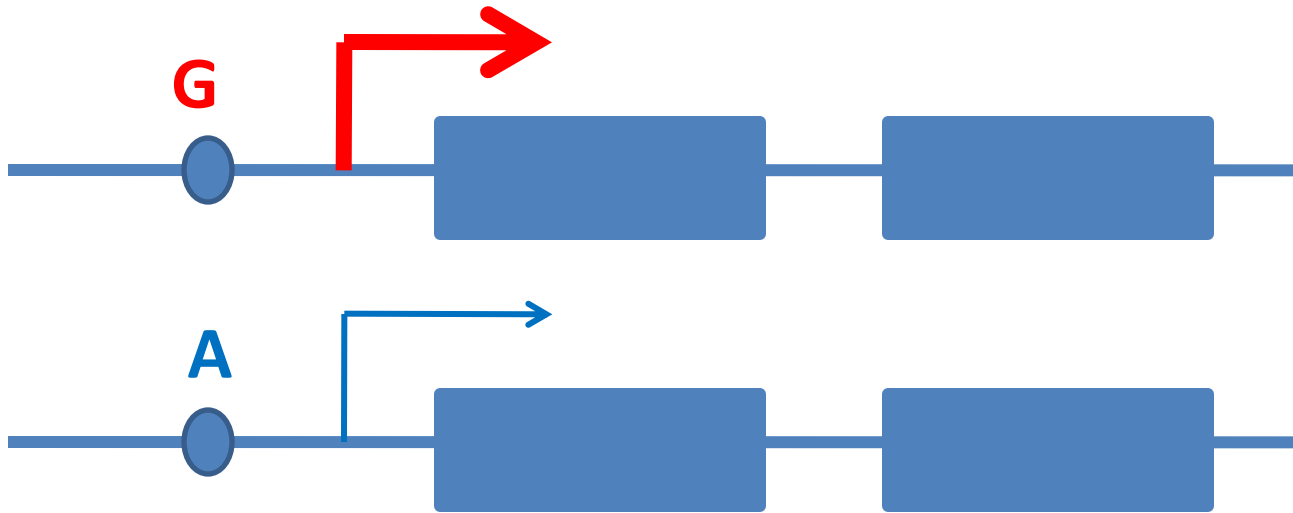
Functional mutations

MMP20



Total Expression Analysis





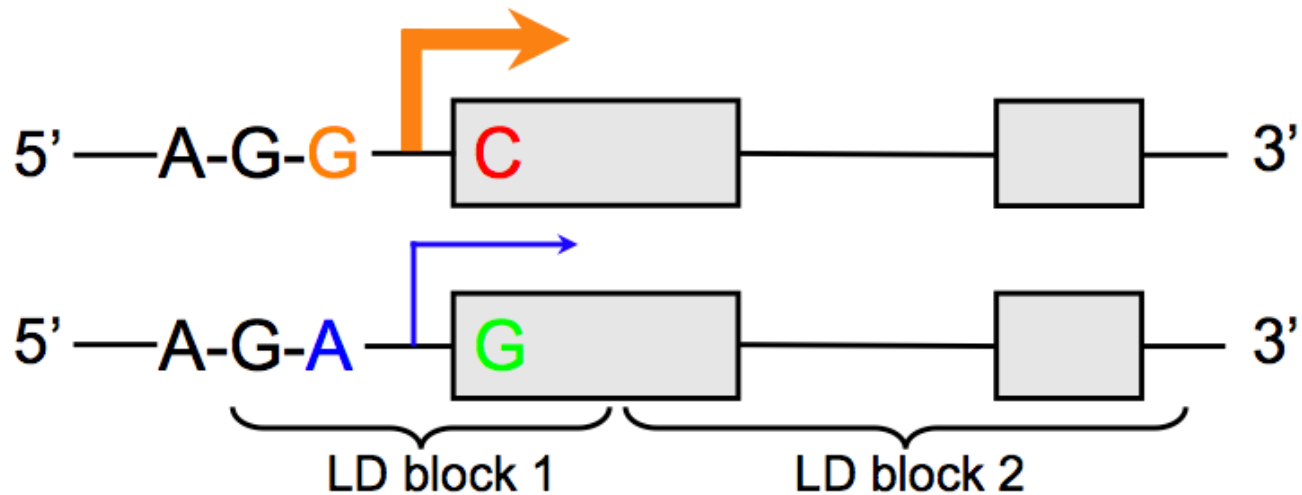
Look at expression in :

