Genomic Prediction Workshop - Palmerston North 2015

Introduction to Genomic Prediction

Dorian Garrick
Lush Endowed Chair in Animal Breeding & Genetics
dorian@iastate.edu

Genomics

▼ *Dictionary*

ge•no•mics | jēˈnōmiks, -ˈnäm- , |
pluralnoun [treated as sing.]
the branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes.

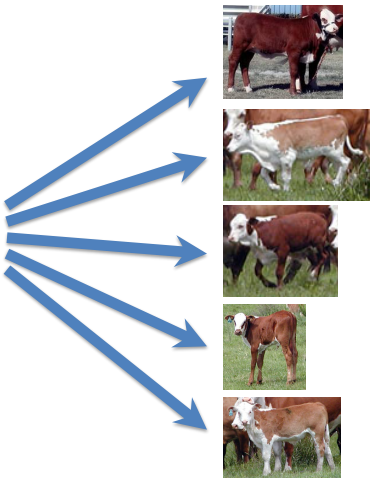
ORIGIN 1980s: from *genome* ***'the complete set of genes present in an organism'*** + *-ics* .

Genomic Prediction

- Ranking candidates for selection using knowledge of the "complete set of genes" *along with conventional pedigree and performance information*
  - Using everything we've got to obtain the most accurate EPD/EBV (at as young an age as possible)

Suppose we generate 100 progeny on 1 bull

Sire

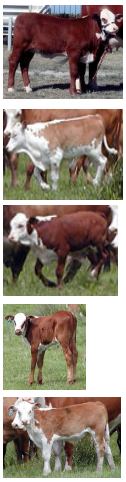


Progeny

Performance of the Progeny

Sire

Offspring of one sire exhibit more than ¾ diversity of the entire population



+30 kg
+15 kg
-10 kg
+ 5 kg
+10 kg

Progeny +10 kg

We Learn about Parents from Progeny

Sire

+30 kg
+15 kg
-10 kg
+ 5 kg
+10 kg

(EBV is "shrunk")
(<2x progeny)

Sire EBV +16-18 kg

Progeny +10 kg

How much we shrink depends upon the number of progeny

EBVs on widely-used old sires are accurate

Sire

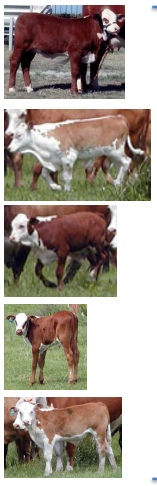
With enough progeny, this is usually close to the bulls true EBV/EPD (not surprisingly!)

Sire EBV +16-18 kg

Suppose we generate new progeny

Sire

Sire EBV +16-18 kg



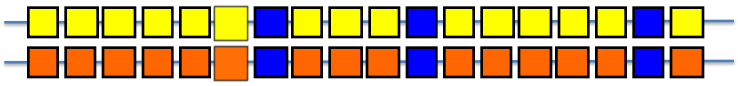
Progeny

Expect them to be 8-9 kg heavier than those from an average sire

Some will be more others will be less but we cant tell which are better without "buying" more information

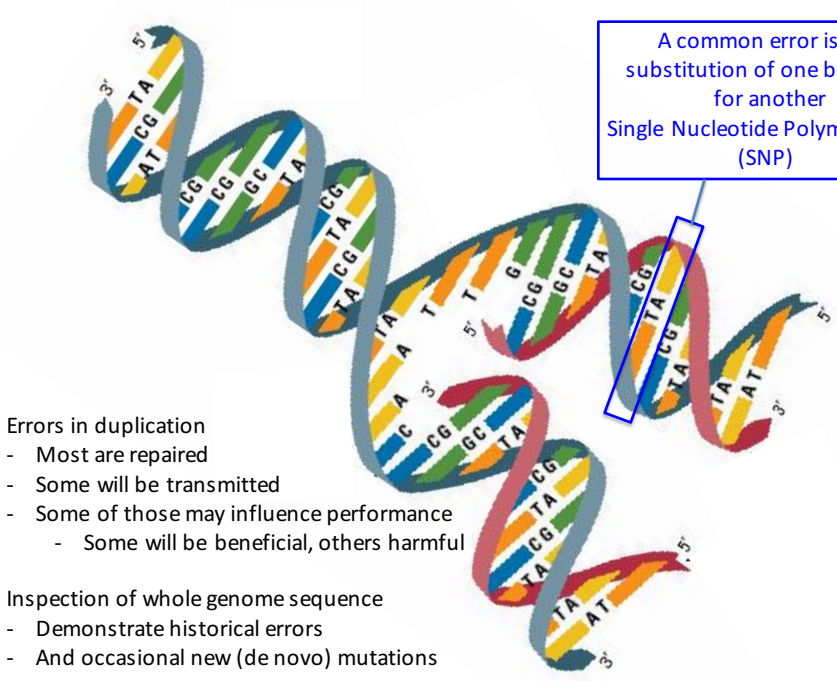
Chromosomes are a sequence of base pairs

