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GWAS Atlas: a curated resource of genome-wide variant-trait associations in plants and animals

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ABSTRACT

GWAS Atlas (https://bigd.big.ac.cn/gwas/) is a manually curated resource of genome-wide variant-trait associations for a wide range of species. Unlike existing related resources, it features comprehensive integration of a high-quality collection of 75 467 variant-trait associations for 614 traits across 7 cultivated plants (cotton, Japanese apricot, maize, rapeseed, rice, sorghum and soybean) and two domesticated animals (goat and pig), which were manually curated from 254 publications. We integrated these associations into GWAS Atlas and presented them in terms of variants, genes, traits, studies and publications. More importantly, all associations and traits were annotated and organized based on a suite of ontologies (Plant Trait Ontology, Animal Trait Ontology for Livestock, etc.). Taken together, GWAS Atlas integrates high-quality curated GWAS associations for animals and plants and provides user-friendly web interfaces for data browsing and downloading, accordingly serving as a valuable resource for genetic research of important traits and breeding application.

INTRODUCTION

Genome-wide association study (GWAS) is a key technique for exploiting the genetic basis of complex traits and diseases by detecting genotype-phenotype associations in a group of individuals or natural inbred lines (1). As a result, GWAS has been widely applied in model organisms, primarily in human (2,3) and Arabidopsis (4). Nowadays, with the rapid development of phenotyping and genotyping technologies, a number of high-quality genotype-phenotype associations have also been identified in plants and animals, including maize, rice, sorghum, cotton, soybean, goat, pig, etc. (5,6). Taking corn as an example, diverse traits ranging from molecular to cellular (i.e. metabolites) and from individual morphological scale (agronomic, yield or reproductive characteristics) to the interaction with different environmental factors (biotic or abiotic stress tolerance), have been comprehensively studied and associated with different genetic variants (5,7). Therefore, a resource that integrates GWAS associations, as well as their associated information, is of fundamental significance to systematically capture the whole picture of genotype-phenotype associations and improve our understanding of genetic architecture of complex quantitative traits.

Over the past decade, several resources, such as GWASdb (8,9), GWAS Catalog (3,10,11), GWASCentral (12) and AraGWAS Catalog (13), have been developed to provide publicly available GWAS associations. Among them, GWAS Catalog and AraGWAS Catalog are two popular representatives. GWAS Catalog, a dedicated resource for human that includes a total of 149 855 significant associations ($P < 1 \times 10^{-5}$) derived from 7230 studies in 4085 publications (as of August 2019) (3), has been widely used by the global community for deciphering genetic basis and molecular mechanisms of human phenotypes and diseases. AraGWAS Catalog (13), a curated and standardized GWAS associations database for Arabidopsis, has integrated more than 167 traits and 222 000 variant-trait associations, making it an important and useful resource for the Arabidopsis community. Despite this, existing resources focused mainly on human and other model organisms and did not comprehensively integrate GWAS associations identified in both crops and domesticated animals. Therefore, a specialized resource that houses comprehensive GWAS associations as well as

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their associated information in a variety of plants and animals is highly desirable.

Here, we present GWAS Atlas (https://bigd.big.ac.cn/gwas), a curated resource incorporating high-quality GWAS associations with particular focus on plants and animals. In the current release, it houses a total of 75 467 GWAS associations in seven cultivated plants and two domesticated animals manually curated from 254 publications. Moreover, all associations and traits are annotated and organized based on a suite of ontologies. To facilitate data access and query, GWAS Atlas is equipped with friendly web interfaces to provide genetic markers and genes that have significant associations ($P < 10^{-3}$) with specific traits of interest. Thus, GWAS Atlas would function as a valuable resource for studying complex agronomic traits and conducting genomic breeding applications in plants and animals.