G/G
High

G/A
Medium

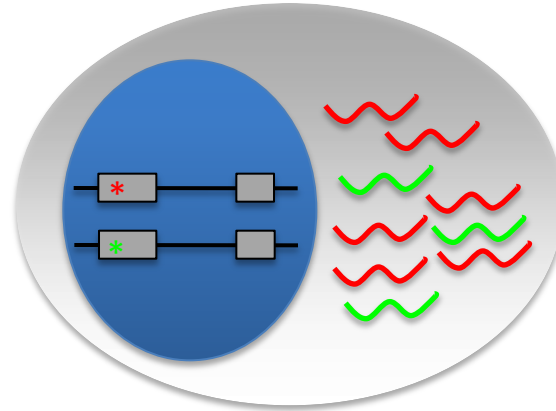
A/A
Low

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.

Allele-specific Expression



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

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: ENSG00000136997

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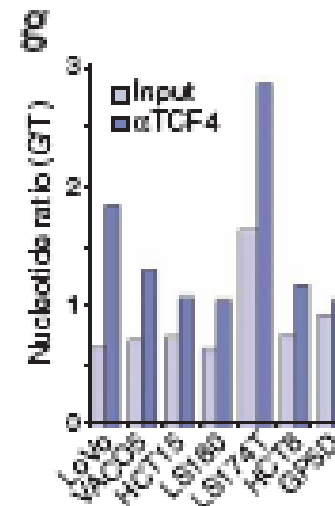
133537 : aggt--at-cgtCCATAAAACgagggatgaataaaactctctctaccactaagggtg
164885 : -gtcccta--tCCATAAAACgagggacgaataaaactctctctaccactaagggtg
133594 : tagccaggttaataccctcaccatcctttgagctccgcSATGAAAAGTactgagaaaa
164842 : tagccaggttaataccctcaccatcctttgagctccgcSATGAAAAGTactgagaaaa
133604 : gtacaaagtATTTTTATGtctattgacTTTTTTTTTTTTATg:ggggagggaggtttg
165002 : gtacaaagtATTTTTATGtctattgacTTTTTTTTTTTTATg:ggggagggagccgg
133714 : ccccagctggaagtTGCCTTTtctgAAACAAGgaggaaccAGCAAGTTTTCAGG
165002 : ccccagctggaagtTGCCTTTtctgAAACAAGgaggaaccAGCAAGTTTTCAGG
133774 : AcaggaccttaggcTGGCTGTGTacaga--gtgccacccacccccacagttcagtt
165122 : AcaggaccttaggcTGGCTGTGTacaga--gtgccacccacccccacagttcagtt
133832 : tctttaacctggtCTCCAGGCataaactgtccaactctgaaTTTAACAAAtgtgttg
165182 : tctttaacctggtCTCCAGGCataaactgtccaactctgaaTTTAACAAAtgtgttg
133892 : ttgtcccCAACTGTtctgtttcgcaatgccaggtaatatggttggccctgtaggaa
165242 : ttgtcccCAACTGTtctgtttcgcaatgccaggtaatatggttggccctgtaggaa
133902 : gagtcAAATAGTTAtgTGGAAAgggttggcat
165302 : gagtcAAATAGTTAtgTGGAAAgggttggcat

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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



polymorphisms



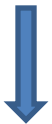
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All genes expressed in cardiovascular disease
Genes that change expression in CVD



