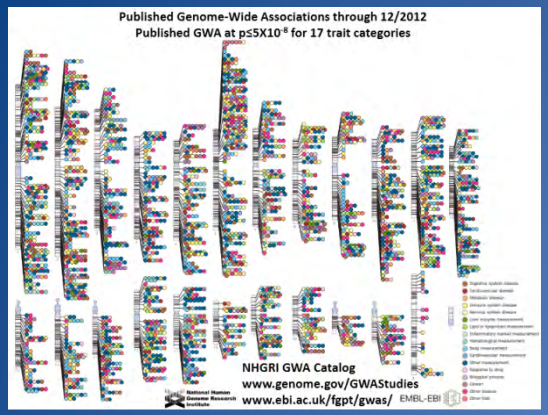


NHGRI GWAS Catalog: Current uses and future directions

Lucia A. Hindorff, PhD, MPH
Division of Genomic Medicine
NHGRI, NIH
July 18, 2013

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH National Human Genome Research Institute

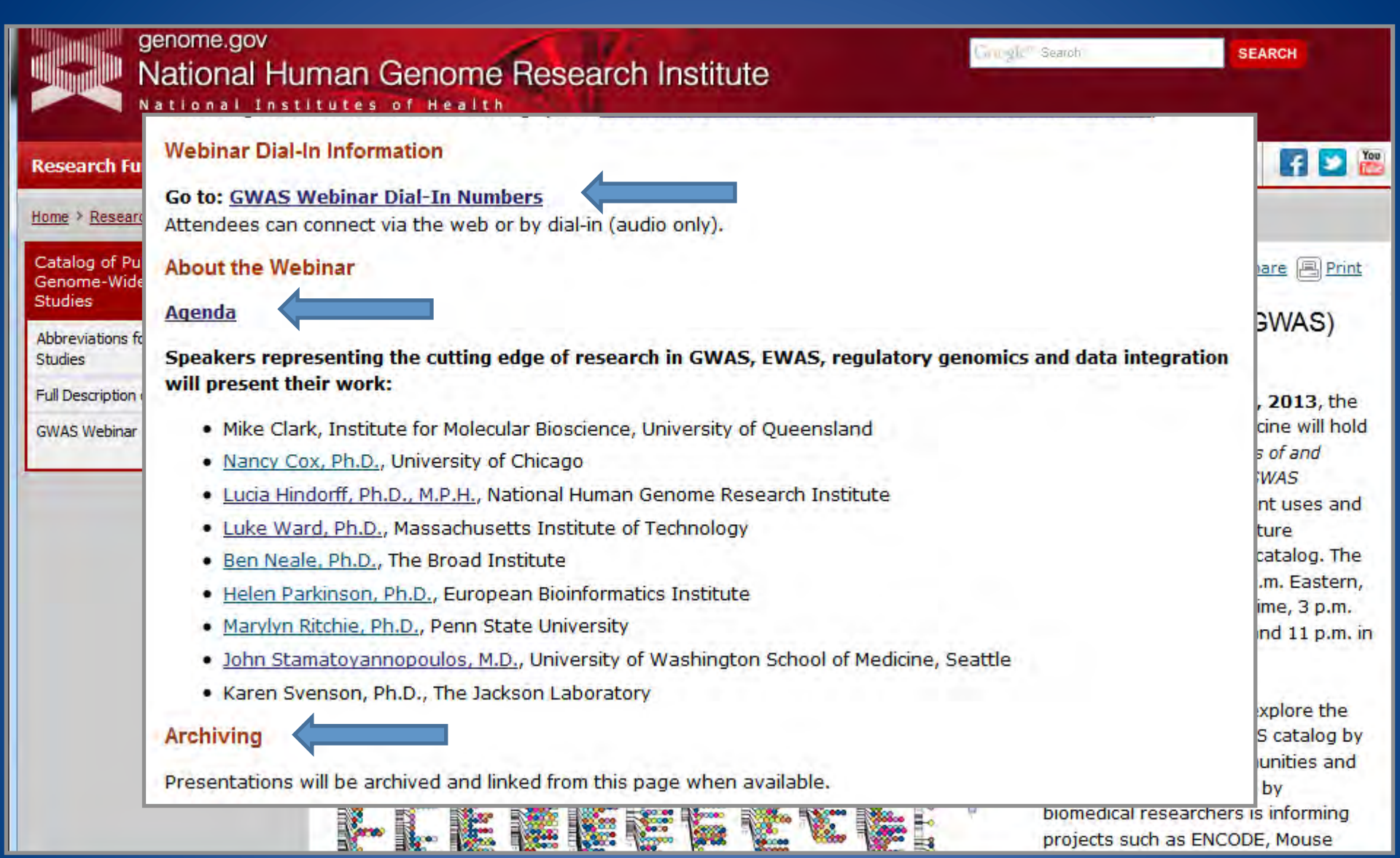
Overview

- Goals and logistics of webinar
- Curation and display
- Recent enhancements
- Community adoption & uptake
- Discussion

Goals for today

- Describe overall goals of the GWAS Catalog
- Review evolution of the GWAS Catalog: history, process, improvements
- Assess community use of Catalog and challenges in its use
- Identify possible future uses and needs
- Obtain advice on useful future directions for the Catalog

Time	Talk	Speaker
09.00	***Introduction to the GWAS Catalog***	**Lucia Hindorff, Ph.D.** National Human Genome Research Institute, NIH
09:40	***Uncovering hidden genes in intergenic GWAS regions with RNA capture-sequencing***	**Michael Clark, Ph.D.** University of Queensland, Australia
10:20	***GWAS and prior knowledge to uncover gene-gene interactions***	**Marylyn Ritchie, Ph.D.** Pennsylvania State University
11:00	***Gene regulation and common diseases and traits***	**John Stamatoyannopoulos, M.D.** University of Washington, Seattle
11:40	***Regulatory genomics and epigenomics of complex disease genetics***	**Luke Ward, Ph.D.** Massachusetts Institute of Technology
12:20	***Using human GWAS data to interrogate complex traits in an outbred mouse population***	**Karen Svenson, Ph.D.** The Jackson Laboratory
12:40	***GTEx X NHGRI catalog***	**Nancy Cox, Ph.D.** University of Chicago
13:20	***Ontologising the GWAS Catalog***	**Helen Parkinson, Ph.D.** EMBL-EBI, UK
13:40	***GWAS as a window to genetic architecture***	**Benjamin Neale, Ph.D.** Broad Institute
14:20	***Open Discussion: Feedback and Suggestions***	



http://www.genome.gov/27554296

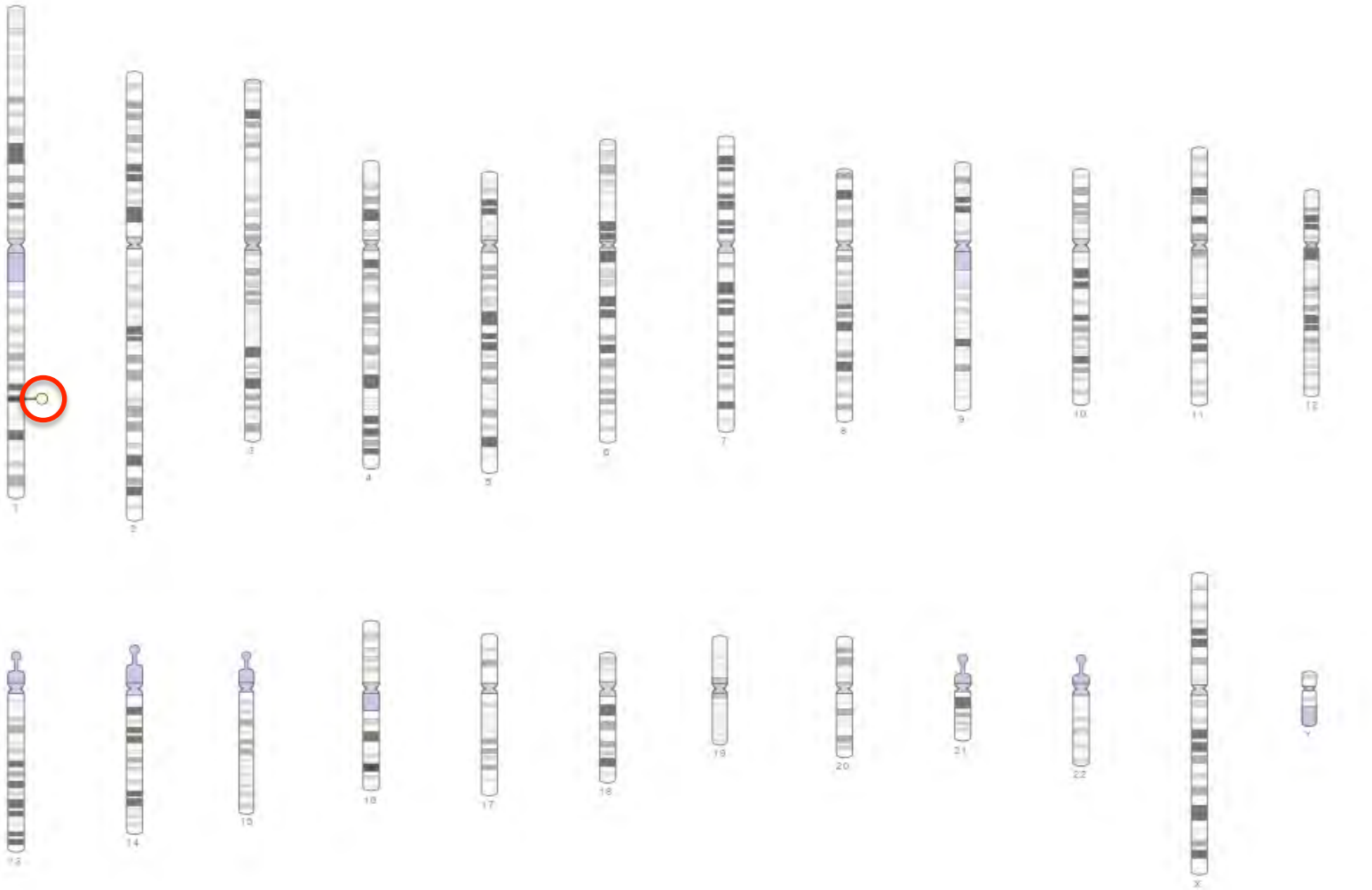
Logistics

- Presenters joining by webinar / phone
- Adherence to agenda times
- Questions
  - Directly after each talk
  - By phone: *1 to reach operator
  - Chat feature in WebEx
  - By email: gwas_table@mail.nih.gov

