



Concept Review

|||||||

Bayer-Russia Molecular
Marker Training

24 July 2023



A purpose-driven pipeline



Farmers need innovation

not only to grow enough but to grow better for our planet and its people

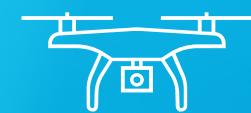
Agricultural Innovations
can be part of the solution



Producing more
on each acre



Reducing the
environmental impact of farming



Enabling **smarter decision-making** and more efficient farming

Combining the best genetics for the best outcomes

Crops have genetic advantages in each region where they're grown based on generations of environmental adaptation. By identifying those strong genes, we can **breed for the strongest crops**

However the number of possible genetic combinations is infinite, so Bayer breeders rely on **AI and advanced analytics to aid selection**

This allows us to develop crops that **leverage the complexity of the genome to its fullest potential**



Asia

Brazil

Mexico

Africa

Argentina

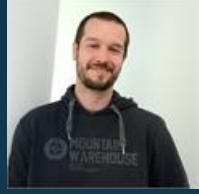
Europe



Meet the Bayer Trainers: Experienced scientific leaders



Amy
Caruano-Yzermans



Chris
Gaynor



Neil
Yu



Jianyi
Yang



Zane
Goodwin

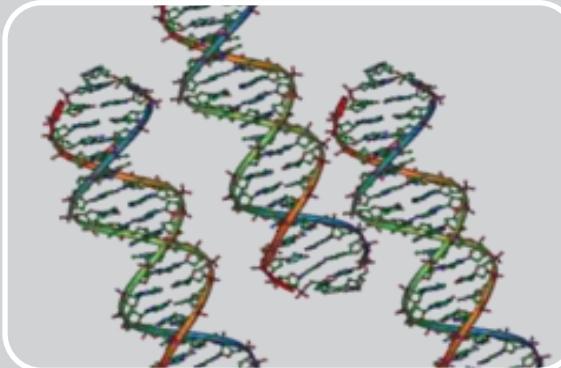


Christopher
Schlosberg

Bayer Trainers

- PhD scientists formally trained in Computational and Systems Biology, Plant Molecular & Cellular Biology, Chemical Biology, Genetics, and Plant Breeding
- Collectively have over 77 years in agriculture academic and industry experience
- Published 64 scientific articles
- Co-authored 6 patents (granted or under review)

Bayer-Russia Molecular Marker Training Content



Day 1

Overview of
Molecular
Breeding &
Application

Day 2

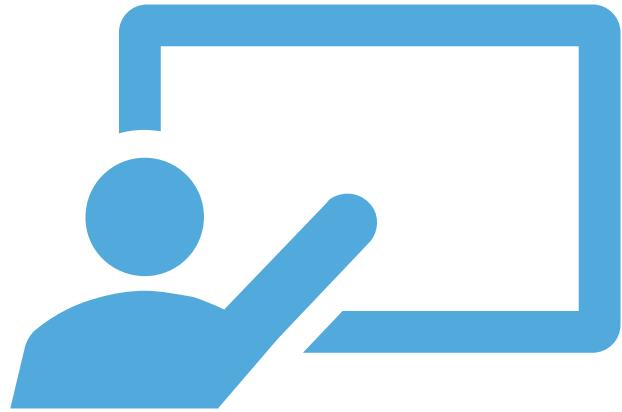
Markers for
Use in High
Throughput
Labs

Day 3

Data
Science &
Engineering
& Summary



Bayer-Russia Molecular Marker Training Format



**Presentations on topic
30-60 minutes**



**Q&A/Discussion after
presentation ~15 min**



**Scheduled break about
halfway through the session**



Bayer Russia Molecular Marker Training: Concept Review

- 1 **Genetic Inheritance**
- 2 **Modern Quantitative Genetics**
- 3 **Mapping Quantitative Trait Loci (QTLs)**
- 4 **Foundational Genomics**
- 5 **Molecular Breeding Workflows (MAS, MABC and GWS)**
- 6 **Public Resources for row and vegetable crops**
- 7 **Bayer's insight into workflows across crops**

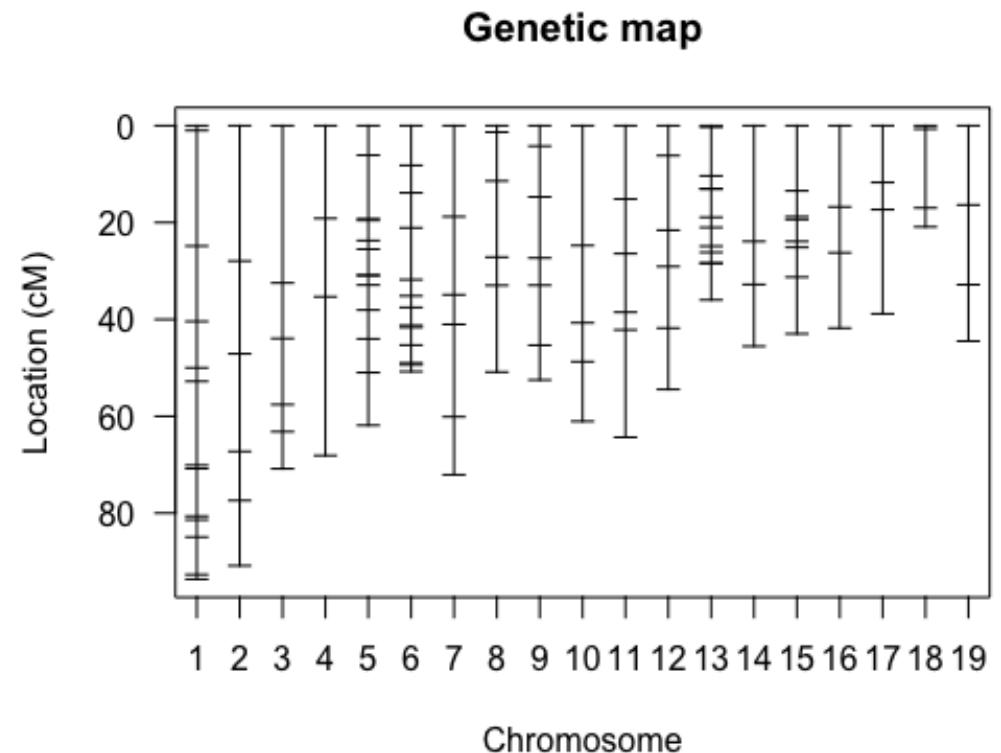
Recombination is Infrequent

Typical average of 1-2 per chromosome per generation



Linkage Mapping

- // Recombination data can order markers
 - // Fewer recombinations when close
- // Easiest with experimental crosses
 - // Designed for linkage mapping
- // A mapping function is required





Common Experimental Crosses for Mapping

- // Recombinant Inbred Lines (RIL)
- // Doubled Haploids (DH)
- // Backcross (BC)
- // F_2
- // Cross pollinated (CP)
- // Nested Association Mapping (NAM)
- // Multiparent Advanced Generation Intercross (MAGIC)



Genetic Mapping Functions

- // Mapping functions account for two important properties of recombination
 - // We only observe odd numbers of recombinations
 - // Recombination rates between loci are not additive
- // Map distances are expressed in Morgans
 - // Expected number of crossovers
- // There are many mapping functions but only two are widely used
 - // Hladane, does not model crossover interference
 - // Kosambi, models crossover interference

Linkage Disequilibrium (LD)

- // Correlation between loci
 - // One locus can predict another
 - // Caused by genetic linkage
 - // Caused by drift and selection
- // High in typical breeding programs
 - // Few parents
 - // Small effective population (N_e)
- // Lower in diversity populations
 - // High N_e



$$D_{AB} = p_{AB} - p_A p_B$$



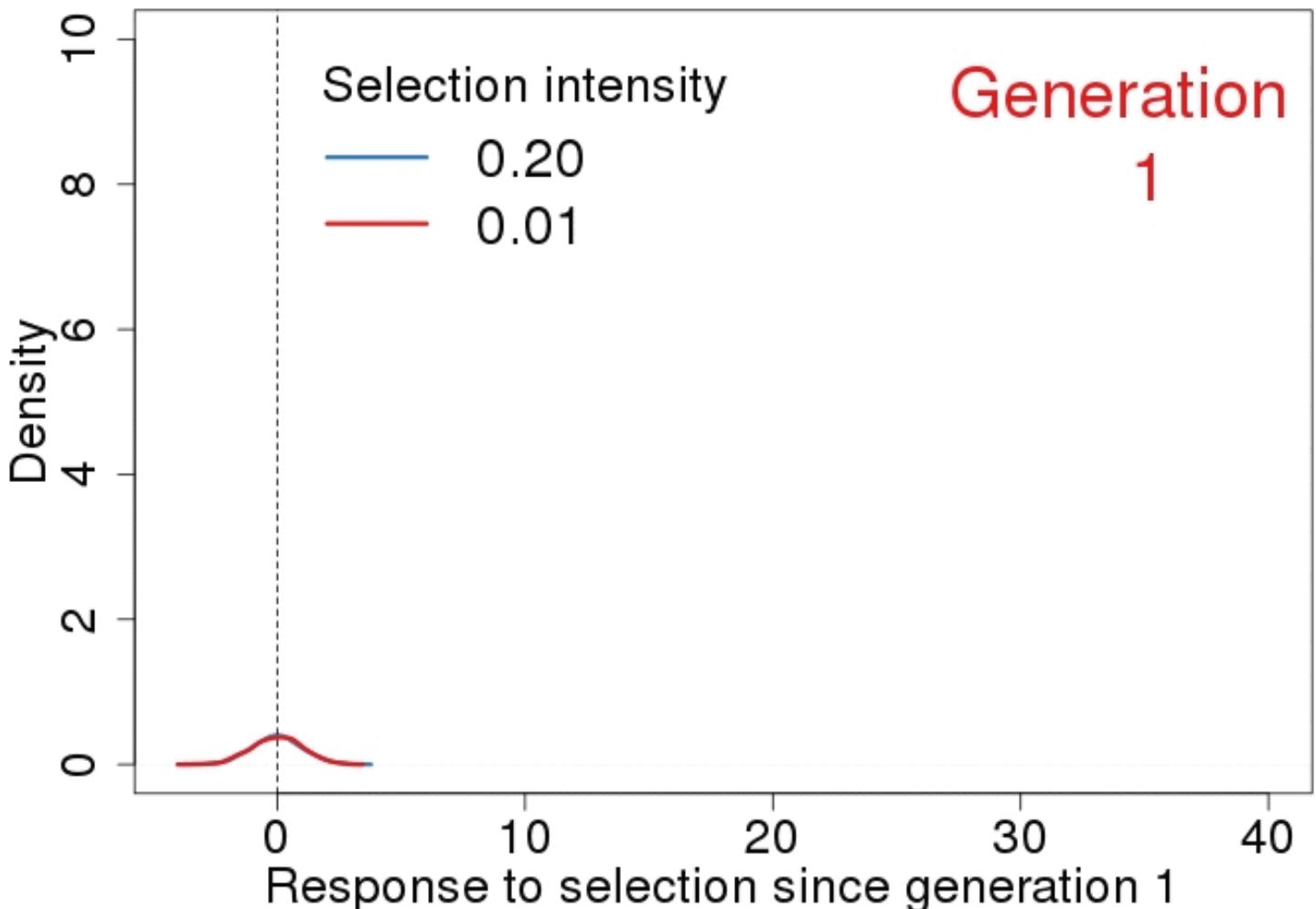
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Breeder's Equation

