

The 2013 *Nucleic Acids Research* Database Issue and the online Molecular Biology Database Collection

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ABSTRACT

The 20th annual Database Issue of *Nucleic Acids Research* includes 176 articles, half of which describe new online molecular biology databases and the other half provide updates on the databases previously featured in *NAR* and other journals. This year's highlights include two databases of DNA repeat elements; several databases of transcriptional factors and transcriptional factor-binding sites; databases on various aspects of protein structure and protein–protein interactions; databases for metagenomic and rRNA sequence analysis; and four databases specifically dedicated to *Escherichia coli*. The increased emphasis on using the genome data to improve human health is reflected in the development of the databases of genomic structural variation (NCBI's dbVar and EBI's DGVa), the NIH Genetic Testing Registry and several other databases centered on the genetic basis of human disease, potential drugs, their targets and the mechanisms of protein–ligand binding. Two new databases present genomic and RNAseq data for monkeys, providing wealth of data on our closest relatives for comparative genomics purposes. The *NAR* online Molecular Biology Database Collection, available at <http://www.oxfordjournals.org/nar/database/a/>, has been updated and currently lists 1512 online databases. The full content of the Database Issue is freely available online on the *Nucleic Acids Research* website (<http://nar.oxfordjournals.org/>).

NEW AND UPDATED DATABASES

This 1300-page virtual volume represents the 20th annual Database Issue of *Nucleic Acids Research* (*NAR*). It includes descriptions of 88 new online databases, 77 update articles on databases that have been previously featured in the *NAR* Database Issue (Table 1) and 11 articles with updates on database resources whose descriptions have been previously published in other journals (Table 2).

At this point it might be instructive to look back at the origin and evolution of the *NAR* Database Issue. Its history started from two supplementary issues that were published in *NAR* in April of 1991 and in May of 1992 and consisted of 18 and 19 articles, respectively (see <http://nar.oxfordjournals.org/content/19/supplement.toc> and <http://nar.oxfordjournals.org/content/20/supplement.toc>). These articles offered descriptions of several nucleotide sequence databases, such as GenBank, the EMBL Data Library, compilations of small RNA, tRNA, and 5S, 16S, and 23S rRNA sequences (including the Ribosomal Database Project), DNA sequences from *Escherichia coli* and a human genome database (GDB). Those first issues also included descriptions of several protein databases, such as SWISS-PROT, PIR, PROSITE, Restriction Enzyme Database (REBASE), Transcription Factors Database (TFD) and Histone database. There was also a medical genetics database, Haemophilia B, listing point mutations and indels in the coagulation factor IX (*F9*) gene that caused this blood clotting disorder, which has affected the royal families of several European countries.

The next issue, published on July 1, 1993, was the first one formally labelled as the Database Issue. It consisted of 24 articles, which added databases of RNA and protein structure and the ENZYME database. It was followed by

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Table 1. New online databases featured in the 2013 NAR Database issue