Part of 1 pair
of chromosomes



Cattle usually have 30 pairs of chromosomes
One member of each pair inherited from the sire, one from the dam
Each chromosome has about 100 million base pairs (A, G, T or C)
About 3 billion describe the animal

Blue base pairs represent genes
Yellow represents the strand inherited from the sire
Orange represents the strand inherited from the dam



Errors in duplication
- Most are repaired
- Some will be transmitted
- Some of those may influence performance
  - Some will be beneficial, others harmful

Inspection of whole genome sequence
- Demonstrate historical errors
- And occasional new (de novo) mutations

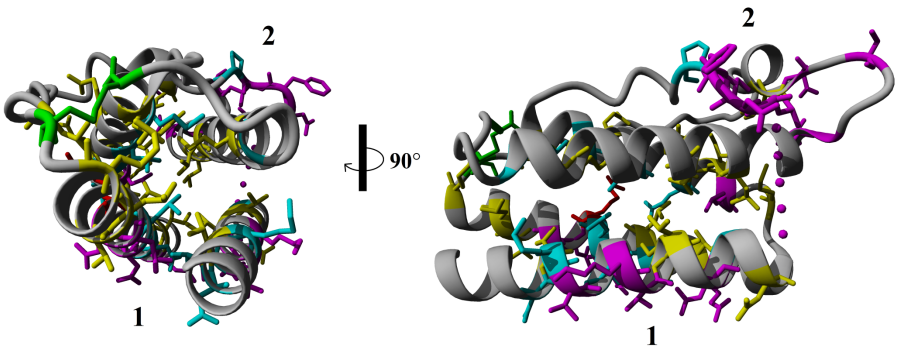
Mutations

- Could cause complete loss-of-function of the gene (ie the gene is "broken")
  - These can sometimes be catastrophic when an individual is homozygous and carries 2 copies of the broken gene
    - For examples DUMPS, Citrullinemia, BLAD, etc

Mutations

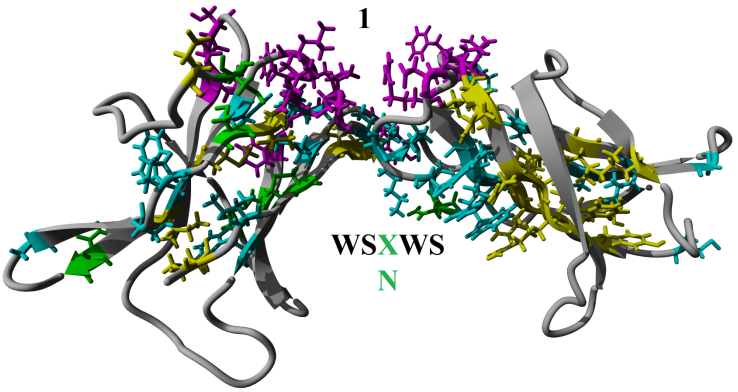
- Could cause complete loss-of-function of the gene (ie the gene is "broken")
- Could increase or decrease expression level
- The variant might change amino acid sequence to cause subtle changes to the shape of the protein products making them function a little better or a little worse
  - Natural or artificial selection will favour the variants that improve fitness in that particular climatic and environmental circumstance