Cholesterol levels



Cardiovascular disease

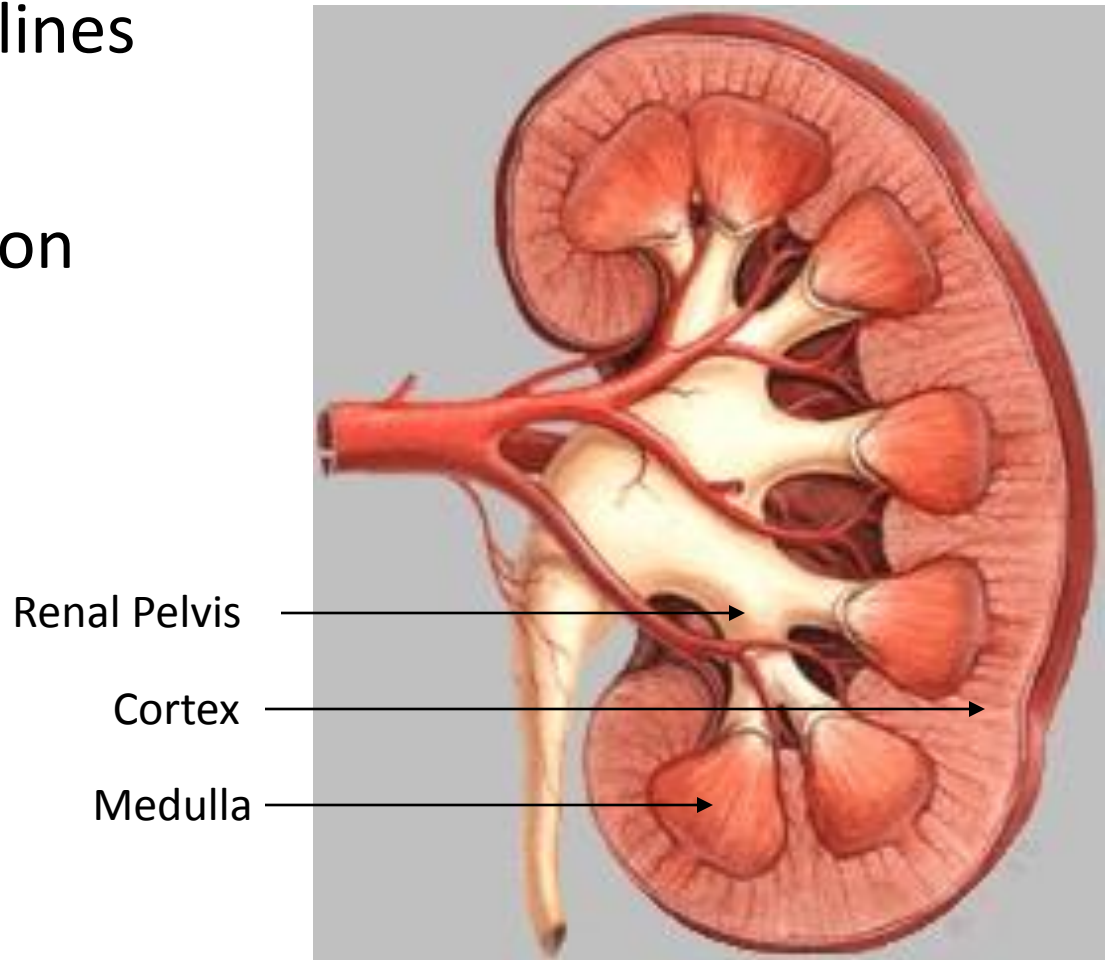
Sequential Use of Transcriptional Profiling, Expression Quantitative Trait Mapping, and Gene Association Implicates *MMP20* in Human Kidney Aging

Heather E. Wheeler¹, E. Jeffrey Metter^{2,3}, Toshiko Tanaka^{2,3}, Devin Absher⁴, John Higgins⁵, Jacob M. Zahn⁶, Julie Wilhelmy⁶, Ronald W. Davis⁶, Andrew Singleton⁷, Richard M. Myers⁴, Luigi Ferrucci^{2,3}, Stuart K. Kim^{1,8*}

