AgBioData SGV

Towards Standards for Biocuration & Interoperability of Genetic Variation Data

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Cold Spring Harbor Laboratory

Standards for Genetic Variation Working Group
AgBioData Consortium

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Genotyping at our Finger Tips - DIY SNP Kits

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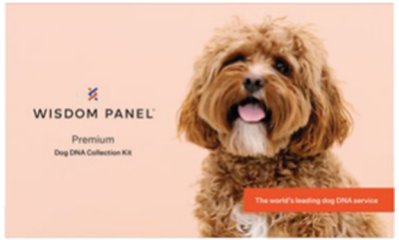

Increased number & quality of plant genome assemblies

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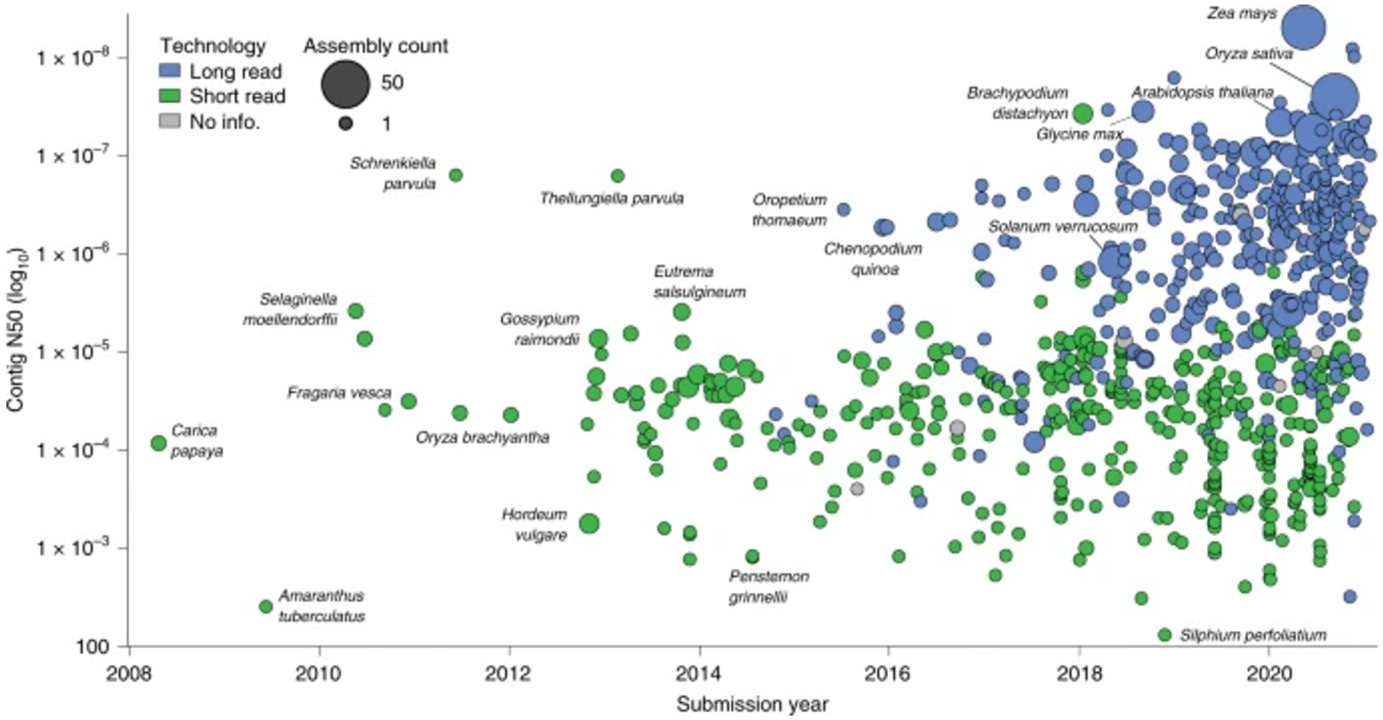

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Marks et al (2021). *Nat. Plants*. doi: 10.1038/s41477-021-01031-8

AgBioData Standards for Genetic Variation WG

AgBioData SGV

Chair: Doreen Ware

Co-Chair: Timothee Cezard

Members:

- Alexey Sokolov
- Andria Harkey
- Doreen Ware
- Emily Grau
- Kazim Wazir
- Kelly Vining
- Marcela K. Tello-Ruiz
- Mazdak Salavati
- Melanie Harrison
- Nahla Bassil
- Rajdeep S. Khangura
- Sarah Dyer
- Sebastian Beier
- Sharon Wei
- Shaun Clare
- Vivek Kumar
- Yogendra Khedikar

Past members:

- Tao-Ho Chang (Rice)

For more information, visit https://www.agbiodata.org/working_groups/sgv

AgBioData SGV Working Group Goals

AgBioData SGV

- Support the harmonization and adoption of standards for genetic variation (GV) data from various platforms in Plants & Animals
- Bring together a community of data providers, biocurators & computer scientists to promote interoperability and access to GV datasets

https://www.agbiodata.org/working_groups/sgv

Standards for Genetic Variation Working Group

AgBioData SGV

- **Specific objectives**:
  - Enable sharing of GV data to support agriculture
  - Identify existing GV and technical barriers for data exchange
  - Review technical standards for GV to support adoption
  - Review GV workflows
  - Engage community to support ingestion and usability of GV data into community and archival resources