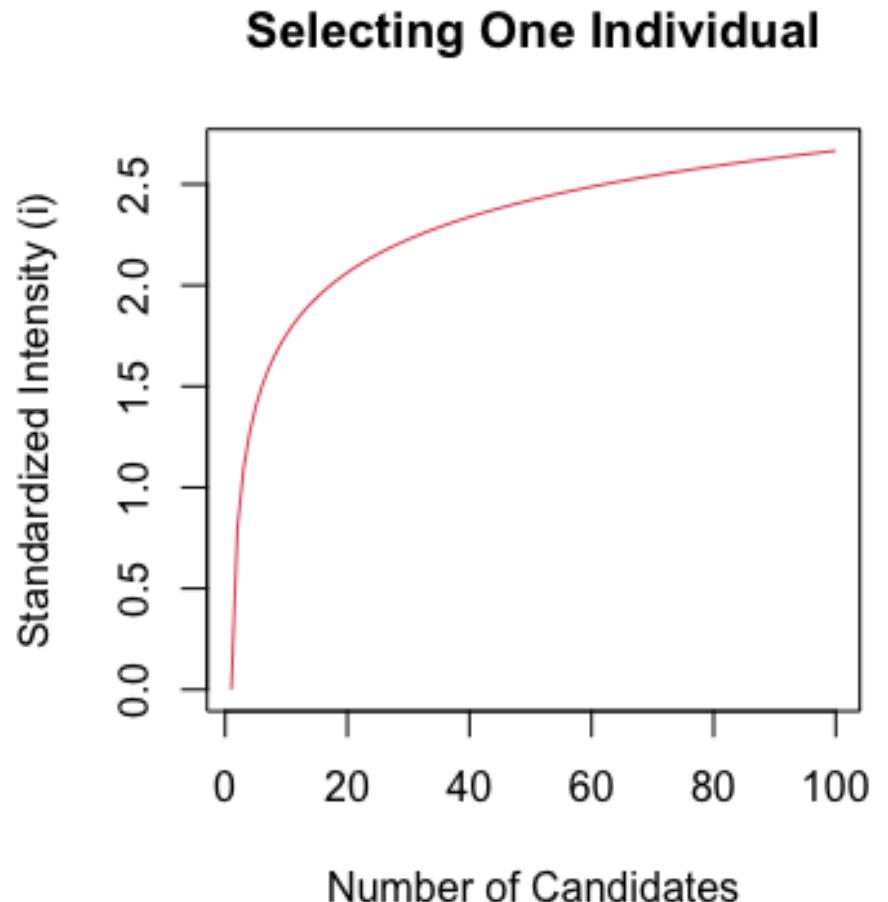
$$R = \frac{ih\sigma_A}{L}$$

- // Selection intensity (i)
- // Selection accuracy (h)
- // Genetic diversity (σ_A)
- // Generation interval (L)



Markers to improve selection intensity (i)

- // Expands pool of selection candidate
 - // Markers cheaper than phenotyping
 - // May be the only way to select
- // Subject to diminishing returns
 - // Less improvement at higher intensity





Markers to improve selection accuracy (h)

// “Borrow” data using mixed models

// Originated with animal breeding

// Pedigree BLUP -> GBLUP

VanRaden, P. M. 2008. Efficient Methods to Compute Genomic Predictions. Jour of Dairy Sci 91(11): 4414.

$$y = X\beta + Zu + \varepsilon$$

$$u \sim N(0, G\sigma_G^2)$$

$$\varepsilon \sim N(0, R\sigma_E^2)$$

// Shrinkage effect from mixed models

// Helps truncation selection

Markers to improve genetic diversity (σ_A)

// Selection for diverse crosses

// Simulation to estimate usefulness

Bernardo, R. 2014. Genomewide Selection of Parental Inbreds: Classes of Loci and Virtual Biparental Populations. *Crop Science* 54(6): 2586.

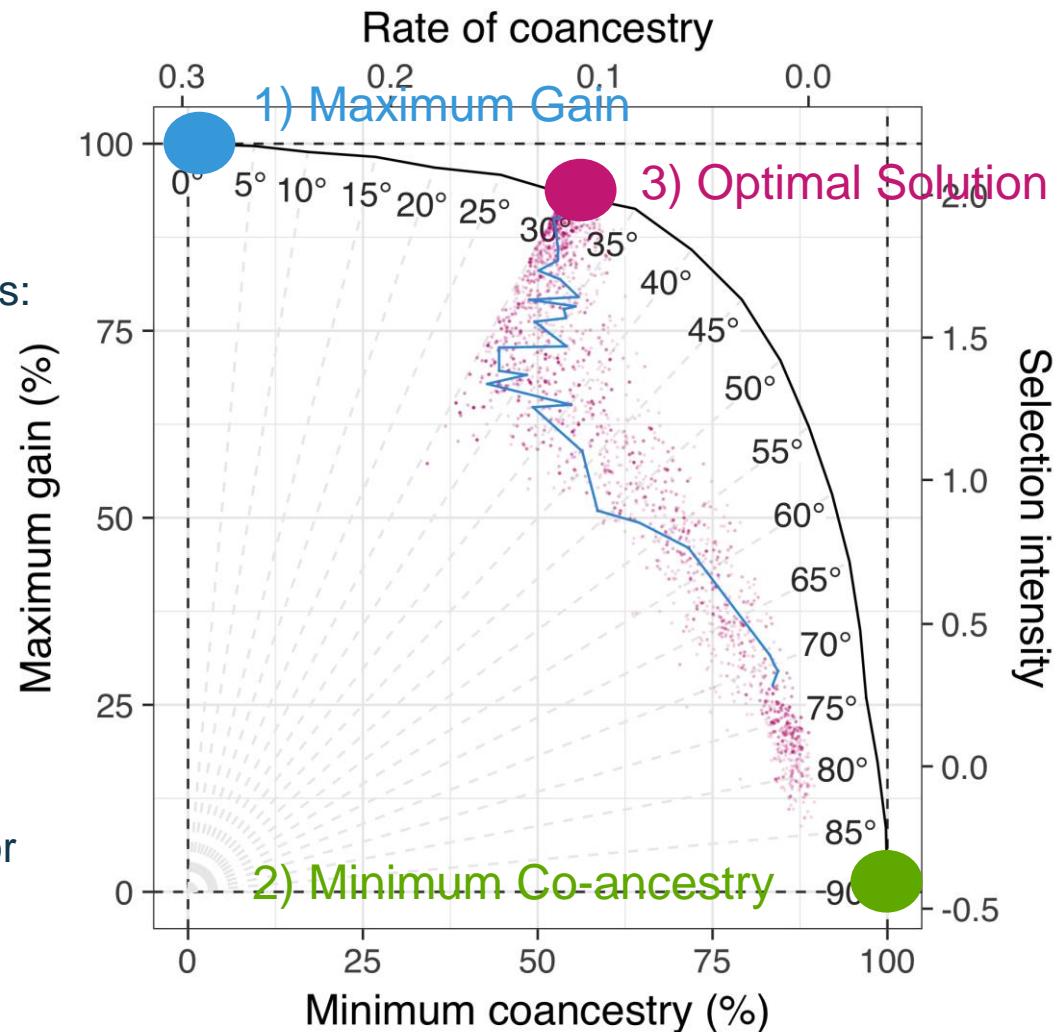
// Optimal contribution selection

// Maximize genetic gain

// Minimize co-ancestry

Gorjanc, G., R.C. Gaynor, and J.M. Hickey. 2018. Optimal cross selection for long-term genetic gain in two-part programs with rapid recurrent genomic selection. *Theor Appl Genet* 131(9): 1953–1966.

$$f(\mathbf{c}) = \mathbf{c}^T \mathbf{a} - \lambda \mathbf{c}^T \mathbf{A} \mathbf{c}$$

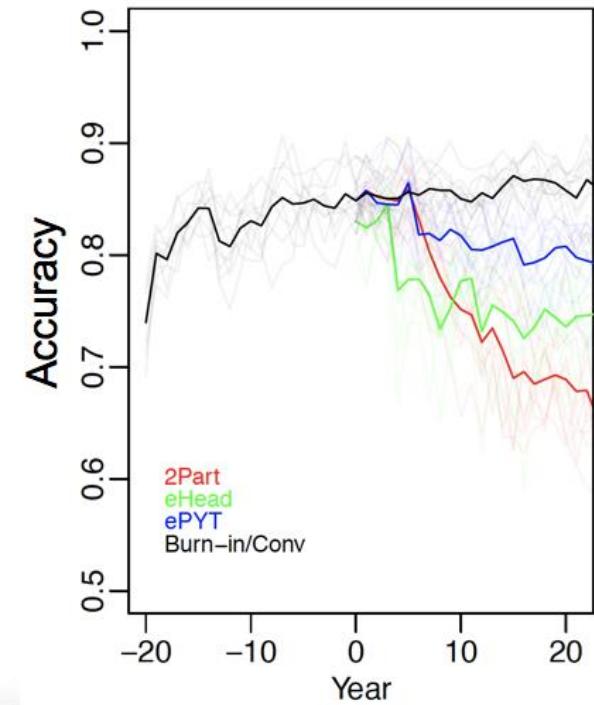
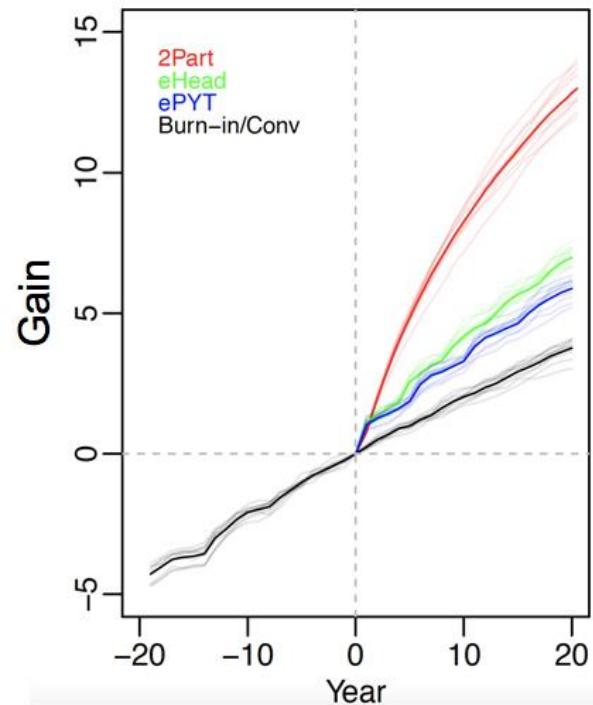


Markers to decrease generation interval (L)

// Large potential for gain
// Linear response

// Selection with only markers
// Greatly reduces accuracy

Gaynor, R. C., G. Gorjanc, A. R. Bentley, E. S. Ober, P. Howell, R. Jackson, I. J. Mackay, and J. M. Hickey. 2017. A Two-Part Strategy for Using Genomic Selection to Develop Inbred Lines. *Crop Science* 57(5): 2372.