IMPLEMENTATION

GWAS Atlas is implemented using MySQL (http://www.mysql.org; a free and popular relational database management system) and Apache Tomcat Server (http://tomcat.apache.org; an open source software implementation of Java Servlet and Java Server Pages). Web user interfaces are developed using JSP (Java Server Pages; a technology facilitating rapid development of dynamic web pages based on the Java programming language), HTML5, CSS3, AJAX (Asynchronous JavaScript and XML; a set of web development techniques to create asynchronous applications without interfering with the display and behavior of the existing page), JQuery (a cross-platform and feature-rich JavaScript library; http://jquery.com, version 3.2.1) as well as BootStrap (an open source toolkit for developing web projects with HTML, CSS and JS; https://getbootstrap.com, version 3.3.7). For dynamic data visualization, ECharts (a declarative framework for rapid construction of web-based visualization; http://echarts.baidu.com, version 4.1.0) is adopted to generate interactive charts.

DATA CURATION

To provide high-quality information curated from GWAS publications, we set up a standardized curation process involving four major steps, viz., literature search, information retrieval, integration & annotation and database construction (Figure 1). Briefly speaking, first, we perform literature search in PubMed using species name and GWAS as keywords and accordingly obtain a total of 1850 publications. Among them, 1767 publications published after 2009 are retained. Publications are eligible for inclusion in GWAS Atlas if they contain significant GWAS associations with necessary description on biological traits. Consequently, a total of 254 publications are qualified and their basic bibliographic information (e.g. title, journal, year, citation) are automatically obtained through Europe PMC API (https://europepmc.org/developers/) (14,15). Then, we manually curate the study and genotype-to-phenotype (G2P) association information from publications. As one publication may contain multiple studies with different experimental designs, we record species name, sampling spot, year, condition, population, sample size, genotyping technology, association model, association number, and PMID for each study. Regarding GWAS association, we collect species name, genome version, genomic position, variant ID, traits, GWAS association P-value, R^2 and mapped genes. Considering the possible inconsistency of reference genome versions used in different studies, all genomic variants for a given species are annotated based on the latest version. Finally, to unify the representation of biological traits, trait entities are mapped to a suite of reference ontologies (PTO, Plant Trait Ontology; ATOL, Animal Trait Ontology for Livestock) (16–18) and species-specific ontology (CO, Crop Ontology) (19) using the 'term search' in Planteome API and Livestock Ontologies. Since not all curated traits are included in existing ontologies, we additionally establish PPTO (Plant Phenotype and Trait Ontology) and APTO (Animal Phenotype and Trait Ontology) by integrating more comprehensive terms based on Open Biological and Biomedical Ontologies (OBO) format.

DATABASE CONTENT AND USAGE

Based on the standardized curation process, GWAS Atlas integrates a high-quality collection of 75 467 variant-trait associations for 614 traits across seven cultivated plants and two domesticated animals, which were manually curated from 254 publications (Table 1). To facilitate users in browsing these data, GWAS Atlas provides eight modules, where data are organized and presented in terms of species, associations, variants, genes, traits, ontologies, studies and publications, respectively.

The 'Associations' module provides a comprehensive overview of associated hits ($P < 10^{-3}$) for each species, where data are organized in a tabular table (Figure 2A) and displayed in a heatmap at a chromosome-scale (Figure 2B). Each association contains its variant ID, chromosomal position, consequence type(s), mapped gene(s), associated trait, P-value and PMID. And links to external web sites are provided to help users easily access more details about variants and genes. Besides, a set of filters in light of P-value, trait and variant position are provided to help users narrow down the browsing list. Moreover, associations could also be sorted by a variety of keywords, including VarID, traits, species, P-Value and R^2%. In the 'Variants' (Figure 2C) and 'Genes' modules (Figure 2D), we summarize all associated hits detected in non-redundant variants and genes (or in close proximity to genes) and group the results by variant ID and gene name, respectively. Detailed information can be obtained by clicking on any variant ID or gene ID. Through sorting by trait or association count, users can swiftly get shared genes or sites with multiple different effects.