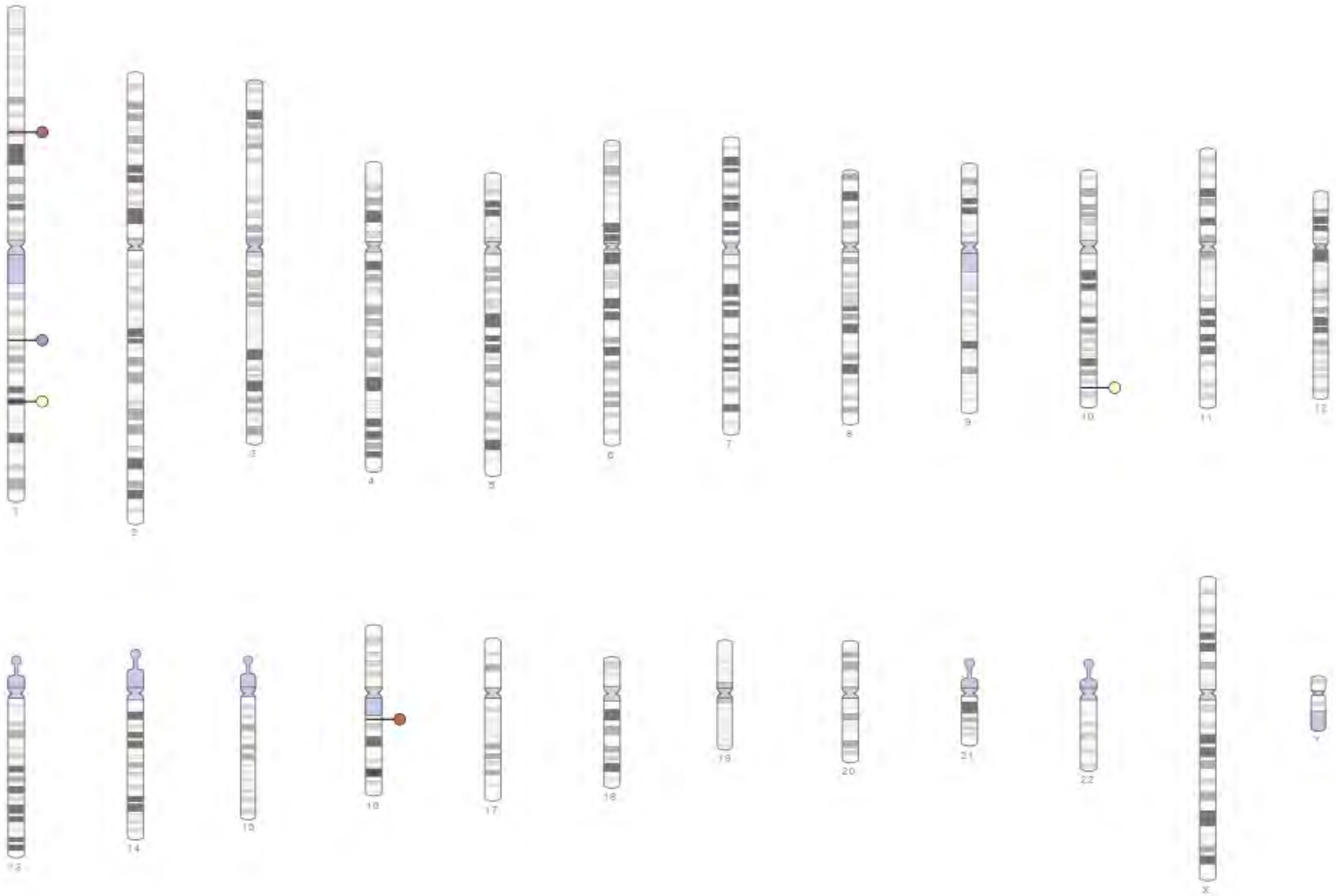
Overview

- Goals and logistics of webinar
- Curation and display
- Recent enhancements
- Community adoption & uptake
- Discussion