- **Activities**:
  - Regular monthly meetings (break July-September)
  - Biocurators & smaller group meetings
  - AgBioData annual workshop
  - Community surveys
  - Webinar “Biocurating Genetic Variation” (8 speakers)

AgBio Community Surveys

AgBioData SGV

Goals:

- Identify existing & anticipated GV data sets for agriculturally important species
- Identify challenges & propose solutions for data integration & interoperability
- Recruit WG members

Live Poll - Feb 2022 (15 participants)

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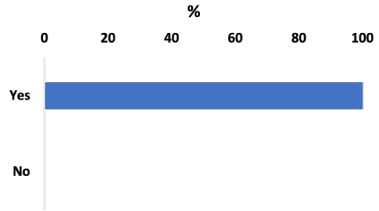
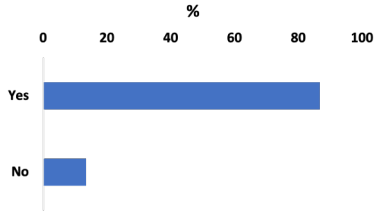
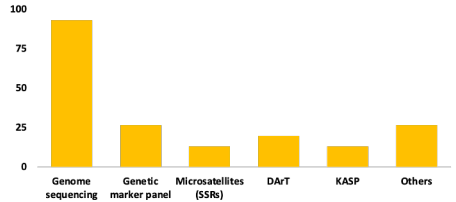
- Are you aware of/or working on genetic variation?



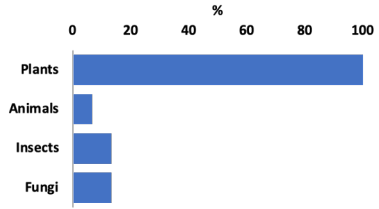
- Is there a community resource to host your GV data?



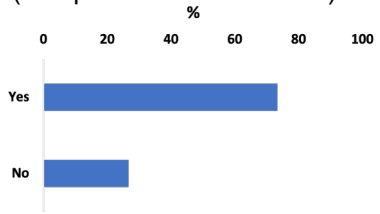
- If generating the data what type of technology are you using?



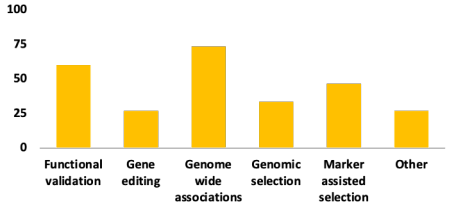
- What type of species are you working on?



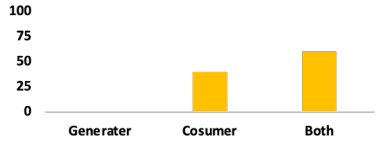
- Have you heard of the EVA (European Variation Archive)?



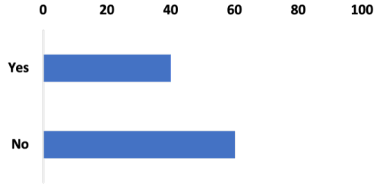
- What are you using the genetic variation information for?



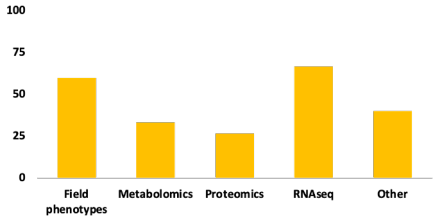
- Are you a data generator, consumer or both?



- Are there standards to name samples (i.e., standard identifiers) for your species community(ies)?



- What other data types are you generating from the same germplasms/biosamples?



Survey - Feb. 2022 (11 participants)

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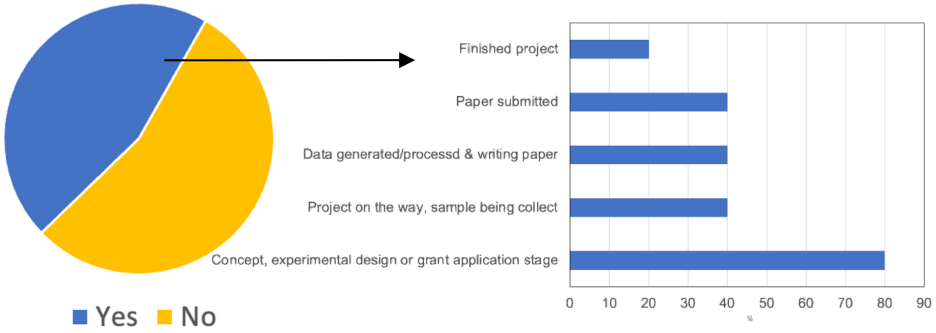
Generate or process variation data that could be submitted to EVA



Interest in specific data types

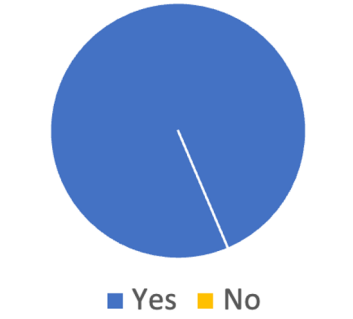
53%
Variant definitions found in one species (clustered variant or #rs)

27%
Variant definitions found in one study (submitted variant or #ss)

20%
Genotype of allele frequencies found in one study

Interest in a Biocuration Workshop to support processing and submitting variation data?