Leptin



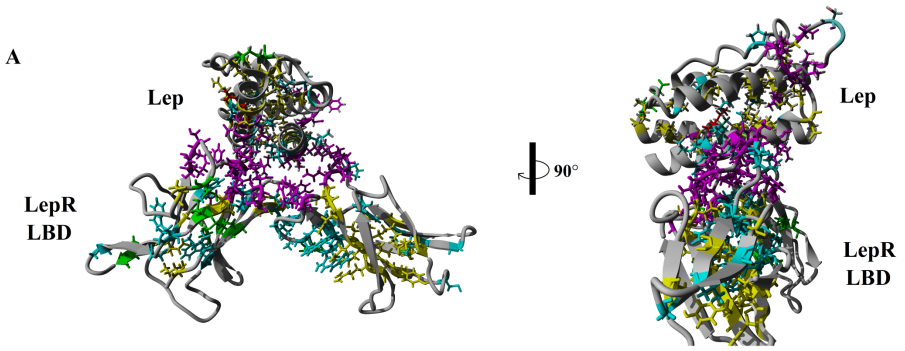
Prokop et al, Peptides, 2012

Leptin Receptor



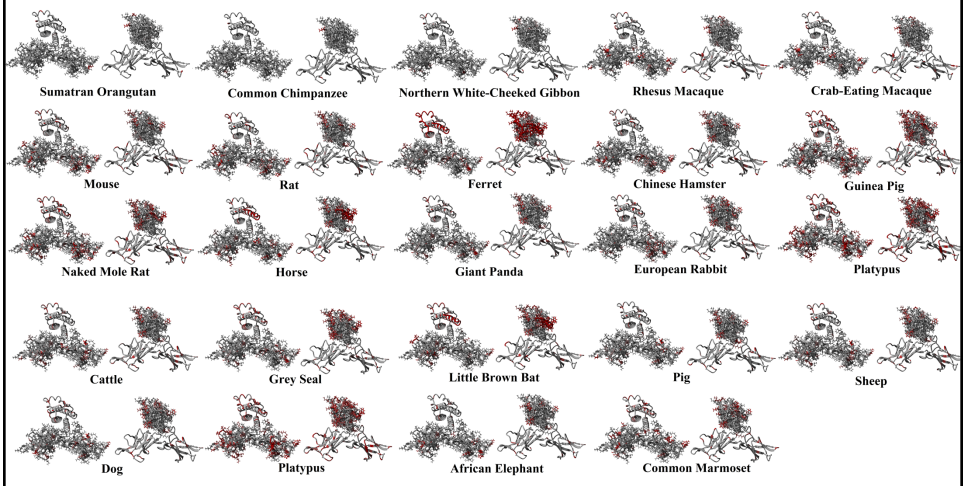
Prokop et al, Peptides, 2012

Joining the two



Prokop et al, Peptides, 2012

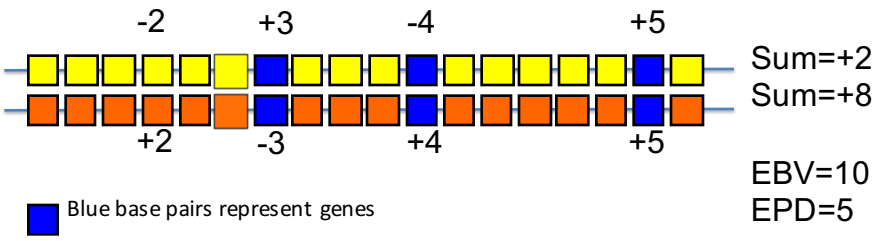
Leptin and its Receptor Across Species



There are small differences (within &) between species in these proteins

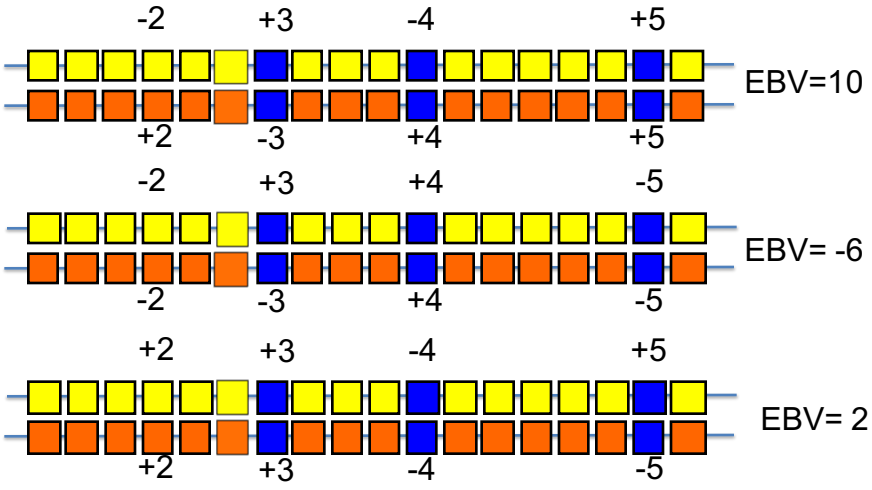
Prokop et al, Peptides, 2012

EBV is sum of the Gene Effects



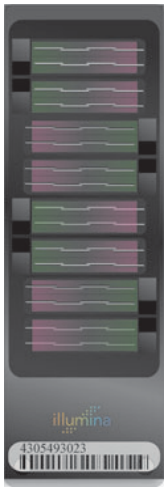
EPD is HALF the sum of the gene effects