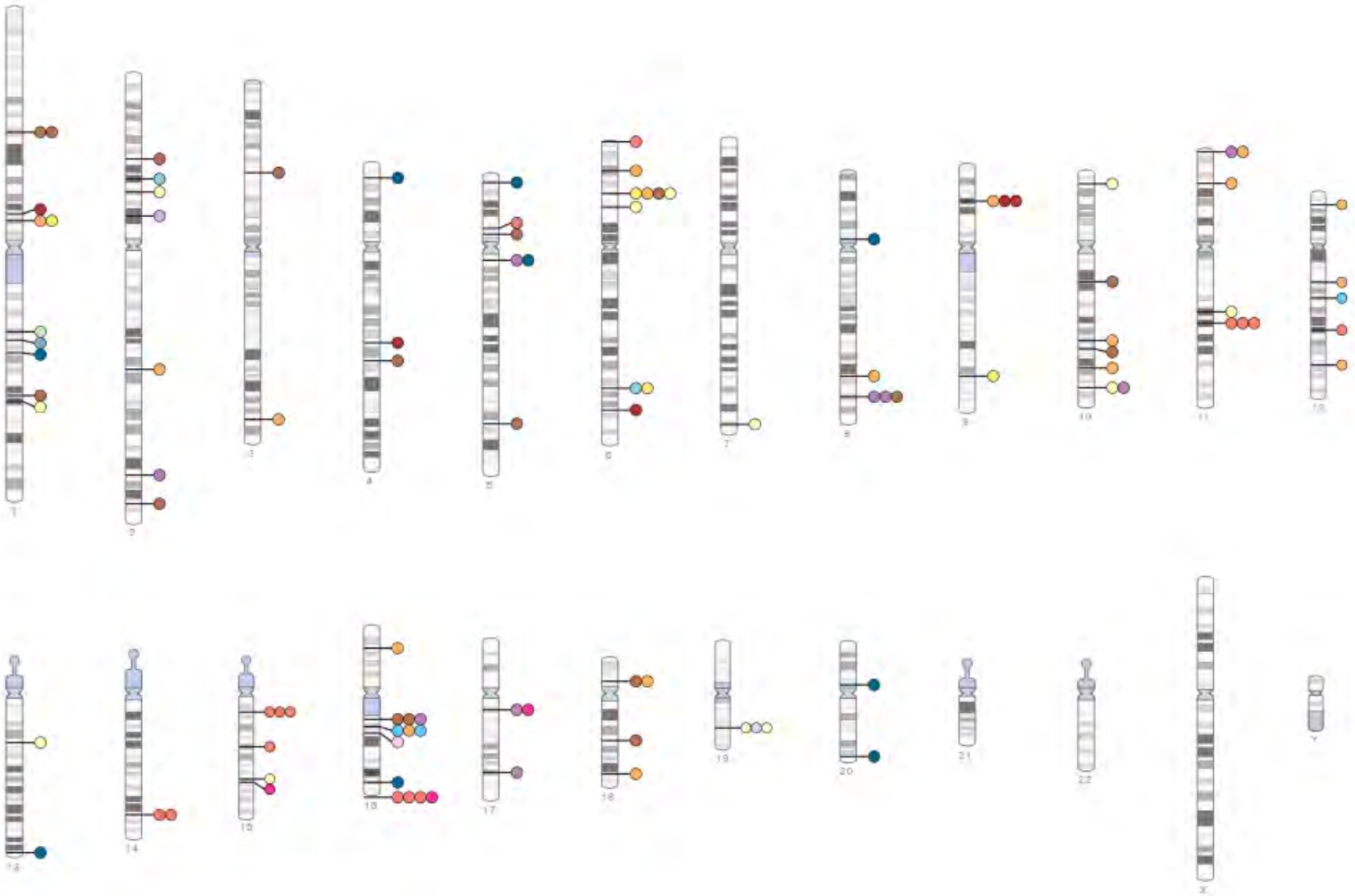
2005



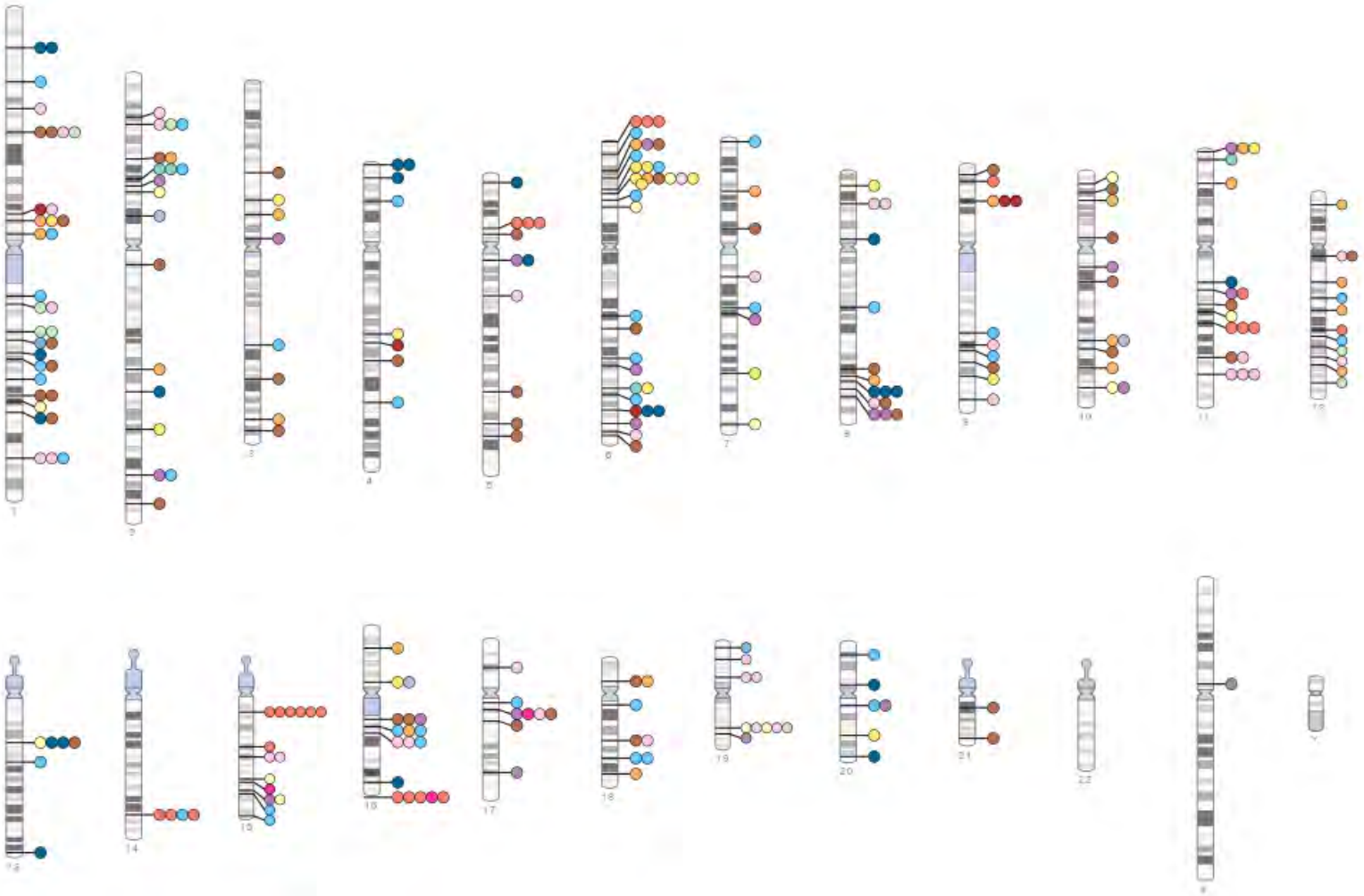
2006



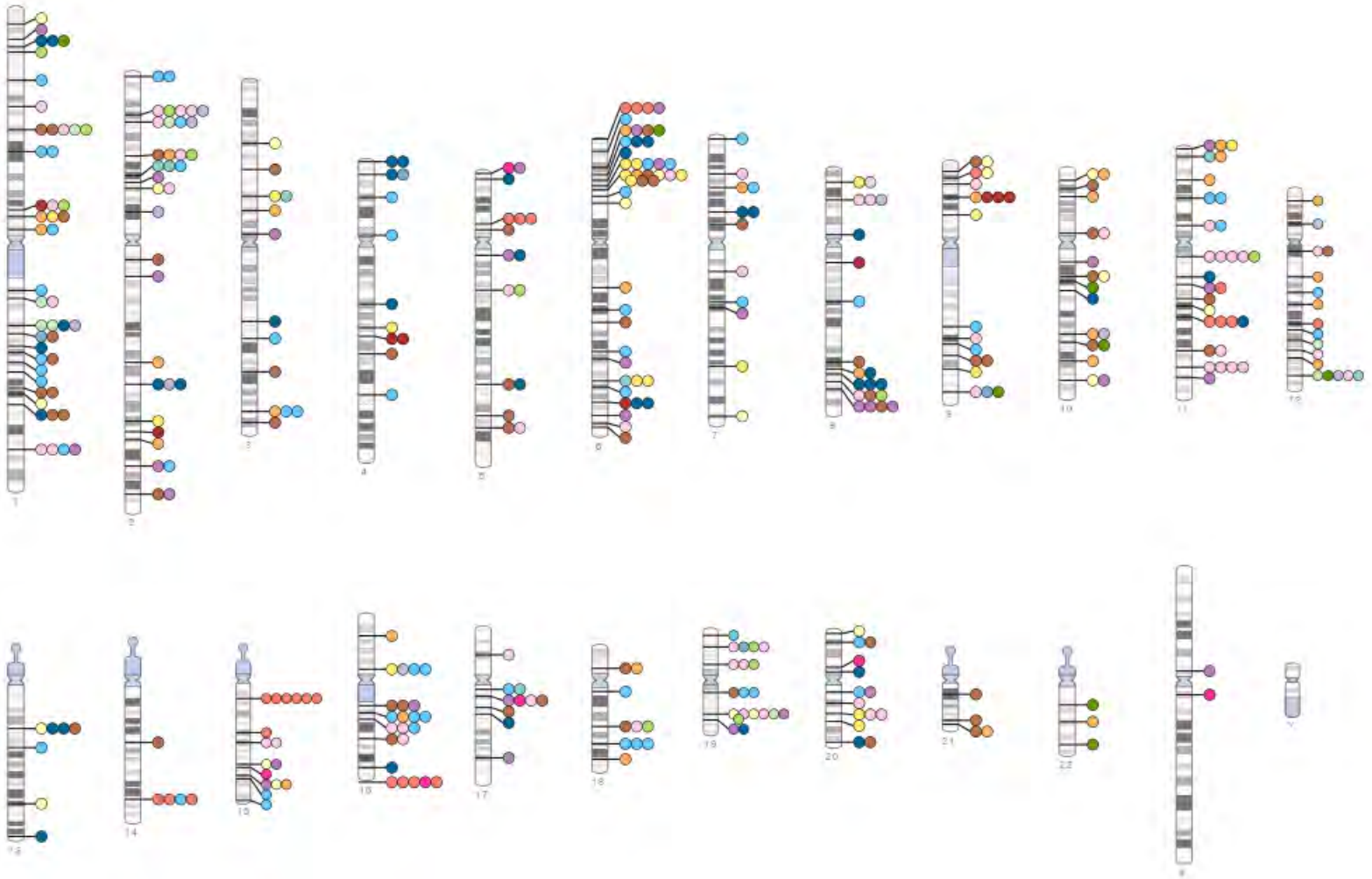
2007



2008 2nd quarter



2008 4th quarter

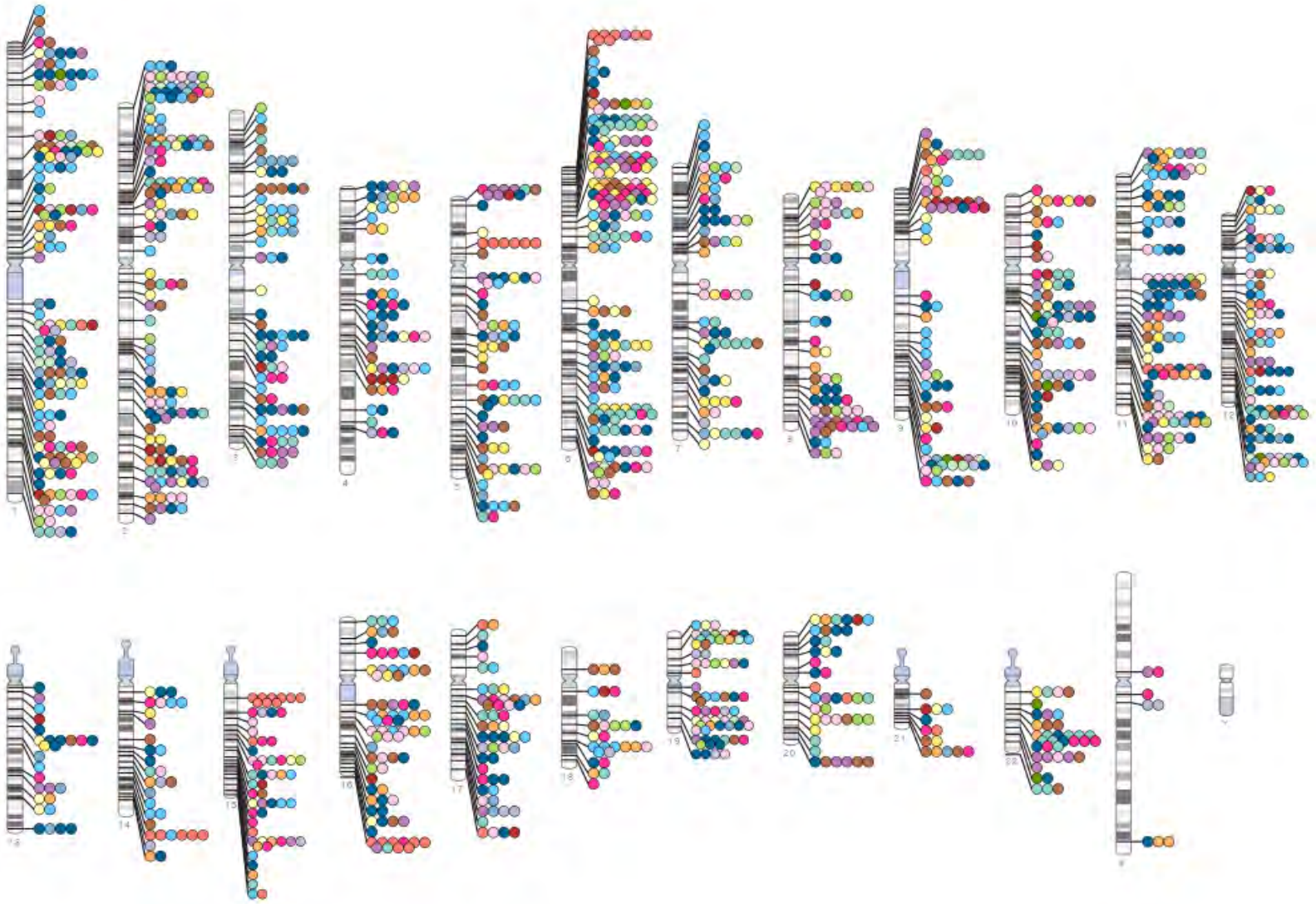


2009 2nd quarter

2009 4th quarter

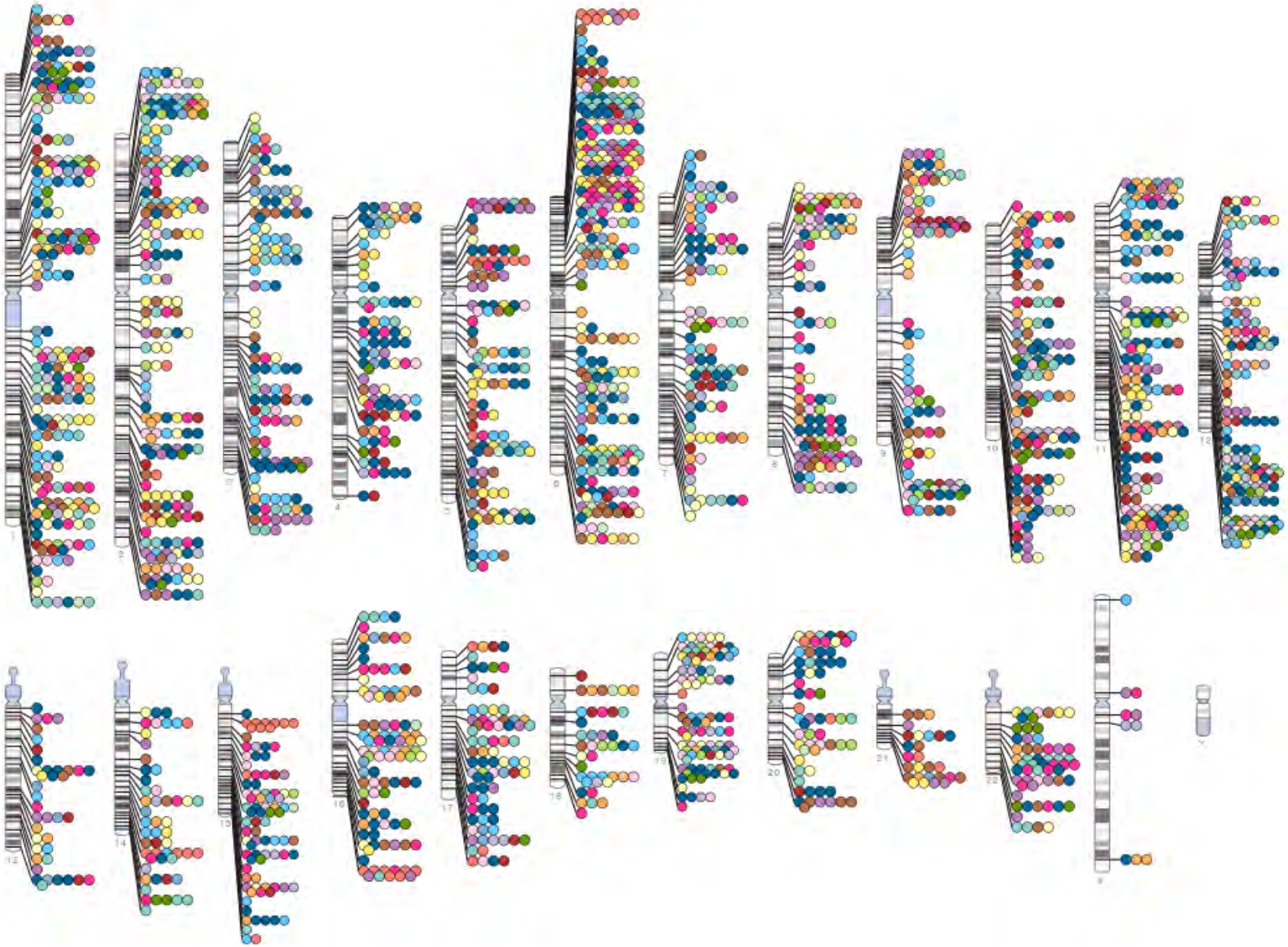
2010 2nd quarter

2010 4th quarter



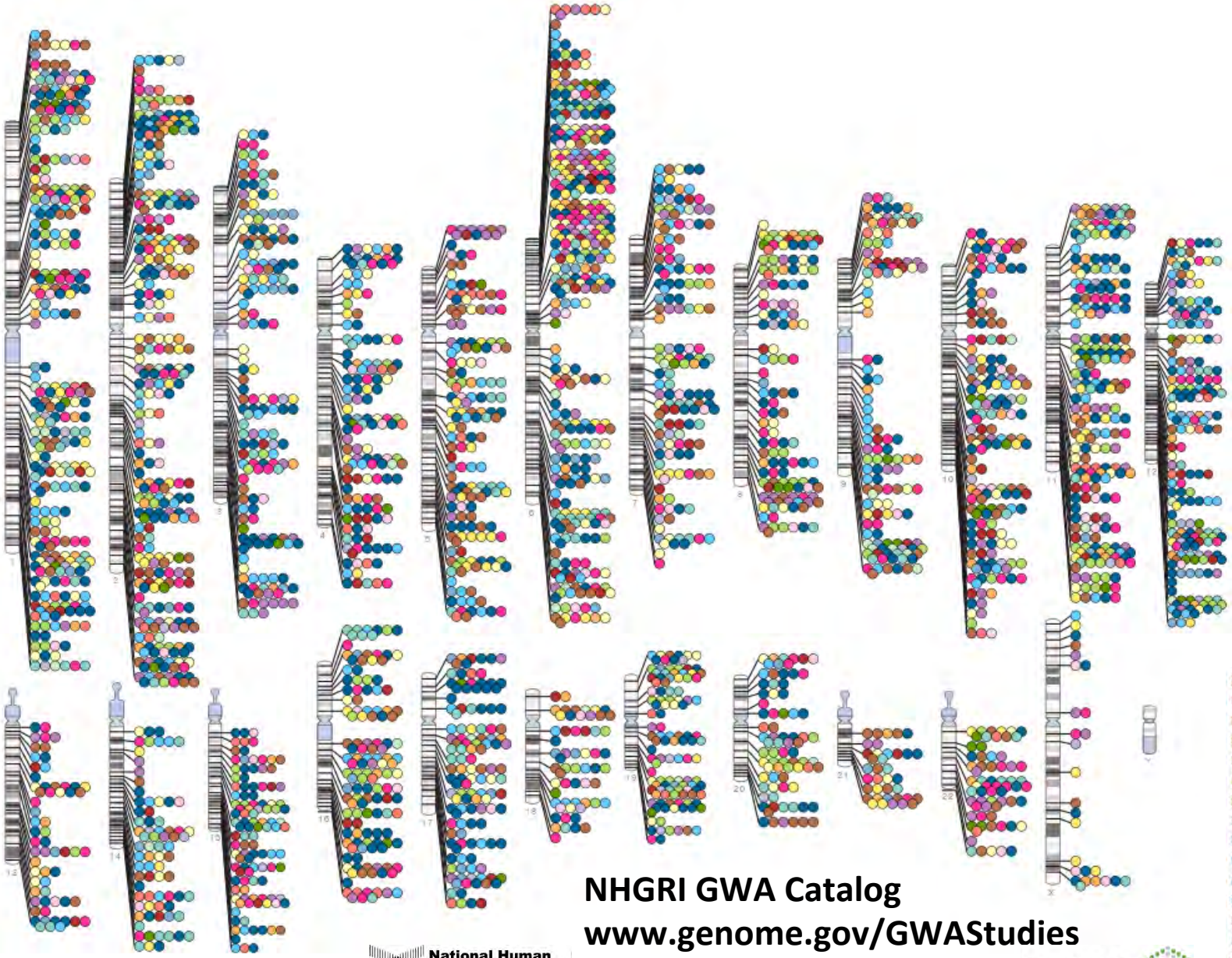
2011 2nd quarter

2011 4th quarter



2012 2nd quarter

Published Genome-Wide Associations through 12/2012
Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories



NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

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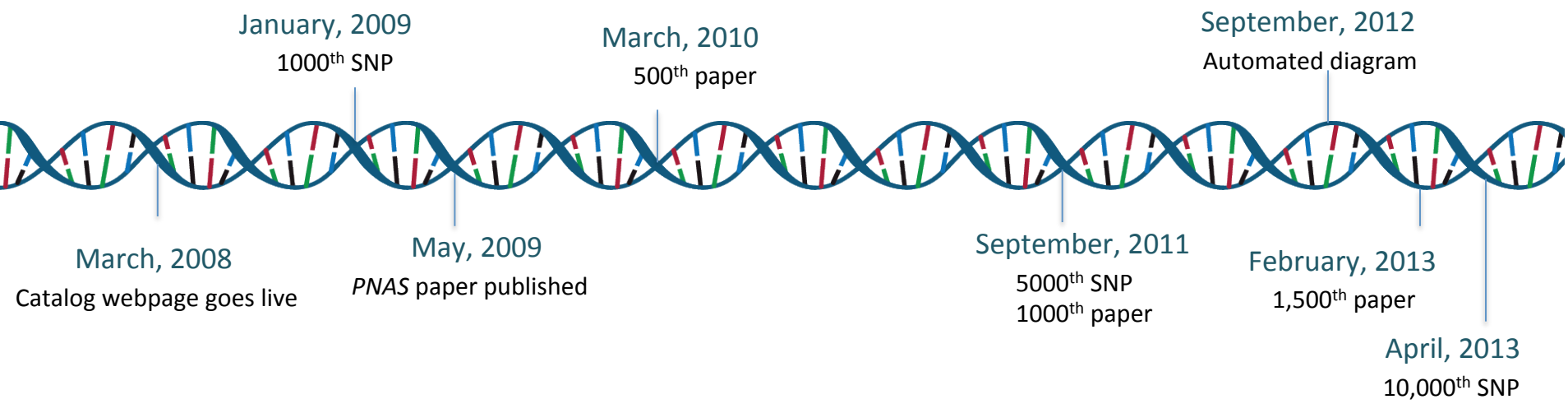
Table 9
GWA studies in various traits

Disease/trait	Sample size Initial	Sample size Replication	Region	Gene	Strongest SNP-risk allele	Risk allele frequency in controls	*P*	OR per copy or for heterozygote (95% CI)	Platform manufacturer and SNPs[A]
Body mass index (93)	10,657 adults	19,424 adults 10,172 children	16q12.2	*FTO*	rs9939609-A	0.39	2×10^{-20}	0.36 (NR)[B] –0.4 (NR)[C]	Affymetrix 490,032
Height (132)	4,921 studied	29,098 studied[D]	12q14.3	*HMGA2*	rs1042725-C	0.51	6×10^{-16}	0.4 (NR)[I]	Affymetrix 364,301
Height (133)	6,669 studied	28,801 studied	20q11.22	*BFZB*	rs6060369-C	0.44	2×10^{-16}	0.44 (NR)[I]	Illumina and Affymetrix[G]
Skin pigmentation by reflectance spectroscopy (134)	363 maxL* <56[H] 374 maxL* >63[H]	116 low maxL* 115 high maxL*	15q21.1 11q14.3 5p13.3	*SLC24A5* *TYR* *SLC45A2*	rs1834640-G rs1042602-C rs16891982-C	0.30 0.90 0.97	1×10^{-30} 4×10^{-10} 3×10^{-11}	12.5 (8.33–20.0) 4.36 (2.64–7.20) 4.86 (2.88–8.21)	Perlegen: 1,502,205[I]
Freckles (135)	2,986 studied	3,932 studied	6p25.3	between *SEC5L1* and *IRF4*	rs1540711-A	0.50	2×10^{-8}	1.40 (1.26–1.57)	Illumina: 317,511
Blond vs. brown hair (135)	2,986 studied	3,932 studied	12q21.33 14q32.12	*KITLG* *SLC24A4*	rs12821256-C rs4904868-C+ rs2402130-A	0.15 0.60	2×10^{-14} 9×10^{-24}	2.32 (1.86–2.92) 2.56 (2.12–3.09)	Illumina: 317,511
Blue vs. green eyes (135)	2,986 studied	3,932 studied	14q32.12	*SLC24A4*	rs4904868-C+ rs2402130-A	0.60	2×10^{-16}	2.06 (1.76–2.42)	Illumina: 317,511
F cell distribution (136)	179 adults[J]	90 adults	2p16.1 6q23.3 11p15.5	*BCL11A* Intergenic *Xmnl-Gγ*	rs1427407-? rs9399137-? NR	0.14 0.23 0.33	6×10^{-31} 3×10^{-26} 2×10^{-08}	13.1% (NR)[K] 15.8% (NR)[K] 10.2% (NR)[K]	Illumina: 308,015
Serum uric acid levels (137)	4,305 Sardinian	1,301 Tuscan	4p16.1	*GLUT9*	rs6855911-A	0.74	2×10^{-16}	0.32 (NR)[I]	Affymetrix 362,129
Serum urate (117)	1,955 hypertensive individ	2,033 individ in 519 families; 1,461 twins[M]	4p16.1	*SLC2A9*	rs7442295-A	0.79	2×10^{-15}	0.024 (0.018–0.030)[N]	Affymetrix 400,496
Recombination	1,887 men	1,248 men	4p16.3	*RNF212*	rs3796619-T	0.33[P]	3×10^{-24}	70.7 (84.3–57.1)[Q]	Illumina:

GWAS Catalog Timeline
2008 - present



www.genome.gov/gwastudies

Division of Genomic Medicine

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A Catalog of Published Genome-Wide Association Studies