Interest in using data already served by EVA?



Preference to access data

37.5% Query and search through the Website

31% Bulk download via FTP

31% Programmatic access via the REST APIs

Preliminary Survey - Jan. 2023 (14 responses)

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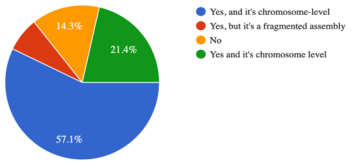
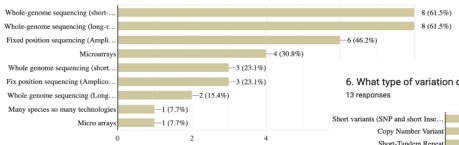
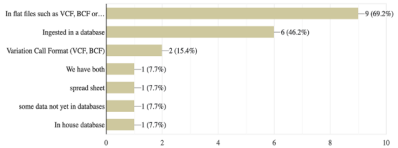
3. Does your species of interest usually have a reference assembly ?
14 responses



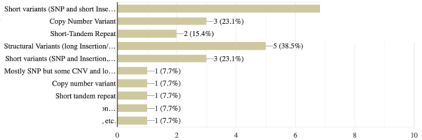
5. What type of technologies are used to generate the variation data ?
13 responses



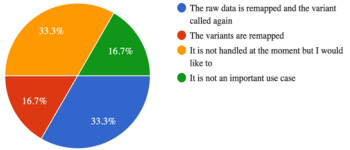
8. How do you keep your variation data ?
13 responses



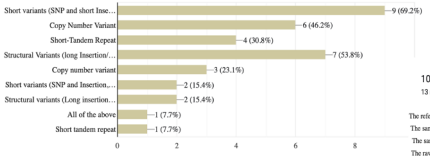
6. What type of variation data are you storing ?
13 responses



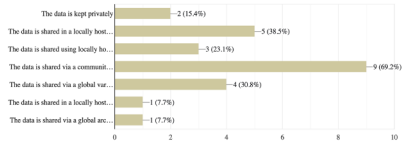
13. If the reference genome changes, how do you handle the update ?
12 responses



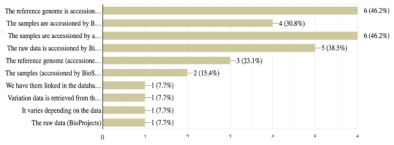
7. What type of variation data are you interested in storing in the future ?
13 responses



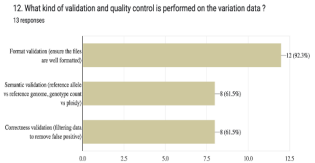
9. How do you share or plan to share your variation data?
13 responses



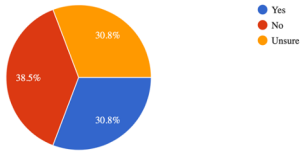
10. Is the variation data linked to other accessioned data ?
13 responses



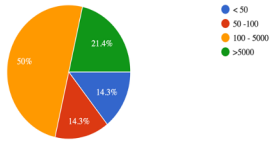
12. What kind of validation and quality control is performed on the variation data ?
13 responses



14. Are there stable variant identifiers associated with the variation data you hold ?
13 responses



11. How many individuals are you working with ?
14 responses



15. Are you interested in participating in the SGV working group?
11 responses

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Biocurating Ag Genetic Variation