Consider 3 Bulls

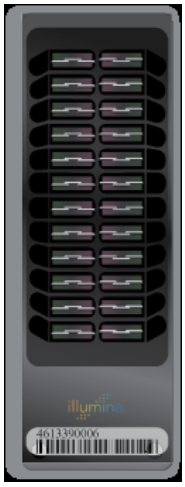


Below-average bulls will have some above-average alleles and vice versa!

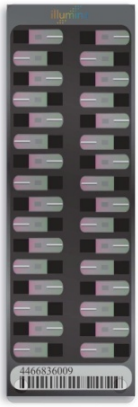
Illumina Bovine 770k, 50k (v2), 3k



700k (HD)



50k (Several versions)

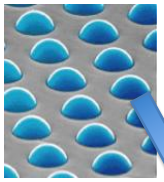


3k (LD)

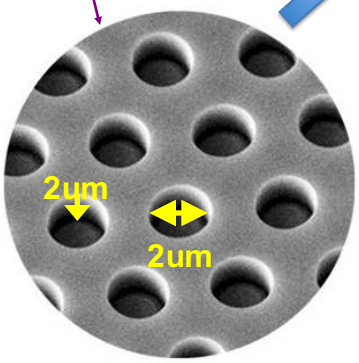
Illumina SNP Bead Chip

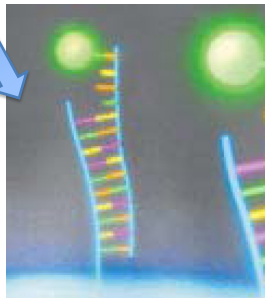
BeadChip

eg 1,000,000 wells/stripe



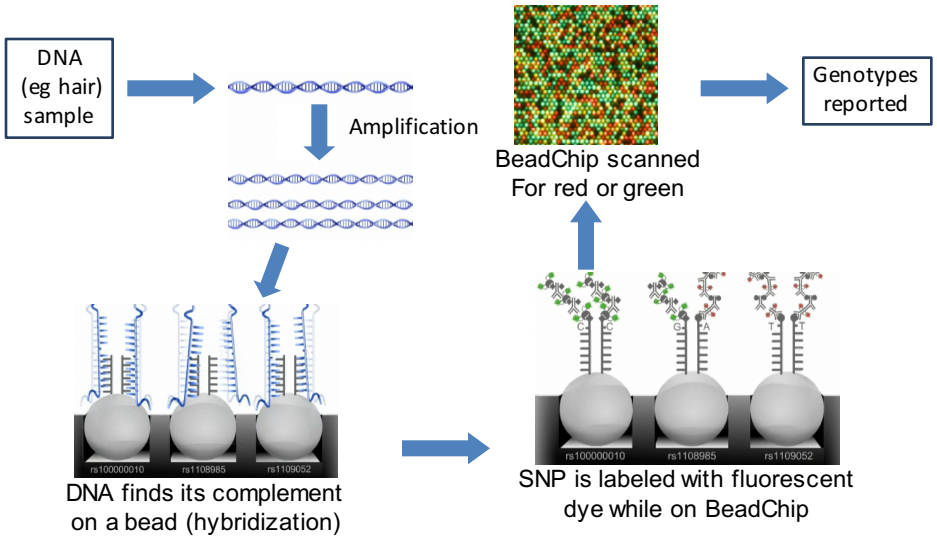
▸Silica glass beads self-assemble into microwells on slides