Division Staff | Funding Opportunities | Genomic Medicine Activities | GWAS Catalog | Meetings & Workshops | Potential Sample Collections for Sequencing | Programs | Publications | Trans-NIH Sequencing Inventory

Additional information has been added to the HTML catalog columns below. For a description of column headings for the HTML catalog, go to: Catalog Heading Descriptions PDF new

Potential etiologic and functional implications of genome-wide association loci for human diseases and traits PDF
Click here to read our recent *Proceedings of the Academy of Sciences (PNAS)* article on catalog methods and analysis.

View the Interactive Diagram new | View the Full Catalog | Download the Catalog | Search the Catalog

Published Genome-Wide Associations
Credit: Darryl Leja and Teri Manolio, NHGRI; Tony Burdett, Dani Welter, and Helen Parkinson, EBI

View as PDF PDF

View PowerPoint slide

The genome-wide association study (GWAS) publications listed here include only those attempting to assay at least 100,000 single nucleotide polymorphisms (SNPs) in the initial stage. Publications are organized from most to least recent date of publication, indexing from online publication if available. Studies focusing only on candidate genes are excluded from this catalog. Studies are identified through weekly PubMed literature searches, daily NIH-distributed compilations of news and media reports, and occasional comparisons with an existing database of GWAS literature (HuGE Navigator).

SNP-trait associations listed here are limited to those with p-values < 1.0 x 10-5 (see full methods for additional details). Multipliers of powers of 10 in p-values are rounded to the nearest single digit; odds ratios and allele frequencies are rounded to two decimals. Standard errors are converted to 95 percent confidence intervals where applicable. Allele frequencies, p-values, and odds ratios derived from the largest sample size, typically a combined analysis (initial plus replication studies), are recorded below if reported; otherwise statistics from the initial study sample are recorded. For quantitative traits, information on % variance explained, SD increment, or unit difference is reported where available. Odds ratios < 1 in the original paper are converted to OR > 1 for the alternate

www.genome.gov/gwastudies

Search By:

Journal: Select Journal

First Author:
(last name)

Disease/Trait:
(string search)

Tip: Expand your search by using the OR operator (returns results with either term), or narrow your search using the AND operator (returns results with both terms).

or

β2-Glycoprotein I (β2-GPI) plasma levels
5-HTT brain serotonin transporter levels
AB1-42
Abdominal aortic aneurysm
Acenocoumarol maintenance dosage
Activated partial thromboplastin time
Acute graft versus host disease
Acute lung injury
Acute lymphoblastic leukemia (childhood)
Addiction
Adiponectin levels
Adiposity

Tip: Hold Ctrl-key to select multiple entries.