Notes on Analysis of Phenotypic Data

- // Be mindful of scope-of-inference
 - // Genotype-by-environment interactions
 - // Greenhouse versus field
- // Mixed models are a good choice
 - // Handles unbalanced data and fits spatial models

Smith A. B., B. R. Cullis, and R. Thompson. 2005. The analysis of cultivar breeding and evaluations trials: an overview of current mixed model approaches. *The Jour of Agri Sci* 143(6).

- // Analyses can be performed in multiple stages
 - // BLUE first, then BLUP

Piepho, H. P., J. Mohring J., T. Schulz-Streeck, and J. O. Ogutu. 2012. A stage-wise approach for analysis of multi-environmental trials. *Biometrics* 54:844-860.



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Common QTL Mapping Approaches

// Interval Mapping

- // Searches for QTL between genetic markers
- // Lots of variations (e.g. composite interval mapping)

Doerge R. W.. 2002. Mapping and analysis of quantitative trait loci in experimental populations. *Nature Reviews Genetics* 3:43-52.

// Genome Wide Association Mapping (GWAS)

- // Tests for associations with genetic markers directly
- // Many different statistical models (e.g. Q+K)

Uffelmann R., et al. 2021. Genome-wide association studies. *Nature Reviews Methods Primers* 1(59).

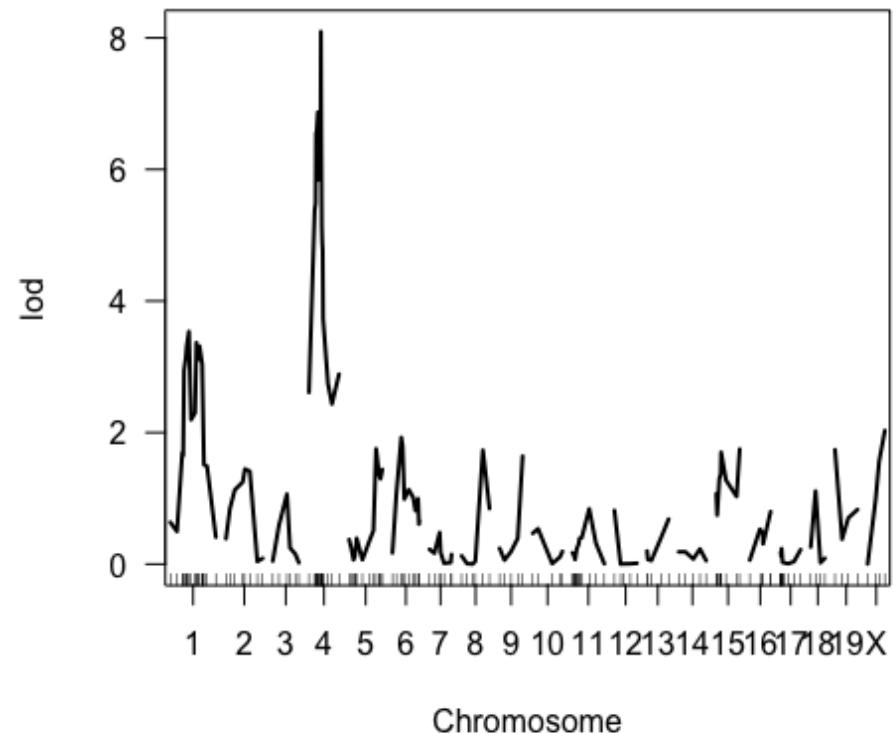
Interval Mapping

// Strengths

- // Requires relatively few markers
- // High statistical power
- // Sets up fine mapping

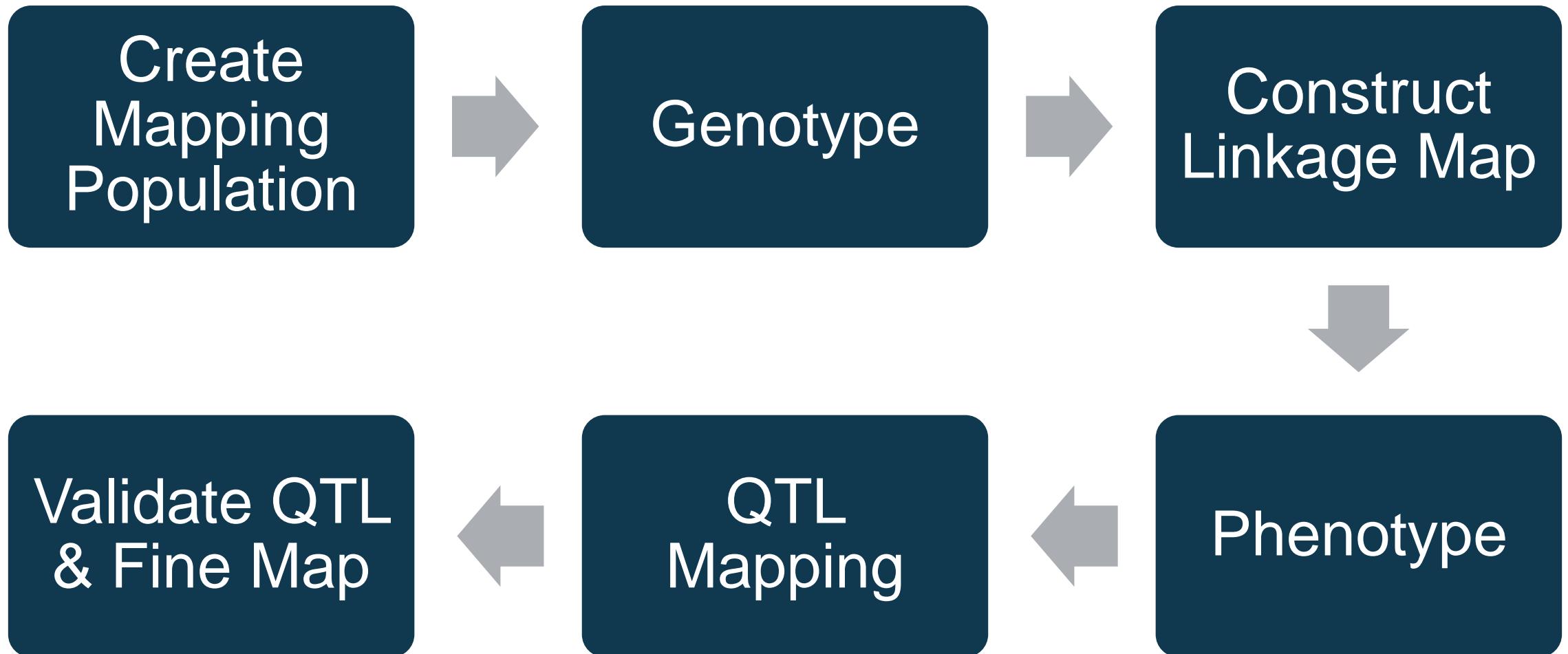
// Weaknesses

- // Requires a mapping population
- // Limited genetic scope-of-inference





Interval Mapping Workflow





Mapping Populations

- // Many different types of populations
 - // RIL, DH, NAM, MAGIC, ...
- // Statistical analysis depends on type of population
- // Statistical power depends mostly on size of population
- // Scope-of-inference limited mostly by number of parents
 - // Usually bi-parental
 - // Some multi-parent types (e.g. NAM and MAGIC)
 - // Phenotyping also limits scope-of-inference

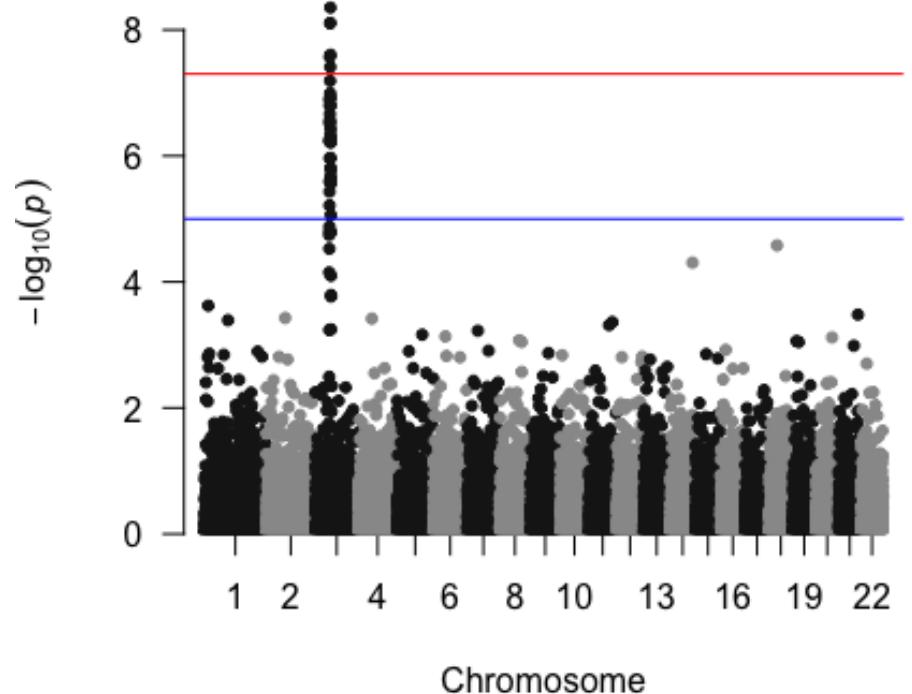
Genome Wide Association Studies (GWAS)

// Strengths

- // Does not require a mapping population
- // Greater genetic scope-of-inference
- // Leverages historic recombinations