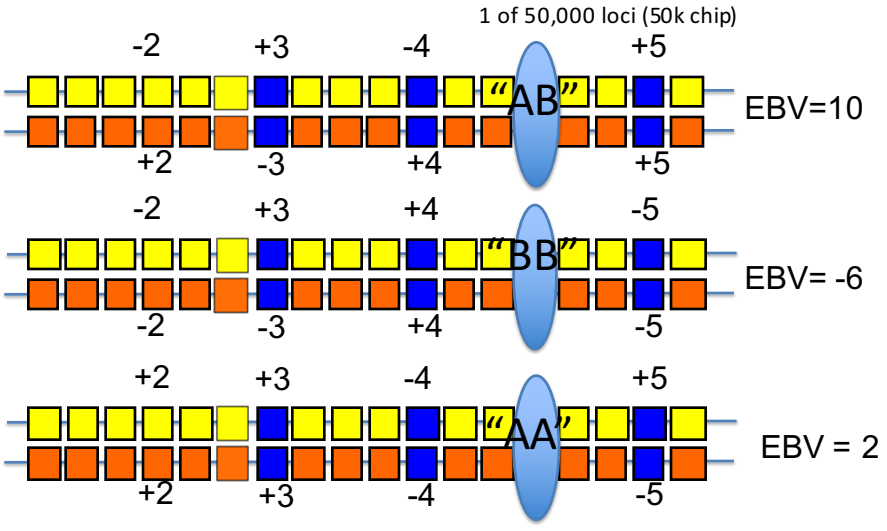


~800,000 copies of specific oligo per bead
50k or more bead types

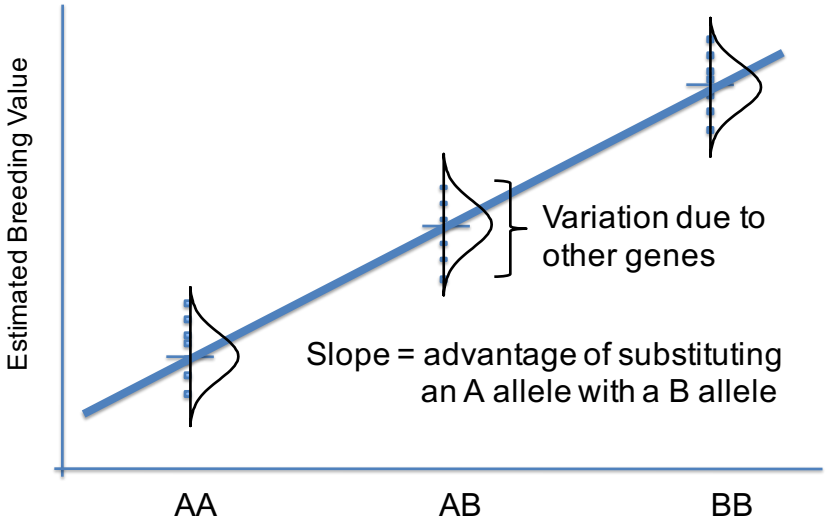
Illumina Infinium SNP genotyping



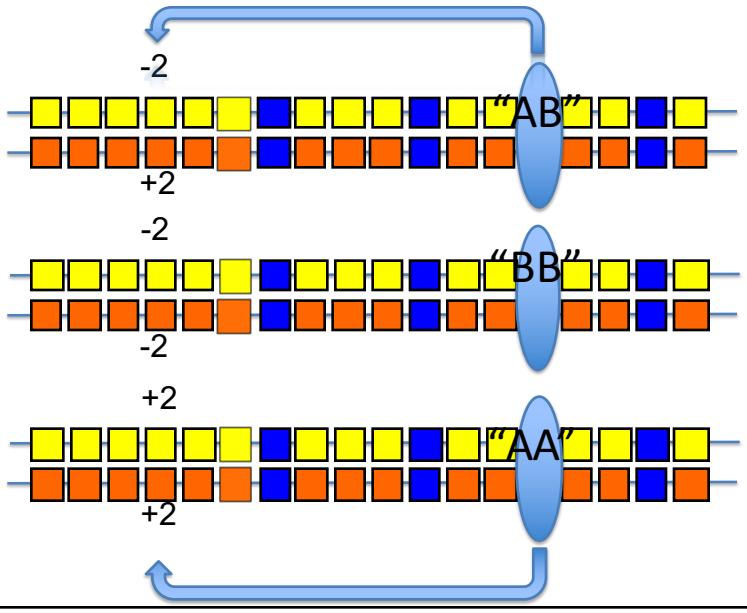
SNP Genotyping the Bulls



Regress performance on SNP genotype

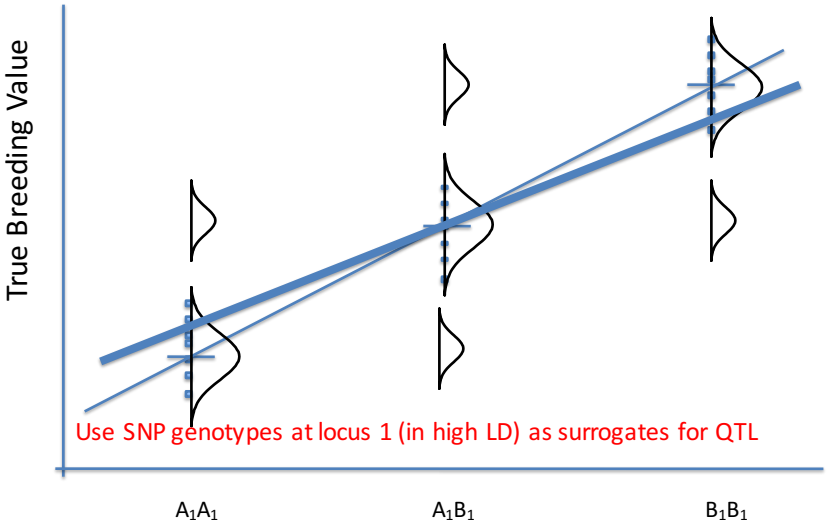


Linkage Disequilibrium (LD)

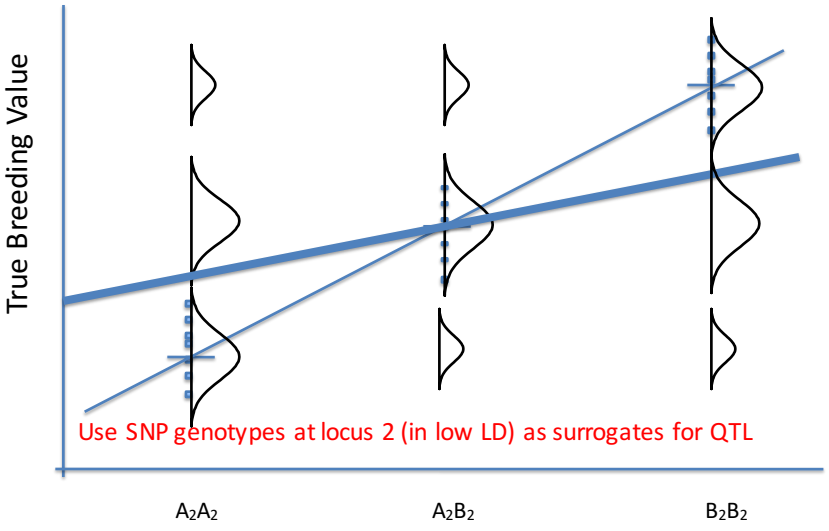


LD occurs when genotypes at one locus are predictive of genotypes at another

Practice – EBV/EPD on SNP



Practice – EBV/EPD on SNP



In practice fitting all SNP simultaneously
Meuwissen, Hayes and Goddard (2001)

www.23andme.com

23andMe

Health Risks

Alzheimer's Disease

Decreased Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Alzheimer's Disease	★★★★	4.9%	7.2%	0.69x

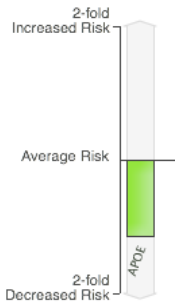
Your Data | How It Works | Technical Report | Community (162)

Technical Report

Gene or region: APOE

	SNPs used	Genotype	Allele	Adjusted Odds Ratio
Dorian Garrick	rs7412 rs429358	*CC* *TT*	ε3/ε3	European: 0.67