Chromosomal Region:
(e.g., "13q21.31")

Gene:
(e.g., "LRP5")

SNP:
(e.g., "rs20755555")

The SNP data in the catalog has been mapped to dbSNP Build 137 and Genome Assembly, GRCh37/hg19.

OR greater than:

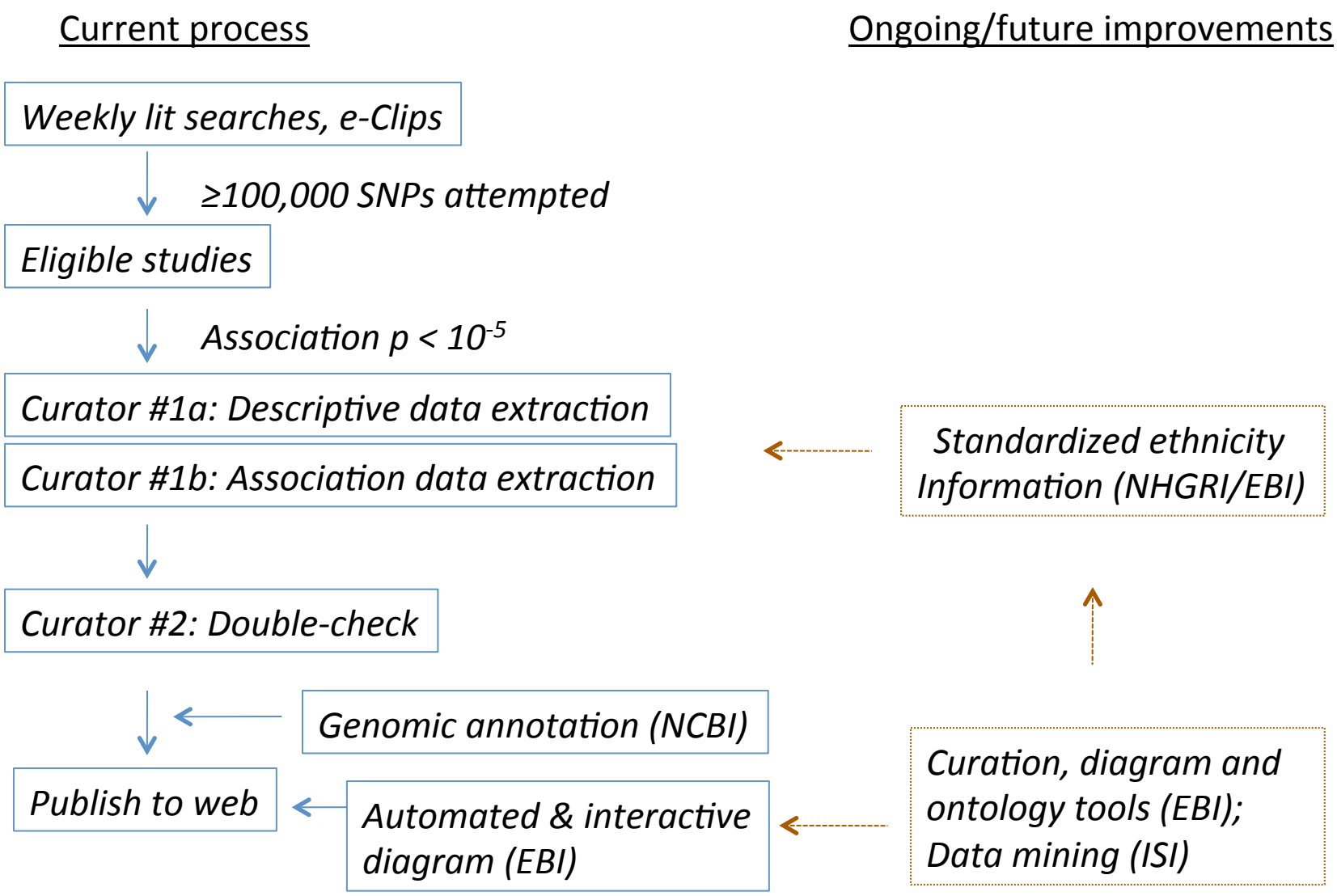
p-Value threshold:
Enter the exponent. For example, enter "5" for $p<10^{-5}$

Search Reset

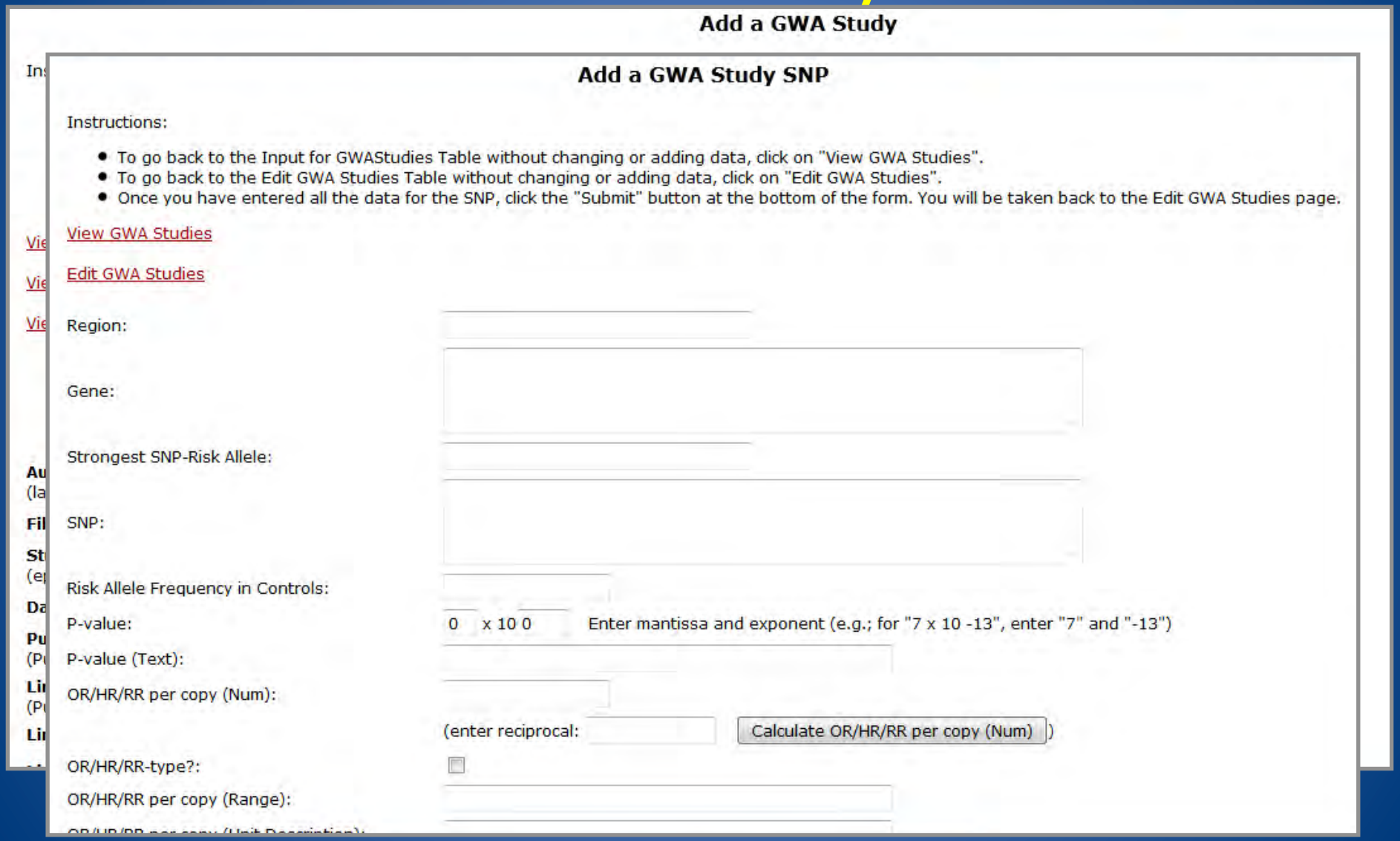
Date Added to Catalog (since 11/25/08)	First Author/Date/ Journal/Study	Disease/Trait	Initial Sample Size	Replication Sample Size

Region	Reported Gene(s)	Mapped Gene(s)	Strongest SNP-Risk Allele	Context	Risk Allele Frequency in Controls	P-value	OR or beta-coefficient and [95% CI]	Platform [SNPs passing QC]	CNV
			View full set of 17 SNPs					Illumina [1,232,008] (imputed)	N
10q25.2	*TCF7L2*	TCF7L2	rs7903146-T	intron	0.5	9×10^{-75} (South Asian, East Asian, Europeans)	1.19 [1.17 - 1.21]		
10q25.2	*TCF7L2*	TCF7L2	rs7903146-T	intron	0.3	2×10^{-38} (South Asians, East Asians)	1.15 [1.12 - 1.17]		
10q25.2	*TCF7L2*	TCF7L2	rs7903146-T	intron	0.3	3×10^{-35} (South Asians)	1.15 [1.13 - 1.18]		
10q25.2	*TCF7L2*	TCF7L2	rs7903146-T	intron	0.31	6×10^{-22} (All Punjabi)	1.3 [1.23 - 1.37]		
3q27.2	*IGF2BP2*	IGF2BP2	rs1470579-C	intron	0.5	2×10^{-19} (South Asian, East Asian, Europeans)	1.08 [1.05-1.09]		
10q25.2	*TCF7L2*	TCF7L2	rs7903146-T	intron	0.31	3×10^{-19} (Punjabi Sikhs)	1.44 [1.33 - 1.56]		
3q27.2	*IGF2BP2*	IGF2BP2	rs1470579-C	intron	0.45	2×10^{-13} (South Asians, East Asians)	1.06 [1.04-1.08]		
3q27.2	*IGF2BP2*	IGF2BP2	rs1470579-C	intron	0.45	4×10^{-9} (South Asians)	1.06 [1.04-1.09]		
13q12.12	*SGCG, SACS*	SGCG	rs9552911-G	intron	0.93	2×10^{-8} (Punjabi Sikhs)	1.49 [1.3-1.72]		
3q27.2	*IGF2BP2*	IGF2BP2	rs1470579-C	intron	0.41	4×10^{-7} (All Punjabi)	.88 [0.83 - 0.92]		

GWAS catalog workflow



Data entry



Add a GWA Study

Add a GWA Study SNP

Instructions:

- To go back to the Input for GWAStudies Table without changing or adding data, click on "View GWA Studies".
- To go back to the Edit GWA Studies Table without changing or adding data, click on "Edit GWA Studies".
- Once you have entered all the data for the SNP, click the "Submit" button at the bottom of the form. You will be taken back to the Edit GWA Studies page.

