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Lnc2Meth: a manually curated database of regulatory relationships between long non-coding RNAs and DNA methylation associated with human disease

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ABSTRACT

Lnc2Meth (http://www.bio-bigdata.com/Lnc2Meth/), an interactive resource to identify regulatory relationships between human long non-coding RNAs (lncRNAs) and DNA methylation, is not only a manually curated collection and annotation of experimentally supported lncRNAs-DNA methylation associations but also a platform that effectively integrates tools for calculating and identifying the differentially methylated lncRNAs and protein-coding genes (PCGs) in diverse human diseases. The resource provides: (i) advanced search possibilities, e.g. retrieval of the database by searching the lncRNA symbol of interest, DNA methylation patterns, regulatory mechanisms and disease types; (ii) abundant computationally calculated DNA methylation array profiles for the lncRNAs and PCGs; (iii) the prognostic values for each hit transcript calculated from the patients clinical data; (iv) a genome browser to display the DNA methylation landscape of the lncRNA transcripts for a specific type of disease; (v) tools to re-annotate probes to lncRNA loci and identify the differential methylation patterns for lncRNAs and PCGs with user-supplied external datasets; (vi) an R package (LncDM) to complete the differentially methylated lncRNAs identification and visualization with local computers. Lnc2Meth provides a timely and valuable resource that can be applied to significantly expand our understanding of the regulatory relationships between lncRNAs and DNA methylation in various human diseases.

INTRODUCTION

Recent studies have identified massive of long RNA transcripts lacking of protein-coding potential, termed long non-coding RNAs (lncRNAs) (1). In view of the considerable diversity of lncRNAs and their involvement in important biological processes, numerous resources specific for lncRNAs have been developed. The primary resources mainly collect or integrate basic annotation and functional information on lncRNA transcripts, such as NONCODE (2), LNCipedia (3), and LNCat (4). Another type of resource lists functional lncRNAs that participate in disease, such as lncRNAdb (5), LncRNADisease (6) and Lnc2Cancer (7). The remaining resources explore the regulatory roles of lncRNAs interacting with other functional elements, such as genetic variants [LincSNP (8), lncRNASNP (9), and LncVar (10)], RNA editing sites [LNCediting (11)], microRNAs [DIANA-LncBase (12) and ChIPBase (13)] and protein-coding genes (PCGs) [LncRNA2Target (14) and LncReg (15)]. However, a resource linking DNA methylation, an essential epigenetic regulator and disease biomarker, with lncRNAs is still lacking.

DNA methylation is a fundamental feature of epigenomes that can affect the expression of protein-coding or non-coding transcripts (16,17). In addition to the direct regulation of lncRNAs by DNA methylation via interactions with their promoter regions, recent research has brought several more intricate regulatory relationships between lncRNAs and DNA methylation to light (18–21). For example, the lncRNA *ecCEBPA* (extra-coding *CEBPA*), transcribed from the *CEBPA* gene locus is reported to be critical for regulation of DNA methylation at this site through interactions with DNA methyltransferase 1, DNMT1 (22). Expression of the lncRNA maternally expressed gene 3 (*MEG3*), a well-

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characterized tumor inhibitor, is associated with its first intron methylation mediated by TET2 (23). However, the wealth of knowledge on lncRNA-methylation regulatory relationships is fragmented, with relevant research findings documented across thousands of different articles in the literature. Therefore, establishing a high-quality database with experimentally verified information on the regulatory relationships between lncRNAs and DNA methylation should greatly facilitate further research on the appropriate regulatory mechanisms and functions.

To address this gap, we developed a manually curated database, Lnc2Meth (http://www.bio-bigdata.com/Lnc2Meth/), with the aim of providing a comprehensive resource and web tool for clarifying the regulatory relationships between human lncRNAs and associated DNA methylation status. With the aid of Lnc2Meth, researchers can identify the lncRNAs dysmethylated in a specific disease or the diseases with a specific dysmethylated lncRNA. Furthermore, Lnc2Meth provides a platform that integrates tools to re-annotate probes from the Illumina Infinium Human Methylation 450k BeadChip (HM450k) array to lncRNA loci and identify differential methylation patterns of the lncRNAs and PCGs with user-supplied external datasets.