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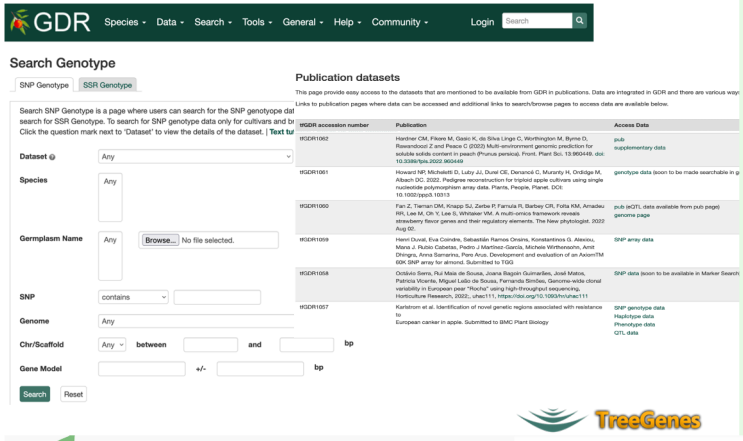
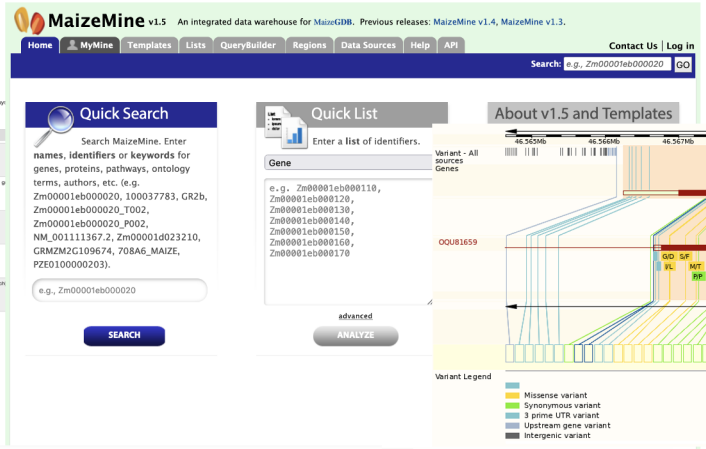
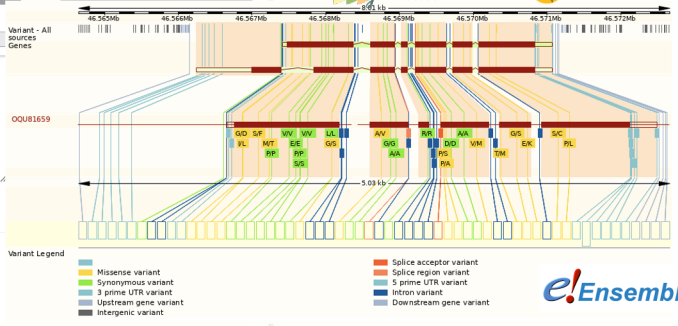
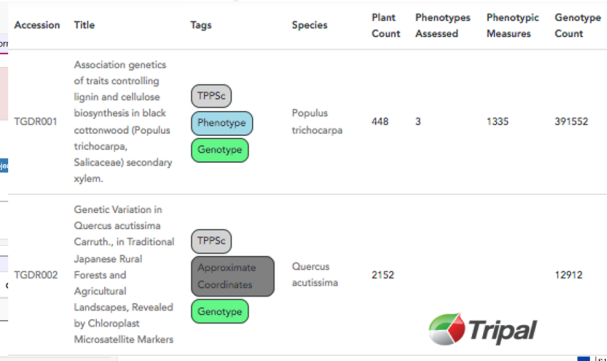
1. GDR (CottonGen, GDV, CGD, PCD) - Sook Jung
2. BreedBase (SGN, CassavaBase, YamBase, SweetPotatoBase, MusaBase) - Lukas Mueller
3. MaizeGDB - Carson Andorf by proxy
4. NCGR Corvallis - Nahla Bassil
5. TreeGenes - Emily Grau
6. TAIR - Tanya Berardini/Leonore Reiser
7. InterMine (MaizeMine, Bovine Genome Database, FAANGMine, Hymenoptera Genome DB) - Chris Elsik by proxy
8. Gramene / Ensembl Plants & SorghumBase - Marcela K. Tello-Ruiz

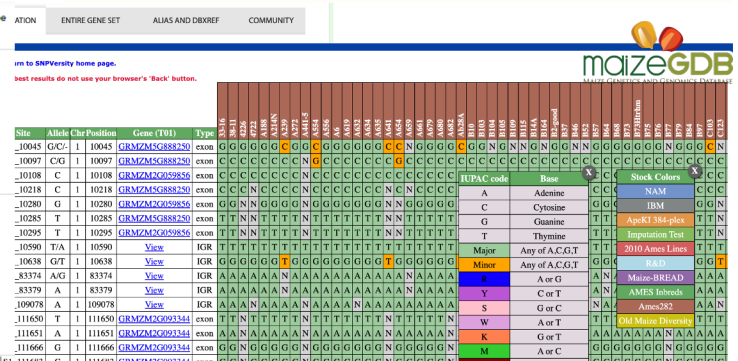
Biocurating Ag Genetic Variation











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Challenges associated with genetic variation

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- All data has a lifecycle. It can become stale & could be reused
- Different versions of an assembly (quality & stability)
  - Remapping to a newer assembly may result in reduced precision & data loss
  - Raw data *vs* processed data
  - Availability & quality of data sets for clustering
- Moving from a single reference to a PanGenome
- Improvements in assays and algorithms to determine GV (GBS, WGS, etc.)
- Converting from SSRs to SNPs
- Integration between studies (new studies, meta-analyses, etc.)
  - Sample identifiers