View GWA Studies

Edit GWA Studies

Region:

Gene:

Strongest SNP-Risk Allele:

SNP:

Risk Allele Frequency in Controls:

P-value: 0 x 10 0 Enter mantissa and exponent (e.g.; for "7 x 10 -13", enter "7" and "-13")

P-value (Text):

OR/HR/RR per copy (Num):

(enter reciprocal:) Calculate OR/HR/RR per copy (Num)

OR/HR/RR-type?:

OR/HR/RR per copy (Range):

Overview

- Goals and logistics of webinar
- Curation and display
- Recent enhancements
- Community adoption & uptake
- Discussion

GWAS diagram improvements

- Automated generation of diagram
- Interactive display
- Consolidation of traits into higher level categories = fewer colors
- Dynamic time-series display
- Interactive filtering on trait (selected browsers)

GWAS Diagram Browser

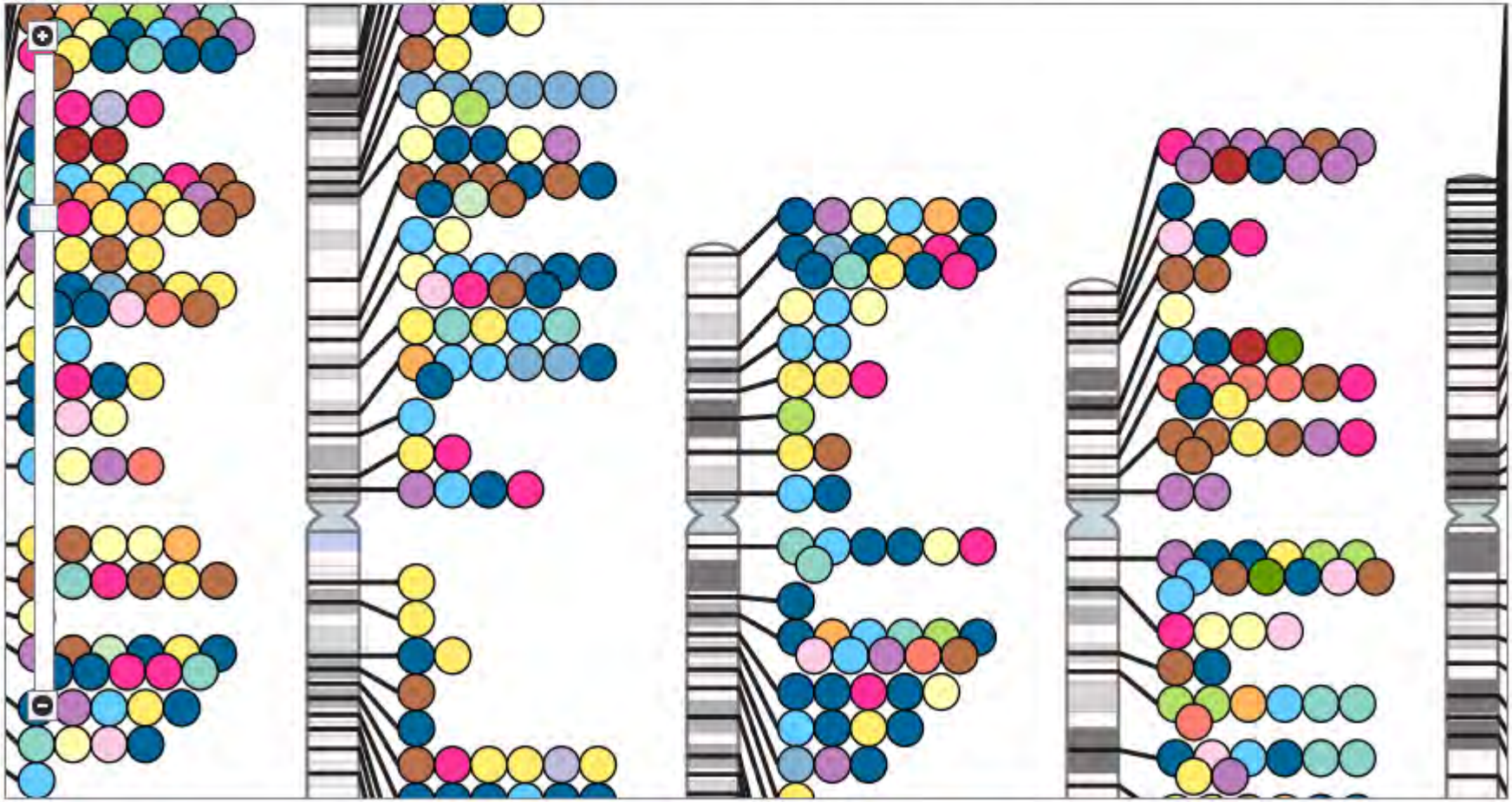
Exploring Genome-wide Association Studies

National Human Genome Research Institute EMBL-EBI

Query by trait | Clear | *To show only one trait, e.g. "breast cancer" or "schizophrenia", type the trait into the box on the left and hit "Query by trait"*

Interactive GWAS Diagram | Trait-specific Views | Time Series Views | Downloads | Help | About | Show Legend

This diagram shows all SNP-trait associations with p-value ≤ 5.0×10^{-8}, published in the GWAS catalogue (http://www.genome.gov/gwastudies) up to the end of December 2012. For information on how to navigate the diagram, see the help tab.



GWAS Diagram Browser

Exploring Genome-wide Association Studies

National Human Genome Research Institute

EMBL-EBI

Query by trait | Clear | *To show only one trait, e.g. "breast cancer" or "schizophrenia", type the trait into the box on the left and hit "Query by trait"*

Interactive GWAS Diagram | Trait-specific Views | Time Series Views | Downloads | Help | About | Show Legend

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Background

The National Human Genome Research Institute (NHGRI) Catalog of Published Genome-Wide Association Studies or GWAS catalogue provides a quality controlled, manually curated, literature-derived collection of all published GWA studies assaying at least 100,000 SNPs and all SNP-trait associations with p-values < 1.0×10^{-5} *(Hindorff et al., 2009)*. The catalogue can be searched by a number of options including journal, first author, trait, chromosomal region, gene, SNP, odds ratio and p-value threshold. As of 20/08/12, it includes 1355 publications and 7226 SNPs. In addition to the SNP-trait association data, the catalogue also publishes the iconic GWAS diagram of all SNP-trait associations, with p-values ≤ 5.0×10^{-8}, mapped to the SNPs' chromosomal locations. The diagram is released quarterly and the latest version of the diagram is made available on the GWAS catalogue website in PDF format and as a PowerPoint slide.

The GWAS diagram browser

This page hosts a novel system that generates the GWAS diagram dynamically using semantic web technologies. The diagram produced in this fashion can be filtered and searched at different levels of granularity and by different criteria, currently including trait (main diagram tab) and publication date (time series tab, currently availabe for a fixed set of time points only). It is possible to zoom in over chromosomes in order to see all SNP-trait associations for a given region. SNP-trait associations are shortly going to be fully interactive. Trait name information is already available on mouse-over and traits being clickable to allow proceeding from an association to the catalogue entry and to the publication is currently under development.

The diagram is generated in SVG (Scalable Vector Graphics) as a web application with a Java back-end using an Apache Tomcat server. The catalogue data is presented as a knowledge base, based on the GWAS Catalog schema ontology, which formalises the relationship between various concepts such as SNP, trait and study. Both the knowledge base and the schema ontology can be

"Enter" or clicking the "Query" button.

Future diagram improvements

- Interactive links to other genome browsers
- Improved filtering features
  - Autocomplete (with synonyms)
  - PubMed ID
  - Combinatorial queries
- More frequent availability of updated data
- Improved browser compatibility
- (Your suggestion here!)

Ethnicity

- Disproportionate disease burdens observed in non-European populations
- Frequency of GWAS variants varies up to 40-fold between different populations (Adeyamo, 2010)
- GWAS performed at a ratio of ~10:1 European ancestry vs. all groups combined (Need, 2009)
- Systematic efforts needed to define and extract ancestry information

Add a GWA Study Ethnicity

Instructions:

- To go back to the Input for GWAStudies Table without changing or adding data, click on "View GWA Studies".
- To go back to the Edit GWA Studies Table without changing or adding data, click on "Edit GWA Studies".
- Once you have entered all the data for the Ethnicity, click the "Submit" button at the bottom of the form. You will be taken back to the Edit GWA Studies page.

Number of Individuals:

Inferred Ethnic/Ancestral Group:
(Press the Ctrl key when selecting multiple groups)

- Select a group
- European
- Sub-Saharan African
- African unspecified

Country of Origin:
(Press the Ctrl key when selecting multiple countries)

- ***Africa***
  - Algeria
  - Angola
  - Benin
  - Botswana
  - Burkina Faso
  - Burundi
  - Cameroon
  - Cape Verde
  - Central African Republic
  - Chad
  - Comoros
  - Congo
  - Côte d'Ivoire
  - Democratic Republic of the Congo

Country of Recruitment:
(Press the Ctrl key when selecting multiple countries)

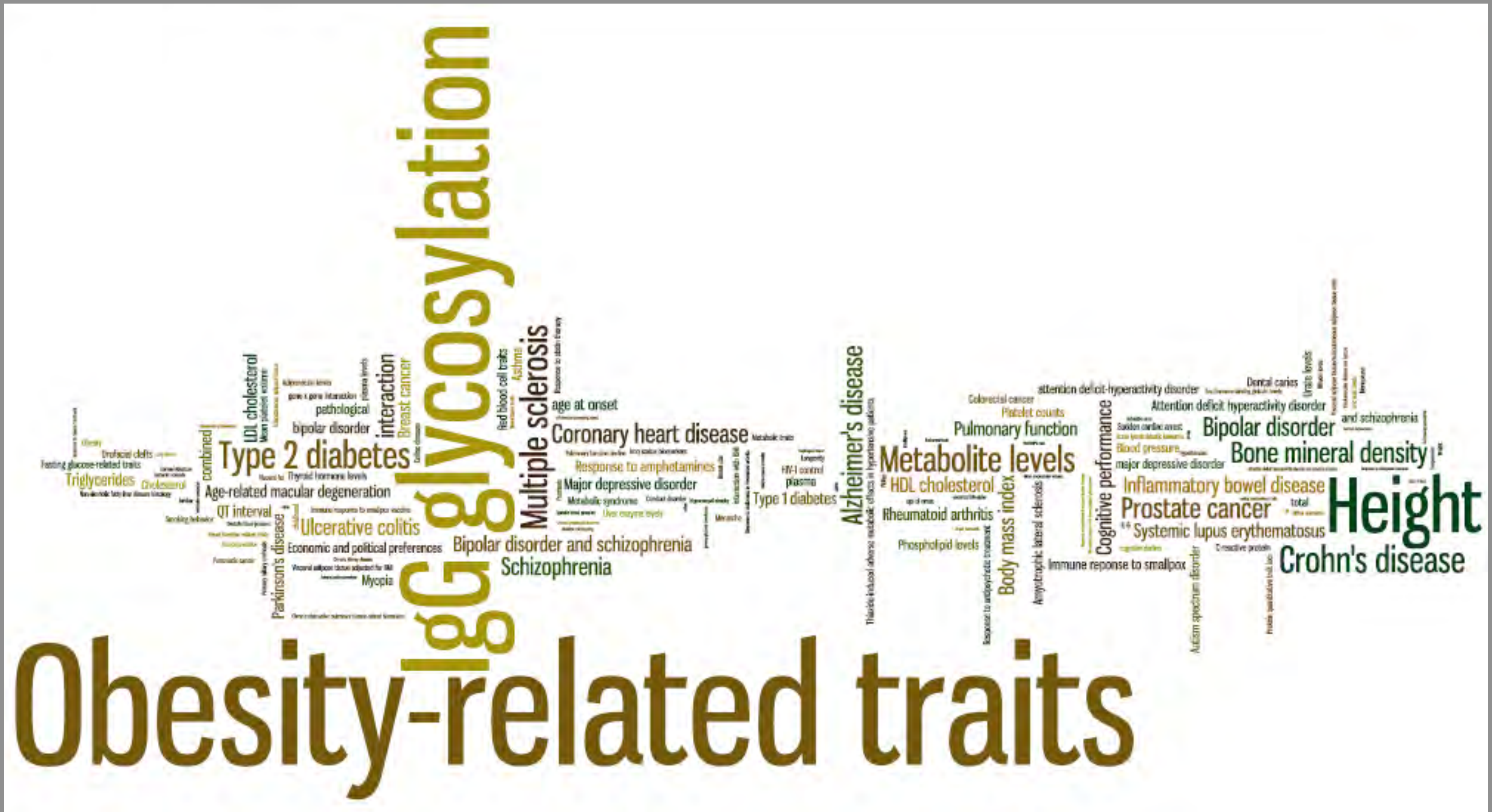
- ***Africa***
  - Algeria
  - Angola
  - Benin
  - Botswana
  - Burkina Faso
  - Burundi
  - Cameroon
  - Cape Verde
  - Central African Republic
  - Chad
  - Comoros
  - Congo
  - Côte d'Ivoire
  - Democratic Republic of the Congo