DATA COLLECTION AND DATABASE CONTENT

Collection of experimentally verified lncRNA-methylation associations

Manually curated lncRNA-methylation associations were systematically refined from the literature obtained by screening the PubMed database (before July 2017) with the following keywords combinations: (i) (long noncoding RNA or long non-coding RNA or long ncRNA or lncRNA or long intergenic noncoding RNA or long intergenic non-coding RNA or large intergenic noncoding RNA or large intergenic non-coding RNA or lincRNA) and (methylation or methylated or epigenetic or epigenetically); (ii) (lncRNA symbols or lncRNA alias or Ensembl gene IDs) and (methylation or methylated or epigenetic or epigenetically). We integrated 16 271 lncRNA symbols/aliases, and 15 693 Ensembl gene IDs, obtained from both lncRNAdb (5) and the Long non-coding RNA gene annotation file in GENCODE (Release 27) (24), as the keywords used in the literature-mining procedure. All selected studies were reviewed by at least two researchers. In this step, we retrieved the lncRNA symbol, transcript information (loci, type), DNA methylation region and pattern, experimental method, tissue/cell type, associated single nucleotide polymorphisms (SNPs)/microRNAs/mRNAs/proteins, disease type, prognostic value, literature reference (PubMed ID, year of publication, title of paper), a brief description of lncRNA and DNA methylation from the original studies, and the regulatory relationships.

Here, the regulatory relationships between lncRNAs and DNA methylation were categorized into three groups: Cis-Methylated LncRNAs (CML), Trans-Methylation Due to LncRNAs (TMDL) and Trans-Methylation Regulated LncRNAs (TMRL). In the CML group, DNA methylation adjacent to/on the lncRNAs loci, such as the promoter or the imprinting control region, directly modulates the expression of target lncRNAs as a cis-regulator (25,26). In the TMDL group, lncRNAs regulate the DNA methylation of a trans- genomic loci as an intermedium by recruiting the DNA (cytosine-5-)-methyltransferase (DNMT) (27,28). In the TMRL group, alteration of the DNA methylation state in specific genomic loci regulates the transcription of its antisense-oriented lncRNAs (29,30). Significantly, these types of regulatory processes are dysregulated in human cancers and implicated in disease progression (31). In addition, the method of disease classification in Lnc2Meth was based on the Disease Ontology database (DO; http://disease-ontology.org) (32). Comprehensive genome annotation files were obtained from GENCODE (https://www.gencodegenes.org/) (24). Furthermore, to facilitate access to information from external resources, we linked GeneCards (33), HGNC (34), Ensembl (35), NCBI GenBank (36), NONCODE (2), LNCipedia (37), lncRNAdb (5), LncRNAWiki (38), Lnc2Cancer (7), GREAT (39), OMIM (40) and COSMIC databases (41), which allowed the efficiently retrieval of a substantial amount of annotation and functional information from external resources.

Prediction of methylation patterns of lncRNAs

The HM450k array datasets were collected systematically from the Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) and The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/). The Whole-Genome Bisulfite Sequencing (WGBS) datasets were collected from the Encyclopedia of DNA Elements (ENCODE; https://www.encodeproject.org/) and TCGA. A re-annotation method was used to predict the methylation patterns for lncRNAs from these datasets (Supplementary Method). The information on the associations with lncRNAs expression status were calculated from the corresponding RNA-sequencing datasets collected from TCGA (Supplementary Method).

Database content and statistics

The current version of the Lnc2Meth documents 471 manually curated lncRNA-methylation associations by reviewing more than 3900 publicly published papers (Table 1). Lnc2Meth additionally provides 301 computationally calculated differential methylation profiles for lncRNAs and PCGs in 11 255 diseases and 1964 normal samples for 72 types of disease (Supplementary Figure S1A and B).

Database implementation

The database was organized with MySQL (version 5.6.25) and queried using JSP scripts. The web interface was developed using HTML with JavaScript. The 'DMBrowser' module was constructed with JBrowse (release 1.12.1) to navigate transcript structure and explore the methylation patterns (42).

DATABASE FEATURES AND APPLICATIONS

Web interface

We provided a user-friendly web interface (Figure 1) for

Table 1. Statistics of the LncRNA-Methylation associations

Regulatory category	Numbers of associations	Numbers of LncRNAs	Numbers of regulating partners/targets				Numbers of diseases
			mRNAs	microRNAs	proteins	[a]SNPs	
[a]CML	427	71	11	11	25	8	93
[a]TMDL	37	25	24	9	8	—	19
[a]TMRL	7	6	1	—	—	—	4
Total	471	95	36	20	30	8	99

[a]SNP is short for single nucleotide polymorphism. CML is short for *cis*-methylated LncRNA. TMDL is short for *trans*-methylation due to LncRNA. TMRL is short for *trans*-methylation regulated LncRNA.