The 'Traits' module provides an overview of all collected traits in GWAS Atlas. For each trait, both general details (e.g. trait label, trait ID, description) and summary information (e.g. association, study, publication) are recorded in the trait table (Figure 3A). As one trait may have multiple associated variants and genes, users could easily access these data by clicking on their hyperlinks. Besides, these traits are sortable by trait label, trait ID and numbers of associations, studies and publications. According to the current collec-

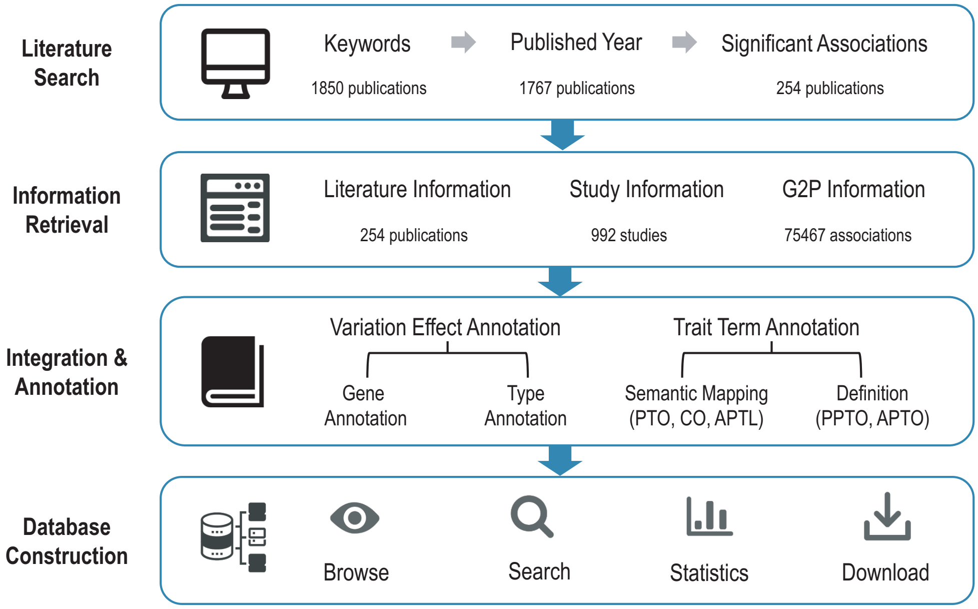


Figure 1. Data curation process adopted by GWAS Atlas.

Table 1. Data statistics in GWAS Atlas (as of 10 August 2019)

Species	# Publications	# Studies	# Traits	# Associations	# Variants	# Genes
Cotton (*Gossypium hirsutum*)	4	23	24	21 955	6115	991
Japanese apricot (*Prunus mume*)	1	2	9	1740	1432	541
Maize (*Zea mays*)	86	308	205	28 310	22 969	13 654
Rape seed (*Brassica napus*)	26	89	67	2396	1709	1791
Rice (*Oryza sativa*)	96	456	284	19 524	14 528	12 803
Sorghum (*Sorghum bicolor*)	13	52	41	754	652	688
Soybean (*Glycine max*)	15	46	40	422	337	354
Goat (*Capra hircus*)	4	6	12	40	40	9
Pig (*Sus scrofa*)	9	10	35	326	284	122

tion in GWAS Atlas (as of August 2019), one of the most extensively studied traits to date is plant height, involving 68 studies, 4238 variants, 2207 genes and 4316 associations. Moreover, we provide an interactive dynamic visualization for each species, to display the count distribution of subtraits and their corresponding associations.