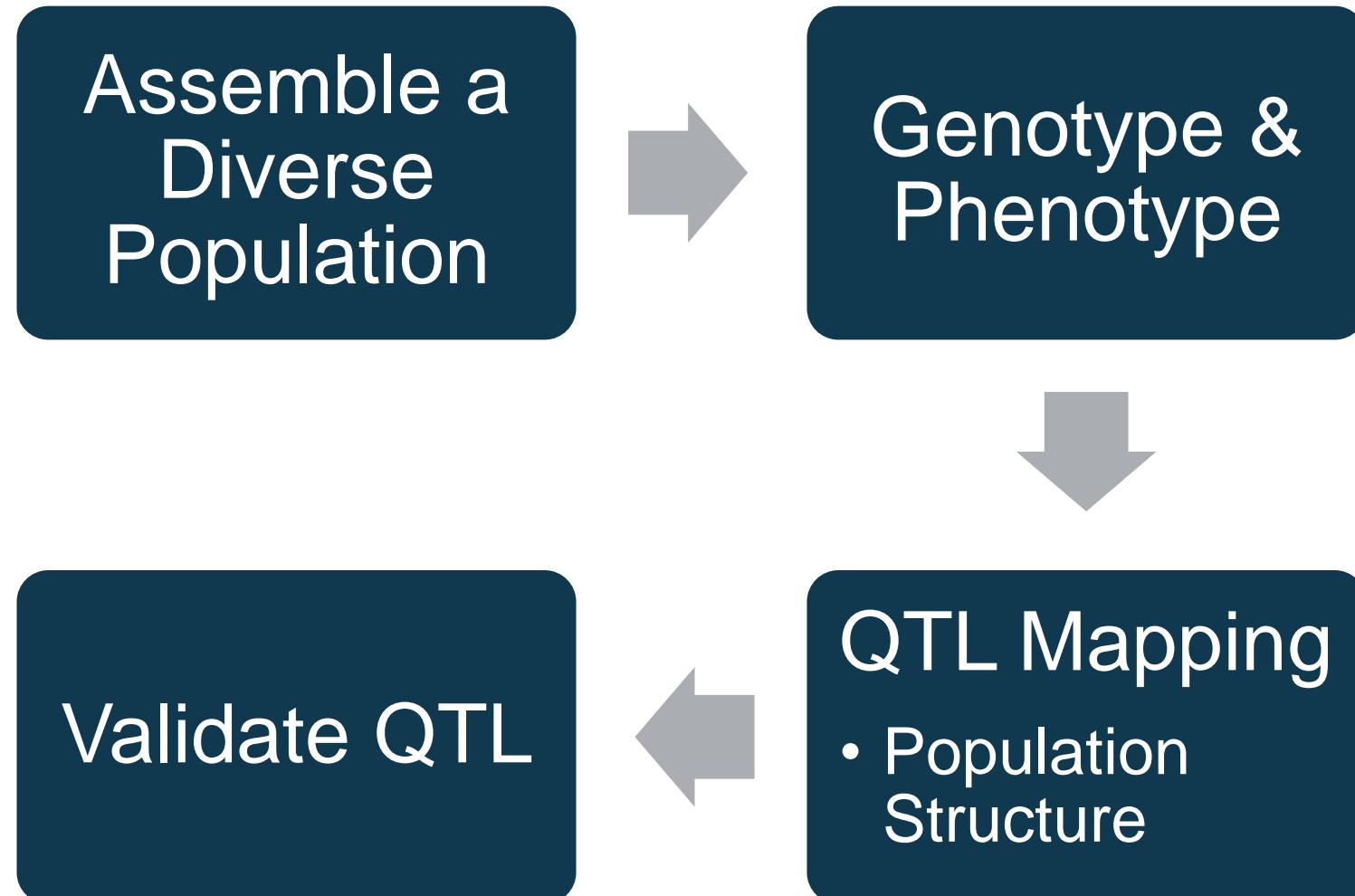
// Weaknesses

- // Limited statistical power
- // Requires lots of markers
- // Prone to false positives





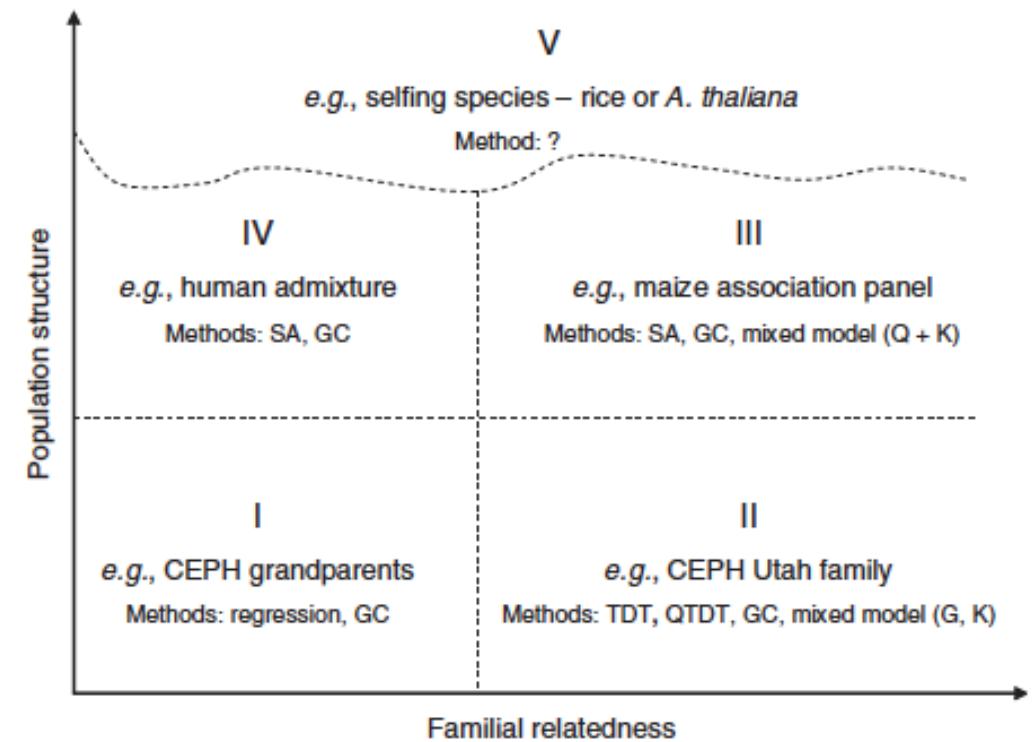
Typical GWAS Workflow



Controlling for False Positives

- // Two primary sources of false positives
 - // Population structure
 - // Familial relatedness
 - // Handled with mixed models

- // “True” positives are not really true
 - // Associations due to short range LD



From: Yu *et al.* 2006.



Concluding Comments on QTL Mapping

- // Effective for genes with large effect
- // Interval mapping approaches have a better record than GWAS

Bernardo R. 2016. Bandwagons I, too, have known. *Theor Appl Genet* 129(12):2323-2332.
- // Genome wide selection is better for highly polygenic traits

Whittaker J. C., R. Thompson, and M. C. Dunham. 2000. Marker-assisted selection using ridge regression. *Genet Res.* 75(2):249-252.



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High-throughput Genotyping

- // Foundation for most modern genomic analyses
 - // Sequencing is a specific example
- // Well established tools and workflows
- // Can operate at greater scale than other types of genomic data
 - // e.g. expression data



Genotyping Platforms

- // Wide variety of platforms are available
 - // Frequently changing

- // Several considerations when choosing a platform
 - // Cost
 - // Number of markers
 - // Dominant or co-dominant
 - // Informativeness of markers
 - // Prior knowledge of variants (causal, physically mapped)



Genotype Imputation

- // Some genomics workflows can not handle missing data
 - // e.g. genome-wide selection
 - // Need to impute sporadic missing data

- // Cost effective to use multiple genotyping platforms
 - // Mix low-density and high-density platforms
 - // Impute low-density genotyping to high-density markers

Gorjanc G., M. Battagin, J. F. Dumasy, R. Antolin, R. C. Gaynor, and J. M. Hickey. 2017. Prospects for Cost-Effective Genomic Selection via Accurate Within-Family Imputation.. *Crop Sci.* 57(1):216-228.



Simulation to Guide Decisions

- // Lots of variables to consider when optimizing genomic workflows
 - // Difficult to make general recommendations

- // Simulations provide a way to prioritize options
 - // Design QTL mapping experiments (example: R/qtl)
 - // Test imputation strategies (example: AlphaSimR)
 - // Test breeding strategies (example: AlphaSimR)



Q&A Discussion



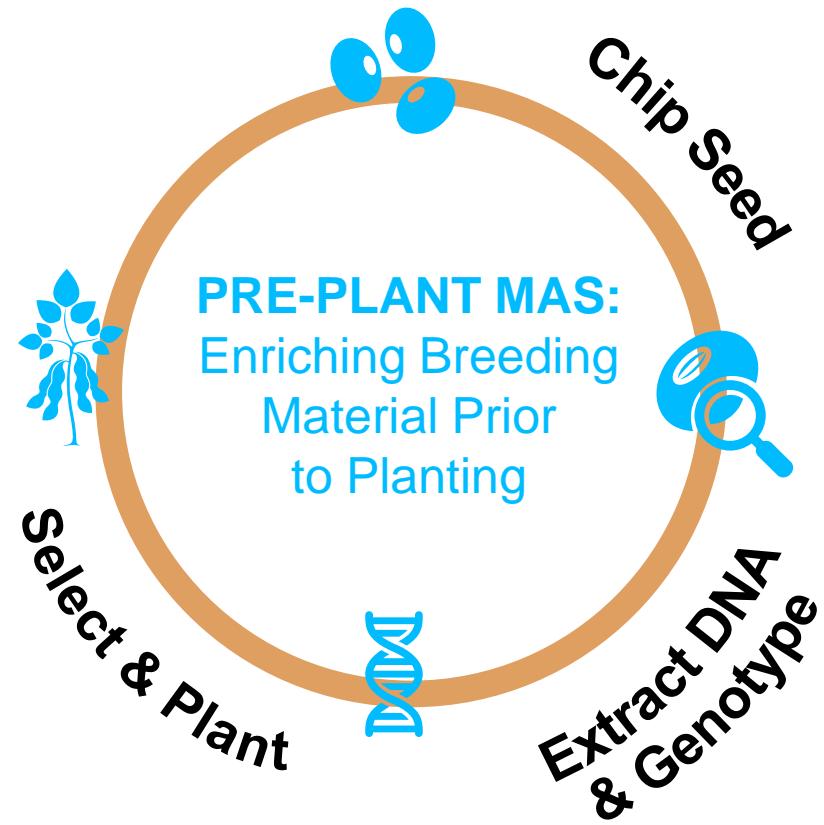
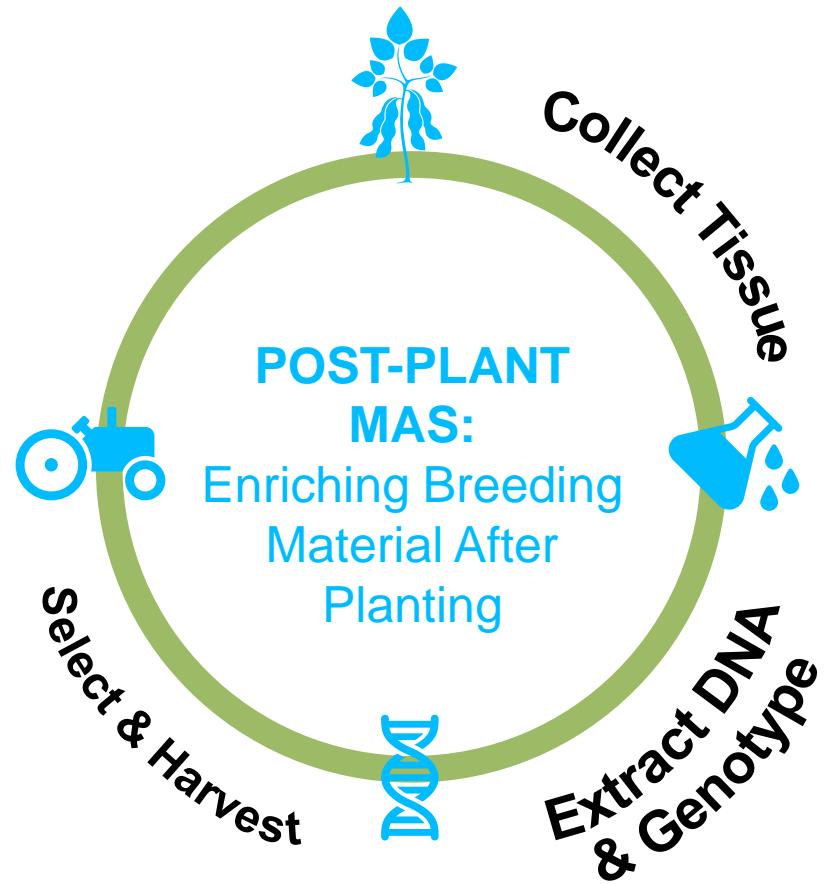