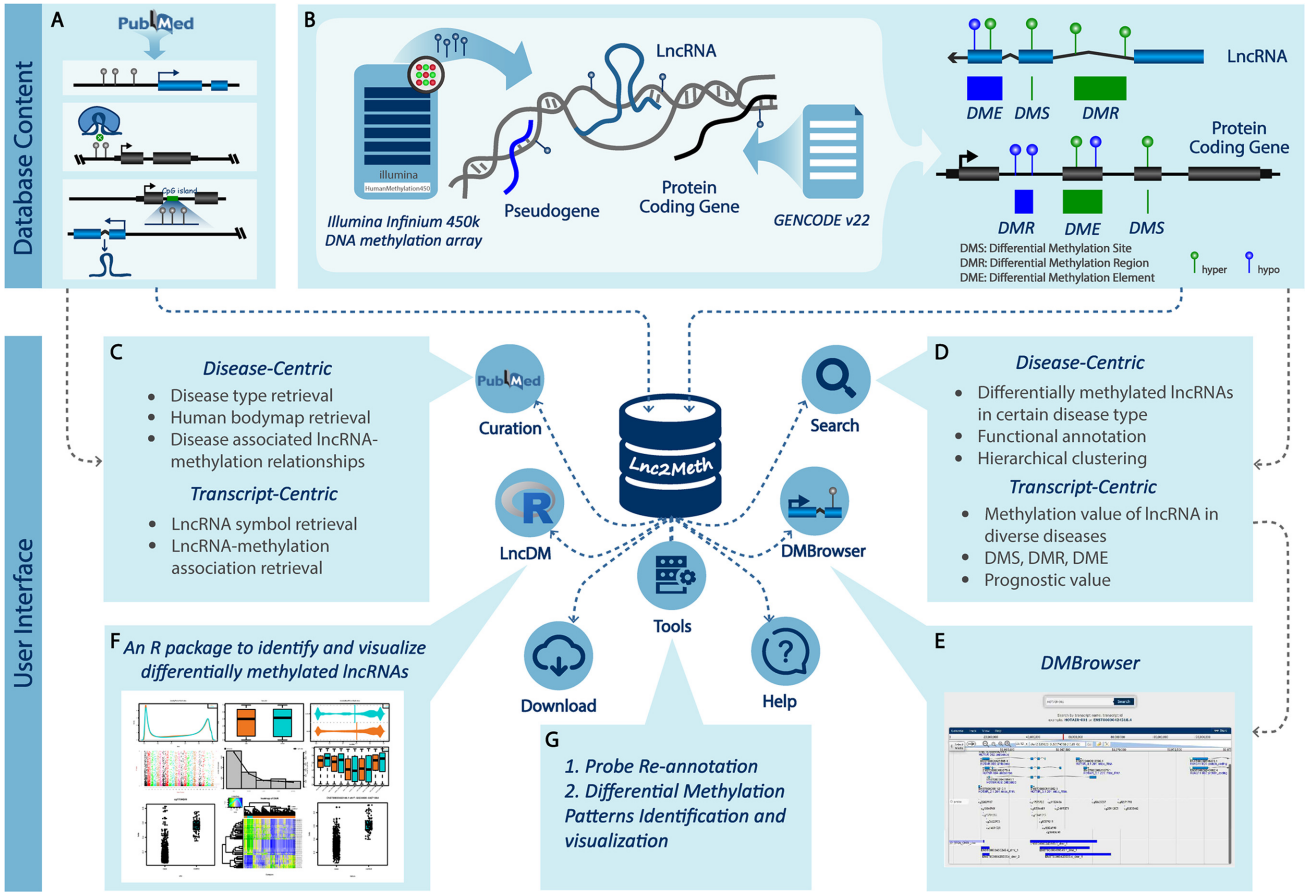

Figure 1. Content and interface of Lnc2Meth. (**A**) Manually curated lncRNA-methylation associations in Lnc2Meth. (**B**) Predicted differential methylation patterns of lncRNAs and PCGs in Lnc2Meth. (**C**) Curation module for manually curated lncRNA-methylation associations. (**D**) Search module for predicted lncRNA/PCG methylation patterns. (**E**) DMBrowser module for illustrating methylation landscape of lncRNAs and PCGs. (**F**) LncDM, an R package for calculating methylation patterns of lncRNAs and PCGs on local computers. (**G**) Tools module for identifying the differential methylation patterns of lncRNAs and PCGs online.