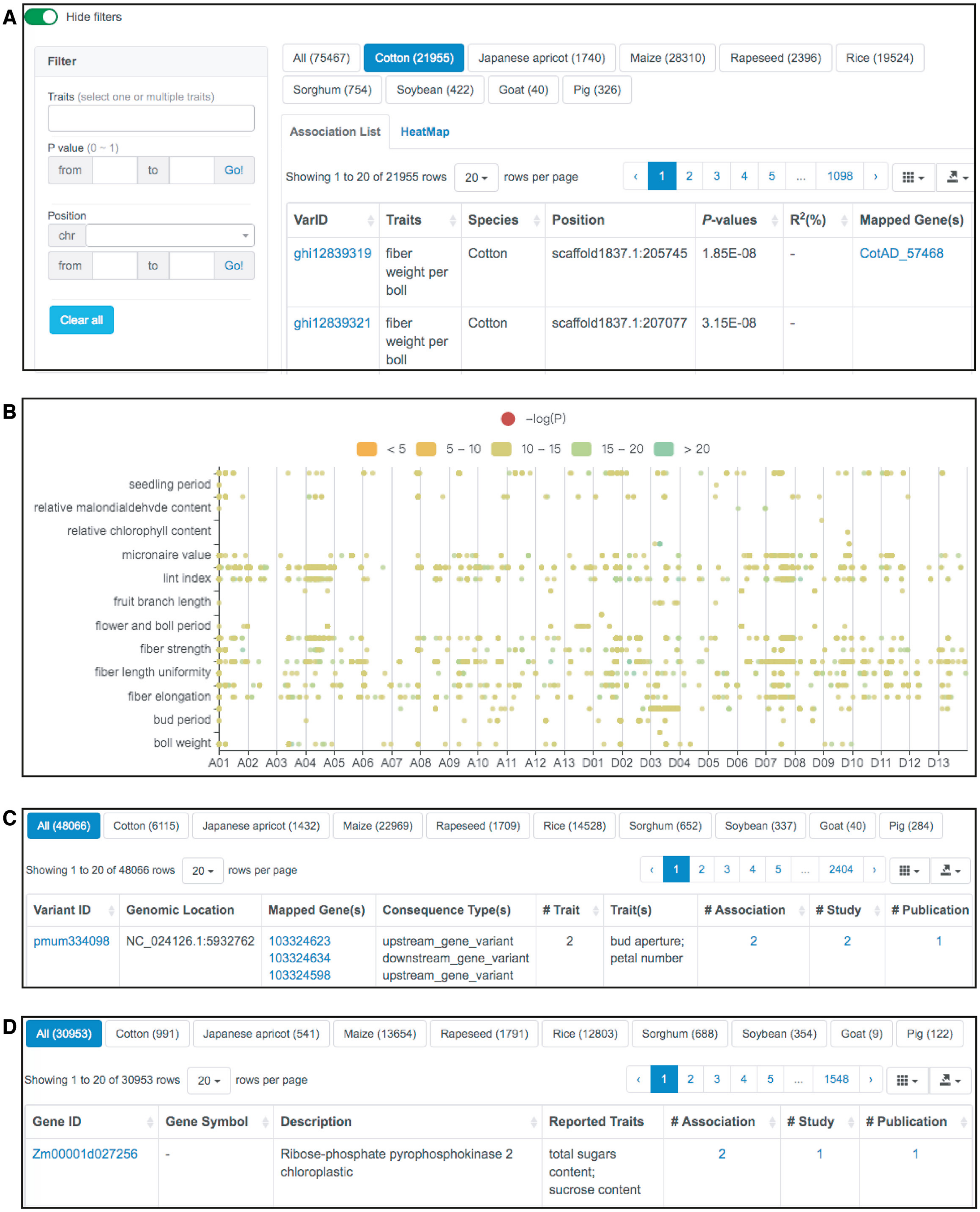
To facilitate structured querying and visualization, we also develop the 'Ontologies' module (Figure 3B) to organize all traits based on a suite of ontologies: PTO, CO and PPTO for plants, and ATOL and APTO for animals (see details in Data Curation). In each ontology module, traits with associations (the number of associations shown in bracket) are displayed in hierarchical structure on the left panel, where users can explore the ontology hierarchy and associated data using the 'drill-down' browser. When a trait term is selected, basic descriptive information on trait, association, study and publication will be automatically mapped and displayed on the right panel, where users could view the detailed information for different species. Therefore, the mapping between GWAS traits and ontology terms in GWAS Atlas would be very useful for identifying new potential genetic variants by providing all related associations across different species. The 'Studies' module displays an overview of all GWAS studies, involving an abundant collection of related information that includes study population, sample size, sampling spot, condition, etc. (Figure 3C). Additionally, for each publication, its bibliographic details (e.g. title, year, journal, PubMed ID, citation) are collectively summarized in the 'Publications' module (Figure 3D).

In all modules, hyperlinks to external databases, such as GVM (20) in BIGD (21), NCBI gene, PubMed, PTO (16) are provided to offer convenient access to additional information.