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

Kidney as a model for human aging

- Filtration rate declines with age
- Easy to test function



Genomic Convergence

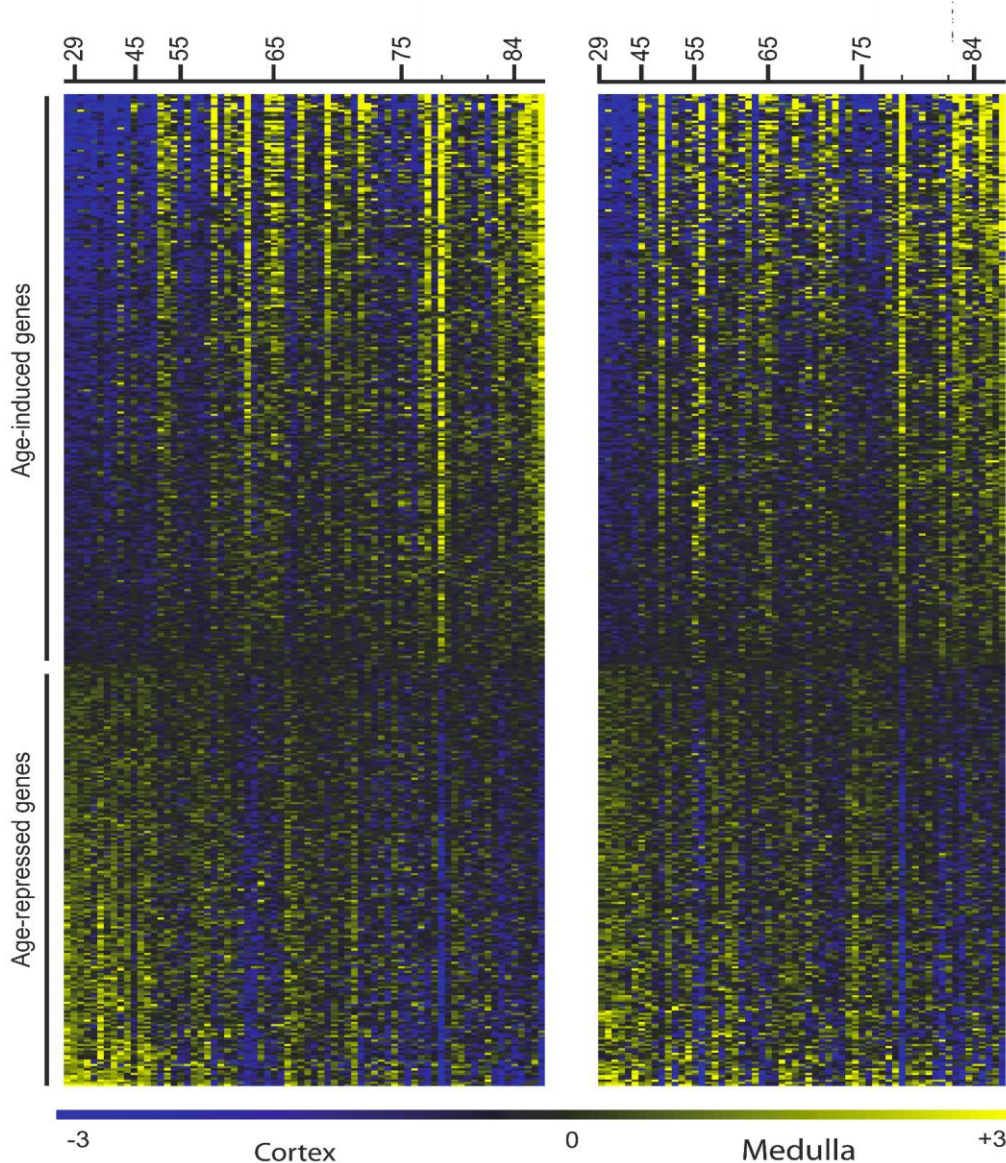
Genome-wide transcriptional profile of human kidney aging

Test age-regulated genes for eSNPs

Test eSNP genes for association with GFR

Aging
SNP!