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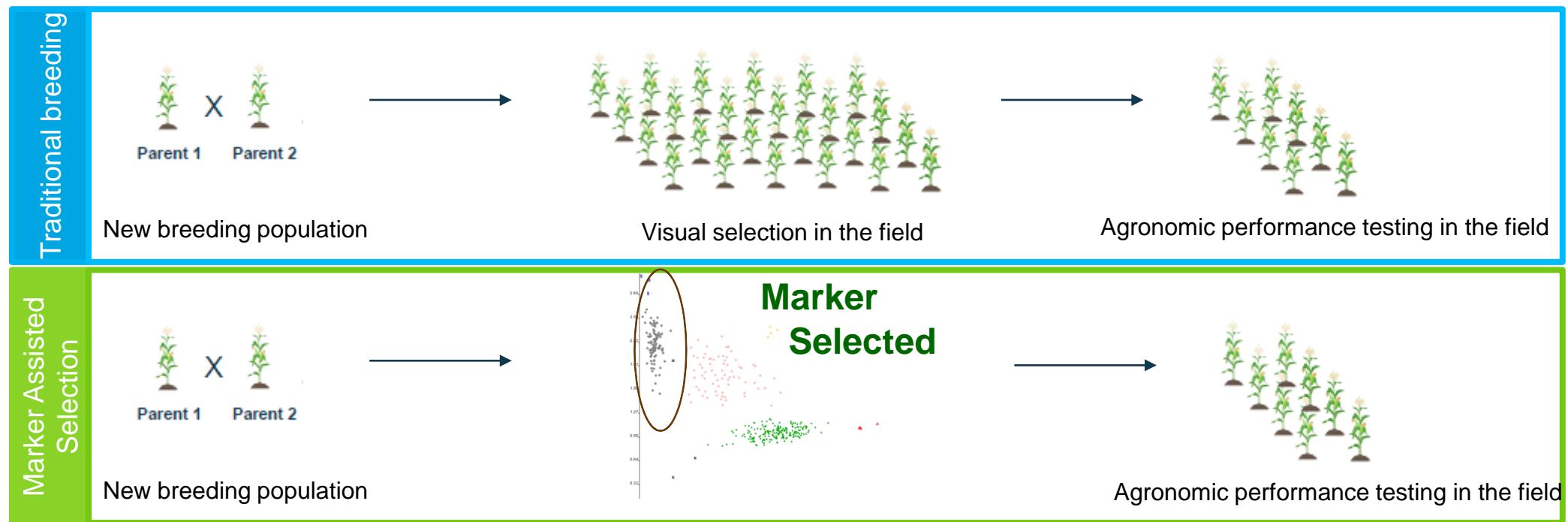
Marker Assisted Selection (MAS)

Marker-Assisted Selection involves genotyping with a small number of markers associated with phenotypic traits and performing selection to enrich a breeding population for the target traits



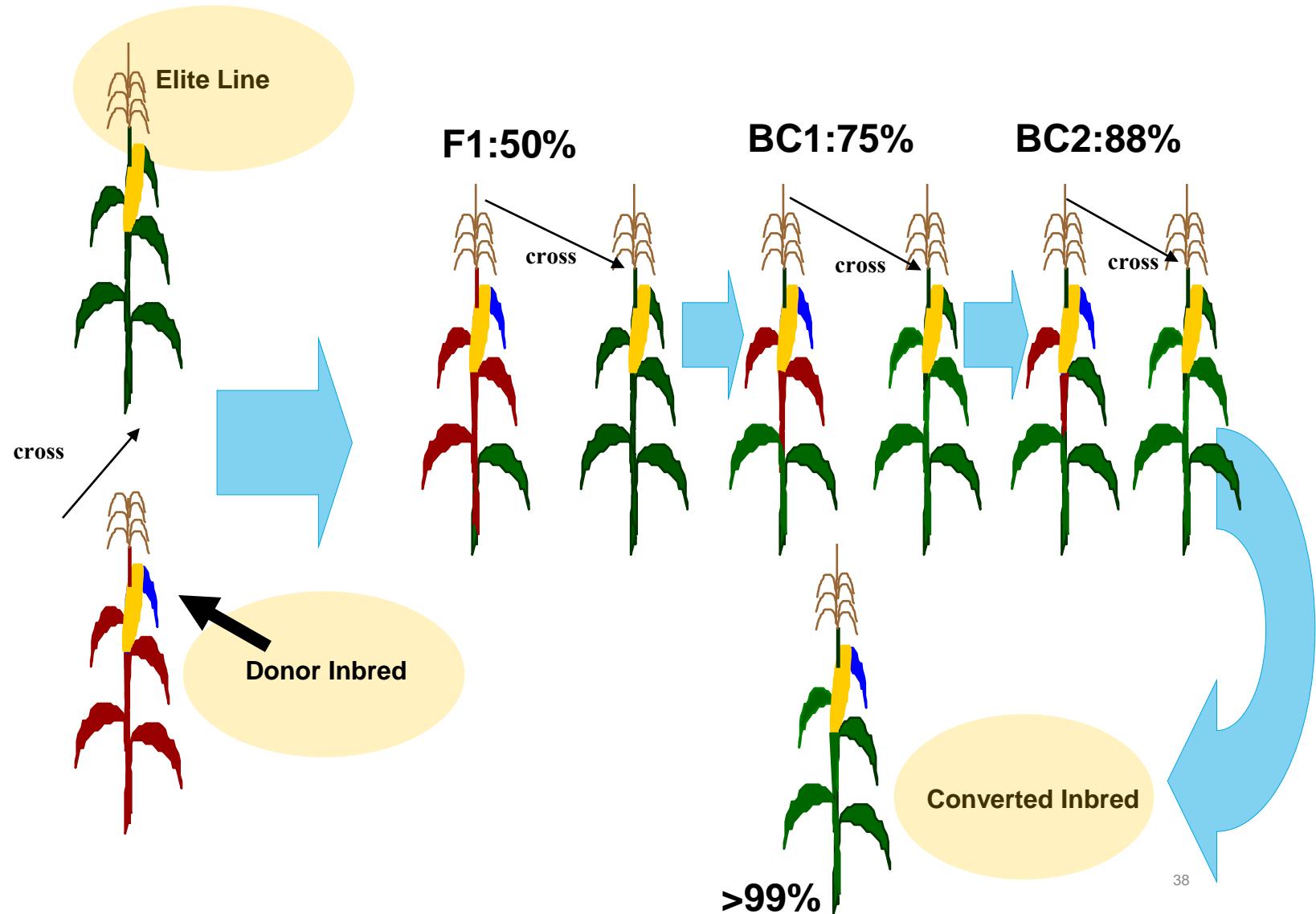
Marker Assisted Selection (MAS)

- // MAS is used to improve the accuracy, speed or costs of selecting for agronomic traits which are under simple genetic control (1-3 genes, require associating a trait with a closely-linked molecular marker)
- // DNA characterization replaces laborious, costly or inefficient phenotypic screens for the trait in breeding programs



Marker Assisted Backcross (MABC)

- The objective of **MABC** projects is to introgress Native traits or transgenes from one inbred (Donor) into another elite line (Recurrent).
- Molecular markers are used, at each backcross generation, for checking the presence of the trait and the similarity with recurrent parent.