Additional Description (free text):

Ethnicity analysis

- 575 GWAS papers, 2011-2012
  - 55% EA only
  - 27% non-EA only
  - 13% both
- 74% of study participants are EA
- Countries of recruitment dominated by Europe, United States


eland
Hong Kong SAR
Slovenia
Mauritius
Gambia
Hungary
Argentina
Ethiopia

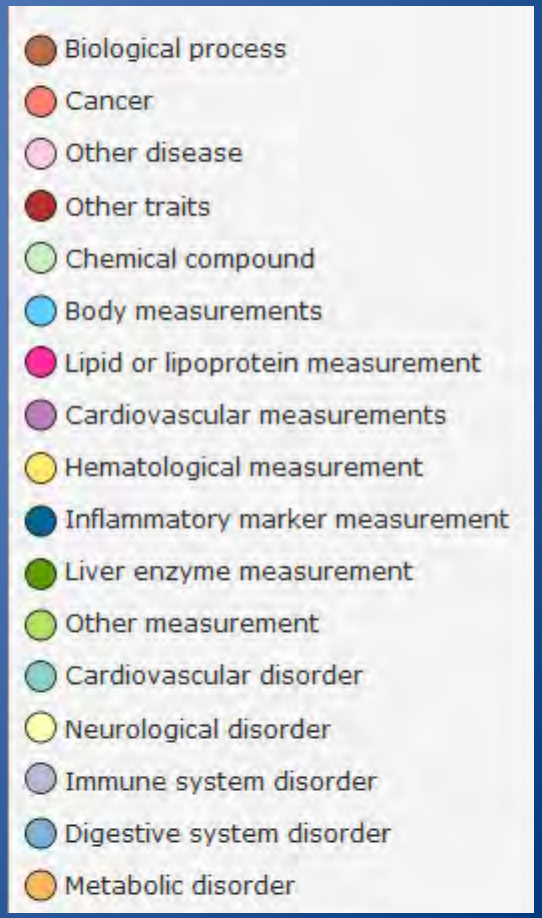

Obesity-related traits
IgG glycosylation
Height
Metabolite levels
Type 2 diabetes
Multiple sclerosis
Coronary heart disease
Crohn's disease
Bone mineral density
Prostate cancer
Bipolar disorder
Alzheimer's disease
Inflammatory bowel disease
Systemic lupus erythematosus
Bipolar disorder and schizophrenia
Schizophrenia
Ulcerative colitis
Body mass index
Cognitive performance
HDL cholesterol
Rheumatoid arthritis
Pulmonary function
Type 1 diabetes
Major depressive disorder
Response to amphetamines
Age-related macular degeneration
LDL cholesterol
interaction
Breast cancer
Triglycerides
QT interval
Parkinson's disease
Economic and political preferences
Myopia
age at onset
Immune reponse to smallpox
Attention deficit hyperactivity disorder
attention deficit-hyperactivity disorder
Phospholipid levels
Platelet counts
Colorectal cancer
Blood pressure
major depressive disorder
Autism spectrum disorder
Amyotrophic lateral sclerosis
Dental caries
Urate levels
and schizophrenia
Fasting glucose-related traits
Orofacial clefts
Cholesterol
Thyroid hormone levels
bipolar disorder
pathological
combined
Asthma
Red blood cell traits
HIV-1 control
plasma
Metabolic syndrome
Liver enzyme levels
Smoking behavior
C-reactive protein
total

Ontology

- Facilitates broad categorization of traits

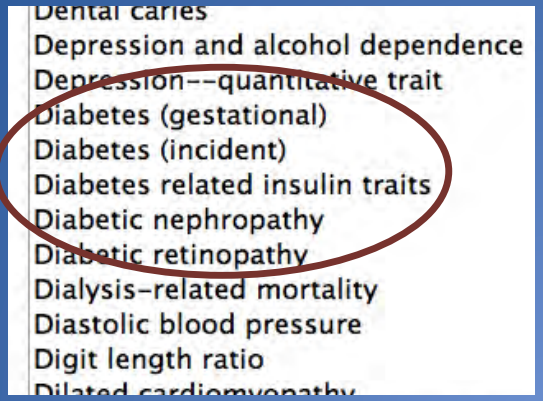
200+ manually-defined traits

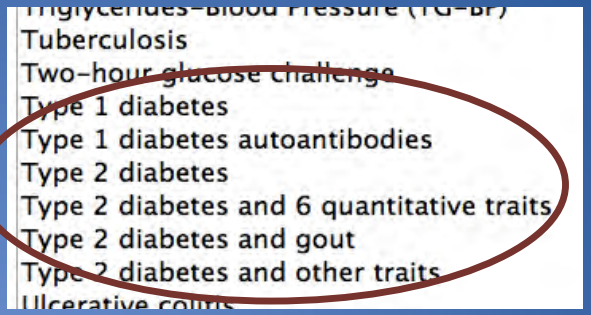
~20 ontology-defined traits



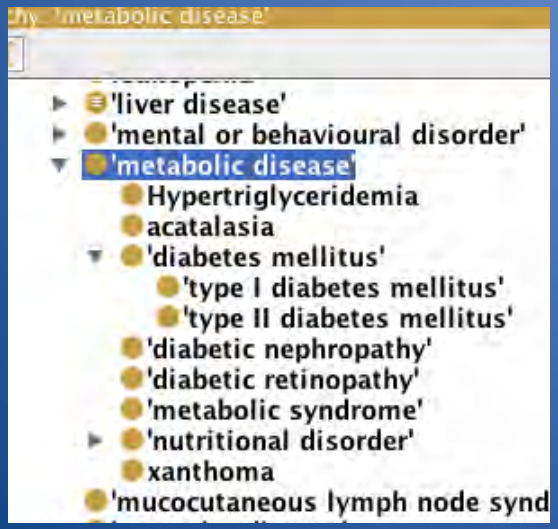
Ontology

- Relatively unstructured trait list





- Integration of traits into existing ontology (EFO) and facilitates systematic and more powerful searches

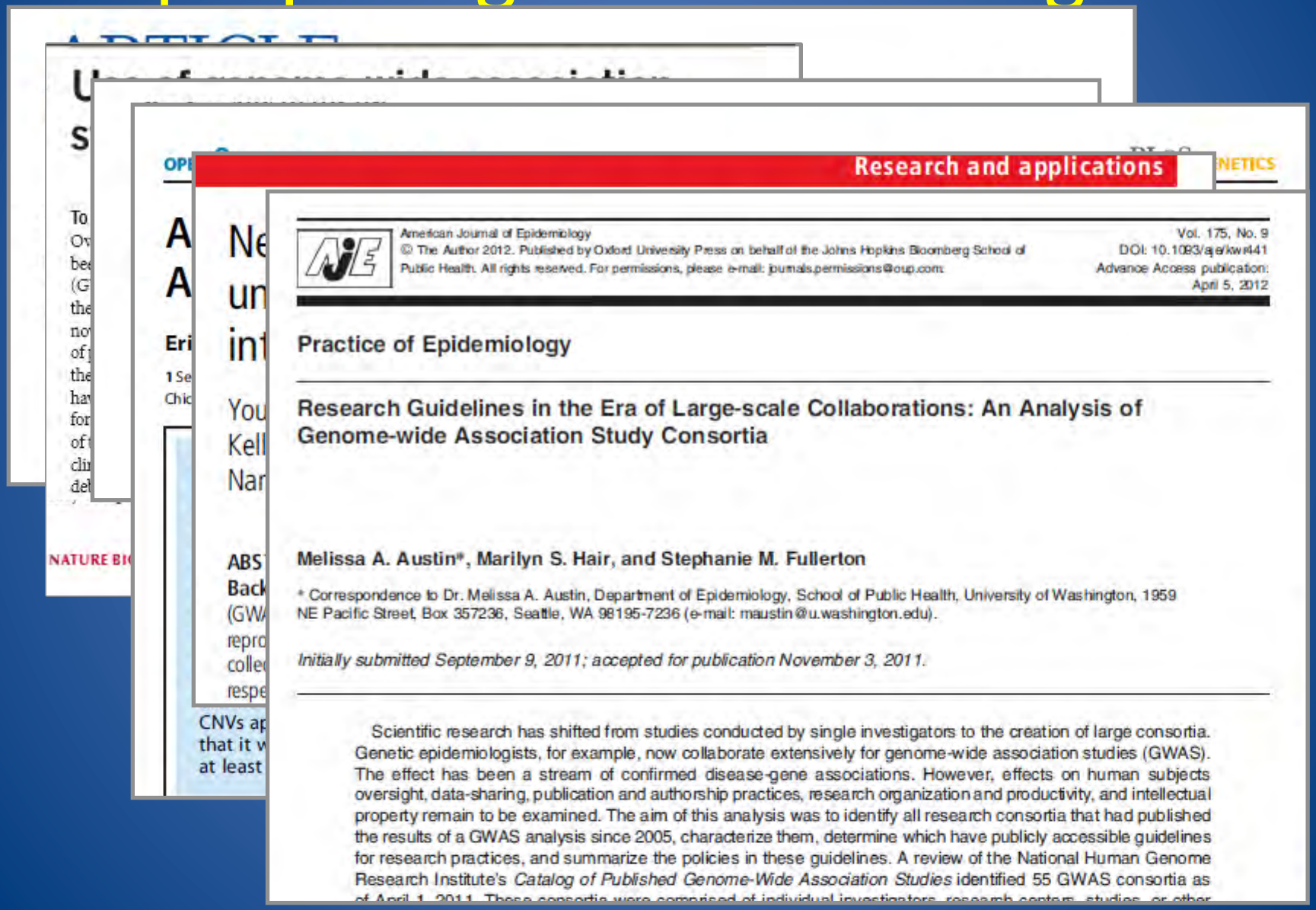


"Show me all SNPs associated with type 2 diabetes and metabolic syndrome."