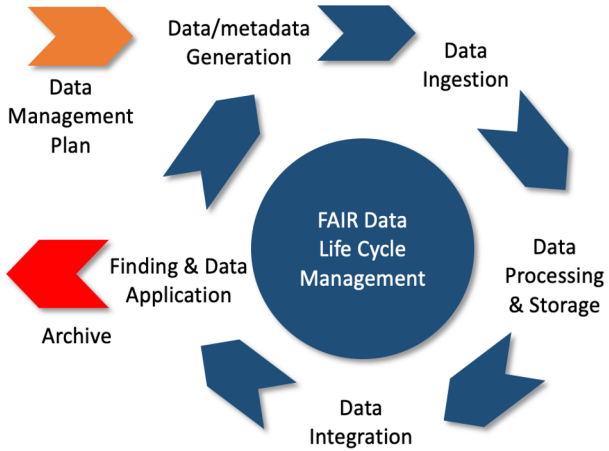

Image credit: FAIRToolkit

Central repositories for genetic variation

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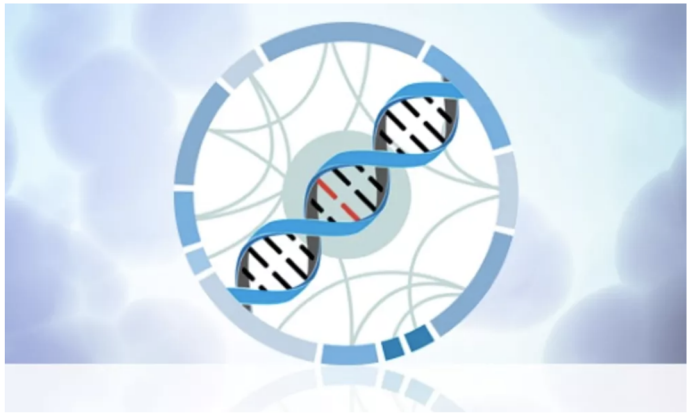
EVA issues long-term IDs for non-human variants

Since Sept. 2017



The European Variation Archive: freely available data on genetic variation

Summary

- New agreement between the NCBI and EMBL-EBI shares responsibility for managing data from genetic variation experiments worldwide.
- From September 2017, EMBL-EBI's European Variation Archive (EVA) will issue locus accession numbers (Reference SNP, rs#) for all non-human

The European Variation Archive: a FAIR resource of genomic variation for all species

Timothe Cezard, Fiona Cunningham, Sarah E Hunt, Baron Koylass, Nitin Kumar, Gary Saunders, April Shen, Andres F Silva, Kirill Tsukanov, Sundararaman Venkataraman ... Show more

Nucleic Acids Research, Volume 50, Issue D1, 7 January 2022, Pages D1216–D1220, https://doi.org/10.1093/nar/gkab960

Published: 28 October 2021 **Article history** ▾

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Abstract

The European Variation Archive (EVA; https://www.ebi.ac.uk/eva/) is a resource for sharing all types of genetic variation data (SNPs, indels, and structural variants) for all species. The EVA was created in 2014 to provide FAIR access to genetic variation data and has since grown to be a primary resource for genomic variants hosting >3 billion records. The EVA and dbSNP have established a compatible global system to assign unique identifiers to all submitted genetic variants. The EVA is active within the Global Alliance of Genomics and Health (GA4GH), maintaining, contributing and implementing standards such as VCF, Refget and Variant Representation Specification (VRS). In this article, we describe the submission and permanent accessioning services along with the different ways the data can be retrieved by the scientific community.

Submission process through EVA

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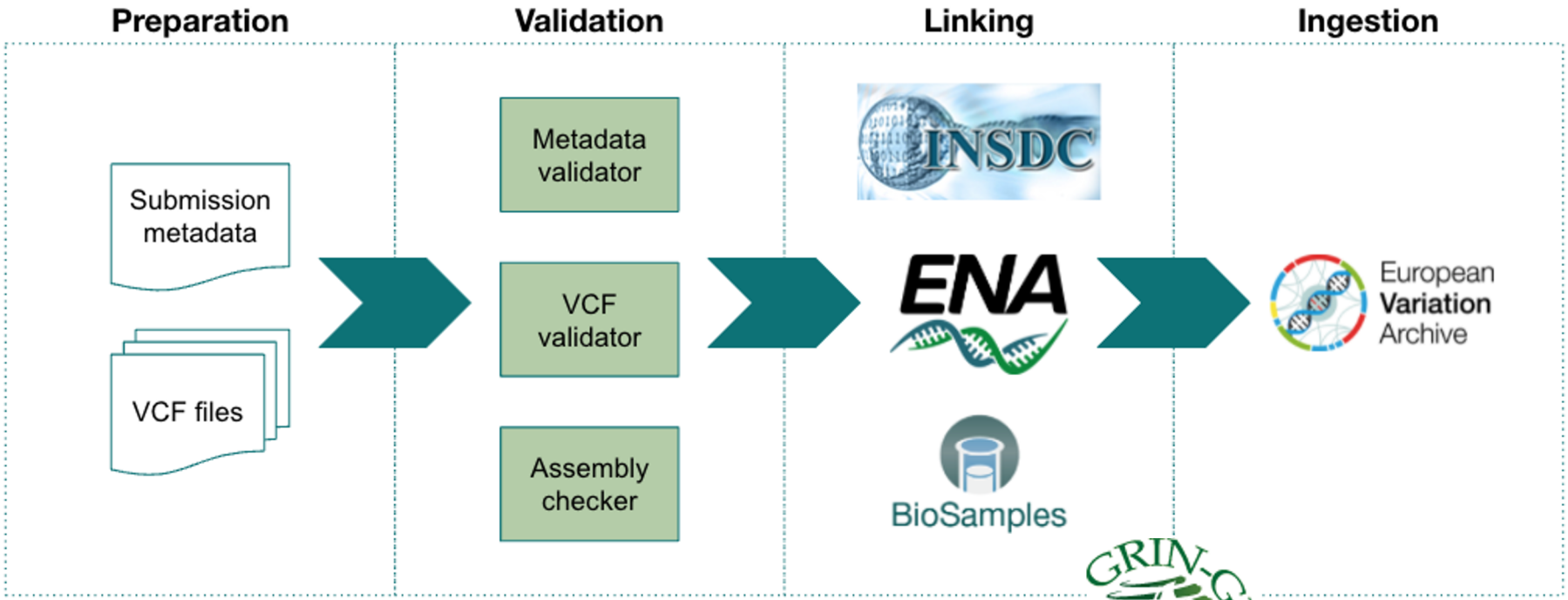