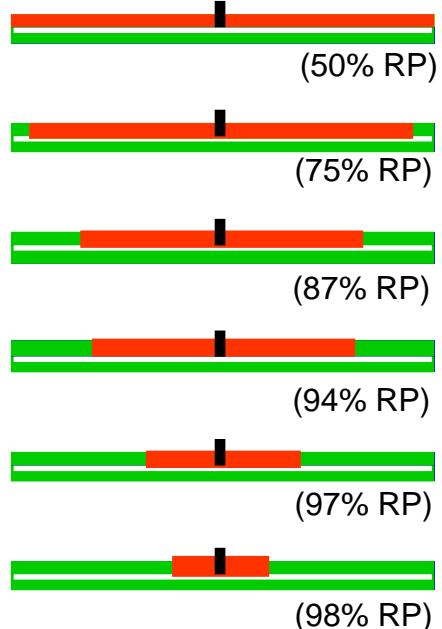




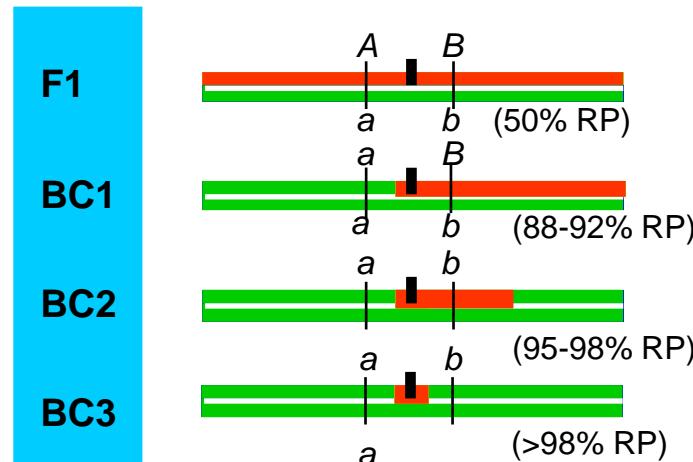
Marker Assisted Backcross (MABC)

Molecular Markers used to identify “elite” vs. “donor” DNA

Traditional Backcross (without markers)



Marker-Assisted Backcross



1. Select for the donor target gene/region
2. Select for progeny that have crossovers near the desired trait gene => Introgression of reduced donor DNA segment
3. Very fast recovery of recurrent parent

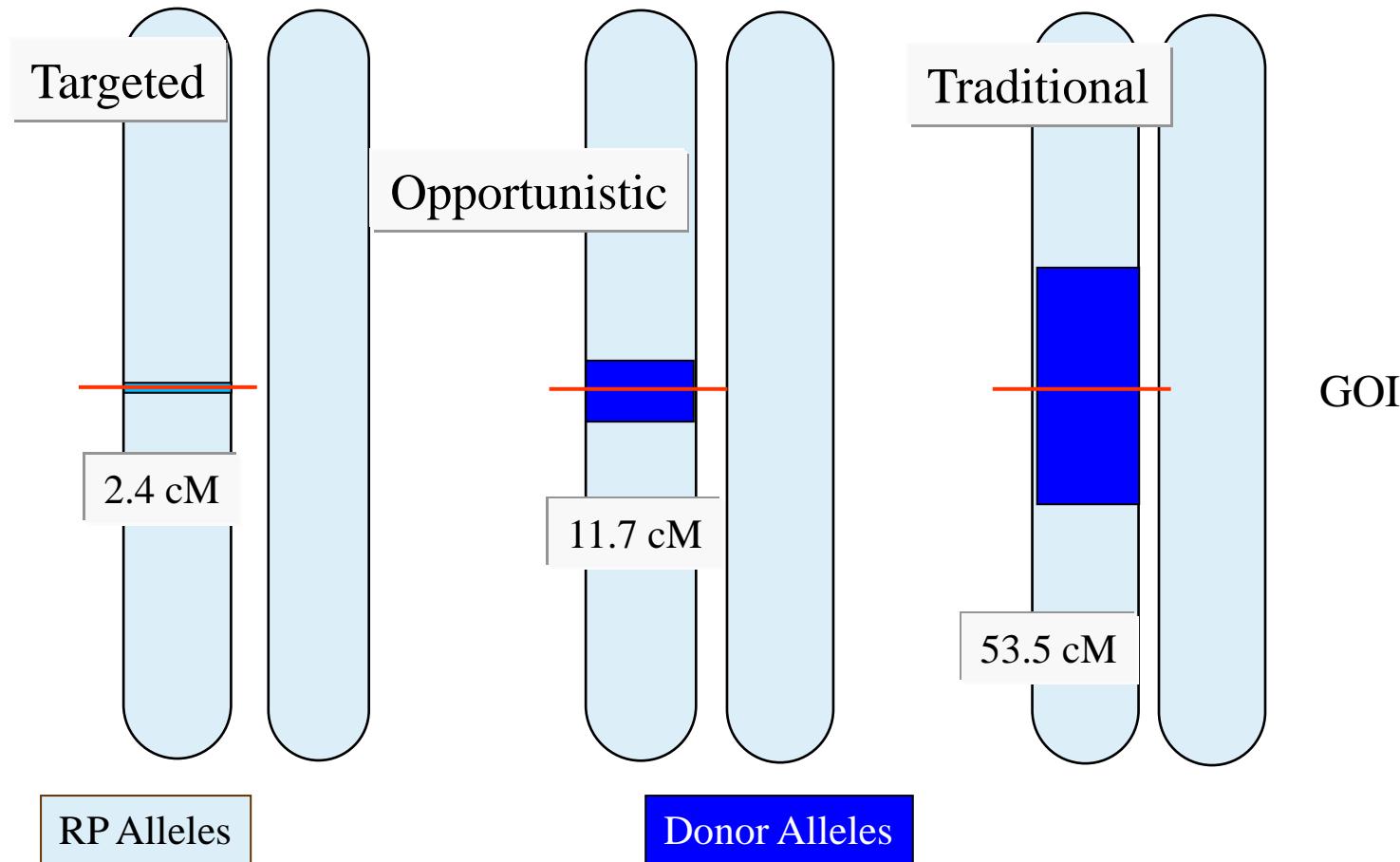
➤ 1-2 year
development
time savings

— DNA from the donor

Marker Assisted Backcross (MABC)

MABC on a chromosomal level

Donor Segment after 3 backcrosses



What is Genome Wide Selection (GWS)?

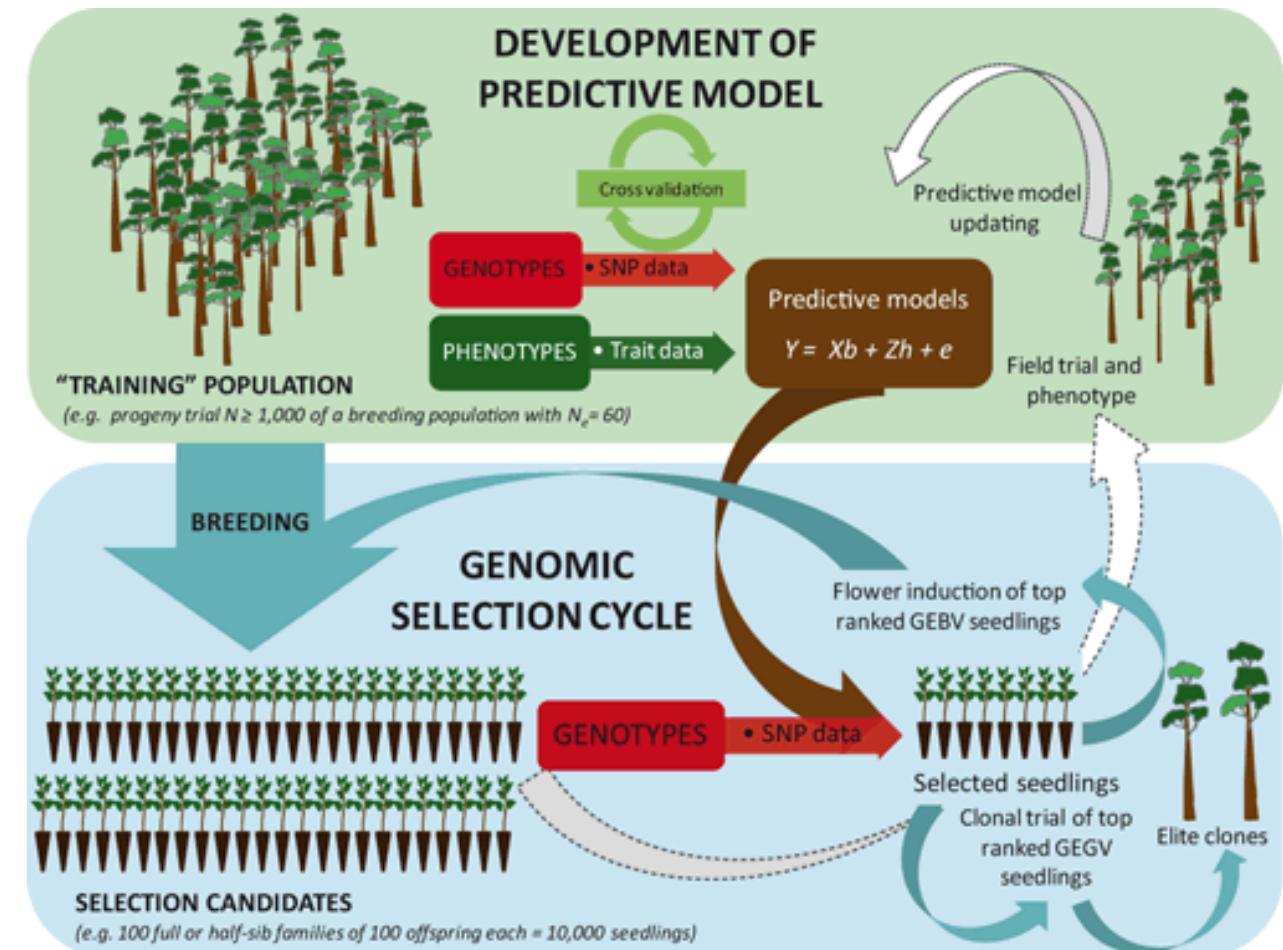
Selection based on genomic estimated breeding value (GEBV)

GWS

Genome wide selection or genomic selection is the selection using genetic evaluation from the whole genome marker-based model.

Pros: improve genetic gain, save resources, works well with complex traits contributed by many small effects

Cons: model accuracy depends on the relationship between training set and prediction set, reduce diversity quickly