Database name	URL	Brief description
APPRIS	http://appris.bioinfo.cnio.es/	A system for annotating alternative splice isoforms
BioLiP	http://zhanglab.cmb.med.umich.edu/BioLiP/	Biologically relevant ligand-protein interactions
BSRD	http://kwanlab.bio.cuhk.edu.hk/BSRD	A repository of bacterial small regulatory RNA
CellLineNavigator	http://www.medicalgenomics.org/celllinenavigator	Cell line expression profiles by microarray analysis
ChIPBase	http://deepbase.sysu.edu.cn/chipbase/	Transcriptional regulation of lncRNA and microRNA genes from ChIP-Seq data
ChiTaRS	http://chimerasrch.bioinfo.cnio.es/	Chimeric RNAs of two or more different transcripts
CIL-CCDB	http://www.cellimagelibrary.org/	Images, videos and animations of various cell types from diverse organisms
CircaDB	http://bioinf.itmat.upenn.edu/circa/	Circadian gene expression profiles in human and mouse
CloneDB	http://www.ncbi.nlm.nih.gov/clone/	Clones and libraries: sequence data, map positions and distributor information
ClusterMine360	http://www.sigma54.ca/microbialclusters/	Microbial PKS/NRPS Biosynthesis
Cyanolyase	http://cyanolyase.genouest.org/	Sequences and motifs of the phycobilin lyase protein family
D2P2	http://d2p2.pro/	Database of Disordered Protein Predictions
dbVar	http://www.ncbi.nlm.nih.gov/dbvar	Structural variation in chromosomes: inversions, translocations, insertions and deletions
DGVa	http://www.ebi.ac.uk/dgva/	domain-centric Gene Ontology
dcGO	http://supfam.org/SUPERFAMILY/dcGO	Human DNA repeat families
Dfam	http://dfam.janelia.org	Disease and Gene Annotations database
DGA	http://dga.nubic.northwestern.edu/	microRNA targets on long noncoding RNAs
DIANA-LncBase	http://www.microrna.gr/LncBase	Database Of Biosynthesis clusters CURated and INtegrated
DoBISCUIT	http://www.bio.nite.go.jp/pks/	Various kinds of information about enzymes: small-molecule chemistry, biochemical pathways and drug compounds
EBI Enzyme Portal	http://www.ebi.ac.uk/enzymeportal	<i>Escherichia coli</i> Metabolome Database
ECMDB	http://www.ecmdb.ca/	Engineered endonucleases: zinc finger nucleases and transcription activator-like effector nucleases
EENdb	http://eendb.zfgenetics.org/	Energy profiles of protein structures
eProS	http://bioservices.hs-mittweida.de/Epros/	Human transcription factor-binding data from ChIP-seq
Factorbook	http://www.factorbook.org/	G-quadruplex Ligands Database
G4LDB	http://www.g4ldb.org/	Genomics of Drug Sensitivity in Cancer: Sensitivity for anti-cancer drugs in various cell lines
GDSC	http://www.cancerRxgene.org/	Genes with frameshifts in prokaryotic genomes and eukaryotic mRNA sequences
GeneTack	http://topaz.gatech.edu/GeneTack/db.html	Domain structure predictions and 3D models for proteins from model genomes
Genome3D	http://genome3d.eu/	Database of glycan 3D structures
Glycan Fragment DB	http://www.glycanstructure.org/fragment-db	Heritability data with trait-associated genomic loci
H2DB	http://tga.nig.ac.jp/h2db/	A knowledge database for the Hepatitis B Virus
HBVdb	http://hbvdb.ibcp.fr/HBVdb/	Gene expression profiles in haematopoiesis
HemaExplorer	http://servers.binf.ku.dk/shs/	Human Exon Splicing Events
HEXEvent	http://hertellab.mmg.uci.edu/cgi-bin/HEXEvent/HEXEventWEB.cgi	HOmo sapiens COmprehensive MOdel COllection of hand-curated transcription factor-binding site models
HOCOMOCO	http://autosome.ru/HOCOMOCO , http://cbrckauust.edu.sa/hocomoco/	Kinase-Inhibitor-Disease Family Map
KIDFamMap	http://gemdock.life.nctu.edu.tw/KIDFamMap/	Library of Apicomplexan Metabolic Pathways
LAMP	http://www.llamp.net/	Human lncRNA gene sequences and structures
Lncipedia	http://www.lncipedia.org/	Long non-coding RNA-associated diseases
LncRNADisease	http://cmbi.bjmu.edu.cn/lncrnadisease	Predicted genome of Last Universal Common Ancestor
LUCApedia	http://eeb.princeton.edu/lucapedia/	Comparative genomic tools for metagenome analysis
meta.MicrobesOnline	http://meta.MicrobesOnline.org/	Metabolomics experiments and associated metadata
MetaboLights	http://www.ebi.ac.uk/metabolights	Metal-binding sites in macromolecular structures
MetalPDB	http://metalweb.cerm.unifi.it/	Spatial organization of metabolic reactions in the mouse
METscout	http://metscout.mpg.de	Genome biology of the monarch butterfly <i>Danaus plexippus</i>
MonarchBase	http://monarchbase.umassmed.edu/	Chemogenomic experiments in yeast: connection of drug response to biological pathways, phenotypes, and networks
NetwoRx	http://ophid.utoronto.ca/networx/	Free online books on the NCBI website
NCBI Bookshelf	http://www.ncbi.nlm.nih.gov/books	Non-human Primate Reference Transcriptome Resource
NHPRTTR	http://nhprtr.org/	Genetic tests and laboratories that perform them
NIH Genetic Testing Registry	http://www.ncbi.nlm.nih.gov/gtr/	Naturally occurring Plant-based Anticancer Compound Targets
NPACT	http://crdd.osdd.net/raghava/npact/	Genome expression database of <i>Oikopleura dioica</i>
OikoBase	http://oikoarrays.biology.uiowa.edu/Oiko/	Microbial orthology resource
OrtholugeDB	http://www.pathogenomics.sfu.ca/ortholugedb/	Small secreted proteins from rice
OrySPSSP	http://genportal.org/SPD/index.do	A database of Papillomaviridae family of viruses
Papillomavirus Episteme	http://PaVE.niaid.nih.gov/	Plant Genome Duplication Database
PGDD	http://chibba.agtec.uga.edu/duplication/	Plant Intron Exon Comparison and Evolution
PIECE	http://probes.pw.usda.gov/piece/	tRNAs of plants and algae
PlantRNA	http://plantrna.ibmp.cnrs.fr/	