447 age-regulated genes in the human kidney



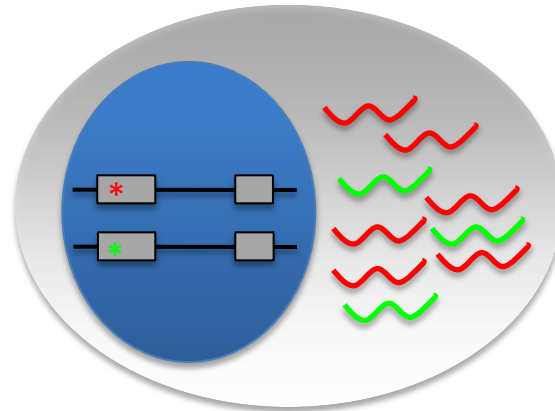
Each row is a gene

Yellow is high level expression
Blue is low level expression

Each column corresponds to a person, youngest to oldest

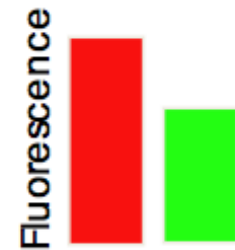
left: Cortex
right: medulla

Differential expression from different alleles



RNA (cDNA)

Genomic DNA



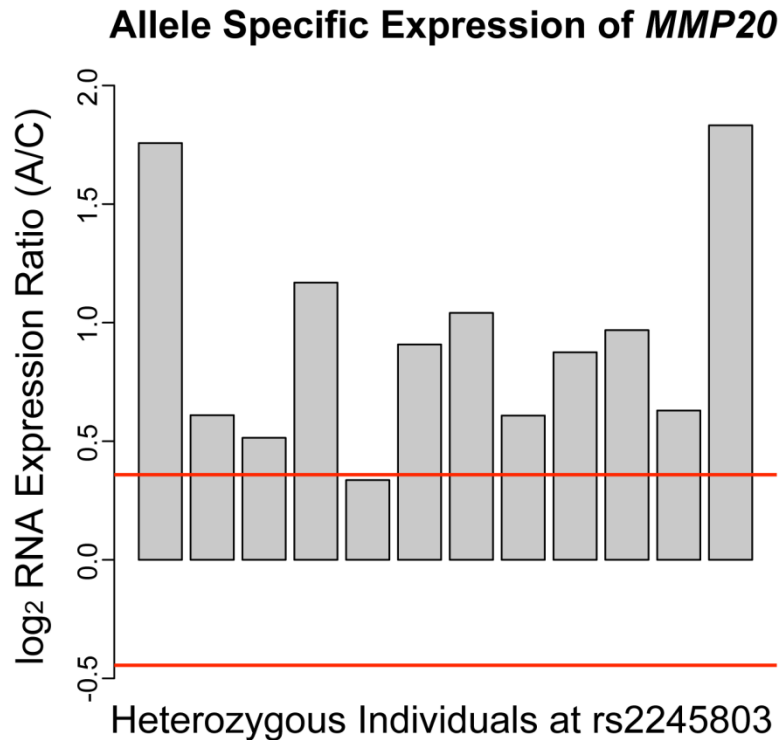
C/G

C/G

Allele-Specific
Expression

1:1 reference

Allele-Specific Expression



- Red lines indicate 95% confidence intervals

- Example shows 11/12 heterozygotes have higher expression of A allele than C allele.