users to query the database through multiple modules and identify differential methylation patterns for a given lncRNA including (i) 'Curation', a retrieval module for experimentally verified lncRNA-methylation associations (Figure 2A–C, Supplementary Method), (ii) 'Search', a retrieval module for predicted differential methylation patterns of lncRNAs and PCGs (Figure 2D-K, Supplementary Method), (iii) 'DMBrowser', a genome browser for illustrating the methylation landscape of lncRNAs and PCGs, (iv) 'Tools', a server for identifying the differential methylation patterns of lncRNAs and PCGs online, (v) 'LncDM', an R package for calculating differential methylation patterns of lncRNAs and PCGs on local computers, (vi) 'Download', a module for downloading the differential methylation pattern profiles of lncRNAs and PCGs and (vii) 'Help', a module with detailed documentation of user tutorials.

Online tools for probe re-annotation and identification of differential methylation patterns for lncRNA/PCG's

Lnc2Meth provides two online tools. One is the 'Probe Re-annotation' tool (PR) and the other is the 'Differential Methylation Identification' tool (DMI). With the PR, users could obtain the annotation information for the

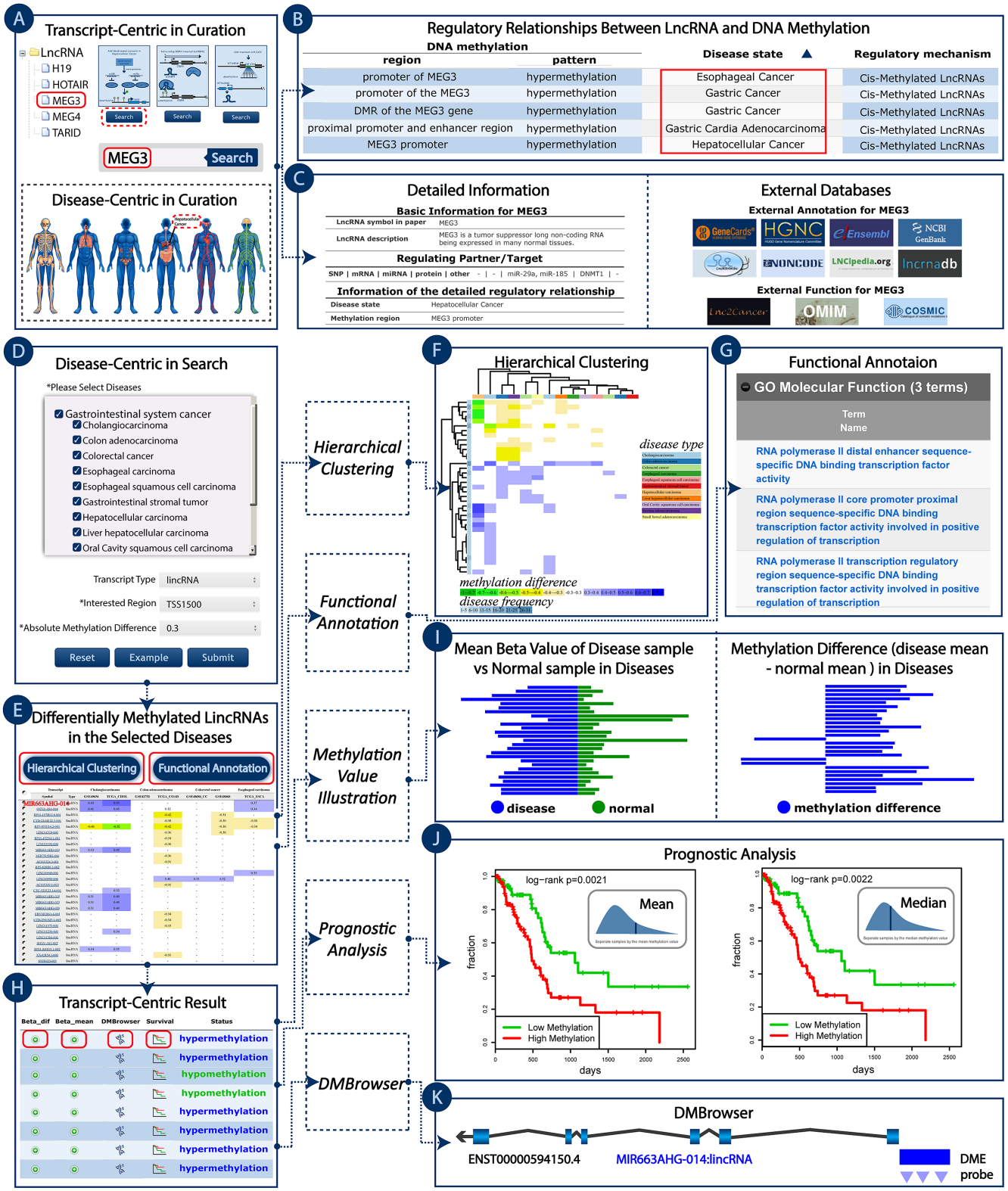

Figure 2. Case study of using Lnc2Meth. (**A**) The interface of the curation module, with *MEG3* input or selected as the retrieved lncRNA in 'Transcript-Centric' page. (**B**) Search result page of *MEG3*. (**C**) Search result page with detailed information. (**D**) The 'Disease-Centric' page of the search module with 'gastrointestinal system cancer' as 'Select Disease', 'lincRNA' as 'Transcript Type', 'TSS1500' as 'Interested Region', '0.3' as 'Absolute Methylation Difference'. (**E**) Search result page of 'gastrointestinal system cancer'. (**F**) Hierarchical clustering heat map of the methylation profile for selected lincRNAs. (**G**) Functional annotation results of the selected lincRNAs using GREAT. (**H**) Search result page of *MIR663AHG-014*. (**I**) Bar plots to illustrate the differentially methylated *MIR663AHG-014* in diseases. (**J**) Two Kaplan–Meier curves for *MIR663AHG-014* in Pancreatic adenocarcinoma. (**K**) DNA methylation landscape of *MIR663AHG-014* in Lnc2Meth DMBrowser.

HM450k array probes located in the functional regions (TSS200, TSS1500, 1_exon, intron, gene body, TSS10kb and TTS10kb) of their interested lncRNA/PCG by searching the gene symbol, Ensembl gene ID or the genomic loci. With the DMI, users could get the calculating results of the differential methylation patterns for their inputting lncRNA/PCG by uploading the user-supplied external HM450k array datasets (Supplementary Figure S2, Supplementary Method). Except for the lncRNAs with known gene symbol or Ensembl Gene ID, users could also re-annotate and calculate methylation patterns for a newly-assembled lncRNA by providing its genomic Loci. These analysis tools allow users to mine their own data to determine whether a given lncRNA is dysmethylated between the case and control samples.