Overview

- Goals and logistics of webinar
- Curation and display
- Recent enhancements
- Community adoption & uptake
- Discussion

“Repurposing” GWAS catalog data



Research and applications

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Practice of Epidemiology

Research Guidelines in the Era of Large-scale Collaborations: An Analysis of Genome-wide Association Study Consortia

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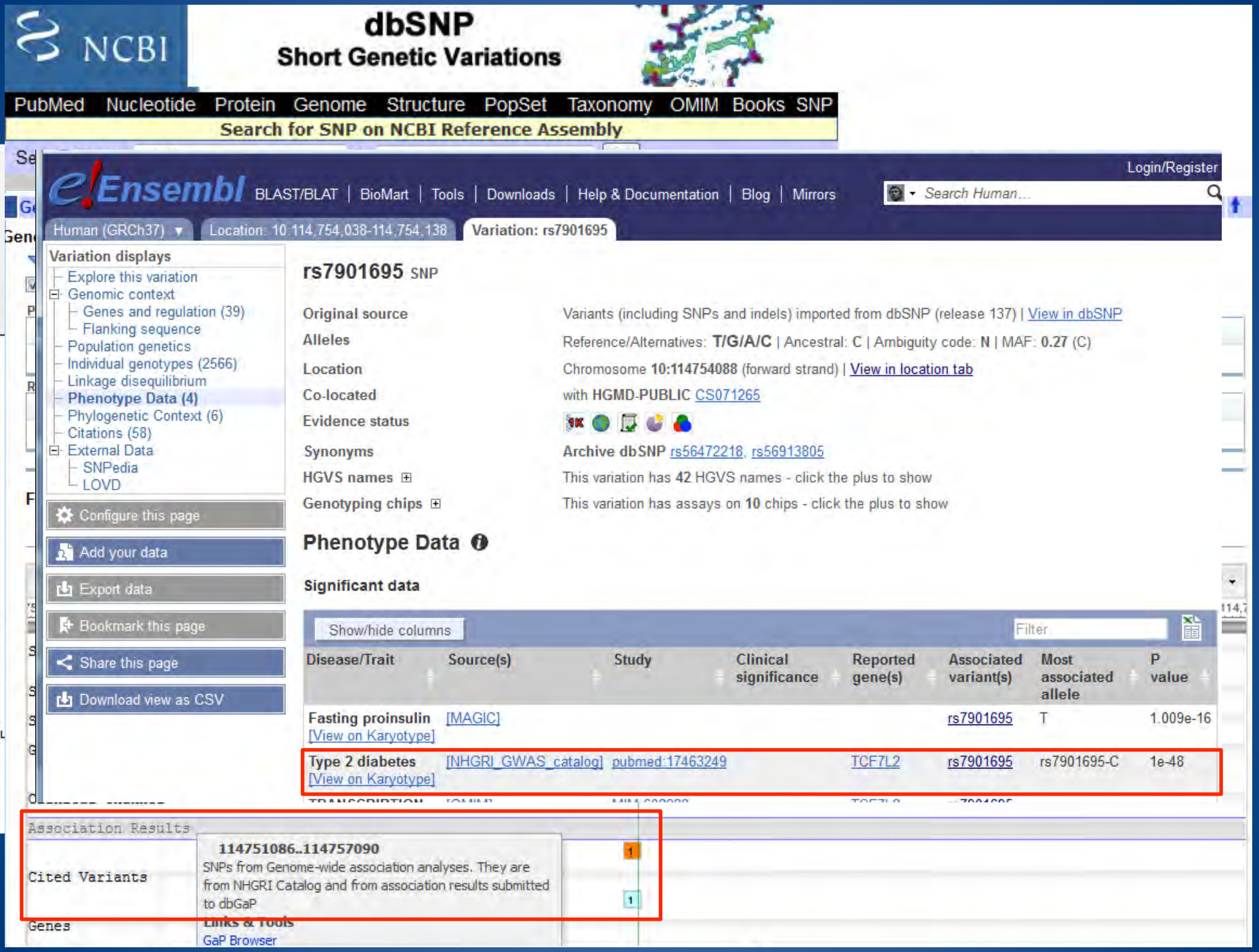
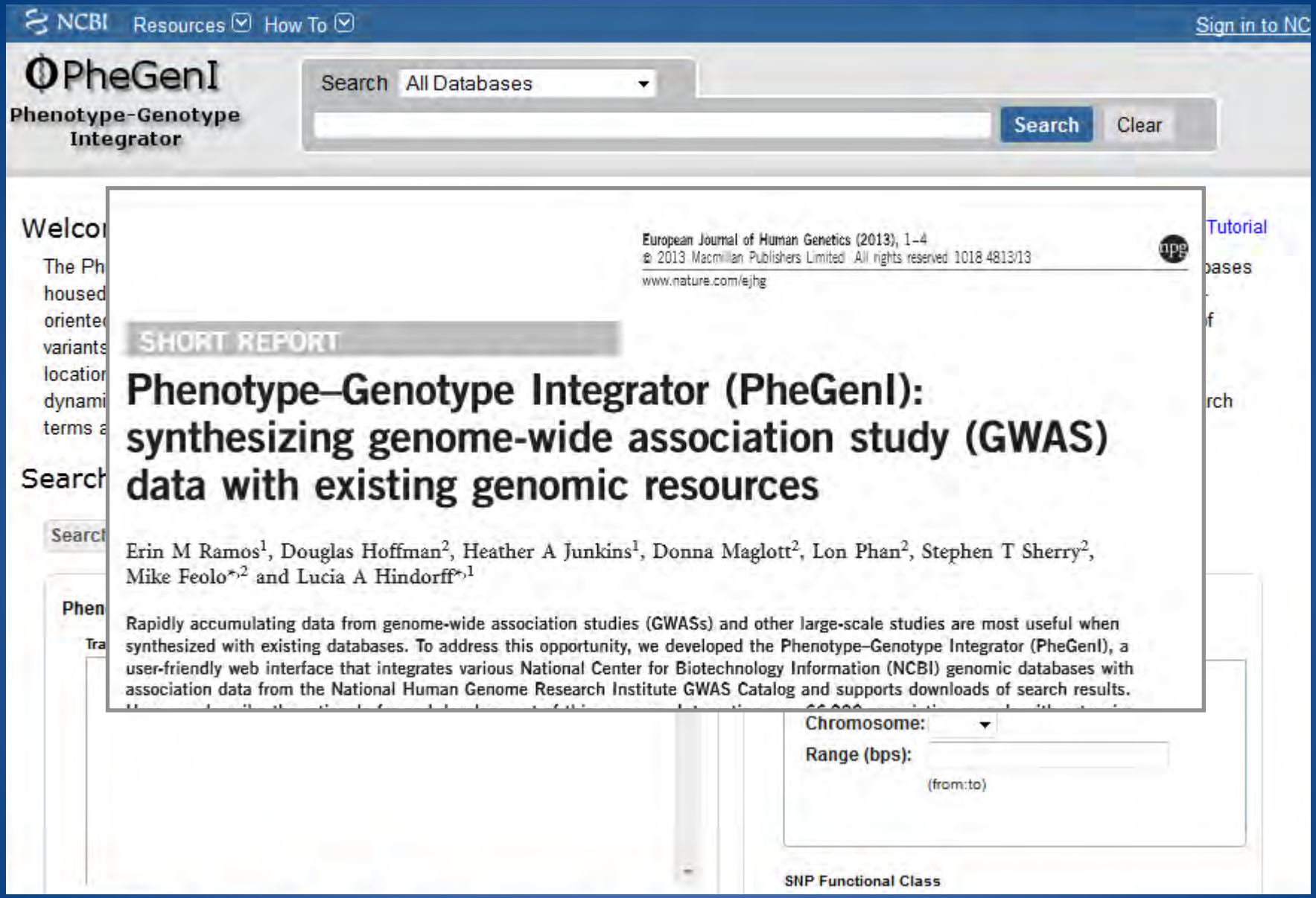
Scientific research has shifted from studies conducted by single investigators to the creation of large consortia. Genetic epidemiologists, for example, now collaborate extensively for genome-wide association studies (GWAS). The effect has been a stream of confirmed disease-gene associations. However, effects on human subjects oversight, data-sharing, publication and authorship practices, research organization and productivity, and intellectual property remain to be examined. The aim of this analysis was to identify all research consortia that had published the results of a GWAS analysis since 2005, characterize them, determine which have publicly accessible guidelines for research practices, and summarize the policies in these guidelines. A review of the National Human Genome Research Institute's *Catalog of Published Genome-Wide Association Studies* identified 55 GWAS consortia as


NCBI
dbSNP
Short Genetic Variations
PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP
Search for SNP on NCBI Reference Assembly
e!Ensembl
BLAST/BLAT | BioMart | Tools | Downloads | Help & Documentation | Blog | Mirrors
Login/Register
Search Human...
Human (GRCh37)
Location: 10:114,754,038-114,754,138
Variation: rs7901695
Variation displays
Explore this variation
Genomic context
Genes and regulation (39)
Flanking sequence
Population genetics
Individual genotypes (2566)
Linkage disequilibrium
Phenotype Data (4)
Phylogenetic Context (6)
Citations (58)
External Data
SNPedia
LOVD
Configure this page
Add your data
Export data
Bookmark this page
Share this page
Download view as CSV
rs7901695 SNP
Original source
Variants (including SNPs and indels) imported from dbSNP (release 137) | View in dbSNP
Alleles
Reference/Alternatives: T/G/A/C | Ancestral: C | Ambiguity code: N | MAF: 0.27 (C)
Location
Chromosome 10:114754088 (forward strand) | View in location tab
Co-located
with HGMD-PUBLIC CS071265
Evidence status
Synonyms
Archive dbSNP rs56472218, rs56913805
HGVS names
This variation has 42 HGVS names - click the plus to show
Genotyping chips
This variation has assays on 10 chips - click the plus to show
Phenotype Data
Significant data
Show/hide columns
Filter
Disease/Trait
Source(s)
Study
Clinical significance
Reported gene(s)
Associated variant(s)
Most associated allele
P value
Fasting proinsulin [View on Karyotype]
[MAGIC]
rs7901695
T
1.009e-16
Type 2 diabetes [View on Karyotype]
[NHGRI_GWAS_catalog]
pubmed:17463249
TCF7L2
rs7901695
rs7901695-C
1e-48
Association Results
Cited Variants
Genes
114751086..114757090
SNPs from Genome-wide association analyses. They are from NHGRI Catalog and from association results submitted to dbGaP
Links & Tools
GaP Browser



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SHORT REPORT

Phenotype–Genotype Integrator (PheGenI): synthesizing genome-wide association study (GWAS) data with existing genomic resources

Erin M Ramos[1], Douglas Hoffman[2], Heather A Junkins[1], Donna Maglott[2], Lon Phan[2], Stephen T Sherry[2], Mike Feolo*[,2] and Lucia A Hindorff*[,1]

Rapidly accumulating data from genome-wide association studies (GWASs) and other large-scale studies are most useful when synthesized with existing databases. To address this opportunity, we developed the Phenotype–Genotype Integrator (PheGenI), a user-friendly web interface that integrates various National Center for Biotechnology Information (NCBI) genomic databases with association data from the National Human Genome Research Institute GWAS Catalog and supports downloads of search results.

www.ncbi.nlm.nih.gov/gap/PheGenI

Key challenges and opportunities

- Curation a key bottleneck; automated data mining may facilitate
- Integration with other resources and data types will further biological understanding
- Providing data in a user-friendly way will increase adoption
- Collaborations can enable high priority improvements

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National Human Genome Research Institute | EMBL-EBI

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