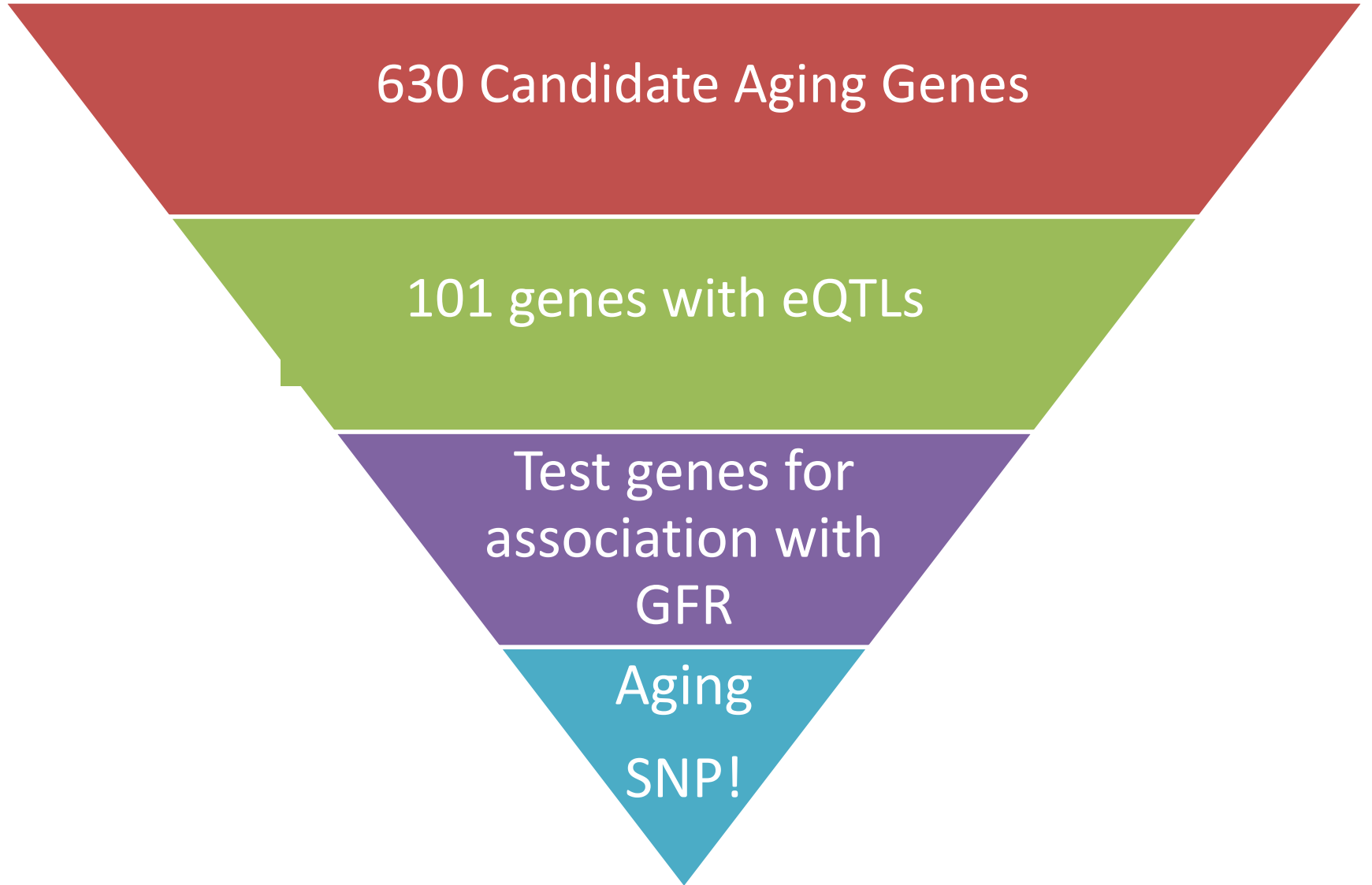
Genomic Convergence

630 Candidate Aging Genes

101 genes with eQTLs

Test genes for
association with
GFR

Aging
SNP!



polymorphisms



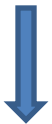
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Protein changes
expression changes



All genes expressed in cardiovascular
Genes that change expression in CVD



GO, KEGG, networks etc.



Cardiovascular disease