(continued)

Table 1. Continued

Database name	URL	Brief description
PR2	http://ssu-rna.org/	Protist Ribosomal reference database
prePPI	http://bhapp.c2b2.columbia.edu/PrePPI	Predicted and experimentally determined protein–protein interactions for yeast and human
PTMcode	http://ptmcode.embl.de/	Functional associations between posttranslational modifications within proteins
Quorumpeps	http://quorumpeps.ugent.be/	A database of quorum-sensing peptides
RhesusBase	http://www.rhesusbase.org/	A Knowledgebase for the Monkey Research Community
RiceFRIEND	http://ricefrend.dna.affrc.go.jp/	Rice Functionally Related gene Expression Network Database
RNApathwaysDB	http://rnb.genesilico.pl/	A database of RNA processing pathways
SecReT4	http://db-mml.sjtu.edu.cn/SecReT4/	Type IV Secretion system Resource
SEVA	http://seva.cnbc.csic.es/SEVA/	Standard European Vector Architecture: a collection of plasmids to analyse complex prokaryotic phenotypes
SIFTS	http://www.ebi.ac.uk/pdbe/docs/sifts/	Structure Integration with Function, Taxonomy and Sequences
SINEBase	http://sines.eimb.ru	A database of short interspersed elements (SINEs)
SomamiR	http://compbio.uthsc.edu/SomamiR/	Somatic mutations that impact microRNA targeting in cancer
Spermatogenesis Online	http://mcg.ustc.edu.cn/sdap1/spermgenes/	Spermatogenesis-related genes
SpliceAid-F	http://mi.caspur.it/SpliceAidF/	Human splicing factors and their RNA-binding sites
Spliceosome Database	http://spliceosomedb.ucsc.edu/	Spliceosome genes and proteins, splicing complexes
StreptomeDB	http://streptomedb.pharmaceutical-bioinformatics.de	Antibiotic, anti-tumour and immunosuppressant drugs produced by <i>Streptomyces</i> spp.
SwissBioisostere	http://www.swissbioisostere.ch/	Molecular replacements for ligand design
SwissSidechain	http://www.swissidechain.ch/	Non-natural amino acid sidechains for protein engineering
SynSysNet	http://bioinformatics.charite.de/synsysnet/	Synapse proteins, their structures and interactions
TCMID	http://www.megabionet.org/tcmid/	Traditional Chinese Medicine Integrated Database
TFClass	http://www.edgar-wingender.de/huTF_classification.html	Human transcription factors classified according to their DNA-binding domains
TissueNet	http://netbio.bgu.ac.il/tissuenet/	Tissue distribution of protein–protein interactions
TOPPR	http://iomics.ugent.be/toppr/	The Online Protein Processing Resource
TSGene	http://bioinfo.mc.vanderbilt.edu/TSGene/	Tumor Suppressor Gene database
UCNEbase	http://cgc.vital-it.ch/UCNEbase/	Ultraconserved non-coding elements and gene regulatory blocks
UUCD	http://uucd.biocuckoo.org/	Ubiquitin and ubiquitin-like conjugation database
ValidNESs	http://validness.ym.edu.tw/	Validated nuclear export signals-containing proteins
Voronia4RNA	http://proteininformatics.charite.de/voronia4rna_tools/v4rna/index	Packing of RNA molecules and complexes
WDDD	http://so.qbic.riken.jp/wddd/	Worm Developmental Dynamics Database
WholeCellKB	http://wholecellkb.stanford.edu/	Pathway and genome database of <i>Mycoplasma genitalium</i> for whole-cell modelling
WormQTL	http://www.wormqtl.org	Natural variation data in <i>Caenorhabditis</i> spp.
YM500	http://ngs.ym.edu.tw/ym500/	smRNA-seq database for miRNA research
ZInC	http://research.nhgri.nih.gov/zinc	Zebrafish Insertions Collection