In addition, to ease data downloading, all query results that are displayed on web pages can be exported as a tab-delimited file (MS-Excel, CSV, TXT) or a JSON-format file. To fully benefit the global scientific community, all relevant data in GWAS Atlas are open access and publicly available at https://bigd.big.ac.cn/gwas/downloads.

DISCUSSION AND FUTURE DIRECTIONS

GWAS Atlas incorporates a large number of high-quality variant-trait associations in multiple plants and animals through manual curation. It equips with friendly web interfaces for browse, search and visualization, thus enabling users to easily maneuver the GWAS associations and uncover molecular mechanisms underlying complex traits. Therefore, GWAS Atlas would be helpful for fully captur-



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VarID	Traits	Species	Position	*P*-values	R^2(%)	Mapped Gene(s)
ghi12839319	fiber weight per boll	Cotton	scaffold1837.1:205745	1.85E-08	-	CotAD_57468
ghi12839321	fiber weight per boll	Cotton	scaffold1837.1:207077	3.15E-08	-	

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Variant ID	Genomic Location	Mapped Gene(s)	Consequence Type(s)	# Trait	Trait(s)	# Association	# Study	# Publication
pmum334098	NC_024126.1:5932762	103324623 103324634 103324598	upstream_gene_variant downstream_gene_variant upstream_gene_variant	2	bud aperture; petal number	2	2	1

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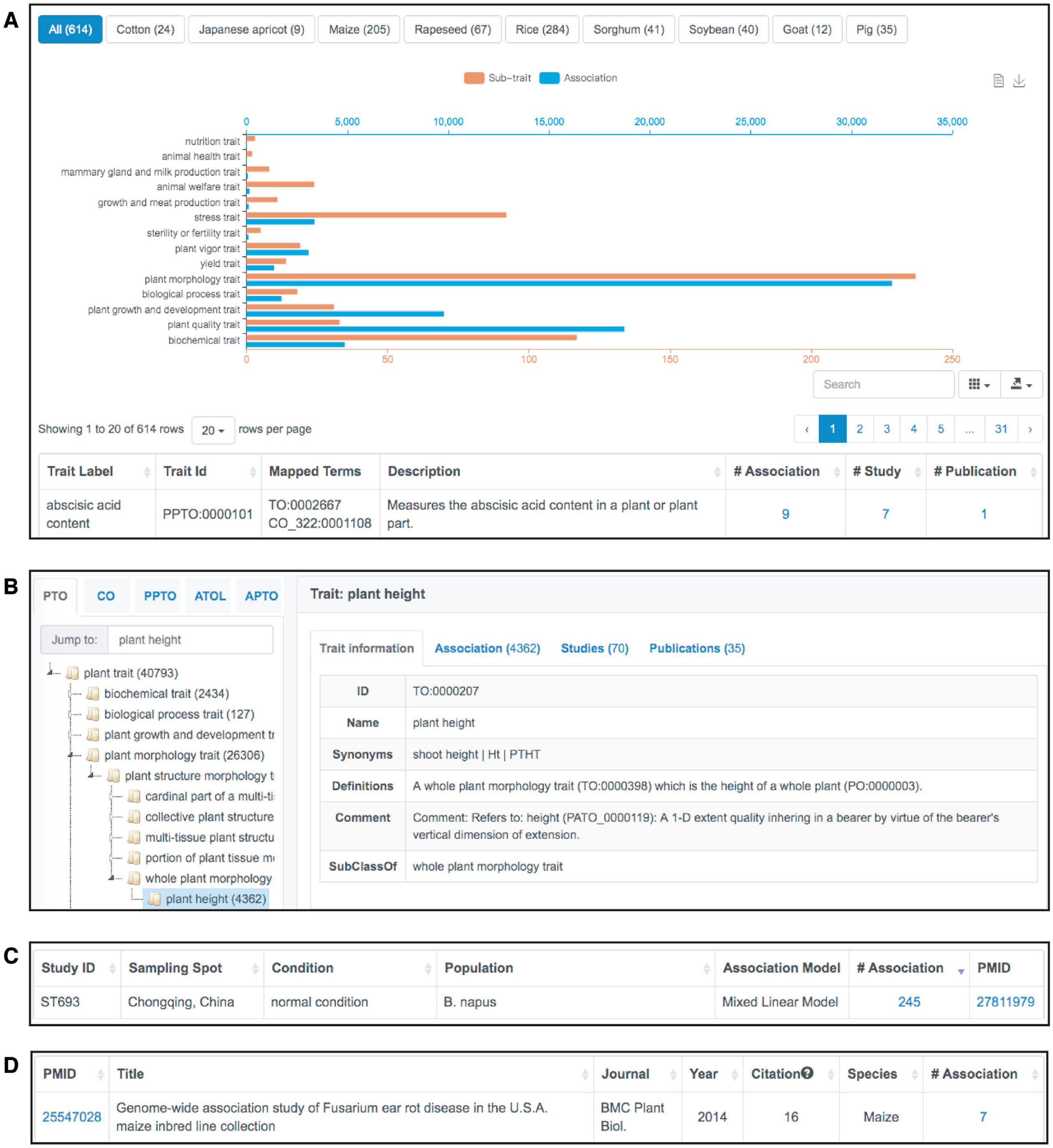
Gene ID	Gene Symbol	Description	Reported Traits	# Association	# Study	# Publication
Zm00001d027256	-	Ribose-phosphate pyrophosphokinase 2 chloroplastic	total sugars content; sucrose content	2	1	1