Slide courtesy of EVA

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Genetic variation data - Standard file format

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Variant Call Format (VCF)

```
##fileformat=VCFv4.3
##fileDate=20090805
##source=myImputationProgramV3.1
##reference=file:///seq/references/1000GenomesPilot-NCBI36.fasta
##contig=<ID=20,length=62435964,assembly=B36,md5=f126cdf8a6e0c7f379d618ff66beb2da,species="Homo sapiens",taxonomy=x>
##phasing=partial
##INFO=<ID=NS,Number=1,Type=Integer,Description="Number of Samples With Data">
##INFO=<ID=DP,Number=1,Type=Integer,Description="Total Depth">
##INFO=<ID=AF,Number=A,Type=Float,Description="Allele Frequency">
##INFO=<ID=AA,Number=1,Type=String,Description="Ancestral Allele">
##INFO=<ID=DB,Number=0,Type=Flag,Description="dbSNP membership, build 129">
##INFO=<ID=H2,Number=0,Type=Flag,Description="HapMap2 membership">
##FILTER=<ID=q10,Description="Quality below 10">
##FILTER=<ID=s50,Description="Less than 50% of samples have data">
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
##FORMAT=<ID=GQ,Number=1,Type=Integer,Description="Genotype Quality">
##FORMAT=<ID=DP,Number=1,Type=Integer,Description="Read Depth">
##FORMAT=<ID=HQ,Number=2,Type=Integer,Description="Haplotype Quality">
#CHROM POS     ID        REF ALT     QUAL FILTER INFO                              FORMAT      NA00001        NA00002        NA00003
20     14370   rs6054257 G   A       29   PASS   NS=3;DP=14;AF=0.5;DB;H2           GT:GQ:DP:HQ 0|0:48:1:51,51 1|0:48:8:51,51 1/1:43:5:.,.
20     17330   .         T   A       3    q10    NS=3;DP=11;AF=0.017               GT:GQ:DP:HQ 0|0:49:3:58,50 0|1:3:5:65,3   0/0:41:3
20     1110696 rs6040355 A   G,T     67   PASS   NS=2;DP=10;AF=0.333,0.667;AA=T;DB GT:GQ:DP:HQ 1|2:21:6:23,27 2|1:2:0:18,2   2/2:35:4
20     1230237 .         T   .       47   PASS   NS=3;DP=13;AA=T                   GT:GQ:DP:HQ 0|0:54:7:56,60 0|0:48:4:51,51 0/0:61:2
20     1234567 microsat1 GTC G,GTCT  50   PASS   NS=3;DP=9;AA=G                    GT:GQ:DP    0/1:35:4       0/2:17:2       1/1:40:3
```

Meta-info lines

Header lines + Sample IDs
Data lines + Genotypes

Genetic variation metadata standards

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EVA metadata submission template

V1.1.4 August 2020

The aim of this sheet is to facilitate effective completion of this template.

The minimum information required to be completed in this template in order for data to be submitted to EVA is: Submitter details, project information, at least data on 1 sample, analysis details, and file entries.
However, we encourage our users to submit as much meta-data as possible. Increased metadata creates much greater visibility of your data and research in our search and analysis platforms. Additionally, such information allows for e

Please email all questions and feedback to eva-helpdesk@ebi.ac.uk

This template is grouped into four sections, split into worksheets. Each worksheet is preceeded by an "HELP" sheet which provides more information and instructions for each column.

Worksheet	Explanation
Submitter Details	This sheet captures the credentials of the submitter.
Project	The objective of this sheet is to gather general information about the Project including submitter, submitting centre, collaborators and publications.
Sample	Projects consist of analyses that are run on samples. We accept sample information in the form of BioSample, ENA or EGA accession(s). We also accept BioSamples sampleset accessions. If your samples a sample(s)" sections of the Sample(s) worksheet to have them registered at BioSamples.
Analysis	For EVA, each analysis is one vcf file, plus an unlimited number of ancillary files. This sheet allows EVA to link vcf files to a project and to other EVA analyses. Additionally, this worksheet contains experimer Important to note; one project can have multiple associated analyses.
Files	Filenames and associated checking data associated with this EVA submission should be entered into this worksheet. Each file should be linked to one, or more, analysis. We accept VCF files along with thei

Each worksheet contains a number of fields -
Completion of the remaining highlighted in **BOLD** is **REQUIRED**. **GREEN** indicates **EITHER/OR** requirement.
Completion of the remaining fields is optional, however please provide as much information as you can and avoid the use of non-ASCII characters in any fields.
An example of a completed template suitable for EVA submission is available at our website (www.ebi.ac.uk/eva/)