Table 2. Database updates new for the NAR Database issue

Database name	URL	Previous article	Brief description
2P2Idb	http://dimr.cnrs-mrs.fr	2010	Structural data on protein–protein interactions and their inhibitors
Allen Brain Atlas	http://www.brain-map.org	2009	Gene expression and neuroanatomical data on human and mouse brain
BioGPS	http://biogps.org	2009	Gene annotation portal and a resource on gene and protein function
DARNED	http://beamish.ucc.ie/	2010	Database of RNA Editing
DoriC	http://tubic.tju.edu.cn/doric/	2007	Replication origin (<i>oriC</i>) regions in bacterial and archaeal genomes
FlyAtlas	http://flyatlas.org/	2007	<i>Drosophila</i> gene expression atlas
GenColors	http://sgb.fli-leibniz.de/	2005	Genome annotation and comparison database for small genomes
Genomicus	http://www.dyogen.ens.fr/genomicus	2010	Syntenic relationships between eukaryote genomes
InnateDB	http://www.innatedb.com/	2008	A database of mammalian innate immune response
MicroScope	http://www.genoscope.cns.fr/agc/microscope/	2009	Microbial genome annotation and analysis platform
NPIDB	http://npidb.belozersky.msu.ru/	2007	Nucleic acids–protein interaction database

NAR Database Issues in September 1994, then in January 1996, and each January after that.

In the past 20 years, the Database Issue has gradually grown in size before stabilizing at the level of ~180 articles. However, despite the almost 10-fold increase in the

number of published articles, the key topics of the current issue remain largely the same as 20 years ago. This issue again features articles from GenBank and the European Nucleotide Archive (formerly the EMBL Data Library), which, together with the DNA Data Bank of Japan, form

the International Nucleotide Sequence Database collaboration, INSDC (1–4). Just as 20 years ago, there are updates from SWISS-PROT and PIR (now combined into UniProt) and PROSITE (5,6).

Continuing the tradition of featuring well-curated databases of RNA sequences, this issue includes an update on SILVA, a widely used comprehensive database of bacterial, archaeal and eukaryotic 16S/18S and 23S/28S rRNA sequences (7), and a description of Protist Ribosomal Reference database (PR2), a new database that catalogs small subunit rRNA sequences from unicellular eukaryotes (8). An update on the Ribosomal Database Project, a constant feature of the *NAR* Database Issue since 1991 (9), was last published in 2009 (10). Other RNA databases in this issue include an update on Rfam (11), the universally acclaimed database of RNA families, as well as several databases on long non-coding RNA, microRNA and their targets. An update of MODOMICS, a database on RNA modification, is now supplemented by RNAPATHWAYSDB, a database of RNA maturation and decay pathways developed by the same group (12,13).

As before, this issue presents several transcription factor (TF) databases. Two of them cover TFs themselves: TFClass offers a classification of human TFs, while NPIDB presents structural information on DNA–protein and RNA–protein complexes (14,15). Several other databases collect information on the TF-binding sites. These include Factorbook, a database of TF-binding data from the ENCODE project; HOCOMOCO, a collection of human TF-binding sites; CTCFBSDB, a database of CCCTC-binding factor (CTCF)-binding sites; RegulonDB, a database of transcriptional regulation in *E. coli*; and SwissRegulon, a database of regulatory sites in human, mouse and yeast genomes and in model bacteria (16–20).

The structural databases featured in this issue all show a trend towards a better integration and cross-referencing tools. This refers both to the updates of well-known databases, such as the RCSB Protein Data Bank (PDB), CATH and PDBTM, and to such databases as EBI's SIFTS, a joint effort of UniProt and PDB to provide a residue level mapping of their entries and supplement it with annotation from other public databases; Genome3D, a recent collaborative project aiming to provide structural annotation from CATH and SCOP to the genomic sequences; and dcGO, which develops domain-centric ontologies to link protein domains with functions, phenotypes and diseases (21–23).

Likewise, with *E. coli* remaining the workhorse of molecular biology, this issue includes update articles on the EcoGene (the first one since 2000), EcoCyc and RegulonDB databases, as well as a description of the newly developed *E. coli* Metabolome Database (20,24–26).

HUMAN DISEASE GENOMICS—THE NEXT FRONTIER?

As discussed earlier (27), the original GDB did not survive the influx of the new data and multiple changes of ownership. Nevertheless, we now have a wide variety of

databases that cover different aspects of human genome and genomes of model organisms. This issue features annual updates from Ensembl and ENCODE projects and from the UCSC Genome Browser and the Japanese H-InvDB database (28–31). The model organism databases are represented by the updates to FlyBase, Mouse Genome database, Xenbase and ZFIN (32–35).