Figure 2. Screenshots for Associations (**A**), GWAS heatmap across chromosomes (**B**), Variants (**C**) and Genes (**D**). Variant-trait associations in cotton are used to depict the GWAS heatmap, where each row represents a trait and each dot illustrates an associated hit. The log(*P*) is adopted to reflect the statistical significance.



Trait Label	Trait Id	Mapped Terms	Description	# Association	# Study	# Publication
abscisic acid content	PPTO:0000101	TO:0002667 CO_322:0001108	Measures the abscisic acid content in a plant or plant part.	9	7	1

B
PTO
CO
PPTO
ATOL
APTO
Jump to:
plant height
plant trait (40793)
biochemical trait (2434)
biological process trait (127)
plant growth and development tr
plant morphology trait (26306)
plant structure morphology t
cardinal part of a multi-ti
collective plant structure
multi-tissue plant structu
portion of plant tissue mo
whole plant morphology
plant height (4362)
Trait: plant height
Trait information
Association (4362)
Studies (70)
Publications (35)

ID	TO:0000207
Name	plant height
Synonyms	shoot height | Ht | PTHT
Definitions	A whole plant morphology trait (TO:0000398) which is the height of a whole plant (PO:0000003).
Comment	Comment: Refers to: height (PATO_0000119): A 1-D extent quality inhering in a bearer by virtue of the bearer's vertical dimension of extension.
SubClassOf	whole plant morphology trait

Study ID	Sampling Spot	Condition	Population	Association Model	# Association	PMID
ST693	Chongqing, China	normal condition	B. napus	Mixed Linear Model	245	27811979

PMID	Title	Journal	Year	Citation	Species	# Association
25547028	Genome-wide association study of Fusarium ear rot disease in the U.S.A. maize inbred line collection	BMC Plant Biol.	2014	16	Maize	7

Figure 3. Screenshots for Traits (**A**), Ontologies (**B**), Studies (**C**) and Publications (**D**).

ing pleiotropic loci and better understanding the similarities and differences in genetic mechanisms between different species and/or traits. So far, the current release of GWAS Atlas includes 9 species, 614 traits and 75 467 variant-trait associations. Accordingly, future directions are integration of more GWAS findings from a broader range of species and continuously updating associations as well as related information. To further evaluate the effect of variants on other biological processes and facilitate the discovery of potential molecular mechanism for these variant sites, we plan to add additional curated information (such as RNA binding protein and microRNA binding site). Besides, as several ontologies used in this study have not been determined their parent-child relationships, we will further optimize and improve their relationships according to the ontology standards and by reference of PTO and ATO. Moreover, we plan to develop the submission functionality to allow users to submit their own data. Meanwhile, we call for worldwide collaborations to work together to build GWAS Atlas into a valuable resource covering more comprehensive associations and traits across a wider range of plants and animals.

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Conflict of interest statement. None declared.

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