Marker Effects



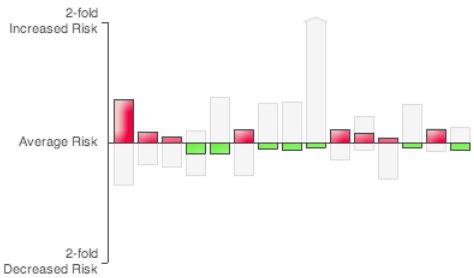
Only significant, validated GWAS findings used in prediction

www.23andme.com

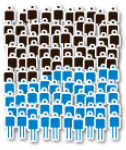
- Coronary Heart Disease

39-56 %
Attributable to Genetics

Marker Effects



Dorian Garrick
55.0 out of 100
men of European ethnicity who share Dorian Garrick's genotype will develop Coronary Heart Disease between the ages of 45 and 79.

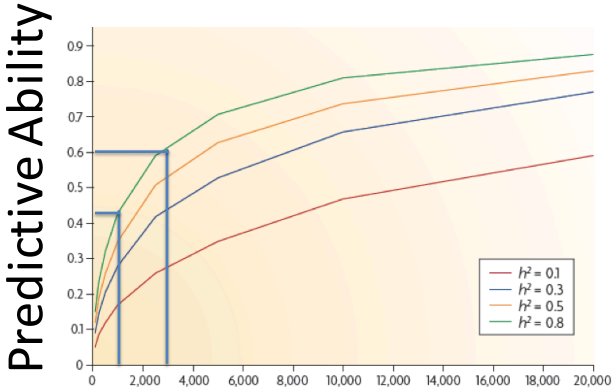


Average
46.8 out of 100
men of European ethnicity will develop Coronary Heart Disease between the ages of 45 and 79.

Each bar represents a different risk QTL allele
(mouseover shows the allele and links to the research publications)
QTL=Quantitative Trait Locus

Only significant, validated GWAS findings used in prediction

Theoretical Basis for Accuracy



Heritability=0.8

N_e=100
like Holsteins & Jerseys

1,000 training animals
r=0.43 20% genetic variance

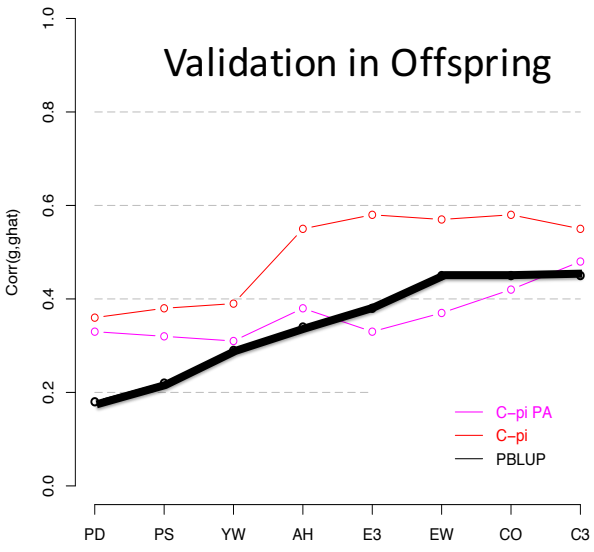
3,000 training animals
r=0.6 36% genetic variance

Goddard & Hayes (Nature Reviews Genetics, 2009)

Reliable prediction requires large training populations of genotyped and phenotyped individuals