Two new databases, RhesusBase and NHPRTR, present extensive genome and RNAseq data for non-human primates, including great apes, old world monkeys, new world monkeys and prosimians (36,37). These data could go a long way towards establishing monkeys as model organisms for comparative genomics studies. One more database is dedicated to a more distant relative of human, the urochordate *Oikopleura dioica* (38).

A potentially important development is the construction of two new databases of repetitive DNA elements, Dfam and SINEBase (39,40). Along with the industry standard Repbase Update (41,42) and monthly RepBase Reports (<http://www.girinst.org/repbase/reports/>), these databases promise to contribute to a better understanding of eukaryotic repeat elements.

With the abundance of databases providing valuable tools for genome analysis, there is a clear trend towards bringing genomics 'from the bench to the bedside', i.e. using genomic data for a better understanding and, hopefully, better treatment of human disease. A number of projects, including ClinSeq (<http://www.genome.gov/20519355>), DDD (<http://www.ddduk.org/>) and UK10K (<http://www.uk10k.org/>) are working towards these goals, and several databases featured in this issue represent important steps in this direction. Last year's issue introduced the GWASdb database of human genetic variants identified by genome-wide association studies (43). GWAS Central, established in 2007 as HGVbaseG2P (44), has been revamped and now includes data from over 1000 studies. Now, a joint article from NCBI and EBI describes their databases of genomic structural variation, dbVar and DGVa (45). These databases cover diverse variation data including inversions, insertions and translocations that are >50 bp in length. NCBI is also developing ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>), a database of relationships between human gene variation and the observed health status (46). The task of streamlining the genetic tests that provide such information is taken up by the recently created NIH Genetic Testing Registry, a database of genetic tests and laboratories that perform them, with detailed information about what exactly is measured in each test and its analytic and clinical validity (47).

The impact of the genomic data on developing targeted approaches for fighting disease is particularly evident in the case of cancer. This issue features updates from three great databases, the UCSC Cancer Genome Browser (48), the Atlas of Genetics and Cytogenetics in Oncology and Haematology (49) and the TP53 website [(50), the first update of the database on tumor factor p53 mutations since 1997]. In addition, there are two new databases dedicated to studying cancer at the level of specific cell lines. The CellLineNavigator database provides gene

expression profiles of different cancer cell lines in different pathological states (51), whereas the Genomics of Drug Sensitivity in Cancer (GDSC) collects the results of high-throughput studies examining the sensitivity for anti-cancer drugs in various cell lines (52).

CURATION OF THE NAR DATABASE COLLECTION

During the past 20 years, all databases featured in the *NAR* Database Issues were added to the *NAR* online Molecular Biology Database Collection, available at <http://www.oxfordjournals.org/nar/database/a/>. With the annual attrition rate of <5%, this Collection has been steadily growing and, in 2012, exceeded 1400 database entries (53). It was clear that the list was due for a serious clean-up, and one of the authors (XMFS) devised and set in motion a semi-automated procedure to identify obsolete and non-responsive websites. Remarkably, >90% of the databases listed in the last year's release of the online Collection were found to be functional. Corresponding authors of close to a hundred non-responsive resources had been contacted and 44 websites (~3.2% of the total) have been approved for deletion. About 100 entries in the Collection have been updated by receiving corrected URLs, summaries highlighting recent developments, or some other changes in the deposited data.

Although deletion of 40 databases was well within the average drop-off rate and was hardly surprising, further analysis revealed that most of these resources were not lost. Instead, in the normal course of database evolution, they have been integrated into larger projects. For example, a couple of segmental duplications databases were merged into the Database of Genomic Variants (54), *NAR* Database Collection entry no. 655, while the NCBI's Cancer Chromosomes database has been merged into dbVar [described in detail in this issue, (45)]. Further, improved annotation of the human genome made redundant a number of resources that covered specific areas of the genome (e.g. the IXDB with its physical maps of human chromosome X).

In one instance, the ExDom database of exon-intron structures of genes in seven eukaryotic genomes (55) had to be removed from the Collection, as it has taken the commercial route and does not provide a free version anymore, although the author's company offered a discounted version for academic users. Unfortunately, the tightening budgets (56) might force other databases to follow the same path.

In total, the *NAR* online Molecular Biology Database Collection now includes 1512 databases sorted into 14 categories and 41 subcategories. The authors wishing to have their databases, published elsewhere, to be included in the Collection are welcome to contact XMFS directly.

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