DMBrowser of Lnc2Meth

JBrowse (release 1.12.1) was applied to develop a genome browser, DMBrowser, to provide a user-friendly interface for navigating the transcript structure and visualizing the differential methylation patterns of the transcript in specific diseases. Users could browse the structures and loci of the lncRNAs and the re-annotated probes by submitting the lncRNAs symbol, transcript ID or genomic interval. Tracks of methylation patterns in diverse diseases could be selected and added into the 'Search' page. The hit transcripts from the transcript-centric search module also contain links to DMBrowser. For the track of lncRNA transcripts, DMBrowser provides links to the UCSC Genome Browser for users further investigating the characteristics of the lncRNAs and methylation.

DISCUSSION AND FUTURE EXTENSIONS

In this study, we developed a database aimed to collect and illustrate the regulatory relationships between lncRNAs and DNA methylation with both experimentally verified and predicted information. Existing methylation-related databases that are widely in use have mainly focused on PCG and seldom contain lncRNA records (Supplementary Table S1). For example, PubMeth (43), MeInfoText (44) and DDMGD (45) amass data on gene-centric methylation data in disease while DiseaseMeth (46) and MethyCancer (47) provided information on disease-associated alterations of DNA methylation patterns with scattered records of lncRNAs. Therefore, Lnc2Meth, a resource for identifying DNA methylation associations with the lncRNAs, represents an early step towards meeting the extensive research interest and should facilitate the generation and systematic analysis of novel hypotheses regarding the regulatory mechanisms of lncRNA-DNA methylation associations.

In the future, we will continue to update and integrate data content in Lnc2Meth by: (i) continuous literature mining and information refining, (ii) expanding the available DNA methylation datasets detected by a variety of techniques, such as the HM450k array, WGBS, reduced representation bisulfite sequencing, and MeDIP-Seq. In addition, we plan to revise information on lncRNA annotation as an improvement of the GENCODE gene annotation catalogues. Lnc2Meth will be maintained and updated to ensure that it remains a useful resource for the research community.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR online.

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