Predictive Ability = Accuracy (r) = correlation true & predicted merit

Accuracy of Genomic Prediction

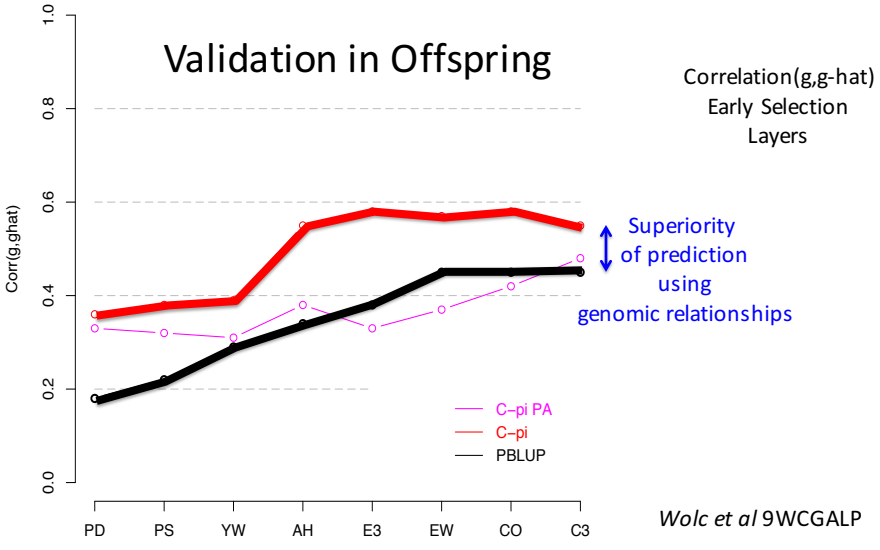


Correlation(g,g-hat)
Early Selection
Layers

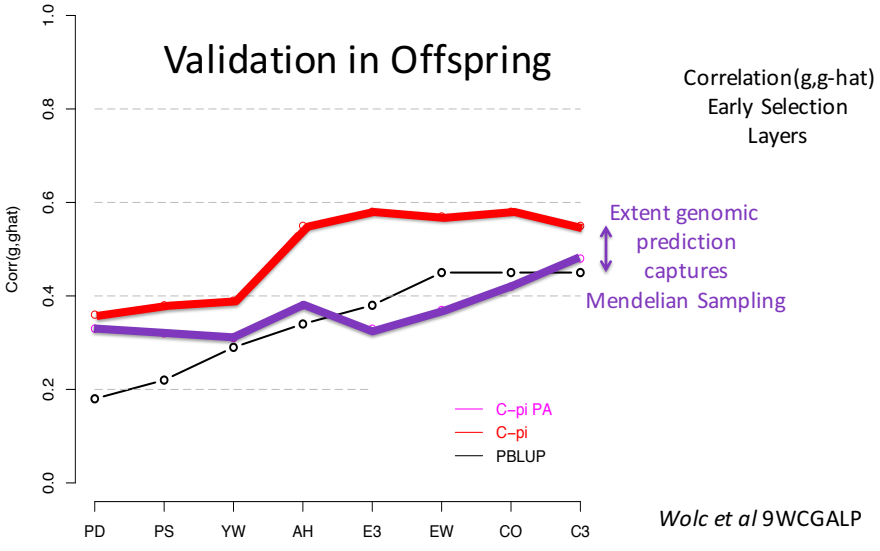
Conventional
pedigree
relationships

Wolc et al 9WCGALP

Accuracy of Genomic Prediction



Accuracy of Genomic Prediction



Genome-Wide Association Studies (GWAS)

- Use a historical population of bulls and cows with EBV information that have been genotyped with 50k panels
- Derive an EBV for every chromosome fragment (we call this training), and find the regions with biggest effects

Cut genome into 2,700 1Mb windows

#SNPs	%Var	Cum%Var	map_pos
11	7.10	7.10	7_93
28	3.70	10.80	20_4
22	1.34	12.14	13_58
22	1.23	13.37	26_34
9	0.92	14.29	6_29
25	0.89	16.09	4_75
26	0.79	16.88	4_114
23	0.65	17.53	2_121
17	0.61	18.14	18_55
25	0.60	18.74	8_88

Regions with biggest effects

Angus Birth Weight

Major Regions for Birth Weight

Genetic Variance %

Chr_mb	Angus	Hereford	Limousin	Simmental	Gelbvieh
7_93	7.10	5.85	0.02	0.18	0.02
6_38-39	0.47	8.48	5.90	16.3	4.75
20_4	3.70	7.99	0.07	1.53	0.03
14_24-26	0.42	0.01	0.71	3.05	8.14

Some of these same regions have big effects on one or more of weaning weight, yearling weight, marbling, ribeye area, calving ease

Iowa State University (ISU)

- A land-grant institution with responsibilities for research, teaching and extension
  - Such activities have been applied to genetic improvement of animals since 1930's when Iowa State Professor, Dr JL Lush, wrote the first textbook on animal breeding
  - That tradition continues just as strongly today as we research the role of genomics for improvement

Summary

- Genomics will increase accuracy of evaluation
  - The technology is starting to mature but works better in some traits and breeds than in others
  - It works better with greater amounts of data
  - Genomic prediction will get more accurate than it is today if we continue to undertake research
- This workshop will explain the statistical basis for methods of genomic prediction and GWAS