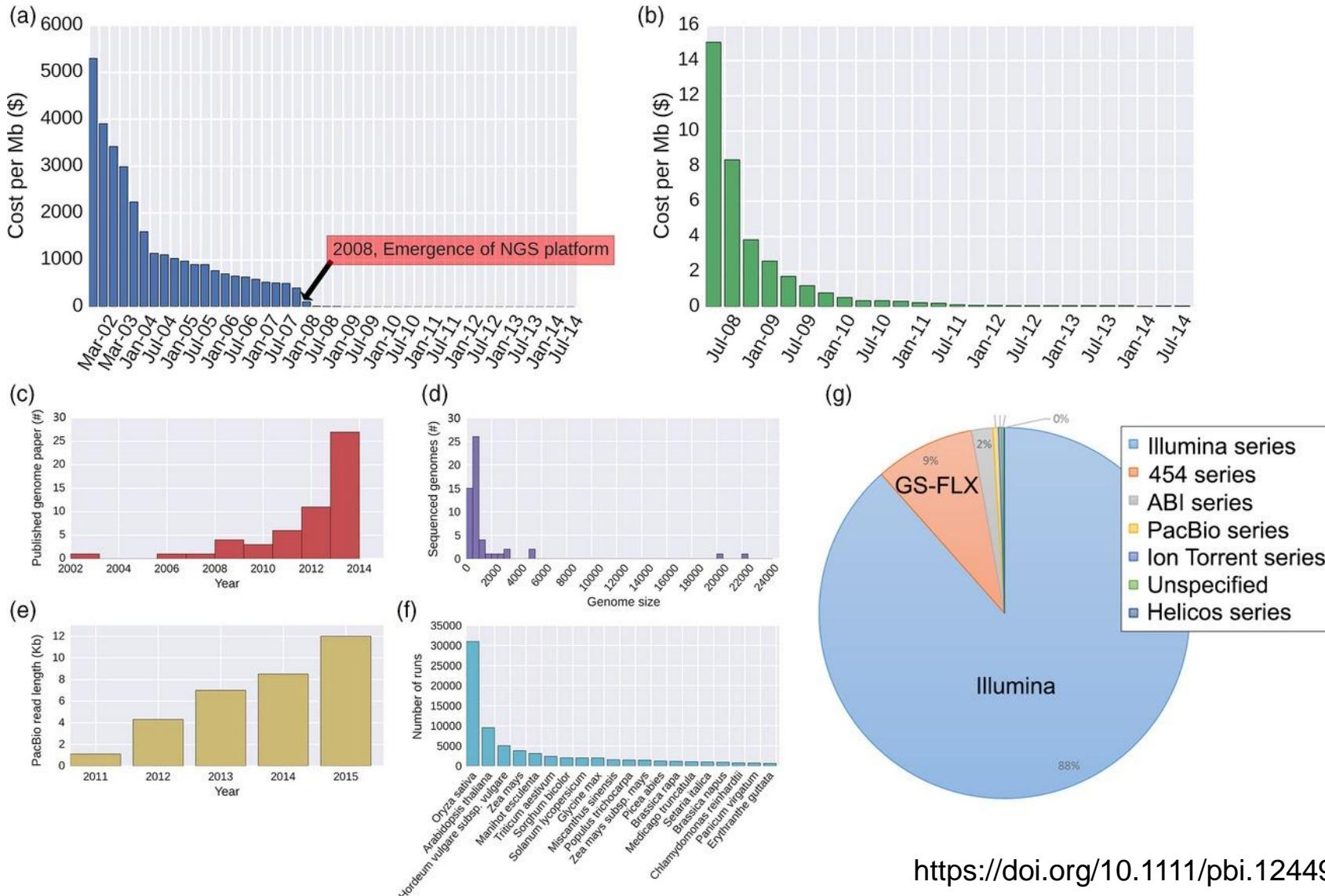
Source: https://doi.org/10.1007/978-94-007-7572-5_26



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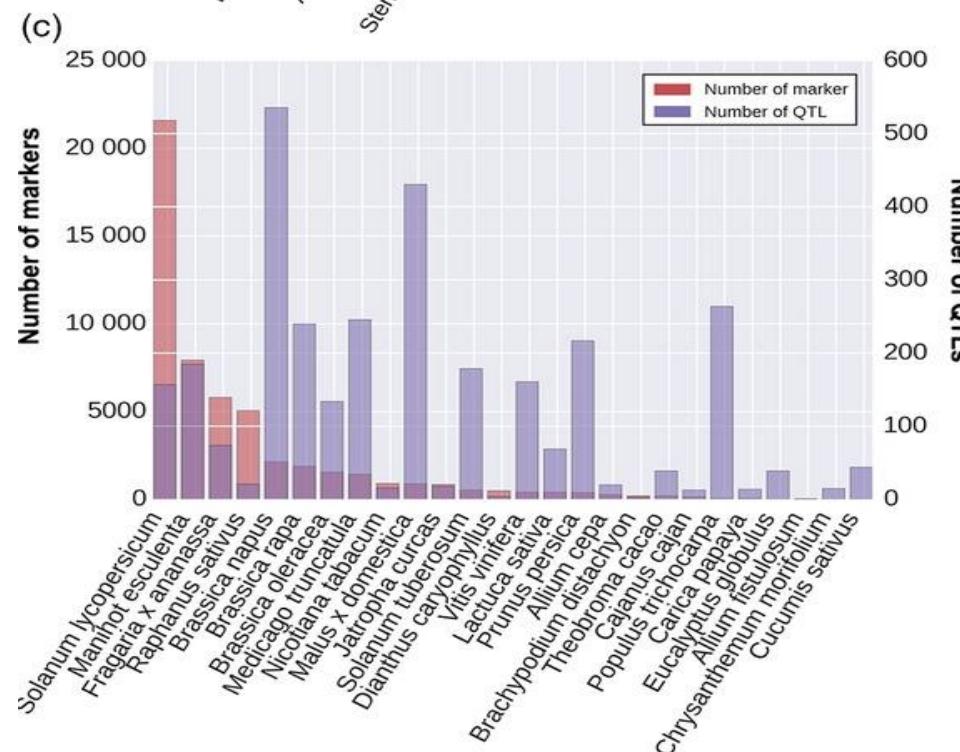
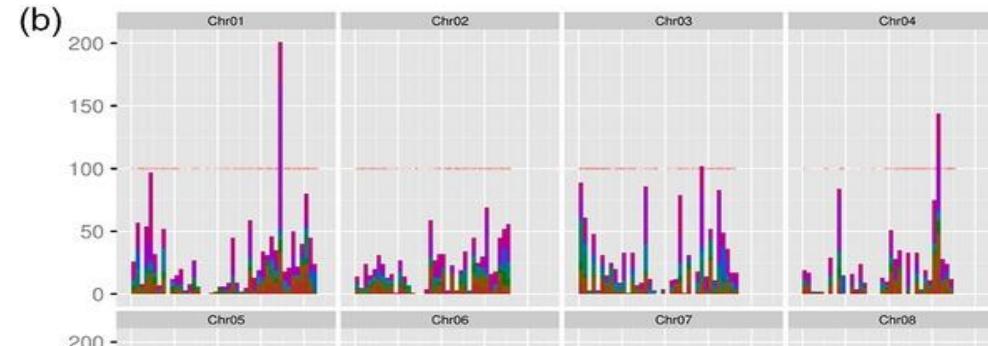
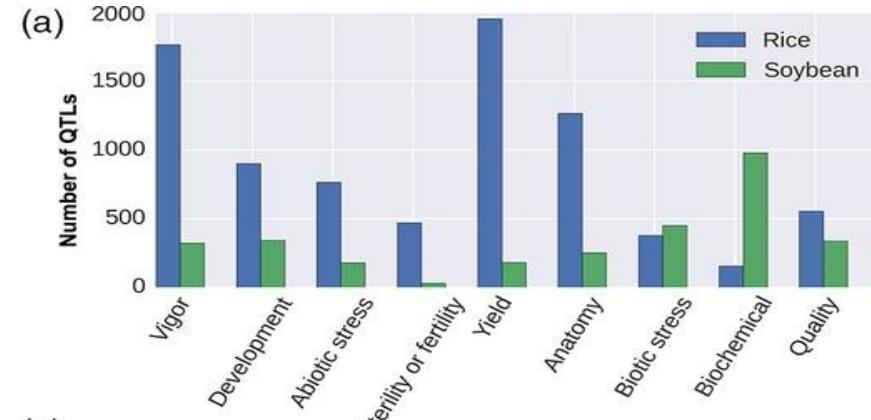
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Dramatic advances in genomics resources in recent decades



<https://doi.org/10.1111/pbi.12449>

Genomic resources that have been deposited in databases



<https://doi.org/10.1111/pbi.12449>



maizeGDB

MAIZE GENETICS AND GENOMICS DATABASE

[Chinese Version \(中文版\)](#) [Download](#)

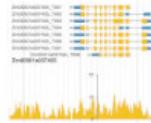


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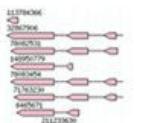
Welcome to MaizeGDB!

MaizeGDB is a community-oriented, long-term, federally funded informatics service to researchers focused on the crop plant and model organism *Zea mays*.

Quick Links



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[GBrowse](#)



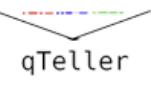
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[Downloads](#)



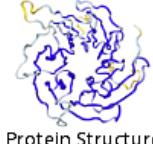
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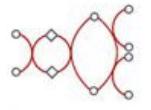
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Reference Assembly



[B73 ASSEMBLY](#)



[B73 ANNOTATION](#)



[ALL GENOMES](#)

[Common genome assembly/annotation tasks](#) | ▾

Contribute data

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@MaizeGDB Tweets



Nothing to see here - yet

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45

/// Bayer-Russia Molecular Markers Training// July 2023



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SoyBase Search HELP

[Advanced Search→](#)

Try pasting a list into the search box!

Examples: BARC-013845-01256 Satt531
Oil Glyma.15g026400

[Click Here For The Advanced Search Interface](#)

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Soybean Data Download Page

Quick Wm82 BLAST

This tool provides a way to BLAST a sequence against the Wm82.a4.v1 coding or protein sequence databases. More options and databases are available in the Full BLAST page. Only blastn and blastp programs are available here

Enter sequence below in FASTA format.

[Full BLAST→](#)

Or load an Example Sequence.

[Clear Sequence](#)

[Click Here For The Full BLAST Interface](#)

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[Linkage Group](#) -OR- [Chromosome](#)

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SoyBase News

2023 Southern Soybean Breeders Tour

June 30 2023

The Sourthern Soybean Breeder's Tour is a unique opportunity to visit multiple local breeding programs and develop collaborations across the soybean breeding industry. The USDA-ARS Soybean & Nitrogen Fixation Research Unit will host the 2023 Southern Soybean Breeder's Tour in Raleigh, NC, from September 5-7, 2023. More details are available on the [registration website](#).

[•Read More](#)

New genomes added to SoyBase

April 26 2023

3 new *G. soja* genomes have been added to the SoyBase [download page](#). The GRIN accessions PI 549046, PI 562565 and PI 578357 genomes, CDS and protein sequences are now available for download.

[•Read More](#)

4 *Glycine max* genomes added to the SoyBase download page

April 18 2023

[•Read More](#)

Registration for Soy2023 is open

March 28 2023

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Soybean Breeders Workshop Favorite Tool

March 13 2023

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Job announcements posted on SoyBase

February 26 2023

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Seed Micro-Dissection Data Added to SoyBase Expression Explorer

February 03 2023

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Summer 2023 Research and Extension Experiences for Undergraduates

January 25 2023

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Upcoming Meetings

National Association of Plant Breeders 2023

Date: 7-16-2023 TO 7-19-2023

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ASPB Plant Biology 2023

Date: 8-5-2023 TO 8-9-2023

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CerealsDB

Tools for the analysis of the wheat genome.

Home Axiom® KASP iSelect TaqMan® DArT Markers Webtools Wheat Sequence TGbyS Publications

Welcome to CerealsDB

This website, created by members of the Functional Genomics Group at the University of Bristol, is aimed at those who information regarding Single Nucleotide Polymorphism (SNP) in the genomes of bread wheat (*Triticum aestivum*) and

These resources are available as an on-line, searchable database. Via this website and associated publications, we hope to data related to each and every SNP, including available flanking sequences (usually 120 base pairs or greater), in the hope that by making this information freely available without restriction, it will encourage other wheat geneticists to do

Wheat development

[This link](#) takes you to the wheat development pages of the WheatBP website which is no longer actively maintained.