EU-FONDUE recommendations data standards for plants

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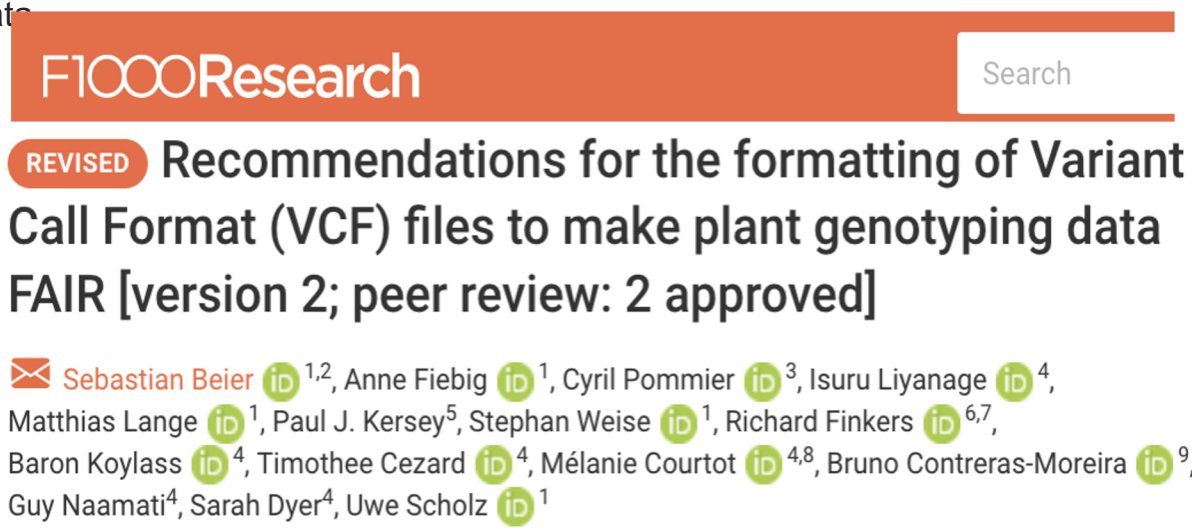
- FONDUE: FAIR-ification of Plant Genotyping Data and its linking to Phenotyping using ELIXIR Platforms
- First guidelines on FAIR handling of GV data published in 2022
- Support data submission to BioSamples & EVA by providing a checklist to classify and validate the data



elixir

doi: 10.12688/f1000research.109080.2

Summary of recommendations for plant metadata formatting

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BioSamples

Table 1. **Summary of recommendations for metadata formatting.**

Metadata field	Definition	Format	Example	Cardinality
##fileDate	Creation date of the VCF file	Date (ISO 8601, YYYYMMDD)	##fileDate=20120921	1
##bioinformatics_source	Chains of bioinformatics tools for creating the VCF file	URL, DOI	##bioinformatics_source="doi.org/10.1038/s41588-018-0266-x"	1
##reference_ac	Accession number of reference genome assembly used in the VCF file	/[(GCA/GCF)_(d){9}\.(0-9)*]/	##reference_ac=GCA_902498975.1	1
##reference_url	URL of the reference genome assembly used in the VCF file	URL, DOI	##reference_url="ftp.ncbi.nlm.nih.gov/genomes/all/GCA/902/498/975/	1
##SAMPLE	Metadata about a single sample genotype that is part of the genotyping experiment in the VCF file	Composite (see below)	##SAMPLE=<ID=SAMEA104646767,DOI="doi.org/10.25642/IPK/GBIS/7811152">	1:N
	The primary identifier (BioSamples Database identifier) of the genotyping sample	/[(SAM)(E|N|D)(A|G)(\d+)]/	ID=SAMEA104646767	1
	The DOI of the genotyping sample (if available)	URL, DOI	DOI="doi.org/10.25642/IPK/GBIS/7811152"	0-1
	The external identifiers under which this genotyping sample is registered in other databases (either 'FAO-WIEWS_instcode:genus:accession_number' or 'DNS: database_identifier:identifier_scheme:identifier')	See Definition	ext_ID="DEU146:Hordeum:HOR 1361 BRG" or ext_ID="ipk-gatersleben.de:GBIS: akzessionId:7811152"	0:N

##SAMPLE	Metadata about a single sample genotype that is part of the genotyping experiment in the VCF file	Composite (see below)	##SAMPLE=<ID=SAMEA104646767,DOI="doi.org/10.25642/IPK/GBIS/7811152">	1:N
	The primary identifier (BioSamples Database identifier) of the genotyping sample	/[(SAM)(E|N|D)(A|G)(\d+)]/	ID=SAMEA104646767	1
	The DOI of the genotyping sample (if available)	URL, DOI	DOI="doi.org/10.25642/IPK/GBIS/7811152"	0-1
	The external identifiers under which this genotyping sample is registered in other databases (either 'FAO-WIEWS_instcode:genus:accession_number' or 'DNS: database_identifier:identifier_scheme:identifier')	See Definition	ext_ID="DEU146:Hordeum:HOR 1361 BRG" or ext_ID="ipk-gatersleben.de:GBIS: akzessionId:7811152"	0:N

elixir

Brier et al (2022). F1000Research. doi: 10.12688/f1000research.109080.2

Suggestions for plant samples meta by our WG

AgBioData SGV

1) Mandatory (1:N): Primary external identifier from major germplasm repository (e.g., GRIN, CGIAR, IPK, CNGB)
2) Recommended (0:N): Inventory or local number
3) Recommended (0:N): Identifier for the specific plant/genotype used in the study