SNP databases

The information regarding SNP markers is grouped according to genotyping platform:

Axiom® 820K and 35K SNP Arrays

Along with researchers at Affymetrix, we have developed both an 820K and a 35K feature wheat SNP array. The code (Affymetrix code, Bristol SNP code and probe sequence containing the SNP ambiguity code) can be downloaded from

KASP probes

We have optimised KASP technology to develop a SNPs database for wheat.

iSelect Array

The iSelect Array contains over 80,000 SNP loci of which 44,000 have been mapped.

TaqMan® probes

In a partnership with [Life Technologies \(Thermo Fisher Scientific\)](#) we have designed a collection of 4,800 TaqMan® varietal markers within the wheat genome.

Agronomically important SNPs (flowering time)

A set of SNPs markers developed as part of the [ADAPTWHEAT project](#) can be viewed [here](#).

Downloadable genome sequence reads

Over 85 gigabases of genomic, 454 sequences (equivalent to 5x genome coverage) of the wheat cultivar 'Chinese Spring' is available to download.

Draft genome assembly

A draft wheat genome assembly based on 5x coverage of 454 reads can be [BLAST searched](#). Alternatively, the raw 454 reads may be searched using the same link.

IPK Galaxy Blast Suite

[Home](#) [Introduction](#) [Blast DBs](#) [Tutorials](#)

Welcome

Webblast Galaxy as part of the IPK Crop Analysis Tools Suite (CATS) offers access to genomic references published by IPK and collaborative projects. It replaces the late viroblast application.



Galaxy is an open source, web-based platform for data intensive biomedical research. If you are new to Galaxy start [here](#) or consult our help resources.



The consortium hosts 40+ database with 200+ members



AgBioData

Toward enhanced genomics, genetics, and breeding research outcomes through standardization of practices and protocols across agricultural databases

Home Community ▾ About Us ▾ Databases ▾ Meetings ▾ Projects ▾ Working Groups ▾ Login

Databases

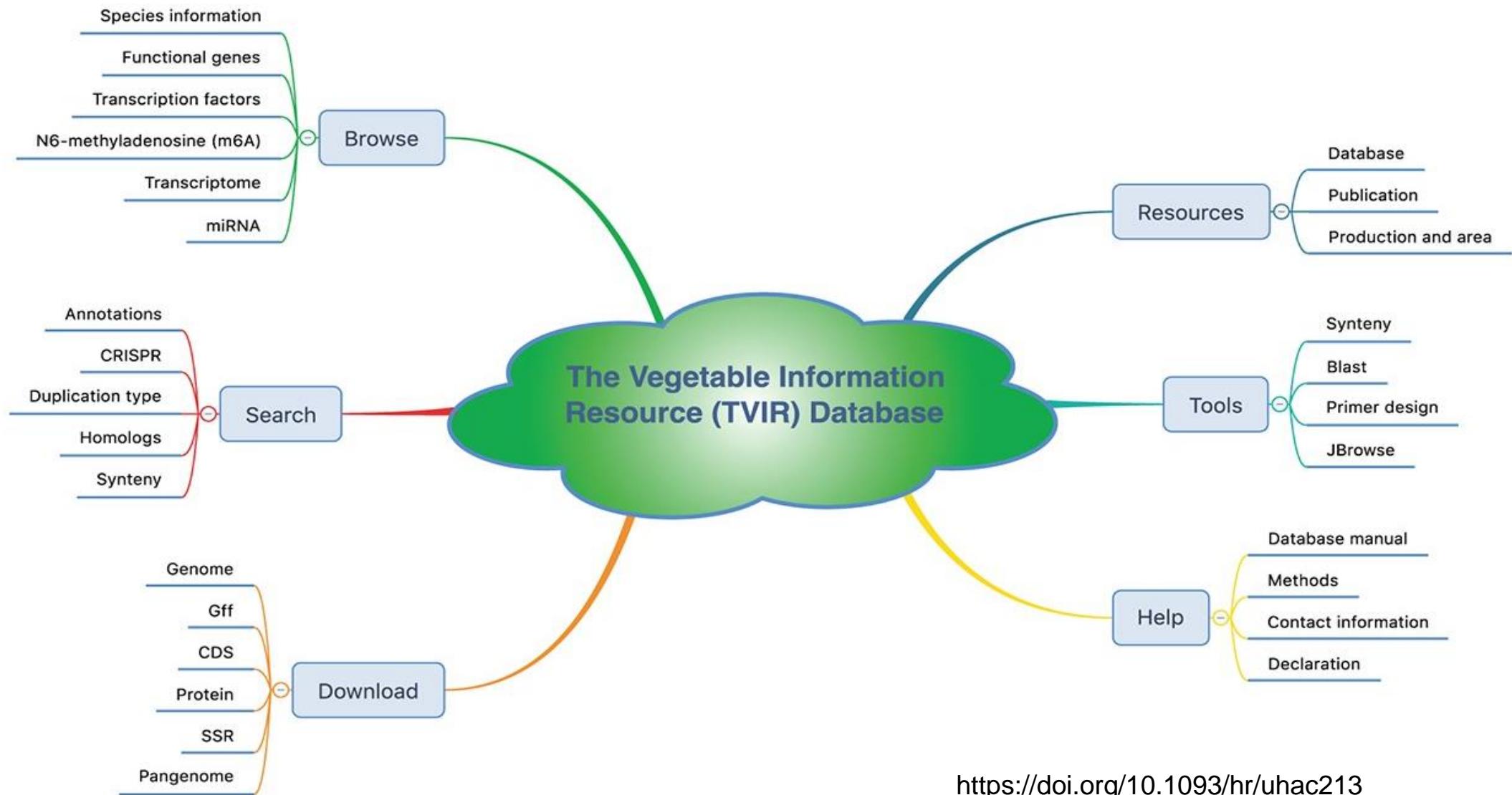
List of the agricultural biological databases involved with the AgBioData consortium.

Name ▾	URL	Contact
Agbase	https://agbase.arizona.edu/	Fiona McCarthy
AgroPortal	http://agroportal.lirmm.fr/	Clement Jonquet
Alfalfa Breeders Toolbox	https://medicago.legumeinfo.org/	Andrew Farmer
Animal QTDb	http://www.animalgenome.org/cgi-bin/QTDb/index	James Reecy
Bovine Genome Database	http://bovinegenome.org/	Christine Elsik
CassavaBase	https://www.cassavabase.org/	CassavaBase
Citrus Genome Database	https://www.citrusgenomedb.org/	Dorrie Main
Citrus Greening	https://www.citrusgreening.org/	Surya Saha
CottonGen	https://www.cottongen.org/	Dorrie Main
Crop Ontology	https://cropontology.org/	Elizabeth Arnaud
Cucurbit Genomics	http://cucurbitgenomics.org/	Zhangjun Fei
CyVerse	http://www.cyverse.org	Jason Williams
EBS (Enterprise Breeding System)	https://ebs.excellenceinbreeding.org/	Elizabeth Jones
Ensembl	https://useast.ensembl.org/index.html	Peter W. Harrison
FAANG	https://data.faang.org/home	Peter W. Harrison
Genome Database for Rosaceae	https://www.rosaceae.org/	Dorrie Main

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/// Bayer-Russia Molecular Markers Training// July 2023

Overview of vegetable genome sequencing and TVIR database



<https://doi.org/10.1093/hr/uac213>

Overview of the database with main interfaces and internal features

Home

The Home page displays a banner image of tomatoes, followed by three statistical charts: Functional genes, N6-methyladenosine, and Transcription factors. Below these are sections for Anthocyanin genes, Allium cepa (Total: 23), and Apium graveolens (Total: 19).

Browse

The Browse page shows a grid of vegetable species with their respective genome, gff, cos, protein, and SSR data.

Search

The Search page includes a search interface for ortho/para homologs across various species, with results for Orthogroup OG0000001.

Download

The Download page provides links to established vegetable databases like Coriander Genome Database (COGB) and Brassica Database (BRAD).

Resources

The Resources page features a section titled "More and more vegetables have established database platforms. Here are some common vegetable databases collected, which can provide users with browsing and retrieval data."

Tools

The Tools page contains two main sections: "MCiscan" and "MCiscanX".

Help

The Help page includes a screenshot of the search interface with annotations: (1) Select the required search type to realize cross species search; (2) Click on the number to view specific information.

<https://doi.org/10.1093/hr/uhac213>



Bayer Russia Molecular Marker Training: Concept Review

- 1 Genetic Inheritance
- 2 Modern Quantitative Genetics
- 3 Mapping Quantitative Trait Loci (QTLs)
- 4 Foundational Genomics
- 5 Molecular Breeding Workflows
- 6 Public Resources for row and vegetable crops
- 7 **Bayer's insight into workflows across crops**



Portfolio of genomics platforms support Bayer's row crop and vegetable breeding programs



Row Crops

Genomics Platform	Application
Single Marker Taqman	Trait integration, QAQC, Purity, Trait verification
Medium density Genotyping by Sequencing (GBS)	Genetic evaluation, Discovery
High density Fingerprinting (FP)	Origin design, Discovery, Haplotype
Resequencing	Novel polymorphism discovery, Haplotype



Vegetables

Crops may use all or some of the genomic platforms depending on breeding objectives, complexity of genome, and foundational genomics

Imputation

- // GWS requires high density markers
 - // 1000s
- // Genotyping with fewer markers with analysis at HD density
 - // Cost effective
- // Imputation implemented
 - // Now need to automate digital workflow to scale

Reference
High Density (HD)

0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	1	1	1	1	1	0	0	1	0	0	1	1	1
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0	1
0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	0	1	1	0	0	1	1	1	0	1	1	1	0
0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0	1
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0
0	0	0	0	1	1	0	0	1	1	1	1	1	1	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

Selection candidates

Medium Density

1	?	?	?	1	?	1	?	0	2	?	?	2	?	0	0
0	?	?	?	2	?	2	?	0	2	?	?	2	?	0	0
1	?	?	2	?	2	?	0	2	1	?	?	2	?	0	0
1	?	?	2	?	1	?	1	2	2	?	?	2	?	0	0
2	?	?	2	?	2	?	1	2	1	?	?	2	?	0	0
1	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	1	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	0
2	?	?	?	2	?	2	?	0	2	1	?	?	2	?	0
1	?	?	?	0	?	0	?	1	2	1	?	?	1	?	0

Inferred HD

Marchini and Howie 2010 Nat Rev Genet 11:499

- // Imputation infers missing marker genotypes in lines genotyped at low/medium density (300 to 2000 markers) with lines genotyped at high density (several 1000s of markers).
- // Makes use of haplotype structure



Q&A Discussion





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