Metadata field	Field Name	Definition	Format	Example	Cardinality
##SAMPLE		Metadata about a single sample genotype that is part of the genotyping experiment in the VCF file	Composite (see below)	##SAMPLE=<ID=SAMN04168247, DOI=doi.org/10.18730/NBYG*, ext_ID=grin-global.org:USA126:PI 276837>	1:N
	BioSample ID	Refers to a biological sample used as a 'reference' (e.g. to sequence its genome) or used in an assay database such as ENA, EVA, ArrayExpress. Always begin with SAM. The next letter is either E or N or D depending if the sample information was originally submitted to EMBL-EBI or NCBI or DDBJ, respectively. After that, there may be an A or a G to denote an Assay sample or a Group of samples. Finally, there is a numeric component that may or may not be zero-padded.	/([SAM)([ENDI)(A/G)(\d+)]/	ID=SAMN04168247	1
	External identifiers	- Primary accession - **One mandatory external ID for plants**. Impractical to enter metadata for each biosample; easier to add as a metadata line in VCF. Impractical for huge data sets as this would significantly increase the size of the VCF file. --- Source of accession [Genebank Name, Original Collection (not in genebank), etc.] Examples: GRIN, ICRISAT, WEIWS code:Species code (IPK), CNGB, GBIS, ORIGINAL COLLECTION --- Accession prefix. Examples: PI, IS, NSSL, GRIF, SOR, Collector ID --- Accession unique identifier or number. Example: six-digit PI number, five-digit IS number, four-digit following WEIWS:species number, collector number - Secondary accession - Sample inventory **if applicable**. Example: CR02, CR03, 07PL. Note: USDA germplasm repositories provide inventory accessions. - Other - Not necessary. Example: Population panel identifiers such as SAP-391, a member of the Sorghum Association Panel are not necessary and are well captured in germplasm registries like GRIN. Identifiers under which this genotyping sample is registered in other databases (either 'FAO-WIEWS_instcode:genus:accession_number' or 'DNS:database_identifier:identifier_scheme:identifier')	ext_ID=registry:identifier	ext_ID=grin-global.org:USA126:PI 276837	1:N
	Study sample identifier	Identifies specific plant/genotype used, **when available**. This will usually be specific to an individual research project and not publicly available. However, the plant or DNA sample may be shared between researchers. Different plant numbers from the same lot. Example: SC103 and SC103-14E share the same PI533752 accession.			0-1
	DOI, URL	DOI for the passport information of the genotyping sample.	URL, DOI	DOI=doi.org/10.18730/NBYG*	0-1

Biocurators meetings

FAANG guidelines for data submission

AgBioData SGV

Understanding the Genome to Phenome link in domesticated animals

The adoption and dissemination of metadata standards for animal genetic variants is relatively advanced. The FAANG online portal can manage metadata in the form of rule sets and provide tools for central validation, and links to public repositories (ENA, EVA).

Different databases are serving different purpose

AgBioData SGV

Central databases

- Long-term archiving of original files
- Accessioning
  - Study
  - Samples
  - Variants
- Update to newer genomes

ENA
European Nucleotide Archive

BioSamples

Community/species databases

- Integration between phenotypes and genotypes
- Tailored feature/toolsets

TreeGenes

BREEDBASE

maizeGDB
Maize Genetics and Genomics Database

SORGHUM BASE

Gramene

EnsemblPlants

Slide courtesy of EVA

Pilot projects based on readiness of the communities

AgBioData SGV

1. Species communities with high-quality reference assemblies in INSDC and GV data in other DBs (e.g., MaizeGDB, GDR, SolGenomics, CassavaBase, TreeGenes)
    - Support interoperability with community resources
    - Demonstrate added value in an archival resource
    - Triage use cases
2. Species with high-quality reference assemblies and population variation data sets without resources to host large GV data sets (i.e., germplasm centers, GRIN)
    - Support for species where infrastructure is not available, capacity building
    - Promote submission of reference assemblies to INSDC
    - FAIR access to data
3. Species developing GV data sets
    - Standards for community & capacity building
    - FAIR access to data

Summary of Outcomes

AgBioData SGV

- Surveys - Identified existing GV datasets, workflows and technical barriers for data exchange
- VCF & metadata for samples - Reviewed guidelines & made additional recommendations to support adoption

Next Steps

AgBioData SGV

Pilot projects - Engaging community to support ingestion and usability of GV data into community & archival resources

- Recruiting WG members
- Recruiting new communities for pilot projects
- Lowering the barrier for generating metadata
- Training materials and virtual hackathons

AgBioData survey

AgBioData SGV

Join our working group, take our survey, meet with us!

AgBioData SGV

Chair: Doreen Ware

Co-Chair: Timothee Cezard

Members:

- Alexey Sokolov
- Andria Harkey
- Doreen Ware
- Emily Grau
- Kazim Wazir
- Kelly Vining
- Marcela K. Tello-Ruiz
- Mazdak Salavati
- Melanie Harrison
- Nahla Bassil
- Rajdeep S. Khangura
- Sarah Dyer
- Sebastian Beier
- Sharon Wei
- Shaun Clare
- Vivek Kumar

Past members:

- Tao-Ho Chang (Rice)

AgBioData Booth #230

Sunday Opening, Monday lunch, Tuesday PM

PAG30